AIOM Post ESMO 2019

Tumori Genitourinari

Nuove prospettive

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Disclosures

Dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

- Ipsen
- Janssen
- MSD
- Novartis
- Pfizer
- Sanofi

Agenda

- The intensification strategy: the TITAN trial
- Management of patients with sRCC
- Sequence in mCRPC
- Olaparib in mCRPC, the new option for DRD patients.
- Atezolizumab ± Chemioterapia nella I linea per neoplasia vescicale

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The intensification strategy: the TITAN trial

STUDY DESIGN AND ENDPOINTS

TITAN

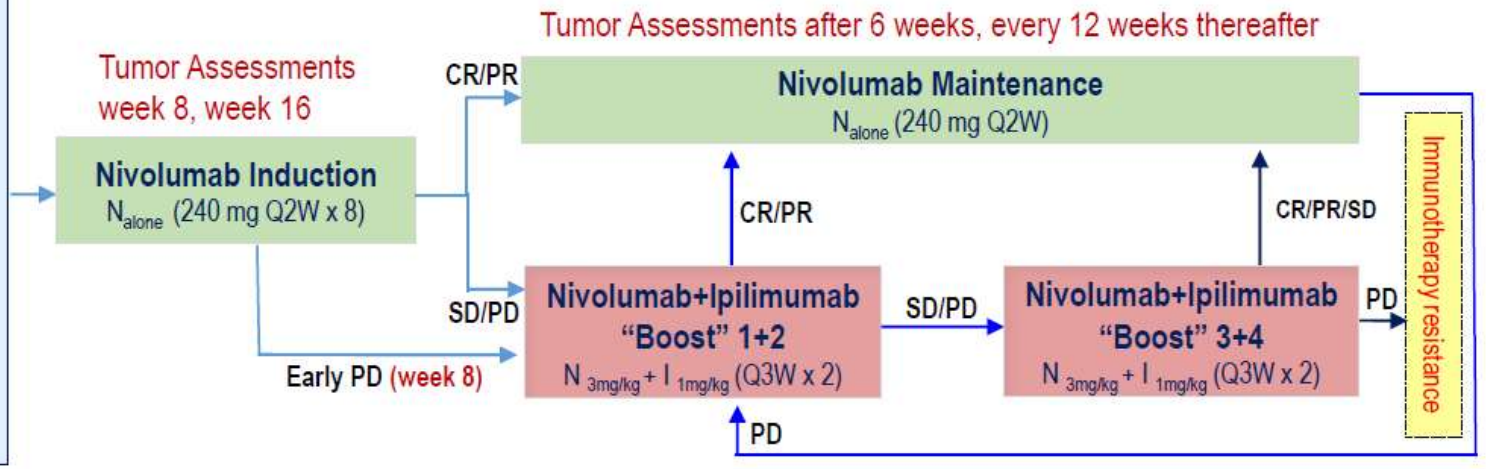
Tailored ImmunoTherapy Approach with Nivolumab in RCC (TITAN-RCC)

n=200

EudraCT number: 2016-002307-26

Key Inclusion Criteria

- Metastatic/locally advanced RCC, histologically confirmed
- Clear cell component
- Intermediate/high risk by IMDC
- Untreated or pretreated with 1 prior TKI (⇨ 1st or 2nd line*)
- Measurable disease as per RECIST v1.1
- KPS ≥ 70
- Evaluable tumor sample for PD-L1 expression (Dako PD-L1 IHC 28-8 pharmDx antibody, central lab)



* Independent cohorts

Primary endpoint: Overall Response Rate (ORR)
Secondary endpoints: PFS, OS, RR after Nivo+Ipi "Boosts"
Safety (TRAE), QoL (FKSI-19)

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IMDC: International Metastatic Renal Cell Carcinoma Database Consortium (Heng DY, *et al*. Lancet Oncol 2013; 14:141-8)

The intensification strategy: the TITAN trial

BASELINE CHARACTERISTICS

Full analysis Set (FAS): **n=207** patients (all patients started nivolumab therapy)

		1L (n=108)	2L (n=99)	Total (n=207)
Median age, years (range)		**63.5** (20-87)	**66** (44-84)	**65** (20-87)
Male gender, n (%)		76 (**70.4**)	71 (**71.7**)	147 (**71.0**)
IMDC Risk factors	**Karnofsky Performance Status 80-100%**, n (%)	86 (**79.6**)	80 (**80.8**)	166 (**80.2**)
IMDC Risk factors	**Initial RCC diagnosis ≤12 months**, n (%)	87 (**80.6**)	57 (**57.6**)	144 (**69.6**)
IMDC Risk factors	**Haemoglobin <LLN***, n (%)	52 (**48.1**)	60 (**60.6**)	112 (**54.1**)
IMDC Risk factors	**Platelet count >ULN†**, n (%)	23 (**21.3**)	17 (**17.2**)	40 (**19.3**)
IMDC Risk factors	**Neutrophil count** (absolute) **> ULN**, n (%)	17 (**15.7**)	9 (**9.1**)	26 (**12.6**)
IMDC Risk factors	**Calcium** (corrected) **> ULN**, n (%)	13 (**12.0**)	14 (**14.1**)	27 (**13.0**)
IMDC Risk group, n (%)	**- Favorable**	3 (**2.8**)	3 (**3.0**)	6 (**2.9**)
	- Intermediate	72 (**66.7**)	74 (**74.7**)	146 (**70.5**)
	- Poor	33 (**30.6**)	22 (**22.2**)	55 (**26.6**)
PD-L1 expression, n (%)#	**≥ 1**	42 (**40.8**)	21 (**22.8**)	63 (**32.3**)

Dako PD-L1 IHC 28-8 pharmDx antibody

* LLN, Lower Limit of Normal; † ULN, Upper Limit of Normal

The intensification strategy: the TITAN trial

EFFICACY – ANTITUMOR ACTIVITY

Median follow-up time: 36.2 weeks (Minimum planned follow-up time: 30 weeks)

	1L (n=108)		2L (n=99)		Total (n=207)	
	N_{alone} #	N ± N+I †	N_{alone} #	N ± N+I †	N_{alone} #	N ± N+I †
ORR (BOR), n (%)	31 (**28.7**)	40 (**37.0**)	18 (**18.2**)	28 (**28.3**)	49 (**22.7**)	68 (**32.9**)
Complete response, n (%)	2 (**1.9**)	2 (**1.9**)	**0**	4 (**4.0**)	2 (**1.0**)	6 (**2.9**)
Partial response, n (%)	29 (**26.9**)	38 (**35.2**)	18 (**18.2**)	24 (**24.2**)	47 (**22.7**)	62 (**30.0**)
Stable disease, n (%)	26 (**24.1**)	26 (24.1)	23 (**23.2**)	25 (**25.3**)	49 (**23.7**)	51 (**24.6**)
Progressive disease, n (%)	13 (**12.0**)	38 (**35.2**)	16 (**16.2**)	43 (**43.4**)	29 (**14.0**)	81 (**39.6**)
Early Progressive disease / 'Boost' Week 8, n (%)	22 (**20.4**)		26 (**26.3**)		48 (**23.2**)	
Not evaluable *, n (%)	16 (**14.8**)	4 (**3.7**)	16 (**16.2**)	3 (**3.0**)	32 (**15.5**)	7 (**3.4**)

- 64.3% of all patients (133/207) received at least one ‚boost' cycle

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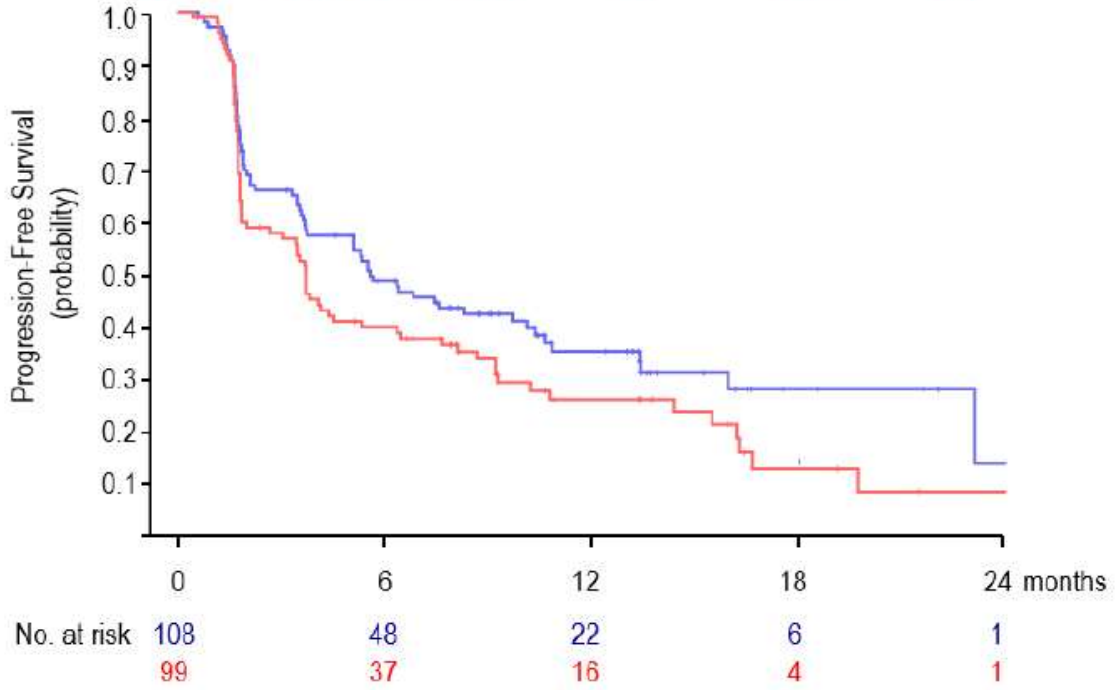
* i.e. including patients with early end of study, e.g. due to death or due to treatment-related adverse event (TRAE);
# Confirmed overall assessment at week 16; † BOR, Best Overall Response

The intensification strategy: the TITAN trial

PROGRESSION-FREE SURVIVAL

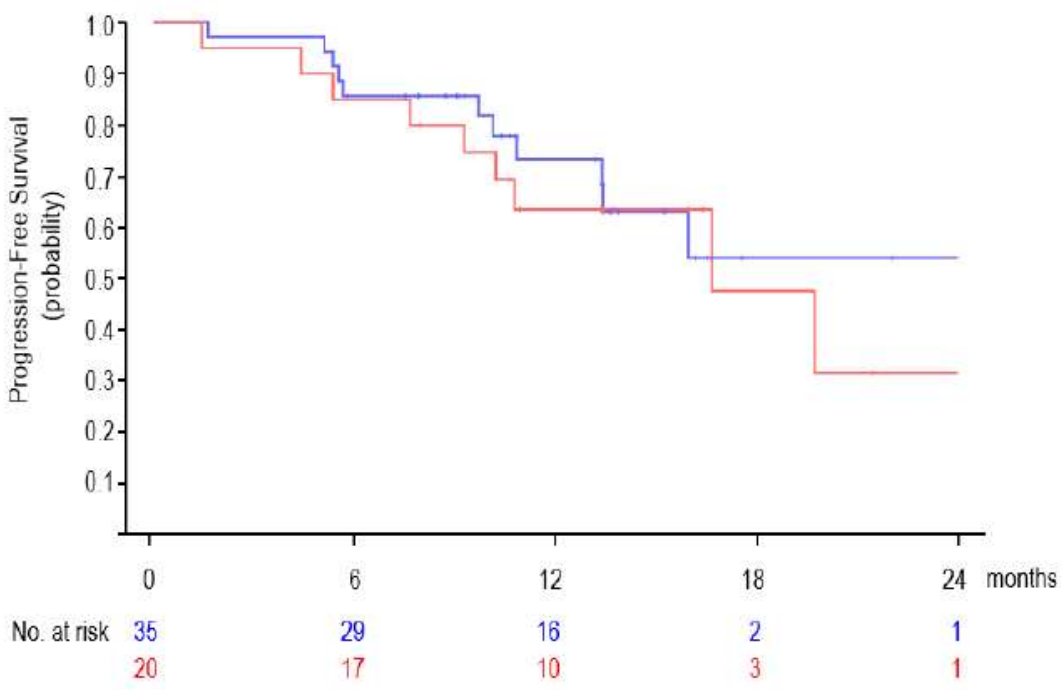
All Patients (Full-analysis set) *

Median PFS, months (95% CI) **		PFS rate	6-months,	12 months
1L	5.54 (3.64 – 10.07)	1L	49%	35%
2L	3.67 (1.84 – 5.31)	2L	39%	25%



Patients with initial response to N_{alone} *

Median PFS, months (95% CI) **		PFS rate	6-months,	12 months
1L	not reached	1L	86%	73%
2L	16.6 (9.2 – n.a.)	2L	85%	64%



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* PFS is calculated from start of therapy

Median follow-up time 8.3 months (36.2 weeks)

The intensification strategy: the TITAN trial

SAFETY OVERVIEW

	1L (n=108)		2L (n=99)		Total (n=207)	
	Events	n (%)	Events	n (%)	Events	n (%)
Treatment-related AE						
Any grade	402	89 (**82.4**)	397	80 (**80.8**)	799	169 (**81.6**)
Grade 3-4	49	29 (**26.9**)	54	34 (**34.3**)	103	63 (**30.4**)
Grade 5	2	2 (**1.9**)	-	-	2	2 (**1.0**)
Serious AE						
Treatment-related serious AE	33	26 (**24.1**)	32	27 (**27.3**)	65	53 (**25.6**)
AE leading to any action regarding study drug(s)						
Dose delayed / interrupted	50	25 (**23.1**)	39	23 (**23.2**)	89	48 (**23.2**)
Discontinued	23	15 (**13.9**)	26	20 (**20.2**)	49	35 (**16.9**)
AE leading to any required treatment						
Drug treatment	136	65 (**60.2**)	134	62 (**62.6**)	270	127 (**61.4**)
Non-drug treatment	6	5 (**4.6**)	14	8 (**8.1**)	20	13 (**6.3**)

One patient may have several events, of several grades and categories

The intensification strategy: the TITAN trial

TREATMENT-RELATED ADVERSE EVENTS IN ≥ 5% OF PATIENTS

Preferred Term (%)		1L (n=108)		2L (n=99)		Total (n=207)	
		Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Total subjects with an event		82.4	26.9	80.8	34.3	81.6	30.4
Endocrine	Hyperthyroidism	8.3	0	2.0	0	5.3	0
	Hypothyroidism	4.6	0.9	10.1	0	7.2	0.5
Gastrointestinal	Diarrhoea	22.2	5.6	18.2	4.0	20.3	4.8
	Nausea	10.2	0	8.1	0	9.2	0
General	Asthenia	21.3	0.9	17.2	0	19.3	0.5
	Fatigue	10.2	0	15.2	0	12.6	0
Investigations	Amylase increased	6.5	2.8	10.1	2.0	8.2	2.4
	Lipase increased	9.3	6.5	8.1	5.1	8.7	5.8
Metabolism and nutrition	Decreased appetite	12.0	0	13.1	0	12.6	0
Mucoskeleton and connective tissue	Arthralgia	6.5	0	9.1	1.0	7.7	0.5
Skin	Pruritus	20.4	0	29.3	0	24.6	0
	Rash	21.3	1.9	10.1	0	15.9	1.0

Further treatment related AEs of interest (any/grade 3/4):				
	Hepatic:	AST increased	3.9	0.5
		ALT increased	4.3	1.4
	Pulmonary:	Pneumonitis	3.4	1.4

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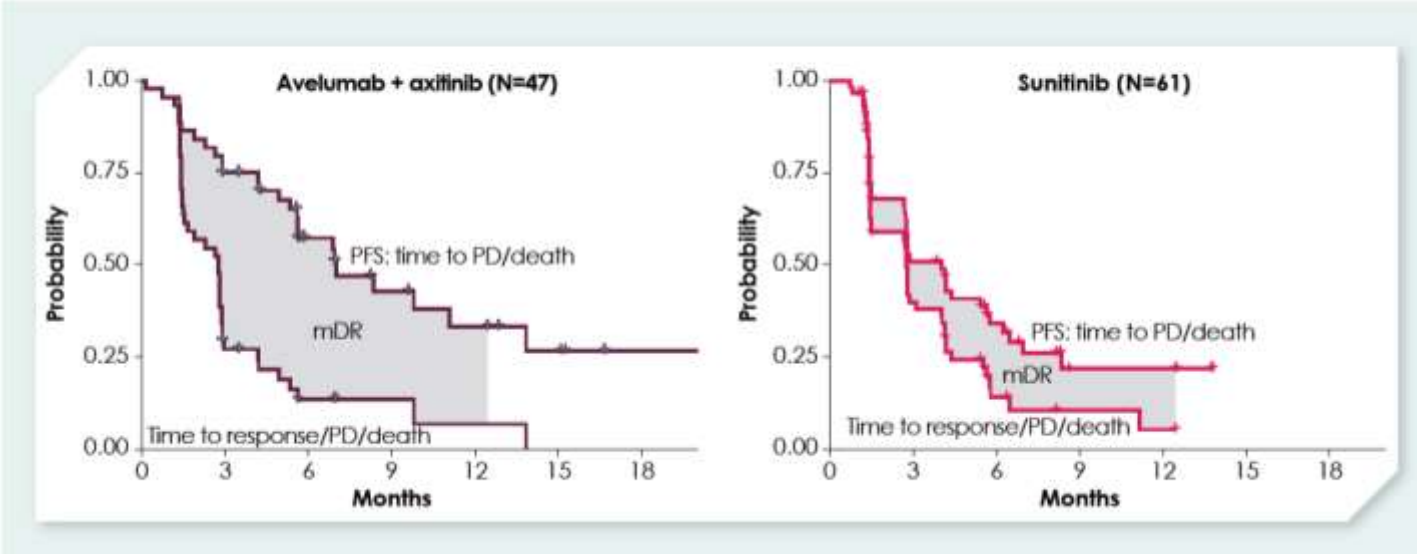
Avelumab+Axitinib in patients with sarcomatoid features

Characteristics	Avelumab + axitinib (N=47)	Sunitinib (N=61)
Median age (range), years	60.0 (29.0-73.0)	57.0 (40.0-80.0)
Sex, n (%)		
Male	35 (74.5)	52 (85.2)
Female	12 (25.5)	9 (14.8)
Prior nephrectomy, n (%)		
Yes	42 (89.4)	55 (90.2)
No	5 (10.6)	6 (9.8)
ECOG PS, n (%)		
0	28 (59.6)	33 (54.1)
1	19 (40.4)	27 (44.3)
2	0	1 (1.6)
IMDC prognostic risk group, n (%)		
Favorable	6 (12.8)	5 (8.2)
Intermediate	28 (59.6)	39 (63.9)
Poor	13 (27.7)	17 (27.9)
MSKCC prognostic risk group, n (%)		
Favorable	6 (12.8)	7 (11.5)
Intermediate	34 (72.3)	44 (72.1)
Poor	7 (14.9)	10 (16.4)
Pooled geographic region, n (%)		
North America	20 (42.6)	31 (50.8)
Europe	12 (25.5)	18 (29.5)
Asia	10 (21.3)	6 (9.8)
ROW	5 (10.6)	6 (9.8)
PD-L1 status, n (%)		
Positive	34 (72.3)	52 (85.2)
Negative	11 (23.4)	7 (11.5)
Unknown	2 (4.3)	2 (3.3)

Table 2. Antitumor activity among patients with sRCC

	Avelumab + axitinib (N=47)	Sunitinib (N=61)
Objective response rate (95% CI), %	46.8 (32.1, 61.9)	21.3 (11.9, 33.7)
Odds ratio (95% CI)	3.249 (1.300, 8.236)	–
Best overall response, n (%)		
Complete response	2 (4.3)	0
Partial response	20 (42.6)	13 (21.3)
Stable disease	13 (27.7)	18 (29.5)
Noncomplete response/ nonprogressive disease	0	1 (1.6)
Progressive disease	7 (14.9)	22 (36.1)
Not evaluable	5 (10.6)*	7 (11.5)†

Figure 4. Mean duration of response in patients with sRCC*



Choueiri TK et al, ESMO 2019 Poster 910 PD

Management of patients with sarcomatoid mRCC

OUTCOMES ACROSS TRIALS IN SARCOMATOID RCC

	Axi/Avelu		Axi/Pembro		Atezo/Bev		Ipi/Nivo (int/poor)	
	All (442)	S (47)	All (432)	S (51)	All (454)	S (68)	All (425)	S (60)
ORR	51%	47%	59%	59%	36%	49%	42%	57%
CR	3%	4%	6%	13%	5%	10%	11%	18%
PFS (months) **HR (95% CI)** **vs Sun**	13.8 0.69 (0.56-0.84)	7 0.57 (0.32-1.003)	15.1 0.69 (0.57-0.84)	NR 0.54 (0.29-1.00)	11,2 0·83 (0·70-0·97)	8.3 0.52 (0.34-0.79)	11.6 0.82 (0.64–1.05)	8.4 0.62 (0.38.0.97)
12 months OS	NA	83%	90%	N/A		56%	80%	73%

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Adapted from J. Brugarolas

De Velasco ESMO 2019

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Lo studio CARD

CARD: STUDY DESIGN

- Multicenter, randomized, open-label study

Patients with mCRPC who progressed ≤ 12 months on alternative ART (before or after docetaxel)

N = 255

RANDOMIZE

1:1

Cabazitaxel (25 mg/m² Q3W) + Prednisone + G-CSF
n = 129

Abiraterone (1000 mg QD) + Prednisone
OR
Enzalutamide (160 mg QD)
n = 126

Endpoints

Primary: rPFS

Key secondary: OS, PFS, PSA response, tumor response

Other secondary: Pain response, time to symptomatic skeletal event, safety

Stratification factors:

- ECOG PS (0/1 vs 2)
- Time to progression on first ART (0–6 vs > 6–12 months)
- Timing of ART (before vs after DOC)

Cycle duration: 3 weeks (both arms)

ECOG PS, Eastern Cooperative Oncology Group performance status; G-CSF, granulocyte-colony stimulating factor; OS, overall survival; PFS, progression-free survival; PSA, prostate specific antigen; QD, daily; Q3W, every 3 weeks; rPFS, radiographic progression-free survival.

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	Cabazitaxel (N = 129)	ART (N = 126)
Median age, years (range)	70.0 (46–85)	71.0 (45–88)
≥ 75 years, n (%)	45 (34.9)	34 (27.0)
ECOG PS 0–1, n (%)	123 (95.3)	119 (94.4)
Visceral metastases, n (%)	21 (16.3)	25 (19.8)
Type of progression at study entry, n (%)		
PSA only	11 (8.5)	10 (7.9)
Radiologic (± PSA), no pain	23 (17.8)	16 (12.7)
Pain (± PSA, ± radiologic)	86 (66.7)	90 (71.4)
Missing	9 (7.0)	10 (7.9)
Gleason 8–10 at diagnosis, n (%)	73 (56.6)	81 (64.3)
M1 disease at diagnosis, n (%)	49 (38.0)	60 (47.6)
Prior ART, n (%)		
Abiraterone / enzalutamide	56 (43.4) / 72 (55.8)	67 (53.2) / 59 (46.8)
Before / after docetaxel	50 (38.8) / 79 (61.2)	49 (38.9) / 77 (61.1)

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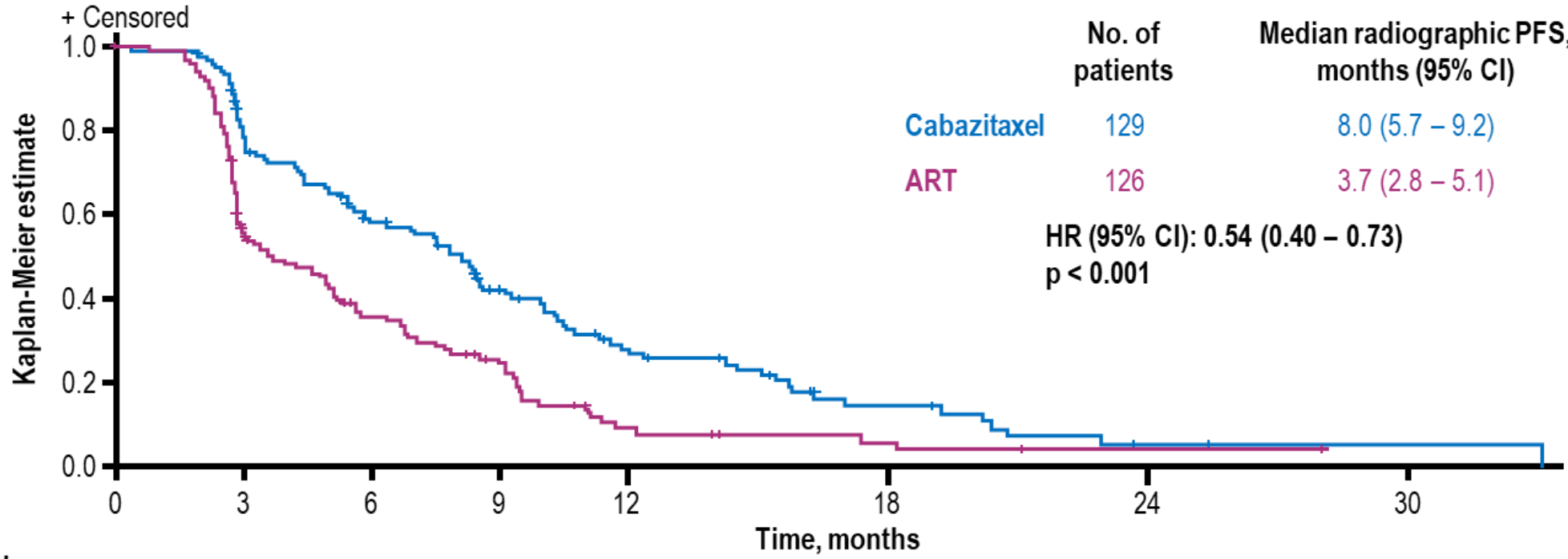
RADIOGRAPHIC PFS (PRIMARY ENDPOINT)



	No. of patients	Median radiographic PFS, months (95% CI)
Cabazitaxel	129	8.0 (5.7 – 9.2)
ART	126	3.7 (2.8 – 5.1)

HR (95% CI): 0.54 (0.40 – 0.73)
p < 0.001

No. at risk								
Cabazitaxel	129	91	64	41	23	9	2	1
ART	126	61	36	22	7	3	1	0

Radiographic PFS: Radiological tumour progression [RECIST 1.1] and/or progression of bone lesions [PCWG2] and/or death from any cause.

Data cut-off date: 27 March 2019.

CI, confidence interval.

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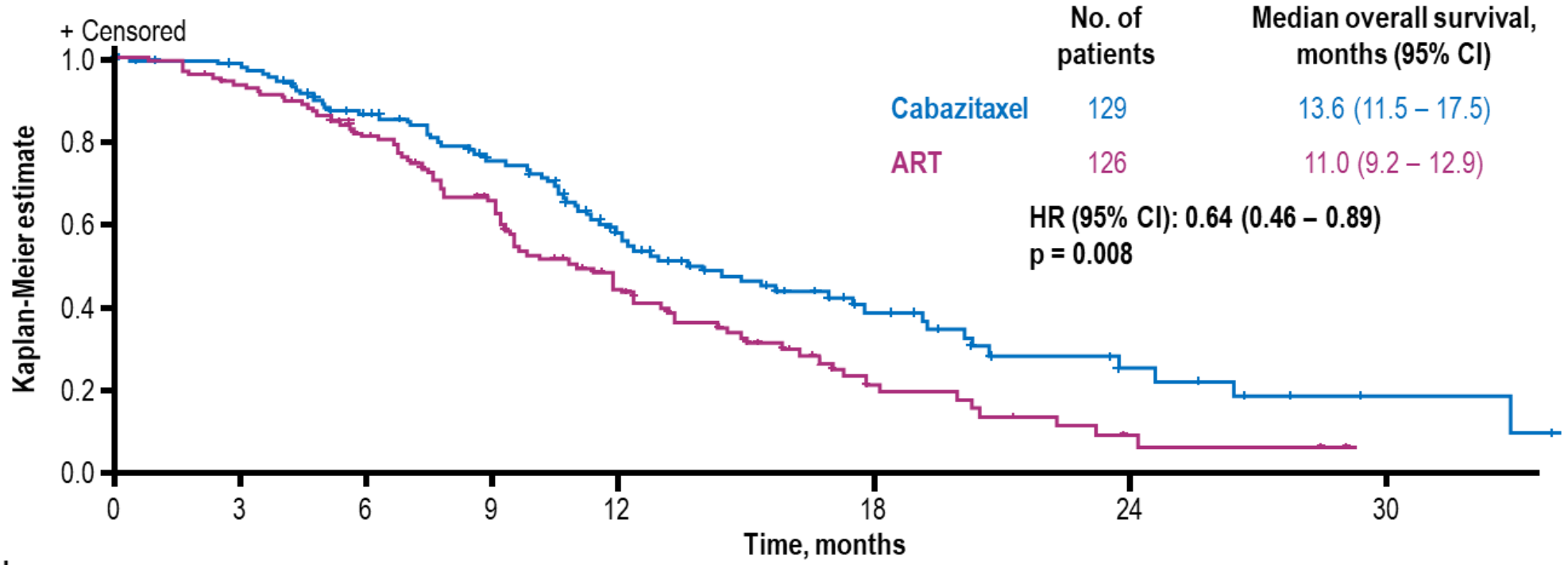
OVERALL SURVIVAL (KEY SECONDARY ENDPOINT)



	No. of patients	Median overall survival, months (95% CI)
Cabazitaxel	129	13.6 (11.5 – 17.5)
ART	126	11.0 (9.2 – 12.9)

HR (95% CI): 0.64 (0.46 – 0.89)
p = 0.008

No. at risk								
Cabazitaxel	129	122	96	77	51	21	8	2
ART	126	116	88	64	39	11	3	0

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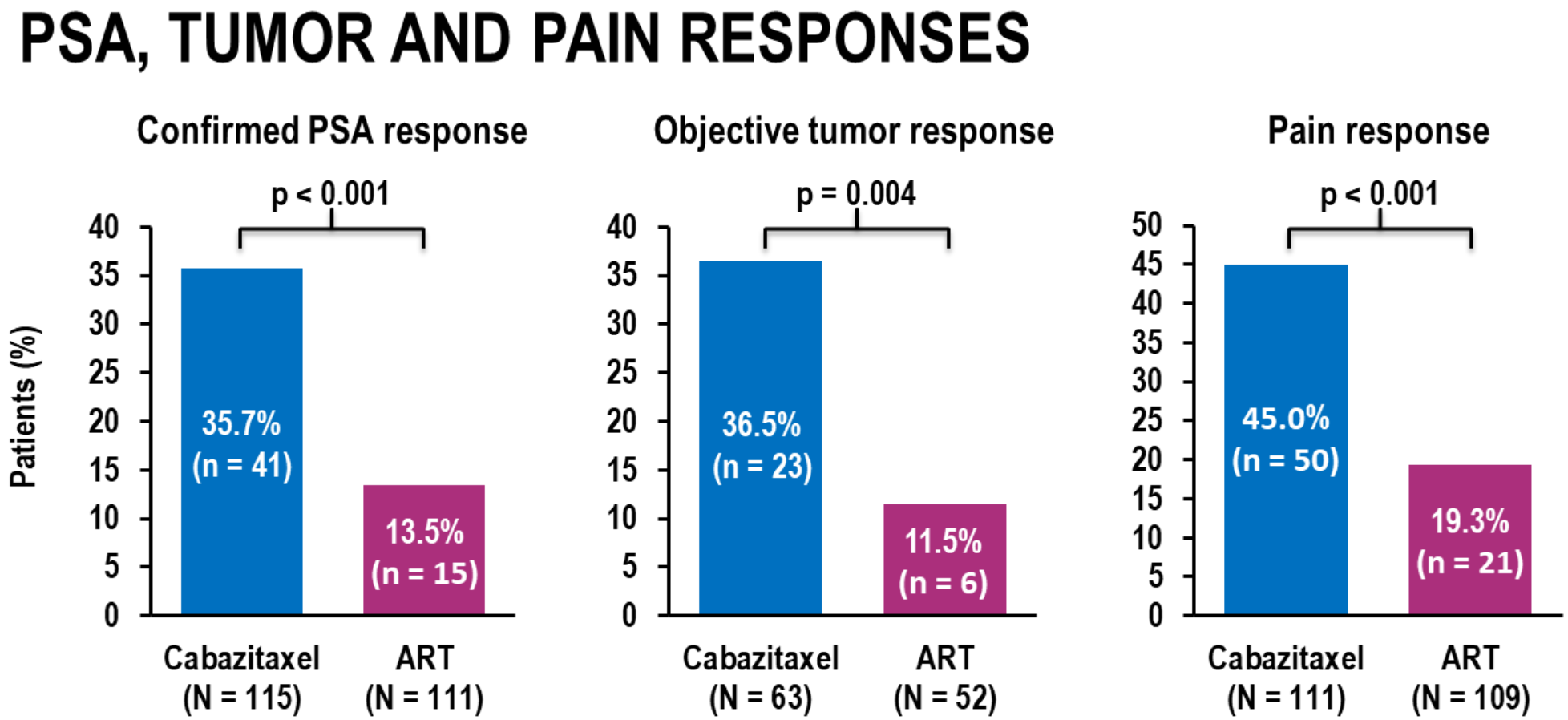

Response definitions:
PSA, PSA reduction ≥ 50% from baseline, confirmed by a second value at least three weeks later. Tumor: Complete or partial responses according to RECIST 1.1 criteria.
Pain: Decrease ≥ 30% from baseline in average BPI-SF pain intensity score at 2 consecutive evaluations ≥ 3 weeks apart without increase in analgesic usage score.

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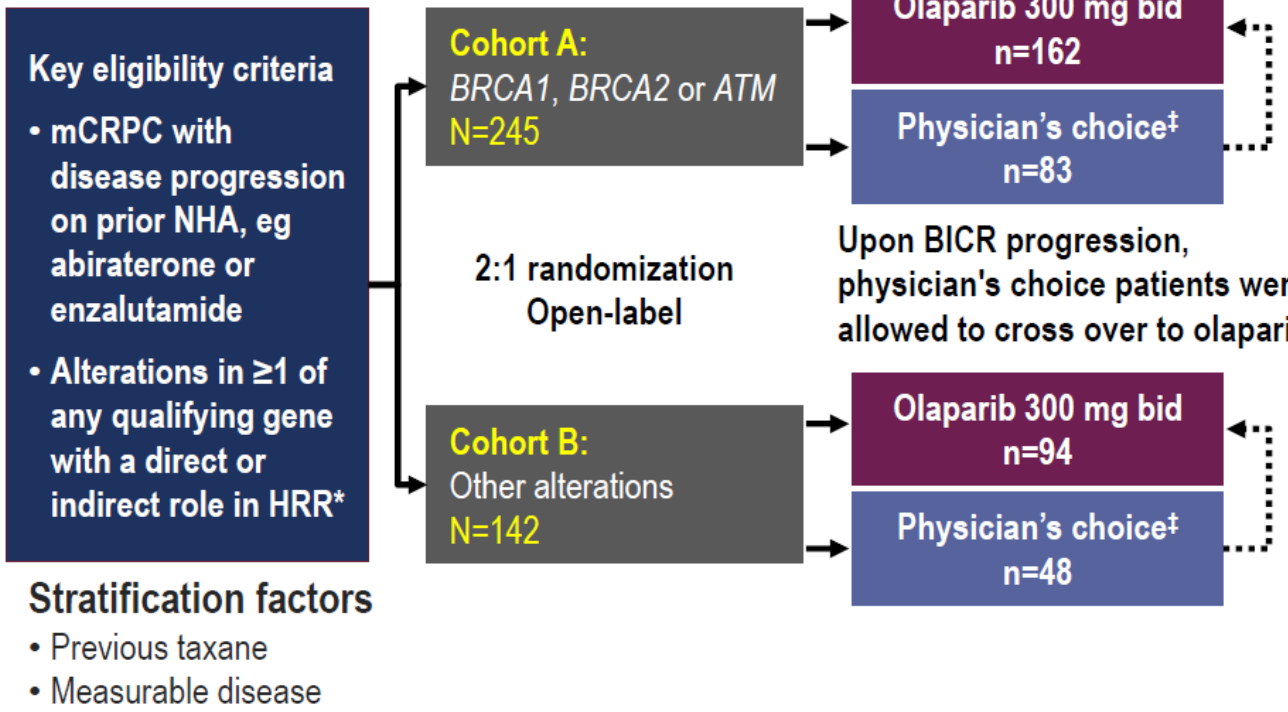
Prostate cancer: *the PROFOUND trial*

PROfound STUDY DESIGN



Primary Endpoint

Radiographic progression-free survival (rPFS) in Cohort A (RECIST 1.1 & PCWG3 by BICR)

Key Secondary Endpoints

- rPFS in Cohorts A+B
- Confirmed radiographic objective response rate (ORR) in Cohort A
- Time to pain progression (TTPP) in Cohort A
- Overall survival (OS) in Cohort A

***An investigational Clinical Trial Assay, based on the FoundationOne® CDx next-generation sequencing test**

Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in ***BRCA1***, ***BRCA2***, ***ATM***, ***BARD1***, ***BRIP1***, ***CDK12***, ***CHEK1***, ***CHEK2***, ***FANCL***, ***PALB2***, ***PPP2R2A***, ***RAD51B***, ***RAD51C***, ***RAD51D*** and/ or ***RAD54L*** in their tumor tissue

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‡Physician's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd + prednisone [5 mg bid])
BICR, blinded independent central review

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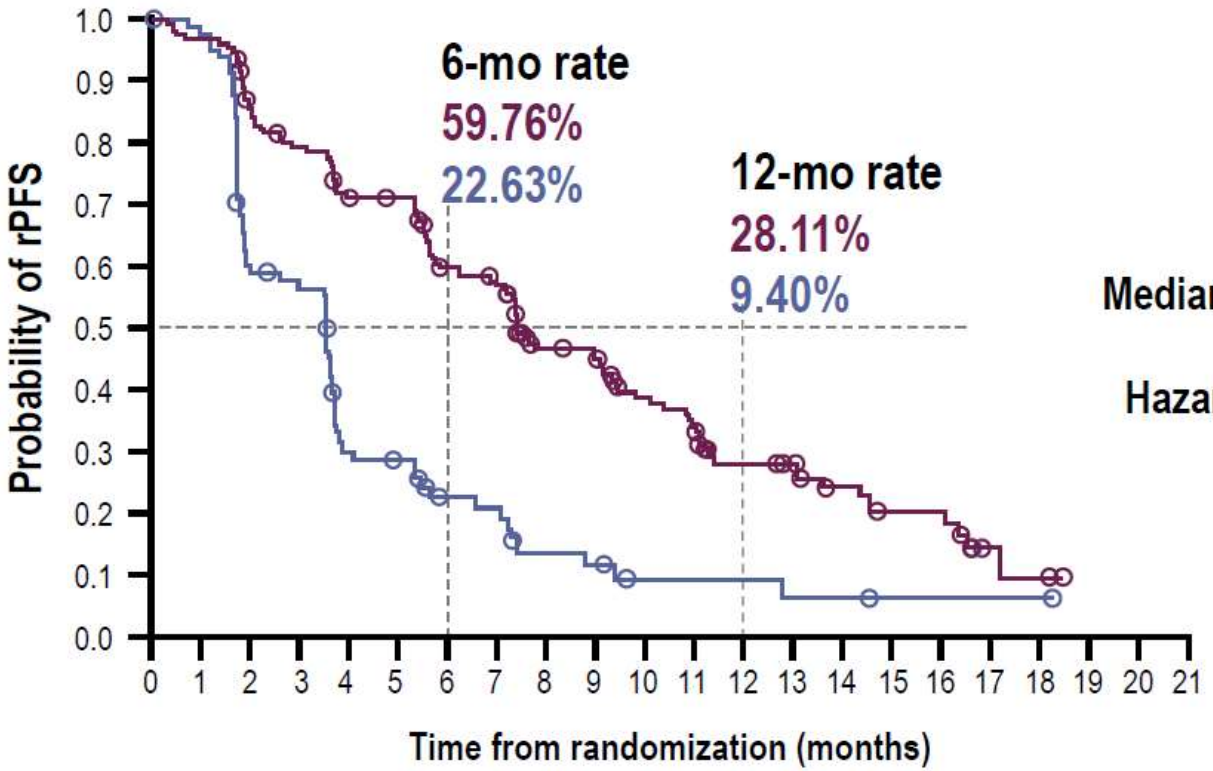
Primary endpoint

rPFS BY BICR IN PATIENTS WITH ALTERATIONS IN *BRCA1*, *BRCA2*, OR *ATM* (COHORT A)



	Olaparib (N=162)	Physician's choice (N=83)
Events (%)	106 (65.4)	68 (81.9)
Median rPFS (months)	7.39	3.55
Hazard ratio (95% CI)	0.34 (0.25, 0.47) *P*<0.0001	

No. at risk																					
Olaparib	162	149	126	116	102	101	82	77	56	53	42	37	26	24	18	11	11	3	2	0	0	0
Physician's choice	83	79	47	44	22	20	13	12	7	6	3	3	3	2	2	1	1	1	1	0	0	0

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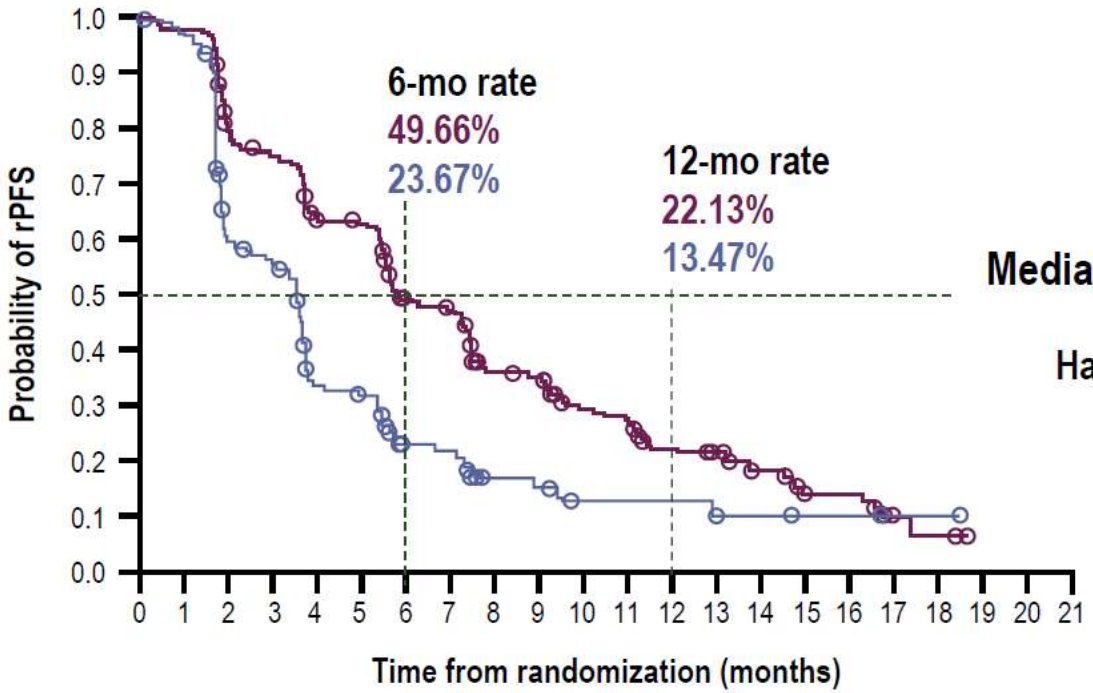
Key secondary endpoint

rPFS BY BICR IN THE OVERALL POPULATION (COHORTS A+B)



No. at risk											
Olaparib	256	188	145	106	67	48	31	21	11	2	0
Physician's choice	131	73	38	20	9	5	5	3	2	1	0

	Olaparib (N=256)	Physician's choice (N=131)
Events (%)	180 (70.3)	99 (75.6)
Median rPFS (months)	5.82	3.52
Hazard ratio (95% CI)	0.49 (0.38, 0.63) *P*<0.0001	

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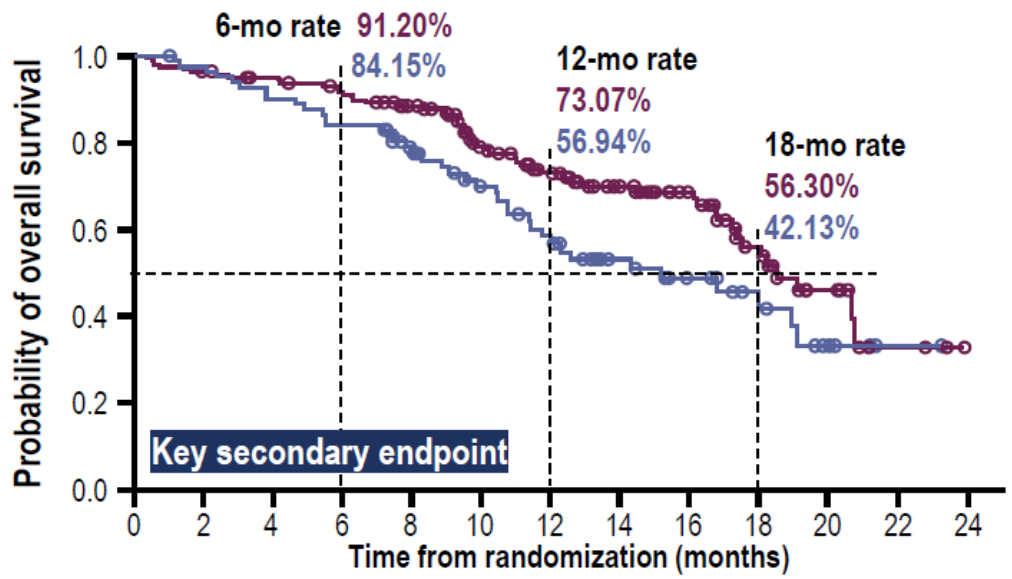
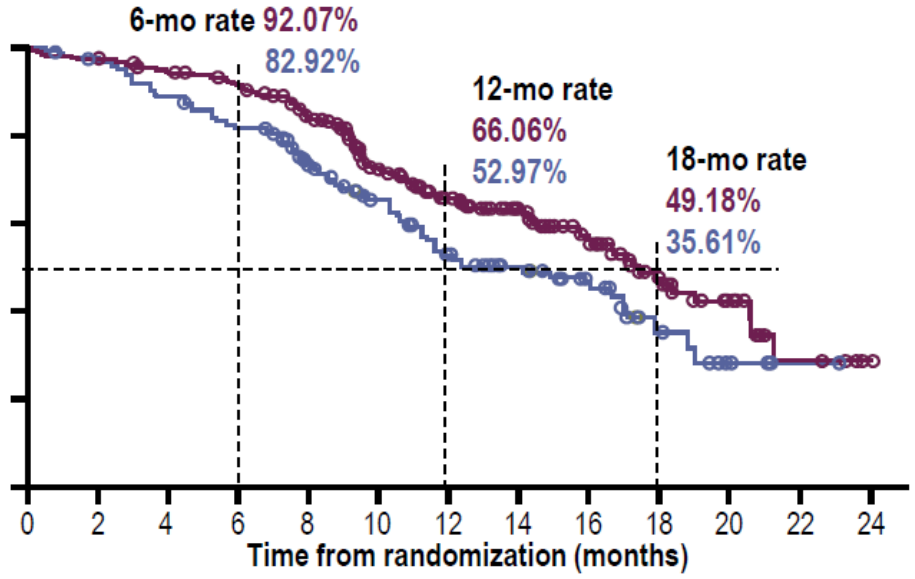
Prostate cancer: *the PROFOUND trial*

INTERIM* OVERALL SURVIVAL

Cohort A	Olaparib (N=162)	Physician's choice (N=83)
Median OS (months)	18.50	15.11
Hazard ratio (95% CI)	0.64 (0.43, 0.97) *P*=0.0173†	

Cohort A+B	Olaparib (N=256)	Physician's choice (N=131)
Median OS (months)	17.51	14.26
Hazard ratio (95% CI)	0.67 (0.49, 0.93) *P*=0.0063 (nominal)	





No. at risk							
Olaparib	162	150	125	76	46	11	0
Physician's choice	83	74	54	34	18	6	0

No. at risk							
Olaparib	256	240	187	106	58	17	1
Physician's choice	131	115	79	46	25	6	0

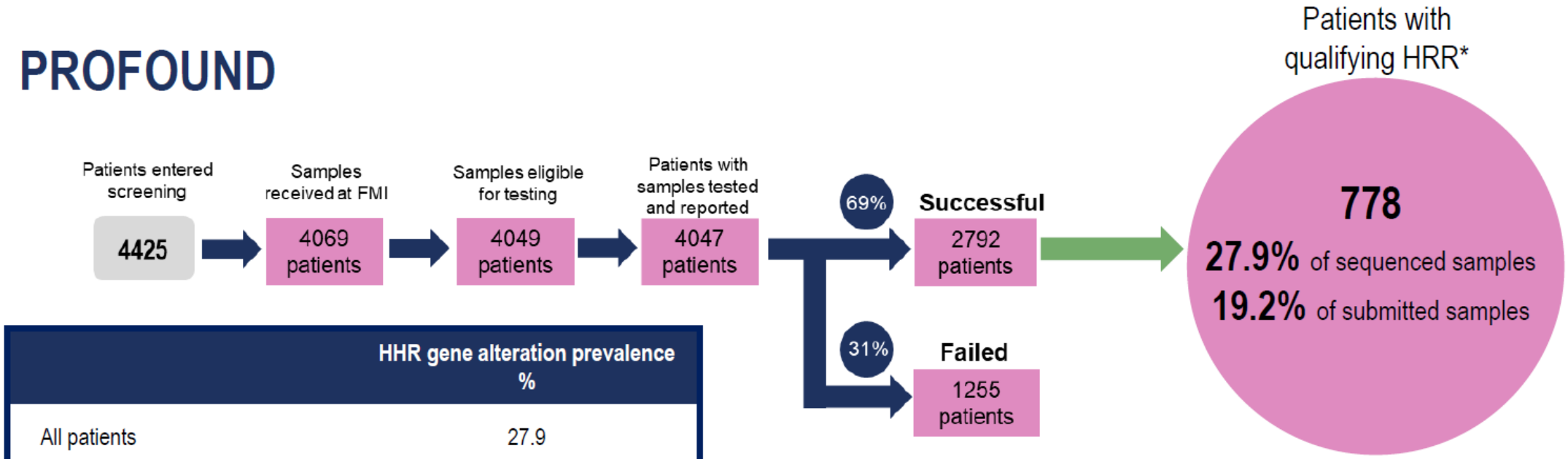
Of the physician's choice arm patients who progressed, 80.6% in Cohort A and 84.6% in Cohort B crossed over to olaparib

*38% maturity in Cohort A; 41% maturity in Cohort A+B; final analysis planned after ~146 deaths in Cohort A (60% maturity)

†Alpha spend at interim was 0.01; statistical significance not reached

Prostate cancer: *the PROFOUND trial*

PREVALENCE OF DDR IN TISSUE



	HHR gene alteration prevalence %
All patients	27.9
All primary tumors	27
Archived primary	27
Newly collected primary	26.5
All metastatic tumors	32.3
Archived metastatic	33.9
Newly collected metastatic	29.7

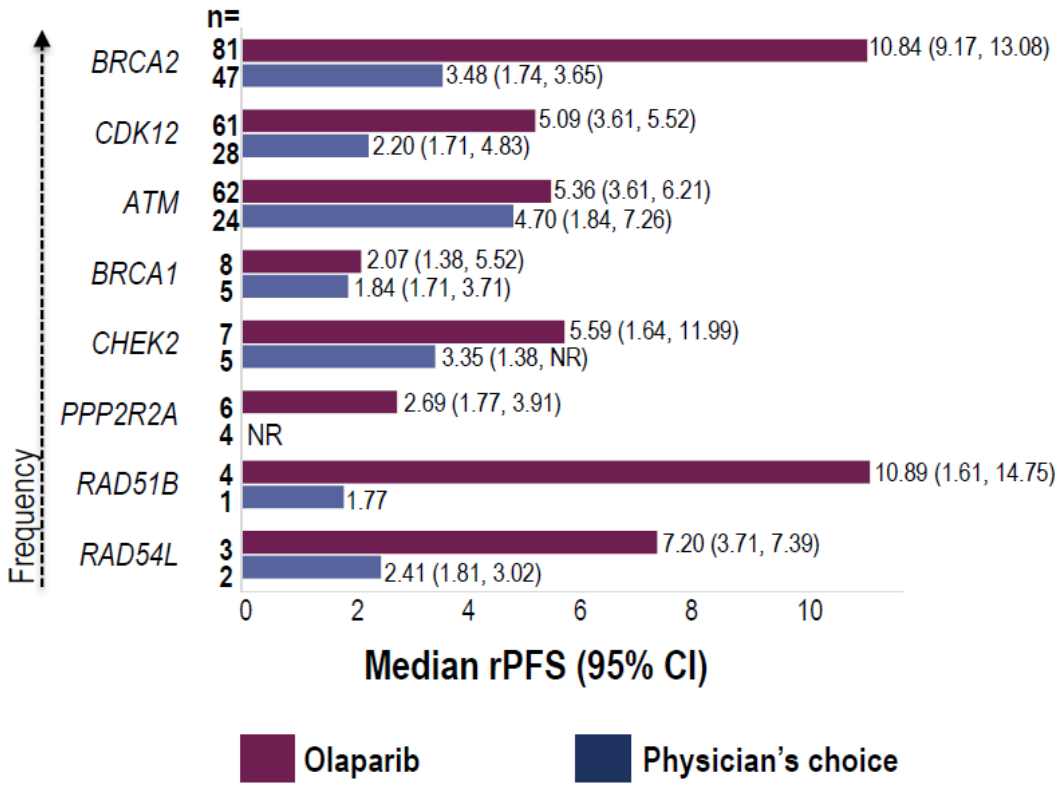
**BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANC, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L*

Prostate cancer: *the PROFOUND trial*

Exploratory analysis

GENE-BY-GENE rPFS

- 7/15 genes had alteration frequencies too low for descriptive statistics (<5 patients)
- 97% of patients were randomized based on alterations in 8/15 single genes
- There is evidence of clinical activity of olaparib in patients with alterations in genes other than *BRCA1* or *BRCA2*
- Gene-level analysis is complex and exploratory, and comparisons may be confounded by multiple factors



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NR, not reached

Agenda

- The intensification strategy: the TITAN trial
- Management of patients with sRCC
- Sequence in mCRPC
- Olaparib in mCRPC, the new option for DRD patients.
- **Atezolizumab ± Chemioterapia nella I linea per neoplasia vescicale**

Bladder cancer: *the IMvigor 130 trial*

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IMvigor130 study design

- Locally advanced or mUC
- No prior systemic therapy in the metastatic setting
- ECOG PS ≤ 2
- 1L platinum-eligible
- N = 1200
- Randomised 1:1:1

→ **Arm A**
Atezo + plt/gem

→ **Arm B**
Atezo monotherapy

→ **Arm C**
Placebo + plt/gem

Stratification factors:
- PD-L1 IC status (IC0 vs IC1 vs IC2/3)
- Bajorin risk factor score including KPS < 80% vs ≥ 80% and presence of visceral metastases (0 vs 1 vs 2 and/or patients with liver metastases)
- Investigator choice of plt/gem (cisplatin + gem or carboplatin + gem)

Co-primary endpoints:
- INV-assessed PFS[a] and OS (Arm A vs C)
- OS (Arm B vs C, hierarchical approach)

Key secondary endpoints:
- INV-ORR[a] and DOR
- PFS[a] and OS (Arm B vs C; PD-L1 IC2/3 subgroup)
- Safety

[a] per RECIST 1.1.

IMvigor130—ESMO 2019 (LBA14): presented by Dr Enrique Grande

http://bit.ly/2Z1bPbD

Bladder cancer: *the IMvigor 130 trial*

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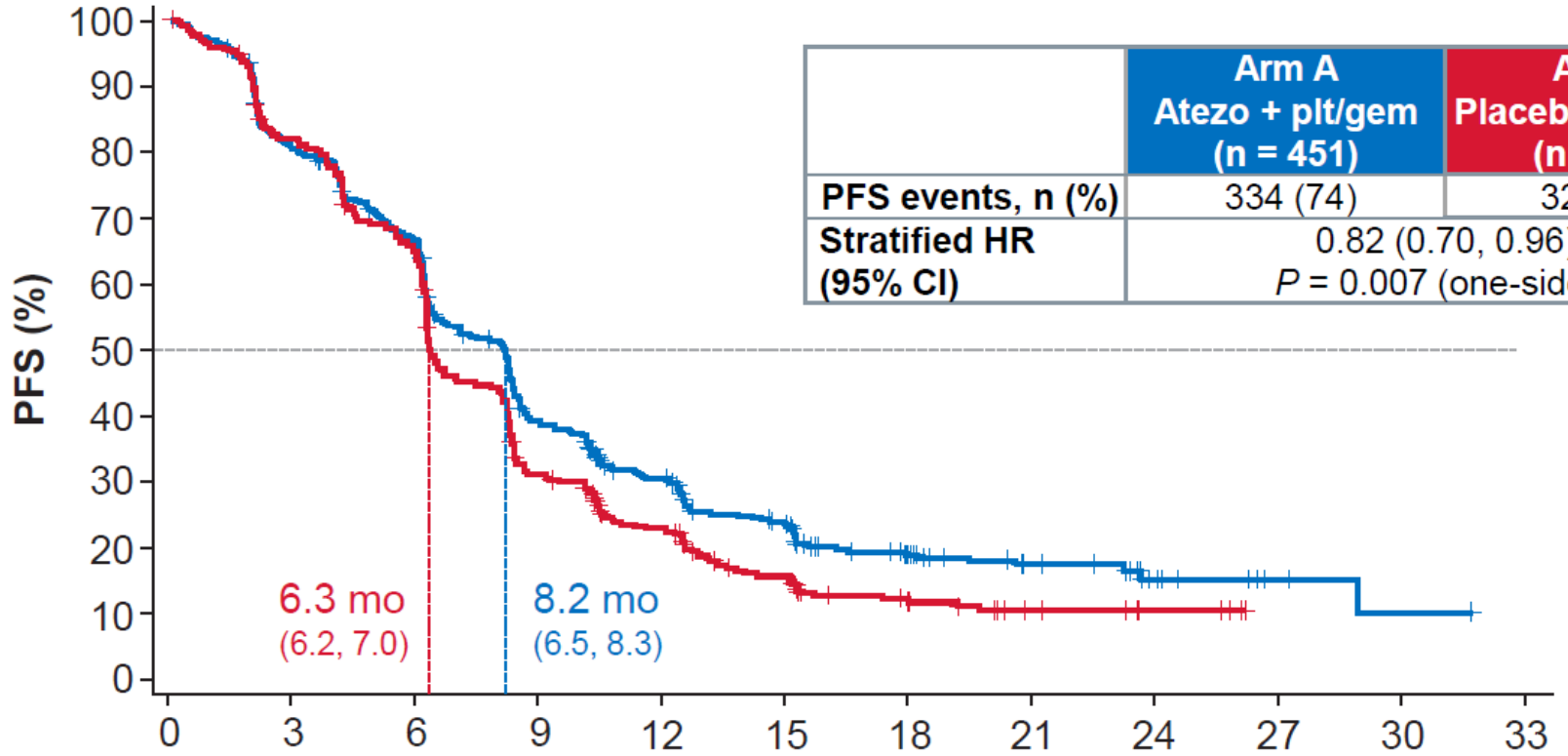
Final PFS: ITT (Arm A vs Arm C)



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	0.82 (0.70, 0.96) *P* = 0.007 (one-sided)	

No. at Risk												
Atezo + plt/gem	451	345	282	160	111	74	42	22	10	4	2	NE
Placebo + plt/gem	400	317	246	116	73	40	18	11	4	NE	NE	NE

NE, not estimable. Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients).

IMvigor130—ESMO 2019 (LBA14); presented by Dr Enrique Grande

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Bladder cancer: *the IMvigor 130 trial*

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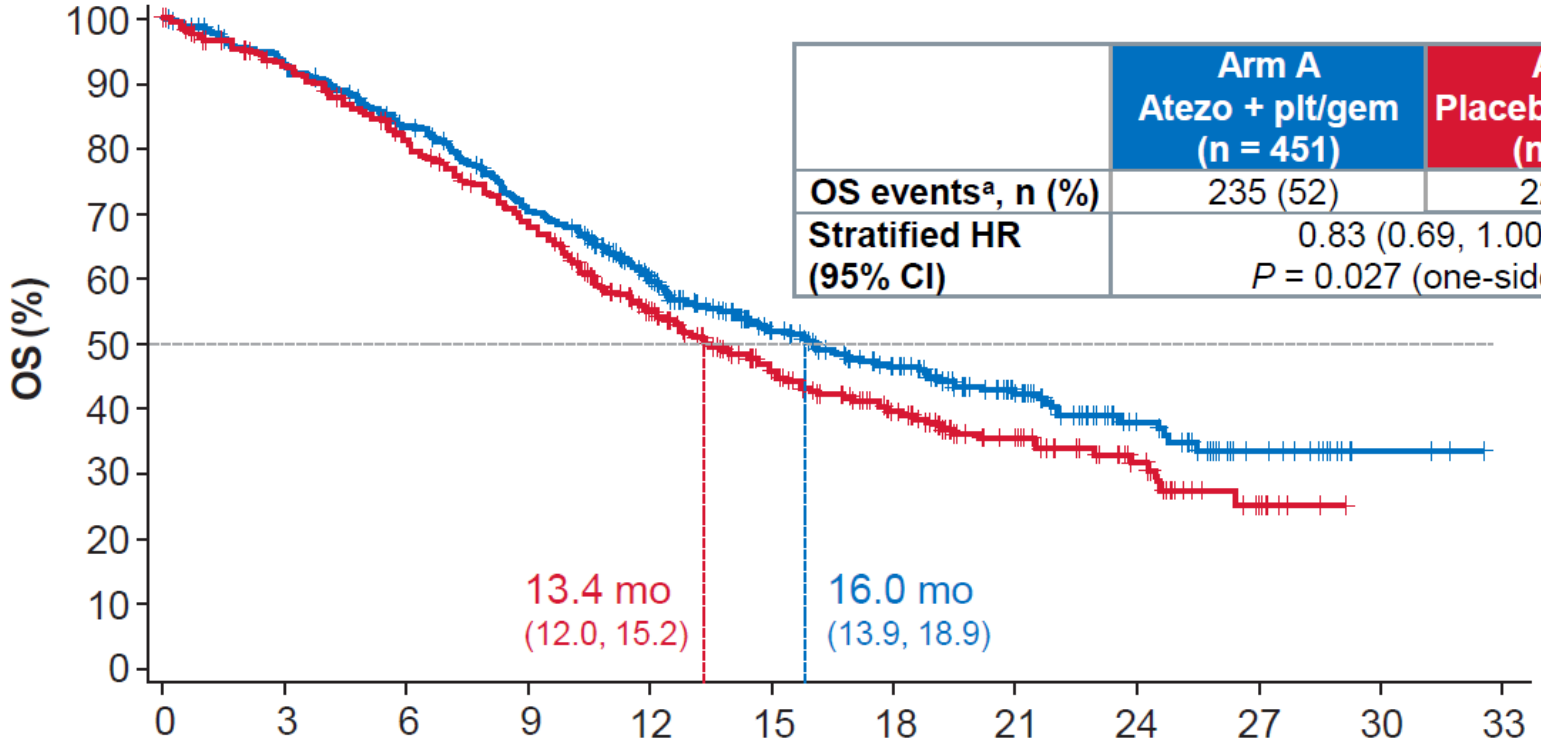
Interim OS: ITT (Arm A vs Arm C)



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	0.83 (0.69, 1.00) *P* = 0.027 (one-sided)[b]	

No. at Risk												
Atezo + plt/gem	451	408	360	301	229	163	117	72	36	16	3	NE
Placebo + plt/gem	400	359	308	255	182	123	79	49	25	8	NE	NE

Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients). [a] 5% of patients from Arm A and 20% of patients from Arm C received non-protocol immunotherapy. [b] Did not cross the interim efficacy boundary of 0.007 per the O'Brien-Fleming alpha spending function.

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Bladder cancer: *the IMvigor 130 trial*

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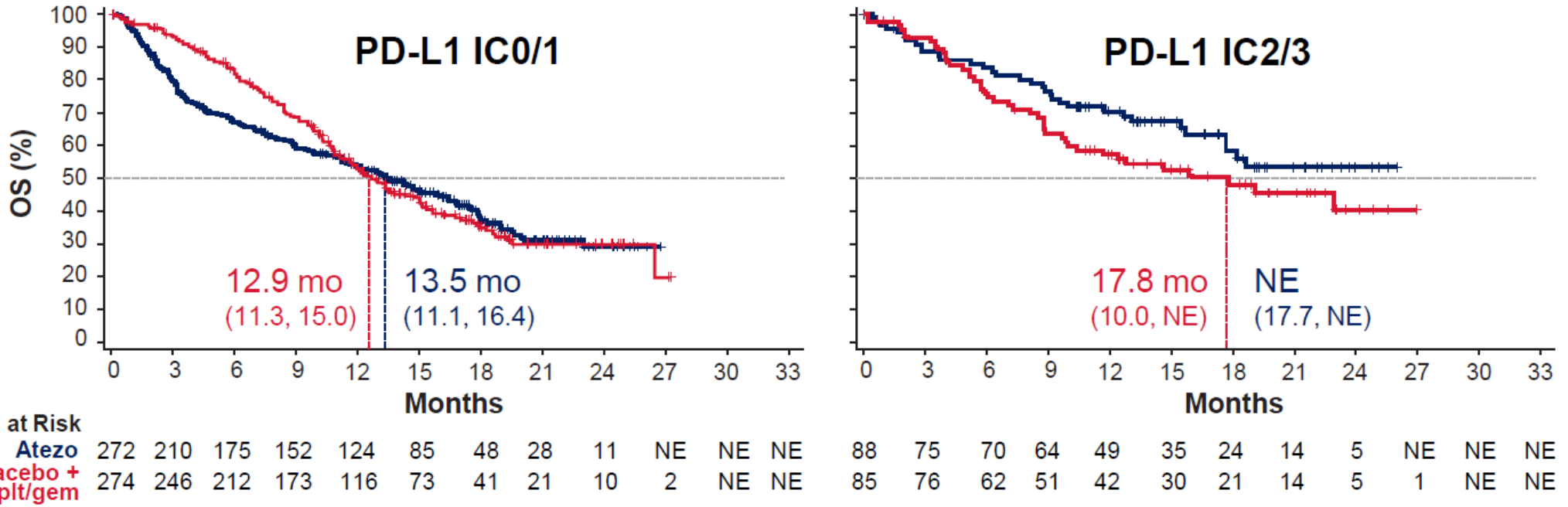
Interim OS: PD-L1 status (Arm B vs Arm C)



No. at Risk												
Atezo	272	210	175	152	124	85	48	28	11	NE	NE	NE
Placebo + plt/gem	274	246	212	173	116	73	41	21	10	2	NE	NE

No. at Risk												
Atezo	88	75	70	64	49	35	24	14	5	NE	NE	NE
Placebo + plt/gem	85	76	62	51	42	30	21	14	5	1	NE	NE

	Arm B Atezo (n = 272)	Arm C Placebo + plt/gem (n = 274)
OS events, n (%)	158 (58)	156 (57)
Unstratified HR (95% CI)	1.07 (0.86, 1.33)	

	Arm B Atezo (n = 88)	Arm C Placebo + plt/gem (n = 85)
OS events, n (%)	33 (38)	42 (49)
Stratified HR (95% CI)	0.68 (0.43, 1.08)	

Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients).

IMvigor130—ESMO 2019 (LBA14): presented by Dr Enrique Grande

http://bit.ly/2Z1bPbD