Safety and efficacy of multi-target TKI combined with nivolumab in checkpoint inhibitor-refractory advanced NSCLC patients: a prospective, single-arm, two-stage study

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BACKGROUND

- Vascular endothelial growth factor (VEGF) inhibition may reverse a proangiogenic microenvironment and recover sensitivity to subsequent immune checkpoint inhibitors (ICIs) treatment.
- Anlotinib is a small molecule tyrosine kinase inhibitor (TKI) inhibiting angiogenesis and has been applied in adjuvant or further-line therapy in Chinese patients with non-small cell lung cancer (NSCLC).

PATIENTS AND METHODS

- This is a phase Ib/II, open-label, single-center study comprising dose finding (part A) and expansion cohort (part B) (Figure 1).
- The primary objective is to determine phase 2 dose (RP2D, part A), safety (part B), and ORR (part B) respectively. The second aim of part B includes disease control rate (DCR), duration of response (DOR), PFS, overall survival (OS) and safety.
- The study included patients with advanced NSCLC who had progressed after prior standard of care and had no driver genes.

RESULTS

- A total of 35 patients were screened and 21 eligible patients enrolled, including 6 patients enrolled in part B. Baseline characteristics were listed in Table 1.
- The median age was 65 years. A total of 47.6% had adenocarcinoma. Among these, 47.6% were smokers, and 85.7% were male patients. Those patients found to have brain metastasis on baseline imaging were 9.5%.
- All patients had been treated with checkpoint inhibitors (at PD-1 inhibitors) and chemotherapy. The median previous treatment line was two.
- None had pathologic response (CR) or minor partial response (PR). Four patients had confirmed partial response (PR), and ORR is 19.0%.
- Three patients (14.3%) had radiographic progression within 2 cycles of study treatment (progressed disease [PD], 15 months) 2
- The median progression-free survival [PFS] was 15 months (95% CI, 4.3 - NE).

Efficacy

- In part A, 4 of the first 2 patients experienced dose-limiting toxicity (DLT, grade 3 or 4) (Figure 1). In addition, 3 patients did not experience DLT, and the RP2D was anlotinib 12 mg daily. 3 days and 8 mg nivolumab every 3 weeks (intravenously) (Table 1).
- Anlotinib and nivolumab showed positive safety and efficacy signals. Further study is warranted.

Table 1. Baseline characteristics

<table>
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<th>Characteristics</th>
<th>No.</th>
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<tr>
<td>Prior treatment line</td>
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</table>

- There were 6 and 4 patients experiencing anlotinib and nivolumab disruption due to TDIAD. Dose reduction to 10 mg at any time was required in 5 patients, and no patients decreased to 8 mg.

CONCLUSION

- Our study suggested that full dose anlotinib combined with nivolumab showed positive safety and efficacy signals. Further study is warranted.

Exploratory biomarker analyses

- TP53 alterations is the most common mutation (12/18) and showed a trend toward association with worse OS (HR, 0.1; 95% CI, 0.01 - 0.6).
- Patients with wild-type IDH4 concentrations (cut-off to cohort median) had better OS (HR, 0.2; 95% confidence interval [0.03 - 0.23] or p = 0.147) and PFS (HR, 0.35; 95% CI, 0.17 to 0.68; 2.5) than those with higher levels.
- Baseline brain-hiT high-potential patients showed longer OS (HR, NE; p = 0.005) but not PFS (HR, 0.71; 95% CI, 0.23 to 1.89; p = 0.246) compared with nivolumab-low patients with the checkpoint inhibition in the cohort median.

REFERENCES


Conflict of interest

- All the authors declare that they have no conflict of interest to declare.