Supplementary Table 1: Baseline characteristics on the ITT population, by gene subgroup (not-mutually exclusive groups*, pooled 300mg and 400mg BID cohorts)

	BRCA1/2 (N=32)		ATM (N=21)		CDK12 (N=21)		PALB2 (N=7)		Other (N=18)	
Age, mean (SD)	65.7 (7.2)		68.7 (6.6)		68.1 (7.3)		65.4 (7.8)		69.4 (8.9)	
Years from initial diagnosis - median (Q1-Q3)	3.8 (2.1-6.0)		5.2 (3.3-8.2)		4.9 (3.3-6.7)		4.6 (1.4-6.5)		4.6 (2.8-7.6)	
Years from diagnosis of CRPC - median (Q1-Q3)	2.4 (1.6-3.8)		2.5 (1.4-4.6)		2.6 (1.7-3.7)		2.9 (0.3-4.0)		2.9 (2.0-3.8)	
Metastatic disease at diagnosis										
No	15	46.9	9	42.9	8	38.1	4	57.1	10	47.6
Yes	16	50	11	52.4	12	57.1	3	42.9	10	47.6
Not available	1	3.1	1	4.8	1	4.8	0	0	1	4.8
Gleason score at diagnosis										
≤7	10	31.3	7	33.3	0	0	0	0	2	9.5
≥8	20	62.5	11	52.4	20	95.2	6	85.7	18	85.7
Not available	2	6.3	3	14.3	1	4.8	1	14.3	1	4.8
Previous hormonal and systemic treatment										
Docetaxel	32	100	21	100	21	100	7	100	21	100
Cabazitaxel	12	37.5	9	42.9	8	38.1	2	28.6	6	28.6
Abiraterone	15	46.9	8	38.1	9	42.9	5	71.4	11	52.4
Enzalutamide	17	53.1	12	57.1	14	66.7	3	42.9	13	61.9
Abiraterone and/or Enzalutamide	28	87.5	18	85.7	19	90.5	6	85.7	21	100
Evidence of progression at trial entry										
PSA only	6	18.8	8	38.1	7	33.3	3	42.9	3	14.3
Radiographic progression (+/- PSA progression)	26	81.3	13	61.9	14	66.7	4	57.1	18	85.7
Site of metastatic disease at trial entry[(1)]										
Lung	6	18.8	0	0	2	9.5	0	0	2	9.5
Lymph nodes	22	68.8	15	71.4	12	57.1	6	85.7	14	66.7
Liver	9	28.1	0	0	6	28.6	2	28.6	7	33.3
Bone	27	84.4	17	81	19	90.5	4	57.1	15	71.4
PSA at trial entry (ng/ml) – median (Q1-Q3)	148.5 (38.9-473.0)		168.0 (52.0-399.2)		248.1 (28.5-506.8)		144.0 (14.0-196.0)		139.1 (41.0-540.0)	
CTC count at trial entry										
CTC<5	10	31.3	8	38.1	6	28.6	4	57.1	8	38.1
CTC >= 5	22	68.8	12	57.1	15	71.4	3	42.9	13	61.9
Not available[(2)]	0	0	1	4.8	0	0	0	0	0	0
RECIST soft tissue disease at trial entry										
Bone lesions only	4	12.5	3	14.3	1	4.8	0	0	2	9.5
Non-measurable disease only (+/- bone lesions)	5	15.6	4	19	2	9.5	1	14.3	1	4.8
Measurable disease (+/- bone lesions)	23	71.9	14	66.7	18	85.7	6	85.7	18	85.7

Q1: 25% percentile, Q3: 75% percentile

* Non-mutually exclusive subgroups - one patient had BRCA1/2, CDK12 and 'Other mutations', and two patients had PALB2 and other mutations included in analysis for each subgroup separately

(1) More than one site could be reported.

(2) Screening CTC assessment not possible due to CTC kit shortage. Patient allowed to be randomised as he had RECIST measurable disease; for randomisation CTC assumed <5 but patient was unevaluable for CTC response.

Source: Mateo et al. Lancet Oncol 2020; 21: 162–74

Supplementary Table 2. TOPARP-B: Updated time-to-event outcomes

	Total	Randomised dose Group		Gene subgroup (mutually exclusive*)				
		300 mg	400 mg	BRCA1/2	ATM	CDK12	PALB2	Other
N	98	49	49	32	21	20	7	18
Radiographic progression-free survival								
Median (95% CI)	5.5 (4.6-7.5)	5.4 (4.2-8.1)	5.5 (3.6-9.3)	8.4 (5.5-14.0)	5.8 (4.4-10.9)	2.9 (2.6-5.6)	5.3 (0.4-NE)	2.8 (2.6-4.3)
Q1 - Q3	2.8-13.0	2.8-9.9	2.8-14.4	5.5-16.4	4.4-10.9	2.6-7.5	2.8-16.7	2.6-4.3
Progression-free survival								
Median (95% CI)	5.4 (3.7-5.6)	5.4 (3.0-5.6)	5.5 (3.6-6.5)	8.2 (5.5-13.0)	5.5 (3.7-6.5)	2.9 (2.6-5.4)	5.3 (0.4-20.6)	2.7 (2.6-3.6)
Q1 - Q3	2.8-9.9	2.7-8.5	2.8-11.5	5.4-14.5	3.7-9.5	2.6-5.4	2.8-20.6	2.6-3.7
Overall survival								
Median (95% CI)	12.8 (9.9-16.6)	10.1 (9.0-14.7)	14.8 (10.1-18.3)	17.7 (9.9-22.2)	16.6 (10.3-22.6)	9.5 (8.2-10.1)	13.9 (0.4-NE)	7.7 (4.3-19.1)
Q1 - Q3	7.7-21.7	7.2-22.4	8.2-20.6	9.7-22.4	10.3-23.2	8.2-10.1	6.4-NE	4.3-19.4

One BRCA1/2 patient with CDK12 and Other mutation analysed with BRCA1/2. Two patients with PALB2 and Other mutations analysed in the PALB2 subgroup
95%CI: 95% confidence interval. Q1= 25% percentile, Q3=75% percentile, NE= not estimable
Radiographic Free Survival is defined as time from randomisation to first evidence of radiographic progression (by RECIST 1.1 or bone scan as per PCWG2 criteria) or death; patients alive and without radiological progression were censored at the last scheduled disease assessment on study, at time of treatment discontinuation (in case of clinical progression not leading to death) or at time of starting a new treatment for mCRPC.
Progression free survival was defined as time from randomisation until radiographic progression, unequivocal clinical progression or death; patients alive and without progression were censored at the last scheduled disease assessment on study.

Supplementary Table 3. Origin and type of gene alteration by gene subgroup

	Total (N=98)		Gene subgroup (mutually exclusive)									
			BRCA1/2 (N=32)		ATM (N=21)		CDK12 (N=20)		PALB2 (N=7)		Other (N=18)	
Origin/type alteration	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Germline mutation	30	30.6	13	40.6	5	23.8	0	0	6	85.7	6	33.3
Bi-allelic hit detected	*17*	*17.4*	*8*	*25.0*	*4*	*19.1*	*0*	*0*	*4*	*57.1*	*1*	*5.6*
Mono - allelic hit detected	*13*	*13.3*	*5*	*15.6*	*1*	*4.8*	*0*	*0*	*2*	*28.6*	*5*	*27.8*
Somatic Homozygous deletion	16	16.3	11	34.4	1	4.8	0	0	0	0	4	22.2
Bi-allelic hit detected	*16*	*16.3*	*11*	*34.4*	*1*	*4.8*	*0*	*0*	*0*	*0*	*4*	*22.2*
Somatic mutation	52	53.1	8	25.0	15	71.4	20	100	1	14.3	8	44.4
Bi-allelic hit detected	*31*	*31.6*	*5*	*15.6*	*7*	*33.3*	*18*	*90.0*	*0*	*0*	*1*	*5.6*
Mono - allelic hit detected	*21*	*21.4*	*3*	*9.4*	*8*	*38.1*	*2*	*10.0*	*1*	*14.3*	*7*	*38.9*
Mono/Bi-allelic?	n	%	n	%	n	%	n	%	n	%	n	%
Bi-allelic hit detected	64	65.3	24	75.0	12	57.1	18	90.0	4	57.1	6	33.3
Mono - allelic hit detected	34	34.7	8	25.0	9	42.9	2	10.0	3	42.9	12	66.7

*Mutually exclusive subgroups - one patient with BRCA1/2+CDK12+Other mutations analysed with BRCA1/2 subgroup, and two patients with PALB2+Other mutations included in the PALB2 subgroup only.

Supplementary Table 4 : ATM patients – summary of outcomes

	Composite Overall response		RECIST 1.1 Objective Response		PSA fall ≥50%		CTC conversion		RECIST 1.1 or PSA response		Radiographic Progression Free Survival	
	resp/n	**RR**	**resp/n**	**RR**	**resp/n**	**RR**	**resp/n**	**RR**	**resp/n**	**RR**	**Median (95%CI)**	**Q1-Q3**
All ATM patients	**8/21**	**38.1**	**1/14**	**7.1**	**1/21**	**4.8**	**6/11**	**54.5**	**2/21**	**9.5**	**5.8 (4.4-10.9)**	**4.4-10.9**
By origin												
Germline	4/5	80	0/2	0	0/5	0	4/4	100	0/5	0	5.4 (5.2-NE)	5.2-13.5
Somatic	4/16	26	1/12	8.3	1/16	6.3	4/4	100	2/7	28.7	5.8 (3.7-9.5)	4.3-9.5
IHC												
ATM no loss	1/6	16.7	0/3	0	0/6	0	1/4	25	0/6	0	3.7 (2.7-NE)	2.8-NE
ATM loss	7/15	46.7	1/11	9.1	1/15	6.7	5/7	71.4	2/15	13.3	5.8 (5.2-13.5)	5.4-13.5

Resp=number of responses, n=patients available, RR=response rate (%)
Q1: 1st quantile (25% centile); Q3: 3rd quantile (75% centile)