Highlights in Genitourinary Cancers from ASCO 2020

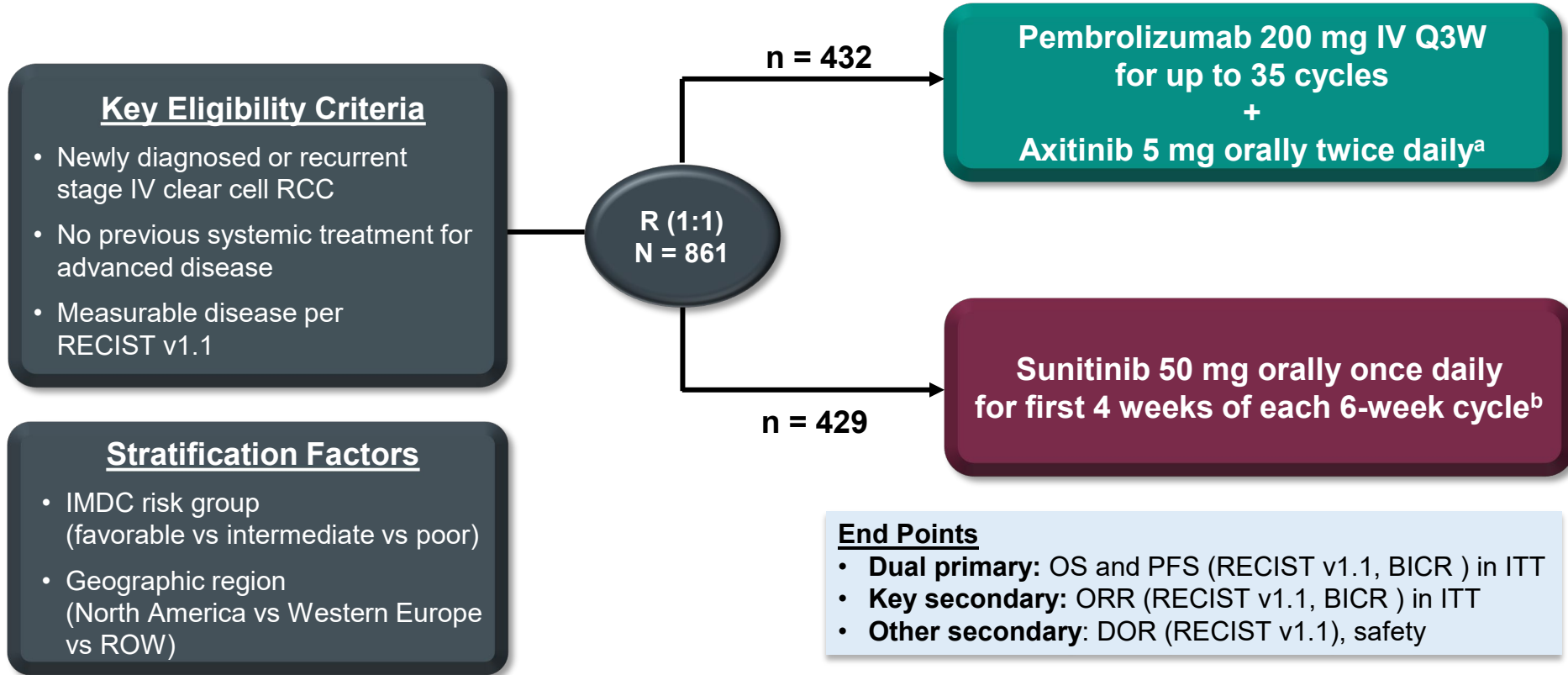Nicholas J. Vogelzang MD FASCO FACP

Comprehensive Cancer Centers of Nevada, Vice chair SWOG
GU Committee, Clinical Professor of Medicine UNLV SOM

Pembrolizumab Plus Axitinib Versus Sunitinib as First-Line Therapy for Advanced Renal Cell Carcinoma: Updated Analysis of KEYNOTE-426

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KEYNOTE-426 Study Design

Key Eligibility Criteria

- Newly diagnosed or recurrent stage IV clear cell RCC
- No previous systemic treatment for advanced disease
- Measurable disease per RECIST v1.1

Stratification Factors

- IMDC risk group (favorable vs intermediate vs poor)
- Geographic region (North America vs Western Europe vs ROW)

R (1:1)
N = 861

n = 432

Pembrolizumab 200 mg IV Q3W for up to 35 cycles + Axitinib 5 mg orally twice daily[a]

n = 429

Sunitinib 50 mg orally once daily for first 4 weeks of each 6-week cycle[b]

End Points
- **Dual primary:** OS and PFS (RECIST v1.1, BICR) in ITT
- **Key secondary:** ORR (RECIST v1.1, BICR) in ITT
- **Other secondary**: DOR (RECIST v1.1), safety

[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity. [b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 weeks of each 6-week cycle to manage toxicity. Data cutoff: January 6, 2020.
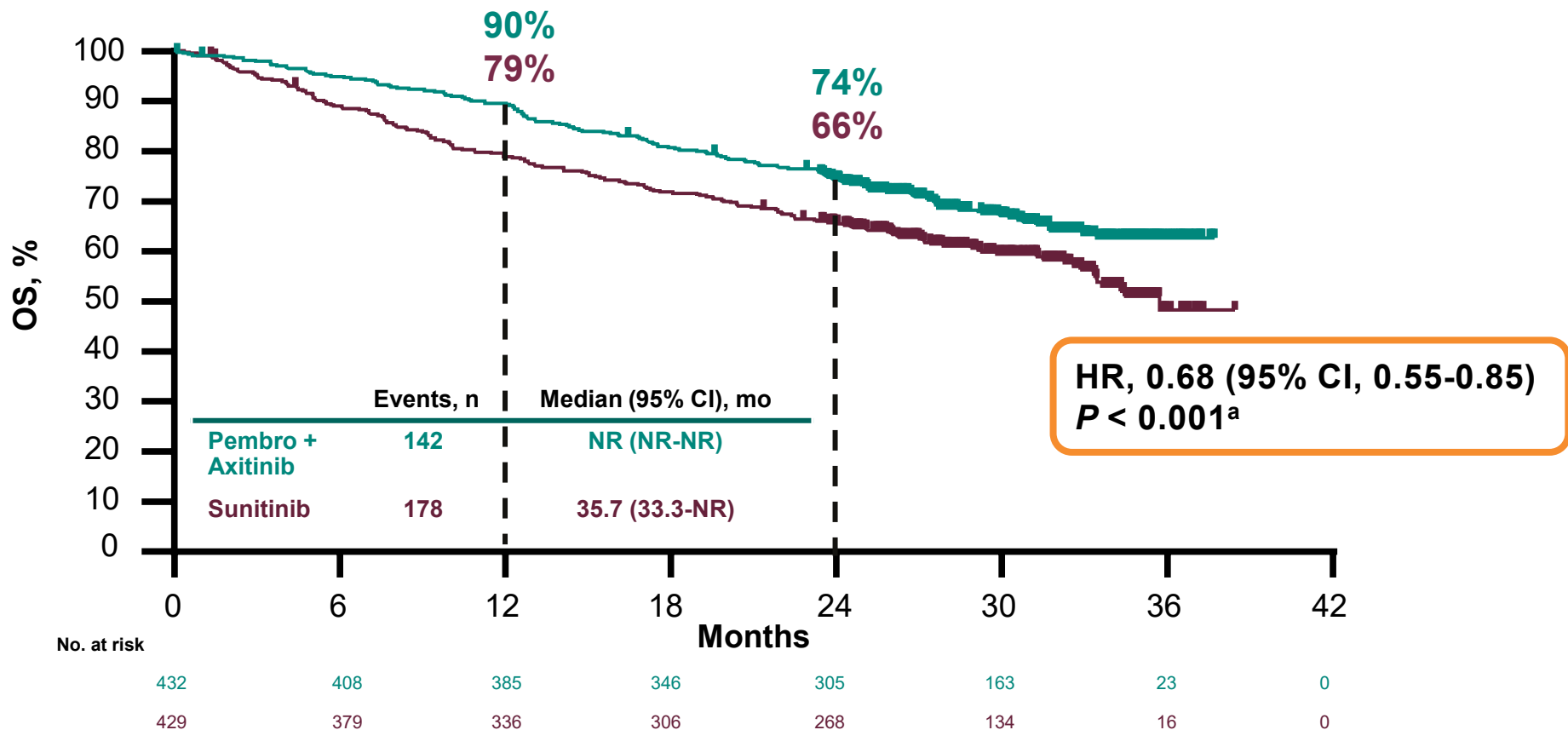
Confirmed Objective Response Rate
ITT Population
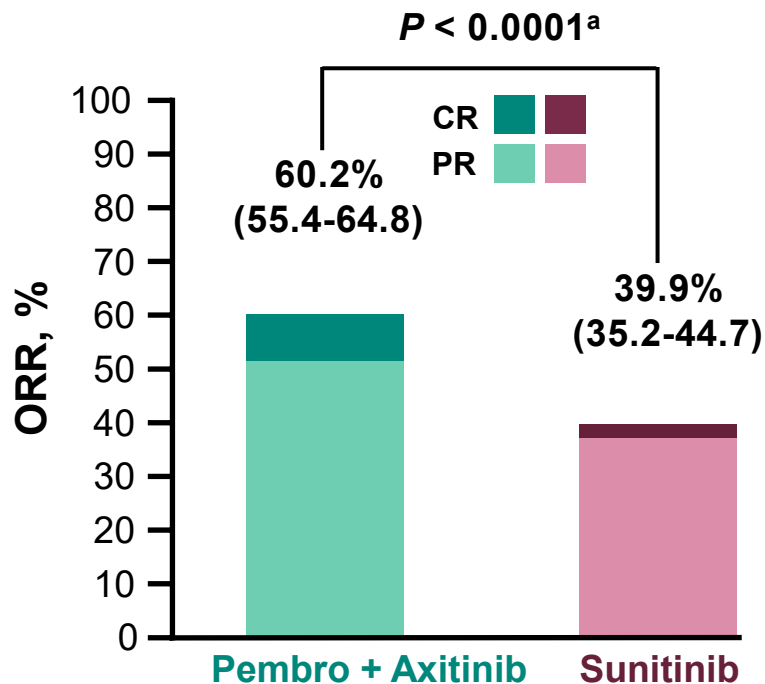
	Pembro + Axitinib n = 432	Sunitinib n = 429
Best response, n (%)		
CR	38 (8.8)	13 (3.0)
PR	222 (51.4)	158 (36.8)
SD	100 (23.1)	150 (35.0)
PD	49 (11.3)	74 (17.2)
NE[b]	16 (3.7)	28 (6.5)
NA[c]	7 (1.6)	6 (1.4)
Duration of response, median (range), mo	23.5 (1.4+ to 34.5+)	15.9 (2.3 to 31.8+)

[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to confirmed objective response; only nominal *P* values are reported. [b]Postbaseline assessment available but not evaluable (ie, all postbaseline assessments with insufficient data for assessment of response per RECIST v1.1 or CR/PR/SD <6 weeks from randomization). [c]No postbaseline assessment available for response evaluation; + indicates an ongoing response at time of last disease assessment. Data cutoff: January 6, 2020.
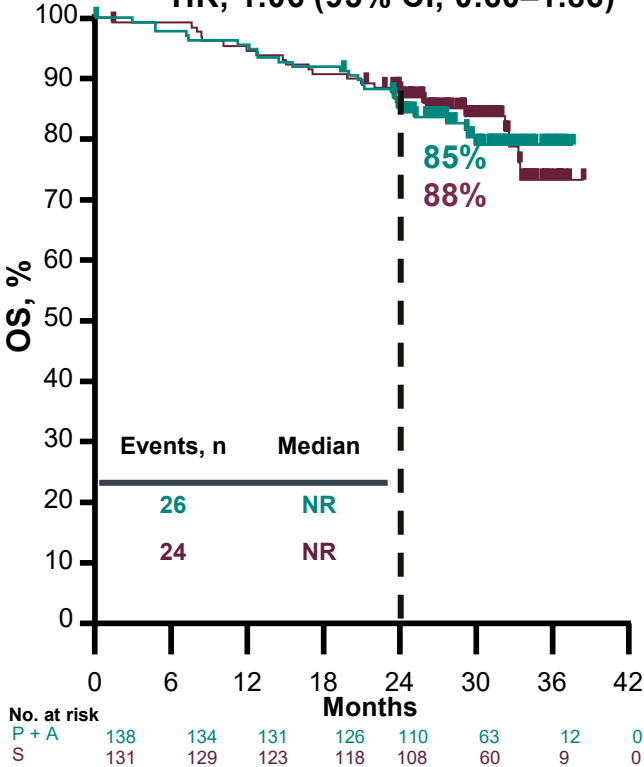
OS in the ITT Population

	Events, n	Median (95% CI), mo
Pembro + Axitinib	142	NR (NR-NR)
Sunitinib	178	35.7 (33.3-NR)

90%
79%
74%
66%

HR, 0.68 (95% CI, 0.55-0.85)
P < 0.001[a]

No. at risk

| 432 | 408 | 385 | 346 | 305 | 163 | 23 | 0 |
| 429 | 379 | 336 | 306 | 268 | 134 | 16 | 0 |

[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported. Data cutoff: January 6, 2020.
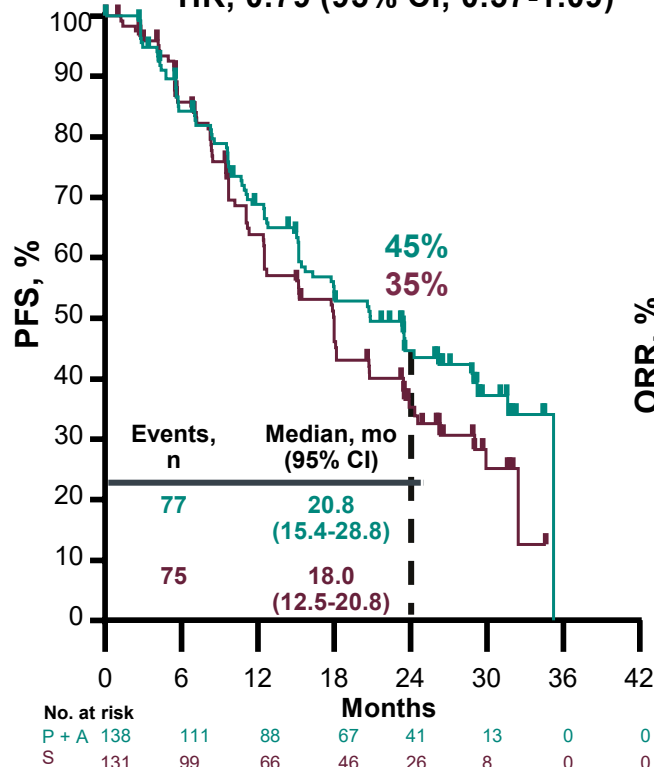
IMDC Favorable Risk: OS, PFS, and ORR
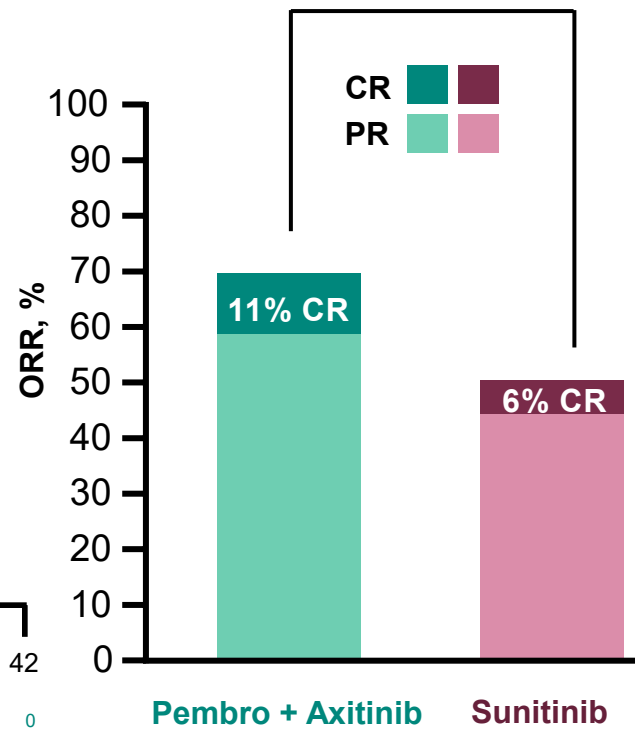
OS
HR, 1.06 (95% CI, 0.60–1.86)

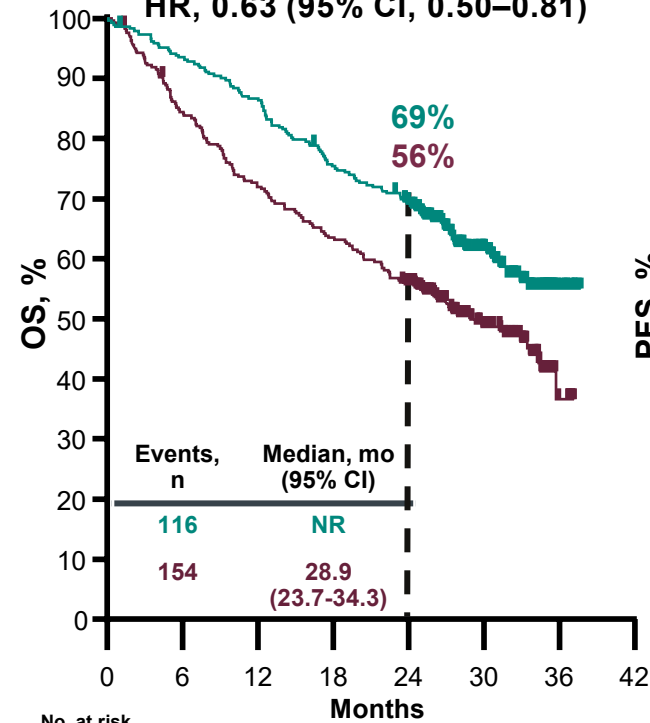**PFS**
HR, 0.79 (95% CI, 0.57-1.09)

ORR
69.6% vs 50.4%

85%
88%

Events, n	Median
26	NR
24	NR

45%
35%

Events, n	Median, mo (95% CI)
77	20.8 (15.4-28.8)
75	18.0 (12.5-20.8)

CR
PR

11% CR
6% CR

Months

No. at risk
P + A	138	134	131	126	110	63	12	0
S	131	129	123	118	108	60	9	0

Months

No. at risk
P + A	138	111	88	67	41	13	0	0
S	131	99	66	46	26	8	0	0

Pembro + Axitinib **Sunitinib**

Data cutoff: January 6, 2020.
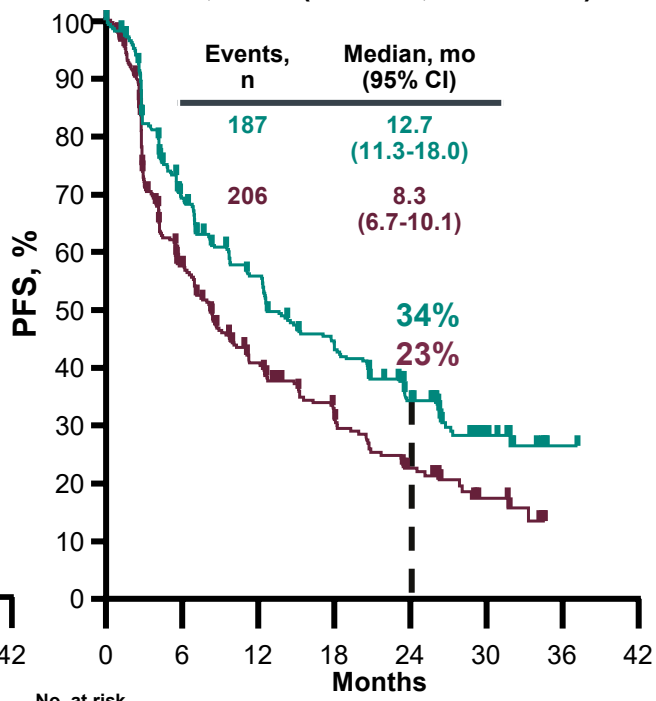
IMDC Intermediate/Poor Risk: OS, PFS, and ORR

OS
HR, 0.63 (95% CI, 0.50–0.81)

PFS
HR, 0.69 (95% CI, 0.56-0.84)

ORR
55.8% vs 35.2%

OS chart:
69%
56%

Events, n	Median, mo (95% CI)
116	NR
154	28.9 (23.7-34.3)

PFS chart:
Events, n	Median, mo (95% CI)
187	12.7 (11.3-18.0)
206	8.3 (6.7-10.1)

34%
23%

ORR chart:
CR PR
8% CR
2% CR
Pembro + Axitinib   Sunitinib

No. at risk

OS:
P + A	294	274	254	220	195	100	11	0
S	298	250	213	188	160	74	7	0

PFS:
P + A	294	189	146	113	68	23	2	0
S	298	149	93	66	35	11	0	0

Data cutoff: January 6, 2020.
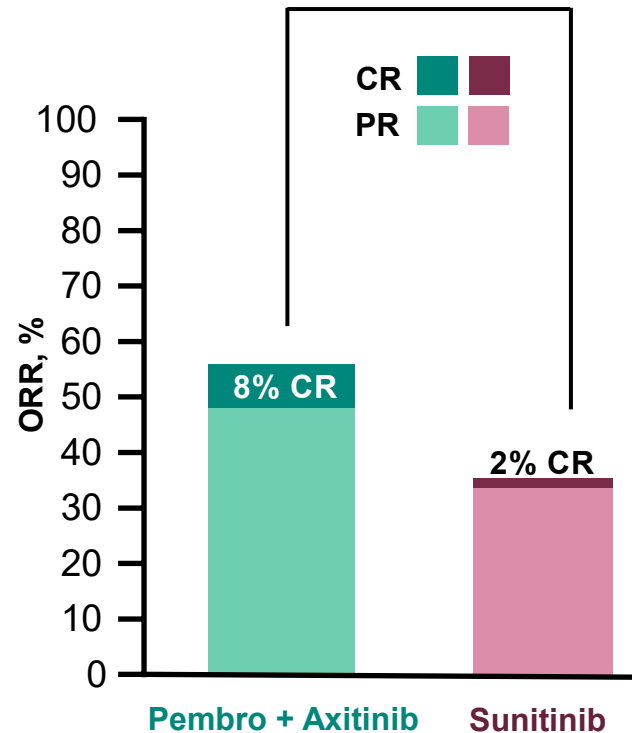
Depth of Response and Overall Survival
6-Month Landmark Analysis (post hoc)

Randomization

6-month landmark

All randomized patients

All survivors at 6 months
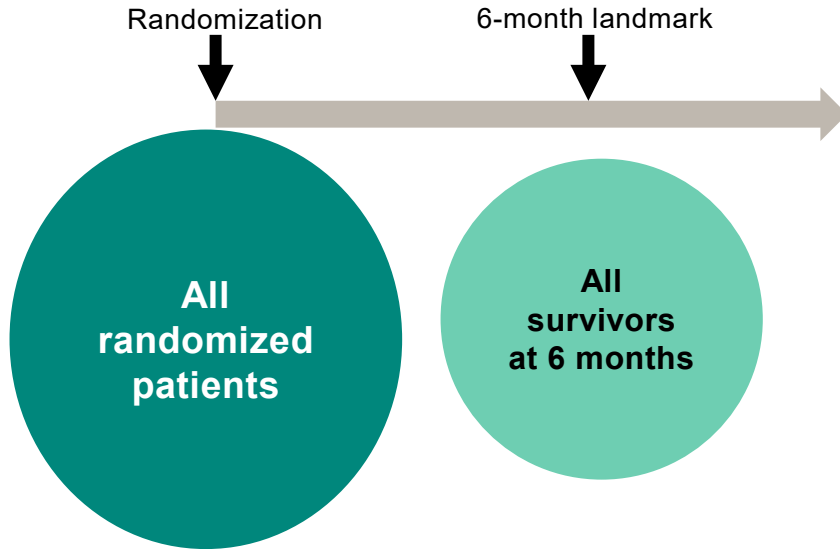
- **Purpose: to explore the relationship between depth of response and survival**
- All patients who were alive at the 6-month landmark and who underwent ≥1 postbaseline imaging up to the landmark were included (745 of 861 randomly assigned patients)
- Patient subgroups were based on maximum sum target lesion reduction from baseline up to the landmark:
  - Confirmed CR at 6 months
  - >80% to 100% (non-CR)
  - >60% to 80%
  - >30% to 60%
  - 0% to 30%
- Survival was analyzed after the 6-month landmark for each subgroup

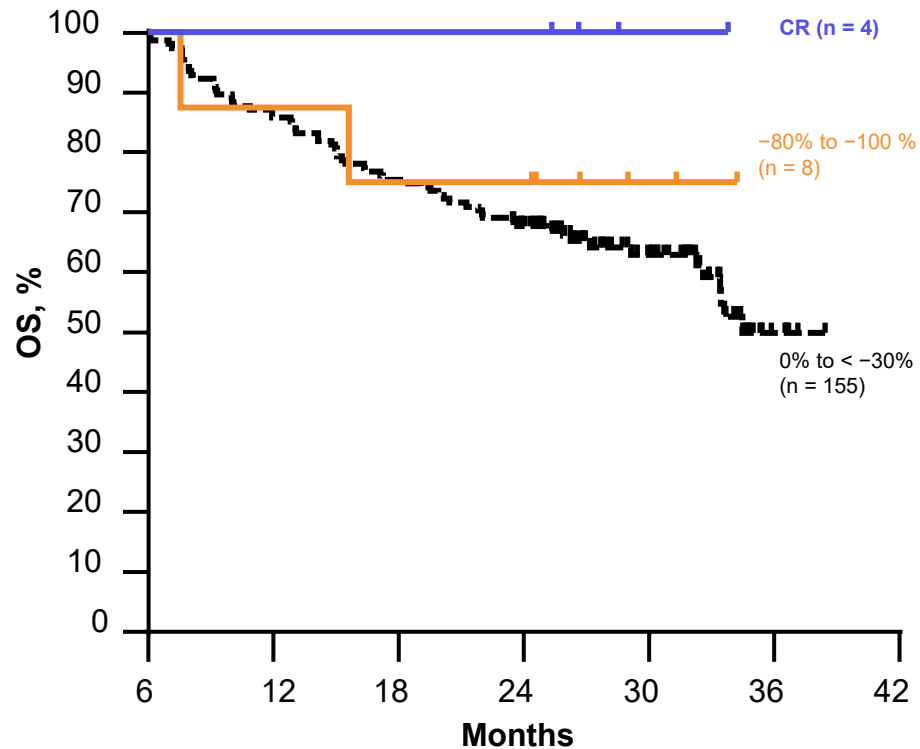# Overall Survival Post-Landmark by Depth of Response Pre-Landmark
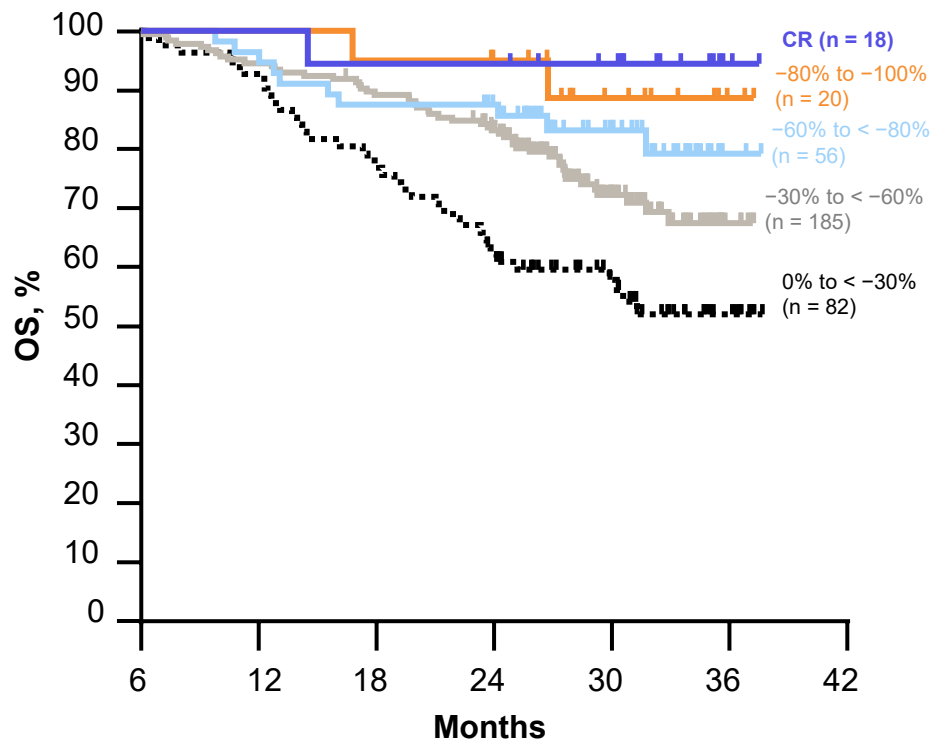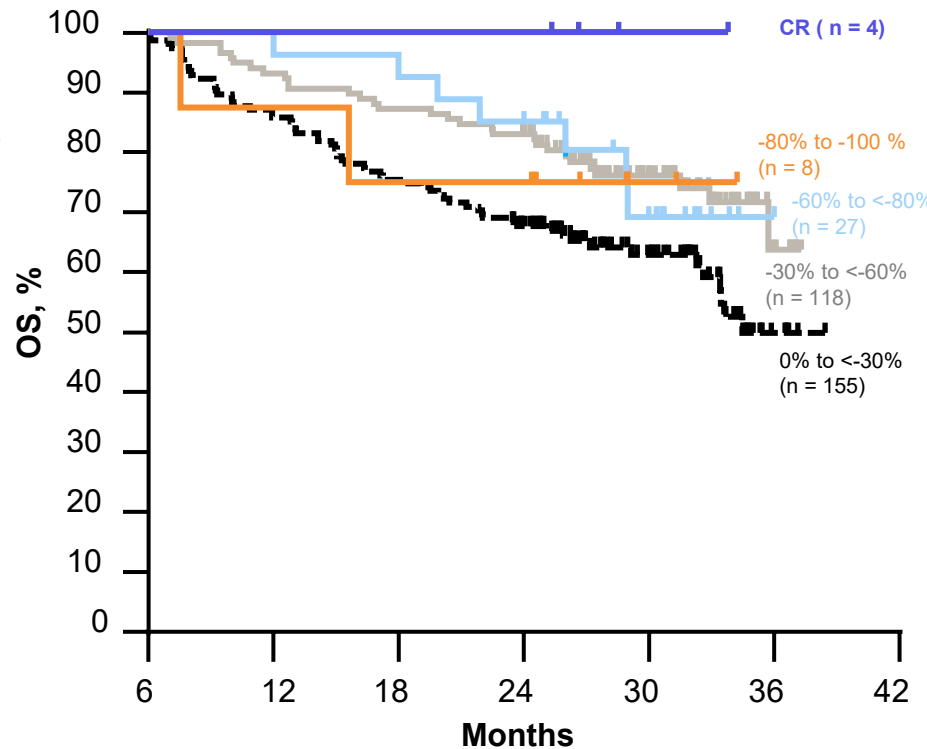

Pembrolizumab + Axitinib

Sunitinib

Data cutoff: January 6, 2020.

Overall Survival Post-Landmark by Depth of Response Pre-Landmark

Pembrolizumab + Axitinib

Sunitinib

Data cutoff: January 6, 2020.
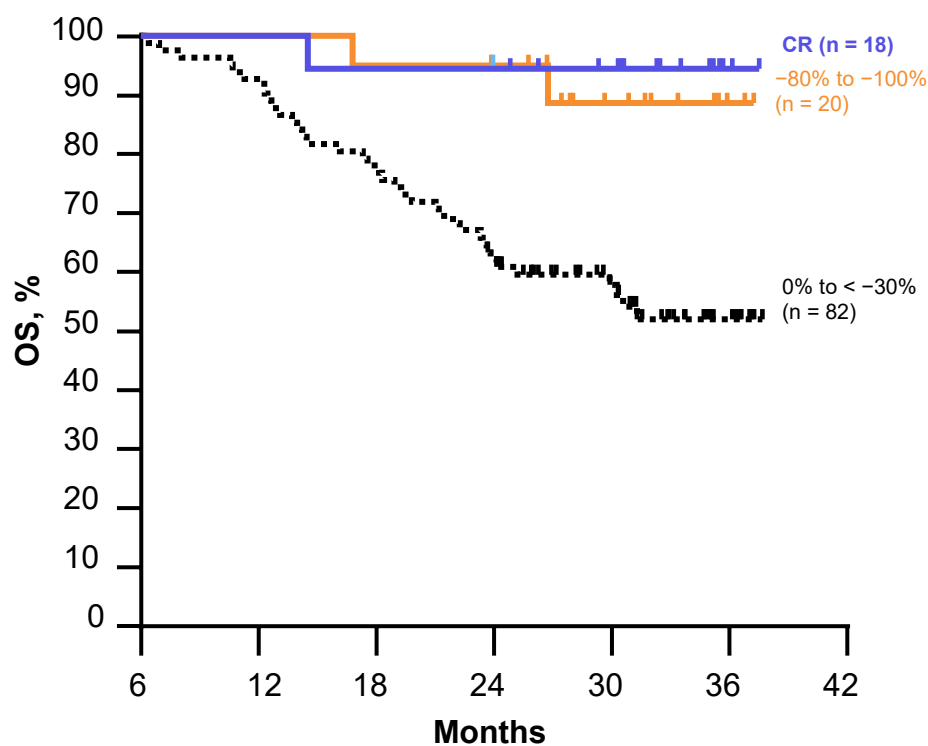
Summary and Conclusions

- With extended follow-up, pembrolizumab + axitinib continued to demonstrate clinically significant improved efficacy compared with sunitinib for previously untreated, advanced RCC
  - OS: HR, 0.68; *P* < 0.001[a]; 24-month rate, 74% vs 66%
  - PFS: HR, 0.71; *P* < 0.0001[a]; 24-month rate, 38% vs 27%
  - ORR: 60% vs 40%; *P* < 0.0001[a]
  - CR rate: 9% vs 3%

- Exploratory landmark analysis demonstrated that greater depth of tumor shrinkage was associated with increased OS in the pembrolizumab + axitinib arm

  - Patients with ≥80% tumor reduction had similar survival rates as patients who achieved confirmed CR by RECIST v1.1 within 6 months after randomization

- These results continue to support pembrolizumab + axitinib as a standard of care for patients with previously untreated advanced RCC

[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated; only nominal *P* values are reported.

Phase II Study of Nivolumab and Salvage Nivolumab + Ipilimumab in Treatment-Naïve Patients with Advanced Renal Cell Carcinoma (HCRN GU16-260)

Michael B. Atkins[1], Opeyemi A. Jegede[2], Naomi B. Haas[3], David F. McDermott[4], Mehmet A. Bilen[5], Charles G. Drake[6], Jeffrey A. Sosman[7], Robert Alter[8], Elizabeth R. Plimack[9], Brian Rini[10], Michael Hurwitz[11], David Peace[12], Sabina Signoretti[13], Catherine J. Wu[2], Paul J. Catalano[2], Hans Hammers[14]
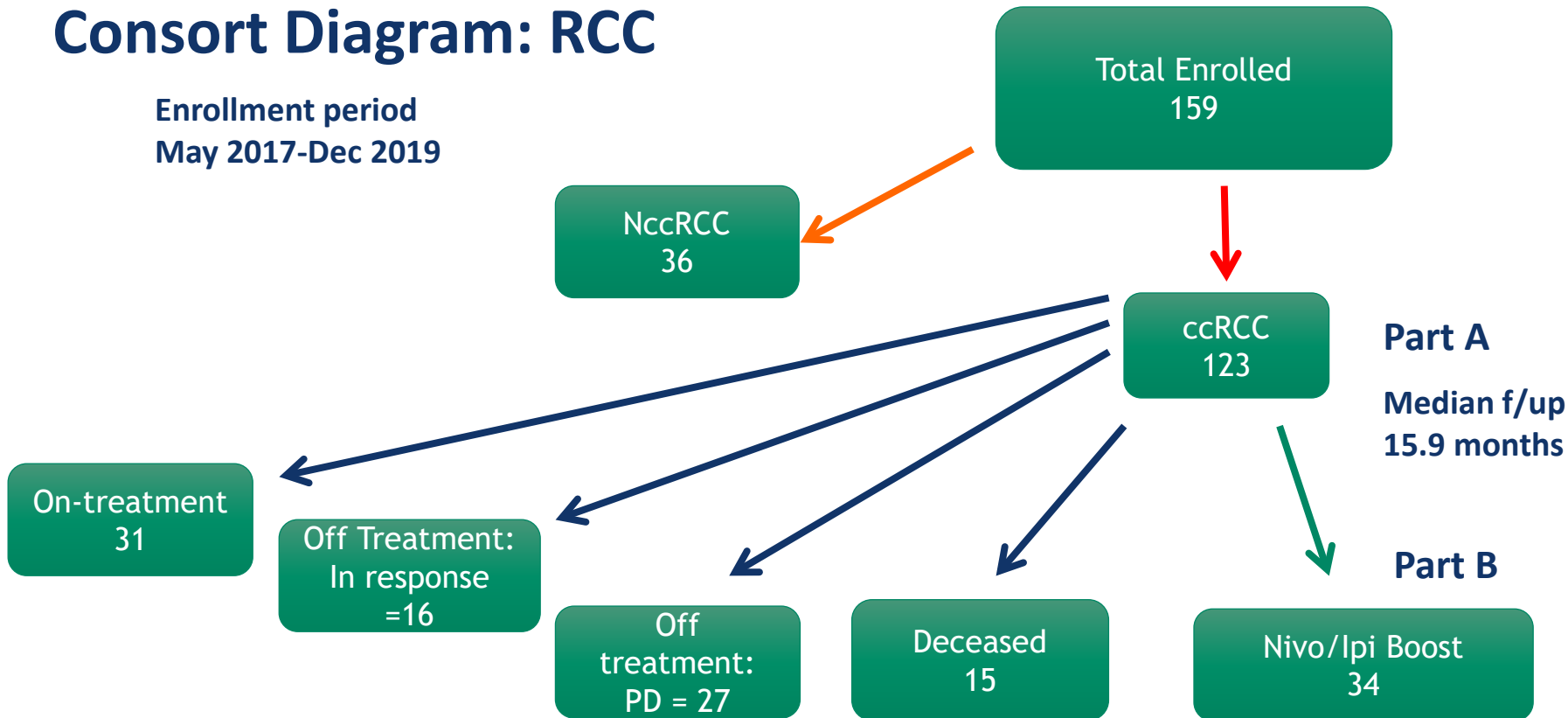
[1]Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC; [2]Dana Farber Cancer Institute, Boston, MA; [3]University of Pennsylvania Abramson Cancer Center, Philadelphia, PA; [4]Beth Israel Deaconess Medical Center, Boston, MA; [5]Winship Cancer Institute of Emory University, Atlanta GA; [6]Columbia Herbert Irving Comprehensive Cancer Center, New York, NY; [7]Northwestern Lurie Comprehensive Cancer Center, Chicago, IL; [8]John Theurer Cancer Center, Hackensack, NJ; [9]Fox Chase Cancer Center, Philadelphia, PA; [10]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH (currently at Vanderbilt-Ingram Cancer Center, Nashville, TN); [11]Yale-Smilow Comprehensive Cancer Center, New Haven, CT; [12]University of Illinois Chicago, Chicago, IL; [13]Brigham and Women's Hospital Boston, MA, [14]University of Texas Southwestern Sammons Cancer Center, Dallas, TX.

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Background/Introduction

- Nivolumab monotherapy (nivo) is approved for VEGFR TKI resistant ccRCC based on the CM 025 Study.

- Combination nivolumab + ipilimumab (Nivo/ipi) is approved for treatment-naïve IMDC intermediate and poor risk ccRCC based on the CM 214 Study.

- Little information was available on the efficacy and toxicity of:
  - Nivo monotherapy in patients with treatment-naïve ccRCC (all IMDC risk groups)
  - Nivo monotherapy in patients with treatment naïve nccRCC
  - Nivo/ipi salvage in patients without response/resistance to Nivo monotherapy
  - Biomarkers predictive of response and resistance to Nivo monotherapy

Consort Diagram: RCC

**Enrollment period
May 2017-Dec 2019**

Total Enrolled
159

NccRCC
36

ccRCC
123

Part A

**Median f/up
15.9 months**

On-treatment
31

Off Treatment:
In response
=16

Off treatment:
PD = 27

Deceased
15

Part B

Nivo/Ipi Boost
34

Data Lock: April 17, 2020

Baseline Characteristics: ccRCC

Characteristic	N=123
Age, median (range), years	65 (32-86)
ECOG PS (0, 1, 2)	79 (64%), 43 (35%), 1 (1%)
Male, n (%)	89 (72%)
IMDC risk category, n* (%)	
Favorable	30 (24%)
Intermediate	80 (65%)
Poor	12 (10%)
Sarcomatoid features	22 (18%)
Liver metastases	28 (23%)

* 1 unknown IDMC class

Objective Response Rates: Nivo Monotherapy: Part A

| Best Response N (%)	IMDC Risk Category (N)			Total (N= 123) N (%)
	Favor (30) N (%)	Interm (80) N (%)	Poor (12) N (%)	
CR	4 (13.3)	3 (3.8)	0	7 (5.7)
PR*	11 (36.7)	17 (21.2)	3 (25)	32 (26.0)
SD	15 (50.0)	26 (32.5)	5 (42)	46 (37.4)
PD	0	34 (42.5)	4 (33)	38 (30.9)
ORR	15/30 (50)	20/80 (25)	3/12 (25)	39/123 (31.7)
(95% CI) %	(31.3,68.7)	(16.6, 35.1)		(23.6, 40.7)

ORR: 39/123 = 31.7% 95% CI (23.6, 40.7%)

Sarcomatoid RCC ORR: 7/22 = 31.8% (all PRs) 95% CI (13.9, 54.9%)

* 1 PR with missing IMDC Risk Category

Best Changes from Baseline: Target Lesions (Part A)
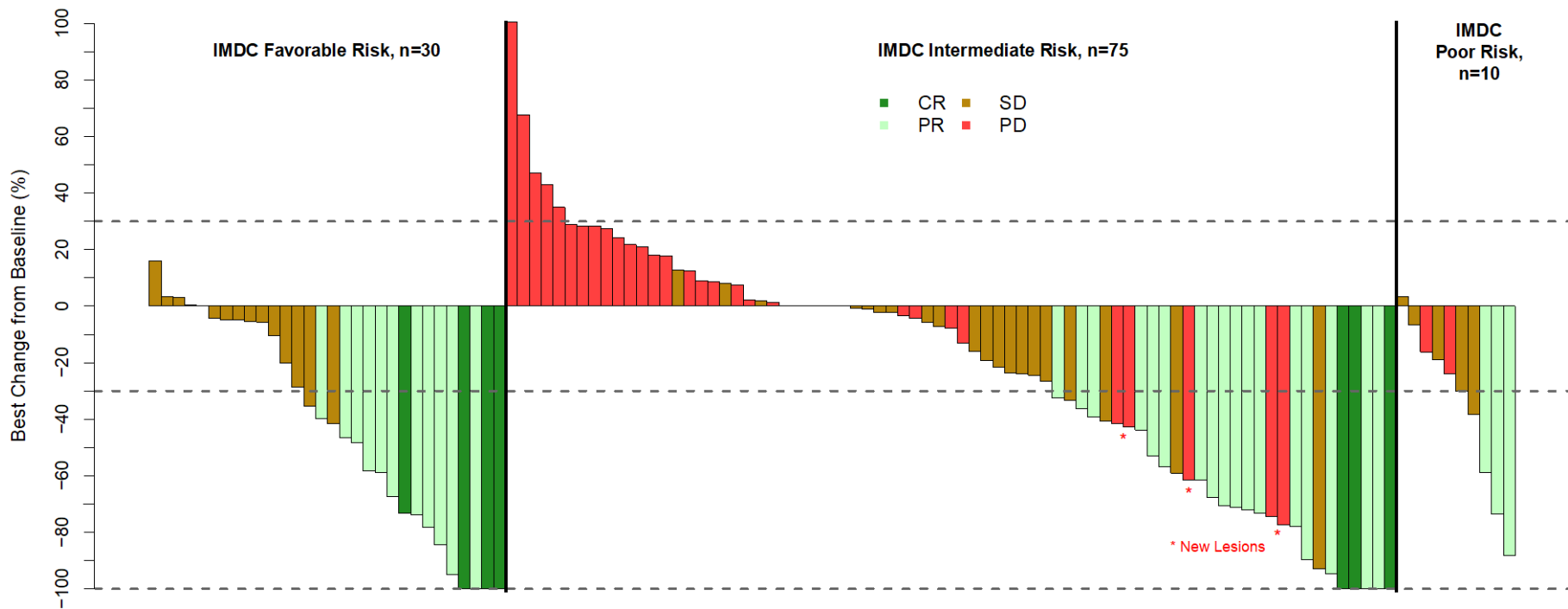
Disposition: Nivo/ipi Salvage (Part B)

- Potentially Eligible for Part B (65)
  - Progressive Disease (n=59)
  - Stable Disease at 48 wks (n=6)

- Not Enrolled: (31)
  - IrAE/AE in Part A (n=4)
  - Symptomatic PD/Alternative Systemic Rx/ Biopsy not possible (n=21)
  - Alternative Rx (surgery, RT) (n=6)

- Enrolled (34)
  - Evaluable (n=30)
  - Inevaluable (n=4) (PD, withdrew, ineligible x2)
  - 26 of 34 (76%) remain alive

Objective Response Rates: Nivo/Ipi Salvage (Part B)

Best Response N (%)	IMDC Risk Category (N=30)			Total N (%)
	Favor (4)	Interm (24)	Poor (2)	
CR	0	0	0	0
PR	2 (50)	2 (8.3)	0	4 (13.3)
SD	1 (25)	6 (25)	0	7 (23.3)
PD	1 (25)	16 (66.7)	2 (100)	19 (63.3)

ORR: 4/30 = 13.3%
95% CI (3.8, 30.7)

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Summary

- Nivo monotherapy has efficacy in treatment naïve ccRCC
  - ORR: 32%; 6% CR
  - Median PFS 8.3 mos; median DOR 19.3 mos
  - Efficacy seen across all IMDC risk categories (especially favorable risk)
  - Typical nivo toxicities

- Nivo/ipi Salvage
  - Due to study design, < 50% of patients with PD/SD were eligible for salvage
  - Salvage ORR: 13%
  - No increased toxicities

Conclusions

- Nivo monotherapy represents an alternative frontline approach
  - Particularly for the ipilimumab or VEGFR TKI averse
  - Possibly for those with IMDC favorable risk or maybe in the adjuvant setting.

- Nivo/Ipi likely preferred over nivo monotherapy
  - Particularly for Intermediate/Poor Risk patients and those with sarcomatoid RCC
  - Higher RR, longer PFS, longer DOR, more CRs

- BMS CM 209-8Y8 study will address this issue directly for IMDC intermediate and poor risk patients (Albiges, Atkins Co-PIs)

- Biologic predictors of response needed (studies ongoing)

Top clinical advances RCC

1. **FDA approval of Nivo/Ipi and Pembro/axitinib both showing survival advantage over sunitunib**
2. Avelumab/axitinib and Atezolizumab/bevacizumab no OS benefit yet over sunitunib
3. Multiple other immune/TKI trials underway/completed but not yet reported (Pembro/lenvantinib,Nivo/Ipi/cabo, Nivo/cabo etc)
4. Pembrolizumab, Nivolumab, cabometyx and lenvantinib/ev all active in metastatic non-clear RCC
5. Decline of use of sunitunib and pazopanib and rise of cabometyx and lenvantinib/everolimus for mRCC
6. Tivozanib (new TKI)> sorafenib in 3-4th line
7. Long term follow up of CARMENA still supports nephrectomy after sunitunib

Diagnostic Performance of ^{18}F-DCFPyL-PET/CT and its Impact on Clinical Management of Patients with Biochemically Recurrent Prostate Cancer: Results from a Phase 3, Prospective, Multicenter Study (CONDOR)

Michael J. Morris*, Peter R. Carroll, Lawrence Saperstein, Frédéric Pouliot, David Josephson, Jeffrey Y.C. Wong, Austin R. Pantel, Steve Y. Cho, Kenneth Gage, Morand Piert, Andrei Iagaru, Janet H. Pollard, Vivien Wong, Jessica Donato Jensen, Nancy Stambler, Michael A. Gorin, Barry A. Siegel

Memorial Sloan Kettering Cancer Center, New York, NY; Dept. of Urology, University of California San Francisco, San Francisco, CA; Yale School of Medicine, New Haven, CT; Cancer Research Center, Centre Hospitalier Universitaire (CHU) de Québec-Université Laval, Quebec City, QC; Tower Urology, Los Angeles, CA; City of Hope, Duarte, CA; University of Pennsylvania, Philadelphia, PA; University of Wisconsin School of Medicine, Madison, WI; Moffitt Cancer Center, Tampa, FL; University of Michigan, Ann Arbor, MI; Stanford University, Stanford, CA; Carver College of Medicine - University of Iowa, Iowa City, IA; Progenics Pharmaceuticals, Inc., New York, NY; Department of Urology, Johns Hopkins University School of Medicine, Baltimore, MD; Siteman Cancer Center/Washington University, Saint Louis, MO

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PRESENTED BY: Michael J. Morris, MD

Background

- Previous data have suggested PSMA-PET is a superior imaging modality for prostate cancer relative to current standards

- ^{18}F-DCFPyL is a PSMA-targeted PET radiopharmaceutical being studied to collect an evidentiary database in support of regulatory approval in the US

- CONDOR is the second of two prospective clinical trials designed in collaboration with FDA to demonstrate the diagnostic performance of ^{18}F-DCFPyL-PET/CT

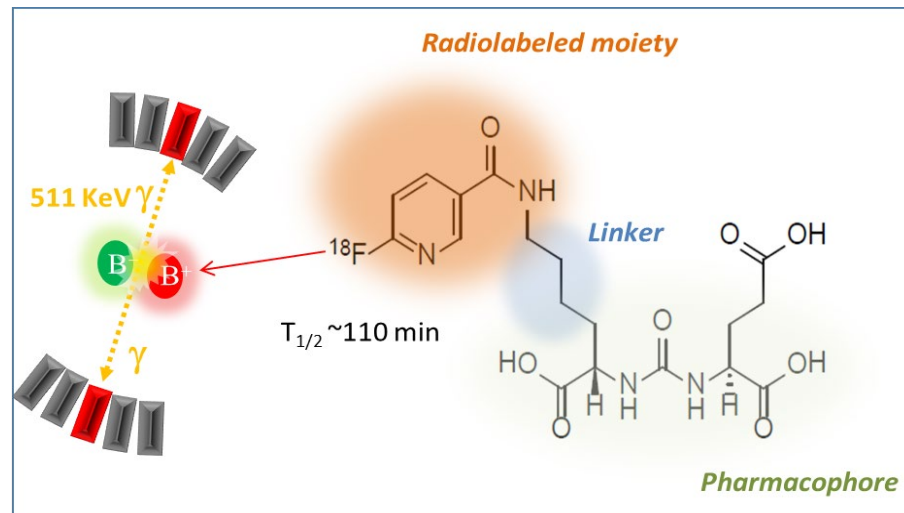# ^{18}F-DCFPyL Clinical Development Program
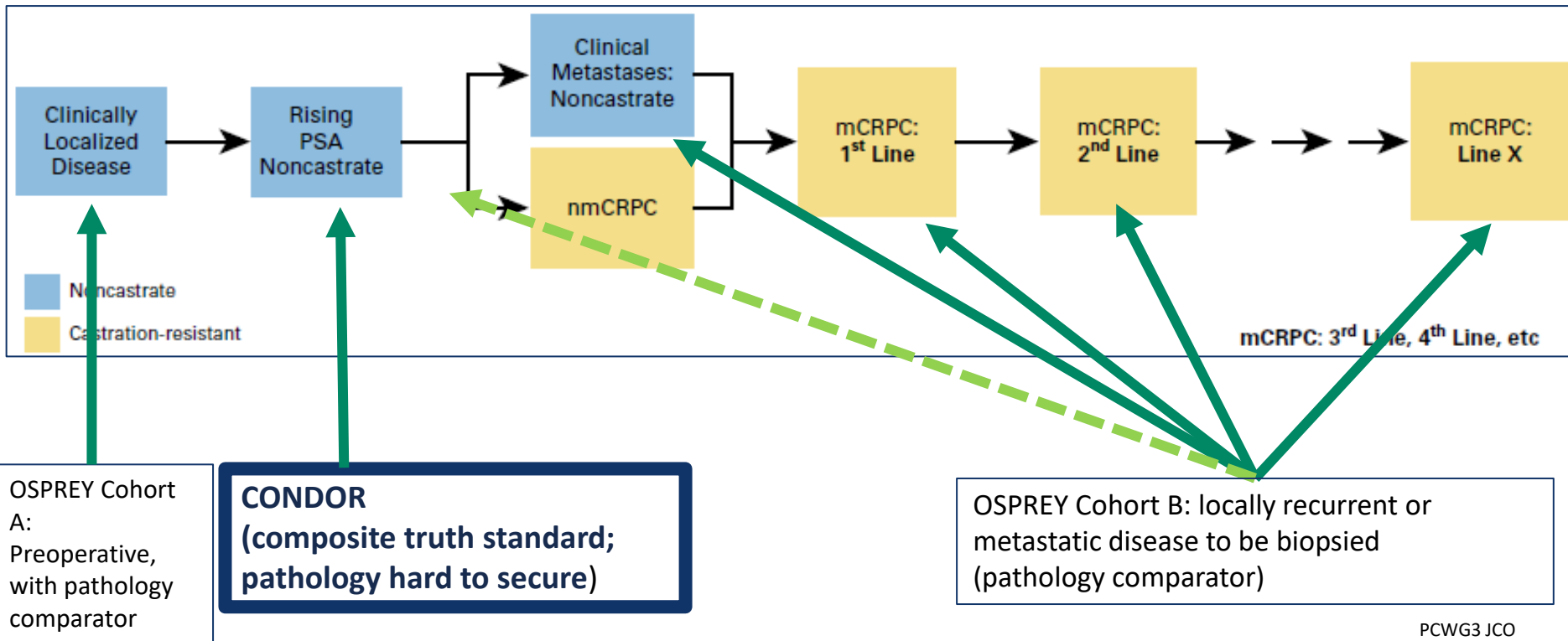
¹⁸F-DCFPyL

- **Lysine-linked, urea-based small molecule**

- **Targets the extracellular domain of PSMA**

- **High specific activity**

- **9 (±20%) mCi administered intravenously as bolus injection**

- **Imaging performed 1-2 hours following administration**

Chen et al. Clin Cancer Res 2011; laboratory of Martin G. Pomper, MD, PhD

Eligibility Criteria

Select Inclusion Criteria

- Post-RP: PSA ≥0.2 ng/mL or

- Post-RT or cryotherapy: PSA ≥2 ng/mL above nadir

- Negative or equivocal imaging per institution's SOC work-up (including bone scan, CT, MRI, FDG PET, ^{18}F-fluciclovine or ^{11}C-choline PET)

Select Exclusion Criteria

- Ongoing treatment with any systemic therapy

- Treatment with ADT within 3 months prior to Day 1

Composite Standard of Truth (SOT)

Defined either as:

1) Evaluable local histopathology findings from surgery/biopsy, **or**

2) Informative conventional imaging [e.g., ^{18}F-fluciclovine PET (preferred if not performed at baseline) or choline PET; targeted MRI/CT], **or**

3) Confirmed PSA response (decline from baseline of ≥50%) in subjects treated with RT only (no concomitant ADT) following ^{18}F-DCFPyL-PET/CT imaging

Select Baseline Characteristics, N=208

Patients Screened/Consented (N)	**217**
Patients dosed (N)	**208**
Age (years): Median (range)	**68 (43, 91)**
Months from Prostate Cancer Diagnosis: Median (range)	**71 (3, 356)**
Prior Prostate Cancer Therapies, N (%)	
RP only	103 (49.5)
RP and RT	74 (35.6)
RT only	31 (14.9)
At least 1 prior systemic therapy	58 (27.9)
Total Gleason Score, N (%)	
< 8	153 (73.6)
≥ 8	55 (26.4)

PSA: Median (range) ng/mL	**0.8 (0.17, 98.45)**
PSA Group (N=202), N (%)	
<2.0 ng/mL	**139 (68.8)**
<0.5 ng/mL	69 (34.2)
0.5 to <1.0 ng/mL	37 (18.3)
1.0 to <2.0 ng/mL	33 (16.3)
≥2.0 ng/mL	**63 (31.2)**
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≥5.0 ng/mL	30 (14.9)

Detection Rate by PSA
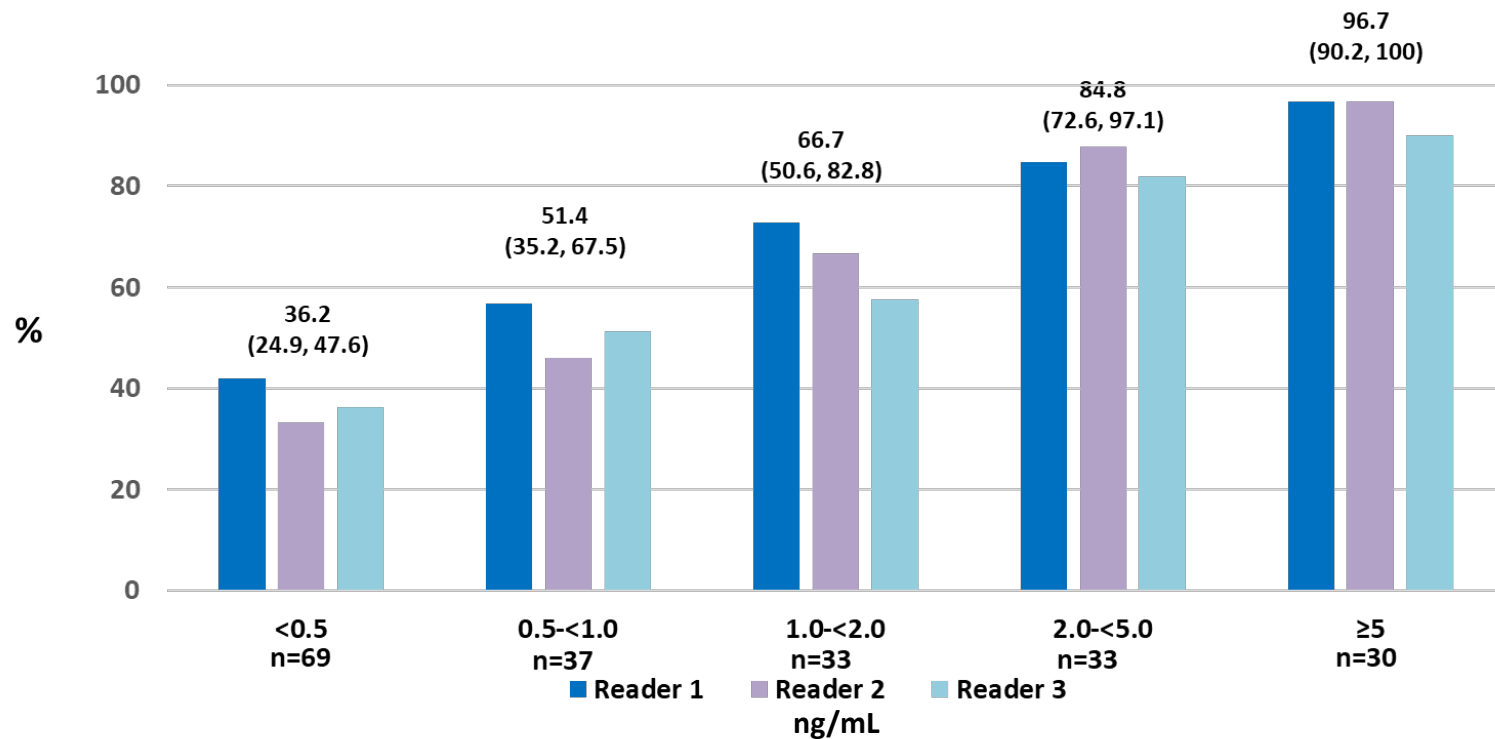
Median values for each group of three readers provided

Change of Management

- 63.9% of evaluable subjects had a change in intended management after ^{18}F-DCFPyL-PET/CT

  o 78.6% were attributable to positive and 21.4% to negative ^{18}F-DCFPyL-PET/CT scans

    - Noncurative systemic therapy to salvage local therapy (n = 43; 21.0%)
    - Salvage local therapy to systemic therapy (n = 58; 28.3%)
    - Observation to initiating therapy (n = 49; 23.9%)
    - Planned treatment to observation (n = 9; 4.4%)

Efficacy Summary

- **The CONDOR study has met its primary endpoint, demonstrating excellent diagnostic performance of ^{18}F-DCFPyL-PET/CT imaging in men with biochemically relapsed prostate cancer, even at low PSA values**

- **^{18}F-DFPyL-PET/CT is superior to standard imaging in men with BCR**

- **The results yielded actionable information clinically significant information. Optimized treatment patterns need to be further defined**

- **This trial, coupled with the OSPREY study, has now established the performance characteristics of ^{18}F-DCFPyL-PET/CT in localized, BCR, and metastatic prostate cancer**

Updated Overall Survival Results From PROSPER: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Enzalutamide in Men With Nonmetastatic Castration-Resistant Prostate Cancer

Cora N. Sternberg,[1] Karim Fizazi,[2] Fred Saad,[3] Neal D. Shore,[4] Ugo De Giorgi,[5] David F. Penson,[6] Ubirajara Ferreira,[7] Petro Ivashchenko,[8] Eleni Efstathiou,[9] Katarzyna Madziarska,[10] Michael Kolinsky,[11] Daniel I. G. Cubero,[12] Bettina Noerby,[13] Fabian Zohren,[14] Xun Lin,[14] Katharina Modelska,[15] Jennifer Sugg,[16] Joyce Steinberg,[16] Maha Hussain[17]

[1]Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, NY, USA; [2]Gustave Roussy, Villejuif Cedex, France; [3]University of Montreal Hospital Center (CHUM), Montreal, QC, Canada; [4]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [5]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; [6]Vanderbilt University, Nashville, TN, USA; [7]State University of Campinas (Unicamp), Campinas, SP, Brazil; [8]Kyiv City Clinical Hospital #3, Kyiv, Ukraine; [9]MD Anderson Cancer Center, Houston, TX, USA; [10]Wroclaw Medical University, Wroclaw, Poland; [11]Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; [12]ABC Foundation School of Medicine, Santo André, Brazil; [13]Sygehus, Lillebælt, Vejle, Denmark; [14]Pfizer Inc., San Francisco, CA, USA; [15]Formerly of Pfizer Inc., San Francisco, CA, USA; [16]Astellas Pharma, Inc., Northbrook, IL, USA; [17]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, USA

PROSPER Study Design

Key Eligibility Criteria
- nmCRPC (central review)
- Rising PSA despite castrate testosterone level (≤ 50 ng/dL)
- Baseline PSA ≥ 2 ng/mL
- PSA doubling time ≤ 10 months

Stratification
- PSA doubling time (< 6 mo vs 6-10 mo)
- Baseline use of bone-targeting agent (Y/N)

N = 1401

Double-blind period

R 2:1

Enzalutamide 160 mg/day + ADT

Placebo + ADT

Open-label extension *(Optional)*

Enzalutamide 160 mg/day + ADT

Crossover Group

Enzalutamide 160 mg/day + ADT
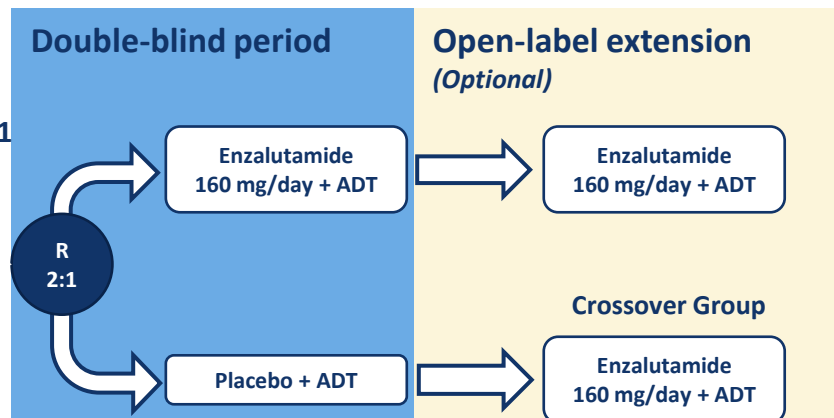
Primary endpoint
- MFS (defined as time from randomization to radiographic progression or death within 112 days of treatment discontinuation without evidence of radiographic progression)

Secondary endpoints
- OS
- Time to PSA progression
- Safety
- PSA response
- Quality of life

ADT, androgen deprivation therapy; MFS, metastasis-free survival; nmCRPC, nonmetastatic castration-resistant prostate cancer; OS, overall survival; PSA, prostate-specific antigen; R, randomization.

PROSPER Final Overall Survival Analysis

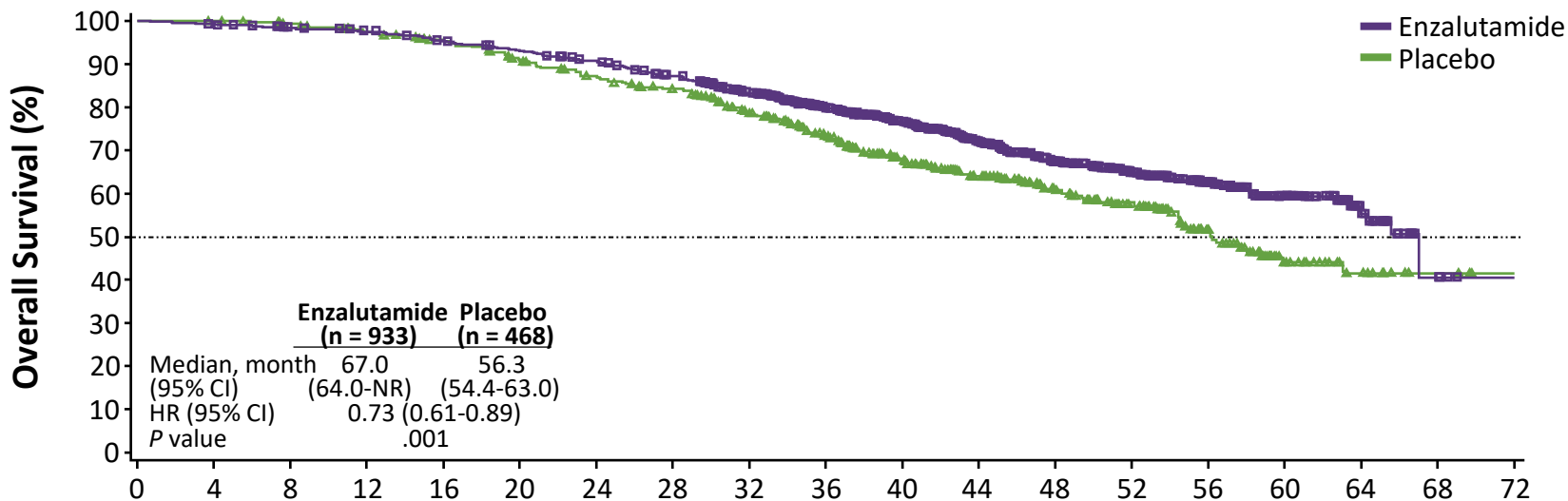**Enzalutamide was associated with a statistically significant 27% reduction in the risk of death**

	Enzalutamide (n = 933)	Placebo (n = 468)
Median, month	67.0	56.3
(95% CI)	(64.0-NR)	(54.4-63.0)
HR (95% CI)	0.73 (0.61-0.89)	
P value	.001	

Patients at risk

	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72
Enzalutamide	933	926	910	897	874	850	822	782	700	608	517	424	327	244	169	89	33	4	0
Placebo	468	467	459	444	428	404	381	363	321	274	219	177	140	106	64	30	16	3	0

CI, confidence interval; HR, hazard ratio; NR, not reached.

PROSPER Subsequent Antineoplastic Therapy

	Enzalutamide Group (n = 930)	Placebo Group (n = 465)
Patients taking ≥ 1 antineoplastic therapy after treatment discontinuation*	**33%**	**65%**
Subsequent therapies used by ≥ 5% of patients in any treatment group†		
Abiraterone acetate	49%	59%
Docetaxel	60%	47%
Enzalutamide‡	14%	36%
Cabazitaxel	15%	16%
Bicalutamide	9%	14%

*Percentages based on the total number of patients in each treatment group.
†Percentages based on the number of patients who received ≥ 1 antineoplastic therapy after treatment discontinuation.
‡Does not include the 87 patients who were randomized to placebo and received enzalutamide in the open-label extension.

PROSPER Time to First Use of Subsequent Antineoplastic Therapy

CI, confidence interval; HR, hazard ratio; NR, not reached.

PROSPER Adverse Events of Special Interest*

	Enzalutamide + ADT (n = 930)		Placebo + ADT (n = 465)	
Fatigue	46%	19 per 100 patient-years	22%	17 per 100 patient-years
Musculoskeletal events	34%	18 per 100 patient-years	23%	23 per 100 patient-years
Fracture	18%	9 per 100 patient-years	6%	5 per 100 patient-years
Hypertension	18%	7 per 100 patient-years	6%	5 per 100 patient-years
Fall	18%	9 per 100 patient-years	5%	4 per 100 patient-years
Cognitive and memory impairment	8%	3 per 100 patient-years	2%	2 per 100 patient-years
Cardiovascular events	6%	3 per 100 patient-years	2%	2 per 100 patient-years
Ischemic heart disease	6%	3 per 100 patient-years	2%	1 per 100 patient-years
Second primary malignancy	5%	2 per 100 patient-years	2%	1 per 100 patient-years

*Occurring in ≥ 5% of patients in either treatment arm. The full list is provided in the manuscript.

Enzalutamide Survival in Nonmetastatic Castration-Resistant Prostate Cancer

- In patients with nmCRPC, enzalutamide treatment resulted in a clinically meaningful and statistically significant 27% lower risk of death than placebo

- These results demonstrate that enzalutamide prolongs overall survival compared with placebo in men with nmCRPC and a rapidly rising PSA

- Adverse events were consistent with the established safety profile of enzalutamide

Enzalutamide Survival in Nonmetastatic Castration-Resistant Prostate Cancer

J.J. McNeil, R.L. Woods, M.R. Nelson, C.M. Reid, B. Kirpach, R. Wolfe, E. Storey, R.C. Shah, J.E. Lockery, A.M. Tonkin, A.B. Newman, J.D. Williamson, K.L. Margolis, M.E. Ernst, W.P. Abhayaratna, N. Stocks, S.M. Fitzgerald, S.G. Orchard, R.E. Trevaks, L.J. Beilin, G.A. Donnan, P. Gibbs, C.I. Johnston, J. Ryan, B. Radziszewska, R. Grimm, and A.M. Murray, for the ASPREE Investigator Group*

ABSTRACT

BACKGROUND

Information on the use of aspirin to increase healthy independent life span in older persons is limited. Whether 5 years of daily low-dose aspirin therapy would extend disability-free life in healthy seniors is unclear.

METHODS

From 2010 through 2014, we enrolled community-dwelling persons in Australia and the United States who were 70 years of age or older (or ≥65 years of age among blacks and Hispanics in the United States) and did not have cardiovascular disease, dementia, or physical disability. Participants were randomly assigned to receive 100 mg per day of enteric-coated aspirin or placebo orally. The primary end point was a composite of death, dementia, or persistent physical disability. Secondary end points reported in this article included the individual components of the primary end point and major hemorrhage.

RESULTS

A total of 19,114 persons with a median age of 74 years were enrolled, of whom 9525 were randomly assigned to receive aspirin and 9589 to receive placebo. A total of 56.4% of the participants were women, 8.7% were nonwhite, and 11.0% reported previous regular aspirin use. The trial was terminated at a median of 4.7 years of follow-up after a determination was made that there would be no benefit with continued aspirin use with regard to the primary end point. The rate of the composite of death, dementia, or persistent physical disability was 21.5 events per 1000 person-years in the aspirin group and 21.2 per 1000 person-years in the placebo group (hazard ratio, 1.01; 99% confidence interval [CI], 0.92 to 1.11; P=0.79). The rate of adherence to the assigned intervention was 62.1% in the aspirin group and 64.1% in the placebo group in the final year of trial participation. Differences between the aspirin group and the placebo group were not substantial with regard to the secondary individual end points of death from any cause (12.7 events per 1000 person-years in the aspirin group and 11.1 events per 1000 person-years in the placebo group), dementia, or persistent physical disability. The rate of major hemorrhage was higher in the aspirin group than in the placebo group (3.8% vs. 2.8%; hazard ratio, 1.38; 99% CI, 1.18 to 1.62; P<0.001).

CONCLUSIONS

Aspirin use in healthy elderly persons did not prolong disability-free survival over a period of 5 years but led to a higher rate of major hemorrhage than placebo. (Funded by the National Institute on Aging and others; ASPREE ClinicalTrials.gov number, NCT01038583.)

Overall Survival (OS) Results of Phase III ARAMIS Study of Darolutamide (DARO) Added to Androgen Deprivation Therapy (ADT) for Non-metastatic Castration-Resistant Prostate Cancer (nmCRPC)

Karim Fizazi,[1] Neal D. Shore,[2] Teuvo Tammela,[3] Albertas Ulys,[4] Egils Vjaters,[5] Sergey Polyakov,[6] Mindaugas Jievaltas,[7] Murilo Luz,[8] Boris Alekseev,[9] Iris Kuss,[10] Marie-Aude Le Berre,[10] Oana Petrenciuc,[11] Amir Snapir,[12†] Toni Sarapohja,[12] Matthew Raymond Smith[13]

[1]Institut Gustave Roussy and University of Paris-Saclay, Villejuif, France; [2]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [3]Tampere University Hospital, Tampere, Finland; [4]National Cancer Institute, Vilnius, Lithuania; [5]Stradins Clinical University Hospital, Riga, Latvia; [6]N.N. Alexandrov National Cancer Centre of Belarus, Minsk, Belarus; [7]Lithuanian University of Health Sciences, Medical Academy, Kaunas, Lithuania; [8]Hospital Erasto Gaertner, Curitiba, Brazil; [9]National Medical Research Radiological Center, Ministry of Health of the Russian Federation, Moscow, Russia; [10]Bayer AG, Berlin, Germany; [11]Bayer HealthCare Pharmaceuticals, Inc., Whippany, NJ, USA; [12]Orion Corporation Orion Pharma, Espoo, Finland [†]; [13]Massachusetts General Hospital Cancer Center, Boston, MA, USA

[†]Present affiliation: PCI Biotech, Oslo, Norway

ARAMIS: Double-Blind, Placebo-Controlled, Phase III Trial to Evaluate Darolutamide vs Placebo in nmCRPC

Darolutamide is a structurally distinct ARI with low BBB penetration and low potential for DDIs[1–4]

Patients
- Men with nmCRPC
- PSADT ≤10 months

Stratification
- PSADT (≤6 months vs >6 months)
- Osteoclast-targeted therapy (yes vs no)

Randomization 2:1

N=1509

Darolutamide 600 mg BID + ADT n=955

Placebo BID + ADT n=554

Primary analysis: MFS

Sep 3, 2018

Unblinding[†]

Final analysis: OS

Nov 15, 2019
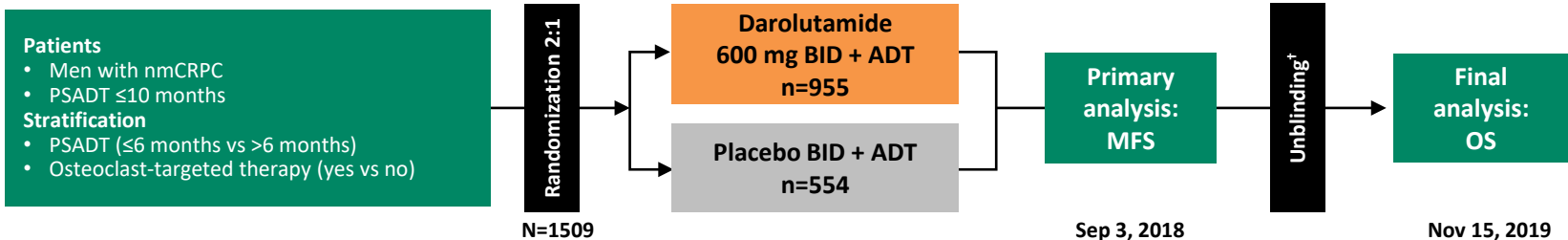
[†]170 patients randomized to placebo crossed over to darolutamide treatment after unblinding

1 **Primary endpoint met at primary analysis (significance level 0.05)[5]**
- MFS median 40.4 months darolutamide vs 18.4 months placebo
- HR 0.41 (95% CI 0.34–0.50); $P<0.0001$

Safety[5]
- Favorable safety profile
- No increased incidence of most ARI-associated AEs with darolutamide

2 **Secondary endpoints assessed for significance at final analysis (hierarchical testing; final α=0.0498)**
- OS
- Time to pain progression
- Time to first cytotoxic chemotherapy
- Time to first SSE

1. Moilanen AM, et al. *Sci Rep.* 2015;5:12007. 2. Williams S, et al. *J Clin Oncol.* 2020;38(suppl 6):abstr 326. 3. Zurth C, et al. *J Clin Oncol.* 2019;37(7_suppl):156. 4. Shore N, et al. *Targ Oncol.* 2019;14:527–539. 5. Fizazi K, et al. *N Engl J Med*. 2019;380:1235–1246.
ADT, androgen deprivation therapy; AE, adverse event; ARI, androgen receptor inhibitor; BBB, blood–brain barrier; BID, twice daily; CI, confidence interval; DDI, drug–drug interaction; HR, hazard ratio; MFS, metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; PSADT, prostate-specific antigen doubling time; SSE, symptomatic skeletal event.

ARAMIS Overall Survival: 31% Reduction in Risk of Death

Survival benefit evident despite many placebo group patients receiving subsequent life-prolonging therapy

HR 0.69 (95% CI 0.53–0.88)
P=0.003

83%

77%

Darolutamide
Placebo

Received subsequent life-prolonging therapy:

Darolutamide	Placebo
141 (15%)	309 (56%)

Patients at risk

	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60
Darolutamide	955	932	908	863	816	771	680	549	425	293	214	129	69	37	12	0
Placebo	554	530	497	460	432	394	333	261	182	130	93	54	28	16	4	0
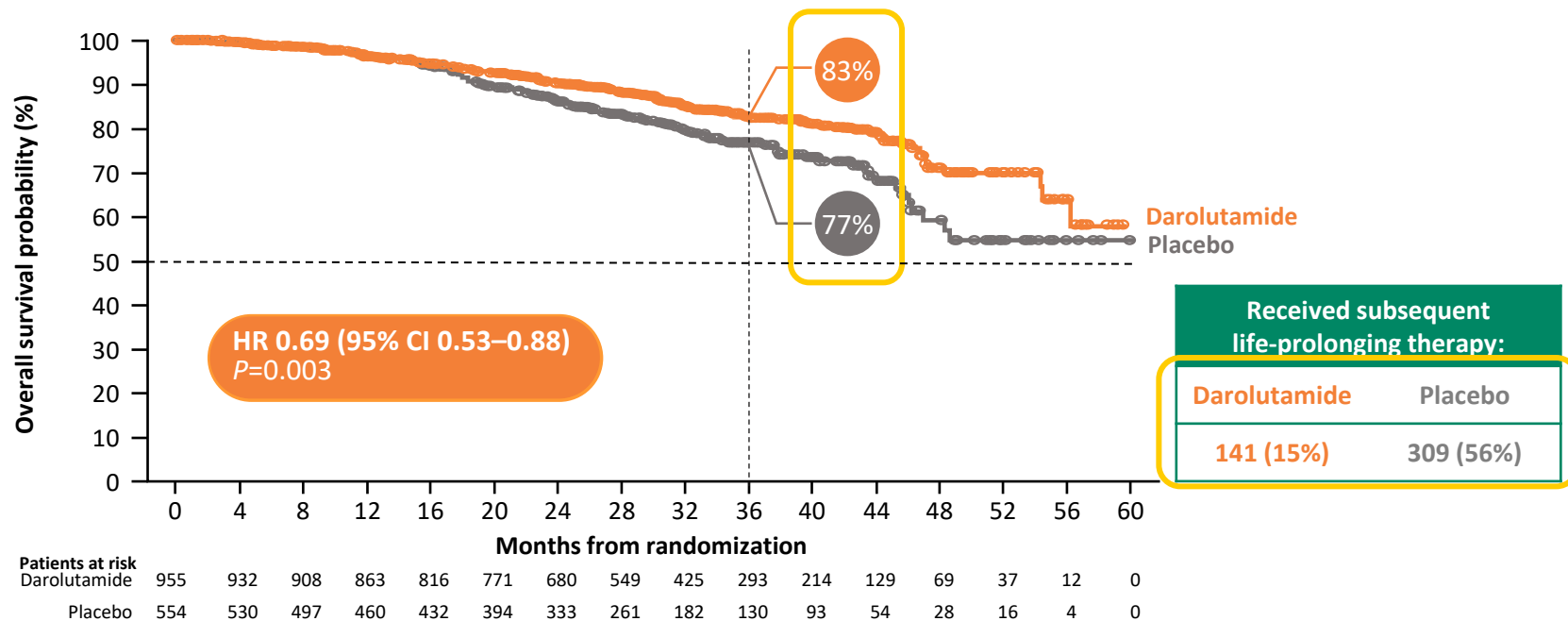
At data cut-off for final analysis (November 15, 2019), median follow-up was 29.1 months. Median treatment duration was 25.8 months for patients randomized to darolutamide (double-blind and open-label periods), 11.0 months for crossover patients receiving darolutamide (open-label period), and 11.6 months for the patients receiving placebo during the double-blind period.
Three-year survival rates are indicated on the Kaplan-Meier curve by a vertical dotted line. CI, confidence interval; HR, hazard ratio.

ARAMIS: All Secondary Endpoints Significantly in Favor of Darolutamide vs Placebo

Time to pain progression†

Darolutamide, median 40.3 months
Placebo, median 25.4 months

HR 0.65 (95% CI 0.53–0.79)
P<0.001

Patients at risk
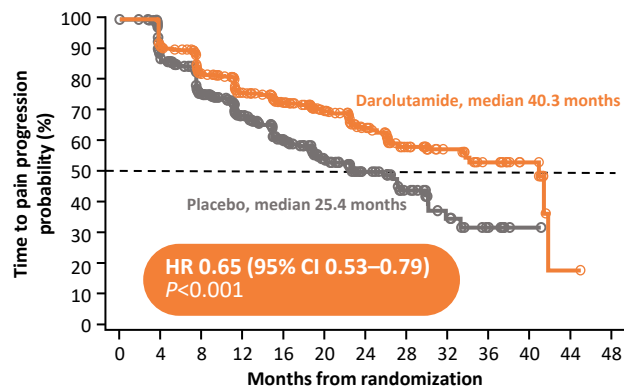
	0	4	8	12	16	20	24	28	32	36	40	44	48
Darolutamide	955	749	585	444	337	238	170	99	59	29	14	1	0
Placebo	554	387	285	198	125	83	54	30	14	6	1	0	0

Time to first cytotoxic chemotherapy

Darolutamide
Placebo

HR 0.58 (95% CI 0.44–0.76)
P<0.001

Patients at risk

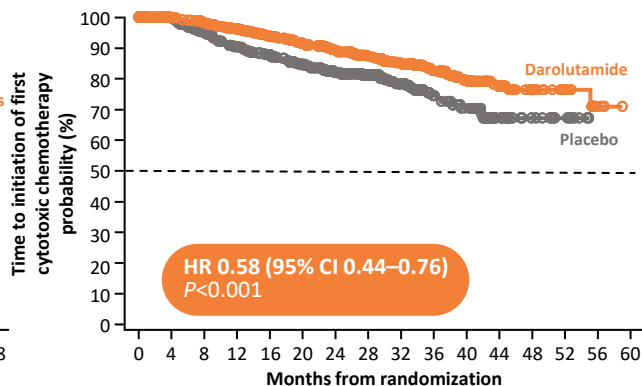|	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60
Darolutamide	955	916	863	805	738	678	578	453	339	232	164	93	45	19	3	0
Placebo	554	511	459	403	364	312	254	183	119	78	58	26	13	7	0	0

Time to first SSE

Darolutamide
Placebo

HR 0.48 (95% CI 0.29–0.82)
P=0.005

Patients at risk
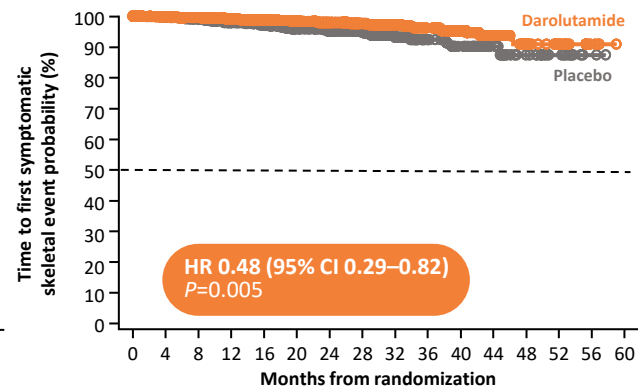
	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60
Darolutamide	955	916	876	823	763	704	601	477	363	253	182	100	46	21	4	0
Placebo	554	511	473	424	388	339	282	210	139	93	71	38	20	11	2	0

†Time to pain progression was evaluated using data from the primary analysis cut-off date of September 3, 2018.
All analyses for the placebo group include the 170 patients who crossed over to darolutamide treatment during the open-label study period.
CI, confidence interval; HR, hazard ratio; SSE, symptomatic skeletal event.

ARAMIS: Incidence of ARI-Associated Adverse Events

	Darolutamide (double-blind) (N=954)		Placebo (double-blind) (N=554)	
	Any grade, n (%)	Grade 3 or 4, n (%)	Any grade, n (%)	Grade 3 or 4, n (%)
Fatigue	126 (13.2)	4 (0.4)	48 (8.3)	5 (0.9)
Asthenic conditions	38 (4.0)	2 (0.2)	17 (3.1)	2 (0.4)
Seizure (any event)	2 (0.2)	0	1 (0.2)	0
Mental impairment disorders	19 (2.0)	3 (0.3)	10 (1.8)	0
Depressed mood disorders	21 (2.2)	1 (0.1)	10 (1.8)	0
Bone fracture	52 (5.5)	10 (1.0)	20 (3.6)	5 (0.9)
Falls (including accident)	50 (5.2)	9 (0.9)	27 (4.9)	4 (0.7)
Weight decreased (any event)	40 (4.2)	0	14 (2.5)	0
Rash	30 (3.1)	2 (0.2)	6 (1.1)	1 (0.2)
Hot flush	57 (6.0)	0	25 (4.5)	0
Hypertension	74 (7.8)	33 (3.5)	36 (6.5)	13 (2.3)
Cardiac arrhythmias [†]	70 (7.3)	17 (1.8)	24 (4.3)	4 (0.7)
Coronary artery disorders [‡]	38 (4.0)	19 (2.0)	15 (2.7)	2 (0.4)
Heart failure [§]	18 (1.9)	4 (0.4)	5 (0.9)	0

At final analysis, median treatment duration during the double-blind period was 18.5 months for the darolutamide group and 11.6 months for the placebo group.
Mental impairment disorders, depressed mood disorders, cardiac arrhythmias, coronary artery disorders, and heart failure are MedDRA High Level Group terms; hot flush and hypertension are group terms based on MedDRA labeling; bone fracture, falls, weight decrease, asthenic conditions, rash, and seizure are grouped terms.
[†] Grade 5 events occurred in two patients receiving darolutamide in the double-blind period and three patients receiving placebo in the double-blind period.
[‡] Grade 5 events occurred in three patients receiving darolutamide in the double-blind period, one patient receiving placebo during the double-blind period and one patient in the crossover group.
[§] Grade 5 events occurred in seven patients receiving darolutamide in the combined double-blind and open-label periods, and three patients receiving placebo during the double-blind period.
ARI, androgen receptor inhibitor; MedDRA, Medical Dictionary for Regulatory Activities.

ARAMIS Final Analysis: Conclusions

- **Darolutamide significantly improved overall survival vs placebo in men with nmCRPC**
  - 31% reduction in risk of death: HR 0.69 (95% CI 0.53–0.88); *P*=0.003

- **Darolutamide significantly delayed the onset of cancer-associated morbidity and subsequent chemotherapy vs placebo**

  - Time to pain progression, subsequent chemotherapy, and SSE were all significantly prolonged vs placebo

- **With extended follow-up, the safety profile of darolutamide was favorable**

  - Incidences of most AEs were not increased with darolutamide vs placebo, taking treatment exposure into account

- **These results provide compelling evidence for early darolutamide treatment in men with non-metastatic castration-resistant prostate cancer**

AEs, adverse events; CI, confidence interval; HR, hazard ratio; nmCRPC, non-metastatic castration-resistant prostate cancer; SSE, symptomatic skeletal event.

ORIGINAL ARTICLE

Nonmetastatic Castration-Resistant Prostate Cancer and Survival with Darolutamide

Karim Fizazi, M.D., Neal Shore, M.D., Teuvo L. Tammela, M.D., Ph.D.,
Albertas Ulys, M.D., Egils Vjaters, M.D., Sergey Polyakov, M.D.,
Mindaugas Jievaltas, M.D., Murilo Luz, M.D., Boris Alekseev, M.D.,
Iris Kuss, M.D., Marie-Aude Le Berre, M.Sc., Oana Petrenciuc, M.D.,
Amir Snapir, M.D., Ph.D., Toni Sarapohja, M.Sc., and
Matthew R. Smith, M.D., Ph.D., for the ARAMIS Investigators*

Figure 2. SPARTAN Study Design[5]

Eligibility
- nmCRPC
  - Pelvic nodes < 2 cm below iliac bifurcation (N1) allowed
- PSADT ≤ 10 months

On-Study Requirement
- Continuous ADT

Stratifications
- PSADT > 6 mos or ≤ 6 mos
- Bone-sparing agents, y/n
- N0 or N1

NCT01946204

Randomization

2:1
(N = 1207)

APA
240 mg QD
+ ADT
(n = 806)

PBO
+
ADT
(n = 401)[a]

MFS

Subsequent Rx at MD's discretion, including open-label ABI/PRED

OS
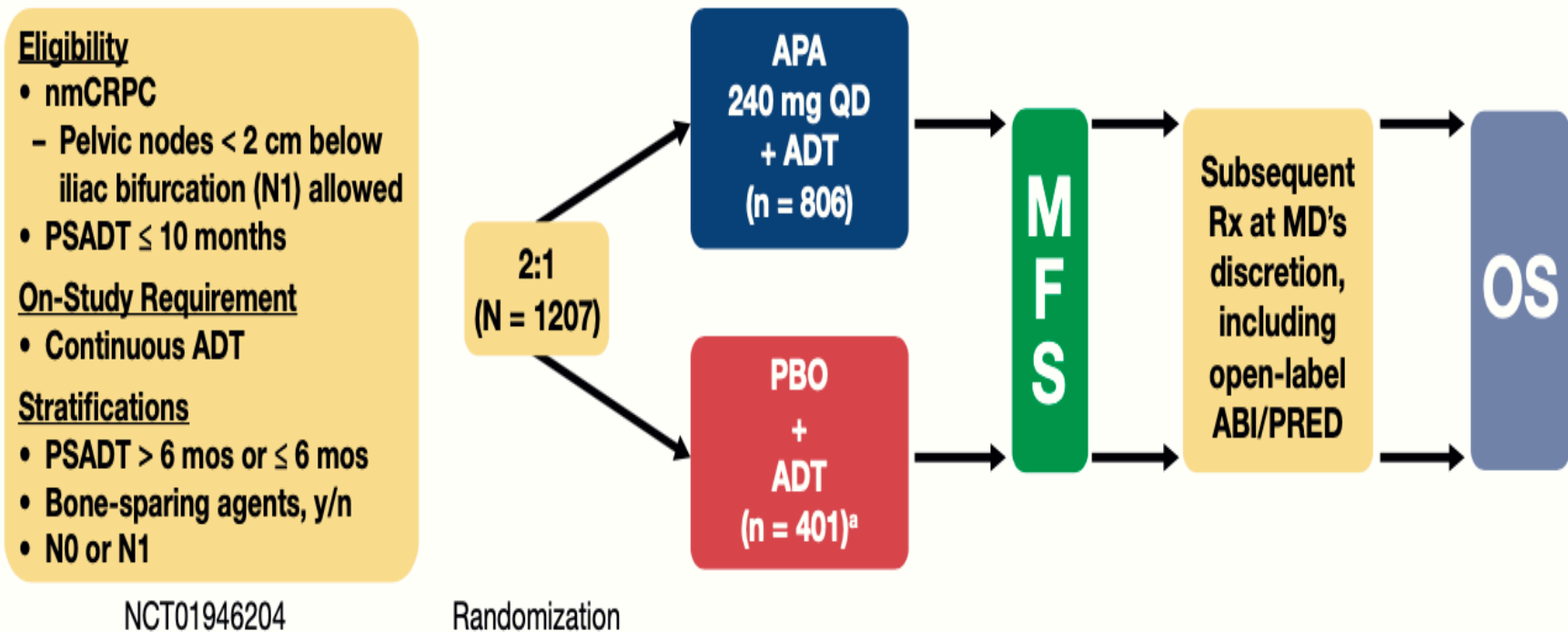
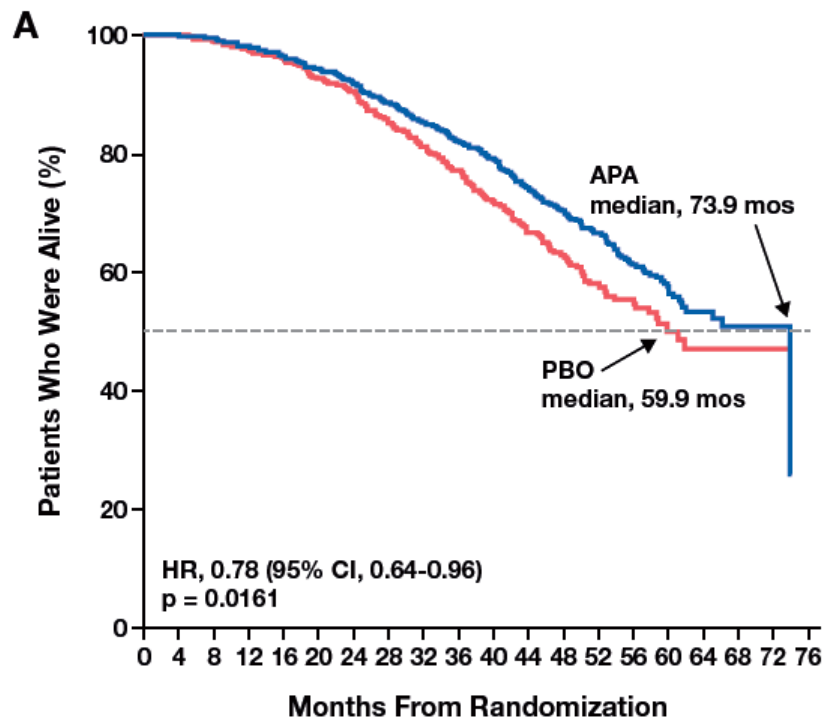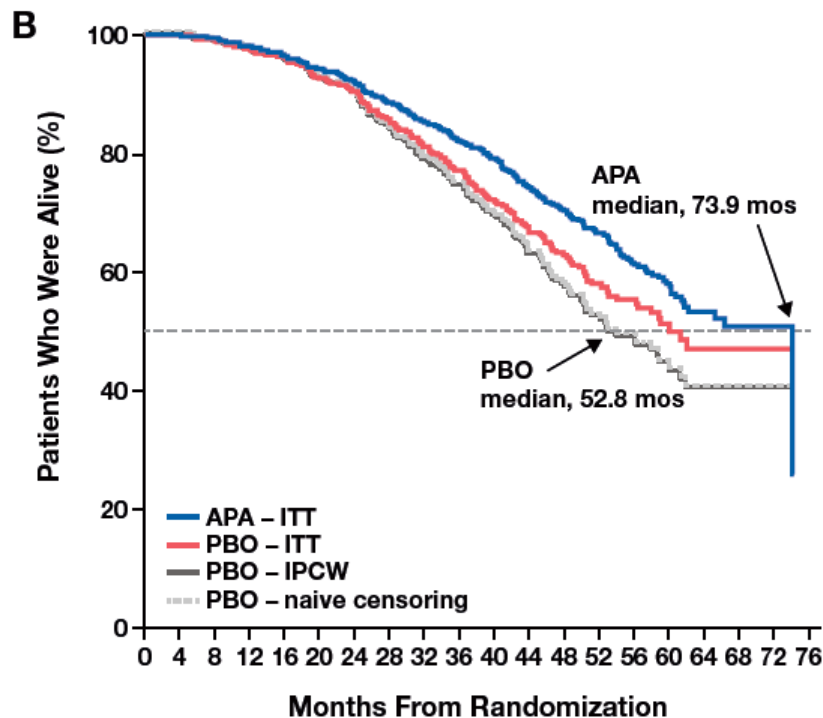PSADT, PSA doubling time; ABI/PRED, abiraterone acetate plus prednisone.

[a]Patients from the PBO group who did not have disease progression at the time of unblinding were allowed to cross over to APA treatment.

Figure 4. Kaplan-Meier Estimate of OS (A), and of OS Adjusted for Patient Crossover From PBO to APA (B), and Forest Plot Subgroup Analysis for OS by Baseline Patient Characteristics (C)

A

APA
median, 73.9 mos

PBO
median, 59.9 mos

HR, 0.78 (95% CI, 0.64-0.96)
p = 0.0161

Months From Randomization

No. at risk
APA   806 791 774 758 739 717 691 658 625 593 558 499 376 269 181 100 47 19   4   0
PBO   401 392 385 373 358 339 328 306 286 263 240 204 156 114 82 38 21   6   2   0

B

APA
median, 73.9 mos

PBO
median, 52.8 mos

APA – ITT
PBO – ITT
PBO – IPCW
PBO – naive censoring

Months From Randomization
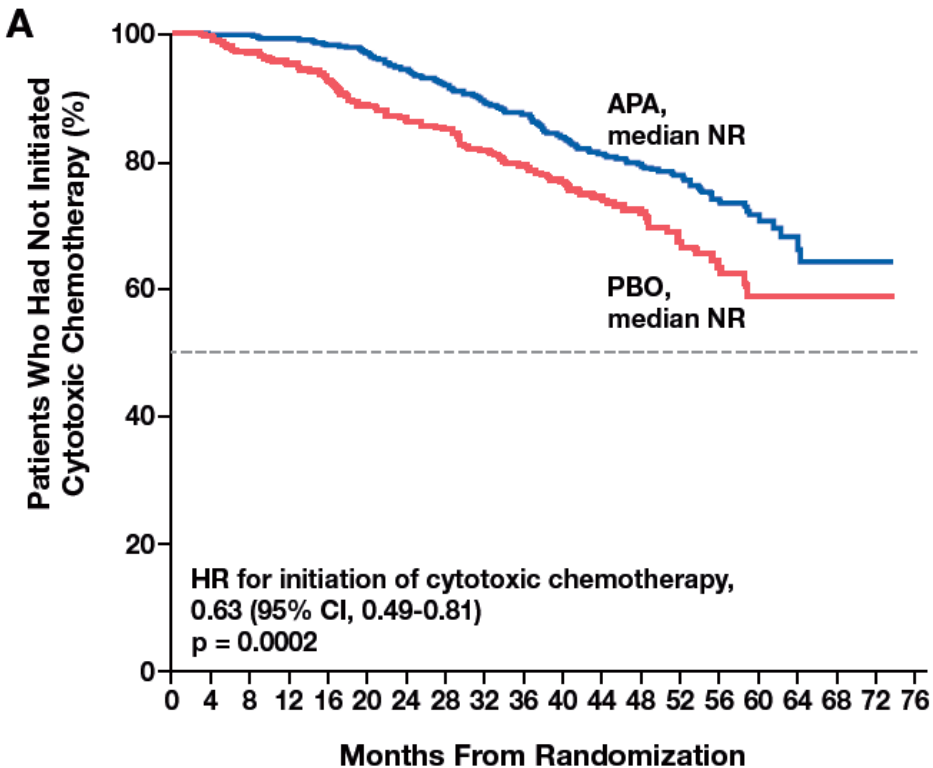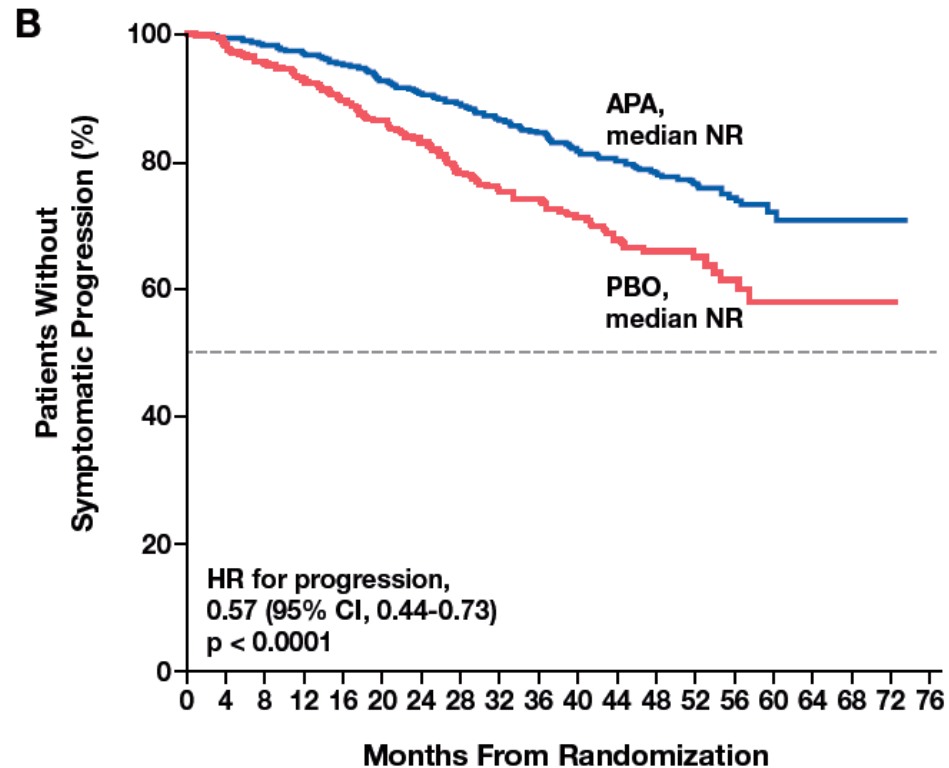
No. at risk
APA   806 791 774 758 739 717 691 658 625 593 558 499 376 269 181 100 47 19   4   0
PBO   401 392 385 373 358 339 328 306 286 263 240 204 156 114 82 38 21   6   2   0
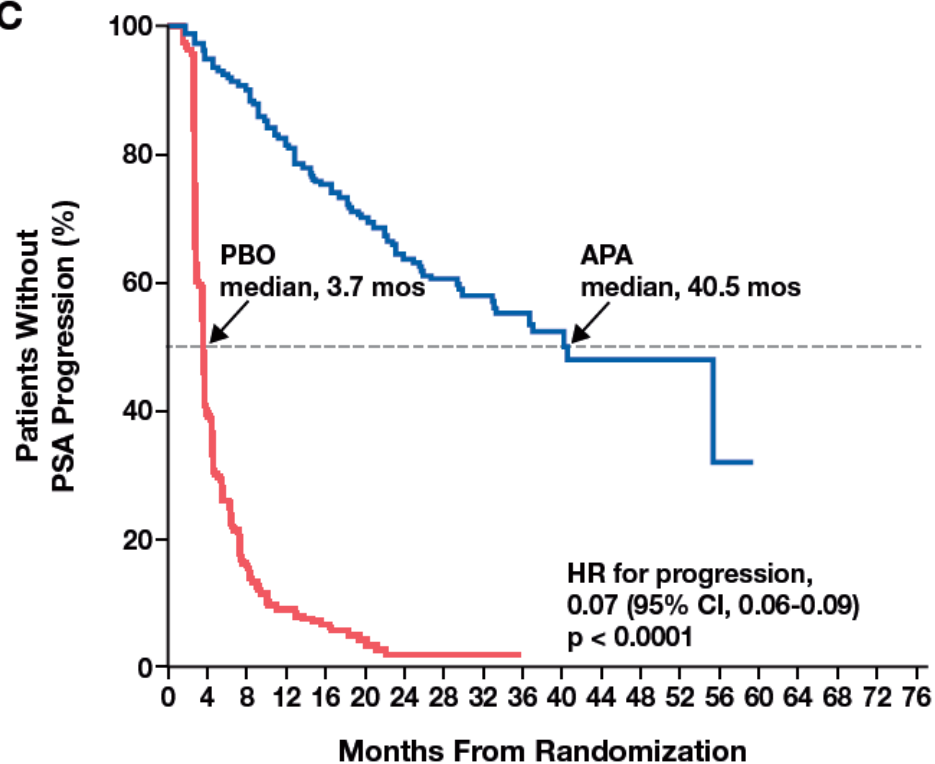
Figure 5. Kaplan-Meier Estimates of Initiation of Cytotoxic Chemotherapy (A), Symptomatic Progression (B), PSA Progression (C), and PFS2 (D)

A

Y-axis: Patients Who Had Not Initiated Cytotoxic Chemotherapy (%)
X-axis: Months From Randomization

APA, median NR
PBO, median NR

HR for initiation of cytotoxic chemotherapy,
0.63 (95% CI, 0.49-0.81)
p = 0.0002

No. at risk

APA	806	787	763	739	711	687	646	610	567	535	492	436	316	225	152	84	35	14	4	0
PBO	401	388	371	352	327	302	283	266	247	224	200	173	128	89	63	26	16	4	2	0

B

Y-axis: Patients Without Symptomatic Progression (%)
X-axis: Months From Randomization

APA, median NR
PBO, median NR

HR for progression,
0.57 (95% CI, 0.44-0.73)
p < 0.0001

No. at risk

APA	806	771	749	721	693	658	620	589	553	520	476	413	289	206	132	65	22	6	1	0
PBO	401	377	355	331	308	279	253	223	206	185	158	126	90	66	45	17	11	5	1	0

C

Patients Without PSA Progression (%)

PBO median, 3.7 mos

APA median, 40.5 mos

HR for progression, 0.07 (95% CI, 0.06-0.09) p < 0.0001

Months From Randomization

No. at risk

APA	806	695	604	508	395	309	211	143	93	46	24	14	6	4	1	0	0	0	0
PBO	401	139	50	23	15	5	2	1	1	0	0	0	0	0	0	0	0	0	0

D

Patients Who Were Alive Without Second Progression or Death (%)

PBO median, 41.2 mos

APA median, 55.6 mos

HR for second progression or death, 0.55 (95% CI, 0.46-0.66) p < 0.0001

Months From Randomization
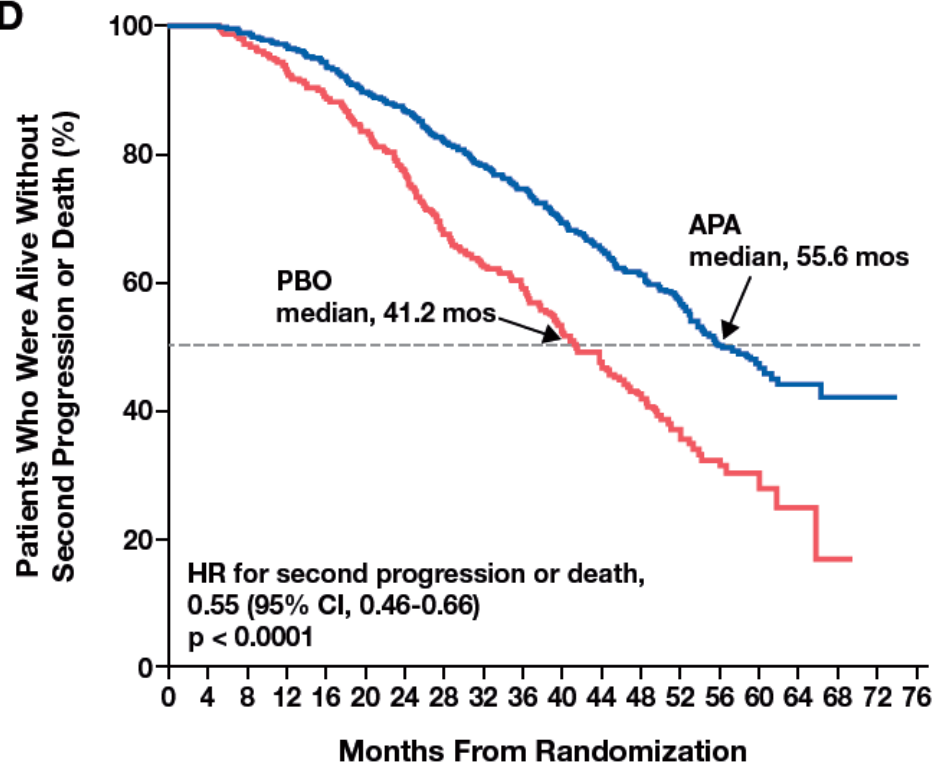
No. at risk

APA	806	783	765	735	704	657	624	582	545	506	453	392	280	195	121	62	27	9	3	0
PBO	401	390	368	338	305	274	236	199	176	153	126	96	68	48	29	12	5	1	0	0

Top 10 clinical advances in Prostate cancer

1. FDA approval of enzalutamide and apalutamide in mHSPC
2. **PSMA scanning is a major advance and expands pool of mHSPC**
3. Oligo mHSPC management is rapidly evolving but probably requires Radiation to disease sites plus ADT. STOMP showed RT to all sites can delay need for ADT
4. Nearly all hormone sensitive metastatic patients should get 2 or more drugs (Leuprolide + 1 is the new standard)
5. FDA approval of enza, apa and darolutamide in non-metastatic CRPC. **All improve OS**
6. Abiraterone and enzalutamide are cross resistant in 90+% of cases, ARV7 identifies some resistant pts
7. Cabazitaxel is superior to 2nd line abi/enza in docetaxel resistant patients CARD trial
8. PARP inhibitors will be FDA approved in 2020 and will require urologists to test for DNA mutations
9. Sip T and Radium continue to be important agents in mCRPC (African American and pain data)
10. New ARi agents are being developed but 20-30% of mCRPC lose AR thru clonal evolution so non-AR targeting is needed (pembrolizumab, cabometyx/atezo, CDK 9, etc)
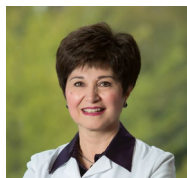
IMvigor010: Primary Analysis From a Phase III Randomized Study of Adjuvant Atezolizumab vs Observation in High-Risk Muscle-Invasive Urothelial Carcinoma

Maha H.A. Hussain,[1] Thomas Powles,[2] Peter Albers,[3] Daniel Castellano,[4] Siamak Daneshmand,[5] Jürgen E. Gschwend,[6] Hiroyuki Nishiyama,[7] Stephane Oudard,[8] Darren Tayama,[9] Nicole Davarpanah,[9] Viraj Degaonkar,[9] Yi Shi,[9] Sanjeev Mariathasan,[9] Petros Grivas,[10] Peter H. O'Donnell,[11] Jonathan E. Rosenberg,[12] Daniel M. Geynisman,[13] Jean H. Hoffman-Censits,[14] Daniel P. Petrylak,[15] Joaquim Bellmunt[16]

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IMvigor010 Study Design

Key eligibility[a]
- **High-risk MIUC (bladder, renal pelvis, ureter)**
- **Radical cystectomy/nephroureterectomy with LN dissection** within ≤ 14 weeks
  - **ypT2-T4a or ypN+** for patients treated with **NAC[b]**
  - **pT3-T4a or pN**+ for patients **not treated with NAC[b]**
- No postsurgical radiation or AC
- If no prior NAC given, patient had to be ineligible for, or declined, cisplatin-based AC
- ECOG PS 0-2
- **Tissue sample for PD-L1 testing**

R 1:1

Atezolizumab 1200 mg q3w *(16 cycles or 1 year)*

No crossover allowed

Observation[c] q3w

Disease recurrence/ survival follow-up

Tumor assessments: q12w for years 1-3, (q24w for years 4-5 and at year 6)

Stratification factors
- Number of LNs resected (< 10 vs ≥ 10)
- Prior NAC (Yes vs No)
- LN status (+ vs –)
- Tumor stage (≤ pT2 vs pT3/pT4)
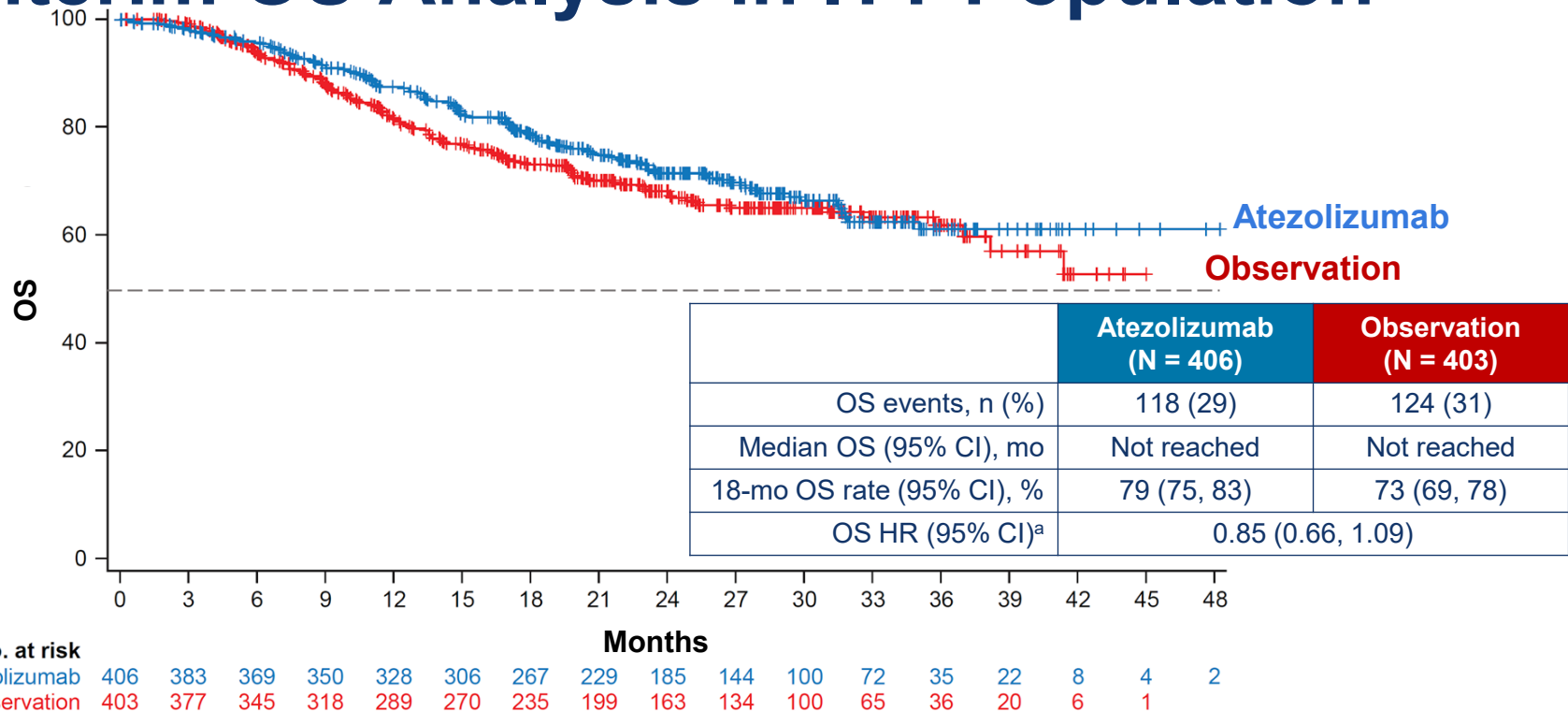- PD-L1 status[a] (IC0/1 vs IC2/3)
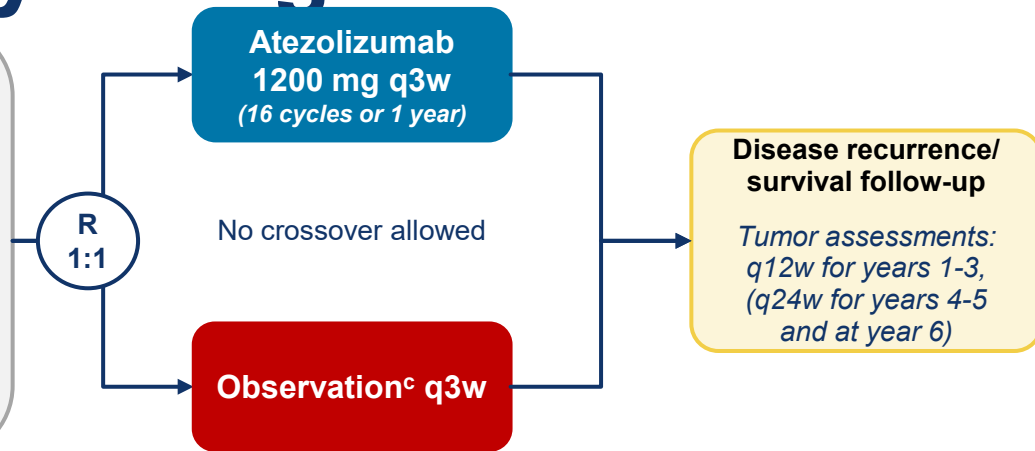
- **Primary endpoint:** DFS (ITT population)
- **Key secondary endpoint:** OS (ITT population)
- **Exploratory analyses:** Biomarkers including PD-L1 status
- **Safety**

AC, adjuvant chemotherapy; DFS, disease-free survival; ITT, intention to treat; LN, lymph node; MIUC, muscle-invasive UC. [a] Protocol amendments broadened eligibility to "all-comers" (initially, only PD-L1–selected patients were enrolled [IC2/3: PD-L1 expression on tumor-infiltrating immune cells (IC) ≥ 5% of tumor area [VENTANA SP142 IHC assay]) and to patients with MIUC (initially, only patients with muscle-invasive bladder cancer were enrolled). [b] Upper-tract UC staging: ypT2-4 or ypN+ (with NAC) and pT3-4 or pN+ (without NAC). [c] Alternating clinic visits and phone calls.
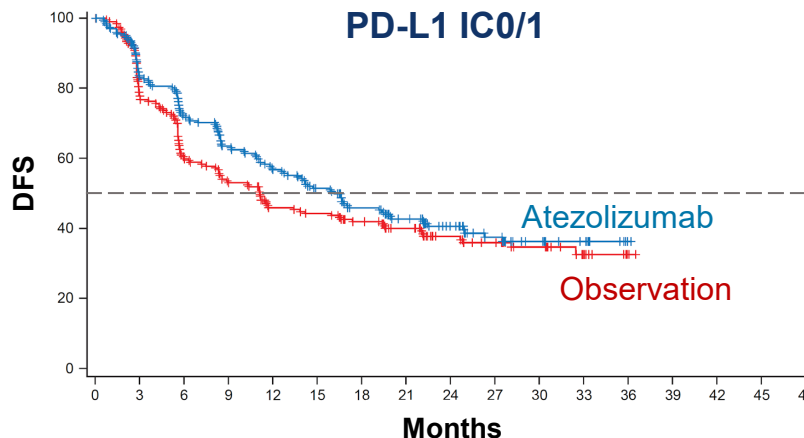
Interim OS Analysis in ITT Population

	Atezolizumab (N = 406)	Observation (N = 403)
OS events, n (%)	118 (29)	124 (31)
Median OS (95% CI), mo	Not reached	Not reached
18-mo OS rate (95% CI), %	79 (75, 83)	73 (69, 78)
OS HR (95% CI)[a]	0.85 (0.66, 1.09)	

No. at risk

| Months	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
Atezolizumab	406	383	369	350	328	306	267	229	185	144	100	72	35	22	8	4	2
Observation	403	377	345	318	289	270	235	199	163	134	100	65	36	20	6	1	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. Most common subsequent non-protocol therapies included immunotherapy (9% in atezolizumab arm vs 21% in observation arm), chemotherapy (27% vs 25%) and targeted therapy (5% vs 2%). [a] OS results are shown for descriptive purposes only. HR stratified by tumor stage, nodal status and PD-L1 status.

DFS by PD-L1 Status

PD-L1 IC0/1
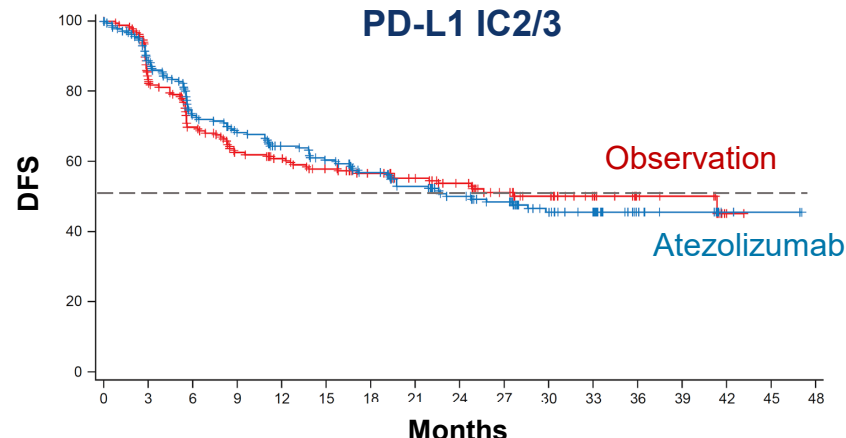
	Atezolizumab (n = 210)	Observation (n = 207)
DFS events, n (%)	118 (56)	120 (58)
HR (95% CI)[a]	0.81 (0.63, 1.05)	

PD-L1 IC2/3

	Atezolizumab (n = 196)	Observation (n = 196)
DFS events, n (%)	94 (48)	88 (45)
HR (95% CI)[a]	1.01 (0.75, 1.35)	

Data cutoff: November 30, 2019. IC2/3, PD-L1–expressing IC on ≥ 5% of tumor area (VENTANA SP142 assay); IC0/1, < 5%. [a] Stratified by tumor stage and nodal status.

IMvigor010: Conclusions

- IMvigor010 is the first Phase III study evaluating the benefit of an adjuvant CPI in MIUC

- The safety profile for atezolizumab monotherapy was consistent with that in prior studies in the advanced setting, with no new safety concerns
  - Higher frequencies of AESIs (mainly Grade 1-2), and treatment discontinuation due to AEs (mainly skin and gastrointestinal) were seen, while corticosteroid use was lower in IMvigor010

- IMvigor010 did not meet its primary endpoint of DFS
  - No pre-specified subgroups (including higher PD-L1 status) showed treatment benefit with atezolizumab
  - OS follow-up is ongoing; additional exploratory biomarker and subgroup analyses may warrant further study

- Other clinical trials with atezolizumab as monotherapy and combination therapy are underway in the metastatic, non-muscle invasive, and bladder-preservation UC settings

Maintenance avelumab + best supportive care (BSC) versus BSC alone after platinum-based first-line chemotherapy in advanced urothelial carcinoma: JAVELIN Bladder 100 phase III results

Thomas Powles,[1] Se Hoon Park,[2] Eric Voog,[3] Claudia Caserta,[4] Begoña P. Valderrama,[5] Howard Gurney,[6] Haralabos Kalofonos,[7] Sinisa Radulovic,[8] Wim Demey,[9] Anders Ullén,[10] Yohann Loriot,[11] Srikala S. Sridhar,[12] Norihiko Tsuchiya,[13] Evgeny Kopyltsov,[14] Cora N. Sternberg,[15] Joaquim Bellmunt,[16] Jeanny B Aragon-Ching,[17] Daniel P. Petrylak,[18] Alessandra di Pietro,[19] Petros Grivas[20]

[1]Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St Bartholomew's Hospital, London, UK; [2]Sungkyunkwan University Samsung Medical Center, Seoul, Korea; [3]Centre Jean Bernard Clinique Victor Hugo, Le Mans, France; [4]Medical Oncology Unit, Azienda Ospedaliera S. Maria, Terni, Italy; [5]Department of Medical Oncology, Hospital Universitario Virgen del Rocío, Sevilla, Spain; [6]Department of Clinical Medicine, Macquarie University, Sydney, New South Wales, Australia; [7]Medical Oncology, University General Hospital of Patras, Patras, Greece; [8]Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [9]Department of Medical Oncology, AZ KLINA, Brasschaat, Belgium; [10]Patient Area Pelvic Cancer, Theme Cancer, Karolinska University Hospital and Department of Oncology-Pathology, Karolinska Institute, Solna, Sweden; [11]Gustave Roussy, INSERMU981, Université Paris-Saclay Villejuif, France; [12]Princess Margaret Cancer Center, University Health Network, Toronto, Ontario, Canada; [13]Department of Urology, Yamagata University Faculty of Medicine, Yamagata, Japan; [14]State Institution of Healthcare Regional Clinical Oncology Dispensary, Omsk, Russia; [15]Weill Cornell Medicine, Hematology/Oncology, New York, New York, USA; [16]Department of Medical Oncology, Beth Israel Deaconess Medical Center; Harvard Medical School, Boston, Massachusetts, USA; [17]Inova Schar Cancer Institute, Fairfax, Virginia, USA; [18]Yale Cancer Center, New Haven, Connecticut, USA; [19]Pfizer srl, Milano, Italy; [20]Department of Medicine, Division of Oncology, University of Washington; Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA
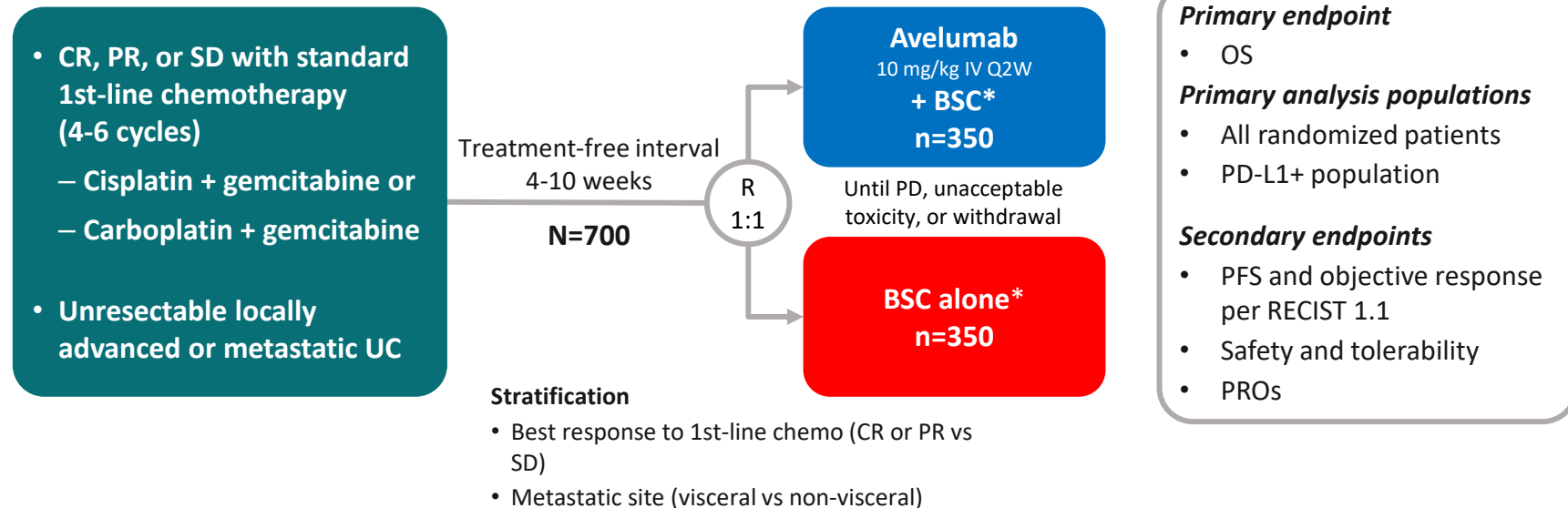
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PRESENTED BY: Thomas Powles, MD

Abstract LBA1

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Background

- PD-L1/PD-1 inhibitors are standard 2nd-line treatment for patients with disease progression after platinum-based chemotherapy[1]
  - This includes the PD-L1 inhibitor avelumab[2]

- Although PD-L1/PD-1 inhibitors have antitumor activity in UC, only a minority of patients obtain a durable clinical benefit with 2nd-line treatment[2-6]

- Avelumab maintenance therapy in patients whose disease has not progressed with 1st-line platinum-based induction chemotherapy is an attractive treatment strategy[7]
  - Disease control achieved with chemotherapy may provide time for immunotherapy to have an antitumor effect
  - Initiating immunotherapy before disease progression occurs may result in more patients receiving treatment

1. NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer, V3.2020. **2.** Patel MR, et al. Lancet Oncol 2018;19:51-64. **3.** Bellmunt J, et al. N Engl J Med 2017;376:1015-26. **4.** Powles, T, et al. Lancet 2018;391:748-57. **5.** Powles T, et al. JAMA Oncol 2017;3:e172411. **6.** Sharma P, et al. Lancet Oncol 2017;18:312-22. **7.** Grivas P, et al. Target Oncol 2019;14:505-525.

JAVELIN Bladder 100 study design (NCT02603432)

**All endpoints measured post randomization (after chemotherapy)** →

CR, PR, or SD with standard 1st-line chemotherapy (4-6 cycles)
- Cisplatin + gemcitabine or
- Carboplatin + gemcitabine

Unresectable locally advanced or metastatic UC

Treatment-free interval 4-10 weeks

N=700

R 1:1

Avelumab
10 mg/kg IV Q2W
+ BSC*
n=350

Until PD, unacceptable toxicity, or withdrawal

BSC alone*
n=350

Primary endpoint
- OS

Primary analysis populations
- All randomized patients
- PD-L1+ population

Secondary endpoints
- PFS and objective response per RECIST 1.1
- Safety and tolerability
- PROs

Stratification
- Best response to 1st-line chemo (CR or PR vs SD)
- Metastatic site (visceral vs non-visceral)

PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

BSC, best supportive care; **CR**, complete response; **IV,** intravenous; **PR**, partial response; **PRO**, patient reported outcome; **Q2W**, every 2 weeks; **R**, randomization; **RECIST 1.1,** Response Evaluation Criteria in Solid Tumors version 1.1; **SD**, stable disease

*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable
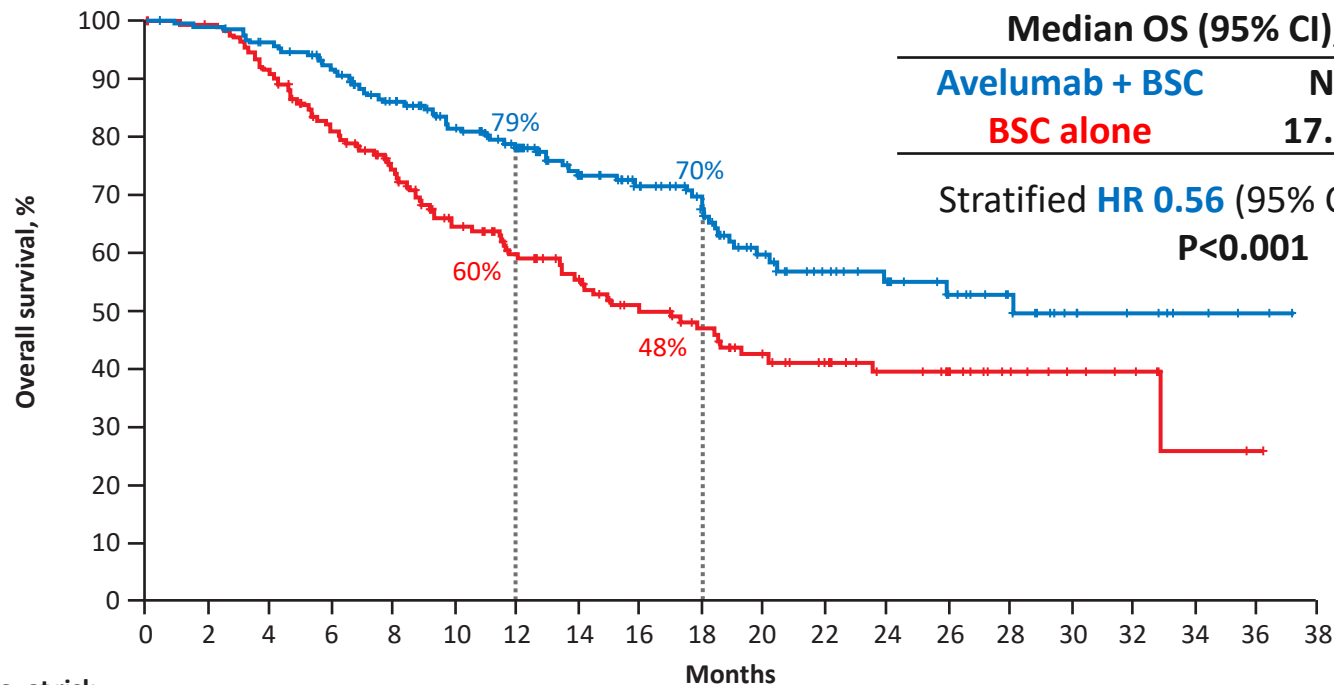
OS in the overall population
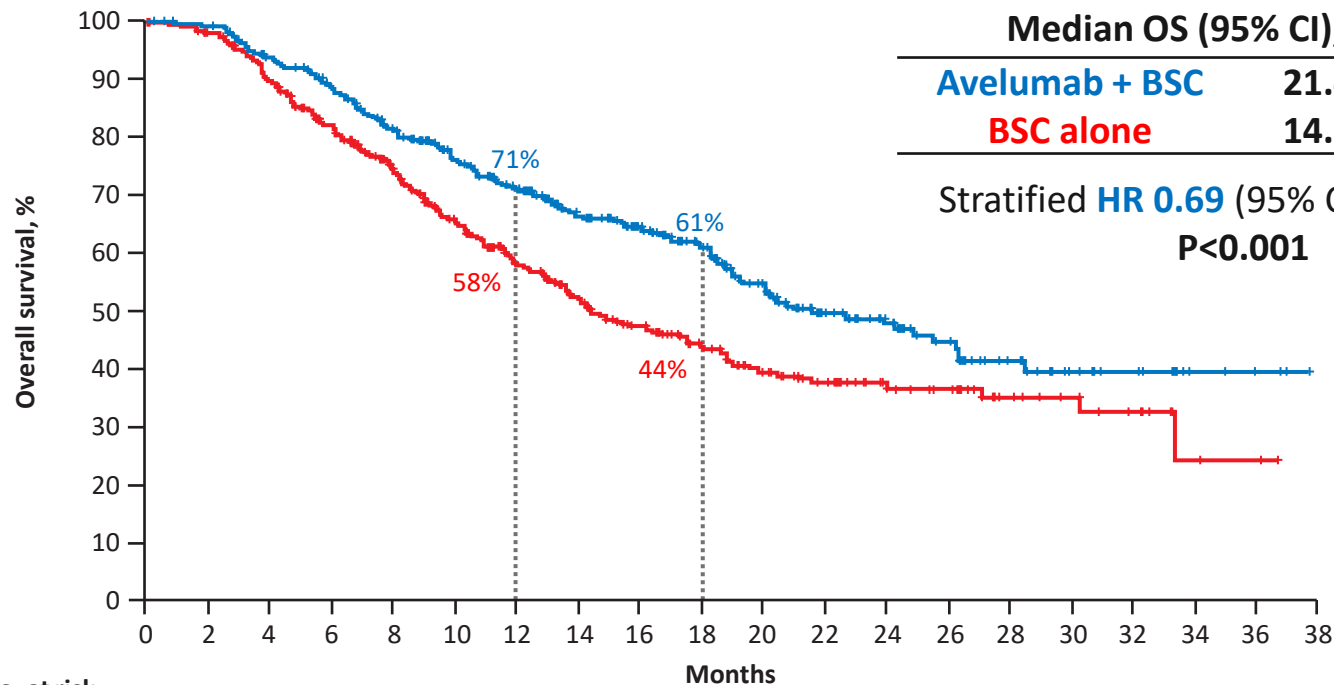
Median OS (95% CI), months	
Avelumab + BSC	**21.4** (18.9, 26.1)
BSC alone	**14.3** (12.9, 17.9)

Stratified **HR 0.69** (95% CI, 0.56, 0.86)
P<0.001

No. at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38
Avelumab + BSC	350	342	318	294	259	226	196	167	145	122	87	65	51	39	26	15	11	5	3	0
BSC	350	335	304	270	228	186	153	125	105	83	68	55	41	33	18	12	9	2	1	0

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)

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OS in the PD-L1+ population

Median OS (95% CI), months	
Avelumab + BSC	**NE** (20.3, NE)
BSC alone	**17.1** (13.5, 23.7)

Stratified **HR 0.56** (95% CI, 0.40, 0.79)

P<0.001

Overall survival, %

79%

70%

60%

48%

No. at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Avelumab + BSC	189	185	177	165	146	129	114	95	81	70	49	38	32	26	18	9	8	4	2	0
BSC	169	165	152	132	113	89	76	67	54	45	37	30	23	21	12	8	6	2	1	0

Months

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0014). **NE**, not estimable

Confirmed objective response

Response to maintenance therapy post randomization

	Overall population		PD-L1+ population	
	Avelumab + BSC (N=350)	**BSC alone (N=350)**	**Avelumab + BSC (N=189)**	**BSC alone (N=169)**
ORR, %	**9.7**	**1.4**	**13.8**	**1.2**
(95% CI)	(6.8, 13.3)	(0.5, 3.3)	(9.2, 19.5)	(0.1, 4.2)
Stratified odds ratio (95% CI)	7.464 (2.824, 24.445)		12.699 (3.160, 114.115)	
Best overall response, %				
Complete response	6.0	0.9	9.5	0.6
Partial response	3.7	0.6	4.2	0.6
Stable disease	12.6	13.1	10.1	13.6
Non-CR/non-PD	18.9	12.9	20.1	13.0
Progressive disease	37.1	48.3	31.2	48.5
Not evaluable*	21.7	24.3	24.9	23.7
Disease control, %[†]	41.1	27.4	43.9	27.8

PD, progressive disease
Objective response was assessed by independent radiology review; in patients with a CR after chemotherapy, best overall response was not evaluable if no evidence of disease at baseline was maintained after randomization, or PD if disease progression occurred after randomization
*Reasons for not evaluable included no evidence of disease at baseline; no post-baseline assessments; SD <6 weeks after randomization; PD >12 weeks after randomization; new anticancer therapy started before first post-baseline assessment; or all post-baseline assessments have objective response of not evaluable
[†]Patients with a best overall response of CR, PR, SD, or non-CR/non-PD

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Conclusions

- JAVELIN Bladder 100 met its primary endpoint by showing significantly longer OS with avelumab 1st-line maintenance vs control, both in the overall population and PD-L1+ population

- OS was longer with avelumab vs control across all prespecified subgroups
  - Includes subgroups defined by cisplatin-based or carboplatin-based chemotherapy, or response or SD with 1st-line induction chemotherapy

- The safety profile of avelumab as 1st-line maintenance was manageable and consistent with previous studies of avelumab monotherapy[1]

- Avelumab 1st-line maintenance in patients whose disease has not progressed with platinum-based induction chemotherapy represents a new 1st-line standard of care for advanced UC

1. Kelly K, et al. Cancer. 2018;124:2010-17.

Top 10 clinical advances TCC 2016-20

1. FDA approval of erdafitanib in FGFR3 fusion + metastatic bladder cancer (MBC)
2. FDA approval of enfortumab 3rd line MBC
3. FDA approval of pembrolizumab for BCG refractory CIS
4. FDA approval of checkpoint inhibitors (CPIs) for Lynch syndrome (upper tract)
5. Long term CR's with CPI monotherapy in MiBC
6. **Maintenance avelumab improves OS after Gem/platin in MBC**
7. Safety and efficacy of CPIs with Gem/platin in MBC
8. Neoadjuvant CPI induces CR in MiBC
9. 50-70% objective response rates in phase 2 trials of CPI combos: (enfortumab, lenvantinib, ephrin inhibitor, sitravatinib, cabometyx, ipilumumab etc)
10. Neoadjuvant chemo for Upper tract high grade TCC