Study Results Synopsis for Public Disclosure

Name of product: [^{177}Lu]Lu-EVS459 (GIZ943), [^{68}Ga]Ga-EVS459 (DZQ109)

Protocol identification number: CGIZ943A12101

EU CT number: 2023-507674-41-00

ClinicalTrials.gov number: NCT06376253

Title of study: A phase I, open-label, multi-center study to evaluate the safety, tolerability, dosimetry, and preliminary activity of [^{177}Lu]Lu-EVS459 in patients with ovarian and lung cancers

Study center(s): 2 centers (1 each in Israel and Switzerland)

Publication (reference): None

Study period:

Study initiation date: 08-Sep-2024 (first patient first visit)

Early termination date: 27-Feb-2025

Study completion date: 10-Jul-2025 (last patient last visit)

Phase of development (phase of this clinical study): I

Objectives:

The purpose of this synopsis is to provide results of the final analysis of the terminated study with a data cut-off date of 10-Jul-2025.

This Phase I study was intended to assess the safety, tolerability, and dosimetry of the folate receptor (FR) targeting radioligand therapy, [^{177}Lu]Lu-EVS459, and identify the recommended dose(s) for further clinical evaluation. This study also aimed to further evaluate the preliminary anti-tumor activity and characterize the pharmacokinetics (PK) of [^{177}Lu]Lu-EVS459. Furthermore, the study also planned to perform an initial evaluation of the radioligand imaging agent [^{68}Ga]Ga-EVS459, its safety and imaging properties. The study was planned in two parts - escalation and expansion parts. Due to the early termination of the study, the dose levels beyond the first level (DL1A) in the escalation part of the study were never conducted. Therefore, this synopsis will report only the primary and secondary endpoints of the escalation part of the study.

Primary and secondary objectives and their related endpoints are provided in the Table 2-1.

Table 2-1 Objectives and their related endpoints:

Objectives	Endpoints
Primary	
Assess the safety and tolerability of [^{177}Lu]Lu-EVS459 Identify the recommended dose(s) of [^{177}Lu]Lu-EVS459 for further clinical evaluation	Safety: Incidence and severity of adverse events (AEs), including dose limiting toxicities (DLTs) and serious adverse events (SAEs) including changes in laboratory values, vital signs and ECGs Tolerability: Frequency of dose interruptions, reductions, dose intensity
Secondary	
Evaluate the preliminary anti-tumor activity of [^{177}Lu]Lu-EVS459	Overall response rate (ORR), disease control rate (DCR), duration of response (DOR), and progression-free survival (PFS) based on RECISTv1.1
Characterize the pharmacokinetics (PK) and radiation dosimetry of [^{177}Lu]Lu-EVS459	PK parameters (e.g., AUC, clearance, Cmax, distribution volume, half-life) of ^{177}Lu-EVS459 Quantification of urinary excretion of [^{177}Lu]Lu-EVS459 (percent of injected dose (%ID), renal clearance) Absorbed radiation dose in normal tissues and tumor lesions Time activity curves (TACs) of [^{177}Lu]Lu-EVS459 uptake in normal tissues and tumor lesions
Characterize the safety and imaging properties of [^{68}Ga]Ga-EVS459	Safety: Incidence and severity of AEs, including SAEs Imaging properties: Visual and quantitative assessment (expressed as standardized uptake values (SUVs)) of [^{68}Ga]Ga-EVS459 uptake in normal tissues and tumor lesions over time

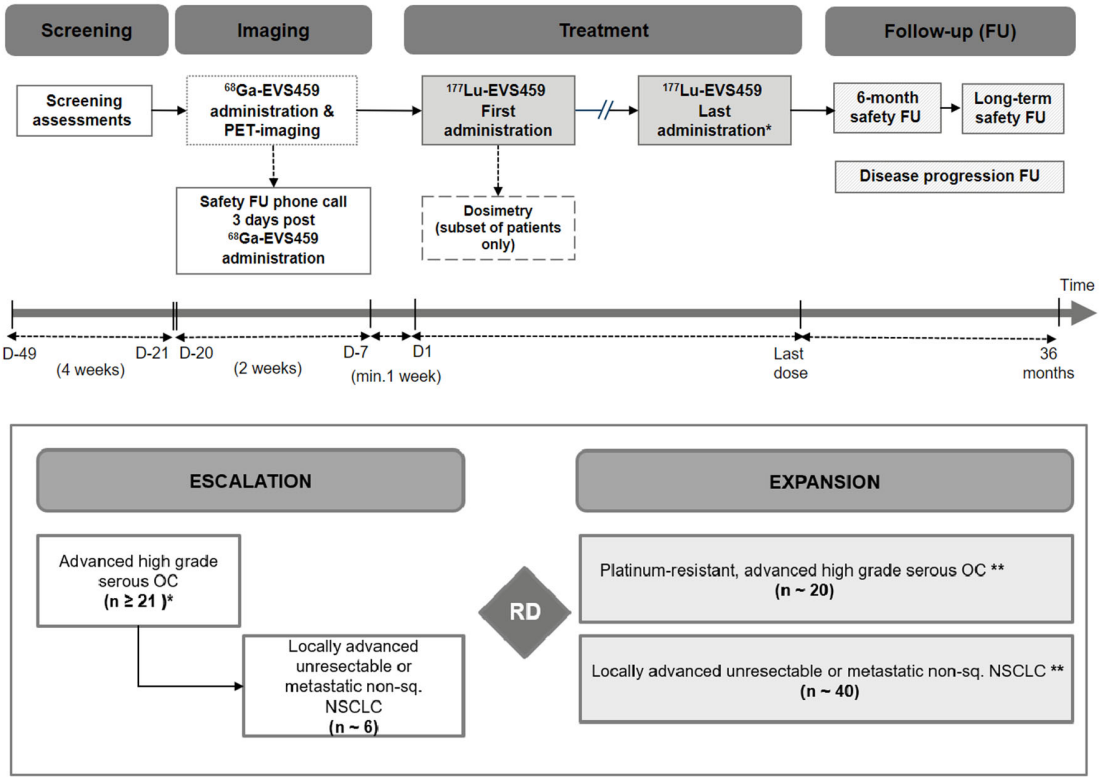
Study design and methodology:

This was a first-in-human (FIH), open-label, non-randomized, phase I, multi-center study, stratified by disease indication in patients with advanced high grade serous ovarian cancer (OC) and locally advanced unresectable or metastatic non squamous non-small cell lung carcinoma (non sq. NSCLC). [^{68}Ga]Ga-EVS459 was administered as radioligand imaging (RLI) agent and [^{177}Lu]Lu-EVS459 as radioligand therapy (RLT).

The study was planned in two parts: dose escalation and dose expansion (of note, the term 'dose' is used as 'dosage' to describe administered activity; 'absorbed dose' will be specified as such and abbreviated as AD). In both parts of the study, patients were planned to initially be imaged with a [^{68}Ga]Ga-EVS459 positron emission tomography (PET)/computed tomography (CT) or PET/magnetic resonance imaging (MRI) scan. In the escalation part, different doses of [^{177}Lu]Lu-EVS459 were planned to be tested to identify recommended dose(s) (RD(s)) for further evaluation. The dose escalation part of [^{177}Lu]Lu-EVS459 was designed to be performed in OC patients and data from this was intended to be used to determine the recommended

radioactive activity and mass dose(s) (RD(s)) of [^{177}Lu]Lu-EVS459 for further evaluation. The expansion part of the study was intended to examine the safety and preliminary efficacy of [^{177}Lu]Lu-EVS459 at the RD(s) determined during the escalation part. The end of study was planned to occur when at least 80% of the patients in the expansion part had completed the follow-up for disease progression or discontinued from the study for any reason, and all patients had completed treatment and the 36-month long-term follow-up period. Refer to Figure 2-1 for the study design. For reporting purpose in this synopsis, [^{177}Lu]Lu-EVS459 will be henceforth referred as ^{177}Lu-EVS459 and [^{68}Ga]Ga-EVS459 will be referred as ^{68}Ga-EVS459.

Figure 2-1 Study design



* 21 is the minimum number of patients required to declare maximum tolerated dose (MTD)

** For both the OC and the non sq. NSCLC expansion arms, approximately 10 of the OC patients and 20 of the non sq. NSCLC were planned to be enrolled in a Pharmacodynamics (PD) cohort

Rationale for synoptic CSR:

Given that the study was terminated early and enrolled only a small number of patients (4 patients), not all data collection planned in the protocol were gathered and, therefore, the volume of data available for analysis is substantially limited. The synoptic CSR documents the analyses of primary and secondary endpoints based on the data collected prior to termination of the study.

Diagnosis and main criteria for inclusion:

This study was planned to include adult patients with OC or non sq. NSCLC. However, due to early termination of the study, the study only comprised of adult patients with OC.

Inclusion criteria:

The key inclusion criteria were as follows:

- Age ≥ 18 years old
- Patients with advanced high-grade serous OC or with locally advanced unresectable or metastatic non sq. NSCLC with disease progression following, or intolerance to, at least 1 line of therapy

Exclusion criteria:

The key exclusion criteria were as follows:

- Absolute neutrophil count (ANC) < 1.5 x 109/L, hemoglobin < 10 g/dL, or platelet count < 100 x 109/L
- QT interval corrected by Fridericia's formula (QTcF) ≥ 470 msec
- Creatinine clearance < 60 mL/min
- Unmanageable urinary tract obstruction or urinary incontinence
- Radiation therapy within 4 weeks prior to the first dose of [^{177}Lu]Lu-EVS459

Test and reference therapies, dose and mode of administration, batch number:

For this study, the term "investigational drug" refers to ^{68}Ga-EVS459 and/or ^{177}Lu-EVS459, and the term "study treatment" refers to ^{177}Lu-EVS459 and unlabeled EVS459. EVS459 is a FR-targeting radioligand, labeled with Lutetium-177 (^{177}Lu) for therapy and with Gallium-68 (^{68}Ga) for imaging as a PET radiotracer.

^{68}Ga-EVS459 (DZQ109), a radiopharmaceutical solution for injection (prepared from a kit for radiopharmaceutical preparation of ^{68}Ga-EVS459), was administered as single dose of 200 – 250 MBq (5.4 – 6.8 mCi). ^{177}Lu-EVS459 (GIZ943), a radiopharmaceutical solution for injection/ infusion (prepared from a kit for radiopharmaceutical preparation of ^{177}Lu-EVS459) , to be given every 6 weeks, at a radioactive dose 1.85 – 8.5 GBq (50 – 230 mCi), and EVS459 dose of 0.125 – 2 mg.

The kits for the radiopharmaceutical preparation of both ^{177}Lu-EVS459 and ^{68}Ga-EVS459 were provided centrally by Novartis. All doses prescribed and administered to patients and all dose changes during the study were recorded on the Dosage Administration Record eCRF.

Protocol amendments and other changes to study conduct:

This synopsis describes the conduct of the study according to protocol amendment v01. The original protocol was dated 15-Sep-2023. Amendment 1, dated 27-Nov-2023, introduced changes made as a response to the Health Authorities (HA) feedback regarding the exclusion of patients with prolonged QTc, the collection of additional safety-related assessments, the safety requirements for intra-patient dose escalation, the criteria for defining DLTs and for ^{177}Lu-EVS459 dose modifications, the maximal allowable number of patients in any additional cohorts, and certain terminologies used in the protocol.

Protocol amendment v02, dated 08-Oct-2024, was shared with EU HAs in response to feedback received during the initial submission. However, this amendment was not submitted, in the countries where patients were enrolled, due to early termination of the study. All patients were consented based on protocol amendment v01.

Changes in study conduct:

Novartis made the decision to halt further enrollment of patients due to observed dose limiting toxicities (DLTs), primarily related to hematological toxicities, on 21 January 2025. A decision of early termination of the study was made on 27 February 2025, on the grounds that no dose with a positive benefit risk ratio could be identified. The escalation part of the study did not proceed beyond dose level 1A (DL1A) and the expansion part of the study was thus not opened.

Criteria for evaluation:

Efficacy assessments:

Efficacy in this study was primarily evaluated through imaging-based assessments of tumor response, conducted at predefined time points as outlined in the protocol.

The planned efficacy assessments included:

- Best overall response (BOR), Overall response rate (ORR), Duration of response (DOR)
- Disease control rate (DCR)
- Progression-free survival (PFS)

Safety and imaging properties of ^{68}Ga-EVS459:

The safety assessments for ^{68}Ga-EVS459 imaging included AE monitoring (incidence and severity of AEs and SAEs).

Imaging assessments:

Imaging assessments were part of both efficacy evaluation and dosimetry analysis in the study and were conducted at predefined time points as outlined in the protocol.

All imaging data were submitted to a central imaging Contract Research Organization (CRO) and interpreted per the Imaging Charter. Standard uptake values i.e., SUVs (SUVmean, SUVpeak, and SUVmax) of lesions and different potential reference organs were calculated as defined in the vendor Imaging Charter.

Pharmacokinetics and dosimetry assessments:

Pharmacokinetic (PK) and dosimetry assessments were planned to be conducted during the dose escalation phase of the study at predefined time points for all patients in DL1A, DL1B, and DL5, and for at least three patients each in DL2, DL3, and DL4. However, due to early termination of the study, patients in the study only participated in DL1A.

Radioactive count rates were measured per Laboratory Manual instructions. Calibration records for well/gamma counters were collected from each site prior to patient enrollment. Blood radioactivity concentrations were analyzed locally.

Patients in the dosimetry subgroup underwent a series of SPECT/CT scans to determine absorbed doses in normal organs and target lesions. Low-dose, non-contrast-enhanced CT scans were acquired concurrently for attenuation correction.

The PK parameters that were planned to be determined included AUClast, AUCinf, Cmax, Tmax, T1/2, CL, and Vz.

Dosimetry assessments included:

- administered activity
- absorbed radiation dose from normal tissues and tumor lesions
- TIAC (Time Integrated Activity Coefficient)
- effective and biological half-life
- percent injected activity

Safety Assessments:

Safety assessments were conducted as outlined in the study protocol. These assessments included

- incidence of dose limiting toxicities (DLTs) during the first 6 weeks of treatment
- AE monitoring (incidence and severity of AEs and SAEs)
- frequency of dose interruptions and reductions, and dose intensities
- ECOG Performance Status
- physical examinations
- vital signs (blood pressure, pulse, and body temperature, height and body weight
- electrocardiograms (ECGs)

- clinical laboratory tests [hematology (hematocrit, hemoglobin, platelets, leukocytes, differential counts), biochemistry (electrolytes, liver and kidney function markers, glucose, enzymes), urinalysis (dipstick and, if abnormal, microscopic panel), coagulation (PT, INR, APTT)].
- pregnancy testing and fertility assessment

Statistical methods

Study data was analyzed by Novartis personnel and/or designated CRO(s). SAS version 9.4 or later and/or R version 4.1 or later was used to perform all data analyses. PK parameters were calculated using non-compartmental methods available in Phoenix WinNonlin version 8.3 or later. The dosimetry estimates were calculated by the vendor (described in the Independent Review Charter from the vendor).

The study data was analyzed and reported in the synoptic CSR based on all patients' data of the dose escalation part up to the time of database lock. Statistical analyses were performed using all data collected in the database up to the data cut-off date.

Analysis set definitions

The Full Analysis Set (FAS) and Safety Set (SS) were the same and comprised all patients who received at least one dose of study treatment ^{177}Lu-EVS459. The ^{68}Ga-EVS459 Safety Set (SS-^{68}Ga-EVS459) includes all patients who received at least one dose of ^{68}Ga-EVS459. The Dose-Determining Set (DDS) for ^{177}Lu-EVS459 with corresponding mass dose included all FAS patients who met the minimum exposure criterion and had sufficient safety evaluations (as determined by Novartis and investigator) or experienced a DLT during the DLT-evaluation period. The Pharmacokinetic analysis set (PAS) included all FAS patients with at least one available valid (not flagged for exclusion) blood radioactivity measurement and with no protocol deviations that impact the interpretability of the data. This analysis set was used for all PK data analysis. The Dosimetry Analysis Set (DAS) included all FAS patients who provided at least one set of dosimetry data.

Demographics and other baseline characteristics

Categorical data was summarized in frequency counts and percentages while continuous data was summarized by descriptive statistics. Disease history, diagnosis, extent of cancer, and medical history were provided in detail in the listings.

Efficacy analysis

The efficacy analysis supporting the secondary objective of demonstration of the anti-tumor activity of ^{177}Lu-EVS459, as measured by BOR and DCR as per RECIST v1.1, was summarized using frequencies and percentages. BOR and overall response assessments were listed for all patients. DOR, PFS rate and median PFS were not summarized because of insufficient data.

Imaging analysis

The statistical analyses of imaging properties of ^{68}Ga-EVS459 was descriptive in nature and were provided as summaries and graphical presentations of data. SUVs (SUVpeak, SUVmean, and SUVmax) and SUVrs of lesions and different organs were provided by the imaging vendor.

Safety analysis

All safety analyses were based on SS and SS-^{68}Ga-EVS459 separately. All analyses were presented by treatment group and overall patients, unless otherwise specified.

The incidence of DLTs was summarized by primary SOC, PT, and maximum grade based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The DDS was used for these summaries.

The assessment of safety was based on the type and frequency of AEs as well as on the number of laboratory values that fall outside of pre-determined ranges (CTCAE grading limits or normal ranges as appropriate). Other safety data included electrocardiograms and vital signs. The safety set was used for summaries and listings of safety data with the exception of DLTs for which the DDS was used.

All adverse events were listed on an individual basis. They were summarized by System Organ Class (SOC) and Preferred Term (PT) at patient level. Patients with more than one adverse event within a particular SOC and PT were counted only once for that SOC and PT. Only treatment emergent events were included in summaries of AEs, but all adverse events were presented in listings.

Clinical laboratory data was summarized to include all assessments available for the laboratory parameter collected no later than 42 days after the last study treatment administration date. Worst post-baseline CTC grade and shift tables summaries were provided separately for hematology parameters (platelets, hematocrit, hemoglobin, leukocytes (WBC), absolute differentials-lymphocytes, monocytes, neutrophils), and biochemistry parameters (albumin, amylase, total lipase, bicarbonate, calcium, chloride, magnesium, phosphate, sodium, creatinine, urea/BUN), by laboratory parameter and treatment. Notable ECG values of QT or QTcF, HR, PR, and QRS were summarized. Notable vital signs were also summarized.

Pharmacokinetic analysis

PK parameters were summarized, using the PAS, by descriptive statistics except for Tmax, where only n, median, minimum, and maximum were presented.

Dosimetry analyses

For dosimetry analyses, the DAS was used. The analysis of biodistribution and dosimetry estimates from normal tissues and tumor lesions were presented as descriptive summaries. Absorbed radiation dose to target organs was calculated by entering the TIAC (residence time) values for all the source organs in the appropriate software program and adjusting the radiation dose reported by the software for individual weight and organ masses for organs of interest (determined from CT), and red marrow in the dosimetry report by the vendor.

Summary - Results

Demographic and background characteristics:

Four patients with OC were administered ^{68}Ga-EVS459 and were treated with ^{177}Lu-EVS459. All four patients completed imaging with ^{68}Ga-EVS459.

All 4 (100.0%) patients discontinued from treatment with ^{177}Lu-EVS459, with the primary reasons being adverse event (1 patient, 25.0%), physician decision (1 patient, 25.0%), and red marrow dosimetry levels that did not allow administration of second radioactive dose based upon protocol criteria (2 patients, 50.0%) (reported as technical problems). The adverse event leading to discontinuation was agranulocytosis. Dosimetry findings showing bone marrow absorbed doses not allowing for a second administration of study drug were recorded as 'technical problem' in the eCRF as a reason, as the event did not fulfill the criteria for Adverse Event or physician decision.

Four patients (100%) discontinued post treatment follow-up, with the primary reasons for discontinuation being death (3 patients died due to progressive disease (PD)- 2 patients with progression of the underlying study indication and 1 patient with worsening of pulmonary embolism, approximately 6 months after the study drug administration, 75.0%) and subject decision (1 patient, 25.0%) (Table 2-2).

Table 2-2 Subject disposition (Full Analysis set)

Disposition/Reason	**[^{177}Lu]Lu-EVS459 N=4 n (%)**
Patients dosed with ^{68}Ga-EVS459	4 (100)
Patients completed imaging	4 (100)
Patients treated with ^{177}Lu-EVS459	4 (100)
Patients discontinued from treatment with ^{177}Lu-EVS459	4 (100)
Primary reason for discontinuation	
Adverse Event	1 (25.0)
Physician Decision	1 (25.0)
Technical Problems*	2 (50.0)
Post-treatment follow-up for patients who discontinued treatment	
Discontinued post treatment follow-up	4 (100)
Primary reason for discontinuation	
Death	3 (75.0)
Subject Decision	1 (25.0)

* bone marrow absorbed doses not allowing for a second administration of ^{177}Lu-EVS459

Data cut-off date: 10Jul2025

All patients were females and White, with a median age of 59.0 years (range: 46-76 years). All assessed patients had ECOG performance status as 0 or 1. At the time of the study entry, all patients had high-grade serous ovarian carcinoma, FIGO stage IIIC to IVB. All patients had peritoneal carcinomatosis. Two patients had disease, limited to the peritoneum. On patient had additionally lung metastases and one patient had liver and lung metastases..

Protocol deviations:

There were no protocol deviations reported in the study.

Prior therapies:

Information pertaining to any prior chemotherapy, anti-cancer hormonal therapy, immunotherapy, radiation, or surgery, including any other anticancer treatment the patient has previously received was reported.

All patients had prior medications started prior to or at the day of first dose of ^{177}Lu-EVS459. Carboplatin, paclitaxel, bevacizumab, and olaparib were the most frequently taken prior medications in these patients. The intent of prior treatment was palliative in one patient, both curative and palliative in one patient and curative in two patients. No prior radiopharmaceutical anti-neoplastic medication was reported.

After discontinuation of the study drug, 2 patients received antineoplastic therapy, namely carboplatin, gemcitabine, paclitaxel, and pembrolizumab.

Concomitant therapies:

All patients (100%) had at least one concomitant therapy during the course of the study. The most common reasons for which the concomitant medications were prescribed were ileus, febrile agranulocytosis, adrenal insufficiency, and fever.

Exposure:
Four patients with OC were administered with ^{68}Ga-EVS459 as RLI at a nominal dose (i.e. administered activity) of 200-250 MBq (5.4 – 6.8 mCi) and were treated with ^{177}Lu-EVS459 at 1.85 GBq (50 mCi) with 500 µg of total mass dose (nominal activity and mass dose), at C1D1.

The median actual cumulative dose (i.e. administered activity) of ^{177}Lu-EVS459 is 1.754 GBq and the median dose (i.e. administered activity) intensity is 1.754 GBq/6 weeks. The median duration of exposure (DOE) of ^{177}Lu-EVS459 is 42.0 days.

Efficacy results:

Limited efficacy analyses were performed due to low patient numbers and treatment duration (4 patients, one treatment cycle) and early termination of the study.

<u>Best overall response (BOR)</u>

Best overall response was analyzed based on local review as per RECIST v1.1, in the full analysis set. Three patients (75.0%) showed progressive disease (PD), while the response was not evaluable in one patient (25.0%). The overall response rate as per the investigator assessment in patients administered with ^{177}Lu-EVS459 was 0 and the disease control rate was 0.

Pharmacokinetic and dosimetry results:

Pharmacokinetic results

Measured radioactivity values were converted to mass units and decay-corrected for PK evaluation. PK parameters derived from AUCinf and/or λz are flagged and excluded from summary of PK parameters (AUCinf, CL/F, and Vz/F), if AUC% extrap > 20% and/or Rsq_adjusted is < 0.75. Renal clearance was not calculated as urine samples were not collected.

The PK of ^{177}Lu-EVS459 was assessed following the dose administration at C1D1. The geo-mean (geo-CV%) of AUClast was 73.2 (4.8) h*ng/mL and the geo-mean (geo-CV%) of Cmax was 3.81 (34.6) ng/ml. The median (min-max) Tmax was 0.867 (0.533-0.967) hours.

The blood mass concentration of ^{177}Lu-EVS459 was at its peak in the first 30 ± 5 mins at C1D1. The blood mass concentration gradually decreased with time and reached < 0.27 ng/mL by 168 h ± 1 day, at C1D8.

Blood radioactivity concentration of ^{177}Lu-EVS459 was at its peak in the first 30 ± 5 mins, at C1D1, and gradually decreased with time to ≤1.14 kBq/mL by C1D8.

Dosimetry results

[^{177}Lu]Lu-EVS459

Absorbed radiation dose:

The median absorbed radiation dose (CV%) of tumors after administration of ^{177}Lu-EVS459 at C1D1 was 2.38 Gy/GBq (111.9).

The median absorbed radiation dose (CV%) after administration of ^{177}Lu-EVS459 at C1D1 for bone marrow (later described also as 'red marrow') was 1.02 Gy/GBq (41.3), for kidneys was 1.27 Gy/GBq (28.5), salivary glands was 1.01 Gy/GBq (37.9), and for liver was 1.12 Gy/GBq (25.6). These four organs showed the highest absorbed doses of all organs reported.

Time integrated activity coefficient:

The median time integrated activity coefficient (TIAC) for tumors after administration of ^{177}Lu-EVS459 at C1D1 was 0.0345 MBq*h/MBq . The median TIAC after administration of ^{177}Lu-EVS459 at C1D1 for liver was 19.0 MBq*h/MBq, for bone marrow was 16.6 MBq*h/MBq, for kidney was 3.58 MBq*h/MBq, and salivary gland was 0.825 MBq*h/MBq.

Effective and biological half-life (h):

The mean (SD) effective half-life of ^{177}Lu-EVS459 for tumors was 57.5 (13.2) h and mean (SD) biological half-life of ^{177}Lu-EVS459 for tumors was 93.6 (33.5) h.

The mean (SD) effective half-life of ^{177}Lu-EVS459 for bone marrow was 72.6 (11.4) h, for liver was 60.3 (2.42) h, for kidney was 52.3 (9.07) h, and for salivary gland was 83.4 (17.0) h. The mean (SD) biological half-life of ^{177}Lu-EVS459 for bone marrow was 136 (37.1) h, for liver

was 96.9 (6.48) h, for kidney was 78.9 (20.5) h, and for salivary glands was 191 (99.1) h.

Percent injected activity (%) vs. time (h):

The mean (SD) percent injected activity (%) vs. time for tumors after the administration of ^{177}Lu-EVS459 at 4 ± 1 h, at C1D1, was 0.0946 (0.133) h, with decay-corrected mean (SD) as 0.0971 (0.136)h. The percent injected activity (%) vs. time for tumors gradually decreased with time and the mean (SD) value at 168 ± 1 h at C1D8 was 0.0195 (0.0317) h, with decay-corrected mean (SD) as 0.0399 (0.0658) h. The mean (SD) volume normalized percent injected activity (%/cm^3) vs. time for tumors after the administration of ^{177}Lu-EVS459 at 4 ± 1 h, at C1D1, was 0.0387 (0.0539) h, with decay-corrected values as 0.0397 (0.0552) h. These values declined with time.

The mean (SD) percent injected activity (%) vs. time after the administration of ^{177}Lu-EVS459 at 4 ± 1 h, at C1D1, for liver was 19.6 (6.46) h, with decay-corrected mean (SD) as 20.1 (6.65) h, for bone marrow was 15.4 (4.92) h, with decay-corrected mean (SD) as 15.8 (5.05) h, for kidney was 4.47 (0.723) h, with decay-corrected mean (SD) as 4.58 (0.725) h, and for salivary glands was 0.480 (0.149) h, with decay-corrected mean (SD) as 0.492 (0.153) h. Mean (SD) percent injected activity (%) vs. time decreased with time in all organs except for salivary glands where there was an increase to 0.555 (0.299) h, at 24 ± 1 h, at C1D2, and then gradually decreased with time.

Imaging analysis results

[^{68}Ga]Ga-EVS459

The tumor visibility score after administration of ^{68}Ga-EVS459 over all time points had a median ranging from 1.5 to 2 [score 1 (Questionable) and score 2 (Acceptable)].

The SUVpeak for tumors gradually declined with time (Table 2-3). The mean (SD) SUVpeak at 25 ± 10 mins was 4.00 (4.38). The mean (SD) SUVmean for tumor at 25 ± 10 mins was 3.33 (3.18) and the SUVmean gradually decreased with time. The mean (SD) SUVmax at 25 ± 10 mins was 5.41 (4.63) and gradually decreased with time.

Table 2-3 Descriptive summary of SUV parameters for tumors- ^{68}Ga-EVS459

SUV parameters	Nominal timepoint	mean (sd)
SUVpeak	25 min +/- 10 min	4.00 (4.38)
	1.5 hour +/- 15 min	3.44 (3.12)
	3 hour +/- 30 min	3.35 (3.00)
SUVmean	25 min +/- 10 min	3.33 (3.18)
	1.5 hour +/- 15 min	2.99 (2.28)
	3 hour +/- 30 min	2.95 (2.23)
SUVmax	25 min +/- 10 min	5.41 (4.63)
	1.5 hour +/- 15 min	4.90 (3.35)
	3 hour +/- 30 min	4.87 (3.36)

The nominal time points are post eoi.

The mean (SD) SUVpeak at 25 ± 10 min was high for right kidney [24.2 (9.12)], left kidney [21.6 (6.26)], and spleen [18.2 (13.7)] while it was low for lungs [0.361 (0.194)], and muscle [0.672 (0.141)]. The mean (SD) SUVmean at 25 ± 10 min was high for right kidney [22.7 (8.79)], left kidney [20.5 (5.97)], and spleen [16.3 (11.9)] while it was low for lung [0.307 (0.160)], blood [0.639 (0.170)], and muscle [0.640 (0.133)]. The mean (SD) SUVmax at 25 ± 10 min was high for right kidney [27.2 (11.2)], left kidney [25.4 (6.72)], and spleen [19.0 (14.1)] while it was low for lung [0.396 (0.201)], muscle [0.757 (0.185)], and blood [0.899 (0.122)].

Safety results:

In patients treated with ^{68}Ga-EVS459, there were no non-serious AEs reported.

In patients treated with ^{177}Lu-EVS459, three patients (75.0%) had at least one AE and experienced AEs grade ≥3. The AEs regardless of study drug relationship included:

- agranulocytosis, anemia (2 patients, 50.0%, each)
- pancytopenia, ascites, intestinal obstruction, ileus, influenza, alanine aminotransferase increased, gamma-glutamyltransferase increased, neutrophil count decreased, platelet count decreased, white blood cell count decreased, acute kidney injury, rash, and rash maculo-papular (1 patient, 25.0%, each)

Of the three patients with at least one AE, two (50.0%) of them experienced AEs reported as related to the treatment: agranulocytosis, anemia, pancytopenia, neutrophil count decreased, platelet count decreased, white blood cell count decreased (1 patient, 25.0%, each). All these were grade ≥3, except for platelet count decreased.

One patient (25.0%) administered with ^{68}Ga-EVS459 experienced an SAE of pyrexia, considered not related to the study treatment per investigator assessment. Three patients (75.0%) treated with ^{177}Lu-EVS459 experienced at least one SAE: agranulocytosis [2 patients (50.0%)], pancytopenia, ileus, and intestinal obstruction, pulmonary embolism [1 patient (25.0%) each]. Except for agranulocytosis and pancytopenia [in one patient (25.0%), each], none of the events were related to the study treatment, as per Investigator assessment. Of these, all SAEs were grade ≥3, except for ileus.

One patient treated with ^{177}Lu-EVS459 died due to SAE worsening pulmonary embolism, considered not related to the study treatment per investigator assessment. This event occurred 60 days after administration of ^{177}Lu-EVS459. The safety summaries include only data from the on-treatment period i.e., 42 days, hence this event is not reflected in the AE summary table. One patient required prolonged hospitalization due to SAEs ileus and febrile agranulocytosis, which were non-fatal. One patient (25.0%) experienced AE agranulocytosis, considered treatment-related by Investigator assessment, leading to treatment discontinuation. Two patients (50.0%) had AEs which required additional therapy (Table 2-4).

Table 2-4 Overview of adverse events- ^{177}Lu-EVS459- Safety Set

Category	[^{177}Lu]Lu-EVS459 N=4 n (%)
Adverse events	3 (75.0)
Treatment-related	2 (50.0)
Adverse events with grade >=3	3 (75.0)
Treatment-related	2 (50.0)
SAEs	3 (75.0)
Treatment-related	2 (50.0)
Fatal SAEs	0
Treatment-related	0
AEs leading to treatment discontinuation	1 (25.0)
Treatment-related	1 (25.0)
AEs leading to dose reduction	0
AEs leading to dose interruption	0
AEs requiring additional therapy	2 (50.0)

Numbers (n) represent counts of patients.

Dose limiting toxicities (DLTs)

Three patients (75.0%) experienced at least one event with dose limiting toxicity. These events included agranulocytosis with grade 4 decrease neutrophil and anemia [2 patients (50.0%), each], and pancytopenia, neutrophil count decreased, and white blood cell count decreased [1 patient (25.0%), each].

All DLTs were hematologic (agranulocytosis with grade 4 decrease neutrophil, pancytopenia, anemia), correlating with Grade 3–4 cytopenias on hematological assessments. Overall, the adverse event reporting and laboratory findings are consistent with AD. Given the administered starting dose of 1.85 GBq, a second dose (Cycle 2) of 3 GBq was not feasible based on EBRT constraints for the bone marrow.

Overall, three patients (75.0%) experienced DLT, while one patient didn't have any DLT.

- One patient (25.0%) experienced DLT due to AE pancytopenia. Worst post-baseline laboratory assessments showed a hemoglobin level of 80 g/L (Grade 2), a markedly reduced leukocyte count of 0.7 $\times 10^9$/L (Grade 4), and a platelet count of 20 $\times 10^9$/L (Grade 4), correlating with higher bone marrow absorbed dose in this patient i.e. 2.91 Gy.
- One patient (25.0%) experienced DLT due to AEs agranulocytosis and anemia. Worst post-baseline laboratory assessments showed a hemoglobin level of 70 g/L (Grade 3), a markedly reduced leukocyte count of 0.3 $\times 10^9$/L (Grade 4), and a platelet count of 8 $\times 10^9$/L (Grade 4), correlating with bone marrow absorbed dose of 1.08 Gy.
- One patient (25.0%) experienced DLT due to AEs neutrophil count decreased, white blood cell counts decreased, agranulocytosis, and anemia. Worst post-baseline laboratory assessments showed a hemoglobin level of 66 g/L (Grade 3), a markedly reduced leukocyte count of 0.8 $\times 10^9$/L (Grade 4), and a platelet count of 7.9 $\times 10^9$/L (Grade 4), correlating with bone marrow absorbed dose of 1.88 Gy

There was one patient with no DLT reported. Worst post-baseline laboratory assessments showed a hemoglobin level of 114 g/L and platelet count of 128 $\times 10^9$/L. The red marrow absorbed dose was 1.74 Gy.

Clinical laboratory evaluation

Hematology

All patients (100%) experienced decrease in lymphocytes and of these three patients (75.0%) had grade ≥3 events. All patients (100%) experienced decrease in platelets and of these three patients (75.0%) had grade ≥3 events. Three patients (75.0%) had decreased hemoglobin, and two of these patients (50.0%) had grade ≥3 events. Three patients (75.0%) had decreased leucocyte count, and all three patients had grade ≥3 events. Two patients (50.0%) experienced decreased neutrophil count, and all two patients had grade ≥3 events.

Clinical chemistry

None of the patients, except for one with elevated ALT levels, treated with ^{177}Lu-EVS459 had Grade ≥ 2 biochemistry events, post-baseline.

Elevated ALT levels of > 5 x ULN was observed in one patient (25.0%), which was Grade 3 AE. Based on the hepatic laboratory values, no patient met the potential Hy's law criteria after receiving any dose of the study treatment. There were no cases suggestive of drug induced liver injury (DILI) observed.

No notable changes in vital signs were observed.

One patient (25.0%) exhibited a new >450 to <=480 ms QTcF interval. No adverse event has been reported in association with the increased QTcF interval.

Conclusions:

In this first-in-human trial of ^{177}Lu-EVS459, a folate receptor–targeting radioligand therapy, in patients with ovarian cancer, three out of the four enrolled patients experienced DLTs related to hematological toxicities after receiving a single cycle of the starting dose (i.e. administered activity) of 1.85 GBq (50 mCi) of ^{177}Lu-EVS459, at dose level 1A. The dose was not escalated further due to DLTs. Based on these findings, Novartis made the decision to terminate the study on the grounds that no dose of ^{177}Lu-EVS459 could be identified with a favourable benefit–risk profile for the studied indication.