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STELLAR-304: a phase III study of zanzalintinib (XL092) plus nivolumab in advanced non-clear cell renal cell carcinoma

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ABSTRACT

Management of advanced non-clear cell renal cell carcinoma (nccRCC) is challenging due to disease rarity and heterogeneity. The combination of multi-targeted tyrosine kinase inhibitor (TKI) with immune checkpoint inhibitor (ICI) has emerged as an effective treatment strategy, but well-designed, phase III randomized clinical trials are needed to demonstrate superiority over current treatment options. Zanzalintinib is a novel, multi-targeted TKI that has demonstrated promising preclinical anti-tumor activity in combination with ICIs. STELLAR-304 is a phase III trial evaluating first-line zanzalintinib plus nivolumab versus sunitinib in advanced nccRCC. Primary endpoints are progression-free survival and objective response rate. Secondary endpoint is overall survival. To our knowledge, STELLAR-304 is the first phase III study assessing a TKI-ICI combination in nccRCC patients across multiple subtypes.

Clinical Trial Registration: This trial is registered at ClinicalTrials.gov (identifier: NCT05678673)

PLAIN LANGUAGE SUMMARY

Advanced non-clear cell renal cell carcinoma (nccRCC) is a group of rare kidney cancers that have spread to other parts of the body. Currently available treatment options for nccRCC are based on results from phase II studies for nccRCC involving small numbers of patients or from studies conducted for all kidney cancers; these treatments may not adequately control the disease. Therefore, new and effective therapies are urgently needed. Zanzalintinib is an investigational oral drug that may reduce or stop cancer cells from growing and spreading. Zanzalintinib may also improve how well the body responds to another type of cancer drug called immune checkpoint inhibitor (ICI), which works by helping the body's own immune system attack cancer cells. STELLAR-304 is a global, phase III study in people who have not been previously treated for advanced nccRCC. The study will test how zanzalintinib plus nivolumab, an ICI, can control the disease compared with sunitinib, a therapy commonly used to treat nccRCC. Participants will be randomly assigned in a 2 to 1 ratio to receive either zanzalintinib plus nivolumab or sunitinib. We will compare how long participants stay alive without nccRCC worsening and evaluate how their tumor responds to the two study treatments. Additionally, we will monitor the side effects in the treatment groups. Approximately 291 participants will be included.

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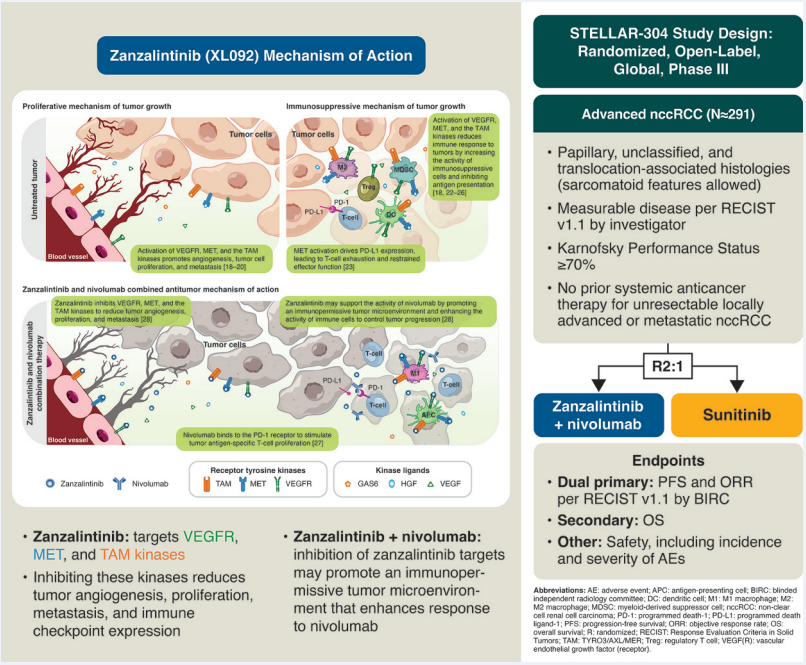

1. Background

1.1. Unmet need and current treatment landscape in non-clear cell renal cell carcinoma

Non-clear cell renal cell carcinoma (nccRCC) is a heterogenous group of cancers that accounts for approximately 25% of all renal cell carcinoma (RCC) cases [1]. Histologic subtypes of nccRCC include papillary (10–20% of all RCC cases), chromophobe (5%), collecting duct (1–2%), translocation-associated (~1%) histology, renal medullary (<1%) and unclassified (<5%), with each subtype showing distinct biologies, presentations, clinical courses, and responses to treatment [1–5]. Due to the rarity of each nccRCC histologic subtype, there have been few dedicated randomized controlled studies in nccRCC [1,6,7]. As a result, management is often based on phase II studies, retrospective analyses, or extrapolation of data from clear cell RCC trials, highlighting the unmet need for a tailored treatment for patients with nccRCC [1,6,7].

Current treatment options for nccRCC include targeted therapies such as tyrosine kinase inhibitors (TKIs), mammalian target of rapamycin (mTOR) inhibitors, angiogenesis inhibitors, and immunotherapy [6,8–10]. However, the optimal treatment strategy remains unclear and practice guidelines recommend enrollment of patients into clinical trials whenever possible [6,8]. Preferred first-line treatment options for nccRCC include TKIs such as sunitinib or cabozantinib, which have shown clinical benefit in phase II clinical trials [6,8,11–13]. In the ASPEN study, patients with previously untreated papillary, chromophobe, or unclassified nccRCC were randomized to receive either sunitinib or everolimus. Sunitinib demonstrated modest progression-free survival (PFS) improvement versus everolimus (8.3 vs 5.6 months; hazard ratio [HR] for everolimus versus sunitinib: 1.41, 80% confidence interval [CI]: 1.03–1.92; $p = 0.16$) [11]. Similarly, in the ESPN study, sunitinib improved median PFS (6.1 vs 4.1 months, respectively; $p = 0.60$) and overall survival (OS, 16.2 vs 14.9 months, respectively; $p = 0.18$) versus everolimus in patients with untreated nccRCC of various histologies [12]. Subsequently, cabozantinib and other MET-targeting TKIs were compared with sunitinib in patients with advanced papillary nccRCC in the SWOG 1500/PAPMET trial [13]. Cabozantinib showed significant benefits in PFS (9.0 vs 5.6 months, respectively; HR for cabozantinib vs sunitinib: 0.60, 95% CI: 0.37–0.97; $p = 0.019$) and objective response rate (ORR, 23% vs 4%; $p = 0.010$) versus sunitinib in patients with advanced papillary nccRCC [13]. However, no significant difference in OS has been observed between cabozantinib and sunitinib based on currently available data [6,8,13].

Immune checkpoint inhibitors (ICIs) such as nivolumab and pembrolizumab (both PD-1 inhibitors) have also been evaluated in patients with nccRCC [3–5,14]. For ICI monotherapy, ORRs ranged from 14% to 27% and were variable by histologic subtype, indicating the need to explore novel combinations to improve efficacy [3–5,14]. In a phase Ib study in advanced solid tumors, cabozantinib plus atezolizumab (a PD-L1 inhibitor) led to an ORR of 31% (80% CI: 20–44) and median PFS of 9.5 (95% CI: 6.4–18.3) months in a cohort of 32 patients with nccRCC [15]. In another phase II single-arm study, treatment with cabozantinib plus nivolumab led to an ORR of 48% (95% CI: 31.5–63.9), a median PFS of 12.5 months (95% CI: 6.3–16.4), and a median OS of 28 months (95% CI: 16.3–not evaluable) in 40 patients with papillary, unclassified, or translocation-associated RCC [16]. The single-arm phase II KEYNOTE-B61 study showed promising antitumor activity with pembrolizumab plus lenvatinib in patients with previously untreated nccRCC [17]. Pembrolizumab plus lenvatinib resulted in a median PFS of 18.0 (95% CI: 14.0–not reached) months and an ORR of 49% (95% CI: 41–57) in 158 patients with nccRCC (28% ORR in the chromophobe subtype; 49–67% in other subtypes) [17]. Taken together, these data support the evaluation of TKI-ICI combination approaches for select nccRCC subtypes.

Article highlights

Background & rationale
- Non-clear cell renal cell carcinoma (nccRCC), a heterogenous group of rare histologic subtypes, accounts for approximately 25% of all renal cell carcinomas.
- Due to the rarity and heterogeneity of histologic subtypes, data supporting the management of nccRCC are limited.
- Single-agent sunitinib, a tyrosine kinase inhibitor (TKI), is commonly used as first-line therapy for patients with nccRCC.
- Combination of tyrosine kinase inhibitor (TKI) with immune checkpoint inhibitor (ICI) has emerged as an effective treatment strategy, but well-designed trials are needed to evaluate superiority over current treatment options.

Mechanism of action for zanzalintinib
- Zanzalintinib (XL092) is a novel, multi-targeted TKI of the vascular endothelial growth factor receptor (VEGFR), MET, and TAM family of kinases, which are involved in tumor cell proliferation, neovascularization, and immune cell regulation.
- Zanzalintinib may promote an immune-permissive microenvironment and enhance response to PD-1/PD-L1 immune checkpoint inhibitors when used in combination.
- Zanzalintinib has demonstrated promising antitumor activity and manageable safety profile as a single agent and in combination with ICIs in preclinical and early phase clinical studies, supporting further clinical research.

STELLAR-304 study design
- STELLAR-304 (NCT05678673) is a global, open-label, randomized, phase III study, which is actively enrolling patients in Europe, Latin America, North America, and the Asia-Pacific region.
- Approximately 291 patients with unresectable, locally advanced or metastatic nccRCC who have not received prior systemic anticancer therapy for advanced disease will be randomized 2:1 to zanzalintinib plus nivolumab or oral sunitinib.
- Patients aged ≥18 years with histologically confirmed nccRCC, with a papillary, unclassified, or translocation-associated histologic subtype are eligible; sarcomatoid features are allowed.
- Patients with chromophobe, renal medullary carcinoma, and pure collecting duct histologic subtypes are excluded.
- Patients may have received one prior systemic adjuvant therapy, including ICI; tumor recurrence must have occurred ≥6 months after the last dose.
- The dual primary endpoints are PFS and ORR per RECIST v1.1 by BIRC
- The secondary endpoint is OS.
- Safety will also be assessed.

Conclusions
- nccRCC is a rare, heterogenous group of RCC with limited treatment options. Novel treatment strategies supported by randomized prospective studies are needed.
- Zanzalintinib is a novel, multi-targeted TKI that has shown promising antitumor activity as a single agent and in combination with an ICI in preclinical and early phase clinical studies.
- STELLAR-304 is a randomized, phase III clinical trial that will evaluate the efficacy and safety of zanzalintinib plus nivolumab compared with sunitinib in patients with previously untreated advanced nccRCC.

1.2. Zanzalintinib's mechanism of action and rationale for combination with ICIs

Zanzalintinib (XL092) is a novel, oral, multi-targeted TKI of vascular endothelial growth factor receptors (VEGFRs), MET, and the TAM family of kinases (TYRO3, AXL, MER) (Figure 1) [28]. These tyrosine kinases are key drivers of RCC pathogenesis, including angiogenesis, tumor cell proliferation, and metastasis; they may also contribute to therapeutic resistance to anti-angiogenic agents [22,28,30,31]. While understanding of the tumor biology is limited across nccRCC subtypes, higher expression levels of VEGFR and AXL have been detected in papillary RCC than that found in ccRCC [32,33]. In addition, aberrant MET expression, which has been reported in papillary and translocation-associated RCC, is associated with poor outcomes [34–36]. Altogether, there is a rationale for targeting VEGFR, MET, and the TAM family of kinases with zanzalintinib to improve treatment outcomes in patients with nccRCC.

The combination of multi-targeted TKIs with ICIs has emerged as a treatment strategy that may potentially overcome the limitations of either agent alone by targeting angiogenesis and the tumor microenvironment [22,28,30]. VEGFR, MET, and the TAM kinases, which are expressed on both tumor cells and endothelial cells of blood vessels, are critical for tumor growth and angiogenesis [22,28,30,31]. These kinases are also expressed on immune cells and their activation leads to impaired dendritic cell maturation, interference with T-cell activation, and proliferation of immunosuppressive cells such as regulatory T cells, myeloid-derived suppressor cells, and M2 macrophages to inhibit immune response to tumors [18,22,28,30]. Furthermore, dysregulation of VEGFR/MET/TAM kinase activity promotes expression of immune checkpoint proteins including PD-1/PD-L1, leading to T-cell exhaustion and restrained effector function [18,22–25,28,30]. Hence, targeting these pathways with a TKI may promote an immune-permissive environment to support the activity of an anti-PD-1/L1 inhibitor (Figure 1) [18,22–25,28,30,37].

Zanzalintinib has demonstrated antitumor activity as a single agent and in combination with ICIs in preclinical studies [28]. In several murine xenograft models of human breast, gastric, and lung cancer, single-agent zanzalintinib inhibited tumor growth in a dose-dependent manner. The immunomodulatory effect of zanzalintinib was evaluated in a colon cancer murine syngeneic model, which showed elevated peripheral CD4+ T-cells and B-cells and decreased peripheral myeloid cells compared with vehicle. In the same mouse model, the combination of zanzalintinib with an ICI (a PD-1, PD-L1, or CTLA-4 inhibitor) led to greater suppression of tumor growth compared with any of these agents alone. Importantly, treatment with zanzalintinib plus a PD-1 or PD-L1 inhibitor showed an immune-permissive effect, with a significant increase in CD8+ T-cell tumor infiltration compared with vehicle. Furthermore, in *in vitro* studies, zanzalintinib treatment led to macrophage repolarization from M2 (immune-suppressive phenotype) to M1 (immune-permissive phenotype) and inhibited primary human macrophage efferocytosis. These results suggest zanzalintinib plus an ICI may provide enhanced antitumor activity and support clinical evaluation of this combination strategy [28].

1.3. Early phase clinical data with zanzalintinib

The safety and antitumor activity of zanzalintinib as a single agent and as part of combination therapies are being investigated in patients with advanced solid tumors in early phase clinical trials [38,39]. The ongoing phase I STELLAR-001 (NCT03845166) study is evaluating zanzalintinib in combination with the PD-L1 inhibitor atezolizumab in patients with advanced solid tumors. In the dose-escalation stage, zanzalintinib demonstrated a half-life of 16–22 hours, supporting once daily dosing [38]. Zanzalintinib as a single agent or in combination showed a manageable safety profile with no

unexpected adverse events reported from the TKI and ICI drug classes [3–5,13,14,38]. The most frequent treatment-emergent AEs were nausea, hypertension, and diarrhea with single-agent zanzalintinib ($n = 47$), and fatigue, diarrhea, and decreased appetite with zanzalintinib plus atezolizumab ($n = 40$). There were no grade 4 or 5 immune-related AEs with zanzalintinib plus atezolizumab and no grade 5 treatment-related AEs with monotherapy or the combination [38]. In an expansion cohort of 32 patients with heavily pre-treated ccRCC, single-agent zanzalintinib resulted in an ORR of 38% and disease control rate (DCR) of 88% [40]. Antitumor activity was observed in patients who had progressed on prior VEGFR-TKIs (ORR of 35%), including cabozantinib. ORR was 57% and DCR was 86% in patients without prior cabozantinib exposure; these rates were 24% and 94%, respectively, in patients who had been previously treated with cabozantinib [40]. Incidence of all-grade (9%) and grade 3 or higher (0%) palmar-plantar erythrodysesthesia was relatively low compared with those reported with other VEGFR-TKIs [40–43]. The cohort-expansion stage is currently ongoing and includes a cohort of patients with nccRCC; data are not yet available [38,40].

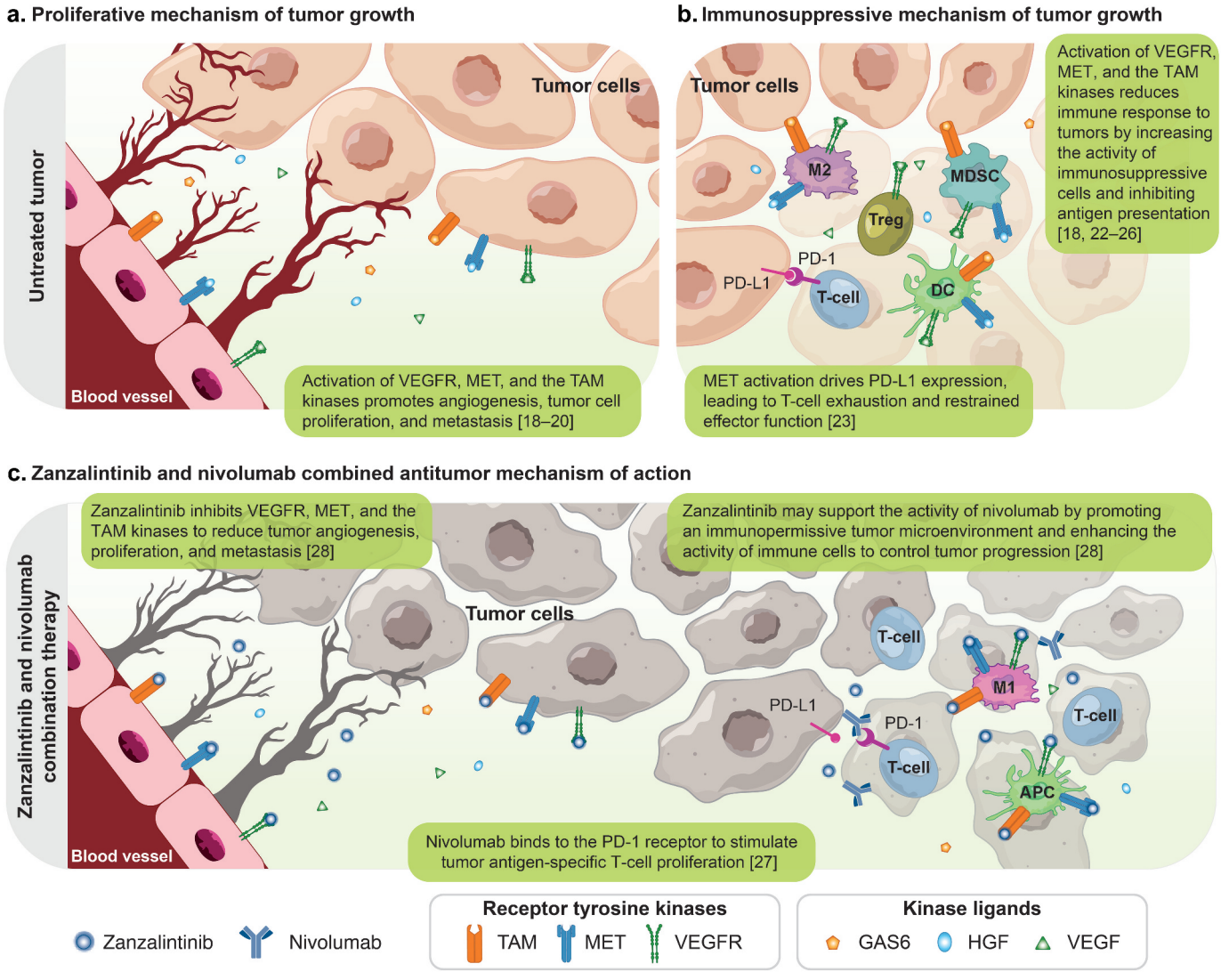

Figure 1. Zanzalintinib inhibits kinases involved in multiple processes.

(a) VEGFR, MET, and the TAM kinases are overexpressed in RCC and their activation by VEGF, HGF, and GAS6 respectively, results in angiogenesis, proliferation, metastasis, and tumor survival [18–21]. (b) VEGFR, MET, and the TAM kinases display immune-modifying activity by increasing the number of immunosuppressive cells, such as myeloid-derived suppressor cells, regulatory T cells, and M2 macrophages, and increasing levels of immune checkpoints including PD-1/PD-L1 in the tumor microenvironment; these kinases also inhibit the maturation and function of antigen-presenting cells and reduce lymphocyte infiltration [18,22–26]. (c) Combining the TKI zanzalintinib and the anti-PD-1 agent nivolumab [27] may create an immune-permissive tumor microenvironment and help overcome immunotherapy resistance [28]. Through inhibition of VEGFR, MET, and the TAM kinases, zanzalintinib may regulate antigen presentation, lymphocyte infiltration, and immune cell expression, which could enhance the activity of nivolumab [28].

The figure was adapted from Saeed et al. [29] with permission of the authors and the publisher (Taylor & Francis Ltd, https://www.tandfonline.com).

APC: antigen-presenting cell; DC: dendritic cell; M1: M1 macrophage; M2: M2 macrophage; MDSC: myeloid-derived suppressor cell; PD-1: programmed cell death protein 1; PD-L1: programmed death ligand 1; RCC: renal cell carcinoma; TAM: TYRO3, AXL, and MER; Treg, regulatory T cell; VEGF(R): vascular endothelial growth factor (receptor).

Based on the preclinical data combining zanzalintinib with ICIs and encouraging preliminary clinical activity of zanzalintinib in RCC, STELLAR-304 (NCT05678673) was initiated.

2. STELLAR-304

2.1. Study design

STELLAR-304 is a global, open-label, randomized, phase III trial evaluating the efficacy and safety of zanzalintinib in combination with nivolumab versus sunitinib in patients with previously untreated advanced nccRCC across different histologic subtypes. Sunitinib was selected as the comparator in the study given its activity across a broad range of nccRCC histological subtypes tested in this trial [11,12]. Sunitinib is a recommended treatment option for nccRCC in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) and for non-papillary nccRCC in the EAU guidelines [44,45]. At the time of conception of the STELLAR-304 study, the ESMO guidelines indicated sunitinib as a standard therapy for papillary RCC [6]. The recently published 2024 ESMO guidelines indicate cabozantinib as the preferred single-agent treatment for papillary RCC, and sunitinib as an alternative single-agent option; lenvatinib plus pembrolizumab and cabozantinib plus nivolumab are suggested as alternatives to single-agent therapy [46]. However, there are no phase III data to date demonstrating OS benefit of cabozantinib or TKI-ICI combinations over sunitinib, and sunitinib remains a standard of care globally [47].

Approximately 291 eligible patients will be randomized 2:1 to receive either zanzalintinib in combination with nivolumab or sunitinib (Figure 2). Randomization will be stratified by histology (papillary without sarcomatoid features vs other subtypes without sarcomatoid features vs any histology with sarcomatoid features) and IMDC prognostic score (favorable vs intermediate vs poor). Zanzalintinib is administered orally once daily, and nivolumab is administered intravenously every 4 weeks. Sunitinib is administered orally once daily for 4 weeks on and 2 weeks off. Patients will be treated until lack of clinical benefit, unacceptable toxicity, or other protocol-defined reason for discontinuation. Post-treatment follow-up visits for safety evaluation are to occur 30 and 100 days following discontinuation of study treatment. In addition, patients are to be contacted every 12 weeks after the second post-treatment visit to assess survival status and receipt of subsequent anticancer therapy. Multiple attempts will be made to contact any patient lost to follow-up.

2.2. Eligibility criteria

Patients must be ≥18 years of age and have histologically confirmed nccRCC that is unresectable, advanced, or metastatic and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by investigators. Patients with papillary, unclassified, or translocation-associated histologic subtypes are eligible; among the eligible nccRCC histologic subtypes, sarcomatoid features are allowed. Patients with chromophobe, renal medullary carcinoma, or pure collecting duct histologic subtypes are not eligible. Patients are excluded if they have had prior systemic anticancer therapy for unresectable, locally advanced or metastatic nccRCC. Receipt of one prior systemic adjuvant therapy is allowed, including ICIs, but excluding sunitinib; for patients who received adjuvant treatment, the recurrence must have occurred ≥6 months after the last dose. Patients must have a Karnofsky performance status of ≥ 70%. Additional key eligibility criteria are shown in Table 1. A retrospective central pathology tissue review will be performed to confirm the nccRCC subtype, and the presence or absence of sarcomatoid features.

2.3. Endpoints

STELLAR-304 has dual primary endpoints of PFS and ORR per RECIST v1.1 as determined by blinded independent radiology committee (BIRC). PFS is defined as the time from randomization to the earlier of either radiographic progressive disease or death from any cause, and ORR is the proportion of patients with the best overall response of complete or partial response that is confirmed at a follow-up assessment ≥28 days later. The secondary endpoint is OS (time from randomization to death from any cause). Safety, including incidence and severity of AEs, will also be evaluated.

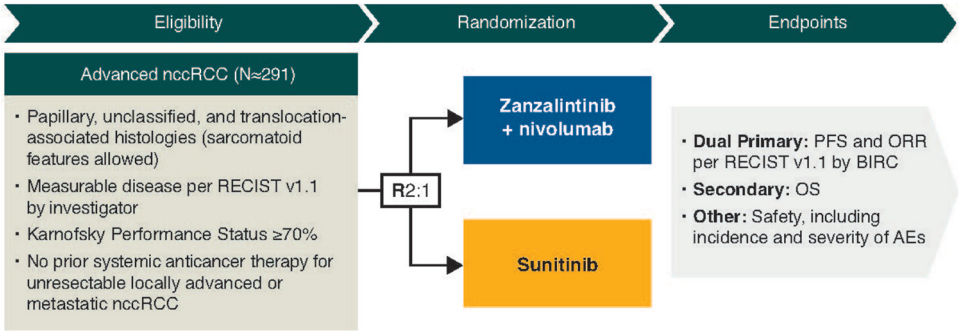

Figure 2. STELLAR-304 study design.

AE: adverse event; BIRC: blinded independent radiology committee; nccRCC: non-clear cell renal cell carcinoma; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; R: randomized; RECIST: Response Evaluation Criteria in Solid Tumors.

Table 1. Key eligibility criteria.

Inclusion
• Histologically confirmed nccRCC that is unresectable, advanced or metastatic
• Papillary, unclassified, and translocation-associated nccRCC histologic subtypes; eligible nccRCC histologies with sarcomatoid features allowed
• Measurable disease per RECIST v1.1 by investigator
• Karnofsky Performance Status ≥ 70%
• Archival tumor tissue available
• Age ≥18 years
• Recovery to baseline or ≤ grade 1 severity per CTCAE v5 from adverse events related to any prior treatments, unless adverse events are clinically nonsignificant and/or stable on supportive therapy
• Adequate organ and marrow function
Exclusion
• Chromophobe, renal medullary carcinoma, and pure collecting duct nccRCC histologic subtypes
• Prior systemic anticancer therapy for unresectable locally advanced or metastatic nccRCC, including investigational agents; one prior systemic adjuvant therapy, including ICI and excluding sunitinib, allowed for completely resected RCC if recurrence occurred ≥6 months after last dose
• Radiation therapy ≤4 weeks (≤2 weeks for bone metastasis) before randomization
• Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery and stable for ≥4 weeks before randomization
• Concomitant anticoagulation with oral anticoagulants and platelet inhibitors
• Major surgery within 8 weeks of randomization
• Corrected QT interval calculated by the Fridericia formula >480 ms within 14 days before randomization
• Pregnant or lactating females
• Administration of a live, attenuated vaccine within 30 days before randomization

CTCAE: Common Terminology Criteria for Adverse Events; ICI: immune checkpoint inhibitor; ms: milliseconds; nccRCC: non-clear cell renal cell carcinoma; RCC: renal cell carcinoma; RECIST: Response Evaluation Criteria in Solid Tumors.

2.4. Statistical methods

A sample size of approximately 291 patients is targeted to yield adequate power for multiple primary efficacy endpoints (PFS and ORR) and the secondary endpoint (OS). The primary ORR analysis will be performed in the first 222 randomized patients, and the PFS and OS endpoints will be performed in all randomized patients. For the primary analysis of ORR, 222 patients are targeted to provide 90% power for a 2-sided test at the 0.5% significance level. A total of 291 patients are targeted for PFS and OS; it will provide 90% power for 2-sided test at 4.5% significance level for PFS and 80% power for 2-sided test at 4.5% significance level for OS.

ORR will be summarized descriptively and will be tested using the Cochran-Mantel Haenszel method to adjust for stratification factors. PFS and OS will be summarized descriptively using the Kaplan-Meier method. The stratified log-rank test will be used for inferential comparisons between treatment arms. Hazard ratios will be estimated using a stratified Cox proportional hazards model.

In general, other than for partial dates, missing data will be treated as missing and will not be imputed.

2.5. Status

The study is actively enrolling. Patients will be recruited from sites across North America, Latin America, Europe, and the Asia-Pacific region. Study sites are listed on clinicaltrials.gov (NCT05678673).

2.6. Patient recruitment

Strategies for achieving adequate patient enrollment include appropriate study site selection globally, increasing patient access by offering transportation per institutional review board guidelines, HCP recruitment toolkit provided to each site, tailoring recruitment tools to participants including multi-ethnic patient brochures, recruitment posters and flyers, HCP recruitment websites in multiple countries, and a patient website in the US.

2.7. Trial oversight

The study was approved by the institutional review board/ethics committee at each site and is being conducted in accordance with Good Clinical Practice guidelines, including International Council for Harmonisation guidelines, and the Declaration of Helsinki. All patients must provide written informed consent. Safety will be monitored by an independent data and safety monitoring committee. The study was designed by members of the steering committee in collaboration with the sponsor (Exelixis) and partner (Bristol Myers Squibb). Data will be collected by the investigators and analyzed by the sponsor. The manuscript was written collaboratively by the authors with medical writing support, funded by the sponsor. All authors approved the manuscript for publication.

3. Conclusion

There is a high unmet need for the treatment of nccRCC due to the rarity of the histologic subtypes and lack of prospective randomized clinical trial data to support current treatment options. Zanzalintinib is a novel, multi-targeted TKI that has shown promising antitumor activity alone and in combination with ICIs in preclinical and early phase clinical studies. STELLAR-304 (NCT05678673) is a global phase III study that is assessing the efficacy and safety of zanzalintinib plus nivolumab versus sunitinib in patients with previously untreated papillary, unclassified, or translocation-associated nccRCC subtypes. Approximately 291 patients will be enrolled globally. The dual primary endpoints are PFS and ORR per RECIST v1.1 by BIRC, and the secondary endpoint is OS. To our knowledge, this is the first phase III

study of a TKI-ICI combination in nccRCC across multiple subtypes.

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Author contributions

All authors contributed to the conception or design of the work, drafting of the manuscript, or revising it critically for important intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure statement

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Ethical disclosure

The authors state that this study adheres to the Good Clinical Practice guidelines, including International Council for Harmonisation guidelines and the Declaration of Helsinki. The study was approved by the institutional review board/ethics committee at each study center, and all patients provided written informed consent.

Data sharing statement

Individual patient data will not be shared.

Information pertaining to writing assistance

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