POSTER #CT059

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

Brian Andrew Van Tine,[1]* Christopher T. Chen,[2] Victor Moreno,[3] Elizabeth J. Davis,[4] Maria J. de Miguel,[5] Antoine Italiano,[6] Esma Saada-Bouzid,[7] Mohammed Milhem,[8] Claudia Valverde,[9] Sant P. Chawla,[10] Abdul Rafeh Naqash,[11] Louise Carter,[12] Robin L. Jones,[13] Ilaria Conti,[14] Joe Boni,[14] Karin Havenith,[15] Yvan LeBruchec,[16] Serafino Pantano,[16] Jean-Yves Blay[17]

[1]Washington University School of Medicine, St. Louis, MO, USA; [2]Stanford University School of Medicine, Palo Alto, CA, USA; [3]START Madrid-FJD, Fundación Jiménez Díaz, Madrid, Spain; [4]Vanderbilt University Medical Center, Nashville, TN, USA; [5]START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Hospital Universitario HM Sanchinarro, Madrid, Spain; [6]Bergonié Institute, Bordeaux, France; [7]Université Cote d'Azur, Centre Antoine Lacassagne, Nice, France; [8]University of Iowa, Iowa City, IA, USA; [9]Vall d'Hebron University Hospital, Barcelona, Spain; [10]Sarcoma Oncology Research Center, Santa Monica, CA, USA; [11]Stephenson Cancer Center, University of Oklahoma, Oklahoma City, OK, USA; [12]The University of Manchester and The Christie NHS Foundation Trust, Manchester, United Kingdom; [13]Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, United Kingdom; [14]ADC Therapeutics, New Providence, NJ, USA; [15]ADC Therapeutics, London, UK; [16]ADC Therapeutics, Épalinges, Switzerland; [17]Centre Léon-Bérard, Lyon, France

Acknowledgments

Funding was provided by ADC Therapeutics. Medical writing support was provided by Citrus Health Group (United States) in accordance with Good Publication Practice (GPP 2022) guidelines.

Disclosures

BA Van Tine: consulting/advisory role with ADRx, Adaptimmune, Apexigen, Ayala Pharmaceuticals, Bayer, Boehringer Ingelheim, Cytokinetics, Daiichi Sankyo, Deciphera, EcoR1 Capital, EMD Serono, Epizyme, GlaxoSmithKline, Immune Design, Intellisphere, Lilly, Novartis, Pfizer, and PTC Therapeutics; leadership role with Polaris; speakers' bureau with Adaptimmune, GlaxoSmithKline, Lilly, and Novartis; travel/accommodations/expenses from Adaptimmune, Advenchen Laboratories, GlaxoSmithKline, and Lilly; expert testimony for Health Advances; patents/royalties/other intellectual property with Accuronix Therapeutics; honoraria from Bionest Partner, Horizon CME, Research to Practice, and Targeted Oncology; research funding from GlaxoSmithKline, Pfizer, Merck, and TRACON Pharma. **CT Chen:** consulting/advisory role for Bower Capital and Guidepoint Global; research funding from ADC Therapeutics, Gilead, Kinnate Biopharma, Mersana Therapeutics, ORIC Pharmaceuticals, Palleon, Rain Oncology, Riboscience, and Takeda. **V Moreno:** consulting/advisory role for Affimed Therapeutics, AstraZeneca, Basilea, Bayer, Bristol-Myers Squibb, Janssen Oncology, Merck, and Roche; speakers' bureau for Bayer and Pierre Fabre; expert testimony for Medscape/Bayer and Nanobiotix; research funding from AbbVie, ACEA Biosciences, Adaptimmune, Amgen, AstraZeneca, Bayer, BeiGene, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eisai, E-therapeutics, GlaxoSmithKline, Janssen, Menarini, Merck, Nanobiotix, Novartis, Pfizer, PharmaMar, PsiOxus Therapeutics, Puma Biotechnology, Regeneron, RigonTEC, Roche, Sanofi, Sierra Oncology, Synthon, Taiho Pharmaceutical, Takeda, Tesaro, and Transgene. **EJ Davis:** consulting/advisory role for Aadi and Deciphera; research funding to institution from Cogent Biosciences, Cornerstone Pharmaceuticals, and Inhibrx. **MJ de Miguel:** no disclosures to report. **A Italiano:** grant of contract with ADC Therapeutics, AstraZeneca, Bayer, Bristol-Myers Squibb, Ipsen, Lilly, Merck Sharp & Dohme, Novartis, Partheon, Roche. **E Saada-Bouzid:** independent contract and travel from Merck Serano and Merck Sharp & Dohme. **M Milhem:** no disclosures to report. **C Valverde:** consulting/advisory role for Bayer, Boehringer Ingelheim, Boxer Capital, Deciphera Pharmaceuticals, and Pharmamar; research funding from Pharmamar, Bayer, Deciphera Pharmaceuticals, Boehringer Ingelheim, Novartis, Pfizer, Bristol Myers Squibb, Monopar Therapeutics, Adaptimmune Therapeutics, GSK, AROG Pharmaceuticals, Blueprint Medicines, and Philogen; non-renumerated leadership role or affiliation with American Society of Clinical Oncology (ASCO), European Organisation for Research and Treatment of Cancer (EORTC), European Society for Medical Oncology (ESMO), Grupo Español de Investigación en Sarcomas (GEIS), and Sociedad Espanola de Oncologia Medica (SEOM); travel/accommodations/expenses from Adaptimmune Therapeutics, Bayer, Pfizer, PharmaMar, and Roche. **SP Chawla:** consulting/advisory role for Advenchen Laboratories, Amgen, Bayer, CytRx Corporation, GlaxoSmithKline, Ignyta, Immune Design, InhibRx, Janssen, Karyopharm Therapeutics, NKMax, Roche, SARC: Sarcoma Alliance for Research through Collaboration, Threshold Pharmaceuticals, and TRACON Pharma; speakers' bureau for Amgen, CytRx Corporation, GlaxoSmithKline, Ignyta, Immune Design, Janssen, Karyopharm Therapeutics, Roche, SARC: Sarcoma Alliance for Research through Collaboration, Threshold Pharmaceuticals, and TRACON Pharma; stockholder ownership interests in Aadi, Cellestia Biotech, and Immix BioPharma; honoraria from Advenchen Laboratories, Amgen, Bayer, CytRx Corporation, GlaxoSmithKline, Ignyta, Immune Design, InhibRx, Janssen, Karyopharm Therapeutics, NKMax, Roche, SARC: Sarcoma Alliance for Research through Collaboration, Threshold Pharmaceuticals, TRACON Pharma, and Tyme; research funding from Advenchen Laboratories, Amgen, Bayer, CytRx Corporation, GlaxoSmithKline, Ignyta, Immune Design, InhibRx, Janssen, Karyopharm Therapeutics, NKMax, Roche, SARC: Sarcoma Alliance for Research through Collaboration, Threshold Pharmaceuticals, and TRACON Pharma. **AR Naqash:** funding to institution for trials from ADC Therapeutics, Calyxe, EMD Serano, Exelexis, IGM Biosciences, Immunophotonics, Inspirna, Jacobio Pharma, Jazz Pharmaceuticals, Loxo@Lilly, NGM Biopharmaceuticals, Nikang Therapeutics, Pionyr Immunotherapeutics, Revolution Medicine, Selexine, and Surface Oncology; travel compensation from American Association for Cancer Research (AACR), BinayTara Foundation, Caris Life Sciences, Conquer Cancer Foundation, Foundation Medicine, Jazz Pharmaceuticals, and Society for Immunotherapy of Cancer (SITC); consulting/advisory role for Foundation Medicine; grant/contract from FDA Broad Agency and SWOG Hope Foundation; consultant editor compensation from JCO Precision Oncology. **L Carter:** no disclosures to report. **R Jones:** consulting/advisory role for Adaptimmune, Astex Pharmaceuticals, Athenex, Bayer, Boehringer Ingelheim, Blueprint Medicines, Clinigen, Eisai, Epizyme, Daichii, Deciphera Pharmaceuticals, Immunedesign, Immunicum, Karma Oncology, Lilly, Merck, Mundipharma, Pharmamar, Springworks Therapeutics, SynOx Therapeutics, TRACON Pharmaceuticals, and UpToDate; grant/contract and research funding from Merck Sharp & Dohme and GSK. **I Conti:** employee of ADC Therapeutics; equity/stock options at ADC Therapeutics, AstraZeneca, and Eli Lilly and Company. **J Boni:** employee of ADC Therapeutics; equity/stock options in ADC Therapeutics. **K Havenith:** employee of ADC Therapeutics; equity/stock options in ADC Therapeutics **Y LeBruchec:** employee of ADC Therapeutics; equity/stock options in ADC Therapeutics. **S Pantano:** employee of ADC Therapeutics; immediate family member employed by Novartis; equity/stock options in ADC Therapeutics, Alcon, Merck, Organon & Co., Novartis, and Sandoz **JY BLAY:** research funding and honoraria from Bayer and PharmaMar.

Contact information

*Brian Andrew Van Tine: bvantine@wustl.edu

References

1. Chen H, et al. *Cancer Treat Rev*. 2016;43:8-18.
2. Schoumacher M, Burbidge M. *Curr Oncol Rep*. 2017;19:19.
3. Zaman A, Bivona TG. *Lung Cancer: Targets Ther*. 2021;12:67-79.
4. Zammarchi F, et al. *Mol Cancer Ther*. 2022;21:582-593.
5. Tolcher AW, et al. Poster presented at: European Society for Medical Oncology; Sep 27-Oct 1, 2019; Barcelona, Spain.
6. Humtsoe JO, et al. Poster presented at: Association for Cancer Research Annual Meeting 2022; Apr 8-13, 2022; Philadelphia, PA.
7. El-Ghazzi N, et al. Oral presentation at: 2023 CTOS Annual Meeting; Nov 1-4, 2023; Dublin, Ireland.

Poster presented at the AACR Annual Meeting 2024.
April 5-10, 2024, San Diego, CA, USA

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

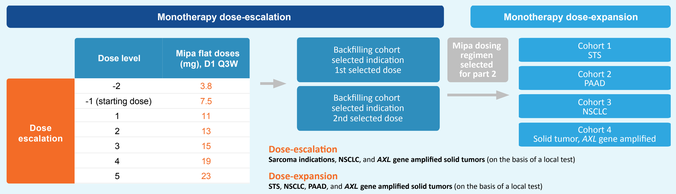
- To characterize the safety and tolerability of Mipa in patients with selected sarcoma indications who have exhausted standard-of-care therapy

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 • History of grade ≥3 hypersensitivity to a therapeutic antibody
• ECOG performance status of 0-1 • 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)

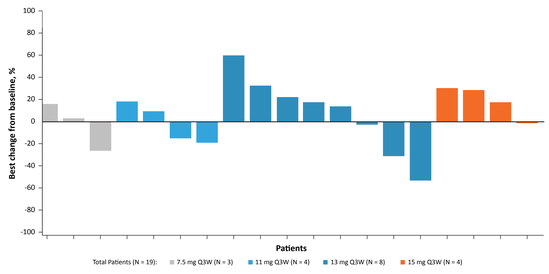
Age, median (range)	57 (30, 80)
Prior systemic therapies, median (range)	3 (1, 10)
Sex, n (%)	
Male	14 (58.3)
Female	10 (41.7)
ECOG performance status, n (%)	
0	13 (54.2)
1	11 (45.8)
Sarcoma subtype, n (%)	
Soft tissue sarcoma	21 (87.5)
Bone sarcoma	3 (12.5)

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]

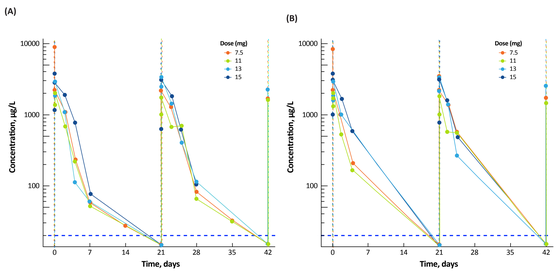


[a]Each bar represents 1 patient in the study. [b]Sum of the longest diameters in multiple target lesions by Investigator.

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

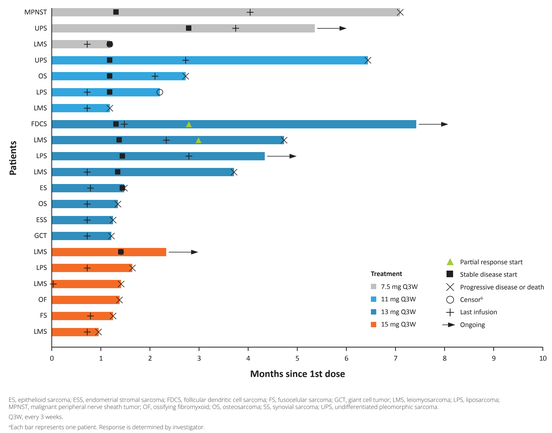
- TEAEs related to the study drug were more prominent in higher doses of Mipa
- Discontinuation from treatment occurred in 75% of patients
  - Reasons for treatment discontinuation included disease progression (12 [50%]), adverse events (4 [16.7%]), and withdrawal of consent (2 [8.3%])
- A TEAE leading 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]

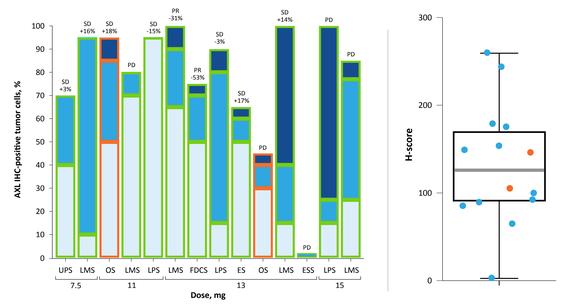


ES, epithelioid sarcoma; ESS, endometrial stromal sarcoma; FDCS, follicular dendritic cell sarcoma; FS, fusocellular sarcoma; GCT, giant cell tumor; LMS, leiomyosarcoma; LPS, liposarcoma; MPNST, malignant peripheral nerve sheath tumor; OF, ossifying fibromyxoid; OS, osteosarcoma; SS, synovial sarcoma; 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.