

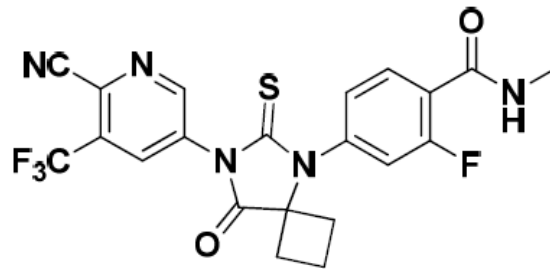
2019 09 05
2020 08 12
2020 11 09
2021 05 06
2022 08 15
2023 04 20

® ERLEADA®

Apalutamide Tablets

Apata'an Pian

4-[7- 6- -5- -3- -8- -6- -5,7- [3.4] -5-]-
2- -N-



C₂₁H₁₅F₄N₅O₂S

477.43

AS

HPMC-

E172)

E172

“AR 60”

- mHSPC
- NM-CRPC

60 mg

240 mg 4 60 mg/

GnRH α

1

≥ 3

≤ 1

180 mg 120 mg

1. 120 mL

2. 15

3. 15

4.

5. 60 mL

60 mL

1

[]

Child-Pugh A B

TITAN SPARTAN 10%
2%

mHSPC

TITAN	1	1	240 mg	TITAN	mHSPC
			GnRHa		
			20	0	34
18	0.1	34			
			10	1.9%	
	n=3		n=2	n=1	n=1
n=1		n=1		n=1	8%
		2%	23%		
	>1%			20%	20%
1	TITAN		10		2
2		15		5	
	1	TITAN			mHSPC

		N=524		N=527	
		%	3-4 %	%	3-4 %
1		17	0.4	15	0.9
2		28	6	9	0.6
		11	0.2	4.6	0.2
		23	0	16	0
		18	8	16	9

1 CTCAE
2

2% 10% 9%
6% 3.1% 1.9% 3.2% 0.6%
3.6% 0.6%

2 TITAN mHSPC 15
5

		N=524		N=527	
		%	3-4 %	%	3-4 %
		27	0.4	19	0.6
	1	17	2.5	12	2.3

1

NM-CRPC

SPARTAN	2	1				NM-
CRPC			240 mg			SPARTAN
			GnRHα			
			33		0.1	75
	11		0.1	37		
			24	3%		2
	n=7		n=3		n=2	n=3 11%
				3.2%	33%	
				1%		

		25%	23%	2%	3.4%
		3.8%			
3	SPARTAN	≥10%		≥2%	
4		≥15%		5%	
		3		SPARTAN	
		N=803		N=398	
		3-4		3-4	
		%	%	%	%
a,b		39	1.4	28	0.3
b		16	0	8	0
c		25	5.2	6	0.3
d		12	0.1	9	0
e		11	0	9	0
b		16	1.7	9	0.8
f		12	2.7	7	0.8
b		16	1.1	6	0.3
		25	14	20	12
		14	0	9	0
		20	1.1	15	0.5
		18	0	16	0
a					
b	CTCAE	3			
c					
d					
e					
f					

≥2%

8% 2% 6% 1.5% 2.2%

1%

4 SPARTAN NM-CRPC %

5%

	N=803		N=398	
	%	3-4 %	%	3-4 %
_____	70	0.4	64	0.5
	47	0.3	29	0
	41	1.8	21	1.6

a	76	0.1	46	0
a	70	2	59	1.0
a	67	1.6	49	0.8
	32	1.9	22	0.5

a

SPARTAN TITAN

26% 8%

6% 0.5% 3 30% [BSA]

83 78%

19%

78

14% 28%

59%

SPARTAN TITAN

4

TSH

8% 1.5%

7% TSH 3 4 25%

4.9%

- /

1
2

		SPARTAN				TITAN			
4%	3%								
			4	2			SPARTAN	TITAN	
6	0.5%			2	0.2%				
	SPARTAN					32.9		11.5	
			4%	1%			TITAN		
	1.5%			1.5%					
SPARTAN	TITAN		2	0.2%					
		SPARTAN	TITAN			6			
							SPARTAN		12%
				7%					

2.7% 0.8% 3-4
314 20 953 SPARTAN
TITAN 9%
6% 3-4
1.5% 56 2 111 TITAN

SPARTAN
16 9

SPARTAN TITAN 5 0.4% 1
0.1% 159
650

SCAR
SCAR([DRESS]
- / [SJS/TEN] SCAR
SCAR

CYP2C9
INR
QT
QT
QT
QT
45 CRPC
240 mg
12.4 ms
90% CI
QTc
16.0 ms
-QT
QTcF
QT

3

/

1327 19% 65 41%

65 74 40% 75

n=1073 65 39% 65-74

41% 75 49% 3-4

65 8% 65-74

10% 75 19%

CYP2C8 CYP3A4

CYP2C8 CYP3A4

N-

CYP2C8 CYP3A4

CYP3A4 CYP2C9 CYP2C19 UGT

CYP3A4 CYP2C19

CYP2C9

CYP3A4 CYP2C19 CYP2C9

UDP-

UGT

UGT

P-gp BCRP OATP1B1

P-

P-gp

BCRP

1B1 OATP1B1

P-gp

BCRP/OATP1B1

P-gp

BCRP OATP1B1

P-gp BCRP

OATP1B1

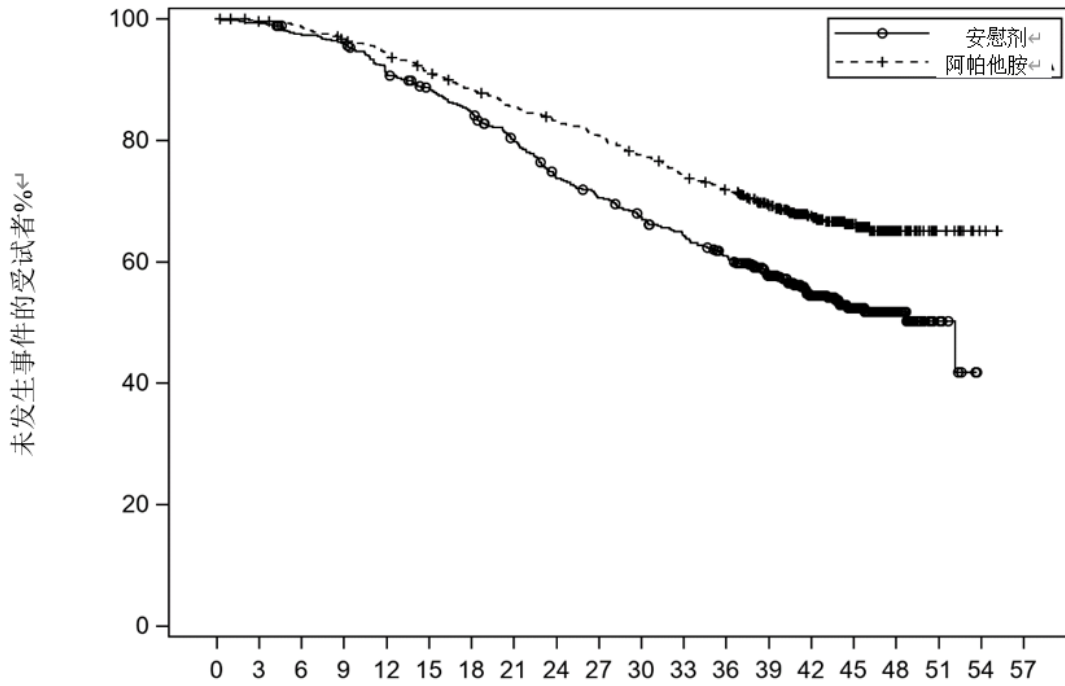
TITAN									
				mHSPC					
	TITAN					1052		mHSPC	
	1 1	240 mg		N=525				N=527	
	TITAN						GnRHα		
				Gleason					
				mHSPC					
		1		4				1	
								68	43-94
	23%	75			68%		22%	2%	63%
		37%				16%			
				Gleason	8	67%	68%		
							1		
				ECOG PS	0	1			
				OS				rPFS	
		2						2	/
								OS	rPFS
	OS								OS
	405			44		39%			
	TITAN	5	1	2					

5 TITAN

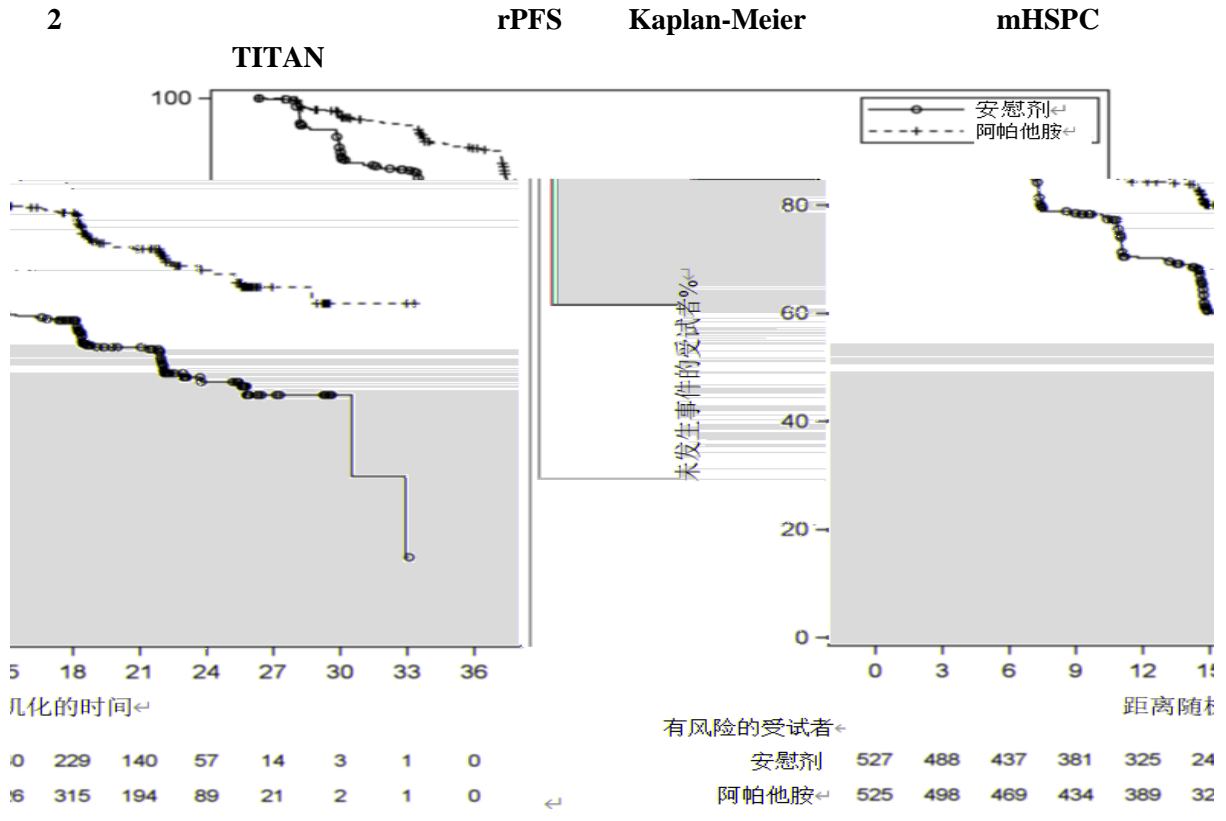
		(N=525)	(N=527)
a	(%)	83 (16%)	117 (22%)
	95% CI ^b	NE (NE, NE)	NE (NE, NE)
	95% CI ^c	0.67 (0.51, 0.89)	
p ^d		0.0053	
	(%)	170 (32%)	235 (45%)
	(95% CI) ^b	NE (NE, NE)	52 (42, NE)
P ^c	(95% CI) ^c	0.651 (0.534, 0.793)	
		<0.0001	
	(%)	134 (26%)	231 (44%)
	95% CI ^b	NE (NE, NE)	22.1 (18, 33)
	95% CI ^c	0.48 (0.39, 0.60)	
p ^d		<0.0001	
a		50%	=0.01
b	NE=		
c		<1	
d	Gleason	7 vs. 7	NA/EU vs.
		p	
		rPFS	vs
		Gleason	7 vs.>7
		OS	Gleason
	7 >7		
			HR=0.39 95%CI=0.27 0.56
			p<0.0001

1

OS Kaplan-Meier mHSPC
TITAN



Time (Weeks)	安慰剂	阿帕他胺
0	524	510
3	510	474
6	474	458
9	436	408
12	374	357
15	330	332
18	301	348
21	281	302
24	242	281
27	227	248
30	139	248
33	52	102
36	15	12
39	3	10
42	0	10
45		10
48		10
51		10
54		10



SPARTAN

NM-CRPC

SPARTAN	ARN-509-003	2	1		
1207	NM-CRPC	2	1	240 mg	
N=806		N=401	SPARTAN		
	GnRH α				
PSA	PSADT				
		PSADT \leq 10		CT	
MRI			BICR		
PSA				BICR	
				74	
48-97	26%	\geq 80	66%	12%	6%
	77%			Gleason	\geq 7
78%		15%	2	73%	
	69%		10%		
	ECOG PS		0	1	

			MFS		BICR
				TTM	PFS
		OS			
				MFS	OS
TTM	PFS		MFS	MFS	TTM
32		OS		3	4
					6
SPARTAN					

6 SPARTAN

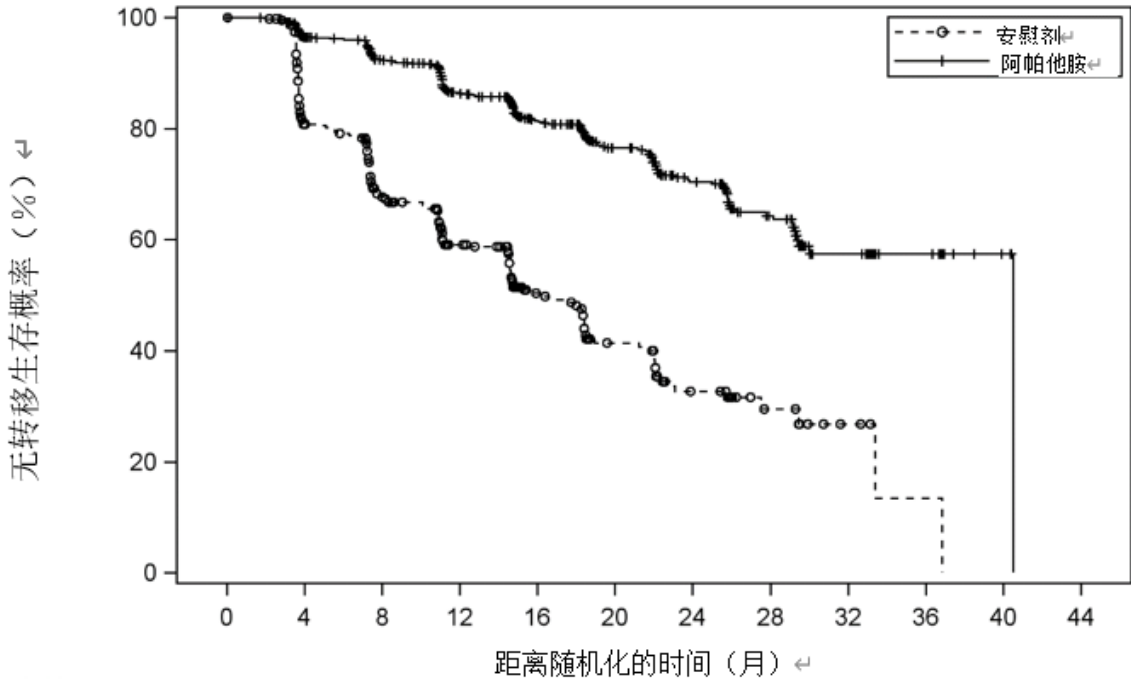
	N=806	N=401
a,b,c		
%	184 (23%)	194 (48%)
95 CI ^d	40.5 (NE, NE)	16.2 (15, 18)
95% CI	0.28 (0.23, 0.35)	
p ^a	<0.0001	
a,b		
%	175 (22%)	191 (48%)
95 CI ^d	40.5 (NE, NE)	16.6 (15, 18)
95% CI	0.27 (0.22, 0.34)	
p ^a	<0.0001	
a,b		
%	200 (25%)	204 (51%)
95 CI ^d	40.5 (NE, NE)	14.7 (14, 18)
95% CI	0.29 (0.24, 0.36)	
p ^a	<0.0001	
%	274 (34%)	154 (38%)
95 CI ^d	73.9 (61, NE)	59.9 (53, NE)
95% CI	0.78 (0.64, 0.96)	
p ^a	0.0161	

a PSA
 b BICR
 c 2.4%
 d NE=

MFS PSADT 6 6
 NO N1

0.81 p=0.0002] [HR=0.63 95% CI=0.49

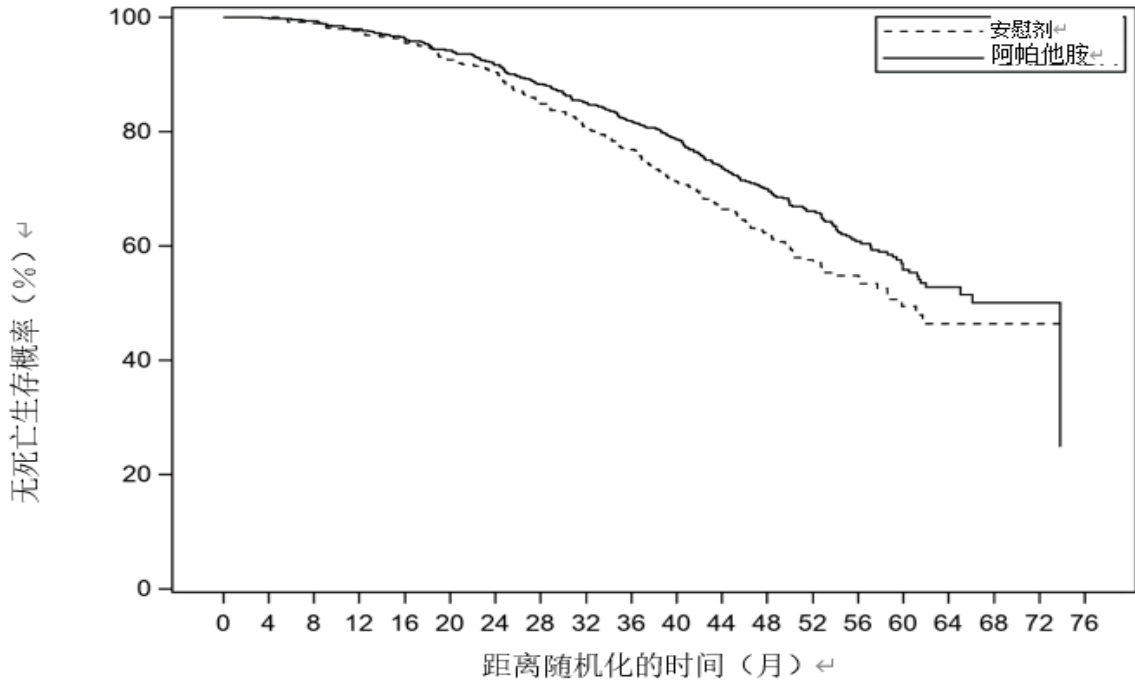
3 SPARTAN MFS Kaplan-Meier



有风险的受试者

安慰剂	401	291	220	153	91	58	34	13	5	1	0	0
阿帕他胺	806	713	652	514	398	282	180	96	36	16	3	0

4: SPARTAN nmCRPC OS Kaplan-Meier



有风险的受试者

安慰剂	401	392	385	373	357	339	328	306	286	263	240	204	155	114	82	38	21	6	2	0
阿帕他胺	806	791	774	758	739	717	691	658	625	593	558	499	374	269	181	100	47	19	4	0

		AR		AR	
AR	DNA		AR		N-
	AR				
	Ames				
		26		39	
	≥ 25 mg/kg/	AUC	1.4		≥ 2.5 mg/kg/
AUC		0.9			/
	/				
		≥ 25 mg/kg/	AUC		0.8
4					
			150 mg/kg/		AUC
	5.7	4	/		
8					
		-			6-20
25	50	100 mg/kg/			25 mg/kg/
/		50 mg/kg/	/		100 mg/kg/
		AUC		2	4
				6	
	2			5	15
	5 mg/kg/	AUC			50 mg/kg/
			0.2		
	rasH2				
		6			30 mg/kg/

[SD] 30 480 mg
 0.125 2 C_{max}
 AUC 4
 5 C_{max} 6.0 µg/mL 1.7 AUC 100 µg.h/mL 32
 1.63 CL/F
 30 480 mg
 N- C_{max} 5.9 µg/mL
 1.0 AUC 124 µg.h/mL 23 N-
 1.27 N- / AUC 1.3
 N-
 100% t_{max} 2 1 5
 4 60 mg / 4
 60 mg / C_{max} AUC
 500 600 250
 150 C_{max} AUC
 t_{max} 2
 276 L
 N- 96% 95%
 CL/F 1.3 L/h 2.0 L/h
 3
 CYP2C8 CYP3A4
 N- CYP2C8 CYP3A4
 58% 13% 40% 37%

240 mg AUC 45% N-
 44%

70 65% 1.2%
 2.7% N- 24% 1.5% 2% N-

18-94 []
 eGFR 30-89 mL/min/1.73 m² [MDRD]
 Child-Pugh A Child-Pugh B N-
 eGFR 29 mL/min/1.73 m² MDRD
 Child-Pugh C

CYP2C8
 240 mg CYP2C8 C_{max}
 21% AUC 68% C_{max} 32% AUC
 44% N-
 C_{max} 19% AUC 23%

CYP3A4
 240 mg CYP3A4 C_{max}
 22% AUC CYP3A4
 AUC 24% C_{max} C_{max} 38% AUC
 51% C_{max} 23% AUC 28%

CYP3A4/CYP2C8
 CYP3A4 CYP2C8
 C_{max} 25% AUC 34% C_{max} 15% AUC 19%

pH
 H₂-

OATP1B3 N- P-gp BCRP OATP1B1
P-gp

CYP

CYP2B6 CYP2C8 N- CYP3A4 CYP2B6
CYP2C9 CYP2C19 CYP3A4
N- CYP1A2 CYP2D6
CYP CYP3A4 AUC
92% CYP2C19 AUC 85% S- CYP2C9 AUC
46% CYP2C8

P-gp BCRP OATP1B1

P-gp AUC 30%
BCRP/OATP1B1 AUC 41% C_{max}

UGT

UGT UGT

OCT2 OAT1 OAT3 MATE

N- 2 OCT2
3 OAT3 MATE 1
OAT3

30°C

160 ml HDPE PP
120 / /

24

JX20190110

H20190050

HJ20200029

Janssen-Cilag International NV