2 SYNOPSIS

SPONSOR: Merck Sharp & Dohme LLC, Rahway, NJ, USA (hereafter called the Sponsor or MSD)

COMPOUND NAME: lenvatinib mesylate (MK-7902/E7080)

PROTOCOL TITLE: An Open-Label, Multicenter Phase 2 Basket Study to Evaluate the Antitumor Activity and Safety of Lenvatinib in Children, Adolescents, and Young Adults with Relapsed or Refractory Solid Malignancies

STUDY IDENTIFIERS:

IND: 147052	EudraCT: 2019-004441-33	WHO: Not applicable	NCT: NCT04447755
JAPIC-CTI: Not applicable	UTN: Not applicable	EU CT: Not applicable	

STUDY PHASE: Phase 2

INDICATION: Neoplasm malignant

STUDY CENTERS: This study was conducted at 49 centers in 20 countries.

STUDY STATUS:

This study is ongoing; this report is based on the primary efficacy analysis (data cutoff date: 16-SEP-2022). Enrollment to the Ewing Sarcoma (EWS) and High-grade Glioma (HGG) Cohorts was stopped (Amendment 4) due to futility observed in Study E7080-A001-216 (lenvatinib in combination with everolimus) in the corresponding tumor types; enrollment to the Rhabdomyosarcoma (RMS) Cohort was stopped due to insufficient antitumor activity observed for participants with RMS in the MK-7902-013 study; enrollment to the Other Solid Tumors cohort was stopped due to insufficient antitumor activity observed in the MK-7902-013 study.

First Participant, First Visit	**Last Participant, Last Visit (for Primary Efficacy Analysis)**	**Database Lock Date**
30-JUL-2020	16-SEP-2022	14-DEC-2022

METHODOLOGY:

This is an ongoing, open-label, multicenter Phase 2 basket study to evaluate the antitumor activity and safety of lenvatinib in children, adolescents, and young adults between 2 and ≤21 years of age with relapsed or refractory malignant solid tumors. Four cohorts are being evaluated: HGG, RMS, EWS/peripheral primitive neuroectodermal tumor (pPNET; hereafter referred to as EWS), and any other solid tumors (aside from osteosarcoma).

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use
Arm 1	Lenvatinib	1 mg, 4 mg, 10 mg	14 mg/m^2	Oral	Once daily	Test Product

Participants were to continue to receive lenvatinib until disease progression was verified by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or Response Assessment in Neuro-Oncology (RANO; for HGG only) criteria, initiation of another anticancer therapy, development of unacceptable toxicity, or withdrawal of consent, whichever occurs first. On-study imaging assessments were performed at screening, every 8 weeks from the date of lenvatinib initiation until Week 24, then every 12 weeks thereafter, or as clinically indicated (±7 days). All responses were confirmed at a follow-up examination ≥28 days after the initial response. Images were collected by a central imaging vendor for possible independent review of response; site assessment (RECIST 1.1 or RANO for HGG) was considered for purposes of satisfying the primary efficacy endpoint.

Part of this study was conducted during the COVID-19 pandemic. The Sponsor continued to follow its standard operating procedures for study conduct, monitoring, and oversight during the pandemic and employed a risk-based approach to assess and mitigate impact on study conduct.

ELIGIBILITY CRITERIA:

Male/female children, adolescents, and young adult participants with relapsed or refractory pediatric solid tumors (excluding osteosarcoma) between the ages of 2 and 21 years, inclusive, were to be enrolled in this study.

OBJECTIVES AND ENDPOINTS:

In children, adolescents, and young adults with relapsed or refractory solid malignancies treated with lenvatinib:

Primary Objective	**Primary Endpoint**
- To determine the ORR at Week 16, by each tumor type, per RECIST 1.1 or RANO (for HGG only) as assessed by the investigator.	- Objective Response, defined as a confirmed (≥4 weeks after initial response) CR or PR.
Secondary Objectives	**Secondary Endpoints**
To evaluate ORR, by each tumor type, per RECIST 1.1 or RANO (for HGG only) as assessed by the investigator.	Objective Response, defined as a confirmed (≥4 weeks after initial response) CR or PR.
To evaluate PFS per RECIST 1.1 or RANO (for HGG only), by each tumor type	PFS defined as the time from the date of the first administration of lenvatinib until the date of first documentation of PD or death (whichever occurs first).
To evaluate the BOR, DOR, DCR, and CBR, by each tumor type.	BOR defined as the participant's best confirmed response (CR or PR) over the treatment period. - DOR defined as the time from the date of the first documented CR or PR to the date first documentation of progressive disease or death (whichever occurs first). - Disease control defined as a BOR of CR or PR, or SD. To be assigned a BOR of SD, the time from the first administration of study drug until the date of documented SD should be ≥7 weeks. - Clinical benefit defined as a BOR of CR or PR, or durable SD (SD duration ≥23 weeks since the first dose of the study treatment).
To evaluate the safety of lenvatinib.	AEs, SAEs, clinical laboratory values, vital signs, 12-lead ECGs, urine dipstick, Lansky play scores or Karnofsky performance status scores, physical examination findings, dental examination findings, height, and closure of proximal tibial plates.
To assess the palatability and acceptability of the suspension formulation of lenvatinib.	Palatability questionnaire using a facial hedonic scale.
To characterize the PK of lenvatinib.	Assessment of population-based PK parameters of lenvatinib.
CCI [redacted]	

The tertiary/exploratory objectives and endpoints analyzed in this CSR are provided above; the full list of tertiary/exploratory objectives for this study is provided in the protocol.

NUMBER OF PARTICIPANTS (planned and analyzed): The planned enrollment total was a minimum of 36 participants with 9 evaluable participants in each of the 4 cohorts: HGG, RMS, EWS, and other solid tumors. A minimum of 6 participants <17 years of age were to be enrolled in HGG, RMS, and EWS cohorts. The final sample size of participants depended on the number of tumor types that met the futility bar and the antitumor activity in evaluable participants observed in the corresponding tumor cohorts in an ongoing study (Study E7080-A001-216). The enrollment in the HGG, RMS, and EWS cohorts was capped at a maximum of 17 evaluable participants each. The efficacy results from all cohorts that enrolled a minimum of 9 evaluable participants were to be presented in this CSR. As of data cutoff date, 127 participants were allocated and received treatment and 124 were included in the Evaluable Analysis Set (EAS) for analysis (9 in EWS, 17 in RMS, 6 in HGG, 9 each in diffuse midline glioma, medulloblastoma, and ependymoma, and 65 in other solid tumors cohort). Three participants (2 from HGG and 1 from other solid tumors cohort) did not meet the criteria for EAS, which requires participants to have measurable disease present at baseline and at least 1 postbaseline efficacy assessment, unless they discontinued prior to the first efficacy assessment due to progressive disease.

STATISTICAL AND ANALYSIS METHODS:

The primary efficacy population was the EAS, which included all evaluable participants, who had measurable disease present at baseline and at least 1 postbaseline efficacy assessment, unless they discontinued prior to the first efficacy assessment due to progressive disease. Objective responses counted only confirmed (≥4 weeks after initial response) complete response (CR) and partial response (PR) at Week 16. Estimated objective response rate (ORR) and its exact 95% confidence interval (CI) using the method of Clopper and Pearson were presented. The ORR, disease control rate (DCR), and clinical benefit rate (CBR) were provided with exact 95% CIs using the method of Clopper and Pearson, and the duration of response (DOR) was analyzed for responders using Kaplan-Meier approach. PFS was analyzed using Kaplan-Meier product-limit estimates. The cumulative progression-free survival (PFS) probabilities were plotted over time as appropriate.

The primary safety population was the Safety Analysis Set, which included all participants who received at least 1 dose of the study drug. Count and percentage of adverse events (AE) by system organ class and preferred term are provided.

RESULTS:

Participant Disposition:

- As of the data cutoff date, 127 allocated, 127 treated, 114 discontinued treatment, 13 ongoing on treatment (10 in the other solid tumors cohort and 1 each in EWS, RMS, and medulloblastoma cohorts), 94 discontinued study, 33 ongoing in the study.

Demographics and Baseline Characteristics:

- **Overall Median Age (Range):** PPD
- **Sex:** 67 (52.8%) male, 60 (47.2%) female
- **Ethnicity:** 77 (60.6%) not Hispanic or Latino, 13 (10.2%) Hispanic or Latino, 37 (29.1%) not reported/unknown/missing
- **Race:** 22 (17.3%) Asian, 3 (2.4%) American Indian or Alaska Native, 2 (1.6%) Native Hawaiian Or Other Pacific Islander, 4 (3.1%) Black or African American, 1 (0.8%) multiple, 63 (49.6%) White, 32 (25.2%) missing
- **Lansky or Karnofsky Scores:** 50 (11 [8.7%]), 60 (13 [10.2%]), 70 (13 [10.2%]), 80 (17 [13.4%]), 90 (34 [26.8%]), 100 (39 [30.7%])

Extent of Exposure: The median duration of exposure to study treatment was 104.0 days (range: 8.0 to 627.0).

Efficacy:

Efficacy results for EWS, RMS, HGG, and other solid tumors cohort that enrolled at least 9 evaluable participants (ie, diffuse midline glioma, medulloblastoma, and ependymoma), are presented in this CSR.

Although objective responses occurred in some participants, antitumor activity could not be concluded for any cohort in this study based on investigator assessment of ORR at Week 16 per RECIST 1.1 or RANO (for HGG only).

Overall, with a median follow-up duration of 7.4 months:

- The ORR observed per RECIST 1.1 or RANO (for HGG only) at Week 16 was 22.2% (2 PRs) in EWS, 11.8% (2 PRs) in RMS, and 7.7% (5 PRs) in the other solid tumors cohort. No objective responses were observed at Week 16 in participants with HGG, diffuse midline glioma, medulloblastoma, and ependymoma cohorts.

- As of the data cutoff date:
  - EWS: The ORR in the EWS Cohort was 22.2% (2 PRs); DOR was not reached. The DCR was 66.7%, with 4 participants exhibiting stable disease (SD) ≥7 weeks and the CBR was 33.3%. The median PFS and overall survival (OS) were 3.0 and 9.4 months, respectively.
  - RMS: The ORR in the RMS Cohort was 11.8% (2 PRs) with a median DOR of 4.6 months. The DCR was 52.9%, with 7 participants exhibiting SD ≥7 weeks and the CBR was 29.4%. The median PFS and OS were 2.6 and 4.9 months, respectively.
  - HGG: No objective responses (PR or CR) were observed in the HGG cohort. The DCR was 33.3%, with 2 participants exhibiting SD ≥7 weeks. The median PFS and OS were 1.9 and 3.8 months, respectively.
  - Diffuse Midline Glioma: No objective responses (PR or CR) were observed in the diffuse midline glioma cohort. The DCR was 22.2%, with 2 participants exhibiting SD ≥7 weeks and the CBR was 11.1%. The median PFS and OS were 1.8 and 3.8 months, respectively.
  - Medulloblastoma: No objective responses (PR or CR) were observed in the medulloblastoma cohort. The DCR was 55.6%, with 5 participants exhibiting SD ≥7 weeks and the CBR was 44.4%. The median PFS and OS were 3.4 and 6.3 months, respectively.
  - Ependymoma: No objective responses (PR or CR) were observed in the ependymoma cohort. The DCR was 55.6%, with 5 participants exhibiting SD ≥7 weeks and the CBR was 33.3%. The median PFS and OS were 2.5 and 7.4 months, respectively.
  - Other solid tumors: The ORR in the other solid tumors cohort was 7.7% (5 PRs) with a median DOR of 4.6 months. The DCR was 64.6%, with 37 participants exhibiting SD ≥7 weeks and the CBR was 40.0%. The median PFS and OS were 3.8 and 10.4 months, respectively.

Safety:

- The types, frequency, and severity of events observed with lenvatinib monotherapy were consistent with the well-established safety profile of lenvatinib monotherapy in adults and pediatric patients (Study E7080-G000-207), and the underlying disease condition.
- Treatment was manageable with standard clinical care and applicable dose modifications for treatment with lenvatinib, as evidenced by the low rate of study intervention discontinuations due to AEs.
- No new safety signals were observed.
- Of the 3 participants who had fatal AEs (sepsis, intracranial pressure increased, and device dislocation), 1 (intracranial pressure increased) was considered to be related to study treatment by the investigator.
- Most clinically significant AEs (CSAE) were Grade 1 or 2 in severity, and no participants died due to a CSAE.

Table 2-1
Adverse Event Summary
(Safety Analysis Set)

	Total	
	n	(%)
Participants in population	127	
with one or more adverse events	126	(99.2)
with no adverse event	1	(0.8)
with drug-related[a] adverse events	116	(91.3)
with toxicity grade 3-5 adverse events	90	(70.9)
with toxicity grade 3-5 drug-related adverse events	61	(48.0)
with serious adverse events	63	(49.6)
with serious drug-related adverse events	24	(18.9)
with any dose reduction due to an adverse event	49	(38.6)
with any dose interruption due to an adverse event	48	(37.8)
with any dose interruption due to an drug-related adverse event	30	(23.6)
with any dose modification[b] due to an adverse event	73	(57.5)
who died	3	(2.4)
who died due to a drug-related adverse event	1	(0.8)
discontinued drug due to an adverse event	8	(6.3)
discontinued drug due to a drug-related adverse event	4	(3.1)
discontinued drug due to a serious adverse event	6	(4.7)
discontinued drug due to a serious drug-related adverse event	3	(2.4)

[a] Determined by the investigator to be related to the drug.
[b] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Non-serious and serious adverse events up to 30 days following the last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 5.0.
Database Cutoff Date: 16SEP2022.

Source: [P013V01MK7902: adam-adsl; adae]

CONCLUSIONS:

Efficacy

Based on the results from this study, the following efficacy conclusions can be made:

- Although objective responses occurred in some participants, antitumor activity could not be concluded for any cohort in this study.
- The ORR at Week 16, based on investigator assessment using RECIST 1.1 or RANO (for HGG only) was 22.2% (2 PRs) in the EWS and 11.8% (2 PRs) in the RMS cohorts. No objective responses were observed in the HGG, diffuse midline glioma, medulloblastoma, or ependymoma cohorts. The ORR at Week 16 was 7.7% (5 PRs) among all other solid tumors.

- The totality of the data demonstrates insufficient antitumor activity for lenvatinib monotherapy in children, adolescents, and young adults with relapsed or refractory solid tumors.

Safety

Based on the results from this study, the following safety conclusions can be made:

- Lenvatinib monotherapy has a clinically manageable safety profile and no new safety signals were identified.
- The safety profile of lenvatinib in Study MK-7902-013 is generally consistent with the established safety profile of lenvatinib in adults as well as in lenvatinib monotherapy studies in pediatric patients and also the underlying disease condition.

The following key safety results were also observed:

- Treatment with lenvatinib monotherapy was manageable, as indicated by the generally low rate of study intervention discontinuations due to AEs.
- Three participants died (sepsis, intracranial pressure increased, and device dislocation) due to AEs during the study, of which 1 (intracranial pressure increased) was considered related to the study intervention by the investigator.
- CSAEs were manageable with dose modification and standard medical practice, as applicable. The majority of CSAEs were Grade 1 or 2 in severity.

PUBLICATION(S): As of the date of this report, there are no publications based on this study.

REPORT DATE: 19-APR-2023

REVISED REPORT DATE: 13-JUN-2023