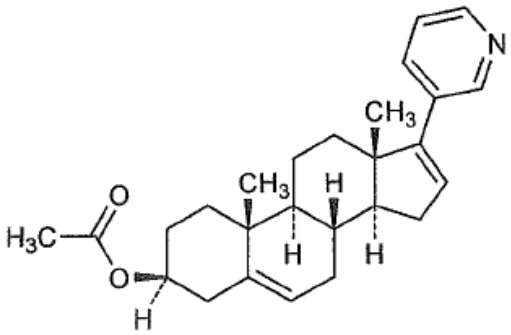
2015 05 06
2015 12 23
2016 02 09
2017 02 24
2018 01 24
2018 11 21
2019 03 06
2019 09 05
2020 06 30
2020 08 18

fi Zytigafi

Abiraterone Acetate Tablets

Cusuan Abitelong Pian

17-(3-)- -5,16- -3



$C_{26}H_{33}NO_2$

391.55

(K29/K32)

mCRPC

mHSPC

3

250mg

1000 mg 4×250mg

5mg 2

mCRPC

5mg 1

mHSPC

GnRHa

1 2

3

3

4.0 mM

3 3

1

Child-Pugh B

250mg Child-Pugh B

1000 mg 4

1 2 2

ALT AST

ALT / AST >5× ULN

>3×ULN

Child-Pugh C 8

Child-Pugh C 8

AUC 7 2

ALT / AST>5×ULN

>3×ULN

AST $ / 7 ” î 8 / 1 ” î 8 / 1

750 mg 1 2 1

3 1

750 mg 1

AST $ / 7 ” î 8 / 1 ” î 8 / 1 500 mg 1

500 mg 1

ALT ALT

3×ULN 2×ULN

CYP3A4

CYP3A4

CYP3A4

2 1000 mg 1 1000 mg

2 CYP3A4

COU-AA-301 COU-AA-

302 mCRPC 1000mg 1

5mg 2 5mg 2

212082PCR3011 mHSPC

1000mg 5 mg 1

mCRPC 2

ABI-PRO-3001 ABI-PRO-3002 5 2230

1~4 1~4

GnRHa

11 0.1 43

7.2 0.1 43

- •

>20% •

53% 46% 3-4

14% 13%

•

7.5 6.6

3.3 >5

COU-AA-301

COU-AA-301 1195

AST / $ / 7 • î 8 / 1

AST / ALT>5×ULN 1

COU-AA-301 •

8

1 301

	+ (N = 791)		+ (N = 394)	
	[1] %	3 4 %	%	3 4 %
/ [2]	30	4.2	23	4.1
[3]	26.2	3.0	23	2.3
[4]	27	1.9	18	0.8
	19	0.3	17	0.3
	8.5	1.3	6.9	0.3
	18	0.6	14	1.3
	6.1	0	3.3	0
	12	2.1	7.1	0.5
	5.4	0	2.5	0
	11	0	7.6	0
	7.2	0.3	5.1	0.3
	6.2	0	4.1	0
[5]	5.9	1.4	2.3	0
[6]	7.2	1.1	4.6	1.0
[7]	3.8	0.5	2.8	0
[8]	2.3	1.9	1.0	0.3

1 NCI CTCAE 3.0

2

3

4

5

6

7

1.3% 1.1%

8

2 COU-AA-301

2 COU-AA-301

	+ (N = 791)		+ (N = 394)	
	%	3 4 %	%	3 4 %
	63	0.4	53	0
AST	31	2.1	36	1.5
	28	5.3	20	1.0
	24	7.2	16	5.8
ALT	11	1.4	10	0.8
	6.6	0.1	4.6	0

COU-AA-302

COU-AA-302 1088

AST / $ / 7 • î 8 / 1

3 COU-AA-302 • •

13.8

3 COU-AA-302

	+ (N = 542)		+ (N = 540)	
	[1] %	3 4 %	%	3 4 %
	39	2.2	34	1.7
[2]	25	0.4	21	1.1
	8.7	0.6	5.9	0.2
/ [3]	30	2.0	25	2.0
	6.6	0.4	4.1	0.7
	23	0.4	19	0.6
	22	0.9	18	0.9
	11	0.0	5.0	0.2
	22	0.2	18	0.0
	22	3.9	13	3.0
	17	0.0	14	0.2
	12	2.4	9.6	0.9
	14	0.2	11	0.0
	13	0.0	9.1	0.0
	5.9	0.0	3.3	0.0
	13	0.0	8.0	0.0
	11	0.0	8.1	0.0
	10.3	1.3	5.6	0.6
	8.1	0.0	3.7	0.0

[1] NCI CTCAE 3.0

[2]

[3]

4 COU-AA-302 15%

>5%

4 COU-AA-302 >15% >5%

	+	(N = 542)	+	(N = 540)
		3 4		3 4
	%	%	%	%
	38	8.7	32	7.4
[1]	57	6.5	51	5.2
ALT	42	6.1	29	0.7
AST	37	3.1	29	1.1
	33	0.4	25	0.2
	17	2.8	10	1.7

[1]

212082PCR3011 mHSPC

212082PCR3011 1199

mHSPC AST / $ / 7 • ULN

GnRHa

24

5 •

•

5 212082PCR 3011 •5% •2%
[1]

/	[2]	N=597 3-4 %	%	N=602 3-4 %
	37	20	13	10
	15	0.0	13	0.2
	20	10	3.7	1.3
ALT [3]	16	5.5	13	1.3
AST [3]	15	4.4	11	1.5
	7.0	1.0	3.7	0.8
	6.7	0.2	4.7	0.2
	7.5	0.3	5.0	0.2
[4]	6.5	0.0	3.2	0

1 GnRH-a
2 CTCAE 4.0
3
4

6

5

6 212082PCR3011 15%
>5%

6 212082PCR3011 >15%

	(N=597)		(N=602)	
	1-4 %	3-4 %	1-4 %	3-4 %
	20	4	14	1.8
	30	9.6	6.7	1.3
ALT	46	6.4	45	1.3

	16	0.2	6.2	0.2

6

5

3 COU-AA-301 ABI-PRO-3001 COU-AA-302 ABI-PRO-3002 212082PCR3011

6

NYHA III IV COU-AA-301 ABI-PRO-3001 II-IV 212082PCR3011 COU-AA-302 ABI-PRO-3002 <50% ADT GnRHa

2.6%vs.0.9% 1.3% 3-4 5 4 0.2% 3-4 2

1-2 1 3 5 7 0.3% 2 0.1% 3 3

-
-
-
-

• < 1/100, • < 1/1000

:

QT

/

–
–
– Child-Pugh C

CYP17

5 mg 1000 mg
4 2 3-4
2 3-4 1
3-4

212082PCR3011 5 mg 1000 mg
10 1 3-4
20 10 3-4
1 3-4

QT

LVEF <50% NYHA III IV
COU-AA-301 NYHA II IV COU-AA-
302 212082PCR3011

2230 1763 0.3% 0.1%
/

3/4 ALT AST 5×ULN
2230 6% 3
ALT AST
2230 1.1% ALT AST

3 2 1 1
ALT AST 250mg
1 1 2 2 1
1 ALT AST
AST ALT AST ALT
AST ALT 5×ULN
3×ULN

AST $ / 7 ” î 8 / 1
” î 8 / 1
AST $ / 7 • î 8 / 1

/

2 1

C_{max} AUC_{0-} , 17

10

223

/ 223

/

223

/

Lapp -

4

1.18mmol 27mg

QT

33 mCRPC 1 2

1000mg 1 5mg 2 2

2 QTc >20ms

QTc <10ms

AUC •0.03

3

70% 65 65 27%
75 75

CYP3A4
CYP3A4 600 mg 6
1000 mg AUC 55%
CYP3A4
[ ]

CYP3A4

CYP2D6 CYP2C8
CYP2D6
AUC 2.9
AUC_{24} 33%
CYP2D6
CYP2D6

CYP2D6

CYP2C8

1000 mg AUC 46%

M-III M-IV AUC 10%

CYP2C8 CYP2C8

OATP1B1 OATP1B1

QT

QT QT

IA

III

PSA

COU-

AA-301 COU-AA-302 212082PCR3011

GnRHa

PSA

COU-AA-301

III

2:1 1195

1000 mg 1 5 mg 2 N=797

1 5 mg 2 N = 398

PSA / 25%

69

39~95 93.3% 3.6% 1.7%

1.6% 89% ECOG 0 1

- 24 45% 90% 30%

70% 30% PSA 70%

30%

552

OS 7 1 775

97% 7

7 GnRHa

	+ (N=797)	+ (N=398)
	333 (42%)	219 (55%)
( )	14.8 (14.1, 15.4)	10.9 (10.2, 12.0)
(95%)		
P [a]	< 0.0001	
[b] (95%)	0.646 (0.543, 0.768)	
	501(63%)	274(69%)
( ) 95%	15.8(14.8 17.0)	11.2(10.4 13.1)
[b] (95%)	0.740(0.638 0.859)	

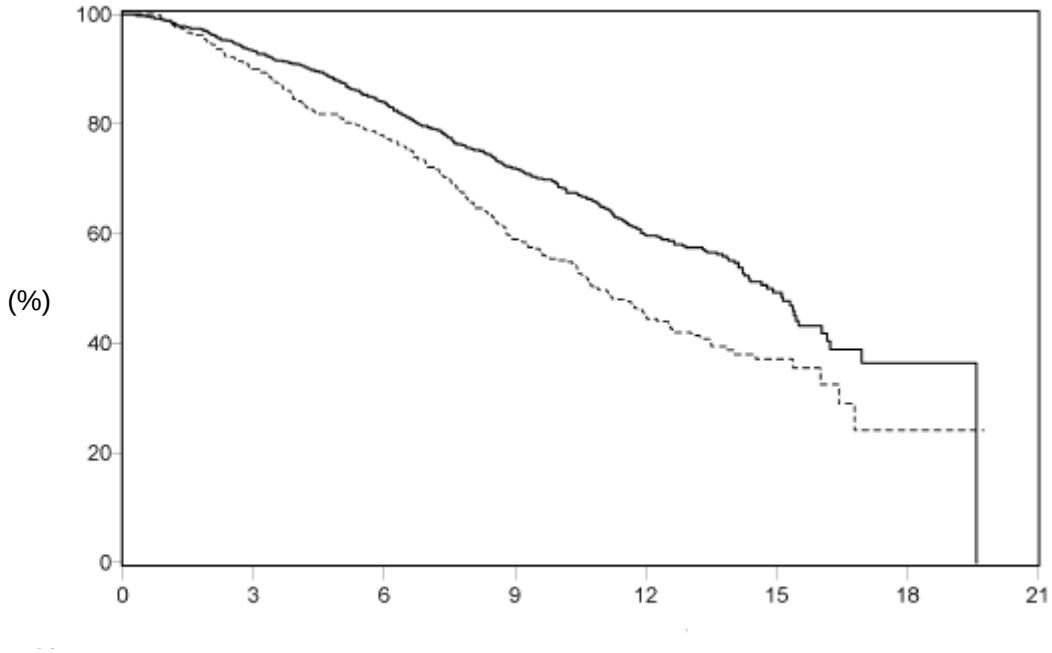
[a] P ECOG 0 1

[b] <1

1

1 GnRHa

Kaplan Meier



797	736	657	520	282	68	2	0
398	355	306	210	105	30	3	0

.....

COU-AA-302

BPI-SF 24

0-1 2-3

1088 1:1 1000mg 1 n=546

1 n=542 5mg 2

ECOG 3

71

70

520 95.4% 15 2.8% 4 0.7% 6

1.1% 76% ECOG 0 24%
1 50% 31% 19%
rPFS

ECOG •
PSA 2[PCWG2]
PCWG2
RECIST 1.1 rPFS

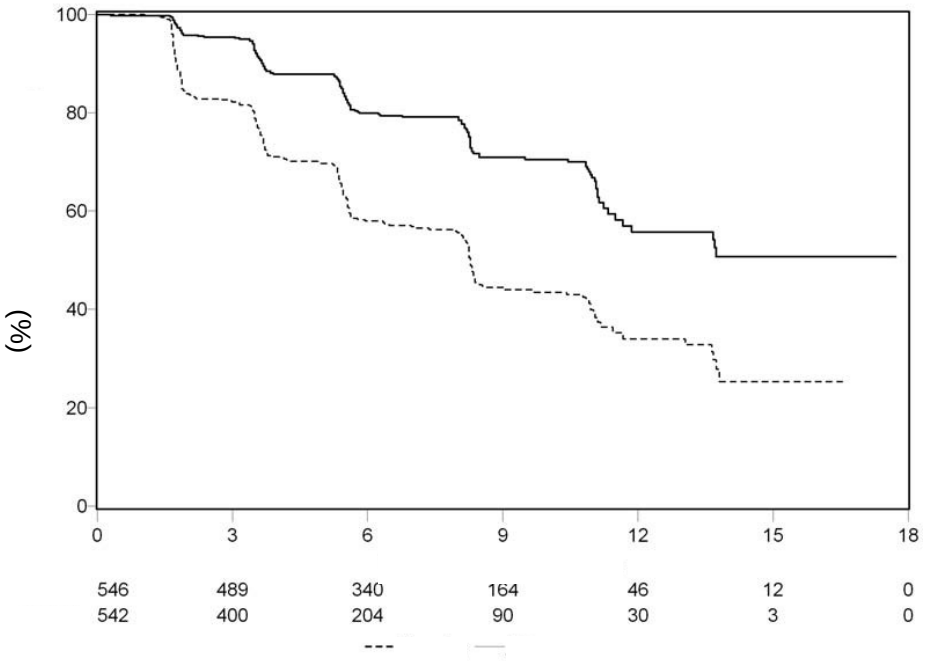
rPFS 401
150 28% 251 46% rPFS
8 2

8 COU-AA-302 GnRHa

	+ (N=546)	+ (N=542)
(rPFS)		
	150(28%)	251(46%)
rPFS( )		8.3
(95% CI)	(11.66 NE)	(8.12 8.54)
P *	<0.0001	
**(95% CI)	0.425(0.347 0.522)	

NE=
*P ECOG 0 1
** < 1

2 GnRHa
Kaplan Meier



OS IA
rPFS 9 3

607 271 50%
336 62% 47%
HR=0.530 95% CI [0.451 0.623] p<0.0001 rPFS
16.5 8.3

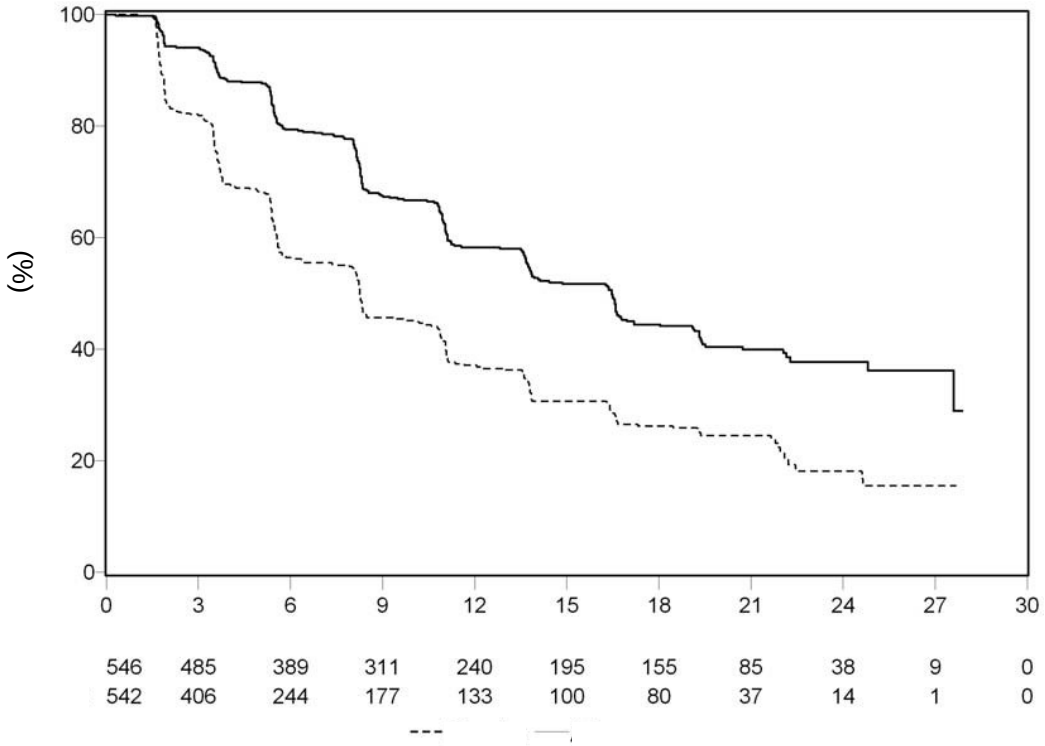
9: COU-AA-302: GnRHa
OS -

	+ (N=546)	+ (N=542)
(rPFS)		
	271(50%)	336(62%)
rPFS( )	16.5	8.3
(95% CI)	(13.80 16.79)	(8.05 9.43)
P *	<0.0001	
**(95% CI)	0.530(0.451 0.623)	

*P ECOG 0 1
** < 1

3: GnRHa

Kaplan Meier OS -



333 OS

25% HR=0.752 95% CI [0.606

0.934] p=0.0097 OS

10 IA

741 OS 49

65% 546 354 71% 542

387 19.4% HR=0.806 95% CI [0.697

0.931] p=0.0033 OS OS 4.4 34.7

30.3 10 4 44%

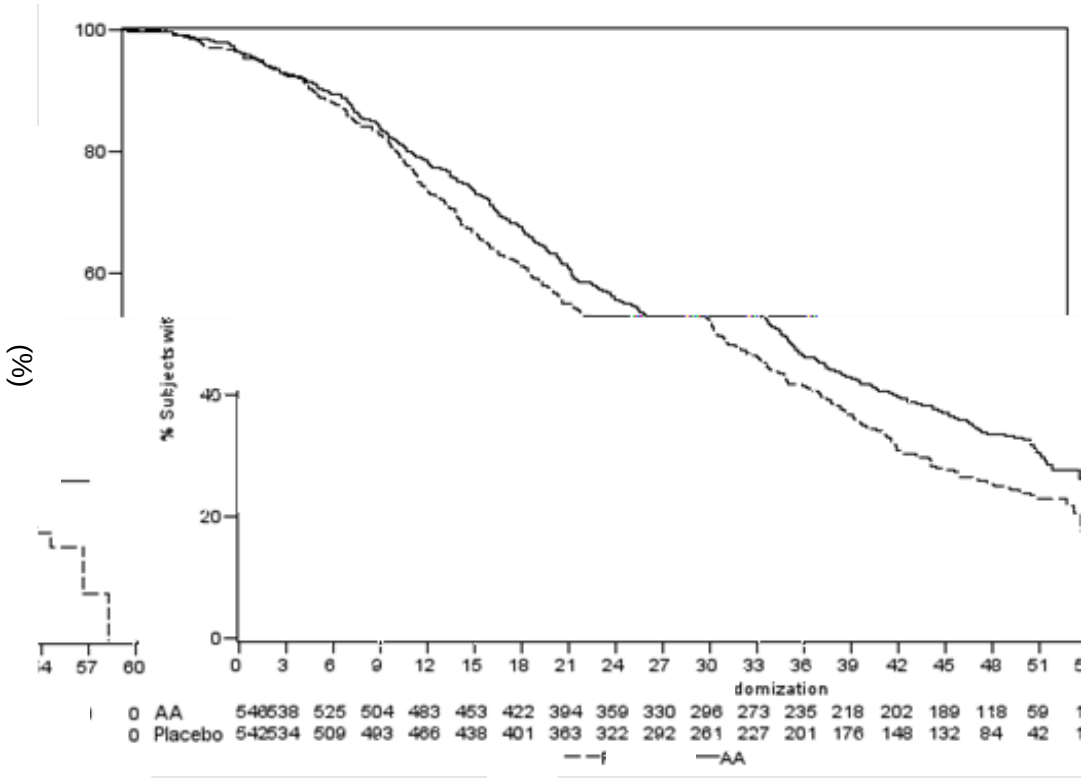
10: COU-AA-302 GnRHa

	+ (N=546)	+ (N=542)
(%)	147(27%)	186(34%)
( )		27.2
(95% CI)	(NE NE)	(25.95 NE)
P *	0.0097	
**(95% CI)	0.752(0.606 0.934)	
(%)	354(65%)	387(71%)
( )	34.7	30.3
(95% CI)	(32.7 36.8)	(28.7 33.3)
P *	0.0033	
**(95% CI)	0.806(0.697 0.931)	

NE=
*P ECOG 0 1
** < 1

4: GnRHa

Kaplan Meier



rPFS

PCWG2 PSA PSA
11.1 5.6 HR=0.488 95% CI [0.420 0.568]
p<0.0001 PSA HR=0.488
PSA 62% vs. 24% p<0.0001

33.4 23.4 HR=0.721 95% CI [0.614 0.846]
p<0.0001

25.2 16.8 HR=0.580 95% CI [0.487 0.691]
p<0.0001

ECOG • ECOG
• 12.3 10.9 HR=0.821 95% CI
[0.714 0.943] p=0.0053

RECIST
• F P
36%
16% p<0.0001

18%
p=0.0490 26.7
18.4

FACT-P
FACT-P 22% p=0.0028
FACT-P 12.7 8.3

212082PCR3011 mHSPC
212082PCR3011 1:1 1199 mHSPC
1000 mg 1 5 mg 1 N=597
1 N=602 mHSPC
ADT GnRHa 3
1 1

Gleason • 3

ECOG 3

67

69% 2.5% 21% 8.1% ECOG

0 76% 1 42% 2 3.5%

24 0~1

50% 2~3 23% • 28% 93.4%

3.8% 3.8% 93.2%

GnRHa 75.0% 12.0%

62.1% 1.4%

406

OS

21% 41

CRPC OS 618

52 11

5 29% 45%

CRPC OS

11 212082PCR3011LATITUDE

	N=597	(N=602)
[1]		
%	169 28%	237 39%
95% CI	NE(NE, NE)	34.7(33.1, NE)
p [2]	<0.0001	
(95% CI)[3]	0.621 (0.509 0.756)	
%	275 (46%)	343 (57%)
95% CI	53.3 (48.2, NE)	36.5 (33.5, 40.0)
(95% CI)[3]	0.66 (0.56, 0.78)	

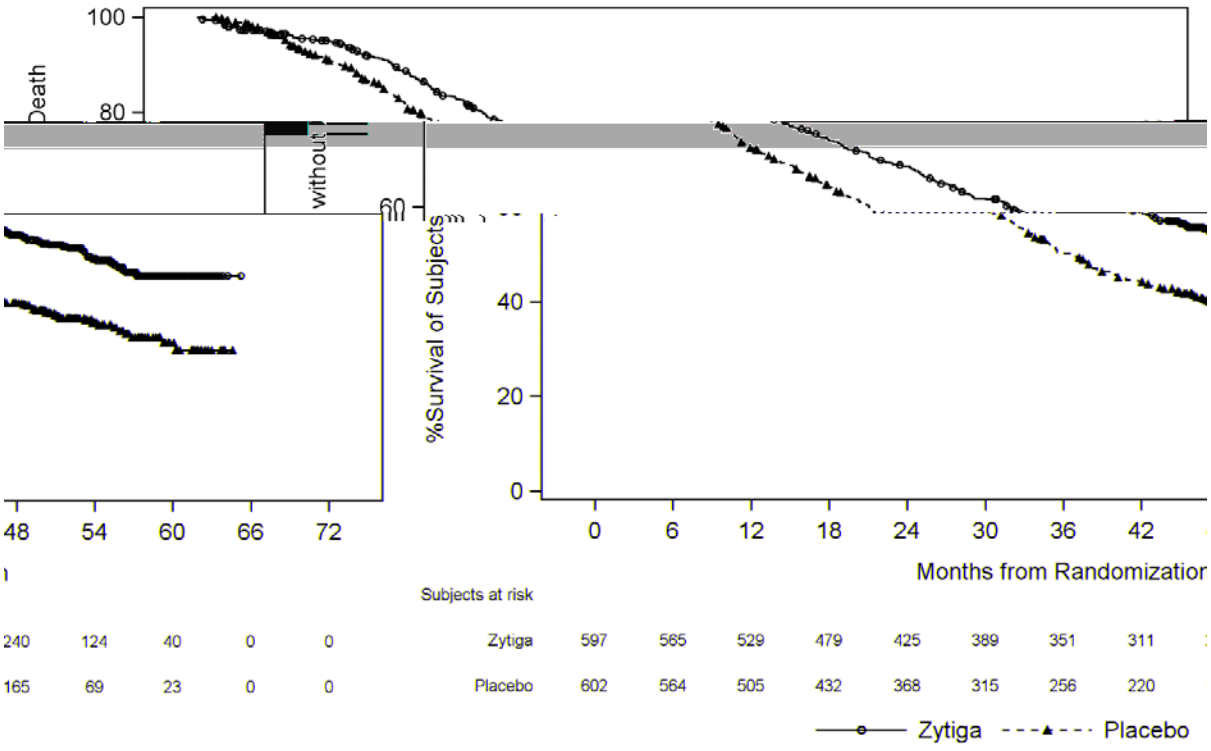
NE=

[1]

[2] p ECOG 0/1 vs2 vs

[3] 1

5 Kaplan-Meier 212082PCR3011/ATITUDE

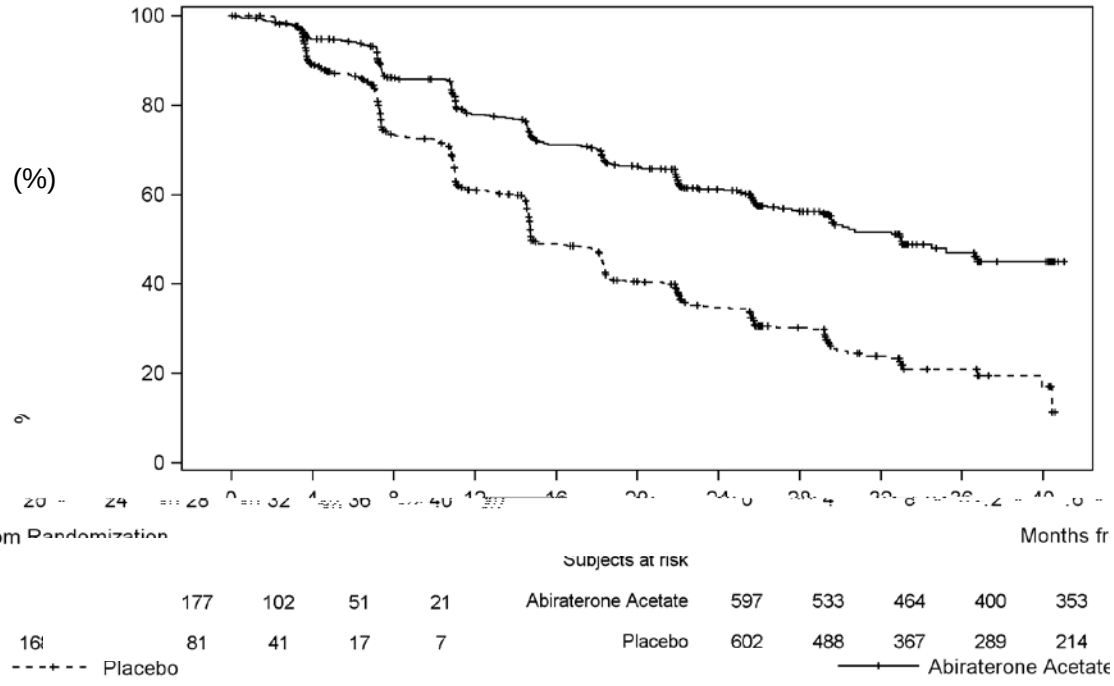


rPFS 593 239
40.0% 354 58.8%
rPFS 12 6
12 212082PCR 3011

	(N=597)	(N=602)
	239 40.0%	354 58.8%
rPFS	33.0	14.8
95% CI	29.57, NE	(14.69 18.27)
p [1]	<0.0001	
[2] (95% CI)	0.466 (0.394 0.550)	

NE=
[1] p ECOG 0/1 2
[2] <1 ADT

6 212082PCR3011 Kaplan-Meier



rPFS

24% HR=0.759; 95% CI:0.601,
0.960; p=0.0208 25
43.0 31.3

PSA PCWG2 PSA

33.3 7.4 HR=0.310; 95% CI:0.266, 0.363; p 0.0001

29.6 AA-P
HR=0.431; 95% CI:0.356, 0.522; p 0.0001

57.6 HR=0.508; 95% CI:0.412, 0.627, p 0.0001

47.4 16.6 HR=0.721; 95% CI:0.607, 0.857; p=0.0002

ABI-PRO-3002

42
/
III
ECOG 0 1 1:1
1000mg 4×250mg
4 1 5mg 2
313 157 156
238
PSA PSA •
• Q J P O •
RECIST 1.1 BPI-SF
•

PSA

ECOG

71

48~90

PSA 58%

HR=0.418 p<0.0001

PSA 44% HR=0.563, p=0.0173

13 ABI-PRO-3002 PSA

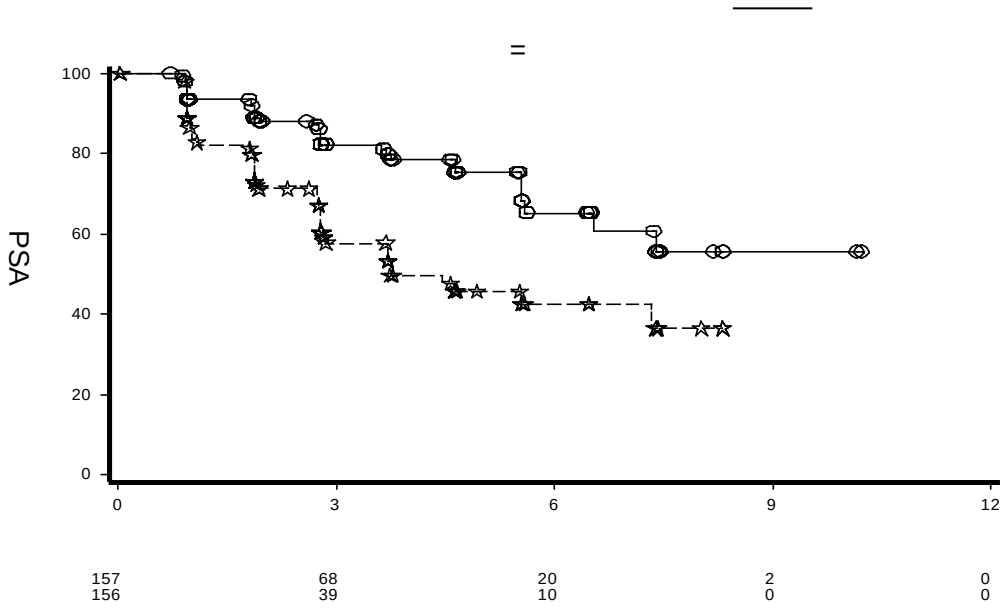
	AA		AA	
[a]	(N=119)	(N=119)	(N=157)	(N=156)
	119	119	157	156
	30 (25.2)	43 (36.1)	34 (21.7)	60 (38.5)
	89 (74.8)	76 (63.9)	123 (78.3)	96 (61.5)
p [b]		0.0173		<0.0001
(95% CI)[c]		0.563 (0.349; 0.909)		0.418 (0.271; 0.646)

[a] Kaplan-Meier

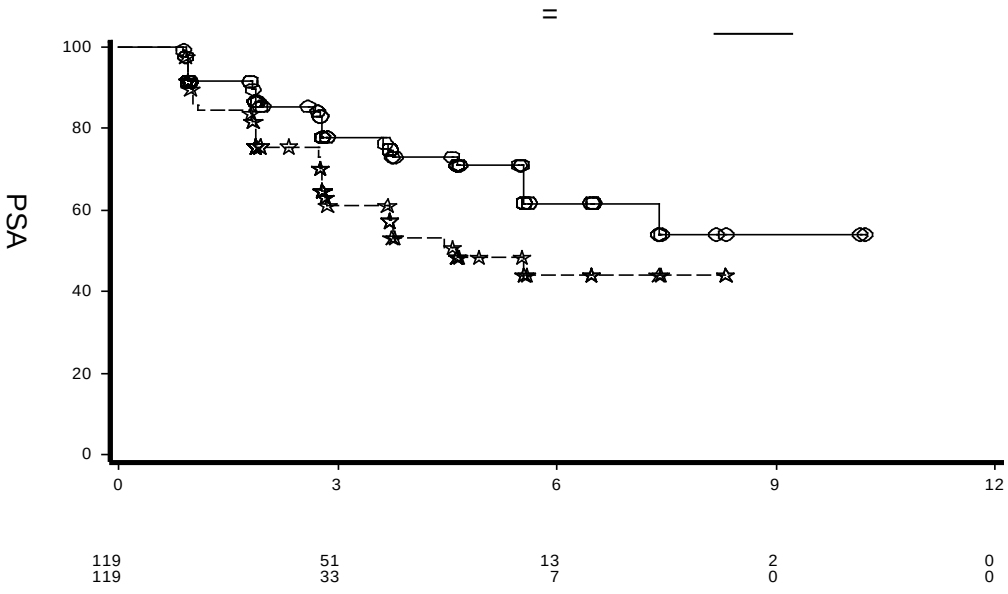
[b] p ( ) ECOG

[c] <1

7 ABI-PRO-3002 PSA Kaplan-Meier (
)



8: ABI-PRO-3002 PSA Kaplan-Meier (
)



31%

PSA 67% p<0.0001

PSA 67% 37%

p<0.0001 CR+PR

23% 5%
4.8 p=0.0369

32% 0% p=0.0052

•

17% 3 4
21% 4% 7%
3% 4% 3% 5%

ABI-PRO-3002 mCRPC
-
III COU-AA-302

ABI-PRO-3001

III
1 1 2:1 1000 mg 4 x 250 mg
1 4 1 5 mg
28

214 ITT
143 71
PSA [PSAWG]
RECIST 1.1
[BPI-SF]

PSA

PSA TTPP
PSA PSAWG
PSA FACT-P
BPI-SF
BFI

68 PSA

95.1% 94.4%

72.7% 66.2% 61.7%

54.7% GnRHa

32.3 16.9

9 5

16.0 4

16

PSA 49%

HR=0.506 p=0.0001 ECOG 2

TTPP

14 PSAWG PSA

ABI-PRO-3001 ITT

	AA (N=143)	(N=71)
	143	71
PSA	109(76.2%)	52(73.2%)
	34(23.8%)	19(26.8%)
PSA ( )[a]		
25 (95% CI)	85.00(83.00, 112.00)	29.00(29.00, 30.00)
(95% CI)	169.00(141.00, 197.00)	84.00(31.00, 113.00)
75 (95% CI)	281.00(252.00, 337.00)	141.00(113.00, 366.00)
	(1.0+, 533.0+)	(22.0+, 533.0+)
3 (95% CI)	0.699(0.614, 0.769)	0.454(0.329, 0.572)
6 (95% CI)	0.446(0.360, 0.528)	0.169(0.082, 0.283)
12 (95%CI)	0.153(0.092, 0.230)	0.145(0.064, 0.257)
p [b]	0.0001	
(95% CI)[c]	0.506(0.356, 0.719)	

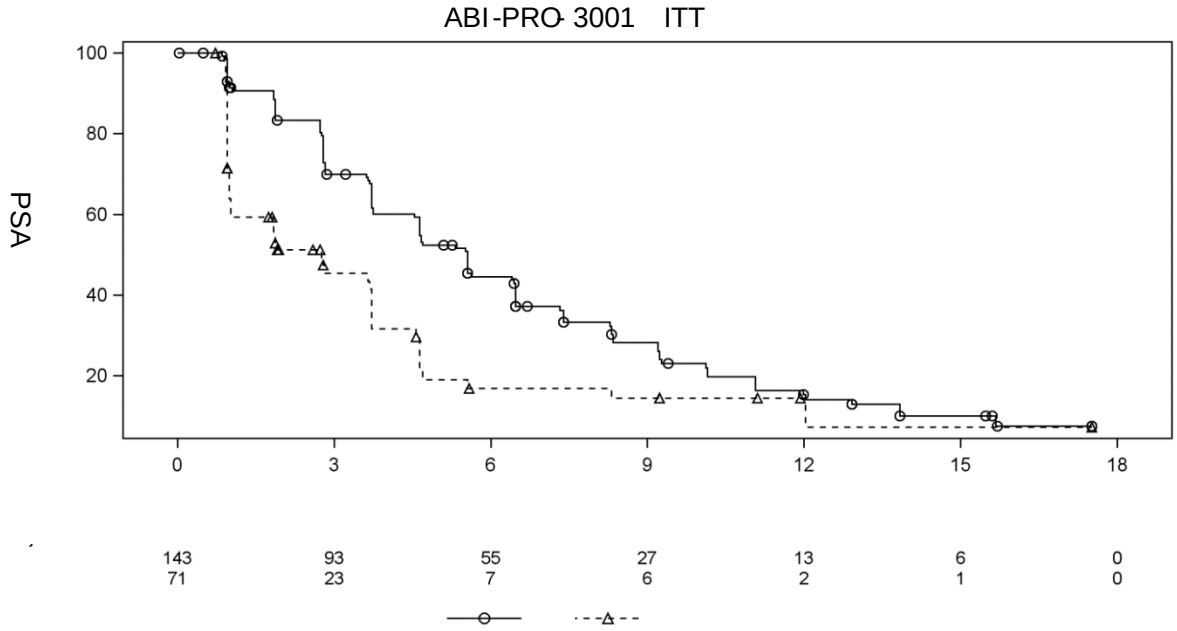
+ = NE=

[a] PSAWG PSA PSA
PSA PSA
PSA

[b] p

[c] <1 AA

9: PSAWG PSA Kaplan-Meier



mCRPC

TTPP PSA OS

HR=0.604 [0.356, 1.026] HR COU-AA-301 HR=0.646 [0.543, 0.768] PSA 49.7% 14.1% =3.525 p<0.0001 37.1% 50.7%

50% HR=0.496 p=0.0014 4 23%

32.2% 3 4 28.2% 14.0% 19.7% 7.0% 9.9% 6.3% 12.7%

ABI-PRO-3001 mCRPC -

III COU-AA-301

212082PCR3011

212082PCR3011 137 69 68

80

GnRHa

28 31 22 24

rPFS 18 26.1 38

55.9

66 HR = 0.341 95 CI 0.193

0.605 rPFS rPFS 18.4

OS 29

14 20.3 15 22.1 OS 0.862 95 CI

0.415 1.788

HR = 0.433 95% CI:

0.146, 1.279

HR = 0.349 95% CI: 0.173, 0.707

HR = 0.680 95% CI: 0.416, 1.111

12.9

PSA HR = 0.261 95% CI: 0.157, 0.433 PSA

9.2

94.2 98.5%

•

37.7 20.6%

ALT 30.4 26.5 AST 27.5 22.1 24.6

20.6 24.6 14.7 10.1 20.6 3 4

60.9 50.0

23.2 32.4 13.0 16.2

8.7

1.5

212082PCR3011

212082PCR3011

mHSPC -

17.- /C17,20- CYP17

CYP17 1 17.-
17.- 2 C17,20
CYP17

GnRHa

PSA

13 26 13 39
AUC

- P J N J AUC 26
  39
  AUC 2
  : Ames

13 26 39 •
mg/kg/ • P J N J/ /

AUC 0.6
30mg/kg/
4

30mg/kg/

16 7

30mg/kg/

300mg/kg/

4

30mg/kg/ 1000mg/ 0.3

/ 6~17 10

30 100mg/kg/ AUC 0.03 0.1 0.3

- P J N J /
- P J N J

100mg/kg/

- P J N J

5 15

50 mg/kg/ 15 50 150mg/kg/

0.8

Tg.rasH2 6

mCRPC

>99%

<0.2 ng/ml

mCRPC 2

AUC 1000 mg 2

mCRPC 1000 mg 1 C_{max} AUC – SD

226–178 ng/ml 993–639ng Âh/ml 250 1000 mg

1000mg 2000mg AUC

8%

7%

300 C_{max} AUC_{0-} 7 5

57% 825 17 10

2 1

.-1 >99%

– SD 19669–13358 L

P- P-

^{14}C-

CYP

N-

43% CYP3A4 SULT2A1 N-

SULT2A1

mCRPC – SD 12–5

^{14}C- 88% 5%

55% 22%

n = 8 n = 8 Child-Pugh A B

8

1000 mg

1.1 3.6

18 19

8 Child-PughC 8

AUC 7

2

n=8 n=8

1

1000 mg 96

1000 mg

15~30℃

120 /

24

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19

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