

A Phase 1, Open-label, Dose-Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of ADCT-601 in Patients with Advanced Solid Tumors

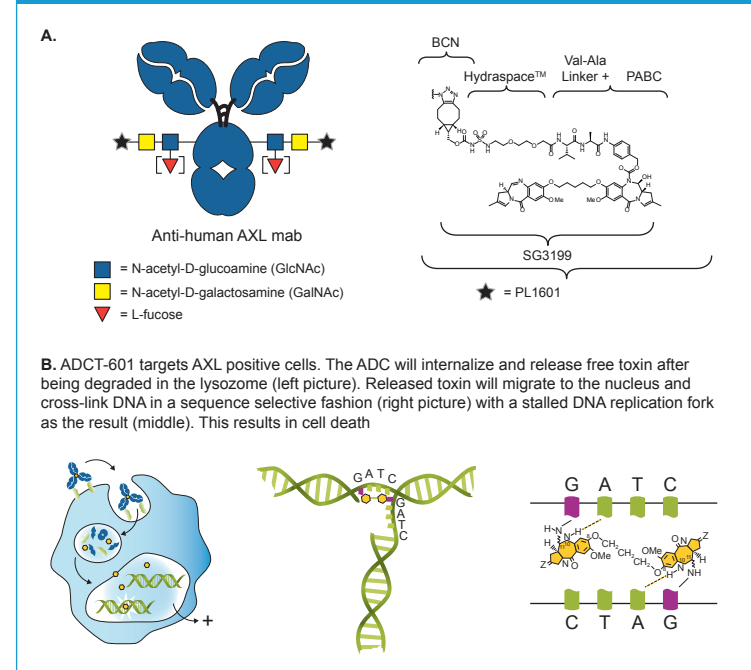
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INTRODUCTION

- AXL, a member of the Tyro-3, Axl, and Mer (TAM) family of receptor tyrosine kinases, is over-expressed in various cancers. Over-expression of AXL is linked to metastasis, poor survival, and drug resistance¹
 - The diverse role of AXL in facilitating cancer progression, and its presence on multiple cell types in the tumor-immune microenvironment, make it an attractive therapeutic target in oncology^{2,3}
- ADCT-601 is an antibody-drug conjugate composed of a humanized IgG1 antibody against human AXL site-specifically conjugated using GlycoConnect™ technology to PL1601, which contains Hydraspase™, a valine-alanine cleavable linker and the pyrrolobenzodiazepine (PBD) dimer cytotoxin SG3199
- ADCT-601 has shown potent and durable antitumor activity in preclinical human cancer models via AXL-mediated delivery of a PBD dimer warhead
 - The structure and mechanism of action of ADCT-601 is presented in **Figure 1**
- Here we report interim data from a Phase 1 clinical trial of ADCT-601 (NCT03700294; ADC Therapeutics) in patients with selected advanced solid tumors

Figure 1. (A) Structure and (B) mechanism of action of ADCT-601



STUDY OBJECTIVES

- Primary objective
 - To characterize the safety and tolerability of ADCT-601 and to identify the recommended dose(s) and schedule(s) for future studies in patients with solid tumors
- Secondary objectives
 - To evaluate the antitumor activity of ADCT-601 (measured by overall response rate, disease control rate, duration of response, progression-free survival, and overall survival)
 - To characterize the pharmacokinetic (PK) profile of ADCT-601
 - To evaluate the immunogenicity of ADCT-601

STUDY DESIGN

- This is a Phase 1, multicenter, open-label, single-arm, dose-escalation (Part 1) and dose-expansion (Part 2) study in eligible patients with relapsed or refractory (R/R) solid tumors. Inclusion and exclusion criteria are presented in **Table 1**
- In Part 1, approximately 30 patients will be enrolled to determine the maximum tolerated dose of ADCT-601 and the recommended dose for expansion
 - Patients will receive 1-hour intravenous infusions of ADCT-601 every 3 weeks (Q3W) starting at 50 μg/kg, with subsequent cohorts enrolled at escalating doses according to a standard 3+3 design
- Treatment for patients in Part 2 will be based on the dose(s) determined in Part 1
 - Part 2 will enrol approximately 45 patients in three additional cohorts (15 patients in each cohort) from one or more selected tumor types

Table 1. Study key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
• Age 18 years or older	• Known history of ≥ Grade 3 hypersensitivity to a therapeutic antibody
• Pathologically confirmed, locally advanced or metastatic solid tumor at the time of screening	• Active second primary malignancy
• Failed or intolerant to any established therapy, or no other treatment options available	• Active autoimmune disease
• Measurable disease, per RECIST 1.1	• Symptomatic CNS metastases or evidence of leptomeningeal disease
• ECOG performance status 0–1	• Significant medical comorbidities
• Absolute neutrophil count ≥ 1.5 × 10 ³ /μL; platelet count ≥ 100 × 10 ³ /μL; ALT, AST and GGT ≤ 2.5 × ULN and ≤ 5 × ULN if there is liver involvement with tumor; total bilirubin and blood creatinine ≤ 1.5 × ULN	• Major surgery, chemotherapy, radiotherapy or other antineoplastic therapy within 14 days prior to Cycle 1 Day 1 treatment

β-HCG, beta-human chorionic gonadotropin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, Central nervous system; ECOG, Eastern Cooperative Oncology Group; GGT, gamma glutamyl transferase; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal

RESULTS

Patient characteristics

- As of July 19, 2019, 13 patients have been treated at doses of 50–150 μg/kg Q3W
 - Baseline characteristics are shown in **Table 2**
 - Patients had received a median of 4 prior systemic therapies (range: 1–7); nine patients had received ≥4 prior systemic therapies
- At data cut-off, patients had received a median (range) of 2 cycles (1–5) of ADCT-601

Table 2. Baseline characteristics and demographic data of study population

Patient characteristics	50 μg/kg (N=3)	100 μg/kg (N=6)	150 μg/kg (N=4)	All doses N=13
Sex, n (%)				
Female	1 (33.3)	2 (33.3)	1 (25.0)	4 (30.8)
Male	2 (66.7)	4 (66.7)	3 (75.0)	9 (69.2)
Age, median (min, max), years	71.0 (65, 77)	58.0 (39, 71)	57.5 (41, 70)	69.0 (39, 77)
ECOG performance status				
0	0	2 (33.3)	0	2 (15.4)
1	3 (100)	4 (66.7)	4 (100)	11 (84.6)
Diagnosis, n (%)				
Colorectal cancer	0	4 (66.7)	0	4 (30.8)
Soft tissue sarcoma	1 (33.3)	1 (16.7)	2 (50.0)	4 (30.8)
Ovarian carcinoma	1 (33.3)	0	0	1 (7.7)
Head and neck carcinoma	0	1 (16.7)	0	1 (7.7)
Esophageal carcinoma	1 (33.3)	0	0	1 (7.7)
Mesothelioma	0	0	1 (25.0)	1 (7.7)
Breast cancer*	0	0	1 (25.0)	1 (7.7)
Number of prior systemic therapies, median (min, max)	5.0 (4, 6)	3.5 (1, 5)	6.5 (2, 7)	4.0 (1, 7)

*ER negative, PR negative and HER2 negative
ECOG, Eastern Cooperative Oncology Group; Q3W, every 3 weeks

Pharmacokinetics

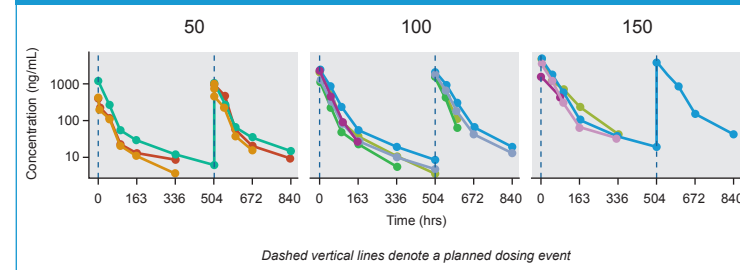
- For ADCT-601, increase in serum exposure and decrease in clearance were observed with increase in the dose from 50 to 150 μg/kg (**Table 3**)
 - Interpatient variability appears moderate (**Figure 2**)
- Consistent with other PBD-conjugated antibodies, SG3199 concentrations in most patients were predominantly below lower limit of quantification
 - Accumulation by Cycle 2 is negligible (**Table 3**)

Table 3. Summary of PK parameters of conjugated antibody by dose group in Cycles 1 and 2

	Cycle 1			Cycle 2		
	50 μg/kg (n=3)	100 μg/kg (n=6)	150 μg/kg (n=4)	50 μg/kg (n=3)	100 μg/kg (n=5)	150 μg/kg (n=2)
C _{max} (ng/mL)	680 (425)	1888 (415)	3678 (1527)	890 (196)	1944 (317)	3895 (49.5)
AUC _{0-∞} (ng·h/mL)	25179 (18372)	81365 (26267)	195085 (77320)	40399 (13318)	94646 (25335)	183295 (104279)
C _{avg} (ng/mL)	50.9 (35.7)	164 (59.4)	456 (93.7)	82.2 (26.9)	190 (70.4)	510 (NA)
T _{1/2} (h)	136 (32.6)	109 (25.4)	123 (56.4)	81.7 (44.1)	34.1 (14.5)	108 (NA)
CL (mL)	190 (88.2)	93.7 (59.0)	50.3 (2.21)	101 (36.4)	99.0 (51.9)	52.5 (NA)
V _d (L)	35.9 (16.0)	13.5 (5.18)	8.91 (4.02)	10.6 (4.48)	4.19 (0.407)	8.17 (NA)
AI	NA	NA	NA	1.03 (0.03)	1.00 (0.0)	1.04 (NA)

Data shown as mean (± SD); AI, accumulation index; AUC_{0-∞}, area under the curve extrapolated to last observable measure; C_{avg}, average concentration; CL_{app}, apparent clearance; C_{max}, maximum observed concentration; T_{1/2}, apparent terminal half-life; V_d, volume of distribution

Figure 2. ADCT-601 conjugated antibody concentration vs time by dose cohort (μg/kg, Q3W)



Q3W, every 3 weeks

Safety

- One patient treated at 100 μg/kg had a dose-limiting toxicity of Grade 3 hematuria, which resulted in hospitalization and was possibly related to ADCT-601
- Treatment-emergent adverse events (TEAEs) were reported in all patients (100%); Grade ≥3 TEAEs were reported in 7/13 (53.8%) patients
- Grade 1/2 and Grade ≥3 TEAEs reported in study patients are shown in **Table 4**
 - The most common TEAEs (>2 patients), regardless of grade or relationship to ADCT-601, were abdominal pain (reported in five patients), decreased appetite, fatigue, nausea (each reported in four patients), constipation, diarrhea, erythema, peripheral edema, maculopapular rash and vomiting (each reported in three patients)
 - The most common Grade ≥3 TEAE (>1 patient) was abdominal pain, which occurred in three patients (23.1%)
- Serious TEAEs were reported in 5/13 (38.5%) patients: abdominal pain in two patients, and upper gastrointestinal hemorrhage, pain, hematuria and urinary tract obstruction, each in one patient
- One patient (7.7%) had TEAEs leading to ADCT-601 dose delay or reduction: peripheral edema and maculopapular rash, both considered related to ADCT-601
- One patient (7.7%) had TEAEs leading to ADCT-601 withdrawal: increased bilirubin and hyponatremia, both considered unrelated to ADCT-601
- Three deaths were reported, all due to progressive disease

Table 4. Grade 1/2 and Grade ≥3 TEAEs occurring in >1 patient

Adverse event by preferred term	50 μg/kg N=3 n (%)		100 μg/kg N=6 n (%)		150 μg/kg N=4 n (%)		All doses N=13 n (%)	
	Grade 1–2	Grade ≥3	Grade 1–2	Grade ≥3	Grade 1–2	Grade ≥3	Grade 1–2	Grade ≥3
Abdominal pain	1 (33.3)	0	1 (16.7)	1 (16.7)	0	2 (50.0)	2 (15.4)	3 (23.1)
Decreased appetite	1 (33.3)	0	2 (33.3)	0	1 (25.0)	0	4 (30.8)	0
Fatigue	2 (66.7)	0	1 (16.7)	0	1 (25.0)	0	4 (30.8)	0
Nausea	1 (33.3)	0	2 (33.3)	0	1 (25.0)	0	4 (30.8)	0
Constipation	1 (33.3)	0	1 (16.7)	0	1 (25.0)	0	3 (23.1)	0
Diarrhea	0	0	2 (33.3)	0	1 (25.0)	0	3 (23.1)	0
Erythema	1 (33.3)	0	1 (16.7)	0	1 (25.0)	0	3 (23.1)	0
Maculopapular rash	1 (33.3)	0	2 (33.3)	0	0	0	3 (23.1)	0
Peripheral edema	1 (33.3)	0	2 (33.3)	0	0	0	3 (23.1)	0
Vomiting	0	0	1 (16.7)	0	2 (50.0)	0	3 (23.1)	0
Hypokalemia	1 (33.3)	0	1 (16.7)	0	0	0	2 (15.4)	0
Hypophosphatemia	1 (33.3)	0	0	1 (16.7)	0	0	1 (7.7)	1 (7.7)

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Disclosures

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Efficacy

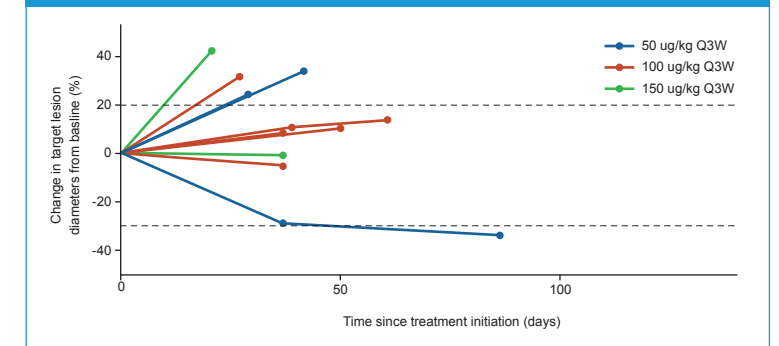
- At data cut-off, 10/13 patients had undergone at least one response evaluation; response has not yet been evaluated in three patients (**Table 5**)
 - There was one unconfirmed partial response (soft tissue sarcoma, 50 μg/kg) and five patients with stable disease
- Percent change in the target lesion observed in different dose cohorts is presented in **Figure 3**

Table 5. Response summary

Response	Cohort			
	50 μg/kg (n=3)	100 μg/kg (n=6)	150 μg/kg (n=4)	All doses (N=13)
CR	-	-	-	-
PR	1 ^a (soft tissue sarcoma)	-	-	1 ^a
SD	-	4 (2 cases of colorectal cancer, 1 case of head and neck carcinoma and 1 case of soft tissue sarcoma)	1 (mesothelioma)	5
PD	2 (esophageal cancer and ovarian cancer)	1 (colorectal cancer)	1 (breast cancer)	4
Not yet evaluated	-	1 (colorectal cancer)	2 (soft tissue sarcoma)	3

^aUnconfirmed
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

Figure 3. Spider plot of percent change in target lesions



Q3W, every 3 weeks

CONCLUSIONS

- ADCT-601 had an acceptable safety profile during dose escalation in patients with R/R solid tumors
- Increase in the dose of ADCT-601 increased serum exposure and decreased clearance with moderate interpatient variability
- There is preliminary evidence of activity of ADCT-601 in the 10 patients with response evaluations, with one unconfirmed partial response and five patients with stable disease
- Patients continue to be enrolled into further dose escalation cohorts to identify the recommended dose of ADCT-601

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