



02139-4616

320

-

128

7

(74)

:

(54)

(Ecteinascidin 743), ET743

(marine source)

ET-743

2000 11 23

WO0069441

743

a) (antimitotic effect)  
xel) )  
bule modulator)

( , , , (taxotere), (doceta  
( , , ) (microtu  
;

b) 5-  
(antimetabolite drug);

(analogue)

c) ( ) (nitrogen mustard)

;

d) ; , , DNA

e) ;

f) , ( ) , , , , ;



9 - (high-dose) 743(ET-743)

가

가 (parenteral) (emulsion)

가

(preparation), 24

2-12 ,가 2-6 12-24 , 2 4

(nanosphere encapsulation)

( *situs* ),

(refractory patient)

. ET-743 WO0069441

(dosing sche

me)

1

가

ET-743

ET-743 가

(Dx)

(soft)

(fibrosarcoma) UV2237, mdr- (rabdomyosarcoma xenograft) TE671 UV2237

. ET-743 Dx (subline) UV2237/ADR

가

. ET-743 Dx UV2237/ADR TE671 3

, ET-743 Dx TE761

TE671가 100mg (i.v.) (tumor weight inhibition)(T WI) 10 (LCK)(Log10 cell kill) , ET-743(0.1mg/kg) 46% 0.132 , Dx (10mg/kg) 50% 0.33 , ET-743 (0.1 mg/kg) Dx (10 mg/kg) 77% 0.924 , Dx (10 mg/kg) 1 ET-743 (0.1 mg/kg) 82% 1.12 , Dx (10 mg/kg) 1 ET-743 (0.1 mg/kg) 75% 0.85

ET-743 Dx

2

743(ET-743)

HT-1080 HS-18

, ET-743 (IC<sub>50</sub> =10ppm) HT 1080 ET-743 (IC<sub>50</sub> =270ppm) E  
 HS-18, ,  
 T-743 가 . ET-743 ,  
 (Chou and Talalay method) , ET-743- , 가  
 (72 ), , ET-743- , 가  
 가 72 ET-743 , ET-743 48 ,  
 , ET-743 가 ET-743 가  
 , ET-743 , ET-743

3

ET-743

743(ET-743) 가  
 . ET-743 (minor groove) N2 ( (Min  
 uzzo) , PNAS, Vol.97, 6780-84, 2000).

(mismatch repair)(MMR) 가 (proficient cell)  
 . ET-743 NER ET-743 6 8  
 가

ET-743  
 Igrove-1 , ET-743 (IG/PSC/ET) , HCT 116, (MMR ) HC  
 T11-ch3 (MMR ) 가

B , ET-743 cisDDP 1 24 ,  
 (colorimetric assay) 가 , cisDDP HCT1 16 , ET-743 24  
 가 (magnally) , E

T-743 cisDDP ,

4

, Sn-38, ET-743  
 가 , Sn-38, ET-743  
 on) - (multiple combinati  
 50:834, 1994) , (model-free design)(Laska , Biometiics  
 가

ET-743 (non-small cell lung)(SN-38 ), (ET-743 ,  
 ), (ET-743 , ), (ET-743 , SN-38 SN-38 )  
 ET-743 , SN-38 ; NSCL SN-38 ; 가/ (NSCL  
 ; NSCL SN-38 ) ; NSCL

가  
 , II ET-743

가 (MDA-435, MDA-231, T-470), (NCI-H522, NC1-H226, NCI-H23), (HCT-116, HT-29, Colo-320), (HOS, U-2, OS, SaOS-2), (RH1, RH30, RD), 10%  
 2mM L- RAMI-1640 37 5% CO  
 2 -95% 75 cm<sup>2</sup> -

IC<sub>50</sub> :

96- , 24  
 ET-743  
 가 , MTT 4 가  
 (570 nm- /630 nm- )

IC<sub>50</sub> ( )

(IC <sub>50</sub> % )	
ET-743	
100	0
75	25
60	40
50	50
40	60
25	75
0	100
0	0

(75:25-ET-743/ ) (100:0-ET-743 0:100- )  
 (ET-743 ) 가 , (ET-743 ) (>5 3 )  
 가 가 , IC<sub>50</sub>

ET-743		
/	/	-
(Osteosarcoma)		
NOS	24 ET-743 24 24 ET-743 24 ET-743 24 ET-743/	가 가

U2-OS	24 ET-743 24 24 24 ET-743 24 ET-743/	가 가 가
Sa06	24 ET-743 24 24 24 ET-743 24 ET-743/	가 가 가/
- (Non-Small Cell)		
NCB-H226	24 ET-743 24 24 24 ET-743 24 ET-743/ 24 ET-743 24 SN-38 24 SN-38 24 ET-743 24 ET-743/SN-38	가 가 가/ 가/ 가
NCB-N522	24 ET-743 24 24 24 ET-743 24 ET-743/ 24 ET-743 24 SN-38 24 SN-38 24 ET-743 24 ET-743/SN-38	가 가 가/ 가/ 가

		가/
NCB-N23	24 ET-743 24 24 24 ET-743 24 ET-743/ 24 ET-743 24 SN-38 24 SN-38 24 ET-743 24 ET-743/SN-38	가 가 가 가/
가 (Brest)		
MDA-435	24 ET-743 24 (gemcitabine) 24 24 ET-743 24 ET-743/	가 가

					가
MDA - 231	24	ET - 743	24		가
	24		24	ET - 743	가
	24	ET - 743/			가
T47-8	24	ET - 743	24		가
	24		24	ET - 743	가
	24	ET - 743/			가
(Colon)					
MCT - 116	24	ET - 743	24	SN - 38	가
	24	ET - 743	24	SN - 38	가
	24	ET - 743/SN - 38			가
NT - 29	24	ET - 743	24	SN - 38	가
	24	ET - 743	24	SN - 38	가
	24	ET - 743/SN - 38			가

Colo - 320	24	ET - 743	24	SN - 38	가
	24	ET - 743	24	SN - 38	가/
	24	ET - 743/SN - 38			
(rhabdomyosarcoma)					
RN1	24	ET - 743	24		가
	24		24	ET - 743	가
	24	ET - 743/			
RD	24	ET - 743	24		가
	24		24	ET - 743	가
	24	ET - 743/			가/
RN30	24	ET - 743	24		가
	24		24	ET - 743	가
	24	ET - 743/			

가 , ET-743 가  
 , NC1-H522 NC1-H23 NSCL SN-38 , HOS  
 ET-743 , T-470 가 , HCT-116  
 SN-38 , Colo-320 SN-38  
 , NC-1H226 NC1-H23 NSCL RHI

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Et-743

ET-743 , ET-743  
 , Chou Talalay (Combination Index, CI) ET-743  
 ; DXR, ; TMTX ; )  
 . ET-743 가 , HT-1080 HS-18 , ET-743 3가  
 SRB , ET-743  
 DXR . ET-743 DXR  
 CIs ( ) HT-1080 , 50, 75, 90 95% 0.86, 0.83, 0.84 0.85 , HS-  
 18 , 50, 75, 90 95% 0.89, 0.74, 0.64 0.60 . DXR ET-743 2  
 4 가, 가 ;  
 90% CI . ET-743  
 ET-743 DXR

ET-743 Pharma-Mar S.A (Tres Cantos, Madrid, Spain) 2 mM  
 DXR Signia chemical Co. (St. Louis, MO) . TMTX  
 Warner-Lambert (ParkeDavis, Ann Arbor, Mich)

, HT-1080 HS-18 10% RP<I-1640

SRB  
 96- SRB  
 (5000 / ) , 50  
 % TCA 1 , 0.4% SRB (Sigma) 가 . 30  
 1% , Biowhitaker microplate reader 2001 570 nm

ET-743 DXR, TMTX

96- 1:100 (ET-743: ) . 72 7가 , SRB

ET-743 DXR, TMTX

C<sub>75</sub> 3가 , ET-743, DXR, TMTX IC<sub>25</sub>, IC<sub>50</sub>, I  
 , 48 가 . ET-743 24 . SRB

70% Becton Dickinson . DNA . 10,000  
 (fluorescence-activated cell sorter, FACS)

(Isobologram)

(Dm IC<sub>50</sub>) (m ) , Chou-Talalay CI  
 (CI=1) † :

$$CI = (D)_1 / (Dx)_1 + (D)_2 / (Dx)_2 \quad (A)$$

(Dx)<sub>1</sub> (Dx)<sub>2</sub> X% D<sub>1</sub> (ET-743) D<sub>2</sub> ( )  
 ( ) , (D)<sub>1</sub> (D)<sub>2</sub> X% ( , ) ET-743  
 . CI<1, CI=1, CI>1 , 가

(Dx)<sub>1</sub> (Dx)<sub>2</sub> Chou Chou - (median-effect equation)

$$Dx = Dm [fa / (1 - fa)]^{1/m} \quad (B)$$

, Dm - , X-log (D) Y-log[fa / (1 - fa)] Dm=10<sup>-(Y- )/m</sup> X-  
 - m, Dm, Dx, CI , m 가 . Chou Chou  
 . (Dm)<sub>1</sub>, (Dx)<sub>2</sub> D1 + D2 , A

가

$$(D1) (D2) / (DX)1 (DX)2 \quad (C)$$

가 A

2 3 , ( ) CI 가

1

HT-1080	S18	4	IC <sub>50</sub>	
			HT-1080	HS-18
ET-743	(nM)		0.01	0.27
DXR	(nM)		25	225
TMTX	(nM)		6	70000

	(nM)	1.3	10
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HT-1080 S18 가 ET-743

IC <sub>50</sub>	24	72	HS-18		
		HR	%G1	%S	%G2-M
			76.3	11.2	12.5
ET-743	270 pM	24 72	32.4 86.7	47.6 8.4	20.0 4.9
DXR	225 nM	24 72	10.1 1.3	64.9 63.8	25.0 34.9
TMTX	70 uM	24 72	44.2 35.5	53.8 57.6	1.9 7.0
	10 nM	24 72	32.8 23.5	52.5 58.7	15.5 26.2

IC <sub>50</sub>	24	72	HT-1080		
		Hr	%G1	%S	%G2-M
			47.5	35.8	16.7
ET-743	10 pM	24 72	42.6 83.1	36.1 10.2	21.3 6.7
DXR	25 nM	24 72	36.1 46.2	17.5 5.3	46.4 48.5
TMTX	6 nM	24 72	31.9 32.0	56.8 53.7	11.3 14.4
	1.3 nM	24 72	45.4 86.0	37.3 9.0	17.3 5.0

2, HT-1080 HS-18 CI, 1 100 E  
 ET-743 DXR, TMTX, .  
 T-743 DXR, CI 1, HT-1080, 50, 75, 90 95%  
 CI ( ) , HT-1080, 50, 75, 90 95% 0.89, 0.74, 0.6  
 0.86, 0.83, 0.84 0.85, HS-18, 50, 75, 90 95%  
 4 0.60, ET-743 DXR, ET-743 TMTX, 가  
 ET-743 24, DXR 48, CI  
 , ET-743 DXR, HT-1080  
 CI 80%, 0.64 ± 0.12, HS-18 88%, 0.24 ± 0.06  
 , DXR ET-743 ( 3a, ) CI  
 , 80%, HT-1080 CI 1.00 ± 0.03, 가 가  
 , 가, 가 CI

ET-743, 0.6, ET-743, HT-1080, CI, HS-18, TMTX, HT-1080, CI, HS-18, TMTX, 1, 1, HS-18, CI, TMTX, 8%, ET-743, HT-1080, CI, 0.92 ± 0.06, 7, ET-743, HT-1080, DXR, ET-743, DXR, ET-743, 6, 743 (Ecteinascidin 743, Et 743), Et 743, MDR1, SXR, DNA, N2, (Jin et. al., PNAS 97, 6775, 2000; Minuzzo et. al., PNAS 97, 6780, 2000), (Synold et. al., Nature Med 7, 584, 2001), (MEXF 989), NSCL (LXFL 529), (HOC 22), (Hendriks et. al., Ann Oncol 10, 1233, 1999), Et743, (compl ete remission, CR), Et 743, (DOX; 8mg/Kg), (DDP; 12mg/Kg), (VINB; 6mg/Kg), (CSHA), (OSA-FH), (SW684), (MRIH-1834), NSCL (LX-1) < 50% T/C, (HF), DOX, Et 743 1, (33% vs. 48%), (20% vs. 34%), (6% vs. 10%), (15% vs. 19%), Et 743, DPP, HF, Et 743, DDP, Et 743, (28% vs. 100%), (36% T/C), (35% vs. 66%), Et 743, CR (<1% T/C), Et 743, Et 743, (22% T/C), Et 743, VINB, CR (<1% T/C), 7, 743 (ET-743), (DOX), ET-743, ET-743, DOX, T-743/DOX, TE671, (1) E, 가, (2), : 1, DOX, TE 671, 가, ET-743, TE

671

가 .

100mg / 10 , (ET -743, 0.1mg/Kg; DOX, 10mg/Kg)  
 50%/0.33, ET -743 DOX ET 46%/0.132, DOX  
 82%/1.12, DOX 1 ET -743 77%/0.924, DOX 1 ET -743  
 UV2237 UV2237/ADR 75%/0.85 가

ET -743/DOX  
 . DOX , DOX가  
 . ET -743 ET -743  
 (PK) 가가 . ET -743 DOX DOX  
 TE 671 . DOX PK ET -743 가 ,

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ET -743 (DDP)

, ET -743 DDP  
 (HCT116), (Igrov -1, A2780), ( , Igrov -1/PSC -ET 1A9),  
 (TE671) , ET -743 DDP ET -743 DDP 2  
 가 . ET743 IC<sub>30</sub> /IC<sub>50</sub> 가

ET -743 DDP , sc TE671 , 가 MTD

ET -743 DDP 1A9 , 50%  
 . (ascitis) (peritoneal cavity) , ET -743 , DDP  
 . (orthotopically) 가 HOC8 , , ET -743 0.05mg/  
 Kg (1/4MTD) 가 , . 0.15mg/  
 Kg ET -743 , 가가 , 가 ,

ET -743 DDP  
 . ET -743 DDP

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(high -dose) (dex) 743(ET -743) (hepatotoxicity)

(tunicate) , ET -743 II .  
 , 가 (transamination)  
 (cholestasis) . , ET -743 (hepatic  
 necrosis) . dex dex가  
 ET -743 (liver damage) , (Wistar)  
 ET -743 (40 µgg/kg) (iv) (dose) . ET -743 24 1, 5, 1  
 0 20mg/kg dex (dose) . ET -743 3 (AL  
 P), (GOT) (TB)

ET -743 2 , ET -743 (biliary epitheli  
 al cell) ET -743 2 TB . ALP GOP 가 2 가 .

-ET-743 ALP, GOT TB 가 10 20 mg/kg dex

1mg/kg dex , 5mg/kg . ET-743 3  
dex (50mg/kg) ET-743 ET-743  
ET-743 B16 (regimen) ET-743

(57)

1. ET-743 ET-743

2. ET-743

3. 1 2 , ET-743

4. 1 , 2 3 , ET-743

5. 1 4 , ET-743

6. 5 , ET-743

7. 1 4 , ET-743

8. 7 , ET-743

9. 1 8 , ET-743

10. ET-743, ET-743

ET-743 ET-743