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Effects of renal impairment on the pharmacokinetics and safety of sorafenib

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Introduction: The effect of renal impairment on sorafenib pharmacokinetics (PK) and safety was evaluated in a dedicated single-dose phase I study, pooled multiple-dose phase I studies, and phase III studies in cancer patients.
Methods: Subjects were classified into 4 renal function groups: normal (Cl_{cr} > 80 mL/min) function, mild impairment (Cl_{cr} 50−80 mL/min), moderate impairment (Cl_{cr} 30−<50 mL/min), and severe impairment (Cl_{cr} < 30 mL/min). The primary statistical analysis was based on Cl_{cr} determined by the Cockroft-Gault equation using subjects' ideal body weight. As a secondary analysis, Cl_{cr} was determined using subjects' actual body weight in an exploratory fashion. Subjects received a single 400 mg dose of sorafenib. Plasma PK samples were collected for up to 144 hours postdose. PK and safety data from sorafenib phase I and III multiple-dose studies, respectively, were also analyzed.
Results: The single-dose phase I study enrolled 32 subjects at 3 centers; mean age was 59 years (range, 39−74), 66% were male. AUC, C_{max}, and half-life values for sorafenib are shown in Table. The primary analysis showed aberrantly high AUC and C_{max} values in the mild group inconsistent with results in the moderate and severe groups. The secondary analysis reclassified some subjects from mild to normal, resulting in a decrease in the AUC and C_{max} of the mild group with greater evidence of PK consistency across all 4 groups. Most common adverse event (AE) was headache. No serious AEs were noted. In pooled sorafenib phase I studies, renal function did not affect sorafenib PK. In a sorafenib phase III trial in advanced RCC, incidence of key AEs did not differ among subjects with normal renal function and those with mild or moderate impairment (data to be shown).
Conclusion: Based on all data assessed, renal impairment did not modulate sorafenib PK parameters. Renal impairment appears to have no clinically relevant effect on sorafenib safety. No dose adjustment is indicated in pts with mild, moderate, or severe renal impairment.

	Normal		Mild		Moderate		Severe	
Parameter	Prim (n = 8)	Sec (n = 12)	Prim (n = 8)	Sec (n = 7)	Prim (n = 8)	Sec (n = 6)	Prim (n = 8)	Sec (n = 7)
AUC, mg.h/L (CV)	62 (72%)	88 (94%)	186 (47%)	133 (62%)	84 (40%)	73 (61%)	74 (84%)	83 (79%)
C_{max}, mg/L (CV)	2.3 (74%)	3.1 (94%)	5.7 (59%)	4.1 (64%)	2.7 (64%)	2.1 (104%)	1.9 (85%)	2.2 (68%)
$t_{1/2}$, h (CV)	23 (31%)	23 (31%)	27 (32%)	31 (29%)	26 (27%)	27 (42%)	25 (41%)	22 (19%)

Prim=primary analysis; Sec=secondary analysis; CV = coefficient of variation

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Randomized, placebo-controlled, phase 3 study of everolimus, a novel therapy for patients with metastatic renal cell carcinoma: subgroup analysis of patients progressing on prior bevacizumab therapy

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Background: Everolimus is an oral inhibitor of mTOR, a protein kinase that regulates cell growth, proliferation, and survival. Results of a phase III study (RECORD-1; NCT00410124) showed that everolimus prolonged progression-free survival (PFS) versus placebo in patients with metastatic renal cell carcinoma (mRCC) whose disease progressed after failure of epidermal growth factor receptor-tyrosine kinase inhibitors, sunitinib and/or sorafenib (*Lancet* 2008;372:449−456). In RECORD-1, prior treatment with bevacizumab also was allowed; this analysis evaluates the effect of everolimus therapy on PFS in the subgroup of patients who received prior bevacizumab therapy.
Materials and Methods: RECORD-1 is a randomized, double-blind, phase III study, in which patients with mRCC who progressed on sunitinib and/or sorafenib therapy received either everolimus 10 mg once daily (n = 272) or placebo (n = 138) in conjunction with best supportive care. Patients were stratified according to a Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score and previous antitumor therapy. In the subgroup of patents whose disease progressed on bevacizumab, differences in PFS between the everolimus group and placebo were estimated using a stratified Cox proportional hazard model and compared with the Log-rank test. Safety and tolerability also were assessed in this patient subgroup.
Results: 24 patients in the everolimus group and 14 patients in the placebo group had received prior bevacizumab therapy. In this subgroup, the median PFS was 5.75 mo (95% confidence interval [CI]: 3.52, 6.90) in patients receiving everolimus versus 1.77 mo (95% CI: 1.02, 3.78) in those receiving placebo (hazard ratio: 0.30 [95% CI: 0.13, 0.68]; $P = 0.001$). Treatment-related grade 3/4 adverse events that occurred in at least 5% of patients who received everolimus included anemia (n = 3), hyperglycemia (n = 2), and lung infiltration (n = 2). The safety profile observed in this subgroup of patients was consistent with previous reports of the safety and tolerability of everolimus therapy.
Conclusions: Everolimus prolonged PFS versus placebo in a subgroup of patients with mRCC who progressed after receiving bevacizumab and was well tolerated. These results and those of the primary analysis suggest that mTOR inhibition with everolimus may be active in patients with mRCC who progressed, regardless of previous therapy.
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Final analysis of a large open-label, noncomparative, phase 3 study of sorafenib in European patients with advanced RCC (EU-ARCCS)

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Background: In the pivotal phase III TARGET study, sorafenib doubled progression-free survival (PFS) and demonstrated an overall survival (OS) advantage in a pre-planned secondary analysis censoring the placebo group at crossover in patients (pts) with clear-cell RCC. The objectives of the present EU-ARCCS trial were to make sorafenib available to European pts prior to regulatory approval, and to collect safety and efficacy data from a large and varied study population reflecting clinical practice.
Methods: Pts with ⩾1 prior failed systemic therapy or unsuitable for cytokine therapy, ECOG PS 0−2, and life expectancy >2 months received sorafenib 400 mg BID until disease progression, intolerable toxicity, or withdrawal of consent. Study assessments were conducted at baseline and once a month. Tumor assessment and radiologic evaluation were conducted ⩽28 days prior to start of sorafenib therapy, then per local standards of care, but at least every 3 months. Endpoints included PFS, disease control rate (DCR; pts who achieved a complete response, partial response, or stable disease by radiologic or clinical assessment for ⩾8 wks), and safety.

Baseline characteristics (n = 1150)	
Median age, y (range)	62 (18−84)
ECOG PS < 2, n (%)	976 (85)
Number of tumor sites ⩾3, n (%)	539 (47)
Pure clear-cell histology, n (%)	909 (79)
Clear-cell w/ papillary features, n (%)	112 (10)
Clear-cell w/ other histologic types, n (%)	66 (6)
Clear-cell w/ sarcomatoid features, n (%)	53 (5)
Prior nephrectomy, n (%)	1020 (89)
Results	
PFS (n = 1150)	
Median PFS, m (95% CI)	6.6 (6.1, 7.4)
PFS rate after 12m, % (95% CI)	29.2 (26.4, 32.1)
DCR (n = 1048) % (95% CI)	85.4 (83.1, 87.5)
Drug-related adverse events (n = 1145)	
Grades 3/4, n (%)	
All categories	507 (44)
Hand-foot skin reaction	149 (13)
Fatigue	81 (7)
Diarrhea	84 (7)
Hypertension	70 (6)
Rash/desquamation	60 (5)

Results: 1159 pts were recruited in 11 European countries; 1150 pts were treated. Baseline pt characteristics, efficacy, and safety results are summarized in the table. The median PFS was 6.6 months (95% CI, 6.1−7.4 months). DCR rate was 85.4%. Hand-foot skin reaction, diarrhea, and fatigue were the most common adverse events.
Conclusions: The efficacy and safety profile of sorafenib in the large, diverse, advanced RCC pt population treated in the clinical practice setting of EU-ARCCS was similar to that seen in the research setting of TARGET study. Both datasets together strongly support the effectiveness of sorafenib in pts with advanced RCC, pretreated or unsuitable for cytokines.

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The effect of zoledronic acid on bone metastasis in patients with metastatic renal cell cancer – a German prospective single-arm clinical trial

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Objective: Over the last decades the incidence of renal cell cancer (RCC) steadily increased. Of these patients about 30% will develop metastases to bone. These patients face considerable skeletal morbidity including bone pain, pathologic fractures, spinal cord compression or tumor induced hypercalcemia (TIH). Therefore patients with metastastic renal cell cancer (mRCC) were included in a prospective, single-arm trial evaluating the SRE (skeletal related event) rate under therapy with zoledronic acid (Zometa®). The study was aimed to assess the proportion of patients who experience at least one SRE during 12 months of treatment with zoledronic acid (ZA).
Material and Methods: Patients with RCC having 1 cancer-related bone lesion and 2 prior applications of a bisphosphonate were eligible. Bone lesions were diagnosed by nucleotide bone scan and 1 lesion was confirmed via X-ray, CT or MRI. Patients passed a 12 months treatment period with ZA (4 mg) every 3 weeks. During a time period of 54 weeks they were followed every 3 weeks for development of SREs (radiation, surgery to bone, spinal cord compression, pathologic bone fractures) and TIH. If AP or LDH were >2×ULN (upper limit of normal) a bone scan or MRI-quickscan was performed. In case of evident SREs or symptoms (e.g. bone pain) confirmatory studies were performed which consisted of X-ray, CT or MRI. After end of treatment patients received a final assessment of disease status and entered a survival follow-up for one year.
Results: 51 patients (median age: 63 years) in 21 centers participated in the study. According to MSKCC score 8%, 56% and 18% showed good, intermediate and poor prognosis. 78% of patients had 6 bone lesions and 18% already experienced at least one SRE prior to study entry. A total of 26% also obtained prior medications, mainly interferon (20%), interleukin (16%) or chemotherapy (16%). 25 patients completed the treatment period and 26 % of them showed 1 SRE according to preliminary analysis. Altogether 23 SREs and no TIH were observed. Final results will be shown at presentation.
Conclusion: Patients with mRCC and bone metastasis are at high risk to experience SREs. Up to 74% of cases were reported in a subgroup analysis of a phase III trial. This is the first study prospectively evaluating the SRE rate in patients with mRCC and bone lesions receiving ZA. Preliminary results indicate a SRE rate of 26% without occurrence of TIH. The results of this trial could further support the use of ZA in this subset of patients.

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Changes in lymphocytic populations and autoantibodies resulting from sunitinib treatment of metastatic renal cell carcinoma (mRCC)

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Background: Immunotherapy was the first and until recently the only therapeutic option for the advanced kidney cancer, a highly resistant to cytotoxic agents neoplasm. Treatment with cytokines has suggested an anticancer role of the immune system in mRCC. This role with the new first line antiangiogenic molecules, mainly sunitinib and bevacizumab with interferon- a (a known immunotropic factor), is now under investigation. The high rate of hypothyroidism, a common adverse event in sunitinib treated patients, is maybe a clinical manifestation of its immunotropic effect.
Materials and Methods: ANA, anti-dsDNA, cANCA, pANCA, AMA, ASMA, C3, C4, RF, anti-Tg and TPO in the serum and lympocytic populations in whole blood, before and during first-line sunitinib therapy (every 12−18 weeks), were analyzed in 27 naive patients with mRCC. Autoantibodies were measured with ELISA, RIA or immunofluoresence, while lymphocytic populations were studied with flow cytometry.
Results: Median values of selected populations and the incidence of positive autoantibodies are shown in Table 1. cANCA, and rheumatoid factor were negative at all measurements before or during treatment. No changes in anti-dsDNA, cANCA and AMA were observed during therapy. There was a significant reduction of CD4 ($p = 0.048$), and HLADR+ CD4 (0.033) and CD8 ($p = 0.018$) cells between baseline and at 12−18 weeks of therapy. During the same time the incidence of ASMA+ cases was also reduced (56% vs. 17%, $p = 0.024$). Nevertheless, there was a significant increase at 3rd measurement (17% vs. 100%, $p = 0.001$), when all patients had positive ASMA. Finally, there was a significant correlation between the occurrence of ANA antibodies and HLADR+ CD8 cells 12−18 weeks after the initiation of treatment with Sunitinib (median 10.2% vs. 8.3% for + and − cases, respectively, $p = 0.032$).
Conclusions: The administration of Sunitinib seems to affect certain immunological markers in patients with metastatic RCC, although some of these changes were transient. Correlation with outcome is currently being studied and will be presented during the meeting.

Table 1. Median pre-treatment (B), 3 months (1) and 6 months (2) values in patients with RCC during Sunitinib therapy

	CD4	CD8	Tregs	HLADR4	HLADR8	ANA	AMA	ASMA
B	67%	33%	3.1%	6.8%	15.5%	55%	17%	57%
1	57%	43%	3.3%	4.7%	9.3%	36%	17%	17%
2	57%	43%	3.5%	5.6%	10.6%	33%	0%	100%

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Analysis of lipid profile of renal cell carcinoma by imaging mass spectrometry

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Background: Although renal cell carcinoma (RCC) had no specific molecular markers, we have reported so far that brain type-free fatty acid binding protein (B-FABP) is highly expressed in RCC and it can be also a useful biomarker. On the other hand, it is known that B-FABP strongly binds to polyunsaturated fatty acid and RCC includes plenty of lipids. However, there is no report about the lipid profile of RCC associated with B-FABP expression. We here demonstrate RCC fatty acid profile by imaging mass spectrometry (IMS).
Materials and Methods: Sample preparation. We used seven frozen sections including tumor and normal tissue in the six removed kidneys and one metastasis site. All tissues were immediately frozen in liquid nitrogen, and stored at −80°C without any fixation. The tissue was sliced into 8 mm-thick sections using a cryostat and mounted onto an indium tin oxide (ITO)-coated slide glass (Bruker Daltonics). A thin matrix layer was applied to the surface of the slide by using an airbrush with a 0.2 mm nozzle and DHB solution (50 mg/mL DHB, 20 mM sodium acetate, 70% methanol, 0.1% TFA) was sprayed.
Imaging mass spectrometry (IMS). MS was performed with a MALDI-TOF/TOF-type instrument: Ultraflex II TOF/TOF (Bruker Daltonics) equipped with a 355 nm Nd:YAG laser with a repetition rate of 200 Hz. Data were acquired in the positive-ion mode by using an external calibration method. The mass spectrometer parameters were set to obtain the highest sensitivity with m/z values in the range of 300−1000. All the spectra were acquired automatically using the Flex Imaging software (Bruker Daltonics).
Results: The uptake of linoleic acids or DHA/EPA in tumor part was increased and decreased than that of normal part, respectively, irrespective of tumor stage and grade.
Conclusions: As far as we know, our study is the first investigation for RCC lipid profile using imaging MALDI-MS. These results may give new aspects in diagnosis and treatment of RCC.