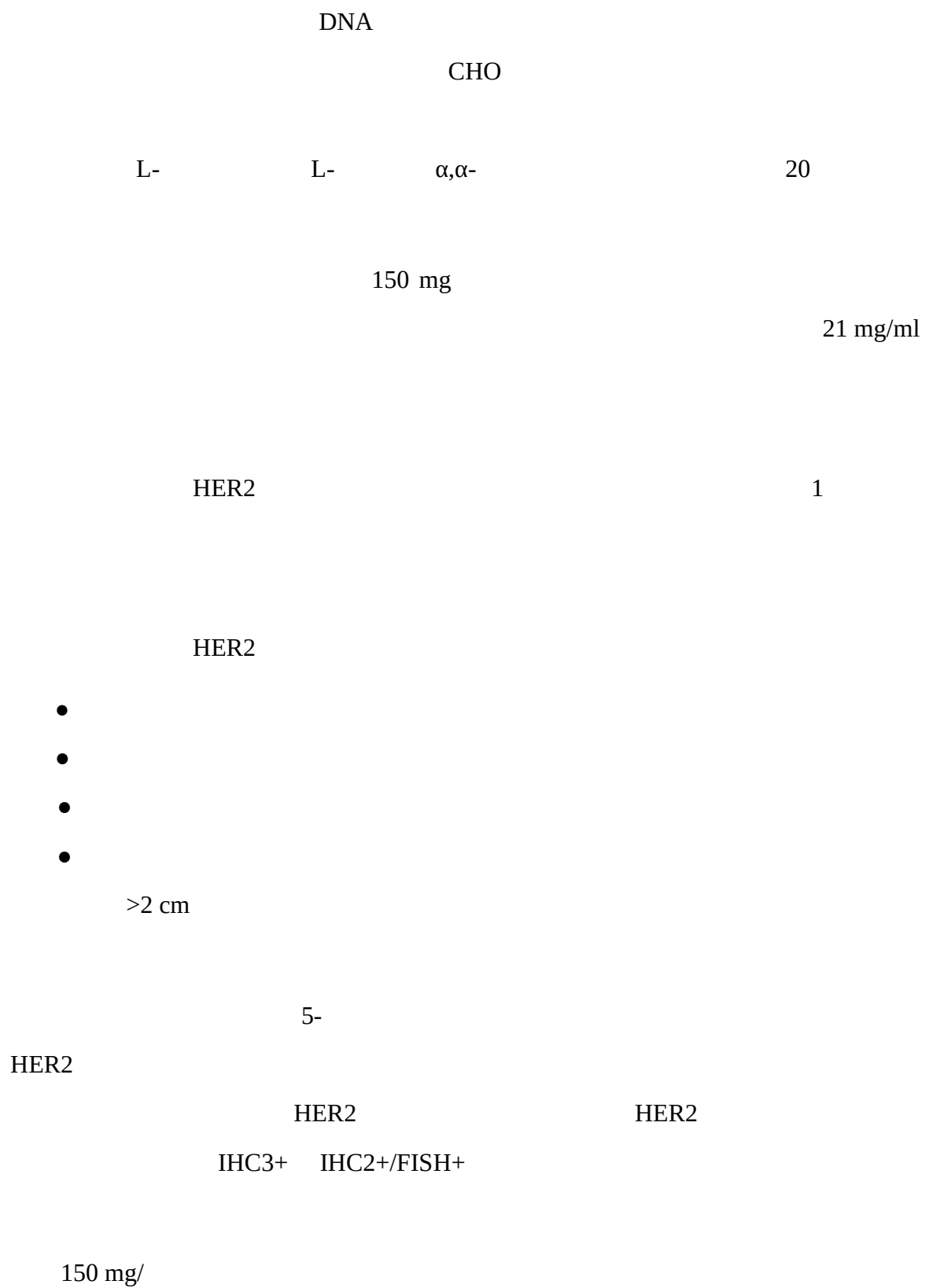


2020



“ ”

HER2

[illegible]

				LVEF					
						4	4	1	
LVEF									
•	LVEF			≥16%					
•	LVEF				LVEF		≥10%		
•	4~8	LVEF			LVEF		≤15%		
•	LVEF		>8	3					

2 mg/kg

6 mg/kg

7

21

4 mg/kg

8 mg/kg

90

7

21

2 mg/kg

6 mg/kg

21 mg/ml pH

6.0

2 8 48
7.2 ml

5

4 mg/kg 1 2 mg/kg

8 mg/kg 3 6 mg/kg

250 ml 0.9% 5%

30 24 2 8 7

5%

/

/

•
•

•
•
•
•
•

$\geq 10\%$

$\geq 5\%$

1

/

$\geq 1/10$

$\geq 1/100$

$< 1/10$

$\geq 1/1,000$

$< 1/100$

$\geq 1/10,000$

$< 1/1,000$

$< 1/10,000$

1

	*	
	/	
	+1	
	+ ()	
	1	
	+1	

	+	
	+	

2 1 2 AC-TH 2.0

AC-TH

64.5%

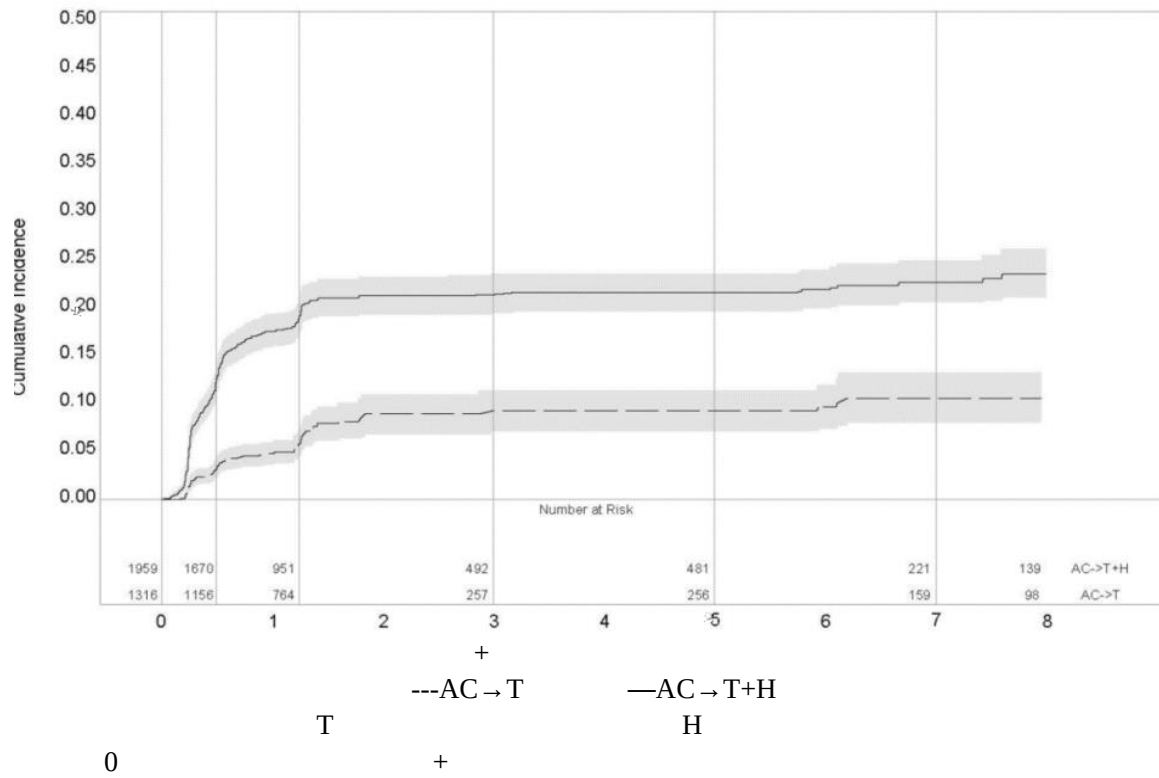
90.3%

2 a

1 NSABP B31 NCCTG N9831

LVEF

50%

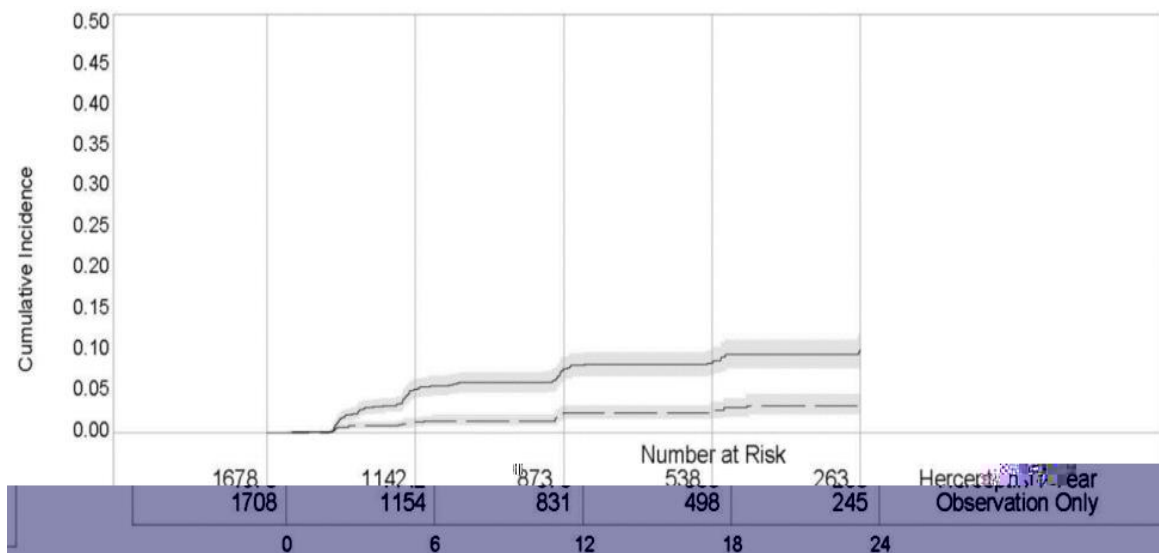


2 BO16348

LVEF

≥ 10%

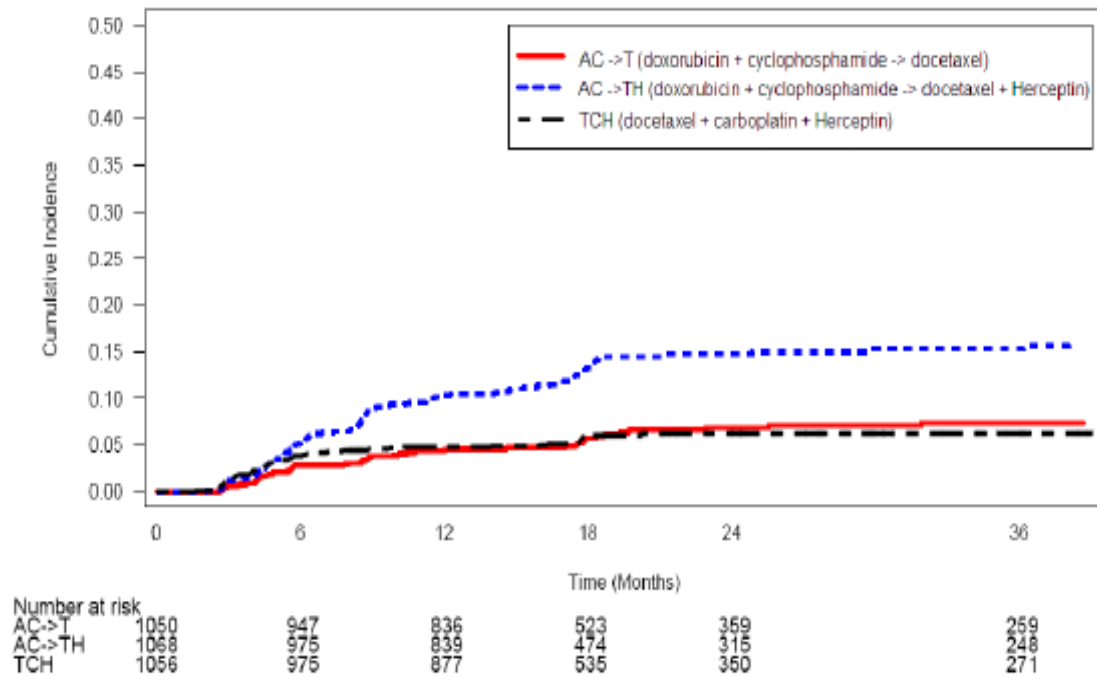
50%



0

1

3 BCIRG006 LVEF ≥ 10% 50%



0

3/4

CHF

0.3 - 0.4%

2.0%

3

AC → P + AC → P + H
3.2% 0.8% 5

5.5 AC → D + AC → DH +

+ DCarbH

LVEF

1.0% 2.3% 1.1%

CHF

NCI-CTC 3-4 AC → D AC → DH DCarbH 5 0.6% 1.9%

0.4% AC → D DCarbH

AC → D DCarbH AC → DH

LVEF

2.3%

AC → D DCarbH 1%

12

1

		NYHA III-IV		0.6%		3.6	
		CHF				0.8%	9.8%
		BO16348		8			CHF
		NYHA III-IV		0.8%			4.6%
				71.4%	CHF		
LVEF	≥50%	79.5%					17%
		NSABP B-31	NCCTG N9831			AC → PH	
+			+	8.1		AC → PH	2.0
					LVEF	18.5%	AC → PH
		LVEF					

3 LVEF

BO18255

LVEF :	/ (N = 290)	/ (N = 294)
	()	()
* LVEF ≥ 10% <50%	1.1%	4.6%
<50%	1.1%	5.9%
* LVEF ≥ 10% ≥ 50%	11.8%	16.5%

FP n=237 LVEF LVEF FP n=187 H

4

BO18255

	/ (N = 290)	/ (N = 294)
	()	()
	6%	6%
≥ 3 NCI CTCAE 3.0	*3%	**1%

* 9 9
** 4 5

IRR /

IRR /

IRR

IRR

IRR 49% 54%

36% 58% IRR

3 5% 7% 5% 6%

IRR 18% 54%

6% 50% IRR 3

0.5% 6% 0.3% 5%

BO22227 IRR

37.2% IRR 3 2.0% 4 5 IRR

WHO 3

1% WHO 4

WHO 3 4

34% 21% 3 4

3/4 32% 22% NCI-CTC

23% 17%

NCI-CTC BO16348 0.4%

3 4 0.6%

30%vs21%[BO16348] NCI-CTC 2~5 12.3%vs

6.7%[NSABP B31] 0.1% vs 0[NCCTG N9831]

H0649g NCI-CTC 3 < 1% BO18255

28% 21% NCI

CTC 3/4 12.2% 10.3%

NCI-CTC 4 5 1.7%vs0.8%[NCCTG N9831] 2 5

6.4%vs4.3%[NSABP B31]

NCI-CTC 3/4

32% vs 22% 23%vs17%

BO18255

NCI CTC 3/4 36.8% 28.9%

5.1% 2.8%

12% WHO 3 4

60%

WHO 3

4 7% vs 15% WHO 3 4

4 18

BO18255

NCI-CTC AE 3.0 ≥3 FP H FP

3% 2%

NCI-CTC AE 3.0 ≥3 SOC

FP H FP

1% <1%

46% vs

30%[H0648g] NCI-CTC 2-5 / 24.3% vs

13.4%[NSABP B31] 3-5 / 2.9% vs

1.4%[NCCTG N9831]

BCIRG006 AC-T

TCH [44% AC-TH 37% TCH 38% AC-T] NCI-

CTC 3-4 [25% AC-TH 21% TCH 23% AC-T]

23% vs 17%

NCI-CTC 2	5	14%vs 5%[NSABP B31]	NCI-CTC 3	5
	2	3.4%vs 1%[NCCTG N9831]		
			NCI-CTC 2	5
4.6%[NSABP B31]	NCI-CTC 2	5	2.4%vs 0.2%[NCCTG N9831]	11.8%vs
/			0.7%	0.3%
	3		1	
	1			

_____/_____

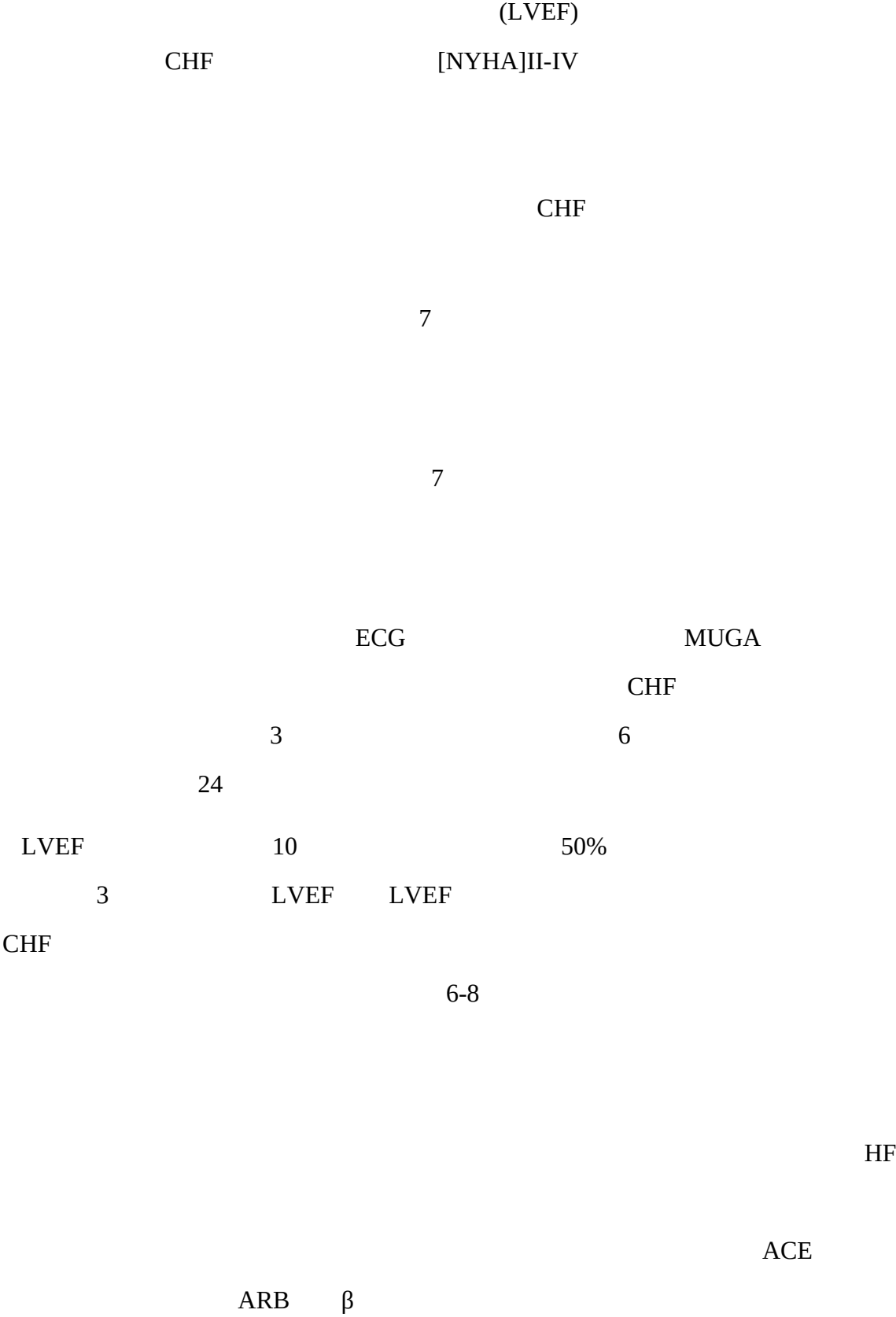
	2.6% vs 1.5%[NSABP B31]	2.5%	3.7% vs 2.2 %[BCIRG006]
2.1% vs 0%[H0648g]			

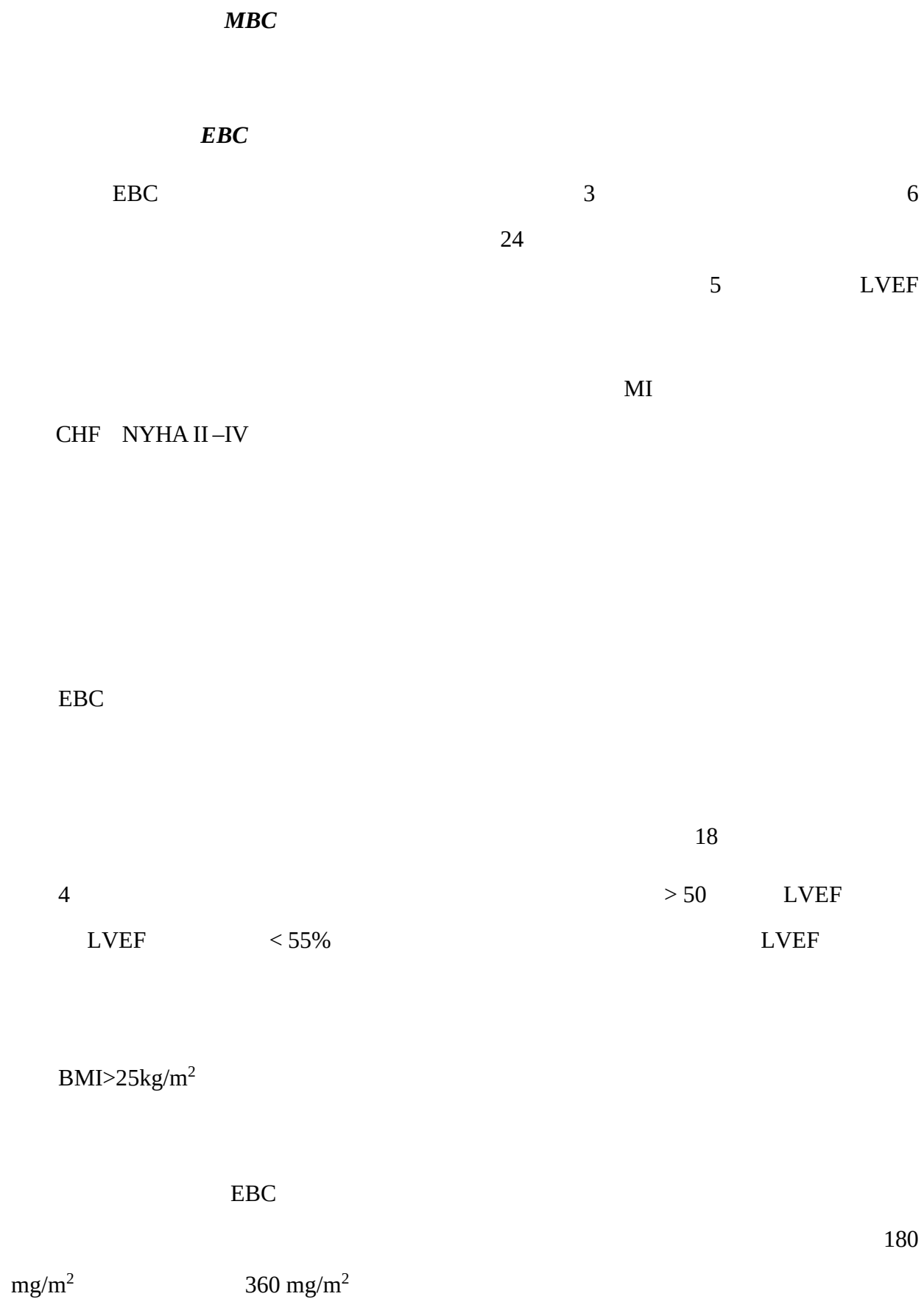
			NCI-
CTC 2	5	6.7% vs 5.4%[NSABP B31]	NCI-CTC 3
vs 0%[NCCTG N9831]			5
	NCI-CTC 1	4	7% vs 1%[BO16348]
BCIRG006		3-4	[5.7% AC-TH
3.0% AC-T]	1-4	[51% AC-TH	63% TCH vs. 43% AC-T]
			27%

	BO18255			109	37%
80	28%			NCI-CTCAE 3.0	
FP	FP+H	4%	9%	≥3	

5

6





MUGA				LVEF				
• • • •	LVEF							
	3			LVEF				
	6			LVEF				
	4			LVEF				
NSABP B31		AC-TH	15%	158/1031	8.7			
LVEF								
BO16348						12.6		
2.6%	44/1678						BCIRG006	
TCH	2.9%	31/1056		1.5%		1.4%	AC-TH	5.7%
61/1068		1.5%		4.2%				
64				CHF		NSABP B31		NCCTG N9831
1				33				
				24%				
≥ 50%				7				
7								

NSABP B31& NCCTG N9831 ^a	AC ^b →	+	3.2%	64/2000	1.3%	21/1655	
BO16348 ^d	→		2%	30/1678	0.3%	5/1708	
BCIRG006	AC ^b →	+	2%	20/1068	0.3%	3/1050	

BCIRG006	+	+	0.4%	4/1056	0.3%	3/1050
----------	---	---	------	--------	------	--------

a	NSABP B31	2	AC → TH	8.3
b				
c	1		1	
d			12.6	NYHA III & IV

BO16348 8

NYHA III	IV	0.8%
----------	----	------

4.6%

8 **a**

		NYHA I-IV		NYHA III-IV	
H0648g	AC ^b	28%	7%	19%	3%
H0648g		11%	1%	4%	1%
H0649g	^c	7%	N/A	5%	N/A

a		LVEF
b		
c	1	

BCIRG006 NCI-CTC 3/4 /

AC-TH 0.3% (3/1068) TCH 0.2% (2/1056) AC-T(0)

IRR

IRR

IRR

IRR

IRR

IRR

 β -

/

7

IRR

NCICTC 3 4

HER2

HER2

HER2

HER2

HER2

HercepTest

IHC

		HER2
0	< 10%	
1+	> 10% /	
2+	> 10%	
3+	> 10%	

HER2

17

2

17

HER2

4

FISH

50%

HER2

5

CISH

FISH

CISH

HER2

HER2

HER2

2+

3+ HER2

HER2

HER2

HER2

HER2

IHC

HER2

SISH

FISH

SISH

HER2

HER2

BO18255

IHC3+ FISH

HER2

HER2

IHC

3+

IHC

2+

FISH

D008548 SISH FISH HER2
>95%

IHC ISH HER2

IHC

	-	-	HER2
0	<10%		
1+	≥ 10% /	/	
2+	≥ 10 %		
3+	≥ 10%		

HER2 17

2 SISH FISH

“ ”

A

1

2mg/kg

25

HER2

20 50

120 150

IgG

120~150

25

2mg/kg

Ç T ,

		[H0648g	H0649g]	[NSABP B31	NCCTG
N9831]	386	65			
	253		133		
				4	

65

1.5

DOL

6- α

POH

7-

-13-

D7D

D7D

PK

5-FU

+

+

	3752				2.0	AC →	
+		DFS			OS	4063	
		8.3	AC →	+		707	
	NSABP B31		NCCTG N9831				
	DFS		49	22-80	6% > 65	84%	
	7%	4%	4%	/		90%	
		38%	T1	91%	27%	66%	
53%	ER+ / PR+		8.3			AC →	+
	BO16348				HER2		IHC
3+	FISH				≥ T1c		
	LVEF <55%						
ECG			(	> 180 mm Hg		> 100 mm Hg)	
	BO16348		HER2				
						1:1:1	
	ER+ / PgR+						8
mg/kg		6 mg/kg					
	DFS		NSABP B31	NCCTG N9831			
		12.6					
					DFS		
	n=1693			n= 1693	3386		
49	21-80	83%	13%		94%		
50%	ER+ / PgR+	57%		32%		11%	
				96%	1055/1098		
		1098		49%	543	ER-	PgR-
47%	512	ER / PgR +					

2 cm

4 8.3 AC → TH 5 BCIRG006

6 DFS

/

/ >65

NSABP B31 NCCTG N9831 OS 0.64 95% CI:0.55 0.74 8.3

[AC → TH] AC → TH 86.9% AC → T 79.4% NSABP

B31 NCCTG N9831 OS

/ OS ≤50

n=2197 OS 0.65 95% CI:0.52 0.81 >50 n=1866

OS 0.63 95% CI:0.51 0.78 ER

/ PR n=2223 0.63 95% CI:0.51 0.78

ER / PR n=1830

0.64 95% CI:0.52 0.80 ≤2 cm n=1604

0.52 95% CI:0.39 0.71 >2 cm n=2448

0.67 95% CI:0.56 0.80

9

NSABP B31 NCCTG N9831 BO16348 BCIRG006

	DFS	DFS 95% CI p	OS	OS	p
<u>NSABP B31 NCCTG N9831^a</u>					
AC → TH n = 1872 ^b n = 2031 ^c	133 ^b	0.48 ^{b,d} 0.39, 0.59 p < 0.0001 ^e	289 ^c	0.64 ^{c,d} 0.55, 0.74 p < 0.0001 ^e	
AC → T n = 1880 ^b n = 2032 ^c	261 ^b		418 ^c		
<u>BO16348^f</u>					
→ n = 1693	127	0.54 0.44, 0.67 p < 0.0001 ^g	31	0.75 p = NS ^h	
→ n = 1693	219		40		
<u>BCIRG006ⁱ</u>					
TCH n = 1075	134	0.67 0.54 - 0.84 p = 0.0006 ^{e,j}	56		
AC → TH n = 1074	121	0.60 0.48 - 0.76 0.0001 ^{e,i}	49		

AC → T n=1073	180		80	
------------------	-----	--	----	--

CI =

a	NSABP B31	NCCTG N9831					AC → T
	AC → TH						
b	h 0 A	1 I	7 f	7 f		7	

HER2		NCCTG N9831	
BO16348	DFS		
10	NCCTG N9831	IHC 3+/FISH+	
81%			
BO16348	IHC 3+/FISH	FISH+/IHC	
DFS			
10	NCCTG N9831	BO16348	HER2
		NCCTG N9831	BO16348 ^c

(HR 0.29, 95% CI 0.08-1.08, p=0.0489)

	BO16348	
	$\rightarrow$ (n = 68)	$\rightarrow$ (n = 54)
<u>DFS</u>	3	8

5gR<A9ES(8p6f9QB!

	EFS	+	
52	/	35%	3
		13	65% vs

52%

(H0648g n=469)

H0649g n=222

2	HER2	
2	3	HER2
		0
		3

H0648g

H0648g 469

IHC	CTA	0	1+	2+	3+	3+
2+	3+					
						33%
						4mg/kg

2 mg/kg

175mg/m ²	3	21	1	6
	AC	60 mg/m ²		75mg/m ²
600 mg/m ²	21	1	6	65%

ORR

13

AC

13 H0648g

		AC					AC
		+		+		+	
		(n=235)	(n = 234)	(n = 92)	(n=96)	AC ^a (n=143)	(n=138)
<u>TTP</u>	b,c	7.2	4.5	6.7	2.5	7.6	5.7
95%		7, 8	4, 5	5, 10	2, 4	7, 9	5, 7
<i>P</i>	d	< 0.0001		< 0.0001		0.002	
<u>b</u>		45	29	38	15	50	38
95%		39, 51	23, 35				

H0649g
H0649g HER2
1 2
222 66% 68% 2
25%
4mg/kg 2 mg/kg
222 ORR 14%
2% 12%
CTA 3+ 18% CTA 2+ 6%
(1:1) III BO18255
5-FU HER2
594 314 53%
351
184 62.2% 167 56.0%
vs.
vs. ECOG 0 1 vs. 2
vs. 5- HER2 FISH+ HER2 IHC
3+ LVEF > 50%
8 mg/kg
6 mg/kg 3 1
80 mg/m² IV 2 3 6
1000 mg/m² 2000 mg/m²
14



	60	21	83	76%	53%	38%	
5%	5%	/	91%	ECOG PS	0	1	82%
18%				23%			7%
/	2%						
	log-rank			OS	351		
OS				0.0193			
OS					15	7	
	15	BO18255	ITT				

	HER2	FISH	IHC
OS	HER2	(IHC 2+ FISH+ IHC 3+)	
		16	11.8
			HR 0.65 (95% CI 0.51-
0.83)	7.6	5.5	HR 0.64 (95% CI 0.51-0.79)
16			

16	HER2	
	FC (N=296) ^a	FC+H (N=298) ^b
<u>FISH+ / IHC 0, 1+ (N=133)</u>		
/n (%)	57/71 (80%)	56/62 (90%)
OS ()	8.8	8.3
95% CI ()	(6.4, 11.7)	(6.2, 10.7)
(95% CI)	1.33 (0.92, 1.92)	
<u>FISH+ / IHC2+ (N=160)</u>		
/n (%)	65/80 (81%)	64/80 (80%)
OS ()	10.8	12.3
95% CI ()	(6.8, 12.8)	(9.5, 15.7)
(95% CI)	0.78 (0.55, 1.10)	
<u>FISH+ or FISH-/IHC3+^c (N=294)</u>		
/n (%)	104/143 (73%)	96/151 (64%)
OS () 9	13.2	18.0
5% CI ()	(11.5 15.2)	(15.5, 21.2)
(95% CI)	0.66 (0.50, 0.87)	

a	FC	FISH+	IHC
b		5	FISH+ IHC
c	6	10	FISH- IHC3+ 8
	IHC 3+		8 FISH

	2009	1	7
15	614	HER2	HER2
22.7%	HER2	85	
36	49		
	ECOG		
95%		80%	80% ECOG
0	1	1	

HER2	12.6	vs 9.7	)
------	------	--------	---

	17	FAS
	N=48	N=36
	28 (58.3%)	19 (52.8%)
*	20 (41.7%)	17 (47.2%)
#	9.7	12.6
95% CI#	[6 ; 18]	[10 ; 18]
95% CI	0.72	[0.40 ; 1.29]

“

4

FAS



PFS TTP

18

18 FAS

	/	/	/
	N = 48	N = 36	
HR 95% CI	5.5	6.8	0.69[0.41 ; 1.15]

Ames

5000 µg/mL

118mg/kg

2mg/kg/ 25

18 I II III

1582

-

MBC/EBC

0.127 L/ 0.176 L/ Vmax

8.81 mg/ Km 8.92 mg/L 2.62 L

AGC 3.63 L

19 1 20 3

5th-95th PK

C_{max} C_{min}

19 1 5th - 95th

		N	C _{min} µg/mL	C _{max} µg/mL	AUC µg. /mL
8mg/kg + 6mg/kg 3	MBC/EBC	1195	29.4 5.8 - 59.5	178 117 - 291	1373 736 - 2245
	AGC	274	23.1 6.1 - 50.3	132 84.2 - 225	1109 588 - 1938
4mg/kg + 2mg/kg	MBC/EBC	1195	37.7 12.3 - 70.9	88.3 58 - 144	1066 586 - 1754

		N	C _{min,ss} (µg/mL)	C _{max,ss} (µg/mL)	AUC _{ss} (µg· /mL)	()	CL (L/)
8mg/kg+ 6mg/kg 3	MBC/ EBC	1195	47.4 (5 - 115)	179 (107 - 309)	1794 (673 - 3618)	12	0.173 - 0.283
	AGC	274	32.9 (6.1 - 88.9)	131 (72.5 - 251)	1338 (557 - 2875)	9	0.189 - 0.337
4mg/kg + 2mg/kg	MBC/ EBC	1195	66.1 (14.9 - 142)	109 (51.0 - 209)	1765 (647 - 3578)	12	0.201 - 0.244

2~8

7.2 ml2~848

0.9%2~8

7

150mg/ 1 /

2~8 48

YBS00182020

S20200019

1289

1289

200233

021-33395800

021-33681208

400--086-6800 24