

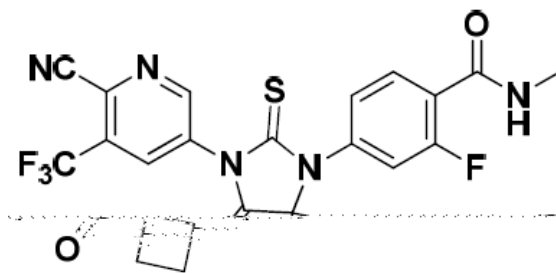
2019 09 05
2020 08 12
2020 11 09
2021 05 06

® 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

≤ 1

Child-Pugh A B

TITAN SPARTAN 10%
2%

mHSPC

TITAN	1	1	240 mg GnRHa	TITAN	mHSPC
18	0.1	34	20	0	34
n=3		n=2	10	2%	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	<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	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		
11	0.1	37			
	24	3%	2		
n=7	n=3		n=2	n=3	11%
			3%	33%	
		1%			

	25%	23%		2%	3%
	4%				
3	SPARTAN		≥10%		≥2%
4		≥15%		5%	
		3	SPARTAN		
				N=803	N=398

		N=803		N=398	
		%	3-4 %	%	3-4 %
4	SPARTAN NM-CRPC	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
	a	67	2	49	0.8
		32	2	22	0.5

a

SPARTAN TITAN

26% 8%
 6% 0.5% 3 30% [BSA]
 83 78%
 78 19%
 14% 28%
 59%

SPARTAN TITAN

4

TSH
 8% 2% 25%
 7% TSH 3 4
 5%

- /

1
2

SPARTAN

4% 3%

TITAN

4 2

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

7

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

		SPARTAN
16	9	

	SPARTAN	TITAN	5		0.4%	1
						159
650	0.1%					

			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

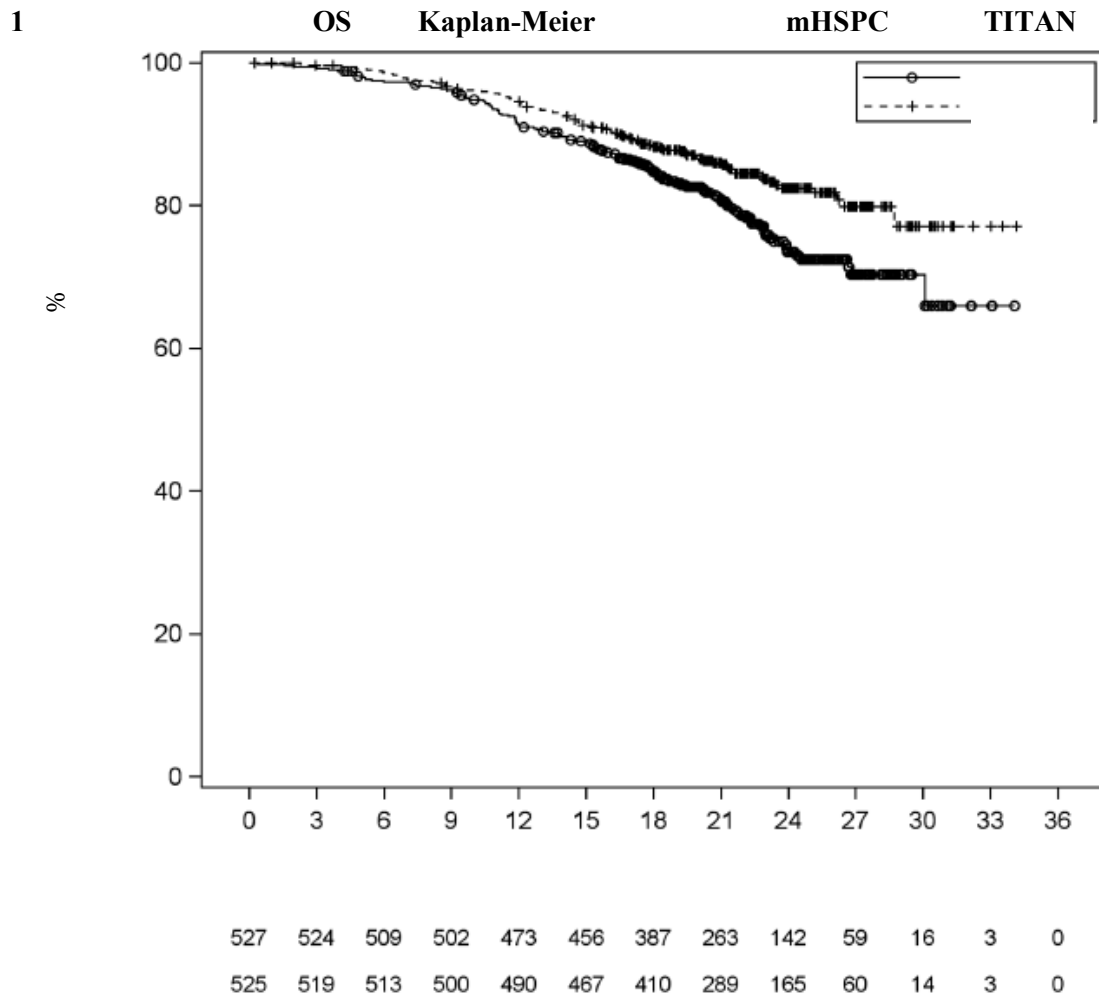
TITAN 1052 mHSPC
1 1 240 mg N=525 N=527
TITAN GnRH α

		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)			
^d	95% CI ^c	0.67 (0.51, 0.89)		0.0053			
^d	(%)	134 (26%)		231 (44%)			
	95% CI ^b	NE (NE, NE)		22.1 (18, 33)			
^d	95% CI ^c	0.48 (0.39, 0.60)		<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

HR=0.39 95%CI=0.27 0.56

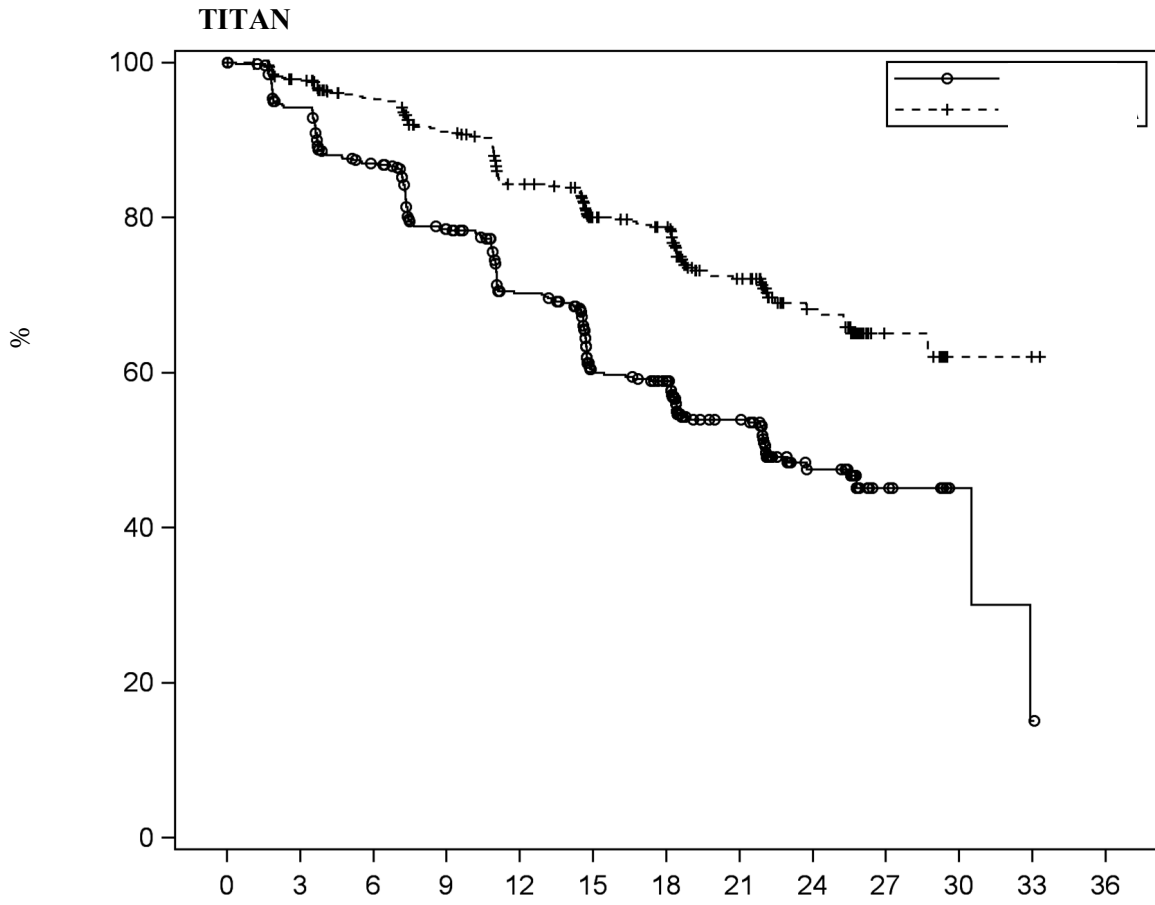
p<0.0001



2

rPFS Kaplan-Meier

mHSPC



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

SPARTAN ARN-509-003 2 1

1207 NM-CRPC 2 1 240 mg

N=806 N=401 SPARTAN

GnRHα

PSA PSADT

PSADT ≤ 10 CT

MRI BICR

PSA BICR

74

48-97 26% ≥ 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=

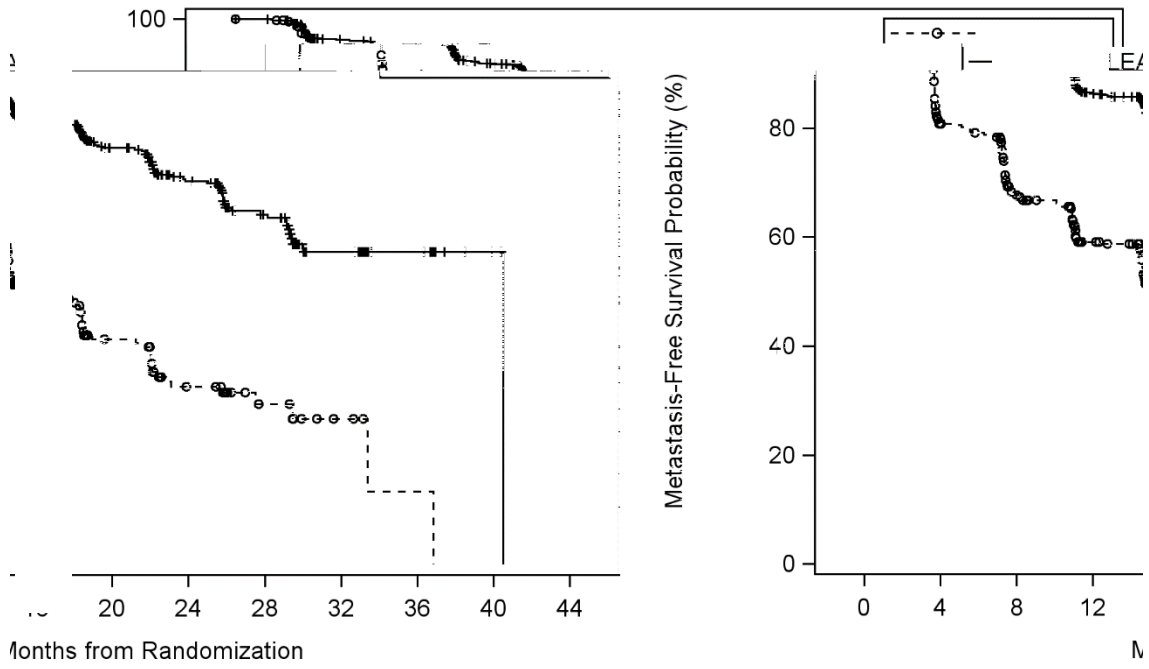
MFS

PSADT 6 6
N0 N1

0.81 p=0.0002]

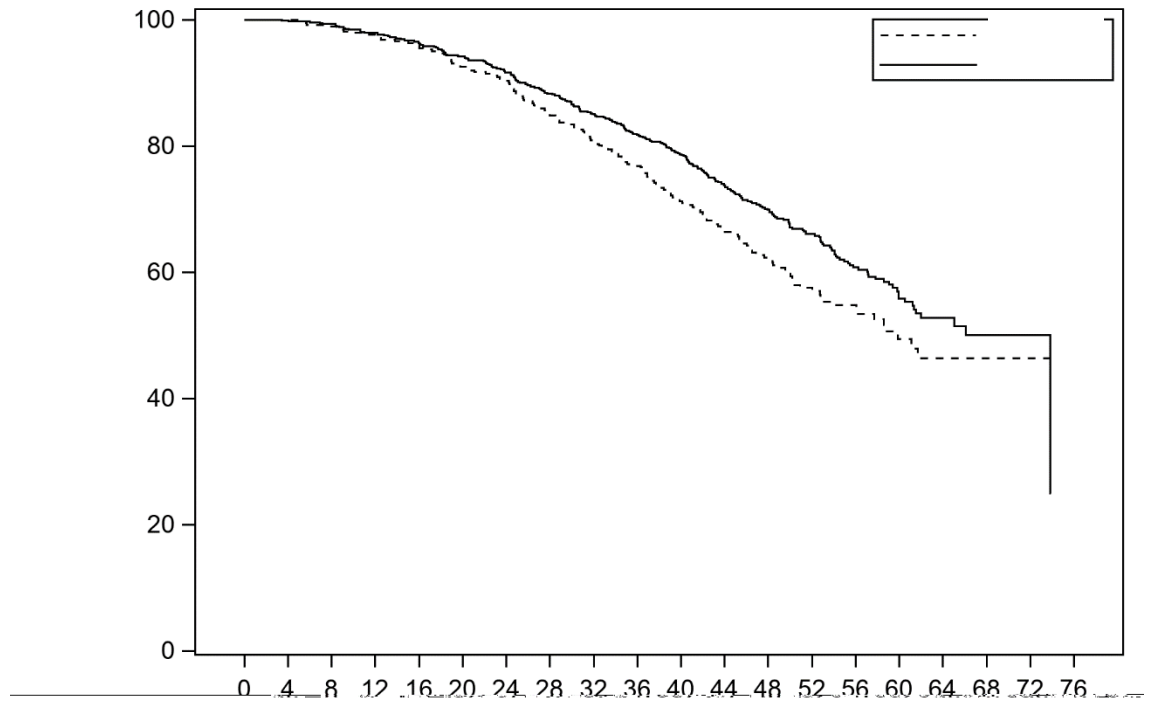
[HR=0.63 95% CI=0.49

3 SPARTAN MFS Kaplan-Meier



Subjects at risk	0	4	8	12	16
Placebo	401	291	220	153	
ERLEADA	806	713	652	514	

4: SPARTAN nmCRPC OS Kaplan-Meier



Subjects at risk	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76
Placebo	401	392	385	373	357	339	328	306	286	263	240	204	155	114	82	38	21	6	2	0
ERLEADA	806	791	774	758	739	717	691	658	625	593	558	499	374	269	181	100	47	19	4	

		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

CYP

			N-		CYP3A4	CYP2B6	
	CYP2B6	CYP2C8			CYP2C9	CYP2C19	CYP3A4
			N-			CYP1A2	CYP2D6
			CYP			CYP3A4	AUC
92%		CYP2C19	AUC	85%	S-	CYP2C9	AUC
46%		CYP2C8					
<i>P-gp</i>	<i>BCRP</i>	<i>OATP1B1</i>					
						P-gp	AUC
							30%
		BCRP/OATP1B1	AUC	41%		C _{max}	

UGT

			UGT		UGT		
<i>OCT2</i>	<i>OAT1</i>	<i>OAT3</i>	<i>MATE</i>				
			N-			2	<i>OCT2</i>
	3	<i>OAT3</i>			<i>MATE</i>		1
		<i>OAT3</i>					

30°C

160 ml		HDPE		PP
120	/	/	/	
24				

JX20190110

H20190050

HJ20200029

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