Highlights of the Post-ASCO Genitourinary regional tour 2019

T. Feys, MSc, MBA[1], J. Beekwilder, PhD[2]

SUMMARY

The 2019 annual American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium was held from February 14-16 in San Francisco. The Belgian Multidisciplinary Meeting on Urological Cancers (BMUC) organised a post-ASCO GU regional tour during which the highlights of the 2019 ASCO GU meeting were discussed. This tour featured four different meetings in four locations in Belgium: Namur, Ghent, Nivelles and Paal. This summary will specifically report on the meeting held in Ghent during which prof. dr Piet Ost (Ghent University Hospital) and prof. dr Sylvie Rottey (Ghent University Hospital) gave a summary of the most important advances in the treatment of prostate, bladder and renal cancer.

(BELG J MED ONCOL 2019;13(3):109-114)

PROSTATE CANCER

LOCALISED PROSTATE CANCER

The most important findings in the localised prostate setting came from the phase III, randomised, open-label, multiple-cohort PACE trial. In the PACE-B cohort, the investigators aimed to demonstrate non-inferiority of stereotactic body radiotherapy (SBRT) compared to conventionally fractionated or moderately hypo-fractionated external beam radiotherapy (CFMHRT) for biochemical or clinical failure.[1] Compared to CFMHRT, SBRT reduces the number of patient visits; but on the other hand, a compressed overall treatment time may influence the severity of acute toxicity. The majority of patients in the CFMHRT arm received 62 Gy in 20 fractions (69%), while 29% was treated with the older scheme consisting of 78 Gy in 39 fractions. During ASCO GU, data on acute toxicity in PACE-B were reported. This is clinically relevant, as it is known that acute toxicity is predictive for late toxicity. No difference in rectal or genitourinary acute toxicity was seen between CFMHRT and SBRT in this trial. The investigators did report a slightly earlier peak in toxicity with SBRT compared to CFMHRT. The vast majority of reported adverse events (AE) were of grade 1, with only a small number of grade 2 AEs (no grade 3/4 AEs).[1] According to Dr Ost, these data fit into the trend of using less and less radiotherapy fractions in this setting. In fact, recent studies with long-term follow-up show encouraging results with as little as five fractions (phase III efficacy data for this strategy are awaited). Of note, the vast majority of patients enrolled in this trial were intermediate risk patients (approximately 92%). In Belgium, we would normally put these patients on six months of hormone therapy. This is not the case in the UK.

METASTATIC HORMONE-SENSITIVE PROSTATE CANCER

For metastatic hormone-sensitive prostate cancer (mHSPC), the treatment used to be limited to androgen deprivation therapy (ADT). The publication of STAMPEDE and CHAARTED data in 2015 changed this situation by showing that the addition of docetaxel to ADT resulted in a significant improvement in overall survival (OS) and other outcome measures.[2,3] In the years following these publications, new data from LATITUDE and results of another STAMPEDE arm also

[1]Ariez International, Ghent, Belgium, [2]Ariez B.V. Zaandam, The Netherlands.

Please send all correspondence to: T. Feys, MBA, MSc, Ariez International, Oude Houtlei 108A, 9000 Ghent, Belgium, tel: +32 (0)479 567890, email: t.feys@ariez.com.

Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: ASCO, bladder cancer, genitourinary, prostate cancer, renal cancer.

showed an OS benefit from adding abiraterone acetate (Abi) to ADT, while a third STAMPEDE arm demonstrated that also adding radiotherapy to ADT led to a significant OS benefit, although this was true only in a pre-specified subgroup analysis looking at patients with low-volume disease.[4-6] Dr Ost particularly emphasised the results of the latter study by underlining the fact that the OS hazard ratio (HR) seen with the addition of radiotherapy to ADT was similar to what was seen with the addition of a systemic therapy (HR with radiotherapy 0.68 *vs* 0.63 and 0.78 with docetaxel in STAMPEDE). During ASCO GU, *Armstrong et al.* presented results of the phase III ARCHES trial, comparing enzalutamide plus ADT with ADT alone.[7] Patients were allowed to have both low- (38%) and high-volume (62%) disease. Seventy percent of the patients were *de novo* and 30% recurrent M1. The primary endpoint of the study, radiographic progression-free survival (rPFS), was met by showing a significantly reduced risk for rPFS with a HR of 0.39 (95% CI: 0.30-0.50; p<0.0001) in favour of the enzalutamide arm. The twelve-month estimates for rPFS event-free rate estimates were 84% *versus* 64% for the experimental and control arm, respectively. OS results were not mature yet. Dr Ost pointed out that the reported effects in this trial are comparable to what was reported with docetaxel and Abi. However, important features of this trial are the fact that 18% of patients in the ARCHES trial previously received docetaxel and the fact that both patients with low- and high-volume disease were included. More research is needed to elucidate the best combination of treatments in this setting.

ASCO GU 2019 also featured the final OS analysis of the LATITUDE trial.[8] The median OS was reported at 53.3 months for patients receiving ADT plus Abi as compared to 36.5 months with ADT alone (HR: 0.66 [95% CI: 0.56-0.78]; p<0.0001). Also secondary endpoints like time to pain progression (47.4 *vs* 16.6 months) and time to subsequent prostate cancer therapy (54.9 *vs* 21.2) were significantly better with Abi-ADT than with ADT alone. No new AEs were reported. Hypertension grade ≥3 (22% *vs* 10%) and hypokalaemia (11% *vs* 2%) were more prevalent with Abi + ADT. Osteoporosis was a rare finding in both study arms.

Several questions regarding mHSPC still remain unanswered. For example, should high-volume patients receive Abi or docetaxel upfront? Can treatments be combined? The latter question may find some answers in the ongoing European PEACE-1 study. Multiple trials are also looking at the role for a radical prostatectomy in this setting, while yet another STAMPEDE arm is assessing the potential of additional radiotherapy to metastases.

Docetaxel has the advantage of being a much cheaper option than Abi and enzalutamide, and also the fact that docetaxel comes with a short treatment course is beneficial. In addition, docetaxel offers the opportunity of having a treatment break, which is not the case for the targeted therapies. Abiraterone acetate on the other hand tends to have milder side effects and patients often perceive the fact that they are not getting chemotherapy as a bonus. In clinical practice it is important to clearly explain the pros and cons of both options and underline that it is not an either/or situation but rather a question of treatment sequence. Also, the fitness of patients should be considered (perhaps better to start with a more intensive therapy upfront in fit patients in order not to lose the chemotherapy option due to declined performance status in later lines?). A final comment referred to the fact that an orchiectomy is nowadays somewhat underused. Lifelong ADT does represent a burden for patients and as such, an orchiectomy might be a better option for older men.

CASTRATION-RESISTANT PROSTATE CANCER WITH M0 DISEASE

Recently, the SPARTAN and PROSPER studies demonstrated a spectacular benefit in metastasis-free survival (MFS) with apalutamide or enzalutamide in non-metastatic (M0) castration-resistant prostate cancer (CRPC).[9,10] In addition, a pooled analysis of both studies also showed a benefit in OS versus placebo.[11] However, the structurally similar apalutamide and enzalutamide were associated with fatigue, falling, fractures, and other AEs compared to placebo.[12] Darolutamide is structurally distinct from apalutamide and enzalutamide and is associated with a low blood-brain barrier penetration. This could potentially lead to less toxicity and an improved tolerability compared to the other two agents. The ARAMIS trial demonstrated that the addition of darolutamide to ADT led to a 59% risk reduction of metastases or death (median MFS: 40.4 *vs* 18.4 months; HR: 0.41 [95% CI: 0.34-0.50]; p<0.0001).[13] OS data are not mature yet, but indicate a 29% risk reduction (36-months OS rates: 83% *vs* 73%; HR: 0.71 [95% CI: 0.50-0.99]; p=0.0452). AEs with darolutamide included fatigue, but overall toxicity was comparable with placebo. The discontinuation rate due to AEs was 8% in both darolutamide and the control arm. The authors concluded that the reported efficacy and the favourable safety profile makes darolutamide an attractive option for the treatment of M0-CRPC patients.

In San Francisco, an update was also given on the SPARTAN study, which investigated the addition of apalutamide to the standard ADT.[14] The most remarkable results included the second-line PFS (PFS2) data, defined as the time from the date of randomisation to discontinuation of next-line treatment. Whereas the median PFS2 was not reached in the apalutamide group, it reached 39.3 months in the placebo group (HR: 0.5 [95% CI: 0.39-0.63]; p<0.0001). Patients from the placebo group were allowed to cross-over to apalutamide af-

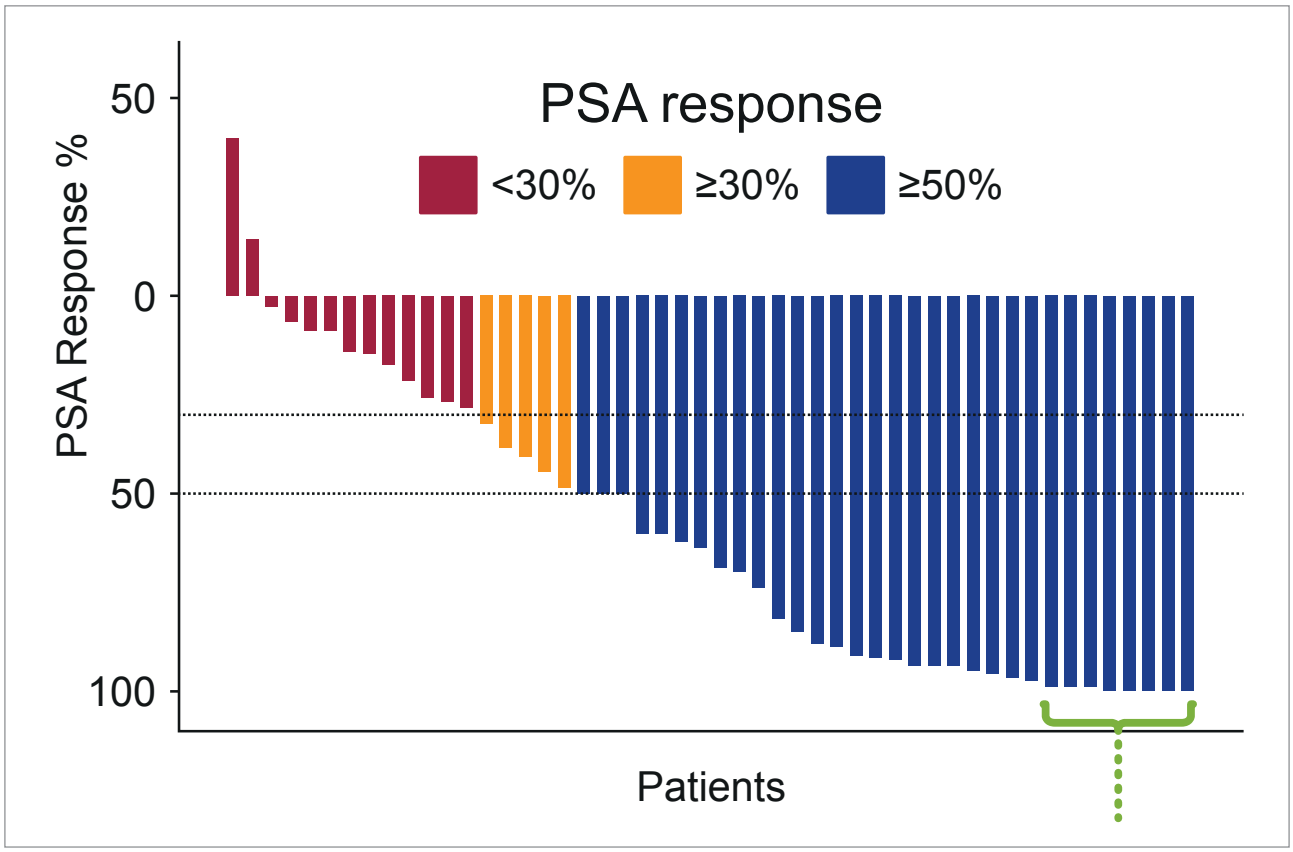

FIGURE 1. Best prostate-specific antigen (PSA) response with Lutetium-177 in metastatic castration-resistant prostate cancer patients (n=50).

ter the unblinding of the study. Therefore, the PFS2 in this study actually reflects a comparison of early versus delayed treatment. In this light, the results suggest that early treatment is associated with a more favourable outcome.

In the discussion of the findings of SPARTAN, PROSPER and ARAMIS, dr Ost underlined that M0 CRPC represents a rare entity. In addition, the increasing use of PSMA scans in PCa will further reduce the incidence of M0 CRPC. In fact, a PSMA PET analysis of the SPARTAN participants revealed that 98% of patients in this trial were actually PSMA positive. In this respect, it is valid to ask the question whether SPARTAN was actually a M0 study. What is the best approach in these PET-CT negative, PSMA-positive patients? Should we treat them as M0 patients? Is there a role for a lymphadenectomy?

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

For more advanced stages of PCa, promising results from a phase II prospective trial were presented. Fifty patients with progressive disease after a second line of androgen receptor pathway inhibition (ARPI) and taxanes were treated with four cycles of Lutetium-177 (177Lu)-PSMA-617 (LuPSMA), a radiolabelled small molecule that binds with high affinity to PSMA enabling targeted delivery of beta-radiation.[15] The median PSA level of included patients was 189.8 ng/mL and the median PSA doubling time was short at 2.6 ng/mL/month. Patients in the trial were heavily pre-treated, with 90% and 84% having received prior Abi/enzalutamide and docetaxel, respectively. Seventy-eight percent of patients received both Abi or enzalutamide and a taxane. In this heavily pre-treated population, the investigators reported an impressive PSA response (PSA decline ≥50% was achieved in 32 of 50 patients; *Figure 1*). Interestingly, eight patients showed a PSA decline of ≥99%. A higher PSA decline was associated with a longer OS, with a median OS of 18 months in patients with a PSA decline of 50% or more (13.3 months in overall patient population). Toxicity was low with the most reported AEs being transient grade 1/2 dry mouth in 68% and grade 1/2 nausea in 48%.[15] Several clinical trials with this treatment modality are ongoing (TheraP, VISION).

BLADDER CANCER

NON-MUSCLE INVASIVE UROTHELIAL CARCINOMA

In patients with bacillus Calmette-Guérin (BCG)-resistant non-muscle invasive urothelial carcinoma, an upregula-

tion of the PD-1 pathway has been observed, which could suggest a potential benefit of pembrolizumab. The phase II KEYNOTE-57 study evaluated the efficacy and safety of pembrolizumab in patients with high-risk BCG-resistant non-muscle invasive urothelial carcinoma. Results of cohort A, including patients with carcinoma *in situ* with or without a papillary tumour, were reported.[16] The three-month complete response (CR) rate in this study was ~40%, which was higher than initially expected. A durable response occurred in 23.5% of patients, and no patients experienced progression to muscle invasive or metastatic bladder cancer while on therapy. The reported AEs were consistent with those of previous studies. Roughly a third of patients had a grade 3/4 treatment-related AE. This grade 3/4 AE incidence is higher than what was seen in other trials with immune checkpoint inhibition. A possible explanation for this could be the limited experience with anti-PD1 agents of the sites involved in the study centres. It is to be expected that this rate would have been lower if pembrolizumab would have been administered in close cooperation with experienced medical oncologists.

The results of this trial generated substantial debate. The standard of care in this setting currently consists of a cystectomy. With pembrolizumab, two thirds of patients did not show a response. In these patients, you are losing precious time and running the risk of no longer have the option do to a cystectomy. A possible solution for this issue would be a thorough response evaluation of patients on pembrolizumab. If there is no evidence for a response, you should stop the immune checkpoint inhibitor and go for a cystectomy.

In locally advanced bladder cancer, chemotherapy alone does not reduce local-regional failure. Local recurrences are associated with high morbidity and mortality. An Egyptian group investigated the hypothesis that adjuvant radiotherapy has a synergistic effect with chemo, improving the prevention of disease recurrence.[17] Results showed a 14% absolute benefit in two-years disease-free survival (62% *vs* 48%) and an 20% absolute benefit in two-years OS (71% *vs* 51%). This could suggest a role for adjuvant therapy in addressing both local and distant disease in patients with locally advanced bladder cancer. However, more evidence is required to substantiate this hypothesis.

RENAL CELL CARCINOMA

FIRST-LINE THERAPY

The phase III CARMENA trial compared nephrectomy plus sunitinib with sunitinib alone in treatment-naïve patients with metastatic renal cell carcinoma (RCC).[18] As reported earlier, patients who were treated with sunitinib alone had a longer median OS than patients who received the tyrosine kinase inhibitor after a nephrectomy (median OS: 18.4 *vs* 13.9 months). However, several issues should be taken into account when interpreting these data. First of all, the study faced a poor accrual. Secondly, 43% of the patients enrolled in the study were poor-risk patients, a group of patients that is nowadays no longer considered for a cytoreductive nephrectomy. Furthermore, recent studies have clearly demonstrated that sunitinib is less effective compared to more recently approved systemic agents (i.e., immune checkpoint inhibitors). Prof. Rottey concluded that there is still a role for a nephrectomy in metastatic RCC. This is particularly the case for patients with a larger primary tumour burden (less sensitive to systemic treatments) and in the palliative setting (e.g., refractory pain or bleeding, symptomatic paraneoplastic syndromes) as well as patients with oligometastatic diasease or intermediate risk patients who do not need immediate systemic therapy (e.g. patients with small lung metastases only).

Several drug combinations with immune checkpoint inhibitors have been compared to sunitinib in patients with clear-cell advanced RCC. The CheckMate 214 trial compared nivolumab plus ipilimumab with sunitinib in treatment-naïve patients with clear-cell advanced RCC.[19] Nivolumab plus ipilimumab was associated with a significantly longer OS compared to sunitinib (median OS not reached *vs* 37.9 months; HR: 0.71 [95% CI: 0.59-0.86]; p=0.0003). However, stratification by International mRCC Database Consortium (IMDC) risk revealed that the benefit of ipilimumab-nivolumab over sunitinib was restricted to intermediate-/poor-risk patients. In this group, the median OS was not reached with the immune checkpoint combination *versus* 26.6 months with sunitinib (HR: 0.66 [95% CI: 0.54-0.80]; p<0.0001). In contrast, no OS difference was seen in the favourable risk group (HR: 1.22 [95% CI: 0.73-2.04]). Importantly, with nivolumab/ipilimumab, the responses were deeper (CR rate: 10.5 *vs* 1.8%) and more durable (duration of response ≥18 months: 53% *vs* 39%) than what was seen with sunitinib. No new safety signals emerged. The nivolumab/ipilimumab combination will soon be available in Belgium for the treatment of intermediate-/poor-risk RCC patients. Pembrolizumab has been studied in combination with axitinib in patients with stage IV clear-cell RCC. Pembrolizumab/axitinib in KEYNOTE-426 was also associated with a good OS and durable responses.[20] Toxicity in general was low, with manageable AE profiles. A third study discussed a drug combination for treatment-naïve patients with advanced RCC, the JAVELIN Renal 101 trial.[21] In this trial the combination avelumab plus axitinib was compared with sunitinib. Avelumab/axitinib was associated with an improved PFS, OS and response rate. In addition, the PFS2 data was presented. The median PFS2 was not reached for avelumab/axitinib as compared to 18.4 months for sunitinib (HR: 0.56 [95% CI: 0.42-0.74]).

All three combinations have shown to be superior to sunitinib in efficacy. The CR rate for the nivolumab/ipilimumab combination seems to be the highest, but this drug combination will only be indicated for intermediate-/poor-risk patients. In order to keep the costs and toxicity to a minimum, it will be a challenge to identify responders before treatment. More combinations are currently being investigated. Prof. Rottey pointed out that an important issue with these drug combinations in clinical practice is that it is not always clear which agent causes the AE that is encountered.

Monotherapy with pembrolizumab, which results in a 38% response rate in clear-cell RCC, has been studied in non-clear cell RCC as well.[22] In this population, which generally has a worse prognosis, pembrolizumab monotherapy resulted in a response rate of 24.8% with a CR in 4.8%. The responses seen in these patients were also durable, lasting for more than 15 months in multiple cases. The safety profile was as expected for pembrolizumab.

LATER TREATMENT LINES

ASCO GU also featured the presentation of a large prospective French study with nivolumab in a 'real world setting' (GETUG AFU 26 – NIVOREN).[23] Inclusion criteria allowed metastatic RCC patients with more than two prior lines of therapy, asymptomatic brain metastases and impaired renal function. Importantly, almost half of the patients received treatment beyond progression. The primary outcome of the study was safety. As expected, the results revealed slightly more AEs than in the pivotal trials. This is likely due to the selection of 'good' patients in the clinical trials. Of note, the occurrence of grade ≥3 treatment-related AEs was found to be associated with a longer PFS.

The TIVO-3 study investigated tivozanib in a group of patients who failed on two or three prior regimens, including at least one VEGF receptor tyrosine kinase inhibitor.[24] Tivozanib, a potent inhibitor of VEGF receptor 1, 2 and 3, was compared with sorafenib in refractory advanced RCC. The median PFS with tivozanib was significantly longer with 5.6 months, compared to the 3.9 months median seen with sorafenib. The OS data were premature at the time of analysis. Tivozanib was well tolerated.

The combination atezolizumab and bevacizumab has been tested in a phase II study with non-clear cell RCC patients.[25] Patients, both treatment-naïve and with prior treatment, with clear cell RCC and sarcomatoid differentiation were also included. Retrospective analysis had shown that the subgroup of patients with sarcomatoid differentiation, which is normally associated with inferior survival, reacts well to checkpoint inhibition. Atezolizumab/bevacizumab demonstrated anti-tumour activity in the selected patients with manageable toxicity.

REFERENCES

1. Van As N, Brand D, Tree A, et al. PACE: Analysis of acute toxicity in PACE-B, an international phase III randomized controlled trial comparing stereotactic body radiotherapy (SBRT) to conventionally fractionated or moderately hypofractionated external beam radiotherapy (CFMHRT) for localized prostate cancer (LPCa). ASCO GU 2019; Abstract 1.

2. Sweeney CJ, Chen Y, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med. 2015;373:737-46.

3. James ND, Sydes M, Clarke N, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016;387(10024):1163-77.

4. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med. 2017;377:352-60.

5. James N, de Bono J, Spears M, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med. 2017;377:338-51.

6. Parker C, James N, Brawley C, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet. 2018;392(10162):2353-66.

7. Armstrong A, Szmulewitz R, Petrylak D, et al. Phase 3 study of androgen deprivation therapy (ADT) with enzalutamide (ENZA) or placebo (PBO) in metastatic hormone-sensitive prostate cancer (mHSPC): The ARCHES trial. ASCO GU 2019; Abstract 687.

8. Fizazi K, Tran N, Fein LE, et al. Final analysis of phase III LATITUDE study in patients (pts) with newly diagnosed high-risk metastatic castration-naïve prostate cancer (NDx-HR mCNPC) treated with abiraterone acetate + prednisone (AA+P) added to androgen deprivation therapy (ADT). ASCO GU 2019; Abstract 141.

9. Smith M, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med. 2018;378:1408-18.

10. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2018;378:2465-74.

11. Bhindi B, Karnes J. Novel nonsteroidal antiandrogens and overall survival in nonmetastatic castration-resistant prostate cancer. Eur Urol. 2018;74(4):534-5.

12. Mateo J, Fizazi K, Gillessen S, et al. Managing nonmetastatic castration-resistant prostate cancer. Eur Urol. 2019;75(2):285-93.

13. Fizazi K, Shore N, Tammela T, et al. ARAMIS: Efficacy and safety of darolutamide in nonmetastatic castration-resistant prostate cancer (nmCRPC). ASCO GU 2019; Abstract 140.

14. Small E, Saad F, Chowdhury S, et al. Updated analysis of progression-free survival with first subsequent therapy (PFS2) and safety in the SPARTAN study of apalutamide (APA) in patients (pts) with high-risk nonmetastatic castration-resistant prostate cancer (nmCRPC). ASCO GU 2019; Abstract 144.

15. Hofman M, Vioelt J, Hicks R, et al. Results of a 50 patient single-centre phase II prospective trial of Lutetium-177 PSMA-617 theranostics in metastatic castrate-resistant prostate cancer. ASCO GU 2019; Abstract 228.

16. Balar A, Kulkarni G, Uchio E, et al. Keynote 057: Phase II trial of pembrolizumab (pembro) for patients (pts) with high-risk (HR) nonmuscle invasive bladder cancer (NMIBC) unresponsive to bacillus calmette-guérin (BCG). ASCO GU 2019; Abstract 350.

17. Zaghoul M, Christodouleas J, Hwang W-T, et al. Randomized phase III trial of

adjuvant sequential chemotherapy plus radiotherapy versus adjuvant radiotherapy alone for locally advanced bladder cancer after radical cystectomy: Urothelial carcinoma subgroup analysis. ASCO GU 2019; Abstract 351.

18. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med. 2018;379:417-27.

19. Tannir N, Frontera O, Hammers H, et al. Thirty-month follow-up of the phase III CheckMate 214 trial of first-line nivolumab + ipilimumab (N+I) or sunitinib (S) in patients (pts) with advanced renal cell carcinoma (aRCC). ASCO GU 2019; Abstract 547.

20. Powles T, Plimack E, Stus V, et al. Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for locally advanced or metastatic renal cell carcinoma (mRCC): phase III KEYNOTE-426 study. ASCO GU 2019; Abstract 543.

21. Choueiri T, Motzer R, Campbell M, et al. Subgroup analysis from JAVELIN Renal 101: Outcomes for avelumab plus axitinib (A + Ax) versus sunitinib (S) in advanced renal cell carcinoma (aRCC). ASCO GU 2019; Abstract 544.

22. McDermott D, Lee J-L, Ziobro M, et al. First-line pembrolizumab (pembro) monotherapy for advanced non-clear cell renal cell carcinoma (nccRCC): Results from KEYNOTE-427 cohort B. ASCO GU 2019; Abstract 546.

23. Albiges L, Negrier S, Dalban C, et al. Safety and efficacy of nivolumab in metastatic renal cell carcinoma (mRCC): Final analysis from the NIVOREN GETUG AFU 26 study. ASCO GU 2019; Abstract 542.

24. Rini B, Pal S, Escudier B, et al. TIVO-3: A phase III, randomized, controlled, multicenter, open-label study to compare tivozanib to sorafenib in subjects with refractory advanced renal cell carcinoma (RCC). ASCO GU 2019; Abstract 541.

25. McKay R, McGregor B, Gray K, et al. Results of a phase II study of atezolizumab and bevacizumab in non-clear cell renal cell carcinoma (nccRCC) and clear cell renal cell carcinoma with sarcomatoid differentiation (sccRCC). ASCO GU 2019; Abstract 548.