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

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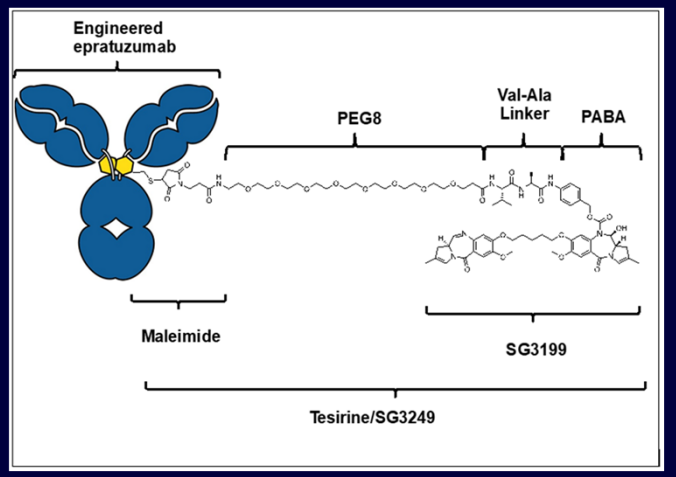
Background

- Outcomes of patients (pts) with R/R B-ALL remain dismal with 5-year survival <20% with chemotherapy
- CD22: expressed in >90% of B-ALL; established target
- ADCT-602: antibody drug conjugate composed of humanized antibody directed against CD22 and conjugated to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin



- ADCT-602 demonstrated potent anti-tumor activity in mouse models of B-cell malignancies
- Loncastuximab (ADCT-402, CD19-directed PBD antibody drug conjugate) is approved for R/R DLBCL and previously investigated in B-ALL
- We present interim data from an ongoing Phase 1/2 trial evaluating ADCT-602 in pts with R/R B-ALL (NCT03698552)

Gokbuget et al. Haematologica. 2016;101(12):1524-1533; Kantarjian et al. N Engl J Med. 2016;375(8):740-53; Gaudio et al. Blood (2020) 136 (Supplement 1): 10-11; Caimi et al. Lancet Oncol. 2021;22(6):790-800; Jain et al. Blood Adv. 2020;4(3):449-457.

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

- Investigator-initiated Phase I-II trial
- Primary objectives
  - 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

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Key Inclusion 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%

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Key Exclusion Criteria

- Known active CNS leukemia
- Isolated extramedullary relapse
- Uncontrolled active infection
- Prior CD22-directed therapy within 3 months
- Allogeneic SCT within 60 days
- Active or severe/extensive chronic GVHD

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Treatment Plan: Dose Levels

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

Currently enrolling dose level

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

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Pretreatment Characteristics

- From November 2018 to September 2022, 24 pts were enrolled

		n (%) or median [range], N=24
Age, years		**34.5 [20-82]**
Gender, F		**12 (50)**
No. prior therapies		**5 [2-9]**
	Blinatumomab	**21 (88)**
	Inotuzumab	**14 (58)**
	Venetoclax	**14 (58)**
	CD19 CAR-T	**11 (46)**
	Allo-SCT	**10 (42)***
Pretreatment marrow blasts, %		**76 [16-96]**
CD22 expression on blasts, %		**96 [33.6-100]**
Genomics		***CRLF2* rearranged, n=4; IGH-EPOR, n=2; SFPQ-ABL1, n=1, PAX5-JAK2, n=1; *TP53* mutated, n=8; *RAS* mutated, n=8**

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* Including 3 pts with 2 prior allo-SCTs

Trial Enrollment Status

- Q3 week schedule (n=11)
  - 30µg/kg, n=3
  - 60µg/kg, n=4*
  - 90µg/kg, n=4*
- Weekly schedule (n=13)
  - 30µg/kg, n=3
  - 40µg/kg, n=4*
  - 50µg/kg, n=6* (dose level currently open for enrollment)

* 4 pts (1 each at 60µg/kg Q3 week, 90µg/kg Q3 week, 40µg/kg weekly, 50µg/kg weekly schedule) did not complete DLT window due to disease progression and were off study prior to end of Cycle 1. None of these 4 pts had a DLT.

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Safety

- One pt at 50µg/kg weekly dose level had a DLT
  - Prolonged myelosuppression with <5% marrow blasts
- One pt at 50µg/kg weekly dose level had grade 3 elevated GGT, possibly related to ADCT-602
- One pt at 30µg/kg weekly dose level had grade 4 thrombocytopenia and grade 4 neutropenia possibly related to ADCT-602
- No pt had VOD

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Preliminary Efficacy

Overall, 4 pts achieved MRD-negative remission

2 pts at 50 µg/kg weekly

- 26-yr-old (PAX5-JAK2 fusion)
  - Prior therapies (COG AALL0232; salvage chemotherapy; CD19 CAR-T x2; allo-SCT)
  - Baseline marrow blasts 80%; CD19 decreased; CD22+ expression 100%
  - MRD+ CR after C1; MRD negative CR after C2
  - Received 8 cycles of treatment
  - Increased GGT (possibly drug-related); course complicated by COVID-19 infection
  - Admitted currently for second allo-SCT while in MRD neg remission for 7+ months
- 66-yr-old (*TP53* mutated, *KRAS* mutated)
  - Prior h/o multiple myeloma; diagnosed with B-ALL while on lenalidomide maintenance
  - Prior therapies (BFM regimen; blinatumomab + anti-PD1)
  - Baseline marrow blasts 27%; CD19 absent; CD22+ expression 100%
  - MRD+ CR after C1; MRD negative CR after C2
  - Received 3 cycles of treatment and underwent allo-SCT while in MRD neg remission. No VOD.

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Preliminary Efficacy

Two pts achieved MRD-negative remission at lower dose levels

- 22-yr-old (complex karyotype) (ADCT-602 30µg/kg weekly)
  - Prior therapies (including pediatric regimen, 2 prior allo-SCT, CD19 CAR-T, inotuzumab, blinatumomab, venetoclax)
  - Baseline marrow blasts 24%; CD22 expression 97%
  - MRD negative CRp after C1; MRD negative CR after C2
  - Grade 4 thrombocytopenia possibly related to ADCT-602
  - Received 4 cycles of ADCT-602.
  - Remission duration 8 months when pt had extramedullary/CNS relapse

- 35-yr-old (complex karyotype, *NRAS* mutation) (ADCT-602 30µg/kg Q3 week)
  - Prior therapies (HCVAD, pegasparaginase-based therapy, allo-SCT, inotuzumab, POMP)
  - Baseline marrow blasts 87%; CD22 expression 99.9%
  - MRD negative CRp after C1; MRD negative CR after C2
  - Received 6 cycles of ADCT-602 before transitioning to second allo-SCT while in MRD neg remission. No VOD.

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Preliminary Efficacy

One additional patient at 50µg/kg weekly dose level had evidence of clinical activity

- 21-yr-old (*TP53* mutated, *KRAS* mutated, complex karyotype)
  - Prior therapies (HCVAD, mini-CVD + inotuzumab, mini-CVD + inotuzumab + venetoclax, CD19 CAR T)
  - Baseline marrow blasts 70%; 53% circulating blasts; CD22+ expression 99%
  - After C1, no morphologic evidence of disease in a hypocellular marrow
  - Patient died on Day 34 from pneumonia and septic shock while still pancytopenic
  - Assessed as DLT (prolonged myelosuppression)

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DLT and Response by Dose Levels

Dose Level	n	DLT, n	CR MRD negative, n (%)
30 µg/kg Q3 week	3	0	1/3 (33%)
60 µg/kg Q3 week	4	0	0
90 µg/kg Q3 week	4	0	0
30 µg/kg weekly	3	0	1/3 (33%)
40 µg/kg weekly	4	0	0
50 µg/kg weekly	6	1	2/6 (33%)*

* One additional pt with clinical activity with blasts <5% without count recovery

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Conclusions

- In this ongoing Phase 1 study in pts with heavily pretreated R/R B-ALL with a median of 5 prior lines of therapy and high baseline bone marrow tumor burden, single-agent ADCT-602 was well tolerated with one DLT noted
- Four pts achieved MRD-negative remission, including 2 of 6 pts at the 50µg/kg weekly dose level; One additional pt at 50µg/kg weekly dose level had marrow blast clearance without count recovery
- Dose escalation continues at 50µg/kg weekly dose level; Phase 2 expansion planned

Acknowledgements

- Department of Leukemia, MDACC
- Department of Hematopathology, MDACC
- Department of Hematology, City of Hope
- IND office, MDACC
- Study funding: ADC Therapeutics
- Patients and their families

Thank you!

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