Poster No.
443TiP

A Multicenter, Open-label, Randomized, Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination With Ifosfamide and Etoposide Versus Ifosfamide and Etoposide in Children, Adolescents, and Young Adults With Relapsed or Refractory Osteosarcoma (OLIE; ITCC-082)

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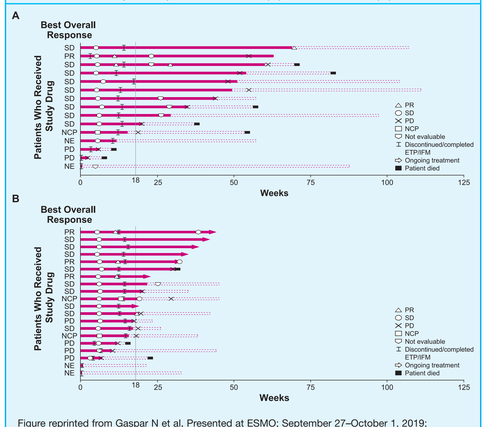
INTRODUCTION

- Osteosarcoma is a bone malignancy that primarily occurs in pediatric and young-adult patients.[1]
- Therapeutic regimens have not been standardized for patients with relapsed osteosarcoma.[1,2]
  - Most regimens include cytotoxic chemotherapy.
  - However, osteosarcomas frequently develop chemotherapy resistance.[2]
- Osteosarcomas are highly vascularized, potentially involving vascular endothelial growth factor (VEGF) receptor and platelet-derived growth factor receptor (PDGFR).[2]
  - VEGF signaling is a key regulator of angiogenesis and expression of these pathway genes has been associated with osteosarcoma.[2]
  - Tyrosine kinase inhibitors (TKIs) that block signaling through this pathway have had modest success in the treatment of osteosarcoma; these agents have typically been associated with stabilizing growth rather than shrinking tumors.[2]
  - In addition to direct effects on the growing tumor, inhibition of angiogenesis may increase uptake of chemotherapy into tumor tissue through vascular normalization.[3]
  - The European Society for Medical Oncology guidelines recommend consideration of TKIs (ie, sorafenib, regorafenib) for second-line therapy for recurrent osteosarcoma.[1]
- Lenvatinib is a TKI of VEGF receptors 1–3, fibroblast growth factor (FGF) receptors 1–4, PDGFRα, RET, and KIT.[4]
  - Importantly, lenvatinib's inhibition of FGF signaling may mitigate the acquired resistance to anti-VEGF therapy that is often observed in osteosarcomas.[5]
- Previously, in a phase 1/2 study (Study 207), the combination treatment of lenvatinib + ifosfamide + etoposide in patients with relapsed/refractory osteosarcoma was assessed.[6]
  - In the phase 1b part of Study 207, the recommended phase 2 dose was determined to be lenvatinib 14 mg/m^2 (orally, once daily) + ifosfamide 3000 mg/m^2 + etoposide 100 mg/m^2 (both IV, days 1–3 of each cycle for up to 5 cycles).
  - At this dose, patients (N = 35) demonstrated a progression-free survival (PFS) rate at 4 months (based on a Kaplan–Meier estimate of the whole population) of 79.9% (95% CI: 60.5–90.5) with a manageable safety profile.
    - PFS at 4 months for evaluable patients (n = 28), based on binomial assessment, was 67.9% (95% CI: 47.6–84.1).
  - Responses over time are shown in **Figure 1**.[6]

Figure 1. Duration of Treatment, Best Overall Response, and Change of Response Over Time (Full Analysis Set; Lenvatinib [14 mg/m^2] + Ifosfamide + Etoposide) for Phase 1b (A) and Phase 2 (B)[6]



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Each bar with a solid line represents treatment duration, while the extended bars with the dashed lines represent the duration that the patient remained on the study after treatment discontinuation.

ETP, etoposide; IFM, ifosfamide; NCP, non-complete response or progressive disease; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

- This multicenter, open-label, randomized, phase 2 study (OLIE) will explore the efficacy and safety of lenvatinib in combination with ifosfamide + etoposide versus ifosfamide + etoposide in children, adolescents, and young adults with relapsed or refractory osteosarcoma, in collaboration with Innovative Therapies for Children with Cancer (ITCC).
  - This will help determine if the addition of lenvatinib to a standard cytotoxic chemotherapy regimen provides a survival benefit.

OBJECTIVES

- The primary objective is PFS rate at 4 months by independent imaging review using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1).
  - PFS rate at 4 months will be determined by a Kaplan–Meier estimate using the full analysis set.
- Secondary objectives include median PFS, differences in overall survival and overall survival rate at 1 year between the study arms, objective response rate, safety and tolerability, characterization of the pharmacokinetics of lenvatinib in the combination treatment, and quality of life.

PATIENT ELIGIBILITY

- Key inclusion and exclusion criteria are listed in **Figure 2**.

Figure 2. Key Inclusion and Exclusion Criteria

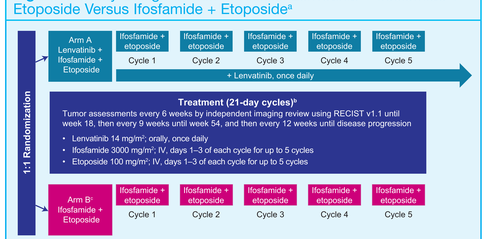
Inclusion Criteria	Exclusion Criteria
Measurable or **evaluable** disease per RECIST v1.1	Active second malignancy within 2 years prior to enrollment
Age 2–25 years (including ≥ 32 patients < 18 years old)	Known hypersensitivity to any component of any study drug
Confirmed diagnosis of high-grade osteosarcoma	History of ifosfamide-related grade ≥ 3 nephrotoxicity or encephalopathy
Refractory or relapsed osteosarcoma after 1–2 prior lines of systemic treatments	Any medical or other condition that would preclude participation in a clinical study
Lansky play score ≥ 50% (patients < 16 years old) or Karnofsky Performance Status score ≥ 50% (patients ≥ 16 years old)	
Adequate organ function	

RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

STUDY DESIGN

- This study will enroll approximately 72 patients, randomized 1:1 to treatment arm A or B (**Figure 3**).
- Randomization will be stratified by time to first relapse/refractory disease (< 18 or ≥ 18 months) and by age (< 18 or ≥ 18 years).

Figure 3. Study Design of Trial to Assess Lenvatinib + Ifosfamide + Etoposide Versus Ifosfamide + Etoposide[a]



[a]A protocol amendment is in the process of being submitted to allow patients in arm B to crossover at disease progression to lenvatinib treatment with or without chemotherapy (there is a maximum of 5 cycles of ifosfamide + etoposide for the duration of the study). This amendment will also update the primary endpoint from PFS at 4 months to PFS, with PFS at 4 months becoming a secondary endpoint.

[b]Patients will receive a maximum of 5 cycles of ifosfamide + etoposide, but patients in arm A can continue to receive lenvatinib until disease progression, development of unacceptable toxicity, patient request, withdrawal of consent, or study termination.

[c]Following completion of 5 cycles, patients in arm B will undergo tumor assessment follow-ups until disease progression.

IV, intravenously; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

- Patients randomly assigned to arm A will continue to receive lenvatinib until disease progression, development of unacceptable toxicity, patient request, withdrawal of consent, or study termination.

STUDY ASSESSMENTS

- Study assessments regarding efficacy, pharmacokinetics, quality of life, and safety, will be carried out according to **Table 1**.

Table 1. Planned Study Assessments

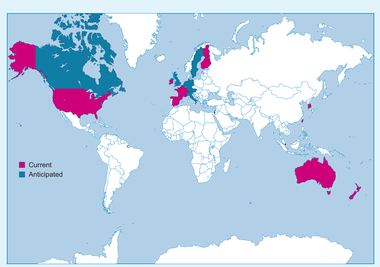
Parameter	Efficacy	Pharmacokinetic	Quality of Life	Safety
Assessment	• Tumor assessments by IIR using RECIST v1.1	• Area under the concentration × time curve	• PedsQL	• Adverse events defined by CTCAE v5.0
Details	• Progression must be confirmed by IIR	• Arm A only (patients who receive lenvatinib)	• Parents and caregivers can provide proxy reports	• Regular laboratory evaluations, performance status scores, and other clinical assessments
Schedule	• Every 6 weeks until week 18 • Every 9 weeks from week 18 until week 54 • Every 12 weeks after week 54 • All patients will be followed for survival for 2 years after the end of treatment, or until death, study termination, withdrawal of consent, or they are lost to follow-up	• Cycle 1 day 1 • Cycle 1 day 15 • Cycle 2 day 1	• Baseline • Cycle 2 day 1 • Cycle 3 day 1 • Week 18 • Cycle 8 day 1 • Cycle 18 day 1	• Ongoing monitoring of adverse events • Routine laboratory evaluations • Lansky play score (patients < 16 years old) • Karnofsky Performance Status score (patients ≥ 16 years old)

CTCAE v5.0, Common Terminology Criteria in Adverse Events, version 5.0; IIR, independent imaging review; PedsQL, Pediatric Quality of Life Inventory; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

CONCLUSIONS

- The study is currently enrolling globally (**Figure 4**).
- A protocol amendment to allow patients in arm B to crossover to lenvatinib, and to update the primary endpoint from PFS at 4 months to PFS, with PFS at 4 months becoming a secondary endpoint, is in the process of being submitted.
- For more information, see www.ClinicalTrials.gov: NCT04154189

Figure 4. Current and Anticipated Countries of Study Sites[a]



[a]Current countries of study sites include Australia, Finland, France, Ireland, New Zealand, Republic of Korea, Singapore, Spain, Switzerland, Taiwan, and the United States of America. Anticipated countries of study sites include Austria, Belgium, Canada, Germany, Israel, Italy, Netherlands, Sweden, and the United Kingdom of Great Britain.

References

1. Casali PG et al. *Ann Oncol*. 2018;29(Suppl 4):iv79–iv95.
2. Xie L et al. *Oncol Rep*. 2017;38(2):625-636.
3. Tuettenberg J et al. *Crit Rev Oncol Hematol*. 2006;59(3):181-193.
4. Lenvima. Package insert. Eisai Inc.; 2020.
5. Ichikawa K et al. *Sci Rep*. 2020;10(1):2939.
6. Gaspar N et al. Presented at the European Society for Medical Oncology meeting; September 27–October 1, 2019; Barcelona, Spain. Poster #1676PD.

Conflict of Interest

Dr Gaspar has a consulting or advisory role with Eisai and Ipsen; and has received funding for travel, accommodations, and expenses from Eisai.

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