

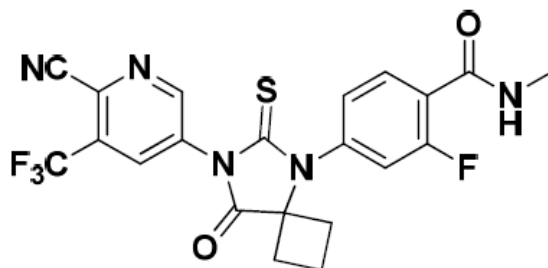
2019 09 05
2020 08 12
2020 10 30
2021 05 28

® ERLEADA®

Apalutamide Tablets

Apata'an Pian

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



$C_{21}H_{15}F_4N_5O_2S$

477.43

HPMC-

AS

E172)

E172

“AR 60”

●

mHSPC

●

NM-CRPC

60 mg

240 mg 4 60 mg/

GnRHa

1

≥ 3

180 mg 120 mg

≤ 1

1. 120 mL

2. 15

3. 15

4.

5. 60 mL

60 mL

1

[]

Child-Pugh A B

		TITAN		SPARTAN		10%	
		2%					
<hr/>							
mHSPC							
TITAN		1	1			mHSPC	
		240 mg				TITAN	
		GnRHα					
		20		0		34	
18		0.1		34			
		10		2%			
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			
<hr/>							
				N=524		N=527	
				3-4		3-4	
				%		%	
<hr/>							

1	17	0.4	15	0.9
2	28	6	9	0.6
	11	<1	5	<1
	23	0	16	0
	18	8	16	9
1	CTCAE		3	2

	2%	10%		9%
6%	3%	2%	3%	1%
4%	1%			
2 TITAN mHSPC		15		
5				

	N=524		N=527	
	%	3-4 %	%	3-4 %
_____	27	0.4	19	0.6
_____ 1	17	3	12	2

NM-CRPC				
SPARTAN	2	1		NM-
CRPC		240 mg		SPARTAN
		GnRHα		
		33	0.1	75

	25%	23%		2%	3%
	4%				
3	SPARTAN		≥10%		≥2%
4		≥15%		5%	
	3	SPARTAN			

	N=803		N=398	
	%	3-4 %	%	3-4 %
a,b	39	1	28	0.3
b	16	0	8	0
c	25	5	6	0.3
d	12	0.1	9	0
e	11	0	9	0
b	16	2	9	0.8
f	12	3	7	0.8
b	16	1	6	0.3
	25	14	20	12
	14	0	9	0
	20	1	15	0.5
	18	0	16	0

a
b
c

d
e

f

CTCAE

3

≥2%

8% 2% 6% 2% 2.2%

1%

4 SPARTAN NM-CRPC ≥15%

5%

	N=803		N=398	
	%	3-4 %	%	3-4 %
	70	0.4	64	0.5
	47	0.3	29	0
	41	2	21	2
a	76	0.1	46	0
a	70	2	59	1
	67	2	49	0.8
a	32	2	22	0.5

SPARTAN TITAN

26% 8%

6% 0.5% 3 30% [BSA]

83 78%

19%

78

14% 28%

59%

SPARTAN TITAN 4

TSH

8% 2%

7% TSH 3 4 25%

5%

- /

1
2

		SPARTAN				TITAN			
	4%	3%							
			4	2			SPARTAN	TTTAN	
	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%							
			3%	1%	3-4				

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

SPARTAN
16 9

	SPARTAN	TITAN	5		0.4%	1
	0.1%					159
650						

CYP2C9
INR
QT
QT
QT
QT

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

3

/

65 74 40% 1327 19% 65 41%
 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 GnRH α

		Gleason		mHSPC			
		1	4	1	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		TITAN	OS	rPFS	
	2				5	1	
5	TITAN						

		(N=525)	(N=527)
a	(%)	83 (16%)	117 (22%)
	95% CI ^b	NE (NE, NE)	NE (NE, NE)
p ^d	95% CI ^c	0.67 (0.51, 0.89)	0.0053
	(%)	134 (26%)	231 (44%)
	95% CI ^b	NE (NE, NE)	22.1 (18, 33)
p ^d	95% CI ^c	0.48 (0.39, 0.60)	<0.0001

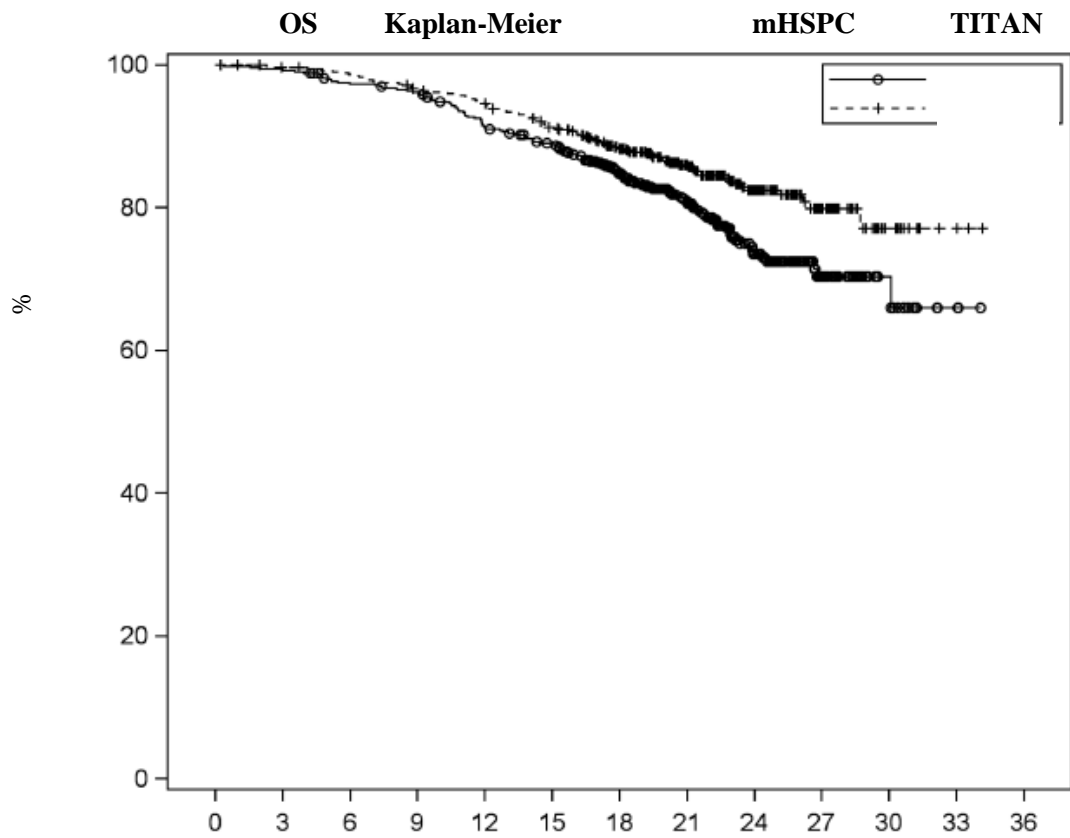
a 50% =0.01
b NE=
c
d Gleason 7 vs. 7 <1 NA/EU vs. p

rPFS vs
 Gleason 7 vs.>7
 OS Gleason

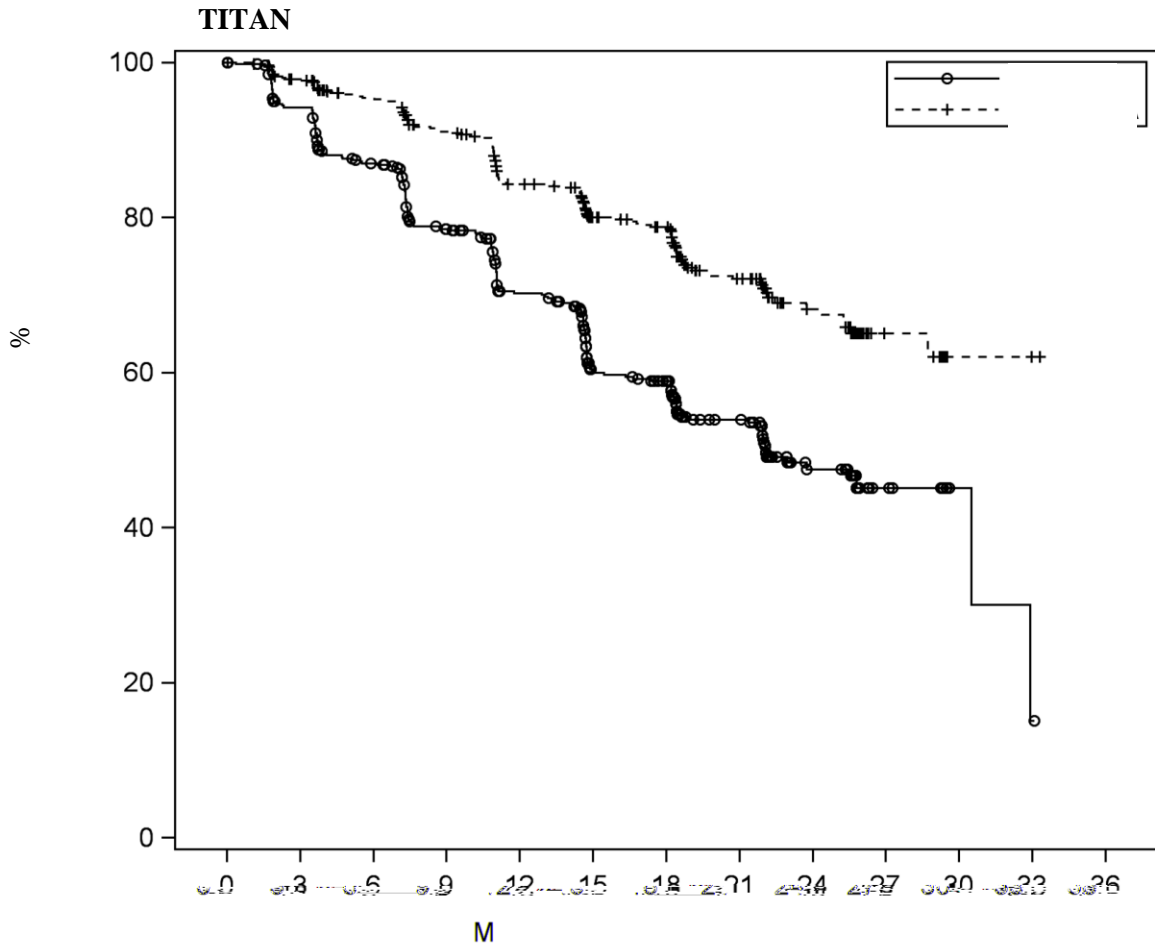
HR=0.39 95%CI=0.27 0.56

p<0.0001

1



527	524	509	502	473	456	387	263	142	59	16	3	0
525	519	513	500	490	467	410	289	165	60	14	3	0



Si													
P	527	488	437	381	325	240	229	140	57	14	3	1	0
EF	525	498	469	434	389	326	315	194	89	21	2	1	0

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 ≥ 7
78% 15% 2 73%
69% 10%
ECOG PS 0 1
MFS BICR
TTM PFS
OS
MFS OS
TTM PFS
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=

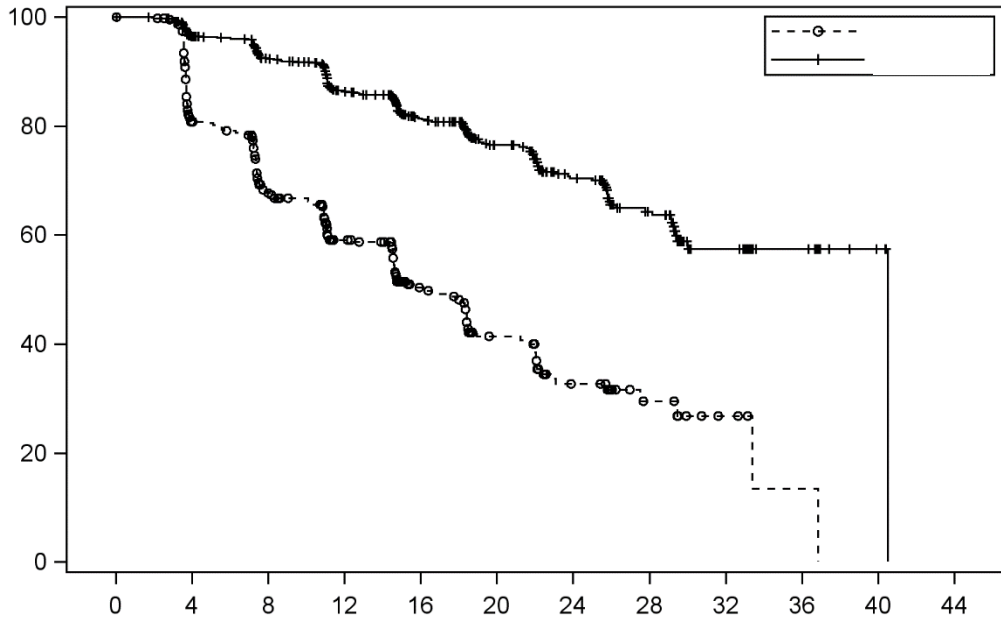
MFS

PSADT 6 6
N0 N1

0.81 p=0.0002]

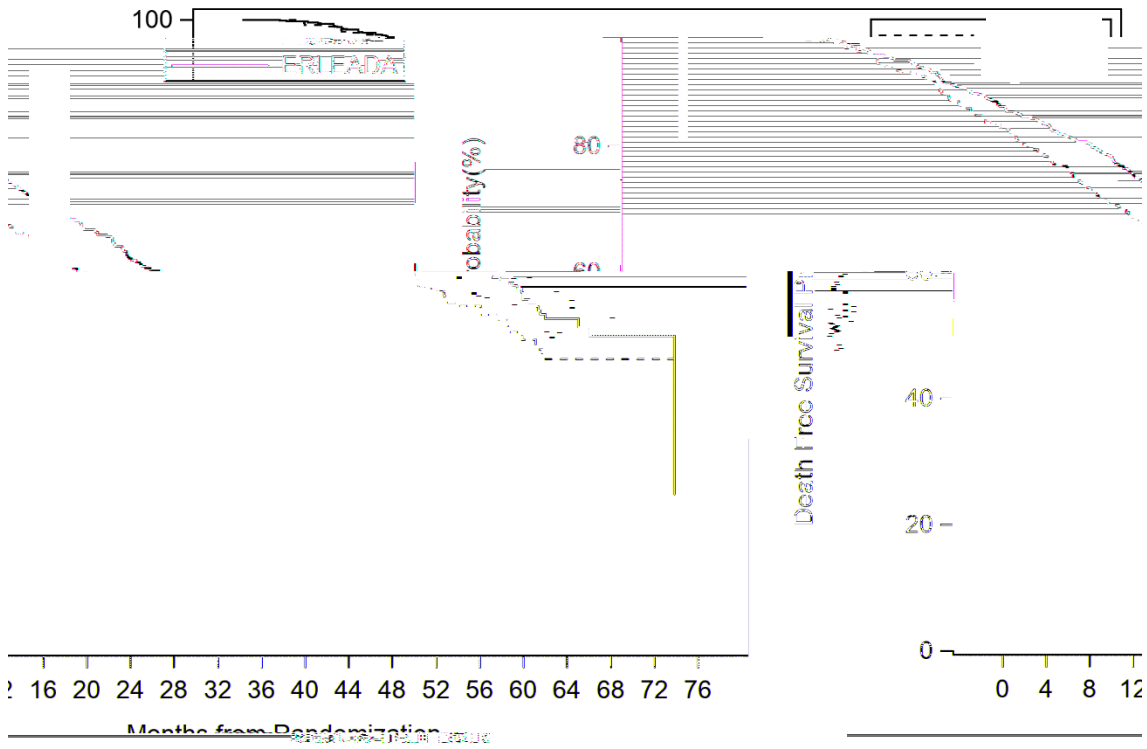
[HR=0.63 95% CI=0.49

3 SPARTAN MFS Kaplan-Meier



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

4: SPARTAN nmCRPC OS Kaplan-Meier



57	339	328	306	286	263	240	204	155	114	82	38	21	6	2	0	Placebo
39	717	691	658	625	593	558	499	374	269	181	100	47	19	4	0	FRIEADA

		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/		AUC	2.3	
					50
mg/kg/		AUC		4.4	100
mg/kg/		AUC		5.6	
		CByB6F1/Tg rasH2			3 10 30 mg/kg/
AUC		1.2 26			
				[SD]	30 480 mg
	0.125 2			C _{max}	
AUC					4

5 C_{max} 6.0 $\mu\text{g/mL}$ 1.7 AUC 100 $\mu\text{g.h/mL}$ 32
1.63 CL/F
30 480 mg

1.0 AUC 124 $\mu\text{g.h/mL}$ 23 C_{max} 5.9 $\mu\text{g/mL}$
1.27 N- / AUC 1.3
N-

100% t_{max} 2 1 5

4 60 mg / 4
60 mg / C_{max} AUC

150 500 600 250
 t_{max} 2 C_{max} AUC

276 L
N- 96% 95%

CL/F 1.3 L/h 2.0 L/h
3

N- CYP2C8 CYP3A4
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-
 N- P-gp BCRP OATP1B1
 OATP1B3 P-gp
 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

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