POSTER #CT059

Phase 1b Trial Mipasetamab Uzoptirine (ADCT-601-102) Dose-Escalation in Patients With Advanced Bone and Soft Tissue Sarcomas

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CONCLUSIONS

- In patients with sarcoma, mipasetamab uzoptirine (Mipa) monotherapy demonstrated an acceptable safety profile and activity with responses, tumor volume reduction, and patients not progressing at week 12 during dose-escalation
- Similar exposures over time between conjugated antibody (Ab) and total Ab demonstrate good in vivo stability of the antibody–drug conjugate (ADC); rapid clearance indicates no accumulation with every 3 week (Q3W) dosing
- Although the non-tolerated dose (NTD) has not been reached and the maximum tolerated dose (MTD) has not been established, due to the preliminary efficacy and incidence of treatment-emergent adverse events (TEAEs), Mipa 15 mg is the highest and last dose explored in a fixed dose every Q3W regimen
- AXL-positive tumor cells (TCs) were present in all patients with sarcoma tested by immunohistochemistry (IHC), with 12/14 patients showing ≥65% AXL-positive TCs; the 2 responding patients have intermediate levels of AXL expression
- The study continues to enroll patients to further optimize the Mipa monotherapy dosing regimen and continues to investigate Mipa in combination with gemcitabine

INTRODUCTION

- AXL is a cell surface receptor tyrosine kinase widely expressed in solid tumors, including sarcomas[1]
- AXL overexpression is linked to increased metastatic potential, chemotherapy resistance, and worse overall survival in some solid tumors, notably sarcoma and non–small cell lung cancer (NSCLC)[1-3]
- ADCT-601 (mipasetamab uzoptirine; Mipa) is an ADC comprising a humanized anti-AXL antibody conjugated via a cleavable linker to the potent chemotherapeutic agent SG3199 (pyrrolobenzodiazepine dimer cytotoxin)[4]
- Mipa demonstrated antitumor activity in preclinical mouse models of sarcoma, adenoid cystic carcinoma, and pancreatic cancer and clinical activity in patients with solid tumors in its first-in-human trial[4-7]

OBJECTIVE

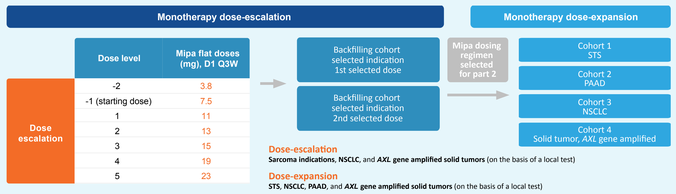
- To characterize the safety and tolerability of Mipa in patients with selected sarcoma indications who have exhausted standard-of-care therapy

METHODS

Study Design

- This is a phase 1b, open-label, dose-escalation (part 1), dose-expansion (part 2) study of Mipa (NCT05389462; EudraCT: 2021-00566-18) (**Figure 1**)
- In part 1, patients with any solid tumor carrying *AXL* gene amplification, patients with sarcoma, or patients with NSCLC received escalating doses of Mipa monotherapy Q3W until disease progression or unacceptable toxicity in a 3 + 3 dose-escalation design
- In part 2, patients will receive the recommended dosing regimen for expansion determined in part 1 or an alternative dosing regimen to support dose optimization
- Patients receive premedication with dexamethasone 4 mg (or prednisone 25 mg) twice daily on the day before, the day of, and the day after administration of Mipa

Figure 1. Phase 1b monotherapy dose-escalation design



D, day; Mipa, mipasetamab uzoptirine; PAAD, pancreatic adenocarcinoma; STS, soft tissue sarcoma; NSCLC, non–small cell lung cancer; Q3W, every 3 weeks.

Outcomes

- The primary endpoints are the frequency and severity of adverse events and serious adverse events; the incidence of dose-limiting toxicity (DLT; dose escalation only); the frequency of dose interruptions and dose reductions; and the changes from baseline in safety laboratory values, vital signs, ECOG performance status, and 12-lead electrocardiograms
- Secondary endpoints include overall response rate (RECIST v1.1), duration of response, progression-free survival, overall survival, pharmacokinetics (PK), and antidrug antibody response

Eligibility Criteria

Table 1. Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
• Adults ≥18 years of age	• Previous AXL-targeting compound
• Pathologic diagnosis of locally advanced or metastatic solid tumor malignancy – Part 1: sarcoma and NSCLC, regardless of *AXL* gene amplification status and solid tumors (excluding lymphomas) with known *AXL* gene amplification	• Significant medical comorbidities • History of SJS/TEN • Symptomatic CNS metastases or evidence of leptomeningeal disease
• Measurable disease (RECIST v1.1) with tumor biopsy showing disease progression and refractory or intolerant to existing therapies	• Clinically significant third space fluid accumulation
• ECOG performance status of 0-1	• History of grade ≥3 hypersensitivity to a therapeutic antibody
• Adequate organ function	• Active second primary malignancy other than nonmelanoma skin cancers, nonmetastatic prostate cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; NSCLC, non–small cell lung cancer; RECIST, response evaluation criteria in solid tumors; SJS/TEN, Stevens–Johnson syndrome or toxic epidermal necrolysis.

RESULTS

Patient Population

- As of February 6, 2024, 24 patients with sarcoma, unselected for *AXL* expression, were enrolled in 4 different dose cohorts to be treated with Mipa: 7.5 mg, 11 mg, 13 mg, and 15 mg Q3W

Table 2. Baseline characteristics of patients (N = 24)

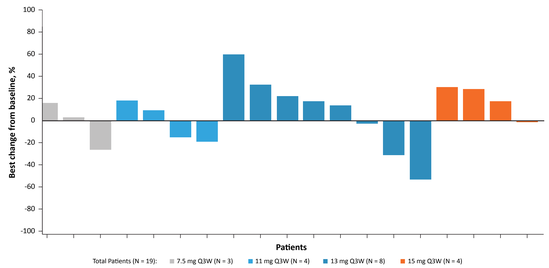
Age, median (range)	57 (30, 80)
Prior systemic therapies, median (range)	3 (1, 10)
Sex, n (%)	
Male	14 (58.3)
Female	10 (41.7)
ECOG performance status, n (%)	
0	13 (54.2)
1	11 (45.8)
Sarcoma subtype, n (%)	
Soft tissue sarcoma	21 (87.5)
Bone sarcoma	3 (12.5)

ECOG, Eastern Cooperative Oncology Group.

Efficacy

- In patients treated with Mipa, the best overall responses were the following:
  - partial response (PR) observed in 2 (9.5%) patients
  - stable disease (SD) observed in 10 (47.6%) patients
  - progressive disease (PD) observed in 8 (38.1%) patients
- Tumor reductions were observed at dose levels of 7.5 mg, 11 mg, and 13 mg (**Figure 2**)
- At week 12, 7/21 (33%) patients did not show radiographic progression (**Figure 3**)

Figure 2. Waterfall plot of best percent change from baseline in tumor volume[a,b]

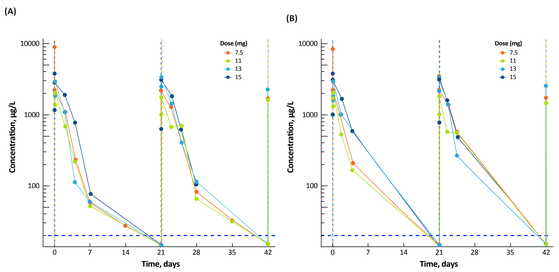


[a]Each bar represents 1 patient in the study. [b]Sum of the longest diameters in multiple target lesions by Investigator.

Pharmacokinetics

- PK data were available from 19 patients in cycle 1 and 17 patients in cycle 2
- Mipa mean exposures tended to increase with dose; Mipa mean exposure demonstrated moderate-to-marked interpatient variability, rapid clearance, and no accumulation by cycle 2 (**Figure 4**)
- Low levels (below limit of quantification) and high variability of SG3199 precluded its characterization for most patients

Figure 4. Median concentration in serum vs time by dose for the (A) Mipa conjugated antibody and (B) total antibody



Dashed vertical lines denote time of a planned dosing events.
Horizontal blue dashed line denotes limit of qualification (20 µg/L).

Cycle	C_{max} (µg/L)	AUC[a] (µg·day/L)	CL (L/day)
1	2136-8775	4245-8977	1.25-2.99
2	2031-4688	6309-9865	1.1-1.83

Dashed vertical lines denote time of a planned dosing events.
Horizontal blue dashed line denotes limit of qualification (28.7 µg/L).

Cycle	C_{max} (µg/L)	AUC[a] (µg·day/L)	CL (L/day)
1	2236-7995	2903-7238	1.88-4.0
2	2347-4346	4149-8733	1.08-2.65

Tabular data shown as range of geometric means.
AUC, area under the curve; CL, apparent clearance; C_{max}, maximum observed concentration; Mipa, Mipasetamab uzoptirine.
[a]Cycle 1 as AUC_{0-21}; cycle 2 as AUC_{ss}.

Safety and Tolerability

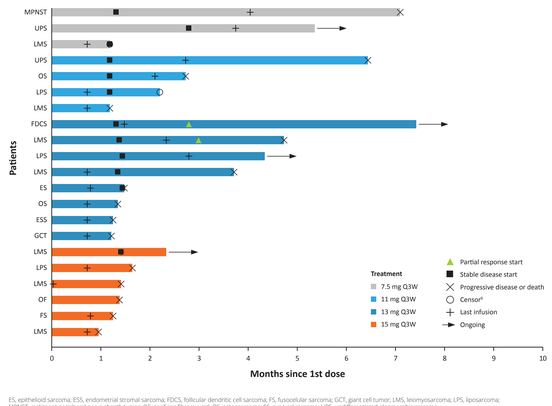
- TEAEs related to the study drug were more prominent in higher doses of Mipa
- Discontinuation from treatment occurred in 75% of patients
  - Reasons for treatment discontinuation included disease progression (12 [50%]), adverse events (4 [16.7%]), and withdrawal of consent (2 [8.3%])
- A TEAE leading to death, acute liver failure, was reported in 1 patient, which was considered not related to the study treatment
- The NTD and MTD have not been reached
  - The following 2 DLTs were reported: cheilitis grade 2 and grade 3 at 15 mg and 13 mg, respectively

Table 3. Summary of treatment-emergent adverse events

	7.5 mg n = 3	11 mg n = 7	13 mg n = 8	15 mg n = 6	Total N = 24
TEAEs, any grade[a]	3 (100)	6 (85.7)	7 (87.5)	6 (100)	22 (91.7)
Anemia	0	4 (57.1)	2 (25.0)	1 (16.7)	7 (29.2)
Dyspnea	1 (33.3)	1 (14.3)	1 (12.5)	4 (66.7)	7 (29.2)
PPE	1 (33.3)	2 (28.6)	3 (37.5)	1 (16.7)	7 (29.2)
Erythema	0	1 (14.3)	1 (12.5)	3 (50.0)	5 (20.8)
Fatigue	0	2 (28.6)	1 (12.5)	2 (33.3)	5 (20.8)
Maculopapular rash	1 (33.3)	0	4 (50.0)	0	5 (20.8)
TEAEs, grade ≥3[b]	3 (100)	3 (42.9)	4 (50.0)	3 (50.0)	13 (54.2)
Pleural effusion	2 (66.7)	0	1 (12.5)	0	3 (12.5)

PPE, palmar-plantar erythrodysesthesia; TEAE, treatment-emergent adverse event.
[a]TEAEs, any grade, occurring in ≥20% of patients. [b]TEAEs, grade ≥3, occurring in ≥10% of patients.

Figure 3. Swimmer plot[a]

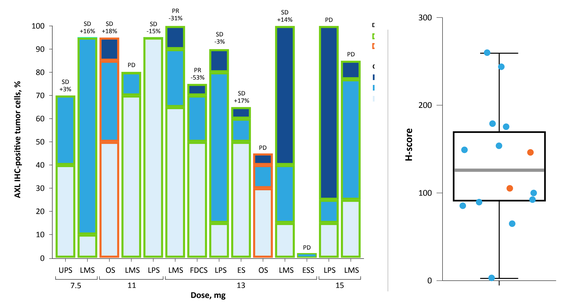


ES, epithelioid sarcoma; ESS, endometrial stromal sarcoma; FDCS, follicular dendritic cell sarcoma; FS, fusocellular sarcoma; GCT, giant cell tumor; LMS, leiomyosarcoma; LPS, liposarcoma; MPNST, malignant peripheral nerve sheath tumor; OF, ossifying fibromyxoid; OS, osteosarcoma; SS, synovial sarcoma; UPS, undifferentiated pleomorphic sarcoma.
Q3W, every 3 weeks.
[a]Each bar represents one patient. Response is determined by investigator.
[b]Only for censored patients who discontinued the trial due to reasons other than disease progression or who went onto a different anticancer treatment.
Soft tissue sarcoma includes LMS, LPS, FDCS, MPNST, UPS, SS, ES, OF, FS, and ESS. Bone sarcoma includes OS and GCT.

AXL Expression by IHC in Sarcoma Baseline Biopsies

- AXL-positive TCs were present in all sarcoma baseline biopsies tested to date (14 biopsies) (**Figure 5A**)
  - 12 of 14 patient biopsies show ≥65% AXL-positive tumor cells
- The 2 responding patients (PR) show intermediate levels of AXL expression by H-score (capturing % positive TCs and staining intensity) (**Figure 5B**)

Figure 5. AXL IHC expression in TCs of sarcoma baseline biopsies (A)[a,b] and intermediate AXL IHC H-score levels in patients with a PR (B)



ES, epithelioid sarcoma; ESS, endometrial stromal sarcoma; FDCS, follicular dendritic cell sarcoma; LMS, leiomyosarcoma; LPS, liposarcoma; OS, osteosarcoma; UPS, undifferentiated pleomorphic sarcoma.
H-score, histoscore; IHC, immunohistochemistry; PD, progressive disease; PR, partial response; SD, stable disease; TC, tumor cells.
[a]Each bar represents 1 patient. [b]Patient best overall response and best percent change from baseline in tumor volume are reported on the top of each bar.
Soft tissue sarcoma includes LMS, LPS, FDCS, UPS, SS, ES, and ESS. Bone sarcoma includes OS.