Highlights in genito-urinary cancers

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From June 1st till June 5th, Chicago was host for the 54th ASCO annual meeting. The theme for this year's venue was 'Delivering Discoveries: Expanding the Reach of Precision Medicine'. With more than 32,000 oncology professionals from around the world to discuss state-of-the-art treatment modalities, new therapies, and ongoing controversies in the field; this year's meeting was a great success. This report will highlight 11 key studies concerning genitourinary cancers presented during the meeting.

PHASE II STUDY BLC2001: FIRST RESULTS OF ERDAFITINIB IN PATIENTS WITH METASTATIC OR UNRESECTABLE UROTHELIAL CARCINOMA AND FGFR ALTERATIONS

Erdafitinib is an FGFR inhibitor with activity in metastatic urothelial carcinoma (mUC) harboring FGFR alterations. Due to low response to immune checkpoint inhibition (ICI) in this population, there is a need for new treatment options. At ASCO 2018, the first efficacy and safety results of a phase II study evaluating this agent were reported. A total of 99 patients with mUC (ECOG 0-2, progression during/following ≥ 1 line of prior chemo or ≤ 12 months of [neo]adjuvant chemo, or cisplatin ineligible, prespecified FGFR alterations) were administered erdafitinib 8 mg daily continuous in 28-day cycles with possible up-titration to 9 mg daily. A median of 5 cycles was administered. There was a 40% confirmed objective response rate (ORR) (3% complete response [CR], 37.4% partial response [PR]) and the disease control rate (DCR) was reported at 82%. Most patients (76%) showed some kind of tumor reduction with a median duration of response of 5.6 months with 21% of patients who remain on treatment. Among patients who received prior ICI (N=21), the ORR was 59. The median progression-free (PFS) and overall survival (OS) were 5.5 months and 13.8 months; respectively. Adverse events (AEs) were manageable with only 7% of patients discontinuing treatment due to a treatment-related AE (TRAE; grade 3/4 stomatitis, diarrhea and hyperphosphatemia).
In conclusion, therapy with erdafitinib yielded a robust ORR and was tolerable in patients with mUC and FGFR alterations, especially in those who received prior ICI. FDA approval has been given based on this phase II trial. Further evaluation in the phase III THOR trial is currently ongoing.[1]

SAFETY AND EFFICACY OF NEOADJUVANT IMMUNOTHERAPY IN MUSCLE INVASIVE UC: FIRST INTERIM RESULTS OF THE ABACUS AND PURE-01 PHASE II STUDIES

Atezolizumab and pembrolizumab are two ICIs used for treatment of mUC. Safety and efficacy results of neoadjuvant atezolizumab (ABACUS) or pembrolizumab (PURE-01) given prior to cystectomy in operable muscle invasive UC were presented at ASCO 2018.
In the ABACUS trial, 74 patients received two cycles of atezolizumab 1200mg q3w prior to cystectomy in muscle

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invasive UC (T2/3/4N0M0; 73%, 20% and 7%, respectively). Imaging was performed at baseline and prior to cystectomy (4-8 weeks after start atezolizumab) to assess radiological response. The median age was 73 years (range 54-88). Fifteen patients (20%) had only 1 cycle of atezolizumab of which 8 due to AEs. Seven patients did not undergo cystectomy. Treatment was manageable with only 9% grade 3/4 TRAEs and one treatment-related death due to dyspnea. The pathological CR (pCR) rate was 29% (20/68) with higher rates for PD-L1-postive patients (40%) versus PD-L1-negative patients (16%). Down-staging to non-muscle invasive disease was seen in 39% of patients. In total, 47 patients had sequential imaging and measurable disease at baseline. Of those, 28% and 17% showed radiological response and progression. Notably, the PD-L1 positivity and the CD8 count increased from pre- to post-treatment. However, the impact of these biomarkers on the treatment outcome is yet to be elucidated.[2]

In the PURE-01 study, a total of 43 patients (predominantly UC histology and cT≤3bN0 stage [63% cT3 versus 37% cT2], regardless of cisplatin eligibility) received 3 cycles of pembrolizumab 200mg q3w before radical cystectomy. Disease assessment as well as biomarker analysis (IHC Dako 22C3 PD-L1 combined positive score [CPS] and genomic sequencing for tumor mutational burden [TMB]) was performed. Sixty-one percent of patients had a tumor mutation burden (TMB) > 10 mutations/megabase (mut/Mb) and 9% had a TMB > 20 mut/Mb. All tumors were microsatellite stable. Pembrolizumab was found to be safe with only one patient suffering from a grade 3 ALT increase and 6 patients reporting reversible grade 2 AEs. At the time of the interim analysis, 25 patients were evaluable. A pCR was observed in 40% of patients with 51% of patients showing down-staging to non-muscle invasive disease. In TURB samples, the mean CPS score for patients with a pCR was 30% as compared to 10% for non-pCR patients (p=0.0549). Median TMB was comparable in both groups. Further genomic analysis showed that *PBRM1* and *RB1* mutations are clearly associated with pCR.[3]

Based on the findings of both trials, atezolizumab and pembrolizumab are safe and clearly show efficacy in this patient cohort urging the need for further follow-up. Biomarker research shows promise for response prediction, but further validation is warranted.[2,3]

KEYNOTE-427: PEMBROLIZUMAB AS MONOTHERAPY FOR ADVANCE CLEAR CELL RENAL CELL CARCINOMA?

ICI combination therapy shows clinical benefit in the first-line advanced clear cell renal cell carcinoma (ccRCC). However, data are scarce on the clinical impact of PD-1 inhibitor monotherapy as a first-line treatment option. In the phase II Keynote-427 trial, the efficacy and safety of pembrolizumab is being assessed in both advanced ccRCC and non-ccRCC. At ASCO 2018, results from the ccRCC cohort were presented. A total of 110 patients (histologically confirmed ccRCC, no prior systemic therapy, measurable disease and Karnofsky performance status ≥70%) were administered pembrolizumab 200 mg q3w for 2 years or until confirmed progressive disease, unacceptable toxicity, or patient withdrawal. In this efficacy analysis, with a median follow-up of 12.1 months, 108 patients with a median age of 64 years (range 29-87) were included. Patients were predominantly male (78%) and were classified as IMDC risk category favorable (37%), intermediate (47%), and poor (16%). The confirmed ORR was 38% (3 CR and 39 PR), 59% showed DCR for more than 6 months and 67% of patients showed a reduction in tumor burden (*Figure 1*). Median duration of response was not reached. ORR for patients with favorable or intermediate/poor risk IMDC was 32% and 42%, respectively. Otherwise, patients with CPS ≥ 1 showed an ORR of 50% whereas this was only half in patients with CPS < 1 (26%). Median PFS and OS were 8.7 months and not reached; respectively. TRAEs occurred in 80% of patients with most commonly reported AEs being pruritus (27%), fatigue (25%), diarrhea (19%), rash (16%), arthralgia (13%), and hypothyroidism (10%). Grade 3-5 TRAEs were noticed in 22% of cases. Monotherapy with pembrolizumab for first-line treatment of advanced ccRCC demonstrated promising efficacy and acceptable tolerability, especially in PD-L1+ tumors. [4]

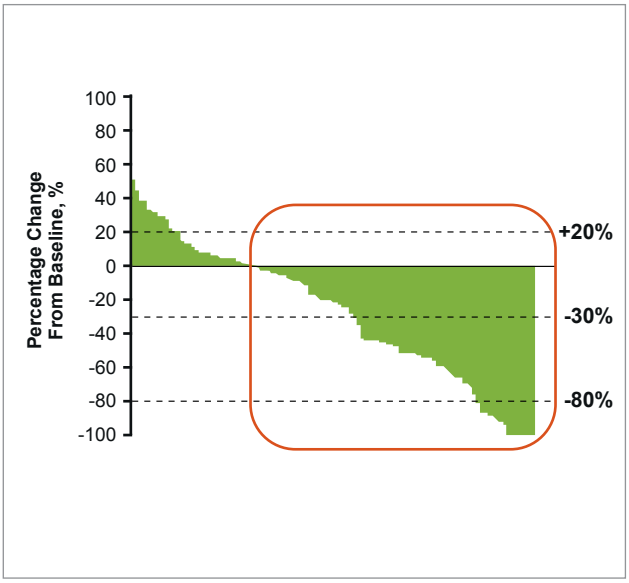

FIGURE 1. Efficacy of pembrolizumab as first-line monotherapy in advanced renal cell carcinoma A total of 74 patients experienced tumor shrinkage of whom 16 experienced a ≥80% reduction and 8 a 100% reduction.[4]

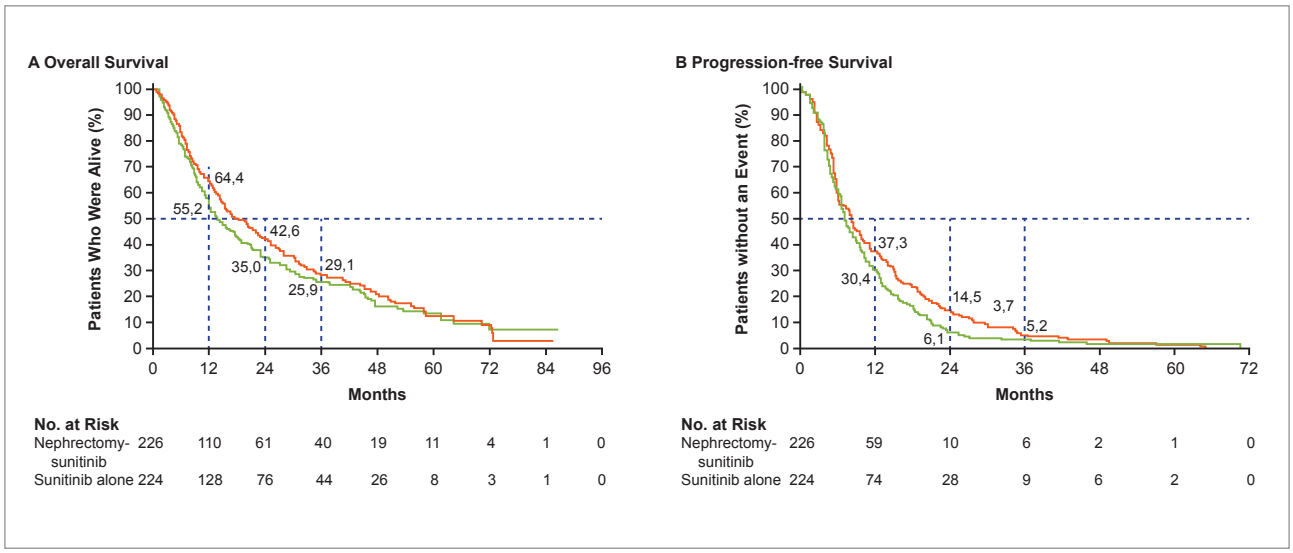

FIGURE 2. Survival outcome of cytoreductive nephrectomy – sunitinib (blue) *vs*. sunitinib alone (red). **A.** Similar OS was noticed for patients who did not undergo cytoreductive nephrectomy. **B.** Radiographic PFS was comparable between both groups. One-, two-, and three-year OS rates are indicated by the vertical dashed lines. The horizontal dashed line indicates the median. Tick marks indicate censored data.[5,6]

TO OPERATE OR NOT TO OPERATE: ROLE OF CYTOREDUCTIVE NEPHRECTOMY IN METASTATIC RCC

Cytoreductive nephrectomy has been the standard-of-care in mRCC for the past twenty years. However, the efficacy of targeted therapies is challenging this standard. The randomized, non-inferiority, phase III CARMENA trial was designed to answer the question whether upfront cytoreductive nephrectomy should continue to be performed before TKI administration. Over a period of 8 years (!), 450 patients with mRCC (ccRCC histology, PS 0-1, absence of symptomatic brain metastasis, acceptable organ function and eligible for sunitinib) were randomized (1:1) to either cytoreductive nephrectomy followed by sunitinib 50 mg daily q4/6w (arm A) or sunitinib alone (arm B). The median age of patients in the trial was 62 years and the intermediate/poor MSKCC risk group distribution was 56%/44% in arm A and in 59%/41% in arm B. Median follow-up was 50.9 months at time of analysis. No difference between arm A and arm B was observed in terms of ORR (27% *vs*. 29%), PFS (7.2 *vs*. 8.3 months; HR[95%-CI]: 0.82[0.67-1.00]), or OS (13.9 *vs*. 18.4 months; HR[95%-CI]: 0.89[0.71-1.10]), independent of the MSKCC risk group (*Figure 2*).

Based on these findings, the authors conclude that sunitinib alone is not inferior to cytoreductive nephrectomy followed by sunitinib and that cytoreductive nephrectomy should no longer be offered as standard-of-care when medical treatment is required. However, this trial population may not be the ideal group to test this hypothesis as the median size of the primary tumor was 89 mm, with a median burden of metastatic disease of 14cm. Furthermore, patients with large primary tumors with only limited metastatic burden were not included. Next, due to the rise of immunotherapy in earlier lines of treatment, the need for TKIs remains unclear. On the other hand, offering sunitinib instead of cytoreductive nephrectomy could lead to the formation of more neoantigens for immunotherapy priming with primary tumor still in place and the inflammation response after surgery could promote tumor growth. It is therefore not clear which option should be presented to the patient at the current time. In diffuse metastatic disease, start of systemic treatment with TKI does not seem inferior to nephrectomy followed by TKI.[5,6]

POST-OPERATIVE SORAFENIB IN PATIENTS WITH RCC WHO UNDERWENT RADICAL METASTASECTOMY: EFFICACY RESULTS FROM THE PHASE II RESORT TRIAL

Radical metastasectomy followed by observation is a commonly used strategy for some patients with mRCC. In the RESORT trial, the clinical benefit of angiogenesis inhibition after radical metastasectomy is prospectively assessed in 132 patients.[7] At the interim analysis, 68 mRCC patients (previous nephrectomy, predominant ccRCC histology, radical excision of no more than 3 metastases) were randomized (1:1) within 12 weeks from surgery to receive sorafenib 400 mg twice daily (N=32) or observation (N=36) for a maxi-

mum of 52 weeks. Patients were stratified according to time from nephrectomy to metastases, site of disease and for the number of lesions. Radiologic restaging was performed every 12 weeks. After a median follow-up of 21 months, the median recurrence-free survival (RFS) was 29 months in the sorafenib arm as compared to 35 months in the observation arm. One-year and 2-year RFS was 62% and 52% in patients treated with sorafenib whereas this was 74% and 59% for patients who were only observed following metastasectomy. No differences in RFS were observed considering the stratification factors. Grade 3 AEs were 22% *vs.* 3% for sorafenib *vs.* observation and only 2 patients received the full sorafenib dose during the course of the trial. Sorafenib did not affect RFS in patients with mRCC after complete metastasectomy and resulted in increased toxicities pointing out that TKIs have no place as adjuvant therapy and watchful waiting remains a valid treatment option in these patients.[8]

SURVIVAL BENEFIT OF ABIRATERONE ACETATE PLUS A LHRH AGONIST ON BIOCHEMICAL RECURRENCE IN HORMONE-SENSITIVE NON-METASTATIC PROSTATE CANCER

Intermittent *vs.* continuous androgen deprivation (ADT) is an acceptable treatment for hormone-sensitive non-metastatic prostate cancer (mPCa) leading to an improved quality of life with no significant survival difference. As abiraterone acetate improves survival in hormone-sensitive mPCa, the survival benefit of the combination of abiraterone acetate and intermittent ADT was evaluated in a non-metastatic setting. Of 200 patients enrolled, 197 patients (hormone-sensitive non-mPCa, no definitive local treatment possible) were randomized (1:1) to 8 months of abiraterone acetate (1 g daily) + prednisone (5 mg daily) + leuprolide (LHRH agonist) *vs.* leuprolide only. Cross-over was allowed upon progression. Stratification factors were radical prostatectomy *vs.* radiation, PSA ≥ *vs.* < 10 µg/L and time to recurrence ≥ *vs.* < 3 years. The median age of patients in the study was 65 years (range 42-85), the median PSA 1 was µg/L (0.3-33.3) and the median testosterone level was reported to be 346 ng/dL (160-946). Th vast majority of patients (94%) had undergone radical prostatectomy. A total of 128 patients had PSA relapse. The PSA PFS was significantly higher in patients receiving the combination for 8 months *vs.* patients receiving only the LHRH agonist (28.3 *vs.* 21.1 months; HR[95%CI]: 0.62[0.44-0.88]) with no difference in time to testosterone recovery. The combination of therapies also proved to be favorable across all stratification factors. The most common grade 3 AEs reported in the combination arm were hypertension (5 patients) and liver function disorders (4 patients).

In summary, 8 months treatment with abiraterone acetate plus a LHRH agonist in hormone-sensitive non-mPCa improves PSA PFS without a delay in testosterone recovery or significant safety concerns.[9]

NOVEL THERAPEUTIC OPTIONS FOR POST-DOCETAXEL METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

The inhibitor olaparib was previously shown to be associated with an improved ORR in patients with metastatic castration-resistant PCa (mCRPC) with a homologous recombination repair mutation.[10] In the currently presented phase II trial, the combination of abiraterone acetate plus olaparib in post-chemotherapy patients with mCRPC was assessed independent of the presence of homologous recombination repair mutations. In total, 142 patients were randomized post-docetaxel (1:1) to receive olaparib (300 mg twice daily) or placebo plus abiraterone acetate (1 g daily) until disease progression. The ORR was similar between olaparib and placebo (27% *vs.* 32%), while the radiographic PFS was significantly higher in the olaparib arm as compared to the comparator arm (13.8 *vs.* 8.2 months; HR[95%CI]: 0.65[0.44-0.97]). This radiographic PFS benefit was seen irrespective of the homologous recombination repair mutation status (wild type [N=35]: 15.0 *vs.* 9.7 months / mutated [N=21]: 17.8 *vs.* 6.5 months / unknown [N=86]: 13.1 *vs.* 6.4 months). The median OS was 22.7 months *vs.* 20.9 months (HR[95%CI]: 0.91[0.60-1.38]). In the olaparib arm, more grade ≥3 (54% *vs.* 28%), serious AEs (34% *vs.* 18%) and treatment discontinuation (30% *vs.* 10%) was reported. The time to quality-of-life deterioration was similar in both arms (5.7 *vs.* 6.0 months). This is the first trial to show a radiographic survival benefit for mCRPC patients treated with a PARP inhibitor combined with abiraterone acetate. Safety data were however less favorable, and no overall survival (OS) benefit was noticed. Although a phase III trial is planned, this combination should not be offered as second-line therapy to patients who progressed on docetaxel.[11]

Secondly, preliminary results have shown antitumor activity of ICI in PD-L1-positive patients with mCRPC (Keynote-028).[12] The phase II Keynote-199 trial evaluates the efficacy and safety of pembrolizumab monotherapy in docetaxel-refractory mCRPC. At ASCO 2018, results from the first 3 cohorts was presented. Patients (ECOG PS 0-2, ≥1 novel endocrine therapy [e.g. abiraterone, enzalutamide], 1-2 prior chemotherapies including docetaxel) were enrolled into three cohorts: RECIST-measurable PD-L1-positive disease (C1; N=131), RECIST-measurable

TABLE 1. Response rates of pembrolizumab in docetaxel-refractory mCRPC.[13]

RECIST v1.1	C1	C2	C3	C1 + C2	C1 + C2 + C3
ORR, %	5 (2-11)	3 (<1-10)	NA	5 (2-8)	NA
DCR, %	22 (15-30)	24 (14-36)	37 (25-50)	23 (17-29)	26 (21-32)
DoR, months	8.4 (1.6-NR)	NR (4.4-NR)	NA	8.4 (1.9-NR)	NA
DCR ≥ 6 months, %	9 (5-16)	6 (2-15)	22 (12-34)	8 (5-13)	11 (8-16)

mCRPC: metastatic castration-resistant prostate cancer; DCR: disease control rate; DoR: duration of response; NA: not applicable; N: not reached; ORR: objective response rate.

PD-L1-negative disease (C2; N=67), and non-measurable, bone-predominant disease (C3; N=60). All patients received pembrolizumab 200 mg q3w until disease progression or intolerable toxicity. The ORR was evaluated every 9 weeks during the first year and every 12 weeks thereafter. The median follow-up for for C1, C2 and C3 was 8.1, 7.9 and 11.8 months, respectively. Antitumor activity was observed in all cohorts (*Table 1*). The ORR was numerically higher in patients with somatic *BRCA1/2* or *ATM* mutations (11%). Median OS was 9.5 months, 8.0 months, and not reached for C1, C2 and C3; respectively. Grade ≥3 TRAEs were similar between cohorts with 14% of grade ≥3 AEs reported in total. Two treatment-related deaths occurred (pneumonitis and sepsis). These data show that pembrolizumab has antitumor activity and disease control with acceptable safety in post-docetaxel patients with mCRPC. Further evaluation and comparison to standard-of-care in large phase III trials is warranted.[13]

CLINICAL OUTCOME OF 3 DIFFERENT RADIUM-223 DOSE REGIMENS IN CHEMOTHERAPY-NAÏVE BONE mCRPC

The standard dose of Radium-223 55 kBq/kg q4w for 6 cycles improved OS and delayed onset of skeletal-related events (SREs) in patients with only bone mCRPC.[14] The current study investigated different Radium-223 treatment regimens in a similar patient population. A total of 391 patients were randomized (1:1:1) to Radium-223 standard dose (SD), Radium-223 high dose 88 kBq/kg q4w for up to 6 cycles (HD), or to Radium-223 standard dose extended q4w for up to 12 cycles (EXT). Treatment completion occurred in 65%, 52% and 22% of patients in the SD, HD and EXT arms, respectively. No significant SRE-free survival differences were observed between SD and HD (12.3 *vs.* 12.9 months; HR[95%CI]: 1.06[0.88-1.27]) and between SD and EXT (13.2 *vs.* 10.8 months; HR[95%CI]: 1.26[0.94-1.69]). Median PFS and OS were 6.3 and 15.8 months, 7.5 and 16.0 months, and 6.1 and 14.4 months in the SD, HD and EXT arms, respectively. The most frequent TRAEs were fatigue, anemia and nausea. Grade ≥3 TRAEs were reported in 34%, 48% and 53% of patients in the SD, HD and EXT arms; with anemia (13%), bone pain (5%), thrombocytopenia (4%) and hypertension (4%) being the most frequent. As the standard dose of Radium-223 is non-inferior to a higher or extent dose with more favorable safety profile, the currently approved dose and schedule of Radium-223 should be maintained as standard therapy.[15]

DOES RACE AFFECT OS IN MEN WITH mCRPC?

Previous reports of relatively small studies have suggested that African-American men with mCRPC have a shorter OS than Caucasian men. The primary goal of the present study was therefore to compare the OS in African-American men to the survival of Caucasian men treated with docetaxel/prednisone or a docetaxel/prednisone containing regimen. Patient data from 8,871 men with mCRPC randomized in nine phase III trials were collected and prognostic importance of race on OS was evaluated, adjusting for established risk factors that were common across the trials (age, PSA, performance status, alkaline phosphatase, hemoglobin, and sites of metastases). In total, 8,452 patients were eligible, namely 7,528 (85%) Caucasian and 500 (6%) African-American men. The median age was 69 years and 94% of patients had a performance status 0-1. The median OS was 21.0 months for African-American as compared to 21.2 months in Caucasian men, respectively. A multivariable analysis adjusting for established risk factors proved favorable for African-American versus Caucasian men (HR[95%CI]: 0.81 [0.72-0.92]). As such, these results are in controversy with previously reported data. Therefore, further understanding of the biological variation by race in men with mCRPC treated with any form of docetaxel/prednisone containing regimen is needed.[16]

KEY MESSAGES FOR CLINICAL PRACTICE

1 Erdafitinib for treatment of mUC with FGFR alterations yields robust ORR, especially when received prior ICI (FDA approval - phase III trial ongoing).

2 Atezolizumab and pembrolizumab are safe and show efficacy as neoadjuvant therapy in muscle invasive UC with down-staging to non-muscle invasive disease – further follow-up needed.

3 Pembrolizumab as first-line monotherapy for advanced ccRCC demonstrated promising efficacy and acceptable tolerability, especially in PD-L1-postive tumors and could become a next treatment in first-line RCC.

4 Sunitinib alone is not inferior to cytoreductive nephrectomy followed by sunitinib for mRCC. However, due to trial shortcomings, cytoreductive nephrectomy followed by TKI administration should remain the standard-of-care in most of our patients.

5 Sorafenib results in increased toxicity without affecting RFS in patients with mRCC after complete metastasectomy. As such, TKIs have no place as adjuvant therapy and a watchful waiting should be offered.

6 Abiraterone acetate plus LHRH agonist in hormone-sensitive non-mPCa improves PSA PFS without a delay in testosterone recovery or significant safety concerns.

7 Pembrolizumab has antitumor activity and disease control with acceptable safety in post-docetaxel patients with mCRPC whereas this is not the case for the combination of abiraterone acetate plus a PARP inhibitor. Further phase III trials are warranted.

8 Standard dose of Radium-223 is non-inferior to a higher or extented dose and is associated with a more favorable safety profile in chemotherapy-naïve bone mCRPC. Therefore, the current schedule of Radium-223 remains standard therapy.

9 Much controversy remains on the effect of race on OS in mCRPC. Further understanding of the biological variation by race in mCRPC is needed.

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