Year in Review

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

October 28, 2017, 8:00 AM – 4:00 PM
Orlando, Florida

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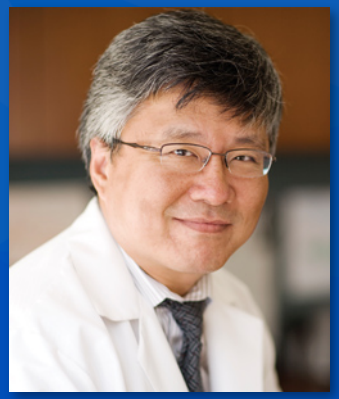

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Disclosures

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Disclosures

Consulting Agreements	Bayer HealthCare Pharmaceuticals, Bellicum Pharmaceuticals Inc, Dendreon Pharmaceuticals Inc, Exelixis Inc, Ferring Pharmaceuticals, Johnson & Johnson Pharmaceuticals, Medivation Inc, a Pfizer Company, Pfizer Inc, Roche Laboratories Inc, Sanofi Genzyme, Takeda Oncology, Tyme Technologies Inc
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Ownership Interest	Bellicum Pharmaceuticals Inc, Tyme Technologies Inc

Select Recently Approved Agents in Genitourinary Cancers

Agent	Approval date	Indication
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 Oh and Petrylak

Renal Cell Carcinoma

Urothelial Bladder Cancer

Prostate Cancer

Cost and reimbursement issues aside, would you recommend an adjuvant tyrosine kinase inhibitor to select patients with renal cell carcinoma (RCC) outside of a trial setting?

a. Yes, pazopanib
b. Yes, sunitinib
c. Yes, either pazopanib or sunitinib
d. No

Randomized Phase III Trial of Adjuvant Pazopanib versus Placebo After Nephrectomy in Patients with Locally Advanced Renal Cell Carcinoma (RCC) (PROTECT)

Motzer RJ et al. *Proc ASCO* 2017;Abstract 4507.

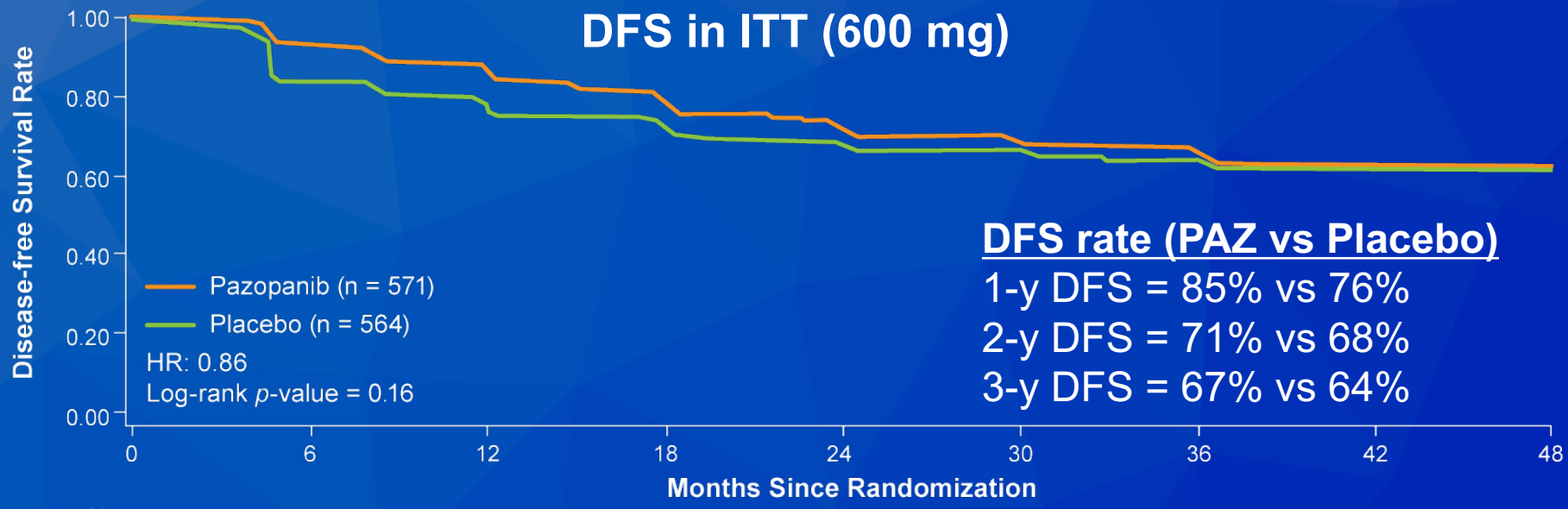
ORIGINAL ARTICLE

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

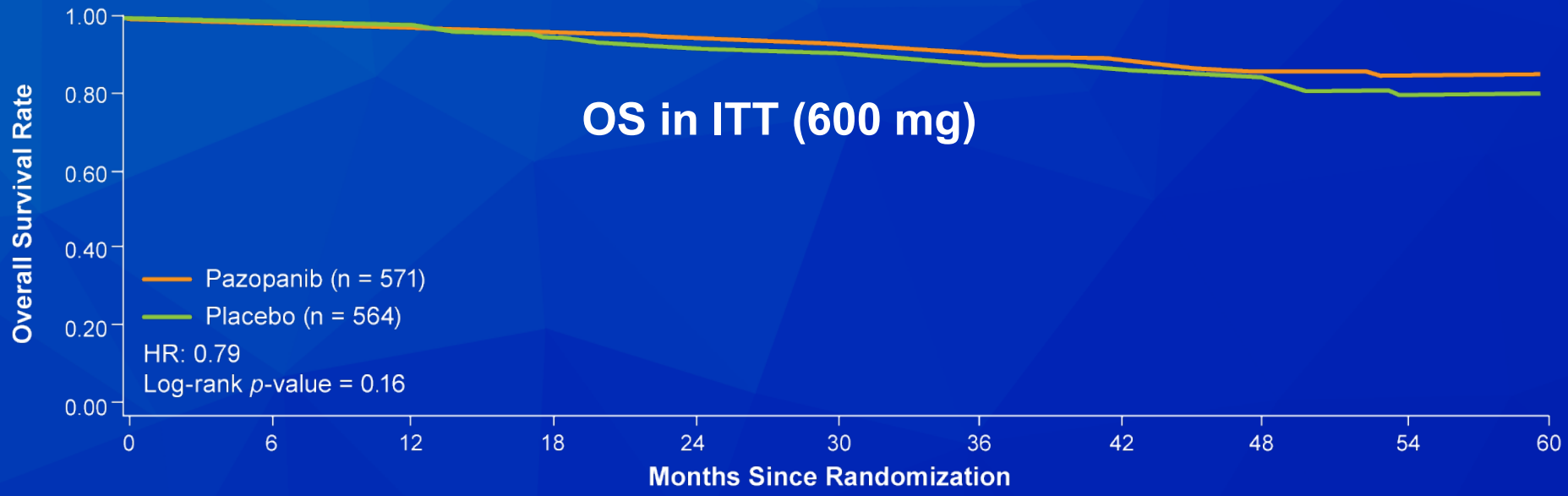


DFS rate (PAZ vs Placebo)

1-y DFS = 85% vs 76%

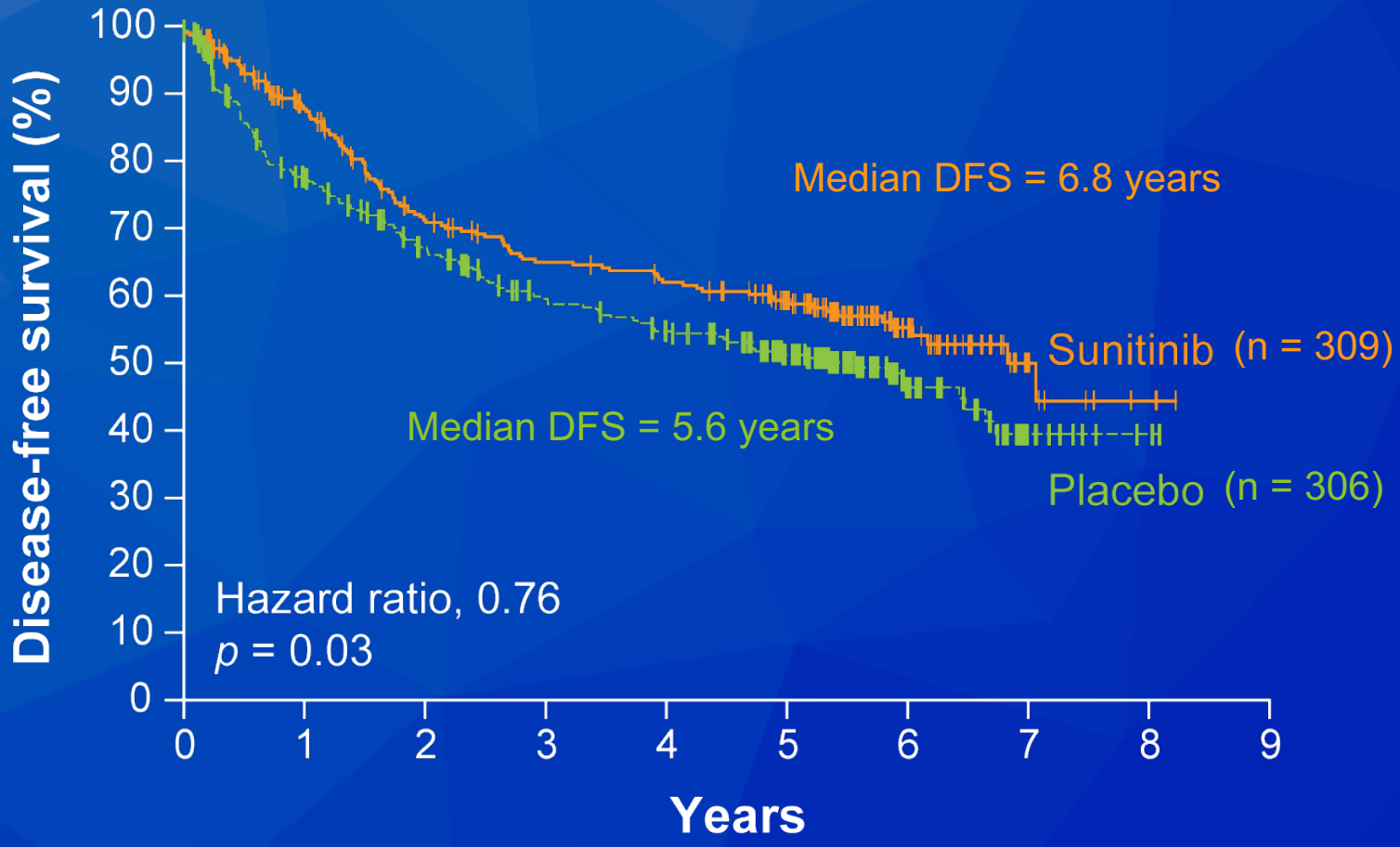
2-y DFS = 71% vs 68%

3-y DFS = 67% vs 64%



Motzer RJ et al. *Proc ASCO* 2017;Abstract 4507.

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.

Editorial — Dr Petrylak

Motzer et al led the PROTECT trial which evaluated the efficacy and safety of pazopanib versus placebo in 1,538 patients with locally advanced renal cell carcinoma (RCC) post-nephrectomy. Patients entered in this study included pT2 (high grade), pT3 or greater clear cell carcinoma. Patients randomized to the pazopanib arm received a starting dose of 800 mg PO QD with the intent to treat for 1 year. Due to lack of tolerability, pazopanib was lowered to 600 mg PO QD in approximately 25% of patients. The primary endpoint, disease-free survival, was not met (HR 0.82).

Editorial — Dr Petrylak (continued)

Rauvaud et al randomized 615 patients with locoregional, high-risk clear-cell renal cell carcinoma to receive either sunitinib (50 mg per day) or placebo on a 4-weeks-on, 2-weeks-off schedule for 1 year or until disease recurrence, unacceptable toxicity, or consent withdrawal. The median duration of disease-free survival was 6.8 years (95% confidence interval [CI], 5.8 to not reached) in the sunitinib group and 5.6 years (95% CI, 3.8 to 6.6) in the placebo group (hazard ratio 0.76; 95% CI, 0.59 to 0.98; *P* = 0.03). Data for overall survival, a secondary endpoint, were not mature at the time of the data cutoff, with deaths reported in 64 patients (20.7%) in the sunitinib group and 64 (20.9%) in the placebo group.

Editorial — Dr Petrylak (continued)

The toxic effects of adjuvant sunitinib were substantial as compared with those of placebo (adverse events of grade 3 or higher, 60.5% vs 19.4%). Dose reductions because of adverse events were more frequent in the sunitinib group than in the placebo group (34.3% vs 2.0%), as were dose interruptions (46.4% vs 13.2%), and more patients who received sunitinib had diarrhea and decreased appetite, in combination with the other serious and rare toxic effects of arterial thromboembolism and treatment-related death.

Thus, given these toxicities and lack of survival benefit, sunitinib should not be considered standard adjuvant therapy for renal cell carcinoma. The author argues that sunitinib should be used as adjuvant therapy for high-risk patients, again without survival data.

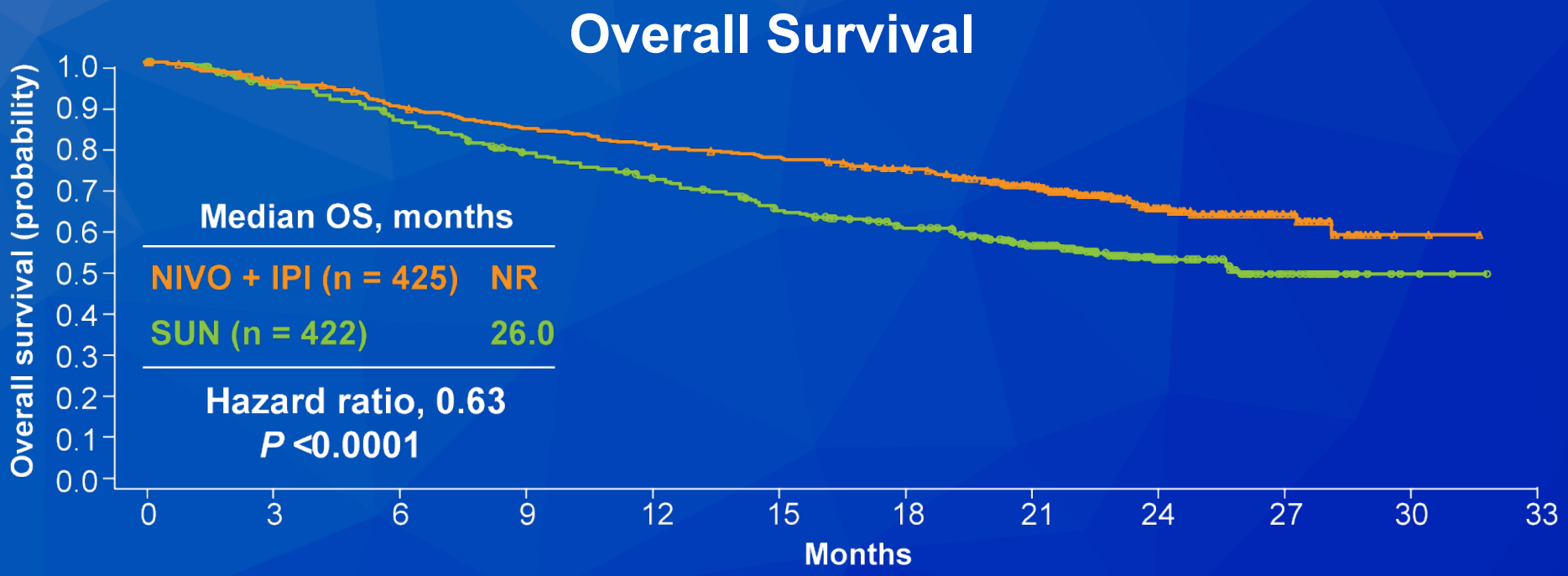
Editorial — Dr Petrylak (continued)

In summary, no survival benefit was gained by the earlier use of TKIs in high-risk renal cell carcinoma, and neither pazopanib nor sunitinib should be considered standard treatment in the adjuvant setting.

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.

Editorial — Dr Oh

Checkpoint inhibitor monotherapy with nivolumab is currently approved for second-line therapy in mRCC. Unresolved questions include whether the combination of anti-PD-1 and anti-CTLA-4 is more active and whether these agents should move into the first line setting. CheckMate 214 addressed both of these issues in a randomized phase 3 trial. 550 treatment-naïve mRCC patients were randomized to either nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks x 4 cycles followed by nivolumab only every 2 weeks or sunitinib 50 mg daily 4 weeks on/2 weeks off (standard of care).

Editorial — Dr Oh (continued)

The co-primary endpoint of ORR in intermediate-high risk disease was noted to be 41.6% (9.4% CR) with ipi/nivo vs 26.5% (1.2%) with sunitinib ($p < 0.0001$). Median PFS was better in the immunotherapy group as well (11.6 vs 8.4 mo, HR 0.82, $p = 0.03$) but in subset analysis of PD-L1 positive tumors only, this difference was significantly higher (22.8 vs 5.9 mo, HR 0.28, $p = 0.0003$). Interestingly, in favorable risk patients, PD-L1 positivity was less common and responses were actually higher in the sunitinib arm.

Bottom line: this is the first trial which “beats” sunitinib in the first line mRCC setting, at least in intermediate and high-risk patients. In the favorable risk patients, sunitinib remains superior.

Editorial — Dr Oh (continued)

However, it is important to remember that the combination has significant additional toxicities compared with single checkpoint agents, and also that the majority of patients still do not respond to therapy. Cost will also be an issue with such combinations.

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)

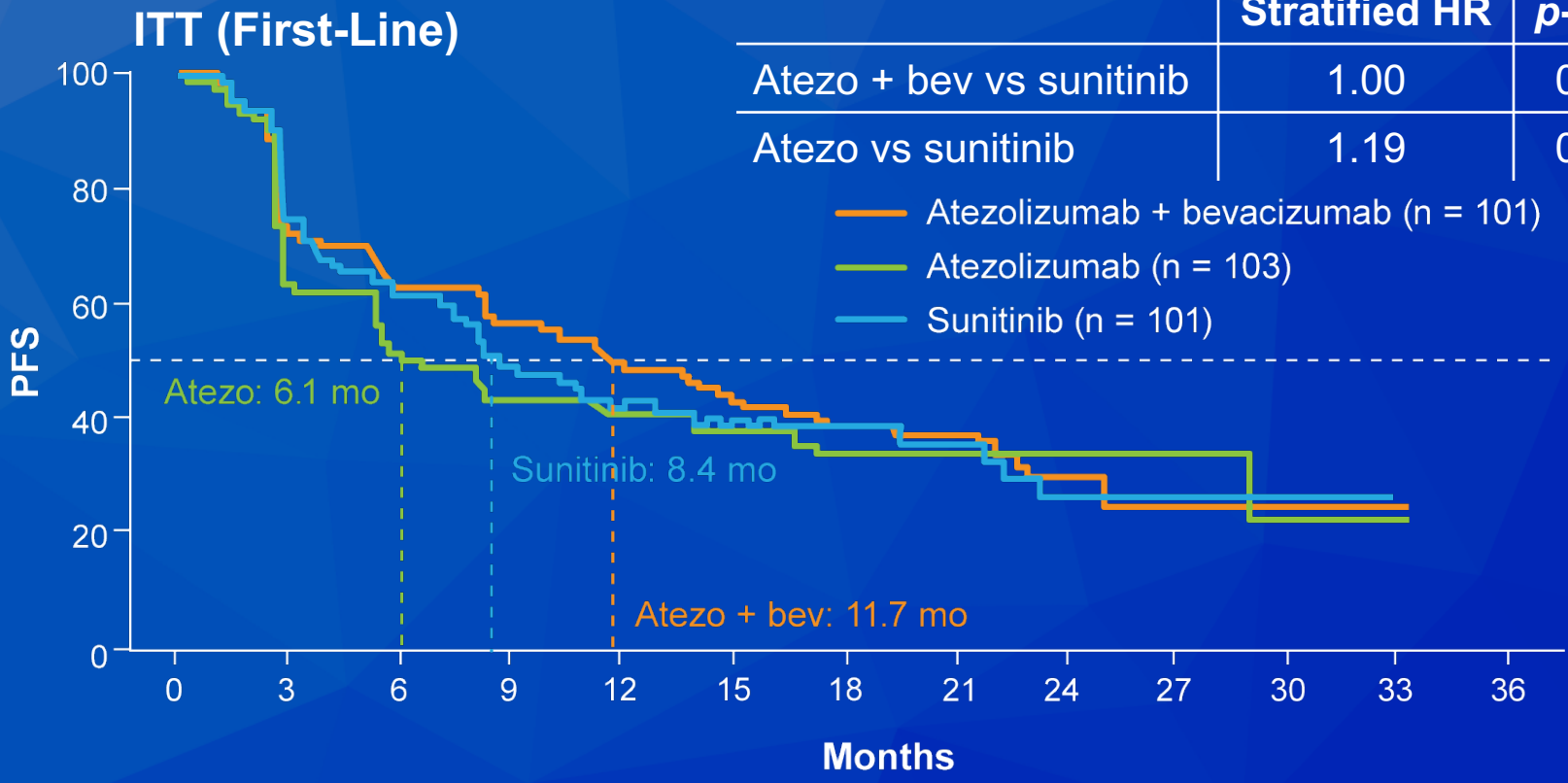
Atkins MB et al.
Proc ASCO 2017;Abstract 4505.

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

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

IMmotion150: PFS

	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 Oh

The comparison of anti-angiogenesis therapies and immunotherapies as first line treatment in mRCC is being explored. This trial looked at that comparison with atezolizumab and sunitinib, but also combined atezo with bevacizumab both up front and after progression on either of the other 2 agents. 305 patients were accrued.

PFS was equivalent across all 3 treatment arms up front (11.7 vs 6.1 vs 8.4 mo for atezo/bev vs atezo vs sun). In the 54% of patients who had PD-L1+ tumors, PFS was longer with the combination compared with sunitinib (14.7 vs 7.8 mo, HR 0.64, 0.38-1.08, $p = 0.095$). After crossover, about one quarter of patients had a subsequent response.

Editorial — Dr Oh (continued)

In this somewhat confusing trial, there appeared to be some slight evidence that the combination of atezo + bev was more active than single agents, particularly if tumors were PD-L1 positive. Also there was evidence that the combination has some salvage response.

Overall this data is not surprising, but it does not suggest that combining checkpoint inhibitors with VEGF inhibitors will have a significant synergistic effect. It seems more consistent with an additive benefit, and toxicity could be limiting. For now, we need more studies.

Editorial — Dr Oh

As discussed with the other trials, combinations of checkpoint inhibitors and anti-angiogenesis agents are being explored, in this case avelumab and axitinib. 55 patients were enrolled, and about 50% had grade 3-4 AEs related to the drug. Confirmed ORR was 54.5% with 2 CRs. Toxicity was considered manageable.

Given the number of checkpoint inhibitors and number of VEGF inhibitors, the mathematical possibilities of combining these are high. The most rational combinations will be determined mostly by safety but also efficacy. Since there is not a strong reason to believe that any of these combinations will a priori be more active than any other, safety will probably be a more significant driver of success. Cost may be as well.

Editorial — Dr Petrylak

Synergy has been observed preclinically when anti-angiogenesis therapy is combined with immune therapy. To evaluate the combination of a TKI with pembrolizumab, Chowdhury et al evaluated 20 patients with pazopanib 800 mg and 600 mg, respectively, both with 2 mg/kg (Q2W and then Q3W) pembrolizumab. Hepatic toxicity was dose limiting at the 2 dose levels tested; sequential administration of pazopanib followed by pazopanib/pembrolizumab was not well tolerated. Thus this combination will not be developed further due to toxicity.

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

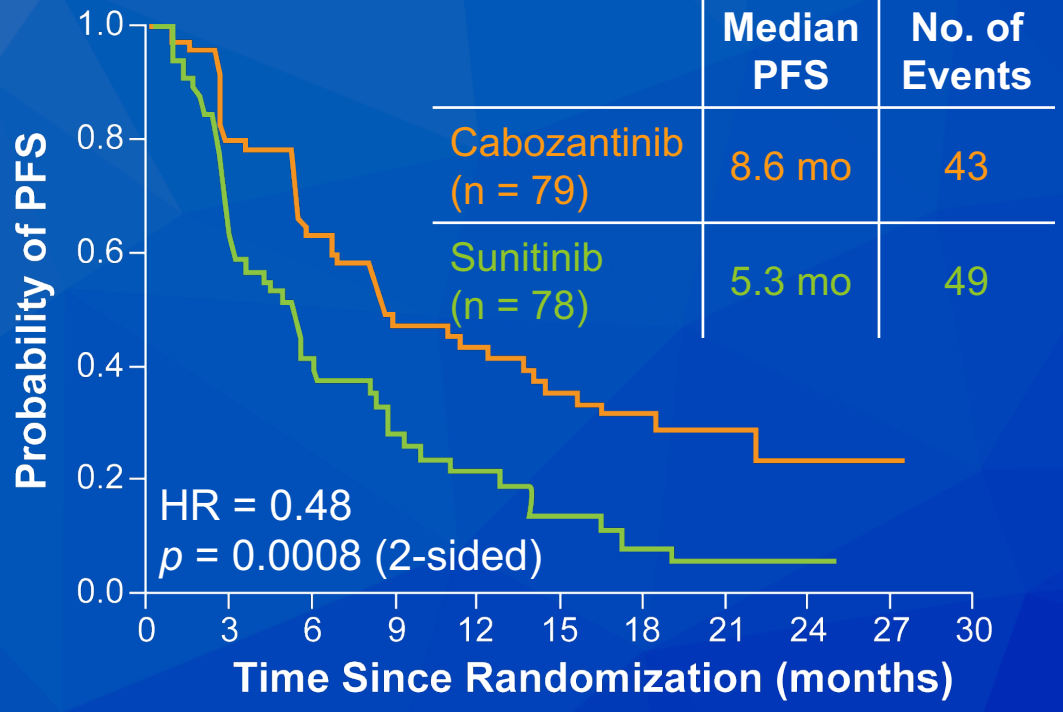
Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial

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.

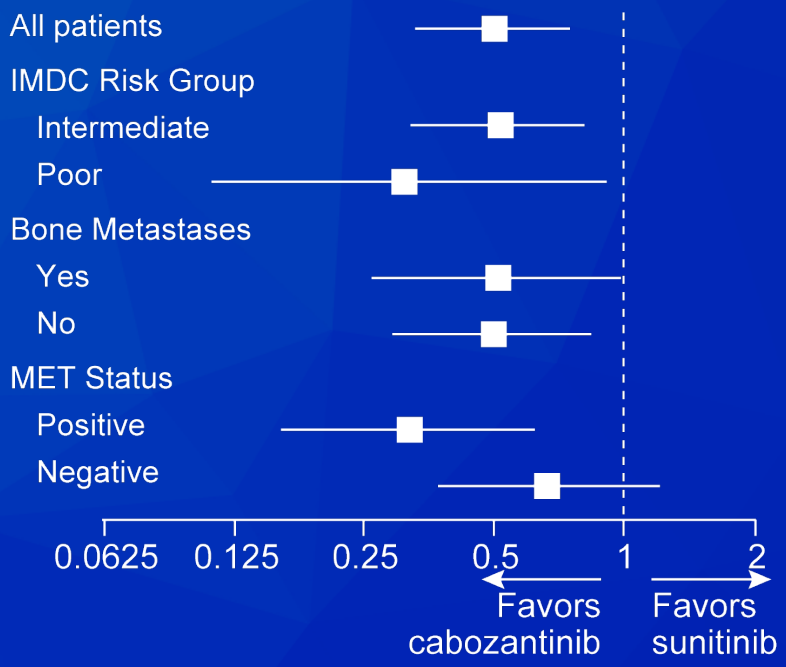
CABOSUN: PFS by Independent Review Committee (IRC) and Updated OS Results

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)

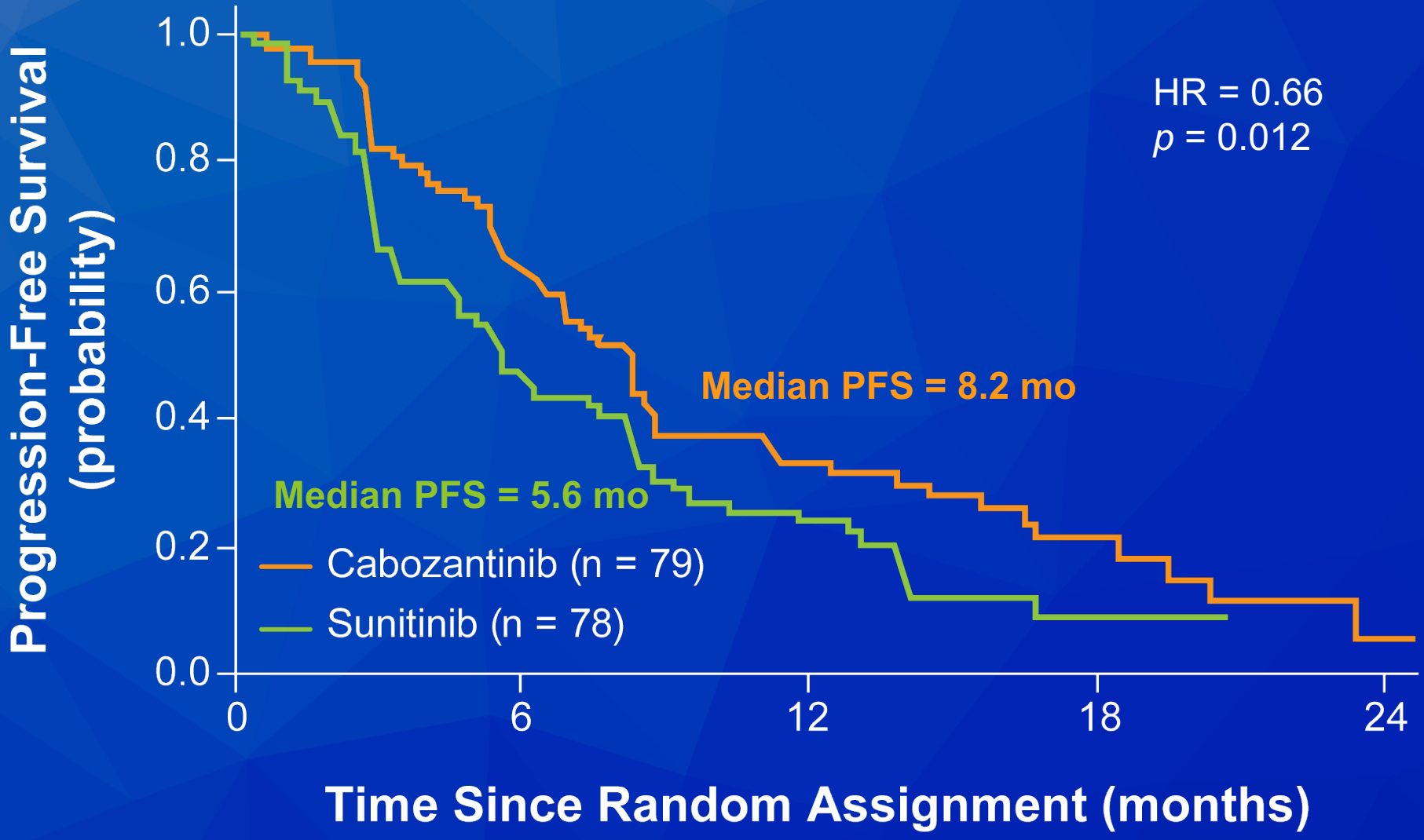
HR = 0.80, p = 0.29 (2-sided)

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 Petrylak

The CABOSUN trial randomized 157 previously untreated patients with intermediate or poor-risk metastatic renal cancer to cabozantinib 60 mg QD or sunitinib 50 mg QD (4 weeks on, 2 weeks off). Cabozantinib reduced the risk for disease progression or death by 52% compared with sunitinib. The initial publication in *JCO* represented the investigator-assessed response and progression-free survival; the ESMO data was derived from an independent radiology review committee (IRC).

The median PFS was 8.6 months for cabozantinib compared with 5.3 months for sunitinib, a 3.3-month improvement. The IRC analysis showed a 52% reduction in the rate of disease progression or death (hazard ratio [HR], 0.48; 95% CI, 0.31-0.74).

Editorial — Dr Petrylak (continued)

In the previously published investigator-assessed analysis, cabozantinib showed a 44% reduction in the risk for disease progression or death (HR, 0.66; 95% CI, 0.46-0.95). Overall survival data was also presented at ESMO. This showed a favorable trend for patients randomized to cabozantinib compared with sunitinib, but the difference was not statistically significant. The median overall survival was 26.6 months for cabozantinib compared with 21.2 months for sunitinib (HR, 0.80; 95% CI, 0.53-1.21).

Editorial — Dr Petrylak (continued)

The most common all-causality grade 3/4 adverse events in more than 5% of patients for cabozantinib (n = 78) and sunitinib (n = 72), respectively, were diarrhea (10% vs 11%), hypertension (28% vs 21%), fatigue (6% vs 17%), increased alanine aminotransferase (ALT; 5% vs 0%), decreased appetite (5% vs 1%), palmar-plantar erythrodysesthesia syndrome (8% vs 4%), decreased platelet count (1% vs 11%), and stomatitis (5% vs 6%). Twenty-one percent of patients in the cabozantinib arm and 22% of patients in the sunitinib arm discontinued treatment due to adverse events.

Thus, based on this data, cabozantinib can be considered as first-line TKI therapy for intermediate/poor-risk renal cell carcinoma.

Genitourinary Cancers — Drs Oh and Petrylak

Renal Cell Carcinoma

Urothelial Bladder Cancer

Prostate Cancer

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 Petrylak

Sharma et al treated 270 refractory urothelial cancer patients with nivolumab, and 265 were evaluated for activity. Median follow-up for overall survival was 7.00 months (IQR 2.96-8.77). Confirmed objective response was achieved in 52 (19.6%, 95% CI 15.0–24.9) of 265 patients. Confirmed objective response was achieved in 23 (28.4%, 95% CI 18.9-39.5) of the 81 patients with PD-L1 expression of 5% or greater, 29 (23.8%, 95% CI 16.5-32.3) of the 122 patients with PD-L1 expression of 1% or greater, and 23 (16.1%, 95% CI 10.5-23.1) of the 143 patients with PD-L1 expression of less than 1%.

Editorial — Dr Petrylak (continued)

Grade 3-4 treatment-related adverse events occurred in 48 (18%) of 270 patients — most commonly grade 3 fatigue and diarrhea, which each occurred in five patients. Three deaths were attributed to treatment (pneumonitis, acute respiratory failure, and cardiovascular failure).

Although the median survival appears to be shorter in duration that other checkpoint inhibitors, the response rates appear to be comparable. No correlation is apparent with PD-L1 expression and response.

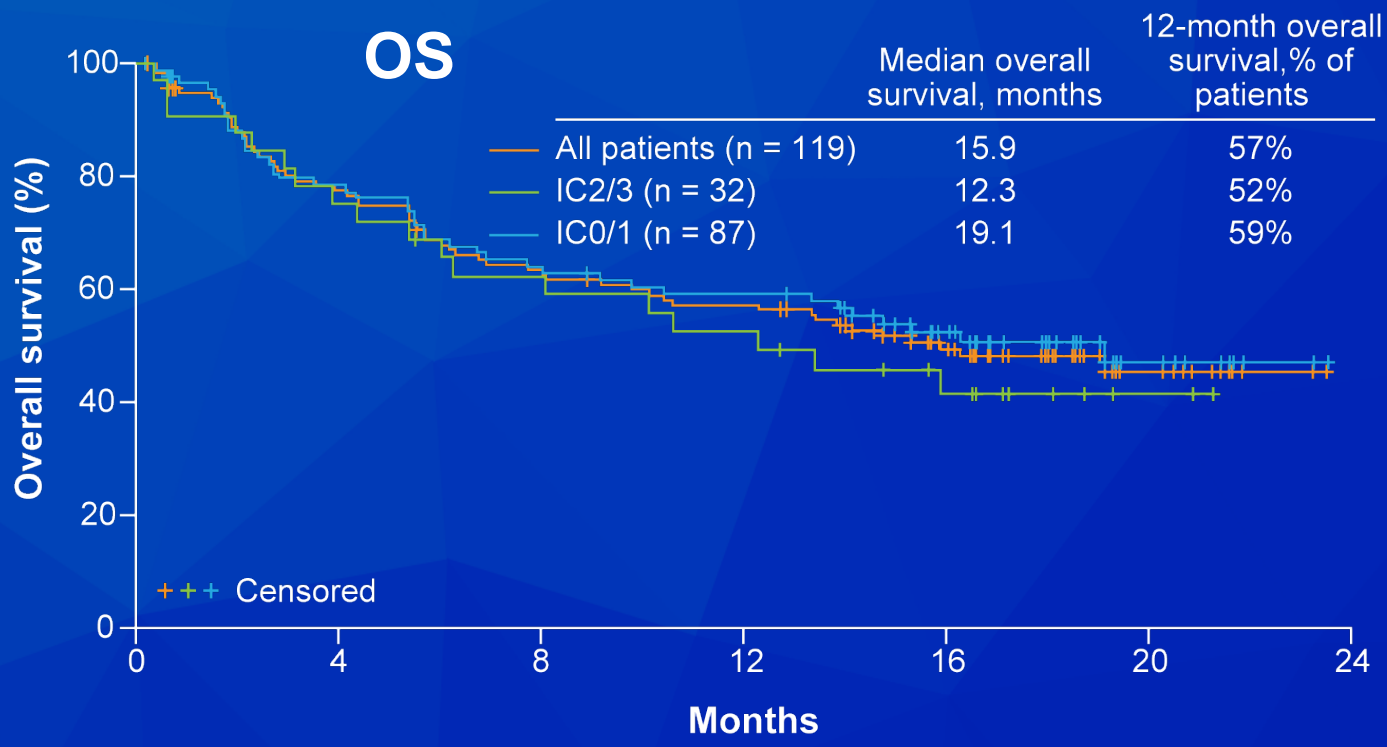
Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial

*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%)



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

Editorial — Dr Petrylak

Cisplatin-ineligible patients include those who have renal dysfunction, peripheral neuropathy, hearing loss, or ECOG performance status of 2. The median survival of patients who are ineligible for cisplatin-based chemotherapy is approximately 9 months. Thus, there is clearly an unmet medical need for active non-cisplatin-based regimens for these patients. IMvigor210 consisted of 2 cohorts. Cohort 1 comprised 119 cisplatin-ineligible patients who had never received treatment for metastatic disease (they were permitted to have received neoadjuvant/adjuvant therapy if >12 months from the end of treatment). Patients were treated with first-line atezolizumab at 1,200 mg IV every 3 weeks until RECIST (Response Evaluation Criteria in Solid Tumors) v1.1 disease progression, assessed by the treating investigator.

Editorial — Dr Petrylak (continued)

At a median follow-up of 17.2 months, the overall response rate was 23%, including 9% complete responses and 14% partial responses. PD-L1 expression on tumor-infiltrating immune cells was assessed by immunohistochemistry and scored as immune cell (IC)0, IC1, or IC2/3. Responses were seen at all levels of PD-L1 expression: 21% who were PD-L1-negative, 23% for those with IC1 expression, and 28% for IC2/3 expression. PDL-1 status therefore did not correlate with response or survival in this group of patients. Tumor mutation load was correlated with response. The median progression-free survival was 2.7 months (2.1 to 4.2). Median overall survival was 15.9 months (10.4 to not estimable).

Editorial — Dr Petrylak (continued)

Caution must be exercised in interpreting survival data from a phase 2 trial, but the survival appears to be better than that seen with carboplatin-based regimens. The FDA has approved atezolizumab for first-line therapy in cisplatin-ineligible patients, and thus it should be considered a treatment option in these patients.

Press Release — Phase III IMvigor211 Trial of Atezolizumab in Previously Treated Bladder Cancer May 9, 2017

The Phase III IMvigor211 study that evaluated atezolizumab in patients with locally advanced or metastatic urothelial cancer (mUC) whose disease progressed during or after prior treatment with a platinum-based chemotherapy did not meet its primary endpoint of overall survival compared to chemotherapy. The safety profile observed in IMvigor211 was consistent with what has been previously observed for atezolizumab.

The results observed in patients treated with atezolizumab in IMvigor211 were generally consistent with those observed in a similar group of patients in the Phase II IMvigor210 study.

https://www.gene.com/media/press-releases/14665/2017-05-09/genentech-provides-update-on-phase-iii-s.

Editorial — Dr Petrylak

IMvigor211 randomized 931 urothelial cancer patients who previously received platinum based chemotherapy to atezolizumab or (vinflunine, paclitaxel or docetaxel).

The primary efficacy endpoint, overall survival, was tested in a successive fashion in study populations defined by PD-L1 expression. The first population tested was people with the highest levels of PD-L1 expression (IC2/3), followed by those with any level of PD-L1 expression (IC1/2/3), and followed by the overall study population (intention-to-treat, ITT). Statistical significance needed to be achieved in the IC2/3 population in order to evaluate the IC1/2/3 population for statistical significance, and similarly achieved in the IC1/2/3 population in order to evaluate the overall study population for statistical significance.

Editorial — Dr Petrylak (continued)

The hazard ratio for the IC2/3 population was 0.87 (95% CI: 0.63, 1.21), *P* = 0.41. Thus the trial failed the first portion of this tiered analysis; thus, even though there was a difference in survival in the ITT patients, it could not be deemed to be significant due to the trial design. The failure of this trial in part may be due to the fact that PD-L1 expression may be both predictive for response as well as prognostic for overall survival. Surprisingly, the median survival with chemotherapy in the IC2/3 patients of 10.6 months was much higher than reported in other trials. Thus, patient selection and trial design may in part account for the fact that IMvigor211 failed to meet its primary endpoint.

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

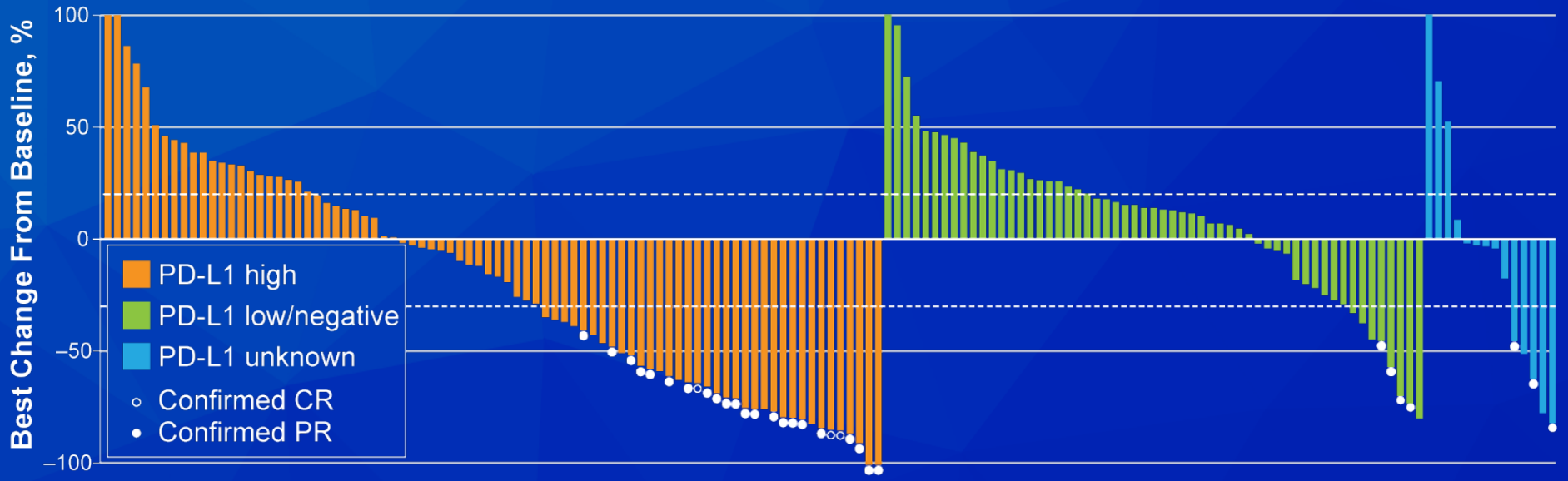
Thomas Powles, MD; Peter H. O'Donnell, MD; Christophe Massard, MD, PhD; Hendrik-Tobias Arkenau, MD, PhD; Terence W. Friedlander, MD; Christopher J. Hoimes, DO; Jae Lyun Lee, MD; Michael Ong, MD; Srikala S. Sridhar, MD; Nicholas J. Vogelzang, MD; Mayer N. Fishman, MD, PhD; Jingsong Zhang, MD, PhD; Sandy 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 Petrylak

Powles et al treated 190 patients with urothelial carcinoma who had prior therapy (1 patient was untreated) with durvalumab 10 mg/kg every other week for up to 1 year.

The objective response rate was 17.8% (34 of 191; 95% CI, 12.7%-24.0%), including 7 complete responses. Responses were early (median time to response, 1.41 months), durable (median duration of response not reached), and observed regardless of programmed cell death ligand-1 (PD-L1) expression (ORR, 27.6% [n = 27; 95% CI, 19.0%-37.5%] and 5.1% [n = 4; 95% CI, 1.4%-12.5%] in patients with high and low or negative expression of PD-L1, respectively). Median progression-free survival and overall survival were 1.5 months (95% CI, 1.4-1.9 months) and 18.2 months (95% CI, 8.1 months to not estimable), respectively.

Editorial — Dr Petrylak (continued)

Thus durvalumab treatment appears to have similar efficacy to other checkpoint inhibitors in second-line urothelial cancer; PD-L1 expression did not correlate with outcome.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

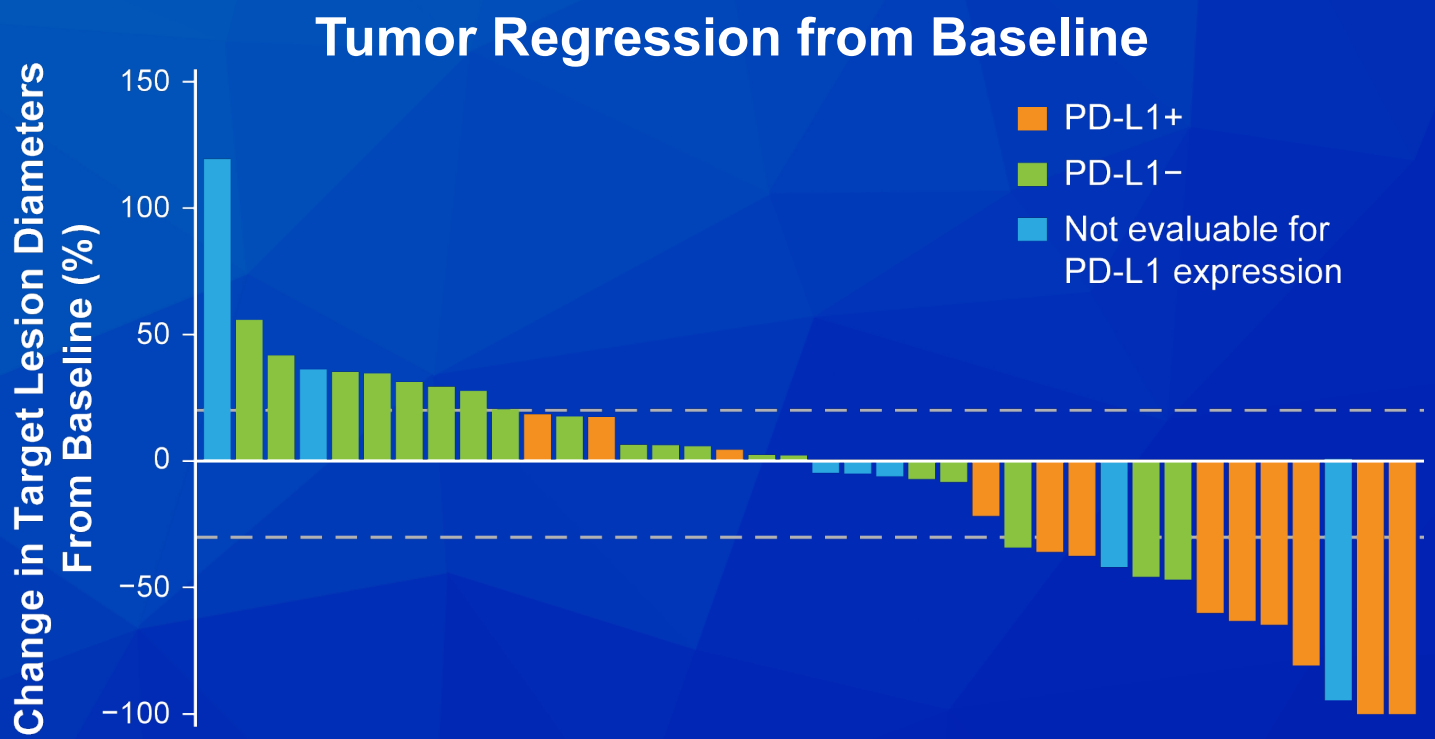
Avelumab, an Anti–Programmed Death-Ligand 1 Antibody, In Patients With Refractory Metastatic Urothelial Carcinoma: Results From a Multicenter, Phase Ib Study

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 Petrylak

Avelumab, a programmed cell death ligand-1 (PD-L1) inhibitor, is approved for second-line use in patients with locally advanced or metastatic urothelial carcinoma whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

This approval was based on a cohort of urothelial cancer patients from a phase I trial, which demonstrated a response rate of 18.2%, with 7 out of 8 responding patients having PD-L1+ tumors. The median progression-free survival was 11.6 weeks (95% CI, 6.1 to 17.4 weeks); the median OS was 13.7 months (95% CI, 8.5 months to not estimable), with a 12-month OS rate of 54.3% (95% CI, 37.9% to 68.1%).

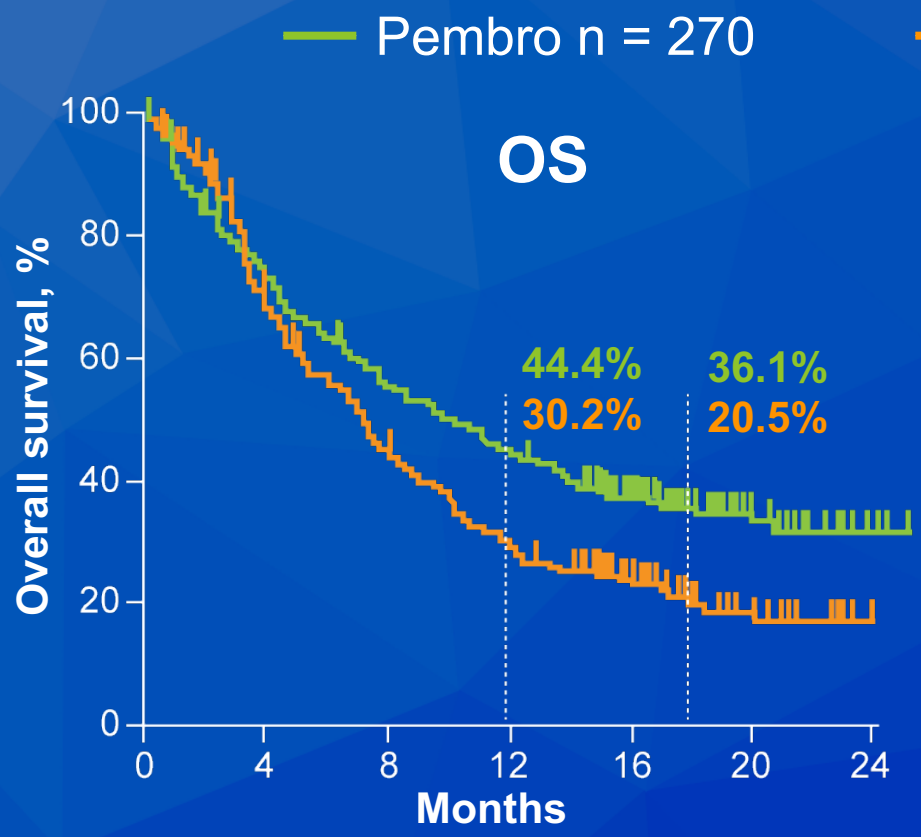
Editorial — Dr Petrylak (continued)

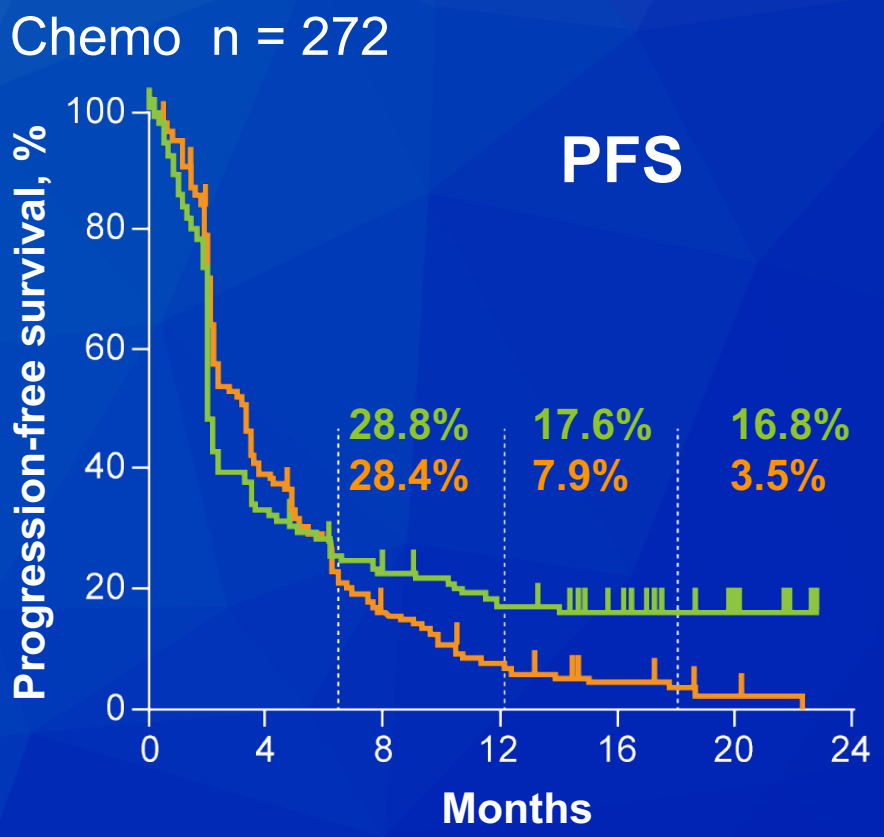
There does appear to be a better correlation of avelumab outcome with PD-L1 expression.

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 Petrylak

To confirm the activity of pembrolizumab in patients with metastatic urothelial carcinoma who progressed after prior platinum-based chemotherapy, KEYNOTE-045 randomized 545 patients to either pembrolizumab monotherapy (200 mg every 3 weeks) or investigator-choice chemotherapy (paclitaxel, docetaxel, vinflunine). The coprimary endpoints were overall survival and progression-free survival; secondary endpoints are overall response rate, duration of response, and safety.

The median survival in the pembrolizumab arm was 10.3 months (95% CI 8.0, 12.3) compared with 7.4 months in the chemotherapy arm (95% CI 6.1, 8.1).

Editorial — Dr Petrylak (continued)

A significant survival benefit was observed in patients across all levels of PD-L1 expression as well as subgroups such as age, ECOG performance status, prior therapy, liver metastases, histology, or investigator choice of chemotherapy. Patients receiving pembrolizumab demonstrated an objective response rate of 21.1% and a complete response rate of 7.8%, compared with 11.0% and 2.9%, respectively, in the chemotherapy arm.

The majority of AEs in the pembrolizumab cohort were pruritus, fatigue, and nausea, most of which were grades 1 and 2. Decreased neutrophil levels and neutropenia were rare among the patients who received pembrolizumab, but developed in approximately 15% of patients receiving chemotherapy, with a 7.5% febrile neutropenia rate.

Editorial — Dr Petrylak (continued)

Immune-related AEs were primarily grade 1 and 2, with hypothyroidism, pneumonitis, and hyperthyroidism as the most common. All immune-related AEs occurred in fewer than 10 patients.

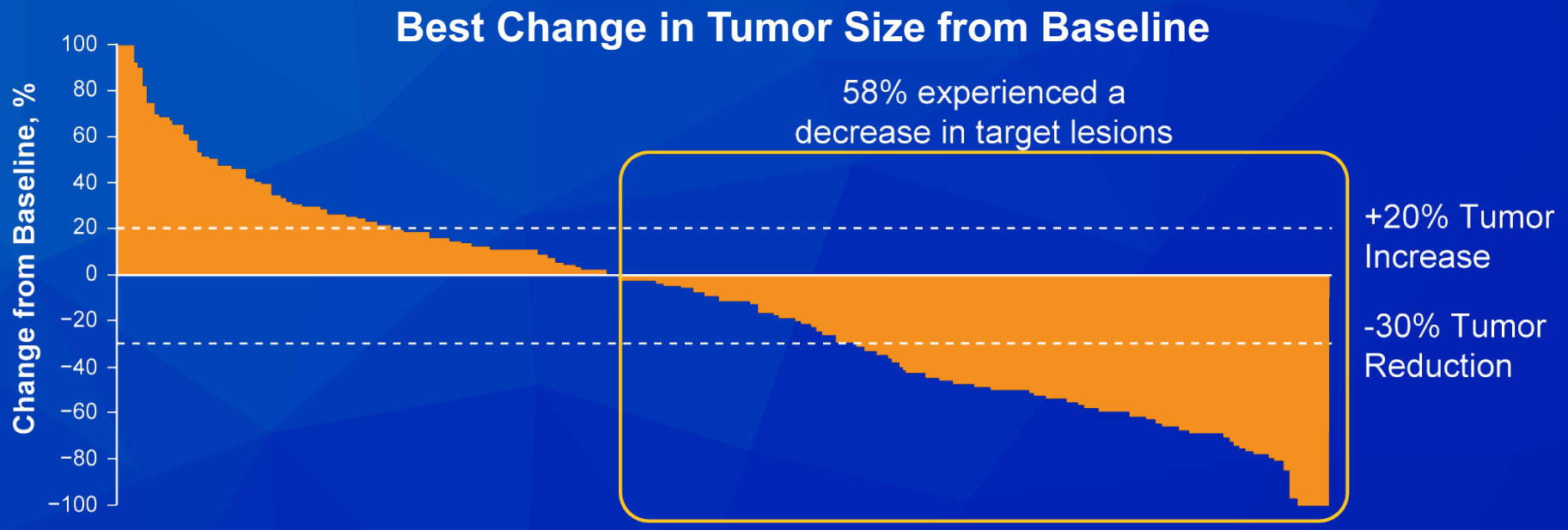
This trial represents the only phase III trial to demonstrate a survival benefit of checkpoint inhibition therapy compared to chemotherapy in metastatic urothelial carcinoma. Of note, while there is no significant PFS difference between chemotherapy and pembrolizumab, the duration of response was longer in those patients treated with checkpoint inhibition therapy. The durability of response is what drives the survival advantage of pembrolizumab.

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.

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 Oh and Petrylak

Renal Cell Carcinoma

Urothelial Bladder Cancer

Prostate Cancer

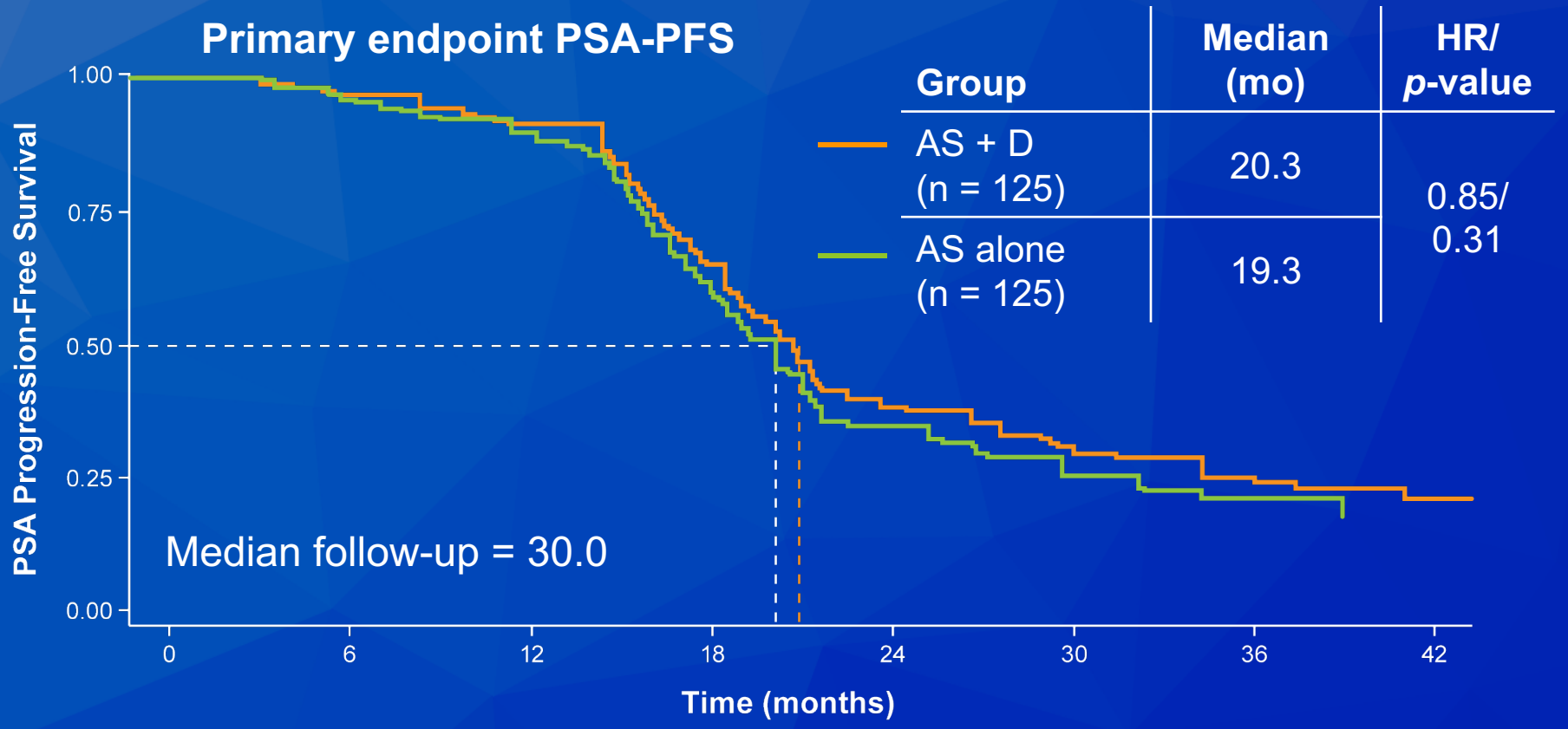
Key Decision Points in the Systemic Treatment of Prostate Cancer

- 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 Oh

Since docetaxel was approved in 2004 based on its OS benefit in mCRPC, efforts to move chemotherapy earlier were initiated. Biochemical relapse (BCR, aka “rising PSA”) seemed to be a perfect opportunity to treat minimal, microscopic disease after local therapy. If those cancer cells which escaped the prostate prior to surgery or radiation represent minimal residual disease, could we target those cells with the combination of ADT and docetaxel? In this phase III trial of 250 men with rising PSA and some high-risk features, patients were randomized to ADT with or without 6 cycles of docetaxel. No differences were seen in PSA response, PSA-PFS and rPFS.

Editorial — Dr Oh (continued)

Other studies done in the setting have also not shown a clinical benefit to adding chemotherapy to ADT in BCR patients. Why? It could be that the cancers were not responsive to chemo, were not high-risk enough (eg, not proliferating adequately), had some interaction with ADT or biologically were not able to target the relapsing cancer cell. In many ways, this result is surprising, considering the results of STAMPEDE, which showed a significant PFS benefit in high-risk localized and node-positive patients treated with a similar course of docetaxel. For now, there is no role for docetaxel in BCR.

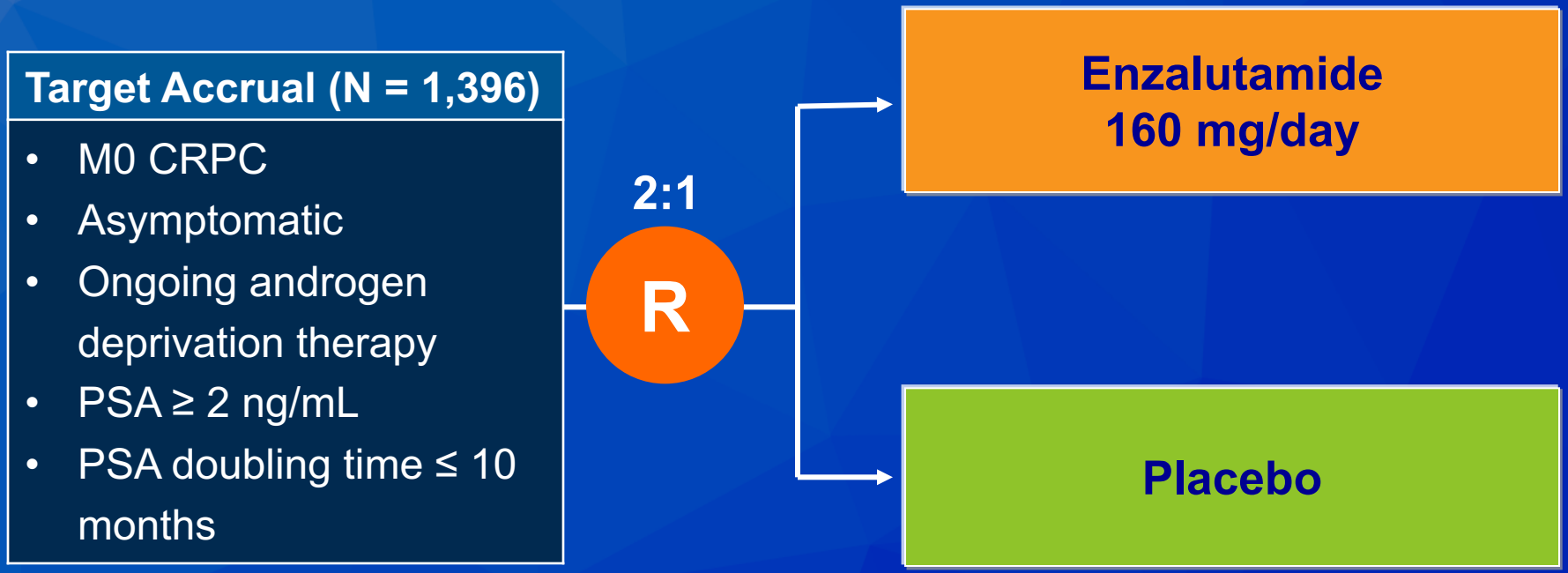
Press Release — Phase III PROSPER Trial of Enzalutamide
September 14, 2017

The Phase III PROSPER trial evaluating enzalutamide plus androgen deprivation therapy (ADT) versus ADT alone in patients with nonmetastatic (M0) castration-resistant prostate cancer (CRPC) met its primary endpoint of improved metastasis-free survival (MFS). The preliminary safety analysis of the PROSPER trial appears consistent with the safety profile of enzalutamide in previous clinical trials.

"*Based on the results of PROSPER, the companies intend to discuss the data with global health authorities to potentially support expanding the label for enzalutamide to cover all patients with CRPC.*"

http://newsroom.astellas.us/2017-09-14-Pfizer-and-Astellas-Announce-Positive-Top-Line-Results-from-Phase-3-PROSPER-Trial-of-XTANDI-enzalutamide-in-Patients-with-Non-Metastatic-Castration-Resistant-Prostate-Cancer

PROSPER: A Phase III Multinational Study of Enzalutamide



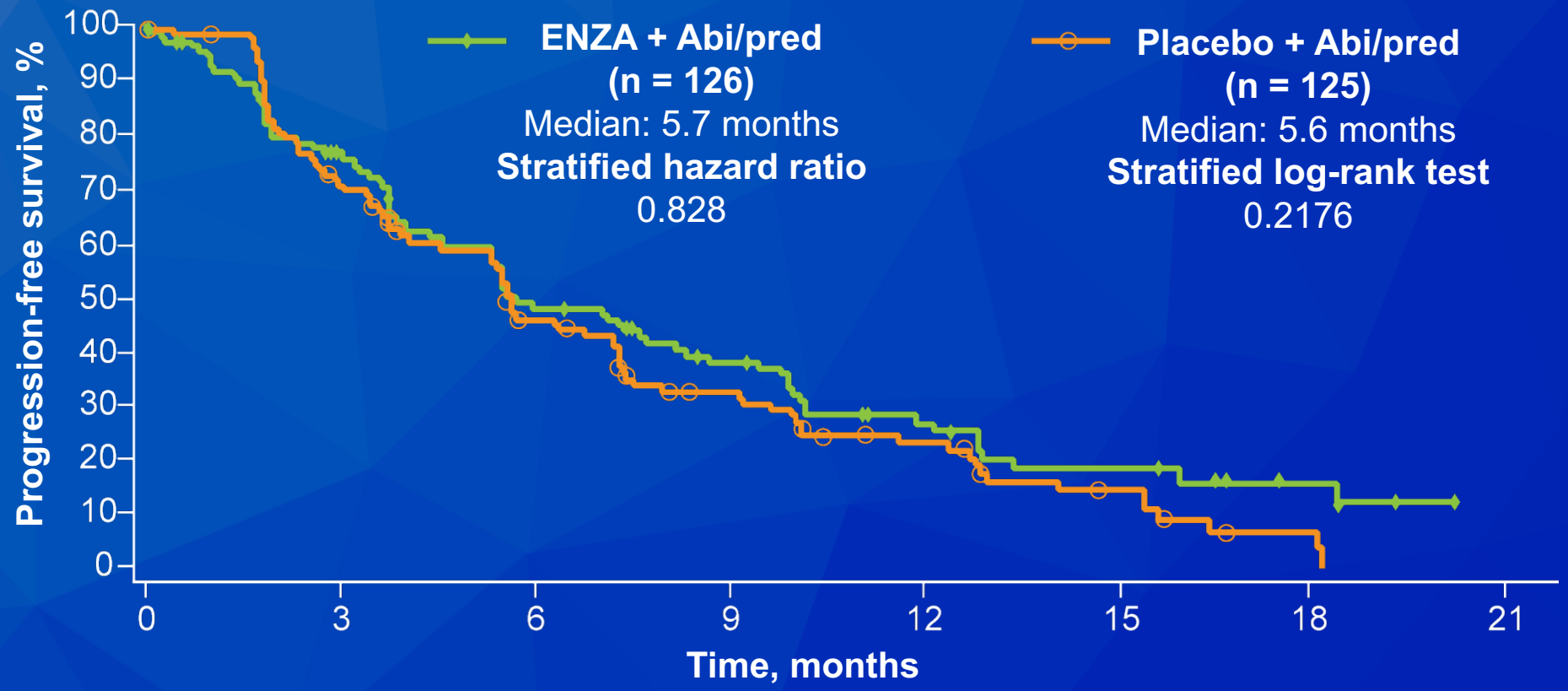
Primary Endpoint: Metastasis-free survival (time to radiographic progression or death)

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

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 Oh

In 2014, AR-V7 came onto the scene in prostate cancer after a paper in *NEJM*. The promise was intriguing — could a blood-based biomarker determine sensitivity to abiraterone or enzalutamide with a compelling biological rationale? Unfortunately 2 things have since been clear. First, a commercially available clinical test has not yet been widely available for clinicians. Second, studies remain unclear about whether AR-V7 is truly a marker of resistance to AR-targeted therapy.

This is a prospective study of 202 patients who had a CTC-based AR-V7 test prior to starting abiraterone or enzalutamide. 29% had no CTCs, and only 12% had CTCs with AR-V7 detected.

Editorial — Dr Oh (continued)

Patients who were AR-V7+ had more advanced disease and were more likely to have been treated previously with abiraterone or enzalutamide or taxanes. Outcomes were best if CTCs were not detected and worse if they were present and AR-V7+.

The major disappointment in this paper is that AR-V7 is clearly prognostic but not necessarily predictive of benefit, at least enough to use it as a clinical test for practitioners. So while a new commercial test may be available soon, it is not clear that oncologists should use it to decide whether to proceed with abiraterone or enzalutamide.

Press Release — Apalutamide New Drug Application Submitted for Nonmetastatic CRPC October 11, 2017

"This submission is based on Phase 3 data from the pivotal ARN-509-003 (SPARTAN) clinical trial, which assessed the safety and efficacy of apalutamide versus placebo, in men with non-metastatic CRPC who have a rapidly rising prostate specific antigen (PSA) despite receiving continuous androgen deprivation therapy (ADT)… The primary endpoint of this study was metastasis free survival."

The SPARTAN study results will be presented at a future medical meeting.

https://www.jnj.com/media-center/press-releases/janssen-submits-new-drug-application-to-us-fda-for-apalutamide-arn-509-to-treat-men-with-non-metastatic-castration-resistant-prostate-cancer

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.

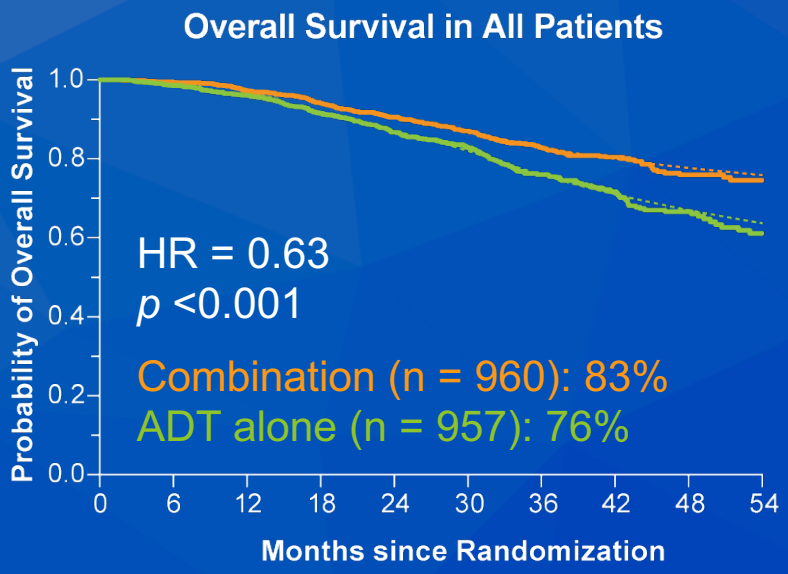
ORIGINAL ARTICLE

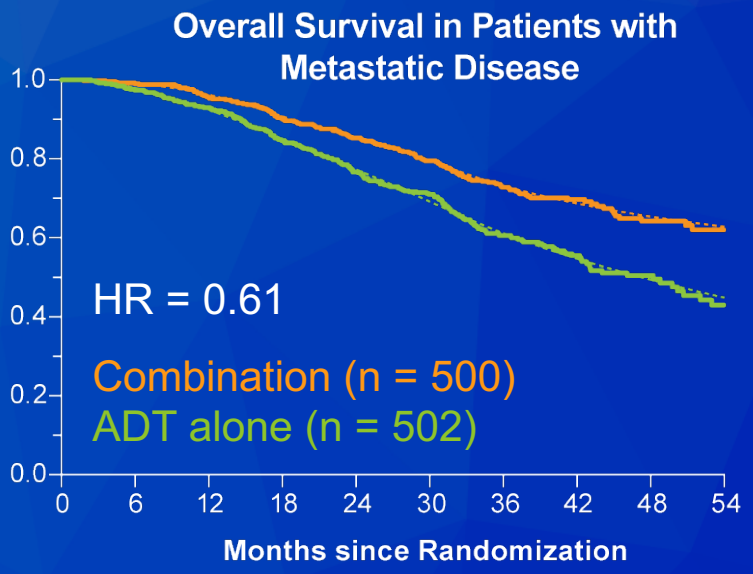
Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

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



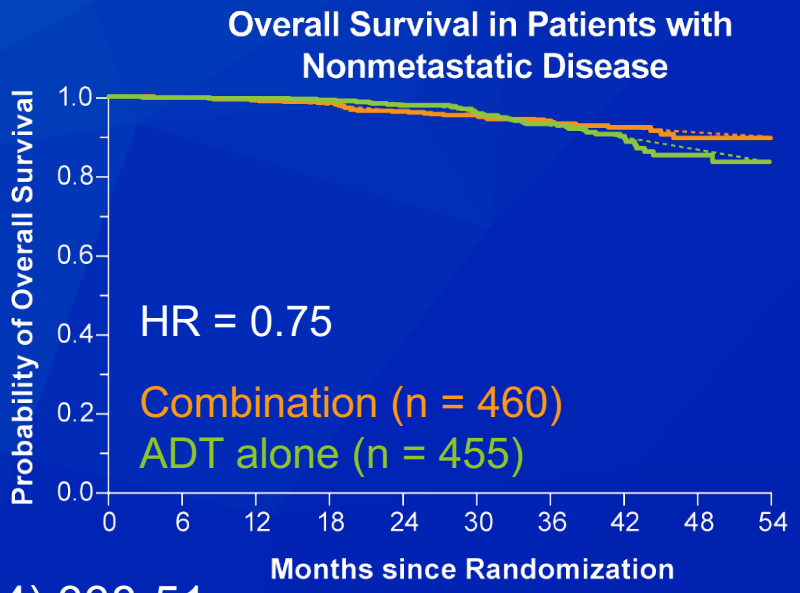


Combination = ADT + Abi + prednisolone

<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%	

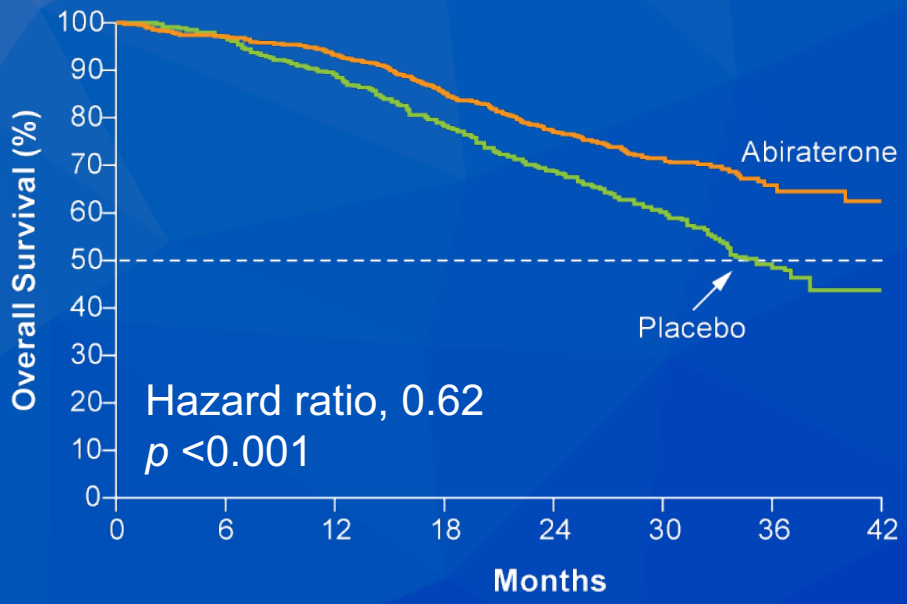
SOC = standard of care; DocP = docetaxel/prednisone; AAP = abiraterone/prednisone

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

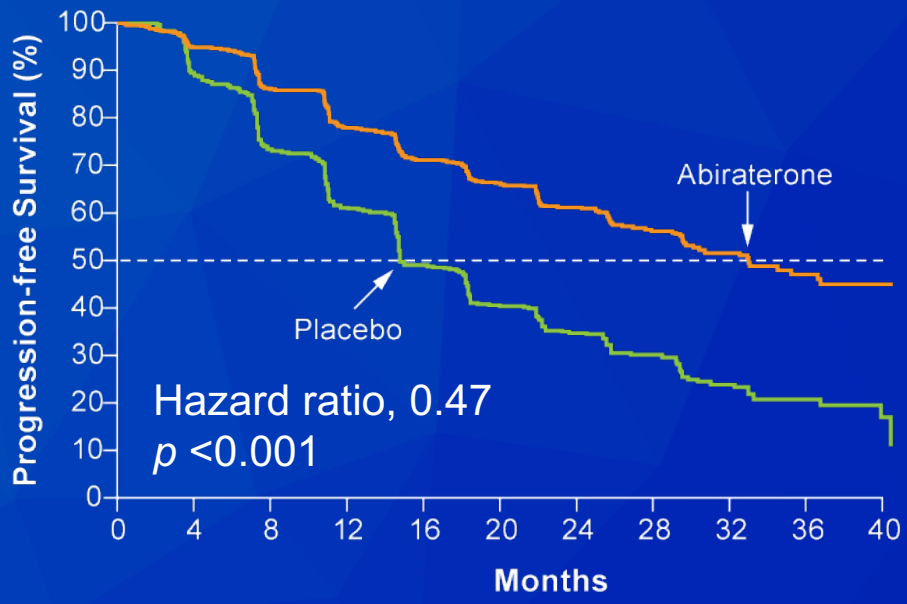
Sydes MR et al. *Proc ESMO* 2017;Abstract LBA31_PR.

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 Oh

Management of metastatic hormone-sensitive prostate cancer (mHSPC) was transformed in 2014 with the publication of CHAARTED and STAMPEDE, which showed that docetaxel x 6 cycles significantly improved survival for these patients. In 2017, the next big step in mHSPC was 2 trials that showed an equivalent dramatic benefit in OS with the use of abiraterone acetate + prednisone. LATITUDE randomized 1,199 mHSPC patients to ADT +/- abiraterone 1,000 mg + prednisone 5 mg (note the lower dose). Hazard ratio (HR) for death was 0.62 (95% CI 0.51-0.75, $p < 0.0001$). rPFS increased from 14.8 to 33 months. Multiple secondary endpoints were better with abiraterone, including SREs.

Editorial — Dr Oh (continued)

STAMPEDE also presented data on 1,917 advanced prostate cancer patients (52% with mets) randomized to the same treatments. In all patients, the HR was 0.63 (95% CI 0.52-0.76, $p < 0.001$) and HR 0.61 in metastatic patients.

The summary of this data is that abiraterone + prednisone has become a choice for a new standard of care for mHSPC. Because this has not been compared with docetaxel chemotherapy per CHAARTED, both abiraterone and docetaxel remain options for therapy to be offered to new patients with mHSPC. Both approaches have toxicity, cost and other issues, so more research is needed to define the benefit of each treatment.

Editorial — Dr Oh (continued)

Molecular markers for benefit may allow us to provide more precise treatment decisions, but do not exist currently. It is possible also that the combination of abiraterone and docetaxel could have a role in the future.

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 Oh

Two taxanes have been approved for use in mCRPC in the US: docetaxel for first line disease (2004) and cabazitaxel for second line disease (2010). Preclinical studies have suggested that cabazitaxel may have activity in docetaxel-resistant cancers. To address the issue of cross-resistance between the taxanes and to explore biomarkers for response, a phase II crossover trial was conducted in 63 patients with mCRPC, assigned 2:1 to receive docetaxel or cabazitaxel up front. If patients did not have a PSA decline >30% by cycle 4, they switched to the alternative taxane: 24.6% of the total. Of those that switched, nearly half did achieve a response to the second taxane.

Editorial — Dr Oh (continued)

In total, the response rate to a taxane either initially or after switching was 56%, higher than historical controls of docetaxel alone. A CTC biomarker on day 8 (% AR nuclear localization) was associated with clinical response.

This study suggests that there is some additional activity with a second taxane in patients who do not have an adequate response to the first. Clinically this may be worth considering in practice, though more typically toxicity is a more common reason to switch. The biomarker is interesting scientifically but unlikely to have any clinical value, especially since CTCs need to be detected (in half of patients currently) and the test is done 1 week after treatment — not a valuable decision aid for whether to start 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.

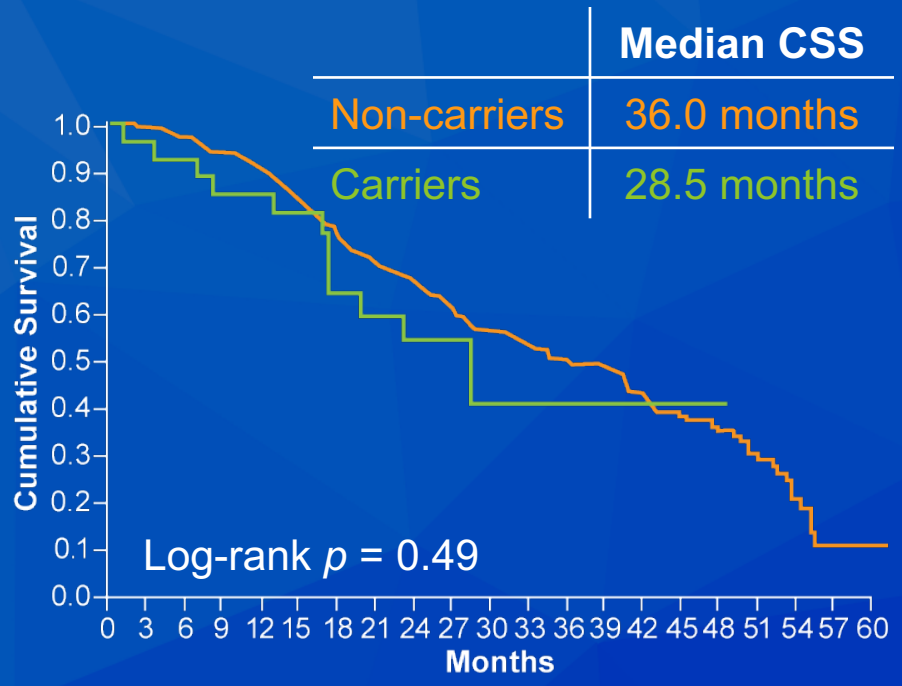
ORIGINAL ARTICLE

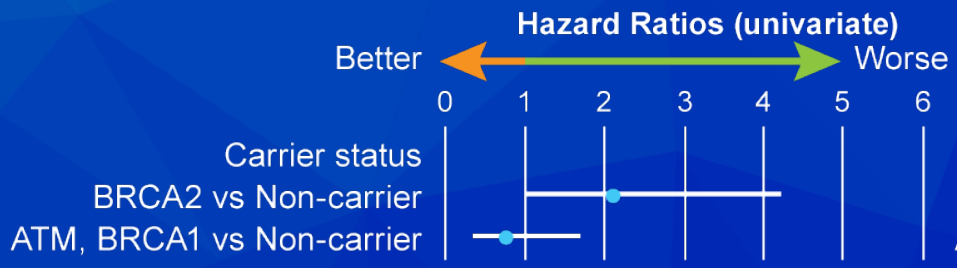
Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

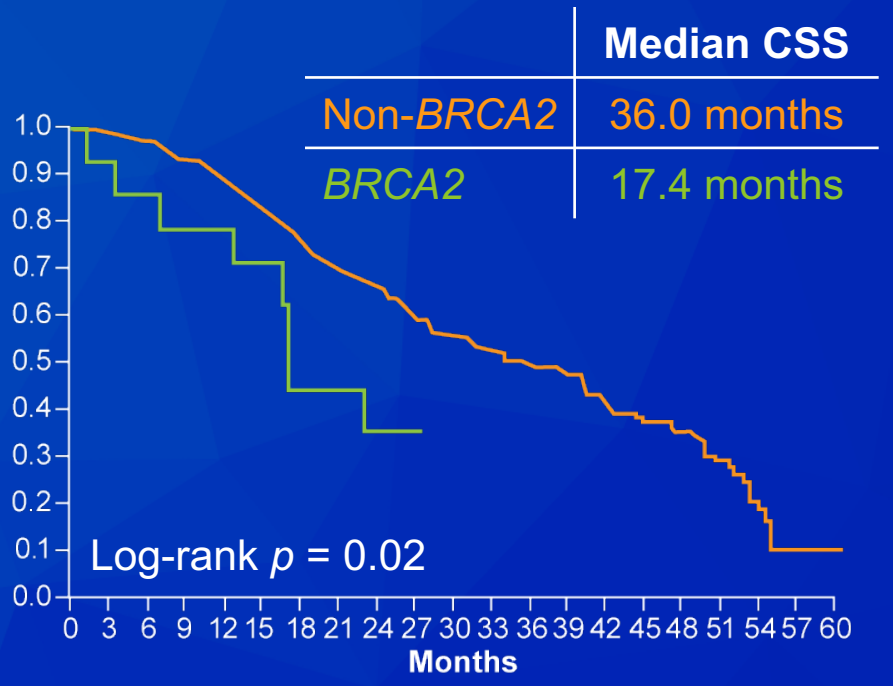
C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, 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

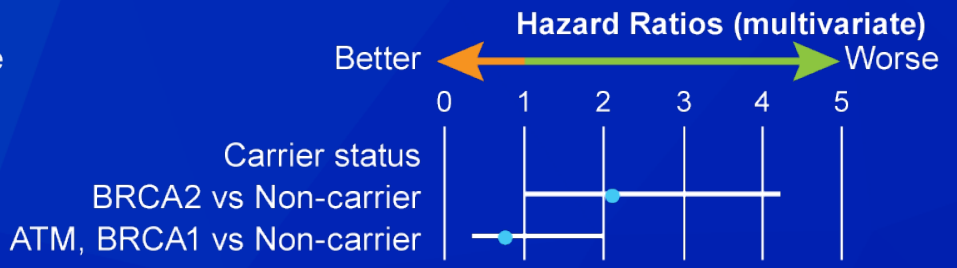
N Engl J Med 2016;375(5):443-53.

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.

Editorial — Dr Oh

The role of DNA repair pathway mutations in prostate cancer has been a very important story recently. Germline mutations in BRCA2 in particular, but also other genes (BRCA1, CHEK2, ATM, PALB2), have been associated with worse outcomes and clinical response to unique therapies, including PARP inhibitors and platinum chemotherapy. Pritchard et al published outcomes in 692 metastatic patients of whom 11.8% had germline mutations in DNA repair pathways (primarily BRCA2). This was much higher than a cohort of localized prostate cancer (4.6%) and non-cancer controls (2.7%) ($p < 0.001$ for both). The Spanish Cancer Consortium prospectively assessed 419 patients from 38 institutions and identified 6.2% as carriers (14 BRCA2, 8 ATM, 4 BRCA1). Any approved mCRPC treatment was allowed.

Editorial — Dr Oh (continued)

There was a trend toward worse cancer-specific survival (CSS), but not significant except for the subgroup of BRCA2 patients only. Median CSS was 28.5 vs 36 months in carriers vs non-carriers (p = NS) but only 17.4 months in BRCA2 carriers (p = 0.02).

In summary, germline mutations in DNA repair pathway genes are more common in metastatic prostate cancer and are associated with worse outcomes in mCRPC. Whether such patients should receive alternative treatment approaches remains unclear. Precision medicine is here for mCRPC!