Year in Review

A Multitumor Regional Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Saturday, January 11, 2020, 8:00 AM – 4:00 PM
Houston, Texas

Faculty

Tanios Bekaii-Saab, MD
Johanna Bendell, MD
Bruce D Cheson, MD
Robert L Coleman, MD
Charles G Drake, MD, PhD
Harry P Erba, MD, PhD
Erika Hamilton, MD
Sara Hurvitz, MD
Mark Levis, MD, PhD
Stephen V Liu, MD, PhD
Kathleen Moore, MD
Loretta Nastoupil, MD
William K Oh, MD
Philip A Philip, MD, PhD, FRCP
Gregory J Riely, MD, PhD
Sonali M Smith, MD

Moderator

Neil Love, MD

Research To Practice®

Agenda

Module 1 — Lymphomas and Chronic Lymphocytic Leukemia: *Drs Cheson, Nastoupil and Smith*

Module 2 — Breast Cancer: *Drs Hamilton and Hurvitz*

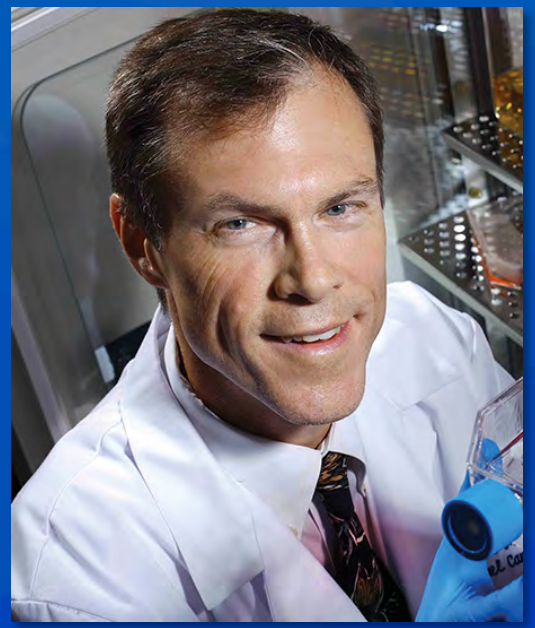
Module 3 — Acute Leukemias: *Drs Erba and Levis*

Module 4 — Gastrointestinal Cancers: *Drs Bekaii-Saab, Bendell and Philip*

Module 5 — Genitourinary Cancers: *Drs Drake and Oh*

Module 6 — Lung Cancer: *Drs Liu and Riely*

Module 7 — Gynecologic Cancers: *Drs Coleman and Moore*



Charles G Drake, MD, PhD
Professor of Medicine
Director, Genitourinary Oncology
Co-Director, Cancer Immunotherapy
Columbia University Medical Center
New York, New York

Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Compugen Inc, F-star Biotechnology Limited, Genentech, Genocea Biosciences Inc, Janssen Biotech Inc, Kleo Pharmaceuticals, Merck, Merck Serono, Pfizer Inc, Pierre Fabre, Roche Laboratories Inc, Shattuck Labs, Tizona Therapeutics Inc, UroGen Pharma, Werewolf Therapeutics
Patents (held by Johns Hopkins University)	Bristol-Myers Squibb Company, Janssen Biotech Inc
Stock Ownership	Compugen Inc, Harpoon Therapeutics, Kleo Pharmaceuticals, Tizona Therapeutics Inc, UroGen Pharma, Werewolf Therapeutics

William K Oh, MD
Chief, Division of Hematology and
Medical Oncology
Professor of Medicine and Urology
Ezra M Greenspan, MD Professor in Clinical
Cancer Therapeutics
Icahn School of Medicine at Mount Sinai
Associate Director of Clinical Research
The Tisch Cancer Institute
Mount Sinai Health System
New York, New York

Disclosures

Consulting Agreements	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, Sanofi Genzyme, Sema4, TeneoBio

Genitourinary Cancers — Drs Drake and Oh

Urothelial Bladder Cancer

Prostate Cancer

Renal Cell Carcinoma

FDA Approves Pembrolizumab for BCG-Unresponsive, High-Risk Non-Muscle Invasive Bladder Cancer

Press Release – January 8, 2020

"The Food and Drug Administration approved pembrolizumab for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

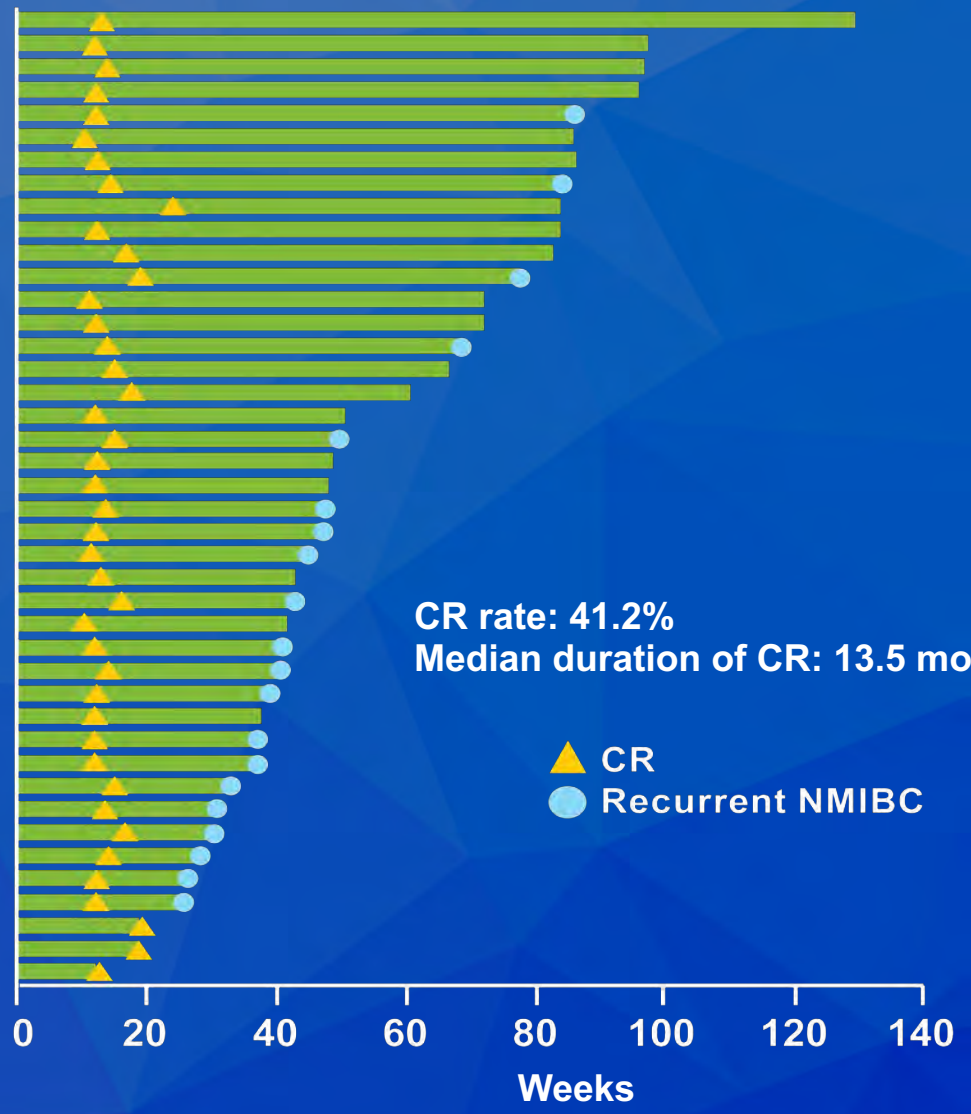
Efficacy was investigated in KEYNOTE-057 (NCT, a multicenter, single-arm trial that enrolled 148 patients with high-risk NMIBC, 96 of whom had BCG-unresponsive CIS with or without papillary tumors. Patients received pembrolizumab 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC or progressive disease, or up to 24 months of therapy without disease progression."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-bcg-unresponsive-high-risk-non-muscle-invasive-bladder-cancer

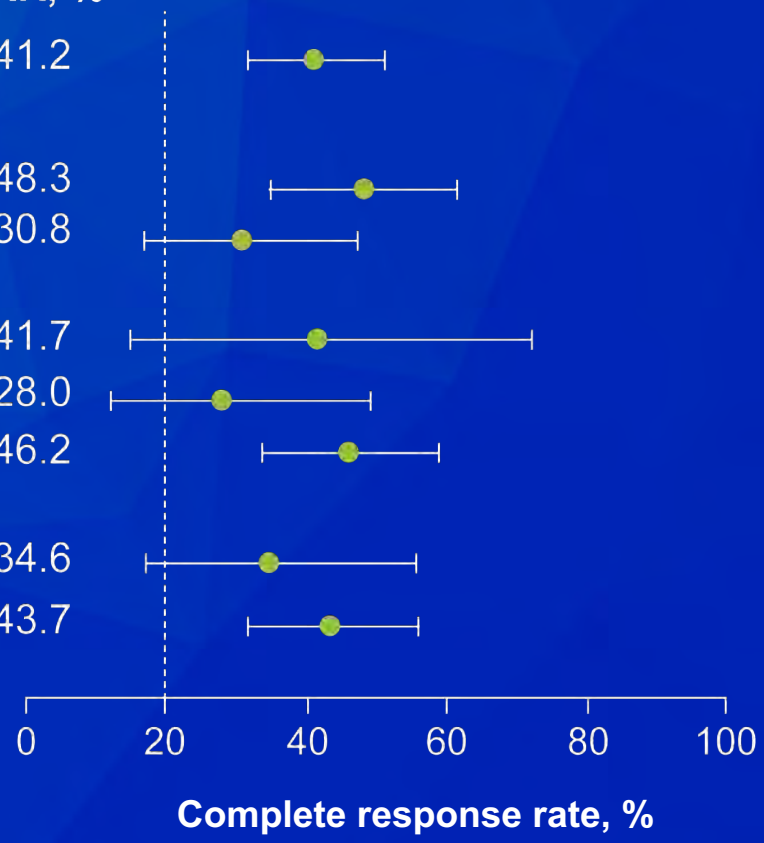
Pembrolizumab (Pembro) for Patients (Pts) with High-Risk (HR) Non-Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guérin (BCG): Updated Follow-Up from KEYNOTE-057

de Wit R et al.
Proc ASCO 2019;Abstract 4530.

KEYNOTE-057: Complete Response Rate to Pembrolizumab



	n/N	CRR, %
Overall	42/102	41.2
PD-L1 status		
PD-L1- (CPS <10)	28/58	48.3
PD-L1+ (CPS ≥10)	12/39	30.8
Tumor pattern at study entry		
CIS with T1	5/12	41.7
CIS with high-grade Ta	7/25	28.0
CIS	30/65	46.2
Baseline disease status		
Persistent HR NMIBC	9/26	34.6
Recurrent HR NMIBC	31/71	43.7



de Wit R et al. *Proc ASCO* 2019;Abstract 4530. *Proc ESMO* 2019;Abstract 916P.

FDA Approval Summary: Atezolizumab or Pembrolizumab for the Treatment of Patients with Advanced Urothelial Carcinoma Ineligible for Cisplatin-Containing Chemotherapy

Suzman DL et al.
Oncologist 2019;24(4):563-9.

FDA Limits the Use of Atezolizumab and Pembrolizumab for Some Patients with Urothelial Cancer

Press Release – July 5, 2018

"FDA has limited the use of atezolizumab and pembrolizumab for patients with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing therapy. The Agency took this action on June 19, 2018, due to decreased survival associated with the use of pembrolizumab or atezolizumab as single therapy (monotherapy) compared to platinum-based chemotherapy in clinical trials to treat patients with metastatic urothelial cancer who have not received prior therapy and who have low expression of the protein programmed death ligand 1 (PD-L1).

The labels of both drugs have been revised to reflect the limitation in the indication:

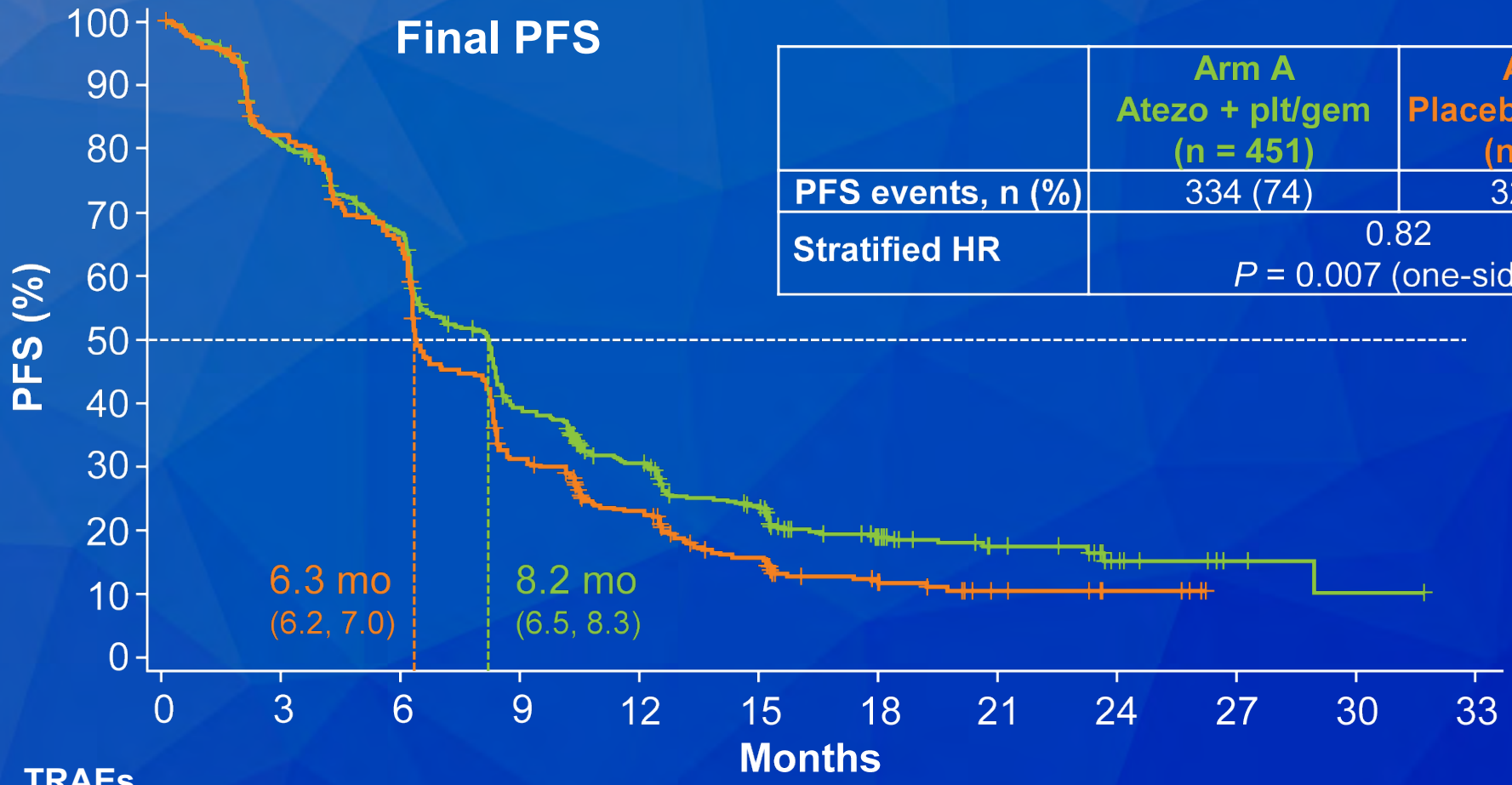
- **Pembrolizumab** is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing therapy and whose tumors express PD-L1 (Combined Positive Score ≥10), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.
- **Atezolizumab** is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
  - Are not eligible for cisplatin-containing therapy, and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥5% of the tumor area), as determined by an FDA-approved test, or
  - Are not eligible for any platinum-containing therapy regardless of PD-L1 status."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-limits-use-tecentriq-and-keytruda-some-urothelial-cancer-patients

IMvigor130: A Phase III Study of Atezolizumab with or without Platinum-Based Chemotherapy in Previously Untreated Metastatic Urothelial Carcinoma

Grande E et al.
Proc ESMO 2019;Abstract LBA14.

IMvigor130: Platinum-Based Chemotherapy with and without Atezolizumab for Previously Untreated Metastatic Urothelial Carcinoma



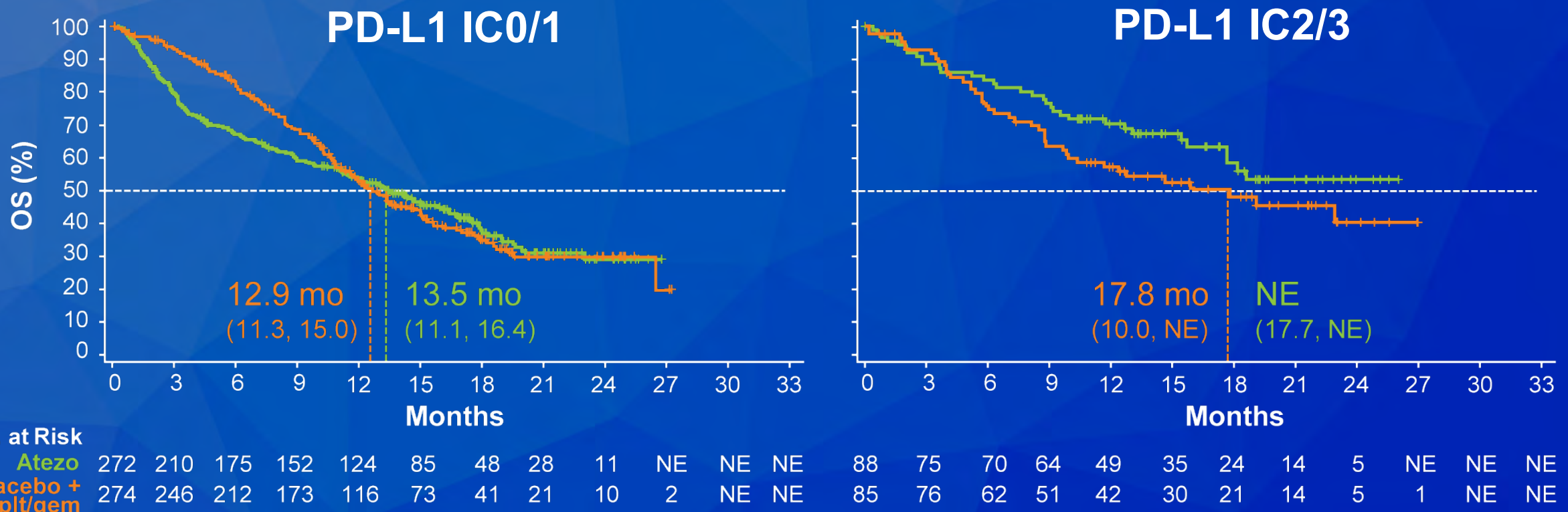
	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR	0.82 *P* = 0.007 (one-sided)	

TRAEs

- Grade ≥3: 83% in atezo + plt/gem arm (plt/gem = cisplatin or carboplatin with gemcitabine)
- Any grade leading to treatment discontinuation: 34% in atezo + plt/gem arm
- Any grade leading to any dose reduction or interruption: 80% in atezo + plt/gem arm

Grande E et al. *Proc ESMO* 2019;Abstract LBA14.

IMvigor130: Interim Overall Survival Analysis by PD-L1 Status



	Atezo (n = 272)	Placebo + plt/gem (n = 274)
OS events, n (%)	158 (58)	156 (57)
Unstratified HR	1.07	

	Atezo (n = 88)	Placebo + plt/gem (n = 85)
OS events, n (%)	33 (38)	42 (49)
Stratified HR	0.68	

Grande E et al. *Proc ESMO* 2019;Abstract LBA14.

Editorial — Dr Quinn

IMVigor 130 was presented at ESMO 2019. It tested the addition of atezolizumab to standard chemotherapy — carboplatin + gemcitabine or cisplatin + gemcitabine — and also had a single-agent atezo arm to compare directly to chemotherapy.

The trial was amended at the end of its accrual based on information the FDA received from the DSMC of this trial and the similar KEYNOTE-361 trial, which incorporated pembrolizumab as the IO.

The IMVigor130 trial achieved one of its primary endpoints — PFS for addition of atezo to chemotherapy with around 2 months' improvement with addition of atezolizumab. There was a trend toward improved OS (HR 0.83), but it did not cross the statistical boundary required for early analysis in the study — further follow-up needed. Toxicity was not significantly increased by adding atezo to chemotherapy.

Editorial — Dr Quinn (continued)

In subgroup analysis, the biggest issue was selection of chemotherapy — 70% of patients go on carboplatin-based chemotherapy, including 52% of patients who were cisplatin eligible at study entry. Based on the forest plots presented, the addition of atezo to cisplatin + gemcitabine yielded a 7-8 month improvement in OS (HR 0.66) compared to no difference when atezo was added to carboplatin + gemcitabine (HR 0.91). The reasons for selection of chemotherapy for given patients will be discussed as part of an ongoing debate, but it is likely that the selection of the type of platinum drug used is important to outcomes with IO agents in UC.

In the single-agent atezo comparison with chemotherapy, patients with PD-L1 high (IC2/3) disease look to benefit from IO over chemotherapy (results still not quite mature), whereas there is no benefit for IO over chemotherapy alone in the low PD-L1-expressing population. This confirms the current agency recommendations for testing for PD-L1 expression in patients who are cisplatin ineligible.

Ongoing Phase III Studies of ICIs in Untreated, Metastatic Urothelial Carcinoma

- **CheckMate 901** (NCT03036098): Nivolumab Combined with Ipilimumab, or with Standard of Care Chemotherapy, versus Standard of Care Chemotherapy
- **KEYNOTE-361** (NCT02853305): Pembrolizumab with or without Platinum-Based Combination Chemotherapy versus Chemotherapy
- **LEAP-011** (NCT03898180): Pembrolizumab in Combination with Lenvatinib versus Pembrolizumab and Placebo in Cisplatin-Ineligible Participants Whose Tumors Express PD-L1, and in Participants Ineligible for Any Platinum-containing Chemotherapy Regardless of PD-L1 Expression
- **DANUBE** (NCT02516241): Durvalumab Monotherapy and Durvalumab in Combination with Tremelimumab versus Standard-of-Care Chemotherapy
- **NILE** (NCT03682068): Durvalumab in Combination with Standard-of-Care Chemotherapy versus Durvalumab in Combination with Tremelimumab and Standard-of-Care Chemotherapy versus Standard-of-Care Chemotherapy Alone

www.clinicaltrials.gov. Accessed January 2020.

Editorial — Dr Quinn

CM901 — accrual complete — examines Nivo + Ipi either with chemotherapy or alone compared to standard chemotherapy in first-line UC.

LEAP-011 — accrual ongoing — tests the addition of lenvatinib to pembrolizumab in the first line for cisplatin-ineligible patients compared with pembro alone.

DANUBE — accrual complete — was the first-line trial in UC, and we have expected results for some time, now predicted in 2020. It tests the CTLA4 + PD-1 doublet of durva + treme compared to durva alone compared to chemotherapy either carboplatin or cisplatin based.

NILE — close to completing accrual — looks at IO with chemotherapy, IO+IO with chemotherapy versus chemotherapy.

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Efficacy was investigated in KEYNOTE-057 (NCT, a multicenter, single-arm trial that enrolled 148 patients with high-risk NMIBC, 96 of whom had BCG-unresponsive CIS with or without papillary tumors. Patients received pembrolizumab 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC or progressive disease, or up to 24 months of therapy without disease progression."

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Pembrolizumab (Pembro) for Patients (Pts) with High-Risk (HR) Non-Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guérin (BCG): Updated Follow-Up from KEYNOTE-057[1]

Health-Related Quality of Life (HRQoL) and Updated Follow-Up from KEYNOTE-057: Phase 2 Study of Pembrolizumab (pembro) for Patients (pts) with High-Risk (HR) Non–Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guérin (BCG)[2]

[1] de Wit R et al.
Proc ASCO 2019;Abstract 4530.

[2] de Wit R et al.
Proc ESMO 2019;Abstract 916P.

Editorial — Dr Drake

Based on the interesting single-arm response rate, approval for pembrolizumab has been sought in BCG-unresponsive bladder cancer. Of note, SOC for these patients generally involves surgery (radical cystectomy), which is poorly accepted by many patients. This study enrolled patients who either were ineligible for or refused cystectomy. Both of those criteria are generally more subjective than objective, i.e., a surgeon's conversation with a patient can greatly influence their acceptance of and interest in potentially life-sparing surgery. Single-agent pembrolizumab showed a CR rate of approximately 40% in these patients, with a safety profile consistent with that observed in multiple other settings. Approximately half of the CRs were durable for at least one year, consistent with clinical benefit in approximately 20% of treated patients. Median overall follow-up, though, was relatively short: 24 months. It is not clear whether pembrolizumab will be approved in this setting.

Editorial — Dr Drake (continued)

On the pro side, systemic treatment with anti-PD-1 may spare a fraction of patients from cystectomy, although that fraction is likely to decrease further from 20% over time. On the con side, systemic anti-PD-1 carries significant risk for systemic toxicities. Surgery, though, is not benign either. Although intravesical valrubicin is approved in this setting, the activity of that approach is far less than that of pembo. It should be noted, the single-arm studies using combination chemotherapy have reported higher response rates than pembrolizumab in this setting; for example, the CGC regimen tested in a small single-institution trial (De Castro et al, AUA 2019) showed a response rate > 90%. Overall, the treatment paradigm for BCG-unresponsive NMIBC is in flux; if anti-PD-1 is approved in this setting, it would represent a significant paradigm shift from local to systemic therapy, with a potential shift in treatment setting from urology to medical oncology.

JAVELIN Bladder 100 Study of Avelumab for Urothelial Cancer Meets Primary Endpoint

Press Release – January 6, 2020

"The phase III JAVELIN Bladder 100 trial met its primary endpoint of overall survival at the planned interim analysis. In this study, patients with previously untreated locally advanced or metastatic urothelial carcinoma whose disease did not progress on induction chemotherapy and who were randomly assigned to receive first-line maintenance therapy with avelumab and best supportive care lived significantly longer than those who received best supportive care alone.

A statistically significant improvement in overall survival was demonstrated in the avelumab arm in each of the co-primary populations: all randomly assigned patients and patients with programmed cell death ligand 1 (PD-L1)-positive tumors…The results of the study will be submitted for presentation at an upcoming medical congress and shared with the US Food and Drug Administration (FDA) and other health authorities."

https://www.ascopost.com/news/january-2020/javelin-bladder-100-study-of-avelumab-for-urothelial-cancer-meets-primary-endpoint/

FDA Grants Accelerated Approval to Erdafitinib for Metastatic Urothelial Carcinoma

Press Release – April 12, 2019

"The Food and Drug Administration granted accelerated approval to erdafitinib for patients with locally advanced or metastatic urothelial carcinoma, with susceptible FGFR3 or FGFR2 genetic alterations, that has progressed during or following platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

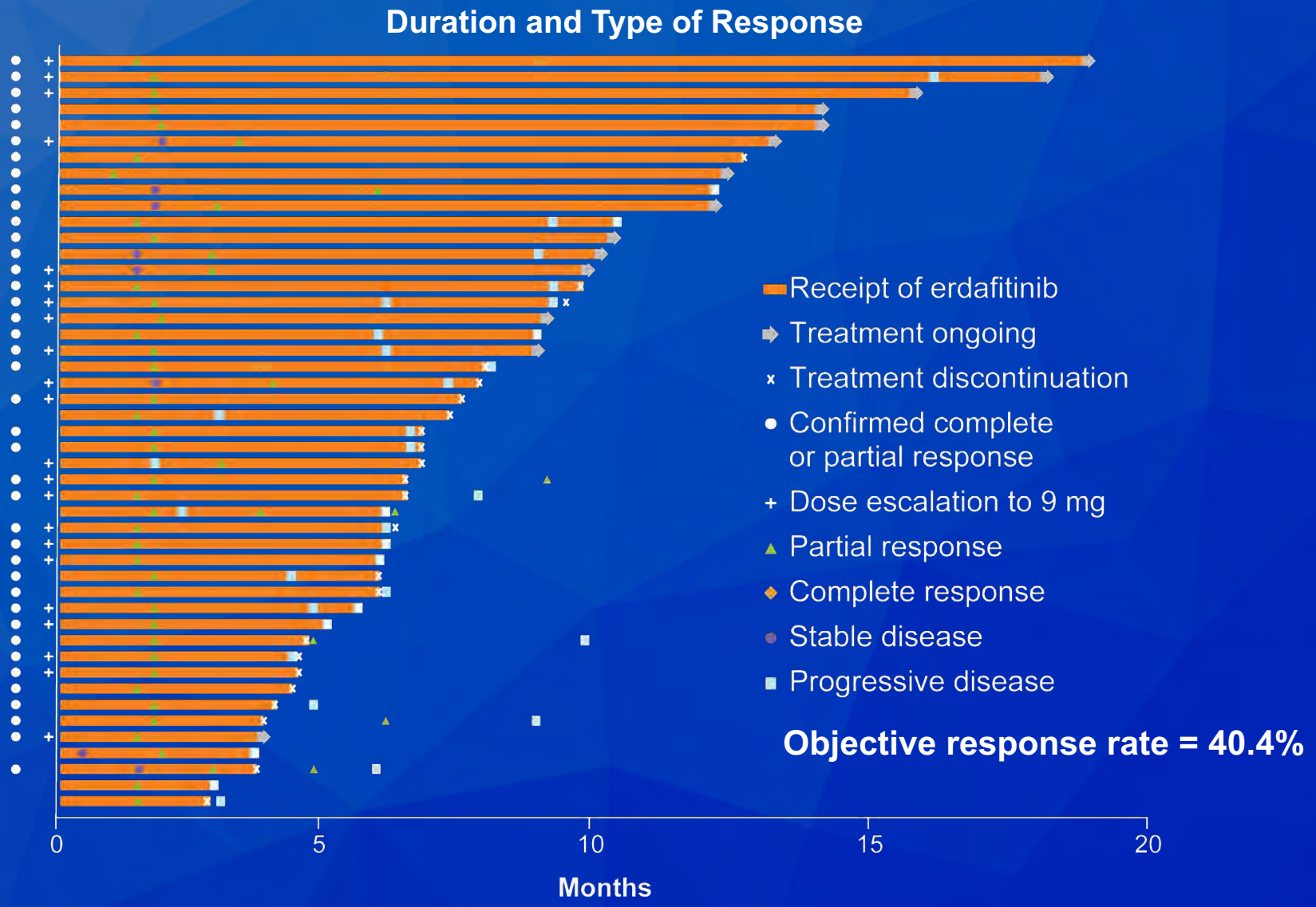
Patients should be selected for therapy based on an FDA-approved companion diagnostic for erdafitinib. Today, the FDA also approved the *therascreen*® FGFR RGQ RT-PCR Kit for use as a companion diagnostic for this therapeutic indication."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-erdafitinib-metastatic-urothelial-carcinoma

Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma

Loriot Y et al; BLC2001 Study Group.
N Engl J Med 2019;381(4):338-48.

BLC2001: Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma



Loriot Y et al; BLC2001 Study Group. *N Engl J Med* 2019;381(4):338-48.

BLC2001: Select Adverse Events with Erdafitinib

Adverse Events in the 99 Patients in the Selected-Regimen Group

Number of patients (%)	Any grade	Grade 1	Grade 2	Grade≥3
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)	0
Hand-foot syndrome	23 (23)	6 (6)	12 (12)	5 (5)
Anemia	20 (20)	9 (9)	7 (7)	4 (4)
Hematuria	10 (10)	7 (7)	1 (1)	2 (2)

Loriot Y et al; BLC2001 Study Group. *N Engl J Med* 2019;381(4):338-48.

Editorial — Dr Quinn

Erdafitinib was the first FGFr TKI to receive accelerated approval. Its indication is for mutations of translations of the FGFr3 gene in met or recurrent UC. The approval came with a companion diagnostic PCR test for FGFr3 alterations in tumor tissue, but insurers will accept other assays such as NGS assays that include FGFr3. FGFr alterations are found in 20% of UC patients; those with these alterations have a 40% response rate and high rates of sustained stable disease. Erdafitinib has side effects that include diarrhea, fatigue, skin rash, hyperphosphatemia and retinopathy.

FDA Approves New Type of Therapy to Treat Advanced Urothelial Cancer

Press Release – December 18, 2019

"The Food and Drug Administration granted accelerated approval to enfortumab vedotin-ejfv, a Nectin-4-directed antibody and microtubule inhibitor conjugate, meaning the drug specifically targets cancer cells – in this case, the cell adhesion molecule Nectin-4, which is highly expressed in urothelial cancers. Enfortumab vedotin is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor and a platinum-containing chemotherapy."

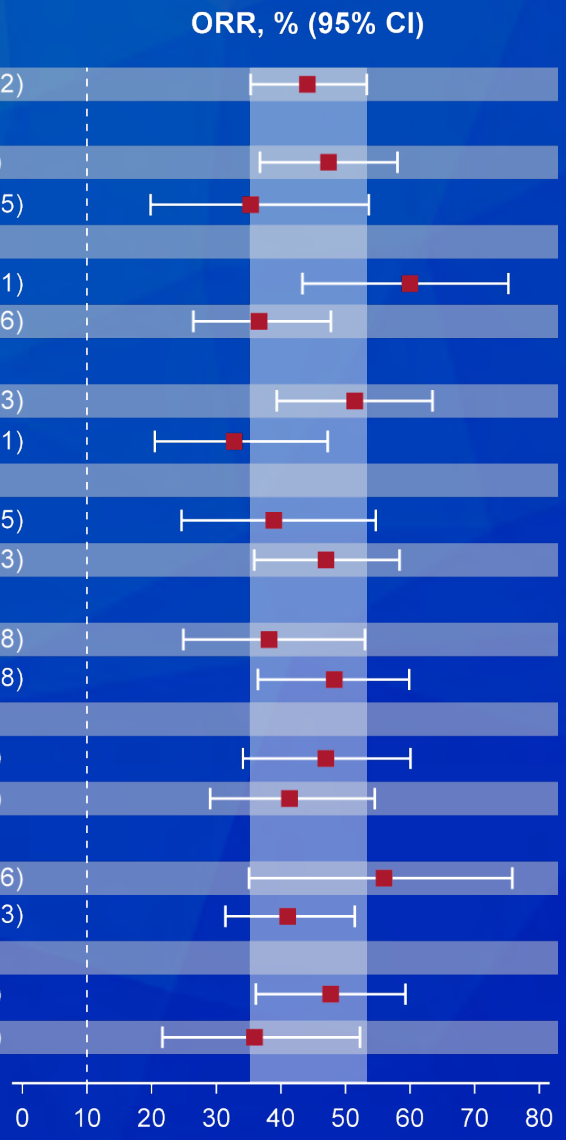
https://www.fda.gov/news-events/press-announcements/fda-approves-new-type-therapy-treat-advanced-urothelial-cancer

Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy

Rosenberg JE et al.
J Clin Oncol 2019;[Epub ahead of print].

Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-PD-1/PD-L1 Therapy: Objective Response

Subgroup	No. of Events/ No. of Patients	% (95% CI)
Overall	55/125	44 (35.1 to 53.2)
Age, years		
<75	43/91	47 (36.7 to 58)
≥75	12/34	35 (19.7 to 53.5)
ECOG performance status		
Grade 0	24/40	60 (43.3 to 75.1)
Grade 1	31/85	36 (26.3 to 47.6)
Bellmunt risk score		
0-1	37/72	51 (39.3 to 63.3)
≥2	17/52	33 (20.3 to 47.1)
Primary tumor sites		
Upper tract	17/44	39 (24.4 to 54.5)
Bladder/other	38/81	47 (35.7 to 58.3)
Liver metastasis		
Yes	19/50	38 (24.7 to 52.8)
No	36/75	48 (36.3 to 59.8)
No. of prior therapies in metastatic UC setting		
1-2	29/62	47 (34 to 59.9)
≥3	26/63	41 (29 to 54.4)
Best response to prior anti-PD-1/L1		
Responder	14/25	56 (34.9 to 75.6)
Nonresponder	41/100	41 (31.3 to 51.3)
PD-L1 expression		
CPS <10	37/78	47 (36 to 59.1)
CPS ≥10	15/42	36 (21.6 to 52)



Rosenberg JE et al. *J Clin Oncol* 2019;[Epub ahead of print].

Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-PD-1/PD-L1 Therapy: Adverse Events

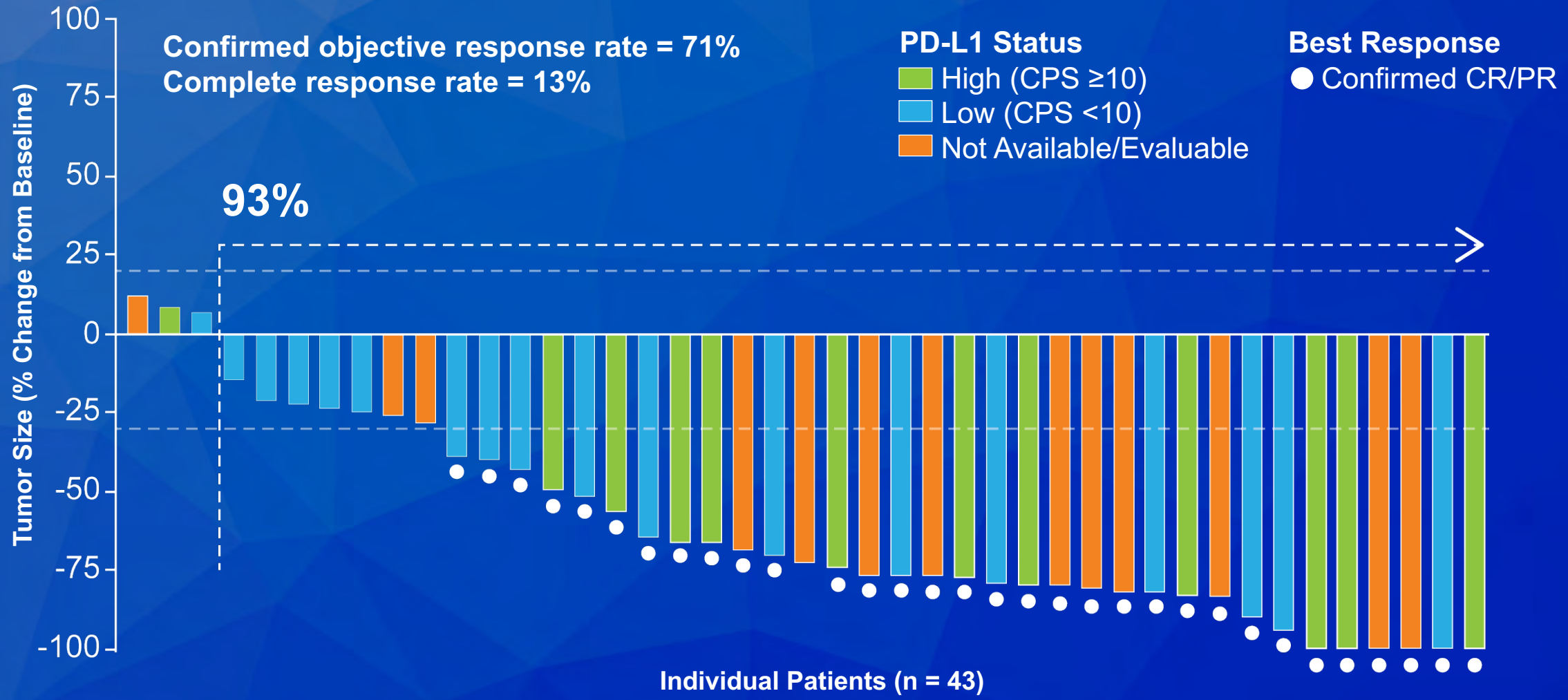
Variable	Patients (N = 125)	
Any adverse event	125 (100)	
Treatment-related adverse events	117 (94)	
Grade ≥3 treatment-related adverse events	68 (54)	
Treatment-related serious adverse events	24 (19)	
Treatment-related adverse events resulting in treatment discontinuation	15 (12)	
Treatment-related adverse events leading to death	0 (0)	
Treatment-related adverse events occurring in ≥20% (preferred term)	Any grade	Grade ≥3
Fatigue	62 (50)	7 (6)
Alopecia	61 (49)	0
Appetite decrease	55 (44)	1 (1)
Dysgeusia	50 (40)	0
Peripheral sensory neuropathy	50 (40)	2 (2)
Nausea	49 (39)	3 (2)
Diarrhea	40 (32)	3 (2)
Rash maculopapular	27 (22)	5 (4)
Weight decrease	28 (22)	1 (1)
Dry skin	28 (22)	0

Rosenberg JE et al. *J Clin Oncol* 2019;[Epub ahead of print].

EV-103: Initial Results of Enfortumab Vedotin plus Pembrolizumab for Locally Advanced or Metastatic Urothelial Carcinoma

Hoimes CJ et al.
Proc ESMO 2019;Abstract 901O.

EV-103: EV with Pembrolizumab as First-Line Therapy for Locally Advanced or Metastatic Urothelial Carcinoma



Hoimes CJ et al. *Proc ESMO* 2019;Abstract 901O.

Editorial — Dr Quinn

Enfortumab vedotin is the most potent single-agent chemotherapy we have seen for UC. It utilizes nectin-4, which is expressed on almost all urothelial cancer cells. Early clinical trials have seen it produce response rates of 40% in settings of platinum +/- CPI pretreated UC, including liver metastases. Side effects include dysgeusia, skin rash and neuropathy that may be related to cumulative dose. An application for accelerated approval is currently with the FDA. A phase III study of EV vs standard single-agent chemotherapy is accruing internationally.

Data from ESMO with EV + pembro in cisplatin-ineligible patients report an ORR of 71% but have only short follow-up.

Genitourinary Cancers — Drs Drake and Oh

Urothelial Bladder Cancer

Prostate Cancer

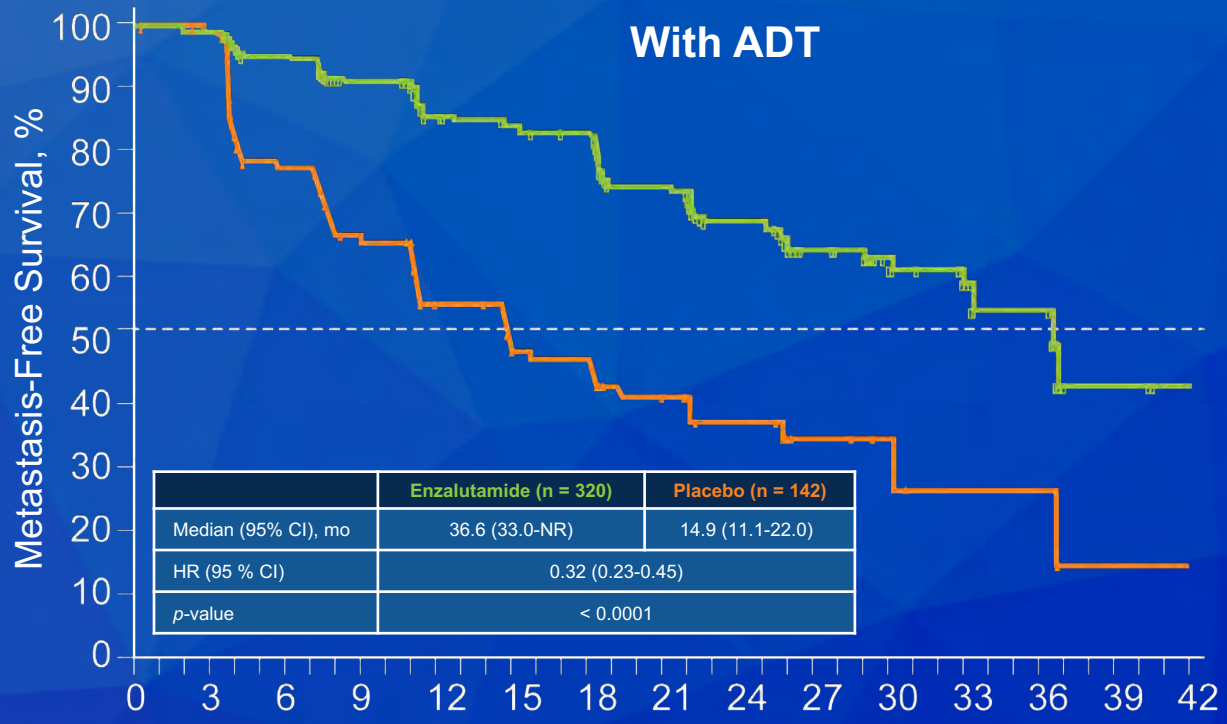
Renal Cell Carcinoma

A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Enzalutamide in Men with Nonmetastatic Castration-Resistant Prostate Cancer: Post-Hoc Analysis of PROSPER by Prior Therapy

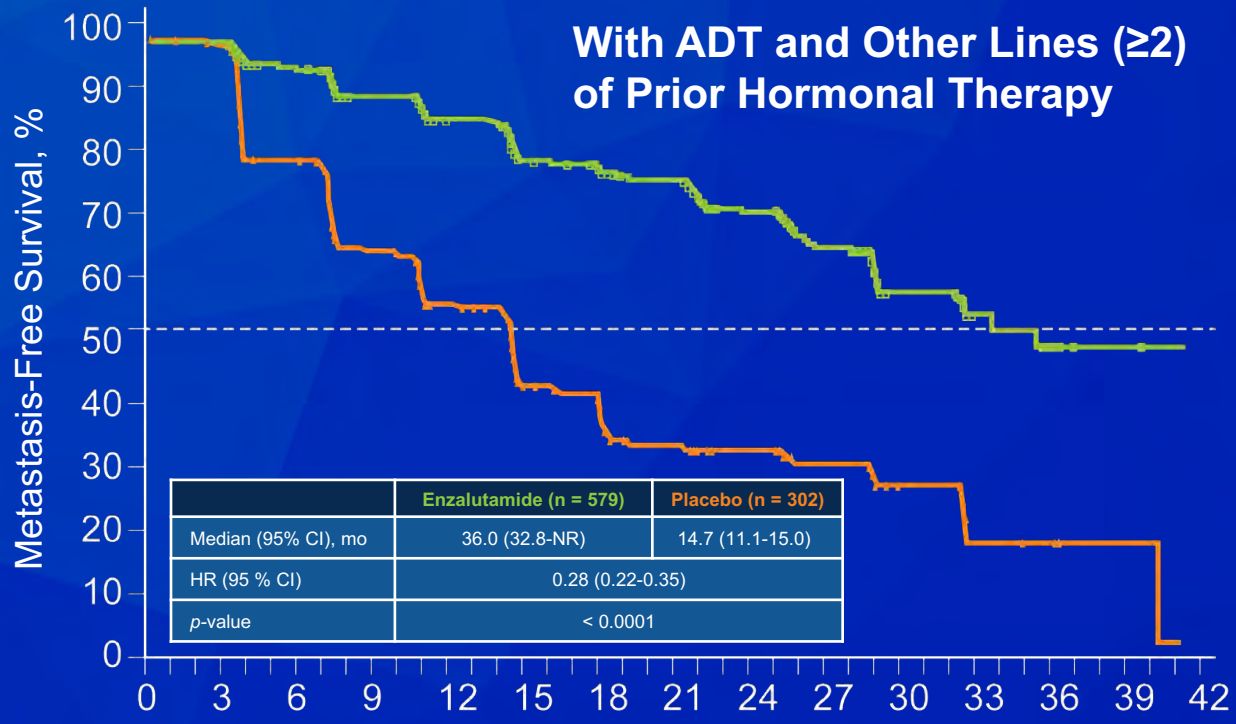
De Giorgi U et al.
Genitourinary Cancers Symposium 2019;Abstract 185.

Post-Hoc Analysis of PROSPER by Prior Lines of Therapy

- In the overall study population, enzalutamide reduced the risk of metastasis or death by 71% (HR 0.29, $p < 0.0001$).
- The median metastasis-free survival (patients who had not received prior bone-targeted therapy): 36.0 mo in the enzalutamide arm vs 14.7 mo in the placebo arm (HR = 0.29; $p < 0.0001$).
- Enzalutamide significantly reduced the risk of metastasis or death, regardless of whether patients had received ADT or ADT with other lines of hormonal therapy.



	Enzalutamide (n = 320)	Placebo (n = 142)
Median (95% CI), mo	36.6 (33.0-NR)	14.9 (11.1-22.0)
HR (95 % CI)	0.32 (0.23-0.45)	
p-value	< 0.0001	



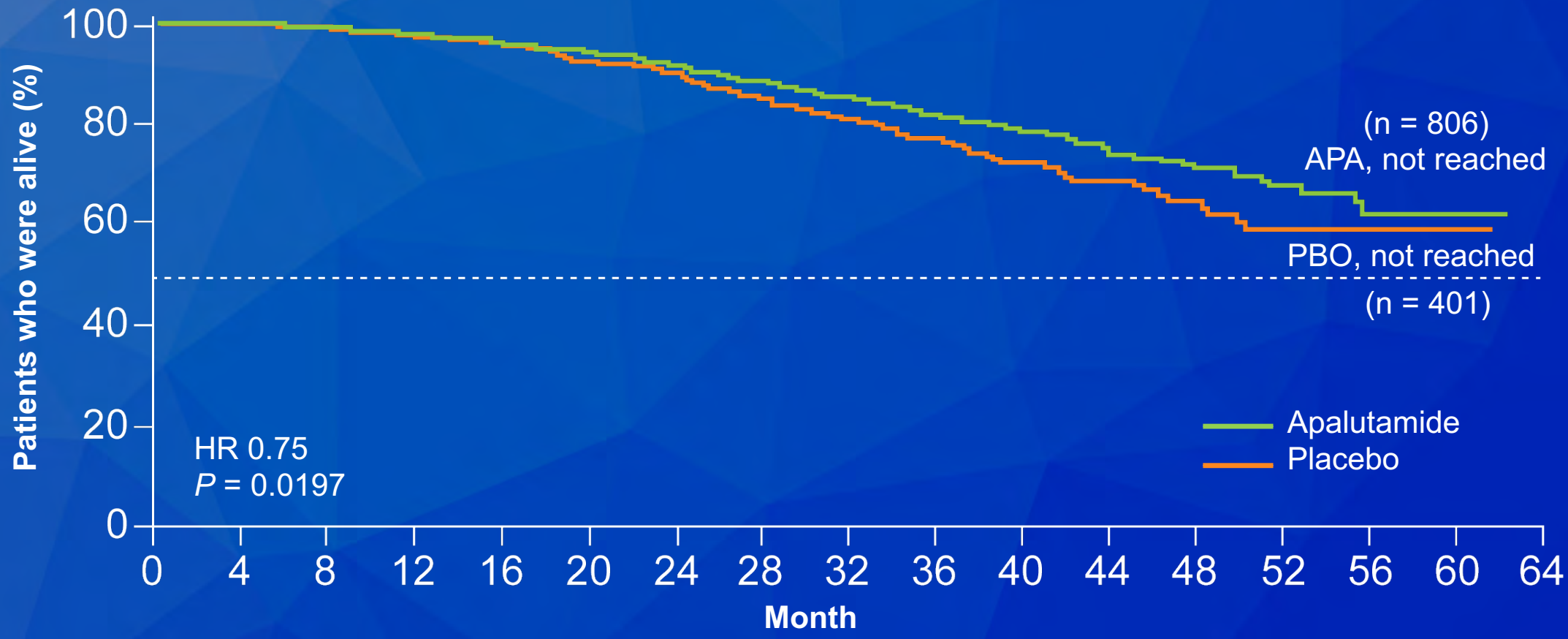
	Enzalutamide (n = 579)	Placebo (n = 302)
Median (95% CI), mo	36.0 (32.8-NR)	14.7 (11.1-15.0)
HR (95 % CI)	0.28 (0.22-0.35)	
p-value	< 0.0001	

De Giorgi U et al. Genitourinary Cancers Symposium 2019;Abstract 185.

Apalutamide and Overall Survival in Non-Metastatic Castration-Resistant Prostate Cancer

Small EJ et al.
Ann Oncol 2019;30(11):1813-20.

SPARTAN: Second Interim Analysis of Overall Survival



OS benefit observed despite crossover of placebo-treated patients and higher rates of subsequent life prolonging therapy for the placebo group

Small EJ et al. *Ann Oncol* 2019;30(11):1813-20.

Editorial — Dr Oh

PROSPER and SPARTAN led to the approval of enzalutamide and apalutamide respectively for nmCRPC based on the endpoint of MFS in patients with PSADT <10 mo. A major concern for using next-gen ART therapies in relatively asymptomatic patients without mets is that the drugs themselves could decrease QOL because of additional side effects. Tombal et al report extensive QOL data from PROSPER that convincingly demonstrates that not only do these patients maintain high HRQOL during treatment, they are less likely to experience pain and deterioration of QOL over time because metastases are delayed. In terms of prior therapies, there seems to be no effect of prior ADT, local therapy, use of BPA or other factors on the benefit from enzalutamide on MFS. A unique aspect of SPARTAN was the reporting of PFS2 (time from randomization to progression on subsequent Rx), since it addresses the question of whether apalutamide was simply delaying MFS at the expense of the next treatment.

Editorial — Dr Oh (continued)

With over 2-yr f/u, Small et al presented updated PFS2 data with HR 0.50 (0.39-0.63, $p < 0.0001$) suggesting that even with salvage Rx, apalutamide significantly delayed secondary progression or death. Waiting until mets develop appears NOT to be the best strategy.

FDA Approves Darolutamide for Nonmetastatic Castration-Resistant Prostate Cancer

Press Release – July 30, 2019

"The Food and Drug Administration approved darolutamide for non-metastatic castration-resistant prostate cancer. Approval was based on ARAMIS (NCT02200614), a multicenter, double-blind, placebo-controlled clinical trial in 1,509 patients with non-metastatic castration resistant prostate cancer. Patients were randomized (2:1) to receive either 600 mg darolutamide orally twice daily (n = 955) or matching placebo (n = 554). All patients received a gonadotropin-releasing hormone (GnRH) analog concurrently or had a previous bilateral orchiectomy. Twelve patients with previous seizure histories were treated on the darolutamide arm.

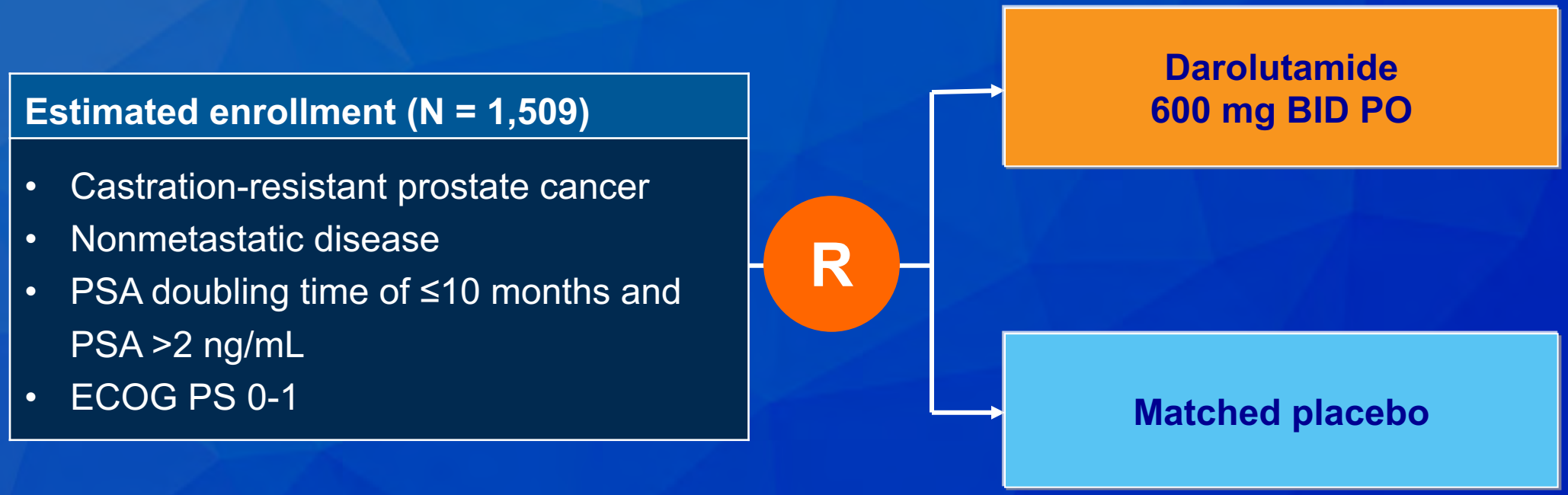
The primary endpoint was metastasis free survival (MFS), defined as the time from randomization to first evidence of distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. The median MFS was 40.4 months for patients treated with darolutamide compared with 18.4 months for those receiving placebo (hazard ratio 0.41; $p < 0.0001$). OS data were not mature."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-darolutamide-non-metastatic-castration-resistant-prostate-cancer

Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer

Fizazi K et al; ARAMIS Investigators.
N Engl J Med 2019;380(13):1235-46.

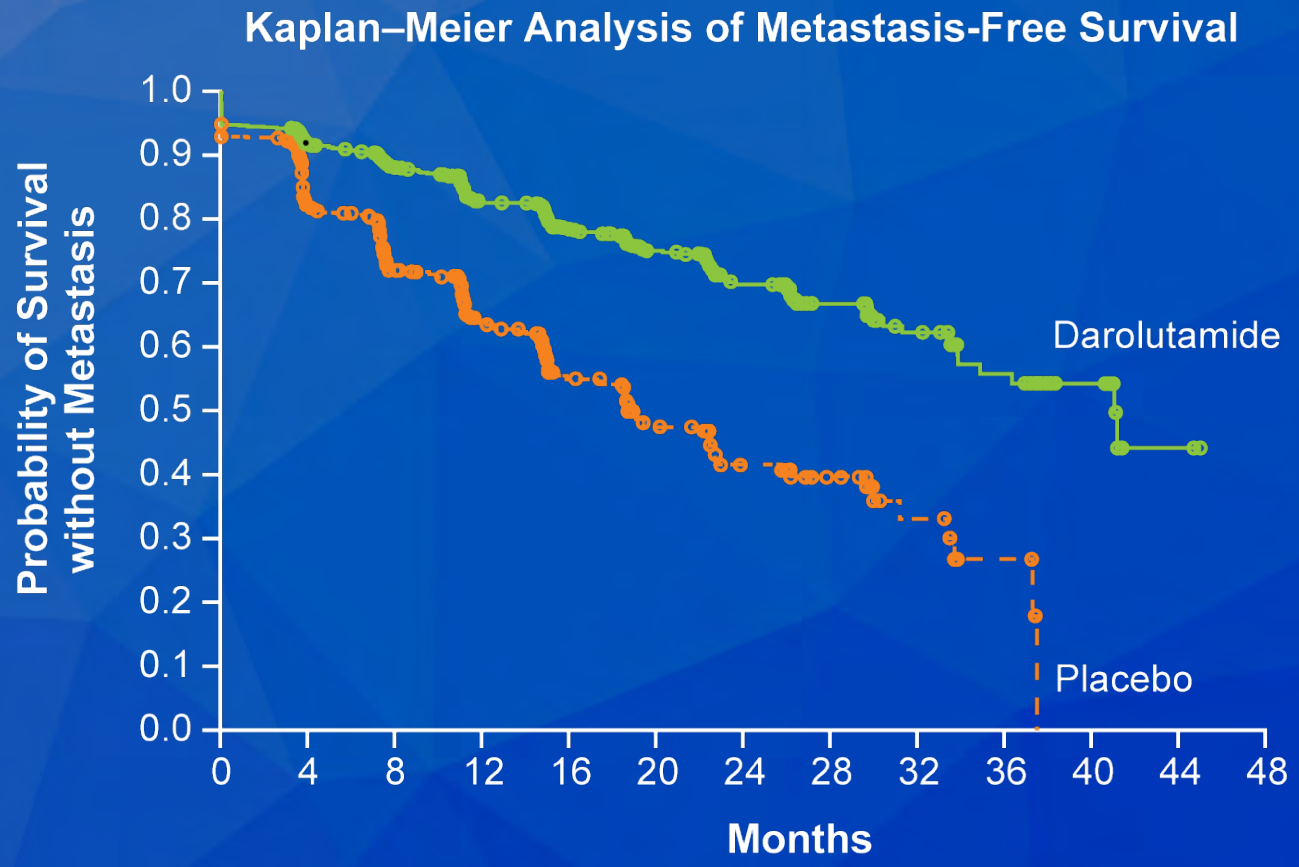
ARAMIS: A Multinational, Randomized, Double-Blind, Placebo-Controlled, Phase III Efficacy and Safety Study of Darolutamide (ODM-201) in Men with High-Risk Nonmetastatic Castration-Resistant Prostate Cancer



Primary endpoint: Metastasis-free survival

www.clinicaltrials.gov (NCT02200614). Accessed September 2019.

ARAMIS: Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer



No. at Risk												
Darolutamide	955	817	675	506	377	262	189	116	68	37	18	2	0
Placebo	554	368	275	180	117	75	50	29	12	4	0	0	0

	Median Metastasis-Free Survival (95% CI)
	mo
Darolutamide	40.4 (34.3–NR)
Placebo	18.4 (15.5–22.3)

Hazard ratio, 0.41 (95% CI, 0.34–0.50)
$p < 0.011$

Fizazi K et al; ARAMIS Investigators. *N Engl J Med* 2019;380(13):1235-46.

ARAMIS: Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer

Adverse event, n (%)	Darolutamide (N = 954)		Placebo (N = 554)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any	794 (83.2)	236 (24.7)	426 (76.9)	108 (19.5)
Serious	237 (24.8)	151 (15.8)	111 (20)	70 (12.6)
Discontinuation	85 (8.9)	32 (3.3)	48 (8.7)	24 (4.3)
Adverse events that occurred in ≥5% of patients in either group				
Fatigue	115 (12.1)	4 (0.4)	48 (8.7)	5 (0.9)
Back pain	84 (8.8)	4 (0.4)	50 (9.0)	1 (0.2)
Arthralgia	77 (8.1)	3 (0.3)	51 (9.2)	2 (0.4)
Diarrhea	66 (6.9)	0 (0)	31 (5.6)	1 (0.2)
Constipation	60 (6.3)	0 (0)	34 (6.1)	0 (0)
Pain in extremity	55 (5.8)	0 (0)	18 (3.2)	1 (0.2)
Anemia	53 (5.6)	8 (0.8)	25 (4.5)	2 (0.4)
Hot flush	50 (5.2)	0 (0)	23 (4.2)	0 (0)
Nausea	48 (5.0)	2 (0.2)	32 (5.8)	0 (0)
Urinary tract infection	47 (4.9)	6 (0.6)	28 (5.1)	3 (0.5)
Urinary retention	33 (3.5)	15 (1.6)	36 (6.5)	11 (2.0)

Fizazi K et al; ARAMIS Investigators. *N Engl J Med* 2019;380(13):1235-46.

Editorial — Dr Oh

The “Third Musketeer” of nmCRPC was approved in July 2019 by the FDA: darolutamide. In the ARAMIS trial of 1,509 pts, darolutamide was associated with MFS of 40.4 months vs 18.4 mo with placebo (HR 0.41, p <0.001). In this regard, the results were comparable to MFS benefits reported in PROSPER and SPARTAN with enzalutamide and apalutamide. What has gotten more attention with darolutamide is the side-effect profile and the possibility that it is better tolerated because it might not cross the blood-brain barrier and induce weakness, fatigue and seizures to the same extent as other ART therapies. In fact, AEs were comparable between the darolutamide and placebo arms, and treatment discontinuations were 8.9% and 8.7% respectively. Fatigue was 15.8% vs 11.4%, slightly favoring placebo. In the QOL presentation of ARAMIS, on-study FACT-P was comparable, but time to deterioration of QOL on FACT-P favored darolutamide (HR 0.80).

Editorial — Dr Oh (continued)

Similarly EORTC QOL surveys showed time to deterioration in bowel and urinary sxs favored darolutamide in a post-hoc analysis. More research will be needed to see if darolutamide is truly better tolerated than enza or apa in head-to-head studies focused on QOL.

FDA Approves Enzalutamide for Metastatic Castration-Sensitive Prostate Cancer

Press Release – December 16, 2019

"The Food and Drug Administration approved enzalutamide for patients with metastatic castration-sensitive prostate cancer (mCSPC). FDA previously approved enzalutamide for patients with castration-resistant prostate cancer.

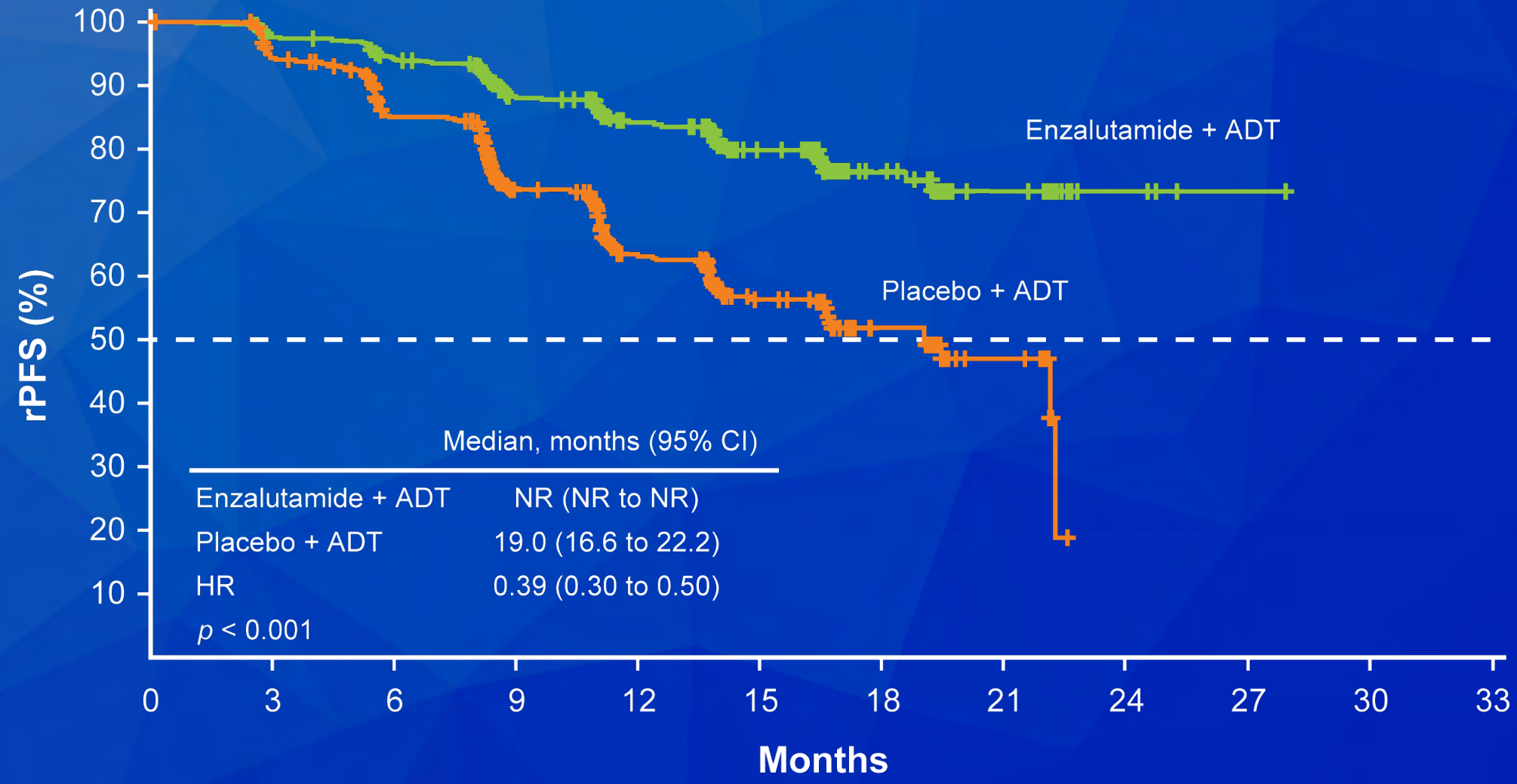
"Efficacy was investigated in ARCHES (NCT02677896), a trial enrolling 1150 patients with mCSPC randomized (1:1) to receive either enzalutamide orally 160 mg once daily (N = 574) or placebo orally once daily (N = 576). All patients received a GnRH analog or had a prior bilateral orchiectomy. The main efficacy outcome measure was radiographic progression-free survival (rPFS). Based on blinded independent central review, rPFS was defined as the time from randomization to radiographic disease progression at any time or death within 24 weeks after drug discontinuation. Radiographic disease progression was defined by identification of 2 or more new bone lesions on a bone scan with confirmation (Prostate Cancer Working Group 2 criteria) and/or progression in soft tissue disease. Time to new antineoplastic therapy was an additional endpoint."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-enzalutamide-metastatic-castration-sensitive-prostate-cancer

ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy with Enzalutamide or Placebo in Men with Metastatic Hormone-Sensitive Prostate Cancer

Armstrong AJ et al.
J Clin Oncol 2019;[Epub ahead of print].

ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy with Enzalutamide or Placebo in Men with Metastatic Hormone-Sensitive Prostate Cancer

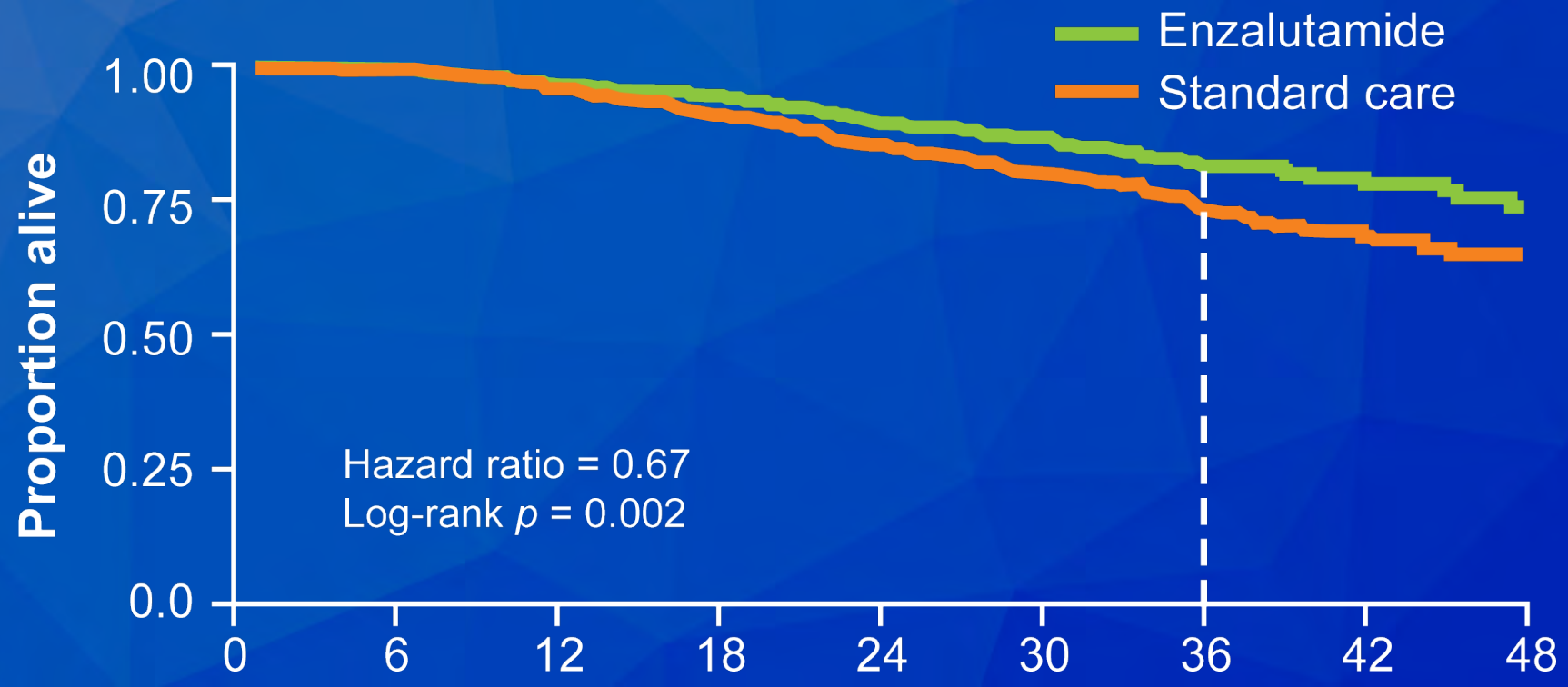


Armstrong AJ et al. *J Clin Oncol* 2019;[Epub ahead of print].

Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer

Davis ID et al.
N Engl J Med 2019;381(2):121-31.

ENZAMET Primary Endpoint: Overall Survival



Number at risk

Standard care	562	551	531	501	452	311	174	86	32
Enzalutamide	563	558	541	527	480	340	189	106	45

Davis ID et al. *N Engl J Med* 2019;381(2):121-31.

FDA Approves Apalutamide for Metastatic Castration-Sensitive Prostate Cancer

Press Release – September 17, 2019

"The Food and Drug Administration approved apalutamide for patients with metastatic castration-sensitive prostate cancer (mCSPC). Apalutamide was initially approved in 2018 for patients with non-metastatic castration-resistant prostate cancer.

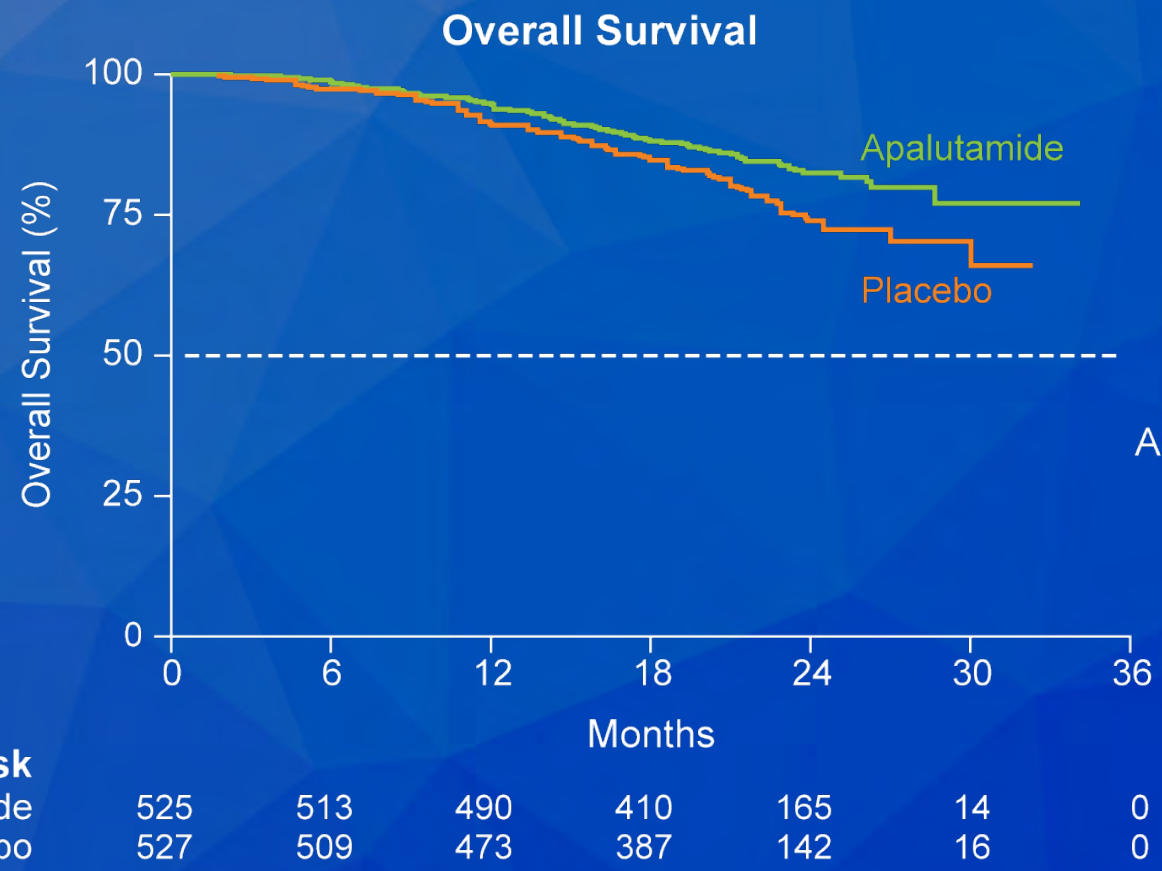
Efficacy was demonstrated in TITAN (NCT02489318), a randomized, double-blind, placebo-controlled, multi-center clinical trial enrolling 1,052 patients with mCSPC. Patients received either apalutamide 240 mg daily or placebo, orally. All patients received androgen deprivation therapy (ADT) — either concomitant gonadotropin-releasing hormone analog or prior bilateral orchiectomy. Patients with both high- and low-volume disease were enrolled in the study."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-apalutamide-metastatic-castration-sensitive-prostate-cancer

Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer

Chi KN et al.
N Engl J Med 2019;381(1):13-24.

TITAN: Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer



	No. of Patients	Median Overall Survival (95% CI)	Patients with Overall Survival at 24 Mo (95% CI)
		mo	%
Apalutamide	525	NE	82.4 (78.4–85.8)
Placebo	527	NE	73.5 (68.7–77.8)

Hazard ratio for death, 0.67 (95% CI, 0.51–0.89)
$p = 0.005$

Chi KN et al. *N Engl J Med* 2019;381(1):13-24.

Health-Related Quality of Life After Apalutamide Treatment in Patients with Metastatic Castration-Sensitive Prostate Cancer (TITAN): A Randomised, Placebo-Controlled, Phase 3 Study

Agarwal N et al.

Lancet Oncol 2019;20(11):1518-30.

Editorial — Dr Oh

ARCHES is a phase III trial of enzalutamide in mHSPC, 1,150 patients (18% with prior docetaxel) which showed a significant PFS benefit, HR 0.39 ($P < 0.0001$). Time to next antineoplastic therapy was also significantly increased (HR 0.28) and objective response rate was 83% vs 63% with addition of enzalutamide. This reinforces the data from ENZAMET, though the primary endpoint was PFS and not OS. QOL was similar between the two arms and was maintained for longer in the enzalutamide arm. TITAN is an additional phase III trial comparing apalutamide to placebo in 1,052 patients with mHSPC. OS was improved with apalutamide (HR 0.67, $p = 0.005$) with 2-yr survival of 82% vs 73%. So how do we decide which therapy to consider for mHSPC if apalutamide is now considered for treatment of mHSPC? The answer is unclear. Without direct comparisons, any of the ART therapies (enza, apa, abi) or docetaxel could be an option. Probably side-effect profiles, cost and patient preference will need to be considered for each patient.

Optimal Sequencing of Enzalutamide and Abiraterone Acetate plus Prednisone in Metastatic Castration-Resistant Prostate Cancer: A Multicentre, Randomised, Open-label, Phase 2, Crossover Trial

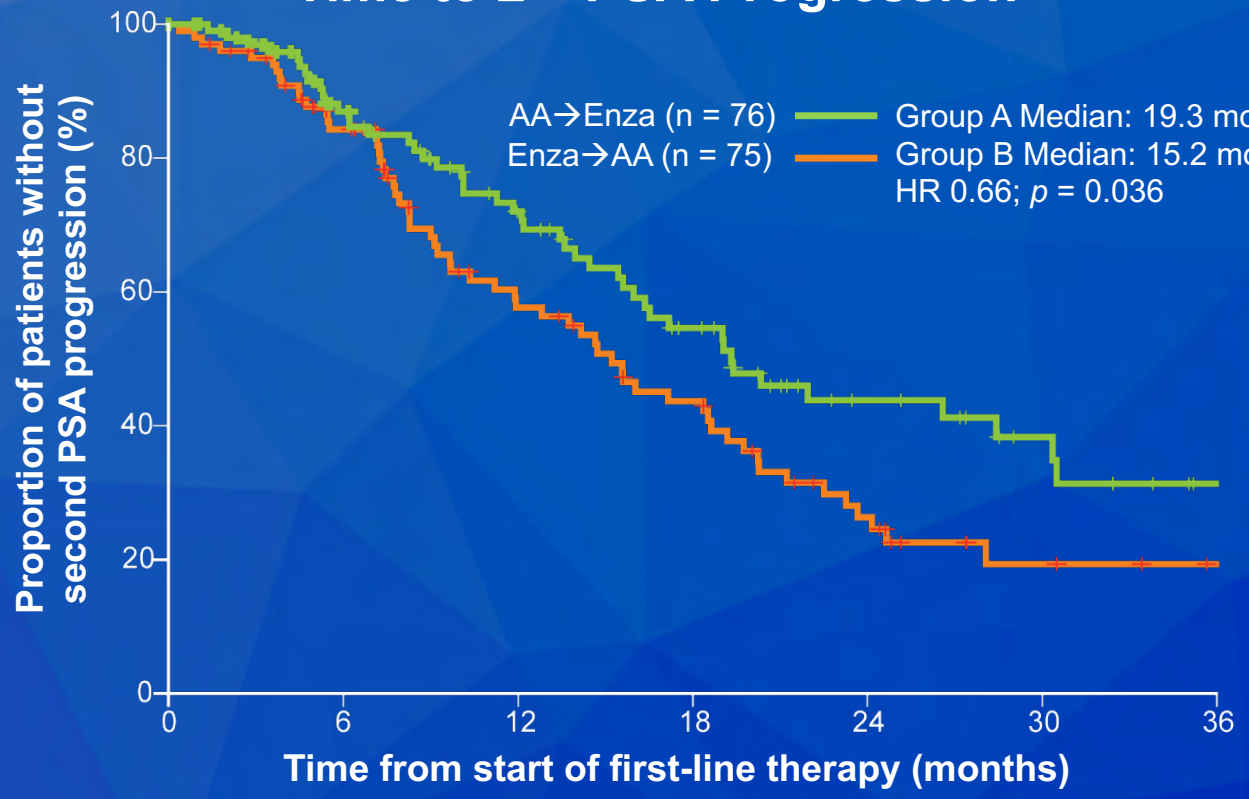
Khalaf DJ et al.

Lancet Oncol 2019;20(12):1730-39.

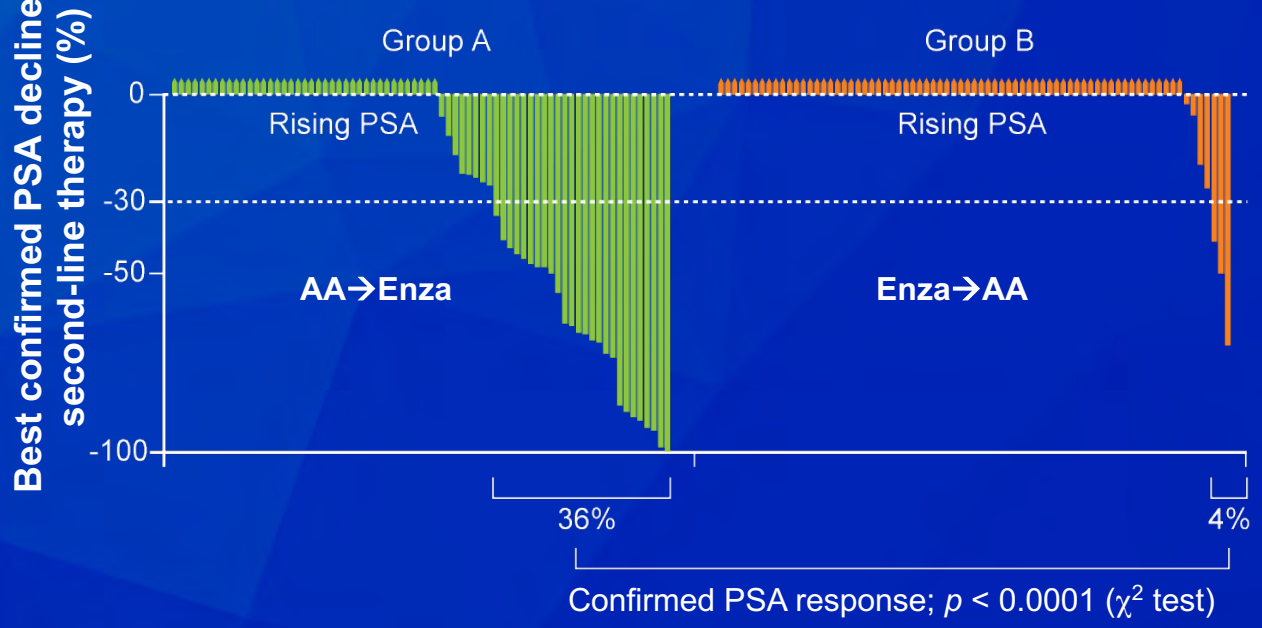
Time From Start of First-Line Therapy to 2nd PSA Progression and Best Confirmed PSA Decline During 2nd-Line Therapy

(Abiraterone Acetate [AA] → Enzalutamide vs Enza → AA)

Time to 2nd PSA Progression



Best Confirmed PSA Decline



Khalaf DJ et al. *Lancet Oncol* 2019;20(12):1730-39.

Editorial — Dr Drake

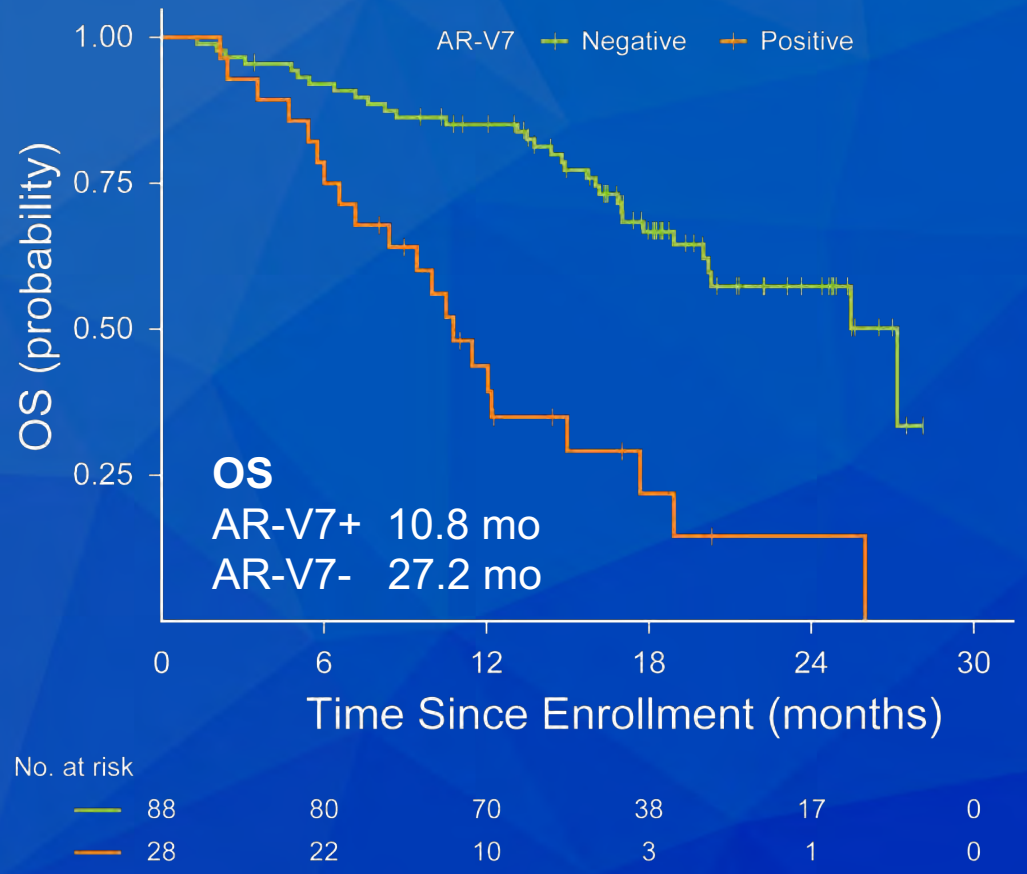
This randomized trial addressed an important clinical question — the relative activity of enzalutamide administered after abiraterone acetate and vice versa. The overall results were clear, showing that abiraterone has negligible activity after enzalutamide, whilst enza retains some activity after abiraterone progression. Thus, patients had a longer time to overall (second) progression when treated with abiraterone → enzalutamide versus the opposite sequence. Thus, strong consideration should likely be given to using abiraterone as a first-line next-gen ADT, unless clinical conditions (for example DM which could be exacerbated by prednisone) are contraindications.

Prospective Multicenter Validation of Androgen Receptor Splice Variant 7 and Hormone Therapy Resistance in High-Risk Castration-Resistant Prostate Cancer: The PROPHECY Study

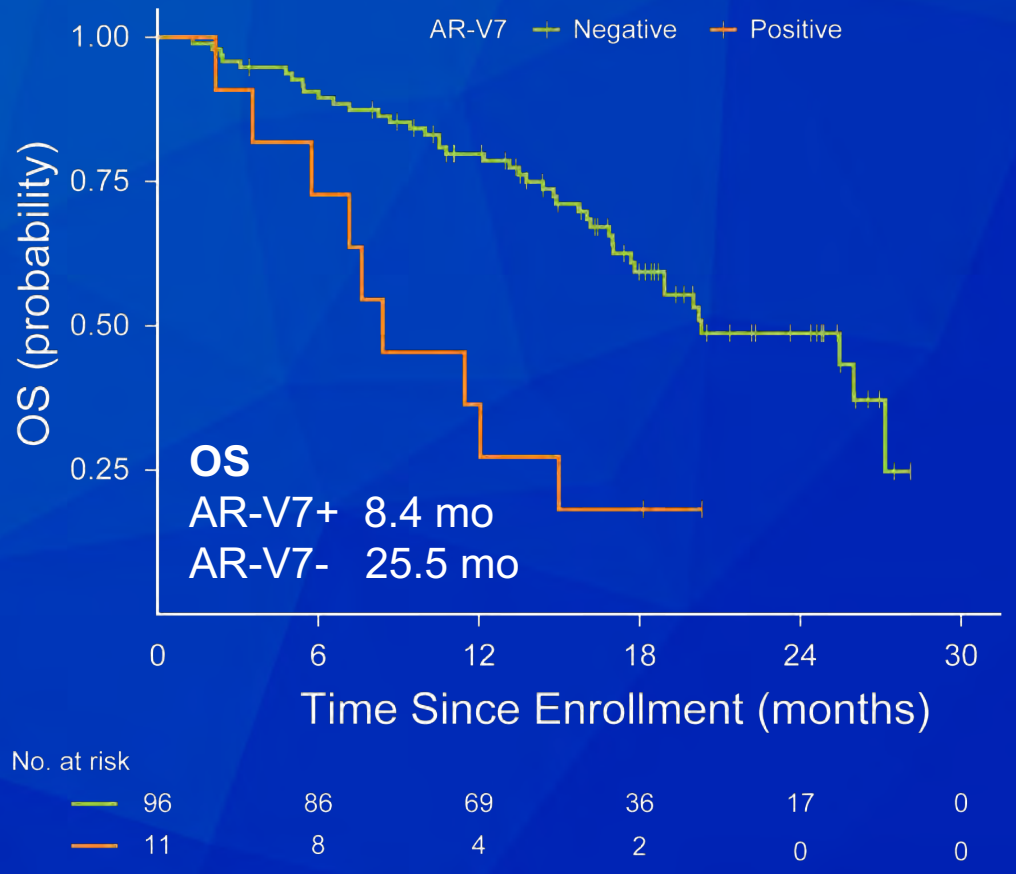
Armstrong AJ et al.
J Clin Oncol 2019;37(13):1120-9.

PROPHECY: OS by Johns Hopkins University and the Epic CTC Nuclear-Specific AR-V7 Protein Assay

Johns Hopkins Univ CTC AR-V7 Assay



Epic CTC AR-V7 Assay



Armstrong AJ et al. *J Clin Oncol* 2019;37(13):1120-9.

Editorial — Dr Oh

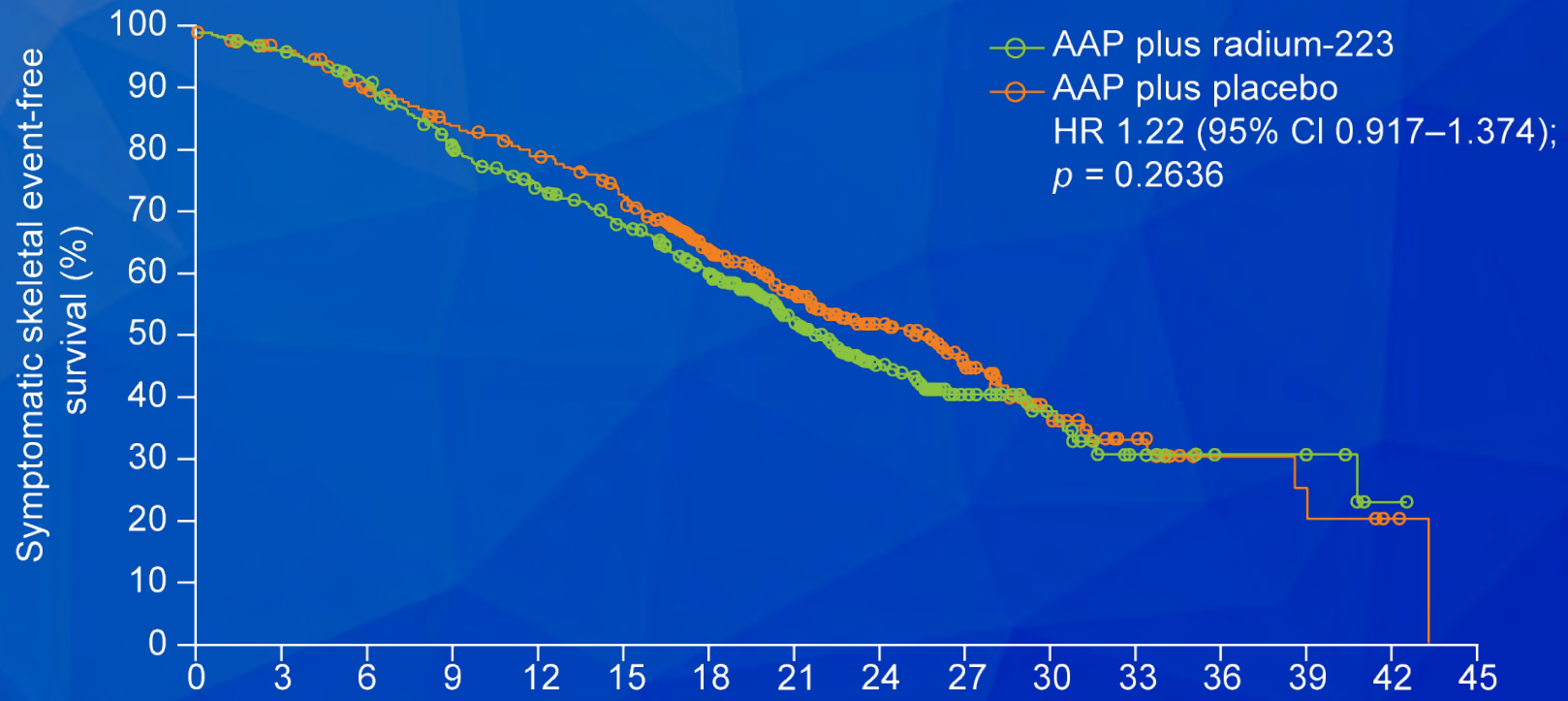
AR-V7 made a big splash in a *NEJM* paper from 2014 that suggested it was highly predictive of benefit from abiraterone or enzalutamide for mCRPC. Its utility as a clinically useful test, however, was hampered by a lack of commercial options until this past year when it became available. So should clinicians use it, and when? This paper from Armstrong et al was a prospective, multicenter study of 118 mCRPC patients starting abiraterone or enzalutamide who were tested for AR-V7 by either the JHU or EPIC Sciences test. It confirmed that detecting AR-V7 was associated with shorter PFS (HR of 1.9-2.4) and OS (HR of 3.5-4.2). PSA and soft-tissue responses in AR-V7+ patients were very low (0-11%), and concordance between the assays was acceptable at 82%. The biggest issues with AR-V7 testing are that (1) a positive test is rare in patients who have not already received abi/enza, (2) when positive, some patients may still respond to therapy, (3) more importantly, even when negative, many patients do not respond to abi/enza and (4) the clinical value of sequential ART therapies remains unclear.

Addition of Radium-223 to Abiraterone Acetate and Prednisone or Prednisolone in Patients with Castration-Resistant Prostate Cancer and Bone Metastases (ERA 223): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial

Smith M et al.

Lancet Oncol 2019;20(3):408-19.

ERA 223: Addition of Radium-223 to Abiraterone Acetate and Prednisone or Prednisolone in Patients with CRPC and Bone Metastases



Number at risk (number censored)																
AAP plus Radium-223 group	401 (0)	380 (10)	355 (16)	310 (21)	272 (32)	245 (38)	202 (56)	126 (110)	78 (142)	44 (168)	25 (185)	12 (194)	7 (199)	6 (200)	1 (204)	0 (205)
AAP plus Placebo group	405 (0)	384 (11)	353 (17)	323 (23)	301 (25)	274 (30)	214 (58)	152 (99)	94 (145)	59 (173)	30 (193)	16 (203)	6 (212)	5 (212)	3 (213)	0 (215)

Smith M et al. *Lancet Oncol* 2019;20(3):408-19.

Decreased Fracture Rate by Mandating Bone-Protecting Agents in the EORTC 1333/PEACE III Trial Comparing Enzalutamide and Ra223 versus Enzalutamide Alone: An Interim Safety Analysis

Tombal BF et al.
Proc ASCO 2019;Abstract 5007.

EORTC-1333/PEACE III: Bone-Protecting Agents (BPA) in a Trial Comparing Enzalutamide and Ra223 to Enzalutamide Alone

Bone fractures and cumulative incidence — Safety population

Cumulative incidence (95% CI)	With exposure to BPA		Without exposure to BPA	
	Enza + Rad (N = 39)*	Enza (N = 49)	Enza + Rad (N = 37)	Enza (N = 35)
3 months	0 (-)	0 (-)	0 (-)	5.7 (1.0-16.7)
6 months	0 (-)	0 (-)	5.6 (1.0-16.3)	8.8 (2.2-21.0)
9 months	0 (-)	0 (-)	22.6 (10.6-37.3)	8.8 (2.2-21.0)
12 months	**0 (-)**	**0 (-)**	**37.4 (21.8-53.1)**	**12.4 (3.9-26.2)**
15 months	0 (-)	0 (-)	43.6 (26.8-59.3)	16.6 (5.9-32.0)
18 months	0 (-)	0 (-)	43.6 (26.8-59.3)	16.6 (5.9-32.0)

* The 1 fracture in this group occurred at month 27

Tombal BF et al. *Proc ASCO* 2019;Abstract 5007.

Editorial — Dr Oh

As new therapies for mCRPC became available, sequencing and combinations became the next step. Combining radium and ART therapies would be an obvious consideration as they have different toxicities and could have a synergistic benefit on OS.

ERA 223 is a somewhat notorious trial that tested this combination of abiraterone +/- radium and suggested in early analyses to be associated with increased fractures and death in the combination arm. However, the final paper in *Lancet Oncology* recently published suggested that the fracture rate was indeed very different (29% with radium vs 11% placebo) though survival was not different. At ASCO 2019, Tombal presented results from PEACE III, which evaluated enzalutamide +/- radium-223 but mandated BPA given the findings of ERA 223. At 12 months, osteoporotic fractures were 37% and 12% in the enza/radium and enza arms respectively WITHOUT BPA, but 0% and 0% in the same groups with BPAs.

Editorial — Dr Oh (continued)

Bone-protecting therapy basically eradicated the risk of fracture in this study! DORA is an ongoing trial looking at whether radium-223 can be combined with docetaxel — endpoint is OS.

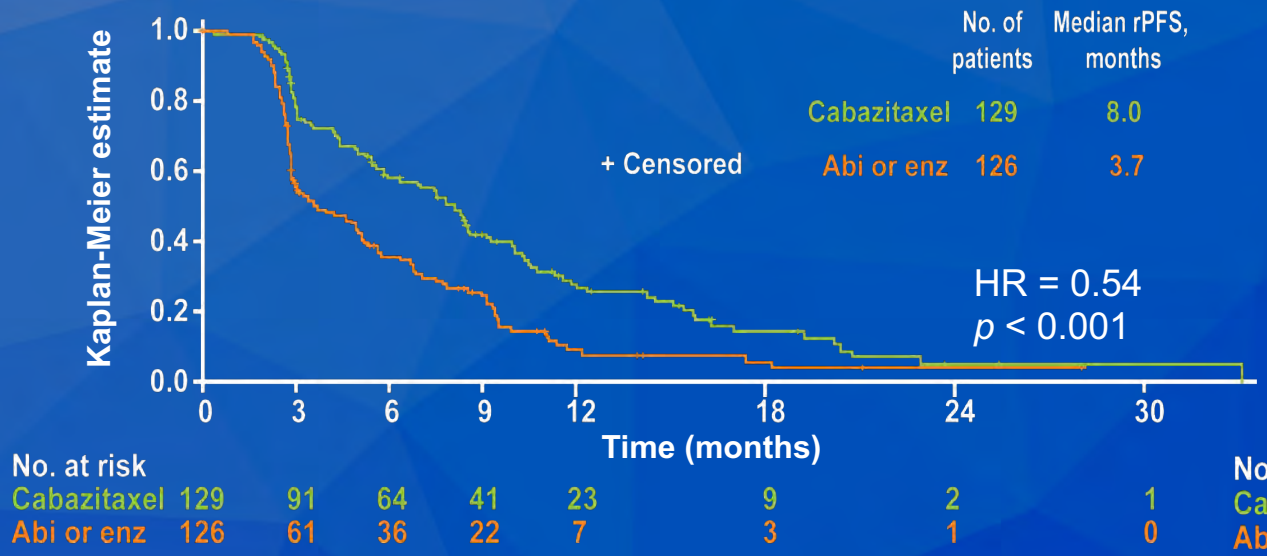
Bottom line: BPAs are critical in mCRPC patients. While checking bone density is important, many osteoporotic fractures cannot be predicted by bone density alone. FRAX scores are more predictive, and clinicians should consider regular assessment of bone density, calculation of risk scores and supplemental vitamin D/calcium. BPAs are important for high-risk patients, esp if combining radium and ART therapies.

Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer

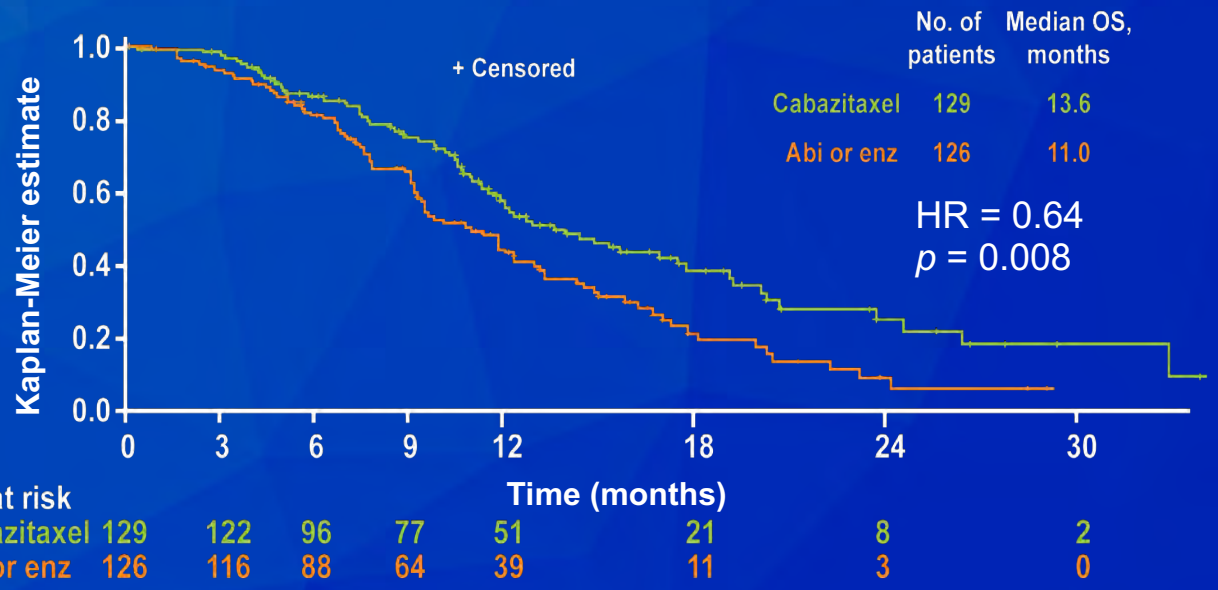
de Wit R et al; CARD Investigators.
N Engl J Med 2019;381(26):2506-18.

CARD: Survival Analyses

Radiographic PFS (primary endpoint)



Overall survival (key secondary endpoint)



rPFS = radiologic tumor progression (RECIST 1.1) and/or progression of bone lesions (PCWG2) and/or death from any cause

- CARD met its primary objective: Cabazitaxel more than doubled rPFS versus abiraterone or enzalutamide
- Cabazitaxel reduced the risk of death by 36% versus abiraterone or enzalutamide

de Wit R et al; CARD Investigators. *N Engl J Med* 2019;381(26):2506-18.

Editorial — Dr Petrylak

Both docetaxel as well as abiraterone/prednisone combined with androgen blockade improve survival over androgen blockade alone in metastatic hormone-sensitive prostate cancer, with a hazard ratio of 0.61 and 0.64, respectively. Chemotherapy has side effects including neutropenia, peripheral neuropathy and fatigue, whereas abiraterone/prednisone has side effects including hypertension, liver function abnormalities and hypokalemia. This is in addition to the known side effects of prednisone. Antiandrogen therapy with apalutamide or enzalutamide theoretically would have a different side-effect pattern, with fatigue, rash and thyroid abnormalities seen with apalutamide and fatigue with enzalutamide. The TITAN trial compared apalutamide combined with androgen blockade to androgen blockade alone and found a 52% reduction in the risk of radiographic progression-free survival or death, with 33% reduction in the risk of death.

Editorial — Dr Petrylak (continued)

The ARCHES trial found a 61% reduction in radiographic progression-free survival or death; however, the survival data is not mature. Thus it seems that antiandrogen therapy has similar survival to abiraterone/prednisone or docetaxel, with different side-effect profiles.

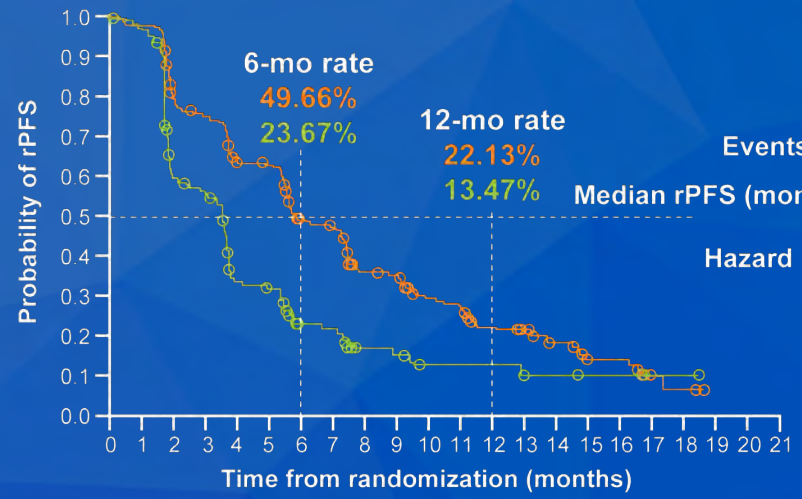
PROfound: Phase III Study of Olaparib versus Enzalutamide or Abiraterone for Metastatic Castration-Resistant Prostate Cancer with Homologous Recombination Repair Gene Alterations

Hussain M et al.

Proc ESMO 2019;Abstract LBA12.

PROfound: Radiographic Progression-Free Survival by BICR

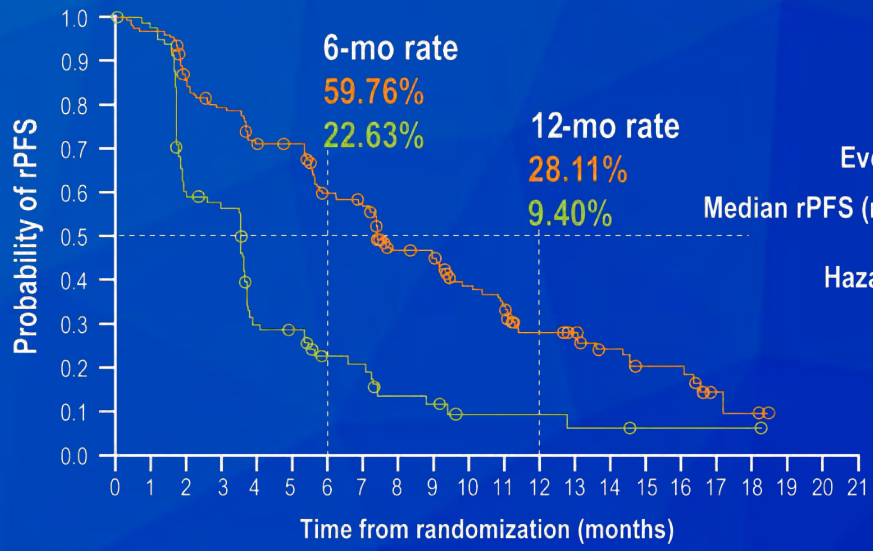
Overall study population



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

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

Patients with BRCA1, BRCA2 or ATM alterations



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

Among patients with mCRPC and disease progression on prior "new hormonal agents," olaparib provided a statistically significant and clinically meaningful improvement in BICR rPFS in comparison to physician's choice of enzalutamide or abiraterone/prednisone for

- Patients with alterations in BRCA1, BRCA2 and/or ATM (primary endpoint)
- The overall population with alterations in any qualifying gene with a role in homologous recombination repair (secondary endpoint)

Hussain M et al. *Proc ESMO* 2019;Abstract LBA12.

Olaparib in Patients with Metastatic Castration-Resistant Prostate Cancer with DNA Repair Gene Aberrations (TOPARP-B): A Multicentre, Open-Label, Randomised, Phase 2 Trial

Mateo J et al.

Lancet Oncol 2020;21(1):162-74.

TOPARP-B: A Phase II Randomized Trial of the PARP Inhibitor Olaparib for mCRPC with DNA Damage Repair Alterations

Primary Endpoint Analysis

	Total (n = 92)		Dose group			
			300 mg (n = 46)		400 mg (n = 46)	
	Resp/n	%	Resp/n	%	Resp/n	%
Composite response (confirmed)	**43/92**	**46.7%**	**18/46**	**39.1%**	**25/46**	**54.3%**
RECIST response	14/70	20.0%	6/37	16.2%	8/33	24.2%
PSA response ≥50%	30/89	33.7%	13/43	30.2%	17/46	37.0%
CTC conversion	28/55	50.9%	13/27	48.1%	15/28	53.6%
RECIST or PSA50 response	32/92	34.8%	13/46	28.3%	19/46	41.3%

Mateo J et al. *Lancet Oncol* 2020;21(1):162-74.

Preliminary Results from TRITON2: A Phase 2 Study of Rucaparib in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Associated with Homologous Recombination Repair (HRR) Gene Alterations

Abida W et al.
Proc ESMO 2018;Abstract 793PD.

TRITON2: Confirmed Investigator-Assessed Responses in Evaluable Patients by HRR Gene Alteration

Response, n (%)	BRCA1/2 (n = 25)	ATM (n = 5)	CDK12 (n = 8)	Other (n = 8)
ORR [95% CI][a]	11 (44.0%) [24.4-65.1]	0 [0.0-52.2]	0 [0.0-36.9]	2 (25.0%) [3.2-65.1]
Complete response	0	0	0	0
Partial response	11 (44.0%)	0	0	2 (25.0%)
Stable disease	9 (36.0%)	4 (80.0%)	5 (62.5%)	5 (62.5%)[b]
Progressive disease	4 (16.0%)	1 (20.0%)	2 (25.0%)	1 (12.5%)
Not evaluable	1 (4.0%)	0	1 (12.5%)	0

Visit cutoff date: 29 June 2018
Includes patients who had measurable disease at baseline per the investigator and ≥16 weeks of follow-up or who discontinued treatment.
[a] Per modified RECIST/PCWG3 criteria
[b] One patient had a BRIP1 alteration and 1 patient had a FANCA alteration
CI, confidence interval; HRR, homologous recombination repair; ORR, objective response rate; PCWG3, Prostate Cancer Clinical Trials Working Group 3; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1

Abida W et al. *Proc ESMO* 2018;Abstract 793PD.

FDA Grants Breakthrough Therapy Designation to Niraparib for mCRPC with BRCA1/2 Mutation

Press Release – October 3, 2019

"The US Food and Drug Administration (FDA) has granted Breakthrough Therapy Designation for niraparib, an orally-administered poly ADP-ribose polymerase (PARP) inhibitor, for the treatment of patients with BRCA1/2 gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have received prior taxane chemotherapy and androgen receptor (AR)-targeted therapy. The Breakthrough Therapy Designation is based on data from the GALAHAD study, a Phase 2, multicenter, open-label clinical trial evaluating the efficacy and safety of niraparib in the treatment of adult patients with mCRPC and DNA-repair gene defects who had received treatment with next-generation androgen-receptor targeting therapies and docetaxel."

https://www.jnj.com/janssen-announces-u-s-fda-breakthrough-therapy-designation-granted-for-niraparib-for-the-treatment-of-metastatic-castration-resistant-prostate-cancer

GALAHAD: Interim Analysis of a Phase II Study of Niraparib for Patients with mCRPC and Biallelic DNA-Repair Gene Defects

Response, n (%)	All biallelic DRD (n = 81)	
	BRCA (n = 46)	Non-BRCA[a] (n = 35)
Objective response rate	12/29 (41%)	2/22 (9%)
PSA_{50}	23/46 (50%)	1/35 (3%)
CTEC conversion[b]	18/38 (47%)	5/24 (21%)
Composite response rate	29/46 (63%)	6/35 (17%)
Median rPFS, mo	8.2	5.3
Median OS, mo	12.6	14.0

[a] Protocol allowed patients with biallelic ATM, FANCA, PALB2, CHEK2, BRIP1 or HDAC2 DRD
[b] CTC conversion from unfavorable (≥5 CTC) to favorable (<5 CTCs confirmed at least by 28 days)
CTC, circulating tumor cells; DRD, DNA repair gene defect; OS, overall survival; PSA_{50}, ≥50% decline in prostate-specific antigen; rPFS, radiographic progression-free survival.

Smith M et al. *Proc ESMO* 2019;Abstract LBA50.

Editorial — Dr Oh

The most promising “precision oncology” option under clinical investigation has been the DNA damage repair (DDR) pathway mutations, which can lead to response to PARP inhibitors. In mCRPC, up to 20% of patients will have germline and/or somatic mutations in DDR genes, most commonly BRCA2. These have led to a series of phase II and III trials of PARP inhibitors in DDR-mutant mCRPC. Rucaparib has been reported in phase 2 trials to have activity in DDR-mutant cancers — TRITON2 reported on 52 patients treated with 600 mg BID in this cohort and demonstrated 48% PSA response rate and 45% measurable response in BRCA1/2 mutant cancers. TOPARP-B evaluated olaparib in a similar population of 92 evaluable patients. RR was 54% and 37% respectively in the 400 BID and 300 mg BID cohorts. The highest RRs were noted in BRCA1/2 and PALB2 subgroups where >2/3 of patients responded. The PROfound trial met its primary endpoint of rPFS in DDR-mutant cancers randomized to olaparib 300 BID vs second ART therapy. This suggests that for this subset of patients, PARP inhibitors will likely become the new SOC.

Pembrolizumab for Treatment-Refractory Metastatic Castration-Resistant Prostate Cancer: Multicohort, Open-Label Phase II KEYNOTE-199 Study

Antonarakis ES et al.

J Clin Oncol 2019;[Epub ahead of print].

KEYNOTE-199: Response and Survival with Pembrolizumab in mCRPC Previously Treated with Docetaxel and Targeted Endocrine Therapy

Endpoint	Cohort 1 (PD-L1 positive)	Cohort 2 (PD-L1 negative)	Cohort 3 (Bone predominant)
Reponse per RECIST v1.1 by central radiology review			
No. of patients	133	66	59
ORR, n (%)	7 (5%)	2 (3%)	—
DCR, n (%)	13 (10%)	6 (9%)	13 (22%)
PSA response in patients with baseline PSA measurement			
No. of patients	124	60	59
PSA response (≥50%)	8 (6%)	5 (8%)	1 (2%)
Median rPFS	2.1 mo	2.1 mo	3.7 mo
Median OS	9.5 mo	7.9 mo	14.1 mo

Antonarakis ES et al. *J Clin Oncol* 2019;[Epub ahead of print].

Editorial — Dr Drake

KEYNOTE-199 was a fairly large 3-cohort trial of pembrolizumab in mCRPC previously treated with docetaxel. The majority of enrolled patients (199 in fact) had RECIST-measurable disease, which is generally not the case for men with mCRPC. Of those, 66 had PD-L1 “positive” disease (Cohort 1). A group of bone-only disease patients was also enrolled. The RECIST response rate was decidedly modest, 5% in Cohort 1 and 3% in Cohort 2. This is far less than that noted with pembro in other GU cancers like bladder cancer and RCC, where ORRs are in the 20-30% range. PSA response rates were also modest — 6% for the PD-L1-positive RECIST-measurable Cohort 1, 8% for Cohort 2 (RECIST disease, PD-L1 negative) and 2% for bone-only disease. Overall these data show that anti-PD-1 has little activity in the post-docetaxel setting and that development of anti-PD-1 monotherapy is unlikely to proceed.

Editorial — Dr Drake (continued)

Of note, much higher response rates were reported (approximately 15%) when anti-PD-1 was added to enzalutamide in progressing patients (Graff et al, *Oncotarget* 2016), suggesting a potentially intriguing biological difference in the prostate cancer tumor microenvironment in these two clinical settings.

Genitourinary Cancers — Drs Drake and Oh

Urothelial Bladder Cancer

Prostate Cancer

Renal Cell Carcinoma

Nivolumab plus Ipilimumab versus Sunitinib in First-Line Treatment for Advanced Renal Cell Carcinoma: Extended Follow-Up of Efficacy and Safety Results from a Randomised, Controlled, Phase 3 Trial

Motzer RJ et al; CheckMate 214 Investigators.
Lancet Oncol 2019;20(10):1370-85.

CheckMate 214: Extended Response and Survival Analyses

	IMDC Intermediate- or Poor-risk		Intention-to-Treat		IMDC Favorable-risk	
	Nivo/Ipi (n = 425)	Sunitinib (n = 422)	Nivo/Ipi (n = 550)	Sunitinib (n = 546)	Nivo/Ipi (n = 125)	Sunitinib (n = 124)
ORR	42%	29%	41%	34%	39%	50%
	P = 0.0001		*P* = 0.015		*P* = 0.14	
30-month OS	60%	47%	64%	56%	80%	85%
	HR: 0.66, *P* < 0.0001		HR: 0.71, *P* = 0.0003		HR: 1.22, *P* = 0.44	
30-month PFS	28%	12%	28%	18%	29%	35%
	HR: 0.77, *P* = 0.0014		HR: 0.85, *P* = 0.027		HR: 1.23, *P* = 0.19	

Motzer RJ et al. *Lancet Oncol* 2019;20(10):1370-85.

Safety and Efficacy of Nivolumab plus Ipilimumab (NIVO+IPI) in Patients with Advanced Renal Cell Carcinoma (aRCC) with Brain Metastases: Interim Analysis of CheckMate 920

Emamekhoo H et al.
Proc ASCO 2019;Abstract 4517.

Interim Analysis of CheckMate 920: Nivolumab with Ipilimumab for Advanced Renal Cell Carcinoma with Brain Metastases

Objective response rate and best overall response in patients with advanced RCC and brain metastases

Response	Cohort 3 (N = 28)
Objective response rate, %	29
95% CI	13-49
Best overall response, n (%)	
Partial response	8 (29)
Stable disease	9 (32)
Progressive disease	6 (21)
Unable to determine	5 (18)

Emamekhoo H et al. *Proc ASCO* 2019;Abstract 4517.

Editorial — Dr Quinn

CheckMate 214 defined immune-oncology therapy in the first-line space for intermediate and poor-risk mRCC. Follow-up at 30 months shows continued improvement in OS between Nivo + Ipi and sunitinib. The OS curves are now quite flat and are likely to remain — most patients are on Nivo either as part of the N + I experimental arm or in the space after sunitinib progression. In good-risk patients, ORR and OS slightly favor sunitinib over the immune combination, meaning that most of us would not give the IO-IO combination to patients who are in the good-risk group.

FDA Approves Pembrolizumab with Axitinib for Advanced Renal Cell Carcinoma

Press Release – April 19, 2019

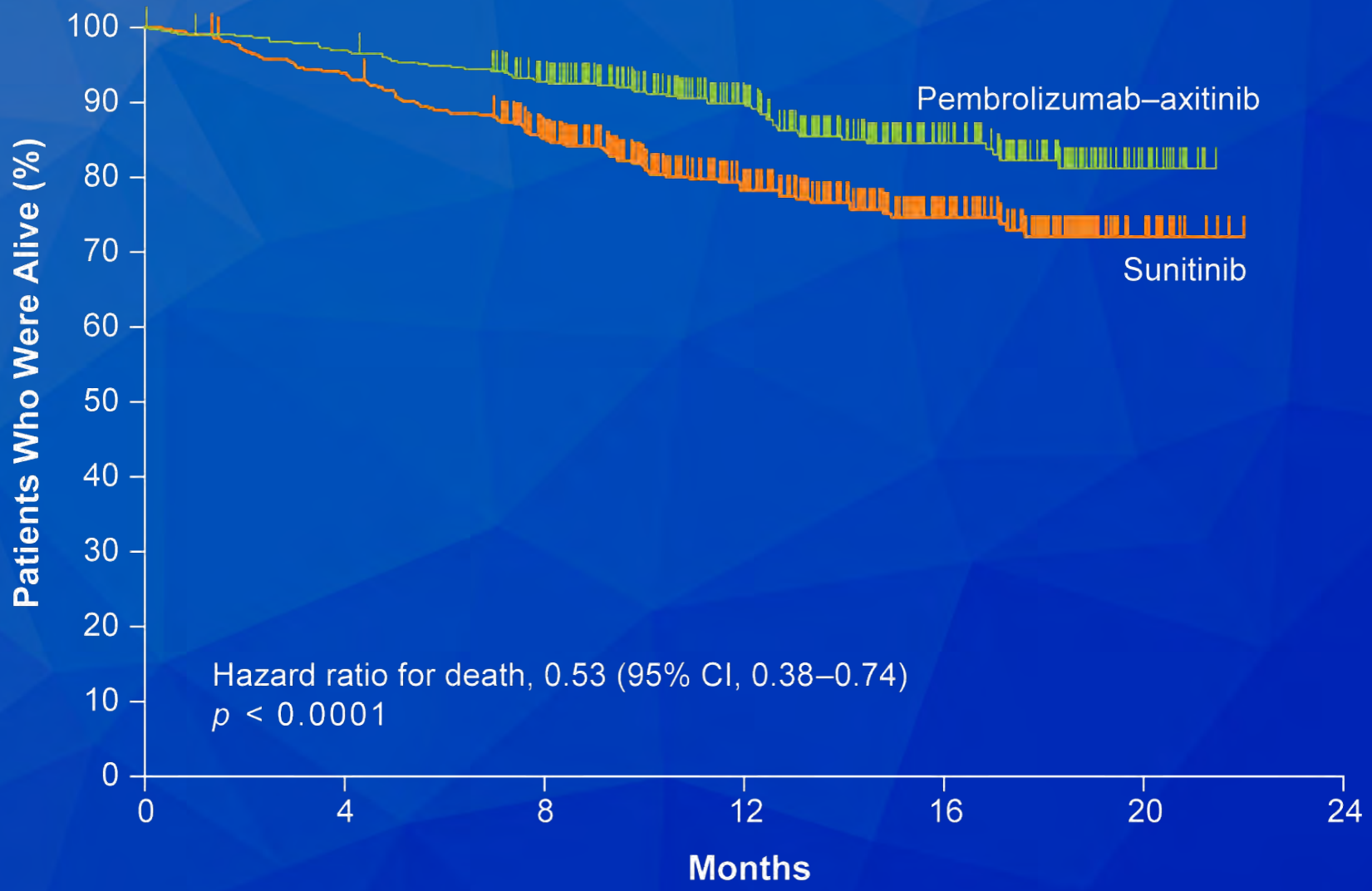
"The Food and Drug Administration approved pembrolizumab plus axitinib for the first-line treatment of patients with advanced renal cell carcinoma (RCC). Approval was based on KEYNOTE-426 (NCT02853331), a randomized, multicenter, open-label trial conducted in 861 patients who had not received systemic therapy for advanced RCC. Patients were enrolled regardless of PD-L1 tumor expression status and were randomly allocated to receive either pembrolizumab 200 mg intravenously every 3 weeks in combination with axitinib 5 mg orally twice daily, or sunitinib 50 mg orally once daily for 4 weeks and then off treatment for 2 weeks. Treatment continued until confirmed disease progression or unacceptable toxicity. Pembrolizumab was received for maximum of 24 months."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-plus-axitinib-advanced-renal-cell-carcinoma

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal Cell Carcinoma

Rini BI et al; KEYNOTE-426 Investigators.
N Engl J Med 2019;380(12):1116-27.

KEYNOTE-426: Pembrolizumab with Axitinib versus Sunitinib for Advanced Renal Cell Carcinoma – Overall Survival



Rini BI et al; KEYNOTE-426 Investigators. *N Engl J Med* 2019;380(12):1116-27.

FDA Approves Avelumab with Axitinib for Renal Cell Carcinoma

Press Release – May 14, 2019

"The Food and Drug Administration approved avelumab in combination with axitinib for first-line treatment of patients with advanced renal cell carcinoma (RCC). Approval was based on JAVELIN Renal 101 (NCT02684006), a randomized, multicenter, open-label trial of avelumab plus axitinib in 886 patients with untreated advanced RCC regardless of tumor PD-L1 expression. Patients were randomized to receive either avelumab 10 mg/kg intravenous infusion every 2 weeks in combination with axitinib 5 mg twice daily orally or sunitinib 50 mg once daily orally for 4 weeks followed by 2 weeks off until radiographic progression or unacceptable toxicity."

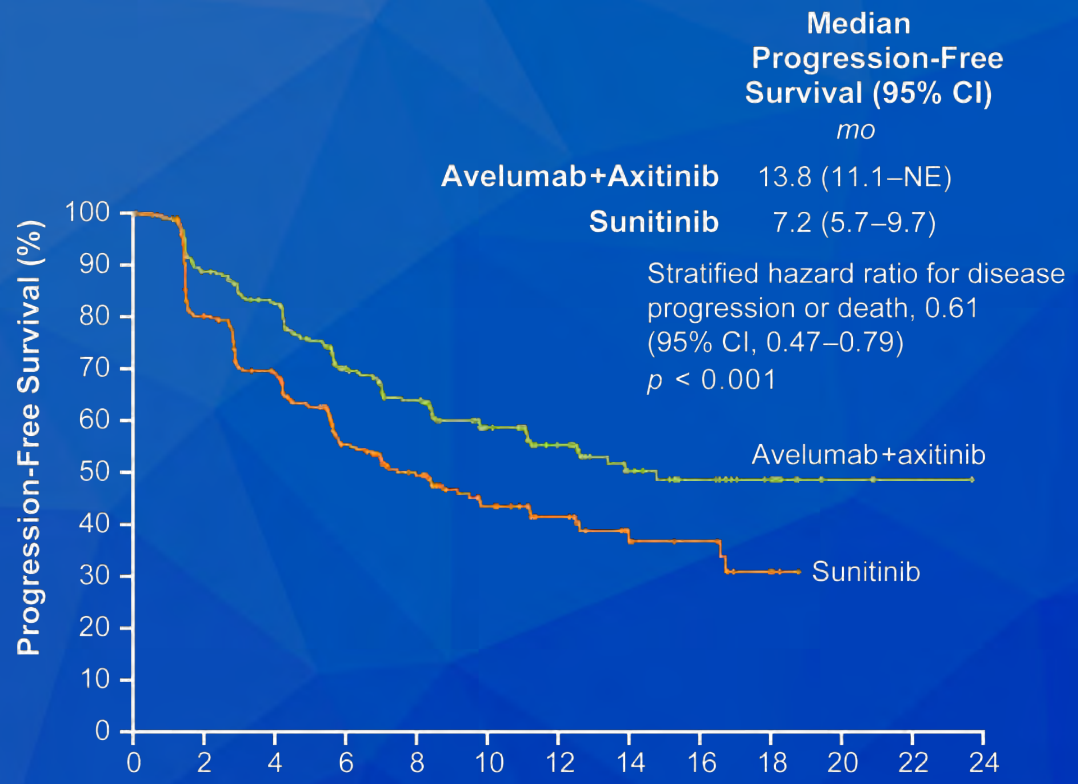
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-avelumab-plus-axitinib-renal-cell-carcinoma

Avelumab plus Axitinib versus Sunitinib for Advanced Renal Cell Carcinoma

Motzer RJ et al.
N Engl J Med 2019;380(12):1103-15.

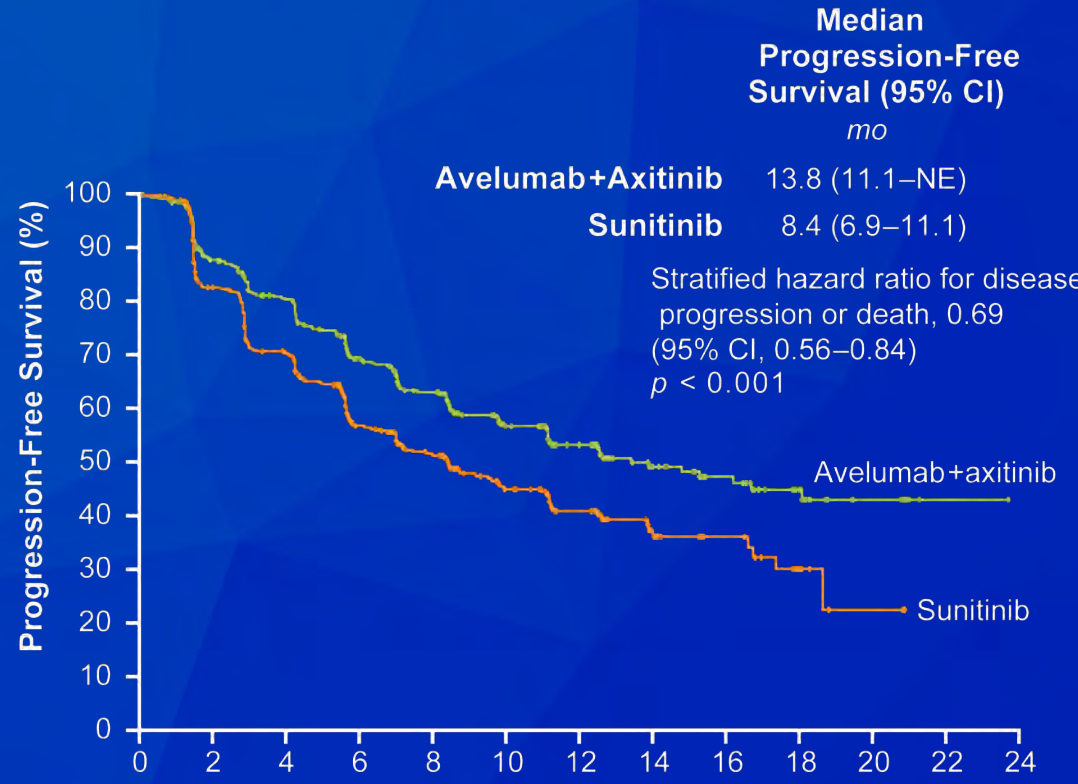
JAVELIN Renal 101: Avelumab/Axitinib versus Sunitinib for Advanced Renal Cell Carcinoma

Patients with PD-L1–Positive Tumors



No. at Risk													
Avelumab+axitinib	270	227	205	154	120	76	53	32	23	13	3	1	0
Sunitinib	290	210	174	119	85	49	35	16	13	5	0		

Overall Population



No. at Risk													
Avelumab+axitinib	442	364	321	250	193	127	94	57	42	24	8	1	0
Sunitinib	444	329	271	192	144	90	64	29	20	8	2	0	

Motzer RJ et al. *N Engl J Med* 2019;380(12):1103-15.

Editorial — Dr Quinn

KEYNOTE-426 demonstrated that axitinib and pembrolizumab was superior to sunitinib for key endpoints of ORR and OS with a HR of 0.53 for the regimen over sunitinib for OS.

The JAVELIN regimen of Axitinib + Avelumab (PD-L1) monoclonal showed superior response rate to sunitinib in all patients and for PFS across all groups. They have not demonstrated an OS advantage over 2 interim analyses.

The toxicity profiles of the 2 VEGF + IO combinations are similar to or slightly worse than sunitinib.

Given the OS advantage for axitinib + pembrolizumab, many favor this as the standard rather than axitinib + avelumab, which also requires 2 weekly infusions compared to every 3 weeks with pembrolizumab.

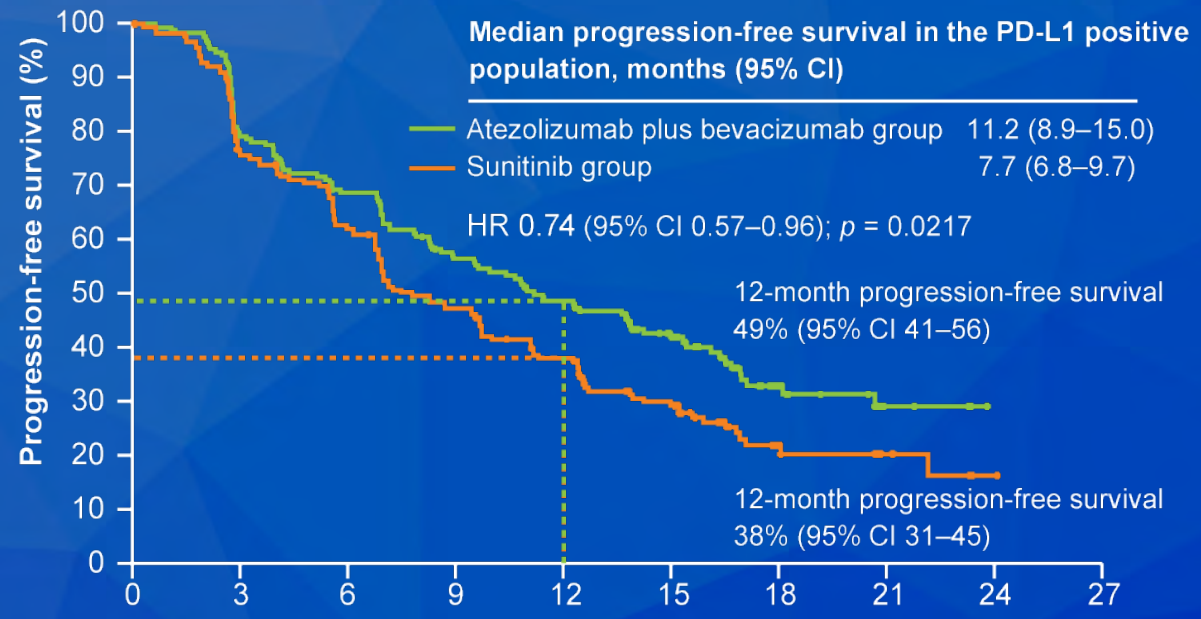
Editorial — Dr Quinn (continued)

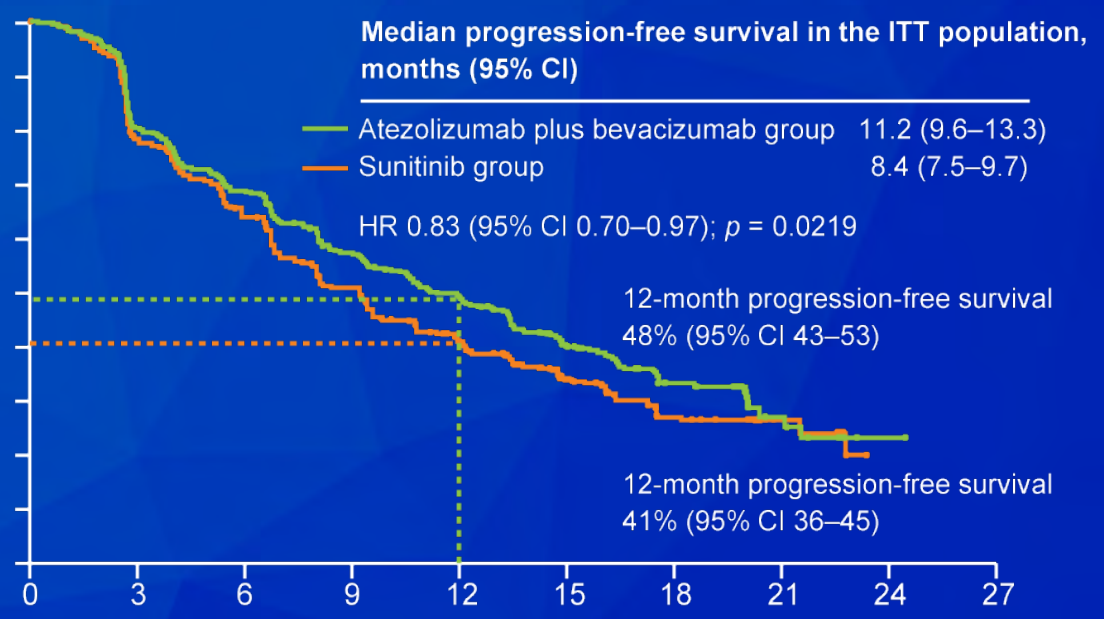
Should axitinib + pembro be used rather than Nivo + Ipi? The answer is not clear — we have follow-up data with the IO + IO combination for 3 years with HRs of 0.66 to 0.69 for OS and toxicity that is mainly in the first 12 weeks when the Ipi is given. Follow-up on the axitinib + pembro data from KEYNOTE-426 was less than 12 months when first reported and 15-16 months for the European filing update, with HRs of 0.53 to 0.59 and toxicity accruing from both agents dosed continuously that is an issue throughout the time of administration.

Atezolizumab plus Bevacizumab versus Sunitinib in Patients with Previously Untreated Metastatic Renal Cell Carcinoma (IMmotion151): A Multicentre, Open-Label, Phase 3, Randomised Controlled Trial

Rini BI et al; IMmotion151 Study Group.
Lancet 2019;393(10189):2404-15.

IMmotion151: Atezolizumab/Bevacizumab versus Sunitinib for Previously Untreated Metastatic Renal Cell Carcinoma





Number at risk (number censored)																				
Atezolizumab plus bevacizumab group	178 (0)	137 (5)	117 (7)	94 (9)	79 (11)	55 (26)	22 (49)	5 (64)	..	..	454 (0)	355 (10)	294 (17)	236 (24)	196 (32)	126 (74)	57 (126)	15 (159)	1 (170)	..
Sunitinib group	184 (0)	135 (5)	110 (6)	83 (7)	64 (10)	44 (17)	15 (37)	7 (44)	1 (49)	..	461 (0)	346 (15)	281 (19)	211 (24)	166 (33)	105 (70)	42 (116)	14 (140)	1 (151)	..

Rini BI et al; IMmotion151 Study Group. *Lancet* 2019;393(10189):2404-15.

Editorial — Dr Quinn

IMmotion151 tested atezolizumab and bev vs sunitinib on the back of data from IMmotion150, a randomized phase 2 study suggesting the combination may be better than SOC single agent. Unfortunately, while the study hit one of its co-primary endpoints of PFS in patients who have tumors that are PD-L1 high at first interim analysis, the study has not met its overall survival endpoint, and the company developing it has indicated that it will not pursue a license in the met RCC indication for this combination. We will not see this impact clinical practice.

CLEAR (NCT02811861): A Multicenter, Open-Label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma

Editorial — Dr Quinn

In this phase III study, which recently completed accrual, lenvatinib + pembro is compared to lenvatinib + everolimus and sunitinib in first-line met RCC. In the basket trial, the combination of len-pem produced high response rates similar to axitinib + pembro and axitinib + avelumab. This makes len + pembro a potentially very interesting combination. However, because the trial was undertaken about 2 years after the axitinib-based combinations, there is potential for the control arm to perform better for OS because nivolumab and other IO agents are given to a larger number of patients as second-line therapy after sunitinib.

The len-pem combination is active in endometrial cancer and HCC and is being tested in a wide range of solid tumors.

- **COSMIC-313** (NCT03937219): A Randomized, Double-Blind, Controlled Phase 3 Study of Cabozantinib in Combination with Nivolumab and Ipilimumab versus Nivolumab and Ipilimumab in Subjects with Previously Untreated Advanced or Metastatic Renal Cell Carcinoma of Intermediate or Poor Risk
- **CheckMate 9ER** (NCT03141177): A Phase 3, Randomized, Open-Label Study of Nivolumab Combined with Cabozantinib versus Sunitinib in Participants with Previously Untreated Advanced or Metastatic Renal Cell Carcinoma
- Zhang T et al. **PDIGREE**: An Adaptive Phase 3 Trial of PD-Inhibitor Nivolumab and Ipilimumab (IPI-NIVO) with VEGF TKI Cabozantinib (CABO) in Metastatic Untreated Renal Cell Cancer (Alliance A031704). *Proc ASCO* 2019;Abstract TPS4596.

Editorial — Dr Quinn

Cabozantinib, nivolumab and the Nivo + Ipi combination all improved OS in mRCC based on the METEOR, CheckMate 025 and CheckMate 214 trials.

The rationale for COSMIC-313 (ongoing) is that both cabozantinib and Nivo + Ipi improved OS in first-line intermediate- and poor-risk mRCC patients — this study tests the addition of cabo to the IO + IO backbone.

Checkmate 9ER (accrued) tests the CaboNivo combination against sunitinib in patients and in parts of the world where single-agent VEGFR TKI is still SOC.

PEDIGREE (accruing) is a cooperative group trial that compares the Nivo + Ipi regimen to cabo single agent.