Highlights in genitourinary cancers

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From the 8th till the 12th of September, Madrid was the host city for the 2017 ESMO Congress. The central theme of the congress was 'Integrating science into oncology for a better patient outcome', as it is crucial that researchers and clinicians exchange knowledge in an era of deep understanding of the molecular biology underlying the development of cancer. ESMO 2017 was attended by almost 24,000 registered attendees. This report will highlight eleven key studies concerning genitourinary cancers presented during the meeting.
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SORAFENIB – PAZOPANIB VERSUS PAZOPANIB – SORAFENIB IN THE SEQUENTIAL TREATMENT OF METASTATIC RENAL CELL CARCINOMA DURING THE SWITCH-II PHASE III TRIAL

The previous SWITCH-I study explored the sequential use of sunitinib and sorafenib for the treatment of metastatic renal cell carcinoma (mRCC) and showed similar survival outcomes.[1] The current trial compared the sequential therapy with sorafenib followed by pazopanib or *vice versa*. A total of 377 treatment-naïve mRCC patients were randomised 1:1 to the sequential use of sorafenib (400 mg twice daily) – pazopanib (800 mg once daily) versus pazopanib – sorafenib. The primary endpoint was non-inferiority in total progression-free survival (PFS). Main secondary endpoints included overall survival (OS), disease control rate (DCR), 1st-line PFS as well as safety and tolerability. Median total PFS was 8.6 months (7.7-10.2) for sorafenib – pazopanib and 12.9 months (10.8-15.2) for pazopanib – sorafenib with a hazard ratio (HR) of 1.36. Based on the pre-set HR, non-inferiority in regard to total PFS was not met. However, marked statistical differences were noted in favour of pazopanib – sorafenib in 1st-line PFS (5.6 versus 9.3 months) and disease control rate (67.7 *vs.* 77.7%) but not for OS (22.7 *vs.* 28.0 months). Most frequent any-grade 1st-line adverse events (AEs) for sorafenib were diarrhoea (56%), fatigue (37%) and hand-foot skin reaction (35%) while diarrhoea (60%), hypertension (48%) and fatigue (45%) were most common with pazopanib. In conclusion, no sequential difference could be demonstrated for sorafenib – pazopanib compared to pazopanib – sorafenib. Due to the higher DCR and the prolonged PFS, pazopanib remains the preferred 1st-line treatment option.[2]

IMMEDIATE VERSUS DEFERRED CYTOREDUCTIVE NEPHRECTOMY IN SYNCHRONOUS mRCC TREATED WITH SUNITINIB? FINDINGS FROM THE EORTC 30073 SURTIME TRIAL

In clinical practice, mRCC patients with the primary tumour *in situ* are offered cytoreductive nephrectomy followed by targeted therapy. This randomised trial explored a period of targeted therapy prior to cytoreductive nephrectomy as an alternative approach. A total of 99 patients with clear-cell mRCC (resectable asymptomatic primary tumour and ≤ 3 surgical risk factors) were randomised (1:1) to immediate cytoreductive nephrectomy followed by sunitinib (50 mg once daily) q4/6w versus three cycles sunitinib followed by cytoreductive nephrectomy and post-operative continuation of sunitinib. Progression-free rate at 28 weeks was the primary endpoint; OS, AEs and post-operative progression in both

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arms were secondary endpoints. Median follow-up was 3.3 years. In the immediate cytoreductive nephrectomy arm, 46 of 50 patients underwent surgery, 40 of 46 had post-operative sunitinib. In the deferred cytoreductive nephrectomy arm, 48 of 49 patients received sunitinib, 40 of 48 underwent surgery and 26 of 40 had post-operative sunitinib. Progression-free rate was 42.0% (28.2-56.8) and 42.9% (28.8-57.8) in the immediate and deferred arms, respectively. The HR for OS in the intention to treat population with deferred versus immediate cytoreductive nephrectomy was 0.57 (0.34-0.95, p= 0.032) with a median OS of 32.4 (14.5-65.3) and 15.1 months (9.3-29.5), respectively. Although these results show no difference between deferred and immediate cytoreductive nephrectomy based on PFS, OS clearly favours deferred cytoreductive nephrectomy. Due to the poor accrual in the study however, no definitive conclusions can be made.[3]

CHECKMATE 214: COMBINATION OF NIVOLUMAB PLUS IPILIMUMAB VERSUS SUNITINIB FOR TREATMENT-NAÏVE mRCC

Combining therapies often shows improved efficacy. At ESMO 2017, the efficacy and safety of nivolumab plus ipilimumab as 1st-line therapy in mRCC was presented. Treatment-naïve patients with clear-cell mRCC (Karnofsky performance status ≥ 70) were randomised (1:1) to nivolumab 3 mg/kg plus ipilimumab 1 mg/kg q3w for four doses followed by nivolumab 3 mg/kg q2w (N= 550), or sunitinib 50 mg daily q4/6w (N= 546). Co-primary endpoints were ORR, PFS and OS in the cohort of patients at intermediate or poor-risk. Efficacy was also evaluated according to IMDC risk group and tumour PD-L1 expression. After 17.5 months of follow-up, ORR in intermediate/poor risk patients (41.6%) was higher compared to the sunitinib arm (26.5%; p < 0.0001) with 9.4% and 1.2% of patients achieving a complete response, respectively. The median duration of response was not reached versus 18.2 months. There was an improvement in PFS of 3.2 months (11.6 *vs.* 8.4 months, HR: 0.82, p= 0.0331; *Figure 1*) and OS (not reached *vs.* 26.0 months, HR: 0.63, p< 0.0001; *Figure 1*). However in patients at favourable risk, both the ORR (29% *vs.* 52%, p= 0.0002) and PFS (15.3 *vs.* 25.1 months, HR: 2.17, p< 0.0001) were higher in the sunitinib arm. Focusing on the intention-to-treat population, the OS was significantly longer with the combination (not reached *vs.* 32.9 months, HR[95%CI]: 0.68[0.49-0.95]) whereas no difference was observed for PFS. Next, ORR and PFS were significantly better with nivolumab plus ipilimumab for intermediate/poor risk patients having baseline PD-L1 expression ≥ 1%. Note hereby that baseline tumour PD-L1 expression was lower in the cohort of patients at favourable risk. Any grade drug-related AEs occurred in 93% (54% grade ≥ 3) of patients in the nivolumab/ipilimumab cohort and in 97% (63% grade ≥ 3) of patients receiving sunitinib.

Findings from the CheckMate 214 phase III trial support the use of combined nivolumab plus ipilimumab as a potential 1st-line treatment for patients with mRCC, with mayor benefit for intermediate/poor risk patients.[4]

IMPACT OF TUMOUR MUTATIONAL BURDEN ON EFFICACY OF NIVOLUMAB IN 2ND-LINE METASTATIC UROTHELIAL CARCINOMA: EXPLORATORY ANALYSIS OF CHECKMATE 275

Nivolumab demonstrated efficacy in patients with surgically unresectable or metastatic urothelial cancer (mUC).[5] At ESMO 2017, the exploratory analysis was presented which explored the potential association between pre-treatment tumour mutational burden (TMB) and response to nivolumab. Tumour DNA from archival tumour tissue and matched whole blood samples was profiled by whole exome sequencing. TMB was defined as the total number of missense somatic mutations per tumour and the association with ORR, PFS and OS was determined. Tumour PD-L1 positivity was assessed by DAKO PD-L1 IHC 28-8 assay (≥ 1%). Baseline characteristics, ORR, PFS, and OS were similar between all treated patients. High TMB showed a statistically significant positive association with ORR (p= 0.002) and PFS (p= 0.005), and a strong association with OS (= 0.067), even when adjusted for baseline tumour PD-L1 expression, liver metastasis status and serum haemoglobin. These exploratory findings suggest that TMB may provide complementary prognostic and predictive information during immunotherapy beyond PD-L1. Further analysis in randomised trials is warranted.[6]

PEMBROLIZUMAB VERSUS INDIVIDUAL INVESTIGATOR'S CHOICE OF CHEMOTHERAPY IN mUC: SUBGROUP ANALYSES FROM KEYNOTE-045

It was previously reported that OS was significantly longer with pembrolizumab versus investigator's choice of chemotherapy in mUC.[7] In a post-hoc analysis, pembrolizumab was compared with the individual agents in the chemotherapy arm. A total of 525 patients with mUC who progressed after platinum-based chemotherapy (ECOG performance status 0-2, measurable disease and ≤ 2 lines of systemic therapy) were assigned 1:1 to pembrolizumab 200 mg q3w (N= 270) or paclitaxel 175 mg/m² q3w (N= 84), docetaxel 75 mg/m² q3w (N= 84), or vinflunine 320 mg/m² q3w (N= 87). Baseline demographics were generally well balanced among cohorts. With median follow-up of fourteen months,

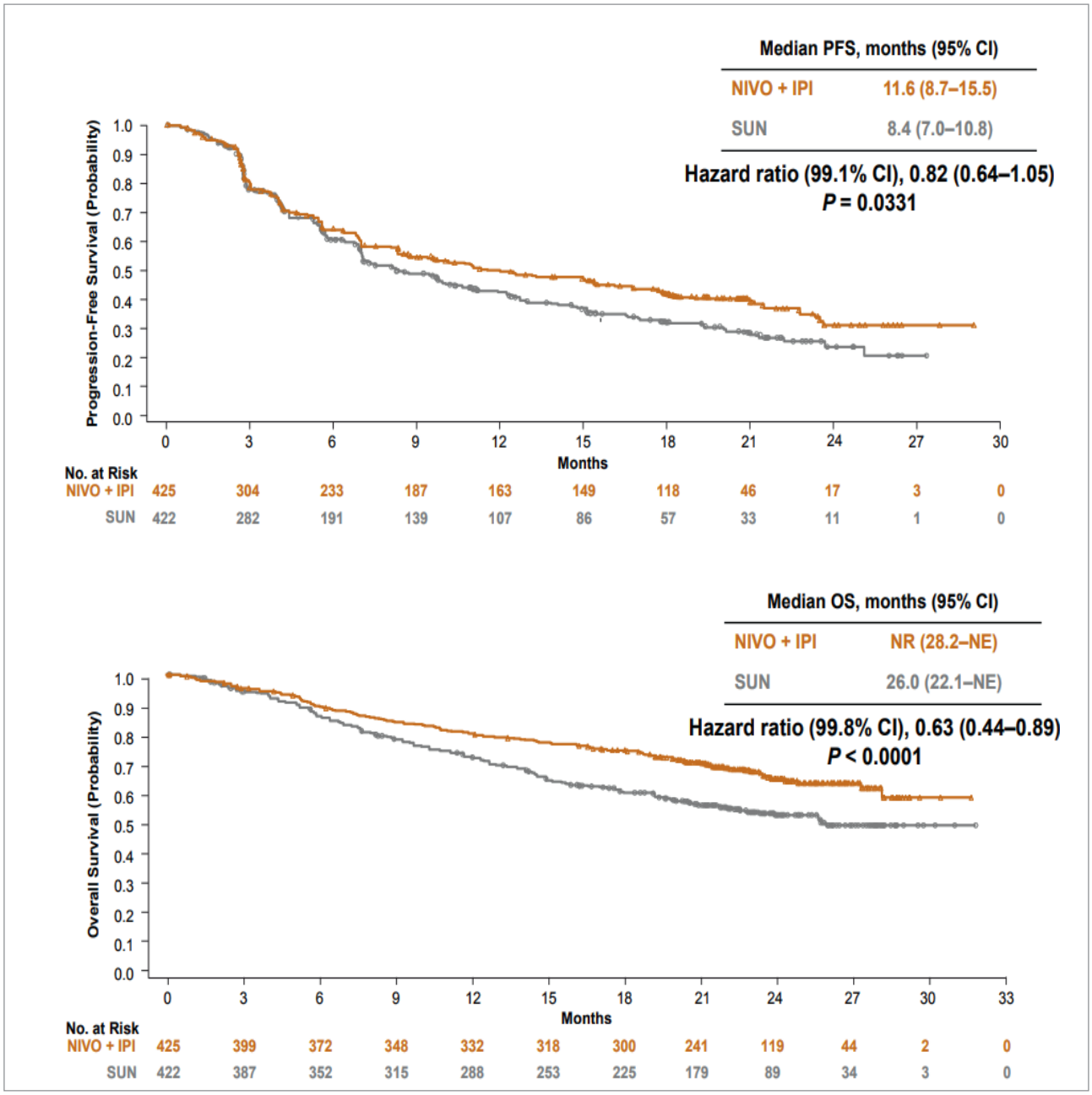

FIGURE 1. Survival outcome of nivolumab plus ipilimumab versus sunitinib for intermediate/poor risk patients with mRCC in the phase III CheckMate 214 trial.[4]

pembrolizumab was associated with an OS benefit over all individual chemotherapeutic agents (HR[95%CI] paclitaxel: 0.77 [0.57-1.06]; HR[95%CI] docetaxel: 0.78 [0.56-1.08]; HR[95%CI] vinflunine: 0.71 [0.52-0.96]). PFS was similar between pembrolizumab and each of the chemotherapeutic agents. ORR was 21% with pembrolizumab versus 12%, 6% and 18% with paclitaxel, docetaxel and vinflunine, respectively. Treatment-related AEs occurred in 61% (15% grade ≥ 3), 88% (44% grade ≥3), 92% (54% grade ≥3), and 91% (51% grade ≥3) of patients for pembrolizumab, paclitaxel, docetaxel and vinflunine, respectively. These results demonstrate that pembrolizumab was associated with longer OS, higher antitumour activity, and lower incidence of toxicities compared to chemotherapy and should therefore be considered as 1st-choice in mUC after progression on platinum.[8]

IMVIGOR 210: POST-PROGRESSION OUTCOMES OF ATEZOLIZUMAB IN PLATINUM-TREATED mUC

Several immunotherapeutic agents have been approved for the treatment of mUC. Now, results on outcome were reported in patients treated beyond progression with atezolizumab. A total of 310 patients who progressed during/

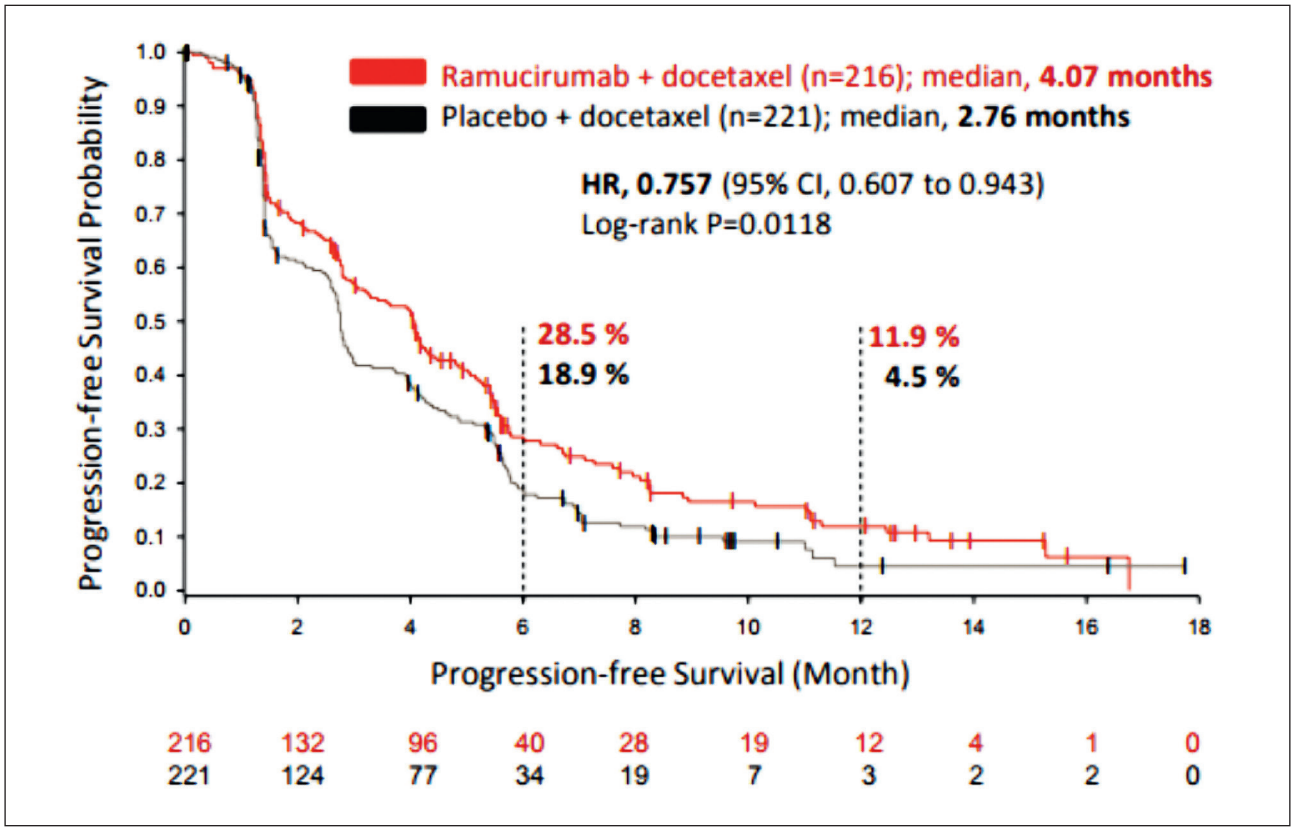

FIGURE 2. PFS outcome of docetaxel plus ramucirumab versus docetaxel plus placebo for mUC in the phase III Range trial.[11]

following platinum were given atezolizumab 1200 mg q3w until loss of clinical benefit. This descriptive, post-hoc analysis reported response (post–first progressive disease), sum of target laesion diameter, OS, post-progression OS and safety. Two-hundred twenty patients who experienced progressive disease were evaluable. Of them, 137 continued atezolizumab and 83 received other (N= 19) or no (N= 64) systemic therapy. Patients continuing on atezolizumab had fewer poor risk factors (ECOG status and visceral mets) compared to other patients. Post-progressive disease ORR was comparable between patients who did or did not receive atezolizumab beyond progression, although a decrease in sum of target laesion diameter was noticed for patients who received atezolizumab beyond progression. Both OS (12.8 *vs.* 3.6 months) and post-progressive disease OS (8.6 *vs.* 1.5 months) were higher for atezolizumab beyond progression compared to no atezolizumab beyond progression. In conclusion, patients who continued atezolizumab beyond progressive disease derived prolonged clinical benefit including tumour burden reduction and numerically longer OS versus patients who discontinued atezolizumab. Administration of additional cycles of immunotherapy should therefore be considered in asymptomatic patients who progress for the first time on anti-PD1/PD-L1 immunotherapy.[9,10]

DOCETAXEL WITH OR WITHOUT RAMUCIRUMAB IN PLATINUM-REFRACTORY mUC: RESULTS OF THE PHASE III RANGE TRIAL

Limited treatment options are available for patients with mUC who progressed on platinum-based chemotherapy. In a previous phase II trial, it has been reported that docetaxel plus the VEGFR2 antibody ramucirumab is effective in this population.[11] The results of the phase III trial were presented at ESMO 2017. In the RANGE trail, 530 mUC patients with progressive disease after platinum were randomised 1:1 to receive docetaxel 75 mg/m² plus ramucirumab 10 mg/kg q3w or docetaxel 75 mg/m² plus placebo q3w until disease progression. Primary endpoint was PFS analysed in the first 437 patients, secondary endpoints included OS, ORR, safety, and quality-of-life. PFS appeared to be significantly prolonged in patients treated with docetaxel plus ramucirumab (4.1 versus 2.8 months; HR[95%CI]: 0.76[0.61-0.94]; *Figure 2*). The ORR was 24.5% in the ramucirumab arm and 14.0% in the placebo arm. OS data are immature. Grade ≥3 AEs were reported at a similar frequency in both arms, with neutropenia being the most common grade ≥3 AE (14-15%), with no unexpected toxicities. Mean scores for global quality-of-life were relatively unchanged over time. Docetaxel plus ramucirumab is the 1st regimen in a phase III trial to show superior

PFS over chemotherapy in patients with platinum-refractory mUC. Data on OS outcome and comparison with checkpoint inhibitors in randomised trials is however needed to determine the place of docetaxel plus ramucirumab in the treatment of mUC.[12,13]

STAMPEDE SUBSET ANALYSIS: ANDROGEN DEPRIVATION THERAPY COMBINED WITH ABIRATERONE ACETATE OR DOCETAXEL FOR HIGH-RISK PROSTATE CANCER

Adding abiraterone acetate (AA) plus prednisone or docetaxel plus prednisone to standard-of-care (SOC, long term androgen deprivation therapy [ADT] with or without radiotherapy) each improved survival versus SOC alone in high-risk prostate cancer (PCa).[14] At ESMO 2017, the 1st direct, randomised data of SOC plus AA or SOC plus docetaxel were shown. Patients were randomised (1:2) to SOC plus docetaxel 75 mg/m² q3w for six cycles plus prednisone 5 mg twice daily (N= 189) or SOC plus AA 1,000 mg plus prednisone 5 mg twice daily (N= 377). The primary outcome measure was death from any cause. Groups were well balanced (60% metastatic disease, 76% Gleason score 8-10, 79% WHO performance status 0). At a median follow-up of four years, the outcome was as follows: HR[95%CI] OS: [0.82-1.65], HR[95%CI] FFS: 0.51 [0.39-0.67], HR[95%CI] PFS: 0.65 [0.48-0.88], HR[95%CI] MFS: 0.77 [0.57-1.03], and HR[95%CI] SRE: 0.83 [0.55-1.25]. This direct comparative analysis of two new standards for high-risk PCa clearly favoured SOC plus AA based FFS and PFS although no difference could be found for OS. Safety profile was similar between treatment arms. Therefore no definitive conclusion can currently be made on which drug should be given 1st in patients with high-risk PCa.[15]

OUTCOME OF DOCETAXEL PLUS ANDROGEN SUPPRESSION FOR HIGH-RISK LOCALISED PCa

Patients with high-risk localised PCa who progress after local therapy have a poor prognosis. In these patients, androgen suppression by means of the gonadotropin-releasing hormone agonist triptorelin may be a therapeutic option. In this phase III trial, 250 patients with PCa who progressed after local therapy (radical prostatectomy and/or radiotherapy and ≥1 of the following criteria: Gleason score ≥8, PSA doubling time ≤6 months, PSA velocity >0.75 ng/mL/year, positive surgical margins, pN1, time from curative therapy to PSA relapse ≤12 months) were randomised (1:1) to triptorelin q3m for one year versus triptorelin plus docetaxel 70 mg/m² q3w for six cycles. The primary endpoint was PSA-PFS, while secondary objectives included PSA response, radiographic PFS, OS and safety. Baseline characteristics were as follows: 38% radical prostatectomy, 28% radiotherapy or 34% radical prostatectomy plus radiotherapy, 29% Gleason score ≥8, 54% PSA doubling time ≤6 months, 84% PSA velocity >0.75 ng/mL/year, 37% positive surgical margins, 4% pN1, 45% PSA relapse ≤ 12 months. Fifty-eight percent of patients had ≥3 risk factors. No significant difference was observed in ORR (94% *vs.* 98%), PSA-PFS (20.7 *vs.* 18.6 months) and radiographic PFS (8.8 *vs.* 9.7 months) for triptorelin plus docetaxel compared to triptorelin alone. OS data was immature. Triptorelin plus docetaxel is therefore not recommended as therapy in patients with high-risk localised PCa who progress after local therapy.[18]

PATIENT REPORTED OUTCOMES FROM LATITUDE

In the LATITUDE study, treatment with ADT plus AA significantly improved OS and delayed disease progression.[16] Here, the impact of ADT plus AA on patient reported outcomes, including symptom and health-related quality-of-life, was reported. One thousand one hundred and ninety nine metastatic castration-sensitive PCa patients were randomised (1:1) to ADT plus AA plus prednisone or ADT plus placebo. Brief Pain Inventory-Short Form, Brief Fatigue Inventory, FACT-P, and EQ-5D-5L questionnaires were taken at baseline, day one of cycles two to thirteen and then every two months until treatment discontinuation. EQ-5D-5L was performed every four months until twelve months after treatment discontinuation. A high questionnaire compliance rate was observed (≥90%). Compared to ADT plus placebo, the ADT plus AA arm had significant delayed time to pain and fatigue intensity and interference progression. FACT-P assessments demonstrated significant delay in degradation for the total score and symptom subscales for the ADT plus AA. Repeated measure analyses showed maintenance or improvement from baseline for the ADT plus AA arm compared to the ADT plus placebo arm as early as cycle two to cycle five (*Figure 3*). ADT plus AA clearly results in improved patient reported outcomes compared to ADT plus placebo and were linked with improvements in clinical outcomes.[17]

DNA REPAIR DEFECTS AS PREDICTIVE AND/OR PROGNOSTIC BIOMARKER IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER (mCRPC): RESULTS FROM THE PROREPAIR-B PROSPECTIVE STUDY

Germline mutations in DNA repair genes have been associated with poor PCa outcomes and progression to metastatic disease, but no conclusive data are available

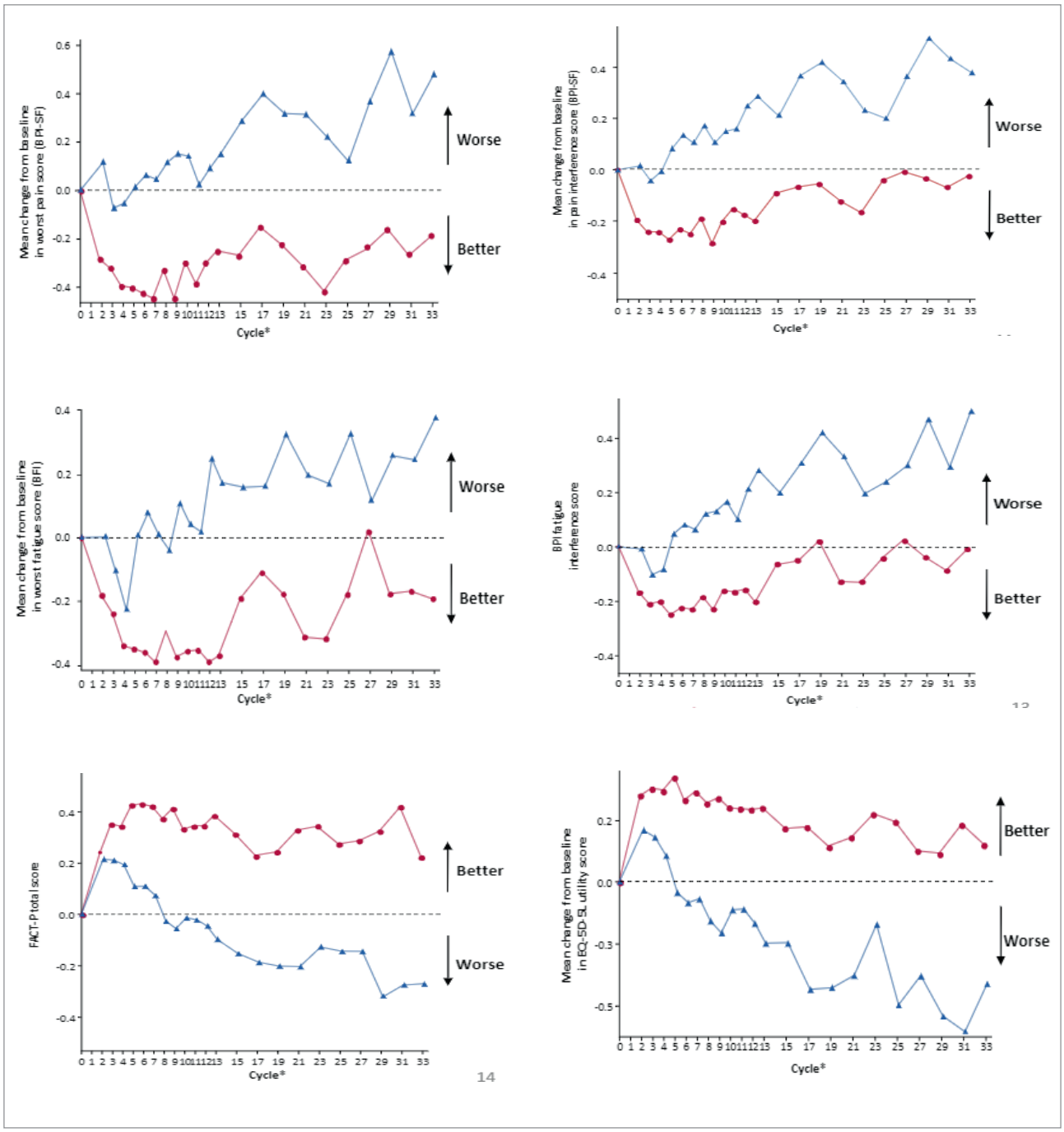

FIGURE 3. Patient reported outcomes in the LATITUDE trial. Comparison between ADT plus AA (red line) and ADT plus placebo (blue line) are depicted for mean change from baseline in worst pain score (top left), mean change from baseline in pain interference score (top right), mean change from baseline in worst fatigue score (middle left), fatigue interference score (middle right), FACT-P score (bottom left) and mean change from baseline in BQ-5D-5L score (bottom right).[17]

for mCRPC. In the prospective multicentre observational study PROREPAIR-B, impact of *BRCA*1, *BRCA*2, *ATM* and *PALB2* germline mutations on cause-specific survival and response to therapy were determined. A total of 419 mCRPC patients were enrolled and were treated at physician-choice's with either AA, enzalutamide, docetaxel, cabazitaxel or Radium-223. In total, 6.2% of patients were identified as germline mutation carriers (fourteen *BRCA*2, eight *ATM* and four *BRCA*1). Median time from ADT initiation to mCRPC was comparable between carriers and non-carriers (23.7 *vs.* 26.7 months). Other baseline characteristics were also not different between carriers and non-carriers at 1st therapy initiation: ECOG 0-1 (92% *vs.* 88%), median PSA (27.9 *vs.* 31.0 µg/L), bone metastases

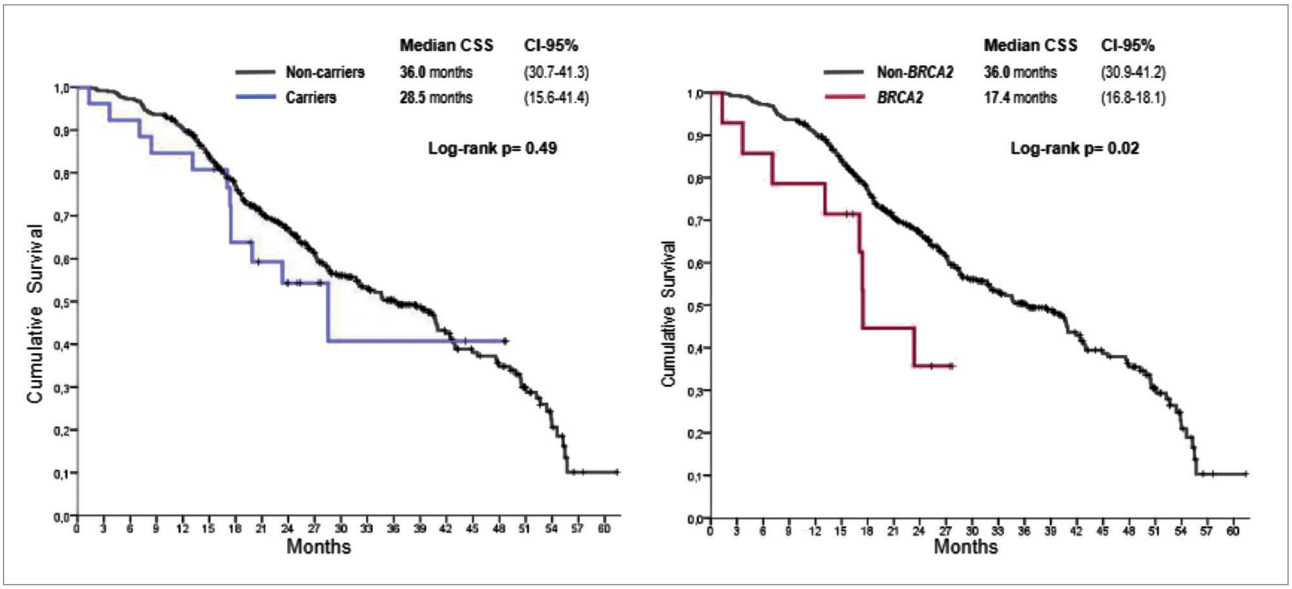

FIGURE 4. Cause-specific survival for presence of germline mutations in mCRPC in the Prorepair-B trial. Survival outcome is depicted for carriers versus non-carriers (left) and for *BRCA2*-carriers versus non-*BRCA-2*-carriers (right).[19]

(96% *vs.* 86%), nodal metastases (48% *vs.* 52%) and visceral metastases (12% *vs.* 16%). After a median follow-up of 36 months, no difference in median cause-specific survival from mCRPC was observed between carriers and non-carriers (28.5 *vs.* 36.0 months; *Figure 4*). Median cause-specific survival and PFS from 1st taxane in carriers and non-carriers as well as 1st androgen receptor targeting therapies were also not different. Patients with a *BRCA2* mutation appeared to have worse outcome (*Figure 4*). However, a larger comparative trial with increased number of carriers is needed to fully assess the impact of germline mutations on the outcome of mCRPC patients.[19]

KEY MESSAGES FOR CLINICAL PRACTICE

1. No survival difference in sorafenib – pazopanib sequence versus pazopanib – sorafenib sequence in 1st-line mRCC treatments can be found. Deferred cytoreductive nephrectomy following neoadjuvant sunitinib in mRCC patients is an option although more data are required concerning effect on OS.
2. Nivolumab plus ipilimumab could become the standard 1st-line treatment option for mRCC as this combination is superior over sunitinib, especially in intermediate/poor-risk patients.
3. TMB can be used for its predictive and prognostic properties during immunotherapy for tumours with a high number of somatic mutations, such as mUC.
4. Pembrolizumab has superiority over various chemotherapeutic agents in mUC after progression on platinum.
5. Post-progression outcome encourages the administration of additional cycles of immunotherapy beyond progression for asymptomatic mUC patients (also applicable for other genitourinary cancers).
6. No definitive conclusion can be drawn for the sequential use of docetaxel and abiraterone acetate in high-risk PCa.
7. DNA repair defects may be used as prognostic markers in mCRPC although further research is needed.

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