Year in Review

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

Saturday, February 24, 2018, 8:00 AM – 4:00 PM
Charlotte, North Carolina

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Research To Practice®

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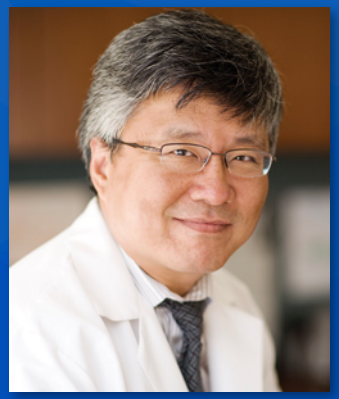
Disclosures

Consulting Agreements	Agenus Inc, Dendreon Pharmaceuticals Inc, Genentech BioOncology, ImmuneXcite, Janssen Biotech Inc, Lilly, Merck, NexImmune, Pierre Fabre, Roche Laboratories Inc
Contracted Research	Aduro Biotech, Bristol-Myers Squibb Company, Janssen Biotech Inc
Patents	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Janssen Biotech Inc
Stockholder	Compugen, NexImmune, Potenza Therapeutics, Tizona Therapeutics Inc
Other	Bristol-Myers Squibb Company



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Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Churchill Pharmaceuticals, Dendreon Pharmaceuticals Inc, Janssen Biotech Inc, Sanofi Genzyme

Select Recently Approved Agents in Genitourinary Cancers

Agent	Approval date	Indication
Renal Cell Carcinoma		
Sunitinib	11/16/17	Adjuvant therapy – patients at high risk for recurrence
Urothelial bladder cancer		
Pembrolizumab	5/18/17	Locally advanced or metastatic urothelial carcinoma not eligible for cisplatin chemotherapy Also approved for patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemo or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemo
Atezolizumab	4/17/17 and 5/18/16	
Avelumab	5/9/17	For patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemo or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemo
Durvalumab	5/1/17	
Nivolumab	2/2/17	

Genitourinary Cancers — Drs Drake and Oh

Renal Cell Carcinoma

Urothelial Bladder Cancer

Prostate Cancer

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma

Robert J. Motzer, Naomi B. Haas, Frede Donskov, Marine Gross-Goupil, Sergei Varlamov, Evgeny Kopyltsov, Jae Lyun Lee, Bohuslav Melichar, Brian I. Rini, Toni K. Choueiri, Milada Zemanova, Lori A. Wood, M. Neil Reaume, Arnulf Stenzl, Simon Chowdhury, Ho Yeong Lim, Ray McDermott, Agnieszka Michael, Weichao Bao, Marlene J. Carrasco-Alfonso, Paola Aimone, Maurizio Voi, Christian Doehn, Paul Russo, and Cora N. Sternberg, on behalf of the PROTECT investigators

Motzer RJ et al. *J Clin Oncol* 2017;35(35):3916-23.

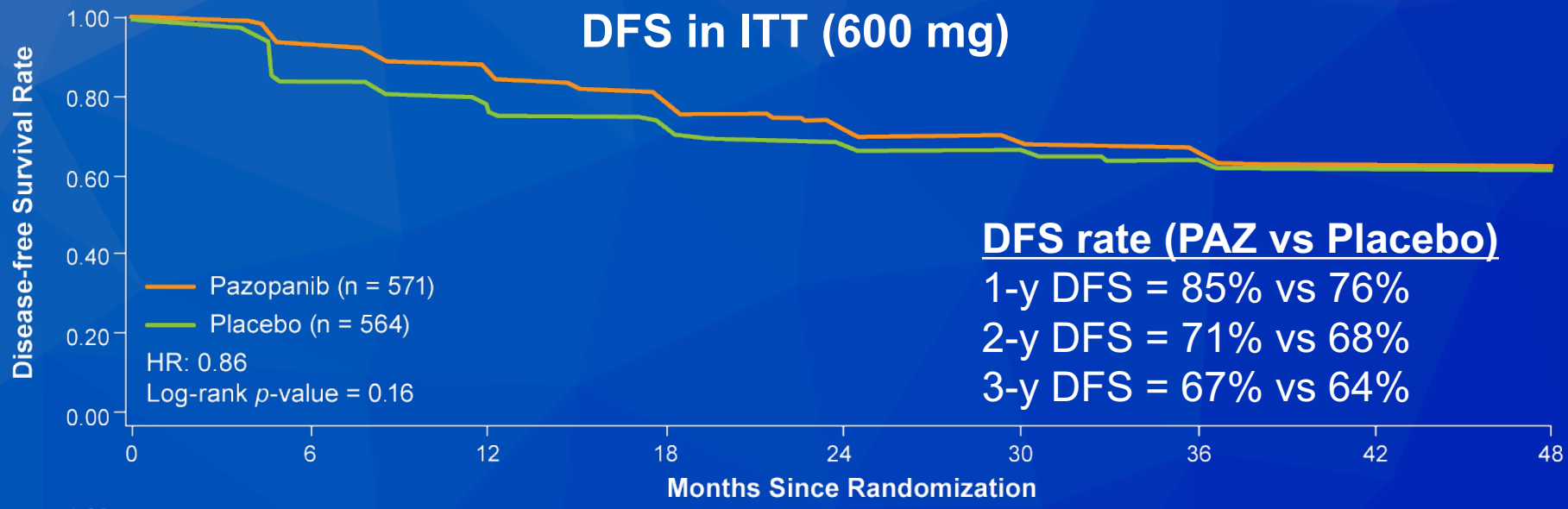
ORIGINAL ARTICLE

Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy

A. Ravaud, R.J. Motzer, H.S. Pandha, D.J. George, A.J. Pantuck, A. Patel, Y.-H. Chang, B. Escudier, F. Donskov, A. Magheli, G. Carteni, B. Laguerre, P. Tomczak, J. Breza, P. Gerletti, M. Lechuga, X. Lin, J.-F. Martini, K. Ramaswamy, M. Casey, M. Staehler, and J.-J. Patard, for the S-TRAC Investigators*

N Engl J Med 2016;375(23):2246-54.

PROTECT: Disease-Free Survival (DFS) and OS

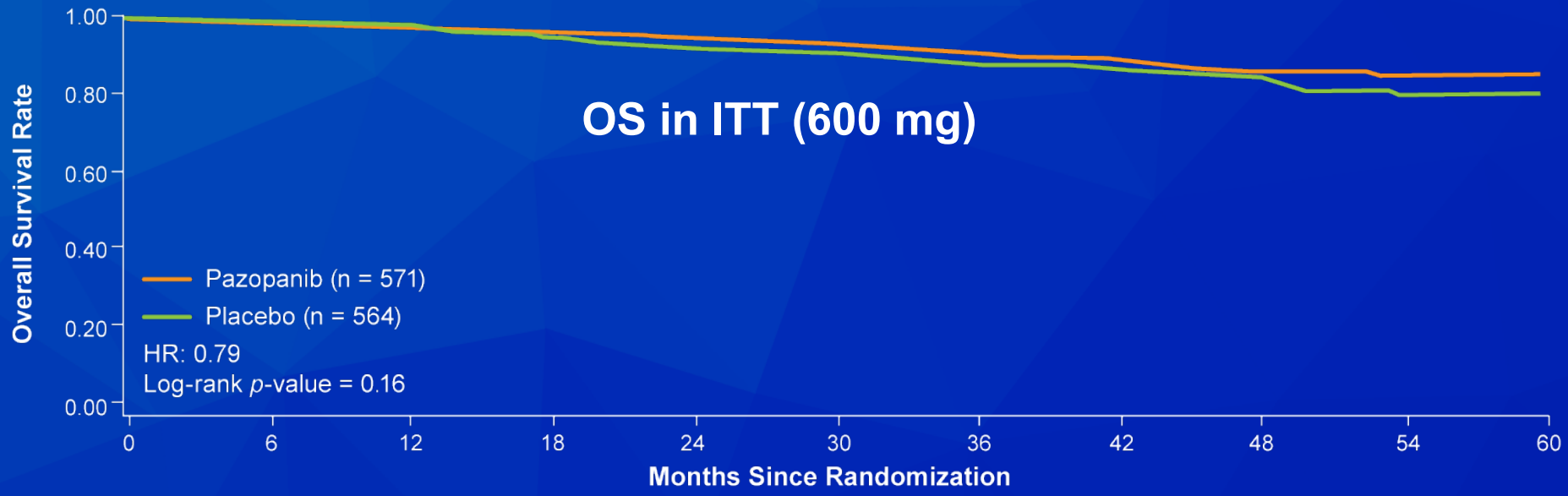


DFS rate (PAZ vs Placebo)

1-y DFS = 85% vs 76%

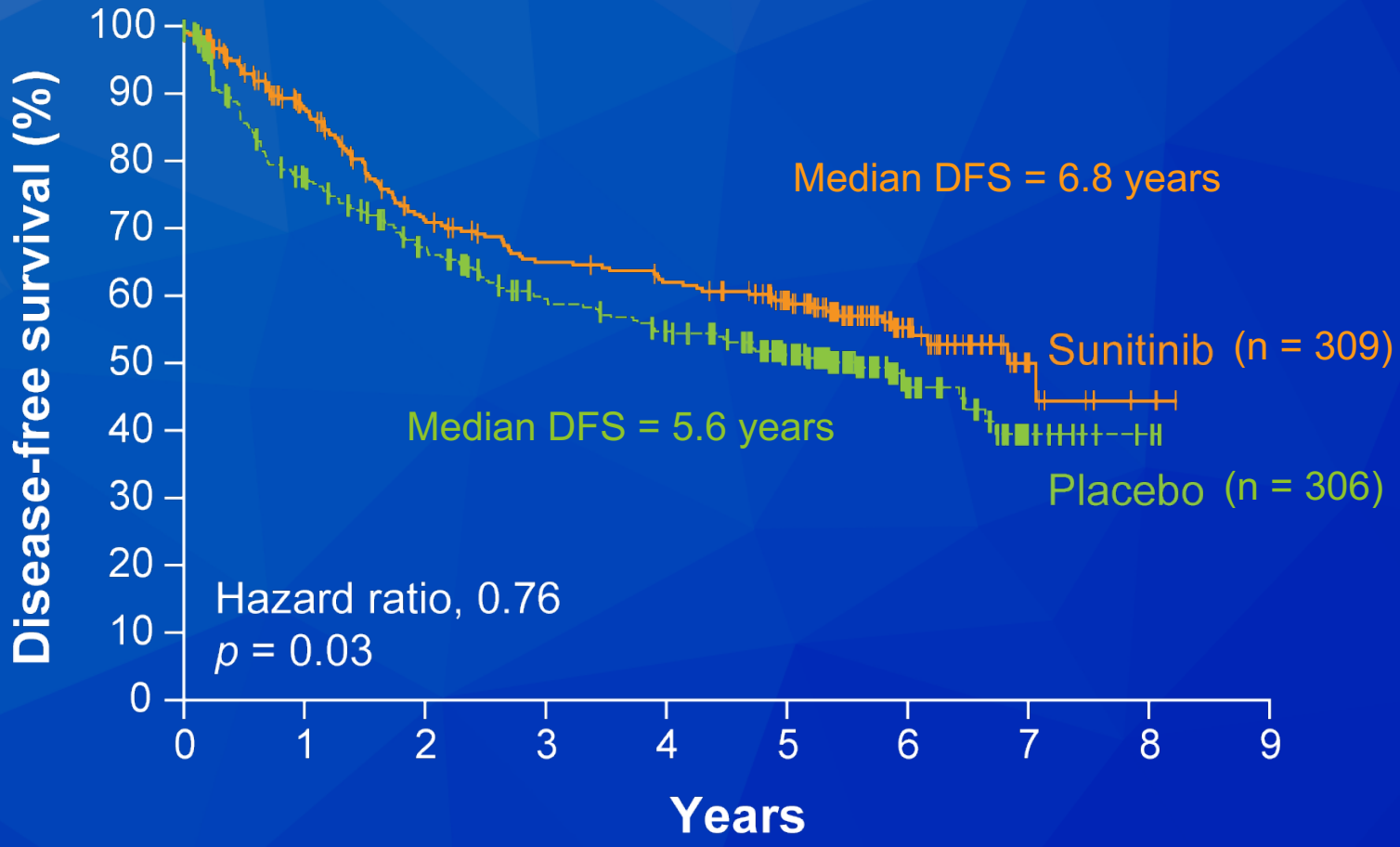
2-y DFS = 71% vs 68%

3-y DFS = 67% vs 64%



Motzer RJ et al. *J Clin Oncol* 2017;35(35):3916-23.

S-TRAC: DFS and Safety



- Grade 3 or 4 AEs were more frequent in the sunitinib group than placebo
  - Grade 3 = 48.4% vs 15.8%
  - Grade 4 = 12.1% vs 3.6%

Ravaud A et al. *N Engl J Med* 2016;375(23):2246-54.

Press Release — FDA Approval of Sunitinib as Adjuvant Therapy for Renal Cell Carcinoma November 16, 2017

“The US Food and Drug Administration has approved a new indication expanding the use of sunitinib malate to include the adjuvant treatment of adult patients at high risk of recurrent renal cell carcinoma following nephrectomy.

The approval was based on results from the S-TRAC trial that demonstrated a significant reduction in the risk of a disease-free survival event (defined as the interval between randomization and tumor recurrence, or secondary primary cancer or death from any cause) for patients at high risk of RCC recurrence who received sunitinib malate compared to placebo in the adjuvant setting.”

https://finance.yahoo.com/news/pfizer-receives-fda-approval-sutent-215800996.html

Editorial — Dr Drake

In addition to the previously published ASSURE trial (Haas et al, *Lancet* 2016) these trials add to the experience of adjuvant VEGF-TKI treatment of RCC. S-TRAC enrolled approximately 600 RCC patients with Stage III and above disease who were randomized 1:1 to either sunitinib (50 mg/day, 4 wks on 2 wks off) with a primary endpoint of DFS. Dose reductions to 37.5 mg/day were permitted, but unlike other trials the starting dose and schedule of the TKI were kept constant throughout the study. PROTECT was a similar trial using pazopanib; the trial originally used a dose of 800 mg/day but the starting dose was lowered to 600 mg/day after enrollment of approximately 400 patients, to improve tolerability. A new primary endpoint (DFS in the 600 mg/day cohort) was put into place, and approximately 1,200 patients total were enrolled.

Editorial — Dr Drake (continued)

S-TRAC met its primary endpoint with a DFS of 6.8 years in the sunitinib group as compared to 5.6 years in the placebo group. OS was not mature at the time of publication. By contrast, PROTECT did NOT meet its primary endpoint. A secondary analysis of DFS at the higher pazopanib dose of 800 mg (400 patients total) showed a small but statistically significant improvement in DFS (HR 0.69, $p = 0.02$), but that was a secondary endpoint.

So, out of the 3 reported adjuvant TKI trials in RCC, only one (S-TRAC) appears to be positive, with an approximate 1.2 year improvement in DFS. What distinguishes S-TRAC from ASSURE is that S-TRAC continued to start with a higher dose of sunitinib (50 mg) throughout the course of the trial and permitted dose reductions to 37.5 mg but not to 25 mg.

Editorial — Dr Drake (continued)

S-TRAC was also limited to patients with clear-cell RCC, whereas ASSURE allowed other histological subtypes. Like ASSURE, PROTECT also changed the starting dose during the trial course; pharmacological analyses suggested that DFS was improved with increased trough concentrations.

Overall, these 3 trials suggest that adjuvant TKI therapy using sunitinib should likely be considered for Stage III+ patients with clear cell RCC who are likely to tolerate full dose treatment and remain on treatment x 1 year.

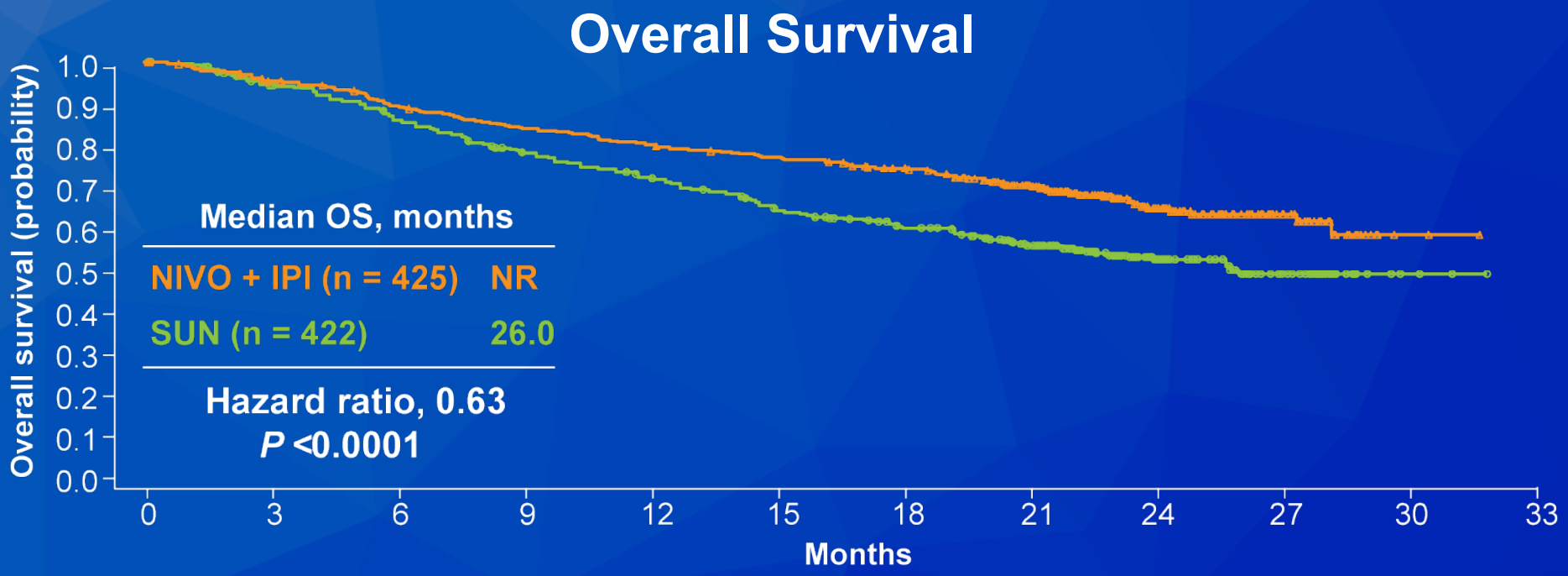
Editorial — Dr Drake (continued)

Patients should also be aware of and willing to tolerate AEs, which were consistent with the known AE profile of sunitinib in the metastatic setting although greater in frequency. In particular, skin toxicity (palmar/plantar erythrodysesthesia), hypertension and fatigue were relatively common.

CheckMate 214: Efficacy and Safety of Nivolumab + Ipilimumab (N+I) v Sunitinib (S) for Treatment-Naïve Advanced or Metastatic Renal Cell Carcinoma (mRCC), Including IMDC Risk and PD-L1 Expression Subgroups

Escudier B et al.
Proc ESMO 2017;Abstract LBA5.

CheckMate 214: Primary Endpoints (IMDC Intermediate/Poor Risk)



By independent review	NIVO + IPI (n = 425)	SUN (n = 422)	HR	*p*-value
PFS	11.6 mo	8.4 mo	0.82	0.0331
Confirmed ORR	42%	27%	—	<0.0001

Escudier B et al. *Proc ESMO* 2017;Abstract LBA5.

CheckMate 214: Treatment-Related Adverse Events (TRAE)

Event	NIVO + IPI N = 547		Sunitinib N = 535	
	Any grade	Grade 3-5	Any grade	Grade 3-5
Any TRAE (in ≥25% of patients)	93%	46%	97%	63%
TRAE leading to discontinuation	22%	15%	12%	7%
Treatment-related deaths	n = 7		n = 4	
Fatigue	37%	4%	49%	9%
Pruritus	28%	<1%	9%	0%
Diarrhea	27%	4%	52%	5%
Nausea	20%	2%	38%	1%
Hypothyroidism	16%	<1%	25%	<1%
Decreased appetite	14%	1%	25%	1%
Hypertension	2%	<1%	40%	16%
Palmar-plantar erythrodysesthesia	1%	0%	43%	9%

Escudier B et al. *Proc ESMO* 2017;Abstract LBA5.

Editorial — Dr Dreicer

The role of immunotherapy in metastatic renal cancer has a long and somewhat tortured history. Until the FDA approval of sorafenib in 2004, interferon-alfa, although never FDA approved, was the most widely used systemic therapy. High-dose interleukin-2 is an FDA-approved therapy with very small numbers of patients achieving long-term disease control.

Following the FDA approval of nivolumab in advanced renal cancer, Escudier and colleagues reported CheckMate 214, which randomized 847 patients with intermediate or poor risk metastatic renal cancer (1,096 total patients) to receive either standard dose/schedule sunitinib or nivolumab 3 mg/kg plus ipilimumab 1 mg/kg x 4 doses followed by nivolumab q2 weeks for 2 years.

Editorial — Dr Dreicer (continued)

Patients receiving the immunotherapy had a 9.4% CR with a PFS improvement >3 months. The median OS for sunitinib was 26 months, not reached with ipi/nivo (HR 0.63, P 0.00003). Of interest in an exploratory analysis, patients with tumor PD-L1 ≥1% demonstrated higher ORR and PFS. Toxicity was consistent with ipi/nivo. More patients had high-grade treatment adverse events with sunitinib but more patients discontinued ipi/nivo secondary to toxicity.

Following the presentation of this data, the DMC stopped the study, noting that it had met its co-primary endpoint demonstrating superior overall survival in intermediate and poor risk patients.

Editorial — Dr Dreicer (continued)

After likely FDA approval of ipi/nivo for advanced renal cancer, clinicians will now need to begin to assess subsets of patients for this therapy option. In CheckMate 214, the median age of enrolled patients was 61-62, much younger than many patients we see in day to day practice. Although not as toxic as HD-IL2, clinicians will need to use clinical judgement re whom to offer ipi/nivo to up front, including perhaps patients with good-risk disease.

IMmotion150: A Phase II Trial in Untreated Metastatic Renal Cell Carcinoma (mRCC) Patients (pts) of Atezolizumab (atezo) and Bevacizumab (bev) vs and Following Atezo or Sunitinib (sun)

First-Line Avelumab + Axitinib Therapy in Patients (pts) with Advanced Renal Cell Carcinoma (aRCC): Results from a Phase Ib Trial

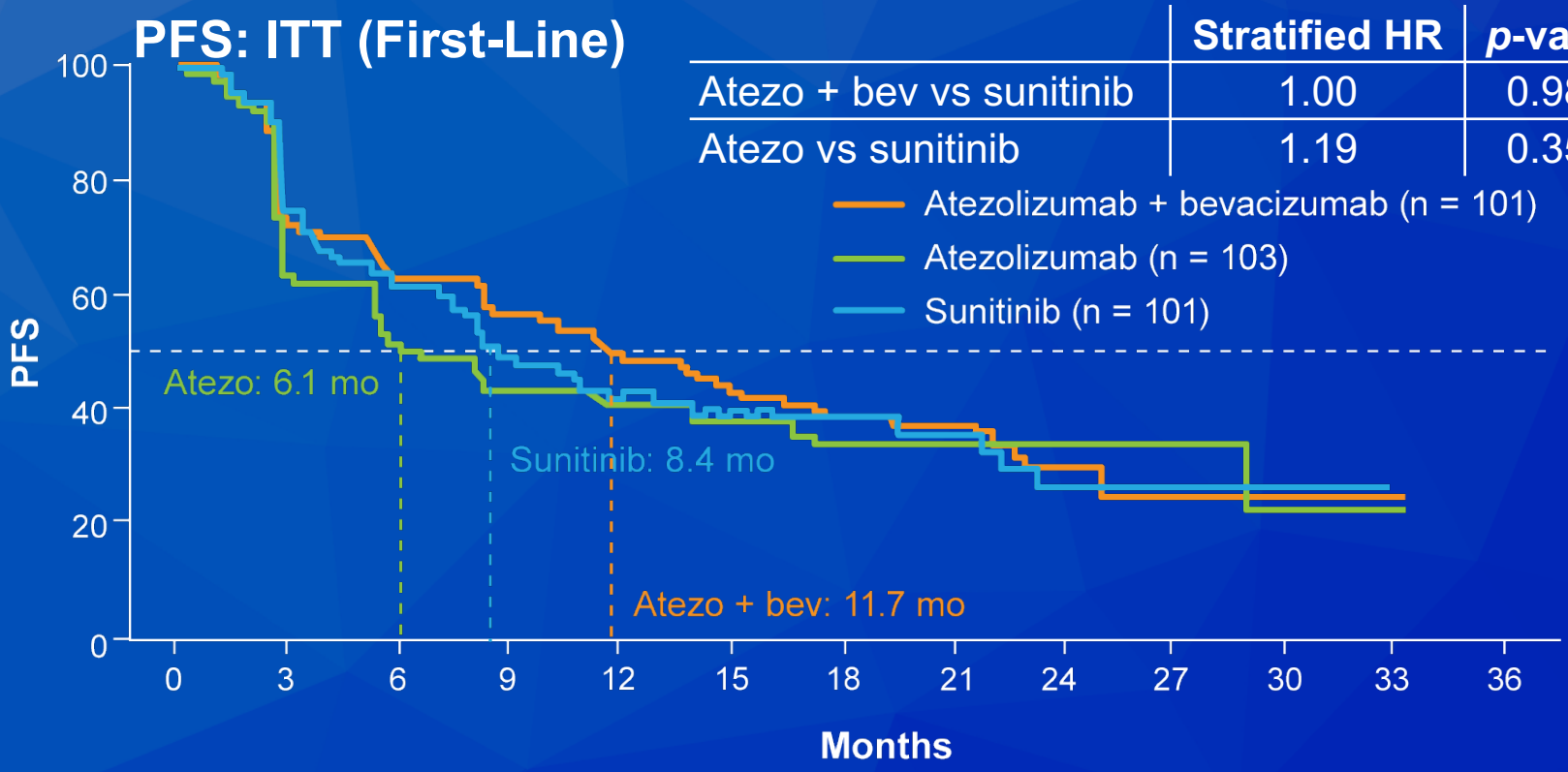
A Phase I/II Study to Assess the Safety and Efficacy of Pazopanib (PAZ) and Pembrolizumab (PEM) in Patients (pts) with Advanced Renal Cell Carcinoma (aRCC)

Atkins MB et al.
Proc ASCO 2017;Abstract 4505.

Choueiri TK et al.
Proc ASCO 2017;Abstract 4504.

Chowdhury S et al.
Proc ASCO 2017;Abstract 4506.

IMmotion150: Atezolizumab with or without Bevacizumab vs Sunitinib for Untreated Metastatic RCC



	Stratified HR	*p*-value
Atezo + bev vs sunitinib	1.00	0.982
Atezo vs sunitinib	1.19	0.358

First line (n = 54, 60, 50)	Atezo	SUN	Atezo/bev
≥1% PD-L1 (IC)	5.5 mo	7.8 mo	14.7 mo
After crossover to atezo/bev	**Post atezo**	**Post SUN**	**All**
Median PFS (n = 44, 57, 101)	12.6 mo	8.3 mo	8.8 mo

IC = tumor-infiltrating immune cells

Atkins MB et al. *Proc ASCO* 2017;Abstract 4505.

JAVELIN Renal 100: Clinical Outcomes

Outcome	All patients (n = 55)	≥1% PD-L1 (IC) (n = 41)	PD-L1-negative (n = 11)
ORR	32 (58.2%)	27 (65.9%)	4 (36.4%)
Complete response	3 (5.5%)	Not reported	Not reported
Partial response	29 (52.7%)	Not reported	Not reported

- Disease control rate (n = 55) = 43 (78.2%)
- The safety profile of avelumab + axitinib appears manageable and is consistent with the safety profile for each agent as monotherapy.
- Most common AE reported: diarrhea (n = 31)
- Grade 3-4 AEs include: hypertension (n = 16), hepatitis (n = 2), increased amylase (n = 3) and lipase (n = 4)
- Grade 5 AE: myocarditis (n = 1)

Choueiri TK et al. *Proc ASCO* 2017;Abstract 4504.

Phase I/II Trial of Pazopanib (PAZ) and Pembrolizumab (PEM): Clinical Outcomes

Outcome	Cohort A (n = 10)	Cohort B (n = 10)	Cohort C (n = 9)	
			PAZ/PEM (n = 5)	PEM (n = 4)
ORR	6 (60%)	2 (20%)	1 (20%)	0
Complete response	2 (20%)	1 (10%)	0	0
Partial response	4 (40%)	1 (10%)	1 (20%)	0

Cohort A = PAZ 800 mg + PEM; Cohort B = PAZ 600 mg + PEM; Cohort C = PAZ 800 mg → PAZ + PEM

- Dose-limiting toxicities in Cohort C combination group include: pneumonitis, bowel perforation and increased lipase
- The PAZ/PEM combination in patients with advanced RCC is not feasible due to hepatotoxicity
- **Conclusion:** Pazopanib is not recommended in combination with pembrolizumab in this population of patients.

Chowdhury S et al. *Proc ASCO* 2017;Abstract 4506.

Editorial — Dr Dreicer

Despite the potential for checkpoint inhibitors in advanced renal cancer, the proportion of patients responding remains modest in the 20%-25% range. There is ongoing need to both improve the proportion of patients who respond and develop new options for patients who either fail to respond or progress on checkpoint inhibitors.

IMmotion 150 randomized 305 previously untreated patients to receive either atezolizumab plus bevacizumab (AB), atezolizumab (A) or sunitinib (S). Upon progression patients treated with either A or S could crossover to AB.

Although this study was hypothesis generating in intent, there was activity seen in both A and S treated patients when they were crossed over to receive AB, with 24% and 28% of patients achieving a PR respectively.

Editorial — Dr Dreicer (continued)

In this small experience tumor PD-L1 status modestly enriched for crossover therapy response. The toxicity of the AB combination was acceptable.

This study and others are testing the theoretical potential for VEGFR-targeted agents to enhance the immune response to checkpoint inhibitors. With many trials of the oral TKIs in combination with checkpoint inhibitors ongoing, it will be challenging to sort out the optimal agents and sequence. IMmotion 151 randomizes patients to receive AB vs S in untreated metastatic renal cancer. This trial has completed its enrollment.

Editorial — Dr Dreicer

In an effort to further expand the response rates to checkpoint inhibitors, investigators have combined avelumab, an anti-PD-L1 antibody, with the potent VEGFR-TKI axitinib in 55 untreated patients with metastatic renal cancer. Following a dose escalation component, patients received axitinib 5 mg BID and avelumab 10 mg/kg every 2 weeks. Responses were seen in 20 of 32 patients, many ongoing at the time of the report. There was an intriguing high objective response rate in the 59% range. Although there was a grade 5 myocarditis event, in general immune AEs seemed consistent with toxicity seen with each individual agent.

Editorial — Dr Dreicer (continued)

This combination of a checkpoint inhibitor plus a VEGFR-TKI provides some early evidence of a higher objective response rate than would be expected for either agent. The challenge of this combination, however, is the requirement for ongoing administration of the TKI, which for many patients is problematic given the life-altering chronic toxicities experienced by many patients. Among the most important observations in CheckMate 025 (nivo vs everolimus) was the durability of response in a subset of patients, highlighting the potential as these agents move up earlier to administer 1 therapy and have long-term disease control without the toxicity burden of TKIs. JAVELIN Renal 101 is a phase III trial comparing the avelumab plus axitinib regimen versus sunitinib as first line therapy. This trial is open and actively recruiting patients.

Editorial — Dr Drake

This was a small (25 pts reported on) study to assess whether the standard-of-care VEGF-TKI pazopanib could be co-administered with the anti-PD-1 antibody pembrolizumab. Two doses of pazopanib (600 and 800 mg) were tested, and a third cohort tested sequential administration of pazopanib → pembrolizumab.

The results were clear: the concomitant combination is not tolerable primarily due to liver toxicity. Grade III/IV AE rates were 90% in cohorts 1 and 2 respectively.

Comment: These results are strikingly consistent with a prior study in which the anti-PD-1 antibody nivolumab was administered along with pembrolizumab in a Phase II trial.

Editorial — Dr Drake (continued)

In that trial (Amin et al, ASCO 2014), the combination showed a 70% rate of Grade III/IV AE and the pazopanib + nivolumab arm was discontinued due to toxicity. It's a bit puzzling why this trial was initiated; since nivolumab and pembrolizumab are biologically similar, it would have been incredibly surprising if pembro + pazo was better tolerated than nivo + pazo.

IMmotion151: A Randomized Phase III Study of Atezolizumab plus Bevacizumab versus Sunitinib in Untreated Metastatic Renal Cell Carcinoma

Motzer RJ et al.
Genitourinary Cancers Symposium 2018;Abstract 578.

IMmotion151: Clinical Outcomes and Safety

PD-L1-positive population	Atezo + Bev (n = 178)	Sunitinib (n = 184)	HR	*p*-value
Median PFS	11.2 mo	7.7 mo	0.74	0.0217
ORR	43%	35%	—	NR
ITT population	**Atezo + Bev (n = 454)**	**Sunitinib (n = 461)**	**HR**	***p*-value**
Median PFS	11.2 mo	8.4 mo	0.83	0.0219
ORR	37%	33%	—	NR

- OS was immature at time of first interim analysis.
- Grade 3/4 AEs: 40% (Atezo/bev) vs 54% (sunitinib)
- Discontinuations due to AEs: 12% (Atezo/bev) vs 8% (sunitinib)

Motzer RJ et al. Genitourinary Cancers Symposium 2018;Abstract 578.

FDA grants regular approval to cabozantinib for first-line treatment of advanced renal cell carcinoma

Press Release — December 19, 2017

"On December 19, 2017, the Food and Drug Administration granted regular approval to cabozantinib for treatment of patients with advanced renal cell carcinoma (RCC).

The FDA previously approved cabozantinib in 2016 for treatment of patients with advanced RCC who have received prior anti-angiogenic therapy. Today's approval provides for treatment in the first-line setting.

This approval was based on data from CABOSUN (NCT01835158), a randomized, open-label phase 2 multicenter study in 157 patients with intermediate and poor-risk previously untreated RCC."

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm589842.htm

Progression-Free Survival (PFS) by Independent Review and Updated Overall Survival (OS) Results from Alliance A031203 Trial (CABOSUN): Cabozantinib versus Sunitinib as Initial Targeted Therapy for Patients (pts) with Metastatic Renal Cell Carcinoma (mRCC)

Choueiri TK et al. *Proc ESMO* 2017;Abstract LBA38.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

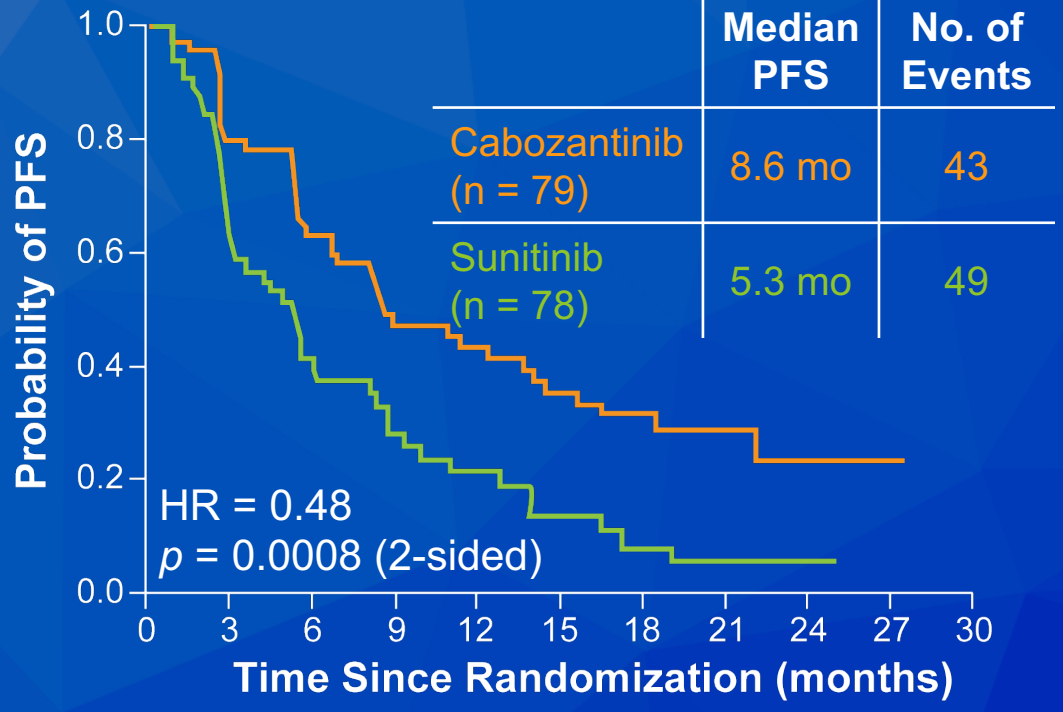
Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial

Toni K. Choueiri, Susan Halabi, Ben L. Sanford, Olwen Hahn, M. Dror Michaelson, Meghara K. Walsh, Darren R. Feldman, Thomas Olencki, Joel Picus, Eric J. Small, Shaker Dakhil, Daniel J. George, and Michael J. Morris

J Clin Oncol 2017;35(6):591-7.

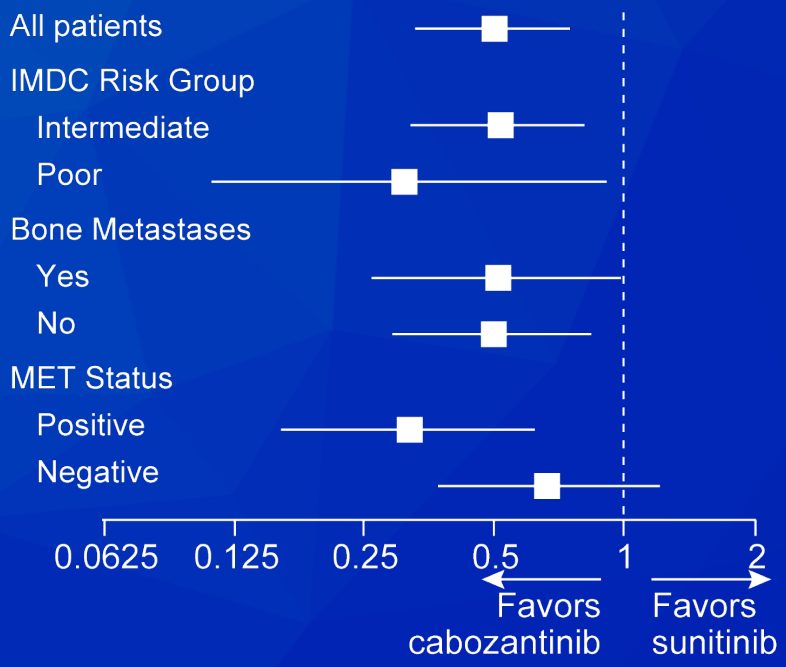
CABOSUN: PFS by Independent Review Committee (IRC) and Updated OS Results

PFS by IRC



	Median PFS	No. of Events
Cabozantinib (n = 79)	8.6 mo	43
Sunitinib (n = 78)	5.3 mo	49

Subgroup Analyses of PFS per IRC



Overall Survival (OS)

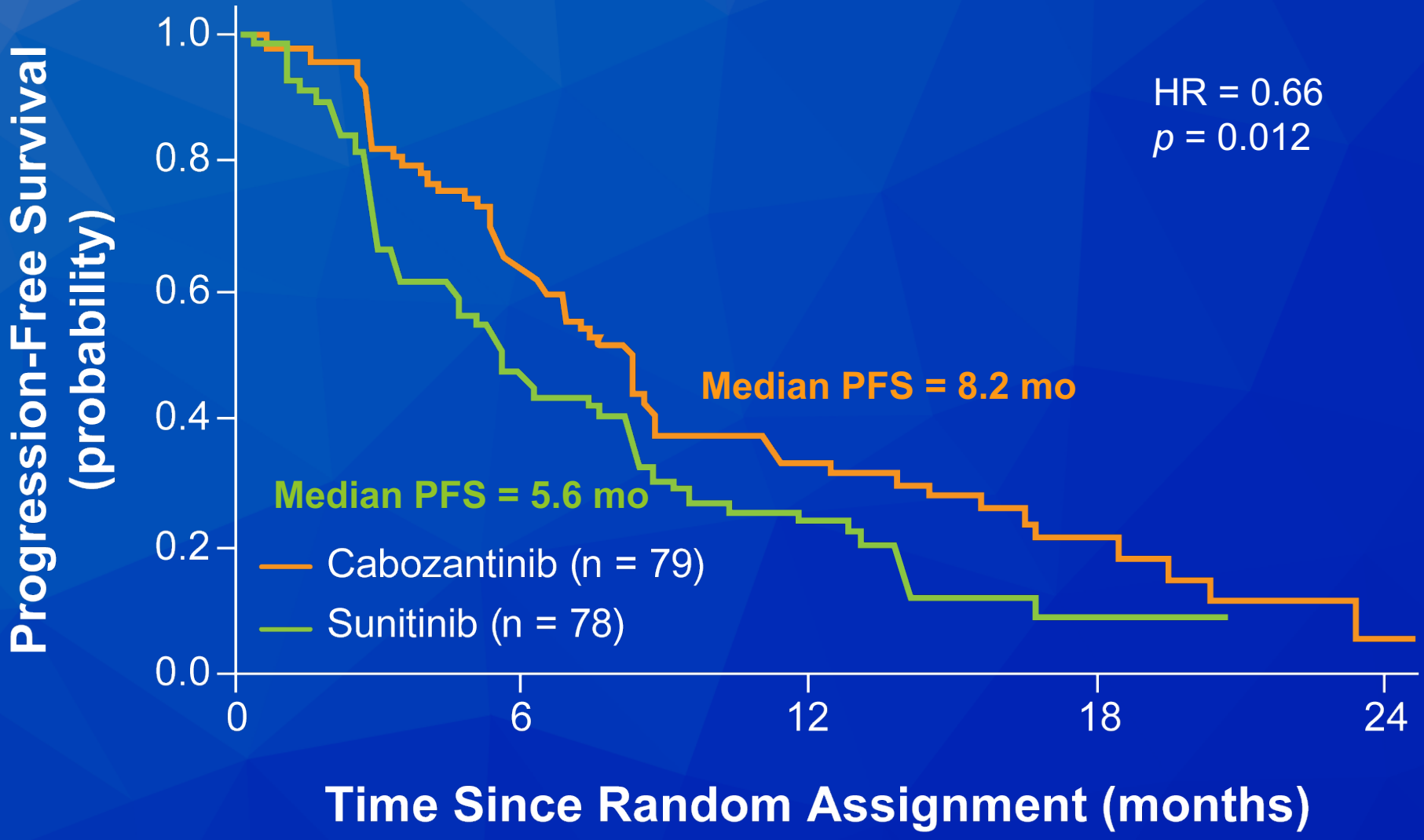
HR = 0.80, p = 0.29 (2-sided)

Median OS: Cabozantinib 26.6 mo, sunitinib 21.2 mo

IMDC = International Metastatic RCC Database Consortium

Choueiri T et al. *Proc ESMO* 2017;Abstract LBA38.

CABOSUN: PFS by Investigator Assessment (INV)



Choueiri TK et al. *J Clin Oncol* 2017;35(6):591-7.

Editorial — Dr Drake

CABOSUN was a relatively small (approx 160 pts) randomized Phase II trial attempting to bring cabozantinib to the first line setting in RCC. Cabozantinib inhibits MET and AXL in addition to VEGF-RII signaling and is FDA approved in the second line setting based on the Phase III METEOR study. This trial randomized patients 1:1 to cabozantinib vs sunitinib, with a primary endpoint of PFS (investigator assessed); secondary endpoints included ORR, safety and OS.

The trial met its primary endpoint, significantly increasing OS (from 5.6 to 8.2 months). ORR was also higher with cabo (46% vs 18%). Tolerability of the two agents was nearly identical, with grade III/IV rates of approx 68% for both agents.

Editorial — Dr Drake (continued)

Fatigue and hematologic toxicity were perhaps a bit more common with sunitinib, whereas hand/foot syndrome was potentially increased with cabo. Re-analysis of PFS by central review was consistent with the investigator-assessed data.

Overall, these data likely establish cabo as a potential treatment modality for first line RCC. The ORR was reasonable, and in fact similar to recently reported data from the immunological combination of anti-PD-1 and anti-CTLA-4 (CheckMate 214, Escudier at al, ESMO 2017).

Editorial — Dr Drake (continued)

What was perhaps a bit surprising was the performance of sunitinib in this setting: in the ipi/nivo study the first line ORR of sunitinib was 28% — similar to the 29% reported in the COMPARZ trial (Motzer et al, *NEJM* 2013), whereas in CABOSUN ORR for sunitinib was only 18%. That's possibly explained by the patient population under study: CABOSUN included no low-risk patients. The overall tolerability of the two agents was also quite similar; it should be noted that although sunitinib is FDA approved using the 4 weeks on, 2 week off schedule, some clinicians use a 2 weeks on, 1 week off schedule with improved tolerability (Sidaway P, *Nat Rev Urol* 2015).

Genitourinary Cancers — Drs Drake and Oh

Renal Cell Carcinoma

Urothelial Bladder Cancer

Prostate Cancer

Immune Checkpoint Inhibitors in Urothelial Bladder Cancer

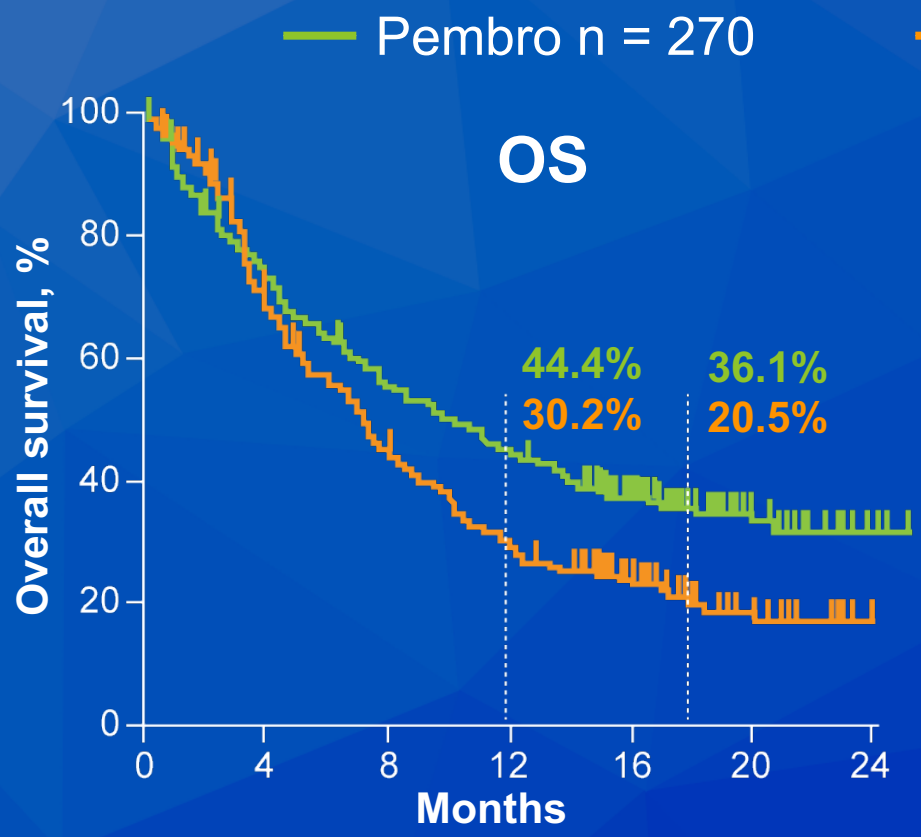
Agent	Antibody target	Approval date	Key studies	Administration schedule	Setting
Atezolizumab	PD-L1	5/18/16 and 4/17/17	IMvigor210	q3wk	First line for patients ineligible for cisplatin chemotherapy Second line after platinum-containing chemotherapy
Pembrolizumab	PD-1	5/18/17	KEYNOTE-052 KEYNOTE-045	q3wk	
Avelumab	PD-L1	5/9/17	JAVELIN	q2wk	Second line after platinum-containing chemotherapy
Durvalumab	PD-L1	5/1/17	Study 1108	q2wk	
Nivolumab	PD-1	2/2/17	CheckMate 275	q2wk	

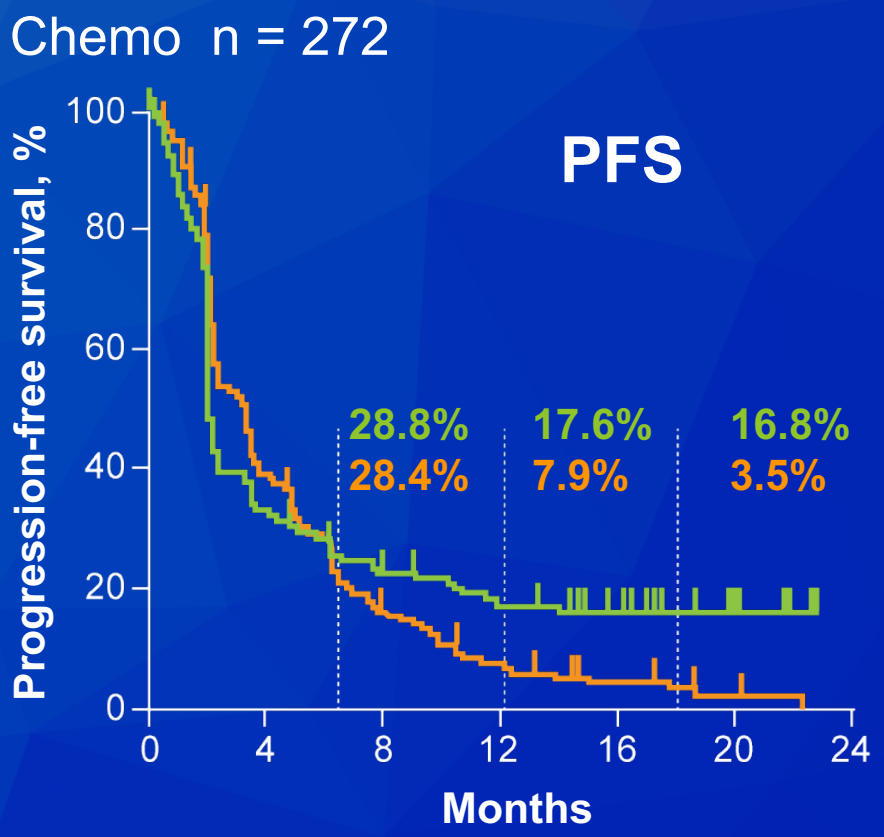
https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm

Updated Survival Analysis from KEYNOTE-045: Phase 3, Open-Label Study of Pembrolizumab (pembro) versus Paclitaxel, Docetaxel, or Vinflunine in Recurrent, Advanced Urothelial Cancer (UC)

Bajorin DF et al.
Proc ASCO 2017;Abstract 4501.

KEYNOTE-045: PFS and OS Results





	Pembro (n = 270)	Chemo (n = 272)	HR	*p*-value
Median OS	10.3 mo	7.4 mo	0.7	0.0004
Median PFS	2.1 mo	3.3 mo	0.96	0.32

Bajorin DF et al. *Proc ASCO* 2017;Abstract 4501.

Editorial — Dr Drake

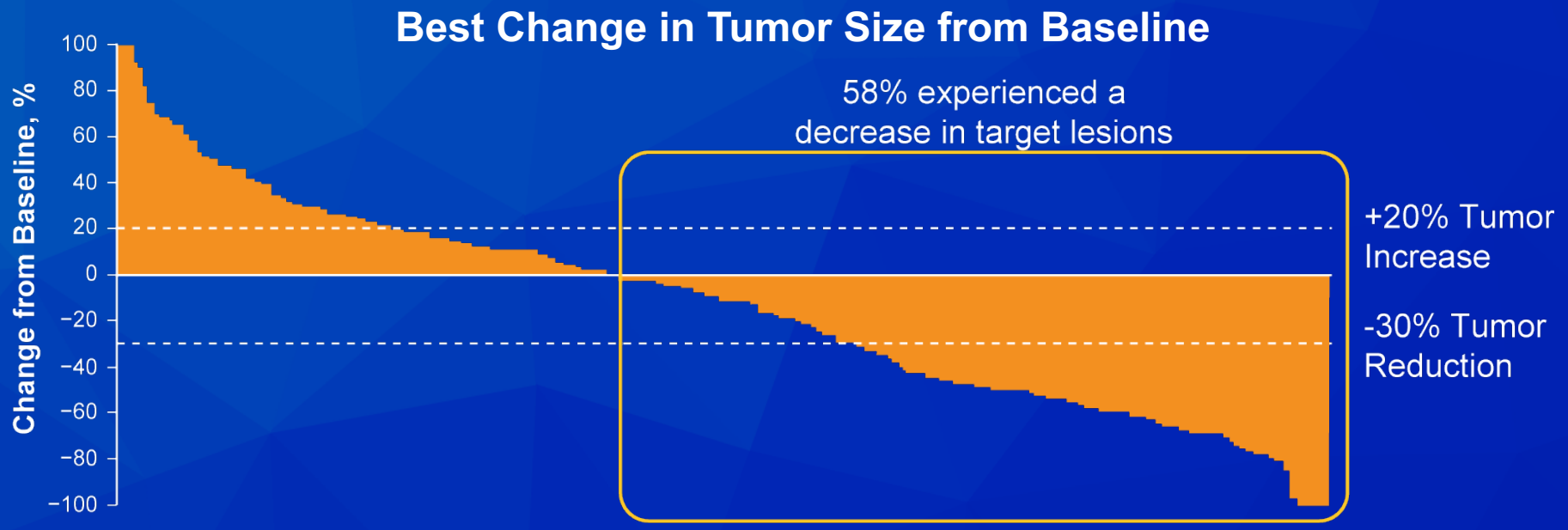
Pembrolizumab is a humanized IgG4 anti-PD-1 antibody that is FDA approved for multiple indications, most notably NSCLC where first line administration is limited to PD-L1+ patients. This randomized controlled Phase III trial compared pembrolizumab to chemotherapy in second line UBC. 542 patients were randomized to pembro vs investigator's choice chemotherapy (docetaxel, vinflunine, paclitaxel). There were co-primary endpoints of OS and PFS; OS was met with a median OS of 10.3 months in the pembro arm as compared to 7.4 months in the chemo arm. PFS was not significantly different between arms. Grade III/IV AE for pembro were similar to that observed in other studies (15% here), whilst chemotherapy had a 49% rate of Grade III/IV/V AE. Overall, this study provided the first Level I evidence for ICB in second line UBC.

Biomarker Findings and Mature Clinical Results from KEYNOTE-052: First-Line Pembrolizumab (pembro) in Cisplatin-Ineligible Advanced Urothelial Cancer (UC)

O'Donnell PH et al.
Proc ASCO 2017;Abstract 4502.

KEYNOTE-052: Response

Outcome	All (n = 370)	Validation set (n = 265)	
		≥10% PD-L1 (n = 80)	<10% PD-L1 (n = 185)
Confirmed ORR	108 (29%)	41 (51%)	42 (23%)
Complete response	27 (7%)	14 (18%)	5 (3%)
Partial response	81 (22%)	27 (34%)	37 (20%)



O'Donnell PH et al. *Proc ASCO* 2017;Abstract 4502.

Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial

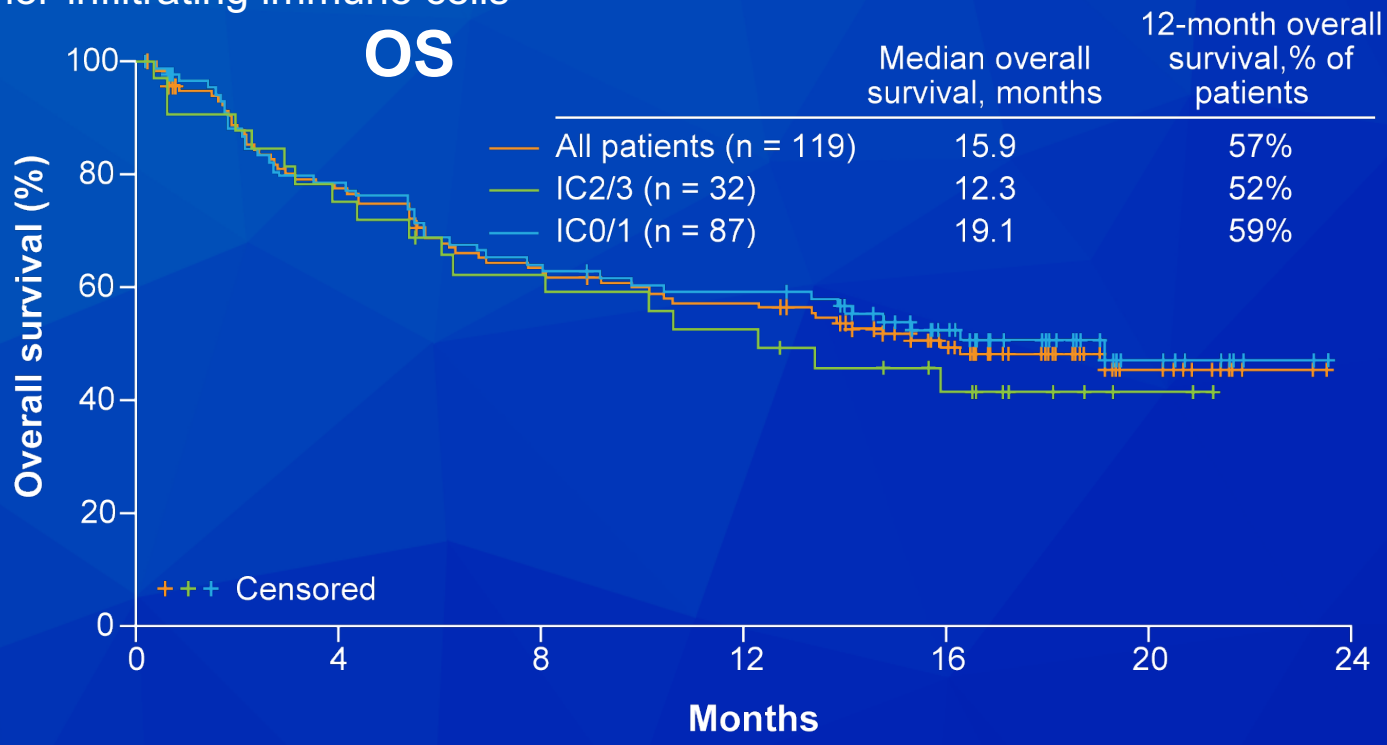
*Arjun V Balar, Matthew D Galsky, Jonathan E Rosenberg, Thomas Powles, Daniel P Petrylak, Joaquim Bellmunt, Yohann Loriot, Andrea Necchi, Jean Hoffman-Censits, Jose Luis Perez-Gracia, Nancy A Dawson, Michiel S van der Heijden, Robert Dreicer, Sandy Srinivas, Margitta M Retz, Richard W Joseph, Alexandra Drakaki, Ulka N Vaishampayan, Srikala S Sridhar, David I Quinn, Ignacio Durán, David R Shaffer, Bernhard J Eigl, Petros D Grivas, Evan Y Yu, Shi Li, Edward E Kadel III, Zachary Boyd, Richard Bourgon, Priti S Hegde, Sanjeev Mariathasan, AnnChristine Thåström, Oyewale O Abidoye, Gregg D Fine, Dean F Bajorin, for the IMvigor210 Study Group**

Lancet 2017;389(10064):67-76.

IMvigor210: Response and OS

Outcome	All (n = 119)	IC2/3 (n = 32)	IC1/2/3 (n = 80)	IC1 (n = 48)	IC0 (n = 39)
Confirmed ORR	27 (23%)	9 (28%)	19 (24%)	10 (21%)	8 (21%)
CR	11 (9%)	4 (12.5%)	8 (10%)	4 (8.3%)	3 (7.7%)
PR	16 (13%)	5 (15.6%)	11 (13.8%)	6 (12.5%)	5 (12.8%)

IC = tumor-infiltrating immune cells



Balar AV et al. *Lancet* 2017;389(10064):67-76.

Editorial — Dr Drake

IMvigor 210 was a single-armed Phase II trial that evaluated the anti-PD-L1 antibody atezolizumab in both first and second line UBC. This manuscript reports on the IMvigor cohort 1 patients; these 123 patients were ineligible for platinum-based chemotherapy and received atezolizumab in the first line setting. ORR was 23%, with a median PFS of 2.7 months and an OS of 16 months. This study also reported some biomarker data: ORR was associated with tumor mutational burden as well as with the luminal subgroup. PD-L1 expression *on immune cells* using the VENTANA PD-L1 (SP142) assay was surprisingly not associated with ORR in this first line setting.

Editorial — Dr Drake (continued)

These Level II data established atezolizumab as a potential first line treatment option for patients with metastatic UBC who were deemed to be platinum ineligible.

Since both cohorts of IMvigor 210 were non-randomized, confirmatory randomized Phase III studies were considered important in developing level 1 evidence for atezolizumab in UBC. The first of these, IMvigor 211, enrolled 900 second line patients — comparing atezolizumab to dealer's choice chemotherapy (vinflunine, docetaxel or paclitaxel) with a primary endpoint of OS. Patients were enrolled regardless of PD-L1 IC status.

Editorial — Dr Drake (continued)

A recent press release reported that trial as negative for its primary readout, although data have not been presented or published. A second randomized ‘confirmatory’ trial, IMvigor 130, comparing atezolizumab to chemotherapy to atezolizumab *plus* chemotherapy in the first line setting, is ongoing.

Atezolizumab (atezo) vs. Chemotherapy (Chemo) in Platinum-Treated Locally Advanced or Metastatic Urothelial Carcinoma (mUC): Immune Biomarkers, Tumor Mutational Burden (TMB), and Clinical Outcomes from the Phase III IMvigor211 Study

Powles T et al.
Genitourinary Cancers Symposium 2018;Abstract 409.

IMvigor211: OS Results

Median OS	Atezo	Chemo	HR
ITT (N = 931)	8.6 mo	8.0 mo	0.85
IC2/3 (n = 234)	11.1 mo	10.6 mo	0.87
IC1/2/3 (n = 625)	8.9 mo	8.2 mo	0.87
tGE3-high (n = 397)	9.2 mo	9.3 mo	0.77
TMB-high (n = 274)	11.3 mo	8.3 mo	0.68

tGE = immune transcriptional gene expression; TMB = tumor mutational burden; IC = immune cells

Powles T et al. Genitourinary Cancers Symposium 2018;Abstract 409.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

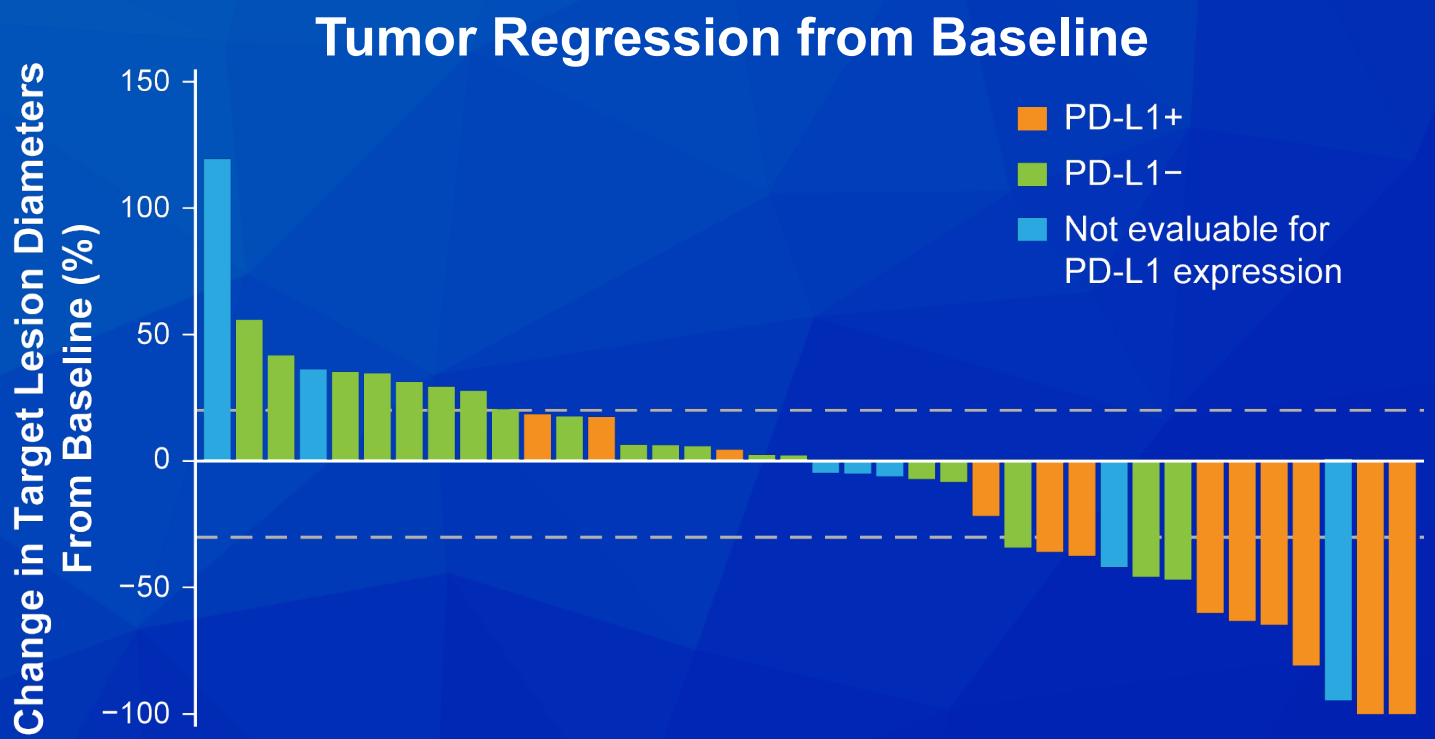
Avelumab, an Anti–Programmed Death-Ligand 1 Antibody, In Patients With Refractory Metastatic Urothelial Carcinoma: Results From a Multicenter, Phase Ib Study

Andrea B. Apolo, Jeffrey R. Infante, Ani Balmanoukian, Manish R. Patel, Ding Wang, Karen Kelly, Anthony E. Mega, Carolyn D. Britten, Alain Ravaud, Alain C. Mita, Howard Safran, Thomas E. Stinchcombe, Marko Srdanov, Arnold B. Gelb, Michael Schlichting, Kevin Chin, and James L. Gulley

J Clin Oncol 2017;35(19):2117-24.

Phase Ib Trial of Avelumab: Efficacy

Outcome	All (n = 44)
Confirmed ORR	8 (18.2%)
Median OS	13.7 mo
Median PFS	11.6 weeks



Apolo AB et al. *J Clin Oncol* 2017;35(19):2117-24.

Phase Ib Trial of Avelumab: Safety Results

Adverse event (n = 44)	All grades	Grade 3	Grade 4
Fatigue	9 (20.5%)	0	0
Infusion-related reaction	9 (20.5%)	0	0
Asthenia	5 (11.4%)	1 (2.3%)	0
Rash	4 (9.1%)	0	0
Hypothyroidism	3 (6.8%)	0	0
Elevated CPK	1 (2.3%)	0	1 (2.3%)
Pneumonitis	1 (2.3%)	0	0
Uveitis	1 (2.3%)	0	0

CPK = creatinine phosphokinase

- Avelumab was well tolerated.

Apolo AB et al. *J Clin Oncol* 2017;35(19):2117-24.

Editorial — Dr Drake

Avelumab is a third anti-PD-L1 antibody, and this agent is a little different than other PD-L1 antibodies in that it is of the human IgG1 isotype and this may have the potential to mediate antibody dependent cellular cytotoxicity (ADCC). This manuscript reports on a small (44 patient) expansion cohort from a larger trial. The confirmed ORR for avelumab in second line (and beyond) UBC was 18%, similar to that of the other PD-1/PD-L1 targeted agents. Tolerability was similar as well, with 7% Grade III/IV treatment-related AE. Although the rate of Grade III/IV events may seem promising here, the relatively small patient number needs to be factored; a larger cohort of 200 patients is being enrolled.

JAMA Oncology | Original Investigation

Efficacy and Safety of Durvalumab in Locally Advanced or Metastatic Urothelial Carcinoma

Updated Results From a Phase 1/2 Open-label Study

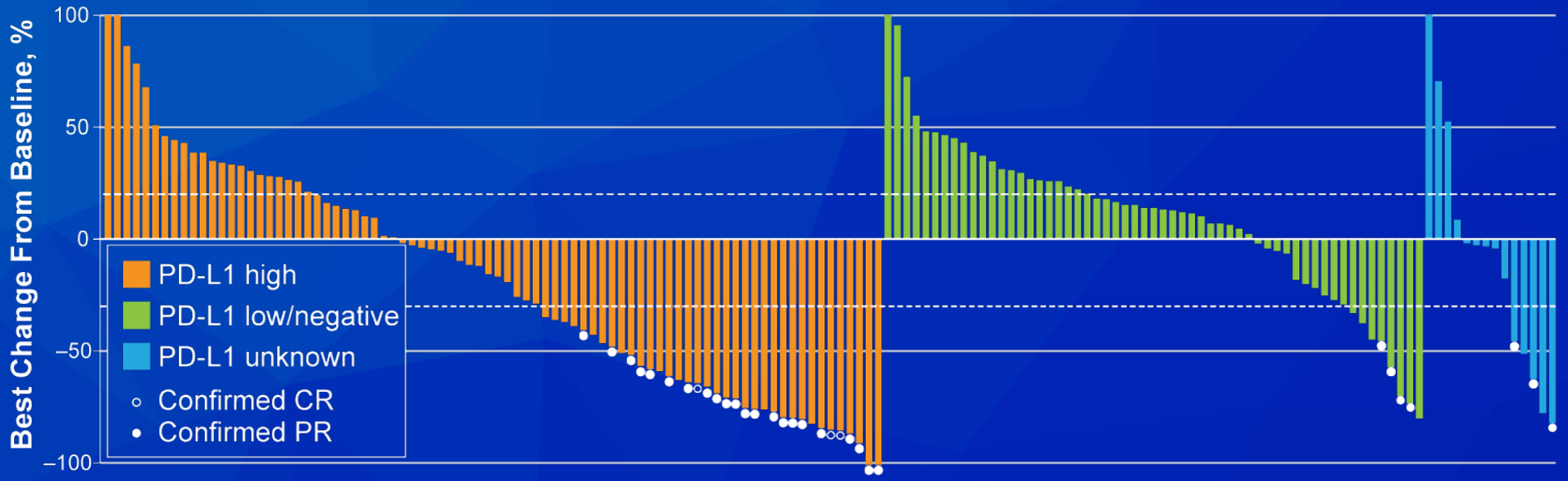
Thomas Powles, MD; Peter H. O'Donnell, MD; Christophe Massard, MD, PhD; Hendrik-Tobias Arkenau, MD, PhD; Terence W. Friedlander, MD; Christopher J. Hoimes, DO; Jae Lyun Lee, MD; Michael Ong, MD; Srikala S. Sridhar, MD; Nicholas J. Vogelzang, MD; Mayer N. Fishman, MD, PhD; Jingsong Zhang, MD, PhD; Sandy Srinivas, MD; Jigar Parikh, MD; Joyce Antal, MS; Xiaoping Jin, PhD; Ashok K. Gupta, MD, PhD; Yong Ben, MD; Noah M. Hahn, MD

JAMA Oncol 2017;3(9):e172411.

Phase I/II Trial of Durvalumab: Response and OS

Outcome	All (n = 191)	PD-L1 high (n = 98)	PD-L1 low/neg (n = 79)
Confirmed ORR	34 (17.8%)	27 (27.6%)	4 (5.1%)
Median duration of response	Not reached	Not reached	12.25 mo
Median OS	18.2 mo	20.0 mo	8.1 mo

Best % change from baseline



Powles T et al. *JAMA Oncol* 2017;3(9):e172411.

Editorial — Dr Drake

Durvalumab is an anti-PD-L1 antibody; this manuscript reports data on the activity and tolerability of this agent in a second line cohort of patients from a non-randomized Phase I/II study. 192 UBC patients are described; the ORR was 18%. Safety and tolerability were similar to other PD-1/PD-L1 agents, and as with other agents PD-L1 expression (SP263 assay from Ventana) was associated with both ORR and outcome. These level II data established durvalumab as a second line treatment option for patients with UBC.

Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial

Padmanee Sharma, Margitta Retz, Arlene Siefker-Radtke, Ari Baron, Andrea Necchi, Jens Bedke, Elizabeth R Plimack, Daniel Vaena, Marc-Oliver Grimm, Sergio Bracarda, José Ángel Arranz, Sumanta Pal, Chikara Ohyama, Abdel Saci, Xiaotao Qu, Alexandre Lambert, Suba Krishnan, Alex Azrilevich, Matthew D Galsky

Lancet Oncol 2017;18(3):312-22.

CheckMate 275: Response

Outcome	All (n = 265)	≥5% PD-L1 (n = 81)	≥1% PD-L1 (n = 122)	<1% PD-L1 (n = 143)
Confirmed ORR	52 (19.6%)	23 (28.4%)	29 (23.8%)	23 (16.1%)
Complete response	6 (2.3%)	4 (4.9%)	5 (4.1%)	1 (0.7%)
Partial response	46 (17.3%)	19 (23.5%)	24 (19.7%)	22 (15.4%)

- Median duration of response was not reached in the overall population.
- At the time of the analysis, responses were ongoing in 40 (77%) of the 52 patients with a confirmed response.
- Follow-up is ongoing.

Sharma P et al. *Lancet Oncol* 2017;18(3):312-22.

Editorial — Dr Drake

CheckMate 275 was a single-armed Phase II trial evaluating anti-PD-1 (nivolumab) in second line UBC. The primary endpoint was OS in either all patients or in patients with PD-L1 expression >1% or >5%. Median follow-up for OS was only 7 months, ie, this is a relatively early readout. ORR was 20% (all comers) and 28% in patients with PD-L1 expression >5% using the 28-8 Dako assay. Tolerability was similar to the experience with nivolumab in other settings, with a Grade III/IV AE rate of 18% overall, primarily Grade III fatigue and diarrhea.

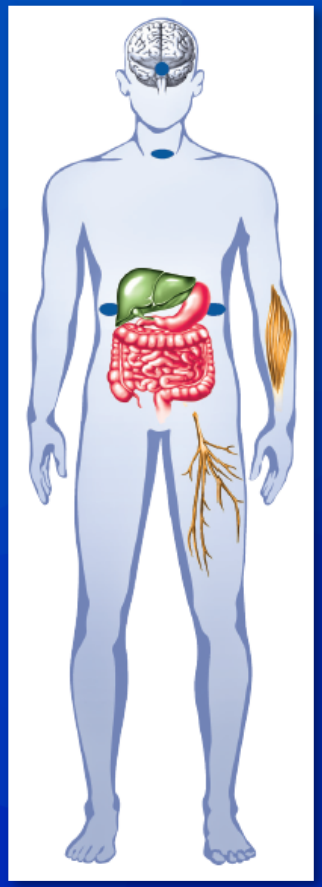
Editorial — Dr Drake (continued)

These data are similar to those previously observed for atezolizumab in the second line setting (IMvigor 210, Rosenberg JE et al, *Lancet* 2016) and establish nivolumab as a treatment option for patients with UBC that progresses on a platinum-based regimen. Like the IMvigor data, these results also suggest that PD-L1 expression enriches (slightly) for patients more likely to respond to PD-1 blockade. Like the IMvigor 210 data, these are not Level 1 data since this was not a randomized controlled trial.

Immune-Related Adverse Events (irAEs)

Activation of the immune system against tumors can result in a novel spectrum of irAEs

- May be due to cytokine release by activated T cells
- May be unfamiliar to clinicians
- Requires a multidisciplinary approach
- Can be serious
- Requires prompt recognition and treatment
- Requires patient and HCP education



Occasional (5%-20%) irAEs

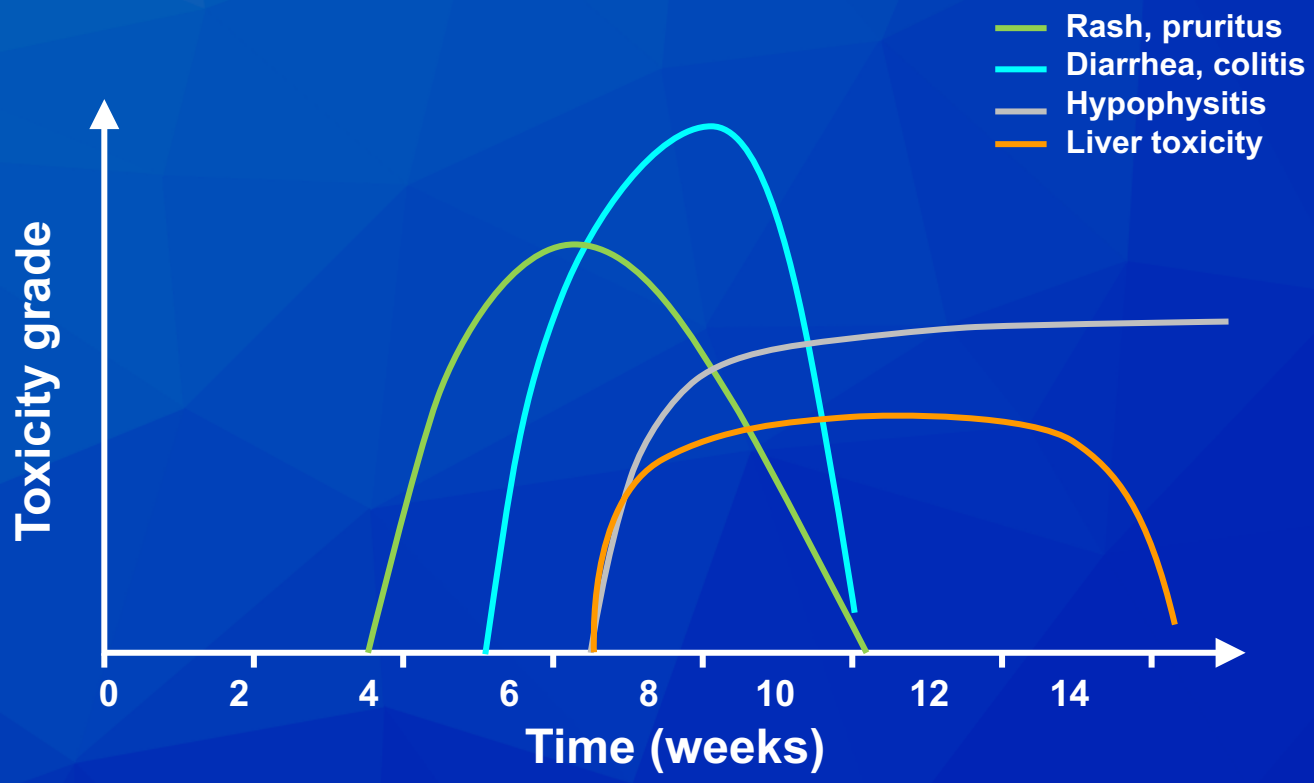
Grade 3/4 Uncommon

- Hypophysitis
- Thyroiditis
- Adrenal insufficiency
- Colitis
- Dermatitis
  - Macropapular/pruritus
- Pneumonitis
- Hepatitis
- Pancreatitis
- Arthritis
- Neuropathies

Amos SM, et al. *Blood* 2011;118:499–509; YERVOY immune-related adverse reactions management guide. October 2012. Available at https://www.yervoy.co.uk/Images/6682_IrAR%20management%20guide%20731EMEA12PM014.pdf. Accessed September 2014; Chin K, et al. Poster presented at ESMO 2008 (abstr. 787P).

Time of Onset and Resolution of irAEs

- Each irAE has different kinetics of onset
- Rash first, followed by colitis, hypophysitis and finally hepatitis



Weber JS et al. *J Clin Oncol* 2012;30(21):2691-7.

General Management of irAEs According to Severity

Grade 1	• Supportive care ± withhold drug
Grade 2	• Withhold drug • Re-dose if toxicity resolved to Grade ≤1 • Low-dose corticosteroids if symptoms do not resolve in 1 week (prednisone 0.5 mg/kg/d)
Grade 3/4	• Discontinue drug • High-dose corticosteroids tapered over ≥1 month until toxicity resolves to Grade ≤1 (prednisone 1-2 mg/kg/d or equivalent)

- **Immunosuppressives (eg, infliximab) may be considered if steroids not effective**
- **Standard algorithms available for management of irAEs**

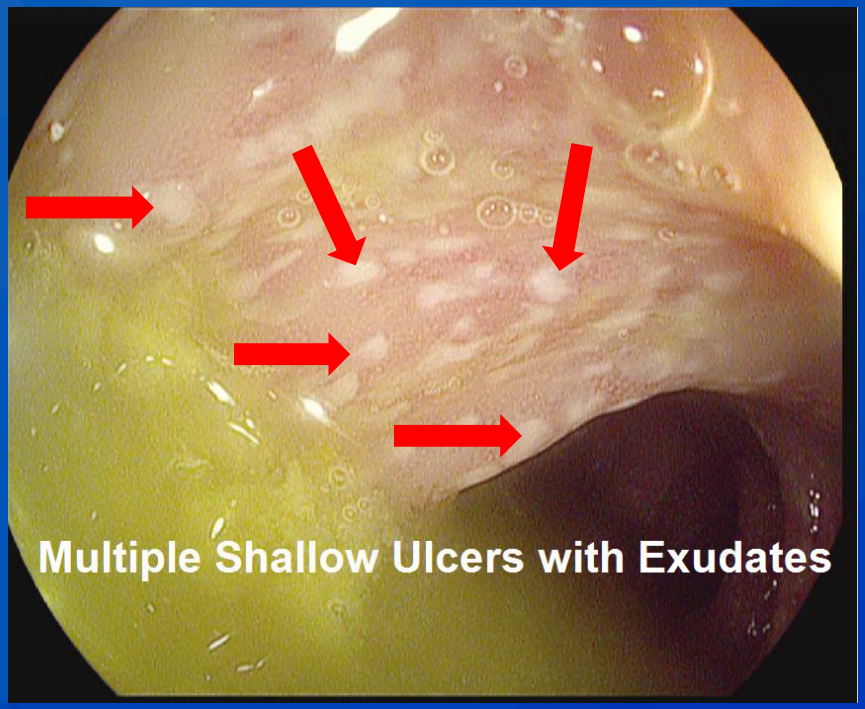
Courtesy of Evan J Lipson, MD, David R Spigel, MD

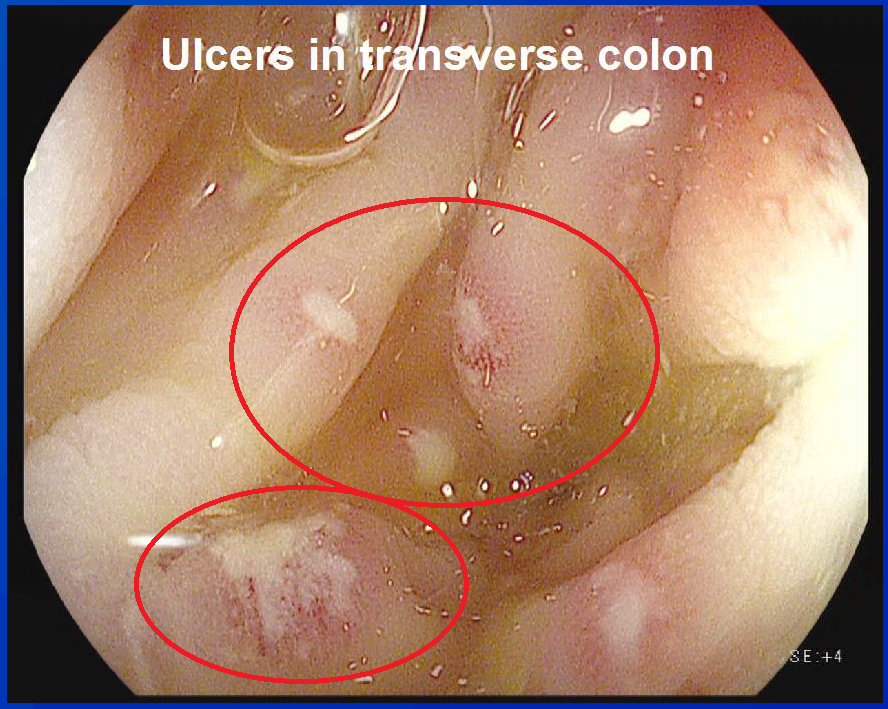
Immune-Mediated Colitis: Incidence, Signs and Symptoms

- Incidence: 2% to 3%
- Diarrhea (loose stools) or more bowel movements than usual
- Blood in stools or dark, tarry, sticky stools
- Severe stomach area (abdomen) pain or tenderness

Nivolumab package insert 2016; Nivolumab Immune-Mediated Adverse Reactions Management Guide. Available at www.opdivohcp.bmscustomerconnect.com/metastatic-nsclc/opdivo-resources-support

Autoimmune Colitis



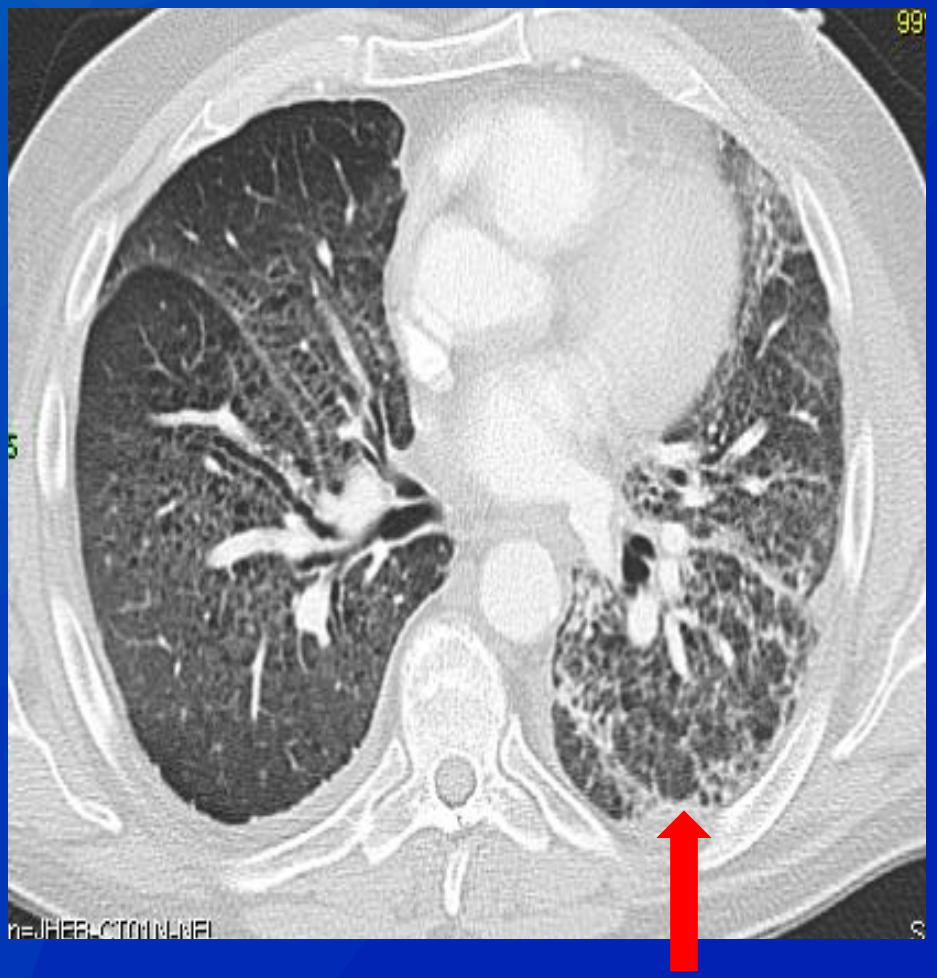


Colonoscopy performed on a 51-year-old man with metastatic melanoma who developed watery diarrhea after receiving an immune checkpoint-blocking drug

Images courtesy of Animesh Jain, MD, Johns Hopkins University School of Medicine

Pneumonitis

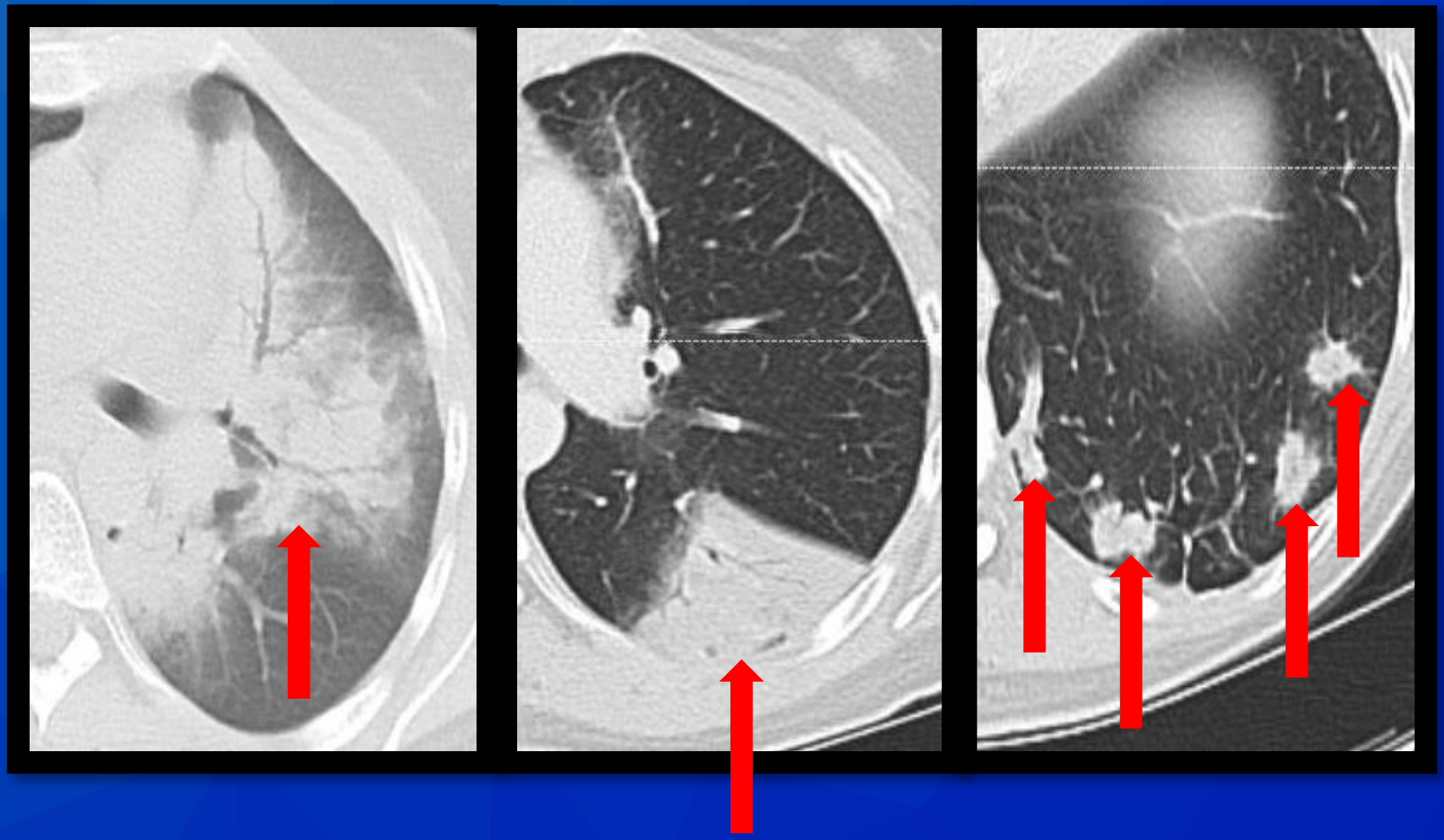
- Radiographs
  - New or changes
    Ground-glass changes
    Nodular or interstitial
- Symptoms
  - New or worsening
    Cough, shortness of breath
- Signs
  - Decrease in oxygen saturation



Diffuse interstitial infiltrates L > R

Courtesy of Julie R Brahmer, MD, MSc

Highly Variable Radiographic Appearance of Pneumonitis



Courtesy of Evan J Lipson, MD

Pneumonitis Treatment

Grade	Management
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider pulmonary and ID consults
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1 mg/kg/day of prednisolone IV or oral equivalent • Consider bronchoscopy, lung biopsy
Grade 3-4 Severe new symptoms; new/worsening hypoxia; life-threatening	• Permanently discontinue I-O therapy • Hospitalize • Pulmonary and ID consults • 1-2 mg/kg/day methylprednisolone IV or IV equivalent • Prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy

Courtesy of Evan J Lipson, MD

FDA Analysis of Patients with Baseline Autoimmune Diseases Treated with PD-1/PD-L1 Inhibitors

Weinstock C et al.
Proc ASCO 2017;Abstract 3018.

RANGE: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Docetaxel (DOC) with or without Ramucirumab (RAM) in Platinum-Refractory Advanced or Metastatic Urothelial Carcinoma

Petrylak DP et al.
Proc ESMO 2017;Abstract LBA4_PR.

RANGE: Efficacy and Safety Results

ITT population	DOC + RAM (n = 263)	DOC + placebo (n = 267)	HR	*p*-value
Median PFS by INV	4.1 mo	2.8 mo	0.757	0.0118
ORR	24.5%	14.0%	NR	NR

ORR = objective response rate; NR = not reported

- OS data were immature at time of analysis.
- Grade ≥3 AEs occurred at a similar frequency in both arms with no unexpected toxicities.
  - Most common = neutropenia (15% RAM vs 14% placebo)

Petrylak DP et al. *Proc ESMO* 2017;Abstract LBA4_PR.

Genitourinary Cancers — Drs Drake and Oh

Renal Cell Carcinoma

Urothelial Bladder Cancer

Prostate Cancer

Management of M0 Prostate Cancer

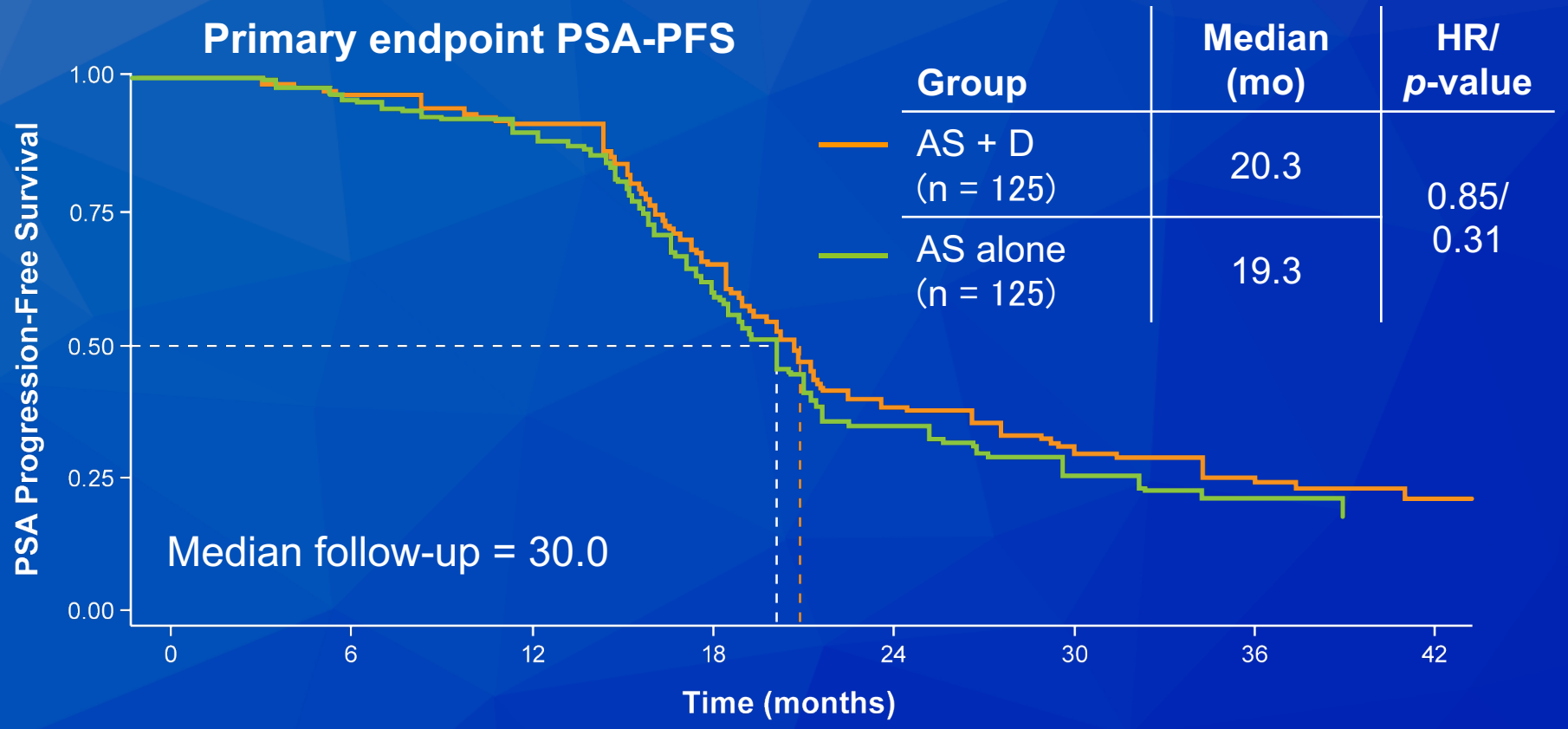
Key Decision Points in the Systemic Treatment of Prostate Cancer

- Adjuvant therapy (with radiation therapy or surgery)
- Locally advanced disease (with radiation therapy)
- M0 disease (PSA-only)
  - Hormone sensitive
  - Hormone resistant
- M1 disease
  - Hormone sensitive
  - Hormone resistant (1st, 2nd, 3rd-line therapies)

Docetaxel (D) with Androgen Suppression (AS) for High-Risk Localized Prostate Cancer (HrPC) Patients (pts) Who Relapsed PSA After Radical Prostatectomy (RP) and/or Radiotherapy (RT): A Randomized Phase III Trial

Oudard S et al.
Proc ESMO 2017;Abstract 784O.

Phase III Trial: Clinical Outcomes



Group	Median (mo)	HR/ *p*-value
AS + D (n = 125)	20.3	0.85/ 0.31
AS alone (n = 125)	19.3	

Outcome	AS + D (n = 125)	AS alone (n = 125)	HR	*p*-value
Radiographic PFS	10.5 years	10.0 years	1.01	0.95

At time of data analysis, OS data were not yet mature.

Oudard S et al. *Proc ESMO* 2017;Abstract 784O.

Editorial — Dr Dreicer

Patients with locally advanced prostate cancer have a relatively high rate (25%-40%) of PSA progression following curative-intent local therapy and present clinicians with a management challenge given the absence of level 1 evidence to guide optimal therapy.

A multicenter French clinical trial randomized 250 patients treated with curative intent with either surgery or radiotherapy to receive androgen deprivation therapy (ADT) with an LHRH agonist with or without docetaxel x 6 cycles. Eligible patients had no evidence of metastases and at least 1 of the following: positive nodes, positive surgical margins, Gleason ≥8, PSA DT ≤6 months, and PSA velocity >0.75 ng/mL/yr or a time of ≤12 months to PSA failure.

Editorial — Dr Dreicer (continued)

The primary endpoint of the study was PSA-PFS, which was defined as a 50% increase of nadir PSA + 0.2 ng/ml confirmed x 2. The majority (90%) of patients underwent radical prostatectomy, with the median time from RP or RT to PSA relapse being 27-30 months. Approximately 95% of patients completed 6 cycles of docetaxel. With a median follow-up of 30 months, PSA-PFS was 20.3 and 19.3 months for the ADT plus docetaxel vs ADT arms respectively (P=0.31). With a median follow-up of 10.5 years, survival data remains immature.

What are the take-away messages from this small randomized trial? It is clear that even in this study of “high risk patients” there is significant heterogeneity.

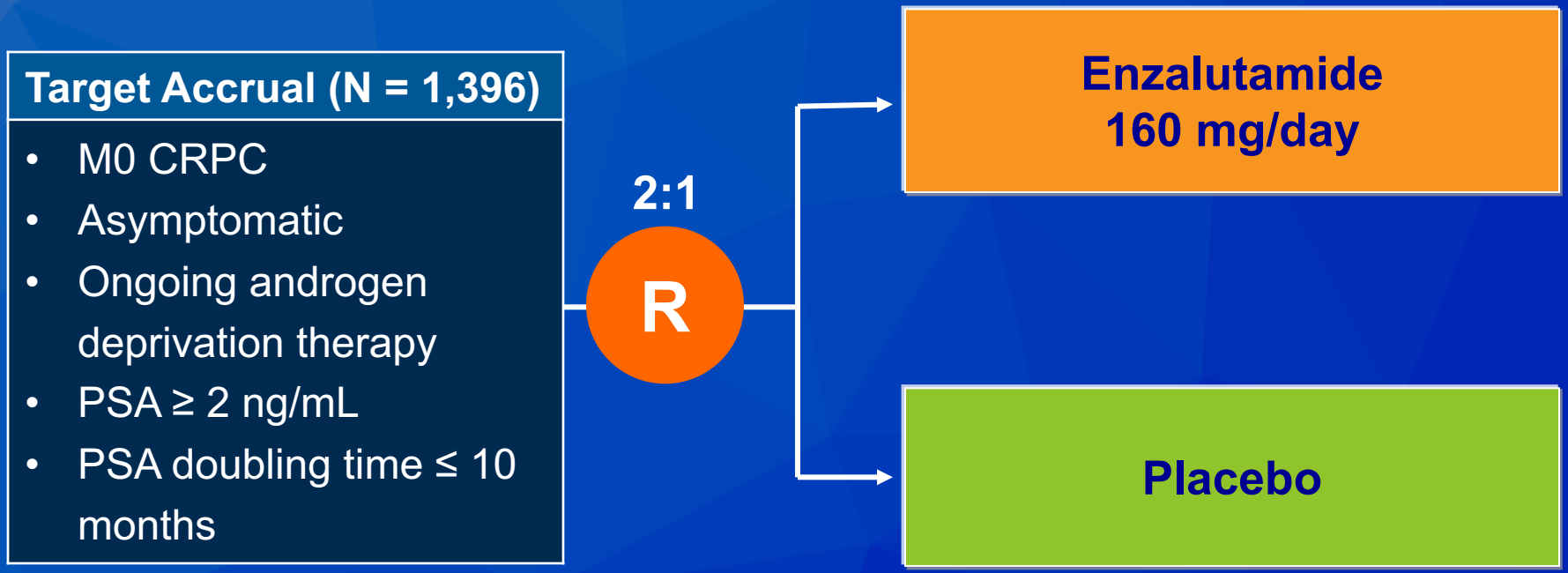
Editorial — Dr Dreicer (continued)

The “control” arm of this study was a year of ADT, which is not a “validated” therapy in this setting. The authors in their own conclusions question the need for ADT given that 70% of patients were alive at 10 years.

PROSPER: A Phase 3, Randomized, Double-Blind, Placebo (PBO)-Controlled Study of Enzalutamide (ENZA) in Men with Nonmetastatic Castration-Resistant Prostate Cancer (M0 CRPC)

Hussain M et al.
Genitourinary Cancers Symposium 2018;Abstract 3.

PROSPER: A Phase III Multinational Study of Enzalutamide



Primary Endpoint: Metastasis-free survival (time to radiographic progression or death)

Sternberg CN et al. *Proc ESMO* 2014;Abstract 802TiP. Clinicaltrials.gov (NCT02003924)

PROSPER: Clinical Outcomes

Survival	ENZA + ADT (n = 933)	PBO + ADT (n = 468)	HR	*p*-value
Median metastasis-free survival (MFS)	36.6 mo	14.7 mo	0.29	<0.0001
Median time to first use of new antineoplastic therapy	39.6 mo	17.7 mo	0.21	<0.0001
Median time to PSA progression	37.2 mo	3.9 mo	0.07	<0.0001
Median OS	Not reached	Not reached	0.80	0.1519

Hussain M et al. Genitourinary Cancers Symposium 2018;Abstract 3.

FDA approves apalutamide for nonmetastatic castration-resistant prostate cancer

Press Release — February 14, 2018

"On February 14, 2018, the Food and Drug Administration approved apalutamide for patients with non-metastatic castration-resistant prostate cancer (NM-CRPC).

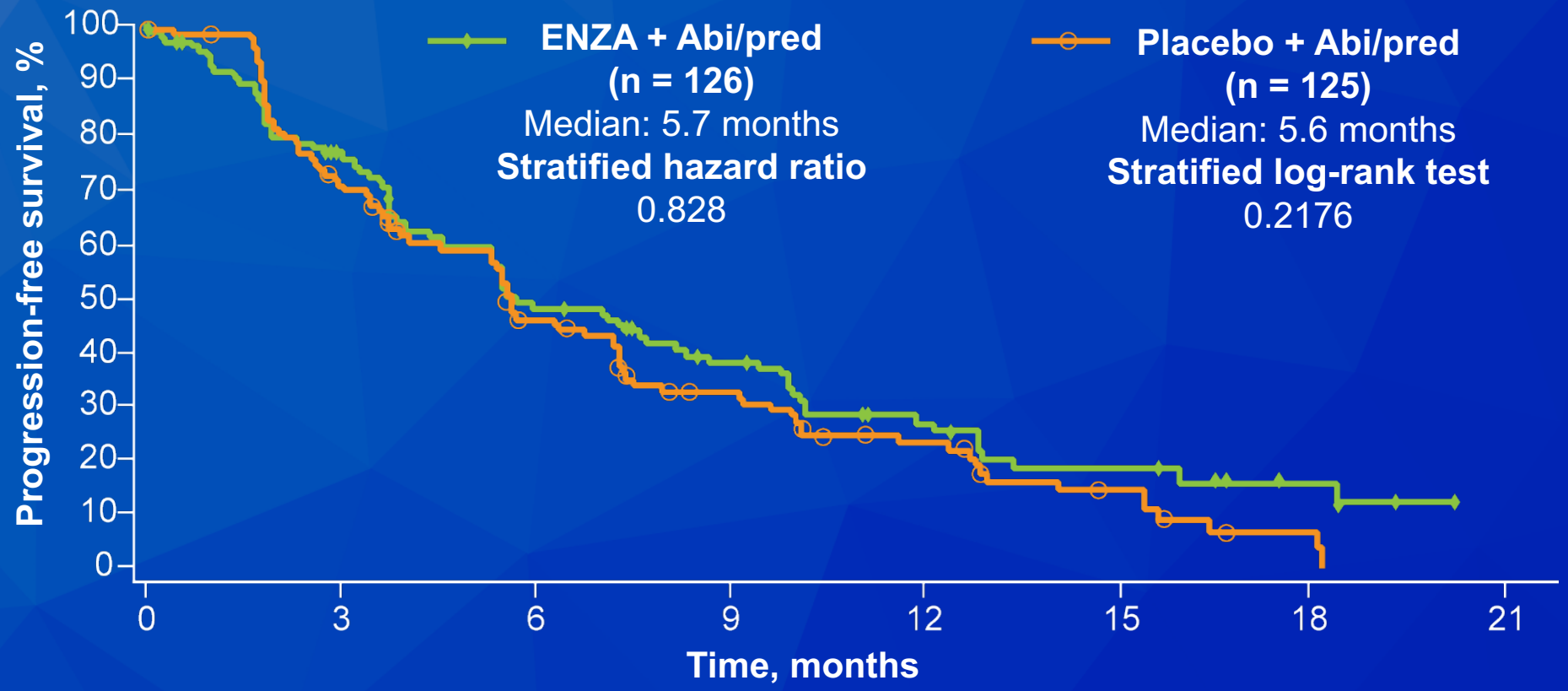
Approval was based on a multicenter, double-blind, clinical trial (SPARTAN, NCT01946204) randomizing 1,207 patients with NM-CRPC (2:1) to receive either apalutamide, 240 mg orally once daily in combination with ADT (medical castration or surgical castration) (n = 806), or placebo once daily with ADT (n = 401)."

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm596796.htm

A Phase IV, Randomized, Double-Blind, Placebo (PBO)-Controlled Study of Continued Enzalutamide (ENZA) Post Prostate-Specific Antigen (PSA) Progression in Men with Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Attard G et al.
Proc ASCO 2017;Abstract 5004.

PLATO: Primary Endpoint (PFS)



- Median rPFS: enza arm 10.0 mo, placebo arm 7.0 mo (HR 0.66)

Attard G et al. *Proc ASCO* 2017;Abstract 5004.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Clinical Significance of Androgen Receptor Splice Variant-7 mRNA Detection in Circulating Tumor Cells of Men With Metastatic Castration-Resistant Prostate Cancer Treated With First- and Second-Line Abiraterone and Enzalutamide

Emmanuel S. Antonarakis, Changxue Lu, Brandon Luber, Hao Wang, Yan Chen, Yezi Zhu, John L. Silberstein, Maritza N. Taylor, Benjamin L. Maughan, Samuel R. Denmeade, Kenneth J. Pienta, Channing J. Paller, Michael A. Carducci, Mario A. Eisenberger, and Jun Luo

J Clin Oncol 2017;35(19):2149-56.

Study Outcomes

All patients (n = 202)	CTC- (n = 53)	CTC+/AR-V7- (n = 113)	CTC+/AR-V7+ (n = 36)	*p*-value
Median PFS	13.9 mo	7.7 mo	3.1 mo	<0.001
Median PSA-PFS	11.3 mo	6.2 mo	2.1 mo	<0.001
Median OS	28.7 mo	29.5 mo	11.2 mo	<0.001
PSA response*	75.5%	52.2%	13.9%	<0.001

* Proportion of patients with a ≥50% PSA decline from baseline at any time after therapy (and maintained for ≥3 weeks)

- Biomarker status generally remained independently prognostic for PFS, PSA-PFS and OS.

Antonarakis ES et al. *J Clin Oncol* 2017;35(19):2149-56.

Editorial — Dr Dreicer

Almost immediately following the broad approval of enzalutamide (E) and abiraterone (A), clinicians noted a much lower likelihood of response when patients were crossed over from E to A or A to E. Among the multiple mechanisms proposed for potential cross-resistance was the abnormal AR splice variant AR-V7, which remains constitutively active irrespective of the presence/absence of the ligand and appears to drive castration-resistant prostate cancer progression.

In their previous work Antonarakis and colleagues demonstrated that AR-V7 expression in circulating tumor cells (CTC) predicted for a low likelihood of response to either abiraterone acetate or enzalutamide.

Editorial — Dr Dreicer (continued)

In the current analysis the investigators prospectively enrolled 202 patients initiating therapy with either abiraterone acetate or enzalutamide and tested the ability of baseline CTC status (+/-) and AR-V7 status (+/-) to predict response to either of these therapies by means of clinical and radiographic progression-free survival.

Median follow-up times ranged from 15-22 months for each of three groups (CTC-, CTC+/AR-V7-, CTC+/AR-V7+). Of the 202 patients, 26% had no detectable CTCs. Response rates to abiraterone/enzalutamide were 75%, 52% and 14% of patients CTC-, CTC+/AR-V7-, CTC+/AR-V7+, respectively.

Editorial — Dr Dreicer (continued)

The broad clinical utility of this assay may be limited as in this experience patients who have not received either abiraterone or enzalutamide have lower rates of AR-V7 + CTCs and in this study almost 1/3 of patients responded to therapy in any case, calling into question the utility of this assay in making day-to-day management decisions.

SPARTAN, A Phase 3 Double-Blind, Randomized Study of Apalutamide (APA) versus Placebo (PBO) in Patients (pts) with Nonmetastatic Castration-Resistant Prostate Cancer (nmCRPC)

Small EJ et al.
Genitourinary Cancers Symposium 2018;Abstract 161.

SPARTAN: Clinical Outcomes

Outcome (N = 1,207)	Apalutamide (n = 806)	PBO (n = 401)	HR	*p*-value
Median MFS	40.5 mo	16.2 mo	0.28	<0.0001
Patients still on treatment at median follow-up of 20.3 mo	61%	30%	—	—
Of patients with disease progression, those who received therapy for mCRPC	56%	80%	—	—

- Time to metastases, PFS, and symptomatic progression were all significantly improved.
- At interim analysis for OS, there was a trend favoring apalutamide.

Small EJ et al. Genitourinary Cancers Symposium 2018;Abstract 161.

SPARTAN: Safety and Health-Related Quality of Life

Outcome	Apalutamide (n = 803)	PBO (n = 398)
Discontinuation due to AEs	10.7%	6.3%

- Mean baseline health-related quality of life scores were maintained with treatment, with no difference between groups over time.

Small EJ et al. Genitourinary Cancers Symposium 2018;Abstract 161.

Treatment of Hormone-sensitive Metastatic Disease

FDA approves abiraterone acetate in combination with prednisone for high-risk metastatic castration-sensitive prostate cancer

Press Release — February 7, 2018

"On February 7, 2018, the Food and Drug Administration (FDA) approved abiraterone acetate tablets in combination with prednisone for metastatic high-risk castration-sensitive prostate cancer (CSPC).

FDA initially approved abiraterone acetate with prednisone in 2011 for patients with metastatic castration-resistant prostate cancer (CRPC) who had received prior chemotherapy, and expanded the indication in 2012 for patients with metastatic CRPC.

Today's approval was based on LATITUDE (NCT01715285), a placebo controlled international clinical trial that randomized 1,199 patients with metastatic high-risk CSPC."

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm596015.htm

ORIGINAL ARTICLE

Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

N.D. James, J.S. de Bono, M.R. Spears, N.W. Clarke, M.D. Mason, D.P. Dearnaley, A.W.S. Ritchie, C.L. Amos, C. Gilson, R.J. Jones, D. Matheson, R. Millman, G. Attard, S. Chowdhury, W.R. Cross, S. Gillessen, C.C. Parker, J.M. Russell, D.R. Berthold, C. Brawley, F. Adab, S. Aung, A.J. Birtle, J. Bowen, S. Brock, P. Chakraborti, C. Ferguson, J. Gale, E. Gray, M. Hingorani, P.J. Hoskin, J.F. Lester, Z.I. Malik, F. McKinna, N. McPhail, J. Money-Kyrle, J. O'Sullivan, O. Parikh, A. Protheroe, A. Robinson, N.N. Srihari, C. Thomas, J. Wagstaff, J. Wylie, A. Zarkar, M.K.B. Parmar, and M.R. Sydes, for the STAMPEDE Investigators*

N Engl J Med 2017;377(4):338-51.

Adding Abiraterone Acetate plus Prednisolone (AAP) or Docetaxel for Patients (pts) with High-Risk Prostate Cancer (PCa) Starting Long-Term Androgen Deprivation Therapy (ADT): Directly Randomised Data from STAMPEDE

Sydes MR et al. *Proc ESMO* 2017;Abstract LBA31_PR.

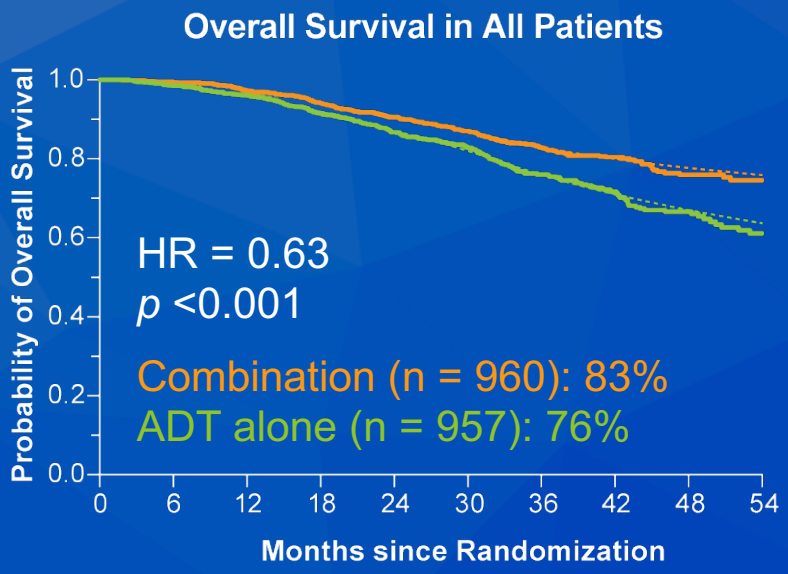
ORIGINAL ARTICLE

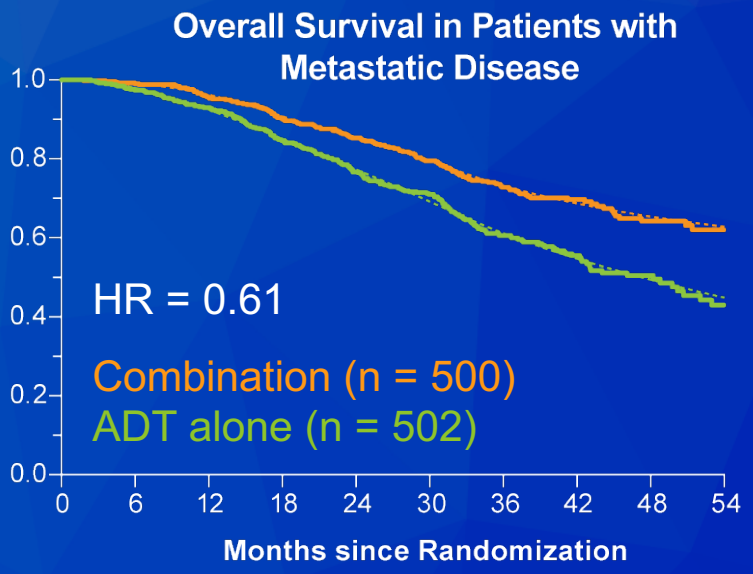
Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Boris Y. Alekseev, M.D., Mustafa Özgüroğlu, M.D., Dingwei Ye, M.D., Susan Feyerabend, M.D., Andrew Protheroe, M.D., Ph.D., Peter De Porre, M.D., Thian Kheoh, Ph.D., Youn C. Park, Ph.D., Mary B. Todd, D.O., and Kim N. Chi, M.D., for the LATITUDE Investigators*

N Engl J Med 2017;377(4):352-60.

STAMPEDE: 3-Year Overall and Failure-Free Survival



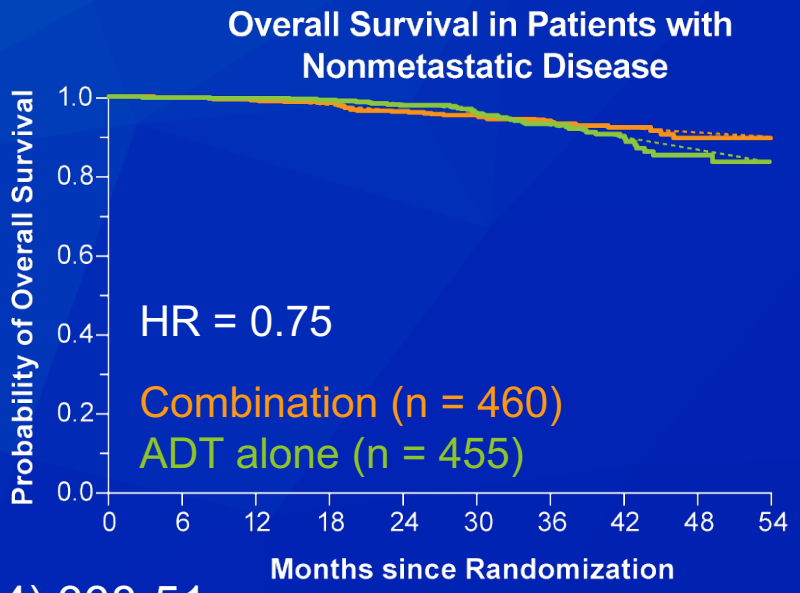


Combination = ADT + Abi + prednisolone

<u>3-year failure-free survival</u>

All patients

- Combination (n = 960) = 75%
- ADT alone (n = 957) = 45%
  - HR = 0.29
  - *p* < 0.001



James ND et al. *N Engl J Med* 2017;377(4):338-51.

STAMPEDE: Efficacy and Safety Results After a Median Follow-Up of 4 Years

Survival	SOC + DocP (n = 189)	SOC + AAP (n = 377)	HR	95% CI
Number of deaths	45	111	1.16	0.82-1.65
Adverse events	**SOC + DocP (n = 189)**		**SOC + AAP (n = 377)**	
Grade 3	36%		40%	
Grade 4	13%		7%	
Grade 5	1%		1%	

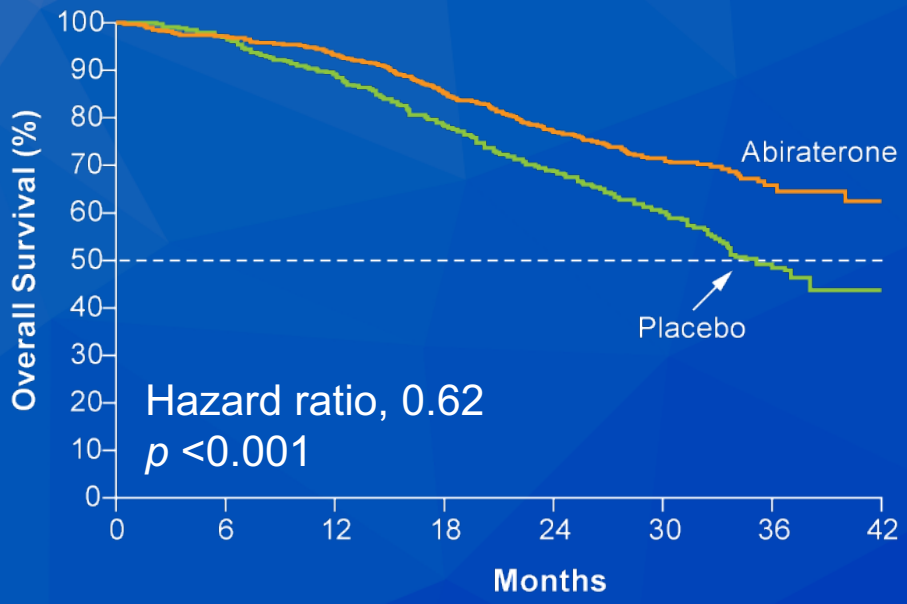
SOC = standard of care; DocP = docetaxel/prednisone; AAP = abiraterone/prednisone

- Failure-free survival HR = 0.51 in favor of SOC + AAP
- PFS HR = 0.65 in favor of SOC + AAP

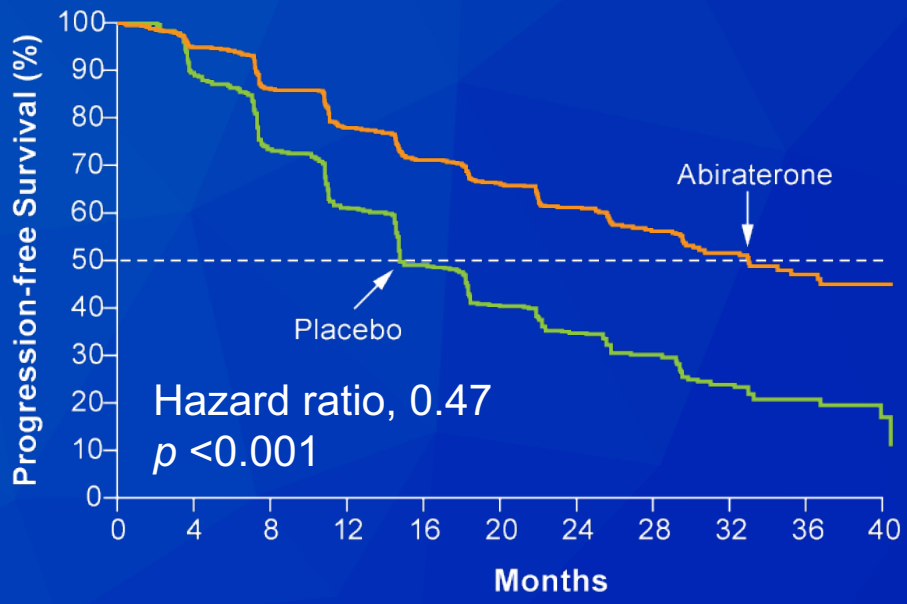
Sydes MR et al. *Proc ESMO* 2017;Abstract LBA31_PR.

LATITUDE: OS and Radiographic PFS (rPFS)

Overall Survival



Radiographic Progression-Free Survival



The treatment effect of abiraterone on overall survival was consistently favorable across nearly all prespecified subgroups

Outcome	Abi (n = 597)	Placebo (n = 602)
3-y OS	66%	49%
Median rPFS	33.0 mo	14.8 mo

Fizazi K et al. *N Engl J Med* 2017;377(4):352-60.

Editorial — Dr Dreicer

Following the dissemination of the paradigm shifting data from the CHAARTED and STAMPEDE docetaxel studies, the addition of docetaxel to ADT rapidly became a standard of care for many patients with hormone sensitive metastatic prostate cancer. Two studies initiated before the data from the docetaxel studies were available randomized a similar group of patients to receive ADT with or without abiraterone and prednisone. In the LATITUDE study approximately 1,200 patients with de novo poor risk (positive imaging studies with at least 2 of the following: Gleason ≥8, at least 3 bone mets or visceral disease) were enrolled. Stampede enrolled 1,917 patients, including a broader group of patients with metastases or locally advanced/node positive disease.

Editorial — Dr Dreicer (continued)

Both studies demonstrated significant survival benefit in the range of 37% improvement in OS. A statistically significant benefit in SSE/SRE was demonstrated in both studies in the abiraterone arms. The STAMPEDE investigators noted that there appeared to be a slightly increased effect of abiraterone on survival compared to docetaxel, with a larger impact on failure free survival.

Given this new data, clinicians are now challenged to make management recommendations for patients whose clinical presentation overlaps the eligibility requirements for both CHAARTED/LATITUDE and the STAMPEDE studies.

Editorial — Dr Dreicer (continued)

Among the issues that need be considered are the differences in toxicity profiles, the differences in therapy duration (18 weeks vs 2 years), economic toxicities as well as exposure to low dose prednisone for a protracted time frame. Studies such as PEACE 1 and others are comparing these two treatment options, and other trials are addressing the question of adding next generation AR drugs to docetaxel/ADT.

Press Release – Phase III Trial of Radium-223 Dichloride in Combination with Abiraterone Acetate and Prednisone/Prednisolone Unblinded Early
November 30, 2017

"*An Independent Data Monitoring Committee (IDMC) has recommended to unblind a Phase III trial of radium (Ra) 223 dichloride (radium-223) in combination with abiraterone acetate and prednisone/prednisolone in prostate cancer. The IDMC recommendation is due to the observation of an imbalance of more fractures and deaths in the treatment arm investigating radium-223 in combination with abiraterone and prednisone/prednisolone in patients with asymptomatic or mildly symptomatic, chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC).*" Data from other types of studies in which this combination treatment was evaluated did not show new safety signals.

https://www.prnewswire.com/news-releases/phase-iii-trial-of-radium-ra-223-dichloride-in-combination-with-abiraterone-acetate-and-prednisoneprednisolone-for-patients-with-metastatic-castration-resistant-prostate-cancer-unblinded-early-300564844.html.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized, Noncomparative, Phase II Trial of Early Switch From Docetaxel to Cabazitaxel or Vice Versa, With Integrated Biomarker Analysis, in Men With Chemotherapy-Naïve, Metastatic, Castration-Resistant Prostate Cancer

Emmanuel S. Antonarakis, Scott T. Tagawa, Giuseppe Galletti, Daniel Worroll, Karla Ballman, Marie Vanhuyse, Guru Sonpavde, Scott North, Costantine Albany, Che-Kai Tsao, John Stewart, Atef Zaher, Ted Szatrowski, Wei Zhou, Ada Gjyrezi, Shinsuke Tasaki, Luigi Portella, Yang Bai, Timothy B. Lannin, Shalu Suri, Conor N. Gruber, Erica D. Pratt, Brian J. Kirby, Mario A. Eisenberger, David M. Nanus, Fred Saad, and Paraskevi Giannakakou on behalf of the TAXYNERGY Investigators

J Clin Oncol 2017;35(28):3181–8.

TAXYNERGY: Primary Endpoints

- Prostate-specific antigen (PSA) response rate (proportion of pts who achieved a confirmed ≥50% PSA response)
- ITT population = 35/63 (55.6%)
  - On or before cycle 4 (C4) = 25 (39.7%)
  - After C4 = 10 (15.9%)
- PSA response exceeded the historical control rate of 45.4% (TAX 327)
- Pts who switched treatment after C4 = 15/61 (24.6%)
  - Achieved ≥50% PSA decrease = 7 (46.7%)
- In 26 CTC-evaluable pts, taxane-induced decrease in % androgen receptor nuclear localization associated with a higher rate of ≥50% PSA decrease at C4 (p = 0.009)

Antonarakis ES et al. *J Clin Oncol* 2017;35(28):3181-8.

Editorial — Dr Dreicer

It has long been suspected that some degree of taxane (docetaxel/cabazitaxel) anti-tumor activity in advanced prostate cancer was in part an androgen receptor (AR)-directed mechanism. There is some preclinical evidence that AR splice variants such as AR-V7, which lack microtubule binding domains for nuclear import of the AR, might have lower response rates to taxane therapy.

The TAXYNERGY study randomized men with metastatic castration-resistant prostate cancer (mCRPC) 2:1 to receive docetaxel or cabazitaxel. Patients who did not manifest a ≥30% PSA decline by cycle 4 were switched to the alternative taxane. In this non-comparative randomized study, the primary endpoint of the study was confirmed ≥50% PSA decline.

Editorial — Dr Dreicer (continued)

An integrated biomarker analysis used CTCs to assess changes in AR nuclear localization (ARNL). Sixty-three patients were enrolled and 56% achieved the primary endpoint of PSA response. Fifteen patients were “switched” to the alternative taxane (12 from docetaxel to cabazitaxel). Only 25 patients had evaluable CTCs; interestingly, patients who experienced a rapid decrease in ARNL were more likely to have a ≥50% PSA decline.

While both an innovative and interesting study, the results from this study must be placed into a clinical context. Although PSA response to docetaxel is associated with a survival benefit, it is not a defined surrogate.

Editorial — Dr Dreicer (continued)

The data from this study does NOT support switching taxanes in this clinical setting. While the CTC data is of interest, as we have seen in other studies only a modest subset of patients actually have measurable CTCs, and the small numbers in this study preclude any definitive conclusions regarding the predictive or prognostic role of decrease in ARNL from therapy.

PROREPAIR-B: A Prospective Cohort Study of DNA Repair Defects in Metastatic Castration Resistant Prostate Cancer (mCRPC)

Castro Marcos E et al. *Proc ESMO* 2017;Abstract LBA32.

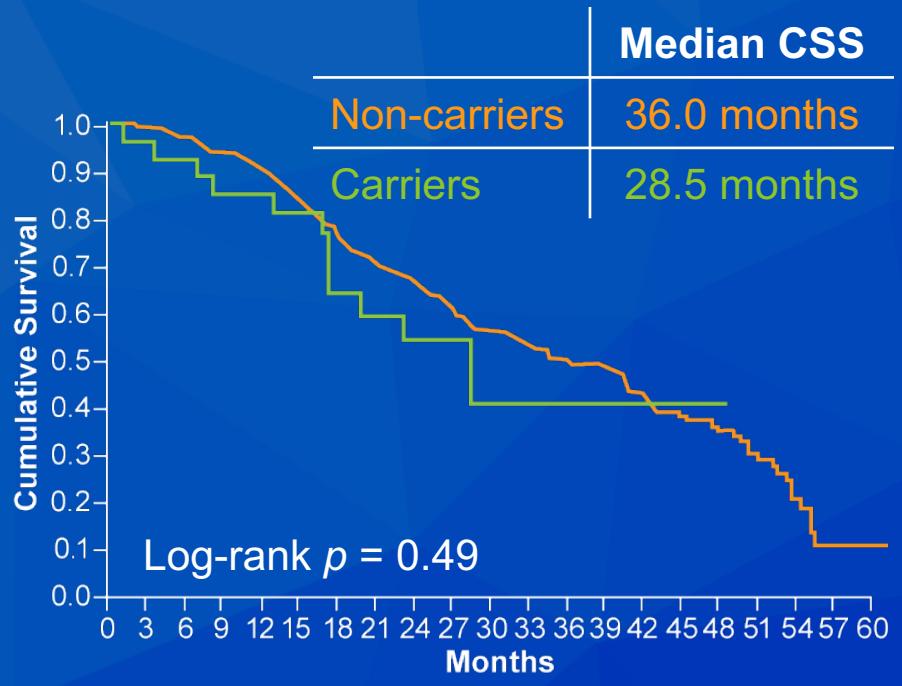
ORIGINAL ARTICLE

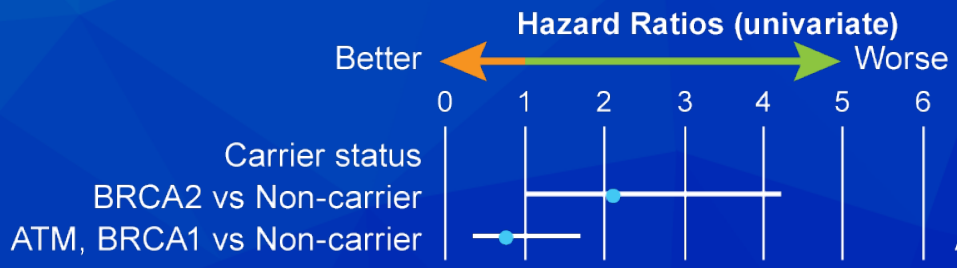
Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

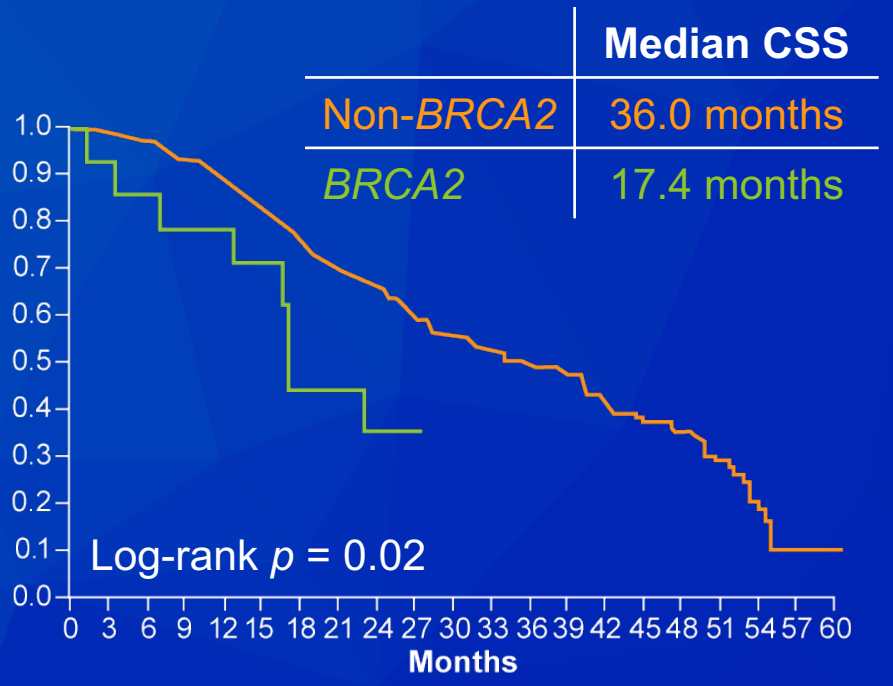
C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson

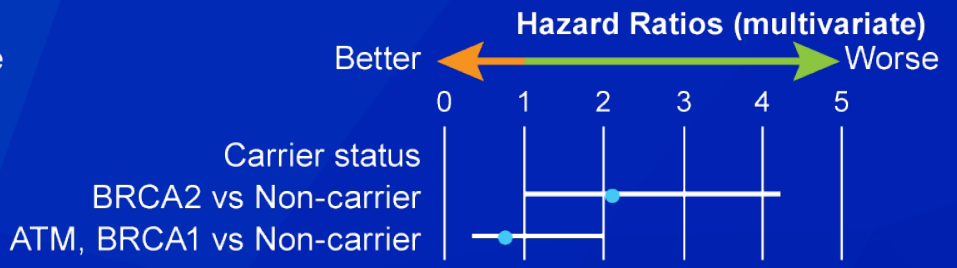
N Engl J Med 2016;375(5):443-53.

PROREPAIR-B: Impact of BRCA1/2, ATM, PALB2 Germline Mutations on Cause-Specific Survival (CSS) from Diagnosis of mCRPC (N = 419)









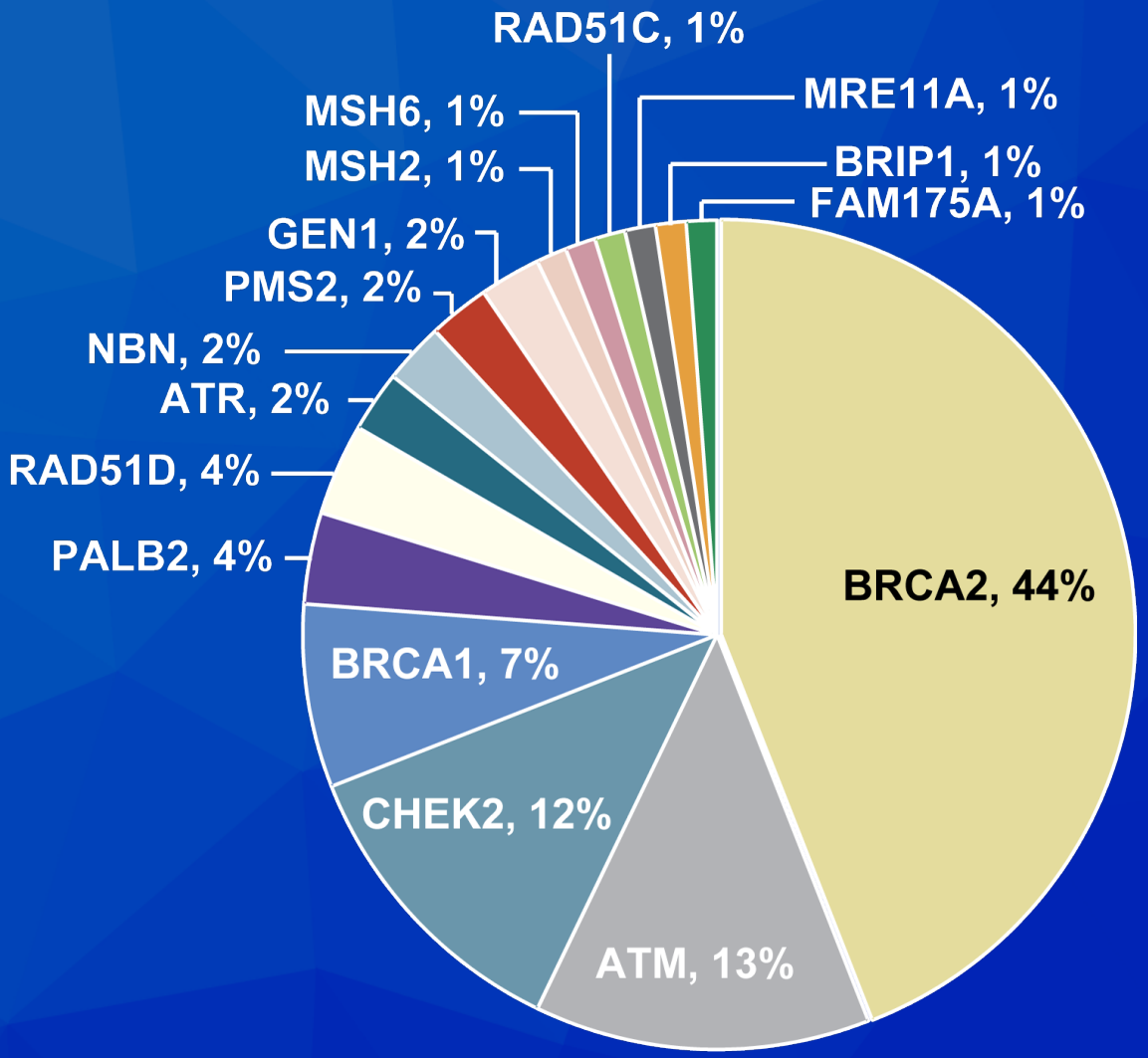
Castro Marcos E et al. *Proc ESMO* 2017;Abstract LBA32.

DNA-Repair Gene Mutations in Metastatic Prostate Cancer (mPC)

- Men with mPC unselected for family history of cancer or age at diagnosis (n = 692)
- 84 deleterious germline DNA-repair gene mutations found
  - Men harboring these mutations = 82 (11.8%)
- Mutations were found in 16 genes, including:
  - BRCA2 = 37/692 (5.3%)
  - CHEK2 = 10/534 (1.9%)
  - ATM = 11/692 (1.6%)
  - BRCA1 = 6/692 (0.9%)
  - RAD51D and PALB2 = 3 (0.4%) each
- Incidence did not differ according to the presence or absence of family history of prostate cancer or age.
- Frequency in men with mPC significantly exceeded the prevalence of 4.6% in 499 men with localized PC ($p < 0.001$).

Pritchard CC et al. *N Engl J Med* 2016;375(5):443-53.

Distribution of Presumed Pathogenic Germline Mutations



82/692 men with germline gene mutations (11.8%)

Pritchard CC et al. *N Engl J Med* 2016;375(5):443-53.

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Pritchard CC et al. *N Engl J Med* 2016;375(5):443-53.

Editorial — Dr Dreicer

The recognition that both somatic and germline mutations in DNA repair genes are both clinically relevant and targetable is beginning to influence clinical management in patients with mCRPC. PROREPAIR-B is a multicenter study in which men with mCRPC and unknown germline mutation status were treated with physician-choice therapy with any of the following: abiraterone, enzalutamide, docetaxel, radium-223 or cabazitaxel. The primary endpoint of the study was to assess the impact of BRCA1 or 2, ATM and PABL2 germline mutations on prostate cancer specific survival. Of the 419 eligible patients, 9.1% had evidence of germline DNA damage repair mutations.

Editorial — Dr Dreicer (continued)

Initial observations include no difference in prostate cancer survival between carriers and non-carriers, shorter survival in BRCA2 carriers and no difference in response to therapeutic agents.

Pritchard and colleagues, building upon their previous reported work, added 6 different international cohorts with 692 patients unselected with regard to family history, age or genetic background and used next-generation sequencing to analyze DNA-repair genes associated with autosomal dominant cancer-predisposition syndromes. Of the 692 men evaluated, 82 (11.8%) had at least one presumed pathogenic germline mutation in a gene involved in DNA-repair processes.

Editorial — Dr Dreicer (continued)

Mutations were identified in 16 different genes with BRCA2 and ATM representing more than 50% of the total mutations.

Given the increasing recognition that identification of mutations in DNA repair genes may lead to identifying patients who may benefit from PARP1 inhibition/cisplatin-based chemotherapy, NCCN Prostate Cancer Version 2.2017 now states, “due to the high prevalence of germline mutations the panel recommends consideration of germline testing for all men with metastatic and high/very high-risk clinically localized prostate cancer.”