Drugs 2009; 69 (15): 2115-2124
0012-6667/09/0015-2115/$55.55/0

Everolimus
In Advanced Renal Cell Carcinoma

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Contents

Abstract

▲ Everolimus is an orally administered, targeted therapy indicated for the treatment of advanced renal cell carcinoma. It inhibits the mammalian target of rapamycin, an integral component of multiple pathways involved in cell growth and proliferation.

▲ Median progression-free survival was significantly longer with everolimus 10 mg once daily than with placebo in both second interim (4.0 vs 1.9 months) and updated (4.9 vs 1.9 months) analyses of a randomized, double-blind, placebo-controlled, multicentre, phase III trial in patients with metastatic renal cell carcinoma that had progressed while receiving sunitinib and/or sorafenib treatment.

▲ At the second interim analysis, median overall survival was 8.8 months for placebo recipients; at this analysis, overall survival had not yet been reached for everolimus recipients.

▲ With regard to objective response at the second interim analysis, 64% of everolimus and 32% of placebo recipients had either a partial response (1% and 0%) or stable disease (63% and 32%).

▲ The tolerability profile of everolimus was largely manageable in the phase III trial, with most treatment-related adverse events being of grade 1 or 2 severity.

Features and properties of everolimus (Afinitor®)	
Indication	
Advanced renal cell carcinoma after failure of vascular endothelial growth factor receptor tyrosine kinase inhibitor treatment	
Mechanism of action	
Mammalian target of rapamycin (mTOR) inhibitor	
Dosage and administration	
Recommended dose	10 mg
Dose in presence of severe and/or intolerable adverse reactions	5 mg
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile of everolimus 5 and 10 mg/day at steady state in patients with advanced solid tumours	
Mean maximum serum concentration (C_{max})	5 mg/day: 32 ng/mL; 10 mg/day: 61 ng/mL
Median time to C_{max}	5 and 10 mg/day: 1 h
Mean area under the serum concentration-time curve	5 mg/day: 238 ng • h/mL; 10 mg/day: 514 ng • h/mL
Most common treatment-emergent adverse events (≥15% of patients) and laboratory abnormalities (≥30% of patients) in patients with metastatic renal cell carcinoma	
Adverse events (all grades)	Stomatitis, rash, fatigue, asthenia, diarrhoea, anorexia, nausea
Laboratory abnormalities (all grades)	Anaemia, hypercholesterolaemia, hypertriglyceridaemia, hyperglycaemia, raised creatinine levels, lymphopenia, raised alkaline phosphatase levels, hypophosphataemia

About 2–3% of all cancers are renal;[1] in the US, 85% of all kidney tumours are renal cell carcinomas.[2] In 2006, the EU had 63 000 new cases of renal cell carcinoma and 26 000 people died of the disease.[1,3] Corresponding numbers in the same year for the US were 39 000 diagnosed, with 13 000 deaths.[1] The incidence of renal cell carcinoma peaks in patients aged 60–70 years.[1] Renal cell carcinomas can be classified as clear cell (70–85% of cases), chromophil (papillary) [10–15%], chromophobe (5%), collecting duct (<1%) and unclassified (3–5%);[2] Xp11 translocation renal cell carcinomas are an additional, recently described, category.[2]

Up to 30% of patients presenting with renal cell carcinoma have metastatic disease; thus, systemic treatment is often required.[1,2] Historically, the only treatment available for renal cell carcinoma was cytokine therapy[1-3] with either interferon or interleukin-2;[2,3] however, such therapy had little impact on survival,[1,3] was limited to those patients with clear-cell disease[1] and was associated with significant toxicity.[1,3]

In a normal cell, when growth factors or nutrients activate the mammalian target of rapamycin (mTOR), thus prompting the upregulation of hypoxia inducible factor (HIF) gene expression,[2,4,5] the von Hippel Lindau protein (VHL) promotes the degradation of HIF.[2,4] However, when VHL becomes dysfunctional through mutation or other mechanisms (common in clear-cell renal cell carcinoma),[4] the resulting increased levels of HIF act to increase the production of various cell proliferation proteins, such as vascular endothelial growth factor (VEGF), thus stimulating angiogenesis and aiding cancer growth.[2,4] Targeted treatment options have been developed to act against various stages of this disease pathway.[1-3]

In terms of targeted therapies, the VEGF receptor tyrosine kinase (RTK) inhibitors sunitinib and sorafenib are recommended as first-line treatments in stage IV renal cell carcinoma (sorafenib in selected patients),[6] but there is a need for additional targeted therapies for patients who have not responded to VEGF RTK inhibitor therapy. National Comprehensive Cancer Network guidelines recommend the use of everolimus as subsequent therapy in patients with stage IV disease when disease progression has occurred despite treatment with VEGF RTK inhibitors.[6] Other targeted therapies (the mTOR inhibitor temsirolimus and the anti-angiogenic monoclonal antibody bevacizumab) are also available.[6]

Everolimus has been previously reviewed with regard to its use as immunosuppressant therapy in renal and cardiac transplantation;[7,8] this article provides an overview of the pharmacological properties of oral everolimus and reviews the clinical trial data available on the efficacy and tolerability of the drug in advanced renal cell carcinoma. Medical literature on the use of everolimus in advanced renal cell carcinoma was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

- Everolimus is an orally bioavailable derivative of rapamycin (sirolimus), exerting its effect by entering the cell and binding to the immunophilin FK506 (tacrolimus)-binding protein 12 Da isoform (FKBP12),[9,10] forming a complex that binds to the FKBP-rapamycin-binding domain[9] of mTOR, when that protein is part of a multiprotein complex (mTOR complex 1),[9] thus inhibiting downstream signalling events.[9,10] Another multiprotein complex, mTOR complex 2, holds mTOR in a form that does not allow inhibition by rapamycin or rapamycin-related compounds.[9] The everolimus concentration at which FK506 binding to FKBP12 was inhibited by 50% (IC_{50}) was 1.8–2.6 nmol/L.[11] Thus, the binding ability of everolimus to FKBP12 is approximately 3-fold weaker than that of rapamycin (IC_{50} 0.4–0.9 nmol/L).[11]
- Everolimus is associated with cell growth retardation.[10] Phosphorylation of the translational repressor eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) was reduced and the translational activator ribosomal protein S6 kinase 1 (S6K1) showed reduced activity in tumour, skin and

peripheral blood mononuclear cell (PBMC) extracts when CA20948 pancreatic tumour-bearing rats were administered everolimus compared with placebo (both 4E-BP1 and S6K1 are downstream mTOR effectors).[10] These changes have been shown to lead to accumulation of cells at the G_1 phase and growth retardation.[12,13]

- The antitumour activity of everolimus treatment was correlated with the prolonged inactivation of S6K1 in PBMCs in CA20948 pancreatic tumour-bearing rats; a prolonged inactivation of S6K1 was also observed in tumours and skin.[10] Antitumour activity was dose dependent in this study; this dose dependency occurred with either daily or weekly treatment schedules.[10]
- Everolimus also demonstrates antiangiogenic activity.[14,15] An *in vitro* study, using tumours derived from cell lines viewed as sensitive or resistant to everolimus, demonstrated that tumour vascularization and plasma and tumour VEGF levels were reduced on administration of everolimus.[15] Another *in vitro* study revealed that the apoptosis of irradiated human umbilical vein endothelial cells was increased with administration of everolimus; *in vivo* studies in mice showed reduced tumour vascularization with everolimus, with or without irradiation.[14]
- This antiangiogenic activity of everolimus is similar to, but also distinct from, that observed with a VEGF RTK inhibitor.[15] *In vivo* studies in mice showed that everolimus was associated with reduced levels of Tie-2 (a cell surface RTK that binds angiopoietin), reduced numbers of mature and immature vessels, and reduced total plasma and tumour VEGF levels, but did not affect blood vessel leakiness in normal vessels acutely exposed to VEGF and did not affect tumour vascular permeability. However, the VEGF RTK inhibitor vatalanib inhibited migration of endothelial cells and vascular permeability, and had a lesser effect on mature vessels than everolimus.[15]
- Single oral doses of everolimus 20 or 50 mg did not appear to be associated with prolongation of the QT or corrected QT interval, in a randomized, placebo-controlled, crossover study in 59 healthy volunteers.[16]

Optimal Dosage Studies

Two clinical trials investigated the optimal biologically effective dosage of oral everolimus in patients with advanced solid tumours (including breast, colorectal, pancreatic and renal cancer).[17,18] In one study, patients received everolimus 5, 10, 20 or 30 mg once weekly for 4 weeks ($n = 18$)[17] and in the other study patients received everolimus 20, 50 or 70 mg once weekly or 5 or 10 mg once daily for ≈4 weeks ($n = 55$).[18] These studies used biomarkers as surrogate markers of anti-tumour activity.[17,18] A modelling study also used biomarker data to evaluate the optimal everolimus dosage.[19]

- Everolimus 5–30 mg once weekly suppressed S6K1 activity in PBMCs; however, 20 mg once weekly was the minimum dosage shown to maintain S6K1 inhibition throughout the dosage interval (i.e. over 7 days).[17]
- Everolimus 20–70 mg once weekly or 5 or 10 mg once daily inhibited mTOR signalling in tumour and skin biopsies.[18] Phosphorylation of S6 and eukaryotic initiation factor 4G was almost completely inhibited ($p < 0.001$) in both tumour and skin samples, whereas phosphorylation of 4E-BP1 was significantly ($p < 0.001$) reduced in skin but not tumour samples.[18] Cellular proliferation was also significantly ($p < 0.05$) reduced by everolimus in both tumour and skin samples.[18]
- Both this study[18] and the modelling study[19] suggested that daily administration of everolimus resulted in more profound inhibition of the mTOR pathway than weekly administration. In addition, inhibition was more complete with everolimus 10 mg once daily than with 5 mg once daily.[18] Thus, everolimus 10 mg once daily was the dosage selected for further study.[20]
- One of these studies[18] and another study in patients with advanced solid tumours who were receiving everolimus[21] revealed that phosphorylation of Akt significantly ($p < 0.05$) increased in tumour[18,21] and skin[18] samples. Akt activation

is a potentially deleterious event associated with cancer cell survival, proliferation and growth.[21]

2. Pharmacokinetic Profile

This section focuses on pharmacokinetic data from the manufacturer's prescribing information for everolimus,[16] supported by data from various clinical trials,[17,22,23] including a phase I study of everolimus in patients with advanced solid tumours.[17] These studies are fully published[17,23] or available as an abstract.[22]

Absorption and Distribution

- In patients with advanced solid tumours receiving oral everolimus 5 or 10 mg once daily, steady state was achieved after 2 weeks of once-daily dosing.[16] Mean maximum serum concentration values (C_{max}) at steady state ($C_{max,ss}$) of 32 and 61 ng/mL were reached in a median of 1 hour.[17] Mean everolimus area under the serum concentration-time curve (AUC) values at steady state (AUC_{ss}) were 238 and 514 ng • h/mL.[17] $C_{max,ss}$ and AUC_{ss} were dose proportional.[16,17]
- Following a high-fat meal, healthy volunteers (n = 24) receiving everolimus 2 mg showed a 60% reduction in everolimus C_{max} (fed : fasting ratio 0.40; 90% CI 0.35, 0.46) and a 16% reduction in everolimus AUC from time zero to infinity (fed : fasting ratio 0.84; 90% CI 0.74, 0.95) compared with in the fasting state in a randomized, open-label, crossover trial.[16,23]
- In healthy volunteers and in patients with moderate hepatic impairment, plasma protein binding for everolimus is ≈74%.[16] In patients with cancer who were administered everolimus 10 mg/day, ≈20% of the dosage is confined to plasma; everolimus has a blood : plasma ratio of 17% : 73% (concentration dependent from 5 to 5000 ng/mL).[16]

Metabolism and Elimination

- There are six main metabolites of everolimus detectable in blood: three monohydroxylated metabolites, two hydrolytic ring-opened metabolites and one phosphatidylcholine conjugate.[16] On oral administration, everolimus is the most common circulating component in human blood.[16] In animal studies, the metabolites demonstrated ≈100-fold less activity than the parent drug.[16]
- Everolimus is a substrate of cytochrome P450 (CYP) 3A4 and P-glycoprotein (P-gp).[16] An effect of everolimus on the metabolism of CYP3A4 or CYP2D6 is unlikely as, while *in vitro* studies demonstrated a potential inhibitory effect, the mean $C_{max,ss}$ after an oral dose of everolimus 10 mg/day in humans is well below the dissociation constant values required for *in vitro* inhibition.[16]
- Everolimus has a mean elimination half-life of ≈30 hours.[16,17]
- While no specific excretion studies have been undertaken in patients with cancer, in patients receiving ciclosporin who were administered an oral dose of [^{14}C]-labelled everolimus 3 mg, 80% of total radioactivity was recovered from the faeces and 5% from the urine.[16] No parent drug was detected in either urine or faeces.[16]

Potential Drug Interactions

- In healthy subjects receiving strong or moderate CYP3A4 inhibitors and P-gp inhibitors, everolimus exposure was significantly increased.[16] Patients receiving concomitant ketoconazole demonstrated a 3.9-fold increase in everolimus C_{max} and a 15.0-fold increase in everolimus AUC; corresponding increases for concomitant erythromycin recipients were 2.0- and 4.4-fold, and for concomitant verapamil recipients were 2.3- and 3.5-fold.[16] As a result, strong or moderate inhibitors of CYP3A4 or P-gp inhibitors should not be used concomitantly with everolimus (section 5).[16]
- Strong CYP3A4 inducers may decrease everolimus exposure.[16] Healthy volunteers receiving concomitant everolimus and rifampicin (rifampin) demonstrated a 64% reduction in everolimus AUC and an 58% reduction in C_{max} compared with those receiving everolimus alone.[16]
- Everolimus appeared to have no clinically significant pharmacokinetic interactions with atorvastatin or simvastatin (CYP3A4 substrates) or pravastatin (a non-CYP3A4 substrate) in healthy volunteers,[16]

or with sorafenib in patients with metastatic clear-cell renal cell carcinoma.[22]

Special Populations

- No clinical studies have been conducted investigating the pharmacokinetics of everolimus in patients with renal impairment. However, creatinine clearance (CL_{CR}) did not appear to have a significant effect on oral clearance of everolimus in a population pharmacokinetic analysis including 170 patients with advanced cancer and CL_{CR} ranging from 25 to 178 mL/min (1.5–10.7 L/h).[16] No dosage adjustment is required in patients with renal impairment.[16]
- Patients with hepatic impairment had increased everolimus exposure.[16] Eight patients with moderate (Child-Pugh class B) hepatic impairment had an AUC value that was ≈2-fold greater than that of eight volunteers with normal hepatic function. Positive correlations between the serum bilirubin level and everolimus AUC, and prolongation of prothrombin time and everolimus AUC was observed, as was a negative correlation between the serum albumin level and everolimus AUC.[16] The everolimus dosage should be decreased in this patient population (section 5).[16]
- Patient age and sex appeared to have no effect on everolimus oral clearance;[16] however, everolimus has not been investigated in paediatric patients.[16]
- There is a potential for increased everolimus exposure among Japanese patients (vs non-Japanese patients) and an increased everolimus oral clearance among Black patients (vs Caucasian patients); however, the potential significance of these differences has not yet been established.[16]

3. Therapeutic Efficacy

The efficacy of oral everolimus in patients with advanced renal cell carcinoma has been investigated in one randomized, double-blind, placebo-controlled, multicentre, phase III trial (second interim analysis[24] and updated[16,25] results are presented) and one noncomparative, phase II, two-part trial, investigating patients who had received up to one[26] or up to two (at least one being a VEGF RTK inhibitor)[27] prior treatments for renal cell carcinoma. Part 1 is fully published[26] and part 2 is available as an abstract plus poster.[27] Several phase II trials have investigated or are investigating the use of everolimus in combination with other drugs (e.g. bevacizumab, imatinib) for the treatment of renal cell carcinoma; these trials will not be discussed further.[28,29]

Phase II Trial

Part 1 of the phase II study recruited 41 patients, with 37 patients evaluable for efficacy endpoints;[26] part 2 had 26 evaluable patients.[27] All had metastatic renal cell carcinoma with ≥75%[26] or predominantly[27] clear-cell characteristics. Most patients were male (78%[26] and 69%[27]), the median age was 57[27] and 60[26] years, and all patients had a Zubrod performance status of ≤2.[26,27] Patients received oral everolimus 10 mg once daily for a 28-day cycle; the dosage was modified for toxicity.[26,27] In part 1, 17% of patients had received no prior systemic therapy, 61% had received interleukin-2- and/or interferon-based therapy, and 22% had received other systemic therapies.[26] In part 2, patients had previously received either sorafenib (n = 21) or sunitinib (n = 5).[27] Response was assessed using Response Evaluation Criteria in Solid Tumours (RECIST).[26,27]

- Patients receiving everolimus 10 mg once daily who had been exposed to up to one previous treatment (part 1) for metastatic renal cell carcinoma had median progression-free (primary endpoint) and overall survivals of 11.2 and 22.1 months.[26] Investigator-assessed partial response was observed in 13.5% (5 of 37) of patients; 73.0% (27 of 37) and 56.8% (21 of 37) had stable disease for ≥3 and ≥6 months.[26]
- Patients with metastatic renal cell carcinoma receiving everolimus 10 mg once daily who had been previously exposed to VEGF RTK inhibitors (part 2) had median progression-free (primary endpoint) and overall survivals of 6.5 and 16.3 months.[27] Investigator-assessed complete or partial response

was not observed in any patients; 84.6% (22 of 26) demonstrated stable disease for >3 months.[27]

Phase III Trial

Two interim analyses were planned after observing ≈30% and ≈60% of the targeted 290 events required, with the first allowing the study to be stopped for futility or safety reasons; the second interim analysis also permitted the study to be stopped because of superior efficacy and the results for this analysis have been fully published.[24] Updated results have been presented in abstract form[25] and in the manufacturer's prescribing information,[16] including the period from the second interim analysis to the unblinding of the patients.

Patients in the phase III trial were randomized (2 : 1) to continuous treatment with oral everolimus 10 mg or placebo once daily (either in a fasting state or with a fat-free light meal), plus best supportive care, in 28-day cycles.[24] Treatment continued until disease progression, unacceptable toxicity, death or discontinuation for any other reason.[24] Following investigator-assessed documented progression, treatment assignment was disclosed and placebo recipients could receive everolimus.[24] In the case of clinically significant haematological or other treatment-related adverse events, the everolimus dosage was reduced to 5 mg/day.[24] 272[24] and 277[25] patients were randomized to everolimus in the second interim[24] and updated[25] analyses, and 138[24] and 139[25] patients were randomized to placebo. The median duration of treatment at the second interim analysis was 95 (range 12–315) days for everolimus recipients and 57 (21–237) days for placebo recipients.[24]

Randomization was stratified according to Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score (favourable, intermediate or poor risk) and the number of previous treatments with VEGF RTK inhibitors (one or two previous treatments).[24]

Eligible patients were aged ≥18 years and had metastatic renal cell carcinoma that showed a clear-cell component and that had progressed either while receiving or within 6 months of ceasing treatment with sunitinib, sorafenib or sunitinib plus sorafenib.[24] The disease was required to be measurable (using RECIST), and patients were required to have a Karnofsky performance status score of ≥70% and adequate hepatic, renal and bone marrow function.[24] Exclusion criteria included previous treatment with an mTOR inhibitor (e.g. temsirolimus), the presence of untreated CNS metastases and uncontrolled medical conditions.[24]

The primary endpoint was progression-free survival (time from randomization to the first documentation of disease progression or death), classified using RECIST and assessed by independent central review.[24] Secondary endpoints included objective tumour response rate, overall survival and health-related quality of life (HR-QOL), assessed using the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-30 and the Functional Assessment of Cancer Therapy Kidney Symptom Index Diseased-Related Symptoms questionnaire (FKSI-DRS).[24] Assessments were based on the intent-to-treat population.[24]

The median age of patients at baseline was ≈61 years and 77% were male.[24] With regard to MSKCC risk factors for second-line therapy, 29% of patients were classed as favourable, 56% as intermediate and 15% as poor risks.[24] Common sites of metastases included lymph nodes, lung, bone and liver; 10% of patients had one disease site, 25% had two, 31% had three and 32% had at least four.[24]

With regard to previous VEGF RTK inhibitor therapy, 26% of patients had received previous treatment with both sunitinib and sorafenib; 45% had been treated with sunitinib only and 29% had been treated with sorafenib only.[24] Other previous systemic therapy included interferon (51% of patients), interleukin-2 (23%), chemotherapy (14%) and bevacizumab (9%); 96% of patients had undergone prior surgery and 30% had undergone prior radiotherapy.[24]

- The trial was terminated after the second interim analysis (involving 66% of the targeted events), as the pre-specified early stopping boundary had been crossed (the criteria for a positive study had been met).[24] There was an additional 4.5 months of

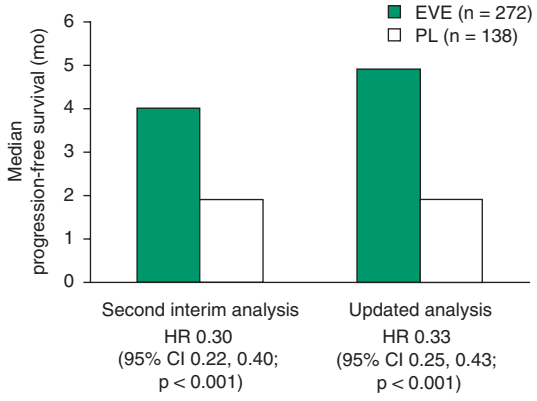

Fig. 1. Efficacy of oral everolimus (EVE) 10 mg/day vs placebo (PL) in patients with metastatic renal cell carcinoma. Median progression-free survival assessed by independent central review (primary endpoint) at a second interim[24] and an updated[16,25] analysis timepoint in a randomized, double-blind, PL-controlled, multicentre, phase III trial. **HR** = hazard ratio.

follow-up in the updated analysis.[25] Placebo recipients crossed over to everolimus post-unblinding.

- Everolimus 10 mg/day was associated with significantly ($p < 0.001$) longer progression-free survival (primary endpoint) than placebo in patients with metastatic renal cell carcinoma that had progressed while receiving sunitinib and/or sorafenib treatment, according to the results of the second interim[24] and updated[16,25] analyses (figure 1). The probability of being progression free at 6 months was 26% in everolimus recipients and 2% in placebo recipients.[24]

- In both analyses, the improvement in progression-free survival occurred regardless of MSKCC subgroup or previous VEGF RTK inhibitor treatment.[16,24,25]

- In the second interim analysis, median overall survival was 8.8 months for placebo recipients; it had not yet been reached for everolimus recipients (hazard ratio 0.83; 95% CI 0.50, 1.37; $p = 0.23$).[24] The crossing over of placebo recipients to everolimus following disease progression may have confounded results.[24] Of the 98 everolimus recipients who had progressed by the time of the second interim analysis, 79 had crossed over to everolimus.[24] At the time of the second interim analysis, mortality was 15% in everolimus recipients and 19% in placebo recipients.[24]
- In terms of objective response, 1% of everolimus recipients and 0% of placebo recipients had a partial response, 63% and 32% had stable disease, 19% and 46% had progressive disease, and disease could not be assessed in 17% and 22% in the second interim analysis.[24] In the updated analysis, everolimus recipients had an objective response rate of 2%; 0% of placebo recipients showed an objective response.[16]
- HR-QOL (EORTC QLQ-30 and FKSI-DRS scores) did not differ significantly between groups in the second interim analysis.[24]

4. Tolerability

Tolerability data for everolimus are available from the phase III clinical trial discussed in section 3. This section focuses mainly on data from the second interim analysis,[24] supplemented by additional data from the prescribing information.[16] Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0.

- Everolimus had a largely manageable tolerability profile in patients with metastatic renal cell carcinoma.[24] The most commonly occurring treatment-related adverse events are shown in figure 2, and included stomatitis, rash, fatigue, asthenia, diarrhoea, anorexia and nausea, and the most commonly occurring laboratory abnormalities included anaemia, hypercholesterolaemia, hypertriglyceridaemia, hyperglycaemia, raised creatinine levels, lymphopenia, raised alkaline phosphatase levels and hypophosphataemia. Most adverse events were of grade 1 or 2 severity.[24]
- Grade 3 treatment-related adverse events occurring in ≥1% of everolimus recipients included stomatitis, fatigue and pneumonitis (each occurring in 3% of patients), infections (2%) and asthenia, diarrhoea, mucosal inflammation and dyspnoea (each occurring in 1%).[24] The only grade 3 treatment-related adverse events to occur in placebo recipients were fatigue and asthenia (each occurring in <1% of patients). The only grade 4 treatment-related adverse event reported in either treatment arm was

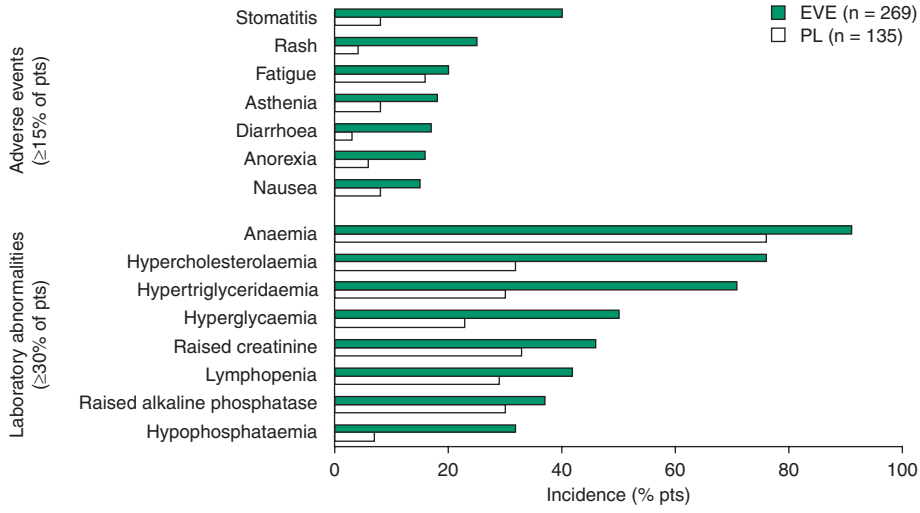

Fig. 2. Tolerability of oral everolimus (EVE) 10 mg once daily vs placebo (PL) in patients (pts) with metastatic renal cell carcinoma. Incidence of treatment-related adverse events (occurring in ≥15% of EVE recipients) and laboratory abnormalities (occurring in ≥30% of EVE recipients) of any grade in a randomized, double-blind, PL-controlled, multicentre, phase III trial.[16]

infections (1% of everolimus recipients). When the incidence of grade 3 and 4 treatment-related adverse events was combined, stomatitis and infections occurred in significantly ($p = 0.03$) more everolimus than placebo recipients.[24]

- Grade 3 laboratory abnormalities occurring in ≥3% of patients included lymphopenia (14% of everolimus recipients vs 5% of placebo recipients), hyperglycaemia (12% vs 1%), anaemia (9% vs 5%), hypophosphataemia (4% vs 0%) and hypercholesterolaemia (3% vs 0%).[24] In terms of grade 4 laboratory abnormalities, lymphopenia occurred in 1% of everolimus recipients, anaemia occurred in <1% of everolimus recipients and leukopenia and thrombocytopenia each occurred in <1% of placebo recipients. When the incidence of grade 3 and 4 laboratory abnormalities was combined, lymphopenia, hyperglycaemia, hypophosphataemia and hypercholesterolaemia occurred in significantly ($p < 0.05$) more everolimus than placebo recipients.[24]

- Of the 5% ($n = 14$) of everolimus and 4% ($n = 6$) of placebo recipients that died within 28 days of the last dose, one everolimus recipient died from candidal sepsis complicated by acute respiratory failure (potentially related to study drug) and one placebo recipient died from myocardial infarction.[24] The underlying malignancy was determined to be the cause of the remaining deaths.[24]

- Discontinuation as a result of treatment-related adverse events occurred in 10% of everolimus and 4% of placebo recipients in the phase III trial; the most common of these adverse events in everolimus patients were pneumonitis, dyspnoea, lung disorder and fatigue.[24] Dose interruption was required in 34% of everolimus and 15% of placebo recipients; 5% and <1% had a dose reduction with no previous interruption.

- Specific warnings and precautions in the manufacturer's prescribing information for everolimus[16] include the risk of non-infectious pneumonitis (a class effect of rapamycin derivatives; 14% of everolimus recipients reported this in the phase III trial), infections (as a result of immunosuppressive properties of the drug; 37% of everolimus recipients reported this) and oral ulceration (44% of everolimus recipients reported mouth ulcers, stomatitis or oral mucositis).[16]

- Additional warnings for everolimus include increased risks of mild elevations in serum creatinine, hyperglycaemia, hyperlipidaemia, hypertriglyceri-

daemia, and decreased haemoglobin, lymphocytes, neutrophils and platelets.[16]

5. Dosage and Administration

The currently recommended everolimus dosage in the US[16] in patients with advanced renal cell carcinoma is 10 mg orally, swallowed whole once daily, at the same time every day, either with or without food.[16] The duration of treatment should be as long as a clinical benefit exists or until unacceptable toxicity occurs.[16] If severe and/or intolerable adverse effects occur, treatment should be interrupted or the everolimus dosage modified (reduced to 5 mg once daily).[16]

Patients with moderate (Child-Pugh class B) hepatic impairment should receive a reduced dosage of everolimus 5 mg once daily.[16] As everolimus has not been evaluated in patients with severe (Child-Pugh class C) hepatic impairment, it should not be used in this patient population.

Concomitant use of strong CYP3A4 inducers (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, rifabutin, phenobarbital) should be avoided;[16] however, if concomitant treatment with these drugs is required, consideration may be given to increasing the dosage of everolimus up to 20 mg once daily in 5 mg increments (although it should be noted that clinical data to support this increase do not exist).[16] When strong CYP3A4 inducers are discontinued, the dosage of everolimus should be returned to the previous dosage.[16]

Local prescribing information should be consulted for detailed information, including contraindications, warnings and precautions, drug interactions, monitoring recommendations and use in special patient populations.

6. Everolimus in Advanced Renal Cell Carcinoma: Current Status

Everolimus is approved in the US for use in patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.[16] In the EU, everolimus is approved for use in patients with advanced renal cell carcinoma whose disease has progressed on or after treatment with VEGF-targeted therapy.[30]

Everolimus is effective, prolonging progression-free survival, and has a largely manageable tolerability profile in patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

Acknowledgements and Disclosures

The manuscript was reviewed by: ***D. Cho***, Division of Hematology and Oncology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA; ***I. Davis***, Ludwig Institute for Cancer Research, Melbourne, Victoria, Australia.

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

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