VIRTUAL 2020 ESMO congress

IPATential150: efficacy and safety from the Phase III study of ipatasertib plus abiraterone vs placebo plus abiraterone in metastatic castration-resistant prostate cancer

Johann De Bono[1], Sergio Bracarda[2], Cora N. Sternberg[3], Kim Chi[4], David Olmos[5], Shahneen Sandhu[6], Christophe Massard[7], Nobuaki Matsubara[8], Boris Alekseev[9], Rustem Gafanov[10], Francis Parnis[11], Gary L. Buchschacher Jr[12], Luis Corrales[13], Michael Borre[14], Gustavo Alves[15], Josep Garcia[16], Marie-Laurence Harle-Yge[16], Geng Chen[17], Matthew J. Wongchenko[17], Christopher Sweeney[18]

[1]The Institute of Cancer Research and the Royal Marsden Hospital, London, UK; [2]Azienda Ospedaliera S. Maria, Terni, Italy; [3]Englander Institute for Precision Medicine, Weill Cornell Medicine, New York-Presbyterian, New York, NY, USA; [4]BC Cancer Agency, Vancouver, Canada; [5]Spanish National Cancer Research Center (CNIO), Madrid, Spain; [6]Peter MacCallum Cancer Centre, Melbourne, Australia; [7]Institut Gustave Roussy, Villejuif, France; [8]National Cancer Center Hospital East, Chiba, Japan; [9]P.A. Herzen Research Institute, Moscow, Russia; [10]Russian Scientific Center of Roentgenoradiology, Moscow, Russia; [11]Ashford Cancer Centre Research, Kurralta Park, SA, Australia; [12]Southern California Permanente Medical Group, Los Angeles Medical Center, Los Angeles, CA, USA; [13]Department of Medical Oncology, Centro de Investigación y Manejo del Cáncer CIMCA, San José, Costa Rica; [14]Aarhus University Hospital, Aarhus, Denmark; [15]Hospital Nossa Senhora da Conceicao, Porto Alegre, RS, Brazil; [16]F. Hoffmann-La Roche, Ltd., Basel, Switzerland; [17]Genentech Inc, South San Francisco, CA, USA; [18]Dana-Farber Cancer Institute, Boston, MA, USA.

Disclosures

- Dr Johann de Bono has the following financial relationships to disclose:

- Honoraria for advisory boards and/or lectures:
  - Astellas Pharma, AstraZeneca, Bayer HealthCare, BioXcel Therapeutics, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eisai, Genentech/F. Hoffmann LaRoche, Genmab, GlaxoSmithKline, Janssen Oncology, Menarini Silicon Biosystems, Merck Serono, Merck Sharp & Dohme, Orion, Pfizer, Sanofi, Sierra Oncology, and Taiho Pharmaceutical
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- Stocks or ownership interest:
  - None

Background

- Metastatic castration-resistant prostate cancer (mCRPC) is a heterogenous disease[1-4]
  - 40%-50% of mCRPCs have lost the AKT phosphatase PTEN, hyperactivating oncogenic PI3K/AKT signalling[1,5-7]
  - PTEN loss in mCRPC is associated with worse prognosis and reduced benefit from androgen receptor (AR) blockade[4]
- Reciprocal cross talk has been demonstrated between AR and PI3K/AKT signalling[8-10]
  - AR blockade can activate PI3K/AKT signalling, enabling prostate cancer cell surival[8-10]
- A Phase II study of dual AR and PI3K/AKT inhibition with abiraterone (and prednisone) plus ipatasertib (400 mg) resulted in prolonged rPFS versus AR inhibition alone (placebo plus abiraterone and prednisone), with a greater impact observed among patients with PTEN-loss tumours[11]
- The Phase III IPATential150 study (NCT03072238) was designed to evaluate the efficacy and safety of ipatasertib with abiraterone and prednisone in patients with previously untreated mCRPC

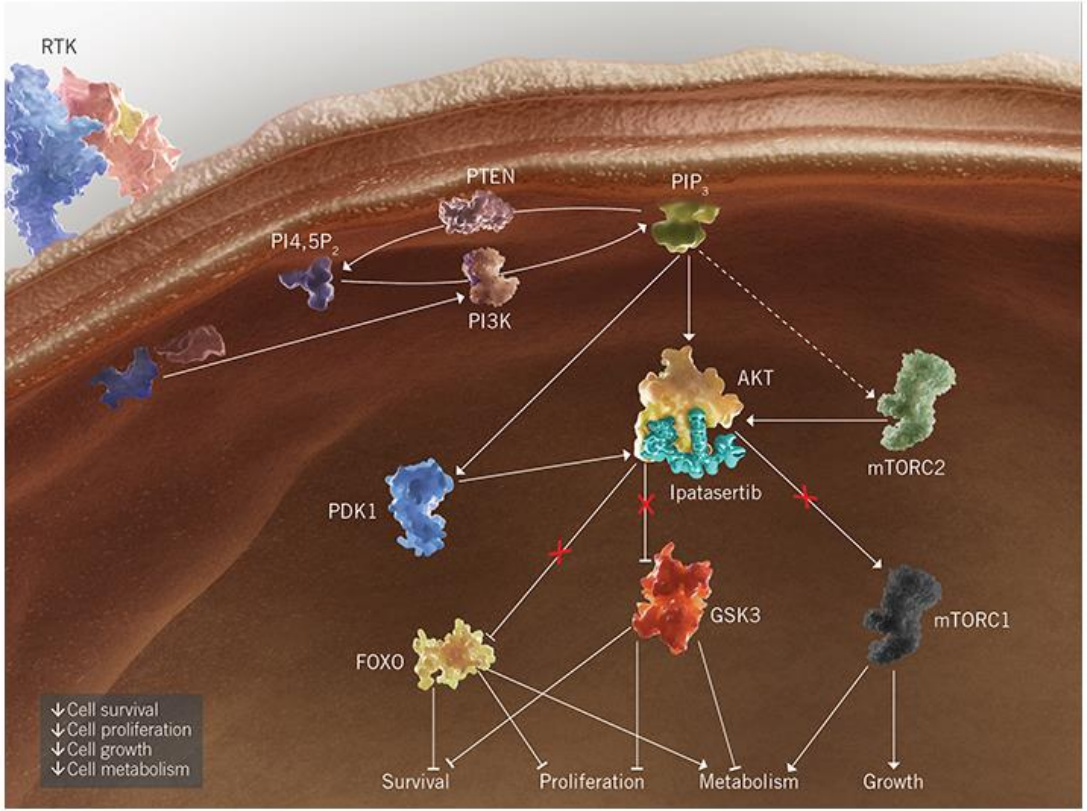
PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homologue.

1. Robinson D, et al. *Cell* 2015; 2. Sartor O, et al. *N Engl J Med* 2018; 3. Nuhn P, et al. *Eur Urol* 2019; 4. Jamaspsihili T, et al. *Nat Rev Urol* 2018; 5. Taylor BS, et al. *Cancer Cell* 2010; 6. Miller TW, et al. *Breast Cancer Res* 2011; 7. Nagata Y, et al. *Cancer Cell* 2004; 8. Sarker D, et al. *Clin Cancer Res* 2009; 9. Carver BS, et al. *Cancer Cell* 2011; 10. Mulholland DJ, *J Med Chem* 2012; 11. de Bono JS, et al. *Clin Cancer Res* 2019.

de Bono J. IPATential150. ESMO 2020. https://bit.ly/31s8gje

Ipatasertib mechanism of action

- Ipatasertib is an oral investigational small molecule that binds to the ATP-binding pocket of all 3 isoforms of AKT[1,2]
- Ipatasertib inhibits AKT serine-threonine kinase activity and can improve the anti-tumour activity of AR blockade in prostate cancer models[1-3]



https://www.genentechoncology.com/pipeline-molecules/ipatasertib.html

1. Lin J, et al. *Clin Cancer Res.* 2013; 2. Nitulescu GM, et al. *Int J Oncol.* 2016; 3. Slomovitz BM, Colemen RL. *Clin Cancer Res.* 2012.

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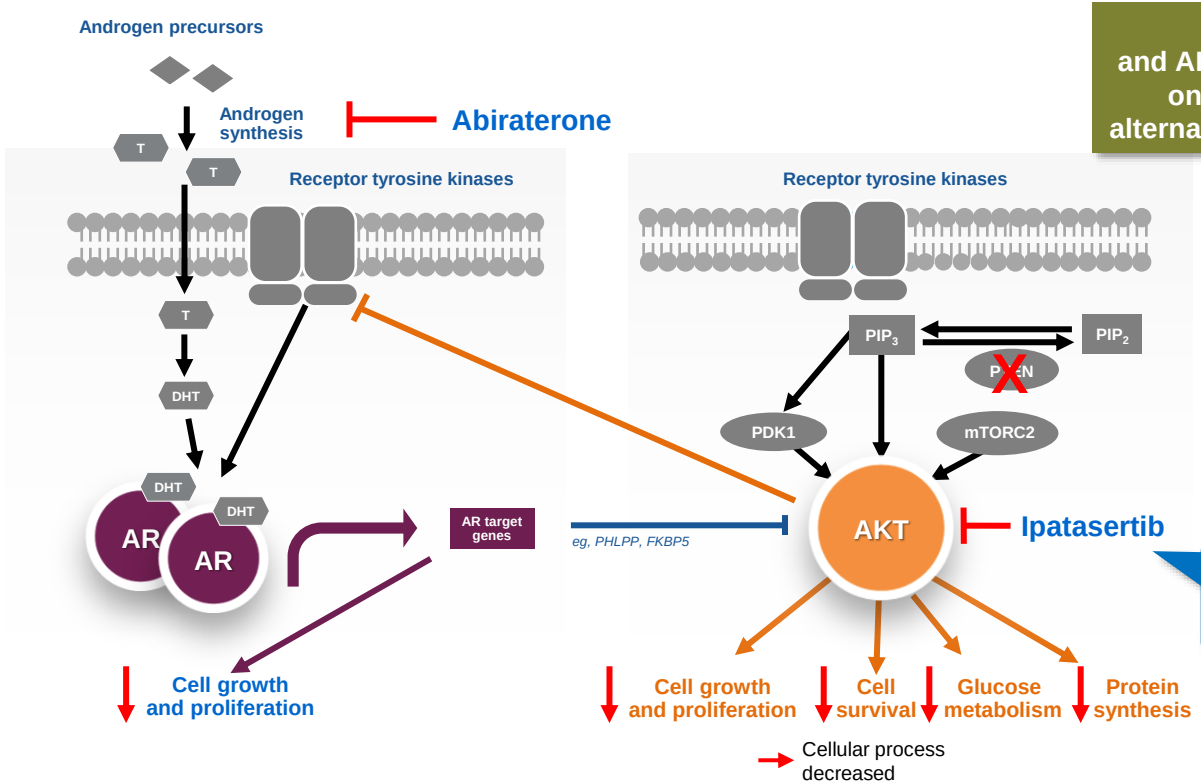
Rationale for dual pathway inhibition



Cross talk between the PI3K/AKT and AR pathways leads to reciprocal activation when one of the pathways is inhibited, providing an alternative mechanism for tumour growth and survival

Dual targeting of both pathways may increase anti-tumour activity

Ipatasertib is a potent, novel, selective, ATP-competitive inhibitor of all 3 isoforms of AKT

1. Lin J, et al. *Clin Cancer Res.* 2013; 2. Carver BS, et al. *Cancer Cell.* 2011; 3. Bitting RL, Armstrong AJ. *Endocr Relat Cancer.* 2013; 4. Hodgson MC, et al. *Cancer Res.* 2011; 5. Mulholland DJ, et al. *Cancer Cell.* 2011; 6. Jamaspishvili T, et al. *Nat Rev Urol.* 2018.

IPATential150 study design

Patients with asymptomatic or mildly symptomatic mCRPC (no prior treatment for mCRPC)

Stratification factors
- Tumour PTEN loss by IHC[a]
- Prior docetaxel in HSPC setting
- Progression by PSA only
- Presence of liver/lung metastases
- Geographic region

N = 1101

R 1:1

Ipatasertib (400 mg qd) + Abiraterone (1000 mg qd)[b]

Placebo + Abiraterone (1000 mg qd)[b]

Radiographically assessed disease progression

Post-treatment follow-up

- Co-primary endpoints: investigator-assessed rPFS (PCWG3 criteria) in ITT and PTEN-loss (by IHC) populations
- Secondary endpoints included: OS, time to pain progression, time to initiation of chemotherapy, ORR, investigator-assessed rPFS in PTEN-loss (by NGS) population

HSPC, hormone-sensitive prostate cancer; NGS, next-generation sequencing; PCWG3, Prostate Cancer Working Group 3; R, randomised.
[a] PTEN loss was defined as a minimum of 50% of the specimen's tumour area with no detectable PTEN staining (by Ventana IHC assay using SP218 antibody).
[b] Abiraterone (1000 mg qd) plus prednisone/prednisolone (5 mg bid).

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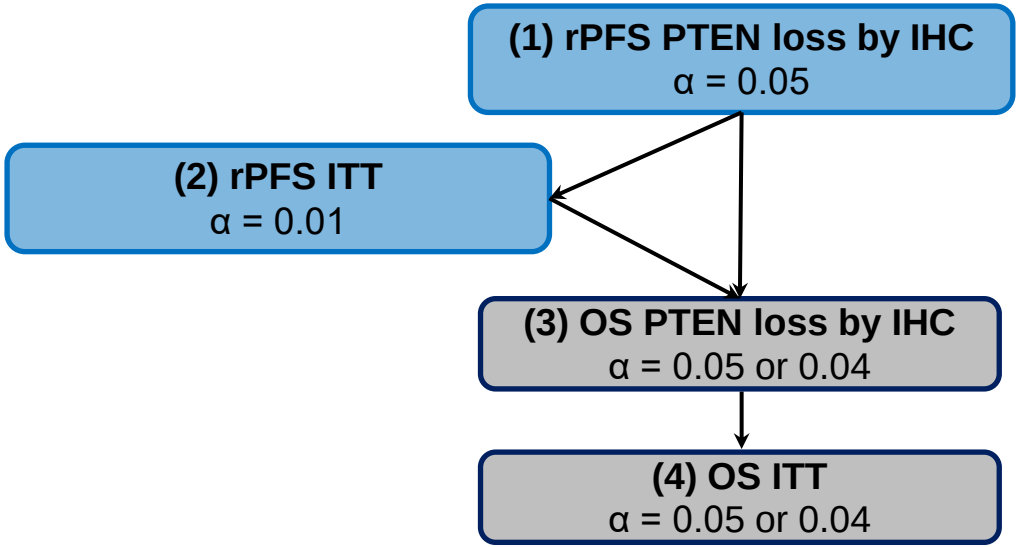
IPATential150 statistical testing hierarchy



- **If rPFS ITT is positive, OS PTEN loss α = 0.05**
- **If rPFS ITT is negative, OS PTEN loss α = 0.04**

	rPFS		OS	
Population	**PTEN by IHC**	**ITT**	**PTEN by IHC**	**ITT**
Target number of events	275	550	327	660
Observed number of events[a]	278	558	140	267

[a] At time of primary analysis.

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Demographics and baseline characteristics

Characteristic	ITT (N = 1101)		PTEN loss by IHC (n = 521)	
	Pbo + abi n = 554	Ipat + abi n = 547	Pbo + abi n = 261	Ipat + abi n = 260
Age, median (range), y	70 (44-90)	69 (47-93)	70 (47-87)	70 (48-92)
Race, n (%)				
White	386 (69.7)	376 (68.7)	195 (74.7)	197 (75.8)
Asian	109 (19.7)	110 (20.1)	41 (15.7)	36 (13.8)
Prior taxane-based therapy, n (%)	99 (17.9)	98 (17.9)	47 (18.0)	47 (18.1)
PSA-only progression factor, n (%)	277 (50.0)	273 (49.9)	125 (47.9)	124 (47.7)
Site of metastatic disease, n (%)				
Lung or liver	67 (12.1)	64 (11.7)	33 (12.6)	28 (10.8)
Bone	468 (84.5)	459 (83.9)	222 (85.1)	213 (81.9)
Lymph nodes	230 (41.5)	200 (36.6)	110 (42.1)	93 (35.8)
Other	36 (6.5)	37 (6.8)	16 (6.1)	19 (7.3)

Abi, abiraterone; ipat, ipatasertib; pbo, placebo.

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Patient disposition

Characteristic	Pbo + abi n = 554	Ipat + abi n = 547
Still on study as of clinical cutoff, n[a]	377	367
On treatment, n (%)	185 (33)	198 (36)
In survival follow-up, n (%)	192 (35)	169 (31)
Discontinued study as of clinical cutoff, n[a]	177	180
Death, n (%)	139 (25)	121 (22)
Lost to follow-up, n (%)	7 (1)	4 (1)
Withdrawal by patient, n (%)	30 (5)	51 (9)
Physician decision, n (%)	1 (0.2)	3 (1)
Other, n (%)	0	1 (0.2)[b]

Abi, abiraterone; ipat, ipatasertib; pbo, placebo.
[a] Data cutoff, 16 Mar 2020. [b] Screen failure but accidentally randomised.

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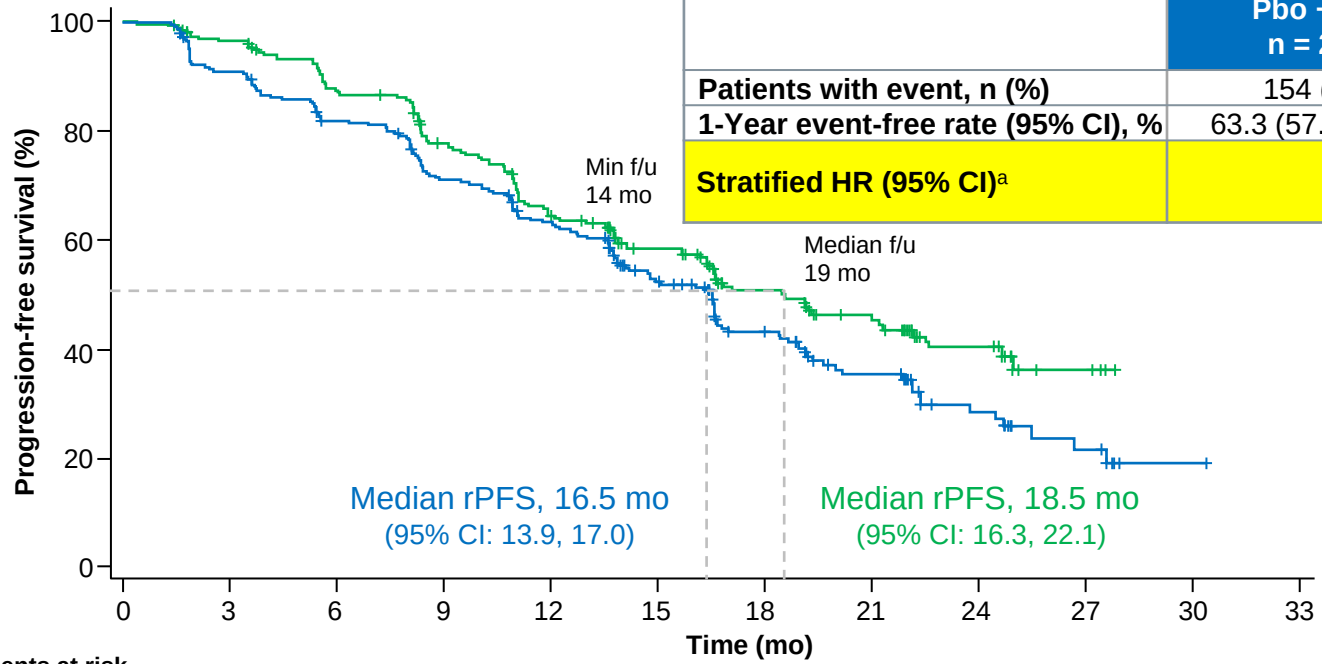
rPFS in the PTEN-loss by IHC population

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



Patients at risk

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

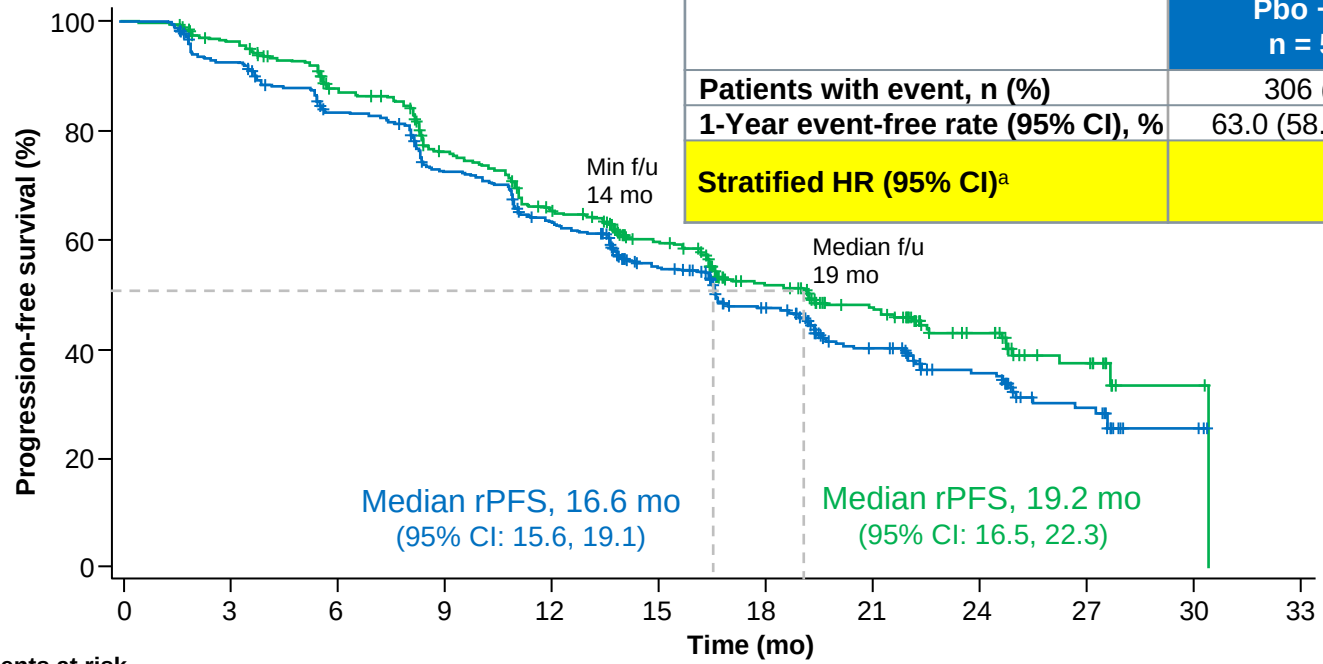
Data cutoff, 16 Mar 2020; median f/u 19 months. f/u, follow-up.

[a] Stratified for prior taxane-based therapy and PSA-only progression factor.

[b] **Statistically significant at α = 0.05 level.**

rPFS in the ITT population

	Pbo + abi n = 554	Ipat + abi n = 547
Patients with event, n (%)	306 (55)	252 (46)
1-Year event-free rate (95% CI), %	63.0 (58.9, 67.1)	65.3 (61.1, 69.5)
Stratified HR (95% CI)[a]	**0.84 (0.71, 0.99)** *P* = 0.0431[b]	



Patients at risk

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

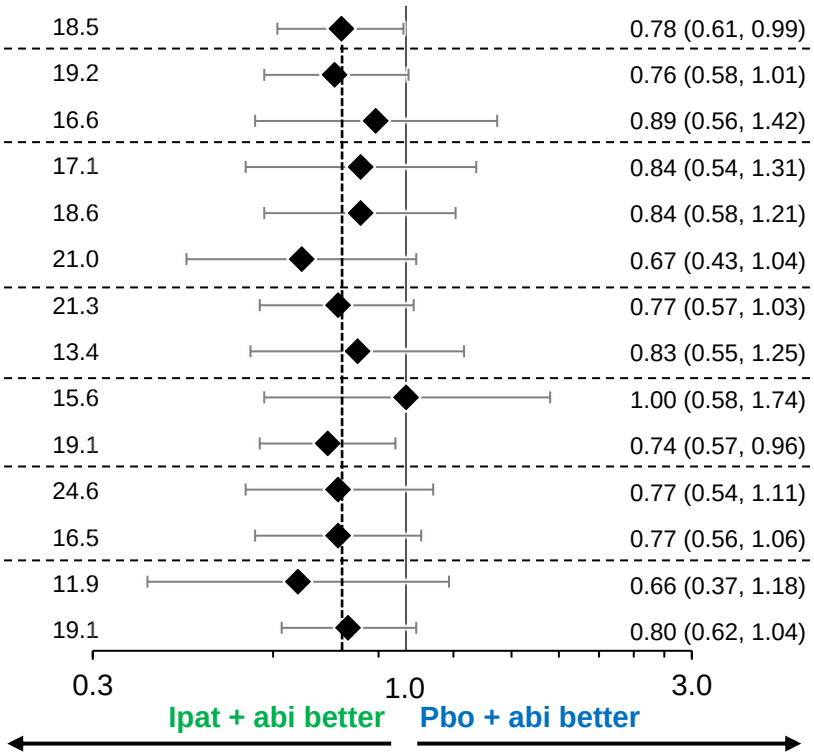
Data cutoff, 16 Mar 2020; median f/u 19 months. f/u, follow-up.

[a] Stratified for prior taxane-based therapy, PSA-only progression factor and tumour PTEN loss status by IHC.

[b] Did not meet statistical significance at α = 0.01 level.

rPFS in key subgroups of the PTEN-loss by IHC population

Characteristic		Patients, n	Pbo + abi Median, mo	Ipat + abi Median, mo	HR (95% CI)
All patients (PTEN loss)		521	16.5	18.5	0.78 (0.61, 0.99)
ECOG PS	0	397	16.6	19.2	0.76 (0.58, 1.01)
	1	123	13.6	16.6	0.89 (0.56, 1.42)
Age, y	< 65	145	18.4	17.1	0.84 (0.54, 1.31)
	65 to < 75	229	16.6	18.6	0.84 (0.58, 1.21)
	≥ 75	147	13.7	21.0	0.67 (0.43, 1.04)
Lactate dehydrogenase level	≤ ULN	376	16.7	21.3	0.77 (0.57, 1.03)
	> ULN	141	10.9	13.4	0.83 (0.55, 1.25)
Prior taxane-based therapy	Yes	94	18.4	15.6	1.00 (0.58, 1.74)
	No	427	16.5	19.1	0.74 (0.57, 0.96)
Progression factor	PSA only	249	16.6	24.6	0.77 (0.54, 1.11)
	Other	272	14.2	16.5	0.77 (0.56, 1.06)
Liver or lung metastases	Yes	74	8.4	11.9	0.66 (0.37, 1.18)
	No	447	16.6	19.1	0.80 (0.62, 1.04)



ULN, upper limit of normal.

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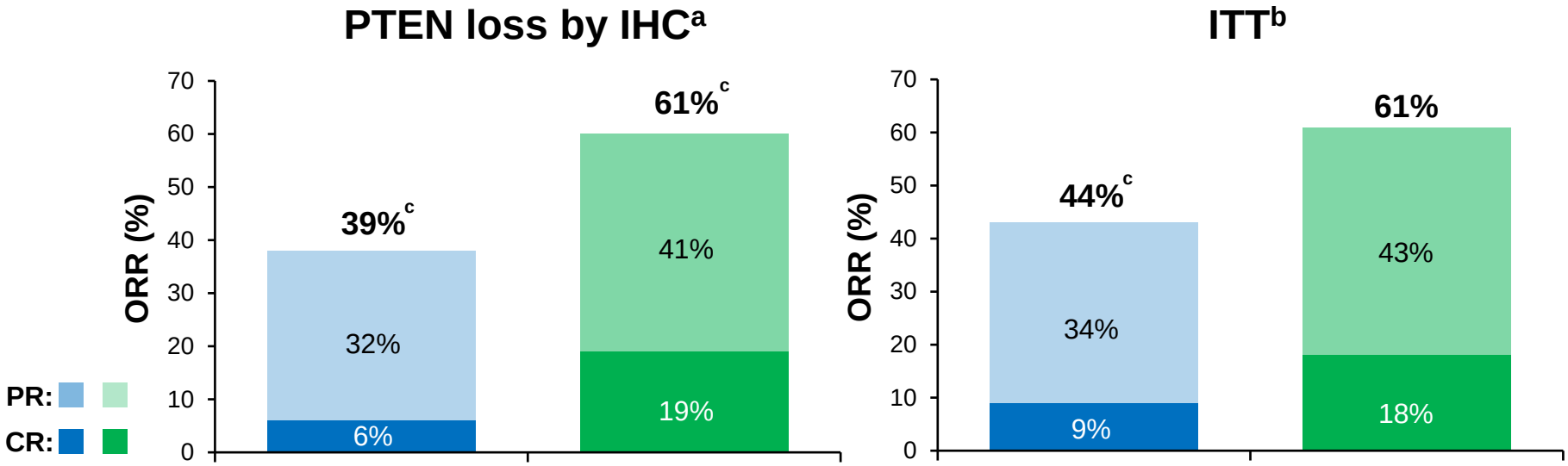
Confirmed ORR and DOR



	Pbo + abi	Ipat + abi	Pbo + abi	Ipat + abi
DOR, median (95% CI), mo	13.9 (12.1, 18.0)	17.7 (14.0, NE)	16.2 (12.9, 19.2)	15.9 (13.0, 20.5)

CR, complete response; DOR, duration of response; ORR, objective response rate; PR, partial response.
[a] In PTEN-loss tumour by IHC patients with baseline measurable disease (n = 195; n = 99 in ipat + abi and n = 96 in pbo + abi).
[b] In ITT patients with baseline measurable disease (n = 426; n = 201 in ipat + abi and n = 225 in pbo + abi).
[c] Sum of PR and CR does not equal ORR due to rounding.

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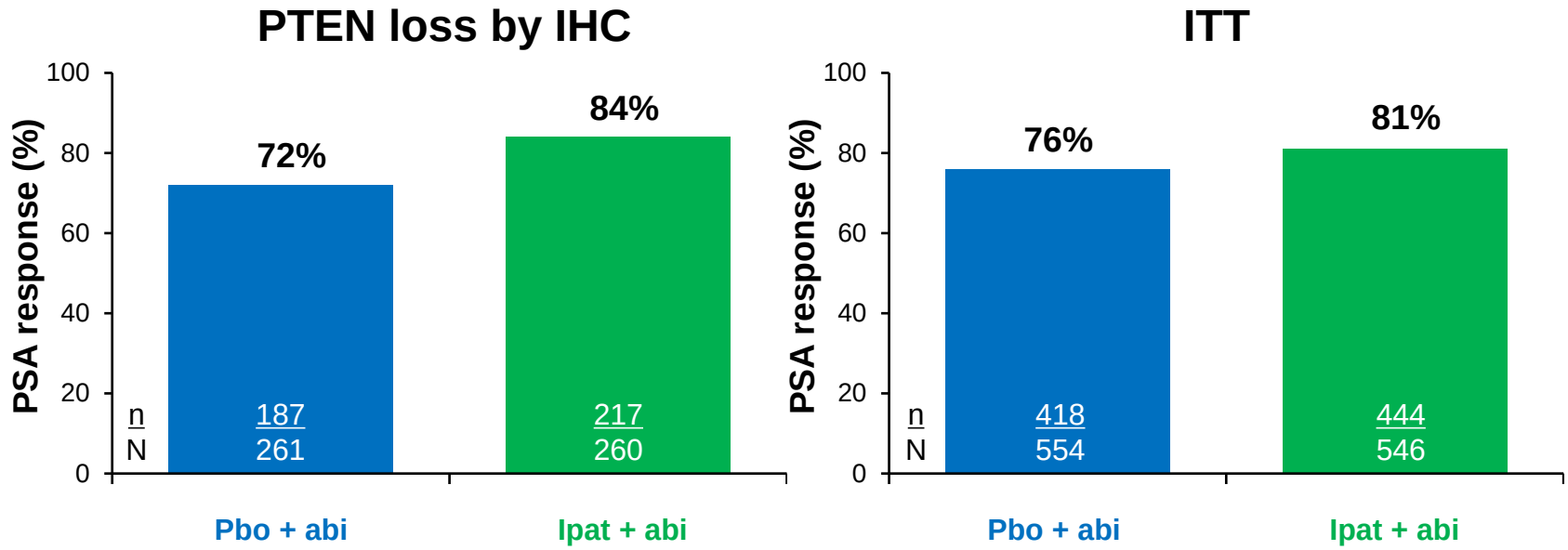
PSA response rate



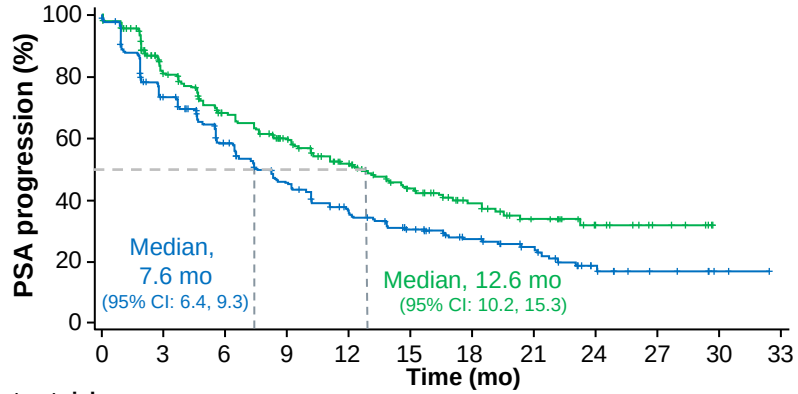
	PTEN loss by IHC	ITT
Difference, % (95% CI)	11.8 (4.3, 19.3)	5.9 (0.8, 10.9)
P value	*P* = 0.0012[a]	*P* = 0.0183[a]

[a] Descriptive.

Time to PSA progression

PTEN loss by IHC

	Pbo + abi n = 261	Ipat + abi n = 260
Patients with event, n (%)	176 (67)	130 (50)
Stratified HR (95% CI)[a]	0.69 (0.55, 0.87) *P* = 0.0013[c]	

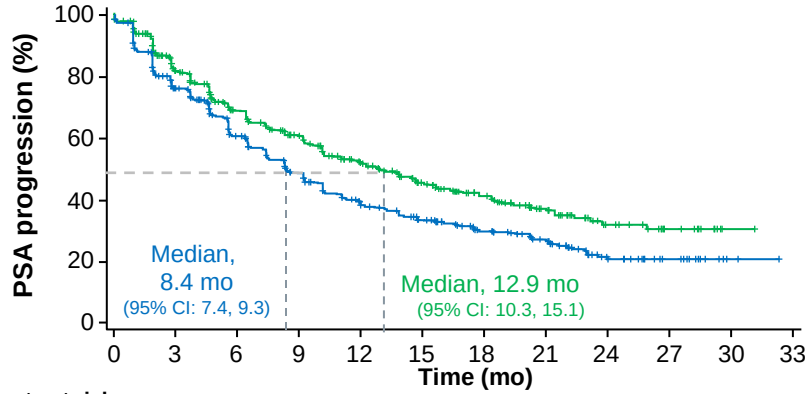


Patients at risk

Pbo + abi	261	180	132	99	73	55	36	25	11	5	2
Ipat + abi	260	161	138	114	69	66	42	25	12	6	

ITT

	Pbo + abi n = 554	Ipat + abi n = 547
Patients with event, n (%)	364 (66)	267 (49)
Stratified HR (95% CI)[b]	0.73 (0.62, 0.85) *P* < 0.0001[c]	



Patients at risk

Pbo + abi	554	396	293	226	169	134	93	62	28	14	2
Ipat + abi	547	281	293	241	184	136	95	56	25	12	1

Data cutoff, 16 Mar 2020; median follow-up, 19 months.

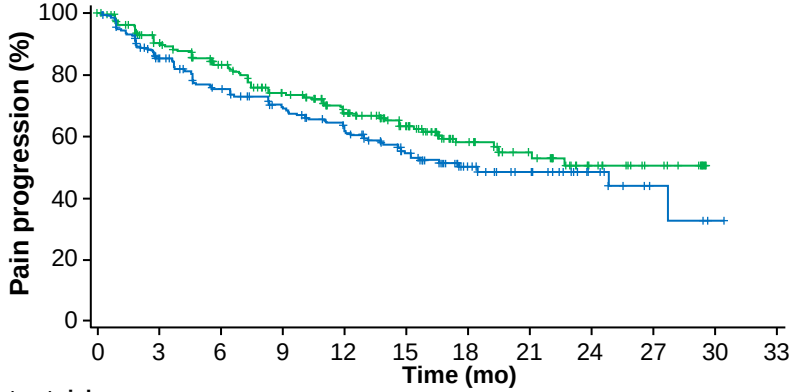
[a] Stratified for prior taxane-based therapy and PSA-only progression factor.

[b] Stratified for prior taxane-based therapy, PSA-only progression factor and tumour PTEN loss status by IHC. [c] Descriptive.

Time to pain progression

PTEN loss by IHC

	Pbo + abi n = 261	Ipat + abi n = 260
Patients with event, n (%)	95 (36)	73 (28)
Stratified HR (95% CI)[a]	0.77 (0.56, 1.04)	

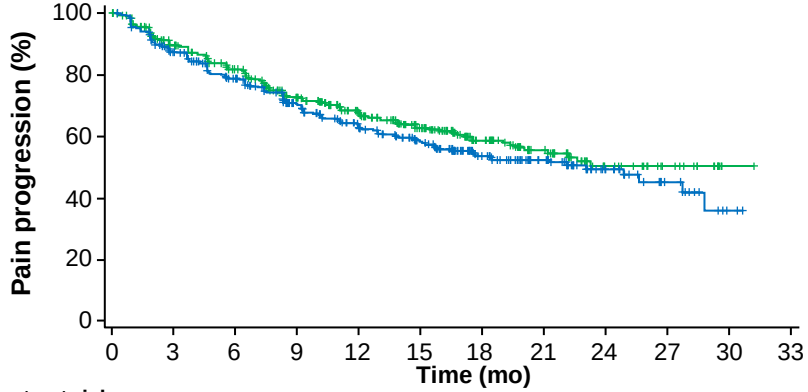


Patients at risk

Pbo + abi	261	177	143	120	99	74	40	26	13	4	1
Ipat + abi	260	175	148	121	101	72	45	30	16	8	

ITT

	Pbo + abi n = 554	Ipat + abi n = 547
Patients with event, n (%)	187 (34)	156 (29)
Stratified HR (95% CI)[b]	0.87 (0.70, 1.08)	



Patients at risk

Pbo + abi	554	380	317	254	206	161	95	61	31	15	2
Ipat + abi	547	372	313	249	196	140	93	58	28	14	1

Data cutoff, 16 Mar 2020; median follow-up, 19 months.

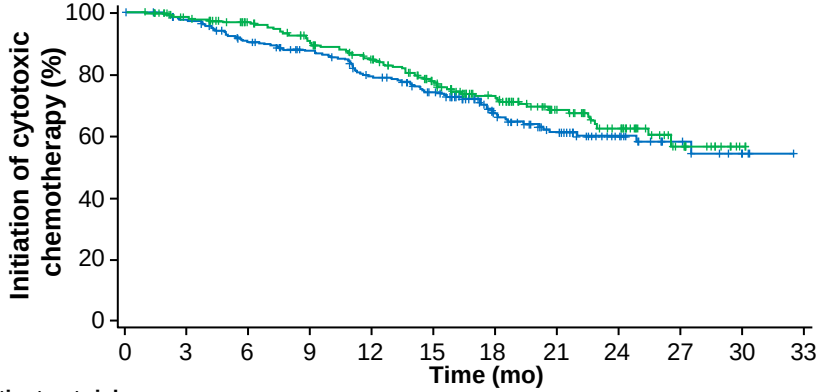
[a] Stratified for prior taxane-based therapy and PSA-only progression factor.

[b] Stratified for prior taxane-based therapy, PSA-only progression factor and tumour PTEN loss status by IHC.

Time to initiation of cytotoxic chemotherapy

PTEN loss by IHC

	Pbo + abi n = 261	Ipat + abi n = 260
Patients with event, n (%)	83 (32)	71 (27)
Stratified HR (95% CI)[a]	0.84 (0.61, 1.15)	

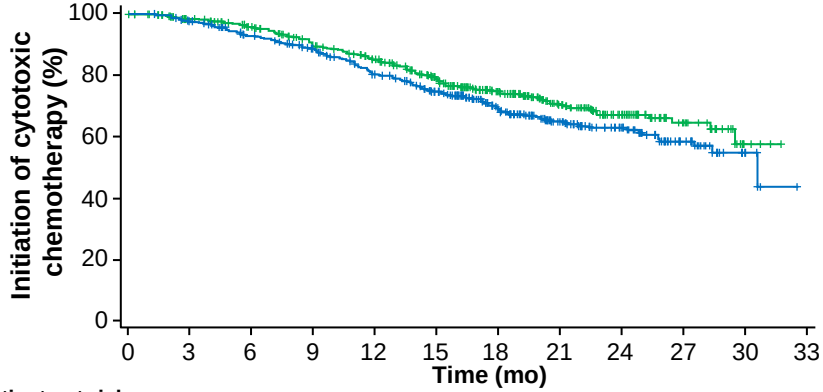


Patients at risk

Pbo + abi	261	249	223	207	182	152	98	67	36	19	6
Ipat + abi	260	243	224	203	181	155	106	70	41	15	2

ITT

	Pbo + abi n = 554	Ipat + abi n = 547
Patients with event, n (%)	172 (31)	138 (25)
Stratified HR (95% CI)[b]	0.80 (0.64, 1.00)	



Patients at risk

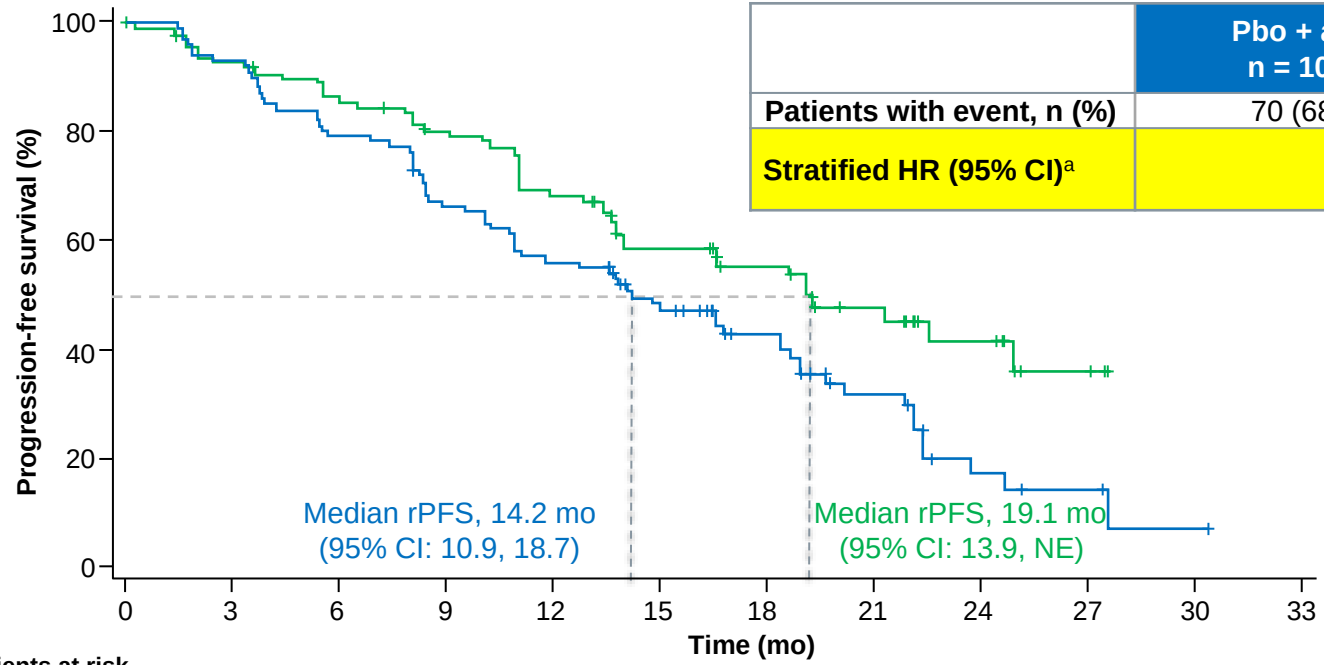
Pbo + abi	554	531	487	449	392	331	231	158	92	44	11
Ipat + abi	547	516	447	431	390	331	236	154	87	41	7

Data cutoff, 16 Mar 2020; median follow-up, 19 months.

[a] Stratified for prior taxane-based therapy and PSA-only progression factor.

[b] Stratified for prior taxane-based therapy, PSA-only progression factor and tumour PTEN loss status by IHC.

rPFS in the NGS-defined PTEN-loss population



	Pbo + abi n = 103	Ipat + abi n = 105
Patients with event, n (%)	70 (68)	47 (45)
Stratified HR (95% CI)[a]	0.65 (0.45, 0.95) *P* = 0.0206[b]	

Patients at risk

Pbo + abi	103	94	80	66	56	40	29	17	6	4	1
Ipat + abi	105	92	83	74	63	45	30	21	12	4	

Data cutoff, 16 Mar 2020; median follow-up, 19 months.

[a] Stratified for prior taxane-based therapy and PSA-only progression factor. [b] Descriptive.

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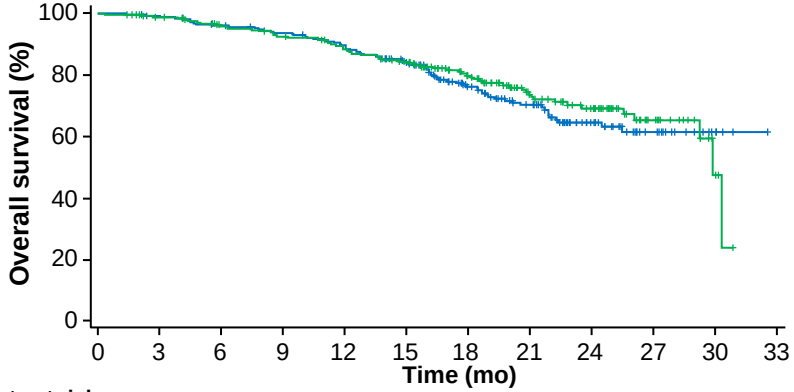
Overall survival

PTEN loss by IHC

	Pbo + abi n = 261	Ipat + abi n = 260
Patients with event, n (%)	75 (29)	65 (25)
Stratified HR (95% CI)[a]	0.91 (0.65, 1.27)	

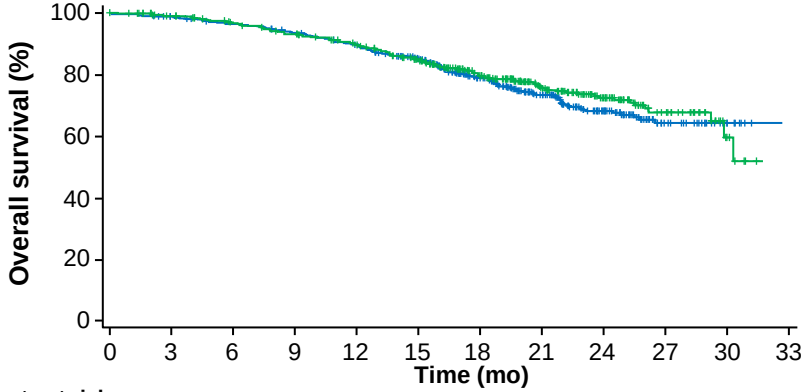


Patients at risk

Pbo + abi	261	254	244	235	224	199	137	98	51	23	8
Ipat + abi	260	247	230	220	206	190	137	91	60	23	4

ITT

	Pbo + abi n = 554	Ipat + abi n = 547
Patients with event, n (%)	143 (26)	124 (23)
Stratified HR (95% CI)[b]	0.93 (0.73, 1.18)	



Patients at risk

Pbo + abi	554	541	520	499	474	424	306	213	123	53	15
Ipat + abi	547	523	497	472	445	399	292	195	118	51	10

Data cutoff, 16 Mar 2020; median follow-up, 19 months.

[a] Stratified for prior taxane-based therapy and PSA-only progression factor.

[b] Stratified for prior taxane-based therapy, PSA-only progression factor and tumour PTEN loss status by IHC.

Drug exposure and safety summary

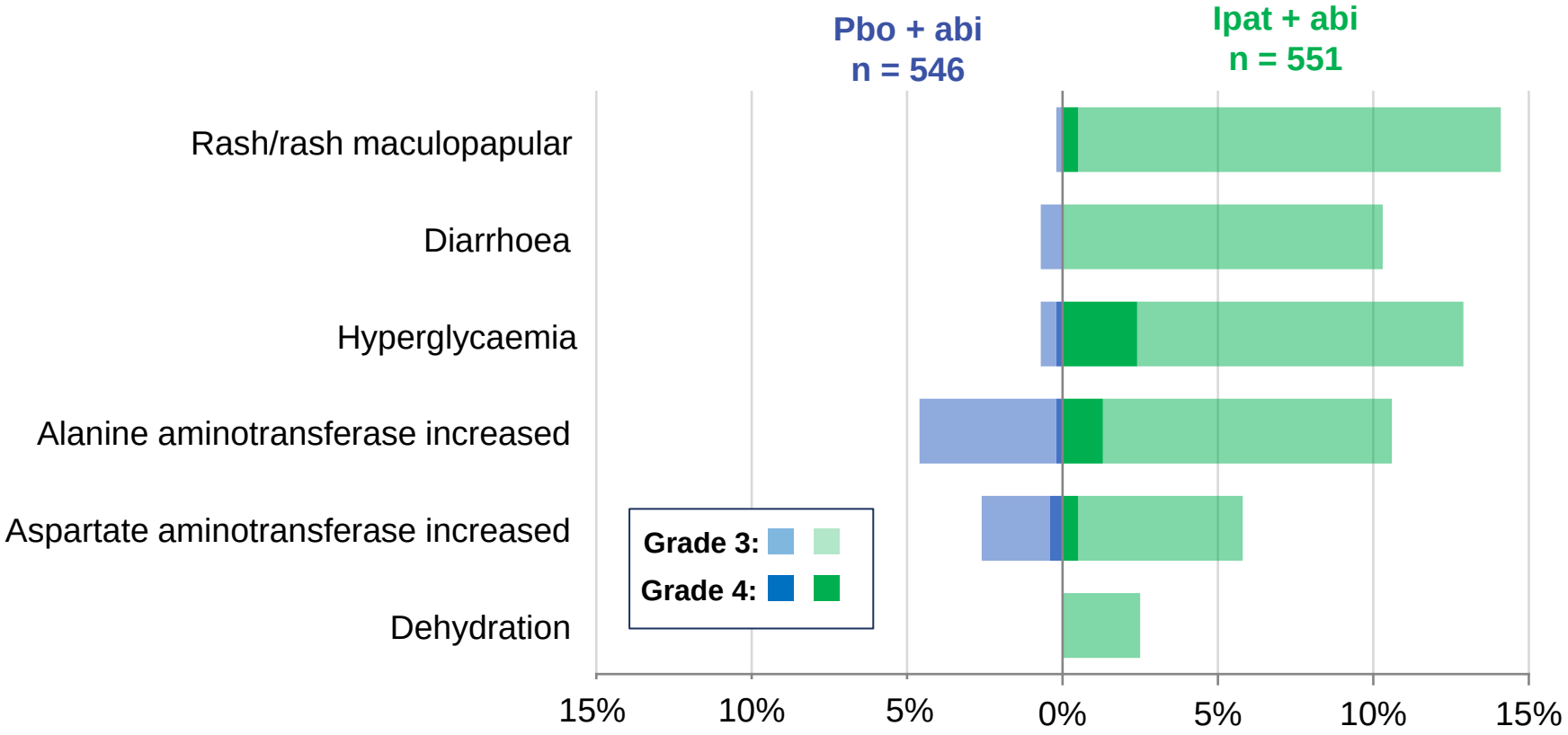
Exposure	Pbo + abi n = 546	Ipat + abi n = 551
Treatment duration, median (range), mo		
Ipat/pbo	14.0 (0-32)	11.1 (0-31)
Abi	14.0 (0-32)	14.2 (0-31)

Safety summary, n (%)	Pbo + abi n = 546	Ipat + abi n = 551
All grade AEs	519 (95.1)	548 (99.5)
Grade 3-5 AEs	213 (39.0)	386 (70.1)
Grade 5 AEs	20 (3.7)	24 (4.4)
Serious AEs	124 (22.7)	218 (39.6)
AEs leading to discontinuation of pbo/ipat	28 (5.1)	116 (21.1)
AEs leading to dose reduction of pbo/ipat	34 (6.2)	220 (39.9)
AEs leading to dose interruption of pbo/ipat	125 (22.9)	319 (57.9)
AEs leading to discontinuation of abi	22 (4.0)	47 (8.5)

de Bono J. IPATential150. ESMO 2020. https://bit.ly/31s8gje

Grade 3 and 4 AEs

≥ 2% difference between treatment arms



de Bono J. IPATential150. ESMO 2020. https://bit.ly/31s8gje

Conclusions

- In this primary endpoint analysis, ipatasertib plus abiraterone as a first-line treatment for mCRPC resulted in significantly superior rPFS and anti-tumour activity compared with placebo plus abiraterone in patients with PTEN-loss mCRPC
  - Improvement of rPFS in the ITT population was not statistically significant
- Ipatasertib was associated with improved time to PSA progression and PSA response, as well as higher ORR in patients with measurable disease at baseline
  - Overall survival and other secondary endpoints remain immature and will require further follow-up
- Increased toxicity was observed with the addition of ipatasertib to abiraterone, in line with prior observations in clinical studies, with a high proportion having dose alterations
  - Drug discontinuations may be avoided by instituting prophylactic loperamide and antihistamine for managing diarrhoea and cutaneous adverse events, respectively
- Combined AR and AKT blockade with ipatasertib plus abiraterone improves clinical outcomes over AR blockade alone for PTEN-loss mCRPC, a poor-prognosis subset

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THANK YOU