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Safety and efficacy of sorafenib in patients with advanced renal cell carcinoma (RCC) with varying histologies: results from the phase 3, open access study of sorafenib in European patients with advanced RCC (EU-ARCCS)

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Background: In the expanded access EU-ARCCS study, 1150 pts with advanced RCC, who failed prior systemic therapy for advanced disease and were not eligible for, or did not have access to sorafenib clinical trials, received sorafenib treatment. The efficacy and safety profile of sorafenib in the clinical practice setting of EU-ARCCS was comparable to the pivotal Phase 3 TARGET study. Because the recent literature notes a change from the era of immunotherapy in reported differences in prognosis for different RCC histologic subtypes (Chowdhary, 2009), we compared the safety and efficacy of sorafenib in the 3 most common histologies recorded in the EU-ARCCS study.
Methods: Pts with $\geqslant$1 prior failed systemic therapy or unsuitable for cytokine therapy, ECOG PS 0–2, and life expectancy >2m received sorafenib 400 mg BID until progression, intolerable toxicity, or consent withdrawal. Study assessments were conducted at baseline and once a month. Tumor assessment and radiologic evaluation were conducted $\leqslant$28d prior to start of sorafenib therapy, then per local standards of care, but $\leqslant$3m. Endpoints included PFS, disease control rate (DCR; pts who achieved a complete response, partial response, or stable disease by radiologic or clinical assessment for $\geqslant$8w), and safety.
Results: 1159 pts were enrolled in EU-ARCCS; 1150 pts were treated. The 3 most common histologies were pure clear cell in 909 (79%) pts, clear cell w/ papillary features in 112 (10%) and clear cell w/ sarcomatoid features in 53 (5%).

	Overall	Clear-Cell		
	(N = 1150)	Pure (n = 909)	w/Papillary features (n = 112)	w/Sarcomatoid features (n = 53)
Efficacy				
Median PFS, m (95% CI)	6.6 (6.1, 7.4)	7.4 (6.6, 8.2)	5.7 (4.5, 6.7)	4.0 (2.8, 4.8)
DCR, % (95% CI)	(n = 1048) 85.4 (83.1, 87.5)	(n = 836) 86.8 (84.4, 89.1)	(n = 101) 82.2 (73.3, 89.1)	(n = 48) 81.3 (67.4, 91.1)
Drug-related AEs (DRAEs) Grades 3/4, n (%)	(n = 1145)	(n = 904)	(n = 112)	(n = 53)
All categories	507 (44)	415 (46)	46 (41)	17 (32)
Hand-foot skin reaction	149 (13)	119 (13)	19 (17)	8 (15)
Fatigue	81 (7)	69 (8)	6 (5)	5 (9)
Diarrhea	84 (7)	71 (8)	7 (6)	2 (4)
Hypertension	70 (6)	62 (7)	5 (5)	0 (0)
Rash/desquamation	60 (5)	49 (5)	4 (4)	3 (6)

Conclusions: Pts with pure clear-cell histology appear to derive the same benefit from sorafenib as the overall population, and median PFS was similar to the TARGET study. PFS of pts with papillary histology is similar to that reported for this subtype (Choueiri, 2008). As expected, pts with sarcomatoid features had a poor prognosis. DRAEs were comparable among the histologic subtypes.

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Burden of bone metastases from renal cell carcinoma: zoledronic acid and functional Independence

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Background: Approximately 30% of patients with advanced renal cell carcinoma (RCC) develop bone metastases. Without bone-targeted therapies, approximately 75% of these patients develop skeletal-related events (SREs) including pathologic fracture, spinal cord compression, requirement for surgery or radiotherapy to bone, and hypercalcaemia of malignancy. Zoledronic acid (ZOL) delays the onset of SREs and reduces pain, enabling patients to maintain functional independence.
Materials and Methods: This was a retrospective assessment of the burden of bone disease from RCC in our practice and whether the activity reported for ZOL in RCC patients in the clinical trial setting (n = 46) translates into benefits during clinical practice.
Results: In our clinic, ZOL 4 mg monthly is used to treat patients with bone metastases from genitourinary cancers such as RCC. Bone lesions associated with RCC are typically highly vascularised and osteolytic. In our clinic, 2 patients with RCC each had a profoundly osteolytic lesion on the lower leg, with amputation recommended at orthopaedic evaluation. The first patient underwent leg amputation and required ambulatory support thereafter. The second patient, who also had lung and liver metastases, refused amputation. Radiotherapy, ZOL (dose-adjusted based on creatinine clearance; 3.5 mg every 4 weeks), dexamethasone (4 mg), and opioid analgesics were prescribed. At the 4-week follow-up, she reported improvement in pain and achieved independence from her walking frame but required crutches. After 12 weeks, her Ntelopeptide levels had normalised (to 42 from 149 nmol/mmol creatinine). More importantly, she sustained no fractures or increases in analgesia before succumbing to her disease ~7 months after initiation of radiotherapy and ZOL. This preservation of mobility with ZOL in clinical practice is consistent with its activity in the phase III trial, in which ZOL delayed times to pathologic fracture (P = 0.003) and bone lesion progression (P = 0.014) versus placebo in the RCC subset.
Conclusions: In our clinical experiences, bone metastases from RCC can be associated with severe morbidity including potentially debilitating destruction of weight-bearing bones. The potential to restore function in bone affected by aggressive tumours with the combination of radiotherapy and ZOL is an important consideration for preserving mobility and quality of life for patients with RCC.

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Evaluation of quality of life in patients with advanced renal cell carcinoma treated with temsirolimus vs interferon-alfa: results from a phase III randomized trial

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Background: Temsirolimus (TEMSR), an mTOR inhibitor, was approved for advanced renal cell cancer (advRCC) treatment based on improvement in overall survival vs. interferon-alfa (IFNa). Previously, we reported improved Q-TWiST in patients with advRCC treated with TEMSR vs. Interferon-alfa (INFa) (Parasuraman et al. J Clin Oncol 2007:5049). We now evaluate quality of life (QoL) changes in these patients using EQ5D.
Methods: Data from a randomized study of advRCC patients were analyzed. Patients included in to the trial had multiple prognostic factors indicating poor risk of survival. EQ5D responses were recorded at baseline, wks 12 and 32, any visit at which a symptomatic National Cancer Institute CTC grade 3 or 4 AE was recorded (if possible, unless the medical condition was prohibitive), and at the withdrawal visit. To be included in the analysis, patients were required to have EQ5D data at baseline, wk 12, and last visit after wk 12 (if alive and not lost to follow-up). EQ5D index scores were used in a repeated measures mixed-effect (RMME) model to evaluate QoL differences between TEMSR vs. IFNa patients, while controlling for baseline covariates.
Results: Of the 416 patients randomized to TEMSR and IFNa arms, 270 met the inclusion criteria for this analysis (n = 115, 155 respectively). At baseline, average age of the patients was 59 yrs (SD = 10), 32% were females, 85% had clear cell carcinoma, 95% had $\geqslant$3 adverse prognostic factors, and mean EQ5D score was 0.62 (SD = 0.24). No systematic differences were identified between groups for the baseline characteristics. Based on the RMME model, the least square means for on-treatment EQ5D in the INFa arm was 0.492 (SE = 0.031) and the TEMSR arm was 0.590 (SE = 0.026) (p-value for diff = 0.0022; 95% CI: −0.162, −0.036). Other significant covariates in the model were: patients in the intermediate-risk group had higher on-treatment EQ5D vs. patients in the poor-risk group (p < 0.001; 95% CI: 0.080 to 0.214), patients at wk 12 had higher on-treatment EQ5D vs. patients at the withdrawal visit (p < 0.001; 95% CI: 0.055 to 0.148), and patients having higher baseline EQ5D had higher on-treatment EQ5D (p < 0.001; 95% CI: 0.470 to 0.733).
Conclusions: Based on EQ5D measurements, TEMSR provides significantly better QoL compared with IFN in poor-prognosis advRCC patients. The difference in EQ5D of 0.098 between TEMSR and INF is considered clinically significant.