2020

DNA

CHO

L- L- α,α- 20

150 mg

21 mg/ml

HER2 1

HER2

-
-
-
-

>2 cm

5-

HER2

HER2 HER2

IHC3+ IHC2+/FISH+

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 ≥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%

2 8 7

30 24

5%

/

/

-
-

-
-
-
-
-

≥10%

≥5%

1

/

≥1/10 ≥1/100

<1/10 ≥1/1,000 <1/100 ≥1/10,000 <1/1,000 <1/10,000

1

	*	
	/	
	+1	
	+ ( )	
	1	
	+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
≥ 16 %) NSABP B31 NCCTG N9831

2 1 2 AC-TH 2.0

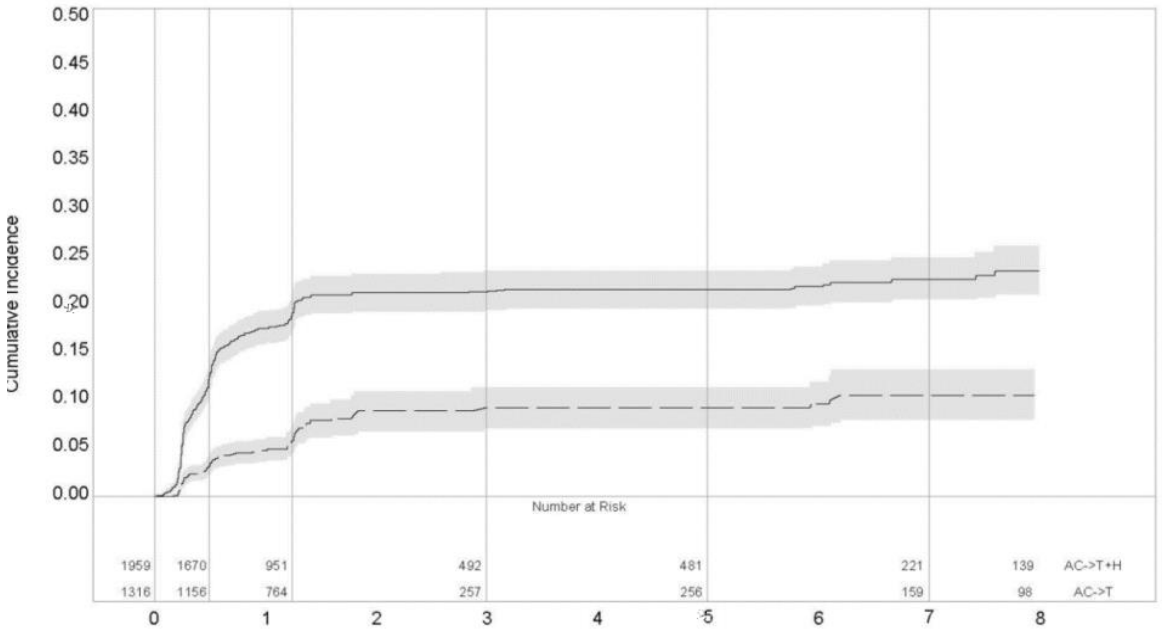
AC-TH

64.5% 90.3%

2 a

9 Tf 1 0 092 r 1 0 0998311 0 595.32 841.92 re W* n BT /F1 9 Tf 1 0 0 1 329.11 39.48 T10.56 Tf 1 0 0 1 246.0 7 BT /F3 10

1 NSABP B31 NCCTG N9831 LVEF 50%



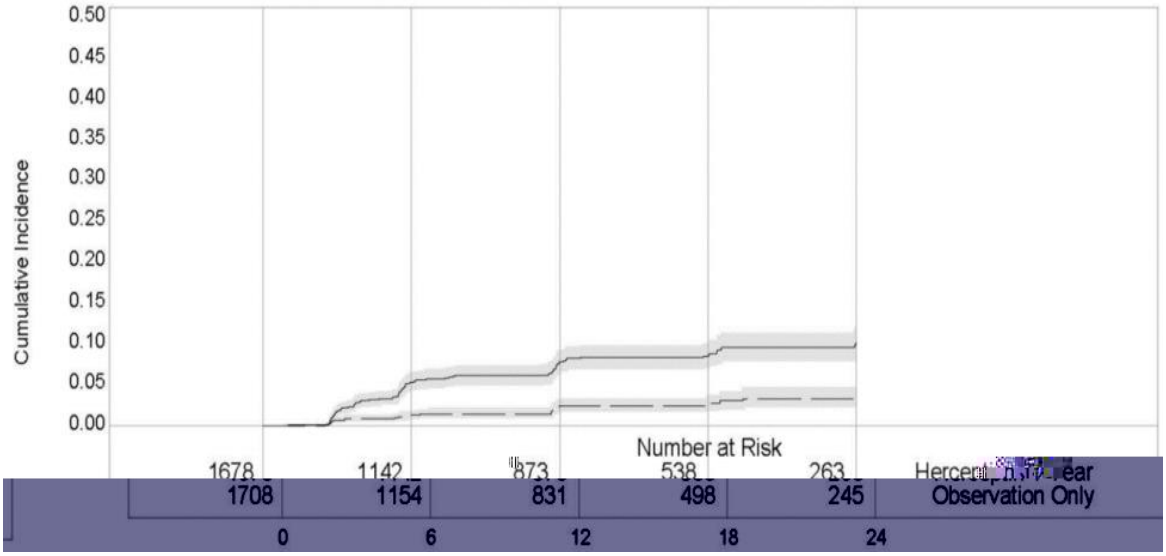
+

---AC→T —AC→T+H

T H

0 +

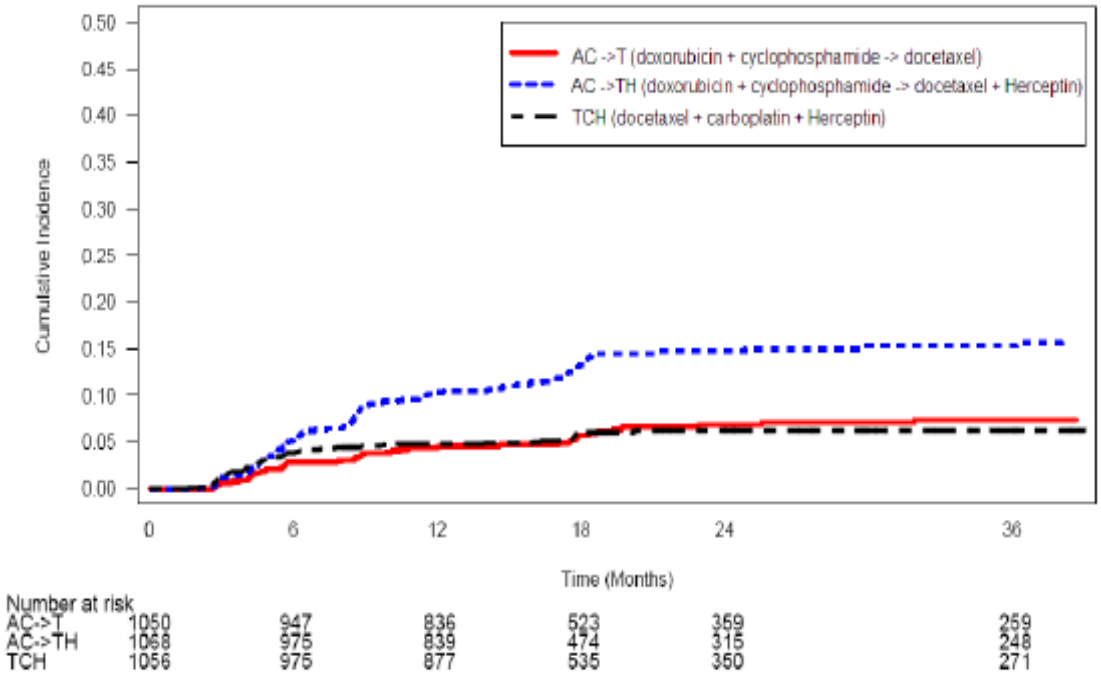
2 BO16348 LVEF ≥ 10% 50%



--- — 1

0

3 BCIRG006 LVEF ≥ 10% 50%



0

3/4

CHF

0.3 - 0.4% 2.0% 3

AC→P + + H

3.2% AC→P 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%

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

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 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]
27%

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

EBC BO22227 70
10.1% 30/296
30 2
[
pCR] EFS [
ARRs]

5

6

(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 β

MBC

EBC

EBC 3 6

24

5 LVEF

MI

CHF NYHA II –IV

EBC

18

4 > 50 LVEF

LVEF < 55% LVEF

BMI>25kg/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%
≥ 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

NCI CTC 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

“ ”

’

1

2mg/kg 25

HER2

20 50 120 150

IgG

120~150 25

2mg/kg

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

65

1.5

6-α POH DOL 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
NSABP B31 NCCTG N9831[a]				
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]	
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	
AC→TH n=1074	121	0.60 0.48 - 0.76 p< 0.0001 [e,i]	49	

AC→T n=1073	180		80	

CI =

[a] NSABP B31 NCCTG N9831 AC→T AC→TH

[b] ˜A Â

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]

50% 40% 10%

41% 91%

26%

BO16348 DFS 1 2

81.4% 92.9% 1

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

BO16348 11

11 BO16348

	BO16348	
	→ (n = 68)	→ (n = 54)
DFS	3	8

EFS +

52 / 35% 3

13 65% vs

52%

(H0648g n=469)

H0649g n=222

2 HER2

2 3 HER2 0 3

H0648g

H0648g 469

13 H0648g

	+ (n=235)	(n = 234)	+ (n = 92)	(n=96)	AC + AC[a] (n=143)	AC (n=138)
TTP 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
P d	< 0.0001		< 0.0001		0.002	
b	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

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

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]
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

=

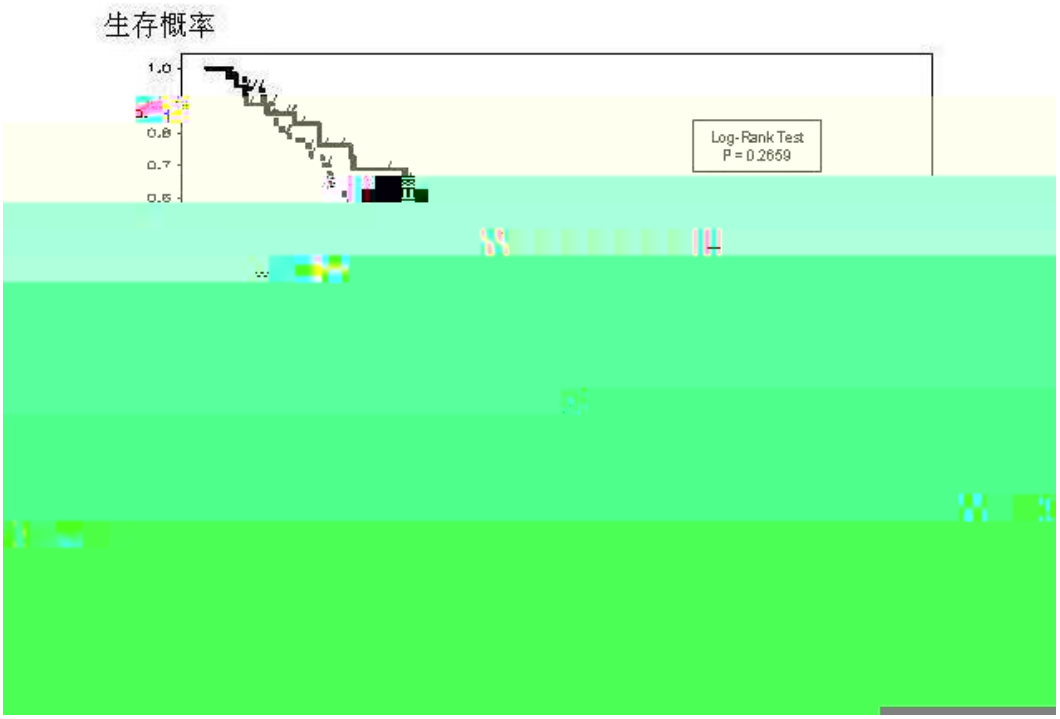
=“ ” “ ” “ ” “

” “ ”

FAS

Kaplan-Meier 8 4

8 Kaplan-Meier FAS



PFS TTP

18

18 **FAS**

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

Ames

5000 μ g/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** **5^{th} - 95^{th}**

		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

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

2~8

7.2 ml 2~8 48

0.9% 2~8

7

150mg/ 1 /

2~8 48

YBS00182020

S20200019

1289

1289

200233

021-33395800

021-33681208

400--086-6800 24