

Supplemental Tables

Table S1. Baseline Characteristics of Men with an Event (CRPC population) Compared to the Overall Population.

	Overall Population			CRPC Population		
	Relugolix (N = 717)	Leuprolide (N = 357)	Total (N = 1074)	Relugolix (N = 88)	Leuprolide (N = 42)	Total (N = 1074)
Age category						
≤ 75 years	509 (71.0%)	254 (71.1%)	763 (71.0%)	60 (68.2%)	26 (61.9%)	86 (66.2%)
> 75 years	208 (29.0%)	103 (28.9%)	311 (29.0%)	28 (31.8%)	16 (38.1%)	44 (33.8%)
Age, years						
Median	71.0	71.0	71.0	72.0	71.5	72.0
Min, Max	48, 91	47, 97	47, 97	54, 91	57, 87	54, 91
Geographic region						
North America	208 (29.0%)	102 (28.6%)	310 (28.9%)	15 (17.0%)	12 (28.6%)	27 (20.8%)
South America	45 (6.3%)	24 (6.7%)	69 (6.4%)	8 (9.1%)	1 (2.4%)	9 (6.9%)
Europe	271 (37.8%)	135 (37.8%)	406 (37.8%)	33 (37.5%)	20 (47.6%)	53 (40.8%)
Asia	155 (21.6%)	86 (24.1%)	241 (22.4%)	26 (29.5%)	7 (16.7%)	33 (25.4%)
Rest of World	38 (5.3%)	10 (2.8%)	48 (4.5%)	6 (6.8%)	2 (4.8%)	8 (6.2%)
Disease stage at study entry						
Metastatic	290 (40.4%)	144 (40.3%)	434 (40.4%)	68 (77.3%)	32 (76.2%)	100 (76.9%)
Locally advanced	192 (26.8%)	96 (26.9%)	288 (26.8%)	12 (13.6%)	7 (16.7%)	19 (14.6%)
Localized	178 (24.8%)	83 (23.2%)	261 (24.3%)	8 (9.1%)	1 (2.4%)	9 (6.9%)
Not classifiable	57 (7.9%)	34 (9.5%)	91 (8.5%)	0	2 (4.8%)	2 (1.5%)
Location of metastasis at study entry						
Bone only	161 (22.5%)	70 (19.6%)	231 (21.5%)	29 (33.0%)	14 (33.3%)	43 (33.1%)
Lymph node only	40 (5.6%)	24 (6.7%)	64 (6.0%)	7 (8.0%)	0	7 (5.4%)
Visceral only	8 (1.1%)	3 (0.8%)	11 (1.0%)	0	0	0
Multiple	79 (11.0%)	47 (13.2%)	126 (11.7%)	31 (35.2%)	18 (42.9%)	49 (37.7%)
Clinical disease state presentation						
Evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent	324 (45.2%)	167 (46.8%)	491 (45.7%)	22 (25.0%)	10 (23.8%)	32 (24.6%)
Newly diagnosed androgen-sensitive metastatic disease	219 (30.5%)	109 (30.5%)	328 (30.5%)	56 (63.6%)	27 (64.3%)	83 (63.8%)
Advanced localized disease not suitable for primary surgical intervention with curative intent	174 (24.3%)	81 (22.7%)	255 (23.7%)	10 (11.4%)	5 (11.9%)	15 (11.5%)
ECOG status						
0	619 (86.3%)	307 (86.0%)	926 (86.2%)	69 (78.4%)	28 (66.7%)	97 (74.6%)
1	98 (13.7%)	49 (13.7%)	147 (13.7%)	19 (21.6%)	13 (31.0%)	32 (24.6%)
3	0	1 (0.3%)	1 (0.1%)	0	1 (2.4%)	1 (0.8%)

	Overall Population			CRPC Population		
	Relugolix (N = 717)	Leuprolide (N = 357)	Total (N = 1074)	Relugolix (N = 88)	Leuprolide (N = 42)	Total (N = 1074)
PSA (ng/mL)						
Median	13.4	12.5	13.3	105.9	84.1	103.4
Min, Max	0.2, 10270.0	0.2, 17574.0	0.2, 17574.0	2.8, 7389.0	6.7, 17574.0	2.8, 17574.0
PSA ≥20	289 (40.3%)	144 (40.3%)	433 (40.3%)	71 (80.7%)	34 (81.0)	105 (80.5%)
Testosterone (ng/dL)						
Mean (SD)	436.4 (161.5)	409.0 (152.3)	427.4 (159.0)	418.1 (146.7)	390.7 (139.3)	409.4 (144.4)
Smoking history						
Never smoker	304 (42.4%)	146 (40.9%)	450 (41.9%)	44 (50.0%)	18 (42.9%)	62 (47.7%)
Former smoker	339 (47.3%)	174 (48.7%)	513 (47.8%)	35 (39.8%)	17 (40.5%)	52 (40.0%)
Current smoker	74 (10.3%)	37 (10.4%)	111 (10.3%)	9 (10.2%)	7 (16.7%)	16 (12.3%)
Laboratory Markers						
LDH above ULN	43 (6.0%)	32 (9.0%)	75 (7.0%)	15 (17.0%)	14 (33.3%)	29 (22.3%)
ALP above ULN	74 (10.3%)	39 (10.9%)	113 (10.5%)	30 (34.1%)	11 (26.2%)	41 (31.5%)

Abbreviations: ALP = alkaline phosphatase; CRPC = castrations-resistant prostate cancer; LDH = lactate dehydrogenase; ULN = upper limit of normal.

Table S2. Adverse Events Summary for Men with an Event (CRPC population) Compared to the Overall Population.

	Overall Population				CRPC Population			
	Relugolix (N = 717)		Leuprolide (N = 357)		Relugolix (N = 88)		Leuprolide (N = 42)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Any adverse event	664 (92.6)	136 (19.0)	330 (92.4)	70 (19.6)	80 (90.9)	25 (28.4)	41 (97.6%)	16 (38.1%)
Serious adverse event	89 (12.4)	—	51 (14.3)	—	16 (18.2)	—	17 (40.5)	—
Fatal adverse event	10 (1.4)	—	11 (3.1)	—	4 (4.5)	—	9 (21.4)	—
Adverse events that occurred in >10% of patients in either group								
Hot flush	386 (53.8)	4 (0.6%)	182 (51.0)	0	42 (47.7)	2 (2.3)	20 (47.6)	0
Fatigue	158 (22.0)	4 (0.6)	68 (19.0)	0	24 (27.3)	1 (1.1)	12 (28.6)	0
Arthralgia	87 (12.1)	2 (0.3)	32 (9.0)	0	16 (18.2)	2 (2.3)	4 (9.5)	0
Constipation	91 (12.7)	0	36 (10.1)	0	18 (20.5)	0	5 (11.9)	0
Hypertension	61 (8.5)	15 (2.1)	37 (10.4)	2 (0.6)	6 (6.8)	2 (2.3)	1 (2.4)	0
Nausea	48 (6.7)	0	16 (4.5)	0	10 (11.4)	0	5 (11.9)	0
Diarrhea	82 (11.4)	0	23 (6.4)	0	4 (4.5)	0	2 (4.8)	0
Back pain	61 (8.5)	3 (0.4)	35 (9.8)	3 (0.8)	8 (9.1)	1 (1.1)	4 (9.5)	1 (2.4)

Abbreviations: MACE, major adverse cardiovascular event; SMQ, standardised MedDRA query.

^aSearch criteria included Myocardial Infarction SMQ (broad), Central Nervous System Hemorrhages and Cerebrovascular Conditions SMQ (broad), and deaths due to all causes.

^bNumber of patients without a history of MACE was 538 in relugolix group and 263 in leuprolide group.

^cNumber of patients without a history of MACE was 84 in relugolix group and 45 in leuprolide group.

Adverse event grades are evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

MedDRA Version 22.0.