A Phase 1 Trial of ADCT-602, a CD22 Targeting Antibody Drug Conjugate Bound to PBD Toxin in Adult Patients with Relapsed or Refractory CD22+ B-Cell Acute Lymphoblastic Leukemia

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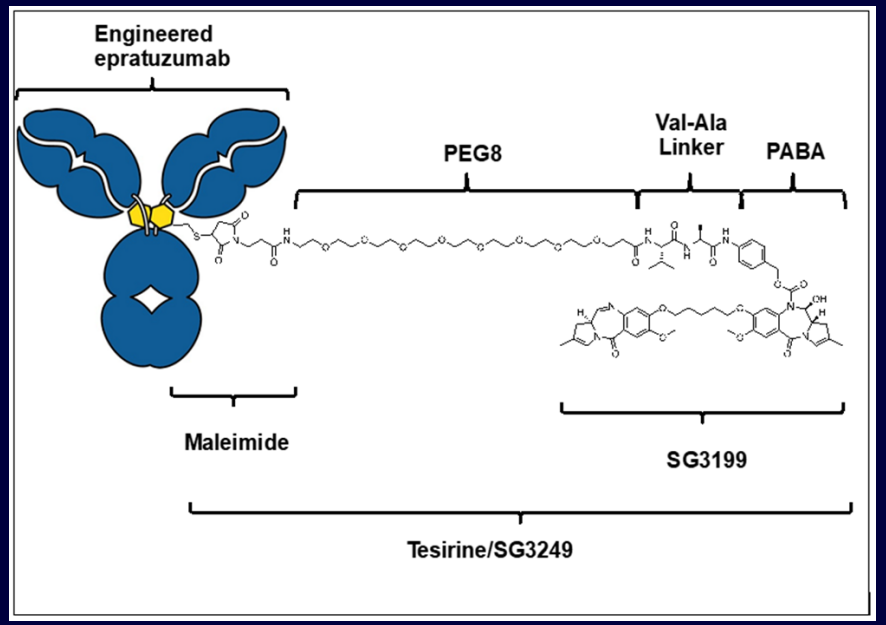
Background

- Outcomes of patients with R/R B-ALL remain dismal, with 5-yr survival <20%
- CD22 is expressed in >90% of pts with B-ALL and is an established therapeutic target
- ADCT-602 is an antibody drug conjugate composed of a humanized monoclonal antibody directed against CD22 and conjugated to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin
- In preclinical studies, ADCT-602 demonstrated potent anti-tumor activity in mouse models of B-cell malignancies
- We present here interim data from an ongoing Phase 1/2 trial evaluating ADCT-602 in pts with R/R B-ALL (NCT03698552)



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Phase I-II Clinical Trial: ADCT-602 in B-ALL

- Investigator-initiated phase I-II trial
- Primary objective
  - Assess the safety and determine the MTD and RP2D of ADCT-602 (Phase 1)
  - Evaluate efficacy (CR/CRi rate) (Phase 2)
- Secondary objectives
  - Duration of response (DOR), PFS and OS
  - Characterize PK profile of ADCT-602

Key Eligibility Criteria

- Age ≥18 years
- Diagnosis of R/R B-ALL with bone marrow blasts ≥5%
- CD22 must be expressed in ≥20% blasts
- Adequate organ function
  - Creatinine ≤1.5 mg/dL
  - ALT and AST ≤2 times upper limit of normal (ULN)
  - Total bilirubin ≤1.5 times ULN
  - LVEF ≥45%

Treatment Plan

Table 1. Planned Dose Levels for ADCT-602 (Q3W and weekly Administration)

Dose Level	*Q3 week Dose of ADCT-602*	*Weekly Dose of ADCT-602*
-1	15 µg/kg	5 µg/kg
1 (starting dose)	30 µg/kg	10 µg/kg
2	60 µg/kg	20 µg/kg
3	90 µg/kg	30 µg/kg
4	120 µg/kg	40 µg/kg
5	150 µg/kg	50 µg/kg

- 3+3 dose-escalation design was used
- ADCT-602 was initially given IV once every 3 weeks (starting dose 30 µg/kg)
- Recently, based on the PK data, the administration schedule was amended to weekly infusions.

Pretreatment Characteristics

- From November 2018 to August 2021, 15 pts with R/R B-ALL were treated with ADCT-602

		n (%) or median [range], N=15
Age, years		**40 [22-82]**
Gender, M		**8 (53)**
No. prior therapies		**4 [2-7]**
	Inotuzumab ozogamicin	**10 (67)**
	Blinatumomab	**14 (93)**
	Venetoclax	**10 (67)**
	CD19 CAR-T	**5 (33)**
	Allo-SCT	**7 (47)**
Pretreatment marrow blasts, %		**77 [16-95]**
CD22 expression on blasts, %		**94 [33.6-100]**

Trial Enrollment and Safety

- Q3 week schedule (n=11)
  - 30µg/kg, n=3
  - 60µg/kg, n=4*
  - 90µg/kg, n=4*
- As PK data indicated rapid clearance of the antibody, the trial was amended to allow for weekly dosing
- Weekly schedule (n=4)
  - 30µg/kg, n=3
  - 40µg/kg, n=1 (dose level currently open for enrollment)

- Safety
  - No pt had a DLT
  - 1 pt (at 30µg/kg weekly dose) had grade 4 thrombocytopenia possibly related to ADCT-602
  - No pt had veno-occlusive disease

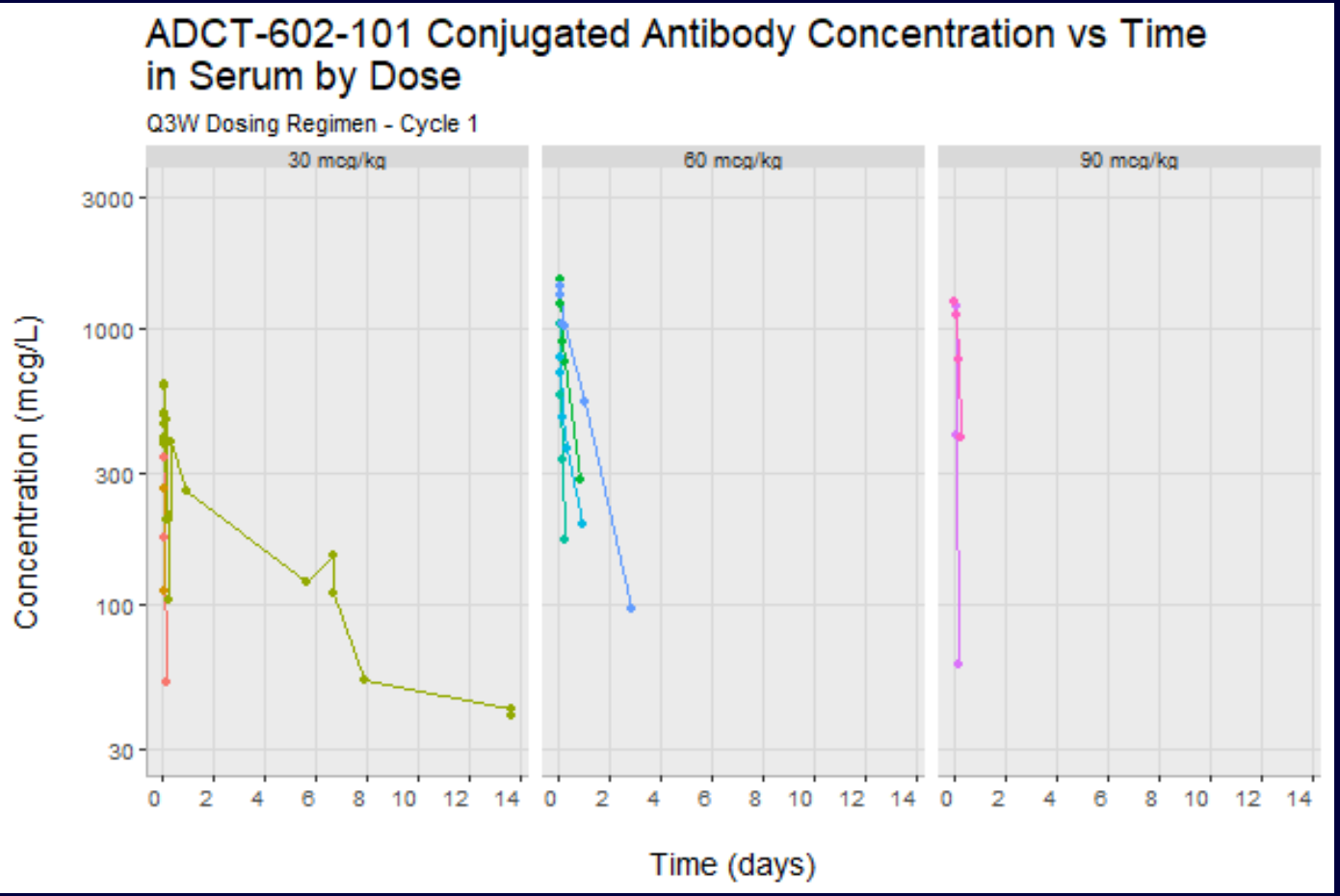
* 2 pts (1 each at 60µg/kg and 90µg/kg Q3 week schedule) did not complete DLT window due to rapid disease progression and were taken off treatment prior to day 28. Both did not experience DLT.

Preliminary Efficacy

Two pts achieved MRD-negative remission

- 35-yr-old with R/R B-ALL (complex karyotype, NRAS mutation)
  - Prior therapies (HCVAD, pegasparaginase-based therapy, allo-SCT, inotuzumab, POMP)
  - Baseline marrow blasts 87%
  - ADCT-602 (30µg/kg Q3W)
  - MRD negative CRp after C1; MRD negative CR after C2
  - Received 6 cycles of ADCT-602 before transitioning to second allo-SCT
- 22-yr-old with R/R B-ALL (complex karyotype)
  - Prior therapies (including 2 prior allo-SCT, CD19 CAR-T, inotuzumab, blinatumomab, pegasparaginase, venetoclax)
  - Baseline marrow blasts 24%
  - ADCT-602 (30µg/kg weekly)
  - MRD negative CRp after C1 and is currently receiving C4

Pharmacokinetic Profile



Conjugated Antibody (Cycle 1)

Parameter	Dose Cohort (mcg/kg, Q3W)		
	30	60	90
C_{max} (mcg/L)	330 (21.2) [3]	1145 (31.0) [4]	1230 (3.45) [2]
AUC_{last} (mcg x day/L)	22.0 (162) [3]	415 (149) [4]	118 (105) [2]
AUC_{inf} (mcg x day/L)	-	459 (435) [2]	-
CL (L/day)	-	8.85 (479) [2]	-
T_{half} (day)	-	0.285 (238) [2]	-
V_{ss} (L)	-	3.27 (44.2) [2]	-

Data denote as Geometric Mean (CV%) [n]

Cmax=maximum observed concentration; AUClast=area under the curve vs. time curve to last measurable time point; AUCinf=area under the curve to infinity; CL=apparent systemic clearance; Thalf=apparent terminal half-life; Vss=volume of distribution at steady-state;

- Mean exposures appear dose-related; high inter-patient variability
- Clearance very rapid; no accumulation by cycle 2
- No substantial differences apparent between Conjugated and Total Ab profiles

Conclusions

- In this Phase 1 study in pts with very heavily pretreated R/R B-ALL with a median of 4 prior lines of therapy and high baseline bone marrow tumor burden, single-agent ADCT-602 was well tolerated with no DLTs noted
- Two pts achieved MRD-negative remission
- Dose escalation continues at 40µg/kg weekly dose level and a subsequent dose level of 50µg/kg weekly is planned