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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).[1]
  - Solid tumors comprise approximately 30–43% of all childhood cancers.[2,3]
- Despite conventional multimodal therapy (chemotherapy, surgery, and radiation), children with high-risk metastatic and/or relapsed disease continue to have poor outcomes.[4]
- Proangiogenic signaling pathways cooperate with mammalian target of rapamycin (mTOR)-mediated regulation to drive cell growth and therapy resistance in pediatric cancers.[5]
  - Lenvatinib is an oral multityrosine kinase inhibitor with single-agent antitumor activity, targeting vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT.[6]
  - Everolimus is an mTOR inhibitor with antitumor effects and is approved in the United States for the treatment of pediatric subependymal giant cell astrocytoma.[7]
  - In clinical studies, the combination of lenvatinib with everolimus suggests synergistic antitumor and antiangiogenic activity, and is FDA-approved for treatment of advanced renal cell carcinoma in adults.[6,8]
- 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 (NCT03245151) conducted by the Children's Oncology Group. The study design is shown in **Figure 1**.

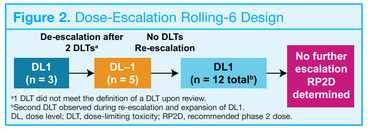
Figure 1. Study Design

[a]Inclusion criteria: Patients aged ≥ 2 and < 18 years (phase 1) or < 21 years (phase 2), with recurrent or refractory solid tumors, histologically or cytologically confirmed diagnosis (phase 1), measurable disease by RECIST version 1.1 (phase 2; all tumors except high-grade glioma) or RANO (high-grade glioma), Lansky/Karnofsky performance score ≥ 50. Patients with lymphoma or radiographic evidence of major blood vessel invasion, untreated CNS metastases, or new intracranial hemorrhage of more than punctate size for patients with high-grade glioma were excluded.
[b]Once-daily dosing for continuous 28-day cycles.
DLT, dose-limiting toxicity; ORR, objective response rate; RANO, Response Assessment in Neuro-Oncology criteria; RECIST, Response Evaluation Criteria In Solid Tumors; RP2D, recommended phase 2 dose.

RESULTS

- The phase 1 part of the study enrolled 17 patients. Demographics and baseline clinical characteristics are shown in **Table 1**.
  - Lansky/Karnofsky performance scores of ≥ 80 were reported in 15 of 17 patients; 1 patient each had a score of 60 or 70.
- All 17 patients enrolled were evaluable for dose-limiting toxicity (DLT) assessments (**Table 2**).
  - 2 DLTs (proteinuria, n = 1; headache, n = 1) observed in the initial 3 patients enrolled into dose-level (DL) 1 (lenvatinib 11 mg/m^2 plus everolimus 3 mg/m^2) resulted in de-escalation (**Figure 2**).
    - On review, 1 DLT (headache) did not meet the definition of a DLT.
  - No DLTs were observed in 5 patients then treated at DL–1 (lenvatinib 8 mg/m^2 plus everolimus 3 mg/m^2).
  - DL1 was expanded to 12 patients total, with a second DLT observed (hypertriglyceridemia and hypercholesterolemia).
- The median number of cycles received was 1 (range: 1–10) in DL–1 and 1 (range: 1–5) in DL1.
- The numbers of dose modifications for lenvatinib and everolimus are shown in **Table 2**.
  - Median treatment duration was 7.0 weeks (range: 3.3–40.0) in DL–1 and 4.9 weeks (range: 3.3–34.0) in DL1.
- Treatment-related adverse events (TRAEs) are shown in **Table 3**.
  - No grade 5 TRAEs were observed.
- Plasma concentrations of lenvatinib and everolimus are shown in **Table 4**.
- DLTs occurring in patients treated with DL1 were not correlated with high plasma concentrations of either lenvatinib or everolimus (**Figure 3**).
- After review of cumulative DLTs, TRAEs, and pharmacokinetic data, no further dose escalation of lenvatinib plus everolimus was recommended.
- Stable disease responses (as determined by investigator assessment) were observed at DL–1 (n = 1) and DL1 (n = 2).

Figure 2. Dose-Escalation Rolling-6 Design



[a]1 DLT did not meet the definition of a DLT upon review.
[b]Second DLT observed during re-escalation and expansion of DL1.
DL, dose level; DLT, dose-limiting toxicity; RP2D, recommended phase 2 dose.

The recommended phase 2 dose is lenvatinib 11 mg/m^2 plus everolimus 3 mg/m^2 for children with solid tumors, including CNS tumors. Treatment was well-tolerated, with no unexpected toxicities.

Pharmacokinetic exposures were similar to those observed in children receiving single-agent lenvatinib and in adults receiving lenvatinib plus everolimus combination therapy.

https://go.aws/2SCpiXd

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CONCLUSIONS

- The recommended phase 2 dose (RP2D) of combined lenvatinib plus everolimus for children with solid and CNS tumors is lenvatinib 11 mg/m^2 plus everolimus 3 mg/m^2 once daily for 28-day continuous cycles.
- RP2D determined after 2 DLTs (proteinuria and lipid abnormalities) and several dose and schedule modifications occurred in DL1.
- Pharmacokinetic exposures following treatment with the RP2D were comparable to those observed in children receiving single-agent lenvatinib and also in adults receiving lenvatinib plus everolimus combination therapy.[8]
  - There was no clear relationship between dose and toxicity.
  - Enrollment to a phase 1 pharmacokinetic expansion cohort (ages 2 to 6 years) is ongoing (NCT03245151).
- Enrollment to the phase 2 portion of the study is ongoing for patients with recurrent/refractory Ewing sarcoma, rhabdomyosarcoma, and high-grade glioma.

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RESULTS (continued)

Table 1. Patient Demographics and Baseline Characteristics

Parameter	Dose-level –1 LEN 8 mg/m^2 + EVE 3 mg/m^2 (n = 5)	Dose-level 1 LEN 11 mg/m^2 + EVE 3 mg/m^2 (n = 12)	Total (N = 17)
Median age, years (range)	15.0 (12–21)	9.5 (3–19)	10.0 (3–21)
Age group, years, n (%)			
≥ 2 to < 6 years	0	1 (8.3)	1 (5.9)
≥ 6 to < 18 years	4 (80.0)	10 (83.3)	14 (82.4)
≥ 18 to < 21 years	1 (20.0)	1 (8.3)	2 (11.8)
Male/female, n/n (%/%)	3/2 (60.0/40.0)	6/6 (50.0/50.0)	9/8 (52.9/47.1)
Median body surface area, m^2 (range)	1.56 (1.5–1.9)	1.04 (0.7–2.1)	1.09 (0.7–2.1)
Diagnosis, n (%)			
CNS	3 (60.0)	5 (41.7)	8 (47.1)
Astrocytoma	1 (20.0)	0	1 (5.9)
Medulloblastoma	1 (20.0)	1 (8.3)	2 (11.8)
High-grade glioma	1 (20.0)	4 (33.3)	5 (29.4)
Extracranial	2 (40.0)	7 (58.3)	9 (52.9)
Ewing sarcoma	0	1 (8.3)	1 (5.9)
Osteosarcoma	1 (20.0)	2 (16.7)	3 (17.6)
Rhabdomyosarcoma	1 (20.0)	1 (8.3)	2 (11.8)
Wilms tumor	0	2 (16.7)	2 (11.8)
Alveolar soft-part sarcoma	0	1 (8.3)	1 (5.9)
Previous therapy regimens, median (range)	2.0 (2.0–3.0)	3.0 (1.0–5.0)	2.5 (1.0–5.0)
Previous VEGF-targeted therapy, n (%)[a]	1 (20.0)	3 (25.0)	4 (23.5)
Previous mTOR-targeted therapy, n (%)[b]	1 (20.0)	1 (8.3)	2 (11.8)
Median time from end of last treatment to first dose, months (range)	0.8 (0.5–4.2)	1.7 (0.3–48.7)	1.5 (0.3–48.7)

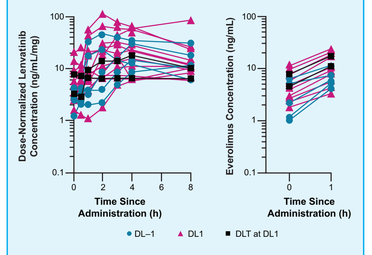
[a]Includes cabozantinib, pazopanib, sorafenib, and sunitinib.
[b]Temsirolimus.
EVE, everolimus; LEN, lenvatinib; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor.

Table 4. Plasma Concentrations of Lenvatinib and Everolimus (Cycle 1, Day 15)

Parameter, mean (SD)	Dose-level –1 (n = 5)	Dose-level 1 (n = 12)
C_{max}, ng/mL	314 (150)	359 (270)
AUC_{0-8}, h*ng/mL	1570 (935)	1780 (1100)

AUC_{0-8}, area under the concentration–time curve from zero to 8 hours; C_{max}, maximum observed concentration; SD, standard deviation.

Figure 3. Plasma Concentrations of Lenvatinib and Everolimus Over Time (Cycle 1, Day 15)



DL–1, lenvatinib 8 mg/m^2 + everolimus 3 mg/m^2; DL1, lenvatinib 11 mg/m^2 + everolimus 3 mg/m^2; DLT, dose-limiting toxicity.

Table 2. Dose-Limiting Toxicities and Dose Modifications

Parameter, n (%)	Dose-level –1 LEN 8 mg/m^2 + EVE 3 mg/m^2 (n = 5)		Dose-level 1 LEN 11 mg/m^2 + EVE 3 mg/m^2 (n = 12)		Total (N = 17)	
Patients evaluable	5 (100.0)		12 (100.0)		17 (100.0)	
DLTs	0		2 (16.7)		2 (11.8)	
Grade ≥ 3	0		2 (16.7)		2 (11.8)	
Serious AE as DLT	0		0		0	
DLT outcome						
Recovered/resolved	0		2 (16.7)		2 (11.8)	
Dose modifications due to DLT						
Interruption	0		2 (16.7)		0	
Discontinuation	0		0		0	
Treatment	**Lenvatinib**	**Everolimus**	**Lenvatinib**	**Everolimus**	**Lenvatinib**	**Everolimus**
Dose modifications due to AEs						
Interruptions[a]	2 (40.0)	2 (40.0)	4 (33.3)	5 (41.7)	6 (35.3)	7 (41.2)
Reductions[a]	0	0	3 (25.0)	0	3 (17.6)	0
Discontinuations	0	0	0	1 (8.3)	0	1 (5.9)

[a]Either lenvatinib or everolimus treatment was interrupted or reduced because of AEs (proteinuria, n = 2; headache, hypercholesterolemia, hypertension, hypertriglyceridemia, myalgia, myositis, pain in extremity, periostitis, decreased platelet count, seizure, weight loss, and wrist fracture, all n = 1); Lenvatinib treatment was also interrupted or reduced due to hypocholesterolemia (n = 1).
AE, adverse event; DLT, dose-limiting toxicity; EVE, everolimus; LEN, lenvatinib.

Table 3. Treatment-Related Adverse Events[a]

Parameter, n (%)	Dose Level –1 LEN 8 mg/m^2 + EVE 3 mg/m^2 (n = 5)		Dose Level 1 LEN 11 mg/m^2 + EVE 3 mg/m^2 (n = 12)		Total (N = 17)	
Patients with TRAEs						
Any grade	5 (100.0)		12 (100.0)		17 (100.0)	
Grade 3 or 4	0		8 (66.7)		8 (47.1)	
Most common TRAEs[b]	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Hypertension	3 (60.0)	0	8 (66.7)	1 (8.3)	11 (64.7)	1 (5.9)
Diarrhea	2 (40.0)	0	7 (58.3)	1 (8.3)	9 (52.9)	1 (5.9)
Hypothyroidism	2 (40.0)	0	7 (58.3)	0	9 (52.9)	0
Hypertriglyceridemia	1 (20.0)	0	7 (58.3)	1 (8.3)	8 (47.1)	1 (5.9)
Abdominal pain	3 (60.0)	0	4 (33.3)	0	7 (41.2)	0
Decreased appetite	4 (80.0)	0	2 (16.7)	0	6 (35.3)	0
Fatigue	2 (40.0)	0	4 (33.3)	0	6 (35.3)	0
Nausea	4 (80.0)	0	2 (16.7)	0	6 (35.3)	0
Stomatitis	3 (60.0)	0	3 (25.0)	0	6 (35.3)	0
Lymphocyte count decreased	2 (40.0)	0	3 (25.0)	0	5 (29.4)	0
Neutrophil count decreased	2 (40.0)	0	3 (25.0)	0	5 (29.4)	0
Proteinuria	1 (20.0)	0	4 (33.3)	2 (16.7)	5 (29.4)	2 (11.8)
Vomiting	2 (40.0)	0	3 (25.0)	0	5 (29.4)	0
Anemia	1 (20.0)	0	3 (25.0)	1 (8.3)	4 (23.5)	1 (5.9)
Blood cholesterol increased	1 (20.0)	0	3 (25.0)	0	4 (23.5)	0
Dry skin	1 (20.0)	0	3 (25.0)	0	4 (23.5)	0
Headache	1 (20.0)	0	2 (16.7)	1 (8.3)	4 (23.5)	1 (5.9)
White blood cell count decreased	1 (20.0)	0	3 (25.0)	0	4 (23.5)	0

[a]TRAEs were coded using the Medical Dictionary for Drug Regulatory Affairs version 22.1, and graded using the Common Terminology Criteria for Adverse Events (version 4.03).
[b]Most common TRAEs ≥ 20% any grade.
EVE, everolimus; LEN, lenvatinib; TRAE, treatment-related adverse event.