Highlights in genitourinary cancers

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The central theme of ESMO 2016 was 'From disease treatment to patient care', and the congress aimed at further integrating clinical research with patient needs. This report will highlight 9 key studies concerning renal cell carcinoma and metastatic prostate cancer, some of which were presented during one of the presidential sessions of the meeting.

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Disease-free survival of adjuvant sunitinib following nephrectomy: results of the S-TRAC phase III trial

Currently, the tyrosine kinase inhibitor sunitinib is only given in case of advanced or metastatic renal cell carcinoma (mRCC). This randomized, double-blind phase III trial examined the efficacy and safety of sunitinib *vs.* placebo in patients with locoregional RCC who underwent nephrectomy and are at high risk of tumor recurrence. Treatment-naïve patients with locoregional RCC (≥T3 and/or N1–2, no metastases; N = 615) received a daily dose of 50mg sunitinib (N= 309) or placebo (N= 306) q4w-on/2w-off for 1 year until disease recurrence, occurrence of secondary malignancy, significant toxicity, or consent withdrawal.[1] The primary endpoint of the study was disease-free survival (DFS), while secondary objectives included, overall survival (OS), safety, and patient-reported outcomes. The reported median DFS of 6.8 months (95%CI[5.8 months – not reached]) with sunitinib was significantly longer than the mDFS of 5.6 months (95%CI[3.8 months –6.6 months]) seen with placebo (Hazard Ratio [HR] = 0.76 [0.59 – 0.98]; p= 0.030; *Figure 1*). No OS data were presented at this time. Grade ≥3 adverse events (AEs) were more frequent with sunitinib (62.1%) than with placebo (21.1%) although no difference was observed in the frequency of serious AEs (21.9% *vs.* 17.1%, respectively).

These data might indicate that sunitinib is a potential adjuvant therapy in this cohort of patients.[1] However, these results are contradictory to what was reported in the ASSURE trial. A possible explanation for this difference might be that in the S-TRAC trial no T1-2 tumors were included, less dose reduction of sunitinib was allowed and no patients with non clear-cell RCC were enrolled.[2] As such, more data are needed before sunitinib could be considered as a standard adjuvant therapy following nephrectomy.

Shift in initial targeted therapy in mRCC? Findings from the phase II ALLIANCE A031203 trial

Cabozantinib, an oral, potent inhibitor of MET, AXL and VEGFR2, has previously shown its potential as second-line therapy in mRCC patients after prior VEGF-targeted therapy.[3,4] The goal of the presented randomized phase II multicenter trial was to assess the efficacy of cabozantinib as frontline targeted therapy in patients with mRCC. Treatment-naïve patients (clear-cell mRCC, ECOG performance status 0-2, and intermediate or poor risk according to the Heng criteria; N=157) were randomized 1:1 to receive either cabozantinib (60 mg daily), or sunitinib (50 mg daily, q4w-on/2w-off). Patients were stratified for risk groups and the presence of bone metastases. The objective response rate (ORR, according to RECIST v1.1) was 46% for cabozantinib *vs.* 18% for sunitinib. The median progression-free survival (PFS) was significantly higher in the cabozantinib cohort (8.2 months, 95%CI[6.2 months – 8.8 months]) compared to the sunitinib cohort (5.6 months, 95%CI[3.4 months – 8.2 months]). This corresponds with a 31% reduc-

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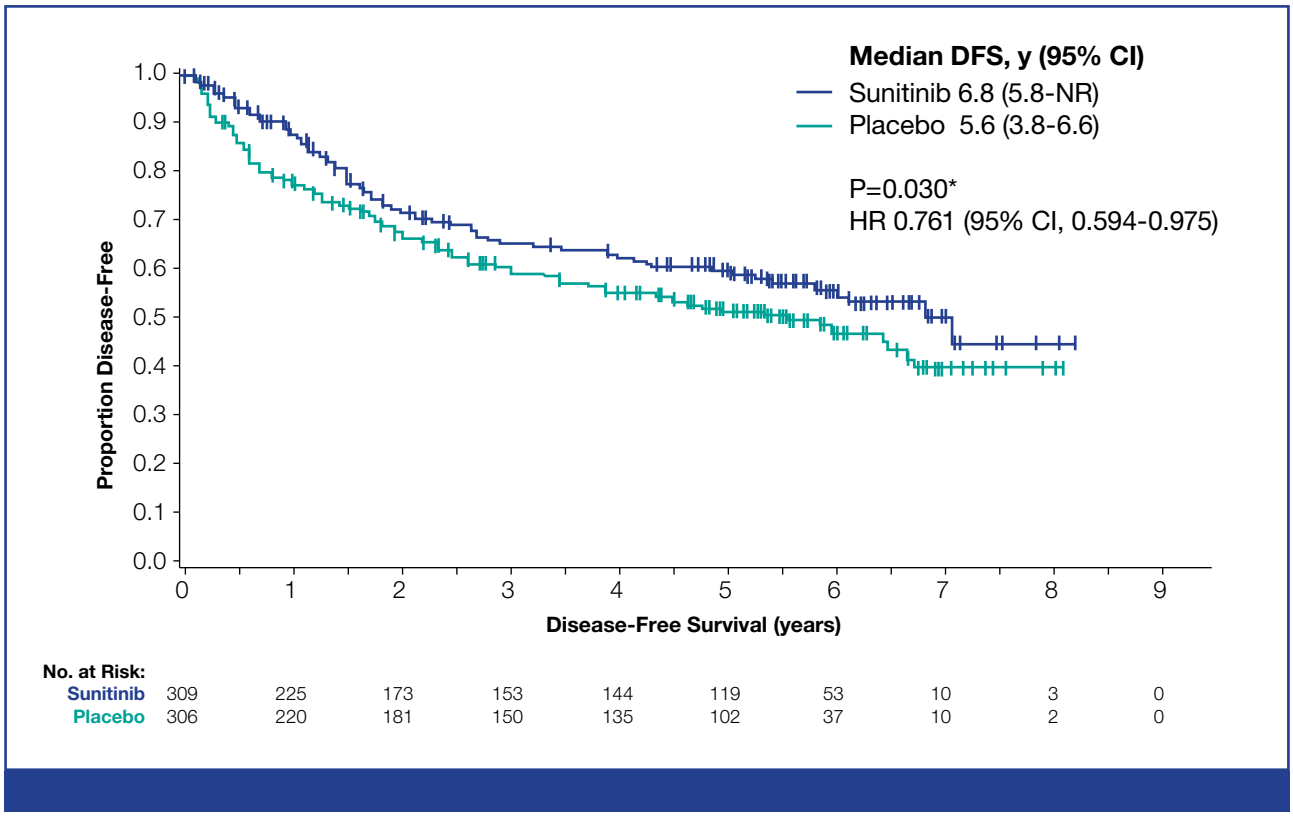

Figure 1. DFS for sunitinib versus placebo as adjuvant therapy in high-risk RCC following nephrectomy.[1] A significant difference was observed in DFS between adjuvant sunitinib and placebo in high-risk RCC following nephrectomy.

tion in risk of disease progression or death with cabozantinib (adjusted HR[95%CI]: 0.69[0.48 – 0.99], p= 0.012; *Figure* 2A). The benefit of cabozantinib was especially prominent in patients with bone metastases (HR[95%CI]: 0.51[0.29 – 0.90]), but was not observed in any of the other subgroups. No difference was observed with respect to OS (median OS 26.4 months *vs.* 23.5 months; adjusted HR[95%CI]: 0.87[0.55 – 1.4]; *Figure* 2B). The toxicity profile also proved to be similar for both TKIs, with 70.5% and 72.2% grade ≥3 AEs for cabozantinib and sunitinib respectively. Although these data favor for cabozantinib as first-line targeted therapy in mRCC, larger comparative studies are needed in order to adapt the current standard therapy. Also the specific toxicity profile of cabozantinib requires further follow-up should it be implemented as first-line therapy.[5]

Combination of targeted therapies in various solid tumors

Combining different therapies often leads to an improved efficacy when compared to monotherapy. In this light, combining a kinase inhibitor with an immune-checkpoint inhibitor has the potential to improve patient outcomes. At ESMO 2016, several ongoing phase I trials were presented that are investigating this hypothesis.

Firstly, an ongoing, open-label, multicenter, phase 1b trial assessed the maximum tolerated dose, safety, tolerability, and ORR (irRECIST) of lenvatinib plus pembrolizumab in metastatic solid tumors. Thirteen patients were enrolled (2 non-small cell lung carcinomas [NSCLC], 8 RCC: 2 endometrial carcinomas, and 1 melanoma) and received pembrolizumab (200mg IV q3w) and 1 of 2 lenvatinib dose levels (DL, orally daily): DL1 = 24mg (N=3), or DL2 = 20mg (N=10). Two dose limiting toxicities were reported for DL1, while none were observed with DL2. All patients experienced at least 1 treatment-related AE. DL1 was associated with an ORR of 100% (all partial responses [PR]), while DL2 showed an ORR of 40% (all PR). PRs were reported for 4 RCC, 1 NSCLC, 1 endometrial carcinoma, and 1 melanoma. In conclusion, the authors stated that combining 20mg of lenvatinib at a dose of 20mg per day with pembrolizumab shows promising activity with manageable toxicity.[6]

In a second study, it was suggested that the multiple receptor TKI cabozantinib has immunomodulatory properties. This phase I trial reported the safety and clinical activity of cabozantinib (orally daily) in com-

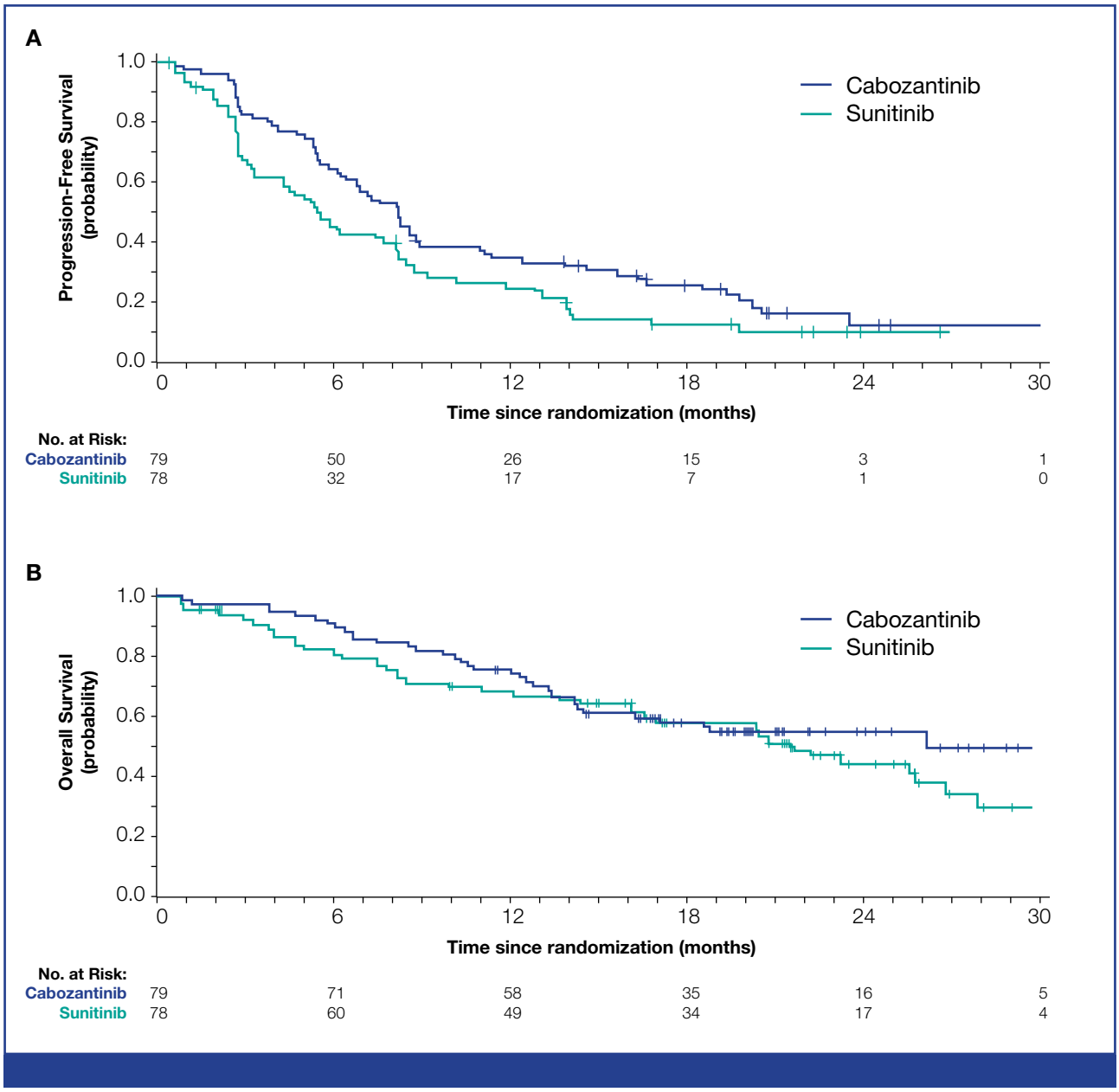

Figure 2. PFS and OS of cabozantinib versus sunitinib as first-line therapy in mRCC.[5] **Top**. PFS was significantly longer in the cabozantinib group (8.2 months, 95%CI[6.2 months – 8.8 months]) vs. the sunitinib group (5.6 months, 95%CI[3.4 months – 8.2 months]; adjusted HR[95%CI]: 0.69[0.48 – 0.99], p= 0.012). **Bottom**. OS was comparable between both therapies (26.4 months vs. 23.5 months, respectively; adjusted HR[95%CI]: 0.87[0.55 – 1.4]).

bination with nivolumab (IV q2w), a monoclonal IgG4 antibody to PD-1. A total of 24 patients (6 metastatic urothelial carcinomas, 4 urachal bladder carcinomas, 3 bladder squamous cell carcinomas, 5 germ cell tumors, 4 castrate-resistant prostate cancer [CRPC], 1 RCC, and 1 trophoblastic tumor) were treated at 4 dose levels (DL, equal distribution): DL1= cabozantinib 40mg / nivolumab 1mg/kg, DL2= cabozantinib 40mg / nivolumab 3mg/kg, DL3= cabozantinib 60mg / nivolumab 1mg/kg, DL4= cabozantinib 60mg / nivolumab 3mg/kg. Most dose reductions were needed in patients receiving 60mg of cabozantinib. Grade 3 AEs included neutropenia (N=3), fatigue (N=2), mucositis (N=1), and vomiting (N=1). There were no grade ≥4 toxicities. In 18 evaluable patients, the ORR (RECIST v1.1) was 33% including 1 complete response (CR) (a case of bladder squamous cell carcinoma) and 5 PRs (2 metastatic urothelial carcinoma, 1 RCC, 1 urachal bladder carcinoma, 1 bladder squamous cell carcinoma, and 1 CRPC). All responses were ongoing at cutoff. The com-

bination of cabozantinib with nivolumab proves well tolerated at recommended dose of cabozantinib 40mg plus nivolumab 3mg/kg. Expansion studies in patients with mUC and RCC are planned.[7]

Other studies examined the potential benefit of combining targeted therapies in RCC. At ESMO 2016, two ongoing phase Ib trials in treatment-naïve mRCC patients (clear-cell RCC with primary tumor resected, ≥1 measureable lesion, ECOG performance status 0-1) were presented.

The first trial reported the preliminary safety and efficacy results from the combination of axitinib (5 mg orally twice daily), a TKI inhibiting VEGFR approved in second- or further-line, and pembrolizumab (2 mg/kg IV q3w), a humanized monoclonal antibody that blocks binding of the immune-checkpoint receptor programmed death (PD)-1 to its ligand PD-L1/2. A total of 52 patients were eligible. More than half of the patients (67.3%) had an ORR (RECIST v1.1) with 2 CRs and 33 PRs. Eleven patients enrolled in the dose finding phase of the trial, of which 7 remained free of progression free at 11 months (immature median PFS data). The most common grade ≥3 AEs included hypertension, diarrhea, headache, hyponatraemia, increased alanine aminotransferase (ALT), and increased levels of aspartate aminotransferase (AST).[8]

A second trial evaluated the safety and tolerability of axitinib (5 mg orally twice daily) and avelumab (10 mg/kg IV infusion q2w), a fully human IgG1 antibody that inhibits PD-L1. At data cut-off, 6 patients were treated with the combination. The median duration of treatment was 17.0 weeks (range 11.9 weeks – 21.7 weeks) for avelumab and 16.3 weeks (range 12.7 weeks – 22.7 weeks) for axitinib. ORR (RECIST v1.1) was observed in 5 patients, all being PRs, and 1 patients exhibited stable disease with tumour shrinkage not meeting PR. Grade ≥3 AEs occurred in 4 patients: hypertension (N= 2), palmar-plantar erythrodysaesthesia syndrome (N= 1), increased lipase (N= 1), and proteinuria (N= 1).[9]

These results provide a rationale that both combinations of a potent kinase inhibitor and an immune-checkpoint inhibitor prove antitumor activity in various solid tumors. However, combining different drugs usually leads to increased toxicity. Larger trials are warranted to assess this issue and to randomise versus monotherapy.

Long term efficacy and Quality of Life in the E3805 CHAARTED trial

It was previously reported that the combination of docetaxel plus androgen deprivation therapy (ADT) increases the OS when compared to ADT as monotherapy for prostate cancer (PCa) patients with a higher burden of disease.[10] In order to see the benefit of docetaxel in patients with a lower volume disease longer follow-up is needed.[10] The E3805 CHAARTED trial reported the long term efficacy and Quality of Life (QoL) data of chemo-hormonal therapy in patients with high *vs.* low volume disease. A total of 790 men were enrolled and randomized 1:1 to ADT alone or ADT plus docetaxel (75mg/m^2 q3w for 6 cycles within 4 months of ADT). The median OS was 57.6 months (95%CI[52.0 months – 63.9 months]) for ADT plus docetaxel as compared to 47.2 months (95%CI [41.8 months – 52.8 months]) for ADT alone (HR [95%CI]: 0.73[0.59 – 0.89], p= 0.0018). This benefit was however only observed for patients with a high volume disease (HR[95%CI]: 0.63[0.50 – 0.79], p<0.0001), while this was not seen in patients having a lower disease burden (HR[95%CI]: 1.04[0.70 – 1.55], p= 0.86). QoL was determined using the FACT-P score and showed a decline in QoL from baseline to 3 months in patients with low volume disease receiving ADT plus docetaxel. The lowest FACT-P score at 12 months was seen in patients with high volume disease receiving ADT as monotherapy. Based on these findings, the combination of ADT plus docetaxel should perhaps be limited to patients with a higher volume metastatic PCa.[11]

Survival data and QoL with cabazitaxel in mCRPC

The post-hoc survival analyses and QoL data associated with cabazitaxel therapy in mCRPC from 2 large phase III studies was presented.

The FIRSTANA trial evaluated cabazitaxel *vs.* docetaxel in chemotherapy-naïve mCRPC patients. A total of 1,168 patients were randomized 1:1:1 to cabazitaxel 20mg/m^2 (N=389), cabazitaxel 25mg/m^2 (N=388) or docetaxel (N=391). The primary endpoint was OS, while secondary objectives included safety, PFS, PSA tumor response and QoL. All results concerning efficacy are summarized in *Table 1*. The rate of grade ≥3 treatment-related AEs was highest in the cabazitaxel 25mg/m^2 group (60.1%) when compared to cabazitaxel 20mg/m^2 and docetaxel (41.2% and 46.0%, respectively). Cabazitaxel 20mg/m^2 was associated with a greater QoL benefit as compared to docetaxel (p= 0.019) whereas this benefit was only marginal for cabazitaxel 25mg/m^2 *vs.* docetaxel (p= 0.063).[12]

The PROSELICA trial evaluated the same endpoints for the use of cabazitaxel in mCRPC patients previously treated with docetaxel. In this study, 1,200 patients

Table 1. Efficacy of cabazitaxel in chemo-naïve and chemotherapy pretreated mCRPC patients.

Study		FIRSTANA[12]			PROSELICA[13]	
Cohort		Cabazitaxel 20	Cabazitaxel 25	Docetaxel	Cabazitaxel 20	Cabazitaxel 25
Efficacy						
Median OS (months)		24.5	25.2	24.3	13.4	14.5
Median PFS (months)		4.4	5.1*	5.3	2.9	3.5
Tumour response (%)		32.4	41.6	30.9	18.5	23.4
≥50% PSA decline (%)		60.7	68.7	68.4	29.5	42.9§
Prognostic marker						
Grade ≥3 neutropenia	No	22.3 (19.0 – 24.9)	22.1 (16.7 – 23.7)	22.3 (14.9 – 27.6)	14.8 (12.7 – 16.3)	14.6 (11.8 – 16.5)
	Yes	27.9 (24.6 – 32.8)	30.7 (25.7 – 34.0)	27.3 (23.6 – 30.7)	16.1 (13.7 – 18.3)	16.3 (15.1 – 18.2)
	p-value	0.0193	0.0044	0.021	0.073	0.051
Neutrophil-lymphocyte ratio	<3	29.2 (25.7 – 33.7)	31.6 (26.5 – 34.3)	30.1 (25.1 – 35.7)	17.9 (15.1 – 19.9)	17.6 (15.9 – 20.8)
	≥3	20.6 (15.7 – 22.4)	23.4 (19.5 – 26.6)	23.0 (19.0 – 25.5)	13.6 (12.1 – 15.0)	14.9 (13.5 – 16.0)
	p-value	<0.0001	0.0033	0.0011	<0.001	0.059

* Significantly different between the cabazitaxel 25 mg/m² and the docetaxel regimen (P= 0.037).§ Significantly different between the cabazitaxel 20 mg/m² and the cabazitaxel 25 mg/m² regimen (P< 0.001).

were randomized 1:1 to receive cabazitaxel 20mg/m² (N=598) or cabazitaxel 25mg/m² (N=602). All efficacy data from this trial are depicted in *Table 1*. Grade ≥3 treatment-related AEs were also more common in this cohort (54.5% *vs.* 39.7%), although no difference in QoL, based on FACT-P scores, was demonstrated (p= 0.369). This proves that cabazitaxel 20mg/m² is non-inferior to the 25mg/m² regimen. Combined with the reported efficacy data, this favors the use of the latter regimen in mCRPC patients after progression on docetaxel. 13 Of note, Both studies also indicate the prognostic value of grade ≥3 neutropenia and neutrophil-lymphocyte ratio for OS in mCRPC patients treated with cabazitaxel, despite prior chemotherapy regimens (*Table 1*).[12,13]

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Key messages for clinical practice

1. No clear outcome on the use of sunitinib as adjuvant therapy in RCC patients following nephrectomy with high risk for recurrence.
2. Possible use of cabozantinib as first-line therapy in mRCC patients although further comparison with currently approved first-line targeted agents is needed in larger trials.
3. Combination therapy of kinase inhibitors and immune-checkpoint inhibitors show promising results in various genitourinary tumors but needs thorough assessment of toxicity profile as well as extensive comparison with monotherapy.
4. ADT plus docetaxel only shows benefit in PCa patients with high volume disease whereas patients with low volume disease seem to exhibit loss in QoL due to this combination.
5. Cabazitaxel shows no superiority over docetaxel in chemo-naïve mCRPC patients. The difference in outcome between both cabazitaxel dose regimens (20 and 25 mg/m²) is also marginal, with increased toxicity in the 25mg/m² regimen.
6. Grade ≥3 neutropenia and neutrophil-lymphocyte ratio potentially hold prognostic value in chemo-naïve and pretreated mCRPC patients.

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