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An International Expanded Access Program (EAP) of RAD001 (everolimus) in patients with metastatic renal cell carcinoma (mRCC) who fail, or become intolerant of a prior vascular endothelial growth factor receptor (VEGFr) therapy

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RAD001 (everolimus) is an oral inhibitor of the mammalian target of rapamycin (mTOR), a key kinase regulating cell proliferation, metabolism and angiogenesis. Everolimus is the only therapy with proven efficacy in a randomized, controlled clinical trial in mRCC patients (pts) after progression on sunitinib and/or sorafenib. When compared with placebo everolimus more than doubled the time without tumor growth or death (4.9 vs.1.9 months) and reduced the risk of disease progression or death by 67% (Motzer R, et al, J Clin Oncol, 08, Escudier B, et al, Ann Onc, 08). For these reasons, everolimus is being offered globally in this EAP to fulfill an unmet medical need until approval globally.

Methods: The program was started in July, 2008 and pts with clear cell mRCC who failed or became intolerant of sunitinib and/or sorafenib are treated with once daily, oral doses of 10 or 5 mg. Therapy continues until disease progression based on overall investigator assessment every 3 months. Up to 1000 patients will be treated in this program from 36 countries worldwide.

Results: As of April 3, 2009, 342 pts are enrolled from 22 different countries. Of the 342 patients enrolled, 278 continue treatment today. To date, no new safety issues have been identified. Safety and efficacy data will be presented.

Conclusion: The global EAP is successfully providing everolimus to pts with mRCC before marketing approval. The rapid enrolment rate confirms the unmet medical need after failure of a VEGFr therapy. The program also provides an efficient framework for the development of global expanded programs for innovative anticancer agents in patients without satisfactory therapeutic alternatives.

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Overall survival among metastatic renal cell carcinoma (MRCC) patients corrected for crossover using a rank preserving structural failure time (RPSFT) model: analyses from the everolimus phase III trial

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Background: The pivotal trial for everolimus, RECORD-1, examined the impact of everolimus on progression free survival (PFS) and overall survival (OS) in mRCC patients following failure on a VEGFr-TKI therapy. The study design allowed for crossover to open label everolimus following progression for patients randomized to placebo. The ITT analysis based on updated survival data indicated a positive effect of everolimus on OS (HR = 0.87, 95% CI: 0.65−1.15, p = 0.162). However, the ITT estimate of treatment effect is likely to be confounded by crossover and biased towards the null hypothesis of no difference.

Materials and Methods: An exploratory analysis of OS has been conducted using a rank preserving structural failure time (RPSFT) model (Robins and Tsiatis, 1991; Korhonen, et al 1999). This method provides a randomisation-based treatment-effect estimate corrected for the bias due to crossover (under the assumption that the effect is multiplicative in time). This method has been recently applied in a setting similar to RECORD-1 when analysing data from a phase-III trial of sunitinib vs placebo in advanced GIST after imatinib failure (Demetri, et al 2008; Schöffski, et al 2008).

Results: Estimate of the relative survival time when receiving everolimus therapy is 1.9-fold longer (95% CI: 0.5 to 8.5) than when receiving placebo only. Reconstructing the placebo curve by correcting for the effect of crossover provides an estimated median of 10.0 months instead of the observed 14.4 months. The median for patients randomised to everolimus was 14.8 months.

Conclusions: The RPSFT analysis of RECORD-1 indicates the everolimus treatment is associated with an overall survival benefit for patients who failed VEGFr-TKI.

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Open-label phase II trial of everolimus monotherapy for patients with advanced papillary renal cell cancer (RAPTOR): rationale and design

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Background: Papillary tumors are morphologically and genetically distinct renal cell malignancies, with multiple genetic abnormalities described. Two types of papillary renal cell cancers (RCC) exist: type I tumors are usually low grade and have a better prognosis, whereas type II tumors are high grade and have a poorer prognosis. In general, RCC is resistant to chemotherapy, so newer approaches, such as vascular endothelial growth factor (VEGF)-targeted therapies, have been evaluated and have demonstrated clinical benefit in clear cell RCC. However, limited data exist in patients with papillary RCC. Everolimus is an oral inhibitor of mTOR, a protein kinase that regulates cell growth, proliferation, and survival. Everolimus has demonstrated activity as a single agent in patients with metastatic RCC whose disease progressed on VEGF-tyrosine kinase inhibitor therapy (*Lancet* 2008;372:449−456). The purpose of the current study is to evaluate the safety and efficacy of everolimus monotherapy in previously untreated patients with advanced papillary RCC.

Materials and Methods: This ongoing open-label, multicenter, phase II study includes patients with a histological diagnosis of advanced type I or II metastatic papillary RCC. Other inclusion criteria: ECOG performance status $\leqslant$1, life expectancy $\geqslant$3 months, and adequate bone marrow, liver, and renal function. Patients who received prior systemic treatment for RCC (eg, sorafenib, sunitinib, or bevacizumab) are excluded. Patients will self-administer everolimus 10 mg (2.5 mg tablets) orally daily until disease progression, unacceptable toxicity, or study discontinuation. Tumor assessments will take place every 8 weeks until treatment discontinuation. The primary study endpoint is the percentage of patients with progression-free at 6 months. Secondary endpoints include the disease control rate, objective response rate, median progression-free survival, overall survival, and safety/adverse events.

Results: This study is currently ongoing, with a target accrual of 60 patients.

Conclusion: Papillary RCC is a morphologically distinct type of renal cancer, for which only limited data on potentially effective treatments exist. Results of this trial will determine the efficacy and safety of mTOR inhibition with everolimus in previously untreated patients with papillary RCC.

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Subgroup analysis of French patients from RECORD-1: a randomized, placebo-controlled, phase III study of everolimus, a novel therapy for patients with metastatic renal cell carcinoma

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Background: Everolimus, an oral mTOR inhibitor, has been shown to prolong progression-free survival (PFS) versus placebo in a randomized phase III trial (RECORD-1; NCT00410124) involving patients with metastatic renal cell carcinoma (mRCC) whose disease progressed after sunitinib and/or sorafenib therapy. Epidemiological results indicate that the incidence of renal cell carcinoma can vary greatly by region or country, sparking interest in identifying new and effective therapies. This subgroup analysis evaluates the efficacy and safety of everolimus therapy in French patients who participated in the RECORD-1 study.

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 French patients, between-group differences in median PFS were estimated using an unstratified Cox proportional hazard model and compared with the