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(54) Title: TREATMENT OF CANCER

(57) Abstract: Provided are methods relating to the treatment of cancer with a CDP-topoisomerase inhibitor, e.g., a CDP-camptothecin or camptothecin derivative conjugate, e.g., CRLX101 in combination with an inhibitor of the tryptophan metabolism pathway, e.g., an indoleamine-2,3-dioxygenase (IDO) inhibitor or a tryptophan-2, 3 -dioxygenase (TDO) inhibitor.

TREATMENT OF CANCER

Claim of Priority

This application claims priority to U.S. Patent Application No. 62/428,908, filed December 1, 2016, which is incorporated herein by reference in its entirety.

Background of the Invention

CRLX101 is a nanoparticle drug conjugate comprising the chemotherapeutic camptothecin. CRLX101 is being tested in clinical trials for the treatment of cancer. Indoleamine 2, 3-dioxygenase (IDO) and tryptophan 2, 3-dioxygenase (TDO) are immunomodulatory enzymes and part of the tryptophan metabolism pathway. Many cancers have been shown to overexpress IDO. There are several IDO inhibitors currently being tested in combination with other agents in preclinical and clinical studies for treating cancer. There is still a need for new therapies for the treatment of cancer.

Figures

FIG. 1 shows the tumor volumes of B16.F10 tumor-bearing mice administered vehicle, IDO inhibitor NLG-919 analog, CRLX101 or the combination.

FIG. 2 shows tumor volumes of B16.F10 tumor-bearing mice administered vehicle, IDO inhibitor INCB-024360 analog, CRLX101 or the combination.

FIG. 3 shows the tumor growth curves for B16.F10 tumor-bearing mice administered with vehicle, IDO inhibitor INCB-024360, CRLX101 or the combination.

FIG. 4 shows the tumor growth curves for B16.F10 tumor-bearing mice administered with vehicle, IDO inhibitor indoximod, CRLX101 or the combination.

FIGS. 5A-5B show the tumor growth curves for B16.F10 tumor-bearing mice administered with vehicle, IDO inhibitor NLG-919 analog, CRLX101 or the combination (Fig. 5A) or vehicle, the chemotherapeutic drug irinotecan, the IDO inhibitor NLG-919 analog, or the combination (Fig. 5B).

FIG. 6 shows the tumor growth curves for B16.F10 tumor-bearing mice administered with vehicle, IDO inhibitor NLG-919 analog, CRLX101, anti-PD-1 antibodies, the combination of CRLX101 and NLG-919 (Fig. 6A) or the combination of anti-PD-1 antibodies and an NLG-919 analog (Fig. 6B).

Summary of the Invention

In one aspect, the disclosure features, a method of treating a proliferative disorder, *e.g.*, a cancer, in a subject. The method comprises:

providing an initial administration of a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-topoisomerase I or II inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, to the subject in combination with an inhibitor of the tryptophan metabolism pathway, *e.g.*, an indoleamine-2,3-dioxygenase (IDO) inhibitor or a tryptophan-2,3-dioxygenase (TDO) inhibitor;

optionally, providing one or more subsequent administrations of the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-topoisomerase I or II inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, to thereby treat a proliferative disorder, *e.g.*, cancer.

In one embodiment, the method further comprises optionally providing one or more subsequent administrations of the inhibitor of the tryptophan metabolism pathway, *e.g.*, an indoleamine-2,3-dioxygenase (IDO) inhibitor or a tryptophan-2,3-dioxygenase (TDO) inhibitor. In some embodiments, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered before the inhibitor of the tryptophan metabolism pathway. In other embodiments, the inhibitor of the tryptophan metabolism pathway is administered before the CDP-topoisomerase inhibitor conjugate, particle or composition. In yet other embodiments, the CDP-topoisomerase inhibitor conjugate, particle or composition and the inhibitor of the tryptophan metabolism pathway are administered concurrently. In some embodiments, the inhibitor of the tryptophan metabolism pathway is administered multiple times before or after the administration of the CDP-topoisomerase inhibitor conjugate, particle or composition.

In one embodiment, the inhibitor of the tryptophan metabolism pathway is an IDO inhibitor. In some embodiments, the IDO inhibitor is an IDO1 and/or an IDO2 inhibitor.

In one embodiment, the IDO inhibitor is a small molecule.

In one embodiment, the IDO inhibitor is selected from indoximod, NSC-721782 (1-methyl-D-tryptophan), NLG-919, INCB-024360, INCB-024360 analog, or F001287. In one embodiment, the IDO inhibitor is an NLG-919 analog. In one embodiment, the IDO inhibitor is NLG-919.

In one embodiment, the IDO inhibitor is indoximod, NSC-721782 (1-methyl-D-tryptophan), NLG-919, INCB-024360, INCB-024360 analog, or F001287, and the proliferative disorder is a cancer. Examplary cancers include, but are not limited to, skin cancer (*e.g.,* melanoma and malignant melanoma), lung cancer (*e.g.,* small cell lung cancer and non-small cell lung cancer (*e.g.,* adenocarcinoma, squamous cell carcinoma, bronchoalveolar carcinoma and large cell carcinoma)), gastric and esophageal cancers (*e.g.*, gastroesophageal gastric), colorectal cancer (*e.g.*, colon, small intestine, rectum and/or appendix), bladder cancer, cancer of the genitourinary tract, *e.g.*, ovary (including fallopian, endometrial and peritoneal cancers and uterine sarcoma), cervical cancer, breast cancer, liver cancer, head and neck cancer, kidney cancer (*e.g.*, renal cell carcinoma (*e.g.*, papillary renal cell carcinoma, clear cell carcinoma, chromphobic carcinoma)), lymphoma (*e.g.*, Burkitt's, B-Cell, Hodgkin's or non-Hodgkin's lymphoma), and neural and glial cell cancers (*e.g.*, glioblastoma multiforme and astrocytoma).

In one embodiment, the IDO inhibitor is indoximod, NSC-721782 (1-methyl-D-tryptophan), NLG-919, INCB-024360, INCB-024360 analog, or F001287, and the IDO inhibitor is administered, *e.g.*, orally. In one embodiment, the IDO inhibitor is NLG-919 and is administered, *e.g.*, orally. In one embodiment, the IDO inhibitor is an NLG-919 analog and is administered, *e.g.*, orally.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, is administered at a dosage of 5 mg/m^2, 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, (wherein the dosage is expressed in mg of drug, as opposed to mg of conjugate).

In one embodiment, the one or more subsequent administrations of the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, is administered at a dosage of 5 mg/m^2, 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, wherein each subsequent administration is provided, independently, between 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 days after the previous, *e.g.*, the initial, administration.

In an embodiment, the dosage of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15 or 20 administrations is the same.

In an embodiment, the time between at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, or 20 administrations is the same.

In an embodiment, each subsequent administration is administered 12-16, *e.g.*, 14, days after the previous administration.

In an embodiment, at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20, 50 or 100 administrations are administered to the subject.

In an embodiment, the drug is provided at 12-17 mg/m^2 /administration, *e.g.*, 12 -15 mg/m^2 /administration, *e.g.*, 12 mg/m^2 or 15 mg/m^2.

In an embodiment, the drug is provided at 18-60 mg/m^2 /month, *e.g.*, 18 -30 mg/m^2 /month, 24-30 mg/m2/month or 36-60 mg/m^2/month.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor are administered on the same dosing schedule, *e.g.*, the topoisomerase inhibitor conjugate, particle or composition is administered on the same day, *e.g.*, within 1 hour, 2 hours, 3 hours, 5 hours, 10 hours, 12 hours, 15 hours, 18 hours, 21 hours, 24 hours, as the IDO inhibitor.

In an embodiment, the conjugate includes a topoisomerase I inhibitor and/or a topoisomerase II inhibitor. In an embodiment, the conjugate includes a topoisomerase

I inhibitor or combination of topoisomerase I inhibitors, *e.g.*, camptothecin, irinotecan, SN-38, topotecan, lamellarin D and derivatives thereof. In an embodiment, the conjugate includes a topoisomerase II inhibitor or a combination of topoisomerase II inhibitors, *e.g.*, eptoposide, tenoposide, doxorubicin and derivatives thereof. In one embodiment, the conjugate includes a combination of one or more topoisomerase I inhibitors and one or more topoisomerase II inhibitors. In an embodiment, the CDP-topoisomerase inhibitor conjugate is a CDP-camptothecin or camptothecin derivate conjugate, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate described herein, *e.g.*, CRLX101.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, decreases HIF1α levels in the subject having the proliferative disorder, *e.g.*, cancer. In some embodiments, HIF1α levels are compared to a reference standard, *e.g.*, HIF1α levels in a healthy subject that does not have cancer. In one embodiment, the method includes selecting a subject having increased HIF1α levels (*e.g.*, as compared to a reference standard) for treatment with the conjugate, particle or composition. In one embodiment, the method includes selecting a subject having or at risk of becoming resistant to treatment with a chemotherapeutic agent, *e.g.*, the subject is at risk of developing hypoxia-induced resistance to a chemotherapeutic agent, for treatment with the conjugate, particle or composition. In one embodiment, the method includes selecting a subject having or at risk of developing a metastases. In one embodiment, the method comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, in combination with an agent that increases HIF1α levels.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, is administered by intravenous administration over a period equal to or less than about 30 minutes, 45 minutes, 60 minutes, 90 minutes, 120

minutes, 150 minutes, or 180 minutes. In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, the CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.* CRLX101, is administered at a dosage of 5 mg/m^2, 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2 by intravenous administration over a period equal to or less than about 30 minutes, 45 minutes, 60 minutes or 90 minutes, *e.g.*, a period equal to or less than 30 minutes, 45 minutes or 60 minutes.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, is administered by intravenous administration over a period of about 12 hours, 15 hours, 18 hours, 21 hours, 24 hours, 27 hours, or 30 hours. In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, the CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.* CRLX101, is administered at a dosage of 5 mg/m^2, 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2 by intravenous administration over a period of about 12 hours, 15 hours, 18 hours, 21 hours, 24 hours, 27 hours, or 30 hours. Preferably, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, the CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.* CRLX101, is administered at a dosage of 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, 17 mg/m^2, or 18 mg/m^2 by intravenous administration over a period of about 12 hours, 15 hours, 18 hours, 21 hours, 24 hours, 27 hours, or 30 hours.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle

or composition, *e.g.*, the CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.* CRLX101, is administered at a dosage of 5 mg/m^2, 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, or 14 mg/m^2 twice a day, and optionally, one or more subsequent administrations of the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, is given at a dosage of 5 mg/m^2, 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, or 14 mg/m^2 twice a day, wherein each subsequent administration is provided, independently, between 9, 10, 11, 12, 13, 14, 15 or 16 days after the previous, *e.g.*, the initial, administration, to thereby treat the proliferative disorder. In one embodiment, the second daily dose is given 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20 hours after the initial daily dose.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2 and one or more subsequent administrations of CRLX101 to the subject, at a dosage of 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, *e.g.*, 14, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, lung cancer, *e.g.*, non-small cell lung cancer and/or small cell lung cancer (*e.g.*, squamous cell non-small cell lung cancer or squamous cell small cell lung cancer).

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2 and one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-9 days, *e.g.*, 7, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, lung cancer, *e.g.*, non-small cell lung cancer and/or small cell lung cancer (*e.g.*, squamous cell non-small cell lung cancer or squamous cell small cell lung cancer). In

some embodiments, the subsequent administrations are administered for 1-8 consecutive weeks with and without any rest.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, *e.g.*, 14, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, lung cancer, *e.g.*, non-small cell lung cancer and/or small cell lung cancer (*e.g.*, squamous cell non-small cell lung cancer or squamous cell small cell lung cancer).

In one embodiment, the lung cancer is refractory, relapsed or resistant to a platinum based agent (*e.g.*, carboplatin, cisplatin, oxaliplatin) and/or a taxane (*e.g.*, docetaxel, paclitaxel, larotaxel or cabazitaxel). In one embodiment, the subject has or is at risk of developing increased HIF1α levels, *e.g.*, as compared to a reference standard, *e.g.*, HIF1α levels in a healthy subject that does not have cancer). In one embodiment, the method comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, in combination with an agent that increases HIF1α levels.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, *e.g.*, 14, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, skin cancer.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-9, *e.g.*, 7, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, skin cancer.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, *e.g.*, 14, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, skin cancer.

In one embodiment, the CRLX101 is administered by intraperitoneal administration.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, *e.g.*, 14, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, gastric cancer, *e.g.*, gastroesophageal, gastric cancer.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-9, *e.g.*, 7, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, gastric cancer, *e.g.*, gastroesophageal, gastric cancer.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, *e.g.*, 14, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, gastric cancer, *e.g.*, gastroesophageal, gastric cancer.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2 or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2 or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, *e.g.*, 14, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, bladder cancer.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2 or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2 or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-9, *e.g.*, 7, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, bladder cancer.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, *e.g.*, 14, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, bladder cancer.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, *e.g.*, 14, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, colorectal cancer.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-9, *e.g.*, 7, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, colorectal cancer.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2

or 30 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, *e.g.*, 14, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, colorectal cancer.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, *e.g.*, 14, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, breast cancer, *e.g.*, estrogen receptor positive breast cancer, estrogen receptor negative breast cancer, HER-2 positive breast cancer, HER-2 negative breast cancer, triple negative breast cancer or inflammatory breast cancer.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-9, *e.g.*, 7, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, breast cancer, *e.g.*, estrogen receptor positive breast cancer, estrogen receptor negative breast cancer, HER-2 positive breast cancer, HER-2 negative breast cancer, triple negative breast cancer or inflammatory breast cancer.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, *e.g.*, 14, days after the previous,

e.g., the initial, administration, and the cancer is, *e.g.*, breast cancer, *e.g.*, estrogen receptor positive breast cancer, estrogen receptor negative breast cancer, HER-2 positive breast cancer, HER-2 negative breast cancer, triple negative breast cancer or inflammatory breast cancer.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 12 mg/m2, 13 mg/m2, 14 mg/m2,15 mg/m2, 16 mg/m2, or 17 mg/m2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 12 mg/m2, 13 mg/m2, 14 mg/m2, 15 mg/m2, 16 mg/m2, or 17 mg/m2, e.g., at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, e.g., 14, days after the previous, e.g., the initial, administration, and the cancer is, e.g., endometrial or cervical cancer.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-9, *e.g.*, 7, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, endometrial cancer..

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, *e.g.*, 14, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, endometrial or cervical cancer.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 12 mg/m2, 13 mg/m2, 14 mg/m2,15 mg/m2, 16 mg/m2, or 17 mg/m2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 12 mg/m2, 13 mg/m2, 14 mg/m2, 15 mg/m2, 16 mg/m2, or 17 mg/m2, e.g., at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, e.g., 14, days after the previous, e.g., the initial, administration, and the cancer is, e.g., a neural or glial cell cancers (e.g., glioblastoma multiforme or astrocytoma).

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-9, *e.g.*, 7, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, a neural or glial cell cancers (e.g., glioblastoma multiforme or astrocytoma).

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, *e.g.*, 14, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, a neural or glial cell cancers (e.g., glioblastoma multiforme or astrocytoma).

In one embodiment, the subject has or is at risk of developing increased HIF1α levels, *e.g.*, as compared to a reference standard, *e.g.*, HIF1α levels in a healthy subject that does not have cancer). In one embodiment, the method comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle

or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, in combination with an agent that increases HIF1α levels.

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, *e.g.*, 14, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, kidney cancer, *e.g.*, renal cell carcinoma (*e.g.*, papillary renal cell carcinoma, clear cell carcinoma, chromphobic carcinoma).

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-9, *e.g.*, 7, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, kidney cancer, *e.g.*, renal cell carcinoma (*e.g.*, papillary renal cell carcinoma, clear cell carcinoma, chromphobic carcinoma).

In an embodiment, the method includes an initial administration of CRLX101 to the subject at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 12-16, *e.g.*, 14, days after the previous, *e.g.*, the initial, administration, and the cancer is, *e.g.*, kidney cancer (*e.g.*, renal cell carcinoma or urothelial cell carcinoma).

In one embodiment, the subject has or is at risk of developing increased HIF1α levels, *e.g.*, as compared to a reference standard, *e.g.*, HIF1α levels in a healthy

subject that does not have cancer). In one embodiment, the method comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, in combination with an agent that increases HIF1α levels.

In an embodiment, the cancer is a cancer described herein. For example, the cancer can be a cancer of the bladder (including accelerated and metastatic bladder cancer), blood (*e.g.*, myeloma (*e.g.*, multilple myeloma) and leukemia (*e.g.*, acute myeloid leukemia)), breast (*e.g.*, estrogen receptor positive breast cancer, estrogen receptor negative breast cancer, HER-2 positive breast cancer, HER-2 negative breast cancer, triple negative breast cancer, inflammatory breast cancer), colon (including colorectal cancer, and cancers of the colon, small intestine, rectum and/or appendix), genitourinary tract, *e.g.*, ovary (including fallopian, endometrial and peritoneal cancers), cervix, prostate and testes, head and neck, esophageal, kidney (*e.g.*, renal cell carcinoma (*e.g.*, papillary renal cell carcinoma, clear cell carcinoma, chromphobic carcinoma)), liver (*e.g.,* hepatocellular carcinoma), lung (*e.g.*, small cell lung cancer and non-small cell lung cancer (including adenocarcinoma, squamous cell carcinoma, bronchoalveolar carcinoma and large cell carcinoma)), larynx, leukemia (*e.g.*, acute myeloid leukemia), lymphatic system (*e.g.*, Burkitt's, B-Cell, Hodgkin's or non-Hodgkin's lymphoma), pancreas (including exocrine pancreatic carcinoma), stomach (*e.g.*, gastroesophageal, gastric cancer), gastrointestinal cancer (*e.g.*, anal cancer or bile duct cancer (*e.g.*, Klatskin tumor)), gall bladder, thyroid, Ewing's sarcoma, nasoesophageal cancer, oropharyngeal, nasopharyngeal cancer, neural and glial cell cancers (*e.g.*, glioblastoma multiforme), skin (*e.g.* melanoma and malignant melanoma).

Preferred cancers include lung cancer (*e.g.*, small cell lung cancer and non-small cell lung cancer (including adenocarcinoma, squamous cell carcinoma, bronchoalveolar carcinoma and large cell carcinoma)), skin (*e.g.* melanoma and malignant melanoma), gastric cancer (*e.g.*, gastroesophageal, gastric cancer), bladder, colorectal cancer, breast cancer (*e.g.*, metastatic or locally advanced breast cancer), prostate cancer (*e.g.*, hormone sensitive and castrate-resistant prostate cancer), renal cell carcinoma, squamous cell cancer of the head and neck, lymphoma (*e.g.*, Burkitt's,

Hodgkin's or non-Hodgkin's lymphoma), glioblastoma, endometrial cancer, and kidney cancer.

In an embodiment, the cancer is skin cancer, lung cancer, gastric cancer, esophageal cancer, colorectal cancer, bladder cancer, endometrial cancer, cervical cancer, liver cancer, or head and neck cancer.

In an embodiment, the cancer is melanoma, non small cell lung cancer (adenocarcinoma and squamous cell carcinoma), gastric cancer, esophageal cancer, small cell lung cancer, or colorectal cancer.

In one embodiment, the subject has not been administered a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, prior to the initial administration.

In an embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered as a first line treatment for the cancer.

In an embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered as a second, third or fourth line treatment for the cancer. In an embodiment, the cancer is sensitive to one or more chemotherapeutic agents, *e.g.*, a platinum based agent, a taxane, an alkylating agent, an anthracycline (*e.g.*, doxorubicin (*e.g.*, liposomal doxorubicin)), an antimetabolite and/or a vinca alkaloid. In an embodiment, the cancer is a refractory, relapsed or resistant to one or more chemotherapeutic agents, *e.g.*, a platinum based agent, a taxane, an alkylating agent, an antimetabolite and/or a vinca alkaloid. In one embodiment, the cancer is, *e.g.*, ovarian cancer, and the ovarian cancer is refractory, relapsed or resistant to a platinum based agent (*e.g.*, carboplatin, cisplatin, oxaliplatin), a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel, cabazitaxel) and/or an anthracycline (*e.g.*, doxorubicin (*e.g.*, liposomal doxorubicin)). In one embodiment, the cancer is, *e.g.*, colorectal cancer, and the cancer is refractory, relapsed or resistant to an antimetabolite (*e.g.*, an antifolate (*e.g.*, pemetrexed, floxuridine, raltitrexed) and a pyrimidine analogue (*e.g.*, capecitabine, cytrarabine, gemcitabine, 5FU)) and/or a platinum based agent (*e.g.*, carboplatin, cisplatin, oxaliplatin). In one embodiment, the cancer is, *e.g.*, lung cancer, and the cancer is refractory, relapsed or resistant to a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel, cabazitaxel), a platinum based agent (*e.g.*, carboplatin, cisplatin, oxaliplatin), a vinca alkaloid (*e.g.*, vinblastine, vincristine, vindesine, vinorelbine), a

vascular endothelial growth factor (VEGF) pathway inhibitor, an epidermal growth factor (EGF) pathway inhibitor and/or an antimetabolite (*e.g.*, an antifolate (*e.g.*, pemetrexed, floxuridine, raltitrexed) and a pyrimidine analogue (*e.g.*, capecitabine, cytrarabine, gemcitabine, 5FU)). In one embodiment, the cancer is, *e.g.*, breast cancer, and the cancer is refractory, relapsed or resistant to a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel, cabazitaxel), a vascular endothelial growth factor (VEGF) pathway inhibitor, an anthracycline (*e.g.*, daunorubicin, doxorubicin (*e.g.*, liposomal doxorubicin), epirubicin, valrubicin, idarubicin), a platinum-based agent (*e.g.*, carboplatin, cisplatin, oxaliplatin), and/or an antimetabolite (*e.g.*, an antifolate (*e.g.*, pemetrexed, floxuridine, raltitrexed) and a pyrimidine analogue (*e.g.*, capecitabine, cytrarabine, gemcitabine, 5FU)). In one embodiment, the cancer is, *e.g.*, gastric cancer, and the cancer is refractory, relapsed or resistant to an antimetabolite (*e.g.*, an antifolate (*e.g.*, pemetrexed, floxuridine, raltitrexed) and a pyrimidine analogue (*e.g.*, capecitabine, cytrarabine, gemcitabine, 5FU)) and/or a platinum-based agent (*e.g.*, carboplatin, cisplatin, oxaliplatin).

In one embodiment, the subject has ovarian cancer that is refractory, relapsed or resistant to a platinum-based agent, and the subject is administered a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein. In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, is administered in combination with doxorubicin (*e.g.*, liposomal doxorubicin). In one embodiment, the doxorubicin (*e.g.*, the liposomal doxorubicin) is administered at a dose of about 20 mg/m^2, about 30 mg/m^2 or about 40 mg/m^2, every 24, 25, 26, 27, 28, 29, 30 or 31 days, *e.g.*, 28 days. In one embodiment, when the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with doxorubicin

(*e.g.*, liposomal doxorubicin), the dose at which the CDP-topoisomerase inhibitor conjugate, particle or composition is administered is 1%, 3%, 5%, 10%, 15%, 20%, 25%, 30% less than a dose described herein.

In one embodiment, the subject has gastric cancer and the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with doxorubicin (*e.g.*, liposomal doxorubicin). In one embodiment, the doxorubicin (*e.g.*, the liposomal doxorubicin) is administered at a dose of about 20 mg/m^2, about 30 mg/m^2 or about 40 mg/m^2, every 24, 25, 26, 27, 28, 29, 30 or 31 days, *e.g.*, 28 days.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered at a dose and/or dosing regimen described herein and the doxorubicin (*e.g.*, the liposomal doxorubicin) is administered at a dose of about 20 mg/m^2, about 30 mg/m^2 or about 40 mg/m^2, every 24, 25, 26, 27, 28, 29, 30 or 31 days, *e.g.*, 28 days. In one embodiment, when the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with doxorubicin (*e.g.*, liposomal doxorubicin), the dose at which the CDP-topoisomerase inhibitor conjugate, particle or composition is administered is 1%, 3%, 5%, 10%, 15%, 20%, 25%, 30% less than a dose described herein.

In an embodiment, the cancer has been sensitized to a topoisomerase inhibitor, *e.g.*, the subject has received radiation and/or the subject has received a phosphatase inhibitor (*e.g.*, okadiac acid) prior to the administration of the CDP-topoisomerase inhibitor conjugate, particle or composition. In one embodiment, the cancer is sensitized to topoisomerase inhibitors, *e.g.*, the subject receives radiation in combination with the administration of the CDP-topoisomerase inhibitor conjugate,

particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, and/or the subject is administered a phosphatase inhibitor (*e.g.*, okadiac acid) in combination with the administration of the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein. In one embodiment, the cancer is sensitized or has been sensitized to topoisomerase inhibitors and the cancer is a glial cell cancer (*e.g.*, glioblastoma multiforme) or head and neck cancer.

In one embodiment, the method further comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, in combination with one or more chemotherapeutic agents, *e.g.*, such as a chemotherapeutic described herein (such as an angiogenesis inhibitor) or combination of chemotherapeutic agents described herein.

In some embodiments, the one or more additional chemotherapeutic is selected from AZD4547, AZD9291, bevacizumab, carboplatin, cisplatin, cobimetnib, dabrafenib, dacarbazine, dasatinib, docetaxel, erlotinib, fluorouracil, gefitinib, gemcitabine, ipilimumab, lenalidomide, leucovorin, MEDI0680, MEDI4736, oxaliplatin, paclitaxel, pemetrexed, sunitinib, temozolomide, trametinib, tremelimumab, and vemurafenib.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor are administered in combination with one or more additional chemotherapeutic agent is selected from the group consisting of cisplatin, pemetrexed, carboplatin, paclitaxel, gemcitabine, docetaxel, dacarbazine, temozolomide, erlotinib, gefitinib, dabrafenib, and trametinib.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with one or more of: a platinum-based agent (*e.g.*, carboplatin, cisplatin, oxaliplatin), a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel, cabazitaxel), a vinca alkaloid (*e.g.*, vinblastine, vincristine, vindesine, vinorelbine), an antimetabolite (*e.g.*, an antifolate (*e.g.*, pemetrexed, floxuridine, raltitrexed) and a pyrimidine analogue (*e.g.*, 5FU, capecitabine, cytrarabine, gemcitabine)), an alkylating agent (*e.g.*, cyclophosphamide, decarbazine, melphalan, ifosfamide, temozolomide), a vascular endothelial growth factor (VEGF) pathway inhibitor, a poly ADP-ribose polymerase (PARP) inhibitor and an mTOR inhibitor.

In one embodiment, when the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor are administered in combination with an additional chemotherapeutic agent, the dose at which the CDP-topoisomerase inhibitor conjugate, particle or composition is administered is 1%, 3%, 5%, 10%, 15%, 20%, 25%, 30% less than a dose described herein.

In an embodiment, the method further comprises administering to the subject a treatment that reduces one or more side effect associated with administration of a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a treatment described herein.

In one aspect, the disclosure features, a method of treating a proliferative disorder, *e.g.*, a cancer, in a subject, *e.g.*, a human subject. The method comprises:

providing an initial administration of a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-topoisomerase I or II inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*,

CRLX101, is administered at a dosage of 5 mg/m^2, 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2,12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2, 30 mg/m^2, 31 mg/m^2, 32 mg/m^2, 33 mg/m^2, 34 mg/m^2, 35 mg/m^2 or 36 mg/m^2, (wherein the dosage is expressed in mg of drug, as opposed to mg of conjugate), to the subject in combination with an IDO inhibitor, *e.g.*, a IDO, *e.g.,* an IDO inhibitor, and

optionally, providing one or more subsequent administrations of the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-topoisomerase I or II inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, is administered at a dosage of 5 mg/m^2, 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2,12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2, 30 mg/m^2, 31 mg/m^2, 32 mg/m^2, 33 mg/m^2, 34 mg/m^2, 35 mg/m^2 or 36 mg/m^2, wherein each subsequent administration is provided, independently, between 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or 31 days after the previous, *e.g.*, the initial, administration, to thereby treat the proliferative disorder.

In an embodiment, the IDO inhibitor is indoximod, NSC-721782 (1-methyl-D-tryptophan), NLG-919, INCB-024360, INCB-024360 analog, or F001287. In some embodiments, the IDO inhibitor is an NLG-919 analog. In some embodiments, the IDO inhibitor is NLG-919.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, are administered on the same dosing schedule, *e.g.*, the topoisomerase inhibitor conjugate, particle or composition is administered on the same day, *e.g.*, within 1 hour, 2 hours, 3 hours, 5 hours, 10 hours, 12 hours, 15 hours, 18 hours, 21 hours, 24 hours, as the IDO inhibitor.

In one embodiment, the method further comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and an IDO inhibitor described herein, in combination with one or more chemotherapeutic agent, *e.g.*, such as a chemotherapeutic described herein.

In one aspect, the disclosure features, a method of treating a proliferative disorder, *e.g.*, a cancer, in a subject. The method comprises:

providing an initial administration of a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-topoisomerase I or II inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, is administered at a dosage of 3 mg/m^2, 4 mg/m^2, 5 mg/m^2, 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, or 11 mg/m^2, (wherein the dosage is expressed in mg of drug, as opposed to mg of conjugate), to the subject in combination with a IDO inhibitor, and

optionally, providing one or more subsequent administrations of the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-topoisomerase I or II inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, is administered at a dosage of 3 mg/m^2, 4 mg/m^2, 5 mg/m^2, 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, or 11 mg/m^2, wherein each subsequent administration is provided, independently, between 5, 6, 7, 8, 9 days after the previous, *e.g.*, the initial, administration, to thereby treat the proliferative disorder.

In an embodiment, the IDO inhibitor is a small molecule selected from indoximod, NSC-721782 (1-methyl-D-tryptophan), NLG-919, INCB-024360, INCB-024360 analog, or F001287. In some embodiments, the IDO inhibitor is an NLG-919 analog. In some embodiments, the IDO inhibitor is NLG-919.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin

conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO are administered on the same dosing schedule, *e.g.*, the topoisomerase inhibitor conjugate, particle or composition is administered on the same day, *e.g.*, within 1 hour, 2 hours, 3 hours, 5 hours, 10 hours, 12 hours, 15 hours, 18 hours, 21 hours, 24 hours, as the IDO inhibitor.

In one embodiment, the method further comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, in combination with an inhibitor of the programmed cell death 1 (PD-1)/programmed cell death ligand (PD-L, e.g. PD-L1 or PD-L2) pathway (a PD-1/PD-L pathway inhibitor, e.g., a PD-1, PD-L1, or PD-L2 pathway inhibitor described herein).

In one embodiment, the PD-1/PD-L pathway inhibitor is a small molecule or an antibody, e.g., a monoclonal or polyclonal antibody, e.g., a humanized monoclonal or polyclonal antibody with PD-1, PD-L1, or PD-L2 antagonist activity.

In one embodiment, the PD-1/PD-L pathway inhibitor is a PD-1 inhibitor. In some embodiments, the PD-1 inhibitor is selected from nivolumab (BMS-936558 or MDX1106), pembrolizumab (MK-3475, lambrolizumab, Keytruda), pidilizumab (CT-011), tigatuzumab, PDR001, AMP-224, MEDI0680 (AMP-514), and APE02058.

In one embodiment, the PD-1/PD-L pathway inhibitor is a PD-L1 inhibitor. In some embodiments, the PD-L1 inhibitor is selected from atezolizumab (MPDL3280A, RG7446), durvalumab (MEDI4736), avelumab (MSB0010718C), YW243.55.S70, and BMS-936559 (MDX-1105).

In one embodiment, the method further comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, in combination with an inhibitor of a tumor necrosis factor (TNF) receptor, *e.g.,* an anti-OX-40 monoclonal antibody such as MOXR0916/RG7888 or MEDI6469, an OX40 ligand fusion protein such as MEDI6469; an inhibitor of 4-1BB (also known as CD137 and ILA), such as Urelumab (BMS-663513) or PF-05082566; or chimeric antigen receptor-modified T

cells (CART-19 cells). CART-19 cells are T cells transduced with an antibody against CD19, which is linked to the intracellular signaling domains of 4-1BB and CD3-zeta.

In one embodiment, the method further comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, in combination with an inhibitor of a lymphocyte-activation gene 3 (LAG3), *e.g.,* an antibody such as BMS-986016 or IMP701; or a recombinant protein such as IMP321.

In one embodiment, the method further comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, in combination with an inhibitor of T cell immunoglobulin mucin-3 (TIM-3).

In one embodiment, the method further comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, in combination with an inhibitor of cytotoxic T-lymphocyte-associated protein 4 (CTLA4), *e.g.*, Tremelimumab (formerly CP-675,206 or ticilimumab); or Ipilimumab.

In one embodiment, the method further comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor in combination with one or more chemotherapeutic agent, *e.g.*, such as a chemotherapeutic described herein.

In one aspect, the disclosure features, a method of treating ovarian cancer (*e.g.*, epithelial carcinoma, fallopian tube cancer, germ cell cancer (*e.g.*, a teratoma), sex cord-stromal tumor (*e.g.*, estrogen-producing granulose cell tumor, virilizing Sertoli-Leydig tumor, arrhenoblastoma)), *e.g.*, locally advanced or metastatic ovarian cancer, in a subject, *e.g.*, a human subject. The method comprises administering a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-

topoisomerase I or II inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, in combination with an IDO inhibitor.

In an embodiment, the IDO inhibitor is selected from indoximod, NSC-721782 (1-methyl-D-tryptophan), NLG-919, INCB-024360, INCB-024360 analog, or F001287. In some embodiments, the IDO inhibitor is an NLG-919 analog. In some embodiments, the IDO inhibitor is NLG-919.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, is administered prior to surgery, after surgery or before and after surgery to remove the cancer, *e.g.*, to remove a primary tumor and/or a metastases.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, are administered on the same dosing schedule, *e.g.*, the topoisomerase inhibitor conjugate, particle or composition is administered on the same day, *e.g.*, within 1 hour, 2 hours, 3 hours, 5 hours, 10 hours, 12 hours, 15 hours, 18 hours, 21 hours, 24 hours, as the IDO inhibitor.

In one embodiment, the method further comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, in combination with one or more chemotherapeutic agents, *e.g.*, such as a chemotherapeutic described herein.

In one embodiment, the one or more chemotherapeutic agent is a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel, cabazitaxel). In one embodiment, the one or more chemotherapeutic agent is a platinum-based agent (*e.g.*, cisplatin, carboplatin, oxaliplatin). In one embodiment, the one or more chemotherapeutic agent is an anti-metabolite, *e.g.*, an antifolate (*e.g.*, pemetrexed, floxuridine, raltitrexed) or pyrimidine

analogue (*e.g.*, capecitabine, cytrarabine, gemcitabine, 5FU)). In one embodiment, the one or more chemotherapeutic agent is an anti-metabolite, *e.g.*, an antifolate (*e.g.*, pemetrexed, floxuridine, raltitrexed) or pyrimidine analogue (*e.g.*, capecitabine, cytrarabine, gemcitabine, 5FU)) and folinic acid (leucovorin).

In one embodiment, the chemotherapeutic agent is a MEK inhibitor, *e.g.*, trametinib (Mekinist™).

In one embodiment, the one or more chemotherapeutic agent is an angiogenesis inhibitor (*e.g.*, an angiogenesis inhibitor described herein such as an inhibitor of the VEGF pathway, *e.g.*, a VEGF inhibitor, *e.g.*, a small molecule inhibitor, or an antibody against VEGF, *e.g.*, bevacizumab; or a VEGF receptor inhibitor (*e.g.*, a VEGF receptor 1 inhibitor or a VEGF receptor 2 inhibitor), *e.g.*, a small molecule inhibitor, *e.g.*, sorafenib or sunitinib, or an antibody against VEGF receptor). In one embodiment, the one or more chemotherapeutic agent, *e.g.*, the angiogenesis inhibitor, *e.g.*, sorafenib, is administered at a dose of about 400 mg per day or less, daily, *e.g.*, 350 mg per day, 300 mg per day, 250 mg per day, 200 mg per day, or 150 mg per day. In one embodiment, the one or more chemotherapeutic agent, *e.g.*, the angiogenesis inhibitor, *e.g.*, sunitinib, is administered daily at a dose of about 50 mg per day or less, daily, *e.g.*, 45 mg per day, 40 mg per day, 38 mg per day, 30 mg per day, 25 mg per day, 20 mg per day, or 15 mg per day. In one embodiment, when the one or more chemotherapeutic agent is an angiogenesis inhibitor, *e.g.*, sorafenib or sunitinib, the dose at which the CDP-topoisomerase inhibitor conjugate, particle or composition is administered is 1%, 3%, 5%, 10%, 15%, 20%, 25%, or 30% less than a dose described herein.

In one embodiment, the one or more chemotherapeutic agent is an anthracycline (*e.g.*, doxorubicin (*e.g.*, liposomal doxorubicin), daunorubicin, epirubicin, idarubicin, mitoxantrone, valrubicin). In one embodiment, the cancer is refractory, relapsed or resistant to a taxane and/or a platinum-based agent.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor can be administered with one or more chemotherapeutic agent selected from: an anti-metabolite, *e.g.*, an antifolate (*e.g.*, pemetrexed, floxuridine, raltitrexed) or pyrimidine

analogue (*e.g.*, capecitabine, cytrarabine, gemcitabine, 5FU); an alkylating agent (*e.g.*, cyclophosphamide, decarbazine, melphalan, ifosfamide, temozolomide); a platinum-based agent (carboplatin, cisplatin, oxaliplatin); a vinca alkaloid (*e.g.*, vinblastine, vincristine, vindesine, vinorelbine).

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor can be administered with one or more chemotherapeutic agent selected from: capecitabine, cyclophosphamide, gemcitabine, ifosfamide, melphalan, oxaliplatin, vinorelbine, vincristine and pemetrexed. In one embodiment, the cancer is refractory, relapsed or resistant to a taxane and/or a platinum-based agent.

In one embodiment, the conjugate, particle or composition is administered at a dose and/or dosing schedule described herein. In one embodiment, when the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, are administered in combination with an additional chemotherapeutic agent, *e.g.*, one or more chemotherapeutic agent described herein, the dose at which the CDP-topoisomerase inhibitor conjugate, particle or composition is administered is 1%, 3%, 5%, 10%, 15%, 20%, 25%, 30% less than a dose described herein.

In one embodiment, the IDO inhibitor is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor are administered in combination with a treatment that reduces one or more side effect associated with the administration of a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a treatment described herein.

In another aspect the disclosure features a method of treating colorectal cancer (*e.g.*, colon, small intestine, rectum and/or appendix cancer), *e.g.*, locally advanced or metastatic colorectal cancer, in a subject, *e.g.*, a human subject. The method comprises administering a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-topoisomerase I or II inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, in combination with an IDO inhibitor.

In an embodiment, the IDO inhibitor is selected from indoximod, NSC-721782 (1-methyl-D-tryptophan), NLG-919, INCB-024360, INCB-024360 analog, or F001287. In some embodiments, the IDO inhibitor is an NLG-919 analog. In some embodiments, the IDO inhibitor is NLG-919.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, is administered prior to surgery, after surgery or before and after surgery to remove the cancer, *e.g.*, to remove the primary tumor and/or a metastases.

In one embodiment, the method further comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor in combination with one or more chemotherapeutic agent, *e.g.*, such as a chemotherapeutic described herein.

In one embodiment, the one or more chemotherapeutic agent is an antimetabolite, *e.g.*, an antifolate (*e.g.*, pemetrexed, floxuridine, raltitrexed). In one embodiment, the one or more chemotherapeutic agent is an antimetabolite, *e.g.*, pyrimidine analogue (*e.g.*, capecitabine, cytrarabine, gemcitabine, 5FU) and folinic acid (leucovorin). In one embodiment, the one or more chemotherapeutic agent is a platinum-based agent (*e.g.*, cisplatin, carboplatin, oxaliplatin). For example, in one embodiment, the one or more chemotherapeutic agent is an antimetabolite, *e.g.*, 5FU, folinic acid (leucovorin), and a platinum-based agent, *e.g.*, oxaliplatin. In another

embodiment, the one or more chemotherapeutic agent is an antimetabolite, *e.g.*, a pyrimidine analogue, *e.g.*, capecitabine.

In one embodiment, the chemotherapeutic agent is a MEK inhibitor, *e.g.*, trametinib (Mekinist™).

In one embodiment, the one or more chemotherapeutic agent is an angiogenesis inhibitor (*e.g.*, an angiogenesis inhibitor described herein such as an inhibitor of the VEGF pathway, *e.g.*, a VEGF inhibitor, *e.g.*, a small molecule inhibitor, or an antibody against VEGF, *e.g.*, bevacizumab; or a VEGF receptor inhibitor (*e.g.*, a VEGF receptor 1 inhibitor or a VEGF receptor 2 inhibitor), *e.g.*, a small molecule inhibitor, *e.g.*, sorafenib or sunitinib, or an antibody against VEGF receptor). In one embodiment, the one or more chemotherapeutic agent, *e.g.*, the angiogenesis inhibitor, *e.g.*, sorafenib, is administered at a dose of about 400 mg per day or less, daily, *e.g.*, 350 mg per day, 300 mg per day, 250 mg per day, 200 mg per day, or 150 mg per day. In one embodiment, the one or more chemotherapeutic agent is an angiogenesis inhibitor, *e.g.*, sunitinib, and is administered daily at a dose of about 50 mg per day or less, daily, *e.g.*, 45 mg per day, 40 mg per day, 38 mg per day, 30 mg per day, 25 mg per day, 20 mg per day, or 15 mg per day. In one embodiment, when the chemotherapeutic agent is an angiogenesis inhibitor, *e.g.*, sorafenib or sunitinib, the dose at which the CDP-topoisomerase inhibitor conjugate, particle or composition is administered is 1%, 3%, 5%, 10%, 15%, 20%, 25%, or 30% less than a dose described herein. In one embodiment, the chemotherapeutic agent is a platinum-based agent (*e.g.*, cisplatin, carboplatin, oxaliplatin).

In one embodiment, the one or more chemotherapeutic agent is a vascular endothelial growth factor (VEGF) pathway inhibitor, *e.g.*, a VEGF inhibitor or VEGF receptor inhibitor. In one embodiment, the VEGF inhibitor is bevacizumab or AV-951. In one embodiment, the VEGF receptor inhibitor is selected from CP-547632 and AZD2171. In one embodiment, the one or more chemotherapeutic agent is a VEGF pathway inhibitor, *e.g.*, bevacizumab, and an antimetabolite, *e.g.*, an antifolate (*e.g.*, pemetrexed, floruridine, raltitrexed) or pyrimidine analogue (*e.g.*, capecitabine, 5FU, cytrarabine, gemcitabine). In one embodiment, the one or more chemotherapeutic agent is a VEGF pathway inhibitor, *e.g.*, bevacizumab, an antimetabolite, *e.g.*, a pyrimidine analogue (*e.g.*, 5FU), and folinic acid (leucovorin). In another embodiment, the one or more chemotherapeutic agent is a VEGF pathway inhibitor, *e.g.*, bevacizumab, an antimetabolite, *e.g.*, a pyrimidine analogue (*e.g.*,

5FU), folinic acid (leucovorin), and a platinum-based agent (*e.g.*, cisplatin, carboplatin, oxaliplatin). In one embodiment, the cancer is refractory, relapsed or resistant to an antimetabolite and/or a platinum-based agent.

In another embodiment, the one or more chemotherapeutic agent is a VEGF pathway inhibitor, *e.g.*, bevacizumab, and an antimetabolite wherein the antimetabolite is a pyrimidine analogue, *e.g.*, capecitabine. In one embodiment, the chemotherapeutic agent is a platinum-based agent (*e.g.*, cisplatin, carboplatin, oxaliplatin). For example, in one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor are administered with one or more chemotherapeutic agent: a VEGF pathway inhibitor, *e.g.*, a VEGF inhibitor (*e.g.*, bevacizumab) or a VEGF receptor inhibitor, a pyrimidine analogue (*e.g.*, capecitabine), and a platinum-based agent (*e.g.*, oxaliplatin); or a VEGF pathway inhibitor (*e.g.*, bevacizumab) and a pyrimidine analogue (*e.g.*, capecitabine). In one embodiment, the cancer is refractory, relapsed or resistant to an antimetabolite and/or a platinum-based agent.

In one embodiment, the one or more chemotherapeutic agent is an epidermal growth factor (EGF) pathway inhibitor, *e.g.*, an EGF inhibitor or EGF receptor inhibitor. The EGF receptor inhibitor can be, *e.g.*, cetuximab, erlotinib, gefitinib, panitumumab. In one embodiment, the chemotherapeutic agent is an EGF pathway inhibitor, *e.g.*, cetuximab or panitumumab, and a VEGF pathway inhibitor, *e.g.*, bevacizumab. In one embodiment, the cancer is refractory, relapsed or resistant to an antimetabolite and/or a platinum-based agent.

In one embodiment, the conjugate, particle or composition is administered at a dose and/or dosing schedule described herein. In one embodiment, when the CDP-topoisomerase inhibitor conjugate, particle or composition is administered in combination with an additional chemotherapeutic agent, the dose at which the CDP-topoisomerase inhibitor conjugate, particle or composition is administered is 1%, 3%, 5%, 10%, 15%, 20%, 25%, 30% less than a dose described herein.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate,

particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, is administered in combination with a treatment that reduces one or more side effect associated with the administration of a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a treatment described herein.

In one embodiment, the IDO inhibitor is administered at a dose and/or dosing schedule described herein.

In one aspect, the disclosure features a method of treating lung cancer (*e.g.*, small cell lung cancer and non-small cell lung cancer (*e.g.*, adenocarcinoma, squamous cell carcinoma, bronchoalveolar carcinoma and large cell carcinoma)), *e.g.*, locally advanced or metastatic lung cancer, in a subject, *e.g.*, a human subject. The method comprises administering a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-topoisomerase I or II inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, in combination with an IDO inhibitor.

In an embodiment, the IDO inhibitor is selected from indoximod, NSC-721782 (1-methyl-D-tryptophan), NLG-919, INCB-024360, INCB-024360 analog, or F001287. In some embodiments, the IDO inhibitor is an NLG-919 analog. In some embodiments, the IDO inhibitor is NLG-919.

In one embodiment, the method includes selecting a subject who has squamous cell lung cancer; and

administering a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, to the subject in an amount effective to treat the cancer, to thereby treat the cancer.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, is administered prior to surgery, after surgery or before and after surgery to remove the cancer, *e.g.*, to remove a primary tumor and/or a metastases.

In one embodiment, the method further comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, in combination with one or more chemotherapeutic agent, *e.g.*, such as a chemotherapeutic described herein.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with an EGF pathway inhibitor, *e.g.*, cetuximab, erlotinib, gefitinib, panitumumab, and radiation. In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with an EGF pathway inhibitor, *e.g.*, cetuximab, erlotinib, gefitinib, panitumumab, and one or more additional chemotherapeutic agents. For example, the one or more chemotherapeutic agent can be a platinum-based agent (*e.g.*, cisplatin, carboplatin, oxaliplatin), a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel, cabazitaxel), a vinca alkaloid (*e.g.*, vinblastine, vincristine, vindesine, vinorelbine), an anti-metabolite, *e.g.*, an antifolate (*e.g.*, pemetrexed, floxuridine, raltitrexed) or pyrimidine analogue (*e.g.*, capecitabine, cytrarabine, gemcitabine, 5FU), and combinations thereof.

In one embodiment, the one or more chemotherapeutic agent is a MEK inhibitor, *e.g.*, trametinib (Mekinist™).

In one embodiment, the one or more chemotherapeutic agent is a vascular endothelial growth factor (VEGF) pathway inhibitor, *e.g.*, a VEGF inhibitor or VEGF receptor inhibitor. In one embodiment, the VEGF inhibitor is bevacizumab or AV-951. In one embodiment, the VEGF receptor inhibitor is selected from CP-547632 and AZD2171. In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and

the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with a VEGF pathway inhibitor, *e.g.*, bevacizumab, and radiation. In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with a VEGF pathway inhibitor, *e.g.*, bevacizumab, and one or more additional chemotherapeutic agents. For example, the chemotherapeutic agent can be a platinum-based agent (*e.g.*, cisplatin, carboplatin, oxaliplatin), a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel, cabazitaxel), a vinca alkaloid (*e.g.*, vinblastine, vincristine, vindesine, vinorelbine), an anti-metabolite, *e.g.*, an antifolate (*e.g.*, pemetrexed, floxuridine, raltitrexed) or pyrimidine analogue (*e.g.*, capecitabine, cytrarabine, gemcitabine, 5FU), and combinations thereof. In one embodiment, the cancer is refractory, relapsed or resistant to one or more chemotherapeutic agents, *e.g.*, an EGF pathway inhibitor, *e.g.*, erlotinib.

In one embodiment, the one or more chemotherapeutic agent is an angiogenesis inhibitor (*e.g.*, an angiogenesis inhibitor described herein such as an inhibitor of the VEGF pathway, *e.g.*, a VEGF inhibitor, *e.g.*, a small molecule inhibitor, or an antibody against VEGF, *e.g.*, bevacizumab; or a VEGF receptor inhibitor (*e.g.*, a VEGF receptor 1 inhibitor or a VEGF receptor 2 inhibitor), *e.g.*, a small molecule inhibitor, *e.g.*, sorafenib or sunitinib, or an antibody against VEGF receptor). In one embodiment, the one or more chemotherapeutic agent, *e.g.*, the angiogenesis inhibitor, *e.g.*, sorafenib, is administered at a dose of about 400 mg per day or less, daily, *e.g.*, 350 mg per day, 300 mg per day, 250 mg per day, 200 mg per day, or 150 mg per day. In one embodiment, the one or more chemotherapeutic agent, *e.g.*, the angiogenesis inhibitor, *e.g.*, sunitinib, is administered daily at a dose of about 50 mg per day or less, daily, *e.g.*, 45 mg per day, 40 mg per day, 38 mg per day, 30 mg per day, 25 mg per day, 20 mg per day, or 15 mg per day. In one embodiment, the chemotherapeutic agent, *e.g.*, the angiogenesis inhibitor, *e.g.*, bevacizumab, is administered at a dose of 15 mg/kg or less, *e.g.*, 10 mg/kg or less, *e.g.*, less than 10 mg/kg, *e.g.*, 8 mg/kg, 7 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, or 2 mg/kg.

In one embodiment, one or more subsequent administrations of the chemotherapeutic agent, *e.g.*, angiogenesis inhibitor, *e.g.*, bevacizumab, can be

administered, *e.g.*, wherein each subsequent administration is administered, independently, at 12-16, *e.g.*, 14 days after the previous administration of the angiogenesis inhibitor, *e.g.*, bevacizumab. In one embodiment, when the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with an angiogenesis inhibitor, *e.g.*, sorafenib, sunitinib or bevacizumab, the dose at which the CDP-topoisomerase inhibitor conjugate, particle or composition is administered is 1%, 3%, 5%, 10%, 15%, 20%, 25%, or 30% less than a dose described herein.

In one embodiment, the one or more chemotherapeutic agent is a platinum-based agent (*e.g.*, cisplatin, carboplatin, oxaliplatin). In one embodiment, the one or more chemotherapeutic agent is a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel, cabazitaxel), a vinca alkaloid (*e.g.*, vinblastine, vincristine, vindesine, vinorelbine) and/or an anti-metabolite, *e.g.*, an antifolate (*e.g.*, pemetrexed, floxuridine, raltitrexed) or pyrimidine analogue (*e.g.*, capecitabine, cytrarabine, gemcitabine, 5FU). In one embodiment, the method further includes administering radiation to the subject. In one embodiment, the cancer is refractory, relapsed or resistant to one or more chemotherapeutic agents, *e.g.*, an EGF pathway inhibitor (*e.g.*, erlonitib), a VEGF pathway inhibitor and/or a taxane.

In one embodiment, the one or more chemotherapeutic agent is a MEK inhibitor, e.g., trametinib (Mekinist™).

In one embodiment, the one or more chemotherapeutic agent is a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel, cabazitaxel). In one embodiment, the method further includes administering radiation to the subject. In one embodiment, the cancer is refractory, relapsed or resistant to one or more chemotherapeutic agents, *e.g.*, an EGF pathway inhibitor (*e.g.*, erlotinib), a VEGF pathway inhibitor and/or a platinum-based agent.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*,

an IDO inhibitor described herein, is administered in combination with an-ErBB inhibitor (*e.g.*, PF00299804).

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, is administered in combination with an aromase inhibitor (*e.g.*, MM-10-001).

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, is administered in combination with halichondrin B.

In one embodiment, the chemotherapeutic agent is an anti-metabolite, *e.g.*, an antifolate (*e.g.*, pemetrexed, floxuridine, raltitrexed). In one embodiment, the method further includes administering radiation to the subject. In one embodiment, the cancer is refractory, relapsed or resistant to one or more chemotherapeutic agents, *e.g.*, an EGF pathway inhibitor (*e.g.*, erlotinib), a VEGF pathway inhibitor, a taxane and/or a platinum-based agent.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, decreases HIF1α levels in the subject having lung cancer. In some embodiments, HIF1α levels are compared to a reference standard, *e.g.*, HIF1α levels in a healthy subject that does not have cancer. In one embodiment, the method includes selecting a subject having increased HIF1α levels (*e.g.*, as compared to a reference standard) for treatment with the conjugate, particle or composition. In one embodiment, the method includes selecting a subject having or at risk of becoming resistant to treatment with a chemotherapeutic agent, *e.g.*, the subject is at risk of developing hypoxia-induced resistance to a chemotherapeutic agent, for treatment with the, particle or composition. In one embodiment, the method includes selecting a subject having or at risk of developing a metastases. In

one embodiment, the method comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, in combination with an agent that increases HIF1α levels.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, is administered at a dose and/or dosing schedule described herein. In one embodiment, when the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with an additional chemotherapeutic agent, the dose at which the CDP-topoisomerase inhibitor conjugate, particle or composition is administered is 1%, 3%, 5%, 10%, 15%, 20%, 25%, 30% less than a dose described herein.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, is administered in combination with a treatment that reduces one or more side effect associated with the administration of a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a treatment described herein.

In one embodiment, the IDO inhibitor, *e.g.*, a IDO inhibitor described herein, is administered at a dose and/or dosing schedule described herein.

In one aspect, the disclosure features a method of treating breast cancer (*e.g.*, estrogen receptor positive breast cancer; estrogen receptor negative breast cancer; HER-2 positive breast cancer; HER-2 negative breast cancer; progesterone receptor positive breast cancer; progesterone receptor negative breast cancer; estrogen receptor

negative, HER-2 negative and progesterone receptor negative breast cancer (*i.e.*, triple negative breast cancer)), *e.g.*, locally advanced or metastatic breast cancer, in a subject, *e.g.*, a human subject. The method comprises administering a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-topoisomerase I or II inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, in combination with an IDO inhibitor.

In an embodiment, the IDO inhibitor is selected from indoximod, NSC-721782 (1-methyl-D-tryptophan), NLG-919, INCB-024360, INCB-024360 analog, or F001287. In some embodiments, the IDO inhibitor is an NLG-919 analog. In some embodiments, the IDO inhibitor is NLG-919.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, are administered on the same dosing schedule, *e.g.*, the topoisomerase inhibitor conjugate, particle or composition is administered on the same day, *e.g.*, within 1 hour, 2 hours, 3 hours, 5 hours, 10 hours, 12 hours, 15 hours, 18 hours, 21 hours, 24 hours, as the IDO inhibitor.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, is administered prior to surgery, after surgery or before and after surgery to remove the cancer, *e.g.*, to remove a primary tumor and/or a metastases.

In one embodiment, the method further comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, in combination with one or more chemotherapeutic agent, *e.g.*, such as a chemotherapeutic described herein.

In one embodiment, the one or more chemotherapeutic agent is a HER-2 pathway inhibitor, *e.g.*, a HER-2 inhibitor or a HER-2 receptor inhibitor. For example, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, is administered with trastuzumab.

In one embodiment, the chemotherapeutic agent is a MEK inhibitor, *e.g.*, trametinib (Mekinist™).

In some embodiments, the one or more chemotherapeutic agent is a vascular endothelial growth factor (VEGF) pathway inhibitor, *e.g.*, a VEGF inhibitor (*e.g.*, bevacizumab) or VEGF receptor inhibitor (*e.g.*, CP-547632 and AZD2171). In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, is administered in combination with bevacizumab. In some embodiments, the method further comprises administering one or more additional chemotherapeutic agent, *e.g.*, such as a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel, cabazitaxel). In one embodiment, the method further comprises administering one or more additional chemotherapeutic agent, *e.g.*, such as a poly ADP-ribose polymerase (PARP) inhibitor (*e.g.*, BSI 201, Olaparib (AZD-2281), ABT-888, AG014699, CEP 9722, MK 4827, KU-0059436 (AZD2281), LT-673, 3-aminobenzamide).

In some embodiments, the one or more chemotherapeutic agent is a platinum-based agent (*e.g.*, cisplatin, carboplatin, oxaliplatin). In some embodiments, the method further comprises administering one or more additional chemotherapeutic agent, *e.g.*, such as a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel, cabazitaxel). In some embodiments, the method further comprises administering one or more additional chemotherapeutic agent, *e.g.*, such as an mTOR inhibitor. Non-limiting examples of mTOR inhibitors include rapamycin, everolimus, AP23573, CCI-779 and SDZ-RAD. In one embodiment, the method further comprises administering a PARP inhibitor (*e.g.*, BSI 201, Olaparib (AZD-2281), ABT-888, AG014699, CEP 9722, MK 4827, KU-0059436 (AZD2281), LT-673, 3-aminobenzamide). In some

embodiments, the method further comprises administering one or more additional chemotherapeutic agent, *e.g.*, such as a VEGF pathway inhibitor, *e.g.*, a VEGF inhibitor (*e.g.*, bevacizumab) or VEGF receptor inhibitor (*e.g.*, CP-547632 and AZD2171).

In one embodiment, the one or more chemotherapeutic agent is an angiogenesis inhibitor (*e.g.*, an angiogenesis inhibitor described herein such as an inhibitor of the VEGF pathway). In one embodiment, the angiogenesis inhibitor, *e.g.*, sorafenib, is administered at a dose of about 400 mg per day or less, daily, *e.g.*, 350 mg per day, 300 mg per day, 250 mg per day, 200 mg per day, or 150 mg per day. In one embodiment, the angiogenesis inhibitor, *e.g.*, sunitinib, is administered daily at a dose of about 50 mg per day or less, daily, *e.g.*, 45 mg per day, 40 mg per day, 38 mg per day, 30 mg per day, 25 mg per day, 20 mg per day, or 15 mg per day. In one embodiment, the angiogenesis inhibitor, *e.g.*, bevacizumab, is administered at a dose of 15 mg/kg or less, *e.g.*, 10 mg/kg or less, *e.g.*, less than 10 mg/kg, *e.g.*, 8 mg/kg, 7 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, or 2 mg/kg. In one embodiment, one or more subsequent administrations of the angiogenesis inhibitor, *e.g.*, bevacizumab, can be administered, *e.g.*, wherein each subsequent administration is administered, independently, at 12-16, *e.g.*, 14 days after the previous administration of the angiogenesis inhibitor, *e.g.*, bevacizumab.

In one embodiment, when the chemotherapeutic agent is an angiogenesis inhibitor, *e.g.*, sorafenib or sunitinib, the dose at which the CDP-topoisomerase inhibitor conjugate, particle or composition is administered is 1%, 3%, 5%, 10%, 15%, 20%, 25%, or 30% less than a dose described herein.

In some embodiments, the chemotherapeutic agent is a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel, cabazitaxel). In some embodiments, the method further comprises administering one or more additional chemotherapeutic agent, *e.g.*, such as an mTOR inhibitor. Non-limiting examples of mTOR inhibitors include rapamycin, everolimus, AP23573, CCI-779 and SDZ-RAD. In one embodiment, the method further comprises administering one or more additional chemotherapeutic agent, *e.g.*, such as a PARP inhibitor (*e.g.*, BSI 201, Olaparib (AZD-2281), ABT-888, AG014699, CEP 9722, MK 4827, KU-0059436 (AZD2281), LT-673, 3-aminobenzamide).

In some embodiments, the chemotherapeutic agent is an epothilone (*e.g.*, ixabelipone, epothilone B, epothilone D, BMS310705, dehydelone, ZK-EPO).

In some embodiments, the method further comprises administering one or more additional chemotherapeutic agent, *e.g.*, such as an mTOR inhibitor. Non-limiting examples of mTOR inhibitors include rapamycin, everolimus, AP23573, CCI-779 and SDZ-RAD. In one embodiment, the method further comprises administering one or more additional chemotherapeutic agent, *e.g.*, such as a PARP inhibitor (*e.g.*, BSI 201, Olaparib (AZD-2281), ABT-888, AG014699, CEP 9722, MK 4827, KU-0059436 (AZD2281), LT-673, 3-aminobenzamide). In some embodiments, the method further comprises administering one or more additional chemotherapeutic agent, *e.g.*, such as a VEGF pathway inhibitor, *e.g.*, a VEGF inhibitor (*e.g.*, bevacizumab) or VEGF receptor inhibitor (*e.g.*, CP-547632 and AZD2171). In some embodiments, the method further comprises administering one or more additional chemotherapeutic agent, *e.g.*, such as an anthracycline (*e.g.*, daunorubicin, doxorubicin (liposomal doxorubicin), epirubicin, valrubicin and idarubicin) and/or an anti-metabolite (*e.g.*, floxuridine, pemetrexed, 5FU).

In some embodiments, the chemotherapeutic agent is an anthracycline (*e.g.*, daunorubicin, doxorubicin (liposomal doxorubicin), epirubicin, valrubicin and idarubicin). In one embodiment, the cancer is refractory, relapsed or resistant to one or more chemotherapeutic agents, *e.g.*, a HER-2 pathway inhibitor, a VEGF pathway inhibitor, a taxane, an antimetabolite and/or a platinum-based agent.

In some embodiments, the chemotherapeutic agent is an anti-metabolite, *e.g.*, an antifolate (*e.g.*, floxuridine, pemetrexed) or pyrimidine analogue (*e.g.*, 5FU)). In one embodiment, the cancer is refractory, relapsed or resistant to one or more chemotherapeutic agents, *e.g.*, a HER-2 pathway inhibitor, a VEGF pathway inhibitor, a taxane, an anthracycline and/or a platinum-based agent.

In some embodiments, the chemotherapeutic agent is an anthracycline (*e.g.*, daunorubicin, doxorubicin (liposomal doxorubicin), epirubicin, valrubicin and idarubicin) and an anti-metabolite (*e.g.*, floxuridine, pemetrexed, 5FU). In one embodiment, the cancer is refractory, relapsed or resistant to one or more chemotherapeutic agents, *e.g.*, a HER-2 pathway inhibitor, a VEGF pathway inhibitor, and/or a platinum-based agent.

In some embodiments, the one or more chemotherapeutic agent is an mTOR inhibitor. Non-limiting examples of mTOR inhibitors include rapamycin, everolimus, AP23573, CCI-779 and SDZ-RAD. In some embodiments, the method further comprises administering one or more additional chemotherapeutic agent, *e.g.*, such as

a PARP inhibitor (*e.g.*, BSI 201, Olaparib (AZD-2281), ABT-888, AG014699, CEP 9722, MK 4827, KU-0059436 (AZD2281), LT-673, 3-aminobenzamide).

In some embodiments, the chemotherapeutic agent is a PARP inhibitor (*e.g.*, BSI 201, Olaparib (AZD-2281), ABT-888, AG014699, CEP 9722, MK 4827, KU-0059436 (AZD2281), LT-673, 3-aminobenzamide).

In some embodiments, the one or more chemotherapeutic agent is a pyrimidine analogue, *e.g.*, a pyrimidine analogue described herein (*e.g.*, capecitabine). In some embodiments, the method further comprises administering one or more additional chemotherapeutic agent, *e.g.*, such as a taxane (*e.g.*, docetaxel, paclitaxel, larotaxel, cabazitaxel). In some embodiments, the method further comprises administering one or more additional chemotherapeutic agent, *e.g.*, such as an epothilone (*e.g.*, ixabelipone, epothilone B, epothilone D, BMS310705, dehydelone, ZK-EPO).

In one embodiment, the conjugate, particle or composition is administered at a dose and/or dosing schedule described herein. In one embodiment, when the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor are administered in combination with an additional chemotherapeutic agent, the dose at which the CDP-topoisomerase inhibitor conjugate, particle or composition is administered is 1%, 3%, 5%, 10%, 15%, 20%, 25%, 30% less than a dose described herein.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, decreases HIF1α levels in the subject having lung cancer. In some embodiments, HIF1α levels are compared to a reference standard, *e.g.*, HIF1α levels in a healthy subject that does not have cancer. In one embodiment, the method includes selecting a subject having increased HIF1α levels (*e.g.*, as compared to a reference standard) for treatment with the conjugate, particle or composition. In one embodiment, the method includes selecting a subject having or at risk of becoming resistant to treatment with a chemotherapeutic agent, *e.g.*, the subject is at risk of developing hypoxia-induced resistance to a chemotherapeutic

agent, for treatment with the, particle or composition. In one embodiment, the method includes selecting a subject having or at risk of developing a metastases. In one embodiment, the method comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, in combination with an agent that increases HIF1α levels.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with a treatment that reduces one or more side effect associated with the administration of a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a treatment described herein.

In one embodiment, the IDO inhibitor, *e.g.*, a IDO inhibitor described herein, is administered at a dose and/or dosing schedule described herein.

In one aspect, the disclosure features a method of treating gastric cancer (*e.g.*, gastric adenocarcinoma (*e.g.*, intestinal or diffuse), gastric lymphoma (*e.g.*, MALT lymphoma), carcinoid stromal tumor), *e.g.*, locally advanced or metastatic gastric cancer, in a subject, *e.g.*, a human subject. The method comprises administering a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-topoisomerase I or II inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, in combination with an IDO inhibitor.

In an embodiment, the IDO inhibitor is selected from indoximod, NSC-721782 (1-methyl-D-tryptophan), NLG-919, INCB-024360, INCB-024360 analog, or F001287. In some embodiments, the IDO inhibitor is an NLG-919 analog. In some embodiments, the IDO inhibitor is NLG-919.

In one embodiment, the gastric cancer is gastroesophageal junction adenocarcinoma.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, is administered prior to surgery, after surgery or before and after surgery to remove the cancer, *e.g.*, to remove a primary tumor and/or a metastases.

In one embodiment, the method further comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, in combination with one or more chemotherapeutic agent, *e.g.*, such as a chemotherapeutic described herein.

In one embodiment, the one or more chemotherapeutic agent is an anthracycline (*e.g.*, daunorubicin, doxorubicin (*e.g.*, liposomal doxorubicin), epirubicin, valrubicin, mitoxatrone, and idarubicin), a platinum-based agent (*e.g.*, cisplatin, carboplatin, oxaliplatin) and an anti-metabolite, *e.g.*, an antifolate (*e.g.*, floxuridine, pemetrexed, raltitrexed) or pyrimidine analogue (*e.g.*, 5FU, capecitabine, cytrarabine, gemcitabine)). For example, in one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with an anthracycline (*e.g.*, daunorubicin, doxorubicin (*e.g.*, liposomal doxorubicin), epirubicin, valrubicin, mitoxatrone and idarubicin), a platinum-based agent (*e.g.*, cisplatin, carboplatin, oxaliplatin) and an anti-metabolite, *e.g.*, an antifolate (*e.g.*, floxuridine, pemetrexed, raltitrexed) or pyrimidine analogue (*e.g.*, 5FU, capecitabine, cytrarabine, gemcitabine). In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with an anthracycline (*e.g.*, daunorubicin, doxorubicin (*e.g.*, liposomal doxorubicin), epirubicin, valrubicin, mitoxatrone and idarubicin).In one embodiment, the cancer is refractory, relapsed or resistant to one or

more chemotherapeutic agents, *e.g.*, a platinum-based agent (*e.g.*, cisplatin, carboplatin, oxaliplatin).

In one embodiment, the chemotherapeutic agent is a MEK inhibitor, *e.g.*, trametinib (Mekinist™).

In another embodiment, the one or more chemotherapeutic agent is a platinum-based agent (*e.g.*, cisplatin, carboplatin, oxaliplatin) and an anti-metabolite, *e.g.*, an antifolate (*e.g.*, floxuridine, pemetrexed, raltitrexed) or pyrimidine analogue (*e.g.*, 5FU, capecitabine, cytrarabine, gemcitabine).

In some embodiments, the chemotherapeutic agent is an anti-metabolite, *e.g.*, an antifolate (*e.g.*, floxuridine, pemetrexed, raltitrexed) or pyrimidine analogue (*e.g.*, capecitabine, 5FU, cytrarabine, gemcitabine). In one embodiment, the method further comprises administering one or more additional chemotherapeutic agent, *e.g.*, such as a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel, cabazitaxel). For example, in one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with an anti-metabolite, *e.g.*, an antifolate (*e.g.*, floxuridine, pemetrexed, raltitrexed) or pyrimidine analogue (*e.g.*, capecitabine, 5FU, cytrarabine, gemcitabine) and a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel, cabazitaxel).

In one embodiment, the one or more chemotherapeutic agent is an angiogenesis inhibitor (*e.g.*, an angiogenesis inhibitor described herein such as an inhibitor of the VEGF pathway, *e.g.*, a VEGF inhibitor, *e.g.*, a small molecule inhibitor, or an antibody against VEGF, *e.g.*, bevacizumab; or a VEGF receptor inhibitor, *e.g.*, a VEGF receptor 2 inhibitor, *e.g.*, a small molecule inhibitor, *e.g.*, sorafenib or sunitinib, or an antibody against VEGF receptor 2; or a VEGF receptor 1 inibitor, *e.g.*, a small molecule inhibitor, or an antibody against VEGF receptor 1). In one embodiment, the one or more chemotherapeutic agent, *e.g.*, the angiogenesis inhibitor, *e.g.*, sorafenib, is administered at a dose of about 400 mg per day or less, daily, *e.g.*, 350 mg per day, 300 mg per day, 250 mg per day, 200 mg per day, or 150 mg per day. In one embodiment, the angiogenesis inhibitor, *e.g.*, sunitinib, is administered daily at a dose of about 50 mg per day or less, daily, *e.g.*, 45 mg per day, 40 mg per day, 38 mg per day, 30 mg per day, 25 mg per day, 20 mg per day, or 15

mg per day. In one embodiment, the chemotherapeutic agent, *e.g.*, the angiogenesis inhibitor, *e.g.*, bevacizumab, is administered at a dose of 15 mg/kg or less, *e.g.*, 10 mg/kg or less, *e.g.*, less than 10 mg/kg, *e.g.*, 8 mg/kg, 7 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, or 2 mg/kg. In one embodiment, one or more subsequent administrations of the angiogenesis inhibitor, *e.g.*, bevacizumab, can be administered, *e.g.*, wherein each subsequent administration is administered, independently, at 12-16, *e.g.*, 14 days after the previous administration of the angiogenesis inhibitor, *e.g.*, bevacizumab. In one embodiment, when the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with an angiogenesis inhibitor, *e.g.*, sorafenib or sunitinib, the dose at which the CDP-topoisomerase inhibitor conjugate, particle or composition is administered is 1%, 3%, 5%, 10%, 15%, 20%, 25%, or 30% less than a dose described herein.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with radiation.

In some embodiments, the chemotherapeutic agent is a vascular endothelial growth factor (VEGF) pathway inhibitor, *e.g.*, a VEGF inhibitor (*e.g.*, bevacizumab) or VEGF receptor inhibitor (*e.g.*, CP-547632 and AZD2171). In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with bevacizumab. In one embodiment, the cancer is refractory, relapsed or resistant to one or more chemotherapeutic agents, *e.g.*, an antimetabolite, a platinum-based agent and/or an anthracycline.

In some embodiments, the one or more chemotherapeutic agent is an mTOR inhibitor. Non-limiting examples of mTOR inhibitors include rapamycin, everolimus,

AP23573, CCI-779 and SDZ-RAD. In one embodiment, the cancer is refractory, relapsed or resistant to one or more chemotherapeutic agents, *e.g.*, an antimetabolite, a platinum-based agent and/or an anthracycline.

In some embodiments, the one or more chemotherapeutic agent is a poly ADP-ribose polymerase (PARP) inhibitor (*e.g.*, BSI 201, Olaparib (AZD-2281), ABT-888, AG014699, CEP 9722, MK 4827, KU-0059436 (AZD2281), LT-673, 3-aminobenzamide). In one embodiment, the cancer is refractory, relapsed or resistant to one or more chemotherapeutic agents, *e.g.*, an antimetabolite, a platinum-based agent and/or an anthracycline.

In one embodiment, the conjugate, particle or composition is administered at a dose and/or dosing schedule described herein. In one embodiment, when the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with an additional chemotherapeutic agent, the dose at which the CDP-topoisomerase inhibitor conjugate, particle or composition is administered is 1%, 3%, 5%, 10%, 15%, 20%, 25%, 30% less than a dose described herein.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, decreases HIF1α levels in the subject having lung cancer. In some embodiments, HIF1α levels are compared to a reference standard, *e.g.*, HIF1α levels in a healthy subject that does not have cancer. In one embodiment, the method includes selecting a subject having increased HIF1α levels (*e.g.*, as compared to a reference standard) for treatment with the conjugate, particle or composition. In one embodiment, the method includes selecting a subject having or at risk of becoming resistant to treatment with a chemotherapeutic agent, *e.g.*, the subject is at risk of developing hypoxia-induced resistance to a chemotherapeutic agent, for treatment with the, particle or composition. In one embodiment, the method includes selecting a subject having or at risk of developing a metastases. In one embodiment, the method comprises administering the CDP-topoisomerase

inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, in combination with an agent that increases HIF1α levels.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with a treatment that reduces one or more side effect associated with the administration of a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a treatment described herein.

In one embodiment, the IDO inhibitor, *e.g.*, a IDO inhibitor described herein, is administered at a dose and/or dosing schedule described herein.

In one aspect, the invention features, a method of treating pancreatic cancer in a subject, the method comprising, administering a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-topoisomerase I or II inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, to the subject in combination with an IDO inhibitor.

In one embodiment, the IDO inhibitor is selected from indoximod, NSC-721782 (1-methyl-D-tryptophan), NLG-919, INCB-024360, INCB-024360 analog, or F001287. In some embodiments, the IDO inhibitor is an NLG-919 analog. In some embodiments, the IDO inhibitor is NLG-919.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered on the same dosing schedule, *e.g.*, the topoisomerase inhibitor conjugate, particle or composition is administered on the

same day, *e.g.*, within 1 hour, 2 hours, 3 hours, 5 hours, 10 hours, 12 hours, 15 hours, 18 hours, 21 hours, 24 hours, as the IDO inhibitor.

In one embodiment, the method further comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, in combination with one or more chemotherapeutic agent, *e.g.*, such as a chemotherapeutic described herein.

In one embodiment, the conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the IDO inhibitor, *e.g.*, a IDO inhibitor described herein, is administered at a dose and/or dosing schedule described herein.

In one aspect, the disclosure features, a method of treating a proliferative disorder, *e.g.*, a cancer, in a subject, *e.g.*, a human subject. The method comprises:

providing a subject who has a proliferative disorder, *e.g.*, cancer, associated with an increased level of HIF1α; and

administering a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-topoisomerase I or II inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, to the subject in combination with an IDO inhibitor.

In one embodiment, the IDO inhibitor is selected from indoximod, NSC-721782 (1-methyl-D-tryptophan), NLG-919, INCB-024360, INCB-024360 analog, or F001287. In some embodiments, the IDO inhibitor is an NLG-919 analog. In some embodiments, the IDO inhibitor is NLG-919.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, are administered on the same dosing schedule, *e.g.*, the topoisomerase inhibitor conjugate, particle or composition is administered on the same day, *e.g.*, within 1

hour, 2 hours, 3 hours, 5 hours, 10 hours, 12 hours, 15 hours, 18 hours, 21 hours, 24 hours, as the IDO inhibitor.

In an embodiment, the conjugate includes a topoisomerase I inhibitor and/or a topoisomerase II inhibitor. In an embodiment, the conjugate includes a topoisomerase I inhibitor or combination of topoisomerase I inhibitors, *e.g.*, camptothecin, irinotecan, SN-38, topotecan, lamellarin D and derivatives thereof. In an embodiment, the conjugate includes a topoisomerase II inhibitor or a combination of topoisomerase II inhibitors, *e.g.*, eptoposide, tenoposide, doxorubicin and derivatives thereof. In one embodiment, the conjugate includes a combination of one or more topoisomerase I inhibitors and one or more topoisomerase II inhibitors. In an embodiment, the CDP-topoisomerase inhibitor conjugate is a CDP-camptothecin or camptothecin derivate conjugate, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate described herein, *e.g.*, CRLX101.

In one embodiment, the proliferative disorder is cancer, *e.g.*, a cancer described herein.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, are administered in combination with one or more additional chemotherapeutic agent, *e.g.*, as described herein. In one embodiment, the method comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, in combination with an agent that increases HIF1α levels. In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered at a dose and/or dosing schedule described herein. In one embodiment, the IDO inhibitor, *e.g.*, a IDO inhibitor described herein, is administered at a dose and/or dosing schedule described herein.

In one embodiment, the method further comprises administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described

herein, *e.g.*, CRLX101, and the IDO inhibitor, in combination with one or more chemotherapeutic agent, *e.g.*, such as a chemotherapeutic described herein.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, can be administered in combination with one or more of the agents described herein. For example, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, can be administered in combination with an agent which reduces or inhibits one or more symptom of hypersensitivity. The CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, can be administered in combination with an inhibitor of the programmed cell death 1 (PD-1)/programmed cell death ligand (PD-L, e.g. PD-L1 or PD-L2) pathway (a PD-1/PD-L pathway inhibitor, e.g., a PD-1, PD-L1, or PD-L2 pathway inhibitor described herein).

In one aspect, the disclosure features, a method of treating a proliferative disorder, *e.g.*, a cancer, in a subject, *e.g.*, a human subject. The method comprises:

providing a subject who has a proliferative disorder, *e.g.*, cancer;

administering an agent which ameliorates bladder toxicity associated with therapy, *e.g.*, an agent which increases urinary excretion and/or neutralizes one or more urinary metabolite; and

administering a composition that comprises a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-topoisomerase I or II inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, to the subject in combination with an IDO inhibitor.

In one embodiment, the IDO inhibitor is selected from indoximod, NSC-721782 (1-methyl-D-tryptophan), NLG-919, INCB-024360, INCB-024360 analog, or F001287. In some embodiments, the IDO inhibitor is an NLG-919 analog. In some embodiments, the IDO inhibitor is NLG-919.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, are administered on the same dosing schedule, *e.g.*, the topoisomerase inhibitor conjugate, particle or composition is administered on the same day, *e.g.*, within 1 hour, 2 hours, 3 hours, 5 hours, 10 hours, 12 hours, 15 hours, 18 hours, 21 hours, 24 hours, as the IDO inhibitor.

In one embodiment, the agent which ameliorates bladder toxicity associated with therapy, *e.g.*, the agent which increases urinary excretion and/or neutralizes one or more urinary metabolite, is administered prior to, concurrently with and/or after administration with the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101.

In one embodiment, the agent which ameliorates bladder toxicity associated with therapy is saline, *e.g.*, intravenous saline, D5 half normal saline or D5 water. In one embodiment, the agent which increases urinary excretion and/or neutralizes one or more urinary metabolite is 2-mercaptoethane sulfonate sodium (MESNA). In one embodiment, the agent which ameliorates bladder toxicity associated with therapy is 2-mercaptoethane sulfonate sodium (MESNA) and the MESNA is administered intravenously at a dose of about 10%, 20%, 30% the dose of the camptothecin or camptothecin derivative and/or the MESNA is administered orally at a dose of about 20%, 30%, 40%, 50% the dose of the camptothecin or camptothecin derivative.

In an embodiment, the conjugate includes a topoisomerase I inhibitor and/or a topoisomerase II inhibitor. In an embodiment, the conjugate includes a topoisomerase I inhibitor or combination of topoisomerase I inhibitors, *e.g.*, camptothecin, irinotecan, SN-38, topotecan, lamellarin D and derivatives thereof. In an embodiment, the conjugate includes a topoisomerase II inhibitor or a combination of

topoisomerase II inhibitors, *e.g.*, eptoposide, tenoposide, doxorubicin and derivatives thereof. In one embodiment, the conjugate includes a combination of one or more topoisomerase I inhibitors and one or more topoisomerase II inhibitors. In an embodiment, the CDP-topoisomerase inhibitor conjugate is a CDP-camptothecin or camptothecin derivate conjugate, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate described herein, *e.g.*, CRLX101.

In one embodiment, the proliferative disorder is cancer, *e.g.*, a cancer described herein.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, is administered in combination with one or more additional chemotherapeutic agent, *e.g.*, as described herein. In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered at a dose and/or dosing schedule described herein. In one embodiment, the subject is administered more than one dose of the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, as described herein, and the agent which ameliorates bladder toxicity associated with therapy is administered prior to one or more dose of the CDP-topoisomerase inhibitor conjugate, particle or composition.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, is further administered in combination with one or more of the agents described herein. For example, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, can be administered in combination with an agent which reduces or inhibits one or more symptom of hypersensitivity.

In one embodiment, the method includes selecting a subject who has a proliferative disorder, *e.g.*, cancer, and has experienced cystitis, *e.g.*, has experienced

cystitis as a result of a previous chemotherapeutic treatment, for administration of an agent which ameliorates bladder toxicity associated with therapy and a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein.

In one embodiment, the IDO inhibitor, *e.g.*, a IDO inhibitor described herein, is administered at a dose and/or dosing schedule described herein.

In another aspect, the disclosure features a method of treating a subject, *e.g.*, a human subject, with a proliferative disorder, *e.g.*, cancer, comprising:

selecting a subject who has a proliferative disorder, *e.g.*, cancer, that has increased HIF1α levels, *e.g.*, as compared to a reference standard (*e.g.*, HIF1α levels of a healthy subject that does not have cancer); and

administering a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-topoisomerase I or II inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, in combination with an IDO inhibitor, to the subject in an amount effective to treat the cancer, to thereby treat the cancer.

In one embodiment, the IDO inhibitor is selected from indoximod, NSC-721782 (1-methyl-D-tryptophan), NLG-919, INCB-024360, INCB-024360 analog, or F001287. In some embodiments, the IDO inhibitor is an NLG-919 analog. In some embodiments, the IDO inhibitor is NLG-919.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, are administered on the same dosing schedule, *e.g.*, the topoisomerase inhibitor conjugate, particle or composition is administered on the same day, *e.g.*, within 1 hour, 2 hours, 3 hours, 5 hours, 10 hours, 12 hours, 15 hours, 18 hours, 21 hours, 24 hours, as the IDO inhibitor.

In an embodiment, the conjugate includes a topoisomerase I inhibitor and/or a topoisomerase II inhibitor. In an embodiment, the conjugate includes a topoisomerase I inhibitor or combination of topoisomerase I inhibitors, *e.g.*, camptothecin, irinotecan, SN-38, topotecan, lamellarin D and derivatives thereof. In an embodiment, the conjugate includes a topoisomerase II inhibitor or a combination of topoisomerase II inhibitors, *e.g.*, eptoposide, tenoposide, doxorubicin and derivatives thereof. In one embodiment, the conjugate includes a combination of one or more topoisomerase I inhibitors and one or more topoisomerase II inhibitors. In an embodiment, the CDP-topoisomerase inhibitor conjugate is a CDP-camptothecin or camptothecin derivate conjugate, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate described herein, *e.g.*, CRLX101.

In one embodiment, the subject has lung cancer (*e.g.*, small cell lung cancer and/or non-small cell lung cancer) or kidney cancer (*e.g.*, renal cell carcinoma).

In one embodiment, the cancer is a cancer described herein.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, is administered in combination with one or more additional chemotherapeutic agent, *e.g.*, as described herein. In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered at a dose and/or dosing schedule described herein.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, is administered in combination with one or more of the agents described herein. For example, the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition described herein, *e.g.*, CRLX101, and the IDO inhibitor, *e.g.*, an IDO inhibitor described herein, can be administered in combination with an agent which reduces or inhibits one or more

symptom of hypersensitivity and/or an agent which increases urinary excretion and/or neutralizes one or more urinary metabolite.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and the drawings, and from the claims.

Detailed Description of the Invention

The present invention relates to compositions of therapeutic cyclodextrin-containing polymers (CDP) designed for drug delivery of a topoisomerase inhibitor such as camptothecin or a camptothecin derivative. In certain embodiments, these cyclodextrin-containing polymers improve drug stability and/or solubility, and/or reduce toxicity, and/or improve efficacy of the topoisomerase inhibitor when used *in vivo*.

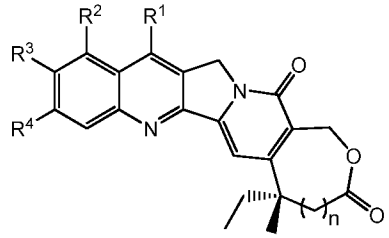
Furthermore, by selecting from a variety of linker groups that link or couple CDP to a topoisomerase inhibitor such as camptothecin or a camptothecin derivative, and/or targeting ligands, the rate of drug release from the polymers can be attenuated for controlled delivery. The invention also relates to methods of treating subjects with compositions described herein. The invention further relates to methods for conducting a pharmaceutical business comprising manufacturing, licensing, or distributing kits containing or relating to the CDP-topoisomerase inhibitor conjugates, particles and compositions described herein.

More generally, the present invention provides water-soluble, biocompatible polymer conjugates comprising a water-soluble, biocompatible polymer covalently attached to the topoisomerase inhibitor through attachments that are cleaved under biological conditions to release the topoisomerase inhibitor.

Polymeric conjugates featured in the methods described herein may be useful to improve solubility and/or stability of a bioactive/therapeutic agent, such as camptothecin, reduce drug-drug interactions, reduce interactions with blood elements including plasma proteins, reduce or eliminate immunogenicity, protect the agent from metabolism, modulate drug-release kinetics, improve circulation time, improve drug half-life (*e.g.*, in the serum, or in selected tissues, such as tumors), attenuate toxicity, improve efficacy, normalize drug metabolism across subjects of different

species, ethnicities, and/or races, and/or provide for targeted delivery into specific cells or tissues.

In preferred embodiments, the topoisomerase inhibitor in the CDP-topoisomerase inhibitor conjugate, particle or composition is camptothecin or a camptothecin derivative. The term "camptothecin derivative", as used herein, includes camptothecin analogues and metabolites of camptothecin. For example, camptothecin derivatives can have the following structure:



wherein

R^1 is H, OH, optionally substituted alkyl (*e.g.*, optionally substituted with NR^a_2 or OR_a, or SiR^a_3), or SiR^a_3; or R^1 and R^2 may be taken together to form an optionally substituted 5- to 8-membered ring (*e.g.*, optionally substituted with NR^a_2 or OR^a);

R^2 is H, OH, NH_2, halo, nitro, optionally substituted alkyl (*e.g.*, optionally substituted with NR^a_2 or OR^a, NR^a_2, $OC(=O)NR^a_2$, or $OC(=O)OR^a$);

R^3 is H, OH, NH_2, halo, nitro, NR^a_2, $OC(=O)NR^a_2$, or $OC(=O)OR^a$

R^4 is H, OH, NH_2, halo, CN, or NR^a_2; or R^3 and R^4 taken together with the atoms to which they are attached form a 5- or 6-membered ring (*e.g.* forming a ring including $-OCH_2O-$ or $-OCH_2CH_2O-$);

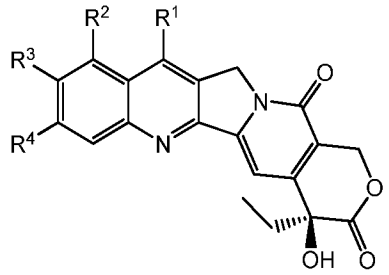
each R^a is independently H or alkyl; or two R^as, taken together with the atom to which they are attached, form a 4- to 8-membered ring (*e.g.*, optionally containing an O or NR^b)

R_b is H or optionally substituted alkyl (*e.g.*, optionally substituted with OR^c or NR^c_2);

R^c is H or alkyl; or, two R^cs, taken together with the atom to which they are attached, form a 4- to 8-membered ring; and

n = 0 or 1.

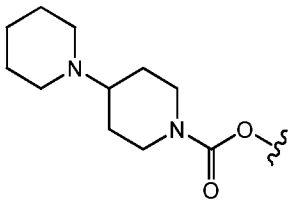
In some embodiments, the camptothecin or camptothecin derivative is the compound as provided below.



In one embodiment, R^1, R^2, R^3 and R^4 of the camptothecin derivative are each H, and n is 0.

In one embodiment, R^1, R^2, R^3 and R^4 of the camptothecin derivative are each H, and n is 1.

In one embodiment, R^1 of the camptothecin derivative is H, R^2 is $–CH_2N(CH_3)_2$, R^3 is –OH, R^4 is H; and n is 0.

In one embodiment, R^1 of the camptothecin derivative is $–CH_2CH_3$, R^2 is H, R^3 is: 

, R^4 is H, and n is 0.

In one embodiment, R^1 of the camptothecin derivative is $–CH_2CH_3$, R^2 is H, R^3 is –OH, R^4 is H, and n is 0.

In one embodiment, R^1 of the camptothecin derivative is *tert*-butyldimethylsilyl, R^2 is H, R^3 is –OH and R^4 is H, and n is 0.

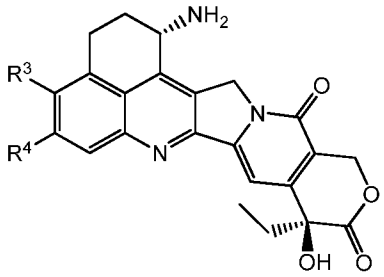
In one embodiment, R^1 of the camptothecin derivative is *tert*-butyldimethylsilyl, R^2 is hydrogen, R^3 is –OH and R^4 is hydrogen, and n is 1.

In one embodiment, R^1 of the camptothecin derivative is *tert*-butyldimethylsilyl, R^2, R^3 and R^4 are each H, and n is 0.

In one embodiment, R^1 of the camptothecin derivative is *tert*-butyldimethylsilyl, R^2, R^3 and R^4 are each H, and n is 1.

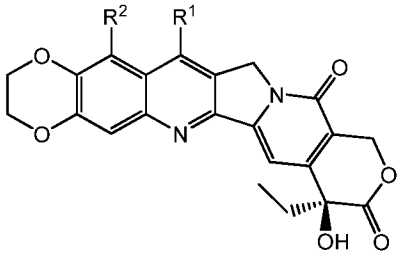
In one embodiment, R^1 of the camptothecin derivative is $–CH_2CH_2Si(CH_3)_3$ and R^2, R^3 and R^4 are each H.

In one embodiment, R^1 and R^2 of the camptothecin derivative are taken together with the carbons to which they are attached to form an optionally substituted ring. In one embodiment, R^1 and R^2 of the camptothecin derivative are taken together with the carbons to which they are attached to form a substituted 6-membered ring. In one embodiment, the camptothecin derivative has the following formula:

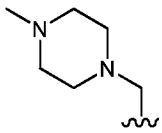


. In one embodiment, R^3 is methyl and R^4 is fluoro.

In one embodiment, R^3 and R^4 are taken together with the carbons to which they are attached to form an optionally substituted ring. In one embodiment, R^3 and R^4 are taken together with the carbons to which they are attached to form a 6-membered heterocyclic ring. In one embodiment, the camptothecin derivative has the following formula:

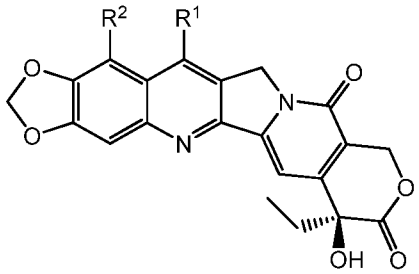


. In one embodiment, R^1 is:

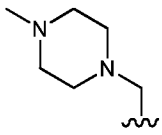


and R^2 is hydrogen.

In one embodiment, the camptothecin derivative has the following formula:

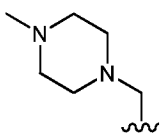


. In one embodiment, R^1 is:



and R^2 is hydrogen.

In one embodiment, R^1 is:



; R^2 is H, R^3 is methyl, R^4 is chloro; and n is 1.

In one embodiment, R^1 is $-CH=NOC(CH_3)_3$, R^2, R^3 and R^4 are each H, and n is 0.

In one embodiment, R^1 is $-CH_2CH_2NHCH(CH_3)_2$, R^2, R^3 and R^4 are each H; and n is 0.

In one embodiment, R^1 and R^2 are H, R^3 and R^4 are fluoro, and n is 1.

In one embodiment, each of R^1, R^3, and R^4 is H, R^2 is NH_2, and n is 0.

In one embodiment, each of R^1, R^3, and R^4 is H, R^2 is NO_2, and n is 0.

An "effective amount" or "an amount effective" refers to an amount of the CDP-topoisomerase inhibitor conjugate, particle or composition which is effective, upon single or multiple dose administrations to a subject, in treating a cell, or curing, alleviating, relieving or improving a symptom of a disorder. An effective amount of the conjugate, particle or composition may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the compound to elicit a desired response in the individual. An effective amount is also one in which any toxic or detrimental effects of the conjugate, particle or composition is outweighed by the therapeutically beneficial effects.

As used herein, the term "subject" is intended to include human and non-human animals. Exemplary human subjects include a human patient having a disorder, *e.g.*, a disorder described herein, or a normal subject. The term "non-human animals" includes all vertebrates, *e.g.*, non-mammals (such as chickens, amphibians, reptiles) and mammals, such as non-human primates, domesticated and/or agriculturally useful animals, *e.g.*, sheep, dog, cat, cow, pig, etc.

As used herein, the term "treat" or "treating" a subject having a disorder refers to subjecting the subject to a regimen, *e.g.*, the administration of a CDP-topoisomerase inhibitor conjugate, particle or composition, such that at least one symptom of the disorder is cured, healed, alleviated, relieved, altered, remedied, ameliorated, or improved. Treating includes administering an amount effective to alleviate, relieve, alter, remedy, ameliorate, improve or affect the disorder or the symptoms of the disorder. The treatment may inhibit deterioration or worsening of a symptom of a disorder.

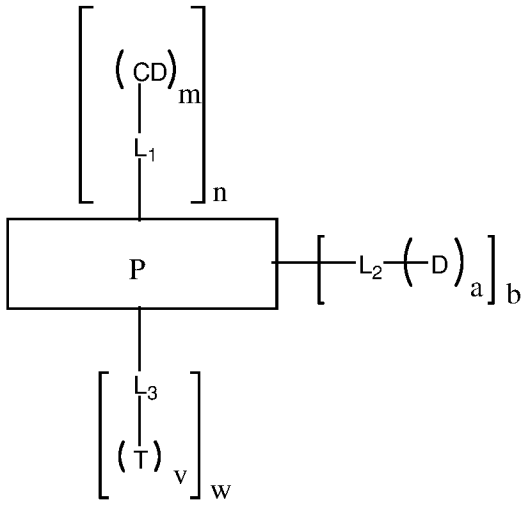
An amount of a CDP-topoisomerase inhibitor conjugate, particle or composition effective to prevent a disorder, or "a prophylactically effective amount" of the conjugate, particle or composition as used in the context of the administration

of an agent to a subject, refers to subjecting the subject to a regimen, *e.g.*, the administration of a CDP-topoisomerase inhibitor conjugate, particle or composition such that the onset of at least one symptom of the disorder is delayed as compared to what would be seen in the absence of the regimen.

CDP-Topoisomerase inhibitor conjugates, particles and compositions

Described herein are cyclodextrin containing polymer ("CDP")-topoisomerase inhibitor conjugates, wherein one or more topoisomerase inhibitors are covalently attached to the CDP (*e.g.*, either directly or through a linker). The CDP-topoisomerase inhibitor conjugates include linear or branched cyclodextrin-containing polymers and polymers grafted with cyclodextrin. Exemplary cyclodextrin-containing polymers that may be modified as described herein are taught in U.S. Patent Nos. 7,270,808, 6,509,323, 7,091,192, 6,884,789, U.S. Publication Nos. 20040087024, 20040109888 and 20070025952.

Accordingly, in one embodiment the CDP-topoisomerase inhibitor conjugate is represented by Formula I:



(I)

wherein

P represents a linear or branched polymer chain;

CD represents a cyclic moiety such as a cyclodextrin moiety;

L_1, L_2 and L_3, independently for each occurrence, may be absent or represent a linker group;

D, independently for each occurrence, represents a topoisomerase inhibitor or a prodrug thereof (*e.g.*, a camptothecin or camptothecin derivative);

T, independently for each occurrence, represents a targeting ligand or precursor thereof;

a, m, and v, independently for each occurrence, represent integers in the range of 1 to 10 (preferably 1 to 8, 1 to 5, or even 1 to 3);

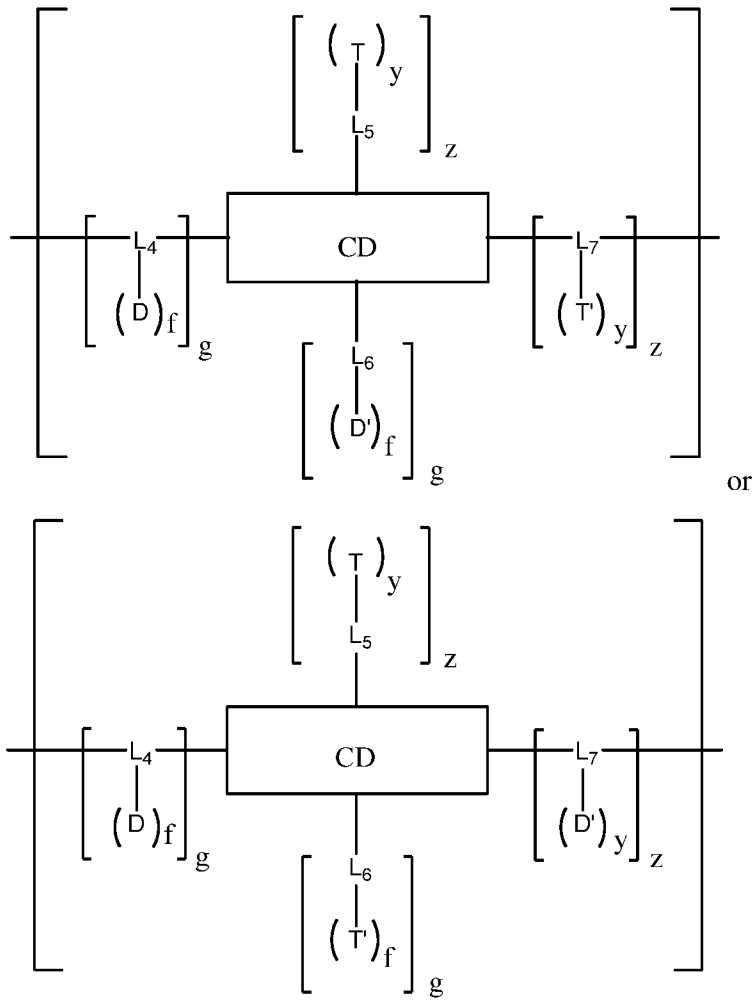
n and w, independently for each occurrence, represent an integer in the range of 0 to about 30,000 (preferably <25,000, <20,000, <15,000, <10,000, <5,000, <1,000, <500, <100, <50, <25, <10, or even <5); and

b represents an integer in the range of 1 to about 30,000 (preferably <25,000, <20,000, <15,000, <10,000, <5,000, <1,000, <500, <100, <50, <25, <10, or even <5),

wherein either P comprises cyclodextrin moieties or n is at least 1.

In some embodiments, one or more of the topoisomerase inhibitor moieties in the CDP-topoisomerase inhibitor conjugate can be replaced with another therapeutic agent, *e.g.*, another anticancer agent or anti-inflammatory agent. Examples of other anticancer agents are described herein. Examples of anti-inflammatory agents include a steroid, *e.g.*, prednisone, and a NSAID.

In certain embodiments, P contains a plurality of cyclodextrin moieties within the polymer chain as opposed to the cyclodextrin moieties being grafted on to pendant groups off of the polymeric chain. Thus, in certain embodiments, the polymer chain of formula I further comprises n' units of U, wherein n' represents an integer in the range of 1 to about 30,000, *e.g.*, from 4-100, 4-50, 4-25, 4-15, 6-100, 6-50, 6-25, and 6-15 (preferably <25,000, <20,000, <15,000, <10,000, <5,000, <1,000, <500, <100, <50, <25, <20, <15, <10, or even <5); and U is represented by one of the general formulae below:



wherein

CD represents a cyclic moiety, such as a cyclodextrin moiety, or derivative thereof;

L_4, L_5, L_6, and L_7, independently for each occurrence, may be absent or represent a linker group;

D and D', independently for each occurrence, represent the same or different topoisomerase inhibitor or prodrug forms thereof (*e.g.*, a camptothecin or camptothecin derivative);

T and T', independently for each occurrence, represent the same or different targeting ligand or precursor thereof;

f and y, independently for each occurrence, represent an integer in the range of 1 and 10; and

g and z, independently for each occurrence, represent an integer in the range of 0 and 10.

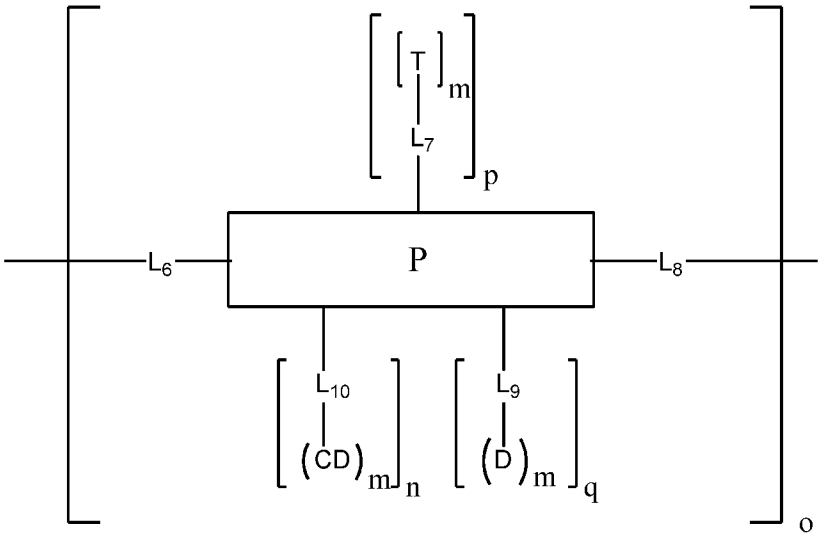
Preferably the polymer has a plurality of D or D' moieties. In some embodiments, at least 50% of the U units have at least one D or D'. In some embodiments, one or more of the topoisomerase inhibitor moieties in the CDP-topoisomerase conjugate can be replaced with another therapeutic agent, *e.g.*, another anticancer agent or anti-inflammatory agent.

In preferred embodiments, L_4 and L_7 represent linker groups.

The CDP may include a polycation, polyanion, or non-ionic polymer. A polycationic or polyanionic polymer has at least one site that bears a positive or negative charge, respectively. In certain such embodiments, at least one of the linker moiety and the cyclic moiety comprises such a charged site, so that every occurrence of that moiety includes a charged site. In some embodiments, the CDP is biocompatible.

In certain embodiments, the CDP may include polysaccharides, and other non-protein biocompatible polymers, and combinations thereof, that contain at least one terminal hydroxyl group, such as polyvinylpyrrollidone, poly(oxyethylene)glycol (PEG), polysuccinic anhydride, polysebacic acid, PEG-phosphate, polyglutamate, polyethylenimine, maleic anhydride divinylether (DIVMA), cellulose, pullulans, inulin, polyvinyl alcohol (PVA), N-(2-hydroxypropyl)methacrylamide (HPMA), dextran and hydroxyethyl starch (HES), and have optional pendant groups for grafting therapeutic agents, targeting ligands and/or cyclodextrin moieties. In certain embodiments, the polymer may be biodegradable such as poly(lactic acid), poly(glycolic acid), poly(alkyl 2-cyanoacrylates), polyanhydrides, and polyorthoesters, or bioerodible such as polylactide-glycolide copolymers, and derivatives thereof, non-peptide polyaminoacids, polyiminocarbonates, poly alpha-amino acids, polyalkyl-cyano-acrylate, polyphosphazenes or acyloxymethyl poly aspartate and polyglutamate *c*opolymers and mixtures thereof.

In another embodiment the CDP-topoisomerase inhibitor conjugate is represented by Formula II:



(II)

wherein

P represents a monomer unit of a polymer that comprises cyclodextrin moieties;

T, independently for each occurrence, represents a targeting ligand or a precursor thereof;

L_6, L_7, L_8, L_9, and L_{10}, independently for each occurrence, may be absent or represent a linker group;

CD, independently for each occurrence, represents a cyclodextrin moiety or a derivative thereof;

D, independently for each occurrence, represents a topoisomerase inhibitor or a prodrug form thereof (*e.g.*, a camptothecin or camptothecin derivative);

m, independently for each occurrence, represents an integer in the range of 1 to 10 (preferably 1 to 8, 1 to 5, or even 1 to 3);

o represents an integer in the range of 1 to about 30,000 (preferably <25,000, <20,000, <15,000, <10,000, <5,000, <1,000, <500, <100, <50, <25, <10, or even <5); and

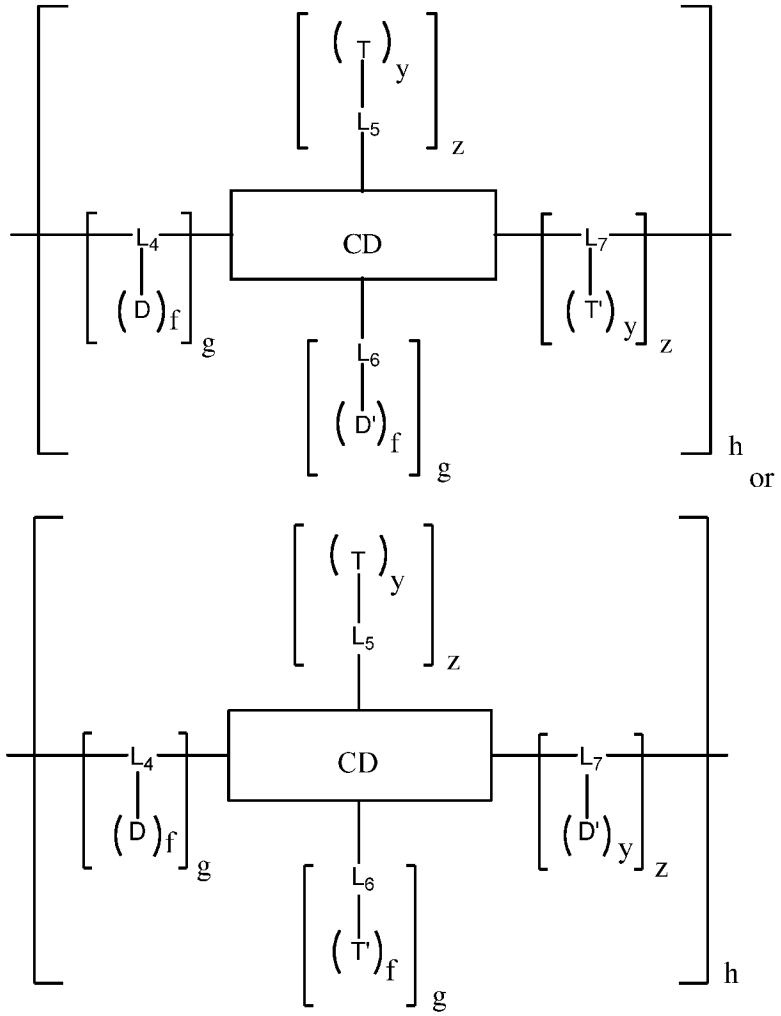
p, n, and q, independently for each occurrence, represent an integer in the range of 0 to 10 (preferably 0 to 8, 0 to 5, 0 to 3, or even 0 to about 2),

wherein CD and D are preferably each present at least 1 location (preferably at least 5, 10, 25, or even 50 or 100 locations) in the compound.

In some embodiments, one or more of the topoisomerase inhibitor moieties in the CDP-topoisomerase inhibitor conjugate can be replaced with another therapeutic

agent, *e.g.*, another anticancer agent or anti-inflammatory agent. Examples of an anticancer agent are described herein. Examples of anti-inflammatory agents include a steroid, *e.g.*, prednisone, or a NSAID.

In another embodiment the CDP-topoisomerase inhibitor conjugate is represented either of the formulae below:



wherein

CD represents a cyclic moiety, such as a cyclodextrin moiety, or derivative thereof;

L_4, L_5, L_6, and L_7, independently for each occurrence, may be absent or represent a linker group;

D and D', independently for each occurrence, represent the same or different topoisomerase inhibitor or prodrug thereof (*e.g.*, a camptothecin or camptothecin derivative);

T and T', independently for each occurrence, represent the same or different targeting ligand or precursor thereof;

f and y, independently for each occurrence, represent an integer in the range of 1 and 10 (preferably 1 to 8, 1 to 5, or even 1 to 3);

g and z, independently for each occurrence, represent an integer in the range of 0 and 10 (preferably 0 to 8, 0 to 5, 0 to 3, or even 0 to about 2); and

h represents an integer in the range of 1 and 30,000 , *e.g.*, from 4-100, 4-50, 4-25, 4-15, 6-100, 6-50, 6-25, and 6-15 (preferably <25,000, <20,000, <15,000, <10,000, <5,000, <1,000, <500, <100, <50, <25, <20, <15, <10, or even <5),

wherein at least one occurrence (and preferably at least 5, 10, or even at least 20, 50, or 100 occurrences) of g represents an integer greater than 0.

Preferably the polymer has a plurality of D or D' moieties. In some embodiments, at least 50% of the polymer repeating units have at least one D or D'. In some embodiments, one or more of the topoisomerase inhibitor moieties in the CDP-topoisomerase inhibitor conjugate can be replaced with another therapeutic agent, *e.g.*, another anticancer agent or anti-inflammatory agent.

In preferred embodiments, L4 and L7 represent linker groups.

In certain such embodiments, the CDP comprises cyclic moieties alternating with linker moieties that connect the cyclic structures, *e.g.*, into linear or branched polymers, preferably linear polymers. The cyclic moieties may be any suitable cyclic structures, such as cyclodextrins, crown ethers (*e.g.*, 18-crown-6, 15-crown-5, 12-crown-4, etc.), cyclic oligopeptides (*e.g.*, comprising from 5 to 10 amino acid residues), cryptands or cryptates (*e.g.*, cryptand [2.2.2], cryptand-2,1,1, and complexes thereof), calixarenes, or cavitands, or any combination thereof. Preferably, the cyclic structure is (or is modified to be) water-soluble. In certain embodiments, *e.g.*, for the preparation of a linear polymer, the cyclic structure is selected such that under polymerization conditions, exactly two moieties of each cyclic structure are reactive with the linker moieties, such that the resulting polymer comprises (or consists essentially of) an alternating series of cyclic moieties and linker moieties, such as at least four of each type of moiety. Suitable difunctionalized cyclic moieties include many that are commercially available and/or amenable to preparation using published protocols. In certain embodiments, conjugates are soluble in water to a concentration of at least 0.1 g/mL, preferably at least 0.25 g/mL.

Thus, in certain embodiments, the invention relates to novel compositions of therapeutic cyclodextrin-containing polymeric compounds designed for drug delivery of a topoisomerase inhibitor. In certain embodiments, these CDPs improve drug stability and/or solubility, and/or reduce toxicity, and/or improve efficacy of the topoisomerase inhibitor when used *in vivo*. Furthermore, by selecting from a variety of linker groups, and/or targeting ligands, the rate of topoisomerase inhibitor release from the CDP can be attenuated for controlled delivery.

In certain embodiments, the CDP comprises a linear cyclodextrin-containing polymer, *e.g.*, the polymer backbone includes cyclodextrin moieties. For example, the polymer may be a water-soluble, linear cyclodextrin polymer produced by providing at least one cyclodextrin derivative modified to bear one reactive site at each of exactly two positions, and reacting the cyclodextrin derivative with a linker having exactly two reactive moieties capable of forming a covalent bond with the reactive sites under polymerization conditions that promote reaction of the reactive sites with the reactive moieties to form covalent bonds between the linker and the cyclodextrin derivative, whereby a linear polymer comprising alternating units of cyclodextrin derivatives and linkers is produced. Alternatively the polymer may be a water-soluble, linear cyclodextrin polymer having a linear polymer backbone, which polymer comprises a plurality of substituted or unsubstituted cyclodextrin moieties and linker moieties in the linear polymer backbone, wherein each of the cyclodextrin moieties, other than a cyclodextrin moiety at the terminus of a polymer chain, is attached to two of said linker moieties, each linker moiety covalently linking two cyclodextrin moieties. In yet another embodiment, the polymer is a water-soluble, linear cyclodextrin polymer comprising a plurality of cyclodextrin moieties covalently linked together by a plurality of linker moieties, wherein each cyclodextrin moiety, other than a cyclodextrin moiety at the terminus of a polymer chain, is attached to two linker moieties to form a linear cyclodextrin polymer.

In some embodiments, the CDP-topoisomerase inhibitor conjugate comprises a water soluble linear polymer conjugate comprising: cyclodextrin moieties; comonomers which do not contain cyclodextrin moieties (comonomers); and a plurality of topoisomerase inhibitor; wherein the CDP-topoisomerase inhibitor conjugate comprises at least four, five six, seven, eight, etc., cyclodextrin moieties and at least four, five six, seven, eight, etc., comonomers. In some embodiments, the topoisomerase inhibitor is a topoisomerase inhibitor described herein, for example,

the topoisomerase inhibitor is a camptothecin or camptothecin derivative described herein. The topoisomerase inhibitor can be attached to the CDP via a functional group such as a hydroxyl group, or where appropriate, an amino group.

In some embodiments, one or more of the topoisomerase inhibitor moieties in the CDP-topoisomerase inhibitor conjugate can be replaced with another therapeutic agent, *e.g.*, another anticancer agent or anti-inflammatory agent.

In some embodiments, the least four cyclodextrin moieties and at least four comonomers alternate in the CDP-topoisomerase inhibitor conjugate. In some embodiments, the topoisomerase inhibitors are cleaved from the CDP-topoisomerase inhibitor conjugate under biological conditions to release the topoisomerase inhibitor. In some embodiments, the cyclodextrin moieties comprise linkers to which topoisomerase inhibitors are linked. In some embodiments, the topoisomerase inhibitors are attached via linkers.

In some embodiments, the comonomer comprises residues of at least two functional groups through which reaction and linkage of the cyclodextrin monomers was achieved. In some embodiments, the functional groups, which may be the same or different, terminal or internal, of each comonomer comprise an amino, acid, imidazole, hydroxyl, thio, acyl halide, -HC=CH-, —C≡C— group, or derivative thereof. In some embodiments, the two functional groups are the same and are located at termini of the comonomer precursor. In some embodiments, a comonomer contains one or more pendant groups with at least one functional group through which reaction and thus linkage of a topoisomerase inhibitor was achieved. In some embodiments, the functional groups, which may be the same or different, terminal or internal, of each comonomer pendant group comprise an amino, acid, imidazole, hydroxyl, thiol, acyl halide, ethylene, ethyne group, or derivative thereof. In some embodiments, the pendant group is a substituted or unsubstituted branched, cyclic or straight chain C1-C10 alkyl, or arylalkyl optionally containing one or more heteroatoms within the chain or ring. In some embodiments, the cyclodextrin moiety comprises an alpha, beta, or gamma cyclodextrin moiety. In some embodiments, the topoisomerase inhibitor is at least 5%, 10%, 15%, 20%, 25%, 30%, or 35% by weight of CDP-topoisomerase inhibitor conjugate.

In some embodiments, the comonomer comprises polyethylene glycol of molecular weight from about 2 to about 5 kDa (*e.g.*, from about 2 to about 4.5 kDa, from about 3 to about 4 kDa, or less than about 4 kDa, (*e.g.*, about 3.4 kDa ± 10%,

e.g., about 3060 Da to about 3740 Da)), the cyclodextrin moiety comprises beta-cyclodextrin, the theoretical maximum loading of the topoisomerase inhibitor on the CDP-topoisomerase inhibitor conjugate is 13% by weight, and the topoisomerase inhibitor is 6-10% by weight of CDP-topoisomerase inhibitor conjugate. In some embodiments, the topoisomerase inhibitor is poorly soluble in water. In some embodiments, the solubility of the topoisomerase inhibitor is <5 mg/ml at physiological pH. In some embodiments, the topoisomerase inhibitor is a hydrophobic compound with a log P>0.4, >0.6, >0.8, >1, >2, >3, >4, or >5.

In some embodiments, the topoisomerase inhibitor is attached to the CDP via a second compound.

In some embodiments, administration of the CDP-topoisomerase inhibitor conjugate to a subject results in release of the topoisomerase inhibitor over a period of at least 6 hours. In some embodiments, administration of the CDP-topoisomerase inhibitor conjugate to a subject results in release of the topoisomerase inhibitor over a period of 2 hours, 3 hours, 5 hours, 6 hours, 8 hours, 10 hours, 15 hours, 20 hours, 1 day, 2 days, 3 days, 4 days, 7 days, 10 days, 14 days, 17 days, 20 days, 24 days, 27 days up to a month. In some embodiments, upon administration of the CDP-topoisomerase inhibitor conjugate to a subject, the rate of topoisomerase inhibitor release is dependent primarily upon the rate of hydrolysis as opposed to enzymatic cleavage.

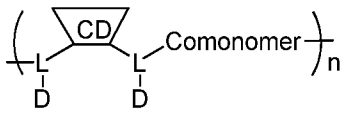
In some embodiments, the CDP-topoisomerase inhibitor conjugate has a molecular weight of 10,000-500,000. In some embodiments, the cyclodextrin moieties make up at least about 2%, 5%, 10%, 20%, 30%, 50% or 80% of the CDP-topoisomerase inhibitor conjugate by weight.

In some embodiments, the CDP-topoisomerase inhibitor conjugate is made by a method comprising providing cyclodextrin moiety precursors modified to bear one reactive site at each of exactly two positions, and reacting the cyclodextrin moiety precursors with comonomer precursors having exactly two reactive moieties capable of forming a covalent bond with the reactive sites under polymerization conditions that promote reaction of the reactive sites with the reactive moieties to form covalent bonds between the comonomers and the cyclodextrin moieties, whereby a CDP comprising alternating units of a cyclodextrin moiety and a comonomer is produced. In some embodiments, the cyclodextrin moiety precursors are in a composition, the composition being substantially free of cyclodextrin moieties having other than two

positions modified to bear a reactive site (*e.g.*, cyclodextrin moieties having 1, 3, 4, 5, 6, or 7 positions modified to bear a reactive site).

In some embodiments, a comonomer of the CDP-topoisomerase inhibitor conjugate comprises a moiety selected from the group consisting of: an alkylene chain, polysuccinic anhydride, poly-L-glutamic acid, poly(ethyleneimine), an oligosaccharide, and an amino acid chain. In some embodiments, a CDP-topoisomerase inhibitor conjugate comonomer comprises a polyethylene glycol chain. In some embodiments, a comonomer comprises a moiety selected from: polyglycolic acid and polylactic acid chain. In some embodiments, a comonomer comprises a hydrocarbylene group wherein one or more methylene groups is optionally replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from, substituted or unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or -O-, C(=X) (wherein X is NR_1, O or S), -OC(O)-, -C(=O)O, -NR_1-, -NR_1CO-, -C(O)NR_1-, -$S(O)_n$- (wherein n is 0, 1, or 2), -OC(O)-NR_1, -NR_1-C(O)-NR_1-, -$NR_1$1-C(NR_1)-NR_1-, and -B(OR_1)-; and R_1, independently for each occurrence, represents H or a lower alkyl.

In some embodiments, the CDP-topoisomerase inhibitor conjugate is a polymer having attached thereto a plurality of D moieties of the following formula:

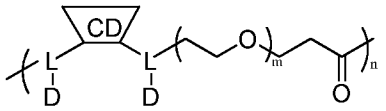


wherein each L is independently a linker, and each D is independently a topoisomerase inhibitor, a prodrug derivative thereof, *e.g.*, a camptothecin or camptothecin derivative, or absent; and each comonomer is independently a comonomer described herein, and n is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, provided that the polymer comprises at least one topoisomerase inhibitor and in some embodiments, at least two topoisomerase inhibitor moieties. In some embodiments, the molecular weight of the comonomer is from about 2 to about 5 kDa (*e.g.*, from about 2 to about 4.5 kDa, from about 3 to about 4 kDa, or less than about 4 kDa, (*e.g.*, about 3.4 kDa ± 10%, *e.g.*, about 3060 Da to about 3740 Da)).

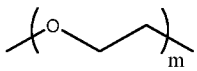
In some embodiments, the topoisomerase inhibitor is a topoisomerase inhibitor described herein, for example, the topoisomerase inhibitor is a camptothecin or camptothecin derivative described herein. The topoisomerase inhibitor can be attached to the CDP via a functional group such as a hydroxyl group, or where

appropriate, an amino group. In some embodiments, one or more of the topoisomerase inhibitor moieties in the CDP-topoisomerase inhibitor conjugate can be replaced with another therapeutic agent, *e.g.*, another anticancer agent or anti-inflammatory agent.

In some embodiments, the CDP-topoisomerase inhibitor conjugate is a polymer having attached thereto a plurality of D moieties of the following formula:



wherein each L is independently a linker, and each D is independently a topoisomerase, a prodrug derivative thereof, *e.g.*, a camptothecin or camptothecin derivative, or absent, provided that the polymer comprises at least one topoisomerase inhibitor and in some embodiments, at least two topoisomerase inhibitor moieties; and

wherein the group 

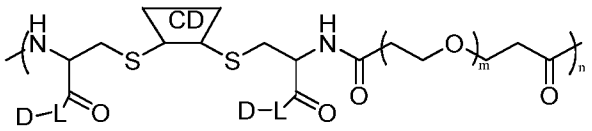
has a Mw of about 2 to about 5 kDa (*e.g.*, from about 2 to about 4.5 kDa, from about 3 to about 4 kDa, or less than about 4 kDa, (*e.g.*, about 3.4 kDa ± 10%, *e.g.*, about 3060 Da to about 3740 Da)) and n is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

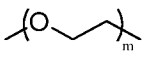
In some embodiments, the topoisomerase inhibitor is a topoisomerase inhibitor described herein, for example, the topoisomerase is a camptothecin or camptothecin derivative described herein. The topoisomerase inhibitor can be attached to the CDP via a functional group such as a hydroxyl group, or where appropriate, an amino group. In some embodiments, one or more of the topoisomerase inhibitor moieties in the CDP-topoisomerase inhibitor conjugate can be replaced with another therapeutic agent, *e.g.*, another anticancer agent or anti-inflammatory agent.

In some embodiments, less than all of the L moieties are attached to D moieties, meaning in some embodiments, at least one D is absent. In some embodiments, the loading of the D moieties on the CDP-topoisomerase inhibitor conjugate is from about 1 to about 50% (*e.g.*, from about 1 to about 25%, from about 5 to about 20% or from about 5 to about 15%). In some embodiments, each L independently comprises an amino acid or a derivative thereof. In some embodiments, each L independently comprises a plurality of amino acids or derivatives thereof. In some embodiments, each L is independently a dipeptide or derivative thereof. In one embodiment, L is one ore more of: alanine, arginine,

histidine, lysine, aspartic acid, glutamic acid, serine, threonine, asparganine, glutamine, cysteine, glycine, proline, isoleucine, leucine, methionine, phenylalanine, tryptophan, tyrosine and valine.

In some embodiments, the CDP-topoisomerase inhibitor conjugate is a polymer having attached thereto a plurality of L-D moieties of the following formula:

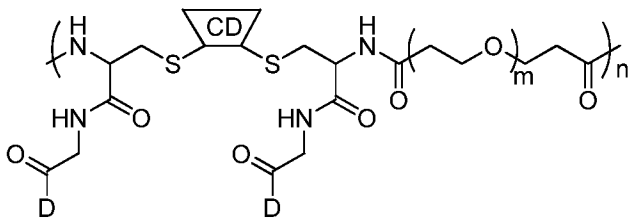


wherein each L is independently a linker or absent and each D is independently a topoisomerase inhibitor, a prodrug derivative thereof, *e.g.*, a camptothecin or camptothecin derivative, or absent and wherein the group  has a Mw of about 2 to about 5 kDa (*e.g.*, from about 2 to about 4.5 kDa, from about 3 to about 4 kDa, or less than about 4 kDa, (*e.g.*, about 3.4 kDa ± 10%, *e.g.*, about 3060 Da to about 3740 Da)) and n is at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, provided that the polymer comprises at least one topoisomerase inhibitor and in some embodiments, at least two topoisomerase inhibitor moieties.

In some embodiments, less than all of the C(=O) moieties are attached to L-D moieties, meaning in some embodiments, at least one L and/or D is absent. In some embodiments, the loading of the L, D and/or L-D moieties on the CDP-topoisomerase inhibitor conjugate is from about 1 to about 50% (*e.g.*, from about 1 to about 25%, from about 5 to about 20% or from about 5 to about 15%). In some embodiments, each L is independently an amino acid or derivative thereof. In some embodiments, each L is glycine or a derivative thereof.

In some embodiments, one or more of the topoisomerase inhibitor moieties in the CDP-topoisomerase inhibitor conjugate can be replaced with another therapeutic agent, *e.g.*, another anticancer agent or anti-inflammatory agent.

In some embodiments, the CDP-topoisomerase inhibitor conjugate is a polymer having the following formula:



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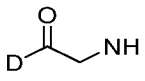
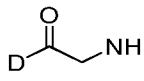
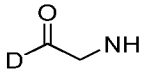
In some embodiments, less than all of the C(=O) moieties are attached to  moieties, meaning in some embodiments,  is absent, provided that the polymer comprises at least one topoisomerase inhibitor and in some embodiments, at least two topoisomerase inhibitor moieties. In some embodiments, the loading of the  moieties on the CDP-topoisomerase inhibitor conjugate is from about 1 to about 50% (*e.g.*, from about 1 to about 25%, from about 5 to about 20% or from about 5 to about 15%).

In some embodiments, one or more of the topoisomerase inhibitor moieties in the CDP-topoisomerase inhibitor conjugate can be replaced with another therapeutic agent, *e.g.*, another anticancer agent or anti-inflammatory agent.

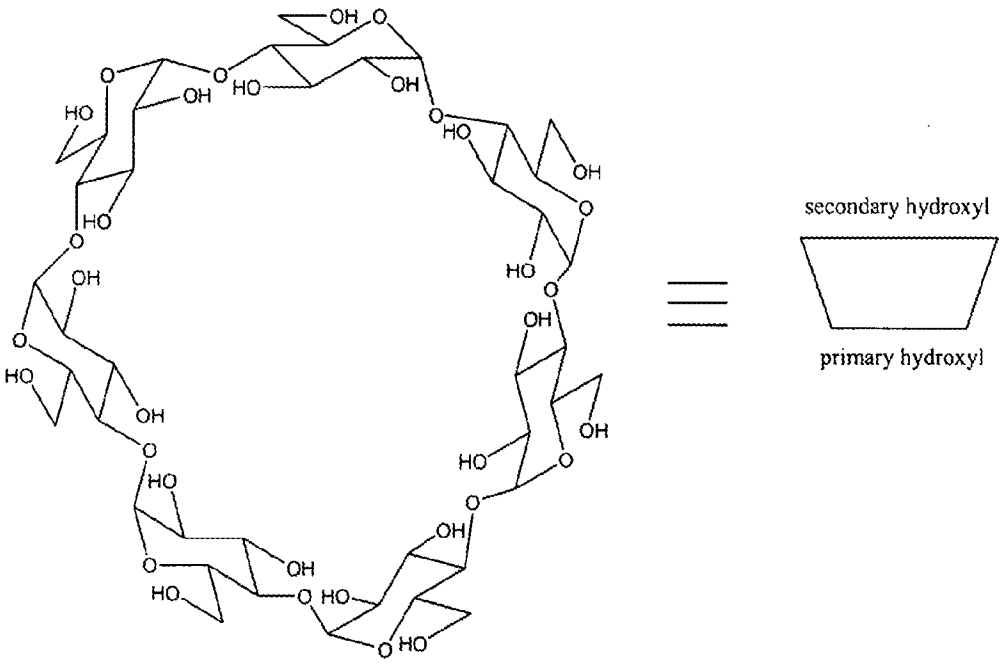
In some embodiments, the CDP-topoisomerase inhibitor conjugate will contain an topoisomerase inhibitor and at least one additional therapeutic agent. For instance, a topoisomerase inhibitor and one more different cancer drugs, an immunosuppressant, an antibiotic or an anti-inflammatory agent may be grafted on to the polymer via optional linkers. By selecting different linkers for different drugs, the release of each drug may be attenuated to achieve maximal dosage and efficacy.

Cyclodextrins

In certain embodiments, the cyclodextrin moieties make up at least about 2%, 5% or 10% by weight, up to 20%, 30%, 50% or even 80% of the CDP by weight. In certain embodiments, the topoisomerase inhibitors, or targeting ligands make up at least about 1%, 5%, 10% or 15%, 20%, 25%, 30% or even 35% of the CDP by weight. Number-average molecular weight (M_n) may also vary widely, but generally fall in the range of about 1,000 to about 500,000 daltons, preferably from about 5000 to about 200,000 daltons and, even more preferably, from about 10,000 to about 100,000. Most preferably, M_n varies between about 12,000 and 65,000 daltons. In certain other embodiments, M_n varies between about 3000 and 150,000 daltons. Within a given sample of a subject polymer, a wide range of molecular weights may be present. For example, molecules within the sample may have molecular weights that differ by a factor of 2, 5, 10, 20, 50, 100, or more, or that differ from the average molecular weight by a factor of 2, 5, 10, 20, 50, 100, or more. Exemplary cyclodextrin moieties include cyclic structures consisting essentially of from 7 to 9

saccharide moieties, such as cyclodextrin and oxidized cyclodextrin. A cyclodextrin moiety optionally comprises a linker moiety that forms a covalent linkage between the cyclic structure and the polymer backbone, preferably having from 1 to 20 atoms in the chain, such as alkyl chains, including dicarboxylic acid derivatives (such as glutaric acid derivatives, succinic acid derivatives, and the like), and heteroalkyl chains, such as oligoethylene glycol chains.

Cyclodextrins are cyclic polysaccharides containing naturally occurring D-(+)-glucopyranose units in an α-(1,4) linkage. The most common cyclodextrins are alpha ((α)-cyclodextrins, beta (β)-cyclodextrins and gamma (γ)-cyclodextrins which contain, respectively six, seven, or eight glucopyranose units. Structurally, the cyclic nature of a cyclodextrin forms a torus or donut-like shape having an inner apolar or hydrophobic cavity, the secondary hydroxyl groups situated on one side of the cyclodextrin torus and the primary hydroxyl groups situated on the other. Thus, using (β)-cyclodextrin as an example, a cyclodextrin is often represented schematically as follows.



The side on which the secondary hydroxyl groups are located has a wider diameter than the side on which the primary hydroxyl groups are located. The present invention contemplates covalent linkages to cyclodextrin moieties on the primary and/or secondary hydroxyl groups. The hydrophobic nature of the cyclodextrin inner

cavity allows for host-guest inclusion complexes of a variety of compounds, *e.g.*, adamantane. (Comprehensive Supramolecular Chemistry, Volume 3, J.L. Atwood et al., eds., Pergamon Press (1996); T. Cserhati, Analytical Biochemistry, 225:328-332(1995); Husain et al., Applied Spectroscopy, 46:652-658 (1992); FR 2 665 169). Additional methods for modifying polymers are disclosed in Suh, J. and Noh, Y., *Bioorg. Med. Chem. Lett.* 1998, *8*, 1327-1330.

In certain embodiments, the compounds comprise cyclodextrin moieties and wherein at least one or a plurality of the cyclodextrin moieties of the CDP-topoisomerase inhibitor conjugate is oxidized. In certain embodiments, the cyclodextrin moieties of P alternate with linker moieties in the polymer chain.

Comonomers

In addition to a cyclodextrin moiety, the CDP can also include a comonomer, for example, a comonomer described herein. In some embodiments, a comonomer of the CDP-topoisomerase inhibitor conjugate comprises a moiety selected from the group consisting of: an alkylene chain, polysuccinic anhydride, poly-L-glutamic acid, poly(ethyleneimine), an oligosaccharide, and an amino acid chain. In some embodiments, a CDP-topoisomerase inhibitor conjugate comonomer comprises a polyethylene glycol chain. In some embodiments, a comonomer comprises a moiety selected from: polyglycolic acid and polylactic acid chain. In some embodiments, a comonomer comprises a hydrocarbylene group wherein one or more methylene groups is optionally replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from, substituted or unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or -O-, C(=X) (wherein X is NR_1, O or S), -OC(O)-, -C(=O)O, -NR_1-, -NR_1CO-, -C(O)NR_1-, -$S(O)_n$- (wherein n is 0, 1, or 2), -OC(O)-NR_1, -NR_1-C(O)-NR_1-, -$NR_1$1-C(NR_1)-NR_1-, and -B(OR_1)-; and R_1, independently for each occurrence, represents H or a lower alkyl.

In some embodiments, a comonomer can be and/or can comprise a linker such as a linker described herein.

Exemplary CDP-topoisomerase inhibitor conjugates, particles and compositions

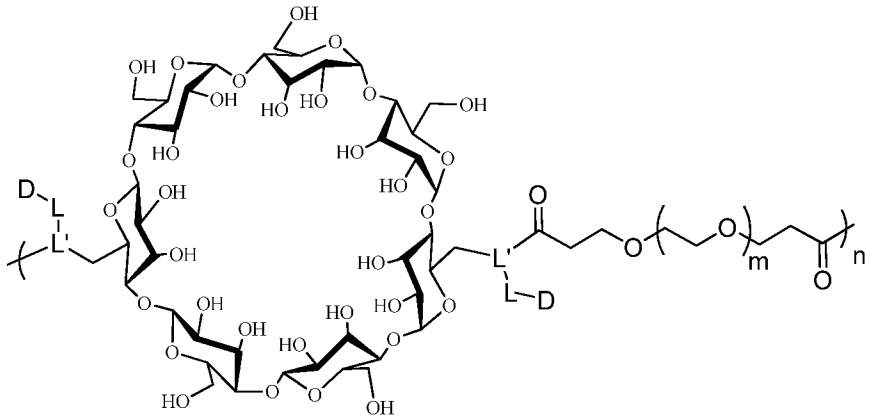
In one embodiment, the CDP-topoisomerase inhibitor conjugate forms a particle, *e.g.*, a nanoparticle. The particle can comprise a CDP-topoisomerase

inhibitor conjugate, *e.g.*, a plurality of CDP-topoisomerase inhibitor conjugates, *e.g.*, CDP-topoisomerase inhibitor conjugates having the same topoisomerase inhibitor or different topoisomerase inhibitors. The compositions described herein comprise a CDP-topoisomerase inhibitor conjugate or a plurality of CDP-topoisomerase inhibitor conjugates. The composition can also comprise a particle or a plurality of particles described herein.

In one embodiment, the CDP-topoisomerase inhibitor conjugate containing the inclusion complex forms a particle, *e.g.*, a nanoparticle. The nanoparticle ranges in size from 10 to 300 nm in diameter, *e.g.*, 20 to 280, 30 to 250, 40 to 200, 20 to 150, 30 to 100, 20 to 80, 30 to 70, 40 to 60 or 40 to 50 nm diameter. In one embodiment, the particle is 50 to 60 nm, 20 to 60 nm, 30 to 60 nm, 35 to 55 nm, 35 to 50 nm or 35 to 45 nm in diameter.

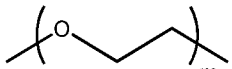
In one embodiment, the surface charge of the molecule is neutral, or slightly negative. In some embodiments, the zeta potential of the particle surface is from about -80 mV to about 50 mV, about -20 mV to about 20 mV, about -20 mV to about -10 mV, or about -10 mV to about 0.

In some embodiments, the CDP-topoisomerase inhibitor conjugate is a polymer having the following formula C:



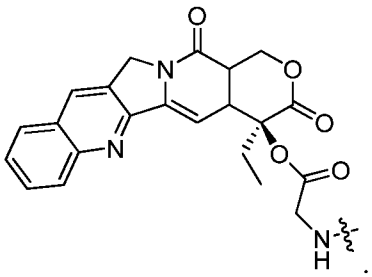
formula C

wherein L and L' independently for each occurrence, is a linker, a bond, or -OH and D, independently for each occurrence, is a topoisomerase inhibitor such as camptothecin ("CPT"), a camptothecin derivative or absent, and

wherein the group  has a Mw of about 2 to about 5 kDa (*e.g.*, from about 2 to about 4.5 kDa, from about 3 to about 4 kDa, or less than about 4 kDa, (*e.g.*, about 3.4 kDa ± 10%, *e.g.*, about 3060 Da to about 3740 Da)) and n is at least 4, provided that at least one D is CPT or a camptothecin derivative. In some embodiments, at least 2 D moieties are CPT and/or a camptothecin derivative.

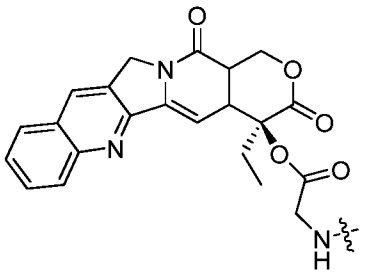
In some embodiments, each L', for each occurrence, is a cysteine. In some embodiments, the cysteine is attached to the cyclodextrin via a sulfide bond. In some embodiments, the cysteine is attached to the PEG containing portion of the polymer via an amide bond.

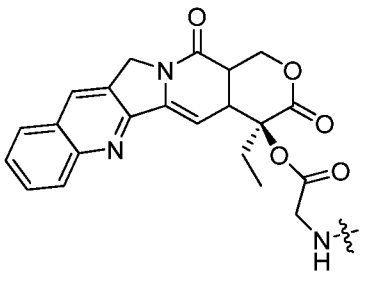
In some embodiments, the L is a linker (*e.g.*, an amino acid such as glycine). In some embodiments, L is absent. In some embodiments, D-L together form

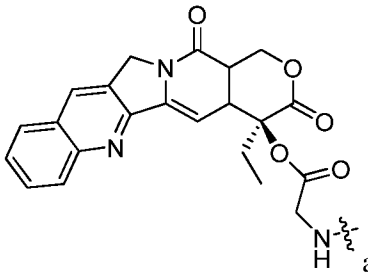
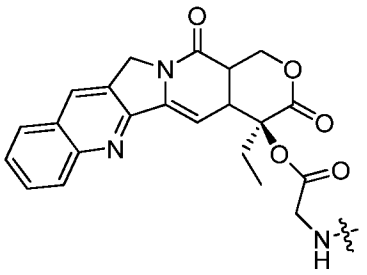
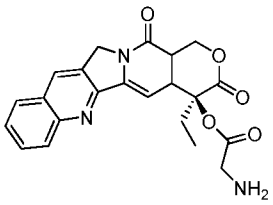
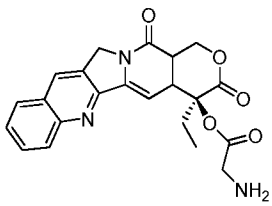


In some embodiments, a plurality of D moieties are absent and at the same position on the polymer, the corresponding L is -OH.

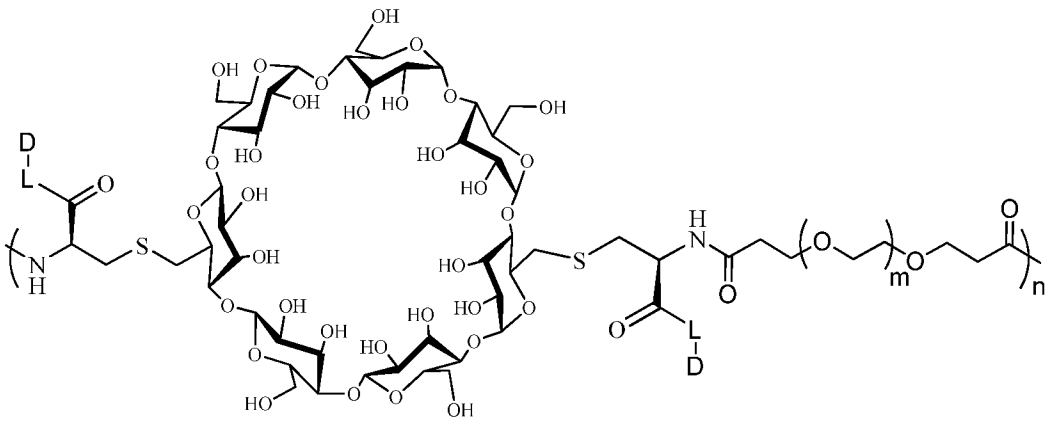
In some embodiments, less than all of the C(=O) moieties of the cysteine residue in the polymer backbone are attached to



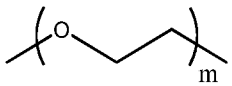
moieties, meaning in some embodiments,  is absent in one or more positions of the polymer backbone, provided that the polymer comprises

at least one  and in some embodiments, at least two  moieties. In some embodiments, the loading of the  moieties on the CDP-topoisomerase inhibitor conjugate is from about 1 to about 50% (*e.g.*, from about 1 to about 25%, from about 5 to about 20% or from about 5 to about 15%, *e.g.*, from about 6 to about 10%). In some embodiments, the loading of  on the CDP is from about 6% to about 10% by weight of the total polymer.

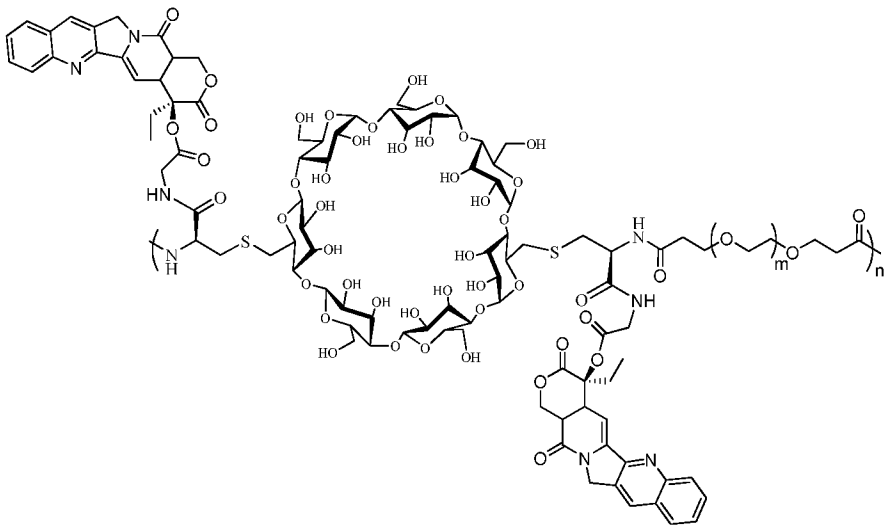
In some embodiments, the CDP-topoisomerase inhibitor conjugate of formula C is a polymer having the following formula:



wherein L, independently for each occurrence, is a linker, a bond, or -OH and D, independently for each occurrence, is camptothecin ("CPT"), a camptothecin derivative or absent, and

wherein the group  has a Mw of about 2 to about 5 kDa (*e.g.*, from about 2 to about 4.5 kDa, from about 3 to about 4 kDa, or less than about 4 kDa, (*e.g.*, about 3.4 kDa ± 10%, *e.g.*, about 3060 Da to about 3740 Da)) and n is at least 4, provided that at least one D is CPT or a camptothecin derivative. In some embodiments, at least 2 D moieties are CPT and/or a camptothecin derivative.

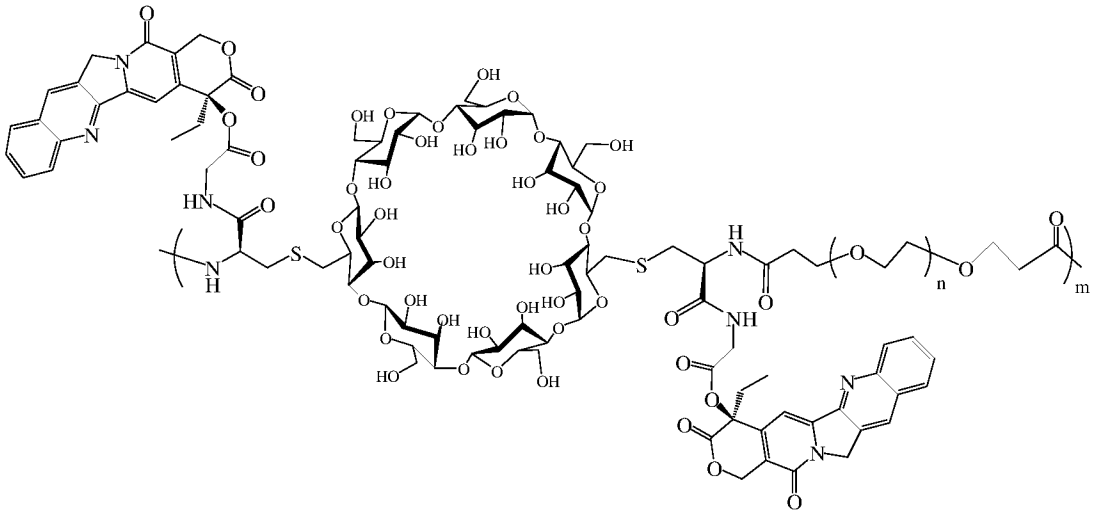
In some embodiments, the CDP-camptothecin conjugate of formula C is a polymer of the following formula:



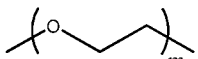
,

wherein m and n are as defined above, and wherein less than all of the C(=O) sites of the cysteine of the polymer backbone are occupied as indicated above with the CPT-Gly, but instead are free acids, meaning, the theoretical loading of the polymer is less than 100%.

In some embodiments, the CDP-camptothecin conjugate is as provided in FIG. 4, and shown below, which is referred to herein as "CRLX101."



In the above structure:

n = about 77 or the group  has a Mw of about 2 to about 5 kDa (*e.g.*, from about 2 to about 4.5 kDa, from about 3 to about 4 kDa, or less than about 4 kDa, (*e.g.*, about 3.4 kDa ± 10%, *e.g.*, about 3060 Da to about 3740 Da));

m = is from about 10 to about 18 (*e.g.*, about 14);

the molecular weight of the polymer backbone (*i.e.*, the polymer minus the CPT-gly, which results in the cysteine moieties having a free -C(O)OH) is from about 48 to about 85 kDa;

the polydispersity of the polymer backbone is less than about 2.2; and

the loading of the CPT onto the polymer backbone is from about 6 to about 13% by weight, wherein 13% is theoretical maximum, meaning, in some instances, one or more of the cysteine residues has a free -C(O)OH (*i.e.*, it lacks the CPT-gly).

In some embodiments, the polydispersity of the PEG component in the above structure is less than about 1.1.

In some embodiments, a CDP-camptothecin conjugate described herein has a terminal amine and/or a terminal carboxylic acid.

Linkers/tethers

The CDPs described herein can include on or more linkers. In some embodiments, a linker can link a topoisomerase inhibitor to a CDP. In some embodiments, a linker can link camptothecin or a camptothecin derivative to a CDP. In some embodiments, for example, when referring to a linker that links a topoisomerase inhibitor to the CDP, the linker can be referred to as a tether.

In certain embodiments, a plurality of the linker moieties are attached to a topoisomerase inhibitor or prodrug thereof and are cleaved under biological conditions.

Described herein are CDP-topoisomerase inhibitor conjugates comprising a CDP covalently attached to a topoisomerase inhibitor through attachments that are cleaved under biological conditions to release the topoisomerase inhibitor. In certain embodiments, a CDP-topoisomerase inhibitor conjugate comprises a topoisomerase inhibitor covalently attached to a polymer, preferably a biocompatible polymer, through a tether, *e.g.*, a linker, wherein the tether comprises a selectivity-determining moiety and a self-cyclizing moiety which are covalently attached to one another in the tether, *e.g.*, between the polymer and the topoisomerase inhibitor.

In some embodiments, such topoisomerase inhibitors are covalently attached to CDPs through functional groups comprising one or more heteroatoms, for example, hydroxy, thiol, carboxy, amino, and amide groups. Such groups may be covalently attached to the subject polymers through linker groups as described herein, for example, biocleavable linker groups, and/or through tethers, such as a tether comprising a selectivity-determining moiety and a self-cyclizing moiety which are covalently attached to one another.

In certain embodiments, the CDP-topoisomerase inhibitor conjugate comprises a topoisomerase inhibitor covalently attached to the CDP through a tether, wherein the tether comprises a self-cyclizing moiety. In some embodiments, the tether further comprises a selectivity-determining moiety. Thus, one aspect of the invention relates to a polymer conjugate comprising a topoisomerase inhibitor covalently attached to a polymer, preferably a biocompatible polymer, through a tether, wherein the tether comprises a selectivity-determining moiety and a self-cyclizing moiety which are covalently attached to one another.

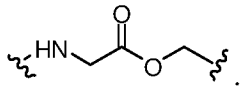
In some embodiments, the selectivity-determining moiety is bonded to the self-cyclizing moiety between the self-cyclizing moiety and the CDP.

In certain embodiments, the selectivity-determining moiety is a moiety that promotes selectivity in the cleavage of the bond between the selectivity-determining moiety and the self-cyclizing moiety. Such a moiety may, for example, promote enzymatic cleavage between the selectivity-determining moiety and the self-cyclizing moiety. Alternatively, such a moiety may promote cleavage between the selectivity-determining moiety and the self-cyclizing moiety under acidic conditions or basic conditions.

In certain embodiments, the invention contemplates any combination of the foregoing. Those skilled in the art will recognize that, for example, any topoisomerase inhibitor of the invention in combination with any linker (*e.g.*, self-cyclizing moiety, any selectivity-determining moiety, and/or any topoisomerase inhibitor) are within the scope of the invention.

In certain embodiments, the selectivity-determining moiety is selected such that the bond is cleaved under acidic conditions.

In certain embodiments, where the selectivity-determining moiety is selected such that the bond is cleaved under basic conditions, the selectivity-determining moiety is an aminoalkylcarbonyloxyalkyl moiety. In certain embodiments, the selectivity-determining moiety has a structure

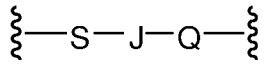


In certain embodiments where the selectivity-determining moiety is selected such that the bond is cleaved enzymatically, it may be selected such that a particular enzyme or class of enzymes cleaves the bond. In certain preferred such embodiments, the selectivity-determining moiety may be selected such that the bond is cleaved by a cathepsin, preferably cathepsin B.

In certain embodiments the selectivity-determining moiety comprises a peptide, preferably a dipeptide, tripeptide, or tetrapeptide. In certain such embodiments, the peptide is a dipeptide is selected from KF and FK, In certain embodiments, the peptide is a tripeptide is selected from GFA, GLA, AVA, GVA, GIA, GVL, GVF, and AVF. In certain embodiments, the peptide is a tetrapeptide selected from GFYA and GFLG, preferably GFLG.

In certain such embodiments, a peptide, such as GFLG, is selected such that the bond between the selectivity-determining moiety and the self-cyclizing moiety is cleaved by a cathepsin, preferably cathepsin B.

In certain embodiments, the selectivity-determining moiety is represented by Formula A:

 (A),

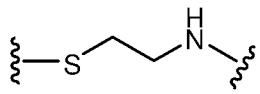
wherein

S a sulfur atom that is part of a disulfide bond;

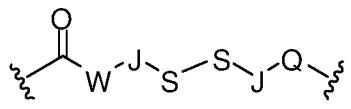
J is optionally substituted hydrocarbyl; and

Q is O or NR^{13}, wherein R^{13} is hydrogen or alkyl.

In certain embodiments, J may be polyethylene glycol, polyethylene, polyester, alkenyl, or alkyl. In certain embodiments, J may represent a hydrocarbylene group comprising one or more methylene groups, wherein one or more methylene groups is optionally replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from, substituted or unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or -O-, C(=X) (wherein X is NR^{30}, O or S), -OC(O)-, -C(=O)O, -NR^{30}-, -NR_1CO-, -$C(O)NR^{30}$-, -$S(O)_n$- (wherein n is 0, 1, or 2), -$OC(O)$-NR^{30}, -NR^{30}-$C(O)$-NR^{30}-, -NR^{30}-$C(NR^{30})$-NR^{30}-, and -$B(OR^{30})$-; and R^{30}, independently for each occurrence, represents H or a lower alkyl. In certain embodiments, J may be substituted or unsubstituted lower alkylene, such as ethylene.

For example, the selectivity-determining moiety may be  .

In certain embodiments, the selectivity-determining moiety is represented by Formula B:

 (B),

wherein

W is either a direct bond or selected from lower alkyl, NR^{14}, S, O;

S is sulfur;

J, independently and for each occurrence, is hydrocarbyl or polyethylene glycol;

Q is O or NR^{13}, wherein R^{13} is hydrogen or alkyl; and

R^{14} is selected from hydrogen and alkyl.

In certain such embodiments, J may be substituted or unsubstituted lower alkyl, such as methylene. In certain such embodiments, J may be an aryl ring. In certain embodiments, the aryl ring is a benzo ring. In certain embodiments W and S are in a 1,2-relationship on the aryl ring. In certain embodiments, the aryl ring may be optionally substituted with alkyl, alkenyl, alkoxy, aralkyl, aryl, heteroaryl, halogen, -CN, azido, $-NR^xR^x$, $-CO_2OR^x$, $-C(O)-NR^xR^x$, $-C(O)-R^x$, $-NR^x-C(O)-R^x$, $-NR^xSO_2R^x$, $-SR^x$, $-S(O)R^x$, $-SO_2R^x$, $-SO_2NR^xR^x$, $-(C(R^x)_2)_n-OR^x$, $-(C(R^x)_2)_n-NR^xR^x$, and $-(C(R^x)_2)_n-SO_2R^x$; wherein R^x is, independently for each occurrence, H or lower alkyl; and n is, independently for each occurrence, an integer from 0 to 2.

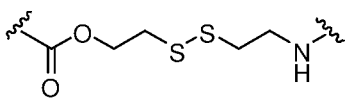
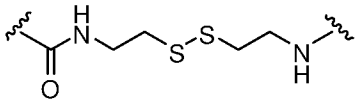
In certain embodiments, the aryl ring is optionally substituted with alkyl, alkenyl, alkoxy, aralkyl, aryl, heteroaryl, halogen, -CN, azido, $-NR^xR^x$, $-CO_2OR^x$, $-C(O)-NR^xR^x$, $-C(O)-R^x$, $-NR^x-C(O)-R^x$, $-NR^xSO_2R^x$, $-SR^x$, $-S(O)R^x$, $-SO_2R^x$, $-SO_2NR^xR^x$, $-(C(R^x)_2)_n-OR^x$, $-(C(R^x)_2)_n-NR^xR^x$, and $-(C(R^x)_2)_n-SO_2R^x$; wherein R^x is, independently for each occurrence, H or lower alkyl; and n is, independently for each occurrence, an integer from 0 to 2.

In certain embodiments, J, independently and for each occurrence, is polyethylene glycol, polyethylene, polyester, alkenyl, or alkyl.

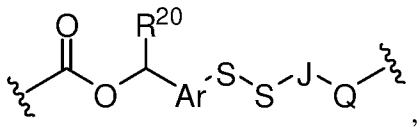
In certain embodiments, independently and for each occurrence, the linker comprises a hydrocarbylene group comprising one or more methylene groups, wherein one or more methylene groups is optionally replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from, substituted or unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or -O-, C(=X) (wherein X is NR^{30}, O or S), -OC(O)-, -C(=O)O, $-NR^{30}-$, $-NR_1CO-$, $-C(O)NR^{30}-$, $-S(O)_n-$ (wherein n is 0, 1, or 2), $-OC(O)-NR^{30}$, $-NR^{30}-C(O)-NR^{30}-$, $-NR^{30}-C(NR^{30})-NR^{30}-$, and $-B(OR^{30})-$; and R^{30}, independently for each occurrence, represents H or a lower alkyl.

In certain embodiments, J, independently and for each occurrence, is substituted or unsubstituted lower alkylene. In certain embodiments, J, independently and for each occurrence, is substituted or unsubstituted ethylene.

In certain embodiments, the selectivity-determining moiety is selected from

 and  .

The selectivity-determining moiety may include groups with bonds that are cleavable under certain conditions, such as disulfide groups. In certain embodiments, the selectivity-determining moiety comprises a disulfide-containing moiety, for example, comprising aryl and/or alkyl group(s) bonded to a disulfide group. In certain embodiments, the selectivity-determining moiety has a structure

 ,

wherein

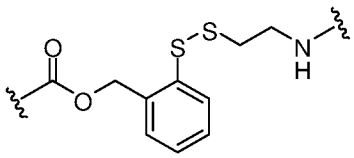
Ar is a substituted or unsubstituted benzo ring;

J is optionally substituted hydrocarbyl; and

Q is O or NR^{13},

wherein R^{13} is hydrogen or alkyl.

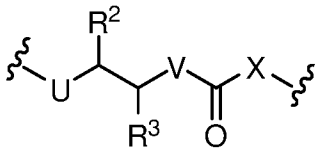
In certain embodiments, Ar is unsubstituted. In certain embodiments, Ar is a 1,2-benzo ring. For example, suitable moieties within Formula B include:

 .

In certain embodiments, the self-cyclizing moiety is selected such that upon cleavage of the bond between the selectivity-determining moiety and the self-cyclizing moiety, cyclization occurs thereby releasing the therapeutic agent. Such a cleavage-cyclization-release cascade may occur sequentially in discrete steps or substantially simultaneously. Thus, in certain embodiments, there may be a temporal and/or spatial difference between the cleavage and the self-cyclization. The rate of the self-cyclization cascade may depend on pH, *e.g.*, a basic pH may increase the rate of self-cyclization after cleavage. Self-cyclization may have a half-life after introduction *in vivo* of 24 hours, 18 hours, 14 hours, 10 hours, 6 hours, 3 hours, 2 hours, 1 hour, 30 minutes, 10 minutes, 5 minutes, or 1 minute.

In certain such embodiments, the self-cyclizing moiety may be selected such that, upon cyclization, a five- or six-membered ring is formed, preferably a five-membered ring. In certain such embodiments, the five- or six-membered ring comprises at least one heteroatom selected from oxygen, nitrogen, or sulfur, preferably at least two, wherein the heteroatoms may be the same or different. In certain such embodiments, the heterocyclic ring contains at least one nitrogen, preferably two. In certain such embodiments, the self-cyclizing moiety cyclizes to form an imidazolidone.

In certain embodiments, the self-cyclizing moiety has a structure



,

wherein

U is selected from O, NR^1 and S;

X is selected from O, NR^5, and S, preferably O or S;

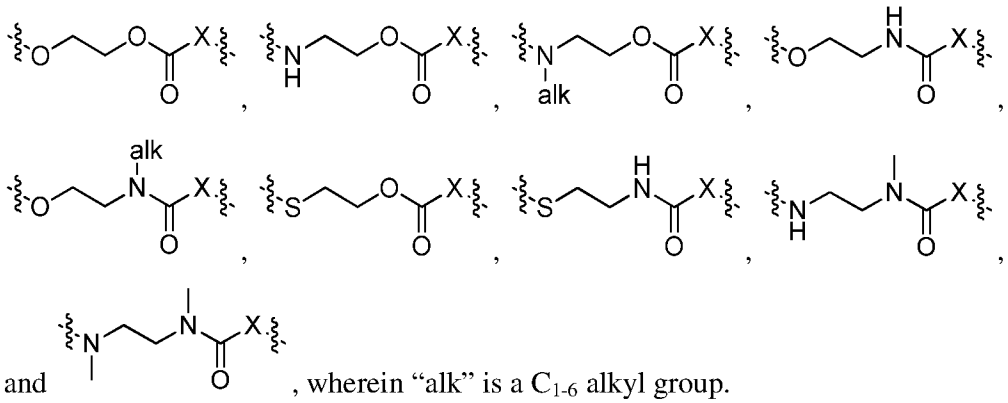
V is selected from O, S and NR^4, preferably O or NR^4;

R^2 and R^3 are independently selected from hydrogen, alkyl, and alkoxy; or R^2 and R^3 together with the carbon atoms to which they are attached form a ring; and

R^1, R^4, and R^5 are independently selected from hydrogen and alkyl.

In certain embodiments, U is NR^1 and/or V is NR^4, and R^1 and R^4 are independently selected from methyl, ethyl, propyl, and isopropyl. In certain embodiments, both R^1 and R^4 are methyl. On certain embodiments, both R^2 and R^3 are hydrogen. In certain embodiments R^2 and R^3 are independently alkyl, preferably lower alkyl. In certain embodiments, R^2 and R^3 together are $-(CH_2)_n-$ wherein n is 3 or 4, thereby forming a cyclopentyl or cyclohexyl ring. In certain embodiments, the nature of R^2 and R^3 may affect the rate of cyclization of the self-cyclizing moiety. In certain such embodiments, it would be expected that the rate of cyclization would be greater when R^2 and R^3 together with the carbon atoms to which they are attached form a ring than the rate when R^2 and R^3 are independently selected from hydrogen, alkyl, and alkoxy. In certain embodiments, U is bonded to the self-cyclizing moiety.

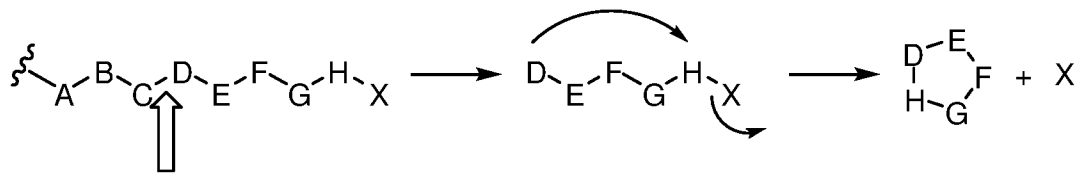
In certain embodiments, the self-cyclizing moiety is selected from



and , wherein "alk" is a C_{1-6} alkyl group.

In certain embodiments, the selectivity-determining moiety may connect to the self-cyclizing moiety through carbonyl-heteroatom bonds, *e.g.*, amide, carbamate, carbonate, ester, thioester, and urea bonds.

In certain embodiments, a topoisomerase inhibitor is covalently attached to a polymer through a tether, wherein the tether comprises a selectivity-determining moiety and a self-cyclizing moiety which are covalently attached to one another. In certain embodiments, the self-cyclizing moiety is selected such that after cleavage of the bond between the selectivity-determining moiety and the self-cyclizing moiety, cyclization of the self-cyclizing moiety occurs, thereby releasing the therapeutic agent. As an illustration, ABC may be a selectivity-determining moiety, and DEFGH maybe be a self-cyclizing moiety, and ABC may be selected such that enzyme Y cleaves between C and D. Once cleavage of the bond between C and D progresses to a certain point, D will cyclize onto H, thereby releasing topoisomerase inhibitor X, or a prodrug thereof.



In certain embodiments, topoisomerase inhibitor X may further comprise additional intervening components, including, but not limited to another self-cyclizing moiety or a leaving group linker, such as CO_2 or methoxymethyl, that spontaneously dissociates from the remainder of the molecule after cleavage occurs.

In some embodiments, a linker may be and/or comprise an alkylene chain, a polyethylene glycol (PEG) chain, polysuccinic anhydride, poly-L-glutamic acid, poly(ethyleneimine), an oligosaccharide, an amino acid (*e.g.*, glycine or cysteine), an

amino acid chain, or any other suitable linkage. In certain embodiments, the linker group itself can be stable under physiological conditions, such as an alkylene chain, or it can be cleavable under physiological conditions, such as by an enzyme (*e.g.*, the linkage contains a peptide sequence that is a substrate for a peptidase), or by hydrolysis (*e.g.*, the linkage contains a hydrolyzable group, such as an ester or thioester). The linker groups can be biologically inactive, such as a PEG, polyglycolic acid, or polylactic acid chain, or can be biologically active, such as an oligo- or polypeptide that, when cleaved from the moieties, binds a receptor, deactivates an enzyme, etc. Various oligomeric linker groups that are biologically compatible and/or bioerodible are known in the art, and the selection of the linkage may influence the ultimate properties of the material, such as whether it is durable when implanted, whether it gradually deforms or shrinks after implantation, or whether it gradually degrades and is absorbed by the body. The linker group may be attached to the moieties by any suitable bond or functional group, including carbon-carbon bonds, esters, ethers, amides, amines, carbonates, carbamates, sulfonamides, etc.

In certain embodiments, the linker group(s) of the present invention represent a hydrocarbylene group wherein one or more methylene groups is optionally replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from, substituted or unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or -O-, C(=X) (wherein X is NR_1, O or S), -OC(O)-, -C(=O)O, -NR_1-, -NR_1CO-, -C(O)NR_1-, -$S(O)_n$- (wherein n is 0, 1, or 2), -OC(O)-NR_1, -NR_1-C(O)-NR_1-, -NR_1-C(NR_1)-NR_1-, and -B(OR_1)-; and R_1, independently for each occurrence, represents H or a lower alkyl.

In certain embodiments, the linker group represents a derivatized or non-derivatized amino acid (*e.g.*, glycine or cysteine). In certain embodiments, linker groups with one or more terminal carboxyl groups may be conjugated to the polymer. In certain embodiments, one or more of these terminal carboxyl groups may be capped by covalently attaching them to a therapeutic agent, a targeting moiety, or a cyclodextrin moiety via an (thio)ester or amide bond. In still other embodiments, linker groups with one or more terminal hydroxyl, thiol, or amino groups may be incorporated into the polymer. In preferred embodiments, one or more of these terminal hydroxyl groups may be capped by covalently attaching them to a therapeutic agent, a targeting moiety, or a cyclodextrin moiety via an (thio)ester,

amide, carbonate, carbamate, thiocarbonate, or thiocarbamate bond. In certain embodiments, these (thio)ester, amide, (thio)carbonate or (thio)carbamates bonds may be biohydrolyzable, *i.e.*, capable of being hydrolyzed under biological conditions.

In certain embodiments, a linker group represents a hydrocarbylene group wherein one or more methylene groups is optionally replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from, substituted or unsubstituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or -O-, C(=X) (wherein X is NR_1, O or S), -OC(O)-, -C(=O)O, -NR_1-, -NR_1CO-, -C(O)NR_1-, -$S(O)_n$- (wherein n is 0, 1, or 2), -OC(O)-NR_1, -NR_1-C(O)-NR_1-, -NR_1-C(NR_1)-NR_1-, and -B(OR_1)-; and R_1, independently for each occurrence, represents H or a lower alkyl.

In certain embodiments, a linker group, *e.g.*, between a topoisomerase inhibitor and the CDP, comprises a self-cyclizing moiety. In certain embodiments, a linker group, *e.g.*, between a topoisomerase inhibitor and the CDP, comprises a selectivity-determining moiety.

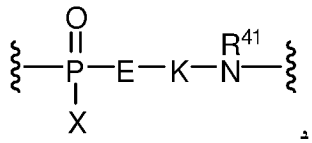
In certain embodiments as disclosed herein, a linker group, *e.g.*, between a topoisomerase inhibitor and the CDP, comprises a self-cyclizing moiety and a selectivity-determining moiety.

In certain embodiments as disclosed herein, the topoisomerase inhibitor or targeting ligand is covalently bonded to the linker group via a biohydrolyzable bond (*e.g.*, an ester, amide, carbonate, carbamate, or a phosphate).

In certain embodiments as disclosed herein, the CDP comprises cyclodextrin moieties that alternate with linker moieties in the polymer chain.

In certain embodiments, the linker moieties are attached to topoisomerase inhibitors or prodrugs thereof that are cleaved under biological conditions.

In certain embodiments, at least one linker that connects the topoisomerase inhibitor or prodrug thereof to the polymer comprises a group represented by the formula



wherein

P is phosphorus;

O is oxygen;

E represents oxygen or NR^{40};

K represents hydrocarbyl;

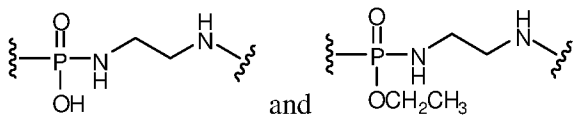
X is selected from OR^{42} or $NR^{43}R^{44}$; and

R^{40}, R^{41}, R^{42}, R^{43}, and R^{44} independently represent hydrogen or optionally substituted alkyl.

In certain embodiments, E is NR^{40} and R^{40} is hydrogen.

In certain embodiments, K is lower alkylene (*e.g.*, ethylene).

In certain embodiments, at least one linker comprises a group selected from



.

In certain embodiments, X is OR^{42}.

In certain embodiments, the linker group comprises an amino acid or peptide, or derivative thereof (*e.g.*, a glycine or cysteine).

In certain embodiments as disclosed herein, the linker is connected to the topoisomerase inhibitor through a hydroxyl group. In certain embodiments as disclosed herein, the linker is connected to the topoisomerase inhibitor through an amino group.

In certain embodiments, the linker group that connects to the topoisomerase inhibitor may comprise a self-cyclizing moiety, or a selectivity-determining moiety, or both. In certain embodiments, the selectivity-determining moiety is a moiety that promotes selectivity in the cleavage of the bond between the selectivity-determining moiety and the self-cyclizing moiety. Such a moiety may, for example, promote enzymatic cleavage between the selectivity-determining moiety and the self-cyclizing moiety. Alternatively, such a moiety may promote cleavage between the selectivity-determining moiety and the self-cyclizing moiety under acidic conditions or basic conditions.

In certain embodiments, any of the linker groups may comprise a self-cyclizing moiety or a selectivity-determining moiety, or both. In certain embodiments, the selectivity-determining moiety may be bonded to the self-cyclizing moiety between the self-cyclizing moiety and the polymer.

In certain embodiments, any of the linker groups may independently be or include an alkyl chain, a polyethylene glycol (PEG) chain, polysuccinic anhydride,

poly-L-glutamic acid, poly(ethyleneimine), an oligosaccharide, an amino acid chain, or any other suitable linkage. In certain embodiments, the linker group itself can be stable under physiological conditions, such as an alkyl chain, or it can be cleavable under physiological conditions, such as by an enzyme (*e.g.*, the linkage contains a peptide sequence that is a substrate for a peptidase), or by hydrolysis (*e.g.*, the linkage contains a hydrolyzable group, such as an ester or thioester). The linker groups can be biologically inactive, such as a PEG, polyglycolic acid, or polylactic acid chain, or can be biologically active, such as an oligo- or polypeptide that, when cleaved from the moieties, binds a receptor, deactivates an enzyme, etc. Various oligomeric linker groups that are biologically compatible and/or bioerodible are known in the art, and the selection of the linkage may influence the ultimate properties of the material, such as whether it is durable when implanted, whether it gradually deforms or shrinks after implantation, or whether it gradually degrades and is absorbed by the body. The linker group may be attached to the moieties by any suitable bond or functional group, including carbon-carbon bonds, esters, ethers, amides, amines, carbonates, carbamates, sulfonamides, etc.

In certain embodiments, any of the linker groups may independently be an alkyl group wherein one or more methylene groups is optionally replaced by a group Y (provided that none of the Y groups are adjacent to each other), wherein each Y, independently for each occurrence, is selected from aryl, heteroaryl, carbocyclyl, heterocyclyl, or -O-, C(=X) (wherein X is NR^1, O or S), -OC(O)-, -C(=O)O-, -NR^1-, -NR^1CO-, -C(O)NR^1-, -$S(O)_n$- (wherein n is 0, 1, or 2), -OC(O)-NR^1-, -NR^1-C(O)-NR^1-, -NR^1-C(NR^1)-NR^1-, and -B(OR^1)-; and R^1, independently for each occurrence, is H or lower alkyl.

In certain embodiments, the present invention contemplates a CDP, wherein a plurality of topoisomerase inhibitors are covalently attached to the polymer through attachments that are cleaved under biological conditions to release the therapeutic agents as discussed above, wherein administration of the polymer to a subject results in release of the therapeutic agent over a period of at least 2, 3, 5, 6, 8, 10, 15, 20, 24, 36, 48 or even 72 hours.

In some embodiments, the conjugation of the topoisomerase inhibitor to the CDP improves the aqueous solubility of the topoisomerase inhibitor and hence the bioavailability. Accordingly, in one embodiment of the invention, the topoisomerase inhibitor has a log P >0.4, >0.6, >0.8, >1, >2, >3, >4, or even >5.

The CDP- topoisomerase inhibitor conjugate of the present invention preferably has a molecular weight in the range of 10,000 to 500,000; 30,000 to 200,000; or even 70,000 to 150,000 amu.

In certain embodiments, the present invention contemplates attenuating the rate of release of the topoisomerase inhibitor by introducing various tether and/or linking groups between the therapeutic agent and the polymer. Thus, in certain embodiments, the CDP- topoisomerase inhibitor conjugates of the present invention are compositions for controlled delivery of the topoisomerase inhibitor.

CDP- topoisomerase inhibitor conjugate characteristics

In some embodiments, the CDP and/or CDP- topoisomerase inhibitor conjugate, particle or composition as described herein have polydispersities less than about 3, or even less than about 2.

One embodiment of the present invention provides an improved delivery of certain topoisomerase inhibitor by covalently attaching one or more topoisomerase inhibitors to a CDP. Such conjugation can improve the aqueous solubility and hence the bioavailability of the topoisomerase inhibitor.

The CDP- topoisomerase inhibitor conjugates, particles and compositions described herein preferably have molecular weights in the range of 10,000 to 500,000; 30,000 to 200,000; or even 70,000 to 150,000 amu. In certain embodiments as disclosed herein, the compound has a number average (M_n) molecular weight between 1,000 to 500,000 amu, or between 5,000 to 200,000 amu, or between 10,000 to 100,000 amu. One method to determine molecular weight is by gel permeation chromatography ("GPC"), *e.g.*, mixed bed columns, CH_2Cl_2 solvent, light scattering detector, and off-line dn/dc. Other methods are known in the art.

In certain embodiments as disclosed herein, the CDP-topoisomerase inhibitor conjugate, particle or composition is biodegradable or bioerodable.

In certain embodiments as disclosed herein, the topoisomerase inhibitor, *e.g.*, the camptothecin, camptothecin derivative, or prodrug thereof makes up at least 3% (*e.g.*, at least about 5%) by weight of the polymer. In certain embodiments, the topoisomerase inhibitor, *e.g.*, the camptothecin, camptothecin derivative or prodrug thereof makes up at least 20% by weight of the compound. In certain embodiments, the topoisomerase inhibitor, *e.g.*, the camptothecin, camptothecin derivative or

prodrug thereof makes up at least 5%, 10%, 15%, or at least 20% by weight of the compound.

CDP-topoisomerase inhibitor conjugates, particles and compositions of the present invention may be useful to improve solubility and/or stability of the topoisomerase inhibitor, reduce drug-drug interactions, reduce interactions with blood elements including plasma proteins, reduce or eliminate immunogenicity, protect the topoisomerase inhibitor from metabolism, modulate drug-release kinetics, improve circulation time, improve topoisomerase inhibitor half-life (*e.g.*, in the serum, or in selected tissues, such as tumors), attenuate toxicity, improve efficacy, normalize topoisomerase inhibitor metabolism across subjects of different species, ethnicities, and/or races, and/or provide for targeted delivery into specific cells or tissues.

In other embodiments, the CDP-topoisomerase inhibitor conjugate, particle or composition may be a flexible or flowable material. When the CDP used is itself flowable, the CDP composition of the invention, even when viscous, need not include a biocompatible solvent to be flowable, although trace or residual amounts of biocompatible solvents may still be present.

While it is possible that the biodegradable polymer or the biologically active agent may be dissolved in a small quantity of a solvent that is non-toxic to more efficiently produce an amorphous, monolithic distribution or a fine dispersion of the biologically active agent in the flexible or flowable composition, it is an advantage of the invention that, in a preferred embodiment, no solvent is needed to form a flowable composition. Moreover, the use of solvents is preferably avoided because, once a polymer composition containing solvent is placed totally or partially within the body, the solvent dissipates or diffuses away from the polymer and must be processed and eliminated by the body, placing an extra burden on the body's clearance ability at a time when the illness (and/or other treatments for the illness) may have already deleteriously affected it.

However, when a solvent is used to facilitate mixing or to maintain the flowability of the CDP-topoisomerase inhibitor conjugate, particle or composition, it should be non-toxic, otherwise biocompatible, and should be used in relatively small amounts. Solvents that are toxic should not be used in any material to be placed even partially within a living body. Such a solvent also must not cause substantial tissue irritation or necrosis at the site of administration.

Examples of suitable biocompatible solvents, when used, include N-methyl-2-pyrrolidone, 2-pyrrolidone, ethanol, propylene glycol, acetone, methyl acetate, ethyl acetate, methyl ethyl ketone, dimethylformamide, dimethylsulfoxide, tetrahydrofuran, caprolactam, oleic acid, or 1-dodecylazacylcoheptanone. Preferred solvents include N-methylpyrrolidone, 2-pyrrolidone, dimethylsulfoxide, and acetone because of their solvating ability and their biocompatibility.

In certain embodiments, the CDP-topoisomerase inhibitor conjugates, particles and compositions are soluble in one or more common organic solvents for ease of fabrication and processing. Common organic solvents include such solvents as chloroform, dichloromethane, dichloroethane, 2-butanone, butyl acetate, ethyl butyrate, acetone, ethyl acetate, dimethylacetamide, N-methylpyrrolidone, dimethylformamide, and dimethylsulfoxide.

In certain embodiments, the CDP-topoisomerase inhibitor conjugates, particles and compositions described herein, upon contact with body fluids, undergo gradual degradation. The life of a biodegradable polymer in vivo depends upon, among other things, its molecular weight, crystallinity, biostability, and the degree of crosslinking. In general, the greater the molecular weight, the higher the degree of crystallinity, and the greater the biostability, the slower biodegradation will be.

If a subject composition is formulated with a topoisomerase inhibitor or other material, release of the topoisomerase inhibitor or other material for a sustained or extended period as compared to the release from an isotonic saline solution generally results. Such release profile may result in prolonged delivery (over, say 1 to about 2,000 hours, or alternatively about 2 to about 800 hours) of effective amounts (*e.g.*, about 0.0001 mg/kg/hour to about 10 mg/kg/hour, *e.g.*, 0.001 mg/kg/hour, 0.01 mg/kg/hour, 0.1 mg/kg/hour, 1.0 mg/kg/hour) of the topoisomerase inhibitor or any other material associated with the polymer.

A variety of factors may affect the desired rate of hydrolysis of CDP-topoisomerase inhibitor conjugates, particles and compositions, the desired softness and flexibility of the resulting solid matrix, rate and extent of bioactive material release. Some of such factors include the selection/identity of the various subunits, the enantiomeric or diastereomeric purity of the monomeric subunits, homogeneity of subunits found in the polymer, and the length of the polymer. For instance, the present invention contemplates heteropolymers with varying linkages, and/or the

inclusion of other monomeric elements in the polymer, in order to control, for example, the rate of biodegradation of the matrix.

To illustrate further, a wide range of degradation rates may be obtained by adjusting the hydrophobicities of the backbones or side chains of the polymers while still maintaining sufficient biodegradability for the use intended for any such polymer. Such a result may be achieved by varying the various functional groups of the polymer. For example, the combination of a hydrophobic backbone and a hydrophilic linkage produces heterogeneous degradation because cleavage is encouraged whereas water penetration is resisted.

One protocol generally accepted in the field that may be used to determine the release rate of a therapeutic agent such as a topoisomerase inhibitor or other material loaded in the CDP-topoisomerase inhibitor conjugates, particles or compositions of the present invention involves degradation of any such matrix in a 0.1 M PBS solution (pH 7.4) at 37 °C, an assay known in the art. For purposes of the present invention, the term "PBS protocol" is used herein to refer to such protocol.

In certain instances, the release rates of different CDP-topoisomerase inhibitor conjugates, particles and compositions of the present invention may be compared by subjecting them to such a protocol. In certain instances, it may be necessary to process polymeric systems in the same fashion to allow direct and relatively accurate comparisons of different systems to be made. For example, the present invention teaches several different methods of formulating the CDP-topoisomerase inhibitor conjugates, particles and compositions. Such comparisons may indicate that any one CDP-topoisomerase inhibitor conjugate, particle or composition releases incorporated material at a rate from about 2 or less to about 1000 or more times faster than another polymeric system.

Alternatively, a comparison may reveal a rate difference of about 3, 5, 7, 10, 25, 50, 100, 250, 500 or 750 times. Even higher rate differences are contemplated by the present invention and release rate protocols.

In certain embodiments, when formulated in a certain manner, the release rate for CDP-topoisomerase inhibitor conjugates, particles and compositions of the present invention may present as mono- or bi-phasic.

Release of any material incorporated into the polymer matrix, which is often provided as a microsphere, may be characterized in certain instances by an initial increased release rate, which may release from about 5 to about 50% or more of any

incorporated material, or alternatively about 10, 15, 20, 25, 30 or 40%, followed by a release rate of lesser magnitude.

The release rate of any incorporated material may also be characterized by the amount of such material released per day per mg of polymer matrix. For example, in certain embodiments, the release rate may vary from about 1 ng or less of any incorporated material per day per mg of polymeric system to about 500 or more ng/day/mg. Alternatively, the release rate may be about 0.05, 0.5, 5, 10, 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 450, or 500 ng/day/mg. In still other embodiments, the release rate of any incorporated material may be 10,000 ng/day/mg, or even higher. In certain instances, materials incorporated and characterized by such release rate protocols may include therapeutic agents, fillers, and other substances.

In another aspect, the rate of release of any material from any CDP-topoisomerase inhibitor conjugate, particle or composition of the present invention may be presented as the half-life of such material in the matrix.

In addition to the embodiment involving protocols for in vitro determination of release rates, in vivo protocols, whereby in certain instances release rates for polymeric systems may be determined in vivo, are also contemplated by the present invention. Other assays useful for determining the release of any material from the polymers of the present system are known in the art.

Physical Structures of the CDP-topoisomerase inhibitor conjugates, particles and compositions

The CDP-topoisomerase inhibitor conjugates, particles and compositions may be formed in a variety of shapes. For example, in certain embodiments, CDP-topoisomerase inhibitor conjugates may be presented in the form of microparticles or nanoparticles. Microspheres typically comprise a biodegradable polymer matrix incorporating a drug. Microspheres can be formed by a wide variety of techniques known to those of skill in the art. Examples of microsphere forming techniques include, but are not limited to, (a) phase separation by emulsification and subsequent organic solvent evaporation (including complex emulsion methods such as oil in water emulsions, water in oil emulsions and water-oil-water emulsions); (b) coacervation-phase separation; (c) melt dispersion; (d) interfacial deposition; (e) in situ polymerization; (f) spray drying and spray congealing; (g) air suspension coating; and (h) pan and spray coating. These methods, as well as properties and

characteristics of microspheres are disclosed in, for example, U.S. Patent No. 4,438,253; U.S. Patent No. 4,652,441; U.S. Patent No. 5,100,669; U.S. Patent No. 5,330,768; U.S. Patent No. 4,526,938; U.S. Patent No. 5,889,110; U.S. Patent No. 6,034,175; and European Patent 0258780, the entire disclosures of which are incorporated by reference herein in their entireties.

To prepare microspheres, several methods can be employed depending upon the desired application of the delivery vehicles. Suitable methods include, but are not limited to, spray drying, freeze drying, air drying, vacuum drying, fluidized-bed drying, milling, co-precipitation and critical fluid extraction. In the case of spray drying, freeze drying, air drying, vacuum drying, fluidized-bed drying and critical fluid extraction; the components (stabilizing polyol, bioactive material, buffers, etc.) are first dissolved or suspended in aqueous conditions. In the case of milling, the components are mixed in the dried form and milled by any method known in the art. In the case of co-precipitation, the components are mixed in organic conditions and processed as described below. Spray drying can be used to load the stabilizing polyol with the bioactive material. The components are mixed under aqueous conditions and dried using precision nozzles to produce extremely uniform droplets in a drying chamber. Suitable spray drying machines include, but are not limited to, Buchi, NIRO, APV and Lab-plant spray driers used according to the manufacturer's instructions.

The shape of microparticles and nanoparticles may be determined by scanning electron microscopy. Spherically shaped nanoparticles are used in certain embodiments, for circulation through the bloodstream. If desired, the particles may be fabricated using known techniques into other shapes that are more useful for a specific application.

In addition to intracellular delivery of a topoisomerase inhibitor, it also possible that particles of the CDP-topoisomerase inhibitor conjugates, such as microparticles or nanoparticles, may undergo endocytosis, thereby obtaining access to the cell. The frequency of such an endocytosis process will likely depend on the size of any particle.

In one embodiment, the surface charge of the molecule is neutral, or slightly negative. In some embodiments, the zeta potential of the particle surface is from about -80 mV to about 50 mV.

CDPs, methods of making same, and methods of conjugating CDPs to Topoisomerase inhibitors

Generally, the CDP-topoisomerase inhibitor conjugates, particles and compositions described herein can be prepared in one of two ways: monomers bearing topoisomerase inhibitors, targeting ligands, and/or cyclodextrin moieties can be polymerized, or polymer backbones can be derivatized with topoisomerase inhibitors, targeting ligands, and/or cyclodextrin moieties. Exemplary methods of making CDPs and CDP-topoisomerase inhibitor conjugates, particles and compositions are described, for example, in U.S. Patent No.: 7,270,808, the contents of which is incorporated herein by reference in its entirety.

The CDPs described herein can be made using a variety of methods including those described herein. In some embodiments, a CDP can be made by: providing cyclodextrin moiety precursors; providing comonomer precursors which do not contain cyclodextrin moieties (comonomer precursors); and copolymerizing the said cyclodextrin moiety precursors and comonomer precursors to thereby make a CDP wherein CDP comprises at least four cyclodextrin moieties and at least four comonomers.

In some embodiments, the at least four cyclodextrin moieties and at least four comonomers alternate in the water soluble linear polymer. In some embodiments, the method includes providing cyclodextrin moiety precursors modified to bear one reactive site at each of exactly two positions, and reacting the cyclodextrin moiety precursors with comonomer precursors having exactly two reactive moieties capable of forming a covalent bond with the reactive sites under polymerization conditions that promote reaction of the reactive sites with the reactive moieties to form covalent bonds between the comonomers and the cyclodextrin moieties, whereby a CDP comprising alternating units of a cyclodextrin moiety and a comonomer is produced.

In some embodiments, the cyclodextrin momomers comprise linkers to which the topoisomerase inhibitor may be further linked.

In some embodiments, the comonomer precursor is a compound containing at least two functional groups through which reaction and thus linkage of the cyclodextrin moieties is achieved. In some embodiments, the functional groups, which may be the same or different, terminal or internal, of each comonomer precursor comprise an amino, acid, imidazole, hydroxyl, thio, acyl halide, -HC=CH-, —C≡C— group, or derivative thereof. In some embodiments, the two functional

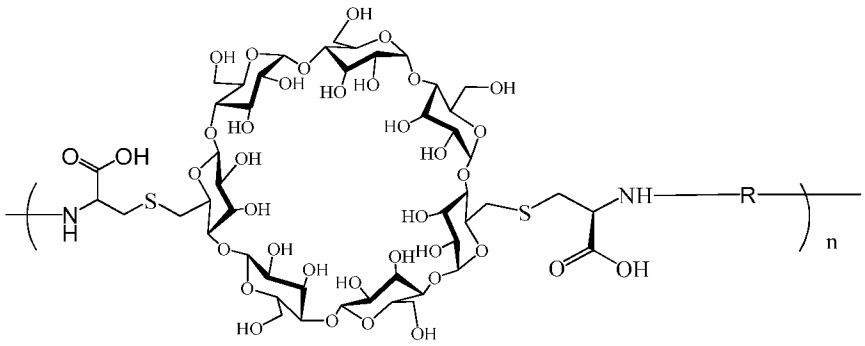
groups are the same and are located at termini of the comonomer precursor. In some embodiments, a comonomer contains one or more pendant groups with at least one functional group through which reaction and thus linkage of a therapeutic agent can be achieved. In some embodiments, the functional groups, which may be the same or different, terminal or internal, of each comonomer pendant group comprise an amino, acid, imidazole, hydroxyl, thiol, acyl halide, ethylene, ethyne group, or derivative thereof. In some embodiments, the pendant group is a substituted or unsubstituted branched, cyclic or straight chain C1-C10 alkyl, or arylalkyl optionally containing one or more heteroatoms within the chain or ring.

In some embodiments, the cyclodextrin moiety comprises an alpha, beta, or gamma cyclodextrin moiety.

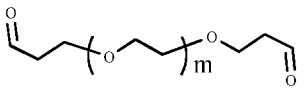
In some embodiments, the CDP is suitable for the attachment of sufficient topoisomerase inhibitor such that up to at least 3%, 5%, 10%, 11%, 12%, 13%, 14%, 15%, 20%, 25%, 30%, or even 35% by weight of the CDP, when conjugated, is topoisomerase inhibitor.

In some embodiments, the CDP has a molecular weight of 10,000-500,000 amu. In some embodiments, the cyclodextrin moieties make up at least about 2%, 5%, 10%, 20%, 30%, 50% or 80% of the CDP by weight.

In some embodiments, a CDP of the following formula can be made by the scheme below:



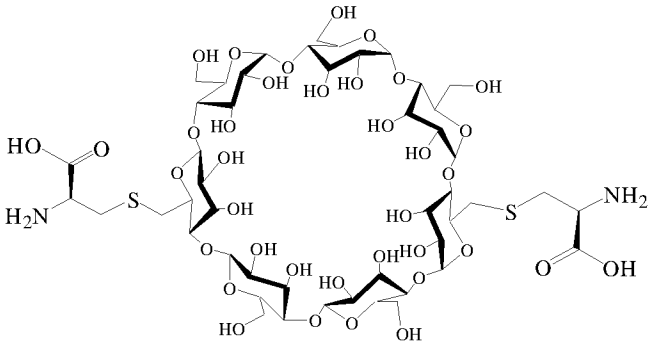
wherein R is of the form:



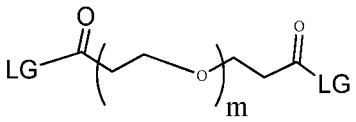
:

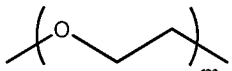
comprising the steps of:

reacting a compound of the formula below:

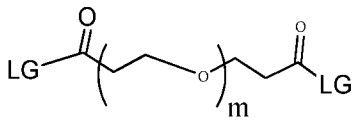
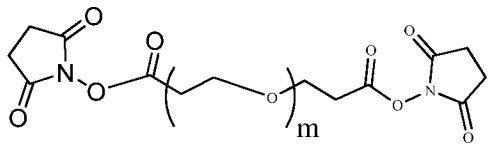


with a compound of the formula below:



wherein the group  has a Mw of about 2 to about 5 kDa (*e.g.*, from about 2 to about 4.5 kDa, from about 3 to about 4 kDa, or less than about 4 kDa, (*e.g.*, about 3.4 kDa ± 10%, *e.g.*, about 3060 Da to about 3740 Da)) and n is at least four,

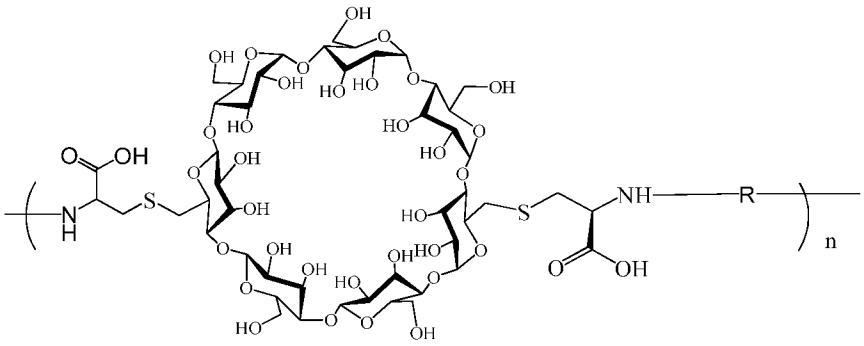
in the presence of a non-nucleophilic organic base in a solvent.

In some embodiments,  is  .

In some embodiments, the solvent is a polar aprotic solvent. In some embodiments, the solvent is DMSO.

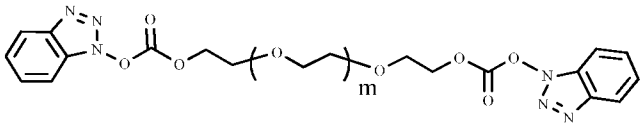
In some embodiments, the method also includes the steps of dialysis; and lyophylization.

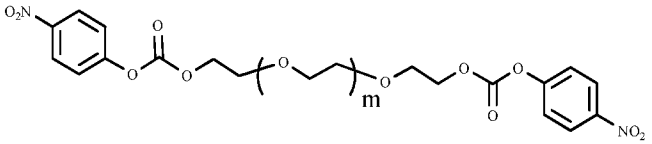
In some embodiments, a CDP provided below can be made by the following scheme:

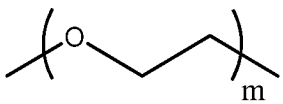


wherein R is of the form:

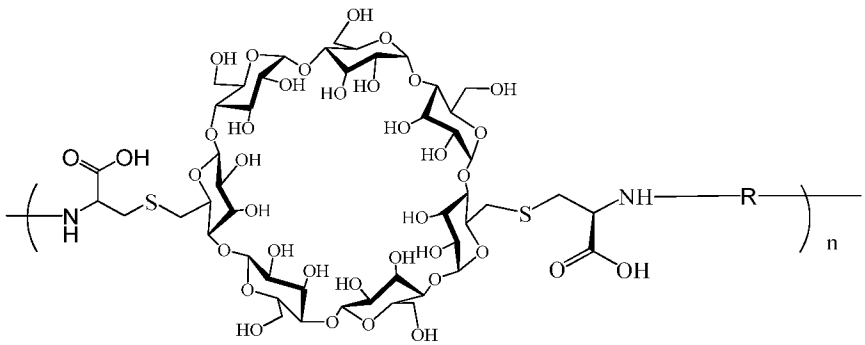
with a compound provided below:





wherein the group  has a Mw of about 2 to about 5 kDa (*e.g.*, from about 2 to about 4.5 kDa, from about 3 to about 4 kDa, or less than about 4 kDa, (*e.g.*, about 3.4 kDa ± 10%, *e.g.*, about 3060 Da to about 3740 Da)); in the presence of a non-nucleophilic organic base in DMSO;

and dialyzing and lyophilizing the following polymer



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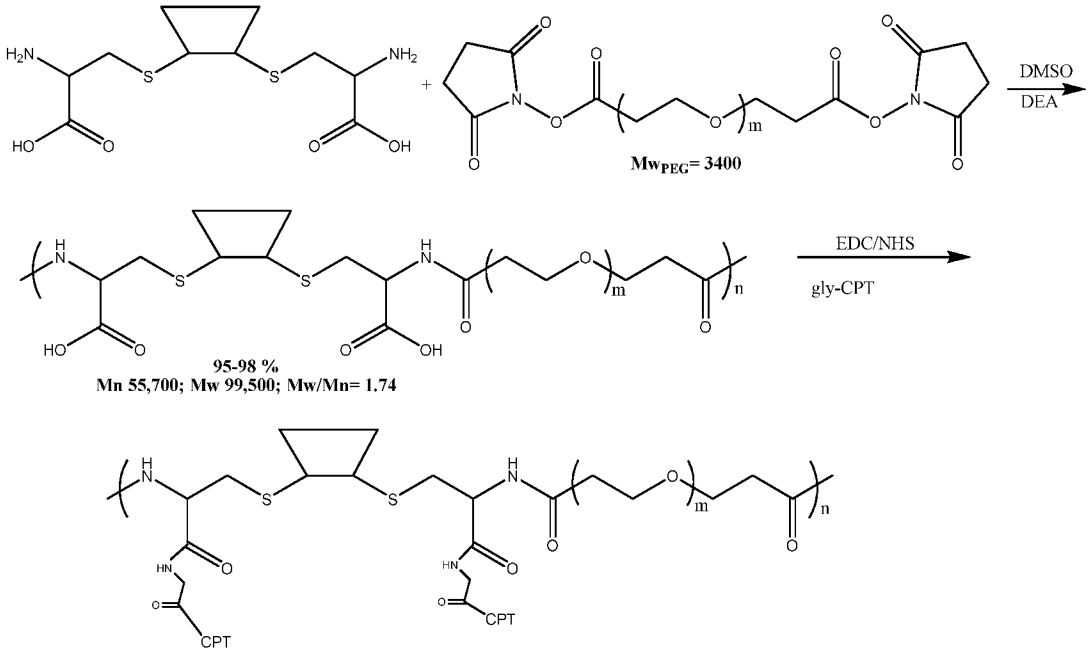
The present invention further contemplates CDPs and CDP-conjugates synthesized using CD-biscysteine monomer and a di-NHS ester such as PEG-DiSPA or PEG-BTC as shown in Scheme I.

Scheme I



Scheme XIII, as provided above, includes embodiments where gly-CPT is absent in one or more positions as provided above. This can be achieved, for example, when less than 100% yield is achieved when coupling the CPT to the polymer and/or when less than an equivalent amount of CPT is used in the reaction. Accordingly, the loading of the topoisomerase inhibitor such as camptothecin, by weight of the polymer, can vary. Therefore, while Scheme XIII depicts CPT at each cysteine residue of each polymer subunit, the CDP-CPT conjugate can have less than 2 CPT molecules attached to any given polymer subunit of the CDP. For example, in one embodiment, the CDP-CPT conjugate includes several polymer subunits and each of the polymer subunits can independently include two, one or no CPT attached at each cysteine residue of the polymer subunit. In addition, the particles and compositions can include CDP-CPT conjugates having two, one or no CPT attached at each cysteine residue of each polymer subunit of the CDP-CPT conjugate and the conjugates include a mixture of CDP-CPT conjugates that can vary as to the number of CPTs attached to the gly at each of the polymer subunits of the conjugates in the particle or composition.

In some embodiments, a CDP-topoisomerase inhibitor conjugate can be made by providing a CDP comprising cyclodextrin moieties and comonomers which do not contain cyclodextrin moieties (comonomers), wherein the cyclodextrin moieties and comonomers alternate in the CDP and wherein the CDP comprises at least four

cyclodextrin moieties and at least four comonomers; and attaching a topoisomerase inhibitor to the CDP.

In some embodiments, one or more of the topoisomerase inhibitor moieties in the CDP- topoisomerase inhibitor conjugate can be replaced with another therapeutic agent, *e.g.*, another anticancer agent or anti-inflammatory agent.

In some embodiments, the topoisomerase inhibitor is attached to the water soluble linear polymer via a linker. In some embodiments, the topoisomerase inhibitor is attached to the water soluble linear polymer through an attachment that is cleaved under biological conditions to release the topoisomerase inhibitor. In some embodiments, the topoisomerase inhibitor is attached to the water soluble linear polymer at a cyclodextrin moiety or a comonomer. In some embodiments, the topoisomerase inhibitor is attached to the water soluble linear polymer via an optional linker to a cyclodextrin moiety or a comonomer.

In some embodiments, the cyclodextrin moieties comprise linkers to which therapeutic agents are linked.

In some embodiments, the CDP is made by a process comprising: providing cyclodextrin moiety precursors, providing comonomer precursors, and copolymerizing said cyclodextrin moiety precursors and comonomer precursors to thereby make a CDP comprising cyclodextrin moieties and comonomers. In some embodiments, the CDP is conjugated with a topoisomerase inhibitor such as camptothecin to provide a CDP-topoisomerase inhibitor conjugate.

In some embodiments, the method includes providing cyclodextrin moiety precursors modified to bear one reactive site at each of exactly two positions, and reacting the cyclodextrin moiety precursors with comonomer precursors having exactly two reactive moieties capable of forming a covalent bond with the reactive sites under polymerization conditions that promote reaction of the reactive sites with the reactive moieties to form covalent bonds between the comonomers and the cyclodextrin moieties, whereby a CDP comprising alternating units of a cyclodextrin moiety and a comonomer is produced.

In some embodiments, the topoisomerase inhibitor is attached to the CDP via a linker. In some embodiments, the linker is cleaved under biological conditions.

In some embodiments, the topoisomerase inhibitor makes up at least 5%, 10%, 11%, 12%, 13%, 14%, 15%, 20%, 25%, 30%, or even 35% by weight of the CDP-topoisomerase inhibitor conjugate.

In some embodiments, the comonomer comprises polyethylene glycol of molecular weight from about 2 to about 5 kDa (*e.g.*, from about 2 to about 4.5 kDa, from about 3 to about 4 kDa, or less than about 4 kDa, (*e.g.*, about 3.4 kDa ± 10%, *e.g.*, about 3060 Da to about 3740 Da)), the cyclodextrin moiety comprises beta-cyclodextrin, the theoretical maximum loading of camptothecin on a CDP-camptothecin conjugate is 13%, and camptothecin is 6-10% by weight of the CDP-camptothecin conjugate.

In some embodiments, the comonomer precursor is a compound containing at least two functional groups through which reaction and thus linkage of the cyclodextrin moieties is achieved. In some embodiments, the functional groups, which may be the same or different, terminal or internal, of each comonomer precursor comprise an amino, acid, imidazole, hydroxyl, thio, acyl halide, -HC=CH-, —C≡C— group, or derivative thereof. In some embodiments, the two functional groups are the same and are located at termini of the comonomer precursor. In some embodiments, a comonomer contains one or more pendant groups with at least one functional group through which reaction and thus linkage of a therapeutic agent is achieved. In some embodiments, the functional groups, which may be the same or different, terminal or internal, of each comonomer pendant group comprise an amino, acid, imidazole, hydroxyl, thiol, acyl halide, ethylene, ethyne group, or derivative thereof. In some embodiments, the pendant group is a substituted or unsubstituted branched, cyclic or straight chain C1-C10 alkyl, or arylalkyl optionally containing one or more heteroatoms within the chain or ring.

In some embodiments, the cyclodextrin moiety comprises an alpha, beta, or gamma cyclodextrin moiety.

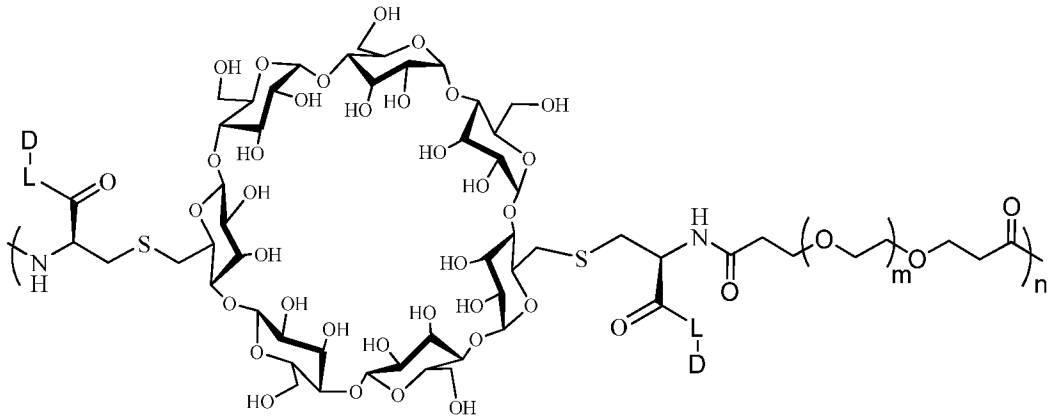
In some embodiments, the topoisomerase inhibitor is poorly soluble in water.

In some embodiments, administration of the CDP-topoisomerase inhibitor conjugate, particle or composition to a subject results in release of the topoisomerase inhibitor over a period of at least 6 hours. In some embodiments, administration of the CDP-topoisomerase inhibitor conjugate, particle or composition to a subject results in release of the topoisomerase inhibitor over a period of 6 hours to a month. In some embodiments, upon administration of the CDP-topoisomerase inhibitor conjugate, particle or composition to a subject the rate of topoisomerase inhibitor release is dependent primarily upon the rate of hydrolysis as opposed to enzymatic cleavage.

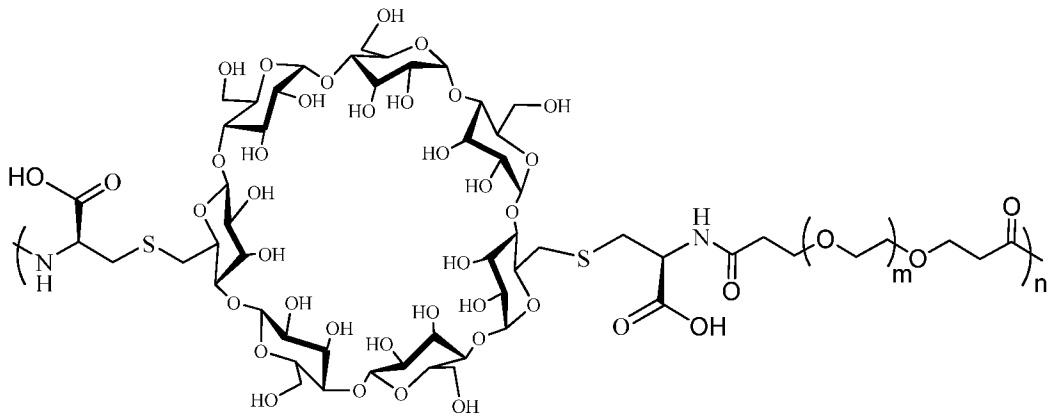
In some embodiments, the CDP-topoisomerase inhibitor conjugate, particle or composition has a molecular weight of 10,000-500,000 amu.

In some embodiments, the cyclodextrin moieties make up at least about 2%, 5%, 10%, 20%, 30%, 50% or 80% of the polymer by weight.

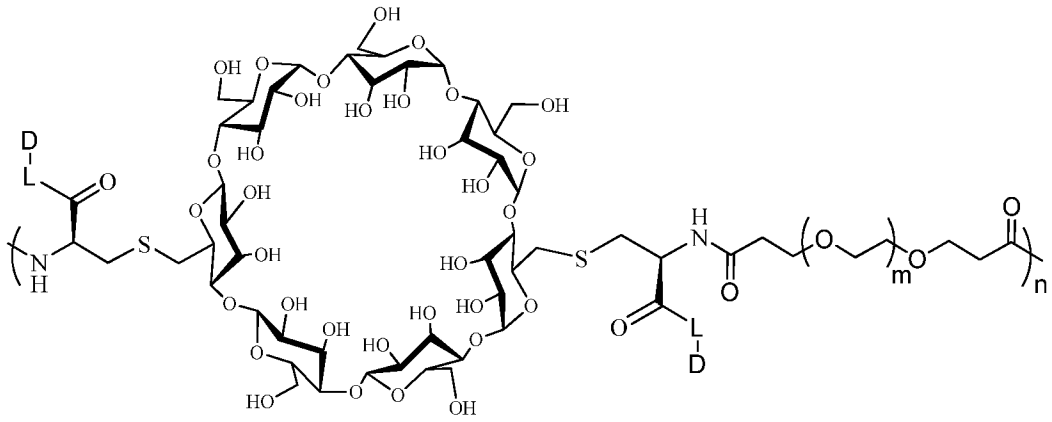
In some embodiments, a CDP-polymer conjugate of the following formula can be made as follows:

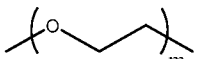


providing a polymer below:



and coupling the polymer with a plurality of L-D moieties, wherein L is a linker, or absent and D is topoisomerase inhibitor such as camptothecin or a camptothecin derivative, to provide:



wherein the group  has a Mw of about 2 to about 5 kDa (*e.g.*, from about 2 to about 4.5 kDa, from about 3 to about 4 kDa, or less than about 4 kDa, (*e.g.*, about 3.4 kDa ± 10%, *e.g.*, about 3060 Da to about 3740 Da)) and n is at least 4, wherein on the final product, L can be a linker, a bond, or OH, and D can be a topoisomerase inhibitor (*e.g.*, camptothecin or a camptothecin derivative) or absent.

In some embodiments, one or more of the topoisomerase inhibitor moieties in the CDP-topoisomerase inhibitor conjugate can be replaced with another therapeutic agent, *e.g.*, another anticancer agent or anti-inflammatory agent.

The reaction scheme as provided above includes embodiments where L-D is absent in one or more positions as provided above. This can be achieved, for example, when less than 100% yield is achieved when coupling the topoisomerase inhibitor -linker to the polymer and/or when less than an equivalent amount of topoisomerase inhibitor-linker is used in the reaction. Accordingly, the loading of the topoisomerase inhibitor, by weight of the polymer, can vary, for example, the loading of the topoisomerase inhibitor can be at least about 3% by weight, *e.g.*, at least about 5%, at least about 8%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, or at least about 20%.

In some embodiments, at least a portion of the L moieties of L-D is absent. In some embodiments, each L is independently an amino acid or derivative thereof (*e.g.*, glycine).

In some embodiments, the coupling of the polymer with the plurality of L-D moieties results in the formation of a plurality of amide bonds.

In certain instances, the CDPs are random copolymers, in which the different subunits and/or other monomeric units are distributed randomly throughout the

polymer chain. Thus, where the formula X_m-Y_n-Z_o appears, wherein X, Y and Z are polymer subunits, these subunits may be randomly interspersed throughout the polymer backbone. In part, the term "random" is intended to refer to the situation in which the particular distribution or incorporation of monomeric units in a polymer that has more than one type of monomeric units is not directed or controlled directly by the synthetic protocol, but instead results from features inherent to the polymer system, such as the reactivity, amounts of subunits and other characteristics of the synthetic reaction or other methods of manufacture, processing, or treatment.

Pharmaceutical Compositions

In another aspect, the present invention provides a composition, *e.g.*, a pharmaceutical composition, comprising a CDP-topoisomerase inhibitor conjugate or particle and a pharmaceutically acceptable carrier or adjuvant.

In some embodiments, a pharmaceutical composition may include a pharmaceutically acceptable salt of a compound described herein, *e.g.*, a CDP-topoisomerase inhibitor conjugate, particle or composition. Pharmaceutically acceptable salts of the compounds described herein include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, benzoate, benzenesulfonate, butyrate, citrate, digluconate, dodecylsulfate, formate, fumarate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, tosylate and undecanoate. Salts derived from appropriate bases include alkali metal (*e.g.*, sodium), alkaline earth metal (*e.g.*, magnesium), ammonium and N-$(alkyl)_4^+$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds described herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate,

sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gailate, aipha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

A composition may include a liquid used for suspending a CDP-topoisomerase inhibitor conjugate, particle or composition, which may be any liquid solution compatible with the CDP- topoisomerase inhibitor conjugate, particle or composition, which is also suitable to be used in pharmaceutical compositions, such as a pharmaceutically acceptable nontoxic liquid. Suitable suspending liquids including but are not limited to suspending liquids selected from the group consisting of water, aqueous sucrose syrups, corn syrups, sorbitol, polyethylene glycol, propylene glycol, and mixtures thereof.

A composition described herein may also include another component, such as an antioxidant, antibacterial, buffer, bulking agent, chelating agent, an inert gas, a tonicity agent and/or a viscosity agent.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition is provided in lyophilized form and is reconstituted prior to administration to a subject. The lyophilized CDP-topoisomerase inhibitor conjugate, particle or composition can be reconstituted by a diluent solution, such as a salt or saline solution, *e.g.*, a sodium chloride solution having a pH between 6 and 9, lactated Ringer's injection solution, or a commercially available diluent, such as PLASMA-LYTE A Injection pH 7.4® (Baxter, Deerfield, IL).

In one embodiment, a lyophilized formulation includes a lyoprotectant or stabilizer to maintain physical and chemical stability by protecting the CDP-topoisomerase inhibitor conjugate, particle or composition from damage from crystal formation and the fusion process during freeze-drying. The lyoprotectant or stabilizer can be one or more of polyethylene glycol (PEG), a PEG lipid conjugate (*e.g.*, PEG-ceramide or D-alpha-tocopheryl polyethylene glycol 1000 succinate), poly(vinyl alcohol) (PVA), poly(vinylpyrrolidone) (PVP), polyoxyethylene esters, poloxomers, Tweens, lecithins, saccharides, oligosaccharides, polysaccharides and polyols (*e.g.*, trehalose, mannitol, sorbitol, lactose, sucrose, glucose and dextran), salts and crown ethers. In one embodiment, the lyoprotectant is mannitol.

In some embodiments, the lyophilized CDP-topoisomerase inhibitor conjugate, particle or composition is reconstituted with a mixture of equal parts by volume of Dehydrated Alcohol, USP and a nonionic surfactant, such as a polyoxyethylated castor oil surfactant available from GAF Corporation, Mount Olive, N.J., under the trademark, Cremophor EL. In some embodiments, the lyophilized CDP-topoisomerase inhibitor conjugate, particle or composition is reconstituted in water for infusion. The lyophilized product and vehicle for reconstitution can be packaged separately in appropriately light-protected vials, *e.g.*, amber or other colored vials. To minimize the amount of surfactant in the reconstituted solution, only a sufficient amount of the vehicle may be provided to form a solution having a concentration of about 2 mg/mL to about 4 mg/mL of the CDP-topoisomerase inhibitor conjugate, particle or composition. Once dissolution of the drug is achieved, the resulting solution is further diluted prior to injection with a suitable parenteral diluent. Such diluents are well known to those of ordinary skill in the art. These diluents are generally available in clinical facilities. It is, however, within the scope of the present invention to package the subject CDP-topoisomerase inhibitor conjugate, particle or composition with a third vial containing sufficient parenteral diluent to prepare the final concentration for administration. A typical diluent is Lactated Ringer's Injection.

The final dilution of the reconstituted CDP-topoisomerase inhibitor conjugate, particle or composition may be carried out with other preparations having similar utility, for example, 5% Dextrose Injection, Lactated Ringer's and Dextrose for Injection (D5W), Sterile Water for Injection, and the like. However, because of its narrow pH range, pH 6.0 to 7.5, Lactated Ringer's Injection is most typical. Per 100 mL, Lactated Ringer's Injection contains Sodium Chloride USP 0.6 g, Sodium Lactate 0.31 g, Potassium chloride USP 0.03 g and Calcium Chloride2H2O USP 0.02 g. The osmolarity is 275 mOsmol/L, which is very close to isotonicity.

The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The dosage form can be, *e.g.*, in a bog, *e.g.*, a bag for infusion or intraperitoneal administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount

of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Routes of Administration

The pharmaceutical compositions described herein may be administered orally, parenterally (*e.g.*, via intravenous, subcutaneous, intracutaneous, intramuscular, intraarticular, intraarterial, intraperitoneal, intrasynovial, intrasternal, intrathecal, intralesional or intracranial injection), topically, mucosally (*e.g.*, rectally or vaginally), nasally, buccally, ophthalmically, via inhalation spray (*e.g.*, delivered via nebulzation, propellant or a dry powder device) or via an implanted reservoir. Typically, the compositions are in the form of injectable or infusible solutions. The preferred mode of administration is, *e.g.*, intravenous, subcutaneous, intraperitoneal, intramuscular.

Pharmaceutical compositions suitable for parenteral administration comprise one or more CDP-topoisomerase inhibitor conjugate(s), particle(s) or composition(s) in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the

like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the agent from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the CDP-topoisomerase inhibitor conjugate, particle or composition then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the CDP-topoisomerase inhibitor conjugate, particle or composition in an oil vehicle.

Pharmaceutical compositions suitable for oral administration may be in the form of capsules, cachets, pills, tablets, gums, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouthwashes and the like, each containing a predetermined amount of an agent as an active ingredient. A compound may also be administered as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered peptide or peptidomimetic moistened with an inert liquid diluent.

Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes

and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the CDP-topoisomerase inhibitor conjugate, particle or composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the CDP-topoisomerase inhibitor conjugate, particle or composition may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Pharmaceutical compositions suitable for topical administration are useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the a particle described herein include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound,

emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active particle suspended or dissolved in a carrier with suitable emulsifying agents. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions described herein may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included herein.

The pharmaceutical compositions described herein may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The pharmaceutical compositions described herein may also be administered in the form of suppositories for rectal or vaginal administration. Suppositories may be prepared by mixing one or more CDP-topoisomerase inhibitor conjugate, particle or composition described herein with one or more suitable non-irritating excipients which is solid at room temperature, but liquid at body temperature. The composition will therefore melt in the rectum or vaginal cavity and release the CDP-topoisomerase inhibitor conjugate, particle or composition. Such materials include, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate. Compositions of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of the invention.

Dosages and Dosing Regimens

The CDP-topoisomerase inhibitor conjugate, particle or composition can be formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active

ingredient which is effective to achieve the desired therapeutic response for a particular subject, composition, and mode of administration, without being toxic to the subject.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered to a subject at a dosage of, *e.g.*, about 1 to 40 mg/m^2, about 3 to 35 mg/m^2, about 9 to 40 mg/m^2, *e.g.*, about 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 mg/m^2 of the topoisomerase inhibitor. Administration can be at regular intervals, such as weekly, or every 2, 3, 4, 5 or 6 weeks. The administration can be over a period of from about 10 minutes to about 6 hours, *e.g.*, from about 30 minutes to about 2 hours, from about 45 minutes to 90 minutes, *e.g.*, about 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours or more. The CDP-topoisomerase inhibitor conjugate, particle or composition can be administered, *e.g.*, by intravenous or intraperitoneal administration.

In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered as a bolus infusion or intravenous push, *e.g.*, over a period of 15 minutes, 10 minutes, 5 minutes or less. In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered in an amount such the desired dose of the agent is administered. Preferably the dose of the CDP-topoisomerase inhibitor conjugate, particle or composition is a dose described herein.

In one embodiment, the subject receives 1, 2, 3, up to 10 treatments, or more, or until the disorder or a symptom of the disorder is cured, healed, alleviated, relieved, altered, remedied, ameliorated, palliated, improved or affected. For example, the subject receives an infusion once every 1, 2, 3 or 4 weeks until the disorder or a symptom of the disorder is cured, healed, alleviated, relieved, altered, remedied, ameliorated, palliated, improved or affected. Preferably, the dosing schedule is a dosing schedule described herein.

The CDP-topoisomerase inhibitor conjugate, particle or composition can be administered as a first line therapy, *e.g.*, alone or in combination with an additional agent or agents. In other embodiments, a CDP-topoisomerase inhibitor conjugate, particle or composition is administered after a subject has developed resistance to, has failed to respond to or has relapsed after a first line therapy. The CDP-topoisomerase inhibitor conjugate, particle or composition can be administered in combination with a

second agent. Preferably, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered in combination with a second agent described herein.

Kits

A CDP-topoisomerase inhibitor conjugate, particle or composition described herein may be provided in a kit. The kit includes a CDP-topoisomerase inhibitor conjugate, particle or composition described herein and, optionally, a container, a pharmaceutically acceptable carrier and/or informational material. The informational material can be descriptive, instructional, marketing or other material that relates to the methods described herein and/or the use of the CDP-topoisomerase inhibitor conjugate, particle or composition for the methods described herein.

The informational material of the kits is not limited in its form. In one embodiment, the informational material can include information about production of the CDP-topoisomerase inhibitor conjugate, particle or composition, physical properties of the CDP-topoisomerase inhibitor conjugate, particle or composition, concentration, date of expiration, batch or production site information, and so forth. In one embodiment, the informational material relates to methods for administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, by a route of administration described herein and/or at a dose and/or dosing schedule described herein.

In one embodiment, the informational material can include instructions to administer a CDP-topoisomerase inhibitor conjugate, particle or composition described herein in a suitable manner to perform the methods described herein, *e.g.*, in a suitable dose, dosage form, or mode of administration (*e.g.*, a dose, dosage form, or mode of administration described herein). In another embodiment, the informational material can include instructions to administer a CDP-topoisomerase inhibitor conjugate, particle or composition described herein to a suitable subject, *e.g.*, a human, *e.g.*, a human having or at risk for a disorder described herein. In another embodiment, the informational material can include instructions to reconstitute a CDP-topoisomerase inhibitor conjugate, particle or composition described herein into a pharmaceutically acceptable composition.

In one embodiment, the kit includes instructions to use the CDP-topoisomerase inhibitor conjugate, particle or composition, such as for treatment of a subject. The instructions can include methods for reconstituting or diluting the CDP-

topoisomerase inhibitor conjugate, particle or composition for use with a particular subject or in combination with a particular chemotherapeutic agent. The instructions can also include methods for reconstituting or diluting the CDP-topoisomerase inhibitor conjugate, particle or composition for use with a particular means of administration, such as by intravenous infusion or intraperitoneal administration.

In another embodiment, the kit includes instructions for treating a subject with a particular indication, such as a particular cancer, or a cancer at a particular stage. For example, the instructions can be for a cancer or cancer at stage described herein, *e.g.*, lung cancer (*e.g.*, non small cell lung cancer and/or small cell lung cancer, *e.g.*, squamous cell non-small cell and/or small cell lung cancer) or ovarian cancer. The instructions may also address first line treatment of a subject who has a particular cancer, or cancer at a stage described herein. The instructions can also address treatment of a subject who has been non-responsive to a first line therapy or has become sensitive (*e.g.*, has one or more unacceptable side effect) to a first line therapy, such as a taxane, an anthracycline, an antimetabolite, a vinca alkaloid, a vascular endothelial growth factor (VEGF) pathway inhibitor, an epidermal growth factor (EGF) pathway inhibitor, an alkylating agent, a platinum-based agent, a vinca alkaloid. In another embodiment, the instructions will describe treatment of selected subjects with the CDP-topoisomerase inhibitor conjugate, particle or composition. For example, the instructions can describe treatment of one or more of: a subject having a cancer that has increased levels of KRAS and/or ST expression, *e.g.*, as compared to a reference standard.

The informational material of the kits is not limited in its form. In many cases, the informational material, *e.g.*, instructions, is provided in printed matter, *e.g.*, a printed text, drawing, and/or photograph, *e.g.*, a label or printed sheet. However, the informational material can also be provided in other formats, such as Braille, computer readable material, video recording, or audio recording. In another embodiment, the informational material of the kit is contact information, *e.g.*, a physical address, email address, website, or telephone number, where a user of the kit can obtain substantive information about a CDP-topoisomerase inhibitor conjugate, particle or composition described herein and/or its use in the methods described herein. The informational material can also be provided in any combination of formats.

In addition to a CDP-topoisomerase inhibitor conjugate, particle or composition described herein, the composition of the kit can include other ingredients, such as a surfactant, a lyoprotectant or stabilizer, an antioxidant, an antibacterial agent, a bulking agent, a chelating agent, an inert gas, a tonicity agent and/or a viscosity agent, a solvent or buffer, a stabilizer, a preservative, a flavoring agent (*e.g.*, a bitter antagonist or a sweetener), a fragrance, a dye or coloring agent, for example, to tint or color one or more components in the kit, or other cosmetic ingredient, a pharmaceutically acceptable carrier and/or a second agent for treating a condition or disorder described herein. Alternatively, the other ingredients can be included in the kit, but in different compositions or containers than a CDP-topoisomerase inhibitor conjugate, particle or composition described herein. In such embodiments, the kit can include instructions for admixing a CDP-topoisomerase inhibitor conjugate, particle or composition described herein and the other ingredients, or for using a CDP-topoisomerase inhibitor conjugate, particle or composition described herein together with the other ingredients. For example, the kit can include an agent which reduces or inhibits one or more symptom of hypersensitivity, a polysaccharide, and/or an agent which increases urinary excretion and/or neutralizes one or more urinary metabolite.

In another embodiment, the kit includes a second therapeutic agent, such as a second chemotherapeutic agent, *e.g.*, a chemotherapeutic agent or combination of chemotherapeutic agents described herein. In one embodiment, the second agent is in lyophilized or in liquid form. In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition and the second therapeutic agent are in separate containers, and in another embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition and the second therapeutic agent are packaged in the same container.

In some embodiments, a component of the kit is stored in a sealed vial, *e.g.*, with a rubber or silicone closure (*e.g.*, a polybutadiene or polyisoprene closure). In some embodiments, a component of the kit is stored under inert conditions (*e.g.*, under Nitrogen or another inert gas such as Argon). In some embodiments, a component of the kit is stored under anhydrous conditions (*e.g.*, with a desiccant). In some embodiments, a component of the kit is stored in a light blocking container such as an amber vial.

A CDP-topoisomerase inhibitor conjugate, particle or composition described herein can be provided in any form, *e.g.*, liquid, frozen, dried or lyophilized form. It is preferred that a composition including the conjugate, particle or composition, *e.g.*, a composition comprising a particle or particles that include a conjugate described herein be substantially pure and/or sterile. When a CDP-topoisomerase inhibitor conjugate, particle or composition described herein is provided in a liquid solution, the liquid solution preferably is an aqueous solution, with a sterile aqueous solution being preferred. In one embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition is provided in lyophilized form and, optionally, a diluent solution is provided for reconstituting the lyophilized agent. The diluent can include for example, a salt or saline solution, *e.g.*, a sodium chloride solution having a pH between 6 and 9, lactated Ringer's injection solution, D5W, or PLASMA-LYTE A Injection pH 7.4® (Baxter, Deerfield, IL).

The kit can include one or more containers for the composition containing a CDP-topoisomerase inhibitor conjugate, particle or composition described herein. In some embodiments, the kit contains separate containers, dividers or compartments for the composition and informational material. For example, the composition can be contained in a bottle, vial, IV admixture bag, IV infusion set, piggyback set or syringe, and the informational material can be contained in a plastic sleeve or packet. In other embodiments, the separate elements of the kit are contained within a single, undivided container. For example, the composition is contained in a bottle, vial or syringe that has attached thereto the informational material in the form of a label. In some embodiments, the kit includes a plurality (*e.g.*, a pack) of individual containers, each containing one or more unit dosage forms (*e.g.*, a dosage form described herein) of a CDP-topoisomerase inhibitor conjugate, particle or composition described herein. For example, the kit includes a plurality of syringes, ampules, foil packets, or blister packs, each containing a single unit dose of a particle described herein. The containers of the kits can be air tight, waterproof (*e.g.*, impermeable to changes in moisture or evaporation), and/or light-tight.

The kit optionally includes a device suitable for administration of the composition, *e.g.*, a syringe, inhalant, pipette, forceps, measured spoon, dropper (*e.g.*, eye dropper), swab (*e.g.*, a cotton swab or wooden swab), or any such delivery device. In one embodiment, the device is a medical implant device, *e.g.*, packaged for surgical insertion.

Combination therapy

The CDP-topoisomerase inhibitor conjugate, particle or composition may be used in combination with other known therapies. Administered "in combination", as used herein, means that two (or more) different treatments are delivered to the subject during the course of the subject's affliction with the disorder, *e.g.*, the two or more treatments are delivered after the subject has been diagnosed with the disorder and before the disorder has been cured or eliminated or treatment has ceased for other reasons. In some embodiments, the delivery of one treatment is still occurring when the delivery of the second begins, so that there is overlap in terms of administration. This is sometimes referred to herein as "simultaneous" or "concurrent delivery". In other embodiments, the delivery of one treatment ends before the delivery of the other treatment begins. In some embodiments of either case, the treatment is more effective because of combined administration. For example, the second treatment is more effective, *e.g.*, an equivalent effect is seen with less of the second treatment, or the second treatment reduces symptoms to a greater extent, than would be seen if the second treatment were administered in the absence of the first treatment, or the analogous situation is seen with the first treatment. In some embodiments, delivery is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one treatment delivered in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The delivery can be such that an effect of the first treatment delivered is still detectable when the second is delivered.

The CDP-topoisomerase inhibitor conjugate, particle or composition and the at least one additional therapeutic agent can be administered simultaneously, in the same or in separate compositions, or sequentially. For sequential administration, the CDP-topoisomerase inhibitor conjugate, particle or composition can be administered first, and the additional agent can be administered second, or the order of administration can be reversed.

In some embodiments, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered in combination with a small molecule. As used herein, the term "small molecule" refers to organic compounds, whether naturally-occurring or artificially created (*e.g.*, via chemical synthesis) that have relatively low molecular weight and that are not proteins, polypeptides, or nucleic acids. Typically, small

molecules have a molecular weight of less than about 1 kilodalton (kDa). For example, small molecules typically have multiple carbon-carbon bonds.

In some embodiments, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered in combination with other therapeutic treatment modalities, including surgery, radiation, cryosurgery, and/or thermotherapy. Such combination therapies may advantageously utilize lower dosages of the administered agent and/or other chemotherapeutic agent, thus avoiding possible toxicities or complications associated with the various monotherapies. The phrase "radiation" includes, but is not limited to, external-beam therapy which involves three dimensional, conformal radiation therapy where the field of radiation is designed to conform to the volume of tissue treated; interstitial-radiation therapy where seeds of radioactive compounds are implanted using ultrasound guidance; and a combination of external-beam therapy and interstitial-radiation therapy.

In some embodiments, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered with at least one additional therapeutic agent, such as a chemotherapeutic agent. In certain embodiments, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered in combination with one or more additional chemotherapeutic agent, *e.g.*, with one or more chemotherapeutic agents described herein. Exemplary classes of chemotherapeutic agents include, *e.g.*, the following:

alkylating agents (including, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes): uracil mustard (Aminouracil Mustard®, Chlorethaminacil®, Demethyldopan®, Desmethyldopan®, Haemanthamine®, Nordopan®, Uracil nitrogen mustard®, Uracillost®, Uracilmostaza®, Uramustin®, Uramustine®), chlormethine (Mustargen®), cyclophosphamide (Cytoxan®, Neosar®, Clafen®, Endoxan®, Procytox®, Revimmune™), ifosfamide (Mitoxana®), melphalan (Alkeran®), Chlorambucil (Leukeran®), pipobroman (Amedel®, Vercyte®), triethylenemelamine (Hemel®, Hexalen®, Hexastat®), triethylenethiophosphoramine, Temozolomide (Temodar®), thiotepa (Thioplex®), busulfan (Busilvex®, Myleran®), carmustine (BiCNU®), lomustine (CeeNU®), streptozocin (Zanosar®), and Dacarbazine (DTIC-Dome®).

anti-EGFR antibodies (*e.g.*, cetuximab (Erbitux®) and panitumumab (Vectibix®).

anti-HER-2 antibodies (*e.g.*, trastuzumab (Herceptin®).

antimetabolites (including, without limitation, folic acid antagonists (also referred to herein as antifolates), pyrimidine analogs, purine analogs and adenosine deaminase inhibitors): methotrexate (Rheumatrex®, Trexall®), 5-fluorouracil (Adrucil®, Efudex®, Fluoroplex®), floxuridine (FUDF®), cytarabine (Cytosar-U®, Tarabine PFS), 6-mercaptopurine (Puri-Nethol®)), 6-thioguanine (Thioguanine Tabloid®), fludarabine phosphate (Fludara®), pentostatin (Nipent®), pemetrexed (Alimta®), raltitrexed (Tomudex®), cladribine (Leustatin®), clofarabine (Clofarex®, Clolar®), mercaptopurine (Puri-Nethol®), capecitabine (Xeloda®), nelarabine (Arranon®), azacitidine (Vidaza®) and gemcitabine (Gemzar®). Preferred antimetabolites include, *e.g.*, 5-fluorouracil (Adrucil®, Efudex®, Fluoroplex®), floxuridine (FUDF®), capecitabine (Xeloda®), pemetrexed (Alimta®), raltitrexed (Tomudex®) and gemcitabine (Gemzar®).

vinca alkaloids: vinblastine (Velban®, Velsar®), vincristine (Vincasar®, Oncovin®), vindesine (Eldisine®), vinorelbine (Navelbine®).

platinum-based agents: carboplatin (Paraplat®, Paraplatin®), cisplatin (Platinol®), oxaliplatin (Eloxatin®).

anthracyclines: daunorubicin (Cerubidine®, Rubidomycin®), doxorubicin (Adriamycin®), epirubicin (Ellence®), idarubicin (Idamycin®), mitoxantrone (Novantrone®), valrubicin (Valstar®). Preferred anthracyclines include daunorubicin (Cerubidine®, Rubidomycin®) and doxorubicin (Adriamycin®).

topoisomerase inhibitors: topotecan (Hycamtin®), irinotecan (Camptosar®), etoposide (Toposar®, VePesid®), teniposide (Vumon®), lamellarin D, SN-38, camptothecin.

taxanes: paclitaxel (Taxol®), docetaxel (Taxotere®), larotaxel, cabazitaxel.

epothilones: ixabepilone, epothilone B, epothilone D, BMS310705, dehydelone, ZK-Epothilone (ZK-EPO).

poly ADP-ribose polymerase (PARP) inhibitors: (*e.g.*, BSI 201, Olaparib (AZD-2281), ABT-888, AG014699, CEP 9722, MK 4827, KU-0059436 (AZD2281), LT-673, 3-aminobenzamide).

antibiotics: actinomycin (Cosmegen®), bleomycin (Blenoxane®), hydroxyurea (Droxia®, Hydrea®), mitomycin (Mitozytrex®, Mutamycin®).

immunomodulators: lenalidomide (Revlimid®), thalidomide (Thalomid®).

immune cell antibodies: alemtuzamab (Campath®), gemtuzumab (Myelotarg®), rituximab (Rituxan®), tositumomab (Bexxar®).

interferons (*e.g.*, IFN-alpha (Alferon®, Roferon-A®, Intron®-A) or IFN-gamma (Actimmune®)).

interleukins: IL-1, IL-2 (Proleukin®), IL-24, IL-6 (Sigosix®), IL-12.

HSP90 inhibitors (*e.g.*, geldanamycin or any of its derivatives). In certain embodiments, the HSP90 inhibitor is selected from geldanamycin, 17-alkylamino-17-desmethoxygeldanamycin ("17-AAG") or 17-(2-dimethylaminoethyl)amino-17-desmethoxygeldanamycin ("17-DMAG").

angiogenesis inhibitors which include, without limitation A6 (Angstrom Pharmacueticals), ABT-510 (Abbott Laboratories), ABT-627 (Atrasentan) (Abbott Laboratories/Xinlay), ABT-869 (Abbott Laboratories), Actimid (CC4047, Pomalidomide) (Celgene Corporation), AdGVPEDF.11D (GenVec), ADH-1 (Exherin) (Adherex Technologies), AEE788 (Novartis), AG-013736 (Axitinib) (Pfizer), AG3340 (Prinomastat) (Agouron Pharmaceuticals), AGX1053 (AngioGenex), AGX51 (AngioGenex), ALN-VSP (ALN-VSP O2) (Alnylam Pharmaceuticals), AMG 386 (Amgen), AMG706 (Amgen), Apatinib (YN968D1) (Jiangsu Hengrui Medicine), AP23573 (Ridaforolimus/MK8669) (Ariad Pharmaceuticals), AQ4N (Novavea), ARQ 197 (ArQule), ASA404 (Novartis/Antisoma), Atiprimod (Callisto Pharmaceuticals), ATN-161 (Attenuon), AV-412 (Aveo Pharmaceuticals), AV-951 (Aveo Pharmaceuticals), Avastin (Bevacizumab) (Genentech), AZD2171 (Cediranib/Recentin) (AstraZeneca), BAY 57-9352 (Telatinib) (Bayer), BEZ235 (Novartis), BIBF1120 (Boehringer Ingelheim Pharmaceuticals), BIBW 2992 (Boehringer Ingelheim Pharmaceuticals), BMS-275291 (Bristol-Myers Squibb), BMS-582664 (Brivanib) (Bristol-Myers Squibb), BMS-690514 (Bristol-Myers Squibb), Calcitriol, CCI-779 (Torisel) (Wyeth), CDP-791 (ImClone Systems), Ceflatonin (Homoharringtonine/HHT) (ChemGenex Therapeutics), Celebrex (Celecoxib) (Pfizer), CEP-7055 (Cephalon/Sanofi), CHIR-265 (Chiron Corporation), NGR-TNF, COL-3 (Metastat) (Collagenex Pharaceuticals), Combretastatin (Oxigene), CP-751,871(Figitumumab) (Pfizer), CP-547,632 (Pfizer), CS-7017 (Daiichi Sankyo Pharma), CT-322 (Angiocept) (Adnexus), Curcumin, Dalteparin (Fragmin) (Pfizer), Disulfiram (Antabuse), E7820 (Eisai Limited), E7080 (Eisai Limited), EMD 121974(Cilengitide) (EMD Pharmaceuticals), ENMD-1198 (EntreMed), ENMD-2076 (EntreMed), Endostar (Simcere), Erbitux (ImClone/Bristol-Myers Squibb), EZN-2208 (Enzon Pharmaceuticals), EZN-2968 (Enzon Pharmaceuticals), GC1008 (Genzyme), Genistein, GSK1363089(Foretinib)

(GlaxoSmithKline), GW786034 (Pazopanib) (GlaxoSmithKline), GT-111 (Vascular Biogenics Ltd.), IMC--1121B (Ramucirumab) (ImClone Systems), IMC-18F1 (ImClone Systems), IMC-3G3 (ImClone LLC), INCB007839 (Incyte Corporation), INGN 241 (Introgen Therapeutics), Iressa (ZD1839/Gefitinib), LBH589 (Faridak/Panobinostst) (Novartis), Lucentis (Ranibizumab) (Genentech/Novartis), LY317615 (Enzastaurin) (Eli Lilly and Company), Macugen (Pegaptanib) (Pfizer), MEDI522 (Abegrin) (MedImmune), MLN518(Tandutinib) (Millennium), Neovastat (AE941/Benefin) (Aeterna Zentaris), Nexavar (Bayer/Onyx), NM-3 (Genzyme Corporation), Noscapine (Cougar Biotechnology), NPI-2358 (Nereus Pharmaceuticals), OSI-930 (OSI), Palomid 529 (Paloma Pharmaceuticals, Inc.), Panzem Capsules (2ME2) (EntreMed), Panzem NCD (2ME2) (EntreMed), PF-02341066 (Pfizer), PF-04554878 (Pfizer), PI-88 (Progen Industries/Medigen Biotechnology), PKC412 (Novartis), Polyphenon E (Green Tea Extract) (Polypheno E International, Inc), PPI-2458 (Praecis Pharmaceuticals), PTC299 (PTC Therapeutics), PTK787 (Vatalanib) (Novartis), PXD101 (Belinostat) (CuraGen Corporation), RAD001 (Everolimus) (Novartis), RAF265 (Novartis), Regorafenib (BAY73-4506) (Bayer), Revlimid (Celgene), Retaane (Alcon Research), SN38 (Liposomal) (Neopharm), SNS-032 (BMS-387032) (Sunesis), SOM230(Pasireotide) (Novartis), Squalamine (Genaera), Suramin, Sutent (Pfizer), Tarceva (Genentech), TB-403 (Thrombogenics), Tempostatin (Collard Biopharmaceuticals), Tetrathiomolybdate (Sigma-Aldrich), TG100801 (TargeGen), Thalidomide (Celgene Corporation), Tinzaparin Sodium, TKI258 (Novartis), TRC093 (Tracon Pharmaceuticals Inc.), VEGF Trap (Aflibercept) (Regeneron Pharmaceuticals), VEGF Trap-Eye (Regeneron Pharmaceuticals), Veglin (VasGene Therapeutics), Bortezomib (Millennium), XL184 (Exelixis), XL647 (Exelixis), XL784 (Exelixis), XL820 (Exelixis), XL999 (Exelixis), ZD6474 (AstraZeneca), Vorinostat (Merck), and ZSTK474.

anti-androgens which include, without limitation nilutamide (Nilandron®) and bicalutamide (Caxodex®).

antiestrogens which include, without limitation tamoxifen (Nolvadex®), toremifene (Fareston®), letrozole (Femara®), testolactone (Teslac®), anastrozole (Arimidex®), bicalutamide (Casodex®), exemestane (Aromasin®), flutamide (Eulexin®), fulvestrant (Faslodex®), raloxifene (Evista®, Keoxifene®) and raloxifene hydrochloride.

anti-hypercalcaemia agents which include without limitation gallium (III) nitrate hydrate (Ganite®) and pamidronate disodium (Aredia®).

apoptosis inducers which include without limitation ethanol, 2-[[3-(2,3-dichlorophenoxy)propyl]amino]-(9Cl), gambogic acid, embelin and arsenic trioxide (Trisenox®).

Auroran kinase inhibitors which include without limitation binucleine 2.

Bruton's tyrosine kinase inhibitors which include without limitation terreic acid.

calcineurin inhibitors which include without limitation cypermethrin, deltamethrin, fenvalerate and tyrphostin 8.

CaM kinase II inhibitors which include without limitation 5-Isoquinolinesulfonic acid, 4-[{2S)-2-[(5-isoquinolinylsulfonyl)methylamino]-3-oxo-3-{4-phenyl-1-piperazinyl)propyl]phenyl ester and benzenesulfonamide.

CD45 tyrosine phosphatase inhibitors which include without limitation phosphonic acid.

CDC25 phosphatase inhibitors which include without limitation 1,4-naphthalene dione, 2,3-bis[(2-hydroxyethyl)thio]-(9Cl).

CHK kinase inhibitors which include without limitation debromohymenialdisine.

cyclooxygenase inhibitors which include without limitation 1H-indole-3-acetamide, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-N-(2-phenylethyl)-(9Cl), 5-alkyl substituted 2-arylaminophenylacetic acid and its derivatives (*e.g.*, celecoxib (Celebrex®), rofecoxib (Vioxx®), etoricoxib (Arcoxia®), lumiracoxib (Prexige®), valdecoxib (Bextra®) or 5-alkyl-2-arylaminophenylacetic acid).

cRAF kinase inhibitors which include without limitation 3-(3,5-dibromo-4-hydroxybenzylidene)-5-iodo-1,3-dihydroindol-2-one and benzamide, 3-(dimethylamino)-N-[3-[(4-hydroxybenzoyl)amino]-4-methylphenyl]-(9Cl).

cyclin dependent kinase inhibitors which include without limitation olomoucine and its derivatives, purvalanol B, roascovitine (Seliciclib®), indirubin, kenpaullone, purvalanol A and indirubin-3'-monooxime.

cysteine protease inhibitors which include without limitation 4-morpholinecarboxamide, N-[(1S)-3-fluoro-2-oxo-1-(2-phenylethyl)propyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-(9Cl).

DNA intercalators which include without limitation plicamycin (Mithracin®) and daptomycin (Cubicin®).

DNA strand breakers which include without limitation bleomycin (Blenoxane®).

E3 ligase inhibitors which include without limitation N-((3,3,3-trifluoro-2-trifluoromethyl)propionyl)sulfanilamide.

EGF Pathway Inhibitors which include, without limitation tyrphostin 46, EKB-569, erlotinib (Tarceva®), gefitinib (Iressa®), lapatinib (Tykerb®) and those compounds that are generically and specifically disclosed in WO 97/02266, EP 0 564 409, WO 99/03854, EP 0 520 722, EP 0 566 226, EP 0 787 722, EP 0 837 063, US 5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 and WO 96/33980.

farnesyltransferase inhibitors which include without limitation A-hydroxyfarnesylphosphonic acid, butanoic acid, 2-[(2S)-2-[[(2S,3S)-2-[[(2R)-2-amino-3-mercaptopropyl]amino]-3-methylpentyl]oxy]-1-oxo-3-phenylpropyl]amino]-4-(methylsulfonyl)-1-methylethylester (2S)-(9Cl), and manumycin A.

Flk-1 kinase inhibitors which include without limitation 2-propenamide, 2-cyano-3-[4-hydroxy-3,5-bis(1-methylethyl)phenyl]-N-(3-phenylpropyl)-(2E)-(9Cl).

glycogen synthase kinase-3 (GSK3) inhibitors which include without limitation indirubin-3'-monooxime.

Heat Shock Protein 90 (Hsp90) chaperone modulators which include without limitation AUY922, STA-9090, ATI13387, MCP-3100, IPI-504, IPI-493, SNX-5422, Debio0932, HSP990, DS-2248, PU-H71, 17-DMAG (Alvespimycin), and XL888.

histone deacetylase (HDAC) inhibitors which include without limitation suberoylanilide hydroxamic acid (SAHA), [4-(2-amino-phenylcarbamoyl)-benzyl]-carbamic acid pyridine-3-ylmethylester and its derivatives, butyric acid, pyroxamide, trichostatin A, oxamflatin, apicidin, depsipeptide, depudecin, trapoxin and compounds disclosed in WO 02/22577.

I-kappa B-alphan kinase inhibitors (IKK) which include without limitation 2-propenenitrile, 3-[(4-methylphenyl)sulfonyl]-(2E)-(9Cl).

imidazotetrazinones which include without limitation temozolomide (Methazolastone®, Temodar® and its derivatives (*e.g.*, as disclosed generically and specifically in US 5,260,291) and Mitozolomide.

Insulin like growth factor pathway inhibitors such as IGF inhibitors or IGF receptor (IGFR1 or IGFR2) inhibitors include without limitation, small molecule inhibitors, *e.g.*, OSI-906; anti-IGF antibodies or anti-IGFR antibodies, *e.g.*, AVE-1642, MK-0646, IMC-A12 (cixutumab), R1507, CP-751,871 (Figitumumab).

insulin tyrosine kinase inhibitors which include without limitation hydroxyl-2-naphthalenylmethylphosphonic acid.

c-Jun-N-terminal kinase (JNK) inhibitors which include without limitation pyrazoleanthrone and epigallocatechin gallate.

mitogen-activated protein kinase (MAP) inhibitors which include without limitation benzenesulfonamide, N-[2-[[[3-(4-chlorophenyl)-2-propenyl]methyl]amino]methyl]phenyl]-N-(2-hydroxyethyl)-4-methoxy-(9Cl).

MDM2 inhibitors which include without limitation trans-4-iodo, 4'-boranyl-chalcone.

MEK inhibitors which include without limitation butanedinitrile, bis[amino[2-aminophenyl)thio]methylene]-(9Cl), and trametinib (Mekinist™).

MMP inhibitors which include without limitation Actinonin, epigallocatechin gallate, collagen peptidomimetic and non-peptidomimetic inhibitors, tetracycline derivatives marimastat (Marimastat®), prinomastat, incyclinide (Metastat®), shark cartilage extract AE-941 (Neovastat®), Tanomastat, TAA211, MMI270B or AAJ996.

mTor inhibitors which include without limitation rapamycin (Rapamune®), and analogs and derivatives thereof, AP23573 (also known as ridaforolimus, deforolimus, or MK-8669), CCI-779 (also known as temsirolimus) (Torisel®) and SDZ-RAD.

NGFR tyrosine kinase inhibitors which include without limitation tyrphostin AG 879.

p38 MAP kinase inhibitors which include without limitation Phenol, 4-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]-(9Cl), and benzamide, 3-(dimethylamino)-N-[3-[(4-hydroxylbenzoyl)amino]-4-methylphenyl]-(9Cl).

p56 tyrosine kinase inhibitors which include without limitation damnacanthal and tyrphostin 46.

PDGF pathway inhibitors which include without limitation tyrphostin AG 1296, tyrphostin 9, 1,3-butadiene-1,1,3-tricarbonitrile, 2-amino-4-(1H-indol-5-yl)-(9Cl), imatinib (Gleevec®) and gefitinib (Iressa®) and those compounds generically

and specifically disclosed in European Patent No.: 0 564 409 and PCT Publication No.: WO 99/03854.

phosphatidylinositol 3-kinase inhibitors which include without limitation wortmannin, and quercetin dihydrate.

phosphatase inhibitors which include without limitation cantharidic acid, cantharidin, and L-leucinamide.

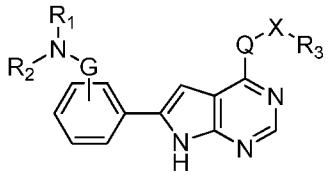
PKC inhibitors which include without limitation 1-H-pyrollo-2,5-dione,3-[1-[3-(dimethylamino)propyl]-1H-indol-3-yl]-4-(1H-indol-3-yl)-(9Cl), Bisindolylmaleimide IX, Sphinogosine, staurosporine, and Hypericin.

PKC deltan kinase inhibitors which include without limitation rottlerin.polyamine synthesis inhibitors which include without limitation DMFO.

proteasome inhibitors which include, without limitation aclacinomycin A, gliotoxin and bortezomib (Velcade®).

protein phosphatase inhibitors which include without limitation cantharidic acid, cantharidin, L-P-bromotetramisole oxalate, 2(5H)-furanone, 4-hydroxy-5-(hydroxymethyl)-3-(1-oxohexadecyl)-(5R)-(9Cl) and benzylphosphonic acid.

protein tyrosine kinase inhibitors which include, without limitation tyrphostin Ag 216, tyrphostin Ag 1288, tyrphostin Ag 1295, geldanamycin, genistein and 7H-pyrollo[2,3-d]pyrimidine derivatives of formula I as generically and specifically described in PCT Publication No.: WO 03/013541 and U.S. Publication No.: 2008/0139587:



(I)

Publication No.: 2008/0139587 discloses the various substituents, *e.g.*, R_1, R_2, etc.

PTP1B inhibitors which include without limitation L-leucinamide.

SRC family tyrosine kinase inhibitors which include without limitation PP1 and PP2.

Syk tyrosine kinase inhibitors which include without limitation piceatannol.

Janus (JAK-2 and/or JAK-3) tyrosine kinase inhibitors which include without limitation tyrphostin AG 490 and 2-naphthyl vinyl ketone.

retinoids which include without limitation isotretinoin (Accutane®, Amnesteem®, Cistane®, Claravis®, Sotret®) and tretinoin (Aberel®, Aknoten®, Avita®, Renova®, Retin-A®, Retin-A MICRO®, Vesanoid®).

RNA polymerase II elongation inhibitors which include without limitation 5,6-dichloro-1-beta-D-ribofuranosylbenzimidazole.

serine/threonine protein kinase inhibitors which include without limitation 2-aminopurine.

sterol biosynthesis inhibitors which include without limitation squalene epoxidase and CYP2D6.VEGF pathway inhibitors which include without limitation anti-VEGF antibodies, *e.g.*, bevacizumab, and small molecules, *e.g.*, sunitinib (Sutent®), sorafinib (Nexavar®), ZD6474 (also known as vandetanib) (Zactima™), SU6668, CP-547632, AV-951 (tivozanib) and AZD2171 (also known as cediranib) (Recentin™).

Examples of chemotherapeutic agents are also described in the scientific and patent literature, see, *e.g.*, Bulinski (1997) J. Cell Sci. 110:3055-3064; Panda (1997) Proc. Natl. Acad. Sci. USA 94:10560-10564; Muhlradt (1997) Cancer Res. 57:3344-3346; Nicolaou (1997) Nature 387:268-272; Vasquez (1997) Mol. Biol. Cell. 8:973-985; Panda (1996) J. Biol. Chem 271:29807-29812.

In some embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered instead of another topoisomerase inhibitor, *e.g.*, instead of a topoisomerase inhibitor as a first line therapy or a second line therapy. For example, the CDP-topoisomerase inhibitor conjugate, particle or composition can be used instead of any of the following topoisomerase inhibitors: a topoisomerase I inhibitor, *e.g.*, camptothecin, irinotecan, SN-38, topotecan, lamellarin D; a topoisomerase II inhibitor, *e.g.*, etoposide, tenoposide, doxorubicin.

In some cases, a hormone and/or steriod can be administered in combination with a CDP-topoisomerase inhibitor conjugate, particle or composition. Examples of hormones and steroids include: 17a-ethinylestradiol (Estinyl®, Ethinoral®, Feminone®, Orestralyn®), diethylstilbestrol (Acnestrol®, Cyren A®, Deladumone®, Diastyl®, Domestrol®, Estrobene®, Estrobene®, Estrosyn®, Fonatol®, Makarol®, Milestrol®, Milestrol®, Neo-Oestronol I®, Oestrogenine®, Oestromenin®, Oestromon®, Palestrol®, Stilbestrol®, Stilbetin®, Stilboestroform®, Stilboestrol®, Synestrin®, Synthoestrin®, Vagestrol®), testosterone (Delatestryl®, Testoderm®, Testolin®, Testostroval®, Testostroval-PA®, Testro AQ®), prednisone (Delta-

Dome®, Deltasone®, Liquid Pred®, Lisacort®, Meticorten®, Orasone®, Prednicen-M®, Sk-Prednisone®, Sterapred®), Fluoxymesterone (Android-F®, Halodrin®, Halotestin®, Ora-Testryl®, Ultandren®), dromostanolone propionate (Drolban®, Emdisterone®, Masterid®, Masteril®, Masteron®, Masterone®, Metholone®, Permastril®), testolactone (Teslac®), megestrolacetate (Magestin®, Maygace®, Megace®, Megeron®, Megestat®, Megestil®, Megestin®, Nia®, Niagestin®, Ovaban®, Ovarid®, Volidan®), methylprednisolone (Depo-Medrol®, Medlone 21®, Medrol®, Meprolone®, Metrocort®, Metypred®, Solu-Medrol®, Summicort®), methyl-testosterone (Android®, Testred®, Virilon®), prednisolone (Cortalone®, Delta-Cortef®, Hydeltra®, Hydeltrasol®, Meti-derm®, Prelone®), triamcinolone (Aristocort®), chlorotrianisene (Anisene®, Chlorotrisin®, Clorestrolo®, Clorotrisin®, Hormonisene®, Khlortrianizen®, Merbentul®, Metace®, Rianil®, Tace®, Tace-Fn®, Trianisestrol®), hydroxyprogesterone (Delalutin®, Gestiva™), aminoglutethimide (Cytadren®, Elipten®, Orimeten®), estramustine (Emcyt®), medroxyprogesteroneacetate (Provera®, Depo-Provera®), leuprolide (Lupron®, Viadur®), flutamide (Eulexin®), toremifene (Fareston®), and goserelin (Zoladex®).

In certain embodiments, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered in combination with an anti-microbial (*e.g.*, leptomycin B).

In another embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered in combination with an agent or procedure to mitigate potential side effects from the agent compositions such as cystisis, hypersensitivity, diarrhea, nausea and vomiting.

Cystisis can be mitigated with an agent that increases urinary excretion and/or neutralizes one or more urinary metabolite. For example, cystisis can be mitigated or treated with MESNA.

Diarrhea may be treated with antidiarrheal agents including, but not limited to opioids (*e.g.*, codeine (Codicept®, Coducept®), oxicodeine, percocet, paregoric, tincture of opium, diphenoxylate (Lomotil®), diflenoxin), and loperamide (Imodium A-D®), bismuth subsalicylate, lanreotide, vapreotide (Sanvar®, Sanvar IR®), motiln antagonists, COX2 inhibitors (*e.g.*, celecoxib (Celebrex®), glutamine (NutreStore®), thalidomide (Synovir®, Thalomid®), traditional antidiarrhea remedies (*e.g.*, kaolin, pectin, berberine and muscarinic agents), octreotide and DPP-IV inhibitors.

DPP-IV inhibitors employed in the present invention are generically and specifically disclosed in PCT Publication Nos.: WO 98/19998, DE 196 16 486 A1, WO 00/34241 and WO 95/15309.

Nausea and vomiting may be treated with antiemetic agents such as dexamethasone (Aeroseb-Dex®, Alba-Dex®, Decaderm®, Decadrol®, Decadron®, Decasone®, Decaspray®, Deenar®, Deronil®, Dex-4®, Dexace®, Dexameth®, Dezone®, Gammacorten®, Hexadrol®, Maxidex®, Sk-Dexamethasone®), metoclopramide (Reglan®), diphenylhydramine (Benadryl®, SK-Diphenhydramine®), lorazepam (Ativan®), ondansetron (Zofran®), prochlorperazine (Bayer A 173®, Buccastem®, Capazine®, Combid®, Compazine®, Compro®, Emelent®, Emetiral®, Eskatrol®, Kronocin®, Meterazin®, Meterazin Maleate®, Meterazine®, Nipodal®, Novamin®, Pasotomin®, Phenotil®, Stemetil®, Stemzine®, Tementil®, Temetid®, Vertigon®), thiethylperazine (Norzine®, Torecan®), and dronabinol (Marinol®).

In some embodiments, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered in combination with an immunosuppressive agent. Immunosuppressive agents suitable for the combination include, but are not limited to natalizumab (Tysabri®), azathioprine (Imuran®), mitoxantrone (Novantrone®), mycophenolate mofetil (Cellcept®), cyclosporins (*e.g.*, Cyclosporin A (Neoral®, Sandimmun®, Sandimmune®, SangCya®), cacineurin inhibitors (*e.g.*, Tacrolimus (Prograf®, Protopic®), sirolimus (Rapamune®), everolimus (Afinitor®), cyclophosphamide (Clafen®, Cytoxan®, Neosar®), or methotrexate (Abitrexate®, Folex®, Methotrexate®, Mexate®)), fingolimod, mycophenolate mofetil (CellCept®), mycophenolic acid (Myfortic®), anti-CD3 antibody, anti-CD25 antibody (*e.g.*, Basiliximab (Simulect®) or daclizumab (Zenapax®)), and anti-TNFα antibody (*e.g.*, Infliximab (Remicade®) or adalimumab (Humira®)).

In some embodiments, a CDP-topoisomerase inhibitor conjugate, particle or composition is administered in combination with a CYP3A4 inhibitor (*e.g.*, ketoconazole (Nizoral®, Xolegel®), itraconazole (Sporanox®), clarithromycin (Biaxin®), atazanavir (Reyataz®), nefazodone (Serzone®, Nefadar®), saquinavir (Invirase®), telithromycin (Ketek®), ritonavir (Norvir®), amprenavir (also known as Agenerase, a prodrug version is fosamprenavir (Lexiva®, Telzir®), indinavir (Crixivan®), nelfinavir (Viracept®), delavirdine (Rescriptor®) or voriconazole (Vfend®)).

When employing the methods or compositions, other agents used in the modulation of tumor growth or metastasis in a clinical setting, such as antiemetics, can also be administered as desired.

When formulating the pharmaceutical compositions featured in the invention the clinician may utilize preferred dosages as warranted by the condition of the subject being treated. For example, in one embodiment, a CDP-topoisomerase inhibitor conjugate, particle or composition may be administered at a dosing schedule described herein, *e.g.*, once every one, two, three or four weeks.

Also, in general, a CDP-topoisomerase inhibitor conjugate, particle or composition and an additional chemotherapeutic agent(s) do not have to be administered in the same pharmaceutical composition, and may, because of different physical and chemical characteristics, have to be administered by different routes. For example, the CDP-topoisomerase inhibitor conjugate, particle or composition may be administered intravenously while the chemotherapeutic agent(s) may be administered orally. The determination of the mode of administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the skilled clinician. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

In one embodiment, a CDP-topoisomerase inhibitor conjugate, particle or composition is administered once every three weeks and an additional therapeutic agent (or additional therapeutic agents) may also be administered every three weeks for as long as treatment is required. Examples of other chemotherapeutic agents which are administered one every three weeks include: an antimetabolite (*e.g.*, floxuridine (FUDF®), pemetrexed (ALIMTA®), 5FU (Adrucil®, Efudex®, Fluoroplex®)); an anthracycline (*e.g.*, daunorubicin (Cerubidine®, Rubidomycin®), epirubicin (Ellence®), idarubicin (Idamycin®), mitoxantrone (Novantrone®), valrubicin (Valstar®)); a vinca alkaloid (*e.g.*, vinblastine (Velban®, Velsar®), vincristine (Vincasar®, Oncovin®), vindesine (Eldisine®) and vinorelbine (Navelbine®)); a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel and cabazitaxel); and a platinum-based agent (*e.g.*, cisplatin (Platinol®), carboplatin (Paraplat®, Paraplatin®), oxaliplatin (Eloxatin®)).

In another embodiment, the CDP-topoisomerase inhibitor conjugate, particle or composition is administered once every two weeks in combination with one or more additional chemotherapeutic agent that is administered orally. For example, the CDP- topoisomerase inhibitor conjugate, particle or composition can be administered once every two weeks in combination with one or more of the following chemotherapeutic agents: capecitabine (Xeloda®), estramustine (Emcyt®), erlotinib (Tarceva®), rapamycin (Rapamune®), SDZ-RAD, CP-547632; AZD2171, sunitinib (Sutent®), sorafenib (Nexavar®) and everolimus (Afinitor®).

The actual dosage of the CDP-topoisomerase inhibitor conjugate, particle or composition and/or any additional chemotherapeutic agent employed may be varied depending upon the requirements of the subject and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small amounts until the optimum effect under the circumstances is reached.

In some embodiments, when a CDP- topoisomerase inhibitor conjugate, particle or composition is administered in combination with one or more additional chemotherapeutic agent, the additional chemotherapeutic agent (or agents) is administered at a standard dose. For example, a standard dosage for cisplatin is 75-120 mg/m^2 administered every three weeks; a standard dosage for carboplatin is within the range of 200-600 mg/m^2 or an AUC of 0.5-8 mg/ml x min; *e.g.*, at an AUC of 4-6 mg/ml x min; a standard dosage for irinotecan is within 100-125 mg/m^2, once a week; a standard dosage for gemcitabine is within the range of 80-1500 mg/m^2 administered weekly; a standard dose for UFT is within a range of 300-400 mg/m^2 per day when combined with leucovorin administration; a standard dosage for leucovorin is 10-600 mg/m^2 administered weekly.

The disclosure also encompasses a method for the synergistic treatment of cancer wherein a CDP- topoisomerase inhibitor conjugate, particle or composition is administered in combination with an additional chemotherapeutic agent or agents. For example, the CDP- topoisomerase inhibitor conjugate, particle or composition can be administered in combination with one of the following chemotherapeutic agents: and a platinum-based agent (*e.g.*, cisplatin (Platinol®), carboplatin (Paraplat®, Paraplatin®), oxaliplatin (Eloxatin®); a taxane (*e.g.*, docetaxel, paclitaxel, larotaxel or cabazitaxel); gemctitabine; sorafenib.

The particular choice of conjugate, particle or composition and anti-proliferative cytotoxic agent(s) or radiation will depend upon the diagnosis of the attending physicians and their judgment of the condition of the subject and the appropriate treatment protocol.

If the CDP- topoisomerase inhibitor conjugate, particle or composition and the chemotherapeutic agent(s) and/or radiation are not administered simultaneously or essentially simultaneously, then the initial order of administration of the CDP-topoisomerase inhibitor conjugate, particle or composition, and the chemotherapeutic agent(s) and/or radiation, may be varied. Thus, for example, the CDP- topoisomerase inhibitor conjugate, particle or composition may be administered first followed by the administration of the chemotherapeutic agent(s) and/or radiation; or the chemotherapeutic agent(s) and/or radiation may be administered first followed by the administration of the CDP-topoisomerase inhibitor conjugate, particle or composition. This alternate administration may be repeated during a single treatment protocol. The determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the subject.

Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of a component (CDP-topoisomerase inhibitor conjugate, particle or composition, anti-neoplastic agent(s), or radiation) of the treatment according to the individual subject's needs, as the treatment proceeds.

The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the subject as well as more definite signs such as relief of disease-related symptoms, inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radiological studies, *e.g.*, CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

Indications

The disclosed CDP-topoisomerase inhibitor conjugates, particles and compositions are useful in treating proliferative disorders, *e.g.*, treating a tumor, *e.g.*, a primary tumor, and/or metastases thereof, wherein the tumor is a primary tumor or a metastases thereof, *e.g.*, a cancer described herein or a metastases of a cancer described herein.

The methods described herein can be used to treat a solid tumor, a soft tissue tumor or a liquid tumor. Exemplary solid tumors include malignancies (*e.g.*, sarcomas and carcinomas (*e.g.*, adenocarcinoma or squamous cell carcinoma)) of the various organ systems, such as those of brain, lung, breast, lymphoid, gastrointestinal (*e.g.*, colon), and genitourinary (*e.g.*, renal, urothelial, or testicular tumors) tracts, pharynx, prostate, and ovary. Exemplary adenocarcinomas include colorectal cancers, renal cell carcinoma, liver cancer, non-small cell carcinoma of the lung, and cancer of the small intestine. The disclosed methods are also useful in evaluating or treating soft tissue tumors such as those of the tendons, muscles or fat, and liquid tumors.

The methods described herein can be used with any cancer, for example those described by the National Cancer Institute. The cancer can be a carcinoma, a sarcoma, a myeloma, a leukemia, a lymphoma or a mixed type. Exemplary cancers described by the National Cancer Institute include:

Digestive/gastrointestinal cancers such as anal cancer; bile duct cancer (*e.g.* Klatskin tumor); extrahepatic bile duct cancer; appendix cancer; carcinoid tumor, gastrointestinal cancer; colon cancer; colorectal cancer including childhood colorectal cancer; esophageal cancer including childhood esophageal cancer; gallbladder cancer; gastric (stomach) cancer including childhood gastric (stomach) cancer; hepatocellular (liver) cancer including childhood hepatocellular (liver) cancer; pancreatic cancer including childhood pancreatic cancer; sarcoma, rhabdomyosarcoma; pancreatic cancer, islet cell; rectal cancer; and small intestine cancer;

Endocrine cancers such as islet cell carcinoma (endocrine pancreas); adrenocortical carcinoma including childhood adrenocortical carcinoma; gastrointestinal carcinoid tumor; parathyroid cancer; pheochromocytoma; pituitary tumor; thyroid cancer including childhood thyroid cancer; childhood multiple endocrine neoplasia syndrome; and childhood carcinoid tumor;

Eye cancers such as intraocular melanoma; and retinoblastoma;

Musculoskeletal cancers such as Ewing's family of tumors; osteosarcoma/malignant fibrous histiocytoma of the bone; rhabdomyosarcoma including childhood rhabdomyosarcoma; soft tissue sarcoma including childhood soft tissue sarcoma; clear cell sarcoma of tendon sheaths; and uterine sarcoma;

Breast cancer such as breast cancer and pregnancy including childhood and male breast cancer;

Neurologic cancers such as childhood brain stem glioma; brain tumor; childhood cerebellar astrocytoma; childhood cerebral astrocytoma/malignant glioma; childhood ependymoma; childhood medulloblastoma; childhood pineal and supratentorial primitive neuroectodermal tumors; childhood visual pathway and hypothalamic glioma; other childhood brain cancers; adrenocortical carcinoma; central nervous system lymphoma, primary; childhood cerebellar astrocytoma; neuroblastoma; craniopharyngioma; spinal cord tumors; central nervous system atypical teratoid/rhabdoid tumor; central nervous system embryonal tumors; and supratentorial primitive neuroectodermal tumors including childhood and pituitary tumor;

Genitourinary cancers such as bladder cancer including childhood bladder cancer; renal cell (kidney) cancer; ovarian cancer including childhood ovarian cancer; ovarian epithelial cancer; ovarian low malignant potential tumor; penile cancer; prostate cancer; renal cell cancer including childhood renal cell cancer; renal pelvis and ureter, transitional cell cancer; testicular cancer; urethral cancer; vaginal cancer; vulvar cancer; cervical cancer; Wilms tumor and other childhood kidney tumors; endometrial cancer; and gestational trophoblastic tumor;

Germ cell cancers such as childhood extracranial germ cell tumor; extragonadal germ cell tumor; ovarian germ cell tumor; and testicular cancer;

Head and neck cancers such as lip and oral cavity cancer; childhood oral cancer; hypopharyngeal cancer; laryngeal cancer including childhood laryngeal cancer; metastatic squamous neck cancer with occult primary; mouth cancer; nasal cavity and paranasal sinus cancer; nasopharyngeal cancer including childhood nasopharyngeal cancer; oropharyngeal cancer; parathyroid cancer; pharyngeal cancer; salivary gland cancer including childhood salivary gland cancer; throat cancer; and thyroid cancer;

Hematologic/blood cell cancers such as a leukemia (*e.g.*, acute lymphoblastic leukemia in adults and children; acute myeloid leukemia, *e.g.*, in adults and children;

chronic lymphocytic leukemia; chronic myelogenous leukemia; and hairy cell leukemia); a lymphoma (*e.g.*, AIDS-related lymphoma; cutaneous T-cell lymphoma; Hodgkin's lymphoma including Hodgkin's lymphoma in adults and children; Hodgkin's lymphoma during pregnancy; non-Hodgkin's lymphoma including non-Hodgkin's lymphoma in adults and children; non-Hodgkin's lymphoma during pregnancy; mycosis fungoides; Sézary syndrome; Waldenstrom's macroglobulinemia; and primary central nervous system lymphoma); and other hematologic cancers (*e.g.*, chronic myeloproliferative disorders; multiple myeloma/plasma cell neoplasm; myelodysplastic syndromes; and myelodysplastic/myeloproliferative disorders);

Lung cancer such as non-small cell lung cancer; and small cell lung cancer;

Respiratory cancers such as malignant mesothelioma including malignant mesothelioma in adults and children; malignant thymoma; childhood thymoma; thymic carcinoma; bronchial adenomas/carcinoids including childhood bronchial adenomas/carcinoids; pleuropulmonary blastoma; non-small cell lung cancer; and small cell lung cancer;

Skin cancers such as Kaposi's sarcoma; Merkel cell carcinoma; melanoma; and childhood skin cancer;

AIDS-related malignancies;

Other childhood cancers, unusual cancers of childhood and cancers of unknown primary site;

and metastases of the aforementioned cancers can also be treated or prevented in accordance with the methods described herein.

The CDP-topoisomerase inhibitor conjugates, particles and compositions described herein are particularly suited to treat accelerated or metastatic cancers of gastric cancer, colorectal cancer, non-small cell lung cancer, ovarian cancer, and breast cancer.

In one embodiment, a method is provided for a combination treatment of a cancer, such as by treatment with a CDP-topoisomerase inhibitor conjugate, particle or composition and a second therapeutic agent. Various combinations are described herein. The combination can reduce the development of tumors, reduces tumor burden, or produce tumor regression in a mammalian host.

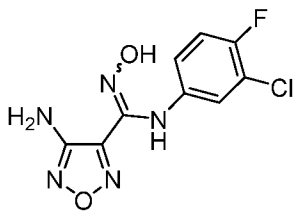
Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents, and other

references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

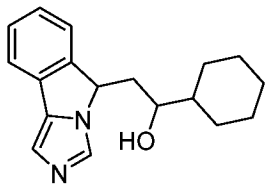
EXAMPLES

Example 1: Increased Efficacy of CRLX101 in Combination with IDO inhibitors (an NLG-919 analog or an INCB-024360 analog) in tumor growth inhibition and delay in a B16.F10 mouse melanoma tumor model

The effects of combining CRLX101 with a mediator of immune biology, specifically an NLG-919 analog or an INCB-024360 analog, on efficacy in the B16.F10 mouse model of melanoma compared to either monotherapy were investigated.



INCB-024360 analog



NLG-919 analog

On Day 1, B16.F10 cells, passage 3, were suspended in DMEM (Dulbecco's Modified Eagle Medium) and implanted subcutaneously (SC) in mice. When the mean tumor volume reached 101 mm^3, the mice were randomized into study groups and given one of the following treatments:

- a control vehicle (20% DMSO/7.5% propylene glycol/5% Tween 80/67.5% PBS) administered IP bid for 14 days, from Day 7 to Day 20 post tumor implantation, with a dose volume of 10 mL/kg

- CRLX101 administered IV at 6 mg/kg q7dx2, i.e. on Day 7 and Day 14 post tumor implantation at a dose volume of 10 mL/kg

- NLG-919 analog (lot # S711102, SelleckChem, Houston, TX) 1.25 mg/mL in 20% DMSO/7.5% propylene glycol/5% Tween 80/67.5% PBS. The dose was 12.5 mg/kg administered IP twice every day with a dose

volume of 10 mL/kg for 14 days, from Day 7 to Day 20 post tumor implantation as a monotherapy and in combination with CRLX101

- INCB-024360 analog (lot # 04, SelleckChem) 10 mg/mL in 3% dimethylacetamide / 97% 5% hydroxypropyl cyclodextrin. The dose was 100 mg/kg administered PO twice every day with a dose volume of 10 mL/kg for 14 days, from Day 7 to Day 20 post tumor implantation as a monotherapy and in combination with CRLX101

Tumor volumes were measured 3 times every week using the equation (width*width*length)/2, in mm^3. Tumor growth inhibition (TGI) was determined by comparing the mean tumor volume of the treated group with the mean tumor volume of the control group, as the decrease in tumor volume of the treated group as a percent of total tumor volume of the control group. The equation to calculate TGI is (1 - (treated volume/control volume)) * 100.

Tumor growth delay (TGD) was determined as the number of days between when the control group reached the tumor volume endpoint and when the treated group reached the tumor volume endpoint.

Results:

	Inhibit tumor growth?	TGI vs. Control (%)	TGI vs. CRLX101 (%)	TGD (Day)
Vehicle	No	N/A	N/A*	N/A
CRLX101	Yes	65	N/A	N/A**
NLG-919 analog	No	23	N/A*	0***
INCB-024360 analog	No	6	N/A*	0
CRLX101 + NLG-919 analog	Yes	85	63	N/A**
CRLX101 + INCB-024360 analog	Yes	81	44	N/A**

*reached tumor volume endpoint prior to Day 21
**did not reach tumor volume endpoint by study end (Day 21)
***TGD was 0 in spite of the TGI because both groups had large mean tumor volumes, above the endpoint when the study ended

The CRLX101-treated group did not reach the tumor volume endpoint in the duration of this study, so the TGD could not be determined. Because neither the NLG-919 analog nor the INCB-024360 analog inhibited tumor growth, there was no TGD for the NLG-919 analog or the INCB-024360 analog.

The combination of CRLX101 and an NLG-919 analog showed increased efficacy, inhibiting tumor growth with a TGI of 85% when the control group reached the tumor volume endpoint. Relative to CRLX101 monotherapy, this combination treatment had improved efficacy. The TGI relative to CRLX101 monotherapy was 63% at the end of the study, Day 21. The CRLX101 + NLG-919 analog group did not reach the tumor volume endpoint in the duration of this study, so the TGD could not be determined.

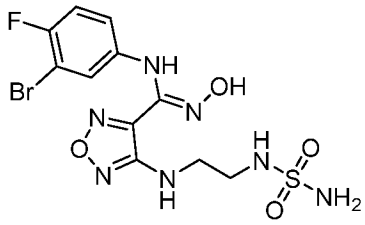
The combination of CRLX101 and the INCB-024360 analog showed increased efficacy, inhibiting tumor growth with a TGI of 81% when the control group reached the tumor volume endpoint. Relative to CRLX101 monotherapy, this combination treatment had improved efficacy, with a TGI of 44% compared to the CRLX101-treated group at the end of the study, Day 21. The CRLX101 + INCB-024360 analog group did not reach the tumor volume endpoint in the duration of this study, so the TGD could not be determined.

FIG. 1 shows the tumor growth curves for B16.F10 tumor-bearing mice administered with vehicle, IDO inhibitor NLG-919 analog, CRLX101 or the combination.

FIG. 2 shows the tumor growth curves for B16.F10 tumor-bearing mice administered with vehicle, IDO inhibitor INCB-024360 analog, CRLX101 or the combination.

The combination of CRLX101 with NLG-919 analog or INCB-024360 analog showed significantly increased tumor growth inhibition compared to CRLX101 monotherapy.

Example 2: Increased Efficacy of CRLX101 in Combination with IDO inhibitor (INCB-024360) in tumor growth inhibition and delay in a B16.F10 mouse melanoma tumor model



INCB-024360

The effects of combining CRLX101 with a mediator of immune biology, specifically the IDO inhibitor INCB-024360, on efficacy in the B16.F10 mouse model of melanoma compared to either monotherapy were investigated.

On Day 1, B16.F10 cells, passage 5, were suspended in DMEM (Dulbecco's Modified Eagle Medium) and implanted subcutaneously (SC) in mice. When the mean tumor volume reached 60 mm^3, the mice were randomized into study groups and given one of the following treatments:

- a control vehicle (20% DMSO/7.5% propylene glycol/5% Tween 80/67.5% PBS) administered IP bid for 13 days, from Day 5 to Day 17, with a dose volume of 10 mL/kg

- CRLX101 administered IV at 6 mg/kg q7dx2, i.e. on Day 5 and Day 12 at a dose volume of 10 mL/kg as monotherapy and in combination

- INCB-024360 (lot #01, SelleckChem, Houston, TX) 10 mg/mL in 20% DMSO/5% propylene glycol/5% Tween 80/67.5% PBS. The dose was 100 mg/kg administered PO twice every day with a dose volume of 10 mL/kg for 13 days, from Day 5 to Day 18 post tumor implantation as a monotherapy and in combination with CRLX101

Tumor volumes were measured 3 times every week using the equation (width*width*length)/2, in mm^3. Tumor growth inhibition (TGI) was determined by comparing the mean tumor volume of the treated group with the mean tumor volume of the control group, as the decrease in tumor volume of the treated group as a percent of total tumor volume of the control group. The equation to calculate TGI is (1 - (treated volume/control volume)) * 100.

Tumor growth delay (TGD) was determined as the number of days between when the control group reached the tumor volume endpoint and when the treated group reached the tumor volume endpoint.

Results:

	Inhibit tumor growth?	TGI vs. Control (%)	TGI vs. CRLX101 (%)	TGD (Day)
Vehicle	No	N/A	N/A*	N/A
CRLX101	Yes	41	N/A	N/A**
INCB-024360	No	20	N/A*	N/A**
CRLX101 + INCB-024360	Yes	88	79	N/A**

*reached tumor volume endpoint prior to Day 18
**did not reach tumor volume endpoint by study end (Day 18)

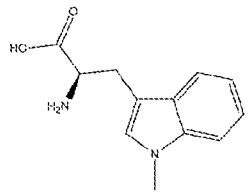
The CRLX101-treated group did not reach the tumor volume endpoint in the duration of this study, so the TGD could not be determined. Since INCB-024360 did not inhibit tumor growth, there was no TGD for INCB-024360.

The combination of CRLX101 and INCB-024360 showed increased efficacy, inhibiting tumor growth with a TGI of 88% when the control group reached the tumor volume endpoint. Relative to CRLX101 monotherapy, this combination treatment had improved efficacy, with a TGI of 79% compared to the CRLX101-treated group at the end of the study, Day 21. The CRLX101 + INCB-024360 group did not reach the tumor volume endpoint in the duration of this study, so the TGD could not be determined.

FIG. 3 shows the tumor growth curves for B16.F10 tumor-bearing mice administered with vehicle, IDO inhibitor INCB-024360, CRLX101 or the combination.

The combination of CRLX101 with NLG-919 or INCB-024360 analog showed significantly increased tumor growth inhibition compared to CRLX101 monotherapy.

Example 3: Increased Efficacy of CRLX101 in Combination with IDO inhibitor (Indoximod) in tumor growth inhibition and delay in a B16.F10 mouse melanoma tumor model



Indoximod

The effects of combining CRLX101 with a mediator of immune biology, specifically the IDO inhibitor Indoximod, on efficacy in the B16.F10 mouse model of melanoma compared to either monotherapy were investigated.

On Day 1, B16.F10 cells, passage 2, were suspended in DMEM (Dulbecco's Modified Eagle Medium) and implanted subcutaneously (SC) in mice. When the mean tumor volume reached 69 mm^3, the mice were randomized into study groups and given one of the following treatments:

- a control vehicle (drinking water with the sweetening agent Equal™ added (2g/L)) was included in the study from Day 7 to Day 19 post tumor implantation.

- CRLX101 administered IV at 6 mg/kg q7dx2, i.e. on Day 7 and Day 14 at a dose volume of 10 mL/kg as monotherapy and in combination.

- Indoximod (lot # MKBQ8091V, Sigma-Aldrich) was administered in the drinking water at a concentration of 2 mg/mL from Day 7 to Day 19 post tumor implantation as a monotherapy and in combination with CRLX101. The water had Equal™ added (2 g/L).

Tumor volumes were measured 3 times every week using the equation (width*width*length)/2, in mm^3. The endpoint for tumor volume was 2000 mm^3. Tumor growth inhibition (TGI) was determined by comparing the mean tumor volume of the treated group with the mean tumor volume of the control group, as the decrease in tumor volume of the treated group as a percent of total tumor volume of the control group. The equation to calculate TGI is (1 - (treated volume/control volume)) * 100.

Tumor growth delay (TGD) was determined as the number of days between when the control group reached the tumor volume endpoint and when the treated group reached the tumor volume endpoint.

Results:

	Inhibit tumor growth?	TGI vs. Control (%)	TGI vs. CRLX101 (%)	TGD (Day)
Vehicle	No	N/A	N/A*	N/A
CRLX101	Yes	55	N/A	N/A**
Indoximod	No	-49	N/A*	0
CRLX101 + Indoximod	Yes	69	31	N/A**

*reached tumor volume endpoint prior to Day 19
**did not reach tumor volume endpoint by study end (Day 19)

The CRLX101-treated group did not reach the tumor volume endpoint in the duration of this study, so the TGD could not be determined. Since Indoximod did not inhibit tumor growth, there was no TGD for Indoximod.

The combination of CRLX101 and Indoximod showed increased efficacy, inhibiting tumor growth with a TGI of 55% when the control group reached the tumor volume endpoint. Relative to CRLX101 monotherapy, this combination treatment had improved efficacy, with a TGI of 69% compared to the CRLX101-treated group at the end of the study, Day 19. The CRLX101 + Indoximod group did not reach the tumor volume endpoint in the duration of this study, so the TGD could not be determined.

FIG. 4 shows the tumor growth curves for B16.F10 tumor-bearing mice administered with vehicle, IDO inhibitor Indoximod, CRLX101 or the combination.

The combination of CRLX101 with Indoximod showed increased tumor growth inhibition compared to CRLX101 monotherapy.

Example 4: Comparison of Efficacy of CRLX101 in Combination with IDO inhibitor (NLG-919 analog) to Irinotecan in combination with the NLG-919 analog in tumor growth inhibition and delay in a B16.F10 mouse melanoma tumor model

The effects of combining CRLX101 with a mediator of immune biology, specifically the IDO inhibitor NLG-919 analog, on efficacy in the B16.F10 mouse model of melanoma compared to the combination of the NLG-919 analog with Irinotecan were investigated.

On Day 1, B16.F10 cells, passage 3, were suspended in DMEM (Dulbecco's Modified Eagle Medium) and implanted subcutaneously (SC) in mice. When the mean tumor volume reached 58 mm^3, the mice were randomized into study groups and given one of the following treatments:

- a control vehicle (20% DMSO/7.5% propylene glycol/5% Tween 80/67.5% PBS) administered IP bid for 14 days, from Day 6 to Day 19, with a dose volume of 10 mL/kg

- CRLX101 administered IV at 6 mg/kg q7dx2, i.e. on Day 6 and Day 13 at a dose volume of 10 mL/kg as monotherapy and in combination

- NLG-919 analog (lot # S711102, SelleckChem, Houston, TX) 1.25 mg/mL in 20% DMSO/7.5% propylene glycol/5% Tween 80/67.5% PBS. The dose was 12.5 mg/kg administered IP twice every day with a dose volume of 10 mL/kg for 14 days, from Day 6 to Day 19 post tumor implantation as a monotherapy and in combination with CRLX101 or Irinotecan.

- Irinotecan (lot # MKBS1158V, Sigma-Aldrich) 10 mg/mL in 5% glucose in water. The dose was 100 mg/kg q7dx2, i.e., administered at a dose volume of 10 mL/kg on Day 6 and Day 13 post tumor implantation as a monotherapy and in combination.

Tumor volumes were measured 3 times every week using the equation (width*width*length)/2, in mm^3. Tumor growth inhibition (TGI) was determined by comparing the mean tumor volume of the treated group with the mean tumor volume of the control group, as the decrease in tumor volume of the treated group as a percent of total tumor volume of the control group. The equation to calculate TGI is (1 - (treated volume/control volume)) * 100.

Tumor growth delay (TGD) was determined as the number of days between when the control group reached the tumor volume endpoint and when the treated group reached the tumor volume endpoint.

Results:

	Inhibit tumor growth?	TGI vs. Control (%)	TGI vs. CRLX101 (%)	TGD (Day)
Vehicle	No	N/A	N/A*	N/A
CRLX101	Yes	56	N/A	N/A**
NLG-919 analog	No	5	N/A*	0
Irinotecan	No	-12	N/A*	0
CRLX101 + NLG-919 analog	Yes	84	63	N/A**
Irinotecan + NLG-919 analog	No	-9	-147	0

*reached tumor volume endpoint prior to Day 21
**did not reach tumor volume endpoint by study end (Day 21)

The CRLX101-treated group did not reach the tumor volume endpoint in the duration of this study, so the TGD could not be determined. Since the NLG-919 analog did not inhibit tumor growth, there was no TGD for the NLG-919 analog.

The combination of CRLX101 and the NLG-919 analog showed increased efficacy, inhibiting tumor growth with a TGI of 84% relative to vehicle control. Relative to CRLX101 monotherapy, this combination treatment had improved efficacy, with a TGI of 63% compared to the CRLX101-treated group at the end of the study, Day 21. The CRLX101 + NLG-919 analog group did not reach the tumor volume endpoint in the duration of this study, so the TGD could not be determined. The combination of Irinotecan and the NLG-919 analog did not show increased efficacy compared to vehicle treated control.

FIG. 5 shows the tumor growth curves for B16.F10 tumor-bearing mice administered with vehicle, IDO inhibitor NLG-919 analog, CRLX101 or the combination.

The combination of CRLX101 with the NLG-919 analog showed significantly increased tumor growth inhibition compared to CRLX101 monotherapy, Irinotecan monotherapy or the combination of Irinotecan + NLG-919 analog.

Example 5: Comparison of Efficacy of CRLX101 in Combination with IDO inhibitor (NLG-919 analog) to anti-PD-1 antibody in combination with the NLG-919 analog in tumor growth inhibition and delay in a B16.F10 mouse melanoma tumor model

The effects of combining CRLX101 with a mediator of immune biology, specifically the IDO inhibitor NLG-919 analog, on efficacy in the B16.F10 mouse model of melanoma compared to the combination of the NLG-919 analog with anti-PD-1 antibody were investigated.

On Day 1, B16.F10 cells, passage 3, were suspended in DMEM (Dulbecco's Modified Eagle Medium) and implanted subcutaneously (SC) in mice. When the mean tumor volume reached 64 mm^3, the mice were randomized into study groups and given one of the following treatments:

- a control vehicle (20% DMSO/7.5% propylene glycol/5% Tween 80/67.5% PBS) administered IP bid for 14 days, from Day 6 to Day 19, with a dose volume of 10 mL/kg

- a control vehicle (isotype IgG2a antibody, clone 2A3, lot # 5679/0415, BioXCell, West Lebanon, NH) was administered IP biweekly, i.e., Day 6, Day 9, Day 13, Day 16 post tumor implantation , with a dose volume of 200 µL per mouse to administer 200 µg per mouse.

- CRLX101 administered IV at 6 mg/kg q7dx2, i.e. on Day 6 and Day 13 at a dose volume of 10 mL/kg as monotherapy and in combination

- Anti-mouse PD-1 antibody (clone RMP1-14, lot # 5311/0215B , BioXCell, West Lebanon, NH) was administered IP biweekly, i.e., Day 6, Day 9, Day 13, Day 16 post tumor implantation, with a dose volume of 200 µL per mouse to administer 200 µg per mouse as a monotherapy and in combination with the NLG-919 analog.

- NLG-919 analog (lot # S711102, SelleckChem, Houston, TX) 1.25 mg/mL in 20% DMSO/7.5% propylene glycol/5% Tween 80/67.5% PBS. The dose was 12.5 mg/kg administered IP twice every day with a dose volume of 10 mL/kg for 14 days, from Day 6 to Day 19 post tumor implantation as a monotherapy and in combination with CRLX101 or Irinotecan.

Tumor volumes were measured 3 times every week using the equation (width*width*length)/2, in mm^3. Tumor growth inhibition (TGI) was determined by

comparing the mean tumor volume of the treated group with the mean tumor volume of the control group, as the decrease in tumor volume of the treated group as a percent of total tumor volume of the control group. The equation to calculate TGI is (1 - (treated volume/control volume)) * 100.

Tumor growth delay (TGD) was determined as the number of days between when the control group reached the tumor volume endpoint and when the treated group reached the tumor volume endpoint.

Results:

	Inhibit tumor growth?	TGI vs. Control (%)	TGI vs. CRLX101 (%)	TGD (Day)
Vehicle	No	N/A	N/A*	N/A
CRLX101	Yes	65	N/A	N/A**
NLG-919 analog	No	15	N/A*	1
Anti-PD-1	No	10	N/A*	1
CRLX101 + NLG-919 analog	Yes	86	60	N/A**
anti-PD-1 + NLG-919 analog	Yes	31	-95	N/A**

*reached tumor volume endpoint prior to Day 21

**did not reach tumor volume endpoint by study end (Day 21)

The CRLX101-treated group did not reach the tumor volume endpoint in the duration of this study, so the TGD could not be determined. Since the NLG-919 analog did not inhibit tumor growth, there was no TGD for the NLG-919 analog.

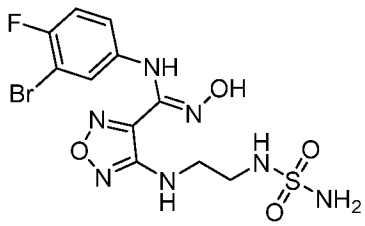
The combination of CRLX101 and the NLG-919 analog showed increased efficacy, inhibiting tumor growth with a TGI of 86% when the control group reached the tumor volume endpoint. Relative to CRLX101 monotherapy, this combination treatment had improved efficacy, with a TGI of 60% compared to the CRLX101-treated group at the end of the study, Day 20. The anti-PD-1 + NLG-919 analog group did not reach the tumor volume endpoint in the duration of this study, so the TGD could not be determined.

FIG. 6 shows the tumor growth curves for B16.F10 tumor-bearing mice administered with vehicle, IDO inhibitor NLG-919 analog, CRLX101, anti-PD-1 antibodies, the combination of CRLX101 and the NLG-919 analog or the combination of anti-PD-1 antibodies and the NLG-919 analog.

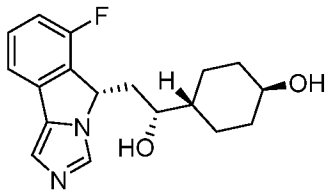
The combination of CRLX101 with NLG-919 showed significantly increased tumor growth inhibition compared to anti-PD-1 and NLG-919.

Example 6: Efficacy of CRLX101 in Combination with IDO inhibitors (NLG-919 or INCB-024360) in tumor growth inhibition and delay in a B16.F10 mouse melanoma tumor model

The effects of combining CRLX101 with a mediator of immune biology, specifically the IDO inhibitor NLG-919 or INCB-024360, on efficacy in the B16.F10 mouse model of melanoma compared to either monotherapy will be investigated.



INCB-024360 (epacadostat)



NLG-919

On Day 1, B16.F10 cells, passage 3, will be suspended in DMEM (Dulbecco's Modified Eagle Medium) and implanted subcutaneously (SC) in mice. When the mean tumor volume reaches 101 mm^3, the mice will be randomized into study groups and given one of the following treatments:

- a control vehicle (20% DMSO/7.5% propylene glycol/5% Tween 80/67.5% PBS) will be administered IP bid for 14 days, from Day 7 to Day 20 post tumor implantation, with a dose volume of 10 mL/kg
- CRLX101 will be administered IV at 6 mg/kg q7dx2, i.e. on Day 7 and Day 14 post tumor implantation at a dose volume of 10 mL/kg
- NLG-919, 1.25 mg/mL in 20% DMSO/7.5% propylene glycol/5% Tween 80/67.5% PBS. The dose will be 12.5 mg/kg administered IP twice every day with a dose volume of 10 mL/kg for 14 days, from Day 7 to Day 20 post tumor implantation as a monotherapy and in combination with CRLX101

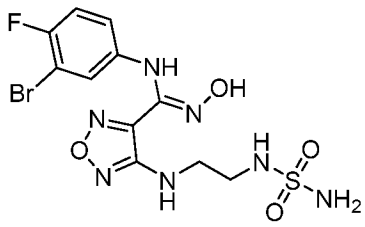
- INCB-024360, 10 mg/mL in 3% dimethylacetamide / 97% 5% hydroxypropyl cyclodextrin. The dose will be 100 mg/kg administered PO twice every day with a dose volume of 10 mL/kg for 14 days, from Day 7 to Day 20 post tumor implantation as a monotherapy and in combination with CRLX101

Tumor volumes will be measured 3 times every week using the equation (width*width*length)/2, in mm^3. Tumor growth inhibition (TGI) will be determined by comparing the mean tumor volume of the treated group with the mean tumor volume of the control group, as the decrease in tumor volume of the treated group as a percent of total tumor volume of the control group. The equation to calculate TGI is (1 - (treated volume/control volume)) * 100.

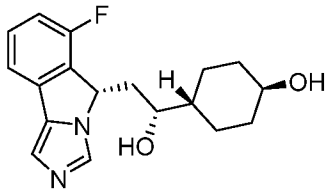
Tumor growth delay (TGD) will be determined as the number of days between when the control group reaches the tumor volume endpoint and when the treated group reaches the tumor volume endpoint.

Example 7: Efficacy of CRLX101 in Combination with IDO inhibitors (NLG-919 or INCB-024360) in tumor growth inhibition and delay in an ovarian tumor model

The effects of combining CRLX101 with a mediator of immune biology, specifically the IDO inhibitor NLG-919 or INCB-024360, on efficacy in an ovarian tumor model compared to either monotherapy will also be investigated.



INCB-024360 (epacadostat)



NLG-919

On Day 1, ovarian tumor cells will be suspended in DMEM (Dulbecco's Modified Eagle Medium) and implanted in mice. When the mean tumor volume reached the appropriate size, the mice will be randomized into study groups and given one of the following treatments:

- a control vehicle (20% DMSO/7.5% propylene glycol/5% Tween 80/67.5% PBS) will be administered IP bid for 14 days, from Day 7 to Day 20 post tumor implantation, with a dose volume of about 10 mL/kg

- CRLX101 will be administered IV at 6 mg/kg q7dx2, i.e. on Day 7 and Day 14 post tumor implantation at a dose volume of 10 mL/kg

- NLG-919, 1.25 mg/mL in 20% DMSO/7.5% propylene glycol/5% Tween 80/67.5% PBS. The dose will be 12.5 mg/kg administered IP twice every day with a dose volume of 10 mL/kg for 14 days, from Day 7 to Day 20 post tumor implantation as a monotherapy and in combination with CRLX101

- INCB-024360, 10 mg/mL in 3% dimethylacetamide / 97% 5% hydroxypropyl cyclodextrin. The dose will be 100 mg/kg administered PO twice every day with a dose volume of 10 mL/kg for 14 days, from Day 7 to Day 20 post tumor implantation as a monotherapy and in combination with CRLX101

Tumor volumes will be measured 3 times every week using the equation (width*width*length)/2, in mm^3. Tumor growth inhibition (TGI) will be determined by comparing the mean tumor volume of the treated group with the mean tumor volume of the control group, as the decrease in tumor volume of the treated group as a percent of total tumor volume of the control group. The equation to calculate TGI is (1 - (treated volume/control volume)) * 100.

Tumor growth delay (TGD) will be determined as the number of days between when the control group reached the tumor volume endpoint and when the treated group reached the tumor volume endpoint.

Other embodiments are in the claims.

Claims

1. A method of treating a cancer, in a subject, comprising:

providing an initial administration of a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, CRLX101, to the subject in combination with an inhibitor of the tryptophan metabolism pathway, *e.g.*, an indoleamine-2,3-dioxygenase (IDO) inhibitor or a tryptophan-2, 3 -dioxygenase (TDO) inhibitor; and

optionally, providing one or more subsequent administrations of the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, CRLX101, to thereby treat the cancer.

2. The method of claim 1, wherein the cancer is selected from skin cancer (*e.g.*, melanoma and malignant melanoma), lung cancer (*e.g.*, small cell lung cancer and non-small cell lung cancer (*e.g.*, adenocarcinoma, squamous cell carcinoma, bronchoalveolar carcinoma and large cell carcinoma)), gastric and esophageal cancers (*e.g.*, gastroesophageal gastric), colorectal cancer (*e.g.*, colon, small intestine, rectum and/or appendix), bladder cancer, cancer of the genitourinary tract, *e.g.*, ovary (including fallopian, endometrial and peritoneal cancers and uterine sarcoma), cervical cancer, breast cancer, liver cancer, head and neck cancer, kidney cancer (*e.g.*, renal cell carcinoma (*e.g.*, papillary renal cell carcinoma, clear cell carcinoma, chromphobic carcinoma)), lymphoma (*e.g.*, Burkitt's, B-Cell, Hodgkin's or non-Hodgkin's lymphoma), and a neural or glial cell cancer (*e.g.*, glioblastoma multiforme and astrocytoma).

3. The method of claim 1, wherein the inhibitor of the tryptophan metabolism pathway is an IDO inhibitor.

4. The method of claim 1, wherein the IDO inhibitor is an IDO1 and/or an IDO2 inhibitor.

5. The method of claim 1, wherein the IDO inhibitor is a small molecule.

6. The method of claim 1, wherein the IDO inhibitor is selected from indoximod, NSC-721782 (1-methyl-D-tryptophan), NLG-919, INCB-024360, INCB-024360 analog, or F001287.

7. The method of claim 1, wherein the the IDO inhibitor is administered orally.

8. The method of claim 1, wherein the inhibitor of the tryptophan metabolism pathway is administered before the CDP-topoisomerase inhibitor conjugate, particle or composition.

9. The method of claim 1, wherein the CDP-topoisomerase inhibitor conjugate, particle or composition and the inhibitor of the tryptophan metabolism pathway are administered concurrently.

10. The method of claim 1, wherein the inhibitor of the tryptophan metabolism pathway is administered multiple times before or after the administration of the CDP-topoisomerase inhibitor conjugate, particle or composition.

11. The method of claim 1, wherein the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, CRLX101, is administered at a dosage of 5 mg/m^2, 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, 17 mg/m^2, 18 mg/m^2, 19 mg/m^2, 20 mg/m^2, 21 mg/m^2, 22 mg/m^2, 23 mg/m^2, 24 mg/m^2, 25 mg/m^2, 26 mg/m^2, 27 mg/m^2, 28 mg/m^2, 29 mg/m^2 or 30 mg/m^2, (wherein the dosage is expressed in mg of drug, as opposed to mg of conjugate).

12. The method of claim 11, wherein each subsequent administration of the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin conjugate, particle or composition or camptothecin derivative conjugate, particle or composition, *e.g.*, CRLX101, is provided, independently, between 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 days after the previous, *e.g.*, the initial administration.

13. The method of claim 1, wherein the dosage of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15 or 20 administrations is the same.

14. The method of claim 1, wherein the time between at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, or 20 administrations is the same.

15. The method of claim 1, wherein each subsequent administration is administered 12-16, *e.g.*, 14, days after the previous administration.

16. The method of claim 1, wherein at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20, 50 or 100 administrations are administered to the subject.

17. The method of claim 1, wherein the CDP-topoisomerase inhibitor conjugate is CRLX101.

18. The method of claim 1, wherein the CDP-topoisomerase inhibitor conjugate is a CDP-camptothecin or camptothecin derivate conjugate, *e.g.*, CRLX101, is administered by intraperitoneal administration.

19. The method of claim 1, wherein the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-16, *e.g.*, 7, days after the previous, *e.g.*, the initial administration, and the cancer is gastric cancer, *e.g.*, gastroesophageal, gastric cancer.

20. The method of claim 1, wherein the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-16, *e.g.*, 7, days after the previous, *e.g.*, the initial administration, and the cancer is, *e.g.*, skin cancer.

21. The method of claim 1, wherein the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-16, *e.g.*, 7, days after the previous, *e.g.*, the initial administration, and the cancer is lung cancer, *e.g.*, non-small cell lung cancer and/or small cell lung cancer (*e.g.*, squamous cell non-small cell lung cancer or squamous cell small cell lung cancer).

22. The method of claim 1, wherein the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-16, *e.g.*, 7, days after the previous, *e.g.*, the initial administration, and the cancer is bladder cancer.

23. The method of claim 1, wherein the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10

mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-16, *e.g.*, 7, days after the previous, *e.g.*, the initial administration, and the cancer is colorectal cancer.

24. The method of claim 1, wherein the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-16, *e.g.*, 7, days after the previous, *e.g.*, the initial administration, and the cancer is breast cancer, *e.g.*, estrogen receptor positive breast cancer, estrogen receptor negative breast cancer, HER-2 positive breast cancer, HER-2 negative breast cancer, triple negative breast cancer or inflammatory breast cancer.

25. The method of claim 1, wherein the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-16, *e.g.*, 7, days after the previous, *e.g.*, the initial administration, and the cancer is endometrial cancer or cervical cancer.

26. The method of claim 1, wherein the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-16, *e.g.*, 7, days after the previous, *e.g.*, the initial administration, and the cancer is a neural or glial cell cancer (e.g., glioblastoma multiforme or astrocytoma).

27. The method of claim 1, wherein the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-16, *e.g.*, 7, days after the previous, *e.g.*, the initial administration, and the cancer is a kidney cancer, *e.g.*, renal cell carcinoma (*e.g.*, papillary renal cell carcinoma, clear cell carcinoma, chromphobic carcinoma).

28. The method of claim 1, wherein the method includes an initial administration of CRLX101 to the subject at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2, 15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, and

one or more subsequent administrations of CRLX101 to the subject, at a dosage of 6 mg/m^2, 7 mg/m^2, 8 mg/m^2, 9 mg/m^2, 10 mg/m^2, 11 mg/m^2, 12 mg/m^2, 13 mg/m^2, 14 mg/m^2,15 mg/m^2, 16 mg/m^2, or 17 mg/m^2, *e.g.*, at the same dosage as the initial dosage, wherein each subsequent administration is administered, independently, 5-16, *e.g.*, 7, days after the previous, *e.g.*, the initial administration, and the cancer is ovarian cancer (*e.g.*, epithelial carcinoma, fallopian tube cancer,

germ cell cancer (*e.g.*, a teratoma), sex cord-stromal tumor (*e.g.*, estrogen-producing granulose cell tumor, virilizing Sertoli-Leydig tumor, arrhenoblastoma)).

29. The method of claim 1, further comprising administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, CRLX101, and the IDO inhibitor, in combination with one or more chemotherapeutic agents, *e.g.*, such as an angiogenesis inhibitor).

30. The method of claim 29, wherein the one or more additional chemotherapeutic agents is selected from AZD4547, AZD9291, bevacizumab, carboplatin, cisplatin, cobimetnib, dabrafenib, dacarbazine, dasatinib, docetaxel, erlotinib, fluorouracil, gefitinib, gemcitabine, ipilimumab, lenalidomide, leucovorin, MEDI0680, MEDI4736, oxaliplatin, paclitaxel, pemetrexed, sunitinib, temozolomide, trametinib, tremelimumab, and vemurafenib.

31. The method of claim 29, wherein the one or more chemotherapeutic agents, is a platinum-based agent (*e.g.*, carboplatin, cisplatin, oxaliplatin), a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel, cabazitaxel), a vinca alkaloid (*e.g.*, vinblastine, vincristine, vindesine, vinorelbine), an antimetabolite (*e.g.*, an antifolate (*e.g.*, pemetrexed, floxuridine, raltitrexed) and a pyrimidine analogue (*e.g.*, 5FU, capecitabine, cytrarabine, gemcitabine)), an alkylating agent (*e.g.*, cyclophosphamide, decarbazine, melphalan, ifosfamide, temozolomide), a vascular endothelial growth factor (VEGF) pathway inhibitor, a poly ADP-ribose polymerase (PARP) inhibitor and an mTOR inhibitor.

32. The method of claim 1, further comprising administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, CRLX101, and the IDO inhibitor in combination with an inhibitor of the programmed cell death 1 (PD-1)/programmed cell death ligand (PD-L, e.g. PD-L1 or PD-L2) pathway (a PD-1/PD-L pathway inhibitor, e.g., a PD-1, PD-L1, or PD-L2 pathway inhibitor).

33. The method of claim 32, wherein PD-1/PD-L pathway inhibitor is a small molecule or an antibody, e.g., a monoclonal or polyclonal antibody, e.g., a humanized monoclonal or polyclonal antibody with PD-1, PD-L1, or PD-L2 antagonist activity.

34. The method of claim 32, wherein the PD-1/PD-L pathway inhibitor is a PD-1 inhibitor.

35. The method of claim 34, wherein the PD-1 inhibitor is selected from nivolumab (BMS-936558 or MDX1106), pembrolizumab (MK-3475, lambrolizumab, Keytruda), pidilizumab (CT-011), tigatuzumab, PDR001, AMP-224, MEDI0680 (AMP-514), and APE02058.

36. The method of claim 33, wherein the PD-1/PD-L pathway inhibitor is a PD-L1 inhibitor.

37. The method of claim 36, wherein PD-L1 inhibitor is selected from atezolizumab (MPDL3280A, RG7446), durvalumab (MEDI4736), avelumab (MSB0010718C), YW243.55.S70, and BMS-936559 (MDX-1105).

38. The method of claim 32, wherein the inhibitor of the programmed cell death 1 (PD-1)/programmed cell death ligand (PD-L, e.g. PD-L1 or PD-L2) pathway (a PD-1/PD-L pathway inhibitor, e.g., a PD-1, PD-L1, or PD-L2 pathway inhibitor) is selected from a tumor necrosis factor (TNF) receptor, *e.g.,* an anti-OX-40 monoclonal antibody such as MOXR0916/RG7888 or MEDI6469, an OX40 ligand fusion protein such as MEDI6469; an inhibitor of 4-1BB (also known as CD137 and ILA), such as Urelumab (BMS-663513) or PF-05082566; or chimeric antigen receptor-modified T cells (CART-19 cells). CART-19 cells are T cells transduced with an antibody against CD19, which is linked to the intracellular signaling domains of 4-1BB and CD3-zeta.

39. The method of claim 1, further comprising administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, CRLX101, and the IDO inhibitor in combination with an inhibitor of a lymphocyte-activation gene 3 (LAG3), *e.g.,* an antibody such as BMS-986016 or IMP701; or a recombinant protein such as IMP321.

40. The method of claim 1, further comprising administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, CRLX101, and the

IDO inhibitor in combination with an inhibitor of a lymphocyte-activation gene 3 (LAG3), *e.g.,* an antibody such as BMS-986016 or IMP701; or a recombinant protein such as IMP321.

41. The method of claim 1, further comprising administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, CRLX101, and the IDO inhibitor in combination with an inhibitor of T cell immunoglobulin mucin-3 (TIM-3).

42. The method of claim 1, further comprising administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, CRLX101, and the IDO inhibitor in combination with an inhibitor of cytotoxic T-lymphocyte-associated protein 4 (CTLA4), *e.g.*, Tremelimumab (formerly CP-675,206 or ticilimumab); or Ipilimumab.

43. A method of treating ovarian cancer (*e.g.*, epithelial carcinoma, fallopian tube cancer, germ cell cancer (*e.g.*, a teratoma), sex cord-stromal tumor (*e.g.*, estrogen-producing granulose cell tumor, virilizing Sertoli-Leydig tumor, arrhenoblastoma)), *e.g.*, locally advanced or metastatic ovarian cancer, in a subject, *e.g.*, a human subject, the method comprising administering a CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-topoisomerase I or II inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, CRLX101, in combination with an IDO inhibitor.

44. The method of claim 43, wherein the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, a CDP-camptothecin or camptothecin derivative conjugate, particle or composition, *e.g.*, CRLX101, is administered prior to surgery, after surgery or before and after surgery to remove the cancer, *e.g.*, to remove a primary tumor and/or a metastases.

45. The method of claim 43, further comprising administering the CDP-topoisomerase inhibitor conjugate, particle or composition, *e.g.*, CRLX101, and the IDO inhibitor, in combination with one or more chemotherapeutic agents.

46. The method of claim 45, wherein the one or more chemotherapeutic agent is selected from a taxane (*e.g.*, paclitaxel, docetaxel, larotaxel, cabazitaxel), a platinum-based agent (*e.g.*, cisplatin, carboplatin, oxaliplatin), an anti-metabolite, *e.g.*, an antifolate (*e.g.*, pemetrexed, floxuridine, raltitrexed) or pyrimidine analogue (*e.g.*, capecitabine, cytrarabine, gemcitabine, 5FU)), folinic acid (leucovorin), a MEK inhibitor, *e.g.*, trametinib (Mekinist™), an angiogenesis inhibitor (*e.g.*, an angiogenesis inhibitor described herein such as an inhibitor of the VEGF pathway, *e.g.*, a VEGF inhibitor, *e.g.*, a small molecule inhibitor, or an antibody against VEGF, *e.g.*, bevacizumab; or a VEGF receptor inhibitor (*e.g.*, a VEGF receptor 1 inhibitor or a VEGF receptor 2 inhibitor), *e.g.*, a small molecule inhibitor, *e.g.*, sorafenib or sunitinib, or an antibody against VEGF receptor).

47. The method of claim 46, wherein the one or more chemotherapeutic agent is bevacizumab.

48. The method of claim 47, wherein bevacizumab is administered at a dose of 15 mg/kg or less, *e.g.*, 10 mg/kg or less, *e.g.*, less than 10 mg/kg, *e.g.*, 8 mg/kg, 7 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, or 2 mg/kg.

49. The method of claim 47, wherein the one or more subsequent administrations of bevacizumab can be administered, *e.g.*, wherein each subsequent administration is administered, independently, at 12-16, *e.g.*, 14 days after bevacizumab.

50. The method of claim 45, wherein the one or more chemotherapeutic agent is an anthracycline (*e.g.*, doxorubicin (*e.g.*, liposomal doxorubicin), daunorubicin, epirubicin, idarubicin, mitoxantrone, valrubicin).

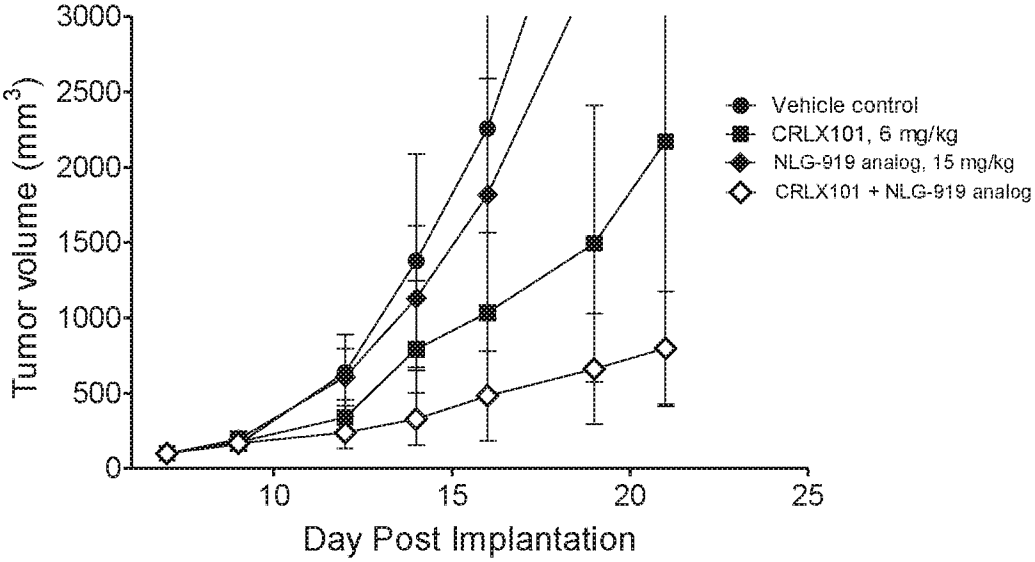

3000
2500
2000
1500
1000
500
0
Tumor volume (mm3)
10
15
20
25
Day Post Implantation
Vehicle control
CRLX101, 6 mg/kg
NLG-919 analog, 15 mg/kg
CRLX101 + NLG-919 analog

FIG. 1

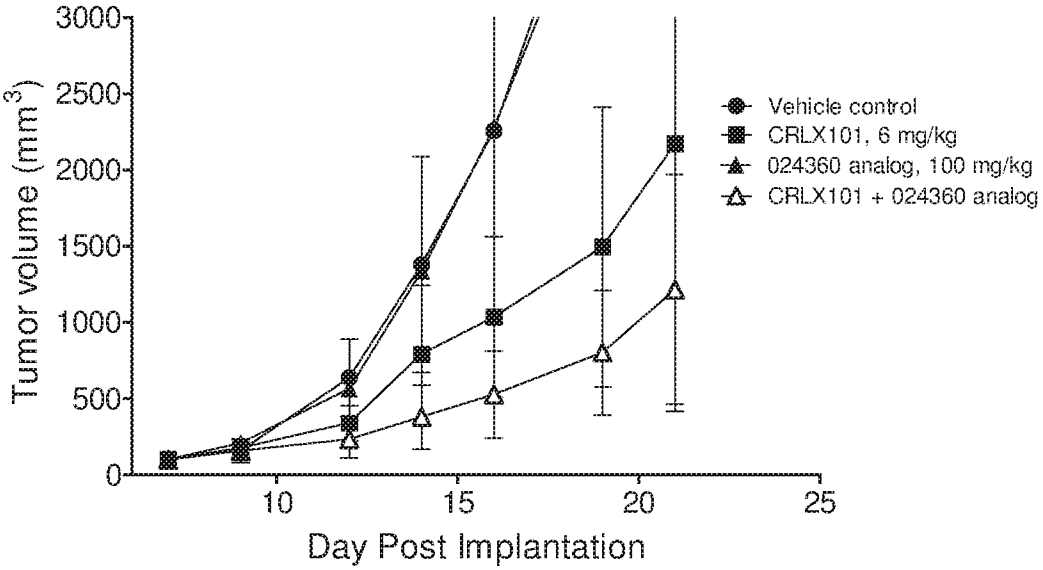

Tumor volume (mm3)
3000
2500
2000
1500
1000
500
0
10
15
20
25
Day Post Implantation
Vehicle control
CRLX101, 6 mg/kg
024360 analog, 100 mg/kg
CRLX101 + 024360 analog

FIG. 2

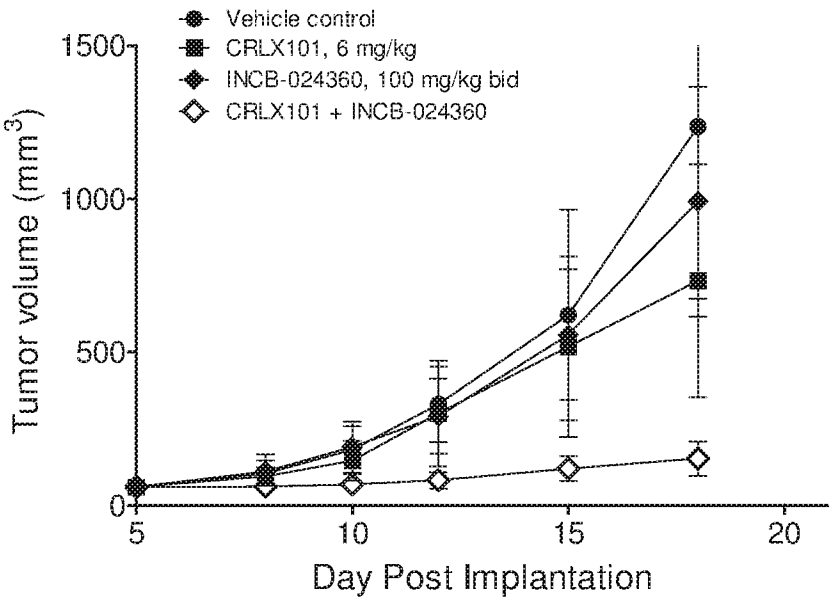

Vehicle control
CRLX101, 6 mg/kg
INCB-024360, 100 mg/kg bid
CRLX101 + INCB-024360
Tumor volume (mm3)
1500
1000
500
0
5
10
15
20
Day Post Implantation

FIG. 3

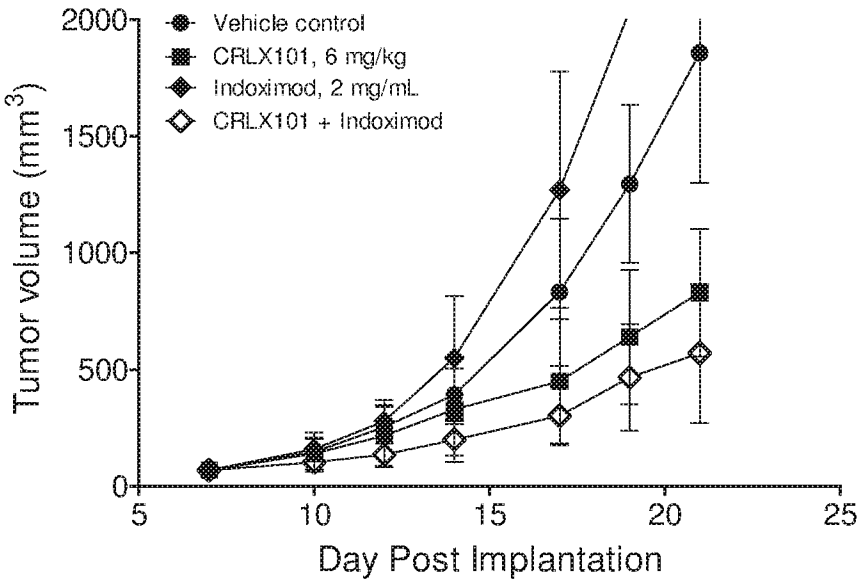

Vehicle control
CRLX101, 6 mg/kg
Indoximod, 2 mg/mL
CRLX101 + Indoximod
Tumor volume (mm3)
2000
1500
1000
500
0
5
10
15
20
25
Day Post Implantation

FIG. 4

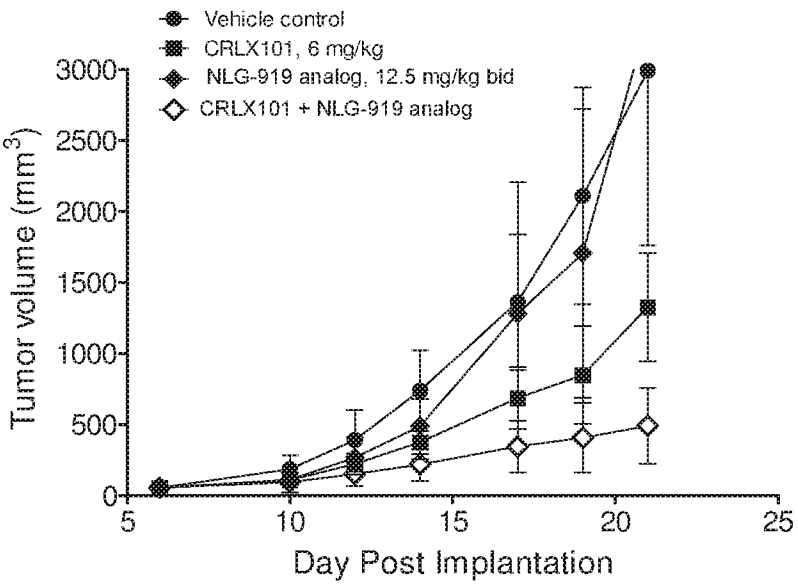

Vehicle control
CRLX101, 6 mg/kg
NLG-919 analog, 12.5 mg/kg bid
CRLX101 + NLG-919 analog
Tumor volume (mm3)
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
Day Post Implantation

FIG. 5A

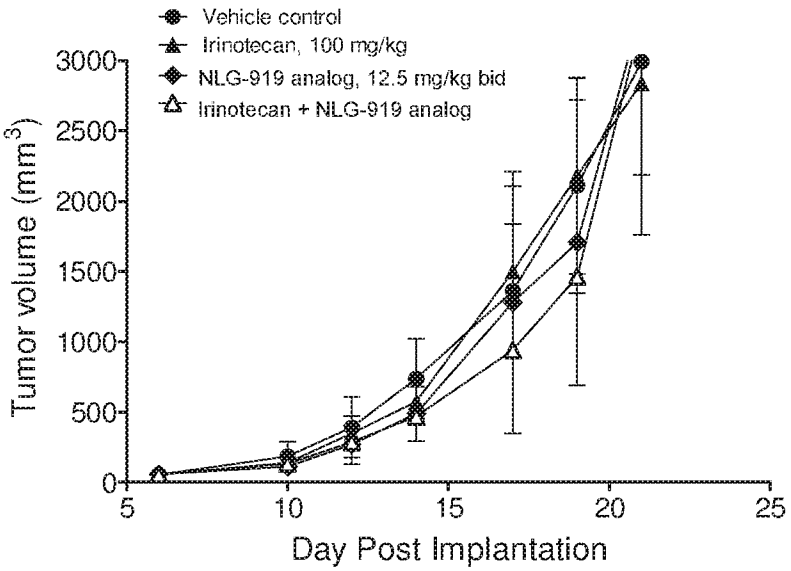

Vehicle control
Irinotecan, 100 mg/kg
NLG-919 analog, 12.5 mg/kg bid
Irinotecan + NLG-919 analog
Tumor volume (mm3)
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
Day Post Implantation

FIG. 5B

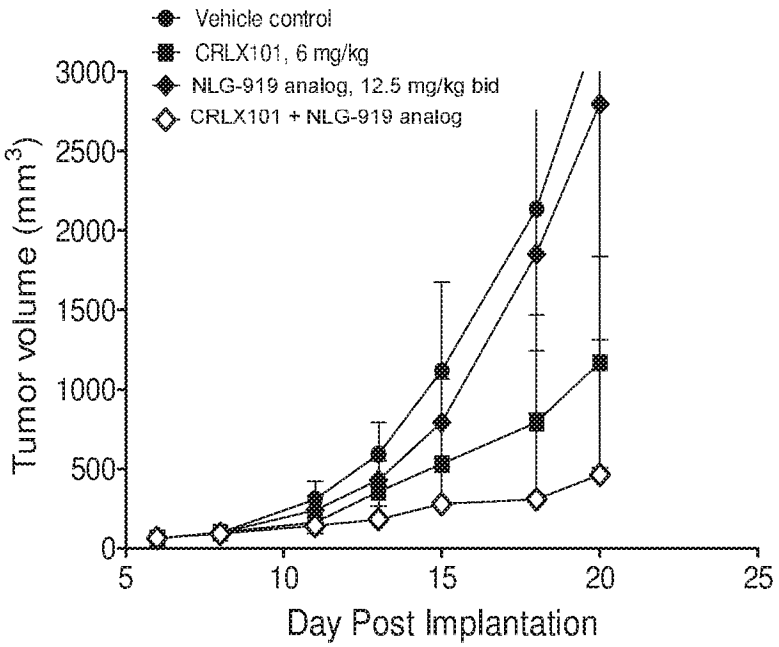

Vehicle control
CRLX101, 6 mg/kg
NLG-919 analog, 12.5 mg/kg bid
CRLX101 + NLG-919 analog
Tumor volume (mm3)
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
Day Post Implantation

FIG. 6A

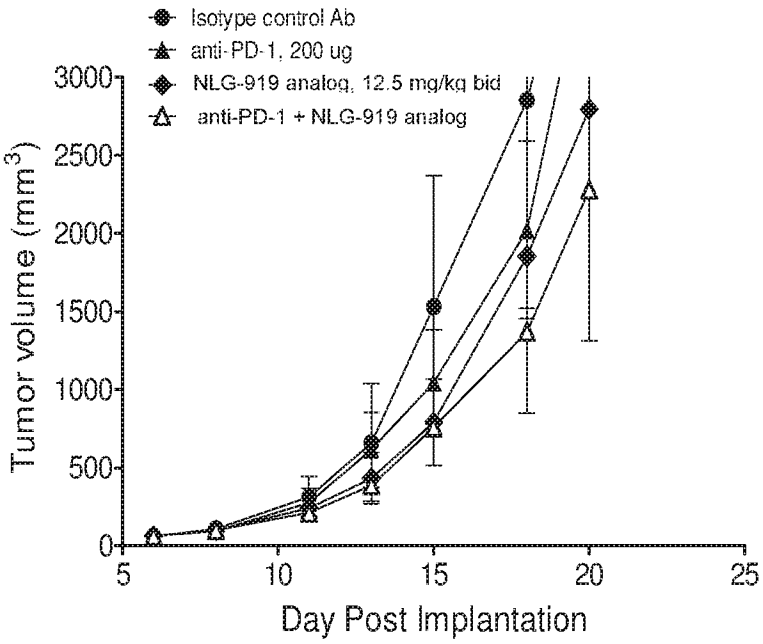

Isotype control Ab
anti-PD-1, 200 ug
NLG-919 analog, 12.5 mg/kg bid
anti-PD-1 + NLG-919 analog
Tumor volume (mm3)
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
Day Post Implantation

FIG. 6B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/64339

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/4745; A61K 31/724; A61K 47/61; A61K 39/395 (2018.01)
CPC - A61K 31/4745; A61K 47/61; A61K 31/724; A61K 39/395; A61K 2300/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	Lazarus et al. 'CRLX101, an investigational nanoparticle-drug conjugate of Camptothecin, demonstrates synergy with Immunotherapy Agents in Preclinical Models'. [abstract], Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2016, April 16-20; New Orleans, LA; Cancer Research July 2016, Vol 76 (14 Suppl); Abstract 3209, pg 1-2. pg. 1	1; 3-6; 17 ---------- 2; 7-16; 18-50
Y	WO 2015/048467 A1 (CERULEAN-467 PHARMA INC.) 02 April 2015 (02.04.2015) pg. 1, para 3-4; pg. 2, para 3 to pg. 3, para 4; pg. 4, para 2; pg. 8, para 3-4; pg 60, para 4; pg. 64, para 1; pg. 69, para 3 to pg. 70, para 2; pg 71, para 1; pg. 72, para 3; pg. 73, para 2	2; 8-16; 18-23; 29-42
Y	SOLIMAN et al. 'A first in man phase I trial of the oral immunomodulator, indoximod, combined with docetaxel in patients with metastatic solid tumors', Oncotarget, 2014, Vol. 5, pp 8136-8146. abstract	7
Y	US 2013/0338103 A1 (CERULEAN PHARMA, Inc.) 19 December 2013 (19.12.2013) para [0021];[0034]; [0037]-[0039];[0112];[0113];[0162];[0163]; [0166]; [0554]; [0557]	24-28; 43-50
Y	US 2016/0176962 A1 (OncoMed Pharmaceuticals, Inc.) 23 June 2016 (23.06.2016) para [0310];[0311];[0314]; [0315];[0319];[0323]	35-42
Y	PHAM et al. 'Preclinical Efficacy of Bevacizumab with CRLX101, an Investigational Nanoparticle -Drug Conjugate, in Treatment of Metastatic Triple-Negative Breast Cancer', American Association for Cancer Research, 2016, Vol 76, pp. 4493-4503. [Published online: 20 June 2016] pg. 4496, Figure 1	48; 49

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 JANUARY 2018	14 FEB 2018
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)