A Phase 1/2 Study of Lenvatinib Plus Everolimus in Recurrent and Refractory Pediatric Solid Tumors Including CNS Tumors


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INTRODUCTION

Cancer is the second leading cause of death in children and adolescents (aged 5–14 years).†

- Solid tumors comprise approximately 30–43% of all childhood cancers.‡

- Lenvatinib is an oral multityrosine kinase inhibitor with single-agent antitumor activity, targeting vascular endothelial growth factor receptor 1/3, fibroblast growth factor receptor 1–4, platelet-derived growth factor receptor β, RET, and KIT.

- Everolimus is an mTOR inhibitor that works systemically by inhibiting mTORC1 and mTORC2 and by decreasing expression of proangiogenic activity, and is FDA-approved for treatment of advanced renal cell carcinoma in adults.§

- The primary objective of the phase 1 portion of the study was the determination of the recommended phase 2 dose (RP2D) and description of toxicities for the combination of lenvatinib plus everolimus in pediatric patients with solid tumors.

- Secondary objectives included characterization of the pharmacokinetics of lenvatinib and everolimus and preliminary evaluation of antitumor activity.

- Data from the phase 1 portion of the study are presented.

METHODS

This was a phase 1/2 multicenter, open-label trial (NCT03449015) conducted by the Children's Oncology Group. The study design is shown in Figure 1.

RESULTS

The phase 1 part of the study enrolled 17 patients. Demographics and baseline clinical characteristics are shown in Table 1.

- Tumor response data are shown in Table 2.

- Phases of the study are shown in Figure 2.

- Concomitant treatment and dose levels for each phase are shown in Table 3.

- Pharmacokinetics of lenvatinib and everolimus are shown in Table 4.

- Treatment-related adverse events (AEs) are shown in Table 5.

- Results of pharmacokinetic samples are shown in Figure 3.

CONCLUSIONS

- The recommended phase 2 dose (RP2D) of combined lenvatinib plus everolimus for children with solid and CNS tumors is lenvatinib 11 mg/m² plus everolimus 3 mg/m² on days 1 and 2 of 28-day cycles.

- RP2D determined after 2 DLTs (proteinuria and lipid abnormalities) and several dose and schedule modifications occurred in DLT 1.

- Pharmacokinetic exposure following treatment with the RP2D was comparable to those observed in children receiving single-agent lenvatinib and also in adults receiving lenvatinib plus everolimus combination therapy.¶

- There was no clear relationship between dose and toxicity.

- Enrollment to phase 1 pharmacokinetic expansion cohort (ages 2 to 6 years) is ongoing (NCT03246155).

- Enrollment to the phase 2 portion of the study is ongoing for patients with recurrent/refractory Ewing sarcoma, rhabdomyosarcoma, and high-grade glioma.

https://go.aws/2SCpIxK

Figure 1. Study Design

Results and interpretations were consistent with expectations of lenvatinib and everolimus as single agents in this phase 1 study. The doses used in this study were generally well tolerated, and toxicity was manageable and predictable.

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REFERENCE


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