KEYNOTE-B61: An Open-Label Phase 2 Study of First-Line Pembrolizumab With Lenvatinib for Non–Clear Cell Renal Cell Carcinoma

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Background

- Most renal cell carcinomas are characterized by clear cell histology (ccRCC); the remainder of cases are characterized as a heterogeneous group of cancers known as non–clear cell renal cell carcinoma (nccRCC)[1]
  - In advanced nccRCC, survival is uniformly worse than with ccRCC because of the aggressiveness of these cancers and a lack of effective systemic treatment options[1]
- Because data are limited for patients with nccRCC, the role of various agents in the treatment of nccRCC is poorly defined, and there is no standard of care; treatment guidelines recommend enrollment in clinical trials as the preferred strategy[2]
- In the phase 2 KEYNOTE-427 study, pembrolizumab, a PD-1 inhibitor, showed promising antitumor activity and manageable safety as first-line therapy in patients with nccRCC[3]
- The vascular endothelial growth factor–tyrosine kinase inhibitor lenvatinib has also shown efficacy, with a tolerable safety profile, as combination therapy with everolimus for nccRCC[4]
- In addition, in the phase 3 KEYNOTE-581/CLEAR study, the combination of pembrolizumab + lenvatinib showed antitumor activity and manageable safety as first-line therapy in patients with metastatic ccRCC, suggesting that this combination is an excellent therapeutic option for nccRCC[5]
- KEYNOTE-B61 (NCT04704219) is a single-arm, open-label, phase 2 trial being conducted to evaluate pembrolizumab + lenvatinib as first-line treatment for nccRCC

Objectives

Primary

- To evaluate the objective response rate (ORR) of pembrolizumab + lenvatinib per RECIST v1.1, by blinded independent central review (BICR)

Secondary

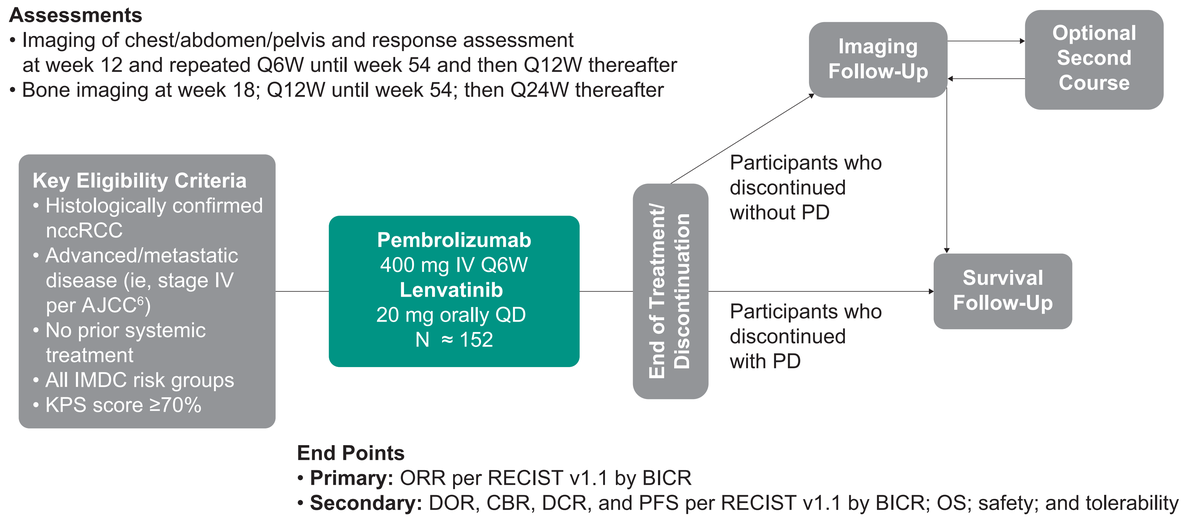
- To evaluate the following for pembrolizumab + lenvatinib:
  - Duration of response (DOR) in patients with confirmed complete response (CR) or partial response (PR) per RECIST v1.1 by BICR
  - Progression-free survival (PFS) per RECIST v1.1 by BICR
  - Overall survival (OS)
  - Clinical benefit rate (CBR), which is the percentage of patients with advanced or metastatic cancer who have achieved CR or PR of any duration or stable disease (SD) of ≥6 months per RECIST v1.1 by BICR
  - Disease control rate (DCR), which is the percentage of patients with advanced or metastatic cancer who have achieved CR, PR, or SD of any duration per RECIST v1.1 by BICR
  - Safety and tolerability

Methods

Study Design

- Approximately 152 participants with histologically confirmed nccRCC, with locally advanced or metastatic disease, who have not previously received systemic treatment will be enrolled and will receive pembrolizumab 400 mg intravenously (IV) every 6 weeks (Q6W) + lenvatinib 20 mg orally once daily (QD) (**Figure 1**)
- Participants will receive pembrolizumab treatment Q6W for up to 18 doses (approximately 2 years) or until progressive disease (PD), unacceptable toxicity, or withdrawal of consent; lenvatinib treatment can continue beyond 2 years until a discontinuation criterion is met
- Participants who stop pembrolizumab treatment after receiving 18 doses of pembrolizumab who have SD or better or participants who have received pembrolizumab for ≥24 weeks with a best response of CR and stop pembrolizumab may be eligible to receive up to 9 additional cycles of pembrolizumab after experiencing PD
  - Participants may also continue lenvatinib treatment; if lenvatinib is continued, participants will be treated at the same dose and frequency that they were receiving when PD occurred
- If pembrolizumab is discontinued because of toxicity, lenvatinib alone can be continued based on physician discretion; if lenvatinib is discontinued because of toxicity, pembrolizumab alone can be continued

Figure 1. Study Design



AJCC, American Joint Committee on Cancer; IMDC, International mRCC Database Consortium; KPS, Karnofsky Performance Status Scale; Q12W, every 12 weeks; Q24, every 24 weeks.

Patient Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 years • Histologically confirmed diagnosis of nccRCC • Locally advanced/metastatic disease • No prior systemic therapy for advanced nccRCC • Measurable disease per RECIST v1.1 by BICR • KPS score ≥70% as assessed within 10 days before the start of study drug • Archival tumor tissue sample or newly obtained core or incisional biopsy specimen of a tumor lesion not previously irradiated	• Collecting duct histology • Left ventricular ejection fraction below the institutional (or local laboratory) normal range, as determined by multigated acquisition scan or echocardiography • Urine protein level ≥1 g/24 hours • Preexisting gastrointestinal fistula grade ≥3 • Radiographic encasement or invasion of a major blood vessel, or intratumoral cavitation • Clinically significant cardiovascular disease within 12 months from the first dose of study drug, including class III or IV congestive heart failure per New York Heart Association criteria, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability • Gastrointestinal malabsorption, gastrointestinal anastomosis, or any condition that might affect the absorption of lenvatinib

Assessment and Follow-Up

- Imaging will occur at 12 weeks from enrollment, then Q6W through week 54, and then Q12W thereafter
- For the second course of tumor imaging, the first on-study imaging assessment should be performed at 12 weeks after restarting treatment
  - Subsequent tumor imaging should be performed Q12W or more frequently if clinically indicated
- Imaging should be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, completion of second-course treatment (9 cycles), or notification by the sponsor, whichever occurs first
- Adverse events (AEs) will be monitored throughout the study and graded using Common Terminology Criteria for Adverse Events (CTCAE), version 5.0

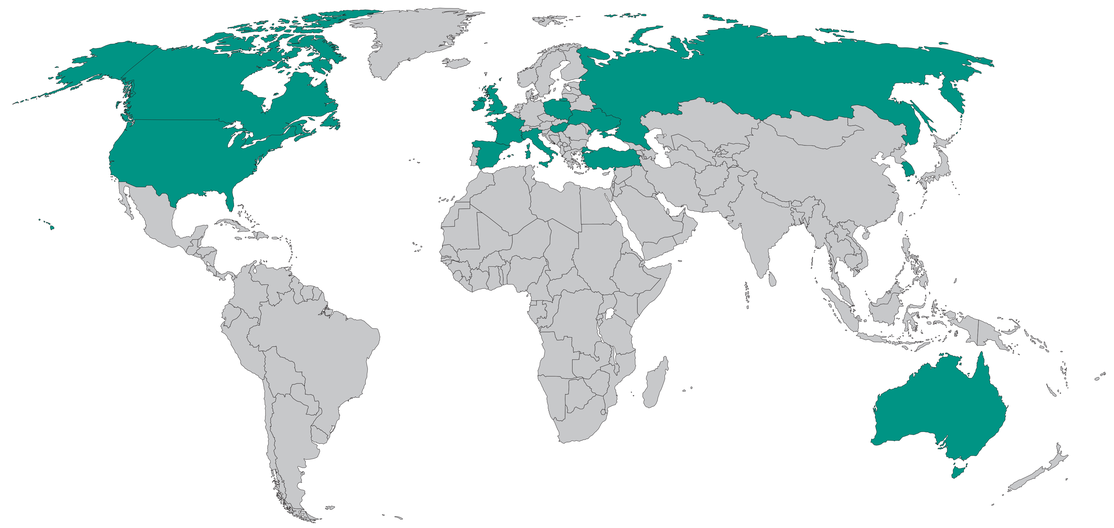
Analyses

- Efficacy analysis will be performed for the all-patients-as-treated population
  - Point estimates of ORR, CBR, and DCR will be provided, along with the 95% CIs, using the Clopper-Pearson exact binomial method
  - DOR, PFS, and OS will be summarized using the nonparametric Kaplan-Meier method
- Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, laboratory parameters, vital signs, and electrocardiographic measurements

Status

- The study is enrolling or planning to enroll in Asia, Australia, Europe, and North America (**Figure 2**)

Figure 2. Countries With Sites of Enrollment (green)



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