Highlights in genitourinary cancers

T. Vermassen[1,2], Rottey S[1,2]
[1]Department of Medical Oncology, Ghent University Hospital, Ghent, Belgium, [2]Drug Research Unit Ghent, Ghent University Hospital, Ghent, Belgium

From the 19th till the 23rd of September, Munich was host for the 2018 ESMO Congress. The central theme of the congress was 'Securing access to optimal cancer care'. This year's venue was attended by more than 25,000 registered attendees. This report will highlight 10 key studies concerning genitourinary cancers presented during the meeting.

DOCETAXEL-BASED CHEMOTHERAPY IN HIGH-RISK LOCALISED PROSTATE CANCER (PCA): UPDATED RESULTS FROM THE GETUG12 PHASE III TRIAL

GETUG-12 assessed docetaxel-estramustine in patients with high-risk localised PCa. A benefit in relapse-free survival (RFS) was reported previously.[1] Updated RFS and assessment of clinical events were presented during ESMO 2018. A total of 413 patients with high-risk localised PCa (treatment-naïve + ≥1 of the following: T3-T4, Gleason ≥8, PSA ≥20 ng/mL, pN+) were randomised to LHRH agonist goserelin for 3 years + 4 cycles of docetaxel 70 mg/m^2 + estramustine 10 mg/kg/day on days 1-5 q3w (ADT+DE arm) or goserelin alone (ADT arm). Local therapy (radiotherapy in 87% of cases) was given at 3 months. After 12 years of follow-up, an event was observed in 233 patients (56%). The twelve-year RFS rate was significantly improved in the ADT+DE arm as compared to the ADT arm: 49% *vs.* 36% (HR: 0.71, p=0.011; *Figure 1*) with a median RFS of 11.6 and 8.1 years, respectively. Subgroup analyses demonstrated a beneficial effect for poor risk tumours (T3-T4, PSA≥20 ng/mL, pN+) except for patient with high Gleason scores. In addition, also the clinical RFS was also significantly improved with ADT+DE (13.9 *vs.* 12.5 years; HR: 0.75; p=0.049; *Figure 1*). The twelve-year metastases-free survival rates (62.2% *vs.* 55.8%) and 12-year PCa-specific survival rates (88.2% *vs.* 83.9%) did not differ significantly between the two study arms.

In conclusion, 4 cycles of docetaxel-based chemotherapy reduce the risk of clinical relapse or death in men with high-risk localised PCa although this provides no benefit for metastases-free and PCa-specific survival.[2]

TREATMENT REGIMENS FOR METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC): WHAT'S NEW?

Abiraterone acetate (AA) is known to improve the progression-free (PFS) and overall survival (OS) in men with mCRPC. Ra-223 also increases the OS and decreases symptomatic skeletal events (SSE) in men with mCRPC and bone metastases. In the ERA223 phase III trial, the concurrent treatment with AA and Ra-223 was evaluated in asymptomatic / mildly symptomatic men with chemotherapy-naïve mCRPC and bone metastases. In total, 806 patients were randomised (1:1) to AA + Ra-223 (N= 401) or AA + placebo (N= 405). Following the complete study-specified Ra-223/placebo treatment, the trial was unblinded as more fractures and deaths were observed in the AA + Ra-223 arm. At the primary analysis, the median SSE-free survival (22.3 *vs.* 26.0 months) and the median OS (30.7 *vs.* 33.3 months) were not significantly different

Please send all correspondence to: Prof. Dr. Sylvie Rottey; Department of Medical Oncology; Ghent University Hospital; C. Heymanslaan 10; B–9000 Ghent; Tel: +32 (0)9/332 26 92; Fax: +32 (0)9/332 62 85; E-mail: Sylvie.Rottey@UGent.be.

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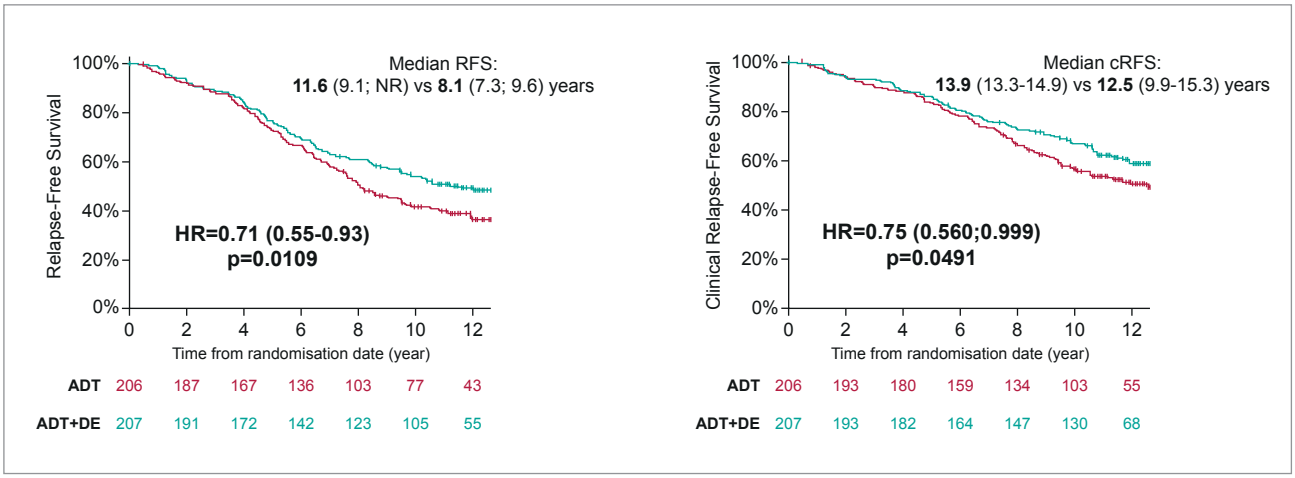

FIGURE 1. Survival outcome of LHRH agonist goserelin for 3 years plus 4 cycles of docetaxel + estramustine vs goserelin alone for high-risk localized PCa. RFS is depicted on the left; clinical RFS is depicted on the right.[2]

between Ra-223 and placebo. No benefits were found for other exploratory endpoints. Fractures occurred in 29% and 11% of patients for Ra-223 and placebo, respectively, with more fractures observed in patients who did not receive bone health agents at baseline. Based on the safety and survival results, the combination of AA and Ra-223 is not recommended for the treatment of asymptomatic / mildly symptomatic bone-predominant mCRPC.[3]

The optimal treatment for poor prognosis mCRPC is undefined and includes either taxane chemotherapy or androgen receptor (AR) targeted therapy, emphasizing the need for predictive biomarkers. A presented phase II trial compared cabazitaxel (CABA) with AA or enzalutamide (ENZ) in this setting and looked for any genomic correlations with the treatment outcome. Patients with poor prognosis mCRPC (i.e. liver metastases, early CRPC [<12 months from ADT start], and/or >3 of 6 poor prognostic criteria[4]) were randomised to receive CABA (N= 45) or AA/ENZI (N= 50) with cross over at progression. No prior AA or ENZ use was permitted. The median duration of therapy was 5.8 with CABA as compared to 4.5 months with AA/ENZ. Treatment discontinuation reasons included disease progression (40% *vs.* 46%) and toxicity (11% *vs.* 4%). The clinical benefit rate was higher with CABA than what was seen with AA/ENZ (90% *vs.* 70%, p= 0.02). No difference was observed in terms of PSA decline ≥50% (56% *vs.* 60%), objective response rate (ORR) (11% *vs.* 12%), time to progression (5.3 *vs.* 4.1 months) and OS (not reached *vs.* 15.5 months). The baseline circulating tumour DNA (ctDNA) fraction (30-100%; 2-30% and undetected) was found to be correlated with both the time to progression (medians 2.8, 5.3 and 8.6 months; respectively) and the OS (medians 9.9, 22.0 months and not reached, respectively). Furthermore, an on-treatment change in the ctDNA fraction appeared also had prognostic value for both PFS and OS (p= 0.001). In addition, AR amplification number showed no effect towards treatment choice.

Based on these findings, no definitive treatment choice can be selected for poor prognosis mCRPC patients as CABA and AA/ENZ resulted in similar outcomes. The study did reveal that ctDNA has potential as a prognostic factor in these patients, but this needs further validation.[5]

TREATMENT OF NEWLY HORMONE SENSITIVE mPCa: WHAT TO CHOOSE?

Based on the LATITUDE trial[6] AA is licenced in the EU for use in high risk newly diagnosed hormone sensitive mPCa, despite contradictory outcomes in the STAMPEDE trial.[7] A study presented at ESMO 2018 retrospectively evaluated the heterogeneity of AA on OS and failure-free-survival (FFS) in patients with LATITUDE defined high & low-risk metastatic disease who were randomised to ADT or ADT + AA in the STAMPEDE trial. Staging scans of 901 eligible patients were evaluated centrally for patients randomised to ADT or ADT + AA. Patients were classified as low (N= 428) or high risk (N= 473) according to the LATITUDE criteria. A secondary differential analysis by tumour volume (high/low) was done using the criteria defined in CHAARTED. The median follow-up for this analysis was 41.5 months. Patients treated with ADT + AA showed clinically and statistically significant FFS and OS improvements in both high- (HR_{FFS} = 0.31 [95%CI: 0.25-0.39]; HR_{OS} = 0.54 [95%CI: 0.41-0.70]) and low- (HR_{FFS} = 0.24 [95%CI: 0.17-0.33]; HR_{OS} = 0.66 [95%CI: 0.44-0.98]) risk groups. In addition, benefits were also observed in terms of PCa-specific survival. No evidence of heterogeneity was detected between risk groups. Similar results were obtained using the CHAARTED definition.[8]

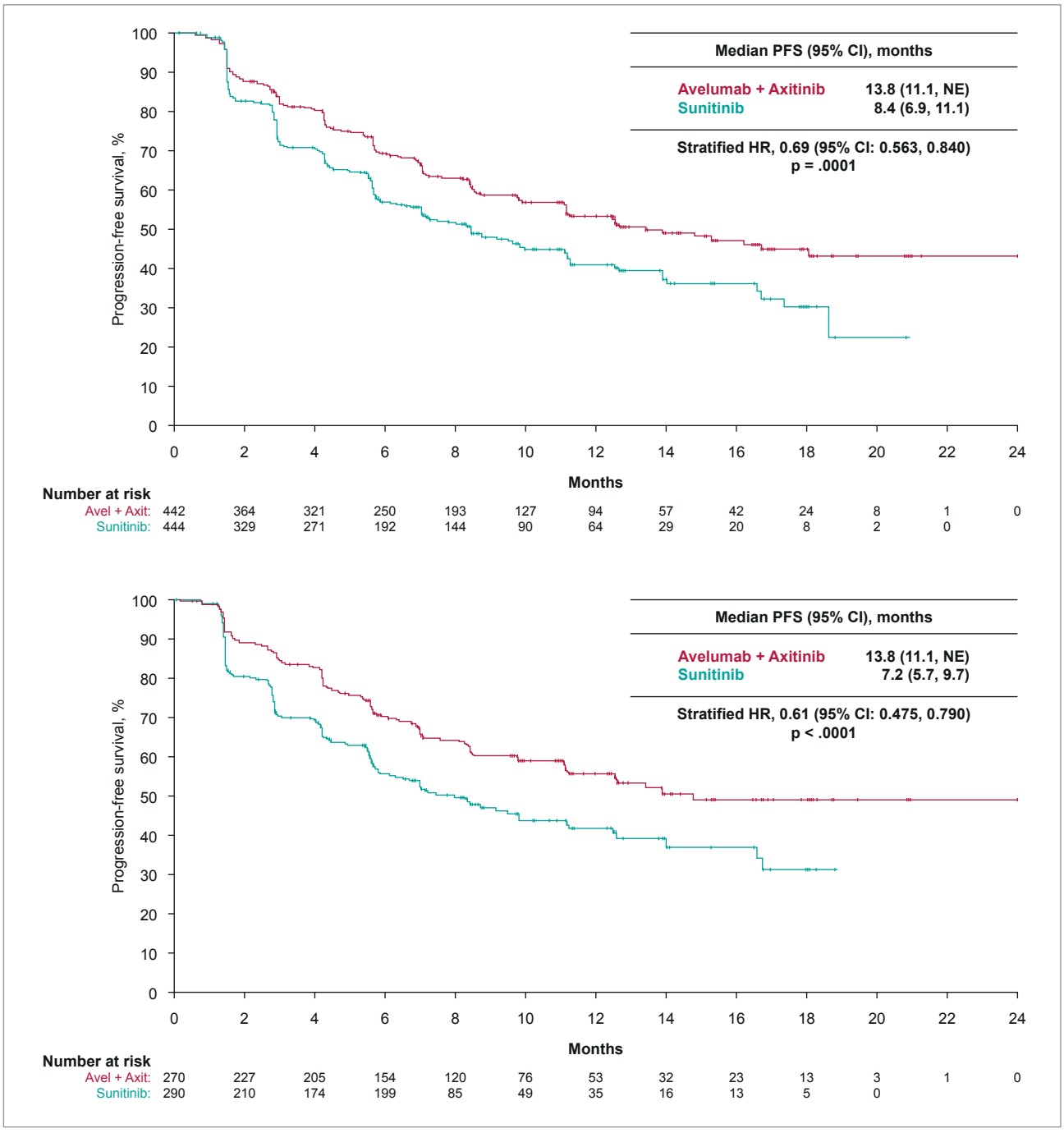

FIGURE 2. Survival outcome between avelumab + axitinib and sunitinib for first-line treatment of advanced RCC. PFS is depicted on the top; PFS in PD-L1+ tumours is depicted on the bottom.[11]

In addition, it was hypothesised that local radiotherapy could improve the OS of men presenting with hormone sensitive mPCa, especially in men with low metastatic burden. In the STAMPEDE trial, 2061 men with newly-diagnosed mPCa were randomised (1:1) to ADT (with early docetaxel) or ADT + radiotherapy (55Gy/20f/4w or 36Gy/6f/6w). Metastatic burden was well balanced (40% low, 54% high, 6% unknown). Local radiotherapy was found to improve the FFS (HR[95%-CI]: 0.76[0.68-0.84]) but not the OS (HR[95%CI]: 0.92[0.80-1.06]). Further analyses highlighted an increased OS in patients with low metastatic burden (HR[95%CI]: 0.68[0.52-0.90]) but this was not the case in the subgroup of patients with a high metastatic burden (HR[95%CI]: 1.07[0.90-1.28]). No difference between both arms was observed in time from randomisation to next life-prolonging treatment nor in time from randomisation to first symptomatic local event. Local radiotherapy was well tolerated with only 5% grade 3/4 adverse events (AEs).[9]

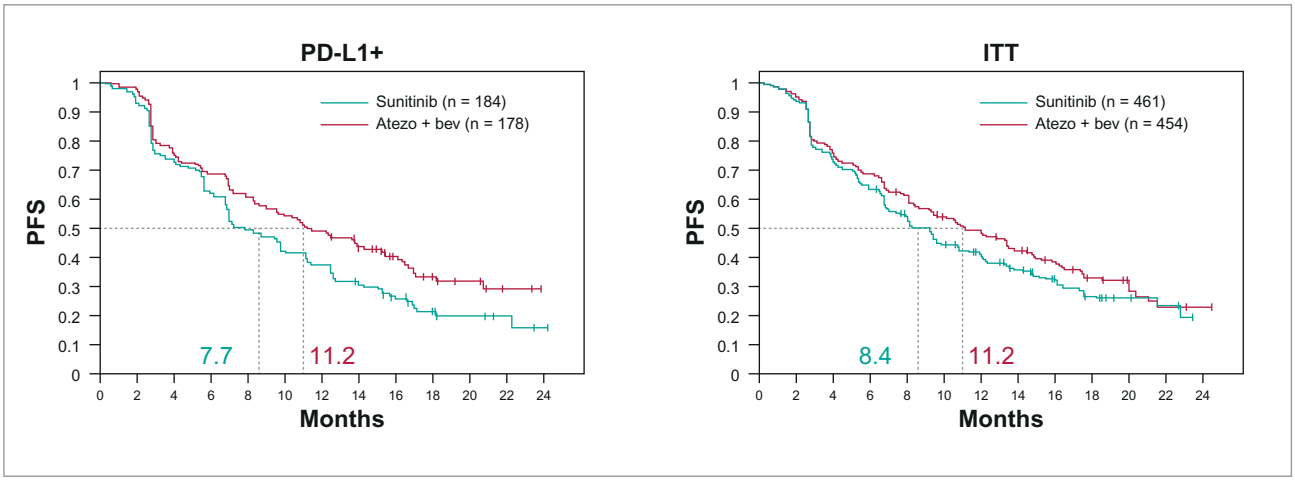

FIGURE 3. PFS outcome between atezolizumab + bevacizumab and sunitinib for first-line treatment of advanced RCC. PFS for PD-L1+ tumours is depicted on the left; PFS for the ITT population is depicted on the right.[13]

Based on these results, ADT + local radiotherapy could be offered to patients presenting with oligometastatic hormone sensitive PCa. On the other hand, adding AA to ADT in the same patient population shows a significant benefit in outcome, irrespective of risk classification.

IMMUNOTHERAPY AS FIRST-LINE TREATMENT FOR ADVANCED RENAL CELL CARCINOMA (RCC)?

A phase Ib trial of first-line avelumab + axitinib showed encouraging antitumour activity for patients with advanced RCC.[10] The outcome with this treatment regimen was further evaluated in the phase III JAVELIN trial. A total of 886 patients (clear-cell, ECOG ≤ 1, no prior systemic therapy) were randomised (1:1) to avelumab (10 mg/kg IV q2w) plus axitinib (5 mg PO BID) or sunitinib (50 mg PO QD q4/6w). Patients were stratified according to IMDC risk criteria (favourable 21%, intermediate 62%, poor 16%). The ORR was 51% with the avelumab-axitinib combination as compared to 26% with sunitinib (p< 0.001). The median PFS was 13.8 months with the immunotherapy-containing regimen, which was significantly longer than the 8.4 months median PFS seen with sunitinib (HR[95%CI]: 0.69[0.56-0.84]; *Figure 2*). Among patients with PD-L1⁺ tumours (≥ 1% of immune cells), the ORR was significantly higher in the avelumab + axitinib arm compared to sunitinib (55% *vs.* 26%) and the median PFS was almost twice as long with the experimental regimen (13.8 *vs.* 7.2 months; HR[95%CI]: 0.61[0.48-0.79]; *Figure 2*). This PFS benefit was seen irrespective of IMDC risk criteria. At the time of the presentation, the OS data were not yet mature. The incidence of grade 3/4 AEs was comparable in both arms (71.2% *vs.* 71.5%), although a higher rate of treatment discontinuation was observed with avelumab + axitinib arm (22.8% *vs.* 13.4%). Nevertheless, due to the promising results avelumab + axitinib can be considered as a first-line treatment option provided that a beneficial result for OS is found.[11]

Atezolizumab + bevacizumab previously demonstrated to induce an improved PFS as compared to sunitinib in the first-line treatment of patients with mRCC expressing PD-L1.[12] The hypothesis that RNA gene expression signatures could be associated with a differential outcome to therapy was tested in the IMmotion 151 trial and the results of this analysis were presented at ESMO 2018. In this study, patients were randomised (1:1) to atezolizumab (1200mg IV q3w) + bevacizumab (15mg/kg IV q3w) (N= 454) or sunitinib (50 mg PO QD q4/6w) (N= 461). Tumour gene expression was performed in 823 patients. Both the angiogenesis and $T_{effector}$ gene expression signatures were distributed equally according to MSKCC risk groups. The median PFS was longer with atezolizumab + bevacizumab than with sunitinib both in the PD-L1⁺ patients (11.2 *vs.* 7.7 months; HR[95%CI]: 0.74 [0.57-0.96]) as in the intention-to-treat (ITT) population (11.2 *vs.* 8.4 months; HR[95%CI]: 0.83[0.70-0.97]; *Figure 3*). This PFS benefit was seen irrespective of MSKCC risk status and was particularly pronounced in patients with sarcomatoid tumour types. Subdividing according to the angiogenesis gene expression resulted in an improved PFS outcome for atezolizumab + bevacizumab in the $angiogenesis^{Low}$ group but not in the $angiogenesis^{High}$ group. Furthermore, focussing within each treatment arm, the PFS was higher for $angiogenesis^{High}$ patients versus $angiogenesis^{Low}$ patients treated with sunitinib, whereas no difference in PFS outcome was found in the atezolizumab + bevacizumab arm according to the angiogenesis gene expression signature. Vice versa, looking at the $T_{effector}$ gene expression resulted in an improved PFS outcome

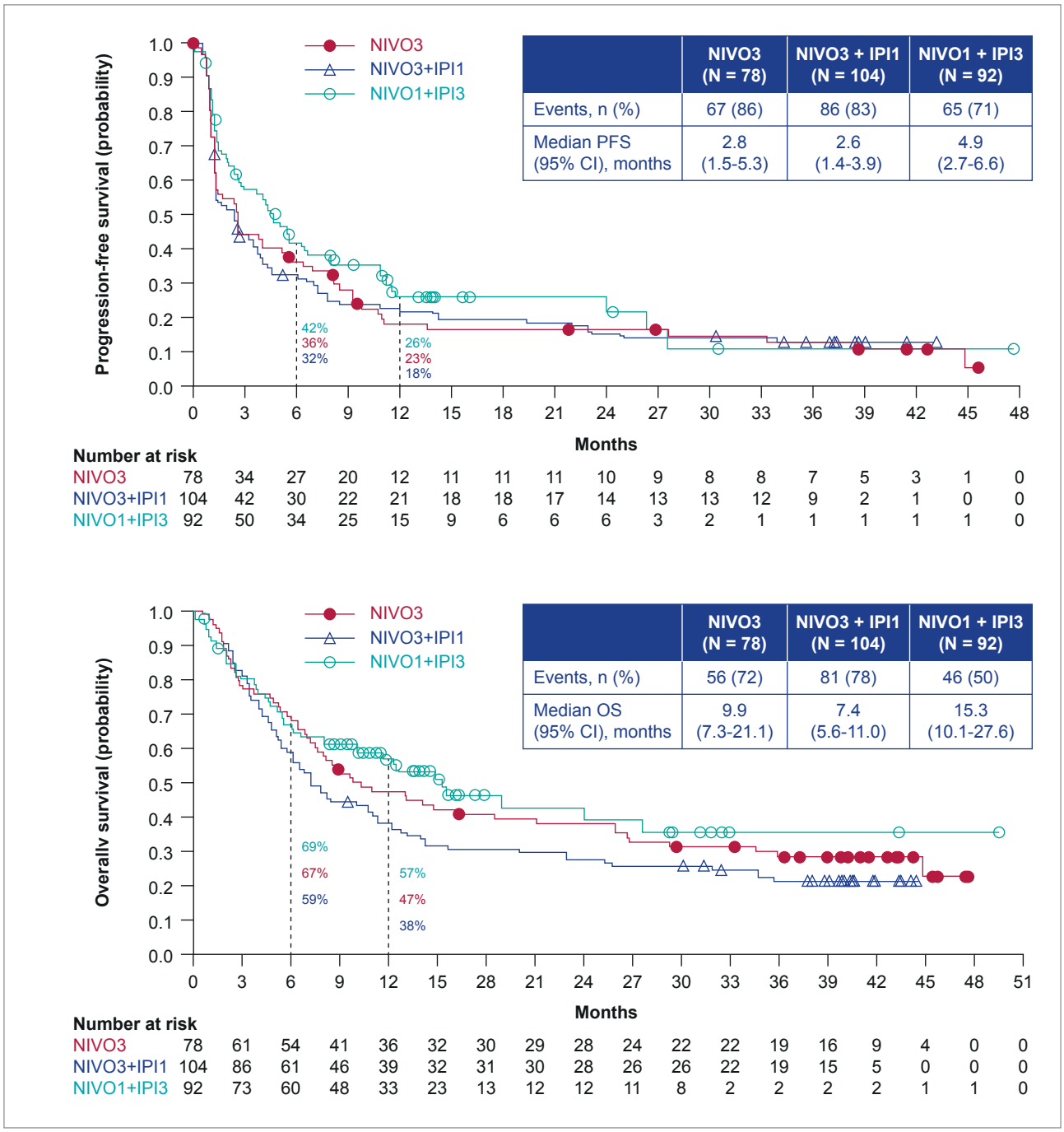

FIGURE 4. Survival outcome between nivolumab NIVO3, NIVO3/IPI1 and NIVO1/IPI3 for platinum pre-treated mUC. PFS is depicted on the top; OS is depicted on the bottom.[16]

for atezolizumab + bevacizumab in the $T_{effector}^{High}$ group but not in the $T_{effector}^{Low}$ group. No PFS benefit was observed for $T_{effector}^{High}$ versus $T_{effector}^{Low}$ in each treatment arm.

These results validate molecular signatures that differentiate clinical outcomes with VEGF inhibition and immunotherapy. This represents a next step towards personalised therapy in patients with mRCC. Further validation of these findings is warranted.[13]

ADJUVANT AXITINIB FOR HIGH RISK OF RECURRENT RCC: OUTCOME IN THE PHASE III ATLAS TRIAL

Axitinib is approved as second-line treatment for patients with advanced RCC. The question remains if this targeted therapy could also be used as an adjuvant therapy in RCC with high risk of recurrence. In the study at hand, 724 patients with RCC (nephrectomy; >50% clear-cell RCC; no re-

KEY MESSAGES FOR CLINICAL PRACTICE

1. Concurrent docetaxel and ADT for high risk localised PCa has no impact on PCa-specific survival and is therefore not considered as viable treatment.
2. Concurrent abiraterone acetate and Ra-223 for (a)symptomatic bone-predominant mCRPC is not recommended due to lack in survival outcome and a worse safety profile.
3. No clear treatment choice exists for AR targeted therapy-naïve poor risk mCRPC as non-inferiority for cabazitaxel vs. abiraterone acetate/enzalutamide was observed.
4. ctDNA fraction might be of use as a prognostic marker for treatment of poor-risk mCRPC although further validation is warranted.
5. Abiraterone acetate + ADT is usable in high-risk, newly diagnosed hormone sensitive mPCa, irrespective of LATITUDE, STAMPEDE or CHAARTED criteria.
6. Both avelumab + axitinib and atezolizumab + bevacizumab yield encouraging results as first-line therapy for mRCC. This further complicates the first-line treatment choice in this setting. Extensive prospective comparison of newly available first-line regimens is therefore warranted.
7. Gene expression signatures for differential outcome in mRCC could be used in several subgroups although further research is still needed.
8. Adjuvant axitinib is not advised for high risk recurrent RCC as no survival benefit is observed with an increase in toxicity profile.
9. Checkpoint inhibition is a valid treatment option in mUC. Furthermore, combination of checkpoint inhibitors (nivolumab + ipilimumab) is effective in platinum pre-treated mUC with a manageable safety profile. Phase III evaluation of this combination in platinum-naïve mUC is ongoing.

sidual disease or mRCC) were randomised (1:1) to receive axitinib 5 mg PO BID (n=363) or placebo (n=361) for up to 3 years. Dose alterations were allowed. Most patients were Asian (73%), their median age was 58 years and highest risk was defined as pT3 with Fuhrman grade ≥3 or pT4 and/or N1 with any Fuhrman grade (57%). No difference in disease-free survival was observed, neither for the ITT population (both not reached; HR[95%CI]: 0.87[0.66-1.15]) nor for the predefined high-risk patients (both not reached; HR[95%CI]: 0.74[0.53-1.03]). OS data were immature at time of the interim analysis. Notably, more AEs (98.6% *vs.* 92.5%), serious AEs (19.4% *vs.* 14.5%), grade 3/4 AEs (61.2% *vs.* 30.1%), dose reductions (56.2% versus 8.4%), dose interruptions (51.4% *vs.* 21.7%) and treatment discontinuations due to AEs (23.3% *vs.* 11.1%) were seen with axitinib than with placebo, with hypertension being the most common AE.

In retrospect to these findings, axitinib should not be considered as adjuvant therapy for patients with RCC at high risk of recurrence.[14]

CHECKPOINT INHIBITION IN UROTHELIAL CANCER (UC): RECENT FINDINGS

Combination of checkpoint inhibitors is promising in several malignancies. Early results from the phase I/II CheckMate 032 trial in platinum-pre-treated mUC have proven effective.[15] At ESMO 2018 results from the expanded cohorts and extended follow-up data were presented. Patients (previously platinum-treated, measurable disease, ECOG ≤1) were randomised to nivolumab (3mg/kg q2w) (NIVO3, N= 78), nivolumab (3mg/kg) + ipilimumab (1mg/kg q3w for 4 cycles) followed by nivolumab (3mg/kg q2w) (NIVO3/IPI1, N= 104), or nivolumab (1mg/kg) + ipilimumab (3mg/kg q3w for 4 cycles) followed by nivolumab (3mg/kg q2w) (NIVO1/IPI3, N= 92) until disease progression or unacceptable toxicity. The reported ORR was 26%, 27%, and 38% for NIVO3, NIVO3/IPI1 and NIVO1/IPI3, respectively, with ongoing responses in 45%, 46% and 66% of patients. The ORR was similar among patients with PD-L1^{+} (≥1%) and PD-L1^{-} tumours for NIVO3 (27% *vs.* 26%) and NIVO3/IPI1 (35% *vs.* 25%) but differed

significantly for NIVO1/IPI3 (58% *vs.* 24%). Next, the median PFS (4.9 *vs.* 2.8 *vs.* 2.6 months) and median OS (15.3 *vs.* 9.9 *vs.* 7.4 months) were also longer with NIVO1/IPI3 than with NIVO3 and NIVO3/IPI1 (*Figure 4*). Grade 3/4 treatment-related AEs occurred in 27%, 31% and 39% of patients for NIVO3, NIVO3/IPI1 and NIVO1/IPI3, respectively.

These results show efficacy of all investigated treatment regimens, with favour for NIVO1/IPI3, in platinum pre-treated mUC with manageable safety profile. A large phase III trial is currently ongoing to compare NIVO1/IPI3 with chemotherapy in previously untreated mUC (CheckMate 901).[16]

Finally, it has been hypothesised that activation of the PD-1/PD-L1 axis is involved in resistance to Bacillus Calmette-Guérin (BCG) therapy. This hypothesis was tested in patients with BCG-unresponsive non–muscle invasive bladder cancer who were treated with checkpoint inhibition. At the time of the analysis, 103 patients (BCG-unresponsive, carcinoma-in-situ ± papillary disease, adequate BCG therapy, no radical cystectomy) were enrolled in the single-arm phase II KEYNOTE-057 trial and received pembrolizumab 200 mg q3w for 24 months or until recurrence, progression, or unacceptable toxicity. At first radiographic evaluation (including 97 evaluable patients) the complete response (CR) rate was 39%. The median duration of response was not reached and 80% of patients had an ongoing response duration of 6 months or more. Treatment-related AEs occurred in 65 patients (immune-mediated in 15 patients), with pruritus (11%), fatigue (10%) and diarrhoea (9%) being the most common. Treatment-related grade 3-5 AEs occurred in 13 patients with 1 treatment-related death.

Given to the encouraging anti-tumour activity of pembrolizumab in this setting, the aforementioned hypothesis might be valid and pembrolizumab could be an ideal treatment option in this patient population. Further research is warranted as the KEYNOTE-057 is ongoing. A phase III trial (KEYNOTE-676) with a similar patient population is planned.[17]

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