Special Edition

Highlights in genitourinary cancer

T. Vermassen, MSc[1], S. Rottey, MD, PhD[1]

From the 26th till the 30th of September, Madrid was host for the 39th annual congress of the European Society of Medical Oncology (ESMO). The theme of this years' meeting, that was hosted at the IFEMA – Feria de Madrid, was 'Precision Medicine in Cancer Care. This report will highlight 10 key studies concerning genitourinary cancers presented during the meeting.

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Clinical activity of PD-L1 inhibition in metastatic urothelial bladder cancer

In this phase I study, 69 heavily pretreated metastatic urothelial bladder cancer (mUBC) patients (measurable disease per RECISTv1.1 and ECOG PS 0 or 1) received MPDL3280A, a human anti-PD-L1 mAb, 15 mg/kg IV q3w for 16 cycles. Patients were subdivided into 2 cohorts: Patients with low immune score (IHC0/1, n=36) or high immune score (IHC2/3, n=33). Rapid response was noticed (median between 6 and 12 weeks). The overall response rate (ORR) was 52% for IHC 2/3 Patients compared to 14% for IHC 0/1 Patients. Median progression free survival (mPFS) was 24 in IHC 2/3 Patients, 8 weeks in IHC 0/1 Patients. Treatment was well tolerated as only 5% of the Patients developed grade 3-4 adverse events (AEs) and no treatment AE-related discontinuation was observed. No renal toxicity has been observed to this date. Additional studies are planned to further evaluate PD-L1 inhibition in UBC.[1]

Dose assessing trial for use of nivolumab in metastatic renal cell carcinoma

Inhibition of the programmed death-1 (PD1) immune checkpoint is a hot topic in new cancer therapies. In this phase II trial 168 clear-cell heavily pretreated metastatic renal cell carcinoma (mRCC) Patients (≥1 agent targeting VEGF pathway) were randomized to the fully human IgG4 monoclonal anti-PD1 antibody nivolumab 0.3 mg/kg (n=60), 2 mg/kg (n=54), or 10 mg/kg (n=54) IV q3w until progression or toxicity. Median PFS was 2.7, 4.0 and 4.2 months for 0.3, 2 and 10 mg/kg, respectively. ORR was approximately 20% for all dosing groups. Median overall survival (OS) was higher for 2 and 10 mg/kg than for 3 mg / kg (25 months *vs.* 18.2 months). Grade 3-4 AEs were ≤17% for all doses with low treatment discontinuation due to treatment-related AEs (for 0.3, 2, and 10mg/kg, 1 (2%), 6 (11%), and 4 (7%) Patients, respectively). These results indicate that nivolumab may be an effective new option for mRCC.[2]

Result of sunitinib rechallenge in mRCC: results of the RESUME study

In this retrospective study, 59 mRCC patients were evaluated who received first-line tyrosine kinase inhibitor (TKI) sunitinib and were rechallenged with sunitinib in third- or further line with another VEGF-inhibitor or an mTOR-inhibitor in between. Objective response for first-line sunitinib was 2% CR, 52% PR, 40% SD and 6% PD. After rechallenge, objective response sunitinib was 0% CR, 16% PR, 46% SD and 38% PD. Median PFS was 7.6 months (4.4-9.7) and OS was 61.9 months (55.5-74.5). Based on these results, rechallenge with sunitinib in mRCC Patients may be possible as resistance to first-line sunitinib is reversible in case of adequately exposing the Patients to the drug. However, as this is a retrospective study with possible selection bias, these results have to be confirmed in a prospective trial.[3]

Possible use of BNC105P with everolimus in mRCC: results of the Disruptor-1 trial

BNC105P is an inhibitor of tubulin polymerization, and preclinical studies suggest possible synergy with the

[1]Department of Medical Oncology, Ghent University Hospital

Please send all correspondence to: S. Rottey, Department for Medical Oncology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium, E-mail: Sylvie.Rottey@UGent.be

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Keywords: urothelial bladder cancer, renal cell carcinoma, immunotherapy, castration-resistant prostate cancer

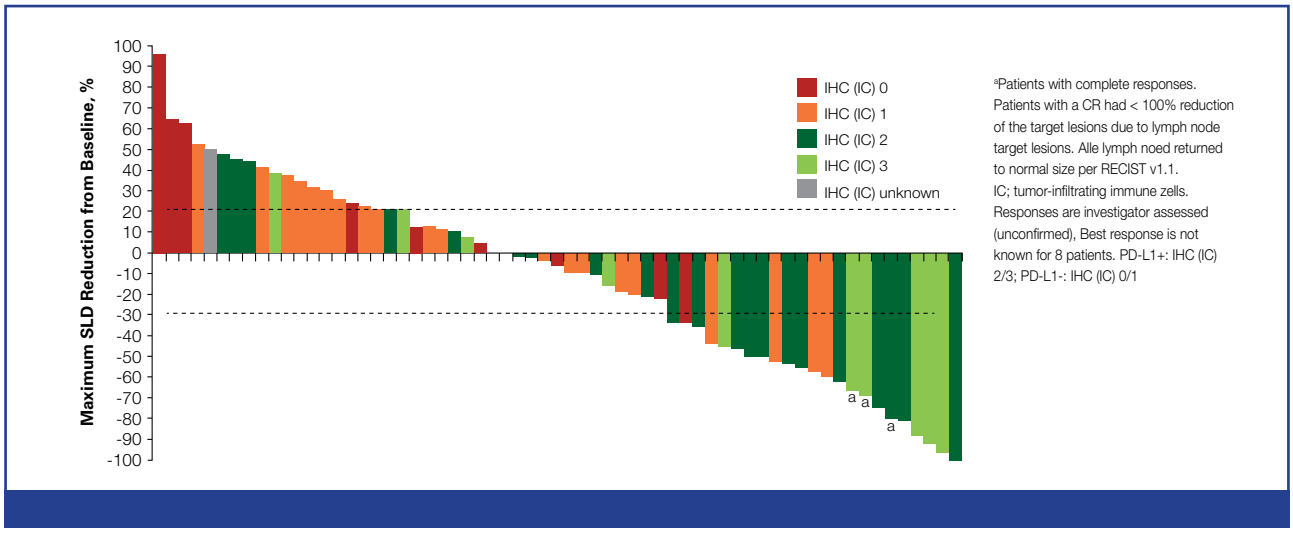

Figure 1. ORR in mBUC Patients, determined by the sum of the longest diameter (SLD).[1]

mTOR inhibitor everolimus. In the phase I component of this study, BNC105P combined with everolimus proved to be well tolerated. Data on the dose regimen are reported in this phase I/II trial. Patients with clear cell mRCC, whom received 1 or 2 prior therapies including minimum 1 VEGF-TKI, were randomized to BNC105P 16 mg/m^2 IV on days 1&8 q3w + everolimus 10 mg/day po (arm A; n=69) or to everolimus alone (arm B; n=67). No difference was observed in the 6 months PFS rate (33% *vs.* 29.8% for arm A and B respectively) nor in PFS (4.7 *vs.* 4.1 months for arm A and B respectively). A trend towards BNC105P benefit in PFS was observed in patients with liver metastates (n=26; 6.6 *vs.* 2.8 months for arm A and B respectively). AEs recorded were related to everolimus toxicity. Although no significant BNC105P benefit was observed, some predictive biomarkers suggested clinical outcome in arm A. Further prospective assessment of BNC105P is therefore warranted.[4]

Influence of brain metastases on outcome of germ cell tumors patients

Treatment and outcome of patients with brain metastases from germ cell tumors GCT are largely unknown due to a lack of data. These characteristics were evaluated in a large international retrospective cohorton behalf of the SWENOTECA and the G3 CONSORTIUM. Data on 523 Patients from 46 international institutions were collected between 1990 and 2013: 228 (44%) Patients with brain metastases at initial diagnosis (group A) and 295 (56%) Patients with brain metastases at relapse (group B). Median follow-up after diagnosis of brain metastases was 7 years. In group A, PFS (6.9 *vs.* 3.6 months, HR=0.60 [0.49-0.73]; p<0.0001) and OS (29.5 *vs.* 8.0 months, HR=0.50 [0.40-0.62]; p<0.0001) were significantly higher compared to group B. Also patients with multiple brain metastases had a worse OS compared to patients with a single brain metastasis. Presence of liver and/or bone metastases also negatively impacted survival. These data suggest that patients with GCT and brain metastases can be cured, especially in cases with brain metastases at initial diagnosis and those with solitary brain metastases. OS of patients with brain metastases at relapse and those with multiple brain metastases could be improved by combination of chemotherapy, radiotherapy and surgery or high-dose chemotherapy.[5]

Impact of enzalutamide on quality of life in the PREVAIL trial

Previous reports of the PREVIAL phase III trial showed improved OS of the androgen receptor antagonist enzalutamide *vs.* placebo in metastatic castration-resistant prostate cancer (mCRPC) patients. Here, results on skeletal related events (SREs), pain and quality of life (QoL) were reported. Patients were randomized to enzalutamide 160mg/day (n=872) or placebo (n=854). Baseline pain and QoL were similar between both arms. Overall, at least one SRE was reported in both enzalutamide (32%) and placebo (37%) patients. Compared to placebo, enzalutamide significantly reduces the risk of 1st SRE occurrence (HR[95%CI]: 0.72[0.61-0.84]; p< 0.0001), QoL deterioration during first 15 months of treatment (FACT-P total scores and subscores were significantly better, all p<0.001) and pain during first 6 months of treatment (p< 0.001). Concluded, in addition to OS benefit, enzalutamide showed significant benefits

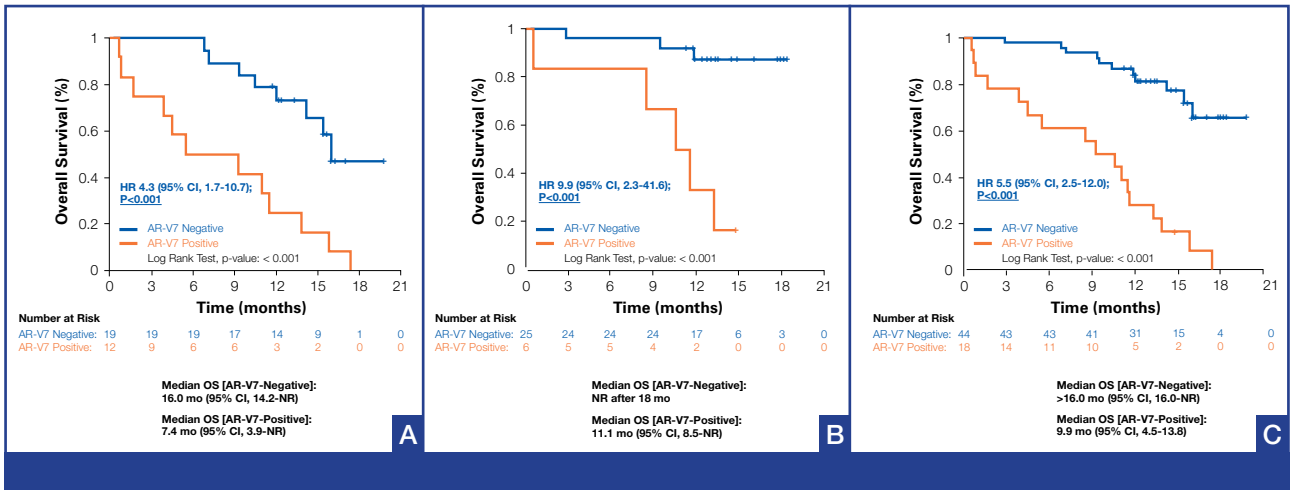

Figure 2. OS rate according to AR-V7 variant in **A**. mCRPC Patients treated with enzalutamide, **B**. mCRPC Patients treated with AA, and **C**. all mCRPC Patients.

in SRE, QoL and pain outcome of mCRPC patients.[6]

Updated OS of ipilimumab in mCRPC in the CA184-043 study

Ipilimumab (Ipi) is a fully human monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 to augment antitumor immune responses. Updated OS (with survival rates up to 3 years) from the phase III trial CA184-043 was reported in post-docetaxel mCRPC patients that received radiotherapy (RT) followed by Ipi or placebo in. Patients were randomized to receive a single dose of RT to bone metastases followed by either Ipi (n= 399) or placebo (n= 400). Median OS was 11.2 months for RT + Ipi compared to 10.0 months for RT + placebo (HR[95%CI]: 0.84[0.72-0.98]; p= 0.03). In patients receiving RT + Ipi, 1-,2-, and 3-year OS rates were 47%, 25% and 12%, respectively, compared to 41%, 17% and 6% for RT + placebo. RT + Ipi showed activity in post-docetaxel mCRPC patients. Long-term OS and Ipi benefit in mCRPC patients with lower disease burden (no visceral metastases) will be evaluated in the ongoing phase III study, CA184-095.[7]

Final OS results from the COU-AA-302 study

Abiraterone acetate (AA) is a prodrug of abiraterone that blocks androgen biosynthesis and is approved, together with the corticosteroid drug prednisone (P), for the treatment of progressive mCRPC patients. Interim analyses of this phase III trial showed that AA + P significantly delayed disease progression and improved OS compared with P alone. Here, final OS and safety outcomes were reported. Patients were randomized 1:1 to receive AA 1g + P 5mg po bid (n=544) *vs.* P alone (n=544). The median follow-up was 49.4 months with 741 deaths observed. Compared to P alone (mOS 30.3 months), AA + P significantly prolonged OS (mOS 34.7 months; HR[95%CI]: 0.80[0.69-0.93]; p= 0.0027). AEs were more common with AA + P compared to P alone. Most reported grade 3-4 AEs in the AA + P group were hypertension (4.6%), hypokalemia (2.6%), increased ALT (5.9%), increased AST (3.3%) and fluid retention/edema (1.1%).

With a median follow-up of 4 years, COU-AA-302 demonstrates a statistically significant OS benefit with AA + P in mCRPC patients with favorable safety profile and is well tolerated.[8]

Influence of custirsen on OS in first-line chemotherapy in the SYNERGY trial

Clusterin is a pro-survival chaperone protein upregulated in response to apoptotic stressors such as chemotherapy. Clusterin blocks block the production of clusterin by inhibiting testosterone-repressed prostate message-2 and thereby sensitizing cells to chemotherapy and resulting in tumor cell death. This randomized, open-label, multicenter, international phase III study determined the added value of clusterin (C) to docetaxel (D) and prednisone (P) in chemotherapy-naive mCRPC patients. From December 2010 to November 2012 Patients were randomized 1:1 to C (640 mg IV weekly after loading dose period) + D (75 mg/m^2 IV day1 q3w) + P (5 mg PO bid) (arm A; n=510) or D+P alone (arm B; n=512) for up to 10 cycles. Median number of cycles received was 8 for arm A and 9 for arm B. mOS was similar between both arms: 23.4 *vs.* 22.2 months for arms A and B respectively

Key messages for clinical practice

1. Revival of immunotherapy is clearly ongoing with encouraging results of immune checkpoint inhibitors in renal cell carcinoma and transitional cell carcinoma of the bladder.
2. The investigations with anti-CTLA-4 in prostate cancer are of interest as well.
3. Very promising is the reported biomarker potential of AR-V7 splice variants in prostate cancer.
4. It is of utmost importance to try to apply personalized treatment.

(HR[95%CI]: 0.93[0.78-1.11]; p= 0.21) as well as reponse to treatment. More AE-related discontinuations were observed in arm A of the study (41% *vs.* 29%). Most common reported grade 3-4 AEs in arm A were neutropenia (43%), lymphopenia (37%), anemia (13%), fatigue (11%), febrile neutropenia (11%) and asthenia (7%). These data suggest no benefit for the addition of C to first-line docetaxel in chemotherapy-naive mCRPC patients. Currently the AFFINITY study is ongoing to determine the clinical benefit of second-line cabazitaxel + C in mCRPC patients previously treated with D + AA or enzalutamide.[9]

OS results from mCRPC Patients with AR-V7 splice variants

At ASCO 2014, it has been reported that detection of AR-V7 in circulating tumor cells (CTCs) from men with mCRPC was associated with resistance to enzalutamide and AA (lower PSA response and PFS). At ESMO 2014, OS data from this study were presented. Thirty-one enzalutamide-treated and 31 AA-treated mCRPC patients were enrolled of which 12 (38.7%) and 6 (19.4%) had detectable AR-V7 in pretreatment CTC samples, respectively. In the enzalutamide-treated group 20 patients had died, compared to 8 patients in AA-treated group. In the enzalutamide arm, AR-V7–positive Patients demonstrated inferior OS compared to AR-V7–negative patients (HR[955CI]: 4.3[1.7-10.7]; p< 0.001) (*Figure 2A*). A similar results was found in the AA arm where AR-V7–negative patients achieved a higher OS compared to AR-V7– positive patients (HR[95%CI]: 9.9 [2.3-41.6]; p< 0.001) (*Figure 2B*). This negative prognostic impact of AR-V7 on OS was maintained in the overall population (HR[95%CI]: 5.5[2.5-12.0]; p<0.001) (*Figure 2C*).

Based on these results, AR-V7 detection in CTCs from mCRPC patients is associated with resistance to enzalutamide and AA, based on lower PSA response, PFS and OS. AR-V7 status might be used as a non-invasive biomarker to predict resistance to androgen receptor targeting agents. However, further multicenter validation is needed to determine the optimal use of AR-V7 status as a predictive or prognostic biomarker.[10]

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