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MEETING SUMMARY
ESMO 2020, VIRTUAL MEETING

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HIGHLIGHTS FROM GU CONNECT
SEPTEMBER 2020

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This content is supported by an Independent Educational Grant from Bayer.

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IPATential150: PHASE 3 STUDY OF IPATASERTIB PLUS ABIRATERONE VS PLACEBO PLUS ABIRATERONE IN mCRPC

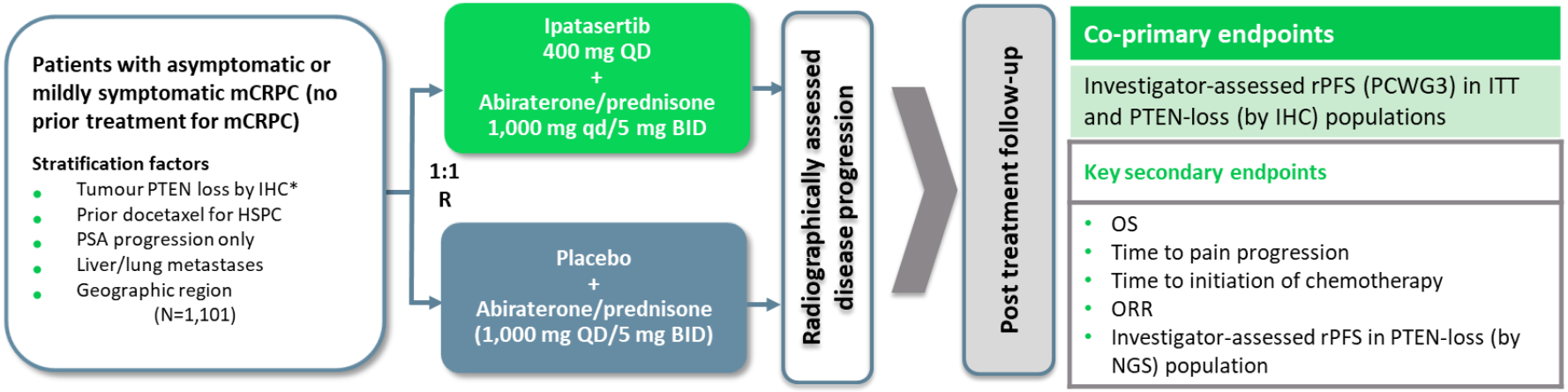
de Bono J, et al.

ESMO 2020. Abstract #LBA4. Oral presentation

mCRPC, metastatic castration resistant prostate cancer

IPATential150: BACKGROUND AND STUDY DESIGN

- **Ipatasertib is an oral adenosine triphosphate-competitive selective inhibitor of AKT1/2/3**, which is the central node of the phosphatidylinositol-3-kinase (PI3K)/AKT signalling pathway – a key driver of cancer cell growth and proliferation in prostate cancer[1,2]
- The **PI3K/AKT pathway** has also been **implicated in resistance to anti-androgen therapy as androgen receptor (AR) inhibition** is associated with an increase in AKT pathway activation[2,3]
- **Approx. 40-60% of patients with metastatic castration-resistant prostate cancer (mCRPC) have lost the AKT phosphatase PTEN. This results in hyperactivation of the PI3K/AKT pathway** and is associated with adverse outcomes such as increased tumour grade and stage, earlier biochemical recurrence after radical prostatectomy, metastasis, prostate cancer–specific death, and androgen-independent progression[4,5]
- **The IPATential150 trial is investigating dual AR and PI3K/AKT inhibition in patients with previously untreated mCRPC**[6]



* PTEN loss defined as minimum of 50% of the specimen's tumour area with no detectable PTEN staining (by Ventana IHC assay using SP218 antibody)

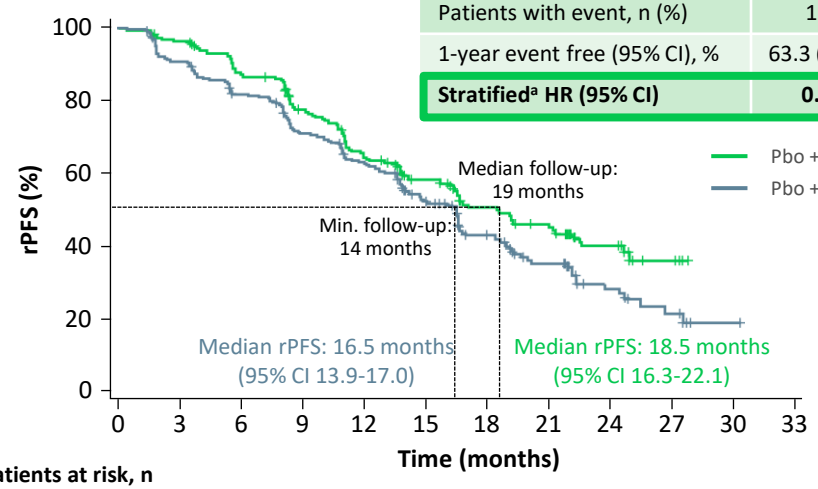
BID, twice daily; HSPC, hormone-sensitive prostate cancer; IHC, immunohistochemistry; ITT, intention to treat; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; PSA, prostate specific antigen; PTEN, phosphatase and tensin homologue; QD, once daily; R, randomisation; rPFS, radiographic progression-free survival; 1. Yang J, et al. Mol Cancer. 2019;18:26; 2. Crumbaker M, et al. Cancers (Basel). 2017;9:34; 3. Wang Y, et al. Current Cancer Drug Targets. 2007;7:591-604; 4. de Bono JS, et al. Clin Cancer Res. 2019;25;928-36; 5. Jamaspishvili T, et al. Nat Rev Urol. 2018;15:222-34; 6. de Bono J, et al. ESMO 2020. Abstract #LBA4. Oral presentation

IPATential150: RESULTS

- Ipatasertib significantly improved radiographic progression-free survival (rPFS) compared to placebo for patients with phosphatase and tensin homologue (PTEN)-loss mCRPC, but not in the intention-to-treat (ITT) population
  - This effect was consistent across all pre-specified subgroups

rPFS in the PTEN-loss (by IHC) population

	Pbo + AAP (N=261)	Ipat + AAP (N=260)
Patients with event, n (%)	154 (59)	124 (48)
1-year event free (95% CI), %	63.3 (57.3-69.3)	64.4 (58.3-70.5)
Stratified[a] HR (95% CI)	**0.77 (0.61-0.98); p=0.0335[b]**	

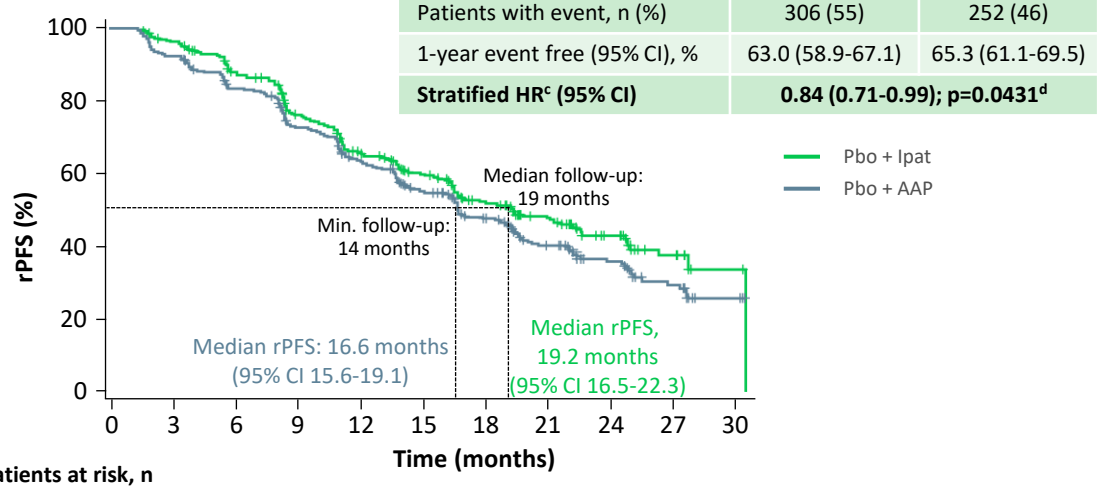


Patients at risk, n

Pbo + AAP	261	233	206	175	151	105	71	41	22	10	3
Ipat + AAP	260	238	211	182	149	113	72	48	25	12	

rPFS in the ITT population

	Pbo + AAP (N=261)	Ipat + AA (N=260)
Patients with event, n (%)	306 (55)	252 (46)
1-year event free (95% CI), %	63.0 (58.9-67.1)	65.3 (61.1-69.5)
Stratified HR[c] (95% CI)	**0.84 (0.71-0.99); p=0.0431[d]**	



Patients at risk, n

Pbo + AAP	554	501	443	377	322	237	165	98	60	29	5
Ipat + AAP	547	495	436	368	310	239	158	103	53	26	2

Data cut-off date: 16 March 2020; [a] Stratified for prior taxane-based therapy and PSA-only progression factor; [b] Statistically significant at α = 0.05 level;
[c] Stratified for prior taxane-based therapy, PSA-only progression factor, and tumour PTEN loss status (by IHC); [d] Did not meet statistical significance α = 0.01 level
AAP, abiraterone acetate + prednisone; CI, confidence interval; HR, hazard ratio; IHC, immunohistochemistry; Ipat, ipatasertib;
mCRPC, metastatic castration-resistant prostate cancer; Pbo, placebo; PSA, prostate specific antigen; de Bono J, et al. ESMO 2020. Abstract #LBA4. Oral presentation

IPATential150: RESULTS (CONT.)

SECONDARY EFFICACY ENDPOINTS

- Secondary endpoints favoured the combination arm

Secondary endpoints (efficacy)	PTEN loss (by IHC) (N=521)		ITT (N=1,101)	
	Pbo + AAP	Ipat + AAP	Pbo + AAP	Ipat + AAP
Time to PSA progression, n	261	260	554	547
Median (95% CI), months	7.6 (6.4-9.3)	12.6 (10.2-15.3)	8.4 (7.4-9.3)	12.9 (10.3-15.1)
Stratified[a,b] HR (95% CI)	0.69 (0.55-0.87); p=0.0013[c]		0.73 (0.62-0.85); p<0.0001[c]	
PSA response, n/N (%)	187/261 (72)	217/260 (84)	418/554 (76)	444/546 (81)
p value	0.0012[c]		0.0183[c]	
Time to pain progression, n/N (%)	95/261 (36)	73/260 (28)	187/554 (34)	156/547 (29)
Stratified[a,b] HR (95% CI)	0.77 (0.56-1.04)		0.87 (0.70-1.08)	
Confirmed ORR, n/N (%)	37/96 (39)	60/99 (61)	98/225 (44)	122/201 (61)
Difference (95% CI), %	22 (7-37)		17 (7-27)	
	PTEN loss (by NGS)			
rPFS, n	103	105	–	–
Median (95% CI), months	14.2 (10.9-18.7)	19.1 (13.9-NE)	–	–
Stratified[a] HR (95% CI)	0.65 (0.45-0.95)		–	–

SAFETY

Safety, %	Pbo + AAP (N=546)	Ipat + AAP (N=551)
SAEs	23	40
AEs leading to treatment discontinuation	5	21

[a] Stratified for prior taxane-based therapy and PSA-only progression factor (PTEN loss [by IHC/NGS]);
[b] Stratified for prior taxane-based therapy, PSA-only progression factor, and tumour PTEN loss (by IHC) (ITT);
[c] Descriptive

AAP, abiraterone acetate + prednisone; CI, confidence interval; HR, hazard ratio; IHC, immunohistochemistry; Ipat, ipatasertib; ITT, intention to treat; NE, not evaluable; NGS, next-generation sequencing; ORR, overall response rate; Pbo, placebo; PSA, prostate specific antigen; rPFS, radiographic progression-free survival; PTEN, phosphatase and tensin homologue

de Bono J, et al. ESMO 2020. Abstract #LBA4. Oral presentation

IPATential150: SUMMARY

- **Ipatasertib plus AAP demonstrated a significantly superior rPFS and anti-tumour activity** compared to placebo plus AAP in patients with PTEN-loss mCRPC
  - Improvement of rPFS in the ITT population was not statistically significant
- **The safety profile of ipatasertib plus AAP was in line with known and potential risks** observed in clinical studies
- While initial data are encouraging, overall survival (OS) benefit and additional secondary endpoints are not yet mature. The trial will continue until the next planned analysis and data will be shared with health authorities

AAP, abiraterone acetate + prednisone; ITT, intention to treat; mCRPC, metastatic castration-resistant prostate cancer; rPFS, radiographic progression-free survival; PTEN, phosphatase and tensin homologue

de Bono J, et al. ESMO 2020. Abstract #LBA4. Oral presentation

FINAL OVERALL SURVIVAL ANALYSIS OF PROfound: OLAPARIB VS PHYSICIAN'S CHOICE OF ENZALUTAMIDE OR ABIRATERONE IN PATIENTS WITH mCRPC AND HOMOLOGOUS RECOMBINATION REPAIR GENE ALTERATIONS

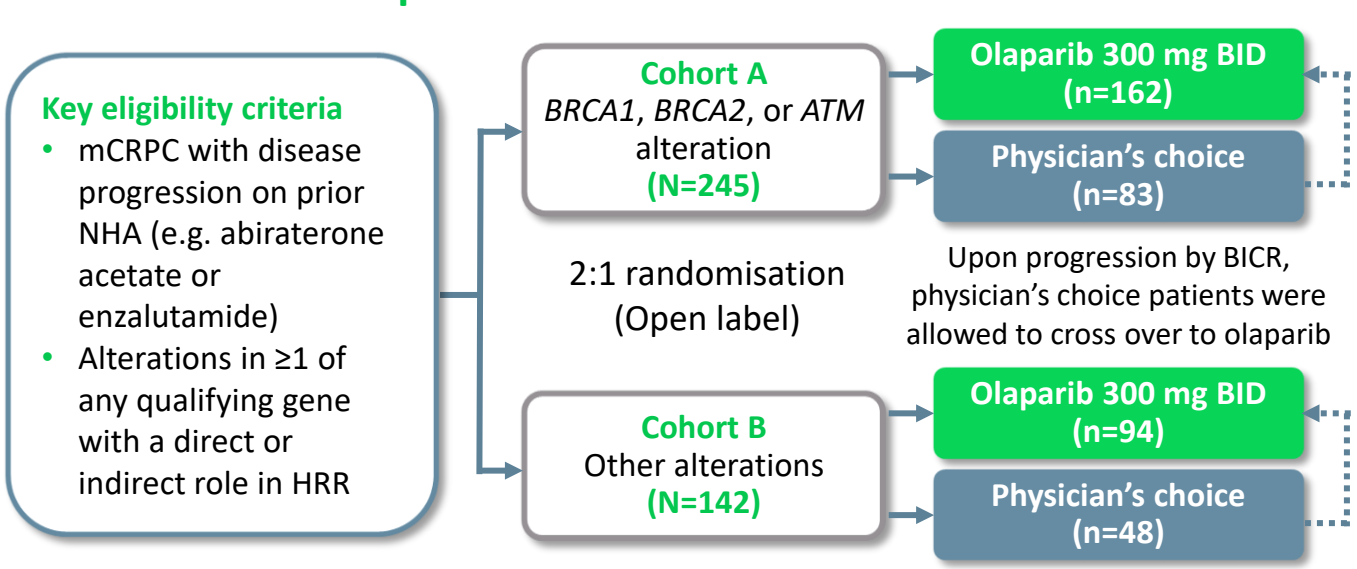
de Bono J, et al.

ESMO 2020. Abstract #610O. Oral presentation by Mateo, J

mCRPC, metastatic castration resistant prostate cancer

PROfound: BACKGROUND AND STUDY DESIGN

- **PROfound was the first** randomised **prostate cancer trial to use biomarker selection** to identify which mCRPC patients may respond to treatment. **Olaparib treatment was associated with statistically significant and clinically relevant improvements in BICR rPFS** compared to enzalutamide/abiraterone acetate in mCRPC patients with:
  - Alterations in *BRCA1*, *BRCA2*, and/or *ATM* (Cohort A)
  - Alterations in any of 15 pre-specified genes with a direct/indirect role in homologous recombination repair (HRR)
- **Final OS data are reported here**



Primary endpoint

rPFS in cohort A (RECIST 1.1 and PCWG3 by BICR)

Key secondary endpoints

- rPFS in cohorts A and B (by BICR)
- Confirmed radiographic objective response rate in cohort A (by BICR)
- Time to pain progression in cohort A
- OS in cohort A

Stratification factors

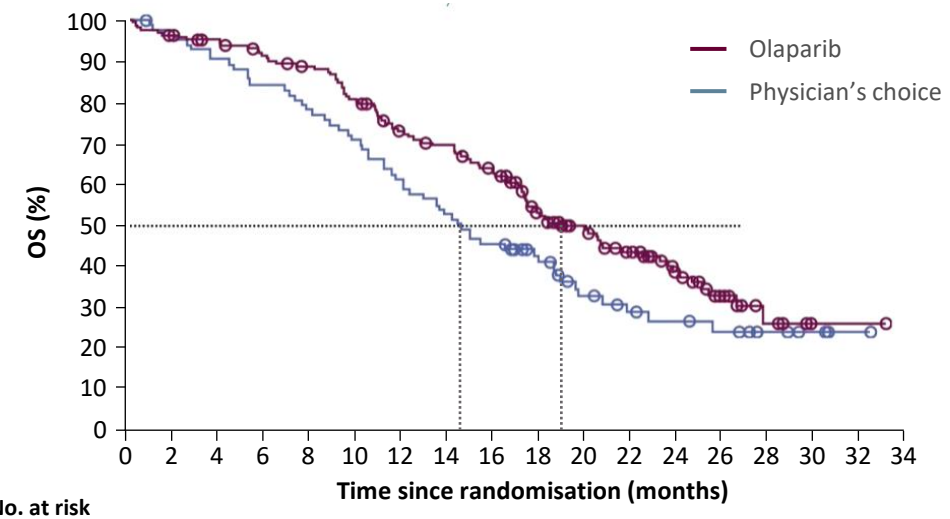
- Previous taxane; measurable disease
- Physicians choice: enzalutamide (160 mg QD) or abiraterone (1,000 mg QD + prednisone 5 mg BID)

ATM, ataxia telangiectasia mutated; BICR, blinded independent central review; BID, twice daily; BRCA1/2, breast cancer 1/2; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression-free survival; QD, once daily

de Bono J, et al. N Engl J Med. 2020;382:2091-102; Hussain M, et al. Ann Oncol. 2019;30 suppl 5:v881-2; abstract LBA12

PROfound: RESULTS

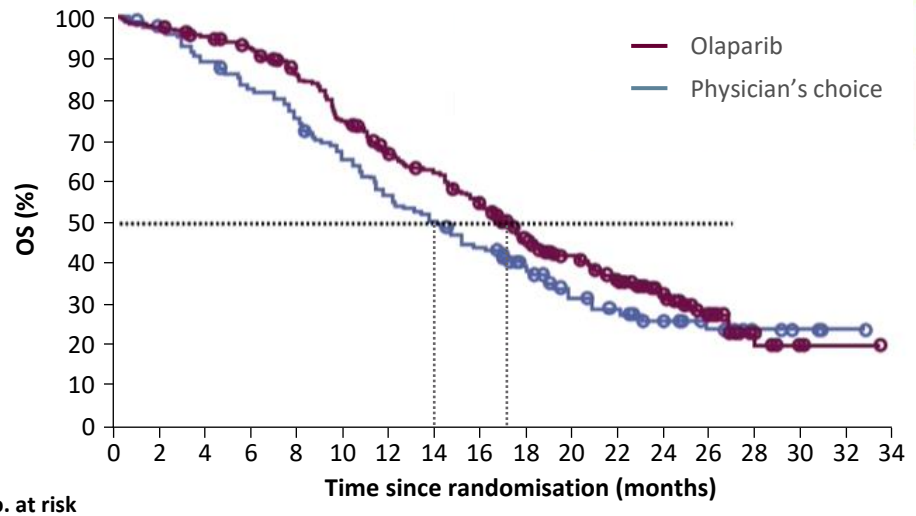
OS IN COHORT A



No. at risk

Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Physician's choice	83	79	74	69	64	58	50	43	37	27	18	15	11	9	6	3	1	0

OS IN OVERALL POPULATION



No. at risk

Olaparib	256	249	240	228	209	182	157	146	126	96	73	56	39	22	7	2	1	0
Physician's choice	131	125	115	106	96	83	71	63	55	37	27	22	15	11	6	3	1	0

	Cohort A	
	Olaparib (N=162)	Physician's choice (N=83)
Median OS, months	19.1	14.7
HR (95% CI)	0.69 (0.50-0.97); p=0.0175	
Median follow-up, months	21.9	21.0

	Overall population	
	Olaparib (N=256)	Physician's choice (N=131)
Median OS, months	17.3	14.0
HR (95% CI)	0.79 (0.61-1.03); p=0.0515	
Median follow-up, months	20.7	20.5

- Patients randomised between April 2017 and November 2018; DCO for final OS: 20 March 2020
- Among patients with disease progression in the physician's choice arm , 67% in cohort A and 66% in the overall population crossed over to olaparib
- Longer follow-up yielded no new safety signals

CI, confidence interval; HR, hazard ratio; OS, overall survival

de Bono J, et al. ESMO 2020. Abstract #610O. Oral presentation by Mateo, J

PROfound: SUMMARY

- **PROfound is the first phase 3 study to show an OS benefit of a PARP inhibitor**
- **Despite extensive crossover** from the control arm, **olaparib demonstrated a statistically significant and clinically relevant prolongation of OS** compared to enzalutamide/abiraterone in patients with mCRPC with alterations in *BRCA1*, *BRCA2,* and/or *ATM*
- Pre-specified sensitivity analysis adjusting for treatment crossover suggests the treatment effect of olaparib will be greater than that observed in the PROfound study
- The safety profile of olaparib was consistent with the primary analysis[1]
- Olaparib is approved by the FDA for patients with mCRPC with alterations in multiple DNA repair genes who have progressed on enzalutamide/abiraterone[2]

ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer 1/2; DNA, deoxyribonucleic acid; FDA, US Food and Drug Administration; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; ; PARP, Poly (ADP-ribose) polymerase; 1. de Bono J, et al. N Engl J Med. 2020;382:2091-102; 2. US FDA. Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer. Last updated May 2020. Accessed September 2020; de Bono J, et al. ESMO 2020 abstract #610O. Oral presentation by Mateo, J

ABIRATERONE ACETATE PLUS PREDNISOLONE FOR HNPC: LONG-TERM RESULTS FROM METASTATIC PATIENTS IN STAMPEDE TRIAL

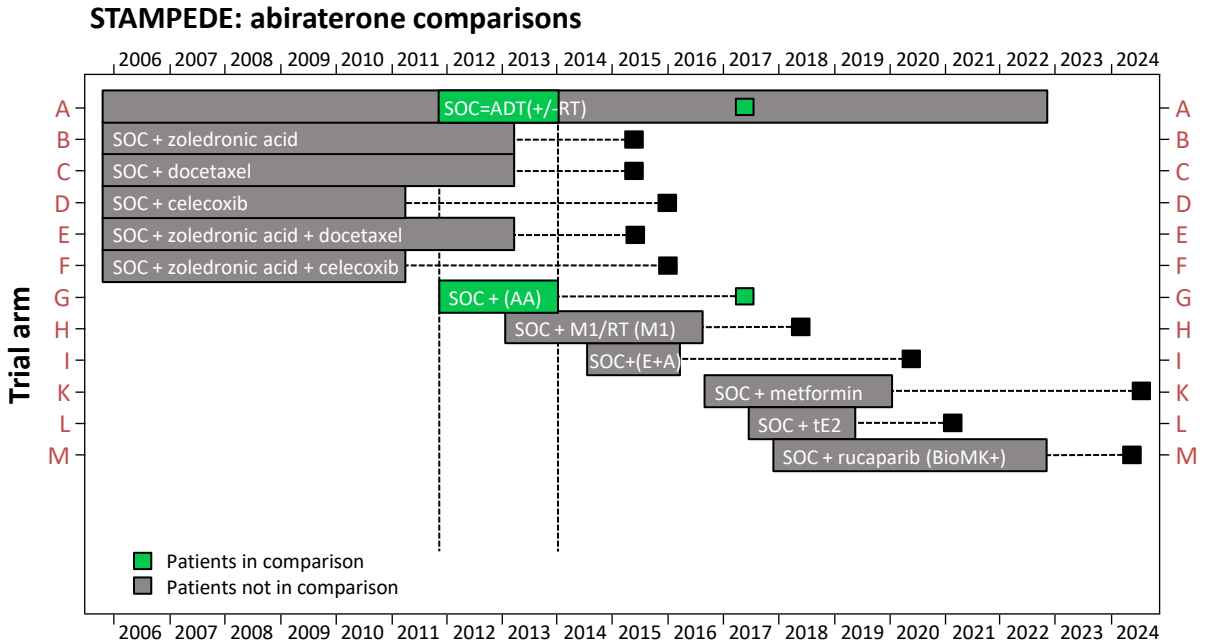
James N, et al.

ESMO 2020. Abstract #611O. Oral presentation

HNPC, hormone-naive prostate cancer

STAMPEDE: BACKGROUND

- In previously reported data from **STAMPEDE, abiraterone acetate plus prednisolone (AAP) showed a clear survival advantage in men starting long-term hormone therapy for prostate cancer[1]**
- STAMPEDE included patients with and without metastatic disease (M1). **Here we report long-term outcomes in the subset of M1 patients[2]**



Patients: standard of care (SOC) (n=957), SOC + AAP (n=960)
Recruitment: November 2011 to January 2014

Long-term follow up analysis

- Database lock: 3 April 2020 (3 years after initial analysis)
- 1,003 patients had M1 disease at baseline
- Median follow-up: 6.1 years
- 329 control arm events
- 125 patients still receiving abiraterone acetate

Primary outcome measure: OS
Secondary outcome measures: FFS, PFS, MFS, SREs, toxicity

A/AA, abiraterone acetate; ADT, androgen deprivation therapy; BioMK+, biomarker positive; E, enzalutamide; FFS, failure-free survival; MFS, metastasis-free survival; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; SRE, skeletal-related event; tE2, transdermal oestradiol

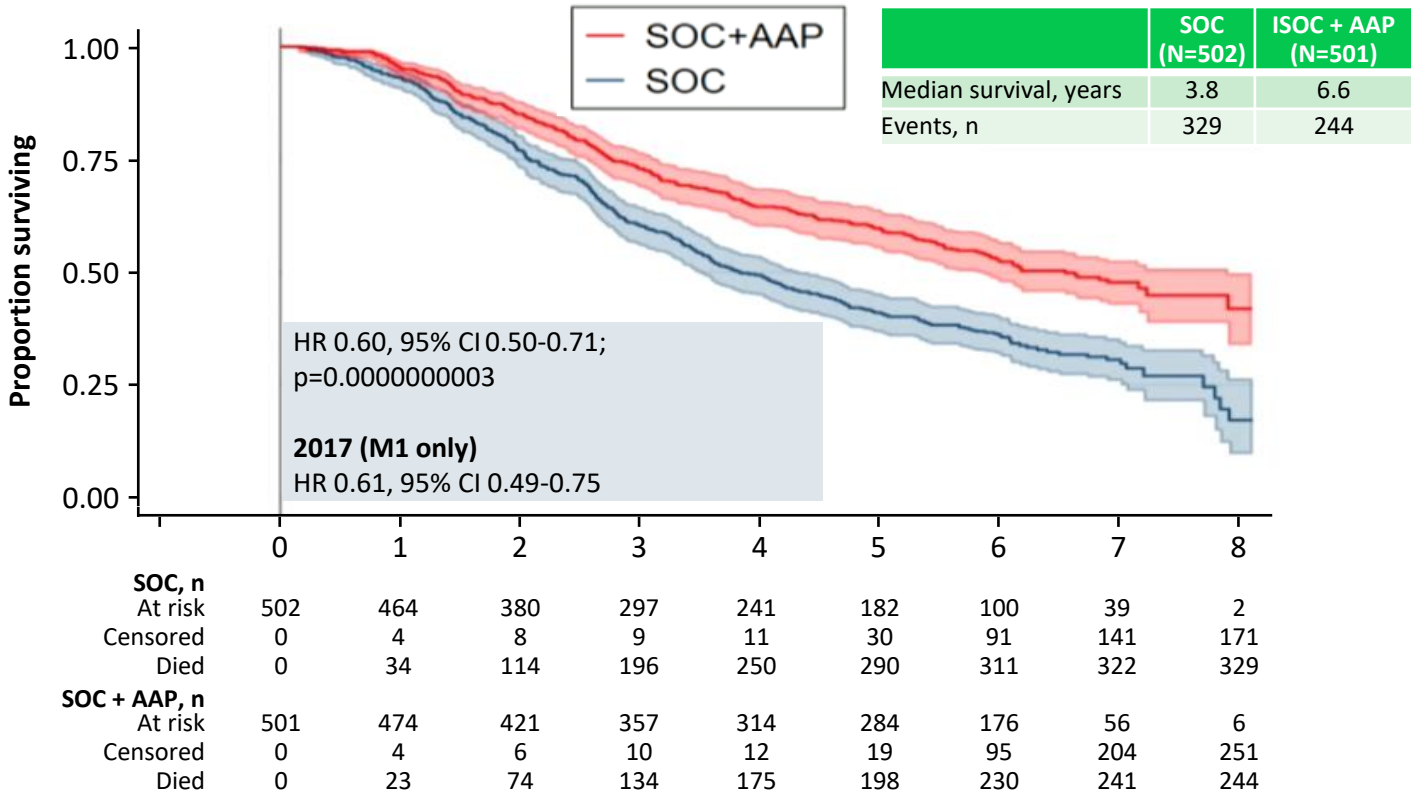
1. James ND, et al. N Engl J Med. 2017;377:338-51; 2. James N, et al. ESMO 2020. Abstract #611O. Oral presentation

STAMPEDE: RESULTS

- 1,003 (52%) of randomised population had metastatic disease

M1 patient characteristics	SOC (N=502)	SOC + AAP (N=501)
Median age (range), years	67 (39-84)	67 (42-85)
Metastatic burden,[a] %		
Low risk	44	43
High risk	46	48
Unclassified	10	9
Eligibility criteria, %		
Newly diagnosed	95	93
Relapsing	5	7
Median PSA (IQR), ng/mL	97.2 (26-358)	96.3 (29-371)

OS: SOC + AAP VS SOC



	SOC (N=502)	ISOC + AAP (N=501)
Median survival, years	3.8	6.6
Events, n	329	244

[a] Per LATITUDE risk criteria

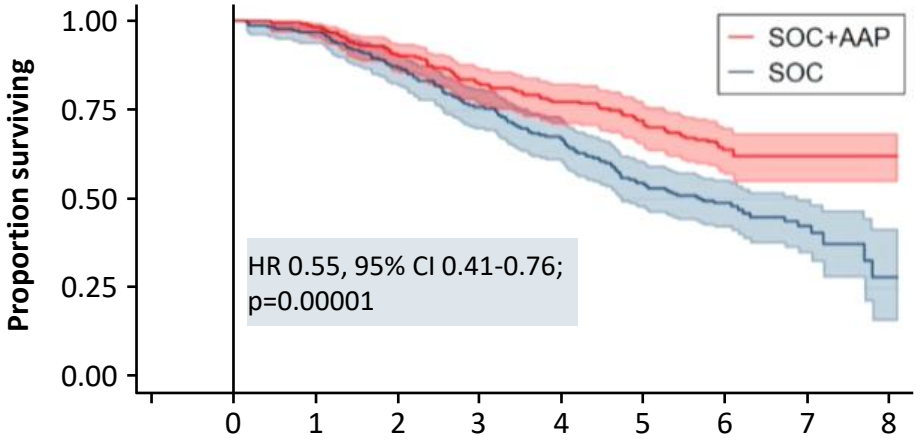
AAP, abiraterone acetate + prednisolone; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; M1, metastatic disease; OS, overall survival; PSA, prostate specific antigen; SOC, standard of care

James ND, et al. N Engl J Med. 2017;377:338-51; James N, et al. ESMO 2020. Abstract #611O. Oral presentation

STAMPEDE: RESULTS (CONT.)

OS BY RISK GROUP (LATITUDE)

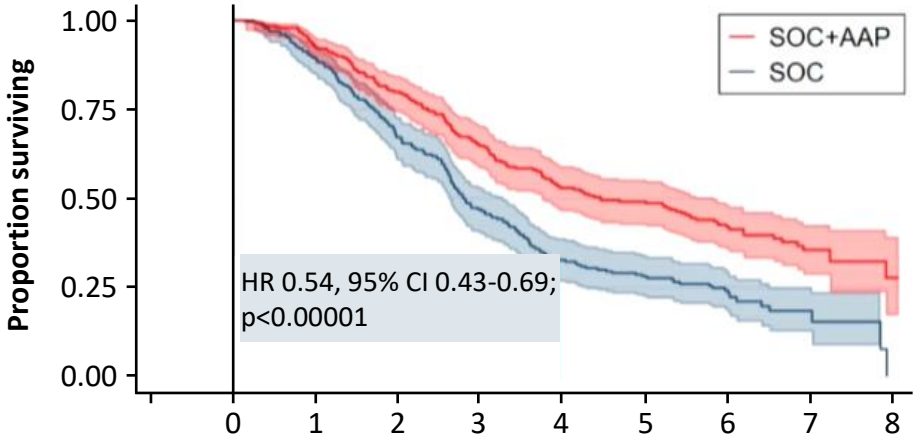
Low Risk



	0	1	2	3	4	5	6	7	8
SOC, n									
At risk	222	213	191	165	146	109	62	29	1
Censored	0	2	3	4	5	14	50	77	101
Died	0	7	28	53	71	99	110	116	120
SOC + AAP, n									
At risk	214	211	192	172	161	149	95	31	5
Censored	0	0	2	5	5	6	44	106	132
Died	0	3	20	37	48	59	75	77	77

2018 analysis
HR 0.66 (0.44-0.98)
P=0.041

High Risk



	0	1	2	3	4	5	6	7	8
SOC, n									
At risk	232	206	152	106	73	56	28	6	0
Censored	0	2	5	5	6	13	33	51	54
Died	0	24	75	121	153	163	171	175	178
SOC + AAP, n									
At risk	241	221	191	154	124	111	66	19	1
Censored	0	2	2	3	5	9	39	79	95
Died	0	18	48	84	112	121	136	143	145

2018 analysis
HR 0.54 (0.41-0.70)
P<0.001

- Toxicity at 4 years post-randomisation was similar between treatment arms, with 16% of patients in each group reporting grade ≥3 toxicity

AAP, abiraterone acetate + prednisolone; CI, confidence interval; HR, hazard ratio; SOC, standard of care

Hoyle AP, et al. Eur Urol 2019;76:719-728; James N, et al. ESMO 2020. Abstract #611O. Oral presentation

STAMPEDE: SUMMARY

- The **results are unchanged** in M1 patients **from the initial analysis in 2017**
- **Highly significant OS benefit was observed** in M1 patients receiving ADT plus AAP
  - Highly significant benefit was also observed for the secondary endpoints of MFS and SREs
- **OS benefit** by LATITUDE risk burden was similar **for both low- and high-risk subgroups**
  - Regulators and payors could consider extending the approval of abiraterone acetate to all patients with mHSPC as opposed to just those in the high-risk subgroup

AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; M1, metastatic disease; MFS, metastasis-free survival; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; SRE, skeletal-related event

James ND, et al. N Engl J Med. 2017;377:338-51; James N, et al. ESMO 2020. Abstract #611O. Oral presentation

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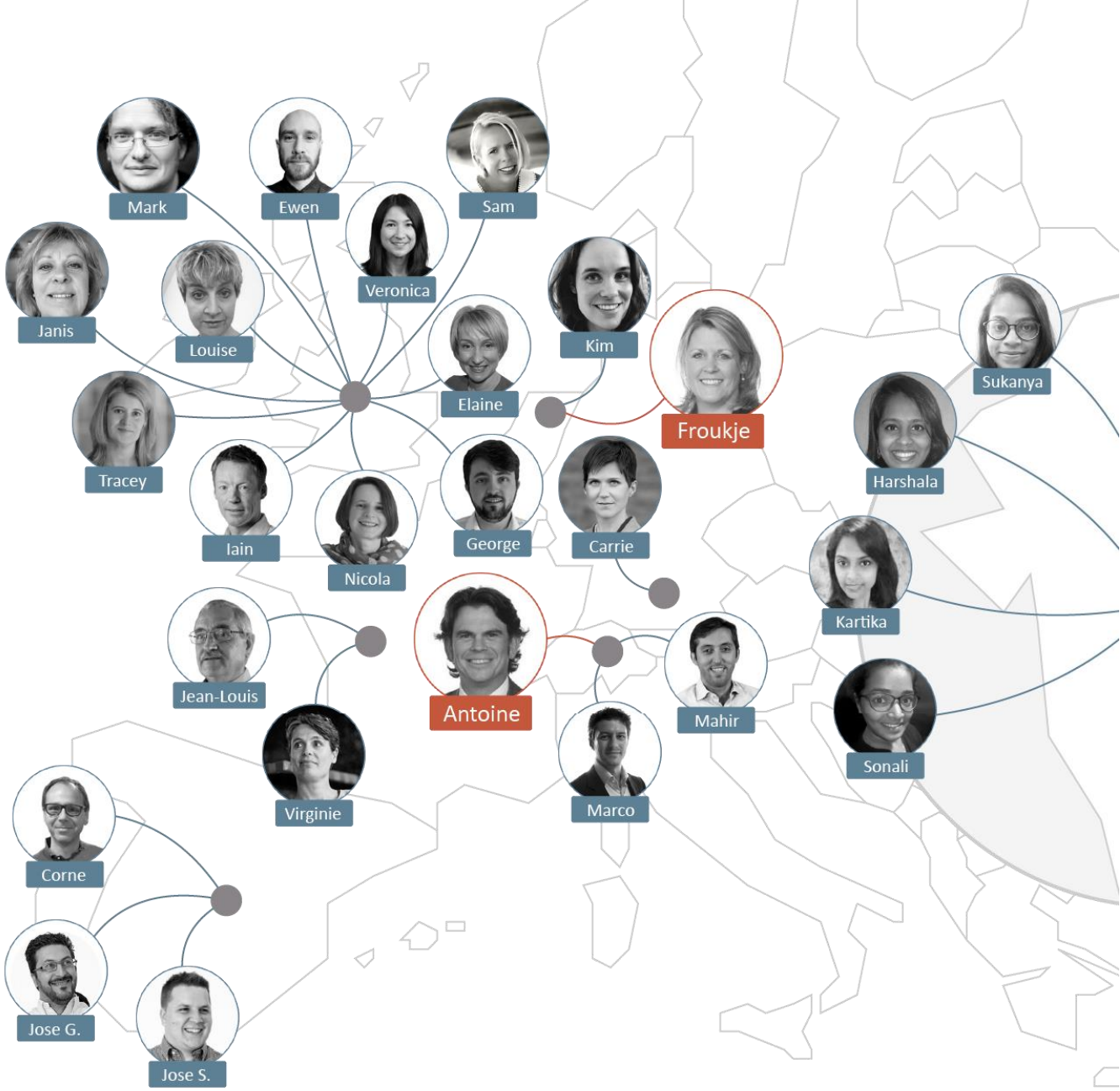

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