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Survival Prediction in Everolimus-treated Patients with Metastatic Renal Cell Carcinoma Incorporating Tumor Burden Response in the RECORD-1 Trial

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Abstract

Background: The phase 3 RECORD-1 study demonstrated clinical benefit of everolimus over placebo (median progression-free survival: 4.9 mo compared with 1.9 mo, $p < 0.001$) in treatment-resistant patients with metastatic renal cell carcinoma (mRCC). However, the Response Evaluation Criteria in Solid Tumors (RECIST) objective response rate was low.
Objective: To explore the potential role of tumor burden response to everolimus in predicting patient survival.
Design, setting, and participants: RECORD-1 patients with at least two tumor assessments (baseline and weeks 2–14) were included ($n = 246$).
Outcome measurements and statistical analysis: A multivariate Cox proportional hazard model was used to assess the impact of various prognostic factors on overall survival (OS). Components of RECIST progression were explored using univariate Cox regression.
Results and limitations: The baseline sum of longest tumor diameters (SLD) and progression at weeks 2–14 were prognostic factors of OS by multivariate analysis. Univariate analysis at weeks 2–14 demonstrated that growth of nontarget lesions and appearance of new lesions were predictive of OS ($p < 0.001$). This retrospective analysis used data from one arm of one trial; patients in the placebo arm were excluded because of confounding effects when they crossed over to everolimus.
Conclusions: This analysis identified baseline SLD as a predictive factor of OS, and the appearance of a new lesion or progression of a nontarget lesion at first assessment after baseline also affects OS in patients with mRCC treated with everolimus.
Trial registration: ClinicalTrials.gov: NCT00410124.

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1. Introduction

The efficacy of anticancer agents in clinical trials is often assessed using Response Evaluation Criteria in Solid Tumors (RECIST) [1,2]. RECIST divides patients into four response categories—complete response, partial response, stable disease, and progressive disease—based on change in the sum of longest tumor diameters (ΔSLD) of target lesions, unequivocal progression or disappearance of nontarget lesions, and appearance of new metastases. RECIST was designed primarily for use with cytotoxic agents and has clear limitations, especially when applied to targeted agents [3,4].

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Recently developed targeted therapies, such as therapies with antiangiogenic or antiproliferative activity, may provide clinical benefit for patients without causing marked tumor shrinkage, resulting in low objective response rates [5,6]. Therefore, alternative means of evaluating tumor response have been explored. The Choi criteria were based on gastrointestinal stromal tumor response to imatinib assessed by computed tomography (CT) and defined *partial response* as ≥10% decrease in tumor size or ≥15% decrease in attenuation at 2 mo after treatment [7]. Subsequently, the Choi criteria demonstrated better predictive value for progression-free survival (PFS) and overall survival (OS) than RECIST at first evaluation of partial response in patients with metastatic renal cell carcinoma (mRCC) treated with sunitinib [8]. In addition, a ΔSLD threshold of −5% or −10% in target lesions was used to differentiate responders from nonresponders in patients with mRCC treated with everolimus or sunitinib, respectively [9,10]. A ≥5% reduction of the sum of longest tumor diameters (SLD) was a better predictor of PFS benefit with everolimus than the ≥30% reduction used in RECIST [9]. The continuous variable ΔSLD has also been analyzed as a phase 2 end point [11] or as input to tumor burden models to predict OS, the phase 3 end point [12–14]. In renal cell cancer, work toward identifying the best measurement and threshold for predicting treatment failure and OS is ongoing [15]. Identifying the optimal measurement will require analysis of a large number of studies.

Identification of prognostic factors that influence OS is critical to distinguish patient subtypes, predict response to agents, and optimize therapeutic regimens [16–18]. We present our efforts to explore additional predictors of survival beyond the SLD of target lesions, including disease status of nontarget lesions and presence or absence of new lesions, using patient data from the phase 3 RECORD-1 (REnal Cell cancer treatment with Oral RAD001 given Daily) trial [19]. In this paper, we extend the original RECORD-1 multivariate Cox model [19] to include baseline SLD, growth of target and nontarget lesions, and appearance of new lesions to assess how tumor burden might predict outcomes for patients with mRCC.

2. Patients and methods

2.1. Patients and study design

RECORD-1 assessed everolimus in patients with mRCC refractory to vascular endothelial growth factor receptor–tyrosine kinase inhibitors [19]. Patients received everolimus (n = 277) or placebo (n = 139), both with best supportive care. Response was assessed according to RECIST v.1.0 [1]; patients who progressed (investigator assessment) were unblinded, with those assigned to placebo offered open-label everolimus. Median PFS was 4.9 mo with everolimus and 1.9 mo with placebo (hazard ratio [HR]: 0.33; 95% confidence interval, 0.25–0.43; $p < 0.001$).

2.2. Exploration data set for testing correlates of overall survival

All everolimus recipients were considered for inclusion in this analysis. Placebo recipients were excluded to minimize confounding the OS analysis with patients who crossed over to everolimus. Patients with at least two tumor assessments, one at baseline and another within 2–14 wk (n = 246), were included in the model. Additional analyses used data from patients with assessments at baseline and either weeks 6–10 (n = 216) or weeks 14–18 (n = 136). We chose weeks 2–14 for the primary analysis because doing so excluded the fewest patients. Using early assessments before month 2 allowed us to include patients who were scheduled for early evaluation because of a safety concern and then underwent a CT scan because of evidence of potential disease progression (eg, clinical deterioration), even though the CT scan was not scheduled per the protocol.

2.3. Statistical analysis

Analyses started with the multivariate Cox proportional hazard model, previously described [19], to assess the impact of various prognostic factors on OS in RECORD-1 patients. Baseline tumor size and progression status at weeks 2–14 were then introduced into the model. The selection level to retain factors in the model was $p < 0.05$. Components of progression at weeks 2–14, based on RECIST (target lesion, nontarget lesions, and new lesions), were explored using univariate Cox regression. For target lesions, different thresholds for the binary Cox analysis were evaluated by plotting HR as a function of percentage change in SLD threshold (%ΔSLD).

3. Results

3.1. Patients

Among 277 everolimus-randomized patients, 246 patients were included in this analysis. Excluded patients did not receive the study medication: 3 patients lacked a week 2–14 tumor assessment; 20 patients had only a baseline assessment (5 patients died and 15 patients discontinued before their first assessment after baseline); and 8 patients had their second assessment at weeks 14–18 or later. There were no major differences in baseline characteristics between patients included in this analysis and patients in the everolimus arm of RECORD-1 (Appendix, Table A1). For comparison, the same sets of analyses were conducted using data from weeks 6–10 (n = 214) or weeks 14–18 (n = 136) (Appendix).

3.2. Adding baseline tumor burden and progression-free survival at weeks 6–10 improves the initial model

In RECORD-1, the initial model indicated prognostic relevance for intermediate or poor Memorial Sloan-Kettering Cancer Center risk, liver or bone metastases, elevated neutrophils or alkaline phosphatase, and prior treatment with sunitinib or interferon [19]. In our restricted patient population, multivariate analysis indicated that liver metastases, prior interferon therapy, and abnormal neutrophils were no longer predictive of survival ($p > 0.05$). However, inclusion of baseline SLD (above or below the median value of 15.9 cm) and progression at weeks 2–14 led to statistically significant improvements over the original prognostic model ($p < 0.05$) (Table 1).

3.3. Progression of target lesions is not predictive of overall survival

To assess which aspects of PFS were predictive of OS, PFS at weeks 2–14 was divided into three RECIST components: