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Quantifying the Effect of Everolimus on Both Tumor Growth and New Metastases in Metastatic Renal Cell Carcinoma: A Dynamic Tumor Model of the RECORD-1 Phase 3 Trial

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ABSTRACT

Background: The randomized, placebo-controlled phase 3 trial RECORD-1 (NCT00410124) established the mammalian target of rapamycin (mTOR) inhibitor everolimus as an effective therapy for prolonging progression-free survival (PFS) in patients with advanced RCC who had progressed after sunitinib or sorafenib. The 10-mg daily everolimus dose administered in RECORD-1 was based on phase 1 studies correlating this regimen with constant and near-complete inhibition of mTOR pathway signaling. Dose reduction to 5 mg daily was allowed for toxicity. We developed a mathematical model of tumor growth in RECORD-1 to evaluate the effect of these 2 everolimus doses on growth of target lesions, nontarget lesions, and new metastases. **Materials and methods:** Tumor growth in all patients with a baseline tumor measurement (n = 407) was described using nonlinear mixed effects modeling. Local radiologic data was collected over time on the sum of the longest target lesion diameters (SLD), progression status of nontarget lesions, and appearance of new lesions. By fitting a mathematical model for tumor growth to each patient, the impact of everolimus dose on all 3 lesion types was investigated. **Results:** At 5 and 10 mg daily, everolimus slowed growth of all 3 lesion types versus placebo (P <.0001). For target lesions, a 10-mg dose had a larger effect than a 5-mg dose (P <.0001). No discernable difference between doses was seen for nontarget and new lesions. The model predicts that after 1 year of continuous dosing, the change in SLD of target lesions in the average patient would be 142.1% ± 98.3% on placebo, 22.4% ± 17.2% for a 5-mg dose, and –15.7% ± 11.5% for a 10-mg dose. **Conclusions:** We developed a dynamic tumor model linking everolimus dosing history with the overall tumor time course for each patient from RECORD-1. These tumor growth biomarkers are closer to the primary clinical end point (PFS) than measures of mTOR pathway inhibition, and thus may provide better predictions of trial success. Our analysis demonstrates a significant drug effect on target, nontarget, and new lesions. Furthermore, an everolimus daily dose of 10 mg is more efficacious than 5 mg in reducing growth of target lesions in metastatic RCC.

INTRODUCTION AND OBJECTIVES

- The phase 3 RECORD-1 trial demonstrated the efficacy and safety of everolimus in patients with metastatic renal cell carcinoma (mRCC) refractory to sunitinib or sorafenib[1,2]
  - Median progression-free survival (PFS) increased from 1.9 months (placebo) to 4.9 months (everolimus) by central radiology review, and from 1.9 months (placebo) to 5.5 months (everolimus) as assessed by local investigators
  - A decrease in the sum of the longest tumor diameters (SLD) was observed in 47% and 10% of everolimus- and placebo-treated patients, respectively
  - Patients treated with everolimus received a daily dose of 10 mg, with a dose reduction to 5 mg daily allowed for toxicity
- We have developed a mathematical model to describe tumor growth dynamics in individual patients from the RECORD-1 trial
  - We used this model to evaluate the effect of 2 different doses of everolimus (10 mg and 5 mg daily) on the growth of target lesions[3]
  - We also explored the effect of everolimus on the growth of nontarget lesions and the appearance of new lesions, and used the projected growth of all 3 lesion types to predict PFS in everolimus-treated patients and patients receiving placebo

METHODS

- Local radiologic data on target lesions (SLD), nontarget lesions, and new lesions were collected over time in RECORD-1 patients
- Tumor growth in RECORD-1 patients was described using nonlinear mixed-effects modeling
- The model of target lesions was defined by the equation[3]:

  $dy/dt = r - E_{dose}y$

  in which:

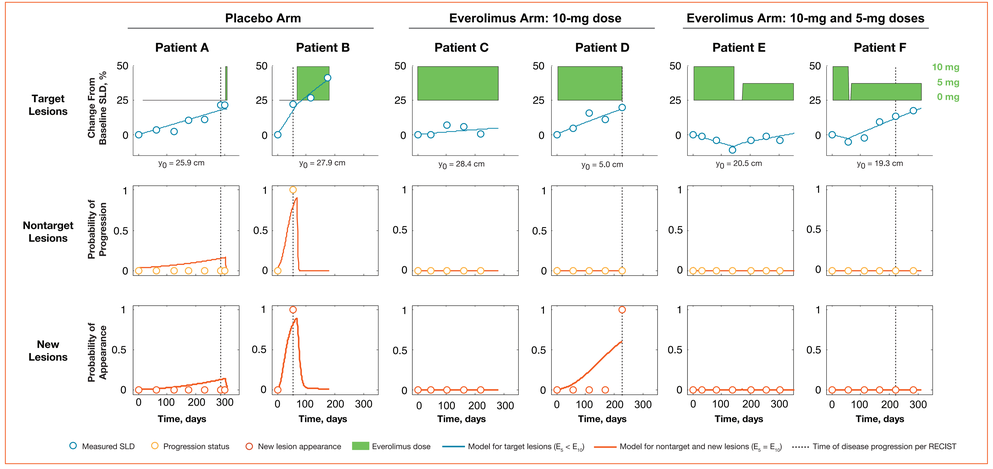
  dy/dt = rate of change of tumor size

  r = tumor growth rate for placebo-treated tumors

  E_{dose} = dose-dependent effect of everolimus on tumor growth

  y = sum of the longest tumor diameters

Figure 1. Change in lesion dynamics over time in relation to everolimus treatment. Top row: target lesions (percent change from baseline SLD); middle row: nontarget lesions (probability of progression; 0 = SD or better, 1 = PD); bottom row: new lesions (probability of appearance; 0 = no new lesion appearance, 1 = new lesion appearance). Six representative patients with very different profiles are shown (patients A–F). Baseline SLD for each patient is shown as y_0. Daily dose of everolimus administered is indicated by barplot as a function of time with a value of 10 mg at its maximum.



- While no lesion diameter was recorded for the nontarget lesions and new lesions, it was assumed that the growth or shrinkage of these lesions over time could be described by the same basic equation used to model the growth dynamics of the target lesions. The sizes of the nontarget lesions and new lesions obtained by the model were then converted to a probability of progression by applying the transformation functions below, which can take values between 0 and 1. These probabilities of progression were then compared with the actual progression outcomes in individual patients
  - Nontarget lesions: $f(\Delta y\%) = \frac{(100\% + \Delta y\%)^8}{(100\% + 50\%)^8 + (100\% + \Delta y\%)^8}$
    - $\Delta y\%$ = percentage change in lesion size from baseline
    - A 50% increase from baseline is associated with a 50% chance of being classified as "unequivocal progression"
    - A 100% increase from baseline is associated with a 90% chance of being classified as "unequivocal progression"
  - New lesions: $f(y) = \frac{y^3}{(0.5\ \text{cm})^3 + y^3}$
    - y = longest diameter of new lesion
    - Assumed to be undetectable and 0.1 cm in size at start of therapy
    - Lesions that reach the imaging resolution of 0.5 cm have a 50% chance of being detected
    - Lesions that reach 2 cm in size are almost certainly detected (98.4% probability)
- For each of these lesion types, the effects of 5 mg everolimus (E_5) and 10 mg everolimus (E_{10}) could be fit as separate parameters. However, nontarget lesions and new lesions, the data did not support this added complexity; thus, it was assumed that 5 mg and 10 mg had the same effect
  - **Target lesions: $E_5 < E_{10}$** (10 mg and 5 mg everolimus have differing effects)
  - **Nontarget and new lesions: $E_5 = E_{10}$** (10 mg and 5 mg everolimus have the same effect)
- Finally, the predicted change in each lesion type was combined to determine the overall response predicted by the model, according to RECIST

RESULTS

- 407 patients had a baseline tumor assessment and were included in the analysis
- **Figure 1** shows plots of SLD of target lesions, probability of progression of nontarget lesions, and probability of progression of new lesions in a set of representative patients over time in relation to everolimus dose received
- As shown in **Figure 2**, the model predicts that for a typical patient maintaining continuous, uninterrupted dosing for 1 year, change in SLD of target lesions would be:
  - Placebo: +142.1% ± 98.3%
  - 5 mg everolimus: +22.4% ± 17.2%
  - 10 mg everolimus: –15.7% ± 11.5%
- As shown in **Figure 3A**, after 1 year of continuous, uninterrupted dosing, the percentage of patients predicted to show nontarget lesion progression (with 90% confidence intervals) would be:
  - Placebo: 95.0% (81.8%, 99.5%)
  - 10 mg or 5 mg everolimus: 64.3% (33.2%, 90.0%)
- As shown in **Figure 3B**, after 1 year of continuous, uninterrupted dosing, the percentage of patients predicted to show progression of new lesions (with 90% confidence intervals) would be:
  - Placebo: 90.1% (76.1%, 96.8%)
  - 10 mg or 5 mg everolimus: 52.6% (20.5%, 82.4%)
- Model qualification showed a strong correlation between predicted PFS and clinically observed PFS in both everolimus-treated patients and patients receiving placebo (**Figure 4**)
  - For everolimus-treated patients, actual dosing history was used
  - For simulation of patients on the placebo arm, patients were treated as not receiving everolimus (ie, no crossover)
  - Patients who died for reasons other than disease progression were excluded from the analysis
- Improved model fits were obtained when the placebo growth rates (r) of all 3 lesion types were correlated (P <.001)

Figure 2. Simulated changes in the SLD of target lesions over 1 year in the average patient treated continuously with either placebo or everolimus (5 mg or 10 mg daily).

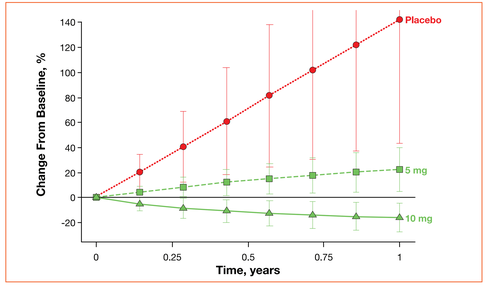


Figure 3. Percentage change in the probability of progression of nontarget lesions (A) and new lesions (B) over 1 year in the average patient treated continuously with either placebo or everolimus (5 mg or 10 mg daily).

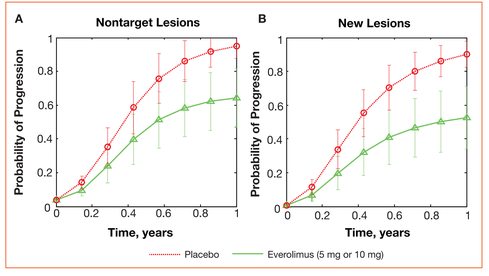
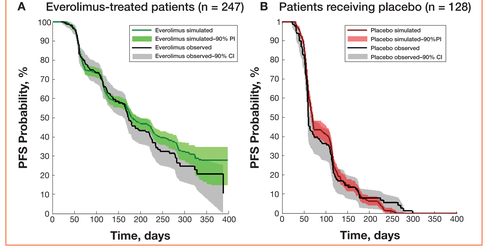


Figure 4. Correlation of PFS predicted by the model (shown in green for everolimus-treated patients [A] and in red for patients receiving placebo [B]) with the actual PFS observed in the RECORD-1 trial (shown in grey). CI, confidence interval; PI, prediction interval.



CONCLUSIONS

- We have developed a model to characterize the tumor response of target lesions, nontarget lesions, and new lesions in the RECORD-1 phase 3 trial
- Everolimus had a significant effect on all 3 lesion types, and the response for each lesion type predicted by the model was integrated according to RECIST into a single prediction of PFS for each patient that showed good correlation with the PFS observed in RECORD-1
- Although RECORD-1 did not have a separate arm in which patients were administered a 5-mg dose of everolimus, the model was able to determine that a 10-mg daily dose of everolimus is more efficacious than a 5-mg daily dose in reducing the growth of target lesions
- Simulations in all 3 lesion types after 1 year of continuous dosing show that a significant antitumor effect is achieved with either 5 mg or 10 mg everolimus compared with placebo
- The model was unable to detect a difference in the effect of a 10-mg versus a 5-mg daily dose of everolimus on the growth of nontarget lesions and new lesions. It may be that 5 mg is as efficient as 10 mg on these types of lesions, it may be that an alternative modeling methodology could detect the difference, or it may be that the less informative nature of the data available for these lesion types (binary or categoric rather than continuous) made the difference more difficult to detect
- Improved methodologies for estimating the growth dynamics of new lesions in patients with mRCC are warranted, given the significant role that such lesions play in metastatic disease. The development of such methods may be enabled by the use of richer datasets that include, for example, measurements from both central and local lesion assessments, or accurate counts of new lesions over time. Further efforts toward this end will be reported in due course

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