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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)