2020 08 12

2021 01 25

2021 08 09

2022 05 06

2022 05 10

2023 01 09

2023 07 03

® ® [1]

24

1

>2 cm

5-

HER2

HER2 HER2

IHC3+ IHC2+/FISH+

60 mg/ 150 mg/

HER2

4 mg/kg 90

2 mg/kg

30

3

8 mg/kg 6 mg/kg 6 mg/kg

90 30

8 mg/kg 6 mg/kg

90

30

1

EBC 1

LVEF

LVEF 4 4 1

LVEF

LVEF

LVEF LVEF

4~8 LVEF LVEF

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

60 mg/ 3.0 ml

150 mg/ 7.2 ml

5

4 mg/kg	1 2 mg/kg
8 mg/kg	3 6 mg/kg

250 ml 0.9% 5%

2 8 7

30 24

5%

/

/

1

/

* ADR 2%
ADRs
SOC
+
1

NYHA II IV

S3

1%-
4% + 9%-12%
6%-9% + / 27%
/ 7%-10%
0% +
2.2%
79%

(LVEF) BO16348
12.6 12.4 1 12.6 NSABP
B31 NCCTG N9831 AC-T 7.9 AC-TH 8.3

NSABP B31 NCCTG N9831 AC

6% AC (AC LVEF < LLN

NSABP B31 NCCTG N9831

+

BO16348

2 1 2 AC-TH 2.0

AC-TH

64.5% 90.3%

2 [a] NSABP B31 NCCTG N9831 BO16348 BCIRG006

LVEF

	LVEF <50%			LVEF	
	LVEF <50%			<20%	
NSABP B31 NCCTG N9831[b c]					
+ - >2	23.1%	18.5%	11.2%	37.9%	8.9%
n=1856	428	344	208	703	166
+ - >	11.7%	7.0%	3.0%	22.1%	3.4%
n=1170	137	82	35	259	40
BO16348[d]					
	8.6%	7.0%	3.8%	22.4%	3.5%
n=1678	144	118	64	376	59
	2.7%	2.0%	1.2%	11.9%	1.2%
n=1708	46	35	20	204	21
BCIRG006[e]					
TCH	8.5%	5.9%	3.3%	34.5%	6.3%
n=1056	90	62	35	364	67
+ - >2	17%	13.3%	9.8%	44.3%	13.2%
n=1068	182	142	105	473	141
+ - >	9.5%	6.6%	3.3%	34%	5.5%
n=1050	100	69	35	357	58

a NSABP B31 NCCTG N9831 BO16348 BCIRG006

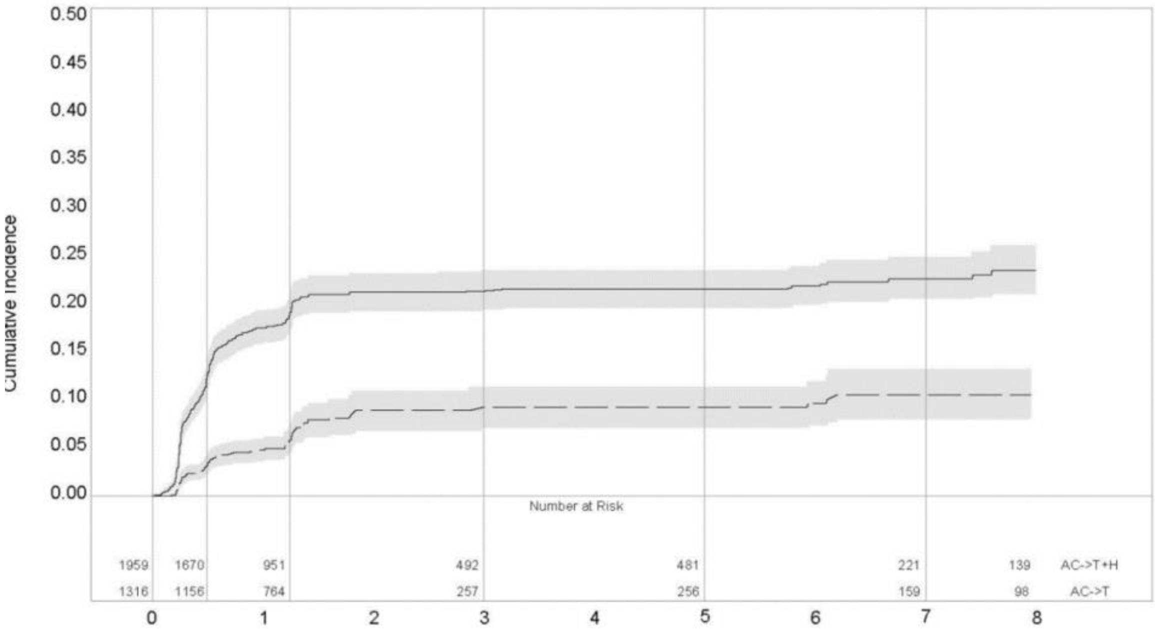
b NSABP B31 NCCTG N9831 + - > + - >2

c NSABP B31 NCCTG N9831 + - >2 8.3

d 12.6

e BCIRG006 + - > AC TH TCH

1 NSABP B31 NCCTG N9831 LVEF 50%



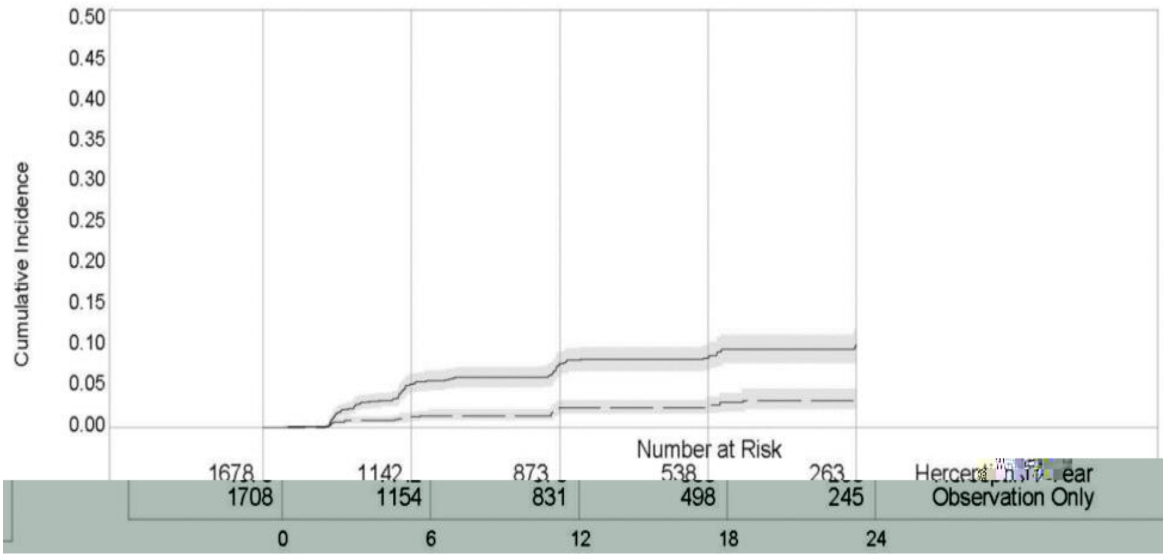
+

---AC T AC T+H

T H

0 +

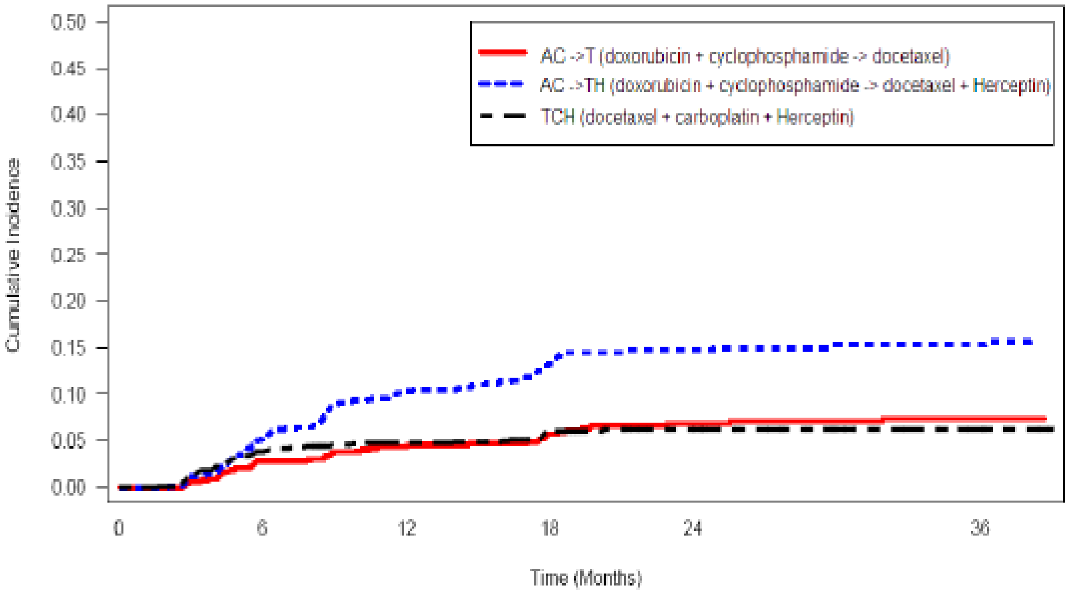
2 BO16348 LVEF 10% 50%



--- 1

0

3 BCIRG006 LVEF 10% 50%



Number at risk

AC->T	1050	947	836	523	359	259
AC->TH	1068	975	839	474	315	248
TCH	1056	975	877	535	350	271

0

3/4

CHF

0.3-0.4% 2.0% 3 + - :

+ +H

3.2% + - : 0.8% 5

5.5 + - . + + - . 2 +

\+ DCarbH

LVEF 1.0% 2.3% 1.1% CHF

NCI-CTC 3-4 + - . + - . 2 DCarbH 5 0.6% 1.9%

0.4% + - . DCarbH

\+ - . DCarbH + - . 2

LVEF 2.3%

\+ - . 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 79.5% 17%

NSABP B-31 NCCTG N9831 + - : 2

+ + 8.1 + - : 2 2.0

LVEF 18.5% + - PH

LVEF 10%~50% + - : 2

64.5% 90.3%

LVEF

MO16432 (3

180 mg/m^2) 1.7%

BO22227 4

30 0mg/m^2 70

/ 0.3%

BO18255 / FP /

H FP LVEF 64% 48%~90% 65% 50%~86%

1 LVEF BO18255

LVEF

3 LVEF BO18255

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

* LVEF LVEF FP n=187 H FP n=237

4 BO18255

/
(N = 290)
(

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 FP H FP

3% 2%

NCI-CTC AE 3.0 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]

NCI-CTC 2 5 14%vs 5%[NSABP B31] NCI-CTC 3 5

2 3.4%vs 0.9%[NCCTG N9831]

NCI-CTC 2 5 11.8%vs 4.6%[NSABP B31] NCI-CTC 2 5 2.4%vs 0.2%[NCCTG N9831]

/ 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 5 2.2% vs 0%[NCCTG N9831] NCI-CTC 1 4 7% vs 1%[BO16348]

BCIRG006 3-4 [5.7% AC-TH 5.5% TCH vs. 3.0% AC-T] 1-4 [51% AC-TH 63% TCH vs. 43% AC-T]

IV 27%

BO18255 109 37%

80 28% NCI-CTCAE 3.0

FP FP+H 4% 9%

EBC BO22227 70

10.1% 30/296

30 2

[

pCR] EFS [

ARRs]

5

[redacted]

(LVEF)

CHF [NYHA]II-IV

CHF

7

7

ECG MUGA

CHF

3 6

24

LVEF 10 50%

3 LVEF LVEF

CHF

6-8

HF

ACE

ARB

MBC

EBC

EBC 3 6 24 5 LVEF

MI

CHF NYHA II IV

EBC

18

4 > 50 LVEF

LVEF < 55% LVEF

BMI>25 kg/m^2

EBC

180 mg/m^2 360 mg/m^2

65

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%

7

7

NSABP B31& NCCTG N9831[a]	AC[b] +	3.2% 64/2000 [c]	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 +- >2 8.3

b

c 1 1

d 12.6 NYHA III & IV

BO16348 8

NYHA III IV 0.8%

4.6%

8 **a**

/

7

IRR

NCI CTC 3 4

HER2

HER2 HER2

HER2 HER2

HercepTest™ CONFIRM anti-HER-2/neu (4B5) Primary Antibody HER-2/NEU

IHC HER2 FISH pharmDx™ INFORM HER2 DNA Probe HER2 DNA

Rabbit anti-DNP Antibody DNP INFORM Chromoso

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+	/	/	
2+			
3+			

HER2 17

2 SISH FISH

7

7

1

2 mg/kg 25

HER2

20 50 120 150

IgG

120~150 25 2

mg/kg

1

7

18

[H0648g H0649g] [NSABP B31 NCCTG N9831] 386 65

253 133

4

65

1.5

6- POH

DOL

7- -13- D7D

D7D

PK 5-FU

+

+

>10 mg/kg

NSABP B31 NCCTG N9831

4063

BO16348 3386

BCIRG006 3222

HER2

NSABP B31 NCCTG N9831 HER2

IHC 3 FISH HER2

NCCTG N9831 NSABP B31

>100mmHg >200mmHg

1 1 + -

+ - + 2 4 21

60 mg/m^2 600 mg/m^2 NSABP B31

80 mg/m^2 3 175 mg/m^2 12 NCCTG N9831

4 mg/kg

2 mg/kg 52 /

ER / PR

DFS

3752 2.0 +-

+ DFS OS 4063

8.3 +- + 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 +- +

BO16348 HER2 IHC

3+ FISH >

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 2-3 < 35 94%

DFS

8

[ITT

DFS = 0.99 95%

CI 0.87 1.13 p = 0.90 OS =0.98 0.83 1.15 p = 0.78]

BCIRG006

BCIRG006 HER2 FISH+

ER/PR >2 cm < 35 /

2 3 3 4

> 100 mmHg T4

N2 N3 M1

1:1:1 AC-T

AC-TH

TCH AC-T AC-TH 3 60 mg/m^2 600 mg/m^2

3 100 mg/m^2 TCH 3

75 mg/m^2 AUC 6 mg/mL/min 30-60

4 mg/kg 2 mg/kg

T TC 3 6 mg/kg 52

ER+ / PR+

DFS

3222 49 22 - 74

54% ER+ / PR+ 71%

DFS NSABP B31 NCCTG N9831 BO16348

BCIRG006 OS NSABP B31 NCCTG N9831 BO16348

9 NSABP B31 NCCTG N9831 2.0 +- >2

4 8.3 +- >2 5 BCIRG006

6 DFS

/

/ >65

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

E+- >2 G +- >2 86.9% +- > 79.4% NSABP

B31 NCCTG N9831 OS

/ OS

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 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
NSABP B31 NCCTG N9831[a]				
+- >2 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]
+- > n = 1880 [b] n = 2032 [c]	261[b]		418[c]	
BO16348[f]				
n =1693	127	0.54 0.44, 0.67 $p< 0.0001$[g]	31	0.75 p=NS[h]
n = 1693	219		40	
BCIRG006[i]				
TCH n=1075	134	0.67 0.54 - 0.84 p=0.0006 [e, j]	56	
+- >2 n=1074	121	0.60 0.48 - 0.76 $p< 0.0001$ [e,i]	49	

+- > n=1073	180		80	

CI =

[a] NSABP B31 NCCTG N9831 +- > +- >2

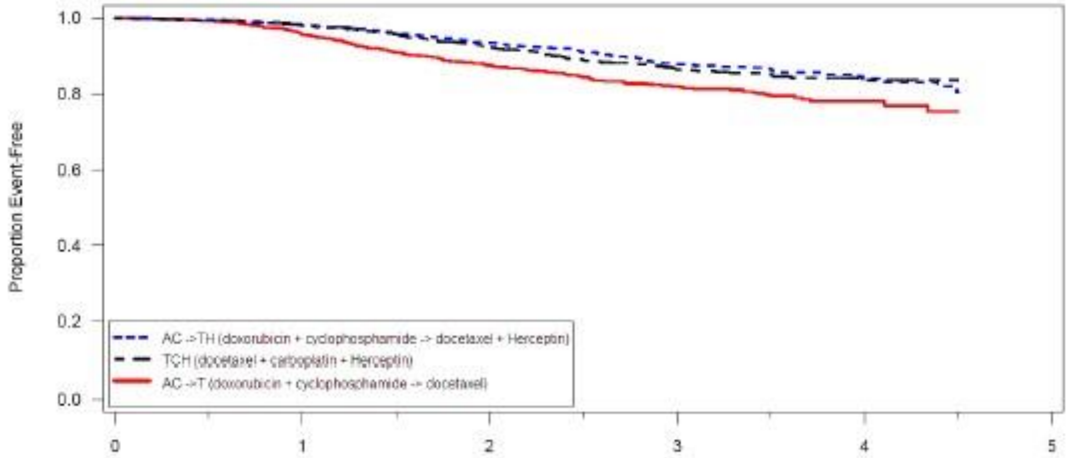
[b] +- >2 2.0 DFS

[c] 707 +- >2 8.3 OS

[d] Cox

[e]

6 BCIRG006



Disease-Free Survival (years)

Number at risk					
AC->T	1073	971	802	417	103
AC->TH	1074	1023	885	457	126
TCH	1075	1018	877	447	126

AC=doxorubicin and cyclophosphamide; T=docetaxel; TCH=docetaxel, platinum salt, and Herceptin; TH=docetaxel and Herceptin.
Kaplan-Meier estimates are shown.

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]		
HER2 [a]		DFS	95% CI		DFS	95% CI
<u>IHC 3+</u>						
FISH +	1170	0.42	0.27, 0.64	91	0.56	0.13, 2.50
FISH -	51	0.71	0.04, 11.79	8		
FISH	51	0.69	0.09, 5.14	2258	0.53	0.41, 0.69
IHC < 3+ / FISH +	174	1.01	0.18, 5.65	299[b]	0.53	0.20, 1.42
IHC / FISH +				724	0.59	0.38, 0.93

[a] HercepTest IHC PathVysion FISH HER2/CEP17
[b] BO16348 IHC 2+
[c] 12.6

BO16348 122 54 1 68

122 46 26 67 92%

50% 40% 10%

41% 91%

26%

BO16348 DFS 1 2

81.4% 92.9% 1

(HR

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

ORR
13
AC

13 H0648g

	AC

H0649g

H0649g HER2

1 2

222 66% 68% 2

25%

4 mg/kg 2 mg/kg

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/m^2 IV 2 3 6

1000 mg/m^2 2000 mg/m^2

14 21 6 1

5 CIV 5- 800 mg/m^2/ 3 6

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

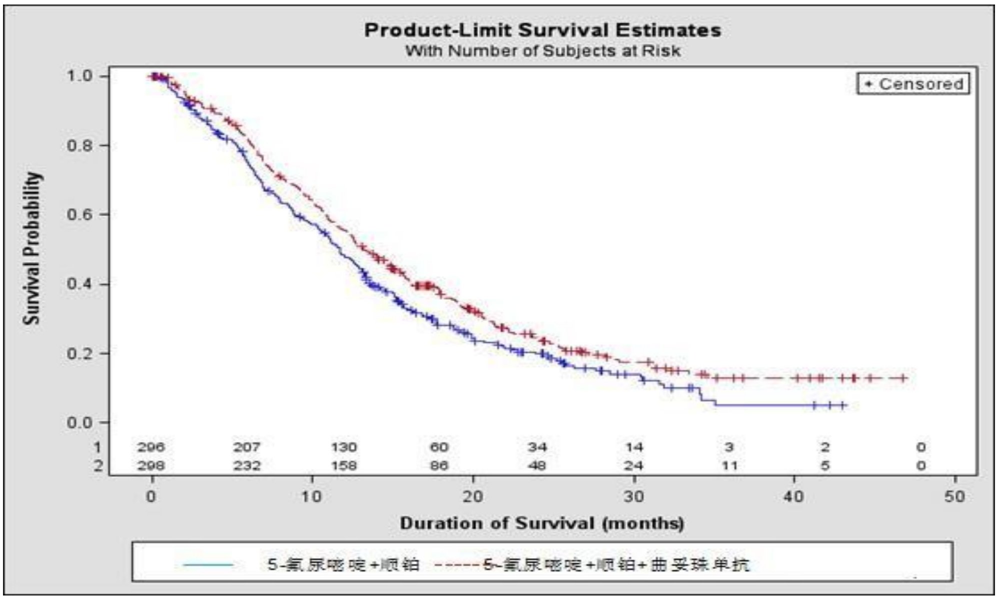
OS 15 7

15 BO18255 ITT

	FC N=296	FC + H N=298
( )		
(%)	184 (62.2%)	167 (56.0%)
	11.0	13.5
95% CI ( )	(9.4, 12.5)	(11.7, 15.7)
	0.73	
95% CI	(0.60, 0.91)	
p *,	0.0038	
(%)	227 (76.7%)	221 (74.2%)
	11.7	13.1
95% CI ( )	(10.3, 13.0)	(11.9, 15.1)
	0.80	
95% CI	(0.67, 0.97)	

* 0.0193

7 ToGA



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]
FISH+ / IHC 0, 1+ (N=133)		
/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)	
FISH+ / IHC2+ (N=160)		
/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)	
FISH+ or FISH-/IHC3+[c] (N=294)		
/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 8 FISH IHC 3+

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)

FP H FP 28% HR 0.72; 95% CI [0.40 1.29]) BO18255 13.8 vs 11.1 HR 0.74; 95% CI [0.60 0.91] 17

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]
	0.72	
95% CI	[0.40 ; 1.29]	

5- FU

*

Kaplan-Meier

=

FAS

Kaplan-Meier 8 4

PFS TTP

18

18 FAS

	/ N = 48	/ / N = 36
HR 95% CI	5.5	6.8
	0.69[0.41 ; 1.15]	
HR 95% CI	5.7	7.2
	0.67[0.39 ; 1.15]	
	2 (4.2%)	2 (5.6%)

3	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

20 AGC 5th - 95th

		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

60 mg/ 3.0 ml

48

150 mg/ 7.2 ml

48

0.9% 2~8

7 30 24

60 mg/ 1 /

150 mg/ 1 /

24

YBS00502022

60 mg/ S20217019

150 mg/ S20200019