Highlights in genitourinary cancers

T. Vermassen, S. Rottey
Department of Medical Oncology, Ghent University Hospital

From June 2nd till June 6th, Chicago was host for the 53rd ASCO annual meeting. The theme for this year's venue was 'Making a Difference in Cancer Care WITH YOU'. With over 35,000 registered attendees from over 100 countries worldwide and almost 6,000 submitted abstracts, this year's meeting was a great success. This report will highlight 7 key studies concerning genitourinary cancers presented during the meeting.

KEYNOTE-052: MATURE RESULTS FROM FIRST-LINE PEMBROLIZUMAB IN CISPLATIN-INELIGIBLE ADVANCED UROTHELIAL CARCINOMA

Comorbidities and renal impairment preclude many with advanced urothelial carcinoma (UC) from receiving platinum-based chemotherapy. Initial results suggested that first-line pembrolizumab is active and safe in cisplatin-ineligible advanced UC.[1] Updated efficacy and safety data as well as biomarker evaluation were presented at ASCO 2017. Eligible patients (ECOG PS 2, CrCl ≥30 and < 60 mL/min, grade ≥2 neuropathy/hearing loss, NYHA Class 3 heart failure) with no prior systemic chemotherapy received pembrolizumab 200 mg q3w (n=370). The primary endpoint of the study was objective response rate (ORR) (RECIST v1.1, independent review) and associations with an 18-gene expression profile (GEP) and PD-L1 combined positive score (≥10%) were evaluated. At data cut-off, ORR was 29%: 27 (7%) and 81 (22%) patients achieved complete responses (CR) and partial responses (PR), respectively. Sixty-seven patients (18%) had stable disease as best response. The median time to response was 2 months and the median duration of response was not reached (range, 1 to 18 months) with 67% of responses ongoing. ORR in 96 patients with a PD-L1 score ≥10% was 47%. Any-grade and grade ≥3 drug-related AEs occurred in 66% (21% immune-mediated) and 19% of patients. A positive association with response was seen for the 18-GEP ($p<0.0001$). Notably, all genes included in this score were separately also significantly associated with response ($p<0.05$). These results confirm that pembrolizumab elicits clinically meaningful, durable responses in and is well tolerated by treatment-naive patients with advanced UC. Pembrolizumab could therefore be an option as first-line therapy in elderly patients and patients with poor performance status who are ineligible for platinum-based chemotherapy. [1,2]

PEMBROLIZUMAB VERSUS PACLITAXEL, DOCETAXEL, OR VINFLUNINE IN RECURRENT ADVANCED UROTHELIAL CARCINOMA: PLANNED 3RD SURVIVAL ANALYSIS OF KEYNOTE-045

Patients with advanced UC who progress after platinum-based chemotherapy have a poor prognosis and limited treatment options. Second-line chemotherapies for advanced urothelial carcinoma (UC) have limited clinical benefit with overall survival (OS) ranging between 7 and 9 months. In Keynote-045, a total of 542 patients who progressed after platinum-based chemotherapy with ECOG PS 0-2, measurable disease and ≤2 lines of systemic therapy were randomized 1:1 to pembrolizumab 200 mg q3w (n=270) or investigator's choice of paclitaxel 175 mg/m² q3w, docetaxel 75 mg/m² q3w, or vinflunine 320 mg/m² q3w (n=272). Primary efficacy endpoints were OS and PFS, with ORR as a key secondary endpoint (RECIST v1.1, independent review). Positive survival outcomes from

Please send all correspondence to: S. Rottey, Department for Medical Oncology, 4B2, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium, E-mail: Sylvie.Rottey@UGent.be

Keywords: Urothelial cancer, hormone-naive prostate cancer, renal cell carcinoma, immunotherapy.

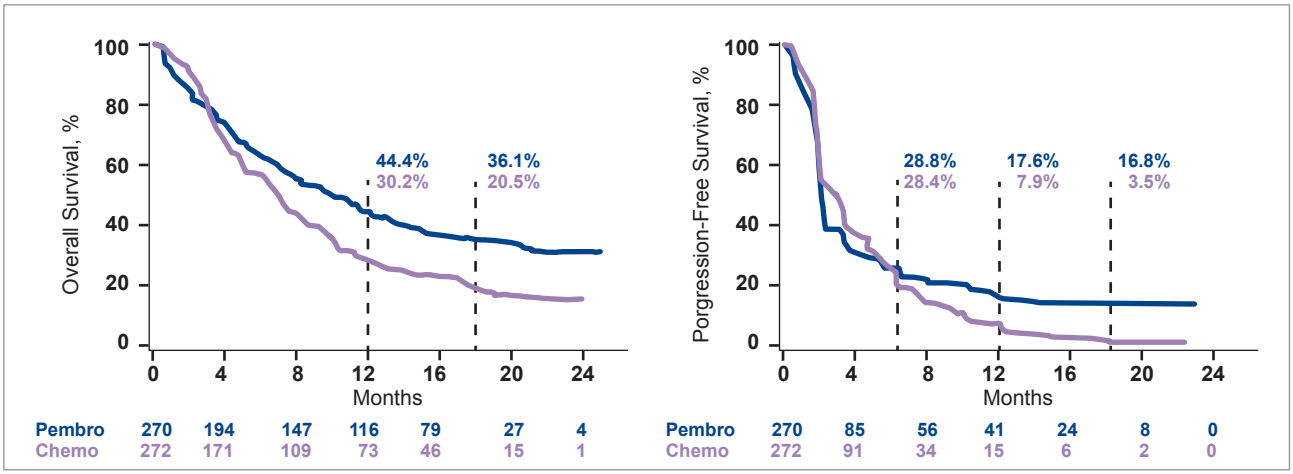

FIGURE 1. Survival outcome of second-line pembrolizumab versus chemotherapy in recurrent advanced urothelial carcinoma. The OS was significantly prolonged for patients who received pembrolizumab (left) while no difference in PFS was observed (right).[4]

the planned 2nd analysis were published recently.[3] The results from the planned 3rd analysis were presented at ASCO 2017. The median follow-up for this updated analysis was 18.5 months. At that point, the median OS was significantly longer with pembrolizumab versus chemotherapy (10.3 versus 7.4 months; HR: 0.70; p=0.0004; *Figure 1A*), regardless of PD-L1 expression, age, ECOG PS, prior therapy, liver metastases, histology, and choice of chemotherapy. The 18-months OS rate was 36.1% with pembrolizumab versus 20.5% with chemotherapy. PFS was not different between both arms (*Figure 1B*). A higher ORR was observed with pembrolizumab (21.1% versus 11.0%) with longer median duration of response. Fewer treatment-related AE occurred in the pembrolizumab arm (any grade, 61.3% versus 90.2%; grade ≥3, 16.5% versus 49.8%). This planned analysis proves that pembrolizumab is superior to second-line chemotherapy for both OS and safety. Based on this level 1 evidence, pembrolizumab should be opted as new standard of care for patients with UC who previously received platinum.[4]

FIRST-LINE AVELUMAB PLUS AXITINIB IN ADVANCED RENAL CELL CARCINOMA: RESULTS FROM THE JAVELIN RENAL 100 PHASE IB TRIAL

The combination of an immune checkpoint inhibitor with a targeted antiangiogenic agent may leverage complementary mechanisms of action for treatment in RCC. Avelumab is a fully human anti–PD-L1 IgG1 antibody with clinical activity in various tumor types.[5] Updated results on safety and clinical activity of avelumab plus axitinib in treatment-naive clear-cell RCC patients were reported. At data cut-off, 55 patients with at least 1 measurable lesion, an ECOG PS ≤1, and no prior systemic therapy received avelumab 10 mg/kg IV q2w plus axitinib 5 mg orally twice daily until progression, unacceptable toxicity, or withdrawal. Endpoints included safety and ORR (RECIST v1.1, independent review). In total, 54 patients were treated with avelumab for a median of 36.5 weeks; 55 patients were treated with axitinib for a median of 34.0 weeks. Seventeen patients (30.9%) had an immune-related AE with hypothyroidism being the most common AE (21.8). Nine patients had a grade ≥3 immune-related AE. Axitinib-related AE were as previously observed in monotherapy. One treatment-relate death occurred due to myocarditis. The confirmed ORR reached 58.2% and included 3 CR and 29 PR. An additional 11 patients showed stable disease. Tumor shrinkage was noticed in 85% of patients (*Figure 2*). This indicated that the safety profile appears manageable. Early encouraging antitumor activity provides rationale for further follow-up.[6]

ATEZOLIZUMAB PLUS BEVACIZUMAB AS FIRST- OR SECOND-LINE THERAPY FOR METASTATIC RENAL CELL CARCINOMA: SURVIVAL OUTCOME IN THE IMMOTION 150 TRIAL

Most patients treated with VEGF-inhibitors develop resistance within the first year of therapy. In this phase II trial, 305 patients were randomized 1:1:1 to atezolizumab 1200 mg IV q3w plus bevacizumab 15 mg/kg IV q3w, atezolizumab 1200 mg IV q3w or sunitinib 50 mg orally daily q4/6w. Crossover to atezolizumab plus bevacizumab was allowed following progression on monotherapy. The co-primary endpoints of this trial were PFS (RECIST v1.1, independent review) in all patients and in the subgroup of PD-L1 positive patients (≥ 1% on IC, 54%). Median PFS was 11.7 months, 6.1 months and 8.4

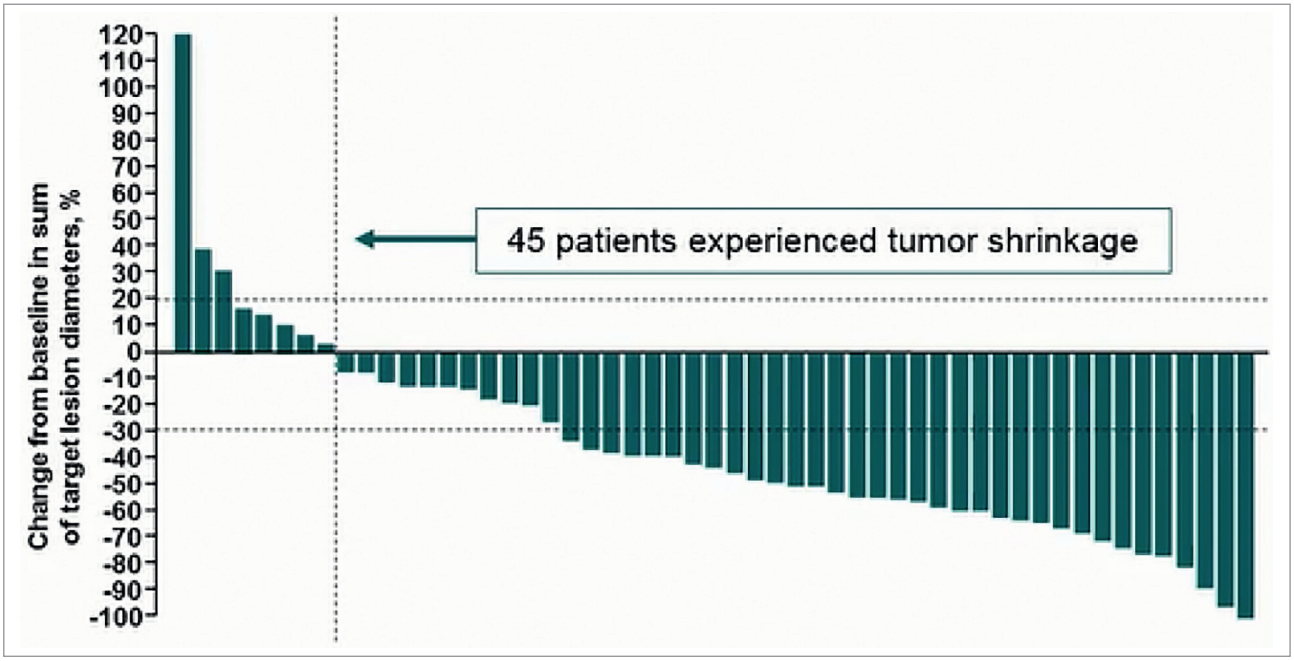

FIGURE 2. Efficacy of avelumab plus axitinib in in advanced renal cell carcinoma. A total of 45 patients experienced any form of tumor shrinkage. Thirty-four patients experienced tumor shrinkage ≥30%. In three patients, tumor volume was grown ≥20%.[6]

months in patients treated with atezolizumab plus bevacizumab, atezolizumab and sunitinib, respectively. In the PD-L1-positive population, the median PFS was 14.7, 5.5 and 7.8 months with atezolizumab plus bevacizumab, atezolizumab and sunitinib, respectively. This resulted in a first-line PFS hazard ratio of 0.64 (95%CI [0.38 – 1.08], p=0.095) for atezolizumab plus bevacizumab versus sunitinib for PD-L1 positive patients. No difference in survival outcome was observed between all other subgroups. Of note, a difference in first-line PFS outcome was observed between patients with low and high T-effector^{high} myeloid inflammation. A total of 101 patients crossed over to atezolizumab plus bevacizumab after progression on atezolizumab (n=44) and sunitinib (n=57). Second-line patients achieved an ORR of 24% and 28%, respectively. The combination of atezolizumab plus bevacizumab shows encouraging antitumor activity although the benefit seems to be limited to PD-L1 positive patients. The proposed combination also proves activity as second-line therapy for patients who progressed on sunitinib or atezolizumab in first-line. Further evaluation of the combination of atezolizumab plus bevacizumab in ongoing in the IMmotion 151 phase III trial.[7]

PROTECT: BENEFIT OF ADJUVANT PAZOPANIB AFTER NEPHRECTOMY IN PATIENTS WITH LOCALLY ADVANCED RENAL CELL CARCINOMA

The question to whether adjuvant treatment can be beneficial following nephrectomy has long been raised. In the phase III PROTECT trial, 1538 patients with resected pT2 or higher clear cell RCC were randomly assigned 1:1 to pazopanib 800 mg daily or placebo for 1 year post-op. In order to improve tolerability, the pazopanib dose was reduced to 600mg following treatment of the first 403 patients. A primary analysis was performed after 350 DFS events. No difference was observed in DFS for patients receiving 600mg pazopanib versus placebo (HR[95%CI]: 0.86[0.70–1.06]; p=0.165) although a 31% risk reduction was observed for patients receiving 800mg pazopanib (HR[95%CI]: 0.69[0.51–0.94]). Comparable results were found after an additional 12 months of follow-up. Mature OS data were not yet available. Sixty percent of patients receiving pazopanib experienced a grade ≥3 AE. Most common AEs leading to treatment discontinuation were increased ALT (16% and 18%) and increased AST (5% and 7%) in both the 600mg and 800mg, respectively which was consistent with previous reported safety profile of pazopanib. These results seem to suggest that adjuvant pazopanib after nephrectomy is only be beneficial if given at dose of 800mg. Hence the treatment discontinuation of 1/4 in this cohort, use of pazopanib as adjuvant therapy following nephrectomy is not recommended. [8]

ALTERNATIVE TREATMENT REGIMEN FOR HIGH-RISK LOCALLY ADVANCED OR METASTATIC HORMONE-NAIVE PROSTATE CANCER: RESULTS FROM THE LATITUDE AND STAMPEDE TRIAL

Patients with newly diagnosed locally advanced or metastatic

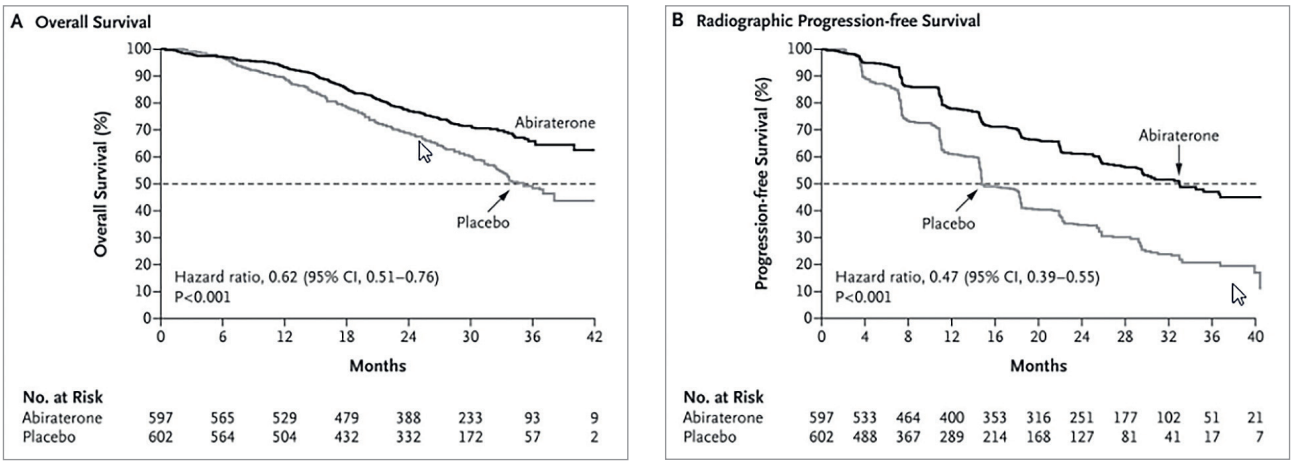

FIGURE 3. Survival outcome of ADT plus abiraterone acetate plus prednisone in metastatic hormone-naive prostate cancer in the LATITUDE trial. A. Significant prolonged OS was noticed for patients who received abiraterone acetate versus standard-of-care. B. Radiographic PFS was doubled in the intervention group versus the control group.[9,10]

hormone-naive prostate cancer (HNPCa) have a poor prognosis. Although androgen deprivation therapy (ADT) combined with docetaxel shows improved outcome, many patients are not eligible for this treatment regimen.

In the LATITUDE phase III trial, 1199 patients with newly diagnosed metastatic HNPCa (less than 3 months), ECOG PS 0-2, ≥ 2 of 3 risk factors (Gleason ≥ 8, ≥ 3 bone lesions, measurable visceral metastases) were randomized (1:1) to ADT plus abiraterone acetate (1g daily) plus prednisone (5mg daily) or to ADT plus placebo. Primary endpoints were OS and radiographic PFS. Results from the first interim analysis (after 48% deaths and median follow-up of 30.4 months) were presented at ASCO 2017. ADT plus abiraterone acetate plus prednisone proved to be highly beneficial with a 48% risk reduction in the risk for death (HR[95%CI]: 0.62[0.51–0.76]; p<0.0001; *Figure* 3A) and a doubling in radiographic PFS (33.0 *vs.* 14.8 months; HR[95%CI]: 0.47[0.39–0.55]; p<0.0001; *Figure* 3B) compared to standard-of-care. Also, time to pain progression, PSA progression, symptomatic skeletal-related event, chemotherapy and subsequent PCa therapy were prolonged in the abiraterone acetate cohort. Most commonly reported grade ≥3 AEs were hypertension (20.3%), hypokalemia (10.4%), increased ALT (5.5%) and increased AST (4.4%). Due to the positive results, the IDMC unanimously recommended unblinding of the study

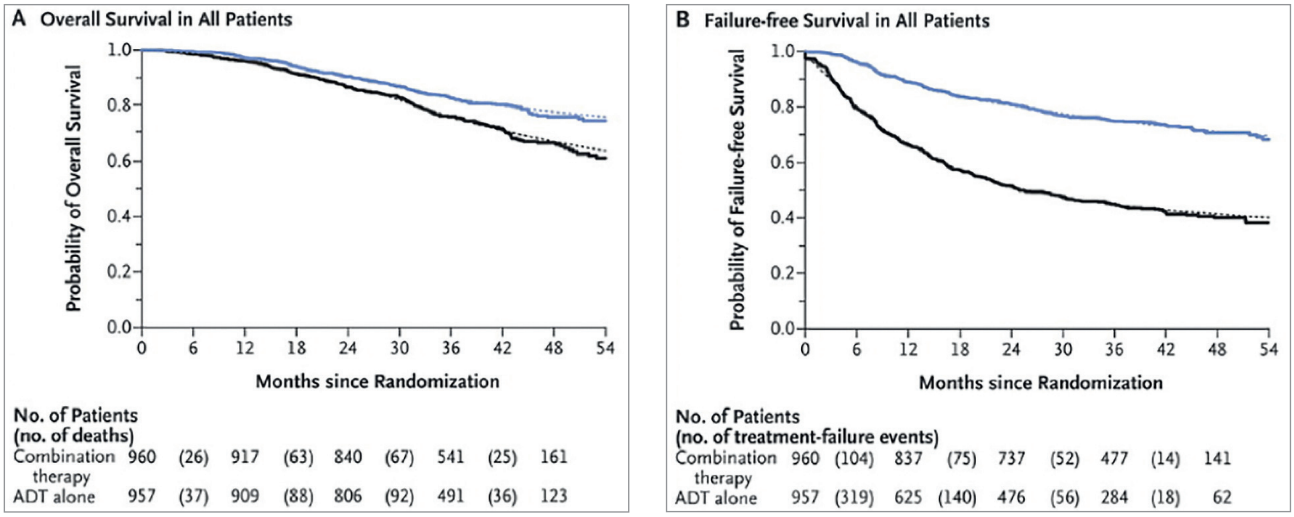

FIGURE 4. Survival outcome of ADT plus abiraterone acetate plus prednisone in locally advanced or metastatic hormone-naive prostate cancer in the STAMPEDE trial. A. Significant longer OS was seen for patients who received abiraterone resulting in an 83% 3-year OS. B. Median FFS was not reached in the intervention group indicating the clinical efficacy of the therapy the control group.[11,12]

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Pembrolizumab is a viable first-line treatment option in patients with advanced urothelial carcinoma, more specifically in patients who are ineligible for platinum-based chemotherapy.**

2. **Pembrolizumab is superior to chemotherapy as second-line treatment in patients with recurrent advanced urothelial carcinoma who advanced after platinum-based chemotherapy and should therefore be preferred as standard-of-care in these patients.**

3. **Hence the effect of immunotherapy and antiangiogenic agents in monotherapy, a great deal of research is going into the combination of both treatments as first- or second-line therapy in metastatic renal cell carcinoma. This shows encouraging antitumor activity with manageable toxicity profiles. Further evaluation in larger phase III trials is warranted and ongoing.**

4. **Adjuvant pazopanib following nephrectomy shows only limited benefit in disease-free survival. Seen the discontinuation in 25% of patients because of side effects, adjuvant administration of pazopanib is not preferred.**

5. **Administration of androgen deprivation therapy plus abiraterone acetate plus prednisone in patients with high-risk locally advanced or metastatic hormone-naive prostate cancer shows to be highly beneficial for overall survival and failure-free survival versus androgen deprivation therapy alone. This regimen is therefore opted for in this patient cohort.**

and crossing patients over to the abiraterone acetate arm.[9,10] On the other hand, the STAMPEDE phase III trial focused on newly diagnosed HNPCa with either locally advanced or metastatic disease. Here, 1,917 patients were randomized (1:1) to ADT plus abiraterone acetate (1g daily) plus prednisone (5mg daily) or to standard-of-care (ADT alone). Adjuvant radiotherapy was performed in patients with locally advanced disease. Primary end-points were OS and failure-free survival (FFS; radiologic, clinical, or PSA progression or death from PCa). After median follow-up of 40 months, a 37% risk reduction for death was noticed in the abiraterone acetate arm (HR[95%CI]: 0.63[0.52–0.76]; p<0.0001; *Figure 4A*), resulting in an 83% 3-year OS. Likewise, a risk reduction of 71% was noticed in FFS for the intervention group versus standard-of-care (HR[95%CI]: 0.29[0.25–0.34]; p<0.0001; *Figure 4B*). Grade ≥3 AEs were more common in the abiraterone acetate arm (47%) versus standard-of-care (33%).[11,12]

As early intervention with ADT plus abiraterone acetate plus prednisone proved clinically and statistically significant, with manageable toxicity profile, this treatment regimen can be opted in newly diagnosed, high-risk locally advanced or metastatic HNPCa.

REFERENCES

1. Balar AV, Bellmunt J, O'Donnell PH, et al. Pembrolizumab (pembro) as first-line therapy for advanced/unresectable or metastatic urothelial cancer: Preliminary results from the phase 2 KEYNOTE-052 study. Ann Oncol 2016;27(6):1-36 (LBA32_PR).

2. O'Donnell PH, Grivas P, Balar AV, et al. Biomarker findings and mature clinical results from KEYNOTE-052: First-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC). J Clin Oncol 2017;35(suppl):abstr 4502.

3. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017;376(11):1015-1026.

4. Bajorin DF, De Wit R, Vaughn DJ, et al. Planned survival analysis from KEYNOTE-045: Phase 3, open-label study of pembrolizumab (pembro) versus paclitaxel, docetaxel, or vinflunine in recurrent, advanced urothelial cancer (UC). J Clin Oncol 2017;35(suppl):abstr 4501.

5. Heery CR, O'Sullivan-Coyne G, Madan RA, et al. Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial. Lancet Oncol 2017;18(5):587-598.

6. Choueiri TK, Larkin JMG, Mototsugu O, et al. First-line avelumab + axitinib therapy in patients (pts) with advanced renal cell carcinoma (aRCC): Results from a phase Ib trial. J Clin Oncol 2017;35(suppl):abstr 4504.

7. Atkins MB, McDermott DF, Powles T, et al. 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). J Clin Oncol 2017;35(suppl):abstr 4505.

8. Motzer RJ, Haas NB, Donskov F, et al. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with locally advanced renal cell carcinoma (RCC) (PROTECT). J Clin Oncol 2017;35(suppl):abstr 4507.

9. Fizazi K, Tran N, Fein LE, et al. LATITUDE: A phase III, double-blind, randomized trial of androgen deprivation therapy with abiraterone acetate plus predni-

sone or placebos in newly diagnosed high-risk metastatic hormone-naive prostate cancer. J Clin Oncol 2017;35(suppl):abstr LBA3.

10. Fizazi K, Tran N, Fein LE, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med 2017;377(4):352-360.

11. James ND, De Bono JS, Spears MR, et al. Adding abiraterone for men with high-risk prostate cancer (PCa) starting long-term androgen deprivation therapy (ADT): Survival results from STAMPEDE (NCT00268476). J Clin Oncol 2017;35(suppl):abstr LBA5003.

12. James ND, De Bono JS, Spears MR, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med 2017;377(4):338-351.