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Mark Markowski , MD

Dr. Mark Markowski is a medical oncologist with the Sidney Kimmel Cancer Center at Sibley Memorial Hospital. A skilled medical oncologist treating numerous types of cancers, he participates in multidisciplinary clinics at Sibley Memorial Hospital as well as at The Johns Hopkins Hospital, and sees patients in the genitourinary clinics of both hospitals. In addition to his patient care services, Dr. Markowski is also a researcher and instructor. Dr. Markowski's major area of research interest is in early phase drug development for prostate cancer.

Dr. Markowski completed both his B.S. (in biochemistry) and his M.D./Ph.D at Georgetown University. He completed his residency in Internal Medicine at Columbia University in New York City, and his Medical Oncology Fellowship training at Johns Hopkins Hospital.

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MEDICINE

Most Important Advances in GU Malignancies

Mark C. Markowski, MD, Ph.D.
Assistant Professor of Oncology
Johns Hopkins University

Outline

- **Prostate Cancer**
- Bladder Cancer
- Renal Cancer

HERO Phase 3 Trial: Relugolix, an Oral GnRH Receptor Antagonist, versus Leuprolide Acetate for Advanced Prostate Cancer

Neal D. Shore,[1] Fred Saad,[2] Michael S. Cookson,[3] Daniel J. George,[4] Daniel R. Saltzstein,[5] Ronald Tutrone,[6] Hideyuki Akaza,[7] Alberto Bossi,[8] David F. van Veenhuyzen,[9] Bryan Selby,[9] Xiaolin Fan,[9] Vicky Kang,[9] Jackie Walling,[9] Bertrand Tombal,[10] for the HERO Study Investigators

1. Carolina Urologic Research Center; 2. University of Montreal Hospital Centre; 3. University of Oklahoma Health Sciences Center; 4. Duke Cancer Institute Center for Prostate and Urologic Cancers; 5. Urology San Antonio; 6. Chesapeake Urology; 7. University of Tokyo; 8. Gustave Roussy Cancer Institute; 9. Myovant Sciences, Inc.; 10. Université Catholique de Louvain

PRESENTED BY: Neal Shore, MD, FACS
Carolina Urologic Research Center, SC, USA

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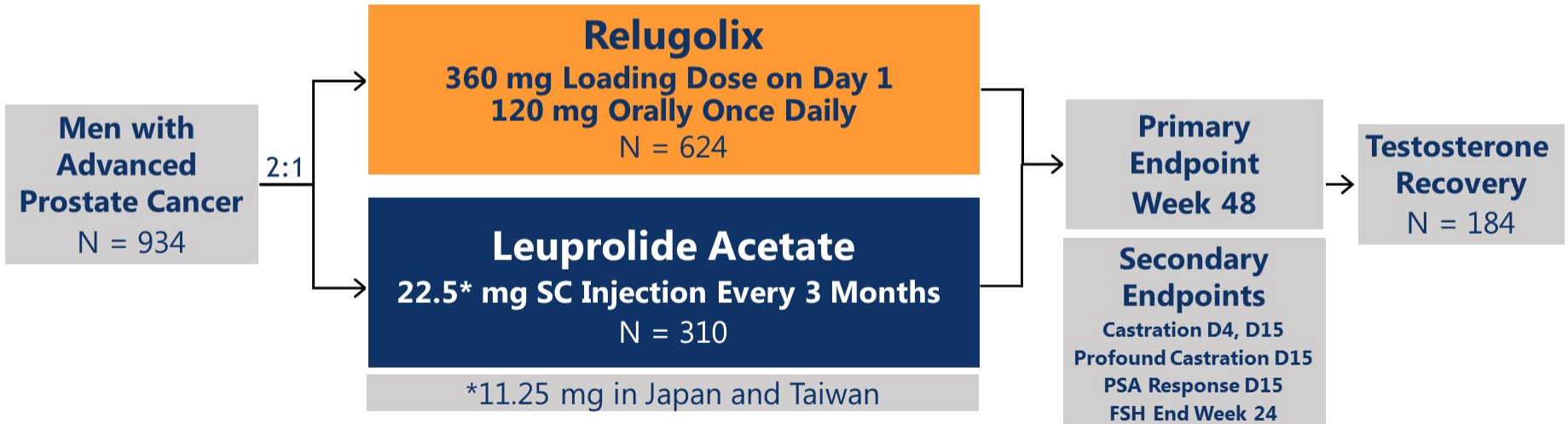
HERO

Phase 3 HERO Study Design

- A multinational phase 3 randomized, open-label, parallel group study to evaluate the safety and efficacy of relugolix in men with advanced prostate cancer
- **Primary Endpoint**: Sustained castration through 48 weeks (< 50 ng/dL)



SC, subcutaneous; D, day

Shore ND, et al NEJM 2020;382:2187-2196

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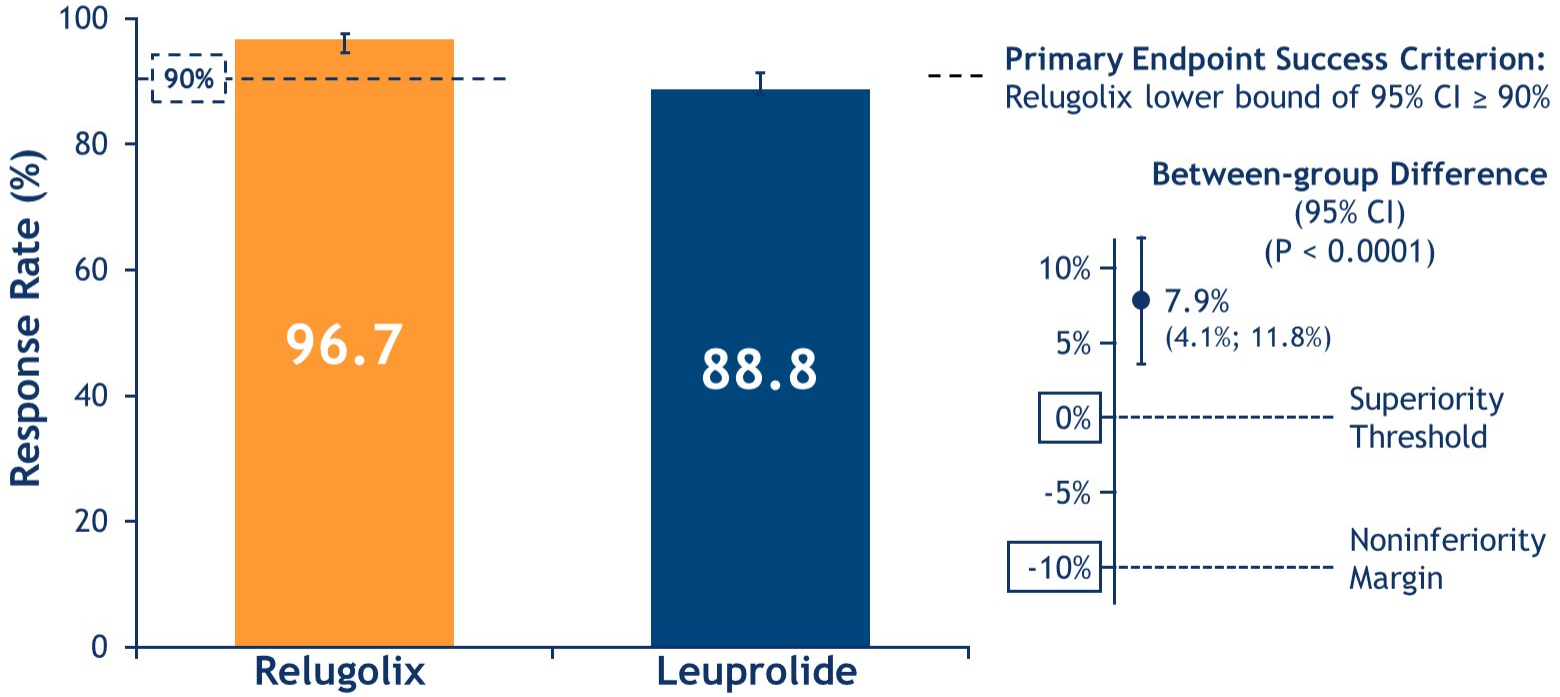
HERO

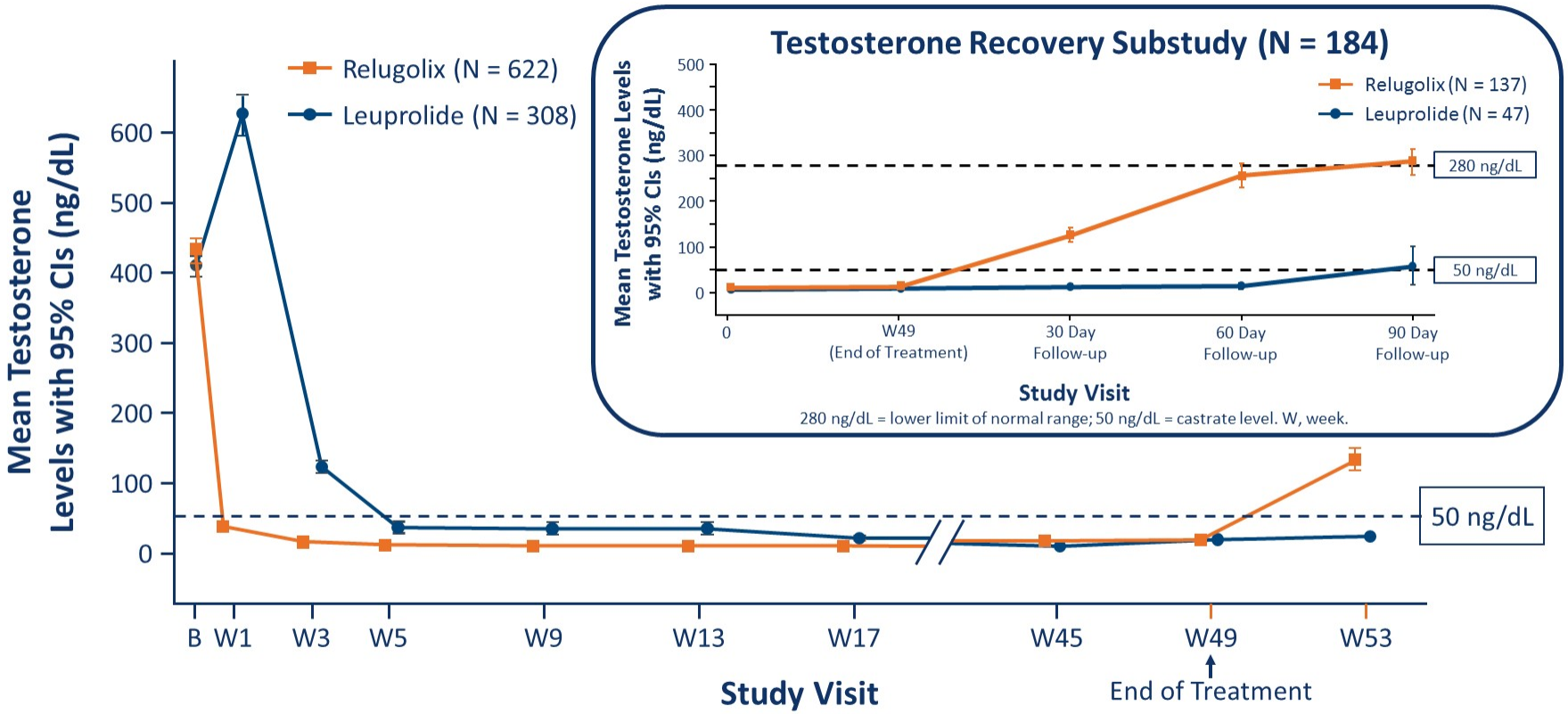
Primary Endpoint – Sustained Castration

Key Secondary Endpoint – Noninferiority to Leuprolide



Shore ND, et al NEJM 2020;382:2187-2196

Time Course of Testosterone Suppression



50 ng/dL = castrate level. B, baseline; W, week

Shore ND, et al NEJM 2020;382:2187-2196

Cardiovascular Adverse Events

	Relugolix (N = 622)	Leuprolide (N = 308)
Adverse Cardiovascular Events	3.9%	7.1%
Major Adverse Cardiovascular Events (MACE)	2.9%	6.2%
Ischemic Heart Disease	2.4%	1.6%

History of MACE	**Yes**		**No**	
N (%)	**Relugolix** 84 (13.5%)	**Leuprolide** 45 (14.6%)	**Relugolix** 538 (86.5%)	**Leuprolide** 263 (85.4%)
MACE	3.6%	17.8%	2.8%	4.2%
Odds Ratio Leuprolide vs Relugolix (95% confidence interval)	5.8 (1.5, 23.3)		1.5 (0.7, 3.4)	

MACE = non-fatal myocardial infarction + non-fatal stroke + all-cause mortality

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Shore ND, et al NEJM 2020;382:2187-2196

Randomized Controlled Trial > Circulation. 2021 Oct 19;144(16):1295-1307.
doi: 10.1161/CIRCULATIONAHA.121.056810. Epub 2021 Aug 30.

Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Prostate Cancer: The Primary Results of the PRONOUNCE Randomized Trial

Renato D Lopes [1], Celestia S Higano [2], Susan F Slovin [3], Adam J Nelson [1], Robert Bigelow, Per S Sørensen [4], Chiara Melloni [1 5], Shaun G Goodman [6 7], Christopher P Evans [8], Jan Nilsson [9], Deepak L Bhatt [10], Noel W Clarke [11], Tine K Olesen [4], Belinda T Doyle-Olsen [4], Henriette Kristensen [4], Lauren Arney [1], Matthew T Roe [1 12], John H Alexander [1], PRONOUNCE Study Investigators

This study was terminated prematurely because of the smaller than planned number of participants and events, and no difference in major adverse cardiovascular events at 1 year between patients assigned to degarelix or leuprolide was observed.

Meta-Analysis > Minerva Urol Nephrol. 2021 Jun;73(3):276-282.
doi: 10.23736/S2724-6051.20.03756-X. Epub 2020 Nov 27.

Comparing the risk of cardiovascular disease following GnRH agonist and GnRH antagonist therapy for patient with prostate cancer: a systematic review and meta-analysis

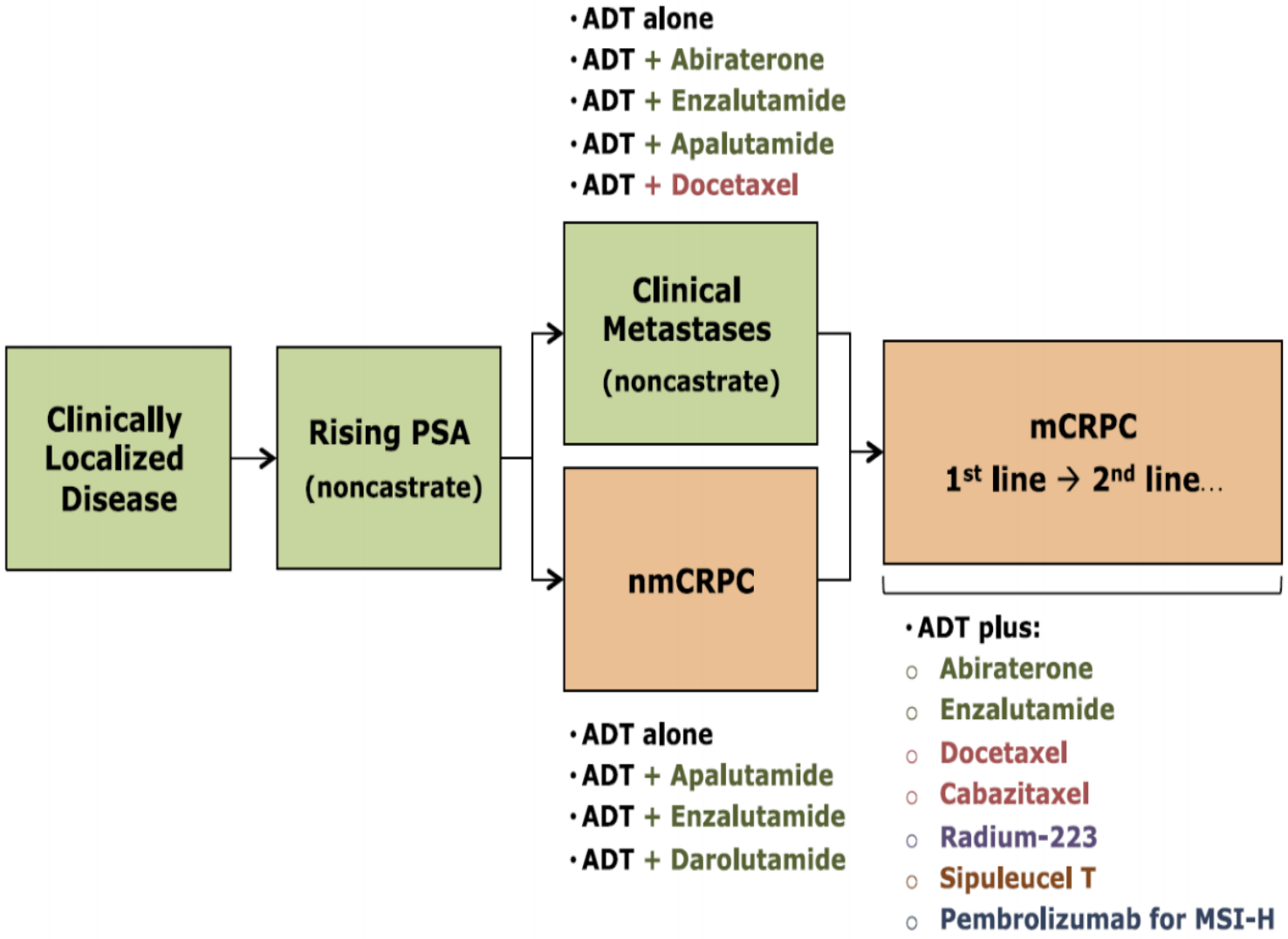
Chengquan Ma [1], Iruni R Abeysekera [2 3], Wenbin Xu [4], Ying Wang [5], Jia Peng [5], Hongjun Li [6]

Conclusions: This meta-analysis indicates that compared treatment with GnRH antagonist, risks of CVD in PCa patients was the same as GnRH agonist. Further RCTs are strongly required to provide more definitive evidence.

Take Home

- Relugolix, an oral GnRH antagonist, leads to testosterone suppression comparable to Leuprolide
- The rate of CV events is lower with Relugolix compared to Leuprolide, especially in the subset or patients with history of MACE
- Positives- Oral agent, early CV improvement
- Negatives- ?compliance, ?cost
- Reasonable in those with limited time frame for ADT- like in conjunction with XRT

Prostate Cancer Treatment Landscape



Bastos DA, Antonarakis ES. Oncotargets & Ther 2019; 12: 8769-8777.

OVERALL SURVIVAL BENEFIT WITH TREATMENT INTENSIFICATION

DOCETAXEL	CHAARTED	Median follow-up: 53.7 months, Median OS: 57.6 months vs 47.2 months	HR=0.72
	STAMPEDE-C	Median follow-up: 78.2 months, Median OS: 59.1months vs 43.1 months	HR=0.81
ABIRATERONE	LATITUDE	Median follow-up: 51.8 months, Median OS: 53.3 months vs 36.5 months	HR=0.66
	STAMPEDE-G	Median follow-up: 73.2 months, Median OS: 79.2 months vs 45.6 months	HR=0.60
ENZALUTAMIDE	ENZAMET	Median follow-up: 34.0 months, OS at 3 years 80% vs 72%	HR=0.67
	ARCHES	Median follow-up: 44.6 months, Median OS: NR vs NR	HR=0.66
APALUTAMIDE	TITAN	Median follow-up: 44.0 months, Median OS: NR vs 52.2 months	HR=0.65

Kyriakopoulos CE et al. J Clin Oncol. 2018 Apr 10;36(11):1080-1087. Clarke NW et al. Annals of Oncology30:1992-2003, 2019. Fizazi K et al. Lancet Oncol 2019 May; 20(5):686-700. James N et al. 2020 ESMO. Davis IA et al. N Engl J Med 2019;381:121-131. Armstrong AJ et al. Annal Oncol 2021;32(5):S1283-S1346, LBA25. Chi KN et al. J Clin Oncol. 2021 39:2294-2303.

ASCO Genitourinary Cancers Symposium

Overall survival with darolutamide versus placebo in combination with androgen-deprivation therapy and docetaxel for metastatic hormone-sensitive prostate cancer in the phase 3 ARASENS trial

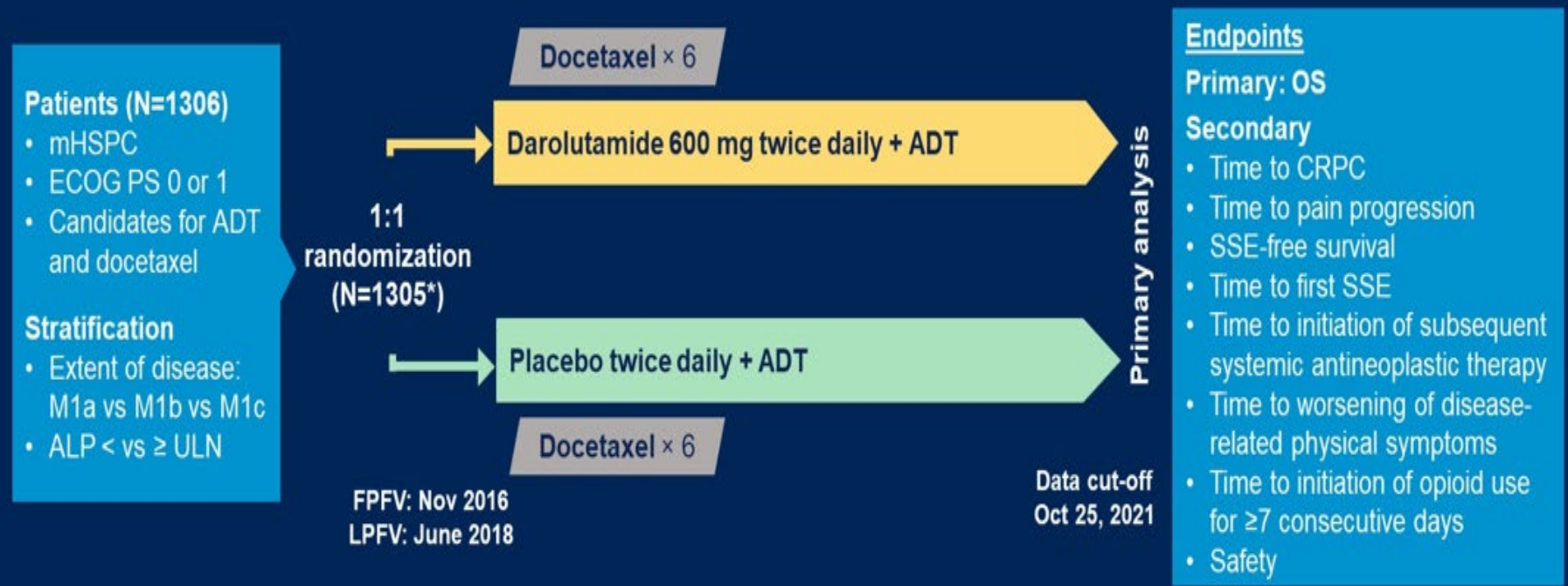
Matthew R. Smith, MD, PhD,[1] Maha Hussain, MD,[2] Fred Saad, MD,[3] Karim Fizazi, MD, PhD,[4] Cora N. Sternberg, MD,[5] E. David Crawford, MD,[6] Evgeny Kopyltsov, MD,[7] Chandler H. Park, MD,[8] Boris Alekseev, MD,[9] Álvaro Montesa Pino, MD,[10] Dingwei Ye, MD,[11] Francis Parnis, MB, BS,[12] Felipe Melo Cruz, MD,[13] Teuvo L.J. Tammela, MD, PhD,[14] Hiroyoshi Suzuki, MD, PhD,[15] Heikki Joensuu, MD,[16] Silke Thiele, MD,[17] Rui Li, MS,[18] Iris Kuss, MD,[17] Bertrand Tombal, MD, PhD[19]

[1]Massachusetts General Hospital Cancer Center, Boston, MA; [2]Northwestern University, Feinberg School of Medicine, Chicago, IL; [3]University of Montreal Hospital Center, Montreal, Quebec, Canada; [4]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France; [5]Englander Institute for Precision Medicine, Weill Cornell Department of Medicine, Meyer Cancer Center, New York-Presbyterian Hospital, New York, NY; [6]UC San Diego School of Medicine, San Diego, CA; [7]Clinical Oncological Dispensary of Omsk Region, Omsk, Russian Federation; [8]Norton Cancer Institute, Louisville, KY; [9]P. Hertsen Moscow Oncology Research Institute, Moscow, Russian Federation; [10]UGC Intercentros de Oncología Médica, Hospitales Universitarios Regional y Virgen Victoria, IBIMA, Málaga, Spain; [11]Fudan University Shanghai Cancer Center, Xuhui District, Shanghai, China; [12]Ashford Cancer Centre Research, Kurralta Park, SA, Australia; [13]Núcleo de Pesquisa e Ensino da Rede São Camilo, São Paulo, Brazil; [14]Tampere University Hospital, Tampere, Finland; [15]Toho University Sakura Medical Center, Chiba, Japan; [16]Orion Corporation Orion Pharma, Espoo, Finland; [17]Bayer AG, Berlin, Germany; [18]Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA; [19]Division of Urology, IREC, Cliniques Universitaires Saint Luc, UCLouvain, Brussels, Belgium

PRESENTED BY: Matthew R. Smith, MD, PhD

ARASENS Study Design

Global, randomized, double-blind, placebo-controlled phase III study (NCT02799602)



- The primary analysis was planned to occur after ~509 deaths
- Secondary efficacy endpoints were tested hierarchically

*One enrolled patient was excluded from all analysis sets because of Good Clinical Practice violations. ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FPFV, first patient first visit; LPFV, last patient first visit; M1a, nonregional lymph node metastases only; M1b, bone metastases ± lymph node metastases; M1c, visceral metastases ± lymph node or bone metastases; Q3W, every 3 weeks; SSE, symptomatic skeletal event; ULN, upper limit of normal.

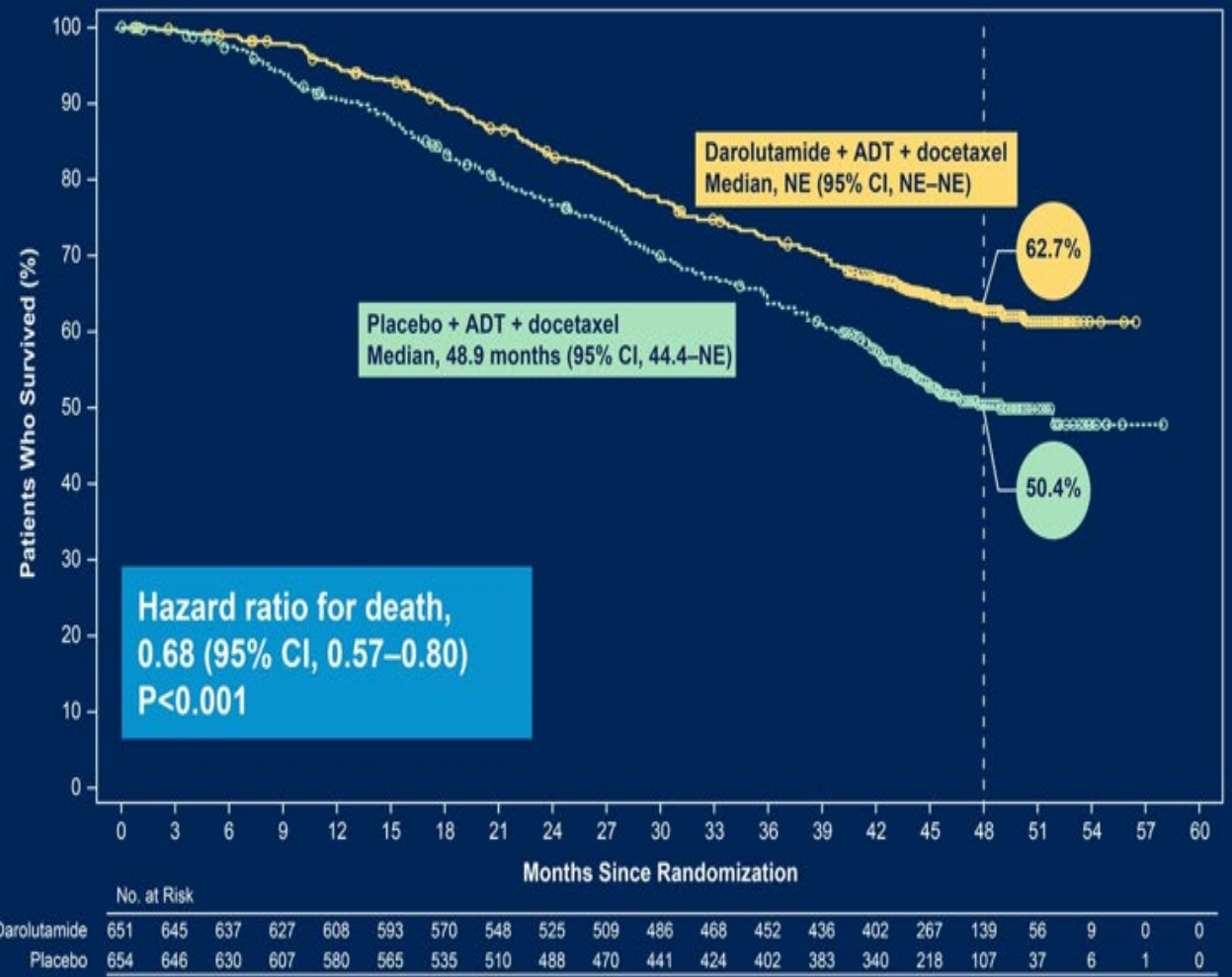
Baseline Demographics and Disease Characteristics

Patient demographics and disease characteristics		Darolutamide + ADT + docetaxel (n=651)	Placebo + ADT + docetaxel (n=654*)
Age, median (range), y		67 (41–89)	67 (42–86)
Region, n (%)	North American	125 (19.2)	119 (18.2)
	Asia Pacific	229 (35.2)	244 (37.3)
	Rest of World	297 (45.6)	291 (44.5)
EGOG performance status, n (%)	0/1	466 (71.6)/185 (28.4)	462 (70.6)/190 (29.1)
Gleason score ≥8 at initial diagnosis, n (%)		505 (77.6)	516 (78.9)
Metastatic stage at initial diagnosis, n (%)	M1	558 (85.7)	566 (86.5)
	M0	86 (13.2)	82 (12.5)
	Mx	7 (1.1)	6 (0.9)
Metastatic stage at screening, n (%)	M1a	23 (3.5)	16 (2.4)
	M1b	517 (79.4)	520 (79.5)
	M1c	111 (17.1)	118 (18.0)
Serum PSA, median (range), ng/mL†		30.3 (0.0–9219.0)	24.2 (0.0–11,947.0)
Serum ALP, median (range), U/L†		148 (40–4885)	140 (36–7680)
ALP stratification, n (%)†	≥ULN	361 (55.5)	363 (55.5)

*One patient randomized to placebo but who received darolutamide was included in the placebo group for the full analysis set. †Centrally assessed; samples were collected while patients were receiving ADT.
PSA, prostate-specific antigen.

ARASENS Primary Endpoint*: Overall Survival

Darolutamide significantly reduced the risk of death by 32.5%

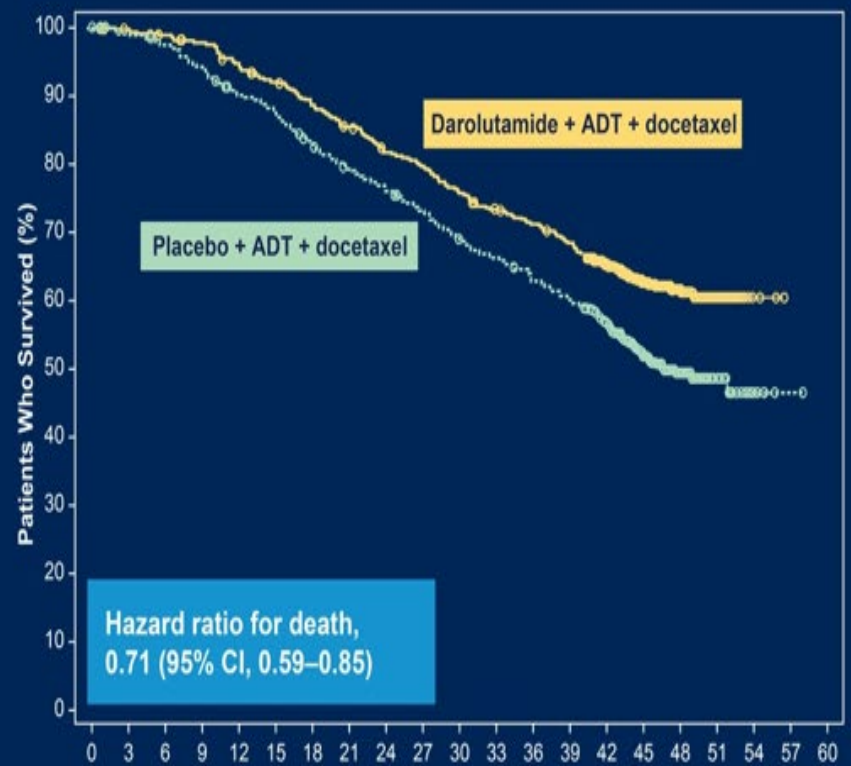


No. at Risk																					
Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

*Primary analysis occurred after 533 deaths (darolutamide, 229; placebo, 304). CI, confidence interval; NE, not estimable.

Overall Survival By Metastatic Stage at Initial Diagnosis

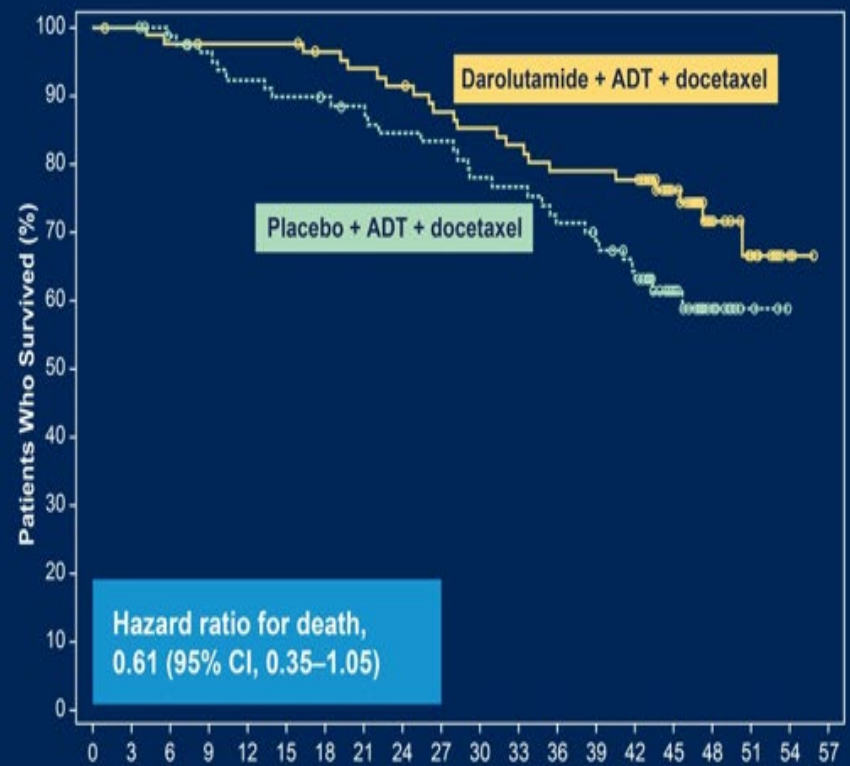
De novo metastatic disease



No. at Risk

Darolutamide	558	553	547	539	520	505	485	466	445	433	412	396	383	367	334	220	116	45	7	0	0
Placebo	566	558	546	526	503	490	461	438	420	403	378	362	344	328	292	190	93	33	6	1	0

Recurrent metastatic disease



No. at Risk

Darolutamide	86	85	83	81	81	81	78	76	74	70	68	66	63	63	62	43	20	11	2	0	
Placebo	82	82	78	75	72	70	69	67	64	63	59	58	54	51	45	26	12	4	0	0	

ARASENS Conclusions

- Darolutamide in combination with ADT and docetaxel significantly improved OS compared with ADT and docetaxel in patients with mHSPC. Darolutamide reduced the risk of death by 32.5%
- Darolutamide improved OS despite a high rate of subsequent life-prolonging systemic therapy in the placebo group
- The OS benefit for darolutamide was consistent across prespecified subgroups
- Darolutamide also significantly improved key secondary endpoints, including time to castration-resistant prostate cancer, time to pain progression, time to first SSE, and time to first subsequent antineoplastic therapy
- Rates of adverse events were similar between the darolutamide and placebo groups

Darolutamide in combination with ADT and docetaxel should become a new standard of care for treatment of mHSPC

OVERALL SURVIVAL BENEFIT WITH TREATMENT INTENSIFICATION

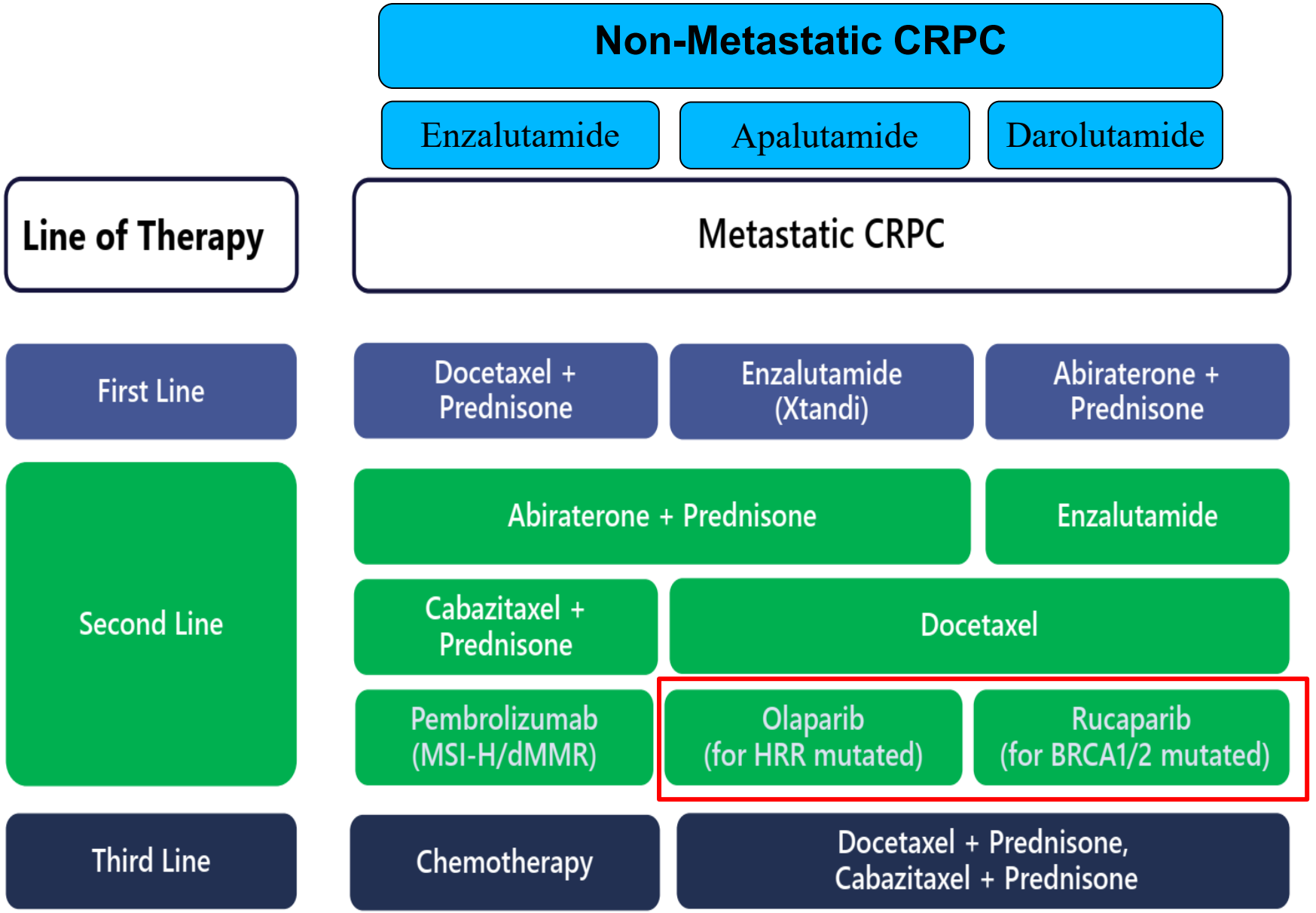
DOCETAXEL PLUS ABIRATERONE	PEACE-1	Median follow-up: 52.8 months, Median OS: NR vs 52.8 months, HR=0.75
DOCETAXEL PLUS DAROLUTAMIDE	ARASENS	Median follow-up: 43.7 months, Median OS: NR vs 48.9 months, HR=0.675

*Prior docetaxel therapy: ENZAMET: 17%, ARCHES: 17.9%, TITAN: 26.8%

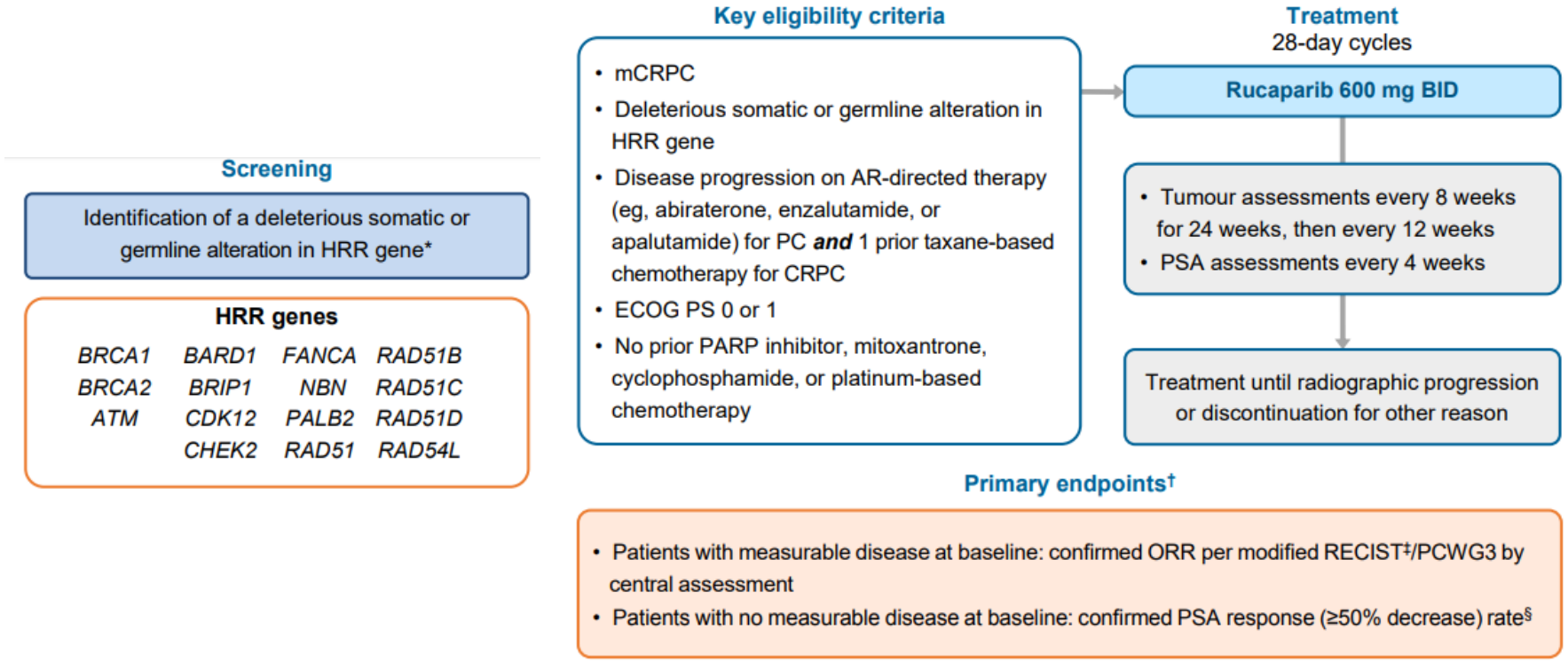
Fizazi K et al. Annal Oncol 2021;32(5):S1283-S1346, LBA5_PR. Smith MR et al. J Clin Oncol 2022, abstract #13.

Metastatic Hormone Sensitive Prostate Cancer- How intense?

- Growing data on improved OS with intensification- now data with combination of chemotherapy and oral AR therapy
- Need to think about
  - De novo versus metastatic over time
  - High volume versus low volume
  - Age, co-morbidities, suitability for docetaxel

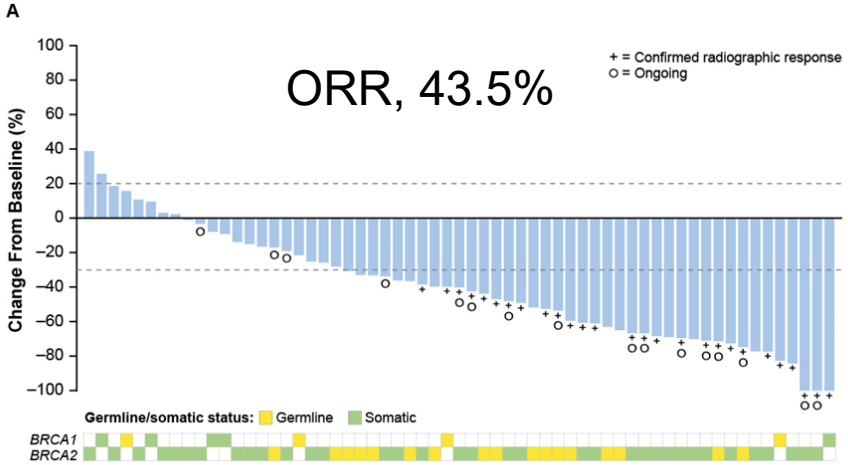

Non-Metastatic CRPC
Enzalutamide
Apalutamide
Darolutamide
Line of Therapy
Metastatic CRPC
First Line
Docetaxel + Prednisone
Enzalutamide (Xtandi)
Abiraterone + Prednisone
Second Line
Abiraterone + Prednisone
Enzalutamide
Cabazitaxel + Prednisone
Docetaxel
Pembrolizumab (MSI-H/dMMR)
Olaparib (for HRR mutated)
Rucaparib (for BRCA1/2 mutated)
Third Line
Chemotherapy
Docetaxel + Prednisone, Cabazitaxel + Prednisone

Phase II TRITON2 Trial of Rucaparib for mCRPC: Study Design

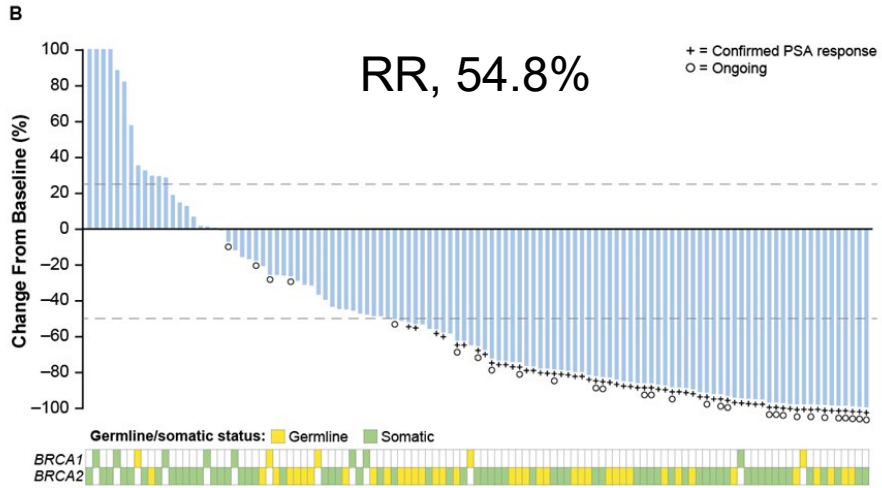


Phase II TRITON2: Radiographic Response—*BRCA1/2*m

Sum of target lesion(s) in IRR-evaluable population



PSA in overall efficacy population (n=115)



	Investigator-evaluable population (n=65)	IRR-evaluable population (n=62)
Confirmed ORR, n (%) [95% CI][a]	33 (50.8) [38.1–63.4]	27 (43.5) [31.0–56.7]
CR, n (%)	4 (6.2)	7 (11.3)
PR, n (%)	29 (44.6)	20 (32.3)
SD, n (%)	25 (38.5)	28 (45.2)
PD, n (%)	6 (9.2)	6 (9.7)
NE, n (%)	1 (1.5)	1 (1.6)

*BRCA1/2*m, *BRCA1* or *BRCA2* mutation; IRR, independent radiology review.

Phase II TRITON2: Response by DDR Gene Alteration—Non-*BRCA*

- 78 patients enrolled based on a non-BRCA DDR gene alteration identified during screening

	By DDR gene group[a]			
	ATM (n = 49)	CDK12 (n = 15)	CHEK2 (n = 12)	Other[b] (n = 14)
Confirmed investigator-assessed objective response	2/19 (10.5) [1.3–33.1]	0/10 (0) [0.0–30.8]	1/9 (11.1) [0.3–48.2]	4/14 (28.6) [8.4–58.1]
CR	0/19 (0.0)	0/10 (0)	0/9 (0)	1/14 (7.1)
PR	2/19 (10.5)	0/10 (0)	1/9 (11.1)	3/14 (21.4)
SD	9/19 (47.4)	6/10 (60.0)	6/9 (66.7)	8/14 (57.1)
PD	7/19 (36.8)	3/10 (30.0)	2/9 (22.2)	1/14 (7.1)
NE	1/19 (5.3)	1/10 (10.0)	0/9 (0)	1/14 (7.1)
6-mo CBR	12/42 (28.6) [15.7–44.6]	3/15 (20.0) [4.3–48.1]	3/8 (37.5) [8.5–75.5]	6/11 (54.5) [23.4–83.3]
12-month CBR	3/18 (16.7) [3.6–41.4]	1/14 (7.1) [0.2–33.9]	0/5 (0) [0.0–52.2]	3/8 (37.5) [8.5–75.5]
Confirmed PSA response	2/49 (4.1) [0.5–14.0]	1/15 (6.7) [0.2–31.9]	2/12 (16.7) [2.1–48.4]	5/14 (35.7) [12.8–64.9]
Median time to PSA progression, mo (95% CI)	3.1 (2.8–4.6)	3.2 (2.8–4.6)	7.4 (2.8–7.4)	11.1 (3.0–NR)

[a] Patients with co-occurring alterations were included in multiple gene groups. [b] Includes patients with alteration in FANCA (n = 4), NBN (n = 4), BRIP1 (n = 2), PALB2 (n = 2), RAD51 (n = 1), RAD51B (n = 1), and/ or RAD54L (n = 1)

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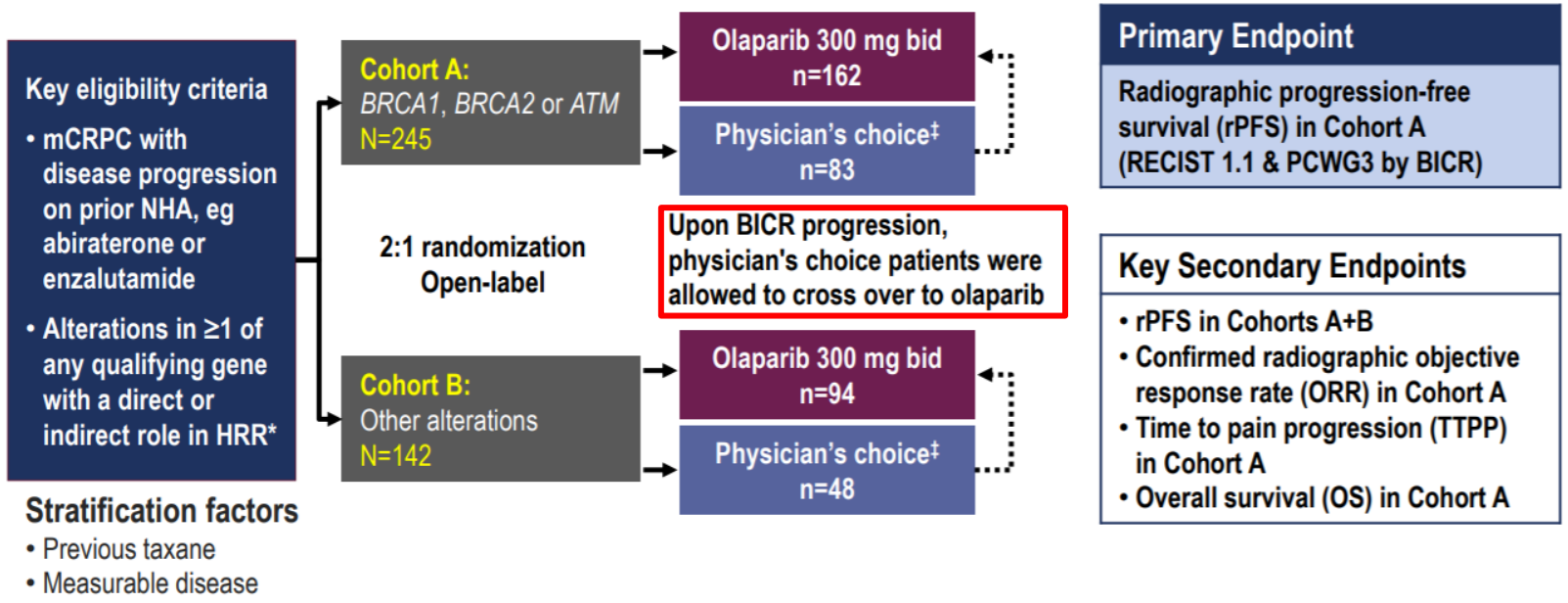
FDA grants accelerated approval to rucaparib for BRCA-mutated metastatic castration-resistant prostate cancer

On May 15, 2020, the Food and Drug Administration granted accelerated approval to rucaparib (RUBRACA, Clovis Oncology, Inc.) for patients with deleterious *BRCA* mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.

Efficacy was investigated in TRITON2 (NCT02952534), an ongoing, multi-center, single arm clinical trial in 115 patients with *BRCA*-mutated (germline and/or somatic) mCRPC who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy. Patients received rucaparib 600 mg orally twice daily and concomitant GnRH analog or had prior bilateral orchiectomy.

Phase III PROfound Study: Study Design

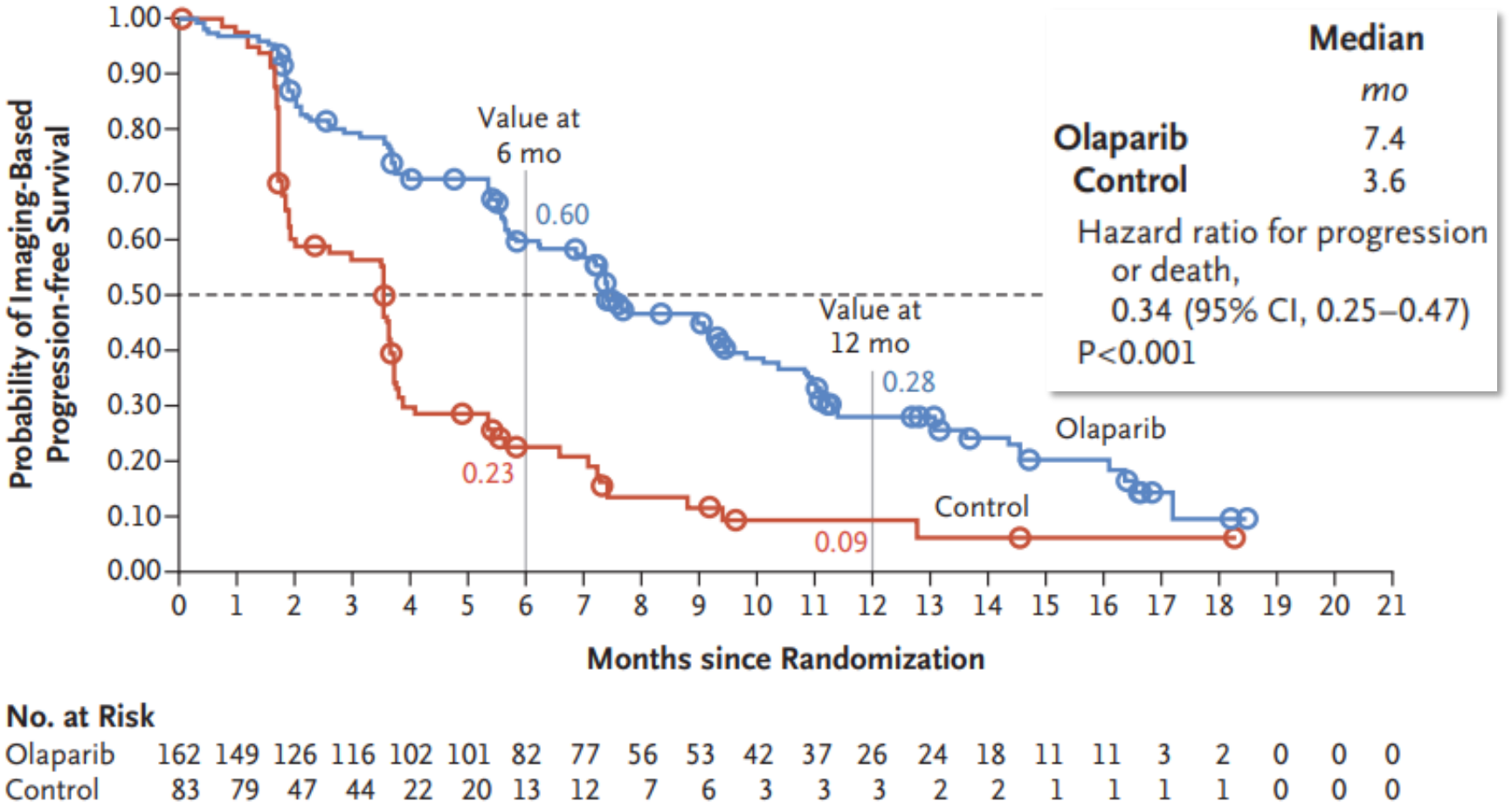


*An investigational Clinical Trial Assay, based on the FoundationOne® CDx next-generation sequencing test

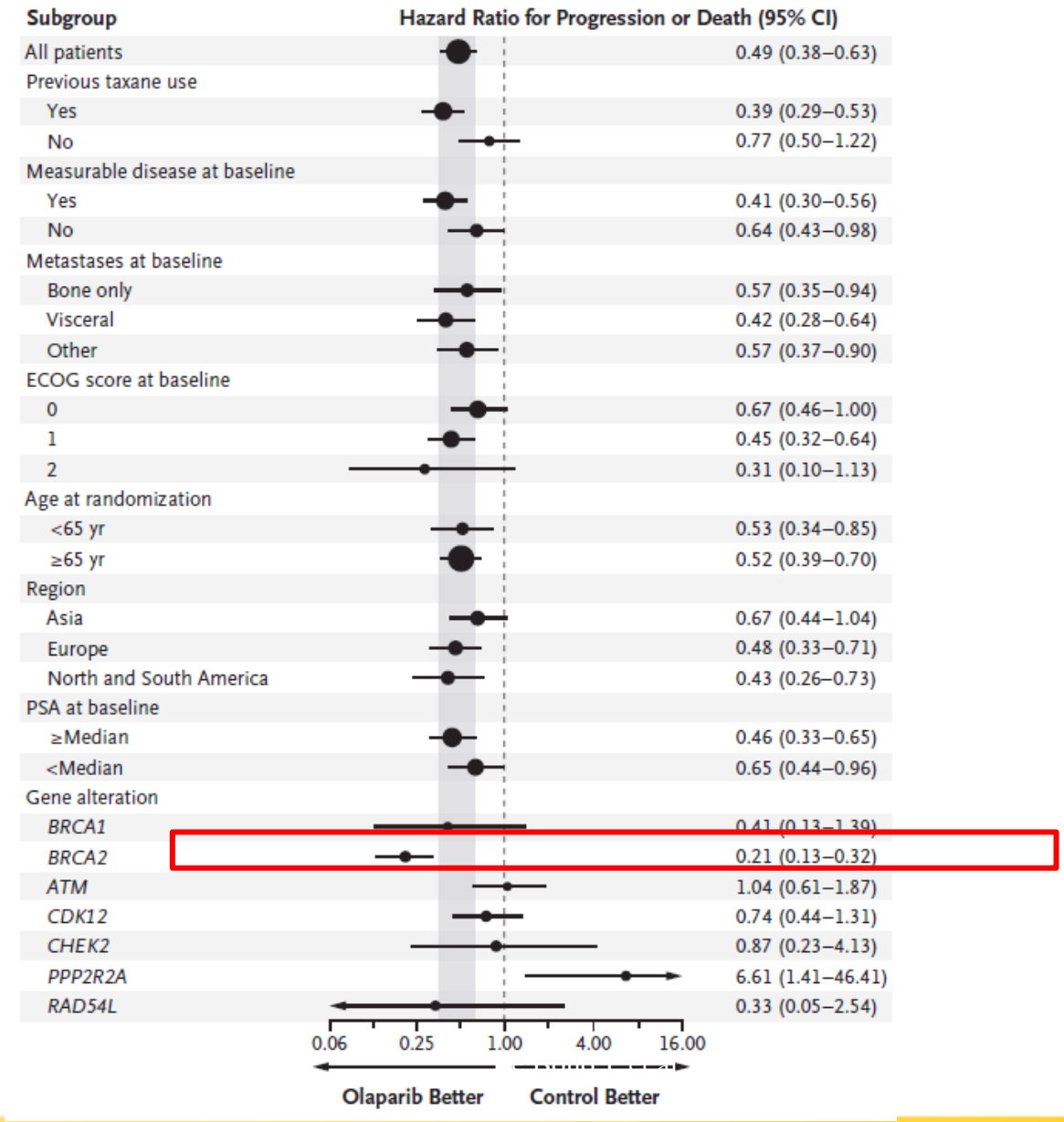
Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and/ or *RAD54L* in their tumor tissue

N Engl J Med. 2020 May 28;382(22):2091-2102.

Phase III PROfound Study: rPFS BY BICR in Cohort A (Patients With *BRCA1/2* or *ATM* Alterations)

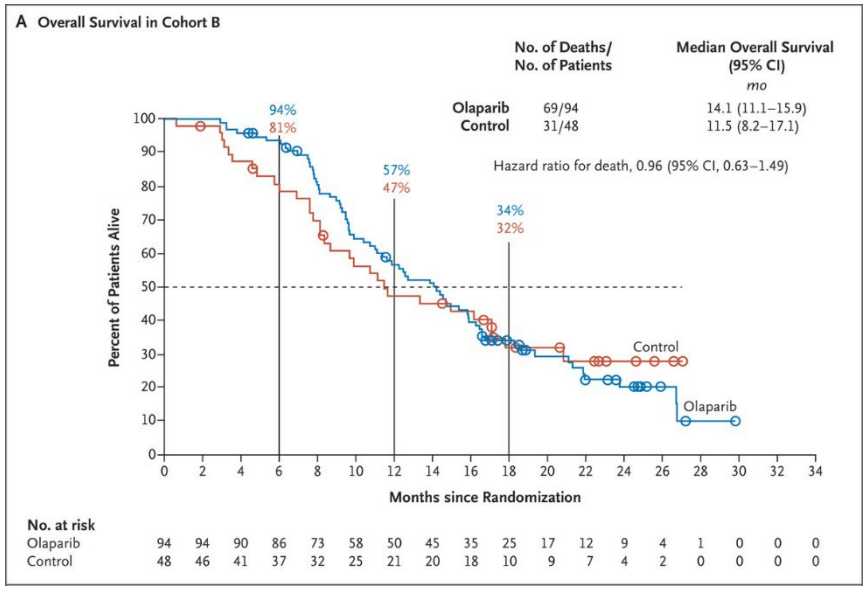


PROfound: PFS by Subgroup (Overall Population)

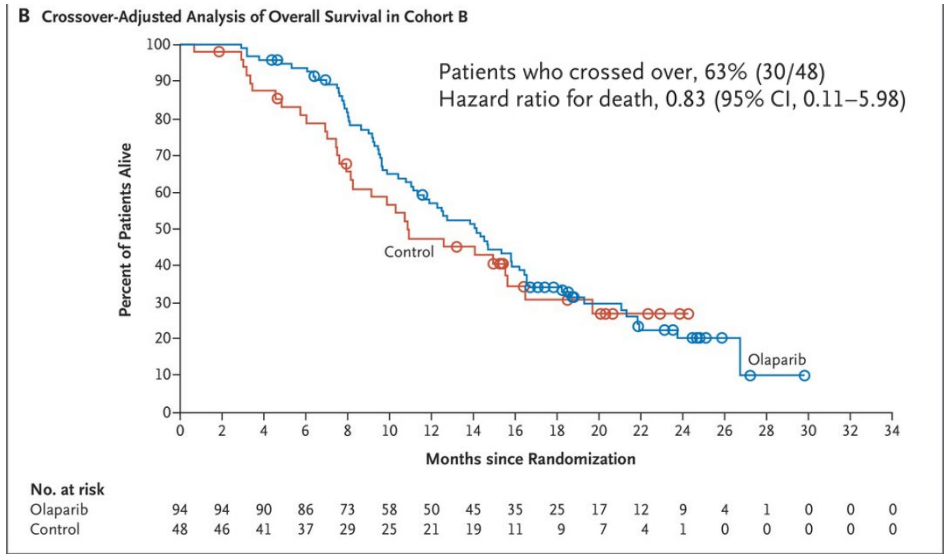


Phase III PROfound Study: OS—Cohort B (non-*BRCA* or *ATM* Alterations)

Cohort B (non-*BRCA1/2* or *ATM* Alterations)



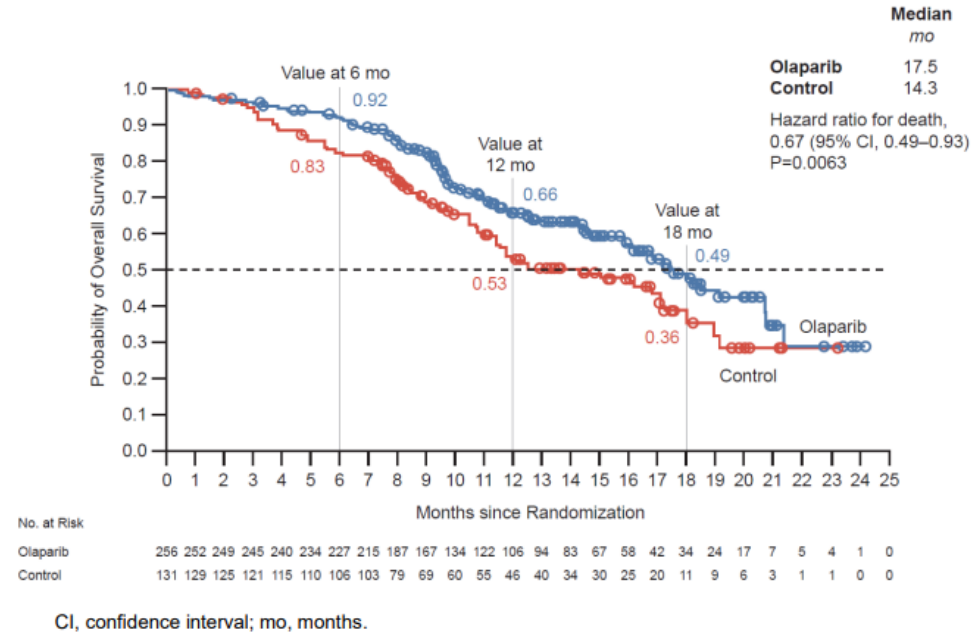
Crossover-Adjusted Sensitivity Analyses



- mOS: 14.1 mo vs 11.5 mo (HR, 0.96; 95% CI 0.63-1.49)

Phase III PROfound Study: OS—Overall Population

Overall Population



CI, confidence interval; mo, months.

mOS: 17.5 mo vs 14.3 mo (HR, 0.67; 95% CI (0.49-0.93); P=0.006

De Bono et al. *N Engl J Med.* 2020. DOI: 10.1056/NEJMoa2022485

JOHNS HOPKINS MEDICINE

FDA approves olaparib for HRR gene-mutated metastatic castration-resistant prostate cancer

On May 19, 2020, the Food and Drug Administration approved olaparib (LYNPARZA, AstraZeneca Pharmaceuticals, LP) for adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC), who have progressed following prior treatment with enzalutamide or abiraterone.

Today, the FDA also approved FoundationOne CDx (Foundation Medicine, Inc.) for selection of patients with mCRPC carrying HRR gene alterations and BRACAnalysis CDx test (Myriad Genetic Laboratories, Inc.) for selection of patients with mCRPC carrying germline *BRCA1/2* alterations as companion diagnostic devices for treatment with olaparib.

ASCO Genitourinary Cancers Symposium

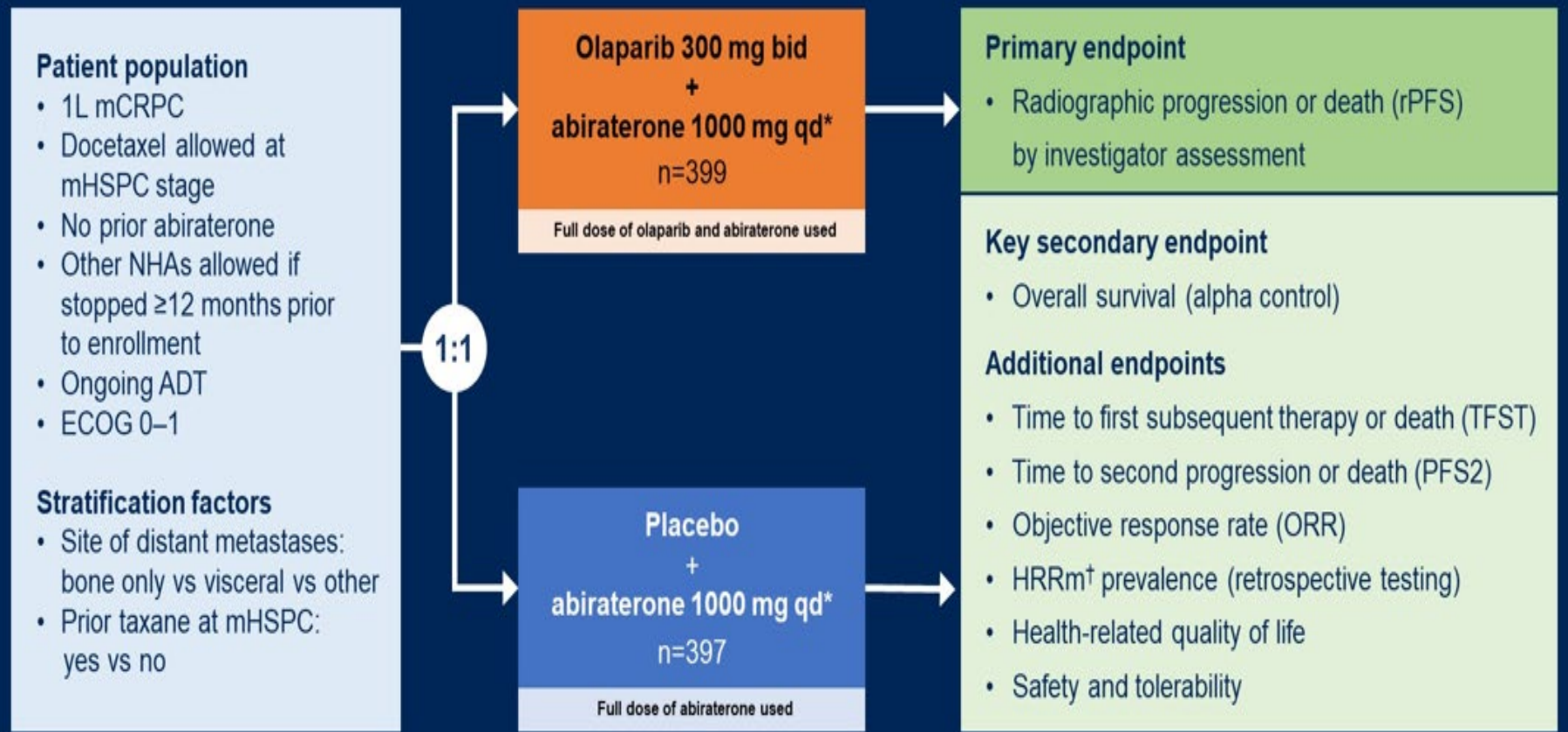
PROpel: phase III trial of olaparib and abiraterone versus placebo and abiraterone as first-line therapy for patients with metastatic castration-resistant prostate cancer

Fred Saad, Andrew J. Armstrong, Antoine Thiery-Vuillemin, Mototsugu Oya, Eugenia Loredo, Giuseppe Procopio, Juliana de Menezes, Gustavo Girotto, Cagatay Arslan, Niven Mehra, Francis Parnis, Emma Brown, Friederike Schlürmann, Jae Young Joung, Mikio Sugimoto, Christian Poehlein, Elizabeth A. Harrington, Chintu Desai, Jinyu Kang, and Noel Clarke

ClinicalTrials.gov identifier: NCT03732820.
This study was supported by AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, who are co-developing olaparib.

PRESENTED BY: Professor Fred Saad

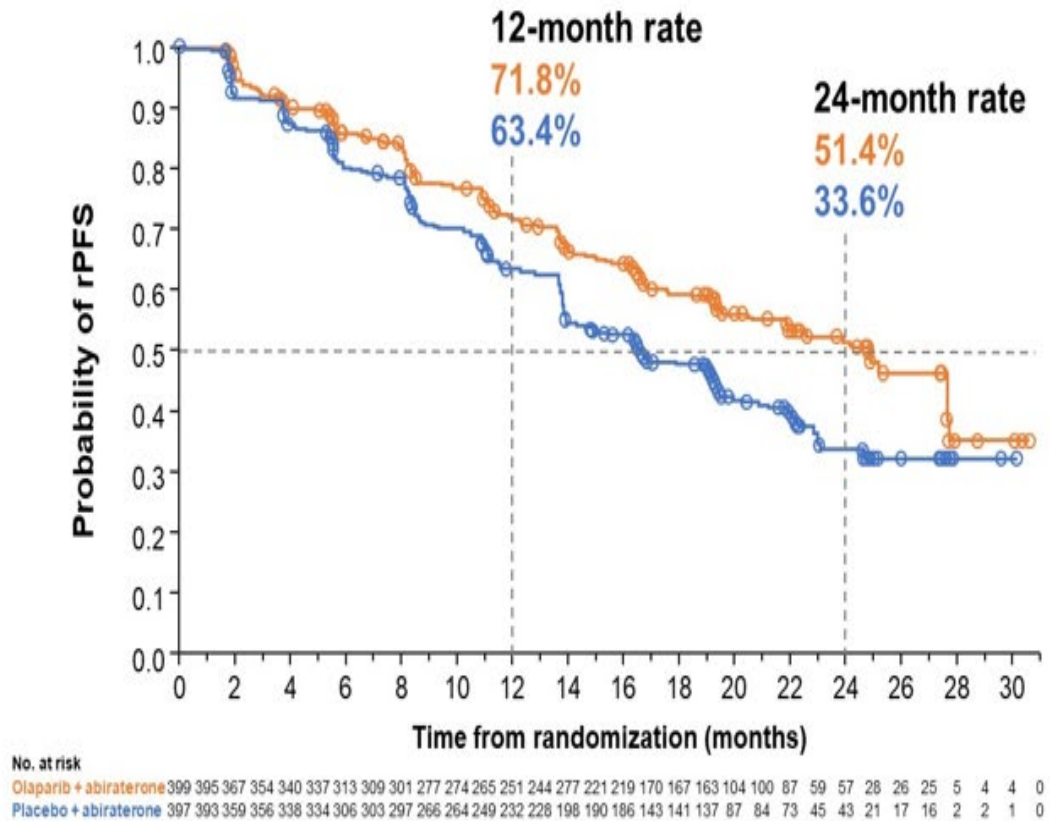
PROpel: a global randomized double-blind phase III trial



First patient randomized: Nov 2018; Last patient randomized: Mar 2020; DCO1: July 30, 2021, for interim analysis of rPFS and OS.
Multiple testing procedure is used in this study: 1-sided alpha of 0.025 fully allocated to rPFS. If the rPFS result is statistically significant, OS to be tested in a hierarchical fashion with alpha passed on to OS.
Please access the ***Supplement*** via the QR code at the end of this presentation for more details.
*In combination with prednisone or prednisolone 5 mg bid. †HRRm, homologous recombination repair mutation, including 14 genes panel.
ADT, androgen deprivation therapy; bid, twice daily; ECOG, Eastern Cooperative Oncology Group; mHSPC, metastatic hormone sensitive prostate cancer; qd, daily

PROpel primary endpoint: rPFS by investigator-assessment

34% risk reduction of progression or death with olaparib + abiraterone



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS (months)	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); *P*<0.0001	

Pre-specified 2-sided alpha: 0.0324

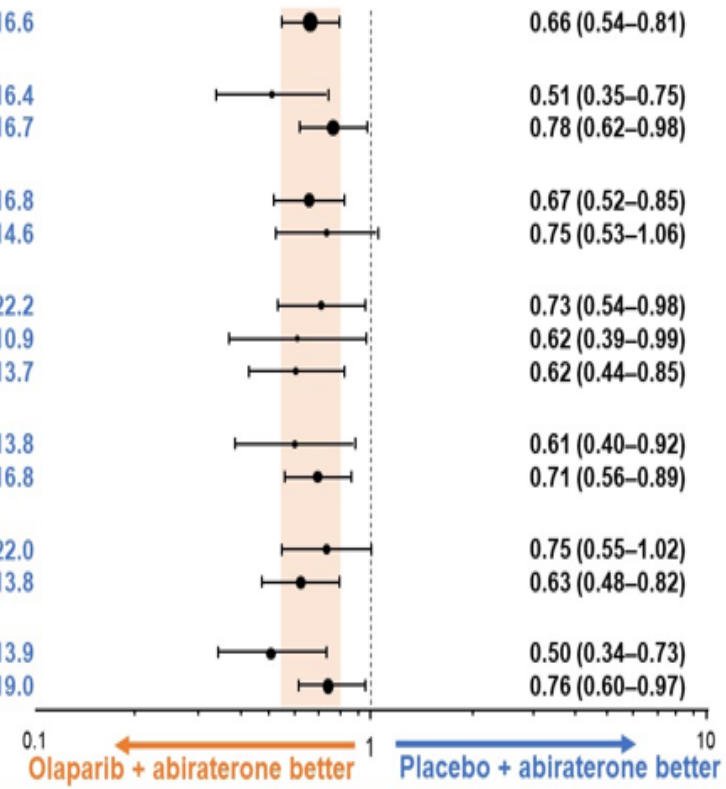
Median rPFS improvement of 8.2 months favors olaparib + abiraterone*

Events: 394; Maturity 49.5%
*In combination with prednisone or prednisolone
CI, confidence interval; HR, hazard ratio.

PROpel: subgroup analysis of rPFS

rPFS benefit observed across all pre-specified subgroups

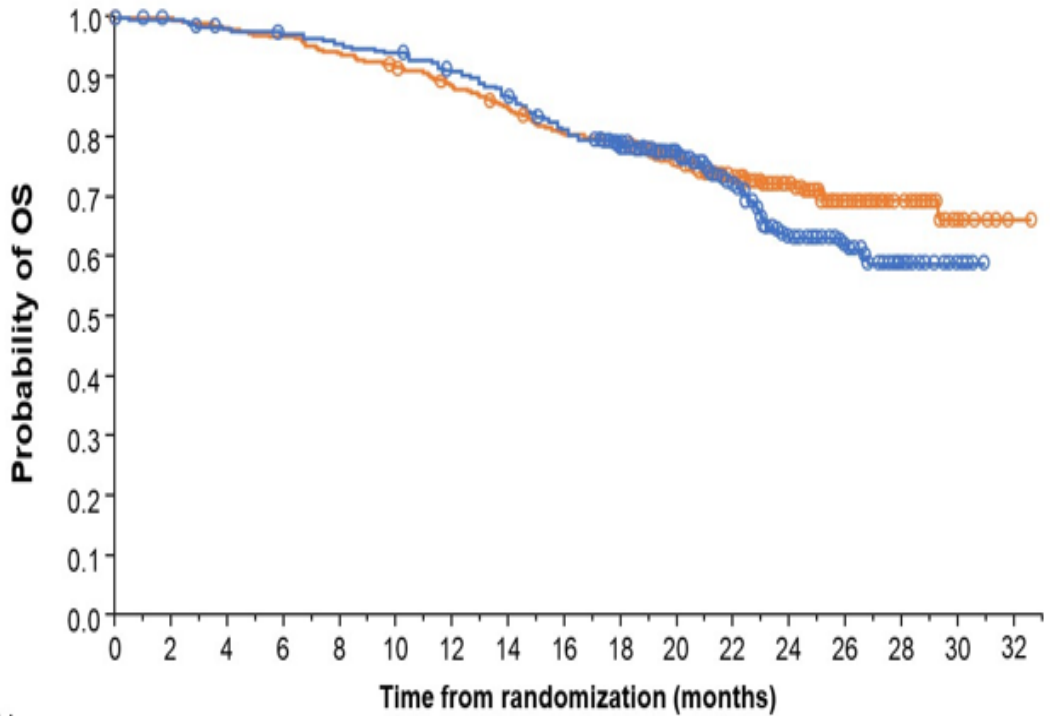
	Number of patients, n	Median rPFS, months		HR (95% CI)
All patients	796	24.8	16.6	0.66 (0.54–0.81)
Age at randomization				
<65	227	NR	16.4	0.51 (0.35–0.75)
≥65	569	22.0	16.7	0.78 (0.62–0.98)
ECOG performance status at baseline				
0	558	24.9	16.8	0.67 (0.52–0.85)
1	236	17.5	14.6	0.75 (0.53–1.06)
Site of distant metastases				
Bone only	434	27.6	22.2	0.73 (0.54–0.98)
Visceral	105	13.7	10.9	0.62 (0.39–0.99)
Other	257	20.5	13.7	0.62 (0.44–0.85)
Docetaxel treatment at mHSPC stage				
Yes	189	27.6	13.8	0.61 (0.40–0.92)
No	607	24.8	16.8	0.71 (0.56–0.89)
Baseline PSA				
Below median baseline PSA	396	25.2	22.0	0.75 (0.55–1.02)
Above or equal to median baseline PSA	397	18.5	13.8	0.63 (0.48–0.82)
HRRm status*				
HRRm	226	NR	13.9	0.50 (0.34–0.73)
Non-HRRm	552	24.1	19.0	0.76 (0.60–0.97)



Global interaction test not significant at 10% level. *The HRRm status of patients in PROpel was determined retrospectively using results from tumor tissue and plasma ctDNA HRRm tests. Patients were classified as HRRm if (one or more) HRR gene mutation was detected by either test; patients were classified as non-HRRm patients if no HRR gene mutation was detected by either test; patients were classified as unknown HRRm if no valid HRR test result from either test was achieved. 18 patients did not have a valid HRR testing result from either a tumor tissue or ctDNA test and were excluded from the subgroup analysis. This subgroup analysis is post hoc exploratory analysis. Please access the Supplement via the QR code at the end of this presentation for more details. NR, not reached.

PROpel: overall survival

28.6% maturity; trend towards improved OS with olaparib + abiraterone



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	107 (26.8)	121 (30.5)
Median OS (months)	NR	NR
HR (95% CI)	0.86 (0.66–1.12) *P*=0.29	

Pre-specified 2-sided alpha: 0.001

Events: 228
NR, not reached.

PROpel: conclusions

- **Olaparib + abiraterone** led to a **significant and clinically meaningful improvement in rPFS (HR 0.66 [95% CI 0.54–0.81])** over placebo + abiraterone in 1L mCRPC
  - Benefit observed led to a **median rPFS beyond 2 years**
  - Benefit was observed **irrespective of HRRm status**
- **Secondary and exploratory endpoints support the treatment benefit** of olaparib + abiraterone over placebo + abiraterone in the overall patient population
- The safety profile of olaparib + abiraterone was **consistent with the safety profile for the individual drugs** and there was **no detriment to quality of life** allowing most patients to stay on therapy
- The phase III PROpel study is the first combination approach to deliver consistent **clinical benefits for patients in the 1L mCRPC setting, irrespective of HRRm status**

PARP Inhibitors in PCA

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- Olaparib and rucaparib- FDA approved with different labels- based on trial designs
- BRCA2 clearly the greatest benefit- seems to drive the results in all 3 of the studies presented today
- Can get responses in non-BRCA2 HRD mutations- but likelihood is low and limited in duration
- PARPi and Abiraterone

Theranostics in Prostate cancer

2021 ASCO ANNUAL MEETING

Phase 3 study of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION)

Presenter: Michael J. Morris, Memorial Sloan Kettering Cancer Center

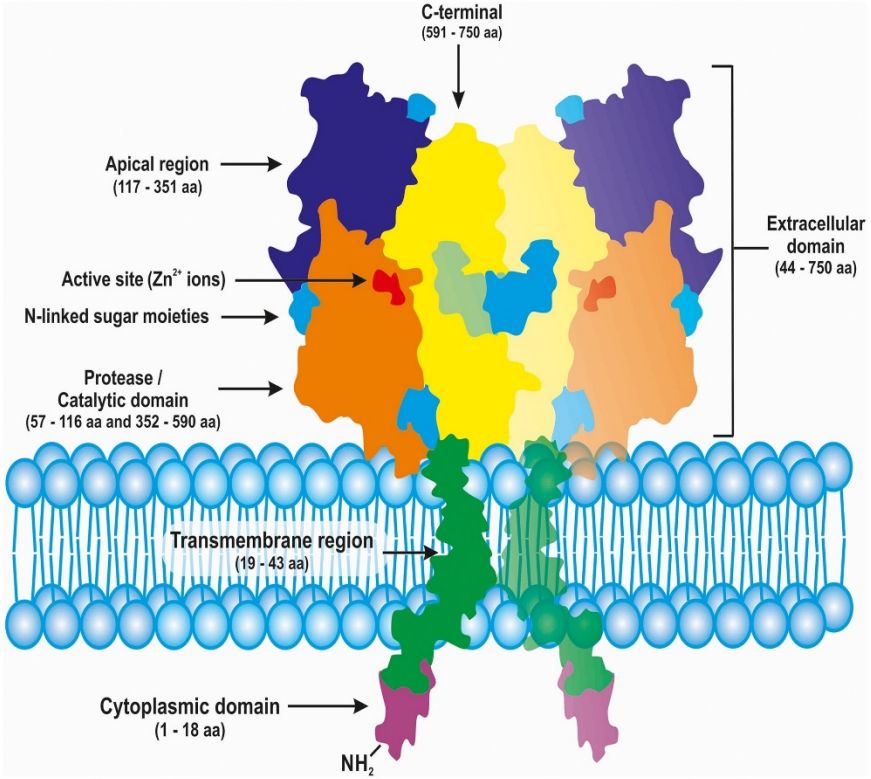
Co-authors: J. de Bono, K. N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S. T. Tagawa, L. T. Nordquist, N. Vaishampayan, G. El-Haddad, C. H. Park, T. M. Beer, W. J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R. A. Messmann, B. J. Krause, O. Sartor, for the VISION investigators

6 June 2021

Study funded by Endocyte, Inc., a Novartis company

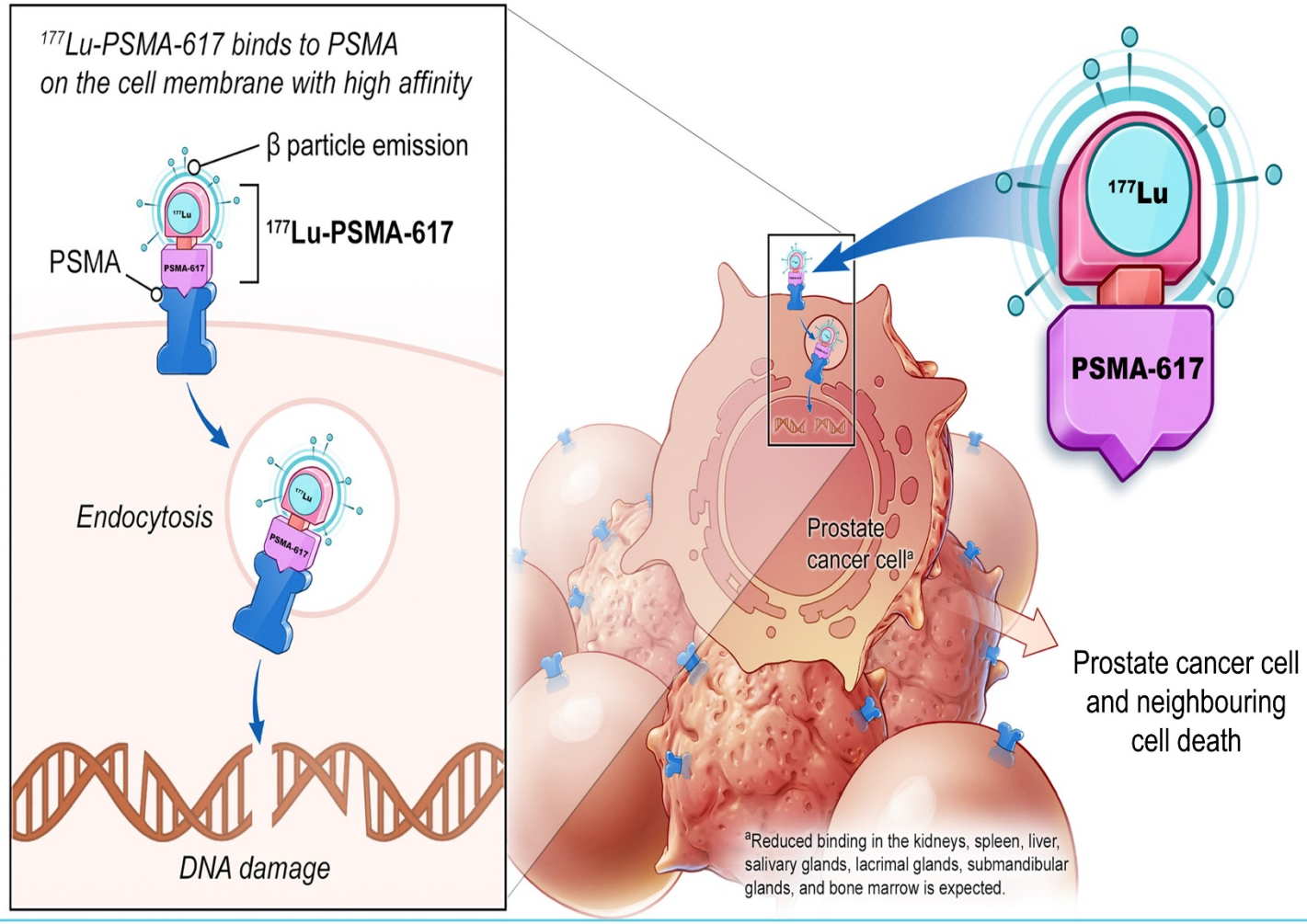
Prostate-specific membrane antigen (PSMA): molecular target for imaging and therapy in prostate cancer

- Transmembrane carboxypeptidase
- Highly expressed in prostate cancer including metastatic lesions
- Relatively restricted normal expression
  - E.g. salivary and lacrimal glands
- Excellent target for PET imaging



From Evans JC *et al. Br J Pharmacol* 2016;173:3041–3079

^{177}Lu-PSMA-617 targeted radioligand therapy



Open-label study of protocol-permitted standard of care ± ^{177}Lu-PSMA-617 in adults with PSMA-positive mCRPC

Eligible patients

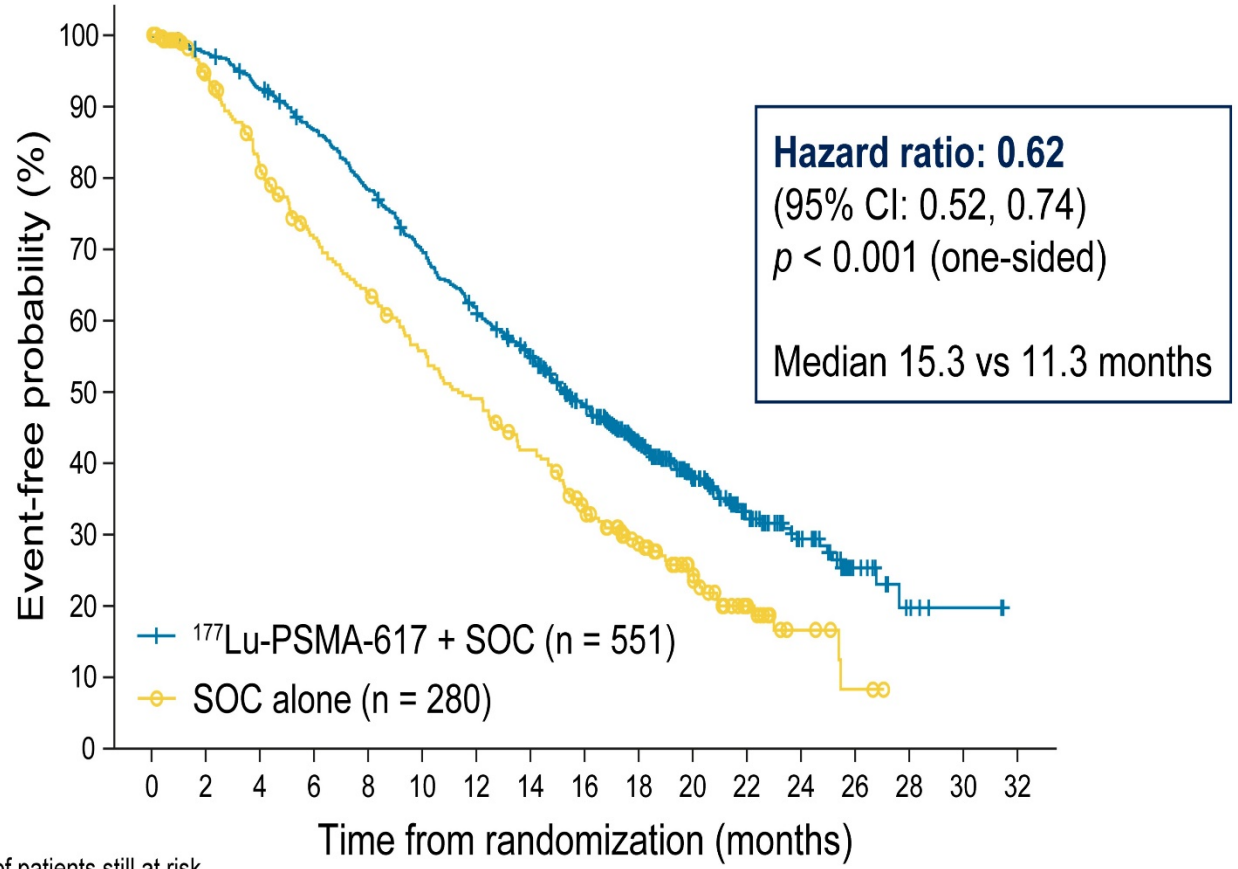
- Previous treatment with both
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11

- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)
- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review

Primary endpoints: ^{177}Lu-PSMA-617 prolonged OS

Primary analysis

All randomized patients
(N = 831)



Number of patients still at risk

^{177}Lu-PSMA-617 + SOC	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
SOC alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

Pluvicto in PCA

- FDA approved 3/23/22 – post AR targeted therapy and taxane chemotherapy
- Manufacturing issues and logistics slow implementation
- Requires PSMA -PET
- Use in early disease space??

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Bladder Cancer

The NEW ENGLAND JOURNAL of MEDICINE

JOHNS HOPKINS MEDICINE

ORIGINAL ARTICLE

Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma

Y. Loriot, A. Necchi, S.H. Park, J. Garcia-Donas, R. Huddart, E. Burgess, M. Fleming, A. Rezazadeh, B. Mellado, S. Varlamov, M. Joshi, I. Duran, S.T. Tagawa, Y. Zakharia, B. Zhong, K. Stuyckens, A. Santiago-Walker, P. De Porre, A. O'Hagan, A. Avadhani, and A.O. Siefker-Radtke, for the BLC2001 Study Group*

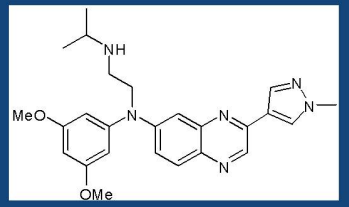
N Engl J Med 2019;381:338-48.

FGFRs induce signaling through networks that regulate cell proliferation, survival, migration, and differentiation

Mutations / fusions in FGFR2/3 present in:
- **~20% bladder cancers**
- **~ 35% of UTUC**

Erdafitinib Is a Potent FGFR Inhibitor

- Erdafitinib* is an oral pan-FGFR (1-4) inhibitor with IC_{50} in the single-digit nanomolar range[1]
- Erdafitinib is taken up by lysosomes, resulting in sustained intracellular release, which may contribute to its long-lasting activity[1]
- Erdafitinib has demonstrated promising activity in patients with metastatic or unresectable UC and other histologies (eg, cholangiocarcinoma) with *FGFR* alterations[2-5]



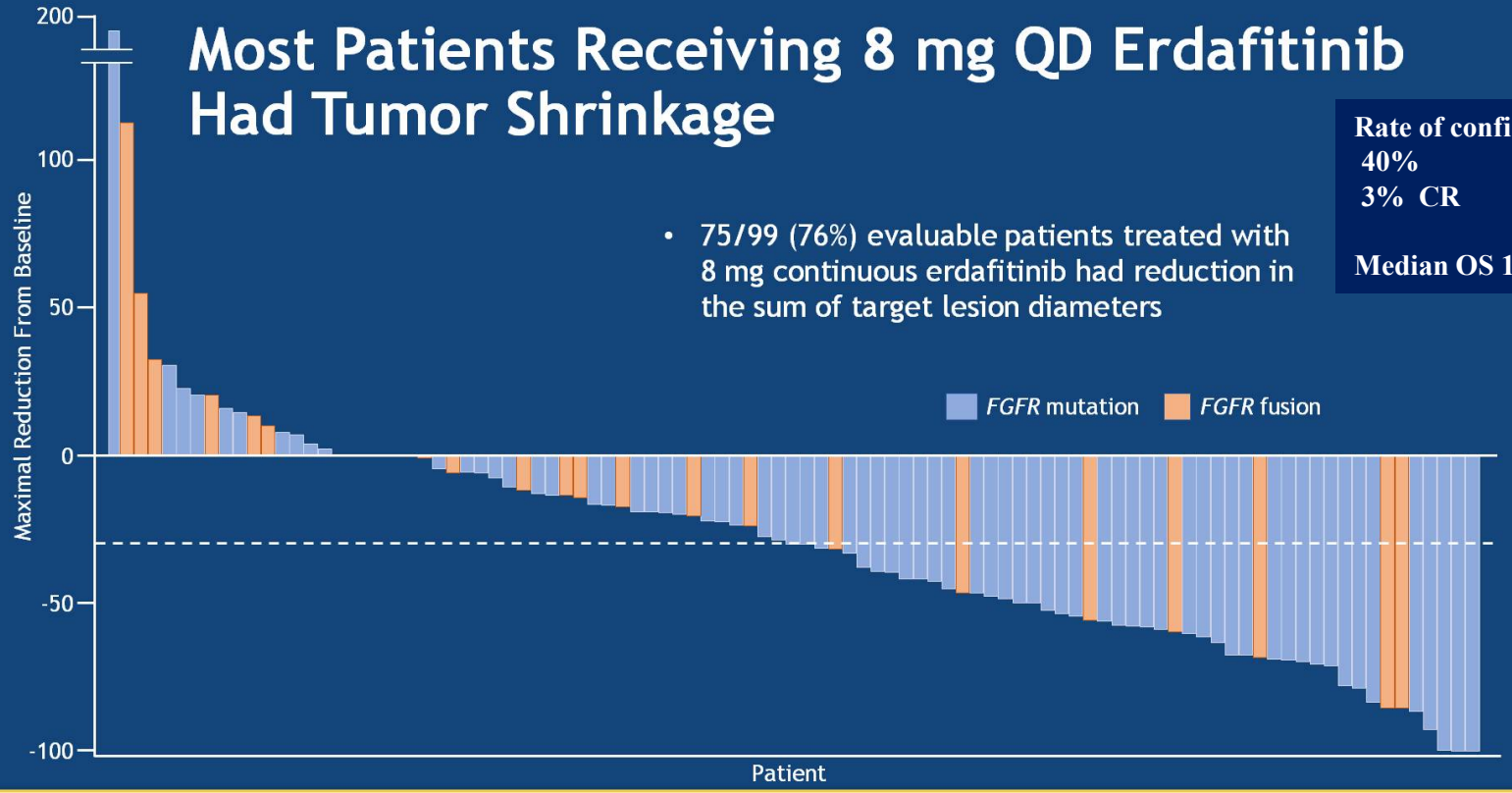
*Investigational compound erdafitinib (JNJ-42756493) was discovered in collaboration with Astex Pharmaceuticals.

Abbreviation: IC_{50}, drug concentration at which 50% of target enzyme activity is inhibited.

1. Perera TPS, et al. *Mol Cancer Ther*. 2017;16:1010-1020.
2. Tabernero J, et al. *J Clin Oncol*. 2015;33:3401-3408.
3. Soria J-C, et al. ESMO 2016. Abstract 781PD.
4. Loriot Y, et al. ASCO GU 2018. Abstract 411.
5. Siefker-Radtke A, et al. ASCO GU 2018. Abstract 450.

Most Patients Receiving 8 mg QD Erdafitinib Had Tumor Shrinkage

- 75/99 (76%) evaluable patients treated with 8 mg continuous erdafitinib had reduction in the sum of target lesion diameters



Rate of confirmed response
40%
3% CR

Median OS 13.8 mos

Table 3. Adverse Events in the 99 Patients in the Selected-Regimen Group.*

Adverse Event	Any Grade	Grade 1	Grade 2	Grade ≥3
		number of patients (percent)		
Hyperphosphatemia	76 (77)	53 (54)	21 (21)	2 (2)
Stomatitis	57 (58)	21 (21)	26 (26)	10 (10)
Diarrhea	50 (51)	31 (31)	15 (15)	4 (4)
Dry mouth	45 (46)	34 (34)	11 (11)	0
Decreased appetite	38 (38)	18 (18)	20 (20)	0
Dysgeusia	37 (37)	23 (23)	13 (13)	1 (1)
Fatigue	32 (32)	12 (12)	18 (18)	2 (2)
Dry skin	32 (32)	24 (24)	8 (8)	0
Alopecia	29 (29)	23 (23)	6 (6)	0
Constipation	28 (28)	19 (19)	8 (8)	1 (1)
Hand–foot syndrome	23 (23)	6 (6)	12 (12)	5 (5)
Anemia	20 (20)	9 (9)	7 (7)	4 (4)
Asthenia	20 (20)	2 (2)	11 (11)	7 (7)
Nausea	20 (20)	13 (13)	6 (6)	1 (1)
Dry eye	19 (19)	14 (14)	4 (4)	1 (1)
Onycholysis	18 (18)	6 (6)	10 (10)	2 (2)
Alanine aminotransferase increased	17 (17)	13 (13)	2 (2)	2 (2)
Paronychia	17 (17)	3 (3)	11 (11)	3 (3)
Blurred vision	17 (17)	10 (10)	7 (7)	0
Nail dystrophy	16 (16)	5 (5)	5 (5)	6 (6)
Urinary tract infection	16 (16)	0	11 (11)	5 (5)
Vomiting	13 (13)	10 (10)	1 (1)	2 (2)
Hyponatremia	12 (12)	1 (1)	0	11 (11)
Hematuria	10 (10)	7 (7)	1 (1)	2 (2)
Dyspnea	8 (8)	4 (4)	2 (2)	2 (2)
Nail disorder	8 (8)	4 (4)	1 (1)	3 (3)
Acute kidney injury	6 (6)	2 (2)	2 (2)	2 (2)
Cataract	6 (6)	3 (3)	1 (1)	2 (2)
Colitis	5 (5)	1 (1)	2 (2)	2 (2)
General deterioration in physical health	5 (5)	0	1 (1)	4 (4)
Keratitis	5 (5)	0	2 (2)	3 (3)
Aphthous ulcer	4 (4)	2 (2)	0	2 (2)
Increase in γ-glutamyltransferase	3 (3)	1 (1)	0	2 (2)
Urosepsis	3 (3)	0	0	3 (3)

- Mucositis / GI toxicity
- Nail changes
- Occular Toxicity

(central Serous retinopathy)

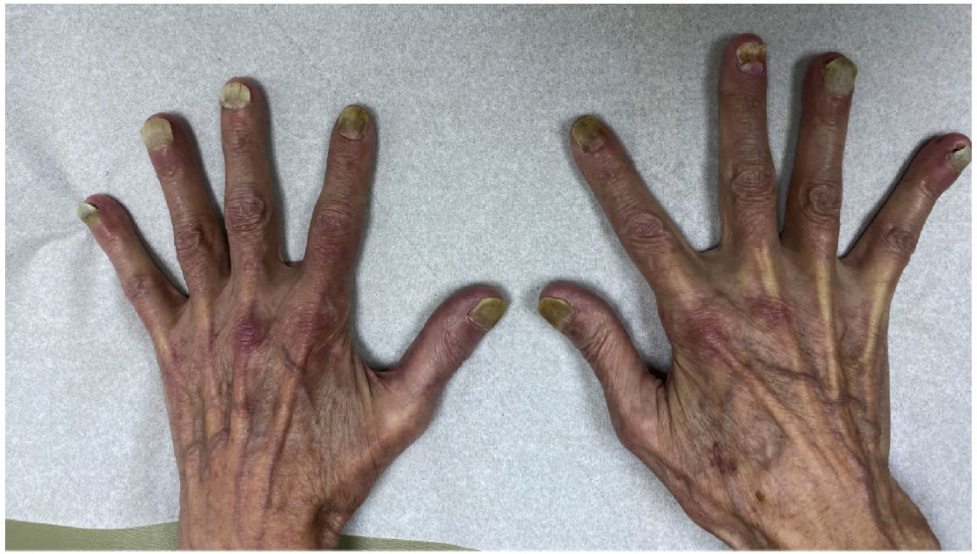


Fig 1. Severe onycholysis and nail bed infection of fingernails. Erythematous patches over metacarpophalangeal joint, distal interphalangeal joint, and periungual areas.

JAAD Case Reports 2020;6:569-71.

Enfortumab Vedotin

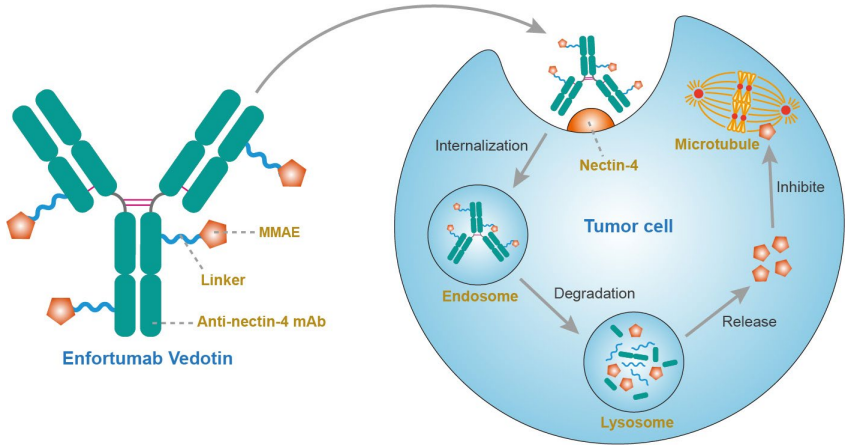


TABLE A2. Summary of Responses Per Investigator in the Full Analysis Set

Response	Patients (N = 125)
Objective response rate	49 (39)
95% CI*	30.6, 48.3
Best overall response,†	
Complete response	9 (7)
Partial response	40 (32)
Stable disease	48 (38)
Progressive disease	17 (14)
Not evaluable‡	11 (9)

NOTE. Data are presented as No. (%).

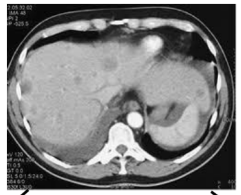
*CI was computed using the Clopper-Pearson method.[22]

†Best overall response according to RECIST v1.1.

‡Includes 10 patients who did not have any response assessment postbaseline and one patient whose postbaseline assessment did not meet the minimum interval requirement for stable disease.

Rosenberg et al, JCO 2019

Bladder Cancer Treatment Algorithm



- Chemotherapy Ineligible
  - CPI
    Pembrolizumab or Atezolizumab
- Chemotherapy Eligible
  - Cisplatin Ineligible
    - Carboplatin and Gemcitabine
      - Pembrolizumab, Atezolizumab, nivolumab, durvalumab, avelumab
  - Cisplatin Eligible
    - Cisplatin and Gemcitabine
      aMVAC
      - Pembrolizumab, Atezolizumab, nivolumab, durvalumab, avelumab
    - CR/PR/SD on 1L Platinum
      - Avelumab Maintenance

PD on 1L Platinum → Pembrolizumab, Atezolizumab, nivolumab, durvalumab, avelumab

- FGFR3 mut/fusion +
  - Erdafitinib
  - Enfortumab Vedotin
- FGFR3 mut/fusion -
  - Enfortumab Vedotin

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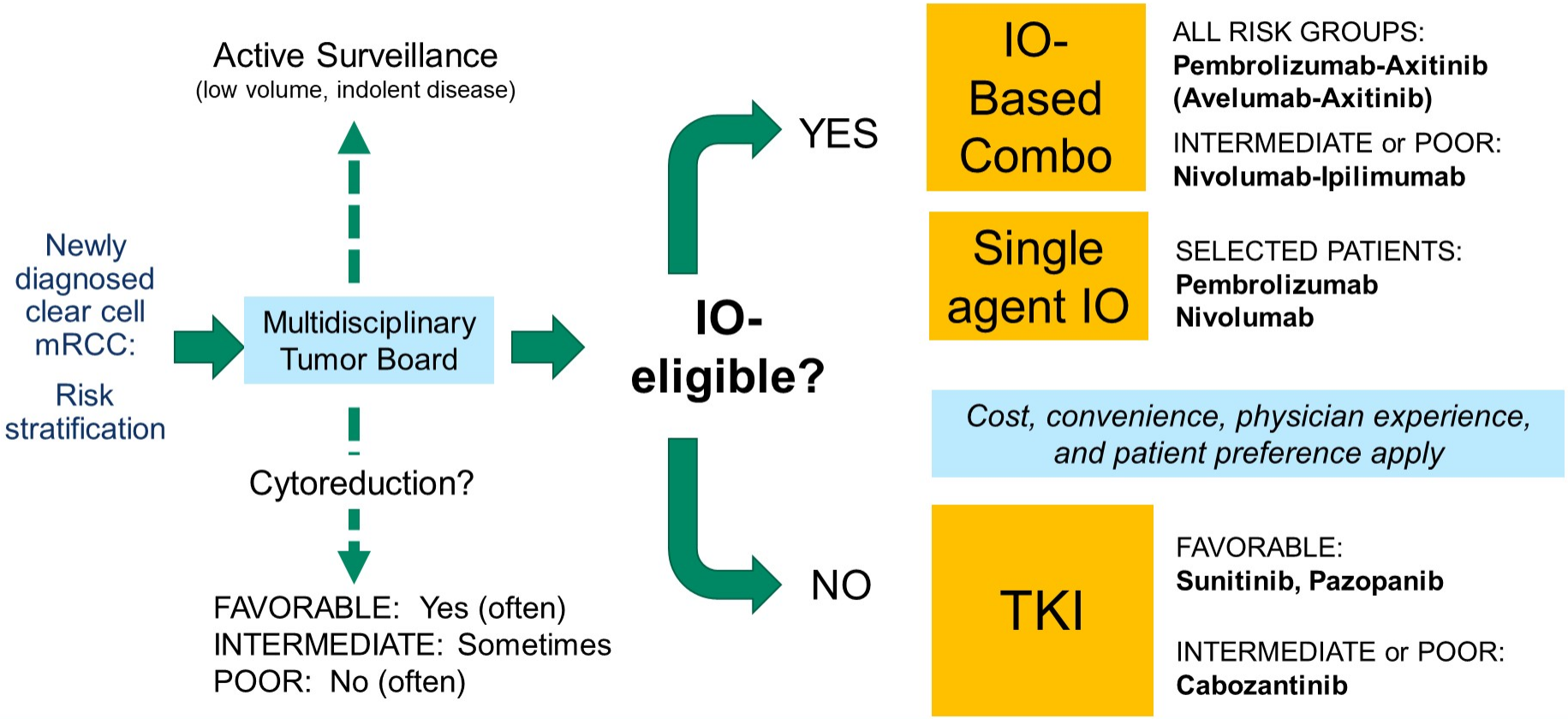
Renal Cancer

mRCC Decision Tree



IO = immuno-oncology

Phase 3 trial of lenvatinib plus pembrolizumab or everolimus versus sunitinib monotherapy as a first-line treatment for patients with advanced renal cell carcinoma (CLEAR study)

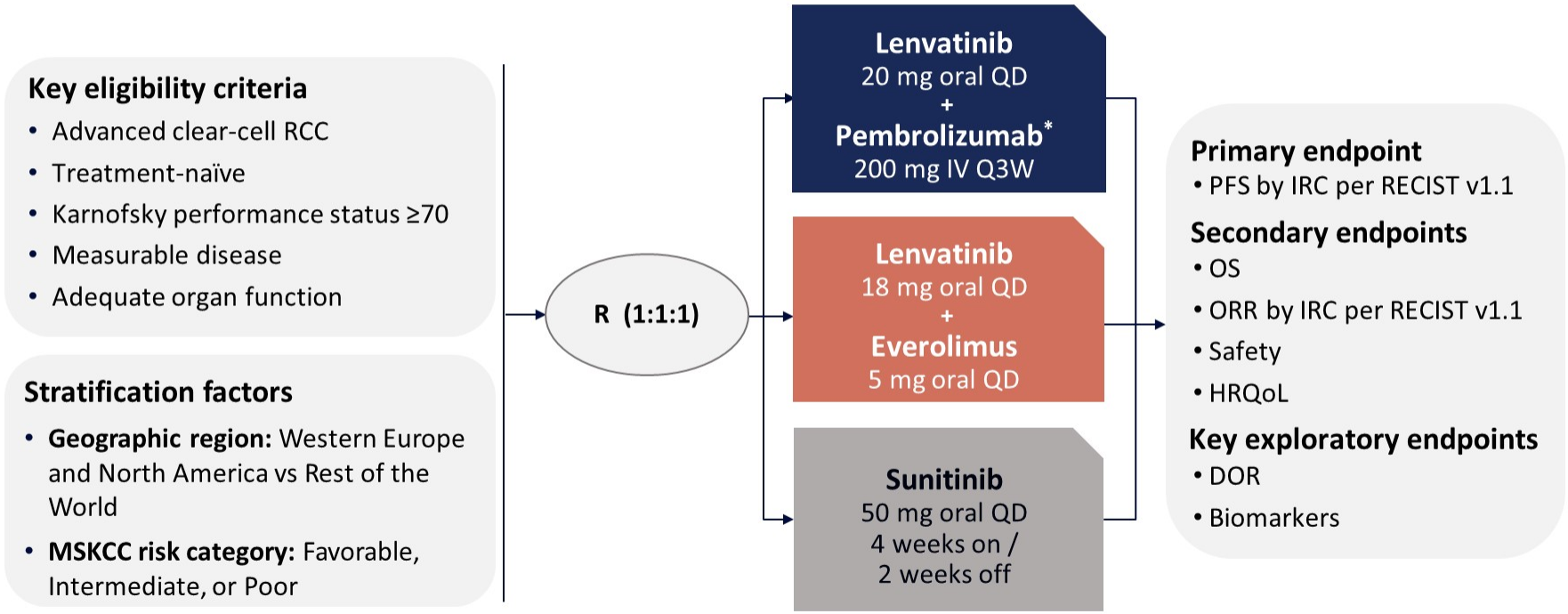
Robert Motzer[1], Camillo Porta[2], Masatoshi Eto[3], Thomas Powles[4], Viktor Grünwald[5], Thomas E. Hutson[6], Boris Alekseev[7], Sun Young Rha[8], Evgeny Kopyltsov[9], María José Méndez-Vidal[10], Sung-Hoo Hong[11], Anil Kapoor[12], Teresa Alonso Gordoa[13], Jeffrey C. Goh[14], Jaime R. Merchan[15], Alan D. Smith[16], Kalgi Mody[17], Rodolfo F. Perini[18], Dongyuan Xing[17], and Toni K. Choueiri[19]

[1]Memorial Sloan Kettering Cancer Center; New York, NY, USA; [2]San Matteo University Hospital Foundation, Pavia, Italy; [3]Kyushu University, Fukuoka, Japan; [4]The Royal Free NHS Trust, London, England, UK; [5]University Hospital Essen, Essen, Germany; [6]Texas Oncology, Dallas, TX, USA; [7]P.A. Hertsen Moscow Cancer Research Institute, Moscow, Russia; [8]Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea; [9]State Institution of Healthcare "Regional Clinical Oncology Dispensary", Omsk, Russia; [10]Maimonides Institute for Biomedical research of Cordoba (IMIBIC) Hospital Universitario Reina Sofía, Medical Oncology Department, Córdoba, Spain; [11]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; [12]McMaster University Hamilton, Ontario, Canada; [13]Hospital Universitario Ramón y Cajal, Madrid, Spain; [14]ICON Research, South Brisbane & University of Queensland, St Lucia, Queensland, Australia; [15]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA; [16]Eisai Ltd., Hatfield, UK; [17]Eisai Inc., Woodcliff Lake, NJ, USA; [18]Merck & Co., Inc., Kenilworth, NJ, USA; [19]Dana-Farber Cancer Institute, Boston, MA, USA.

Presented By Robert Motzer at 2021 Genitourinary Cancers Symposium

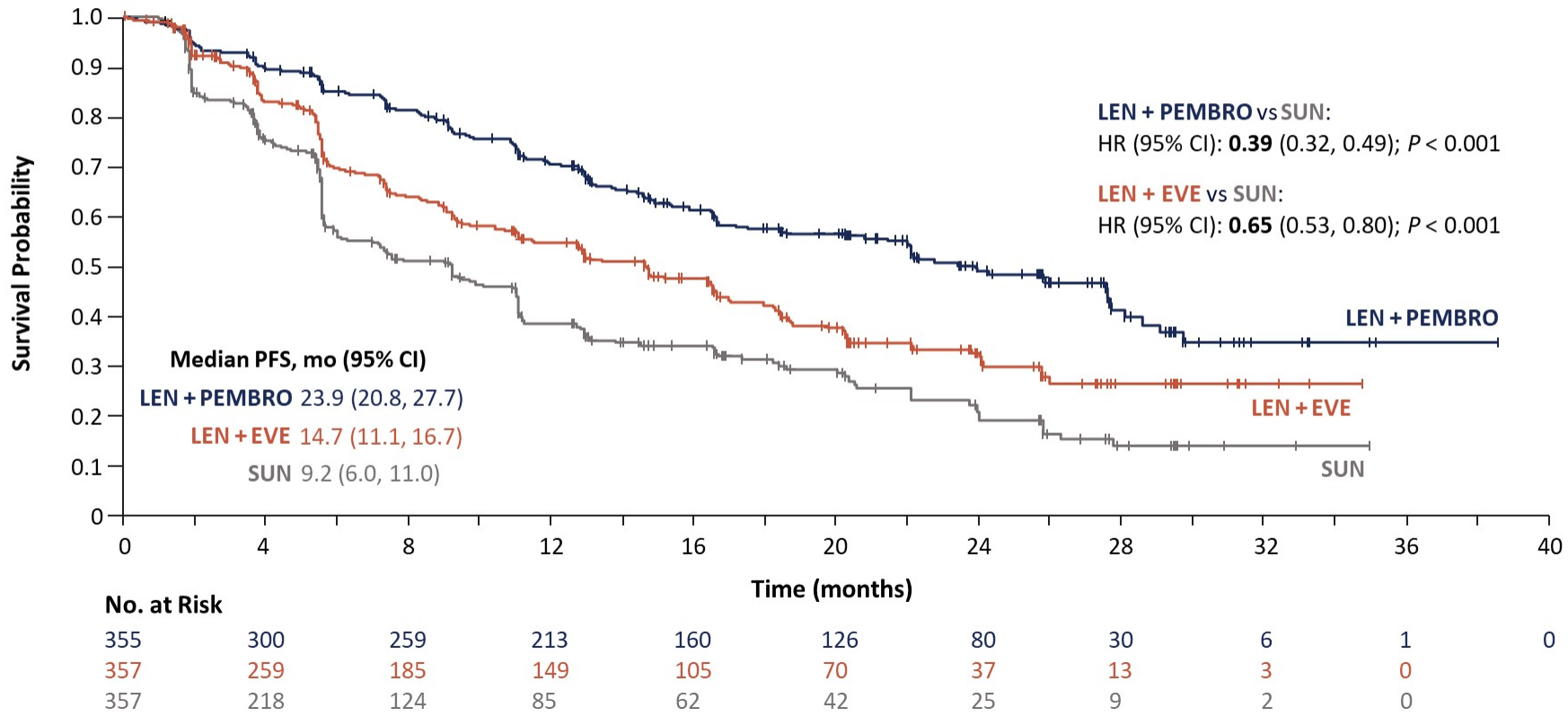
Motzer R, et al. NEJM 2021 Feb 13

Study Design



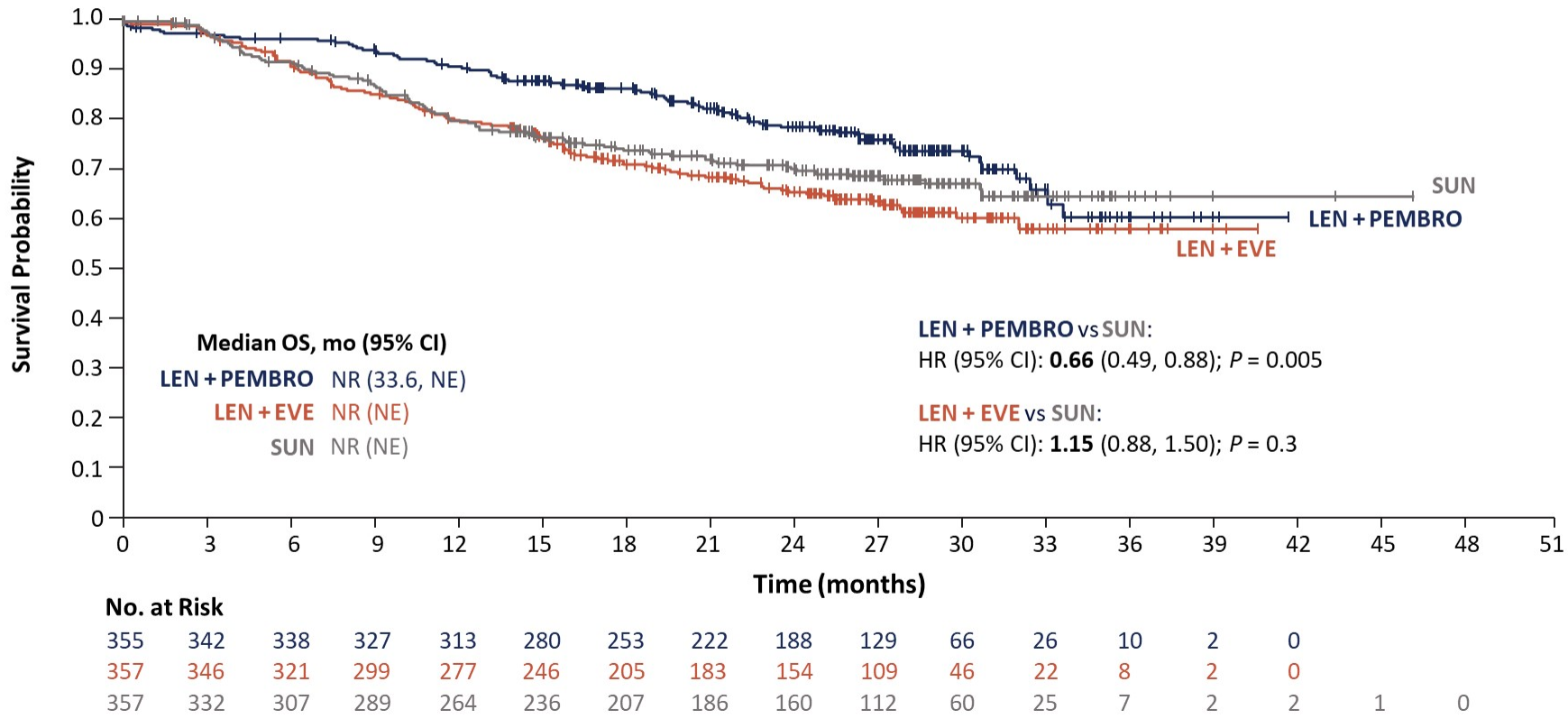
*Patients could receive a maximum of 35 pembrolizumab treatments.
DOR, duration of response; HRQoL, Health-related quality of life; IRC, Independent Review Committee; MKSCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate; OS, overall survival; R, randomization.

Progression-free Survival*



*By Independent Review Committee per RECIST v1.1.

Overall Survival



No. at Risk

355	342	338	327	313	280	253	222	188	129	66	26	10	2	0	
357	346	321	299	277	246	205	183	154	109	46	22	8	2	0	
357	332	307	289	264	236	207	186	160	112	60	25	7	2	2	1	0

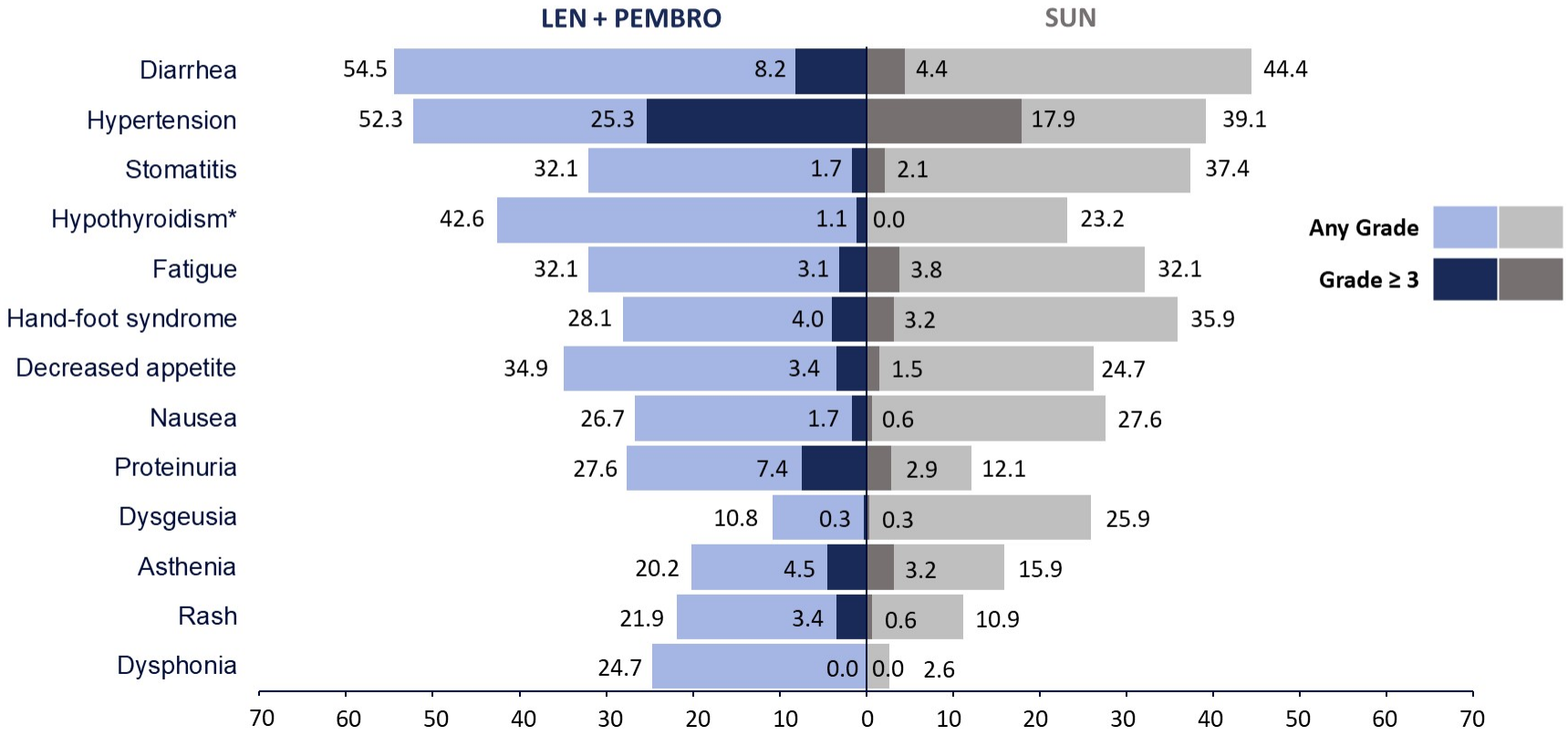
NE, not estimable; NR, not reached.

Confirmed Objective Response Rate*

	LEN + PEMBRO (n = 355)	LEN + EVE (n = 357)	SUN (n = 357)
Objective response rate (95% CI) — %	71.0 (66.3–75.7)	53.5 (48.3–58.7)	36.1 (31.2–41.1)
Best overall response — %			
Complete response	16.1	9.8	4.2
Partial response	54.9	43.7	31.9
Stable disease	19.2	33.6	38.1
Progressive disease	5.4	7.3	14.0
Unknown / not evaluable	4.5	5.6	11.8
Relative risk versus SUN (95% CI)	1.97 (1.69–2.29)	1.48 (1.26–1.74)	--
P-value	< 0.001	< 0.001	--

*By Independent Review Committee per RECIST v1.1.

TRAEs With Frequency ≥ 20%



Alanine aminotransferase/aspartate aminotransferase increased in 9.7/9.4% (grade 3: 3.1/2.6%) of patients in the LEN + PEMBRO arm and 8.8/8.8% of patients (grade 3: 1.8/0.6%) in the SUN arm.
*Adverse event of interest for pembrolizumab.

VIRTUAL 2020 ESMO congress

Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial

Toni K. Choueiri,[1] Thomas Powles,[2] Mauricio Burotto,[3] Maria T. Bourlon,[4] Bogdan Zurawski,[5] Víctor Manuel Oyervides Juárez,[6] James J. Hsieh,[7] Umberto Basso,[8] Amishi Y. Shah,[9] Cristina Suarez,[10] Alketa Hamzaj,[11] Carlos Barrios,[12] Martin Richardet,[13] David Pook,[14] Yoshihiko Tomita,[15] Bernard Escudier,[16] Joshua Zhang,[17] Burcin Simsek,[17] Andrea B. Apolo,[18] Robert J. Motzer[19]

[1]Dana-Farber Cancer Institute, The Lank Center for Genitourinary Oncology, Boston, MA, USA; [2]Barts Cancer Institute, Queen Mary University of London, Royal Free NHS Trust, London, UK; [3]Bradford Hill Clinical Research Center, Santiago, Chile; [4]Urologic Oncology Clinic, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [5]Professor Franciszek Lukaszczyk Oncology Centre, Bydgoszcz, Poland; [6]Centro Universitario contra el Cáncer Hospital Universitario "Dr. José Eleuterio González" Universidad Autónoma de Nuevo León, Nuevo León, Mexico; [7]Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO, USA; [8]Istituto Oncologico Veneto IOV IRCCS, Padova, Italy; [9]MD Anderson Cancer Center, Houston, TX, USA; [10]Vall d'Hebron Institute of Oncology, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [11]Ospedale San Donato, Istituto Toscano Tumori, Arezzo, Italy; [12]Oncology Research Center, Hospital São Lucas, PUCRS, Porto Alegre, Brazil; [13]Fundacion Richardet Longo, Instituto Oncologico de Cordoba, Cordoba, Argentina; [14]Cabrini Monash University Department of Medical Oncology, Cabrini Health, Malvern, VIC, Australia; [15]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [16]Gustave Roussy, Villejuif, France; [17]Bristol Myers Squibb, Princeton, NJ, USA; [18]Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; [19]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Presentation Number 696O

Choueiri TK et al NEJM 2021;384:829-841

CheckMate 9ER: Study design

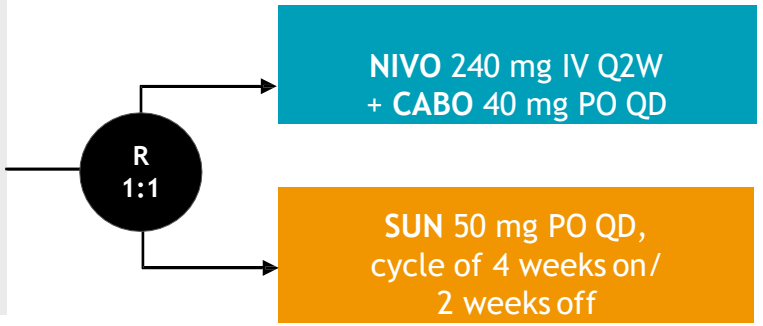
N = 651

Key inclusion criteria[1,2]

- Previously untreated advanced or metastatic RCC
- Clear cell component
- Any IMDC risk group

Stratification factors:

- IMDC risk score
- Tumor PD-L1 expression[a]
- Geographic region



Treat until RECIST v1.1–defined progression or unacceptable toxicity[b]

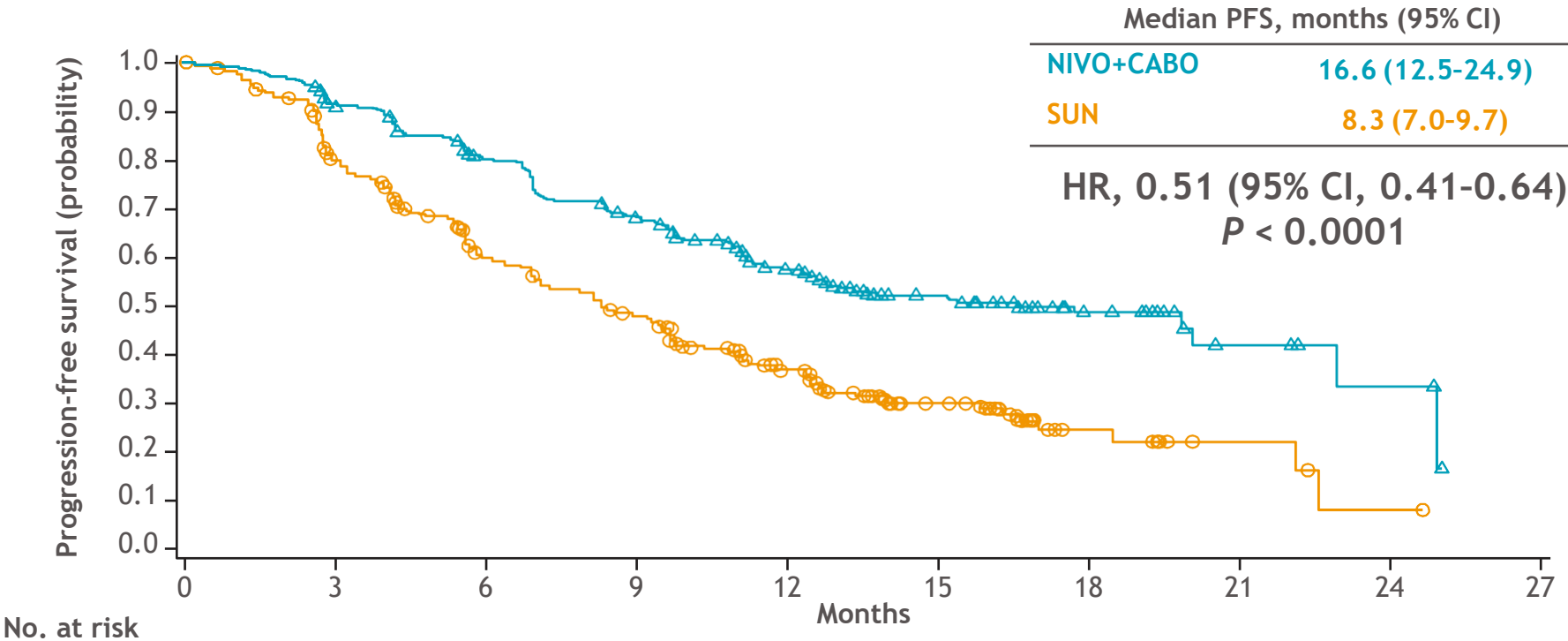
Median study follow-up, 18.1 months (range, 10.6–30.6 months)

Primary endpoint: PFS

Secondary endpoints: OS, ORR, and safety

[a]Defined as the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry 28-8 pharmDx assay.
[b]NIVO dosing may not exceed a total of 2 years (from cycle 1); CABO and SUN treatment may continue beyond 2 years in the absence of progression or unacceptable toxicity. Patients may be treated beyond progression.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IV, intravenously; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; PO, orally; Q2W, every 2 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.
1. Clinicaltrials.gov/ct2/show/NCT03141177. Accessed June 8, 2020; 2. Choueiri TK et al. Poster presented at the American Society of Clinical Oncology Annual Meeting 2018. TPS4598.

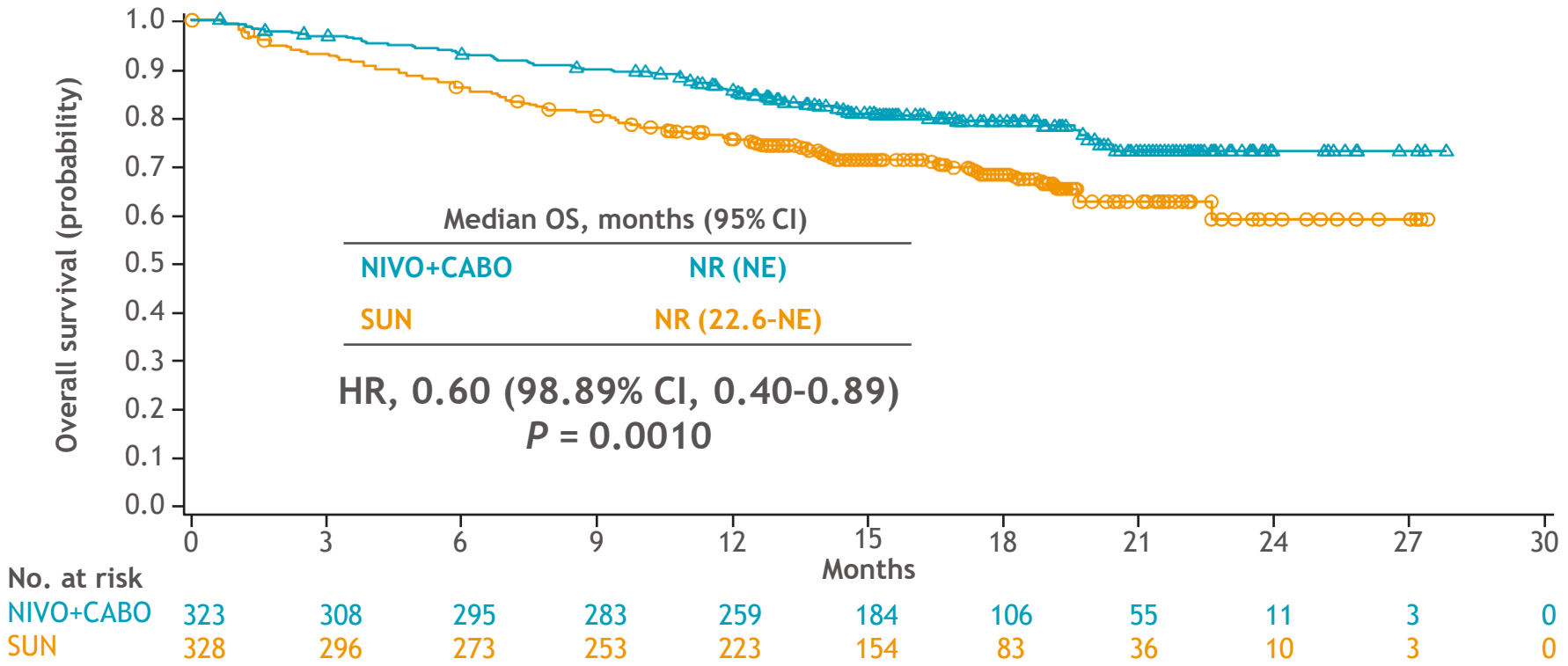
Progression-free survival per BICR



No. at risk										
NIVO+CABO	323	279	234	196	144	77	35	11	4	0
SUN	328	228	159	122	79	31	10	4	1	0

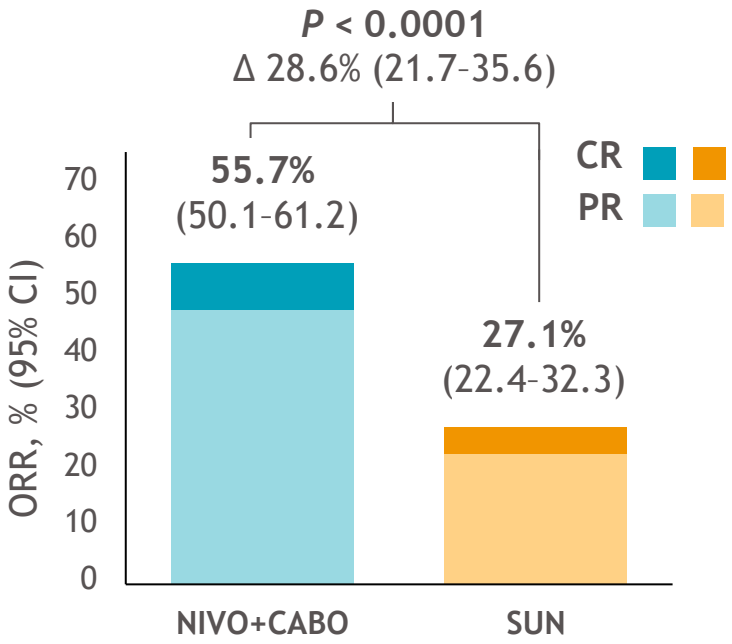
Minimum study follow-up, 10.6 months.

Overall survival



Minimum study follow-up, 10.6 months.
NE, not estimable; NR, not reached.

Objective response and best overall response per BICR



Outcome, %	NIVO+CABO (n = 323)	SUN (n = 328)
Complete response	8.0	4.6
Partial response	47.7	22.6
Stable disease	32.2	42.1
Progressive disease	5.6	13.7
Not evaluable/not assessed[a]	6.5	17.1
Median time to response (range), months[b]	2.8 (1.0–19.4)	4.2 (1.7–12.3)
Median duration of response (95% CI), months[b]	20.2 (17.3–NE)	11.5 (8.3–18.4)

- ORR favored NIVO+CABO over SUN across subgroups including by IMDC risk status, tumor PD-L1 expression (≥ 1% vs < 1%), and bone metastases

BICR-assessed ORR and BOR by RECIST v1.1.
[a]Includes patients who were never treated, those who discontinued/died before disease assessment, those without measurable disease at baseline per BICR, or other reason not reported/specified; [b]Median time to and duration of response were calculated for patients who had a complete or partial response (n = 180 with NIVO+CABO, n = 89 patients with SUN).

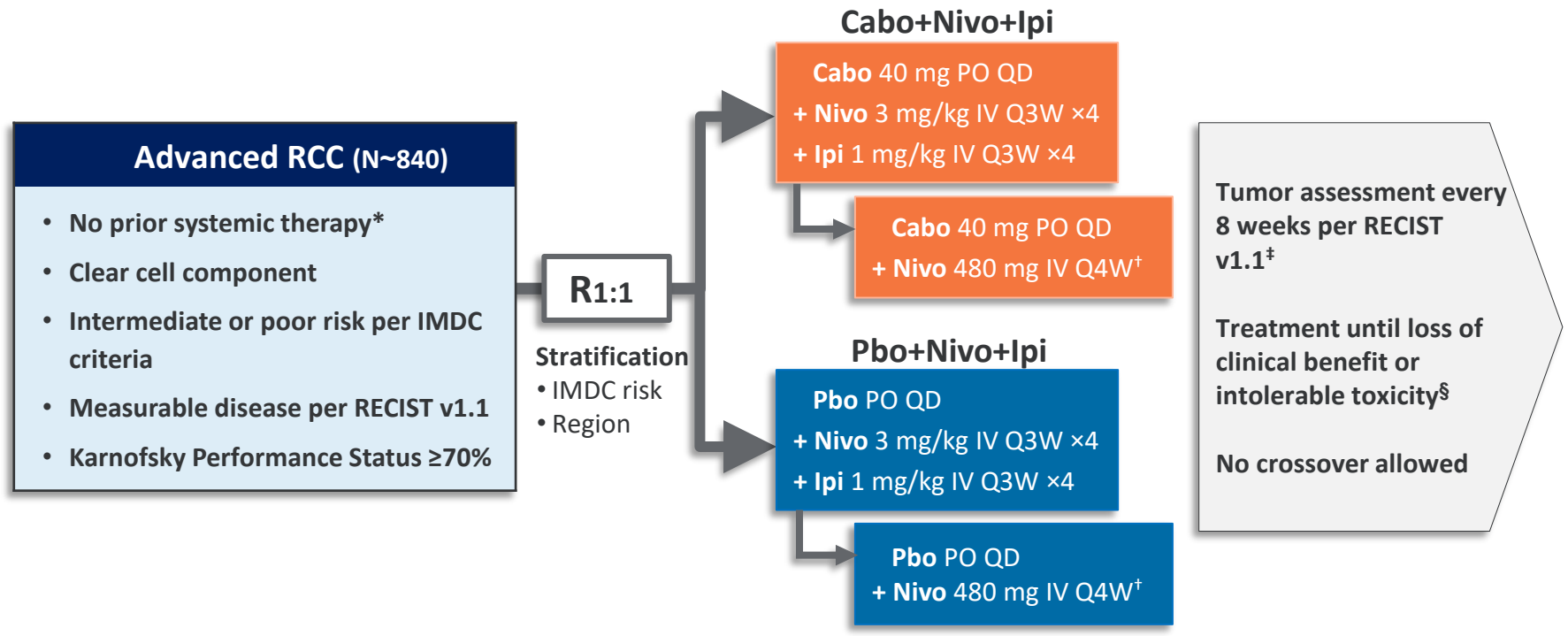
PARIS 2022 ESMO congress

Phase 3 study of cabozantinib in combination with nivolumab and ipilimumab in previously untreated advanced renal cell carcinoma of IMDC intermediate or poor risk (COSMIC-313)

Toni K. Choueiri,[1] Thomas Powles,[2] Laurence Albiges,[3] Mauricio Burotto,[4] Cezary Szczylik,[5] Bogdan Zurawski,[6] Eduardo Yanez Ruiz,[7] Marco Maruzzo,[8] Alberto Suarez Zaizar,[9] Luis Enrique Fein,[10] Fabio A. Schutz,[11] Daniel Y.C. Heng,[12] Fong Wang,[13] Fabio Mataveli,[13] Yu-Lin Chang,[13] Maximiliano van Kooten Losio,[14] Cristina Suarez,[15] Robert J. Motzer[16]

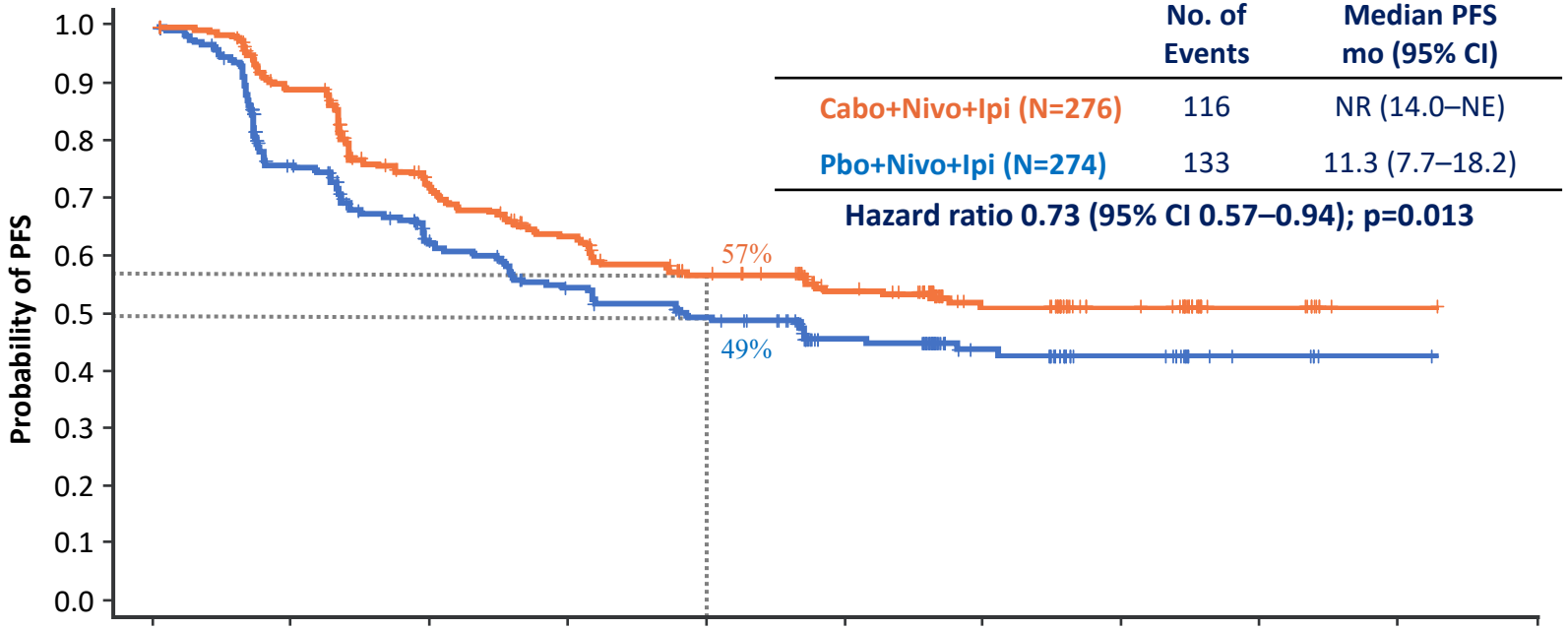
[1]Dana–Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA; [2]Barts Cancer Institute, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, Royal Free National Health Service Trust, London, UK; [3]Institut Gustave Roussy, Université Paris Saclay, Villejuif, France; [4]Bradford Hill Clinical Research Center, Santiago, Chile; [5]European Health Centre, Otwock, Warsaw, Poland; [6]Professor Franciszek Lukaszczyk Oncology Center, Bydgoszcz, Poland; [7]James Lind Centro de Investigacion del Cancer, Temuco, Chile; [8]Oncology Unit 1, Department of Oncology, Istituto Oncologico Veneto IOV - IRCCS, Padua, Italy; [9]Consultorio de Medicina Especializada Dentro de Condominio San Francisco, Benito Juarez, Mexico City, Mexico; [10]Instituto de Oncologia de Rosario, Rosario, Argentina; [11]Beneficência Portuguesa de Sao Paulo, Sao Paulo, Brazil; [12]Tom Baker Cancer Center, University of Calgary, Calgary, Alberta, Canada; [13]Exelixis, Inc., Alameda, CA, USA; [14]Bristol Myers Squibb, Boudry, Neuchâtel, Switzerland; [15]Vall d'Hebron Institute of Oncology, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [16]Memorial Sloan Kettering Cancer Center, New York, NY, USA

COSMIC-313 Study Design



*One prior systemic adjuvant therapy allowed for completely resected RCC and if recurrence occurred ≥6 months after the last dose of adjuvant therapy; adjuvant PD-1 or PD-L1 inhibitor in combination with a CTLA-4 inhibitor not permitted. †Nivolumab given for a maximum of 2 years. ‡Tumor assessment (RECIST v1.1) at week 10, then every 8 weeks through week 50, then every 12 weeks thereafter. §Discontinuation of one agent did not mandate discontinuation of all agents.

Progression-Free Survival: Final Analysis (PITT Population)



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=276)	116	NR (14.0–NE)
Pbo+Nivo+Ipi (N=274)	133	11.3 (7.7–18.2)

Hazard ratio 0.73 (95% CI 0.57–0.94); p=0.013

Number at Risk											
Cabo+Nivo+Ipi	276	234	170	145	119	97	56	33	10	1	0
Pbo+Nivo+Ipi	274	185	136	115	98	69	37	19	5	1	0

PFS per RECIST v1.1 by BIRC.

Date of the 249th event: Aug 23, 2021

Toni K. Choueiri

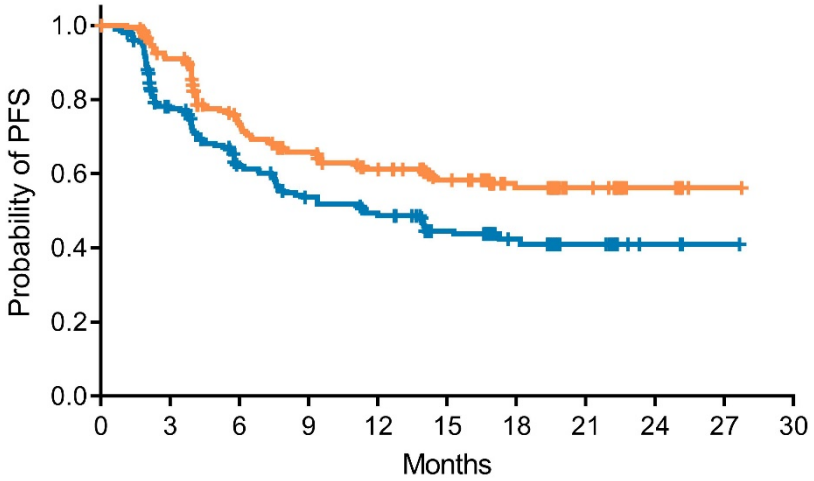
Tumor Response (PITT Population)

	Cabo+Nivo+Ipi (N=276)	Pbo+Nivo+Ipi (N=274)
Objective response rate (95% CI), %	43 (37.2–49.2)	36 (30.1–41.8)
Best overall response, n (%)		
Complete response	7 (3)	9 (3)
Partial response	112 (41)	89 (32)
Stable disease	119 (43)	100 (36)
Progressive disease	23 (8)	55 (20)
Not evaluable	15 (5)	21 (8)
Disease control rate, %	86	72
Median time to objective response (range), mo	2.4 (1.5–17.1)	2.3 (1.9–16.8)
Median duration of response (95% CI), mo	NR (20.2–NE)	NR (NE–NE)

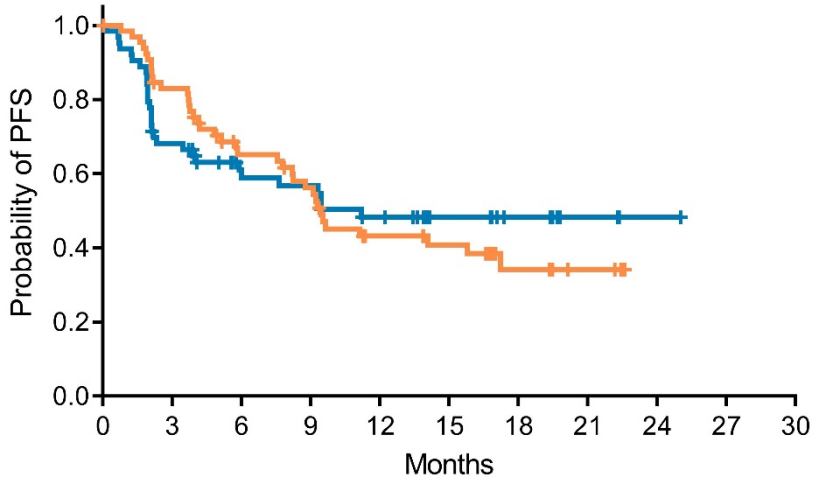
Tumor response per RECIST v1.1 by BIRC
Disease control rate = complete response + partial response + stable disease

Data cut-off: Jan 31, 2022

PFS by IMDC Risk Group (PITT Population)



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=209)	79	NR (16.9–NE)
Pbo+Nivo+Ipi (N=208)	103	11.4 (7.6–17.3)



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=67)	37	9.5 (7.8–17.3)
Pbo+Nivo+Ipi (N=66)	30	11.2 (4.0–NE)

PFS and ORR per RECIST v1.1 by BIRC. IMDC risk group is per IxRS.

Date of the 249th PFS event: Aug 23, 2021
Data cut-off for ORR: Jan 31, 2022

Summary of Adverse Events (Safety Population)

	Cabo+Nivo+Ipi (N=426)		Pbo+Nivo+Ipi (N=424)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse events				
Any event,* %	99	73	91	41
Alanine aminotransferase increased	46	26	17	6
Aspartate aminotransferase increased	44	20	16	5
Diarrhea	41	4	18	3
Palmar-plantar erythrodysesthesia	28	3	4	0
Hypothyroidism	24	<1	15	0
Hypertension	23	8	5	2
Fatigue	22	2	21	1
Lipase increased	22	9	13	6
Amylase increased	20	5	12	2
Rash	20	2	20	1
Pruritus	20	0	26	<1

*Occurring in ≥20% of either treatment group.

Data cut-off: Jan 31, 2022

First Line RCC Comments

- Increasing number of regimens
  - Ipi/Nivo
  - Axi/Pembro
  - Axi/Avelumab
  - Cabo/Nivo
  - Levatinib/Pembro
- Triplet Therapy? Cabo/Ipi/Nivo?

Thank You

- Happy to answer questions

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