Highlights in genitourinary cancers

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From the 25th till the 29th of September, Vienna was host for the 18th ECCO – 40th ESMO European Cancer Congress. Immunotherapy was a very important theme for this year's venue which hosted 18.500 registered attendees. This report will highlight 4 key studies concerning renal cell carcinoma and metastatic prostate cancer presented during the presidential sessions of the meeting.

(Belg J Med Oncol 2015;9:244-49)

Survival benefit of nivolumab (NIVO) compared to everolimus (EVE) in advanced renal cell cancer (aRCC): results of the CheckMate 025 phase III trial

Current treatments for aRCC or metastatic RCC (mRCC) are associated with limited overall survival (OS) in previously treated patients (pts). NIVO is a PD-1 inhibitor which has an acceptable safety profile and proven efficacy in the treatment of melanoma and lung cancer. In this phase III study, 821 pts with clear-cell a/mRCC, 1–2 prior anti-angiogenic therapies and ≤2 systemic therapies, measurable disease (RECIST v1.1), and Karnofsky performance status (KPS) ≥70% were randomized (1:1) to NIVO 3mg/kg intravenously (IV) q2w or EVE 10mg orally once daily and treated to progression or unacceptable toxicity. Median age was 62 years. Seventy-two percent received 1 prior therapy, 28% received 2 prior therapies. OS was higher in pts who received NIVO (25.0 months [21.8 months – not achieved]) compared to EVE (19.6 months [17.6 months – 23.1 months]) which favored NIVO (hazard ratio (HR) [98.5%CI] = 0.73 [0.57-0.93]; P = 0.0018; Figure 1A). Subgroup analyse showed that especially male pts and poor prognosis pts had the greatest advantage in NIVO treatment. Moreover, the benefit in OS was greatest for NIVO versus EVE in pts with PD-L1 expression <1% (27.4 months versus 21.2 months; HR [95%CI] = 0.77 [0.60-0.97]; *Figure 2*). Objective response rate (ORR) was also higher in the NIVO arm (25%) compared to the EVE arm (5%; odds ratio [95%CI] = 5.98 [3.68-9.72]; P < 0.0001) but without difference in time to or duration of response. Progression free survival (PFS) was similar for both treatment arms: 4.6 months versus 4.4 months (HR [95%CI] = 0.88 [0.75-1.03]; P = 0.1135; Figure 1B). Post-hoc analysis in pts without progression or death after 6 months showed a delayed PFS in NIVO pts: 15.6 months versus 11.7 months (HR [95%CI] = 0.64 [0.47-0.88]). Lastly, treatment related adverse events (AEs) and quality of life were also better in the NIVO arm. As NIVO is the 1st therapy that enabled prolonged survival in previously treated a/mRCC pts, this therapy is proposed as novel treatment in mRCC.[3,4]

Survival results from the METEOR trial: cabozantinib (CABO) versus EVE in pts with aRCC

Von Hippel-Lindau tumor suppressor inactivation leads to upregulation of VEGF, MET and AXL which in turn leads to poor prognosis and VEGFR-inhibitor resistance.[5] CABO is a small molecule tyrosine kinase inhibitor (TKI) that blocks VEGFR, MET and AXL. The objective of this phase III trial was to evaluate the efficacy and safety of CABO compared to EVE in pts with cc RCC and disease progression following treatment with one or more VEGFR TKIs. Pts were randomized 1:1 to receive CABO 60mg orally daily (N=330) or

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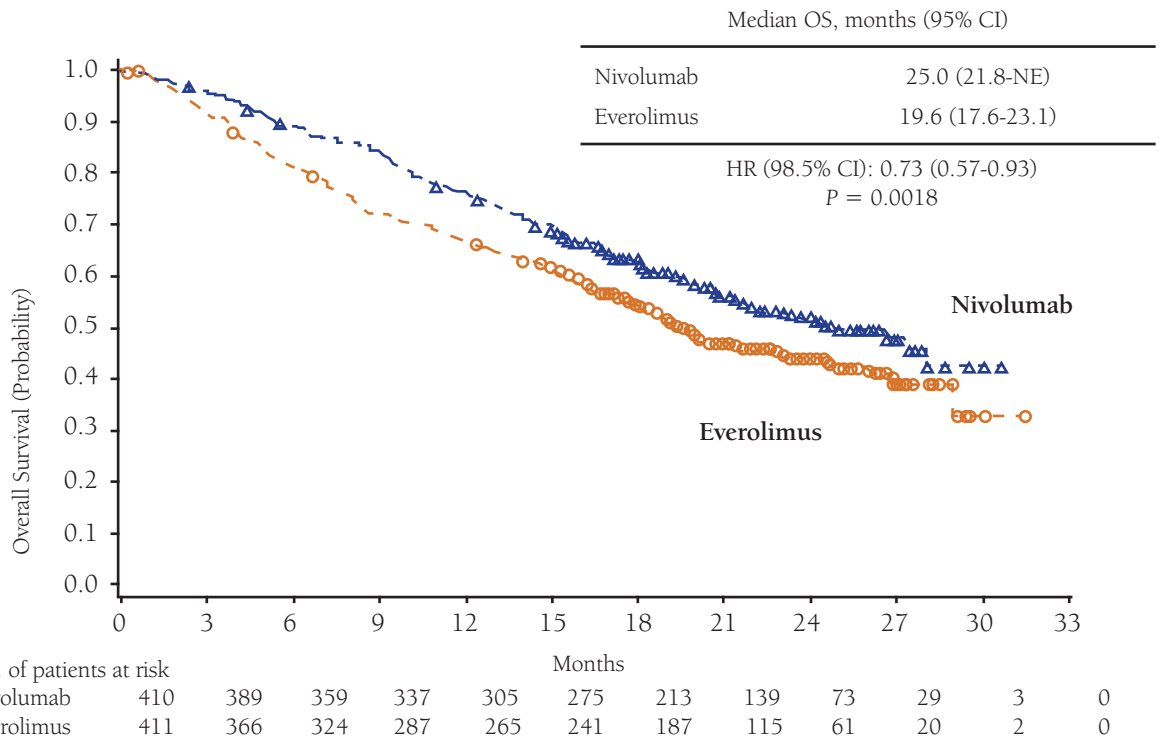
Keywords: renal cell carcinoma, immunotherapy, castration-resistant prostate cancer.

Overall survival



No. of patients at risk

Nivolumab	410	389	359	337	305	275	213	139	73	29	3	0
Everolimus	411	366	324	287	265	241	187	115	61	20	2	0

Minimum follow-up was 14 months
NE, not estimable

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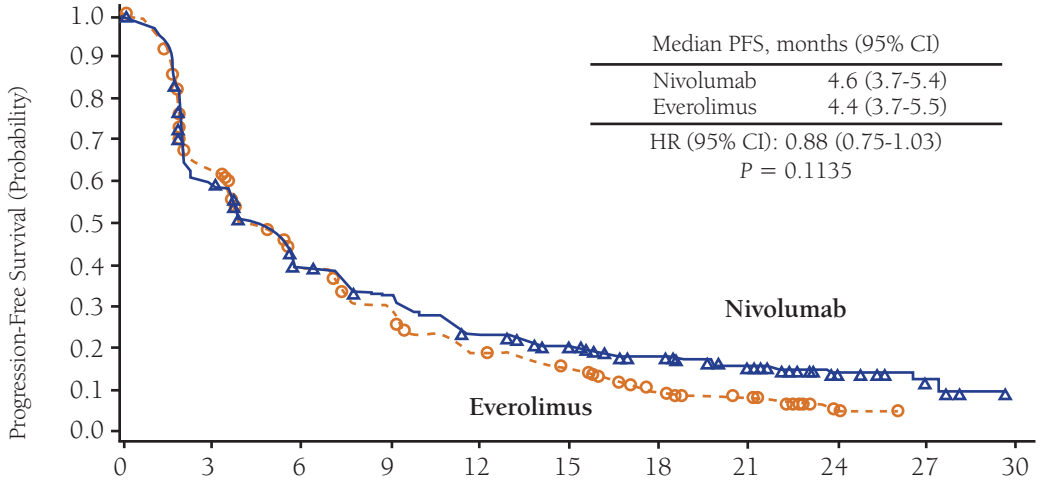
Progression-free survival



No. of patients at risk

Nivolumab	410	230	145	116	81	66	48	29	11	4	0
Everolimus	411	277	129	97	61	47	25	16	3	0	0

- In a post-hoc analysis of patients who had not progressed or died at 6 months, median PFS was 15.6 months for nivolumab vs 11.7 months for everolimus (HR (95% CI): 0.64 (0.47-0.88))

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Figure 1: Survival analyses of nivolumab versus everolimus in aRCC patients (top: OS, bottom: PFS).

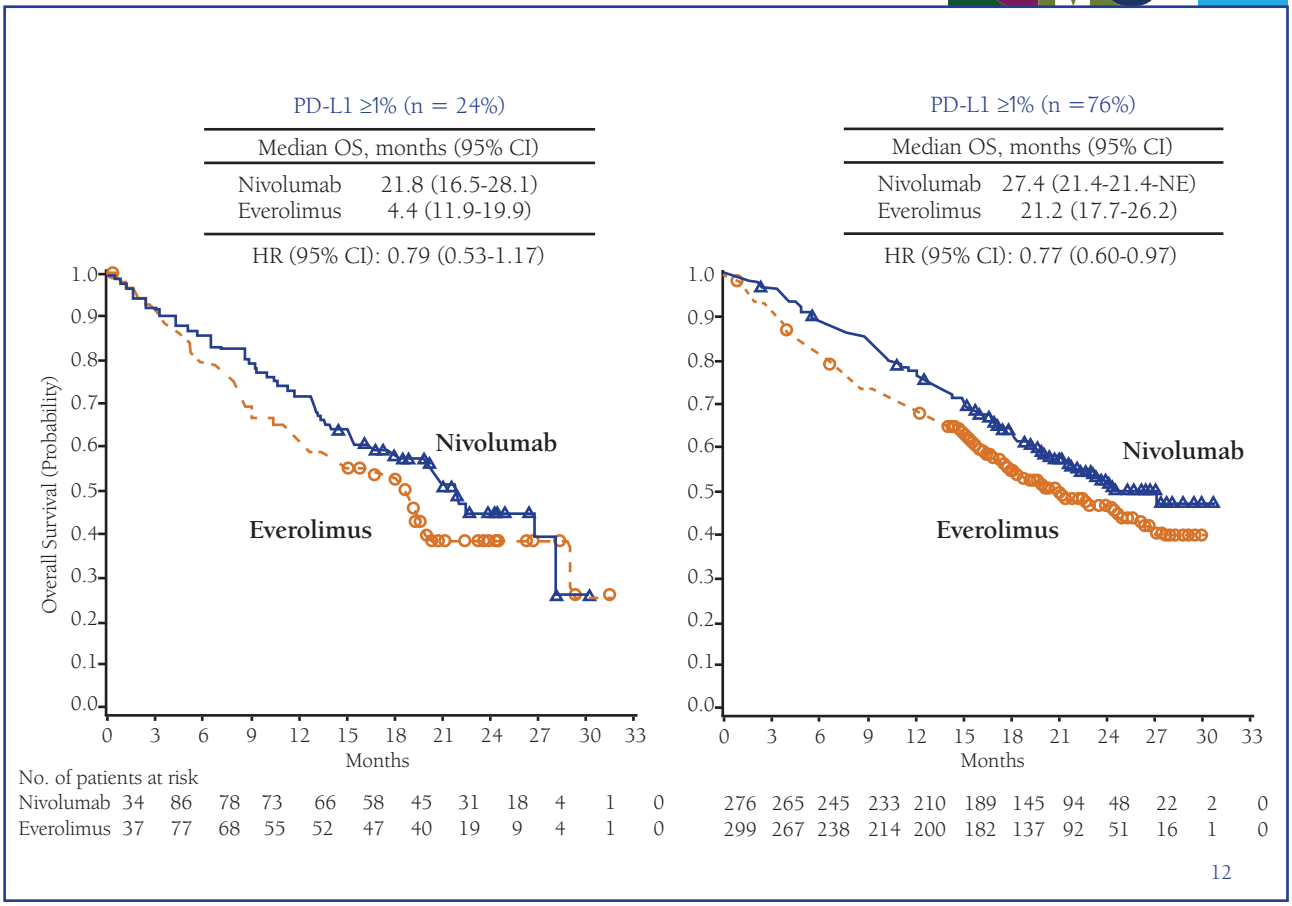


Figure 2. OS analysis in nivolumab versus everolimus according to PD-L1 expression. Left: patients with PD-L1 expression ≥ 1%; Right: patients with PD-L1 expression < 1%.

EVE 10mg daily (N=328). Pts had measurable disease per RECIST 1.1, KPS ≥70%, and were stratified by MSKCC prognostic criteria and number of prior VEGFR TKIs. Patients must have progressed within 6 months of their prior VEGFR TKI. Median age was 63 years. Seventy percent received 1 prior therapy, 30% received 2 or more prior therapies. The PFS was longer in pts with CABO vs EVE: 7.4 months versus 3.8 months (HR [95% CI]= 0.58 [0.45-0.75]; p< 0.001; *Figure 3A*). PFS was primarily longer in pts with only 1 prior treatment, or pts with favorable or intermediate risk to progression. Subanalysis proved highest PFS in pts with 1 prior sunitinib therapy (9.1 months). Next, ORR was higher in pts under CABO (21%) with 84% tumor reduction versus pts treated with EVE (5%; p< 0.001) with 59% tumor reduction (*Figure 3B*). OS analysis was not yet completed at moment of presentation of the study. Finally, both treatments had a similar safety profile.[6,7]

Conventional or hypofractionated radiotherapy (RT) in castration resistant prostate cancer (CRPC): 5 year outcomes of the CHHiP trial

CRPC may be sensitive to radiation fraction size. This multicentric, non-inferiority trial determined the efficacy and safety of hypofractionated RT schedules using intensity modulated radiotherapy (IMRT), thus improving the therapeutic ratio by improving tumor control or reducing side effects. T1b-T3a N0 M0 pts (N3216) with risk of seminal vesical involvement ≤30% and sPSA ≤30μg/L were randomised (1:1:1) to 74 Gray(Gy)/37 fractions (f) (control, N=1065), 60Gy/20f (N= 1074) or 57Gy/19f (N=1077). The median age of patients in the study was 69 years and the median follow-up was 62.4 months. All groups showed comparable clinical stage, Gleason scores and risk to progression. The percentage of pts with 5 year PFS in the control arm was 88.3% [86.0-90.2], while the 5 year PFS for the other arms were 90.5% [88.4-92.2] (HR [95% CI] = 0.83 [0.68-1.02]; P= 0.14); and 85.8% [83.3-87.9] (HR [95% CI]= 1.19 [0.99-1.44]; P= 0.13), for 60 Gy and 57 Gy respectively. All arms showed comparable OS (with biochemical free survival as endpoint). More grade 2 bowel toxicity in the 60 Gy arm was observed versus the control group (36.1% versus 23.8%; P < 0.001) but no difference was observed in late toxicities (bowel, bladder or sexual dysfunction).

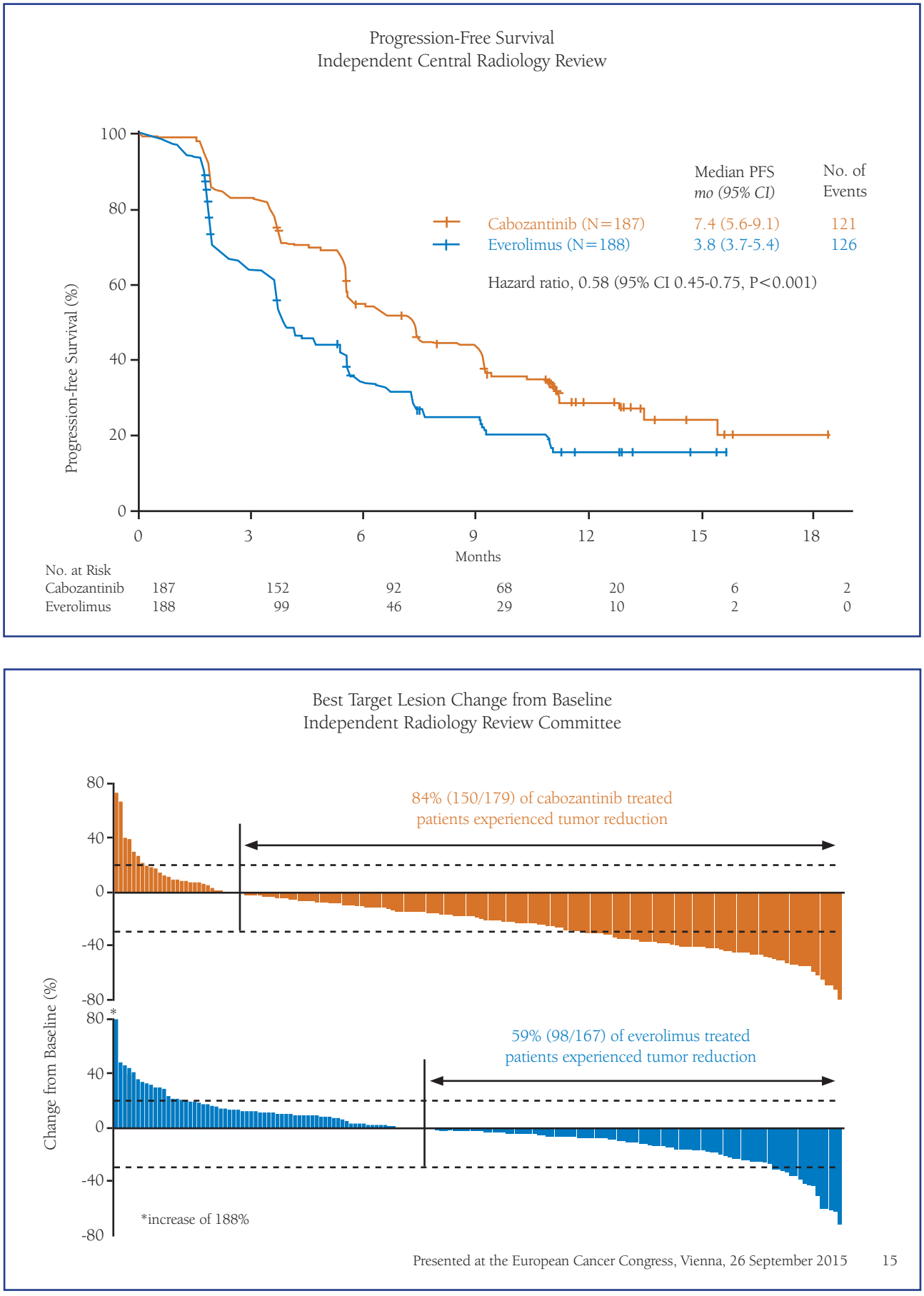
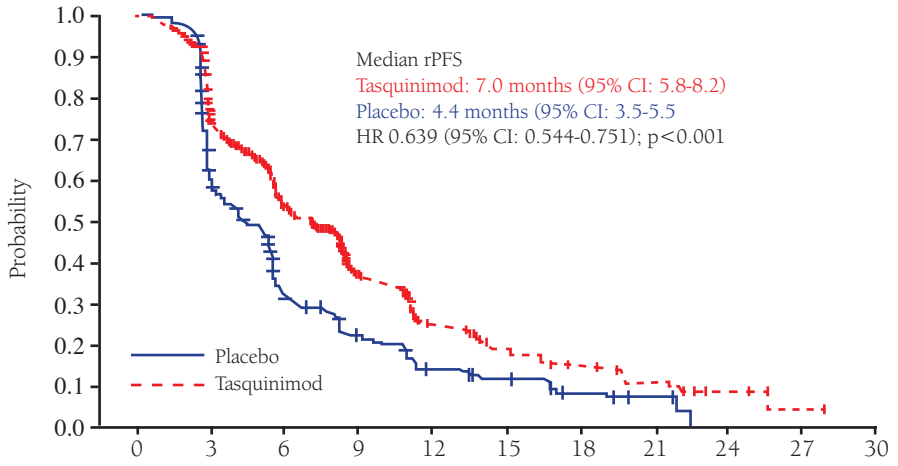


Figure 3. Clinical benefit from cabozantinib treatment. Top: PFS. Bottom: Best target lesion changes to baseline.

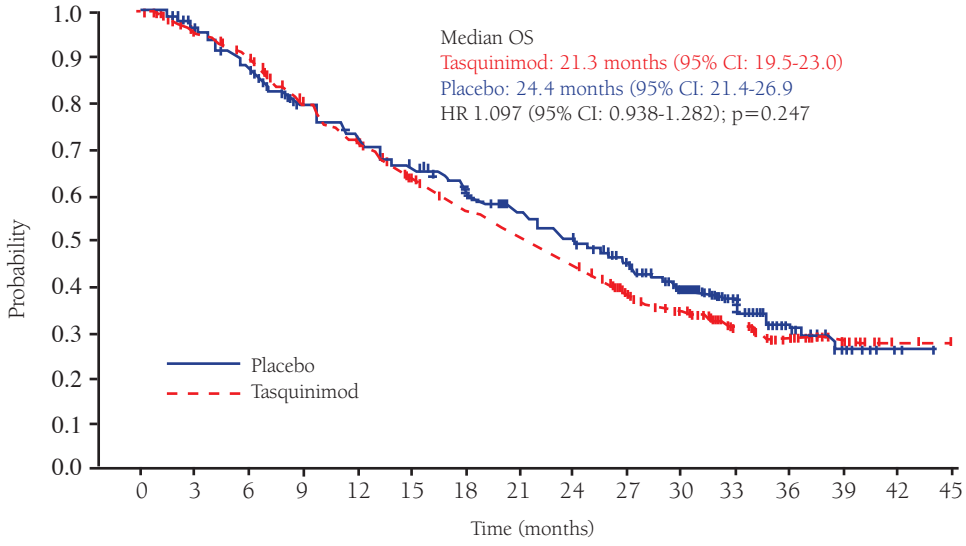
Primary endpoint:
rPFS (ITT) central review*



TASQ: No. of patients at risk	396	235	142	71	35	25	13	5	1
Placebo: No. of patients at risk	181	80	45	22	15	8	3		

*Similar HR by local review

Key secondary endpoint: OS at final analysis



TASQ: No. of patients at risk	767	689	604	532	463	397	353	309	240	144	87	53	26	5
Placebo: No. of patients at risk	391	344	303	273	243	225	199	176	144	89	55	27	11	5

Figure 4. Survival analyses of tasquinimod versus placebo in mCRPC patients. Top: radiological PFS. Bottom: OS.

These results prove that 60 Gy hypofractionated RT is non-inferior to 74 Gy conventional RT and could therefore possible be offered as new standard of care treatment in localized CRPC.[8]

Tasquinimod (TASQ) in metastatic CRPC (mCRPC): final results from a randomized phase III trial

TASQ, a second-generation quinoline-3-carboxamide variant, is a novel oral immunotherapy with immunomodulatory, anti-angiogenic and anti-metastatic properties. It targets the tumor microenvironment by modulating regulatory myeloid cells. In a previously conducted phase II trial in mCRPC, TASQ increased the PFS and showed a trend to an OS benefit in chemotherapy-naive pts vs placebo. Men with asymptomatic to mildly symptomatic chemotherapy-naïve mCRPC and evidence of bone metastases (N= 1245) were assigned (2:1) to receive TASQ once daily (initial dose 0.25mg/d escalating to 1.0mg/d over 4 weeks; N= 832) or placebo (N= 413) until progression or toxicity. Randomization was stratified by KPS (≥90% vs <90%), presence/absence of visceral disease, and geographic region. The most common administered dose in the TASQ arm was 1 mg daily (67%). Similar to the phase II trial [9], radiological PFS was prolonged after TASQ compared to placebo: 7.0 months versus 4.4 months (HR[95% CI] = 0.64 [0.54-0.75]; p< 0.001; Figure 4A). However, no OS benefit was found for TASQ compared to placebo: 21.3 months versus 24.0 months (HR [95% CI]: 1.10 [0.94-1.28]; p= 0.247; *Figure 4B*). Most common all grade AEs were decreased appetite, nausea and fatigue. The authors are inconclusive on whether the dosing of the therapy, or the toxicity of the drug, or the use as a single agent is the reason for the negative results in OS. As a consequence of these results, the use of CABO is no longer pursued in prostate cancer.[10]

Conclusions

Nivolumab proves beneficial as treatment option in advanced or metastatic renal cell carcinoma patients and will become a new standard treatment option in this patient population

Cabozantinib is favored in pts with advanced renal cell carcinoma, particularly in those with only 1 prior systemic treatment and with favorable or intermediate risk to progression

Hypofractionated radiotherapy of 60 gray is non inferior to the current standard treatment option of 70 gray and could possibly be offered as new standard of care;

Tasquinimod, with favorable radiological progression free survival, failed to prolong life expectancy in castration resistant prostate cancer. As a consequence, the drug will not be included in the guidelines for the treatment of CRPC.

References

1. J.Wolchok, H. Kluger, M. Callahan, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369(2):122-133.
2. N. Rizvi, J. Mazières, D. Planchard, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial.Lancet Oncol 2015;16(3):257-65.
3. P. Sharma, B. Escudier, D.F. McDermott, et al. CheckMate 025: a randomized, open-label, phase III study of nivolumab (NIVO) versus everolimus (EVE) in advanced renal cell carcinoma (RCC). Presented at ECCO - ESMO 2015; abstract 3LBA
4. R. Motzer, B. Escudier, D.F. McDermott, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015. [Epub ahead of print]
5. L. Zhou, X. Liu, M. Sun, et al. Targeting MET and AXL overcomes resistance to sunitinib therapy in renal cell carcinoma. Oncogene 2015 [Epub ahead of print]
6. T. Choueiri, B. Escudier, T. Powles, et al. Cabozantinib versus everolimus in patients with advanced renal cell carcinoma: Results of the randomized phase 3 METEOR trial. Presented at ECCO - ESMO 2015; abstract 4LBA.
7. T. Choueiri, B. Escudier, T. Powles, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015. [Epub ahead of print]
8. D. Dearnaley, I. Syndikus, H. Mossop, et al. 5 year outcomes of a phase III randomised trial of conventional or hypofractionated high dose intensity modulated radiotherapy for prostate cancer (CRUK/06/016): report from the CHHiP Trial Investigators Group. Presented at ECCO - ESMO 2015; abstract 8LBA.
9. R. Pili, M. Häggman, W. Stadler, et al. Phase II randomized, double-blind, placebo-controlled study of tasquinimod in men with minimally symptomatic metastatic castrate-resistant prostate cancer. J ClinOncol2011;29(30):4022-4028.
10. M. Carducci, A. Armstrong, R. Pili, et al. A phase 3, randomized, double-blind, placebo-controlled study of tasquinimod (TASQ) in men with metastatic castrate resistant prostate cancer (mCRPC). Presented at ECCO - ESMO 2015; abstract 4BA.