7143 POSTER

Prognosis of Patients With Metastatic Renal Cell Carcinoma (mRCC) With Primary Resistance to Sunitinib: Is There Any Active Treatment?

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Background: Around 20% of patients (pts) with mRCC experience rapidly progressive disease (PD) with sunitinib. Although 2nd line treatment with everolimus is currently the standard of care in this setting, there is no prospective data available in this specific subgroup.
Methods: Pts with mRCC with rapid PD (within 2 or 4 cycles) on first line sunitinib, were retrospectively collected from 17 major european institutions. Clinical data, MSKCC classification and further treatment were assessed; PFS and OS were calculated (Cox model).
Results: 144 mRCC pts with rapid PD on first line sunitinib (2 cycles, n = 89 or 4 cycles, n = 55), were identified. Median age was 59, sex ratio 111 M/ 33W. Histological subtypes were clear cell (77%) and papillary carcinomas (14%), notably 17% of tumours exhibited sarcomatoid features. Nephrectomy had been performed in 85% of pts. Most pts presented with synchroneous metastatic disease (82%), prognostic classification was good in 10%, intermediate in 62% and poor in 20% of pts. Metastatic sites were respectively: lung (70%), bone (32%), liver (26%). Median OS was 6.97 months (m) [1−33], 23/144 (16%) pts are still alive with a median follow up of 9 months after sunitinib stop.
Second line treatment was administered in 82 (57%) pts: 23 with everolimus (E), 20 with temsirolimus (T) and 33 with sorafenib (S), 2 with axitinib (A), 2 with a bevacizumab+sunitinib combination and 2 with chemotherapy.
In pts receiving 2nd line treatment, median OS from beginning of 2nd line was 122 days for mTOR inhibitors (E: 151d and T: 84d), and 194d for S. Interestingly the 2 pts receiving A presented long lasting partial response (PFS: 250 and 195 days). Clinical benefit >3 months was observed in 22 pts (27%). Univariate analysis identified following prognosis factors for OS: prior nephrectomy, Karnofsky index, MSKCC score, number of metastatic sites, number of sunitinib cycles (2 vs 4), second line treatment (yes vs no), none of them remaining in multivariate analysis.
Conclusions: Pts with rapid PD on sunitinib have a very dismal prognosis. The benefit of current second line treatments is questionable. Although retrospective, this study does not suggest that mTOR inhibition is superior to VEGF inhibition. Data from ongoing prospective trials are urgently needed. Better understanding of primary resistance to sunitinib might help to identify new pathways. Therefore this study should push physicians to refer pts to investigational new drug trials.

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Weekly Paclitaxel as Third-line Chemotherapy in Patients With Metastatic Transitional Cell Carcinoma of Urothelial Tract: Results of a Phase II Study

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Background: Few data exist about third-line chemotherapy for metastatic disease. Although administered in up-front and second-line regimens, paclitaxel was never evaluated as third-line treatment. This study assessed the activity of weekly paclitaxel in patients with advanced TCC previously-treated with two chemotherapy regimens.
Materials and Methods: From March 2007 to July 2010, 22 patients with metastatic TCC were recruited: median age was 64 years (45−71 years) with a median ECOG PS of 1. Patients received weekly paclitaxel 80 mg/m^2 dd.1, 8, 15 every 28 days until appearance of progressive disease or unacceptable toxicity.
Results: All patients were evaluable for efficacy and toxicity. No patient showed complete response. Four patients (18%) had partial response, eight patients (36%) reported stable disease for a disease control rate of 54%. The median time to progression (TTP) was 4.4 months with a median overall survival (MOS) of 7.1 months. Treatment was well tolerated: no patient developed grade 4 toxicities.
Conclusions: This is the first study which evaluated the efficacy of paclitaxel as third-line chemotherapy in metastatic TCC. Despite the poor prognosis subset of patients evaluated, weekly paclitaxel showed quite positive results in terms of efficacy with a manageable profile of toxicity: its administration could be of interest in well-selected patients.

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Self Assessment of Buccodental Toxicity − Comparison of Patients With Metastatic Renal-cell Carcinoma (RCC) Treated With Sunitinib to Patients Treated With Chemotherapy

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Background: Sunitinib is a standard of care for first-line treatment of advanced or metastatic RCC. Recently, the association of sunitinib and bisphosphonates has been described to increase osteonecrosis of the jaw (Bozas *and al,* Oncologie 2010). We measured the potential impact of Sunitinib on buccodental toxicities.
Methods: Between Oct and Dec 2010, 58 patients with metastatic RCC treated by Sunitinib (S) and 52 patients treated by chemotherapy (C) agreed to fill a self administered questionnaire assessing buccodental status included varying oral hygiene/care practices, history of bisphosphonate treatment, occurence of dental or gingival pathologies during treatment, and quality of life. T-tests and Chi-square analyses were used to compare differences between the two groups.
Results: Median age of the 110 pts analyzed was 62.5 years (28−84) with majority of male in group S (73%) and female in group C (67%). Smokers were more represented in group C (23.1%) than in group S (8.6%) ($p = 0.036$). Among 58 pts in the group S, 9 had previously received bevacizumab, and 5 Sorafenib. Among 52 pts in the group C, 13 received an adjuvant chemotherapy, 39 had metastatic chemotherapy line, and 8 combination of chemotherapy and bevacizumab. Some pts in each group received bisphosphonates: 8 in group S (13.8%) and 4 in group C (7.7%) ($p = 0.306$). Higher frequencies of dental and gingival toxicities in group S were observed: pain (53.7% *vs* 46.3%, $p = 0.007$), teeth instability (43.1% *vs* 22.5%, $p = 0.037$), gingival bleeding (62% *vs* 42.4%, $p = 0.010$) and cavities (51.6% *vs*25%, $p = 0.005$). Consequently, 62% (S) *vs* 42.3% (C) needed to change their alimentary habits ($p = 0.010$). Indeed, the pts of the group S had more frequently visited their dentist within the few months following treatment to remove pathological teeth (15 patients *vs* 4 patients, $p = 0.013$). Results were similar with or without bisphosphonate treated patients.
Conclusion: Sunitinib seems to increase buccodental toxicity as compared to chemotherapy with or without bisphosphonate association. This work emphasizes the need of an optimal dental care and follow-up for patients treated with Sunitinib.

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Pilot Investigation of Cisplatin, 5-Fluorouracil and a Taxane (TPF) in Patients (pts) With Advanced Squamous-cell Carcinoma (SCC) of the Penis − Results From a Single-Institution Series

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Background: Few sparse data indicate poor to moderate activity of systemic chemotherapy in advanced penile SCC, and no definitive acquisition is available concerning timing for integrated surgery. Pts with metastatic bilateral or pelvic nodes show an overall survival (OS) of 15% and less than 10%, respectively. We evaluated TPF in either neoadjuvant (NA), adjuvant (A) or metastatic (M) setting in a single-center pilot trial.
Methods: 3−4 courses of paclitaxel 120 mg/m^2 d1 or docetaxel 75 mg/m^2 d1 + cisplatin 75 mg/m^2 d1 + 5-FU 750 mg/m^2 96hrs continuous infusion from d1, q3wks were provided. Primary endpoint (EP) was progression-free survival (PFS). Safety profile, response rate (RR) and OS were the secondary EPs. Immunostaining for p53, p16, p63, EGFR, HER2/neu and mutational analysis of EGFR were planned on available tissue.
Results: From 7/2004 to 03/2011, 46 consecutive pts were treated, 40 of them fully evaluable for response and outcome. 8 pts underwent paclitaxel-

PF and 32 docetaxel-PF. Grade $\geqslant$ 3 hematologic toxicity was observed in 4 pts, grade $\geqslant$ 3 renal and neurotoxicity occurred in 1 pt each.
Median PFS and OS in the whole series were 6 (1−73) and 9.5 mos (1−73) respectively. Positive p53 staining significantly associated with better OS and PFS at univariate analysis (Log-Rank test p = 0.0421 and p = 0.0483, respectively).
Adjuvant setting: 17 pts (4 bilateral pN+ and 11 pelvic pN+) underwent adjuvant TPF. Median PFS and OS were 10 mos (1−73) and 13 mos (1−73). 10 pts (59%) were alive with 17 mos (1−73) of median follow-up (f-u).
Neoadjuvant setting: 16 pts with cN2/3 SCC (9 cN3) were treated, either at diagnosis (11) or following recurrence after prior lymphadenectomy (5). Median PFS was 4 mos (1−46). 3 pts achieved a complete response (CR) and 6 pts achieved a partial response (PR, RR = 62%). OS was 5 mos (3−46). 11/16 pts underwent surgery that was radical in 9 (82%). 3 pathologic-CR (27%) have been achieved. 8 pts (50%) were alive with a median f-u of 9 mos (3−46).
Metastatic setting: 7 pts were treated. 2 pts had a PR and 1 a SD that lasted a median of 5 mos (3−8), and all died of disease. Median PFS and OS were 2 mos (1−8) and 5 mos (2−12).
Conclusion: Perioperative TPF was effective in advanced penile SCC, either in A or NA setting. It deserves further investigation including earlier stages (probably all cN+), combined with surgery. Neoadjuvant TPF allowed to obtain a significant number of responses in very advanced pts and to perform radical surgery even in nodal relapses after prior intervention. Mature results on the predictive role of biomarkers will be available in Sept 2011.

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The REACT Expanded-access Program of Everolimus in Patients With Metastatic Renal Cell Carcinoma Refractory to VEGF-targeted Therapy: Subgroup Analyses by Prior Therapy

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Background: Everolimus has demonstrated clinical efficacy in metastatic renal cell carcinoma (mRCC) refractory to vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) therapy, and is approved for use in this indication in 65 countries. The REACT (RAD001 Expanded Access Clinical Trial in RCC) study was initiated to provide patients with VEGFR-TKI-refractory mRCC access to everolimus in advance of regulatory approval.
Materials and Methods: REACT was an open-label, international, expanded-access clinical trial (Clinicaltrials.gov: NCT00655252; Trial sponsor: Novartis Pharmaceuticals) that enrolled patients with measurable or nonmeasurable mRCC of any histology who were intolerant of, or progressed while on, VEGFR-TKI therapy. Everolimus 10 mg/day was administered orally. The long-term safety of everolimus in patients with mRCC, as determined by the overall incidence of grade 3/4 and serious adverse events (AEs), was the primary study objective. RECIST-defined tumour response was also assessed by local investigator. Several subgroup analyses were performed to evaluate the effect of prior treatment on safety and efficacy of everolimus.
Results: From July 2008 to June 2010, 1367 patients were enrolled. Most patients (92.7%) had progressed on prior VEGFR-TKI therapy, and some (24.4%) were VEGFR-TKI intolerant (some patients experienced both VEGFR-TKI intolerance and disease progression). Median everolimus treatment duration was similar across patient subgroups by prior VEGFR-TKI treatment, including VEGFR-TKI intolerant patients (Table). Best overall response rates in the VEGFR-TKI-intolerant subgroup were 1.8% partial response (PR) and 53.5% stable disease (SD), as compared with 1.7% PR and 51.6% SD for the overall population. The incidence of grade 3/4 AEs across all prior treatment subgroups were similar to those of the overall population.

Table: Everolimus treatment duration in REACT by prior therapy

	All	Progression on prior VEGFR-TKI	Intolerant to prior VEGFR-TKI	Treated with only 1 prior VEGFR-TKI	Treated with only prior sunitinib
n	1367	1267	333	895	742
Treatment duration, median (range), weeks	14.0 (0.1–83.7)	14.1 (0.1–83.7)	13.1 (0.6–71.7)	13.7 (0.1–83.7)	13.1 (0.1–83.7)

Conclusions: Patients enrolled in REACT derived benefit from everolimus irrespective of prior VEGFR-TKI therapy, including those who were VEGFR-TKI intolerant. Everolimus is well-tolerated and affords disease stabilization in the majority of patients with VEGFR-TKI-refractory mRCC, and is the standard-of-care in this patient population.

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Hyperglycemia and Hypercholesterolemia and Associated Outcomes of Patients With Metastatic Renal Cell Carcinoma Treated With Everolimus in the Expanded-access Program REACT

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Background: The occurrence of specific adverse events (AEs) has been shown to correlate with clinical efficacy of targeted therapies in the treatment of patients with metastatic renal cell carcinoma (mRCC). Subanalyses of REACT (RAD001 Expanded Access Clinical Trial in RCC) evaluated the potential association of hyperglycemia and hypercholesterolemia with outcomes in mRCC patients treated with everolimus.
Materials and Methods: REACT was an open-label, international, expanded-access clinical trial (Clinicaltrials.gov: NCT00655252; Trial sponsor: Novartis Pharmaceuticals) that evaluated the long-term safety and efficacy of everolimus (10 mg/day) in patients with mRCC who were intolerant of, or progressed while on, VEGFR-TKI therapy. All grade 3/4 AEs and any grade 1/2 AEs resulting in study drug modification were collected. Subgroup analyses of patients who developed hyperglycemia or hypercholesterolemia of any grade were performed.
Results: REACT enrolled 1367 patients from 34 countries. The median everolimus treatment duration was longer for patients who developed hyperglycemia (n = 78) or hypercholesterolemia (n = 14) than for the overall population (19.14, 19.71 vs 14.0 weeks, respectively; Table). Overall, 30.3% of REACT patients remained on therapy for $\geqslant$6 months, as compared with 42.3% and 35.7% of patients with hyperglycemia and hypercholesterolemia, respectively. Best overall response was stable disease in 51.6% of the overall study population, as compared with 65.4% of patients with hyperglycemia and 71.4% of patients with hypercholesterolemia.

Table. Everolimus treatment duration and best overall response in patients with hyperglycemia and hypercholesterolemia

	All n = 1364	Pts with hyperglycemia n = 78	Pts with hypercholesterolemia n = 14
Duration of treatment, median, weeks	14.0	19.14	19.71
Duration of treatment, weeks, %			
$\leqslant$4	8.6	1.3	7.1
>4 to $\leqslant$8	13.8	10.3	14.3
>8 to $\leqslant$16	32.8	35.9	14.3
>16 to $\leqslant$24	14.6	10.3	28.6
>24 to $\leqslant$32	11.7	17.9	14.3
>32 to $\leqslant$52	14.6	14.1	21.4
>2	4.0	10.3	0
Best overall response			
Partial response, n (%)	23 (1.7)	2 (4.6)	0
Stable disease, n (%)	705 (51.6)	51 (65.4)	10 (71.4)

Conclusions: Our results suggest that hyperglycemia and hypercholesterolemia do not lead to permanent everolimus treatment discontinuations, as most patients with these AEs remained on therapy longer than the overall REACT population. Hyperglycemia and especially hypercholesterolemia were observed in low numbers of patients, but they may be associated with improved response to everolimus treatment and should be further explored as putative biomarkers for mTOR inhibition.