

(54) E r b B

가

ErbB

ErbB , ,

ErbB가
ErbB

- HER2 가

ErbB, HER2, , FISH,

S.C. § 119(e) 가 , 2000 5 19 가 60/205,754 35 U.

ErbB , HER2

ErbB , - ErbB
ErbB

가 가 가 가 가 가 가 가 가

her2/neu p185HER2 p185HER2
(EGFR) HER2
(van de Vijer et al. New Eng. J. Med. 317: 1239 (1988) ; Walker et al. Br. J. Cancer 60: 426 (1989); Tandon et al. J. Clin. Invest. 7: 120 (1989); Wright et al. Cancer Res. 49: 2087 (1989); McCann et al. Cancer Res 51: 3296 (1991); Paterson et al. Cancer Res. 51: 556 (1991); and Winstanleyetal. Br. J. Cancer 63 : 447 (1991)) butnotinother s (Zhouetal. Oncogene4 : 105 (1989); Heintz et al. Arch Path Lab Med 114: 160 (1990); Kury et al. Eur.

J. Cancer 26: 946 (1990); Clark et al. Cancer Res. 51: 944 (1991); and Ravdin et al. J. Clin. Oncol. 12: 467 - 74 (1994)).

103 가 , 3 () 3
 HER2 가 (Slamon et al. Science 235
 : 177 (1987)). 86 - 가 ,
 (IHC) 가 HER2
 HER2 (Slamon et al. Science 235: 177 (1987); S
 Slamon et al. Science 244: 707 (1989)). 5
 her2 5
 , 가 mRNA () 가 ()
 (Slamon et al. Science 244: 707 (1989); 4,968,603). (Nel
 son et al.) FISH her2/neu
 (Nelson et al. Modern Pathology 9 (1) 21A (1996)).

가
 (IHC) , 가
 가 (CTA) , IHC IHC
 50 - 80% (Press, Cancer Research 54: 2771 (1994)). , IHC
 가
 (FISH) . FIS
 H , FISH가 ,
 . FISH
 (Anastasi et al., Blood 77:
 2456 - 2462 (1991); Anastasi et al., Blood 79: 1796 - 1801 (1992); Anastasi et al., Blood 81: 1580 - 1585
 (1993); van Lom et al., Blood 82: 884 - 888 (1992); Wolman et al., Diagnostic Molecular Pathology 1 (3)
 : 192 - 199 (1992); Zitzelberger, Journal of Pathology 172: 325 - 335 (1994)).

, her2 - HER2
 IHC . 가 3+ 2+
 (Herceptin,) - HER2
 3+ 2+ , FISH her2 가 , ()
) ErbB 가 .

HER2 IHC (HER2), 0 1
 + HER2 IHC FISH+ () 가
 , 가 IHC 가 (, ErbB 가)
 , IHC ErbB (가 가)
 ; ErbB , - ErbB (- -)
 ; ErbB ; erbB 가

HER, ErbB3 ErbB4 , " ErbB " ErbB , EGFR,
 ; ErbB , TEGFR (5,708,156) ;
 , ErbB ErbB ErbB

ErbB - " "
 , " "
 " ErbB
 MARTI/Melan A, gp - 100 (); MAGE - 1 MAGE - 3 (, -
); HPV EG E7 (); Mucin/MUC - 1 (, ,);
 /PSA (); /CEA (,)가

" " erbB - 가
 , ErbB
 PCR,

7 (1997)]; (CR - 1) [Kannan et al., J. Biol. Chem. 272 (6):3330 - 3335 (1997)] . EGFR
 ErbB EGF, TGF - , , HB - EGF . HER3
 ErbB . HER4 ErbB , ,
 HB - EGF, NRG - 2, NRG - 3 .

" " (HRG) 5,641,869 (Marchionni et al., Nature, 362: 31
 2 - 318 (1993)) ,
 - 1, - 2
 - 3 (Holmes et al., Science, 256: 1205 - 1210 (1992); and U. S. Patent No. 5,641,869); neu
 (NDF) (Peles et al. Cell 69 : 205 - 216 (1992)); - (ARIA) (Falls et al. Cel
 l 72 : 801 - 815 (1993)); (GGF) (Marchionni et al., Nature, 362: 312 - 318 (1993));
 (SMDF) (Ho et al. J. Biol. Chem. 270: 14523 - 14532 (1995)); - (Schae
 fer et al. Oncogene 15: 1385 - 1394 (1997)) HRG /
 EGF - (: HRG - 1, 177 - 244) .

" ErbB - " 2 ErbB
 ErbB 가 ErbB ,
 [Sliwkowski et al. J. Biol. Chem., 269 (20):14661 - 14665 (1994)]
 SDS - PAGE ErbB - EGFR - HER2, HER2 -
 HER3 HER3 - HER4 가 , ErbB - ErbB , HER
 3, HER4 EGFR HER2 (: gp 130)

" ErbB1" , " " EGFR" [Carpenter et al., Ann. Rev. Biochem. 56:881 - 914 (1987)] EGFR
 [(Humphrey et al. PNAS (USA) 87:4207 - 4211 (1990))
 EGFR] . erbB1 EGFR . EGFR
 MAb 579 (ATCC CRL HB 8506), MAb 455 (ATCC CRL HB8507), MAb 225 (ATCC CRL 8508), MAb 528
 (ATCC CRL 8509) (4,943,533) , 225 (C225) 225
 (H225) (PCT WO 96/40210)가 .

" ErbB2" " HER2" , [Semba et al., PNAS (U
 SA) 82:6497 - 8501 (1985) and Yamamoto et al., Nature 319:230 - 234 (1986)] HE
 R2 (X03363) . erbB2 HER2
 , neu p185neu . HER2 HER2 . HER2
 MAbs 4D5 (ATCC CRL 10463), 2C4 (ATCC HB - 12697), 7F3 (ATCC HB - 12216) 7
 C2 (ATCC HB - 12215)가 [5,772,997 ; WO 98/77797; 5,840,525].
 - HER2 huMAb4D5 - 1, huMAb4D5 - 2, huMAb4D5 - 3, huMAb4D5 - 4, huMAb4D5 - 5, huMAb
 4D5 - 6, huMAb4D5 - 7 huMAb4D5 - 8 (()) [5,821,337 3
]; 520C9 (WO 93/21319)가 . - HER2 5,772,997 PCT W
 O 97/00271)

(Baselga et al., J. Clin. Oncol. 14: 737 - 744 (1996)).

() HER2
1998 9 25

IHC HER2

- HER2 가 [Tagliabue et al. Int. J. Cancer 47: 933 - 937 (1991); McK
enzie et al. Oncogene 4: 543 - 548 (1989); Maier et al. Cancer Res. 51: 5361 - 5369 (1991); Bacus et al.
Molecular Carcinogenesis 3: 350 - 362 (1990); Stancovski et al. PNAS (USA) 88: 8691 - 8695 (1991); Ba
cus et al. Cancer Research 52: 2580 - 2589 (1992); Xu et al. Int. J. Cancer 53: 401 - 408 (1993); W094/0
0136; Kasprzyk et al. Cancer Research 52: 2771 - 2776 (1992); Hancock et al. Cancer Res. 51: 4575 - 458
0 (1991); Shawver et al. Cancer Res. 54: 1367 - 1373 (1994); Arteaga et al. Cancer Res. 54: 3758 - 3765 (1
994); Harwerth et al. J. Biol. Chem. 267: 15160 - 15167 (1992); 5,783,186 ; Klapper et al. O
ncogene 14: 2099 - 2109 (1997); PCT WO 98/77797]

, ErbB HER3 (5,183,884 5,480,968 , Kraus et al.
PNAS (USA) 86: 9193 - 9197 (1989)) HER4 (599,274 ; Plowman et al., Proc. Natl. A
cad. Sci. USA, 90: 1746 - 1750 (1993); and Plowman et al., Nature, 366: 473 - 475 (1993))
가

ErbB ErbB
가 (Earp et al. Breast Cancer Research and Treatment 35: 115 - 132
(1995)). EGFR 6가 (EGF), (TGF -),
(HB - EGF), (Groenen et al. Growth Factors 11: 235 -
257 (1994)) HER3
HER4 (Holmes et al., Science, 256: 1205 - 121
0 (1992); 5,641,869 ; and Schaefer et al., Oncogene 15: 1385 - 1394 (1997)); neu
(NDF), (GGF); (ARIA); (SMDF)
가 [(Groenen et al. Growth Factors 11: 235 - 257 (1994); Lemke, G. M
olec. & Cell. Neurosci. 7: 247 - 262 (1996) and Lee et al. Pharm. Rev. 47: 51 - 85 (1995))].
, 가 가 ErbB , HER3 HER4 - 2 (NRG - 2) (Cha
ng et al., Nature 387 509 - 512 (1997); and Carraway et al Nature 387: 512 - 516 (1997)) HER4
- 3 (Zhang et al. PNAS (USA) 94 (18): 9562 - 7 (1997)) . HB - EGF
HER4

EGF TGF - HER2 , EGF EGFR HER2 , H
EGFR HER2 ()
ER2 (Earp et al., supra). 가 , HER3가 HER2
, 가 , HER2 가 (Sliwkowski et al., J.
Biol. Chem., 269 (20): 14661 - 14665 (1994)). , (HRG) HER3 HER2
가 . HER2 - HER3 (Levi et al., Journal o
f Neuroscience 15: 1329 - 1340 (1995); Morrissey et al., Proc. Natl. Acad. Sci. USA 92: 1431 - 1435 (199
5); and Lewis et al., Cancer Res., 56: 1457 - 1465 (1996)) . HER3 HER4 HER2
(Carraway and Cantle, Cell 78 : 5 - 8 (1994)).

1 (2000)).
2: 215 - 36 (1990));

(PCR);
가

(Boxer, J. Clin. Pathol. 53: 19 - 2
(Stoler, Clin. Lab. Med. 1

가

" ,

.

가 가

(,) ,

가

" " (1)

(2)

(,) (Manual of Histological Staining Method of the Ar
med Forces Institute of Pathology, 3rd Edition Lee G. Luna, HT (ASCP) Editor, The Blakston Division Mc
Graw - Hill Book Company: New York; (1960); The Armed Forces Institute of Pathology Advanced Labora
tory Methods in Histology and Pathology (1994) Ulreka V. Mikel, Editor, Armed Forces Institute of Path
ology, American Registry of Pathology, Washington, D. C.).

(Bouin's)

가 가

(Paraplast),

(Broloid)

(Tissuemay)가

(microtome)

3 5

- L -

- L -

가 Houston, Texas) , Hemo - De7 (CMS,

(FISH)

(Leitch et al., In Situ Hybridization : A Practical Guide, Oxford BIOS Scientific Publishers, Microscopy Handbooks v. 27 (1994)).

(FITC))

가

" ErbB . FISH (PCT WO 00/20641).

(duplex)

가

가

가

가

가

(backg

round)

FISH

RNA

DNA

dCTP,

dCTP 7 -

DNA,

(PNA) () 가

()

(Sambrook, J., et al., Molecular Cloning A Laboratory Manual, Cold Spring Harbor Press, (1989)).

her2/neu, n - myc, c - myc , her2/neu (17q 11.2 - 17q12) 17 (arm) 140 kb her2/neu 17 (aneusomy) (D1721) her2/neu 17 (Vysis, Inc.) SPECTRUM ORANGE7 SPECTRUM GREEN7

(spot) (mapping);
 (microdissection), PCR (YAC)
 YAC
 , YAC, (BAC), DNA,
 cDNA RNA , pBR322, M13, SP6 T7
 ()

(), SPECTRUM ORANGE7 SPECTRU
 M GREEN7 () 가
 1
 가 (, + =) (, + =)
 1

가 가
 1
 , her2/neu 17 , 17
 (D17Z1) (Vysis, Inc.) (diploidy)
 () her2/neu 17

FISH (Ploem and Tanke, Introduction
 to Fluorescence Microscopy, Oxford University Press: New York (1987)).
 가
 FISH FISH
 가

IHC FISH 가
 가
 - CCD FISH
 HC FISH

가 2 (her2/neu 2 , ErbB , her2 - HER2)

가 [Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)]

; EDTA ; (: Zn -); () TWEEN (), PLURONICS () (PEG) 가 - ErbB

WO 97/04801

(VEGF) ErbB 가 , EGFR, ErbB2, ErbB3, ErbB4, 가 ()

(coacervation) [Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)]

1980)]

가 (3,773,919), L - (2 - - L -) () , - -

LUPRON DEPOT () (-

가), -D - (-) -3 -

100

가

37

S - S

가

- ErbB

ErbB

- ErbB

, erbB 가

()

(

);

- ErbB

가

()

가

[Chemotherapy Service Ed., M.C.Perry, Williams & Wilkins, Baltimore, MD (1992)]

(EP 616 812)

(

).

() (),

1

1 kg

1 µg

15 mg (: 0.1

20 mg/)

1

1 µg/kg 100 mg/kg

;

가 () . 1 -
 ErbB , - ErbB .
 2 가 2
 가
 , FISH erbB 가 IHC 가
 , - HER2 가 0 1+

(ATCC) (10801 University Boulevard, Manassas, Virgi

nia 20110 - 2209, U. S. A.)

ATCC

7C2 ATCC HB - 12215 1996 10 17

7F3 ATCC HB - 12216 1996 10 17

4D5 ATCC CRL 10463 1990 5 24

1: () (CTA) (CTA) (FISH) (FISH)
 () (CTA) (FISH)
 (IHC) 2+ 3+ HER2 ()
) CB11 ((CTA) 4D5 ()
 가 2+ 3+ IHC IHC
 , 2+ 3+ .

CTA IHC HercepTest (HT) 79% . HT FDA

, CTA , (PathVysion) FISH her2/neu 가 ,
 () , 5998 HER2 , 1915 (32%) CTA ,
 4083 (68%) 623 (1:1 :)
 , 317 가 CTA+ , 306 가 CTA -
 4-6 μ 2 4
 her2/neu 2 2
 1

[1]FISH/CTA

CTA 0 1+ 2+ 3+					
- FISH+	207	28	67	21	
	7	2	21	176	
	4%	7%	24%	89%	529

FISH+ = HER2: CEP17 2 = 82% (79 - 85%)

623 , FISH 529 19.9% CTA - 10.4%
 CTA+ . 0, 1+, 2+ 3+ 4.2%, 6.7%, 23.9% 89.3 %
 79% CTA/HT 81.3% 2+ 31%
 CTA - (4.6%). CTA -
 IHC

her2/neu 가 HercepTest () 가
 4% 2+ FISH+ IHC
 . 1+ 0 FISH+ () IHC
 FISH () 2 IHC

2:FISH/ FISH/

3가 () FISH , 805
 3가 , 167 78
 (9.7%). , 540 2.5 4.5
 (pool)
 가

FISH 2 3 가
 (CTA) 2+ 3+ 2

[2]

	FISH+	FISH -
	21	0
	84	37
	20%	0%
	(12.5 - 27.5%)	(0.7%)

N= 142

FISH+ 20% 2+ 3+ 15% , 2+ 3+
 가 IHC , CTA 1 14% , FISH
 ISH () HercepTest 가 IHC , F
 가 3+ 2+ , FISH+ 20% (3 4).

[3] 2 3 () FISH/ , 3+

	FISH+	FISH -
	18	0
	72	17
	20%	0%
	(12 - 28%)	(0 - 14%)

N=107

[4] 2 3 () FISH/ , 3+

	FISH+	FISH -
	3	0
	12	20
	20%	0%
	(1 - 40%)	(0 - 14%)

N=35

3+ , FISH+ (20%) 3+ 17% , 2+
 FISH+ 20% 9%
 FISH+ (her2)가 () 가 가
 , 1 () 가 (5).

[5]

	FISH+	FISH -
	17	1
	24	20
	41%	20%
	(26 - 56%)	(0 - 14%)

N=62

FISH+ 41% 3+, 2+ 27%

FISH () , 가 FISH+ 7-9 가 FISH- (41%) () , A
 C; , P) (,) , () , A
 ())

[6] 1 +/- () FISH/ , 2+/3+

	C	C+H
FISH -	39%(26 - 52%)	41%(27 - 55%)
FISH+	27%(19 - 35%)	54%(45 - 63%)

N=336

[7]

		H + Ac(n = 143)	AC(n = 138)	H+P(n = 92)	P(n = 96)	H + CT(n = 235)	CT (n = 234)
2+/3+	469	56*	42	41*	17	50*	32
+							
3+	349	60*	42	49*	17	56*	31
FISH	240	58*	40	49*	14	54*	27
+							

*p < 0.05

2 , .

4.

3 , 가 - 0 1+

5.

1 , ErbB 가 - ErbB .

6.

5 , ErbB가 HER2 , 가 (rhuMAb) 4D5 .

7.

1 , erbB - .

8.

7 , erbB 가 her2 .

9.

1 , 가 .

10.

9 , ErbB가 HER2 , .

11.

1 , 가 30% 가 .

12.

- HER2 , her2 가 가 .
, - HER2 가 가

13.

12 , 가 - 0 1+

14.

12 , 가 .

15.

(a) ErbB ;

(b) erbB 가 ErbB

16.

15 , ErbB 가 .

17.

16 , 가 - HER2 .

18.

17 , - HER2 가 rhuMAb 4D5 (()) .

19.

15 , 가 ErbB 가 .

20.

19 , .

21.

B erbB , Erb

22.

21 , 가 - 0 1+ .

23.

21 , erbB가 her2 .