Clinical Trial Protocol

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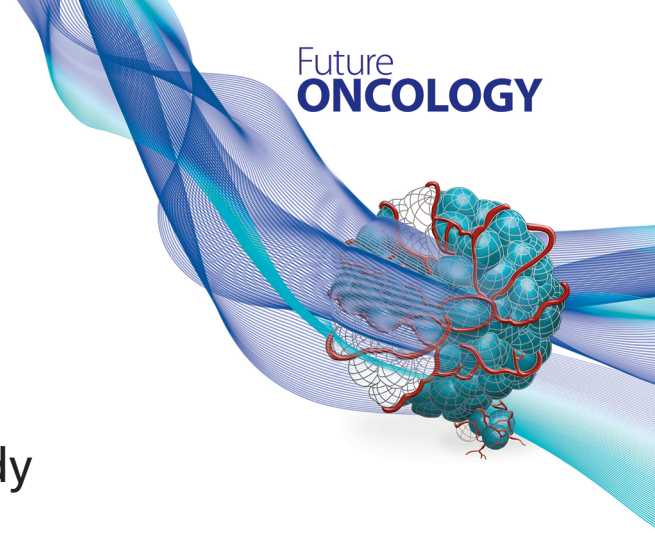

Lenvatinib plus everolimus or pembrolizumab versus sunitinib in advanced renal cell carcinoma: study design and rationale

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Aim: Lenvatinib plus everolimus is approved for the treatment of advanced renal cell carcinoma (RCC) after one prior vascular endothelial growth factor-targeted therapy. Lenvatinib plus pembrolizumab demonstrated promising antitumor activity in a Phase I/II trial of RCC. **Methods:** We describe the rationale and design of the CLEAR study, a three-arm Phase III trial comparing lenvatinib plus everolimus and lenvatinib plus pembrolizumab versus sunitinib monotherapy for first-line treatment of RCC. Eligible patients must have advanced clear cell RCC and must not have received any prior systemic anticancer therapy. The primary end point is progression-free survival; secondary end points include objective response rate, overall survival, safety, health-related quality of life and pharmacokinetics. Biomarker evaluations are included as exploratory end points.

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Keywords: everolimus • first-line treatment • immuno-oncology • lenvatinib • pembrolizumab • renal cell carcinoma • sunitinib • tyrosine kinase inhibitor

Cancers of the kidney and renal pelvis are among the most common cancers worldwide [1]. Regions with the highest estimated incidence rates of kidney cancer include North America, Australia/New Zealand and Europe, with incidence rates much lower in most parts of Africa and Asia [2]. It is the eighth most common cancer in the USA, with 65,340 new diagnoses and 14,970 deaths estimated for 2018 [3]. The most common type of kidney cancer is renal cell carcinoma (RCC), comprising approximately 85% of renal malignancies [4]. The 5-year survival for European patients who were diagnosed between 2000 and 2007 is reported as 60.6%, compared with 72.4% for the US population [5].

Angiogenesis is known to be integral to the development of clear cell RCC [6], and as such, several pathways involved in angiogenesis have been important therapeutic targets. A major component of the angiogenic process in RCC is VEGF [7], which has been a mainstay of anti-angiogenic therapies. Another pathway involved in the development of RCC is mediated by the mammalian target of rapamycin (mTOR), which is downstream of PI3K and protein kinase B and is regulated by *PTEN* [6–8]. Inhibition of the mTOR pathway can inhibit both angiogenesis and tumor cell proliferation [6,8]. The FGF pathway also plays an important role in angiogenesis in RCC, promoting

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vascularization, lymphangiogenesis and cellular growth [9,10]. In RCC, increased plasma concentrations of FGF have been shown to correlate with high tumor grade and stage, metastasis and poor prognosis [11–13].

In addition to angiogenesis and tumor cell growth, exploration of immunological mechanisms has led to the relatively recent identification of the role of different immune checkpoints (e.g., cytotoxic T-lymphocyte associated protein-4 and PD-1) and their role in circumventing the body's antitumor immune response in RCC [14,15]. The PD-1 signaling appears to be an important regulator of tumor immune tolerance in RCC, with increased expression of PD-L1 correlating with poorer survival [14,15]. Interaction of PD-L1 with its receptor PD-1 (expressed on $CD4^+$ and $CD8^+$ T cells, dendritic cells, B cells and natural killer cells) attenuates the antitumor immune response by inhibiting T cell function via induction of apoptosis, inhibition of cytokine release and decreased clonal expansion of T cells [14].

Overall, the measurement of PD-L1 expression by immunohistochemistry to predict response to immuno-oncology therapy in patients with RCC has been confounded due to differences in assays, expression cut-off levels, and the definition of positive (e.g., tumor vs immune) cells [16]. In a Phase III trial comparing nivolumab with everolimus in patients with previously treated advanced RCC (aRCC; CheckMate 025; ClinicalTrials.gov, number NCT01668784), nivolumab improved overall survival (OS) compared with everolimus, irrespective of PD-L1 expression [17]. In a Phase III trial comparing nivolumab plus ipilimumab with sunitinib in patients with previously untreated advanced clear cell RCC (CheckMate 214; ClinicalTrials.gov, number NCT02231749), median progression-free survival (PFS) was improved among patients with ≥1% PD-L1 expression who were treated with nivolumab plus ipilimumab (22.8 months) compared with sunitinib (5.9 months; disease progression or death hazard ratio [HR]: 0.46; 95% CI: 0.31–0.67), whereas median PFS was not improved among patients with <1% PD-L1 expression who were treated with nivolumab plus ipilimumab (11.0 months) compared with sunitinib (10.4 months; disease progression or death HR: 1.00; 95% CI: 0.80–1.26) [18]. However, nivolumab plus ipilimumab therapy improved OS compared with sunitinib, irrespective of PD-L1 expression in patients with intermediate or high risk [16,18]. Thus, the predictive role of PD-L1 in aRCC is not entirely clear and may vary between lines of treatment.

The current treatment approach for patients with aRCC consists of sequential administration of single-agent tyrosine kinase inhibitor (TKI) therapies that target either the VEGF, mTOR or PD-1 pathways [19,20]. Until recently, very few agents proved able to increase OS; despite this, the OS of patients with aRCC has improved over time using sequential administration of single-agent therapy [21]. First-line therapy typically consists of treatment with anti-VEGF agents, typically sunitinib or pazopanib [19,20]. In 2017, in a randomized, Phase II trial, cabozatinib demonstrated superior efficacy compared with sunitinib as first-line therapy for patients with aRCC of intermediate or high risk [22]. In addition, the combination of ipilimumab and nivolumab was approved by the US FDA for the treatment of treatment-naive, intermediate- or poor-risk aRCC in April 2018 [23].

However, existing first-line therapies for RCC are unsatisfactory due to toxicities and the development of drug resistance [24]. Approximately 20–30% of patients do not respond to initial therapy and progress within ≤3 months, indicating primary or intrinsic resistance to molecular-targeted agents [25–30]. Angiogenic escape due to activation of VEGF-independent pathways such as FGF-associated signaling is a major mechanism of such resistance [27,29,31,32]. Optimization of efficacy may be achieved by combining therapeutic agents that have either broader or distinct mechanisms of action. It is thought that the combination of anti-angiogenic agents with mTOR inhibitors may overcome alternative resistance pathways [29].

Until recently, results of most combination-therapy studies (i.e., temsirolimus plus bevacizumab, temsirolimus plus sunitinib, erlotinib plus bevacizumab, sunitinib plus bevacizumab, everolimus plus bevacizumab, everolimus plus sunitinib, everolimus plus dovitinib) have shown no survival advantage over monotherapy with approved single agents and, in some cases, an unacceptably high degree of toxicity [33–40]. Notable exceptions included the successful combination of nivolumab plus ipilimumab for the treatment of intermediate- or poor-risk, previously untreated, aRCC [23], and lenvatinib plus everolimus for the treatment of aRCC following one prior VEGF-therapy [41]. More recently, atezolizumab plus bevacizumab was reported to demonstrate longer PFS versus sunitinib in patients with $PD\text{-}L1^+$ metastatic RCC [42]. The Phase III JAVELIN trial of avelumab plus axitinib also recently reported improved PFS in patients with aRCC irrespective of PD-L1 status [43]. Two other relevant clinical trials of combination therapies are currently underway in aRCC – axitinib plus pembrolizumab, which recently reported improved OS and PFS outcomes versus sunitinib monotherapy (KEYNOTE-426; NCT02853331 [44,45]), and cabozantinib plus nivolumab (CheckMate 9ER; NCT03141177 [46]), indicative of the high degree of interest

and promise held for these combination therapy strategies in this disease space with TKIs, which inhibit VEGF receptors plus immune checkpoint inhibitors.

Lenvatinib

Lenvatinib is a potent multitargeted receptor TKI that selectively inhibits VEGF receptors (VEGFR1, VEGFR2, VEGFR3) in addition to other pro-angiogenic and oncogenic pathway-related tyrosine kinases, including FGFR 1–4, PDGFRα, KIT and RET [47–49]. Lenvatinib inhibited VEGF-driven VEGFR2 phosphorylation and suppressed proliferation and tube formation in human umbilical vein endothelial cell models [47,50,51]. Lenvatinib also inhibited FGF-driven tube formation in human umbilical vein endothelial cell models [52] and inhibited VEGF- and FGF-induced angiogenesis in preclinical models [50]. The antitumor activity of lenvatinib *in vivo* has been shown in numerous xenograft animals [47,50,51,53].

Clinical evidence of the antitumor activity of lenvatinib in aRCC was first provided in an open-label, Phase I, dose-escalation study in patients with advanced solid tumors [54]. Among all the tumor types studied, lenvatinib appeared to be particularly active in RCC, with four of nine patients with RCC achieving a partial response, out of a total of seven partial responses overall [54].

Lenvatinib plus everolimus

In a mouse xenograft model, the combination of lenvatinib and everolimus demonstrated superior antiangiogenic and antitumor activity compared with each single agent alone [51]. However, in another xenograft model, the combination regimen demonstrated enhanced antitumor activity but similar antiangiogenic activity to that of each monotherapy, suggesting that other mechanisms distinct from angiogenesis may underlie the observed antitumor activity of lenvatinib plus everolimus [51]. The mechanism of action of the combination of lenvatinib and everolimus (Figure 1A [53]) was further investigated in cell-based nonclinical models, and it is hypothesized that the dual inhibition of the VEGF- and FGF-driven mitogen-activated protein kinase and mTOR pathways in endothelial cells may contribute to the enhanced antiangiogenic activity of the combination treatment [51]. In addition, dual targeting of the mTOR-S6K-S6 pathway by the lenvatinib plus everolimus combination may contribute toward the superior antitumor activity of the combination [51].

A randomized, open-label, Phase Ib study in 20 patients with metastatic RCC established the maximum tolerated dose and recommended Phase II dose as lenvatinib 18 mg once daily in combination with everolimus 5 mg once daily [56]. In an open-label, randomized, Phase II study, lenvatinib plus everolimus and lenvatinib alone resulted in a PFS benefit over everolimus alone (HR: 0.40; 95% CI: 0.24–0.68; p = 0.0005 and HR: 0.61; 95% CI: 0.38–0.98; p = 0.048, respectively) in patients with advanced or metastatic RCC and disease progression after one previous VEGF-targeted therapy [41]. The combination of lenvatinib plus everolimus also significantly prolonged OS compared with single-agent everolimus (HR: 0.51; 95% CI: 0.30–0.88; p = 0.024) [41]. Based on the results of the Phase II study [41], lenvatinib in combination with everolimus was designated as a breakthrough therapy by the US FDA in July 2015 [57]. The combination was subsequently approved in various countries, including the US and those in Europe, for patients with aRCC following one prior anti-angiogenic therapy [58,59]. An ongoing Phase II study (NCT03173560) is investigating whether a lower dose of lenvatinib can demonstrate the same efficacy as that observed in the Phase II trial, which led to the approval of the combination but with reduced toxicity [60]. Patients with clear cell RCC, who had disease progression following one VEGF-targeted therapy, will be randomized 1:1 to receive either lenvatinib 18 mg/day plus everolimus 5 mg/day or lenvatinib 14 mg/day plus everolimus 5 mg/day [60].

Lenvatinib plus pembrolizumab

In addition to its antitumor and antiangiogenic effects, VEGF-targeted treatments may also act, in part, by preventing VEGF-mediated immune suppression [61]. In syngeneic mouse models, the combination of lenvatinib with monoclonal antibodies against PD-1 resulted in greater antitumor activity than either agent alone and was accompanied by an improved immune response, likely mediated by $CD8^+$ T cells [62]. Lenvatinib treatment also significantly decreased the population of tumor-associated macrophages in tumors, which enhanced the activity of PD-1 signal inhibitors (Figure 1B) [62]. Additionally, treatment with lenvatinib has been shown to inhibit TH2 and enhance TH1 immune response, leading to the activation of memory T cells [63]. Taken together, these preclinical studies demonstrating lenvatinib's immunomodulatory activity provide mechanistic rationale for the study of lenvatinib in combination with an anti-PD-1 agent such as pembrolizumab.

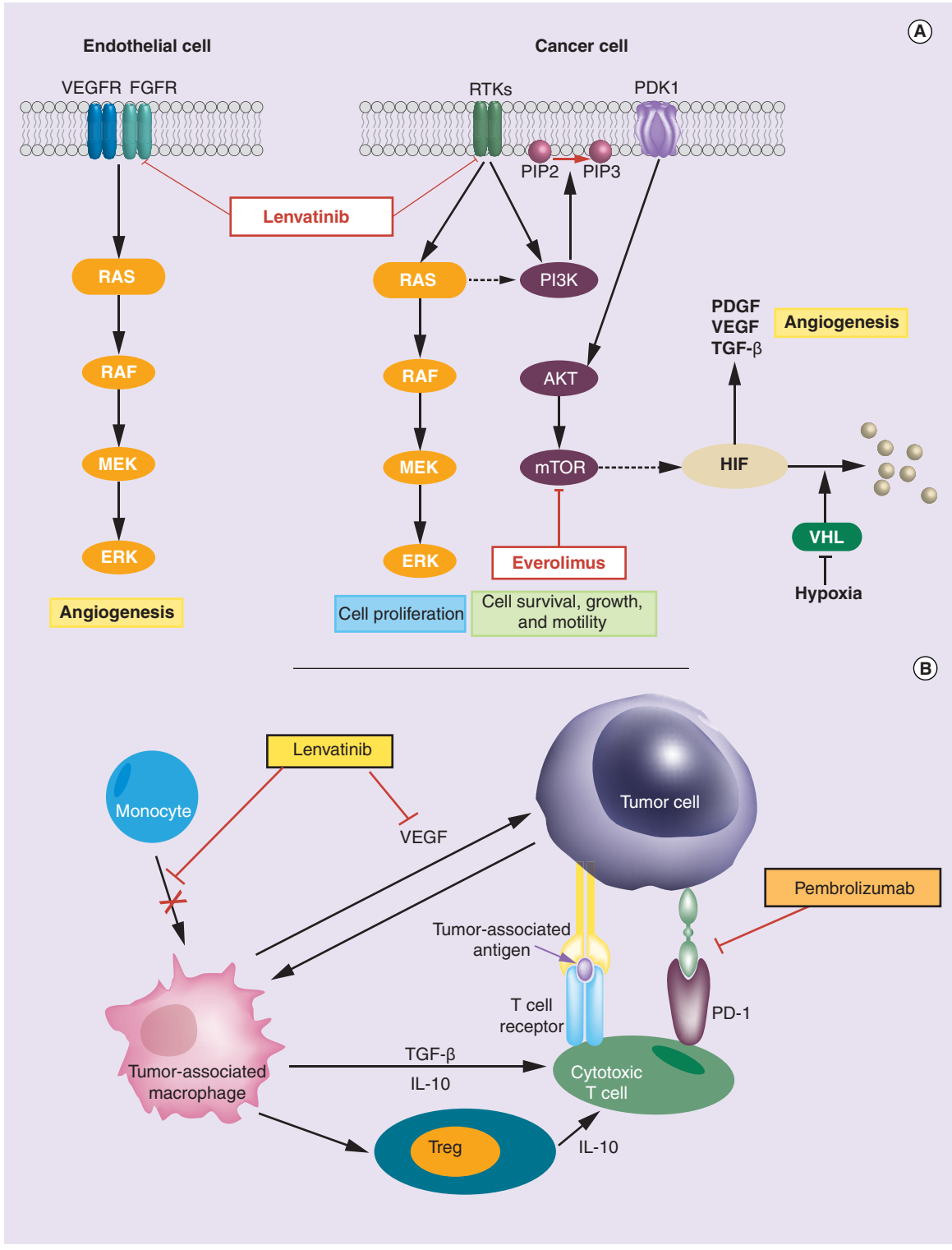

Figure 1. The mechanism of action of lenvatinib with its combination partners. Mechanisms of action of **(A)** lenvatinib plus everolimus and **(B)** lenvatinib plus pembrolizumab combination therapies.
IL: Interleukin; VHL: von Hippel-Lindau.
(A) Reproduced with permission from [53].
(B) Adapted with permission from [55].

Preliminary results from a Phase Ib/II study (n = 13) evaluating the combination of lenvatinib plus pembrolizumab showed promising activity in a range of solid tumor types [64]. Among eight patients with RCC enrolled in the Phase Ib part of the study, five achieved a partial response as their best overall response and three achieved stable disease. The most common treatment-emergent adverse events were decreased appetite, diarrhea and fatigue (each n = 9), and hypertension, hypothyroidism and nausea (each n = 8). Generally, toxicities were managed with dose modifications [64].

An analysis of the RCC cohort of patients enrolled across both phases of the study (n = 30) strengthened the promising antitumor activity and acceptable safety profile of lenvatinib plus pembrolizumab [65]. The objective response rate (ORR) was 63.3% for all patients in the RCC cohort, and 83.3% in the first-line treatment setting [65]. Responses were seen regardless of prior treatment and PD-L1 status [65]. Toxicities (most commonly diarrhea, fatigue, hypothyroidism, nausea and stomatitis) were manageable with lenvatinib dose interruption and/or modification [65]. An updated analysis of the RCC cohort in this ongoing study recently reported an ORR of 70.0%, with a median duration of response of 18.4 months [66]. The combination of lenvatinib plus pembrolizumab has been granted breakthrough therapy designation by the US FDA for patients with advanced or metastatic RCC [67]. Because a significant unmet medical need remains for more effective treatment options with manageable safety profiles for patients with aRCC, these combination therapies are the focus of the CLEAR study.

The CLEAR study

Here, we describe the design and rationale of the CLEAR study (NCT02811861; EudraCT 2016-000916-14), a multicenter, randomized, open-label and Phase III trial, designed to evaluate whether the combination of two targeted therapies (lenvatinib plus everolimus) or the combination of one targeted therapy plus a PD-1 inhibitor (lenvatinib plus pembrolizumab) would be superior to standard first-line therapy with single-agent sunitinib in patients with advanced or metastatic RCC. The study is funded by Eisai Inc., with study support also provided by Merck & Co., Inc.

Objective

The primary objective of this study is to demonstrate superiority of first-line lenvatinib plus everolimus or lenvatinib plus pembrolizumab over sunitinib alone in prolonging PFS, assessed by independent imaging review (IIR) using Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1 in patients with aRCC. Secondary objectives are to compare ORR, OS, safety and tolerability, and health-related quality of life (HRQoL), as well as PFS, in patients on next-line therapy between treatment arms. The pharmacokinetic/pharmacodynamic relationship between exposure and efficacy, biomarkers and safety will also be explored. Exploratory end points include PFS in the lenvatinib plus pembrolizumab arm by immune-related RECIST (irRECIST) [68], duration of response, disease control rates, clinical benefit rates and the relationship between blood biomarkers and efficacy outcomes.

Eligible patients

Patients aged ≥18 years should have histological or cytological confirmation of RCC with a clear cell component and documented evidence of advanced disease. Patients should also have at least one measurable target lesion according to RECIST v1.1, a Karnofsky performance status score of ≥70, adequately controlled blood pressure (with or without the use of antihypertensive medications), and adequate renal, bone marrow, blood coagulation and liver function. Patients should not have received any prior systemic anticancer therapy for RCC. Patients also should not have received any radiation therapy within 21 days prior to the first dose of study drugs, except for palliative radiotherapy to bone lesions, which is permitted if completed 2 weeks prior to the start of study treatment. Patients with untreated CNS metastases or those who had received a live vaccine within 30 days of the planned first dose of study drug(s) are also excluded.

Study design

Patients are being recruited from Australia, Austria, Belgium, Canada, Czech Republic France, Germany, Greece, Ireland, Israel, Italy, Japan, the Netherlands, Poland, Russian Federation, South Korea, Spain, Switzerland, the UK and the USA. Eligible patients will be randomized centrally by an interactive voice- and web-response system in a 1:1:1 ratio to open-label treatment with oral lenvatinib 18 mg/day plus oral everolimus 5 mg/day, oral lenvatinib 20 mg/day plus intravenous pembrolizumab 200 mg every 3 weeks or oral sunitinib 50 mg/day on a schedule of 4 weeks on and 2 weeks off (Figure 2). Randomization will be stratified according to the geographic region

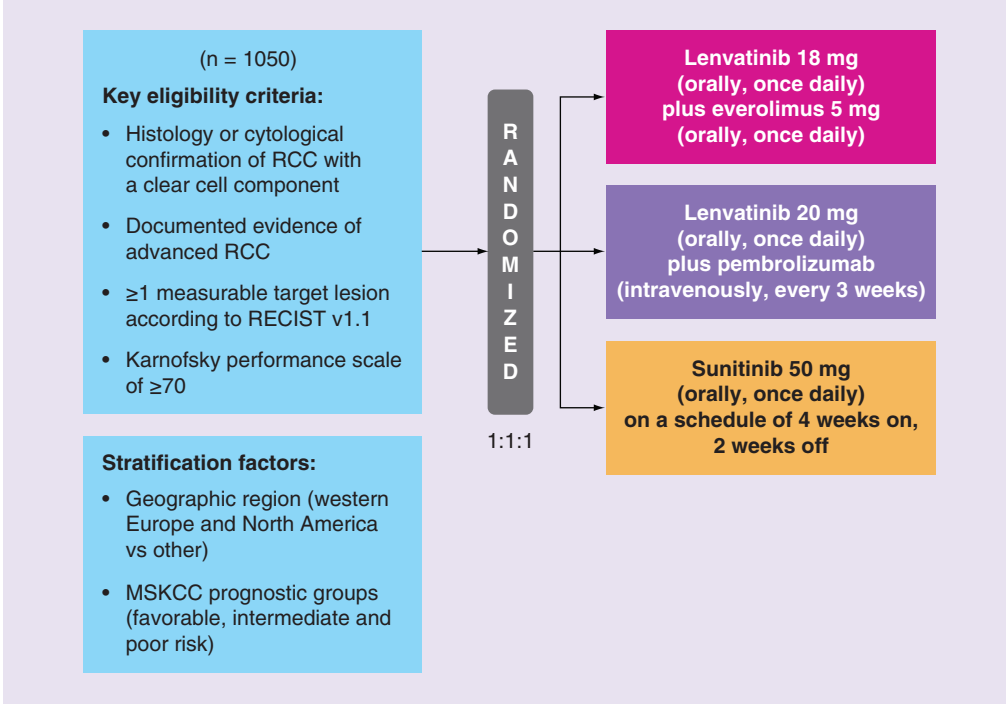

Figure 2. CLEAR study design.
MSKCC: Memorial Sloan Kettering Cancer Center; RCC: Renal cell carcinoma; RECIST v1.1: Response Evaluation Criteria In Solid Tumors version 1.1.

(western Europe and North America vs other) and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favorable, intermediate or poor risk). Patients will continue to receive treatment until disease progression, unacceptable toxicity, patient request, withdrawal of consent, completion of 35 treatments with pembrolizumab or study termination. However, patients may continue treatment beyond initial RECIST v1.1-defined progression so long as an investigator-assessed clinical benefit is observed and the patient is tolerating the study drug. In this case, patients will discontinue study treatment on evidence of further progression and/or loss of clinical benefit.

Outcome evaluations

Tumor assessments, including computed tomography scans of the chest and computed tomography or magnetic resonance imaging scans of the abdomen, pelvis and other areas of known disease, will be performed every 8 weeks according to RECIST v1.1 by the investigator and sent to an imaging core laboratory for IIR. Patients randomized to the lenvatinib plus pembrolizumab treatment arm will also be assessed by IIR using immune-related RECIST. Tumor assessments will be performed at baseline, then every 8 weeks during treatment until disease progression or the start of another anticancer therapy for patients who discontinue study treatment without disease progression.

Safety assessments will consist of monitoring and recording of all adverse events from receipt of informed consent until the last visit; adverse events will be followed until 30 days after the last dose or until resolution, whichever comes first. Serious adverse events will be recorded from the receipt of informed consent until 120 days (or 30 days if the patient initiates new anticancer therapy) after the last dose, regardless of their relationship to the study drugs. Adverse events will be graded according to Common Terminology Criteria for Adverse Events, v4.03. Additionally, hematology and blood chemistry, urine values and vital sign variables will be regularly measured, and physical examinations, electrocardiography and multiple-gated acquisition scans or echocardiograms will be performed periodically. The HRQoL will be assessed at baseline, every 3 weeks, and at the time of withdrawal using several assessments: the Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-related Symptoms, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 and the European Quality of Life (EuroQOL) EQ-SD-3L.

Blood samples will be collected from all lenvatinib recipients at baseline, every 2 weeks of treatment for the first two cycles and then every 3 weeks thereafter. Drug concentrations will be measured and analyzed using a population

pharmacokinetic approach, and serum antidrug antibodies will also be measured for patients in the lenvatinib plus pembrolizumab treatment arm. A biomarker-discovery program is also associated with this clinical trial, focused on biomarker discovery and/or validation to identify potential biomarkers that may be useful to predict patient response, evaluate response-related and/or safety-related outcomes and for potential use in diagnostic development. Additionally, PD-L1 expression by immunohistochemistry will be evaluated.

Statistical analyses

The full analysis set (i.e., all randomized patients regardless of the treatment actually received) will be used for all efficacy analyses. In addition, the per protocol analysis set (i.e., patients who received ≥1 dose of the study drug, had no major protocol deviations and had both baseline and ≥1 postbaseline tumor assessments) will be used in secondary analysis of efficacy end points, and the safety analysis set (i.e., patients who received ≥1 dose of the study drug) will be used for all safety analyses. The sample size was estimated based on the primary end point of PFS; approximately 1050 patients will be randomized. The study is designed to achieve at least 90% statistical power at two-sided $\alpha = 0.0499$ to detect at a difference in at least one of the primary comparisons (lenvatinib plus everolimus vs sunitinib, or lenvatinib plus pembrolizumab vs sunitinib).

The primary efficacy analysis is planned for when approximately 551 PFS events have been observed among the three treatment arms and at least 368 events have been observed for the lenvatinib plus everolimus arm or the lenvatinib plus pembrolizumab arm and sunitinib arm. No comparative statistical analyses are planned between the combination arms. Median PFS will be estimated using the Kaplan–Meier method, with two-sided 95% CIs, and the differences between treatment arms will be evaluated using the stratified log-rank test at two-sided $\alpha = 0.05$, with geographical region and MSKCC prognostic groups as strata. A stratified Cox regression model will be used to estimate the HR and 95% CI. For the secondary efficacy analysis, ORR will be determined with exact 95% CIs using the Clopper–Pearson method, with the difference between treatment arms evaluated using a stratified Cochran–Mantel–Haenszel test. Median OS will be calculated using the same methods used in the primary PFS analysis. Additionally, the primary end point PFS and secondary end points ORR and OS will be tested using a parallel gatekeeping procedure to control the overall family-wise error rate.

Discussion & future perspective

This is a pivotal Phase III study comparing outcomes with the current first-line treatment for aRCC (single-agent sunitinib) versus the combination of either two targeted therapies or one targeted therapy plus an immuno-oncology agent. Patients of all RCC risk groups will be included and stratified based on geographic region and MSKCC prognostic score. Results of the CLEAR study may reshape the approach to first-line treatment of aRCC by introducing a broader range of potential therapies. If the efficacy and safety of either of these combinations is confirmed, then one or two additional first-line treatment options will be available for patients with aRCC. In addition, exploratory analyses will investigate whether differences in biomarkers between TKI plus mTOR inhibitor and TKI plus immuno-oncology therapy combinations exist, and whether different patient populations may derive benefit from them – which could, in turn, inform patient selection. The treatment landscape for aRCC is rapidly evolving, and this study is one of several highly anticipated ongoing clinical trials to examine TKI-IO combination regimens. A key differentiator of the CLEAR study is that lenvatinib has demonstrated immune-modulating activity and has been shown to potentiate the antitumor activity of PD-1 signaling blockade *in vivo* [62]. These preclinical findings form the basis of a solid mechanistic rationale for the combination of these specific agents. Together with the promising anticancer activity observed with lenvatinib plus pembrolizumab in patients with aRCC in a Phase Ib/II study [66], results of the CLEAR study are eagerly awaited.

There were several considerations taken into account during the clinical trial design stage. The first-line treatment paradigm is presently changing, particularly in patients with intermediate- and poor-risk features. However, sunitinib is likely to remain a reasonable first-line treatment option – particularly, but not exclusively, for patients with good risk features – so the use of sunitinib in the control arm of this study is justified, despite recent advancements in the first-line treatment setting. Additionally, tumor assessments will be performed using both investigator and independent reviews. Although independent review is often given more weight due to the lack of potential investigator bias, investigator-reviewed assessments are likely to be more reflective of real-world clinical practice, particularly when immunotherapy is involved [68]. Finally, whether the complete remission rate should be the standard outcome measure to evaluate medical treatment for patients with aRCC remains controversial.

For targeted and cytokine therapies, the amount of tumor shrinkage typically correlates with survival outcomes, particularly if a threshold of 60% tumor shrinkage is reached [69].

Combinations of targeted agents may increase the amount of patients with at least 60% tumor shrinkage, thereby broadening the proportion of patients who may achieve an OS benefit from treatment. However, for checkpoint inhibitor immuno-oncology therapy, the role of tumor shrinkage as an outcome measure is still undefined. In a randomized, Phase III trial, the complete remission rate was higher with TKI plus immuno-oncology combination therapy (nivolumab plus ipilimumab) compared with single-agent TKI use (sunitinib) as first-line treatment for aRCC (9 vs 1%, respectively), indicating a possible advantage with such a combination [18].

As expected with clinical trials of combination therapies, the safety and tolerability profile is of utmost importance to evaluate feasibility as part of the RCC treatment armamentarium. Data regarding HRQoL will also help inform on the usefulness of these therapies.

Conclusion

The CLEAR study will investigate the efficacy and tolerability of lenvatinib in combination with everolimus or pembrolizumab versus standard single-agent sunitinib as first-line therapy for aRCC. The results of this study will help define the roles of these novel combination therapies in the management of aRCC. If positive, the results of this study may change the treatment paradigm in first-line RCC to combination therapy, perhaps irrespective of the prognostic risk group.

Executive summary

Background

- Despite the availability of several first-line targeted treatment options for advanced renal cell carcinoma (RCC), current therapies are unsatisfactory.
- Approximately 20–30% of patients do not respond to initial therapy or progress within ≤3 months, indicating resistance to molecular-targeted monotherapies.

Lenvatinib

- Lenvatinib is a potent, multiple-receptor, tyrosine kinase inhibitor that selectively targets VEGF receptors 1–3, FGF receptors 1–4, PDGFR α, KIT and RET.
- Lenvatinib in combination with everolimus is approved for the treatment of patients with advanced RCC after one prior VEGF-targeted therapy.
- In a Phase I study, lenvatinib in combination with pembrolizumab demonstrated promising antitumor activity in patients with RCC.

The CLEAR study

- The CLEAR study is a three-arm, Phase III clinical trial investigating the combination of lenvatinib plus everolimus and the combination of lenvatinib plus pembrolizumab versus sunitinib monotherapy for the first-line treatment of patients with advanced RCC.
- Eligible patients will have advanced RCC with histologically or cytologically confirmed clear cell component and no prior systemic anticancer therapy.
- The primary end point is progression-free survival, as assessed by independent imaging reviewers using Response Evaluation Criteria In Solid Tumors version 1.1.
- Results of this trial will help define the roles of combination therapies – targeted therapy combinations as well as targeted therapy plus immuno-oncology approaches – in the management of advanced RCC.

Supplementary data

An infographic accompanies this paper at the end of the references section. To download the infographic that accompanies this paper, please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/fon-2018-0745

Financial & competing interests disclosure

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Article details

Title of article
Lenvatinib plus everolimus or pembrolizumab vs sunitinib in advanced renal cell carcinoma: study design and rationale

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Trial registration number
NCT02811861

Primary objectives/rationale

Primary objective

Demonstrate that lenvatinib plus everolimus or lenvatinib plus pembrolizumab is superior compared with sunitinib monotherapy in improving PFS in the first-line treatment of patients with advanced RCC

Secondary objectives

Compare ORR, OS, safety and tolerability, HRQoL, PFS on next line of therapy between treatment arms; characterize the pharmacokinetics of lenvatinib when coadministered with everolimus or pembrolizumab; and assess the pharmacokinetic/ pharmacodynamic relationship between exposure and efficacy, biomarkers, and safety

Study design and treatment including planned sample size, planned study period and study procedures

Patients will be randomized centrally by an interactive voice- and web-response system in a 1:1:1 ratio to open-label treatment with oral lenvatinib 18 mg/day plus oral everolimus 5 mg/day, oral lenvatinib 20 mg/day plus pembrolizumab 200 mg iv. Q3W or oral sunitinib 50 mg/day on a schedule of 4 weeks on and 2 weeks off

Randomization will be stratified according to geographic region (Western Europe and North America versus other), and MSKCC prognostic groups (favorable, intermediate, or poor risk)

Patients will continue to receive treatment until disease progression, unacceptable toxicity, patient request, withdrawal of consent, or study termination.

Key eligibility criteria

Age ≥18 years

Histological or cytological confirmation of RCC with a clear cell component, and documented evidence of advanced disease

≥1 measurable target lesion according to RECIST v1.1, a Karnofsky performance status ≥70, adequately controlled blood pressure (with or without antihypertensive medications), and adequate renal, bone marrow, blood coagulation, and liver function

No prior systemic anticancer therapy for RCC

No radiation therapy within 21 days prior to the first dose of study drugs, except for palliative radiotherapy to bone lesions, which is permitted if completed 2 weeks prior to the start of study treatment

Patients with untreated central nervous system metastases or those who had received a live vaccine within 30 days of the planned first dose of study drug(s) are also excluded

Outcome measures/end points

Primary end point
PFS by independent imaging review using RECIST v1.1

Secondary end points
ORR by independent imaging review using RECIST v1.1; OS; safety and tolerability and HRQoL

Exploratory end points include
PFS in the lenvatinib plus pembrolizumab arm by immune-related RECIST (irRECIST), duration of response, disease control rates, clinical benefit rates, and the relationship between blood biomarkers and efficacy outcomes

Glossary

HRQoL: Health-related quality of life; MSKCC: Memorial Sloan Kettering Cancer Center; ORR: Overall response rate; OS: Overall survival; Q3W: Every 3 weeks; PFS: Progression-free survival; RCC: Renal cell carcinoma