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**EVERSUN: a phase 2 trial of alternating sunitinib and everolimus as first-line therapy for advanced renal cell carcinoma**


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**Background:** We hypothesised that alternating inhibitors of the vascular endothelial growth factor receptor (VEGFR) and mammalian target of rapamycin pathways would delay the development of resistance in advanced renal cell carcinoma (aRCC).

**Patients and methods:** A single-arm, two-stage, multicentre, phase 2 trial to determine the activity, feasibility, and safety of 12-week cycles of sunitinib 50 mg daily 4 weeks on / 2 weeks off, alternating with everolimus 10 mg daily for 5 weeks on / 1 week off, until disease progression or prohibitive toxicity in favourable or intermediate-risk aRCC. The primary end point was proportion alive and progression-free at 6 months (PFS6m). The secondary end points were feasibility, tumour response, overall survival (OS), and adverse events (AEs). The correlative objective was to assess biomarkers and correlate with clinical outcome.

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Results: We recruited 55 eligible participants from September 2010 to August 2012. Demographics: mean age 61, 71% male, favourable risk 16%, intermediate risk 84%. Cycle 2 commenced within 14 weeks for 80% of participants; 64% received ≥22 weeks of alternating therapy; 78% received ≥22 weeks of any treatment. PFS6m was 29/55 (53%; 95% confidence interval [CI] 40% to 66%). Tumour response rate was 7/55 (13%; 95% CI 4% to 22%, all partial responses). After median follow-up of 20 months, 47 of 55 (86%) had progressed with a median progression-free survival of 8 months (95% CI 5–10), and 30 of 55 (55%) had died with a median OS of 17 months (95% CI 12–undefined). AEs were consistent with those expected for each single agent. No convincing prognostic biomarkers were identified.

Conclusions: The EVERSUN regimen was feasible and safe, but its activity did not meet pre-specified values to warrant further research. This supports the current approach of continuing anti-VEGF therapy until progression or prohibitive toxicity before changing treatment.

Australian New Zealand Clinical Trials Registry: ACTRN12609000643279.

Key words: renal cell carcinoma, clinical trial, sunitinib, everolimus, angiogenesis inhibitors, vascular endothelial growth factor receptors

introduction

Several drugs are now available for the treatment of advanced renal cell carcinoma (aRCC) in the first-line setting, although none are curative: at best these agents can lead to long-lasting disease control. Sunitinib targets the vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor (PDGF) receptor families, and improves progression-free survival (PFS) in defined clinical circumstances (clear cell RCC and mainly favourable or intermediate risk) [1–4]. Everolimus is an orally bioavailable mammalian target of rapamycin (mTOR) inhibitor and improves PFS in patients with metastatic RCC who have progressed on sunitinib, sorafenib, or both [5].

The mechanisms of resistance to targeted therapies for RCC remain poorly understood [6]. It is reasonable to hypothesise that cancers upregulate alternative signalling pathways to escape suppression through primary pathways. The concept of planned alternation of blockade of pathways before clinical evidence of treatment resistance had not been previously tested and formed the rationale for the trial.

The current standard of care for aRCC is initial treatment with a VEGFR-targeted therapy in the first line until disease progression or intolerance, followed by switching to another drug. We hypothesised that alternation of treatments with different mechanisms of action would prevent or delay the development of resistance to one or both drugs.

methods

trial design

EVERSUN (ANZUP 0901; Australian New Zealand Clinical Trials Registry ACTRN12609000643279) was a multicentre, single-arm, open-label, phase 2 clinical trial of planned alternation of sunitinib and everolimus in patients with aRCC. The primary end point was the status of being both alive and progression-free (i.e. complete response, partial response, or stable disease) at month 6 (i.e. trial week 22–28), denoted PFS6m. Secondary objectives were to evaluate feasibility, response rate, PFS time, overall survival (OS) time, and safety outcomes. A correlative objective was to assess the prognostic value of possible biomarkers.

Treatment was administered in 12-week cycles, each comprising 6-week subcycles of sunitinib 50 mg once daily for 4 weeks followed by 2 weeks rest, with a subsequent 6-week subcycle of everolimus 10 mg once daily for 5 weeks followed by 1 week rest to allow drug washout. Imaging for assessment of objective tumour response was scheduled at weeks 6, 12, 18, 24, and then 12-weekly. Prohibitive toxicity or progression of disease before the week 24 assessment was attributed to the drug most recently administered, and participants were continued on the other drug and protocol-specified procedures until subsequent progression of disease or prohibitive toxicity on the other drug. Progression of disease after the week 24 assessment (after completion of two full 12-week cycles of therapy) was deemed as failure of both drugs, as patients responding to one drug and not the other should have been identified already by that point. Allowance was made for drug-dose modification or interruptions due to toxicity.

Participants’ eligibility to start cycle 2 within 14 weeks of day 1 cycle 1 was the principal feasibility end point. PFS1 was defined as the interval from registration to the first occasion at which progression or death occurred. PFS2 was defined as time to progression or death for both drugs. Participants who progressed for the first time after the 6-month time point were deemed to have failed both drugs. Thus, in participants progressing before 6 months, PFS1 was always less than PFS2; for participants progressing after 6 months, PFS1 and PFS2 were identical. These measures were censored on the date of last clinical or tumour assessment, whichever was later. The trial was carried out according to the International Conference on Harmonisation guideline for Good Clinical Practice and in accordance with the Australian National Health and Medical Research Council National Statement on Ethical Conduct in Human Research.

participants

Eligible participants had RCC with a clear cell component and metastatic, locally advanced or locally recurrent disease that was not amenable to resection. Key eligibility criteria were: good performance status; favourable or intermediate Memorial Sloan-Kettering Cancer Center prognostic group; expected survival at least 3 months; adequate major organ function; and no contraindications to sunitinib or everolimus. Detailed eligibility criteria are provided in supplementary Table S1, available at Annals of Oncology online. The trial was approved by relevant Human Research Ethics Committees and all participants provided written informed consent.

assessments and outcomes

Safety assessments were carried out at baseline; every 2 weeks during the first 12-week cycle; days 1, 29, 43, and 71 of subsequent cycles; and at the end-of-treatment visit 30–42 days after completion of treatment. Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria v4.0 (CTCAE). Tumour assessments were evaluated according to RECIST 1.1 [7].
biomarker studies

The rationale for the biomarkers evaluated for prognostic significance is summarised in supplementary Table S2, available at *Annals of Oncology* online. Basic fibroblast growth factor (bFGF); platelet-derived growth factor (PDGF)-AA/BB; placental growth factor; VEGF-A, -C, and -D, and soluble VEGFR1 and VEGFR2 were measured by multiplex immunoassays (Bio-Plex and BioRad) according to the manufacturer’s instructions. All samples were assayed in duplicate and the relevant absorbance was measured using the Bio-Plex® 200 system multiwell plate reader (BioRad, CA). Analyte concentrations were calculated from a five-parameter logistic curve of the assay standards using the Bio-Plex Manager software (BioRad). Serum biomarkers carbonic anhydrase 9, vascular cell adhesion molecule, hypoxia inducible factor 1α; neutrophil gelatinase-associated lipocalin, E-selectin and soluble VEGFR-3 were measured by enzyme-linked immunosorbent assay (ELISA; R&D Systems DuoSets). All samples were assayed in duplicate on Nunc C96 Maxisorp plates (Nunc, Denmark). The relevant absorbance was measured using a Synergy HT spectrophotometric multiwell plate reader (Bio-Tek, Winooski, VT) and analyte concentrations were calculated from a linear regression curve of the assay standards using the GraphPad Prism software. Sera from healthy volunteers were used as controls.

Circulating tumour cells (CTCs) were assessed from whole blood (10 mL) samples drawn at baseline into CellSave™ collection tubes and shipped in real time at ambient temperature to the central laboratory at the University of Queensland. CTCs of epithelial origin (CD45−, EpCAM+, and expressing one or more of cytokeratins 8, 18, or 19) were enumerated using the CellSearch® CTC system (Veridex) within 96 h of phlebotomy according to the manufacturer’s instructions.

statistical analysis

A sample size of 55 participants was planned to ensure sufficient data from 50 assessable participants providing 95% power at the 5% significance level to distinguish the observed rate of PFS6m from true rates of 0.84% (indicative of an ‘uninteresting’ low level of efficacy) versus ≤64% (indicative of an ‘interesting’ high level of efficacy) using a Simon 2-stage minimax design. The rates of PFS6m were based on the results of the pivotal trial of single-agent sunitinib as first-line therapy for RCC, in which the proportion alive and PFS6m post randomisation was estimated to be 74% [2]. The Evaluable Analysis Set comprised eligible participants who received ≥70% or greater of at least one 12-week cycle of therapy and had their disease re-evaluated, or who stopped trial treatment before the end of cycle 1 because of disease progression, an AE, or clinician preference. The prognostic value of biomarker levels at baseline, as well as change from baseline to days 29 and 71, was investigated using Cox proportional hazard regression for PFS and OS, and using logistic regression for OR and appreciable toxicity (defined as grade ≥3 AEs during cycle 1). A biomarker change was fitted as a binary covariate constructed by dichotomising change scores relative to the median. All analyses were undertaken in SAS v9.3.

results

Fifty-six participants were enrolled in the trial between September 2010 and August 2012 following the decision to continue accrual beyond the planned interim analysis at stage 1 of the design (comprising 28 assessable patients). One participant withdrew from the trial before receiving any trial medication and was excluded from both the safety and efficacy analyses. The remaining 55 were assessable for analysis. The median follow-up duration for assessable participants was 20 months (95% CI 18–22 months).

Baseline characteristics of the 55 assessable participants are summarized in Table 1. Memorial Sloan-Kettering Cancer Center prognostic group was favourable in 16% and intermediate in 84%. The median time on alternating therapy was 5.8 months, and a median of two treatment cycles were initiated (range 1–10). Seven participants switched from alternating therapy to single-agent sunitinib following disease progression on everolimus. Seventeen participants switched from alternating therapy to single-agent everolimus either because of an AE (n = 9), disease progression on sunitinib (n = 7), or participant preference (n = 1; supplementary Table S3, available at *Annals of Oncology* online). At the time of analysis, four participants continued on alternating therapy and five continued on single-agent everolimus (Figure 1).

Reasons for ceasing all trial treatment were: tumour progression (n = 28), AE (n = 7), clinician preference (n = 4), participant preference (n = 4), and death (n = 3). At the time of analysis, of the 46 participants who had stopped all trial treatment, 26 stopped during alternating treatment (14 while on everolimus and 12 while on sunitinib), 13 stopped while receiving single-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) or N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>61 (10), range 42–84</td>
</tr>
<tr>
<td>Number of male participants</td>
<td>39 (71%)</td>
</tr>
<tr>
<td>Mean systolic blood pressure</td>
<td>132 (11)</td>
</tr>
<tr>
<td>Mean diastolic blood pressure</td>
<td>77 (9)</td>
</tr>
<tr>
<td>Mean time since cancer first diagnosed (months)</td>
<td>48 (118)</td>
</tr>
<tr>
<td>Mean time since diagnosis of advanced disease (months)</td>
<td>12 (25)</td>
</tr>
<tr>
<td>Number of participants with distant metastatic disease at initial diagnosis</td>
<td>33 (60%)</td>
</tr>
<tr>
<td>Number of participants with local disease</td>
<td>30 (55%)</td>
</tr>
<tr>
<td>Number of participants with regional lymph node involvement</td>
<td>27 (49%)</td>
</tr>
<tr>
<td>Number of participants with distant metastases</td>
<td>54 (98%)</td>
</tr>
<tr>
<td>Lung</td>
<td>43 (78%)</td>
</tr>
<tr>
<td>Bone</td>
<td>12 (22%)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>30 (55%)</td>
</tr>
<tr>
<td>Liver</td>
<td>10 (18%)</td>
</tr>
<tr>
<td>Brain</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other*</td>
<td>16 (29%)</td>
</tr>
<tr>
<td>Number of participants with prior radiotherapy</td>
<td>8 (15%)</td>
</tr>
<tr>
<td>Number of participants with prior biological therapy (interferon or interleukin)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Number of participants with prior nephrectomy</td>
<td>34 (62%)</td>
</tr>
<tr>
<td>Mean estimation of LVEFb</td>
<td>64 (5)</td>
</tr>
</tbody>
</table>

*Other sites listed included: thyroid, renal bed, kidney, spleen, peritoneum, pelvis, omentum, breast, adrenal, pericardial effusion, para-aortic lymph nodes, and intra-abdominal.  
*bLeft ventricular ejection fraction expressed as a percentage.
agent everolimus, and 7 stopped while receiving single-agent sunitinib.

efficacy and feasibility

Twenty-nine of the 55 assessable participants (53%, 95% CI 40% to 66%) were alive and free of progression at month 6 (trial week 22–28). This was consistent with a level of efficacy that was pre-specified as uninteresting for further development of the regimen.

Forty-four assessable participants (80%, 95% CI 69% to 91%) were able to start cycle 2 within 14 weeks of day 1 cycle 1; 43 assessable participants (78%, 95% CI 67% to 89%) received at least 22 weeks of treatment (alternating or single agent); and 35 (64%, 95% CI 51% to 76%) received at least 22 weeks of alternating treatment. Patients experiencing treatment delays due to toxicity were included in efficacy and safety analyses.

Seven participants (13%, 95% CI 4% to 22%) experienced objective tumour response before first progression, and 3 of the 14 participants assessable for response after first progression (21%, 95% CI 0% to 43%) experienced a subsequent objective tumour response (Table 2).

The median times to PFS1 and PFS2 were 8 (95% CI 5–10) and 10 months (95% CI 8–11), respectively (Figure 2A and B). Seven participants switched to single-agent sunitinib following progressive disease (PD) on everolimus during the first two cycles of alternating therapy: three after one cycle of alternating therapy and four after two cycles. Seven participants switched to single-agent everolimus following PD on sunitinib during the first two cycles of alternating therapy: two after one cycle of alternating therapy and five after two cycles.

Thirty deaths were recorded with 27 being attributed to cancer. The median OS time was 17 months (95% CI 12–∞; Figure 2C).

safety and toxicity

The most frequent AEs of CTCAE grade 3 or worse were hypertension (n = 13), anaemia (n = 9), mucositis oral (n = 7), fatigue (n = 7), GGT increased (n = 6), pain (n = 5), and platelet count decreased (n = 5; see supplementary Table S4, available at Annals of Oncology online for details). Fifteen participants required additional antihypertensive therapy during cycle 1, but there was no apparent association between the development of hypertension and response to sunitinib.

There were two fatal serious AEs: one due to sepsis in a participant on single-agent everolimus; and the other due to heart failure in a participant on alternating therapy. A third patient died due to cancer while on alternating treatment.

biomarker studies

There was an indication of associations between changes in serum biomarker levels and PFS, OS, and toxicity; however, none of these remained statistically significant after adjusting for multiple comparisons (see Supplementary Tables S5 and S6, available at Annals of Oncology online). CTCs were detected in 5/30 (17%) of patients tested at baseline. The median number of CTCs when detected was 1 per 7.5 ml (range 1–6).

discussion

The observed level of activity of the EVERSUN alternating regimen fell below the pre-specified target; therefore, this trial does not support the use or ongoing investigation of this novel sequencing regimen. The planned interesting level of activity was set high (at least 84% of participants alive and free of progression at 6 months), but we believe that such a level of activity needed to be demonstrated to alter practice and the trial was adequately powered to measure this. The proportion of patients entering the trial with the primary tumour in situ (38%) was high compared with previous studies, and this could potentially have adversely influenced the outcomes. Alternatively, it is possible that the participants in the trial represented a group with relatively indolent biology in view of the long mean times since initial diagnosis or of diagnosis of metastatic disease. We conclude that, at present, there is no reason for clinicians to depart from the current standard of linear sequential treatment with a single agent until failure due to unacceptable toxicity or progressive disease. The choice of subsequent therapy in patients with advanced RCC using a drug with the same or different mechanism of action is currently based on drug availability, tolerance, and prior patterns of response. No validated blood-
based predictive biomarkers are yet known that can guide treatment selection.

Treatment with sunitinib and everolimus in this planned alternating regimen was shown to be safe and well tolerated, with toxicities similar to those expected for either agent alone. The chosen biomarkers did not correlate with outcomes for this specific treatment regimen and schedule. This does not allow conclusions to be drawn about the value of these biomarkers with other regimens. It is possible that an association might have been masked by the alternating use of two drugs with different mechanisms of action.

The observed level of activity was lower than predicted, although the statistical analysis plan was based on early reports of PFS with sunitinib. Subsequent studies suggested that PFS with sunitinib may be lower than first thought [8, 9]. However, we are unable to conclude with statistical confidence that the alternating strategy is inferior to sequential use of single agents until progression. The RECORD-3 trial did not demonstrate non-inferiority of everolimus compared with sunitinib as first-line therapy [8]. If the outcomes demonstrated in EVERSUN represent inferior clinical efficacy, then this might be due to interruption of a more effective therapy. Equal numbers of participants progressed on sunitinib (7) and sorafenib (7) during the first two cycles of treatment. This is a substantial proportion of the total trial population (25%), but it does not suggest that either drug was any more likely to lead to failure.

Recent retrospective studies indicate that the duration of prior response to sunitinib therapy might correlate with a subsequent response [10]. The use of a drug with a different mechanism of action such as an mTOR inhibitor might be preferable in patients with a suboptimal response to first-line therapy. The EVERSUN trial was not designed to determine the answer to this question. New approaches such as immune checkpoint blockade with monoclonal antibodies directed against CTLA-4, PD-1, or PD-L1 may offer additional options for second- and subsequent-line treatment, and perhaps for first-line treatment, after appropriate trials are completed [11].

The EVERSUN trial suggests that clinicians should maximise the value obtained from each line of treatment. This might include judicious and careful assessment of dosing and treatment schedules where appropriate and where high-level evidence supports such modifications. Change to different agents should occur only when it is clear that the first line of therapy is no longer appropriate on the grounds of disease progression or unacceptable toxicity.

**acknowledgements**

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**funding**

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First-line treatment with sunitinib for type 1 and type 2 locally advanced or metastatic papillary renal cell carcinoma: a phase II study (SUPAP) by the French Genitourinary Group (GETUG)†


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Background: Papillary renal cell carcinoma (PRCC), type 1 and type 2, represents 10%–15% of renal cell carcinomas (RCC). There is no standard first-line treatment of metastatic PRCC (mPRCC). Anti-angiogenics have shown activity in

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