7154 POSTER

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

Log-rank test. Safety and tolerability also were assessed in this patient subgroup.
Results: The French subgroup of the RECORD-1 study included 72 patients; 42 received everolimus and 30 received placebo. Median PFS was 5.52 months in French patients who received everolimus versus 1.87 months in those who received placebo (hazard ratio: 0.20; 95% confidence interval: 0.12, 0.34; $P < 0.001$). These results are consistent with those observed in the analysis of the total study population. The safety profile observed in the French subgroup of patients was also consistent with previous reports of the safety and tolerability of everolimus therapy.
Conclusions: Everolimus prolonged PFS versus placebo and was well tolerated in the subgroup of French patients with mRCC from the RECORD-1 trial. Everolimus is a novel therapy for patients with limited treatment options.
Acknowledgment: This study is supported by Novartis Pharmaceuticals Corporation.

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Impact of Tyrosine Kinase Inhibitors (TKIs) in the treatment of patients with advanced renal cell carcinoma (RCC): A single centre retrospective review at the Hospital Universitario Central de Asturias

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Introduction: For almost the last two decades, cytokines (CKs) have been the only systemic treatment options available for advanced RCC. In recent years, TKIs have demonstrated clinical activity in this tumor. Our purpose has been to describe the experience of a single centre with the use of CKs and TKIs in the treatment of patients with advanced RCC.
Methods: This study was designed as a retrospective chart review in RCC patients being treated with CK and or TKI in our department between July 96 and June 08. Efficacy and toxicity were assessed following OMS criteria. The Kaplan-Meier method was used to estimate progression free survival (PFS) and overall survival (OS).
Results: Ninety-four patients were classified in three groups depending on the modality of treatment administered: forty-six treated only with CKs and/or chemotherapy (27 immunotherapy, one chemotherapy and 18 both), 28 only with TKIs (25 sunitinib and 13 sorafenib) and 20 with TKIs in second-line after failure to CKs (17 sunitinib, eight sorafenib, four bevacizumab and one lapatinib). The median of age was 60 years in the CK group and with TKIs 65 and 62 in first and second line respectively. Eighty-five percent of patients treated with CK were men and 75% in the group of TKIs in first and 80% in second line respectively. Overall 89% of patients had a favourable risk and 11% an intermediate risk. All patients were considered evaluable for toxicity. The main toxicity grade 3−4 (%) was asthenia for both groups of treatment, (10) in TKIs and (15) in CKs. Other grade 1−2 toxicities were mucositis (39), bleeding (8), hypertension (19), skin (33) and hypothyroidism (12.5) related with TKIs and anemia (33), cough (29), asthenia (39) and emesis (14) with CKs. The objective response rate among 80 patients evaluable for activity was 10.6% with CK and 46.5% and 35% with TKIs in first and second line respectively. Disease stabilization with CKs was registered in 59% and with CK in 25% and 50% of patients treated in first and second line respectively. The median PFS with CK was 122 days (IC 95%: 82−162) and with TKIs 201 days (65−337) in first and 346 days (256−436) in second line. The median OS was 229 days (142−316) and 2,074 days (1,152−2,996) for patients treated with CK and TKI respectively.
Conclusions: Our results are in agreement with the activity and survival previously reported in the literature for TKIs in patients with advanced RCC in first and second line treatment with an acceptable toxicity.

7159 POSTER

Loss of work activity and productivity in caregivers attending to patients with advanced renal cell carcinoma treated with temsirolimus or interferon-alfa: evaluations from a phase 3 randomized trial

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Background: In cancer, informal caregiving can influence a caregiver's employment, increasing missed work time as well as reducing productivity while at work. We analyzed the impact of informal caregiving on caregiver's workplace productivity. Workplace productivity of caregivers attending to patients (pts) with advanced renal cell cancer (advRCC) treated with temsirolimus (TEMSR) was compared with that of caregivers attending to pts treated with interferon-alfa (INFa). In addition, we evaluated the reaction of informal caregiving in both treatment groups.
Methods: Data were analyzed from a phase 3 trial of pts with previously untreated, poor-prognosis advRCC (N Engl J Med 2007;356:2271). Pts were randomly assigned to receive 25 mg TEMSR IV weekly, or INFa (titrated to 18 mU) SC 3 times weekly, or TEMSR plus IFNa. The combination arm was not included because efficacy was not better than that of the IFNa arm. Caregiver work productivity and activity impairment questionnaire (WPAI-CG), as well as a caregiver reaction assessment instrument (RAI), was administered at baseline and at 4-wk intervals until wk 32. Participation for the caregiver study was on a voluntary basis. For the current analysis, we evaluated WPAI and RAI at pts' last visits. ANCOVA model was used to compare the two treatment groups. Model covariates included baseline WPAI-CG, RAI, and measures of disease severity.
Results: Of 416 pts entered in the TEMSR (n = 209) and IFNa (n = 207) arms, data were available for 174 caregivers. About 50% of participating caregivers were employed (55% in TEMSR arm & 45% in the INFa arm [p = 0.1724]). Caring for advRCC pts was associated with substantial carer burden; on average, caregivers reported absenteeism of 11 hrs per wk and a 27% reduction in productivity at work. Caregivers caring for TEMSR pts reported significantly lower absenteeism (22% vs. 40%, p = 0.0339), lower overall work productivity loss (34% vs. 49%, p = 0.0178), and lower overall impairment in regular activity (29% vs. 38%, p = 0.0305) than caregivers caring for INFa pts. Based on RAI questionnaire, caregivers of TEMSR pts reported a significantly lower burden on their daily schedule compared with caregivers of INFa pts (14.0 vs. 15.9, p = 0.0043).
Conclusions: Although the study had 42% (174/416) caregiver participation rate, TEMSR therapy in advRCC is associated with reductions in caregiver absenteeism, overall impairment in regular activity, overall work productivity loss, and burden on caregiver schedule compared with IFNa therapy.
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Evaluation of adverse event -related hospitalizations in patients with advanced renal cell carcinoma on treatment with temsirolimus or interferon-alfa: results from a phase 3 randomized trial

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Background: First-line immunotherapies for advanced renal cell carcinoma (advRCC) include interleukin-2 and interferon alfa (INFa), administered either alone or in combination. In particular, IFNa has been associated with increased adverse events (AEs) and AE-related hospitalizations. Temsirolimus (TEMSR) is a specific inhibitor of mammalian target of rapamycin kinase and a targeted therapy in advRCC. TEMSR significantly increased overall survival in patients with advRCC compared with INFa in a phase 3 global advRCC (ARCC) trial (N Engl J Med 2007;356:2271). Due to its targeted action, TEMSR could potentially reduce hospitalizations due to AEs. We report evaluation of AE-related hospitalizations for patients on treatment with TEMSR or INFa.
Material and Methods: In the global ARCC trial, patients were randomly assigned to receive 25 mg TEMSR IV weekly, INFa (titrated to 18 mU) 3 times weekly or 15 mg TEMSR IV weekly plus 6 mU INFa 3 times weekly. We evaluated AE-related hospitalizations in TEMSR (n = 209) and INFa (n = 207) groups. AE-related hospitalizations were reported until death or 15 days following the last dose date in case of treatment termination due to disease progression. If last dose date was not available, treatment termination date was used. We analyzed the data using 3 models: Cox model to evaluate the hazard of first hospitalization, Andersen-Gill (AG) proportional rate model, and Prentice-Williams-Peterson (PWP) stratified multiple failure times model. Both AG and PWP models do not discard information past the first hospitalization, unlike the Cox analysis.
Results: A total of 144 AE-related hospitalizations were observed, 80 of these were in INFa group and 64 were in TEMSR group. In time to first hospitalization analysis, the hazard of hospitalization was estimated to be lower by 44% [HR = 0.56; 95% CI (0.402−0.780); p = 0.0006] in TEMSR group vs INFa group. In the AG model, the hazard rate across all hospitalizations was estimated to be lower by 36% [HR = 0.64; 95% CI (0.45−0.92); p = 0.0157] in TEMSR group vs INFa group. Similarly, in the PWP model, the hazard rate across all hospitalizations was estimated to be lower by 28% (HR = 0.72; p = 0.0220) in TEMSR group vs INFa group.
Conclusions: In patients with advRCC, TEMSR-treated patients have significantly longer time to first AE-related hospitalization and significantly fewer AE-related hospitalizations relative to INFa-treated patients.
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