Metastatic Renal Cell Cancer: Summary from ASCO 2015

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Sequencing of Everolimus and VEGF Inhibition in mRCC (RECORD-3)

The *Open-label, Multicenter Phase II Study to Compare the Efficacy and Safety of RAD001 as First-line Followed by Second-line Sunitinib Versus Sunitinib as First-line Followed by Second-line RAD001 in the Treatment of Patients With Metastatic Renal Cell Carcinoma* (RECORD-3) previously supported the sequence of sunitinib followed by everolimus over the opposite sequence in patients with metastatic renal cell carcinoma (mRCC).[1] At American Society of Clinical Oncology (ASCO) 2015, researchers from this study presented the final overall survival (OS) results from this study.

The study population included 471 patients with clear cell or non-clear cell mRCC, who had no prior systemic therapy. They were randomized to receive either first-line everolimus 10 mg/day or sunitinib 50 mg/day (four weeks on, two weeks off) until first occurrence of progressive disease, at which point they were switched to the other therapy. The primary endpoint was progression-free survival (PFS) with the first-line therapies. For the final analysis, the endpoints were overall PFS (combined), OS, and safety. Median duration of follow-up was 3.7 years.

For the combined PFS analysis, median PFS was 22.2 months for the sunitinib → everolimus sequence and 21.7 months for the everolimus → sunitinib sequence (hazard ratio [HR] 1.2, 95% confidence interval [CI] 0.9–1.6).

For the OS analysis at the final evaluation, the proportion of patients who had died in each group was the same (64%); however, there was a suggestion that the sunitinib → everolimus sequence was associated with better result. The median OS was 29.5 months in that group, compared to 22.4 months in the everolimus → sunitinib sequence (HR 1.1, 95% CI 0.9–1.4; Fig. 1).

The rates of Grade 3–4 adverse events suspected to be related to treatment in first-line therapy were 47% with everolimus and 63% with sunitinib; in second-line therapy, these rates were 47% with everolimus and 57% with sunitinib. Within each treatment sequence overall, the rates were 62% with everolimus → sunitinib and 71% with sunitinib → everolimus.

An additional analysis of RECORD-3 presented at ASCO 2015 showed that there may be some particular genetic mutations that could help guide the selection of therapy on a patient-by-patient basis.[2] In RECORD-3, those with KDM5C mutations derived particular benefit (longer PFS) from sunitinib-first sequencing, while those with PBRM1 mutations (41% of the cohort) had comparable PFS benefit from either sequence.

Second-line Everolimus in mRCC (RECORD-4)

The *Open-label, Multicenter Phase II Study to Examine the Efficacy and Safety of Everolimus as Second-line Therapy in the Treatment of Patients With Metastatic Renal Cell Carcinoma* (RECORD-4) evaluated the use of everolimus among patients with mRCC who had previously been treated with a prior vascular endothelial growth factor (VEGF) inhibitor or cytokine therapy.[3] There were a total of 134 patients included in the study, of whom 58 received first-line sunitinib, 62 received another first-line anti-VEGF therapy (sorafenib [n = 23], bevacizumab [n = 16], pazopanib [n = 13], tivozanib [n = 5], axitinib [n = 3], and other [n = 2]) and 14 received a first-line cytokine-based therapy. All patient were treated with everolimus 10 mg per day. The primary efficacy endpoint was PFS.

Regardless of the previous therapy, there was benefit obtained with second-line everolimus (Fig 2). The median PFS overall was 7.8 months; for those previously treated with sunitinib it was 5.7 months, 7.8 months for other anti-VEGFs, and 12.9 months for cytokine-based therapy.

Overall response rate was 8%; most patients (67% overall) achieved stable disease as their best response. There were no new safety signals detected in this study; the adverse event profile was similar to that seen in previous trials with everolimus.

Everolimus or Sunitinib for Non-clear Cell mRCC (ASPEN)

The *Randomized Phase II Study of Afinitor (RAD001) vs. Sutent (Sunitinib) in Patients With Metastatic Non-Clear Cell Renal Cell Carcinoma* (ASPEN) study included 108 subjects with metastatic, non-clear cell RCC (NC-RCC).[4] They were, randomized to either everolimus 10 mg once daily on days 1 to 42 of a six-week cycle or sunitinib 50 mg daily on days 1 to 28 of a six-week cycle. The primary endpoint was radiographic PFS, defined by RECIST 1.1.

For the primary endpoint, the median PFS for sunitinib was longer than for everolimus (8.3 vs. 5.6 months; HR 1.41, $p = 0.16$; Fig. 3). This did meet the pre-specified boundary of $p < 0.20$ for the primary outcome.

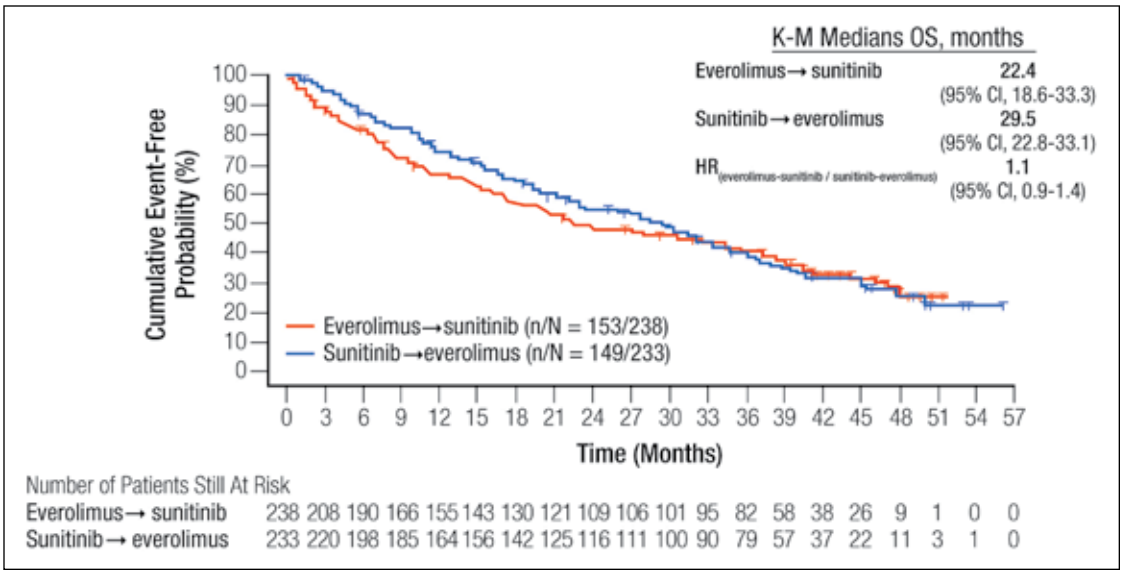

Fig. 1. Overall survival in the RECORD-3 study. K-M: Kaplan-Meier; OS: overall survival.

With respect to OS, the median time was numerically longer with sunitinib versus everolimus (32 months vs. 13 months), but this was not statistically significant (p = 0.60) and the authors provided important data to help manage metastatic non-clear cell renal cell carcinoma (NC-RCC).

With respect to toxicity, sunitinib was associated with a greater incidence of serious adverse events. The proportions of patients with greater than or Grade 3 toxicities were 65% with sunitinib and 47% with everolimus. The pattern of adverse events was similar to that observed in previous studies with these agents.

Checkpoint Inhibition for mRCC

One of the key themes of the entire ASCO conference was the use of immuno-oncology agents for various tumour types. In the genitourinary field, this included the use of nivolumab (a programmed death-1 [PD-1] immune checkpoint inhibitor) alone or in combination with ipilimumab (a cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] inhibitor), for the treatment of mRCC.[5,6]

The *Phase I Study of Nivolumab (BMS-936558) Plus Sunitinib, Pazopanib or Ipilimumab in Subjects With Metastatic Renal Cell Carcinoma* (CheckMate-016) evaluat-

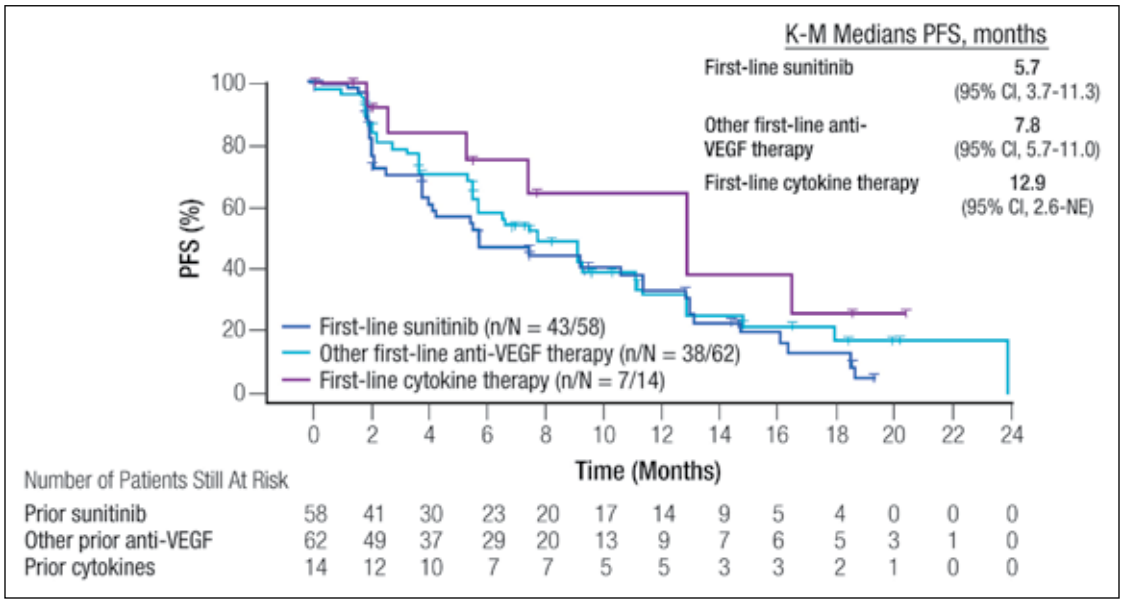

Fig. 2. PFS with everolimus by previous treatment in the RECORD-3 study. K-M: Kaplan-Meier; PFS: progression-free survival; VEGF: vascular endothelial growth factor; CI: confidence interval; NE: not estimable.

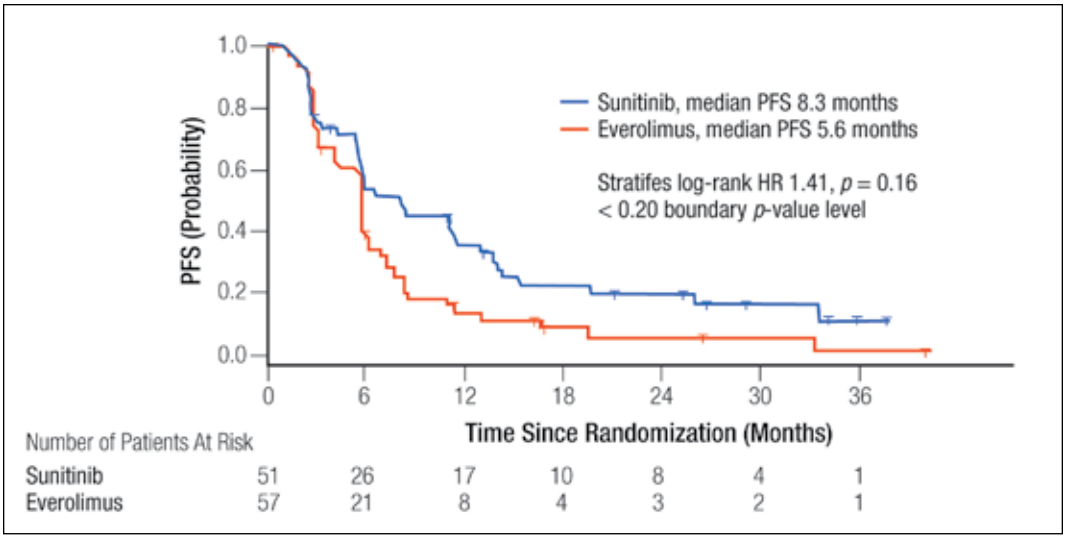

Fig. 3. PFS with sunitinib vs. everolimus in the non-clear cell mRCC (ASPEN). PFS: progression-free survival; mRCC: metastatic renal cell carcinoma; HR: hazard ratio.

ed the combination of nivolumab and ipilimumab in mRCC in three different dosing strategies. Two of these, the nivolumab 1 mg/kg + ipilimumab 3 mg/kg and the nivolumab 3 mg/kg + ipilimumab 1 mg/kg were recommended for cohort expansion. The third arm (nivolumab 3 mg/kg + ipilimumab 3 mg/kg) was stopped for excess toxicity. At ASCO 2015, researchers presented the results from the expanded cohorts.[5]

For this update, there were no new safety signals reported within the two groups. The efficacy of the two combinations appears to be promising. Confirmed objective response was reported in 18 of 47 patients (38.3%, including four complete responses in the nivolumab 3 mg/kg + ipilimumab 1 mg/kg group) and 19 of 47 patients (40.4%, including one complete response in the nivolumab 1 mg/kg + ipilimumab 3 mg/kg group). Among

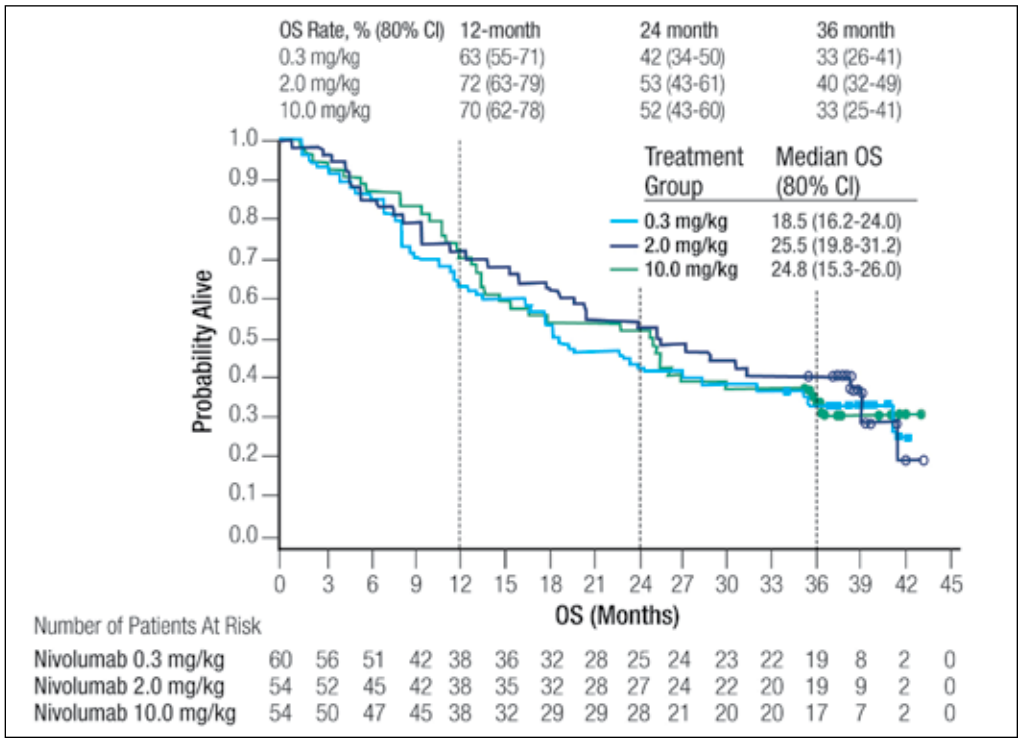

Fig. 4. OS with nivolumab monotherapy in mRCC (Phase II data). OS: overall survival; mRCC: metastatic renal cell carcinoma; CI: confidence interval.

those who responded, the median duration of response was 67.7 weeks in the nivolumab 3 mg/kg + ipilimumab 1 mg/kg arm and 81.1 weeks in the nivolumab 1 mg + ipilimumab 3 mg/kg arm.

Median PFS rates were 33.3 weeks for the nivolumab 3 mg/kg + ipilimumab 1 mg/kg group and 47.1 weeks for the nivolumab 1 mg/kg + ipilimumab 3 mg/kg group. Median OS had not been reached for either group.

Updated results of a Phase II study of nivolumab monotherapy in mRCC were also presented at ASCO 2015.[6] This was a dose-finding study evaluating three different nivolumab regimens, each administered every three weeks: 0.3 mg/kg, 2.0 mg/kg, and 10.0 mg/kg, every six weeks during the first year and then every 12 weeks thereafter until progression or treatment discontinuation. The initial primary endpoint was PFS. Of the 167 patients initially treated, 12 are still receiving nivolumab.

For this long-term analysis, the OS curves are similar for the three treatment arms, and the survival rates are higher than historical rates (Fig. 4). Based on these, and other results in mRCC, nivolumab is now being studied in a comparative, Phase III study versus everolimus.

New Research with VEGF Inhibitors in First-line mRCC

One interesting study with a VEGF inhibitor in first-line treatment of mRCC evaluated whether a dose titration strategy with axitinib based on individual tolerability would optimize plasma drug exposure and improve efficacy compared to a fixed-dose of axitinib with placebo titration.[7] The study included 213 patients with mRCC with no previous systemic treatment for mRCC. Previous reports from this study have shown that objective response rates and PFS were indeed more favorable in the axitinib-titration group. At ASCO 2015, researchers presented an updated analysis of OS. They reported that the median OS for the axitinib titration group was 42.7 months (95% CI, 24.7 to not estimable [NE]), which was numerically higher than the placebo-titration arm, which had a median OS of 30.4 months (95% CI 23.7 to 45.0; $p = 0.162$). There were no new safety signals observed in this longer-term follow-up.

Canadian investigators reported updated results of their Phase II study of individualized sunitinib as first line therapy for mRCC.[8] One of the highest response rates (RR) for mRCC (89.2%) was reported with no new safety signals, further supporting the concept of individualized dose titration for sunitinib therapy in mRCC.

Another poster presented at ASCO 2015 evaluated the prognostic impact of early tumour shrinkage (eTS) with VEGF inhibitors in mRCC.[9] This was a pooled analysis of clinical trials with sunitinib, axitinib, sorafenib, interferon (IFN)-α, bevacizumab, or temsirolimus in patients with mRCC (N = 4,736). For this analysis, eTS was assessed based on percentage change in sum of the longest diameter (SLD) of target lesions at six weeks (± two weeks) after initiation of systemic therapy. The goal was to determine the optimal threshold of eTS to predict prolonged OS or PFS.

The analysis determined that an eTS of 8% was optimal for prediction of OS, while 7% was the optimal threshold for prediction of PFS. The authors concluded that the conventional 30% tumour-shrinkage threshold used by RECIST may not be appropriate for the evaluation of response to systemic therapy.

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