June 3-7, 2016
McCormick Place | Chicago, Illinois
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SPECIAL EDITION

Highlights in genitourinary cancers

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From June 3rd till June 8th, Chicago was host for the 52nd ASCO annual meeting. The theme for this year's venue was 'Collective Wisdom: The Future of Patient-Centred Care and Research'. With almost 35,000 registered attendees from over 100 countries worldwide and about 6,000 submitted abstracts, this year's meeting was a great success. This report will highlight 10 key studies concerning genitourinary cancers presented during the meeting.

(Belg J Med Oncol 2016;10(5):162-169)

Atezolizumab in cisplatin-ineligible locally advanced/metastatic urothelial carcinoma: primary analysis of IMvigor210 cohort 1

Cisplatin-based chemotherapy is a standard first-line treatment for metastatic urothelial carcinoma (mUC) and the only treatment that prolongs the median overall survival (mOS). Due to age or comorbidities, 30-50% of patients are ineligible for this regimen and receive no treatment. A total of 119 chemotherapy-naïve and cisplatin-ineligible mUC patients (renal glomerular filtration rate between 30 and 60 mL/min, hearing impairment, ≥G2 peripheral neuropathy or ≥ Eastern Cooperative Oncology Group performance status [ECOG PS] 2) received atezolizumab, an active and well tolerated immunotherapy in platinum-treated mUC, 1200 mg IV q3w until disease progression. The primary efficacy endpoint was confirmed objective response rate (ORR) according to the RECIST v1.1 criteria while the secondary endpoints included OS. In the cohort, 18% received prior systemic treatment; 10% previously had radiotherapy and 66% suffered from visceral metastases. The median follow-up in the study was 14.4 months (range 0.2-20.1 months). The ORR for all patients was 24% (95% CI[16%-32%]) of which 7% had a complete response (CR). Responses occurred in all investigated subgroups, irrespective of immune cell PD-L1 expression (ORR=21%, 25% and 28% for IC0, IC1/2/3 and IC2/3, respectively) (*Figure 1*) and poor prognostic factors. The mOS was 14.8 months (95%CI: 10.1 months - not estimable). Overall, atezolizumab was well tolerated with 66% and 15% treatment-related all grade and grade 3/4 adverse events (AEs), respectively. These data prove the clinical utility of atezolizumab in first-line cisplatin-ineligible mUC patients, making it an attractive alternative to chemotherapy. Further research comparing atezolizumab to chemotherapy in first-line is however needed.

CheckMate 032: efficacy and safety of nivolumab monotherapy in metastatic urothelial carcinoma

Minimal activity of the existing therapies in combination with the demonstrated immune dysfunction in UC have prompted the evaluation of immunotherapy in this malignancy. Nivolumab, a fully human IgG4 programmed death-1 (PD-1) immune checkpoint inhibitor antibody, previously demonstrated a survival benefit in patients with melanoma, lung cancer, and renal cell carcinoma. Building on this success, the efficacy and safety of this antibody was determined in a multicentre phase I/II study with mUC patients after ≥1 prior line of platinum-based therapy. Seventy-eight patients received nivolumab 3 mg/kg IV q2w until progression or discontinuation. The primary endpoint was ORR (RECIST v1.1), while the other objectives included safety, duration of response, progression-free

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

Keywords: Urothelial cancer, prostate cancer, renal cell carcinoma, immunotherapy, circulating tumour cells.

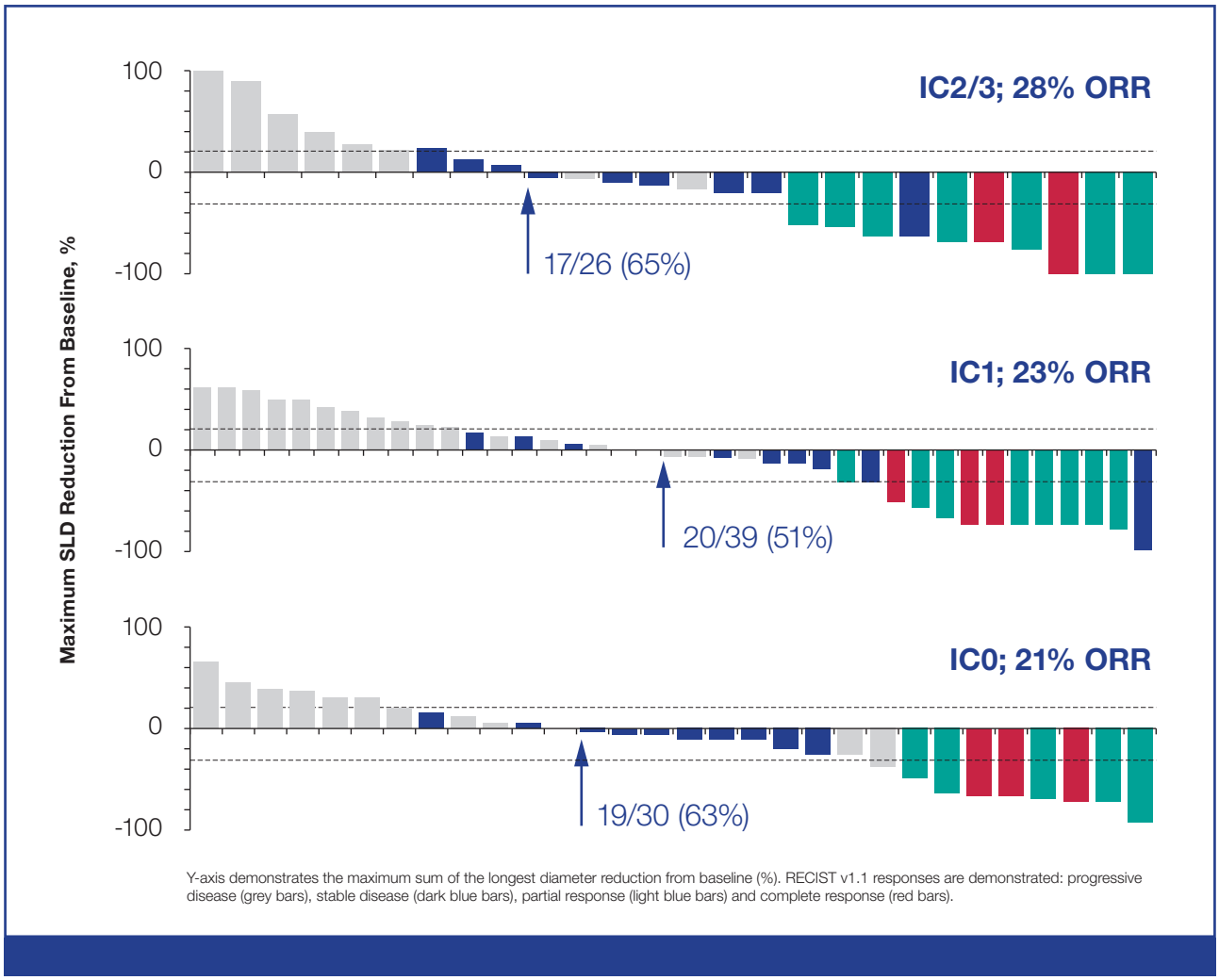

Figure 1. Efficacy of atezolizumab in mUC across subgroups according to immune cell PD-L1 expression.[1]

survival (PFS), and OS. With a median follow-up of 9.0 months (range 0.7-16.6 months), 23.1% of patients remained on nivolumab monotherapy. The ORR was 24.4% (95%CI: 15.3%-35.4%) with a CR in 6.4% and a mPFS of 2.8 months (95%CI: 1.5-5.9 months). The median OS in this study was 9.7 months (95%CI: 7.3-16.2 months). The level of tumoral PD-L1 expression (<1% or ≥1%) was not correlated with the ORR, with an ORR of 26.2% in patients with a PD-L1 expression <1% and of 24.0% in the subgroup expressing PD-L1 in ≥1% of the cells (*Figure 2*). Grade 3/4 treatment-related AEs occurred in 22% of patients, with increased lipase, fatigue, maculopapular rash and nausea as most frequently reported AEs.

In summary, nivolumab monotherapy demonstrated promising efficacy and acceptable safety in previously treated mUC patients and could become a treatment option in these patients.[2]

Safety and efficacy of durvalumab in urothelial carcinoma

Another possible immunotherapy candidate in UC consists of the modified human IgG1 mAb durvalumab, blocking the PD-L1 binding to PD-1 and CD80. In total 61 inoperable or mUC patients (ECOG PS 0-1), who did not previously receive an anti-PD-1/PD-L1 agent, were treated with durvalumab 10 mg/kg IV q2w for up to 12 months. The primary endpoint was ORR (RECIST v1.1). Half of patients (51%) received ≥2 prior systemic treatments. After a median follow-up of 6.5 months (range 0.8-14.8 months), 42 patients were evaluable for response, demonstrating an ORR 31% (N=13). Tumour and immune cell PD-L1 expression both appeared to independently enrich for treatment response as all responders were tumour or immune cell PD-L1 positive (*Figure 3*). Currently, 12 patients continue to respond to treatment with the longest dura-

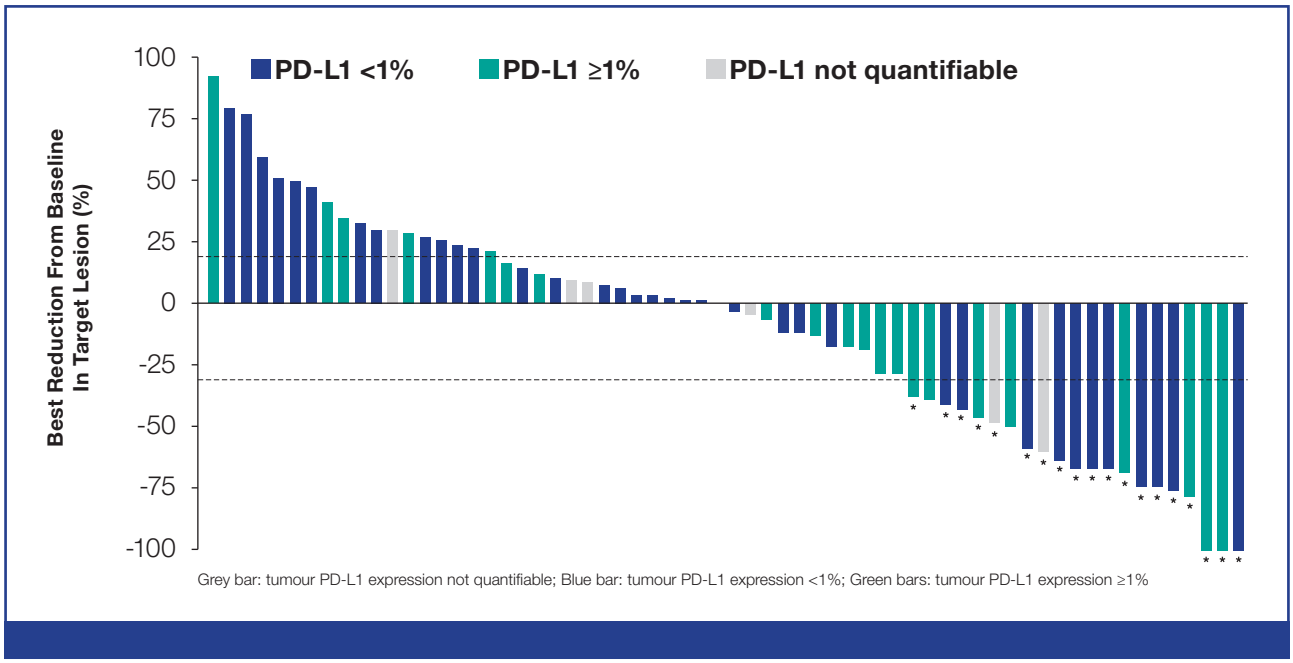

Figure 2. Efficacy of nivolumab in mUC across subgroups according to tumour PD-L1 expression.[2]

tion of response ongoing after more than 11.3 months. Drug-related AEs occurred in 64% of patients with fatigue and diarrhoea as the most frequently reported AEs. Only 5 drug-related grade 3/4 AEs were reported. Durvalumab showed an acceptable safety profile with evidence of clinical activity in heavily pretreated UC patients.[3]

Together with previous described studies, immunotherapies could be a viable treatment option in advanced or mUC.

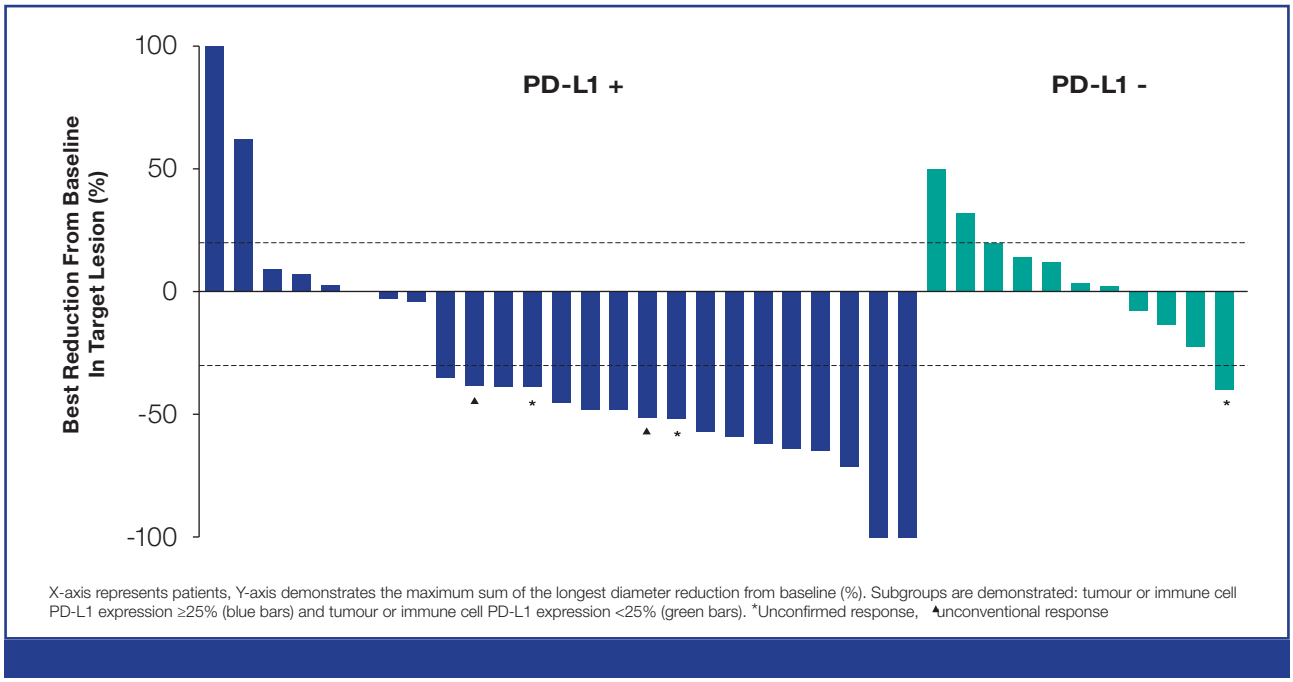

Figure 3. Efficacy of nivolumab in mUC across subgroups according to tumour PD-L1 expression.[2]

CHAARTED: quality of life analysis in chemo-hormonal androgen ablation for prostate cancer

Previously, androgen deprivation therapy (ADT) plus docetaxel for metastatic hormone sensitive prostate cancer was shown to improve the mOS as compared to ADT alone. However, docetaxel shows multiple AEs that can diminish the quality of life (QoL). In this study, 790 prostate cancer patients were randomised 1:1 to 6 cycles ADT plus docetaxel or ADT. The QoL was assessed at baseline and 3, 6, 9 and 12 months post randomisation and compared between both study arms. ADT plus docetaxel was associated with significantly worse FACT-P scores at 3 months (p=0.02), yet significantly better scores were reported after 12 months of therapy (p=0.04). Also FACIT-fatigue at 3 months was worse in patients who received ADT plus docetaxel (p=0.01) compared to ADT. However, after 12 months no difference was observed (p=0.32). FACT-taxane scores were lower in patients receiving ADT plus docetaxel (p<0.02). BPI scores did not differ significantly between arms over time. Emotional well-being was better in patients on ADT plus docetaxel at all time points (p<0.01).

In summary although ADT plus docetaxel was associated with a decreased QoL at 3 months, the 12-month QoL was better for patients receiving ADT plus docetaxel compared to ADT alone.[4]

Survival results from the PRINCE phase III trial

This randomised phase III trial investigated the non-inferiority of intermittent docetaxel compared to a continuous docetaxel treatment for patients with metastatic castration-resistant prostate cancer (mCRPC). A total of 156 eligible patients were randomised 1:1 to docetaxel IV 35 mg/m² q1w or 70 mg/m² q3w. Continuous docetaxel was given until discontinuation while the intermittent arm received docetaxel for 12 weeks and then paused until clinical disease progression (increased serum PSA >4 μg/L with a 50% increase over baseline level, radiological or symptomatic progression). The primary endpoint was one-year OS rate, with OS, PFS, median time to treatment failure and toxicity as key secondary endpoints. The one-year survival rate was 75% (95%CI: 64%-85%) in the continuous arm as compared to 78% (95%CI: 67%-88%) in the intermittent arm. Al-

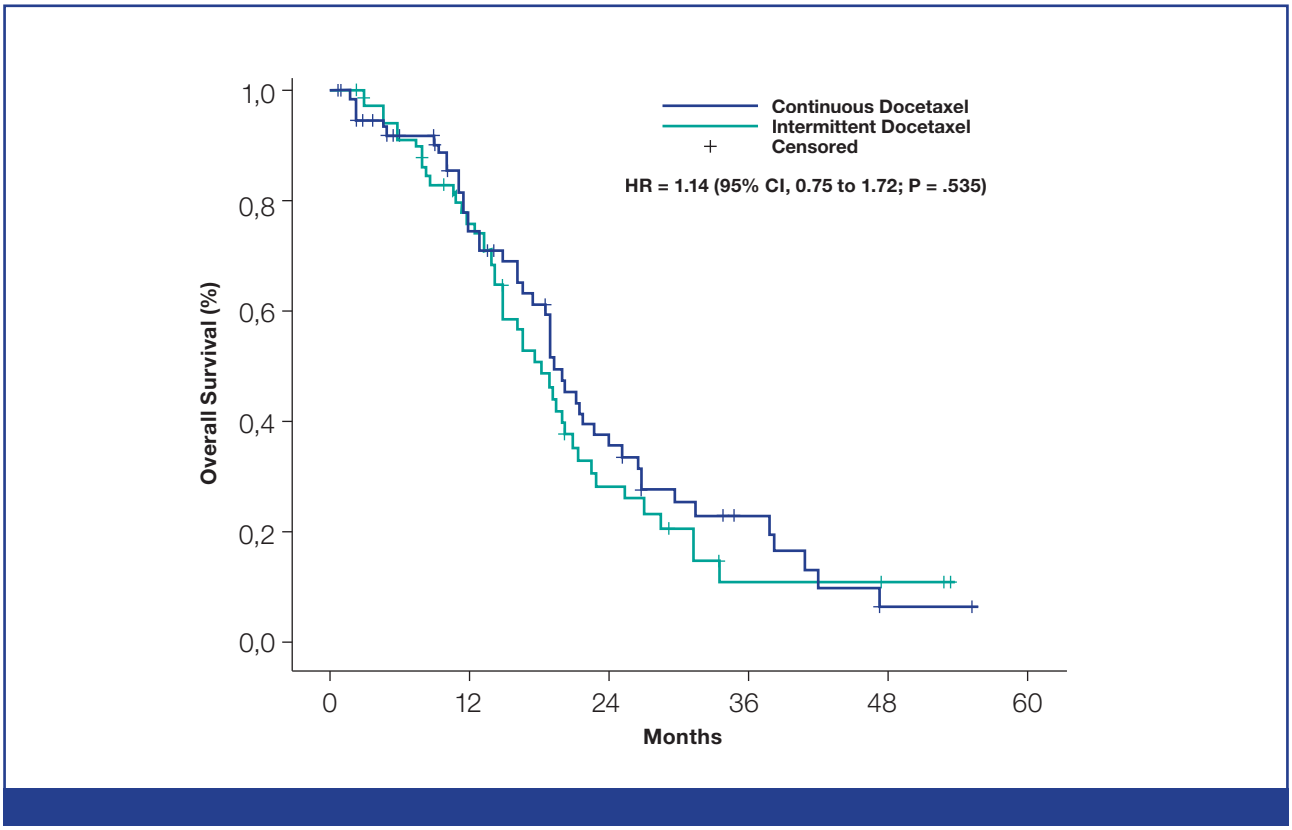

Figure 4. Overall survival of continuous versus intermittent docetaxel in CRPC. No difference was observed in one-year OS or in mOS between continuous and intermittent docetaxel regimen in CRPC.[5]

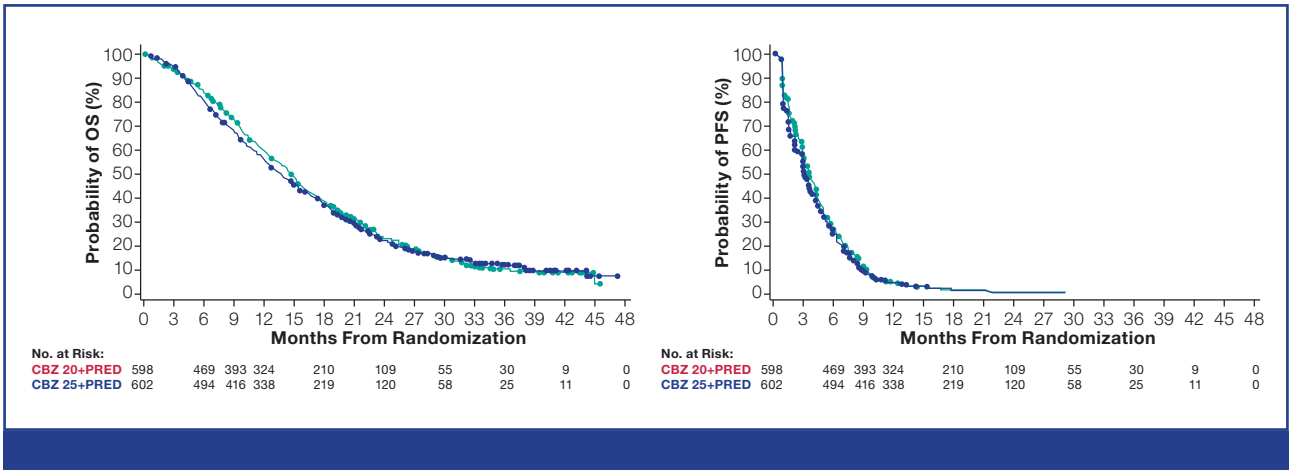

Figure 5. Overall (left) and progression free survival (right) of different cabazitaxel regimens in mCRPC. No difference was observed in mOS or in mPFS between both regimens.[7]

so the median OS was comparable between both arms: 18.3 *vs.* 19.3 months (p=0.535) (*Figure 4*). No significant difference was observed in median PFS or time to treatment failure and the safety profile was comparable for both study arms. As such, intermittent docetaxel was shown to be non-inferior to a continuous therapy with respect to one-year survival and could represent a treatment option for patients with mCRPC.[5]

PROSELICA: Non-inferiority in overall survival for different doses of cabazitaxel in mCRPC

Cabazitaxel showed utility in mCRPC patients previously treated with docetaxel.[6] In the presented phase III study the efficacy and safety profile of 2 different doses of cabazitaxel was determined in 1,200 mCRPC patients who progressed after treatment with docetaxel. Patients with an ECOG PS of 0–2 were randomised 1:1 to cabazitaxel 20 mg/m^2 IV q3w (C20, N=598) or cabazitaxel 25 mg/m^2 IV q3w (C25, N=602). Both groups additionally received prednisone 10 mg PO daily. The primary endpoint was OS, while secondary endpoints included PFS, PSA response, ORR and AEs. Both the median OS (13.4 *vs.* 14.5 months) and median PFS (2.9 *vs.* 3.5 months) did not differ significantly between C20 and C25 (*Figure 5*). Of note, a subgroup analysis favoured C25 in patients who received prior enzalutamide or abiraterone acetate therapy, although this was not significant. In contrast to the findings in OS and PFS, the PSA response (42.9% *vs.* 29.5%) and ORR (23.4% *vs.* 18.5%) were notably higher in C25 as compared to C20. Grade 3/4 AEs were reported more frequently with C25 (54.5%) as compared to C20 (39.7%).[7]

In summary, the non-inferiority to C25 and the improved overall safety profile makes C20 a candidate as treatment option in this cohort of patients.

Comparing cabazitaxel to docetaxel: overall survival results from the FIRSTANA trial

In contrast to PROSELICA, another study assessed the clinical utility of cabazitaxel in chemotherapy-naive mCRPC patients, with little to no patients having received prior enzalutamide or abiraterone acetate treatment. In this three-arm phase III trial 1,168 chemotherapy-naive patients were randomised 1:1:1 to C20 (N=391) or C25 (N=389) or docetaxel 75 mg/m^2 IV q3w (N=388). All groups additionally received prednisone 10 mg PO daily. The primary endpoint was OS, while secondary endpoints included safety, PFS, tumour response (according to RECIST v1.1), PSA response, time to skeletal-related events and QoL. At the time of the analysis, the median OS was 24.5 months for C20, 25.2 months for C25 and 24.3 months for docetaxel. Resulting hazard ratios were 1.01 (95%CI: 0.85-1.20; p=0.997) for C20 *vs.* docetaxel and 0.97 (95%CI: 0.82-1.16, p=0.757) for C25 *vs.* docetaxel. The median PFS was 4.4 months for C20, 5.1 months for C25 and 5.3 months for docetaxel (p>0.05). The rate of tumour response was superior in C25 (41.6%) as compared to docetaxel (30.9%) (p=0.037) while all other secondary endpoints did not differ significantly across the patient cohorts. Grade 3/4 AEs were observed in 41.2% in C20, 60.1% in C25 and 46.0% in docetaxel of patients with

mostly febrile neutropenia, diarrhoea and haematuria in C20/25 compared to peripheral neuropathy, peripheral oedema, alopecia and nail disorders in docetaxel. The authors concluded that C20 and C25 did not demonstrate superiority for OS compared to docetaxel in mCRPC patients.[8]

Correlation between the androgen receptor splice variant 7 and efficacy of abiraterone and enzalutamide

It was previously reported that an association existed between androgen receptor splice variant 7 (AR-V7) detection and poor outcomes with abiraterone and enzalutamide in mCRPC patients.[9] At ASCO 2016, an expanded analysis of the study was presented. A total of 202 mCRPC patients were enrolled and the prognostic value of circulating tumour cell (CTC) detection and AR-V7 detection was examined. Endpoints consisted of PSA response, PFS and OS. CTC positive and AR-V7 positive patients (N=36) were found to be more likely to have a Gleason score ≥8 (p=0.050), present with metastatic disease at diagnosis (p=0.01), have higher PSA concentrations (p<0.01) and were more likely to have received prior treatment with abiraterone/enzalutamide (p=0.03), or with a taxane (p=0.02). Overall, these patients exhibited lower PSA responses (14% *vs.* 52%) and had a shorter median PFS (3.1 *vs.* 7.1 months) and median OS (11.2 *vs.* 29.5 months) than CTC positive and AR-V7 negative patients (all p<0.001). This observation was also true in both first- and second-line novel hormonal therapy. The authors therefore suggest that the CTC-based AR-V7 assay should be interpreted using 3 separate prognostic categories namely CTC negative, CTC positive / AR-V7 negative and CTC positive / AR-V7 positive.[10]

Final overall survival results from the METEOR trial

Last year, *Choueiri et al.* reported that the tyrosine kinase inhibitor cabozantinib (which inhibits MET, VEGF receptors, and AXL) significantly improved the PFS and the ORR as compared to everolimus in previously treated RCC patients.[11] At ASCO 2016, the final OS data of this trial were presented. At the primary analysis, 658 patients with measurable clear cell RCC, Karnofsky performance status ≥70, and ≥1 prior VEGFR tyrosine kinase inhibitor were randomised 1:1 to cabozantinib (60 mg PO daily) or everolimus (10 mg PO daily). Patients were stratified by MSKCC risk group and number of prior VEGFR tyrosine kinase inhibitors (1 or ≥2). The median OS was 21.4 months as compared to 16.5 months. This translates into a 33% reduction in the rate of death (HR[95%CI]: 0.67[0.53-0.83]; p=0.0003) (*Figure 6A*). Landmark estimates of survival at 18 months were 58% in the cabozantinib arm *vs.* 47% in the everolimus arm. The OS benefit with cabozantinib was consistently observed across all pre-specified subgroups, including MSKCC risk group (*Figure 6B-D*), number of prior VEGFR tyrosine kinase inhibitors, prior anti-PD-1/PD-L1 treatment and location and extent of tumour metastases. Furthermore, the median PFS remained higher in the cabozantinib group (7.4 months) as compared to the everolimus group (3.9 months, p<0.0001).

As such, this analysis demonstrated that cabozantinib is the only agent to demonstrate a significant benefit in OS, PFS, and ORR in a phase III trial with previously treated advanced or mRCC patients making it an important new treatment option for these patients.[12]

Summary of long-term overall survival of nivolumab in previously treated RCC patients

The clinical utility of nivolumab in mRCC was reported in the phase III CheckMate 025 study with a significantly longer median OS for nivolumab than with everolimus.[13] At ASCO 2016, the nivolumab long-term OS results from a phase I and II study were reported. In the phase I study, 34 advanced RCC patients (ECOG PS≤2 and 1 to 5 prior systemic treatments) received nivolumab (1 or 10 mg/kg) q2w. After a minimum follow-up of 50.5 months, ORR was 29% and the median duration of response was 12.9 months. The 4- and 5-year OS rates were 38% and 34%.[14] In the phase II study, 167 advanced RCC patients (Karnofsky performance status ≥70 and 1 to 3 prior systemic treatments) received nivolumab (0.3, 2, or 10 mg/kg) q3w. At a minimum follow-up of 38.0 months, the ORR was 21.6%, the median duration of response was 23.0 months and the 4-year OS rate was 29%.[15]

Furthermore, also in the CheckMate 025 trial, prolonged survival during treatment with nivolumab was observed disregarding the MSKCC risk group, Karnofsky performance status or best response to therapy. With approximately 1/3 of patients alive still at 5 years in the phase I study and at 4 years in the phase II study, this is the longest follow-up reported to date with any anti-PD-1/PD-L1 agent in RCC. Potential pre-

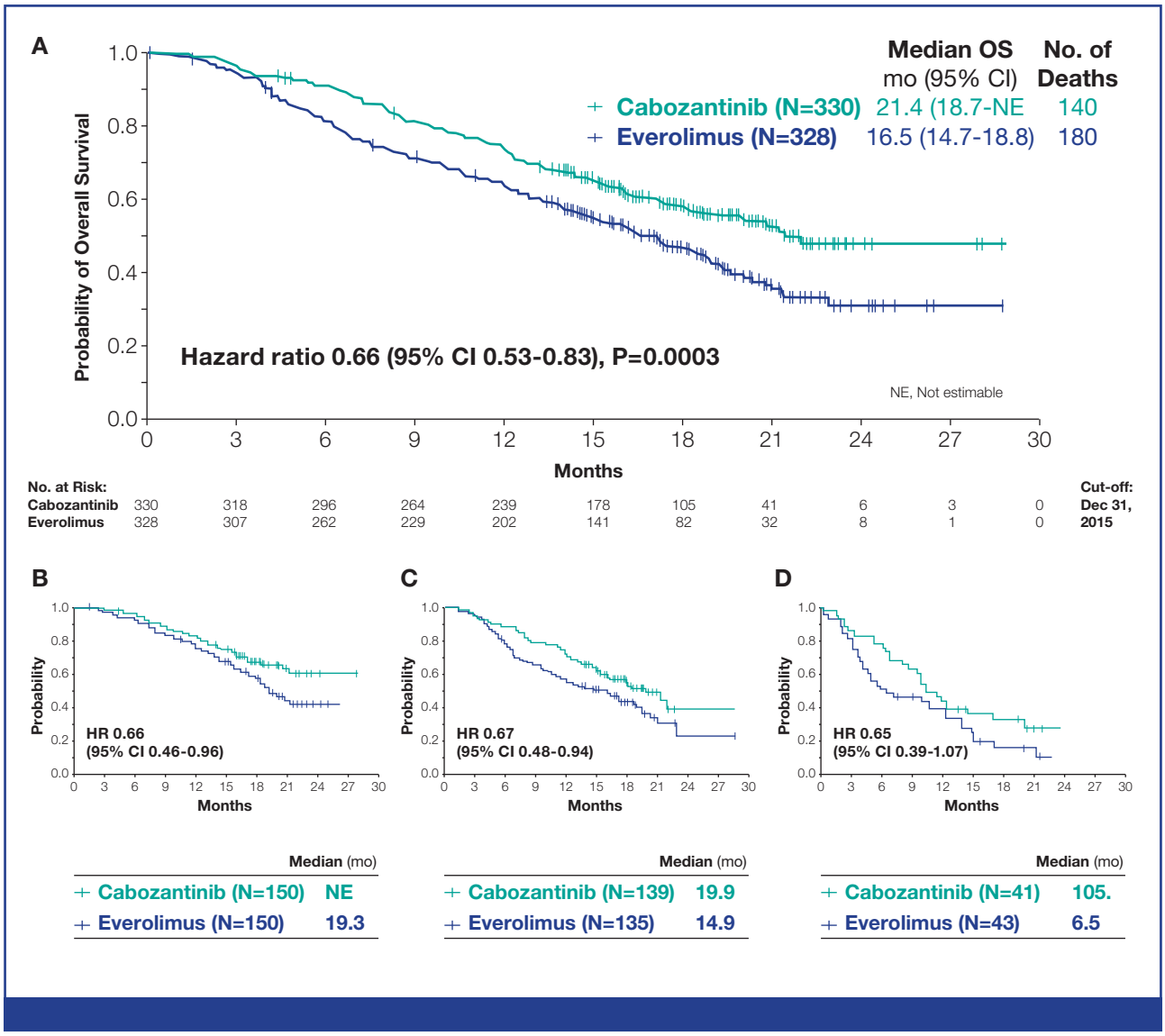

Figure 6. Overall survival of cabozantinib compared to everolimus in mRCC. A significant difference was observed in median OS (A) between the cabozantinib and everolimus cohort. This differences was observed among favourable (B), intermediate (C) and poor risk groups (D).[12]

dictors of long-term survival in this patient population are being explored.[16]

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Key messages for clinical practice

1. Immunotherapy will become a viable treatment option in metastatic urothelial cancer as various anti-PD-1/PD-L1 inhibitors show clinical utility in both chemotherapy-naïve and (heavily) pretreated patients.
2. Androgen deprivation therapy plus docetaxel proves better quality of life over androgen deprivation therapy alone, in hormone responsive metastatic prostate cancer patients, despite a reduction in the quality of life during the first 3 months of therapy.
3. Intermittent docetaxel in mCRPC is non-inferior to the continuous regimen and could be presented as a treatment option for patients, although this did not result in less toxicity.
4. Cabazitaxel was not demonstrated to be superior to docetaxel for treatment of mCRPC. The improved safety profile of 20 mg/m² cabazitaxel versus 25 mg/m² cabazitaxel, makes the former a candidate as second line chemotherapy.
5. Use of the androgen receptor splice variant 7 in mCRPC can predict response to therapy in both first- and second-line novel hormonal therapy.
6. Cabozantinib improves the PFS and OS in metastatic renal cell carcinoma, making this drug an important new treatment option.
7. Long-term survival data of nivolumab confirm the possibility of a shift in the therapeutic landscape of metastatic renal cell carcinoma.

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