Year in Review

Proceedings from a Multitumor CME Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Hormone-Naïve Prostate Cancer and Novel Approaches to the Management of Renal Cell and Urothelial Bladder Cancer — William K Oh, MD

Select Publications

Choueiri TK et al. **Cabozantinib versus everolimus in advanced renal-cell carcinoma.** *N Engl J Med* 2015;373(19):1814-23.

James ND et al. **Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: First overall survival results from STAMPEDE (NCT00268476).** *Proc ASCO* 2015;**Abstract 5001**.

McDermott DF et al. **Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab.** *J Clin Oncol* 2015;33(18):2013-20.

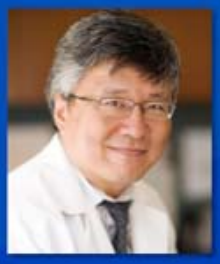
Motzer RJ et al. **Nivolumab versus everolimus in advanced renal-cell carcinoma.** *N Engl J Med* 2015;373(19):1803-13.

Motzer R et al. **Randomized phase II, three-arm trial of lenvatinib (LEN), everolimus (EVE), and LEN+EVE in patients (pts) with metastatic renal cell carcinoma (mRCC).** *Proc ASCO* 2015;**Abstract 4506**.

Petrylak DP et al. **A phase Ia study of MPDL3280A (anti-PDL1): Updated response and survival data in urothelial bladder cancer (UBC).** *Proc ASCO* 2015;**Abstract 4501**.

Plimack ER et al. **Pembrolizumab (MK-3475) for advanced urothelial cancer: Updated results and biomarker analysis from KEYNOTE-012.** *Proc ASCO* 2015;**Abstract 4502**.

Hormone-Naïve Prostate Cancer and Novel Approaches to the Management of Renal Cell and Urothelial Bladder Cancer



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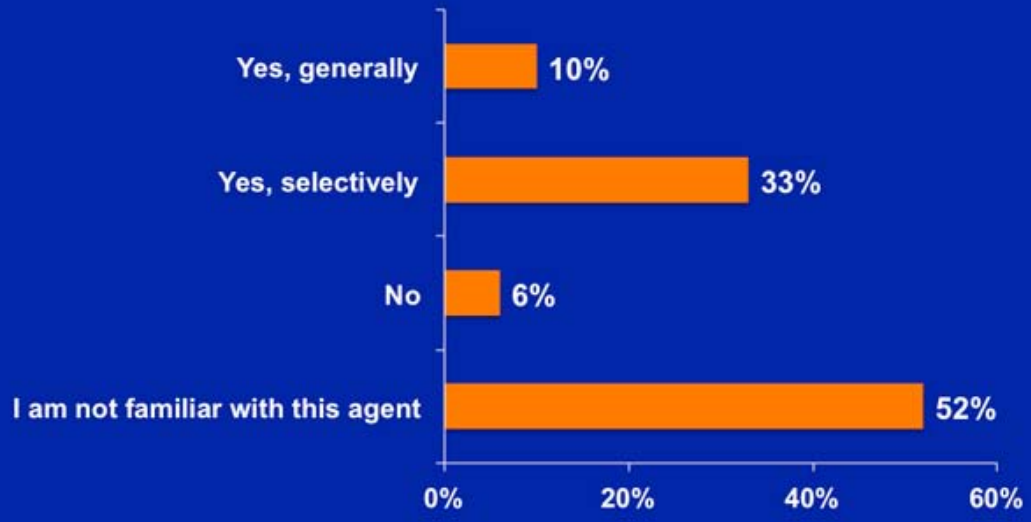
Disclosures

Advisory Committee	Bayer HealthCare Pharmaceuticals, Bellicum Pharmaceuticals Inc, DAVA Oncology, Inovio Pharmaceuticals, Janssen Biotech Inc, Sanofi, Seattle Genetics, Teva Oncology.

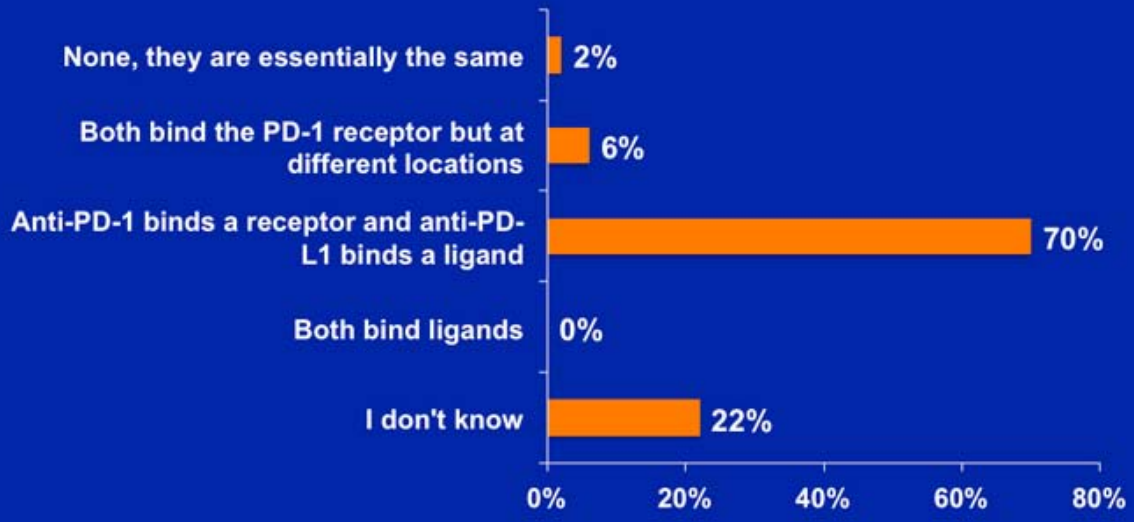
AUDIENCE POLL

If atezolizumab (MPDL3280A) were granted a broad approval for the treatment of metastatic bladder cancer, would you use it as first-line therapy?



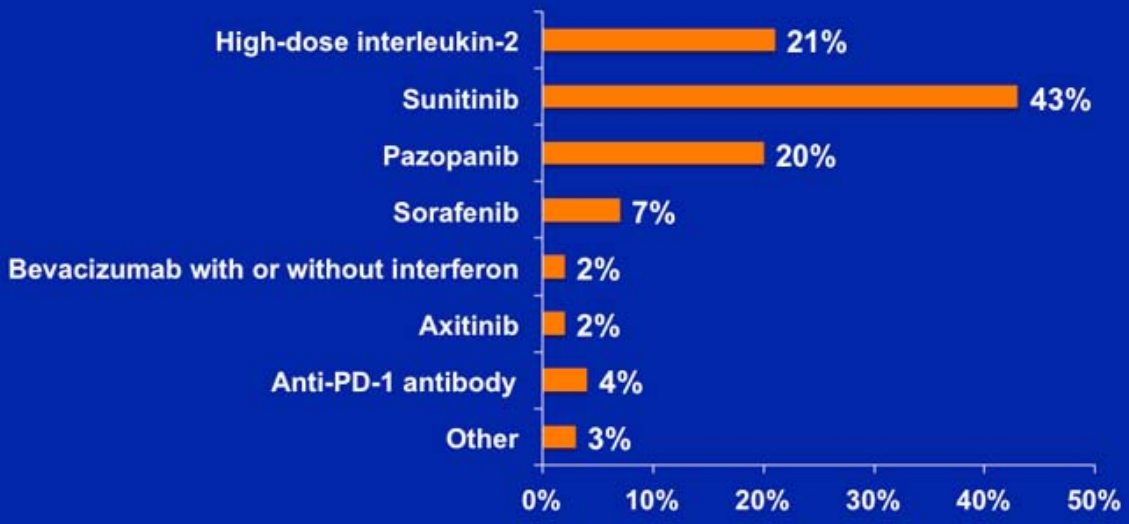
AUDIENCE POLL

What is the difference in the mechanisms of action of anti-PD-1 and anti-PD-L1 antibodies?



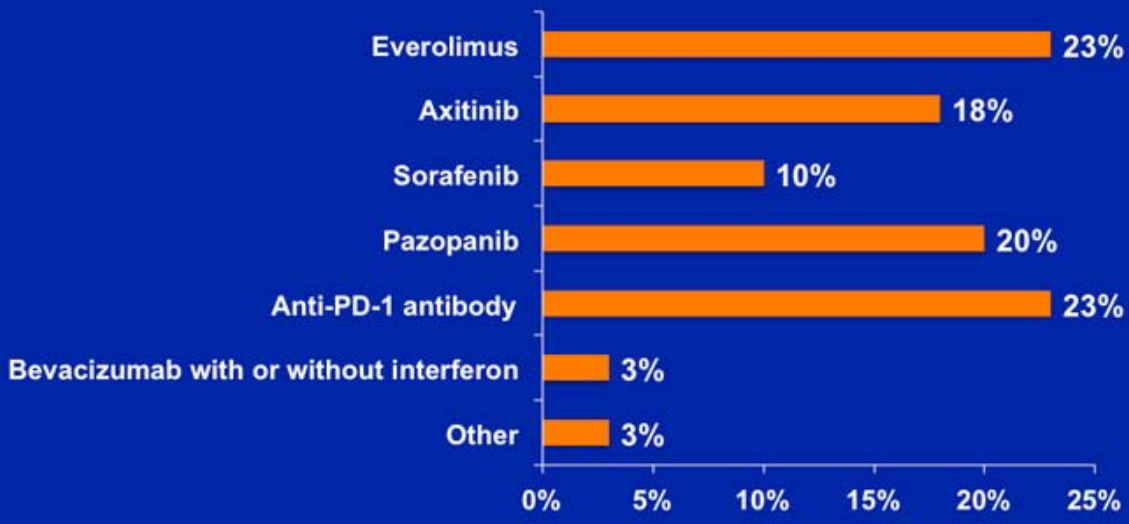
AUDIENCE POLL

Cost and reimbursement issues aside, in general, what is your preferred first-line systemic treatment recommendation for a younger (age 55), otherwise healthy patient with metastatic renal cell carcinoma (mRCC)?



AUDIENCE POLL

Cost and reimbursement issues aside, in general, what is your preferred second-line systemic treatment recommendation for a younger (age 55), otherwise healthy patient with mRCC who initially responds to sunitinib for 7 months and then experiences disease progression?



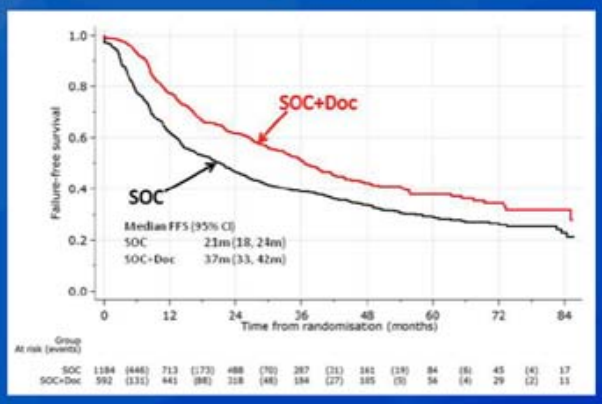
Docetaxel and/or Zoledronic Acid for Hormone-Naïve Prostate Cancer: First Overall Survival Results from STAMPEDE (NCT00268476)

James ND et al.

Proc ASCO 2015;Abstract 5001.

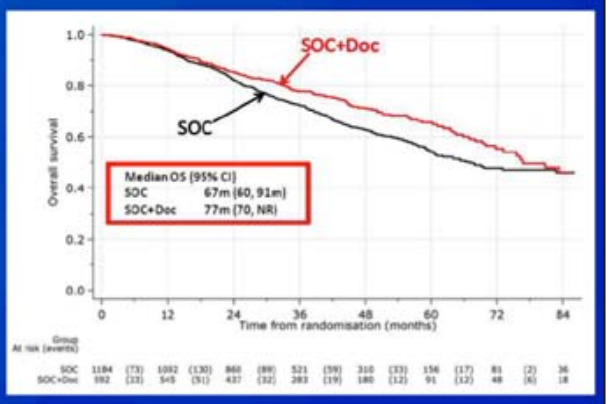
STAMPEDE: Failure-free and Overall Survival with Docetaxel (Doc) versus Standard of Care (SOC)

FFS



SOC	750 FFS events
SOC+Doc	371 FFS events
HR (95%CI)	0.62 (0.54, 0.70)
P-value	<0.0000000001*

OS



SOC	405 deaths
SOC+Doc	165 deaths
HR (95%CI)	0.76 (0.63, 0.91)
P-value	0.003

James ND et al. *Proc ASCO* 2015;Abstract 5001.

Conclusions

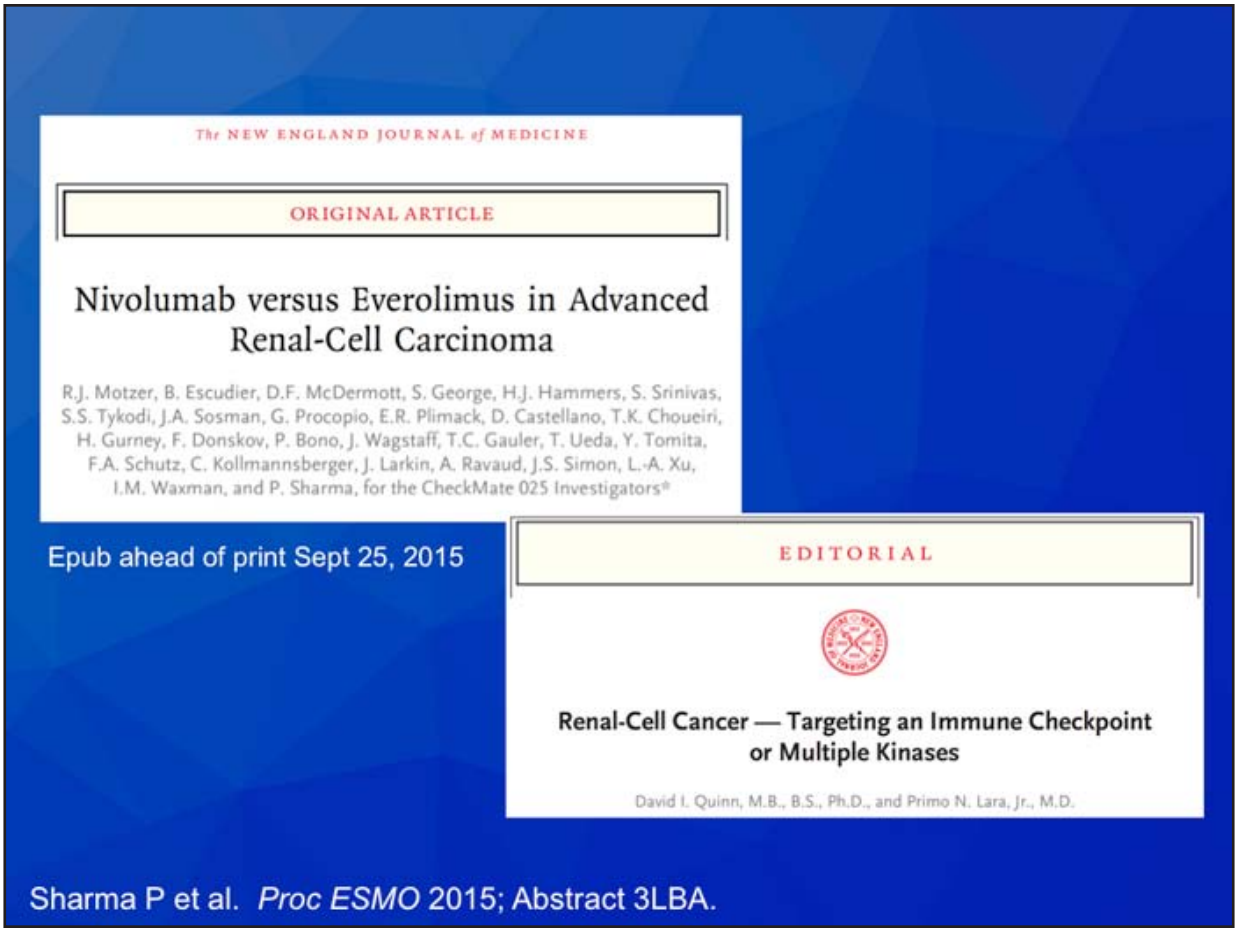
Critical finding(s): The addition of docetaxel to ADT in mHSPC was associated with a 10-month improvement in OS (HR 0.76). In M1 patients, the effect was even greater with a median OS benefit of 22 months. Zoledronic acid had no effect on OS.

Clinical implication(s): Based on STAMPEDE and CHAARTED, the new SOC for mHSPC should be ADT + 6 cycles of docetaxel chemotherapy. STAMPEDE had a 12% rate of febrile neutropenia (CHAARTED 6%), so consideration of growth factors should be given. Patients should be fit for chemotherapy.

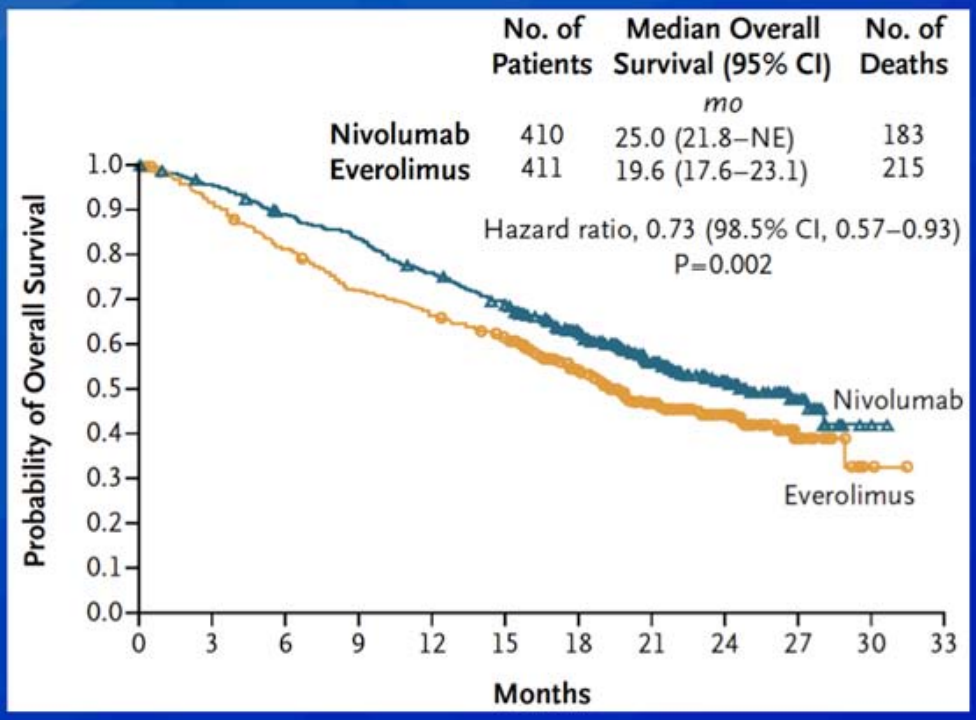
Conclusions

Research relevance: Unanswered questions include: Should high- versus low-volume disease be considered? Is a de novo patient the same as one who progresses to metastasis after local therapy and rising PSA? Would abiraterone or enzalutamide have the same benefit in mHSPC?

RENAL CELL CANCER

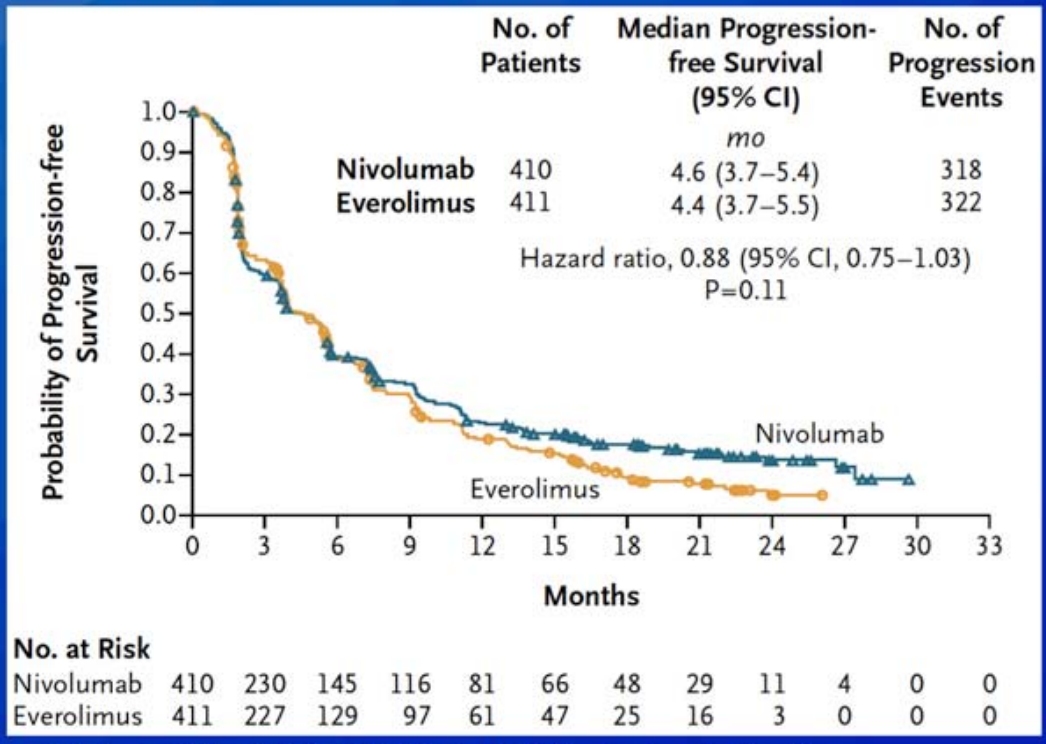


Overall Survival



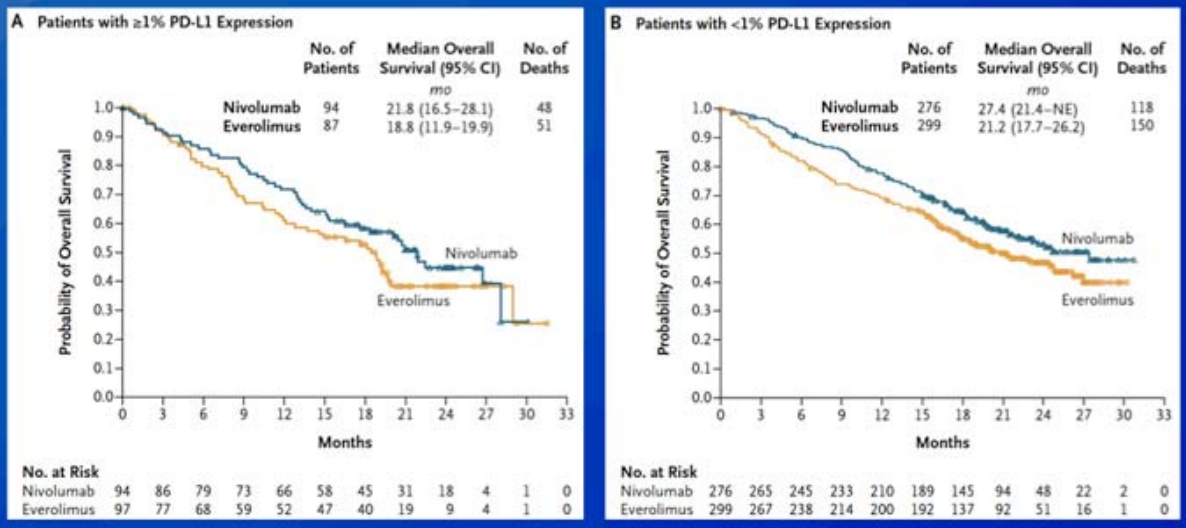
Motzer RJ et al. *N Engl J Med* 2015 Sept 25;Epub ahead of print

Progression-Free Survival



Motzer RJ et al. *N Engl J Med* 2015 Sept 25;Epub ahead of print

PFS by PD-L1 Expression



Motzer RJ et al. *N Engl J Med* 2015 Sept 25;Epub ahead of print

Conclusions

Critical finding(s): Nivolumab, an anti-PD-1 antibody, was superior to everolimus in mRCC after first-line therapy. HR for OS was 0.73, which translated into a 5.4-month improvement in OS. Nivolumab also had fewer Grade 3/4 toxicities.

Clinical implication(s): Based on these findings, nivolumab at 3 mg/kg q2wk should become a standard option for second-line therapy for mRCC after TKIs. The toxicity profile and durable responses noted represent a key new therapeutic option for mRCC.

Conclusions

Research relevance: PD-L1 staining on tumor tissue did not predict benefit for nivolumab, so better predictive biomarkers are needed. Also, it is unclear if nivolumab would be more active if given first line or in combination with TKIs. This will be the subject of future trials.

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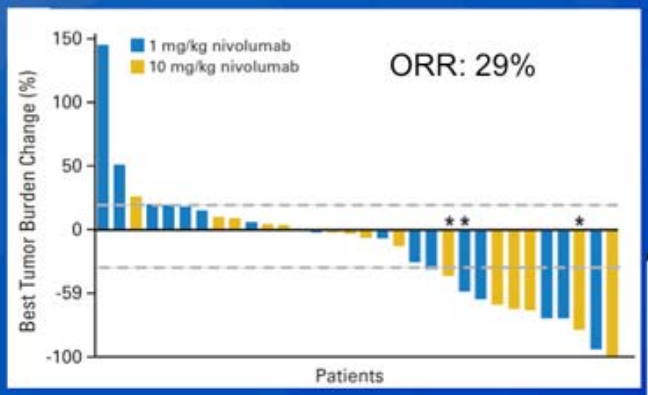
JOURNAL OF CLINICAL ONCOLOGY

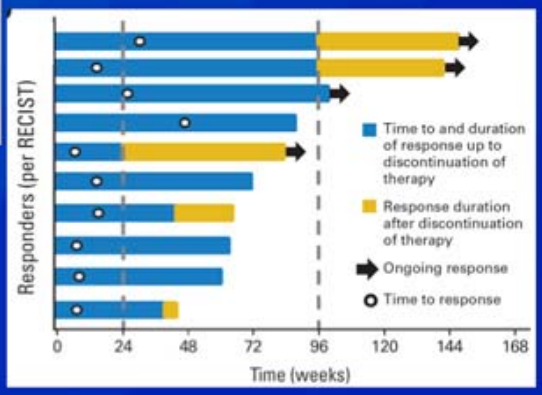
ORIGINAL REPORT

Survival, Durable Response, and Long-Term Safety in Patients With Previously Treated Advanced Renal Cell Carcinoma Receiving Nivolumab

David F. McDermott, Charles G. Drake, Mario Sznol, Toni K. Choueiri, John D. Powderly, David C. Smith, Julie R. Brahmer, Richard D. Carvajal, Hans J. Hammers, Igor Puzanov, F. Stephen Hodi, Harriet M. Kluger, Suzanne L. Topalian, Drew M. Pardoll, Jon M. Wigginton, Georgia D. Kollia, Ashok Gupta, Dan McDonald, Vindira Sankar, Jeffrey A. Sosman, and Michael B. Atkins

Response and Survival (N = 34)





Median response duration:	12.9 mos
Median OS (2-5 prior treatments):	22.4 mos
1-year survival:	71%
2-year survival:	48%
3-year survival:	44%
Grade 3/4 AEs:	18%

McDermott DF et al. *J Clin Oncol* 2015:33(18):2013-20.

Conclusions

Critical finding(s): In a Phase I study of nivolumab, 34 mRCC patients were treated with 1 or 10 mg/kg every 2 weeks. Response rate was 29% with a median response duration of 12.9 months, with an additional 27% having stable disease.

Clinical implication(s): Durable responses are seen with nivolumab in mRCC, similar to those reported in NSCLC and melanoma, even after the drug is discontinued. Responses were seen at both low and high doses, and toxicities were mild.

Research relevance: This Phase I study led to the CheckMate-025 trial, which showed a significant benefit for nivolumab compared to everolimus in second-line treatment of mRCC.

The NEW ENGLAND JOURNAL of MEDICINE

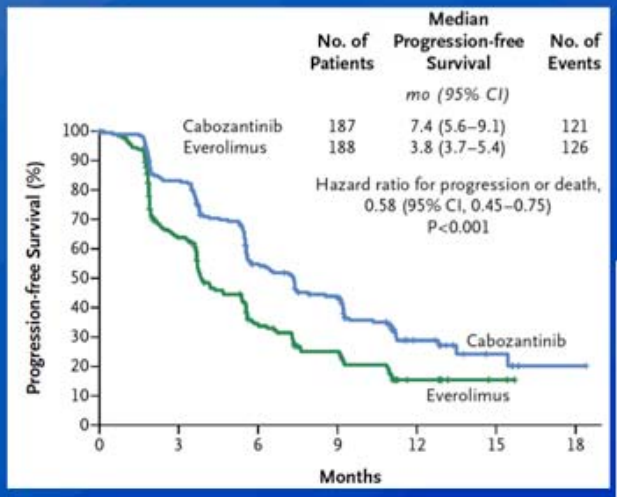
ORIGINAL ARTICLE

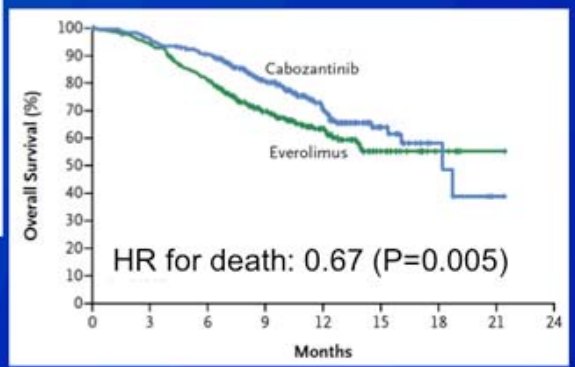
Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma

T.K. Choueiri, B. Escudier, T. Powles, P.N. Mainwaring, B.I. Rini, F. Donskov, H. Hammers, T.E. Hutson, J.-L. Lee, K. Peltola, B.J. Roth, G.A. Bjarnason, L. Géczi, B. Keam, P. Maroto, D.Y.C. Heng, M. Schmidinger, P.W. Kantoff, A. Borgman-Hagey, C. Hessel, C. Scheffold, G.M. Schwab, N.M. Tannir, and R.J. Motzer, for the METEOR Investigators*

Choueiri T et al. *Proc ESMO* 2015; Abstract 4LBA.

Survival Analyses





Choueiri TK et al. *N Engl J Med* 2015 Sept 25; Epub ahead of print

Conclusions

Critical finding(s): Cabozantinib delayed progression compared to everolimus in second-line mRCC by 42% (7.4 versus 3.8 months). The response rate was 21% versus 5% with everolimus. OS was longer also but not yet significant.

Clinical implication(s): Cabozantinib is more active than everolimus in patients who have received prior TKIs. However, 60% of patients needed dose reductions of cabozantinib, although only 9% discontinued therapy because of toxicity.

Conclusions

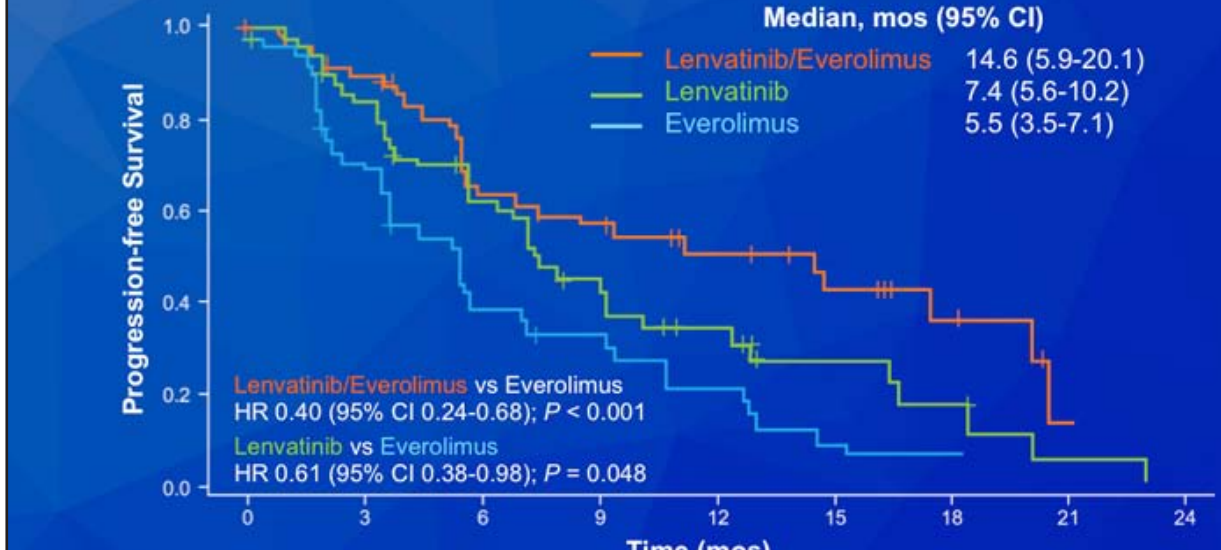
Research relevance: We do not know how cabozantinib would compare with nivolumab as second-line therapy in mRCC. Mechanistically the 2 drugs work very differently, and both drugs show comparable response rates. Combinations versus sequences will need exploration, as will the role, if any, of mTOR inhibitors.

Randomized Phase II, Three-Arm Trial of Lenvatinib (LEN), Everolimus (EVE), and LEN+EVE in Patients (pts) with Metastatic Renal Cell Carcinoma (mRCC)

Motzer R et al.

Proc ASCO 2015;Abstract 4506.

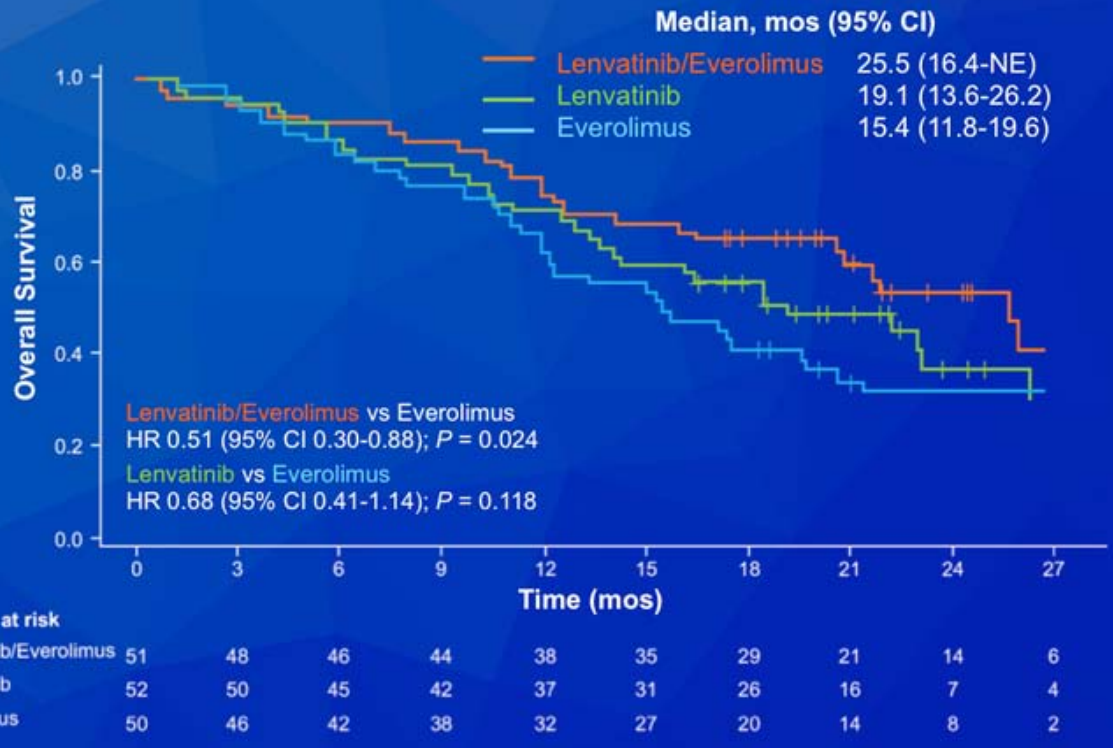
Efficacy: PFS



Number at risk									
Lenvatinib/Everolimus	51	41	27	23	16	10	5	1	0
Lenvatinib	52	41	29	20	11	6	4	1	0
Everolimus	50	29	15	11	7	3	1	0	0

Motzer R et al. *Proc ASCO* 2015;Abstract 4506.

Efficacy: Updated Overall Survival Analysis



Number at risk										
Lenvatinib/Everolimus	51	48	46	44	38	35	29	21	14	6
Lenvatinib	52	50	45	42	37	31	26	16	7	4
Everolimus	50	46	42	38	32	27	20	14	8	2

Motzer R et al. *Proc ASCO* 2015;Abstract 4506.

Conclusions

Critical finding(s): Multitargeted TKI combined with everolimus was associated with significant and intriguing advantages in response rate, PFS and OS in a randomized Phase II trial.

Clinical implication(s): As is the case with cabozantinib, TKIs remain an important therapeutic option in mRCC. Although this is only a randomized Phase II trial, lenvatinib combined with everolimus looks like an active combination of targeted therapies that may improve efficacy.

Research relevance: A randomized Phase III trial is planned of the combination of lenvatinib and everolimus in mRCC. Assessing toxicity carefully will be important — 84% diarrhea and 51% decreased appetite may be intolerable in a larger trial.

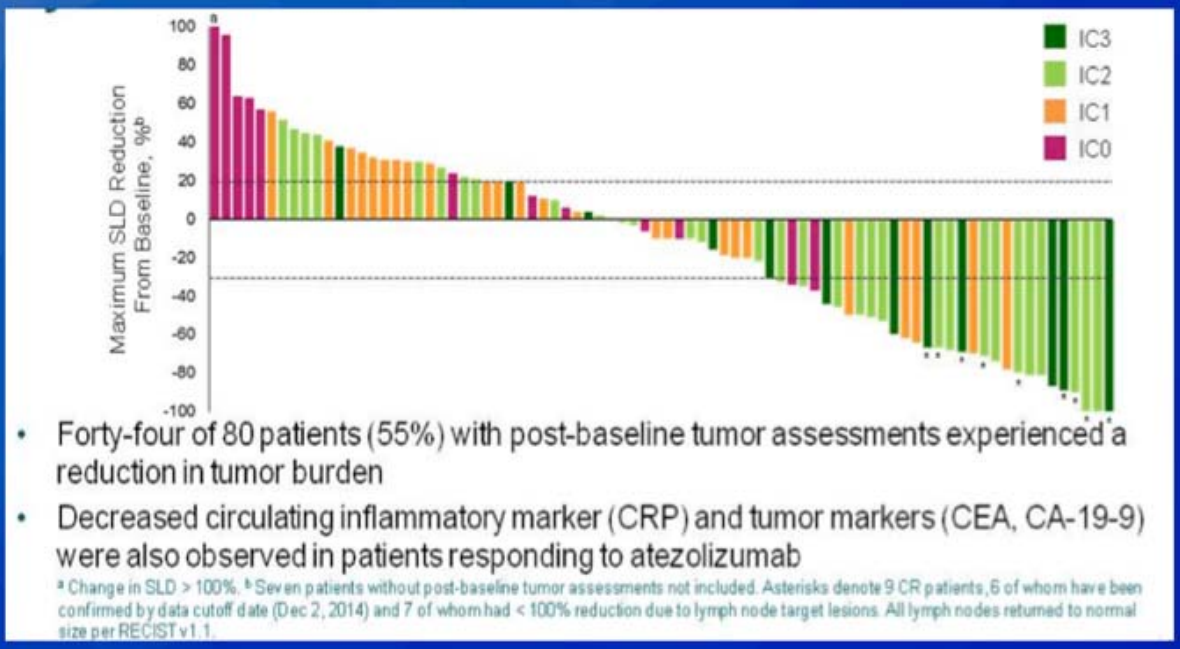
UROTHELIAL BLADDER CANCER

A Phase Ia Study of MPDL3280A (anti-PDL1): Updated Response and Survival Data in Urothelial Bladder Cancer (UBC)

Petrylak DP et al.

Proc ASCO 2015;Abstract 4501.

Atezolizumab (MPDL3280A): Response by PD-L1 Expression in Tumor-Infiltrating Immune Cells (IC)



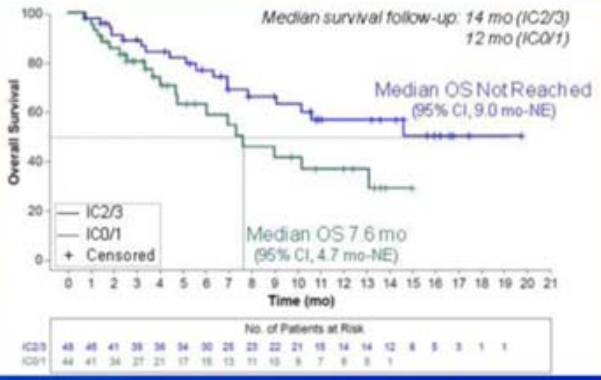
- Forty-four of 80 patients (55%) with post-baseline tumor assessments experienced a reduction in tumor burden
- Decreased circulating inflammatory marker (CRP) and tumor markers (CEA, CA-19-9) were also observed in patients responding to atezolizumab

[a] Change in SLD > 100%. [b] Seven patients without post-baseline tumor assessments not included. Asterisks denote 9 CR patients, 6 of whom have been confirmed by data cutoff date (Dec 2, 2014) and 7 of whom had < 100% reduction due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.

Petrylak DP et al. *Proc ASCO* 2015;Abstract 4501.

Atezolizumab (MPDL3280A): Survival

Survival N = 92	IC2/3 n = 48	IC0/1 n = 44
PFS		
Median PFS (range)	6 mo (0+ to 18)	1 mo (0+ to 14+)
1-y PFS (95% CI)	39% (24-54)	10% (0-21)
OS		
Median OS (range)	Not reached (1 to 20+ mo)	8 mo (1 to 15+ mo)
1-y survival (95% CI)	57% (41-73)	38% (19-56)



- PD-L1 IC status appeared to be predictive of benefit from atezolizumab treatment.
- Preliminary analysis using SP142 (a PD-L1 monoclonal IHC antibody) from an independent sample set (n = 110) suggests that PD-L1 IC status is not prognostic for OS in UBC.

Petrylak DP et al. *Proc ASCO* 2015;Abstract 4501.

Conclusions

Critical finding(s): Anti-PD-L1 (now called atezolizumab) results in 87 UBC patients show significant response, higher in IHC 2/3 (50%) than in 0/1 (17%). PFS was also better in IHC 2/3 patients (6 months versus 1 month).

Clinical implication(s): Some UBCs appear to be responsive to this anti-PD-L1 antibody. Given the poor options for therapy for metastatic disease, this evidence of activity is highly encouraging and has potential to become a new SOC for UBC, particularly for IHC 2/3 patients.

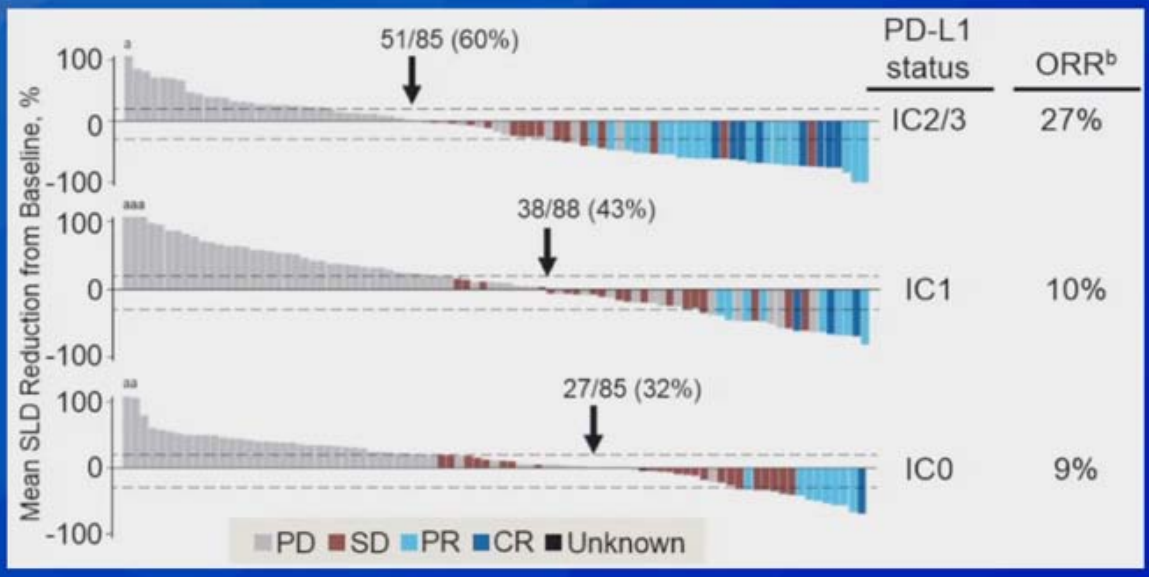
Research relevance: Ongoing Phase III trials are comparing atezolizumab to standard chemotherapy in metastatic UBC after failure of platinum chemotherapy.

Atezolizumab in Patients (pts) with Locally-Advanced or Metastatic Urothelial Carcinoma (mUC): Results from a Pivotal Multicenter Phase II Study (IMvigor 210)

Rosenberg J et al.

Proc ESMO_ECCO 2015;Abstract 21LBA.

IMvigor 210: Response and Changes in Target Lesions by PD-L1 Subgroup



IMvigor 201 met its co-primary endpoints of independent and investigator ORR in all subgroups

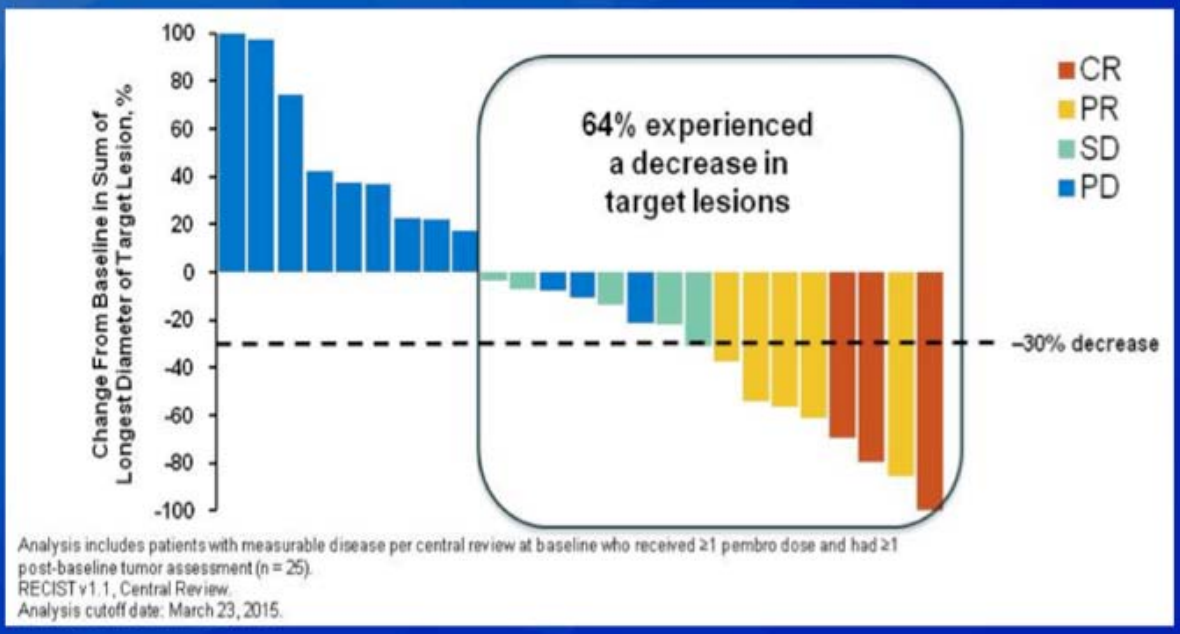
Rosenberg J et al. *Proc ESMO_ECCO* 2015;Abstract 21LBA.

Pembrolizumab (MK-3475) for Advanced Urothelial Cancer: Updated Results and Biomarker Analysis from KEYNOTE-012

Plimack ER et al.

Proc ASCO 2015;Abstract 4502.

Maximum Percent Change from Baseline in Target Lesions



Analysis includes patients with measurable disease per central review at baseline who received ≥1 pembro dose and had ≥1 post-baseline tumor assessment (n = 25).
RECIST v1.1, Central Review.
Analysis cutoff date: March 23, 2015.

Plimack ER et al. *Proc ASCO* 2015;Abstract 4502.

Conclusions

Critical finding(s): Pembrolizumab in 29 patients with advanced UC showed 27.6% response rate (higher in PD-L1-expressing tumors) with 10.3% CRs. Responses are durable and toxicity mild.

Clinical implication(s): PD-1 antibody therapy has activity in UC, a disease without many good therapeutic options.

Research relevance: Phase II and III trials of pembrolizumab are ongoing, including a trial of pembrolizumab versus chemotherapy after first-line chemotherapy.