FIRST-IN-HUMAN STUDY OF AUTOLOGOUS CHIMERIC ENGULFMENT RECEPTOR T-CELL CER-1236 TARGETING TIM-4-L IN ACUTE MYELOID LEUKEMIA (CERTAINT-1)

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Abstract

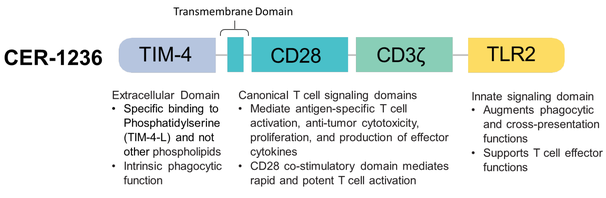
Background:
Acute myeloid leukemia (AML) has high unmet need
- AML is the most common adult acute leukemia.
- Patients with relapsed or refractory (R/R) disease or MRD after treatment have dismal outcomes

CER-1236 is a novel autologous T cell therapy for AML
- A Chimeric Engulfment Receptor (CER) fuses the external domain of TIM-4 with intracellular Toll-like receptor 2 (TLR2), CD28 and CD3ζ.
- CER-1236 binds TIM-4-ligand (phosphatidylserine) on tumor cells leading to phagocytosis, lysis, and cross-presentation to induce an adaptive immune response.
- TIM-4-L is expressed in 88% of primary patient AML samples across mutational subgroups, with significantly higher expression than bone marrow from healthy donors.

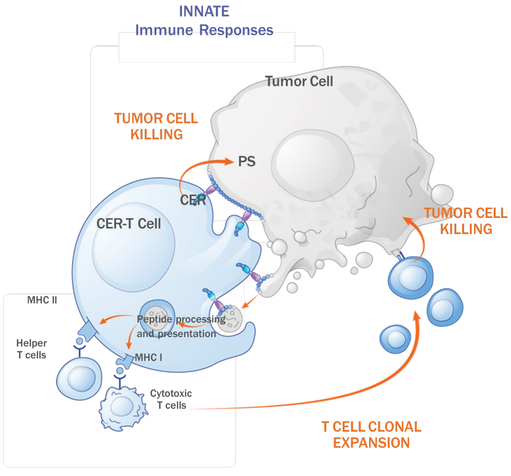
Methods:
CertainT is an open label phase I study to evaluate the safety and preliminary activity of CER-1236 in patients with R/R AML.
- Phase 1 will evaluate 3 doses levels from 1 to 5 x106/kg CER+ T cells using a BOIN dose escalation design.
- Phase 2 will patients in 3 expansion cohorts including R/R AML, TP53 mutated AML, and AML in composite CR (cCR), i.e., CR/CRi/CRh with positive MRD.
- Patients will receive lymphodepleting chemotherapy (LDC) with fludarabine 30 mg/m2/d and cyclophosphamide 400mg/m2/d for 3 days followed by a single infusion of CER-1236 2 days later.

Background

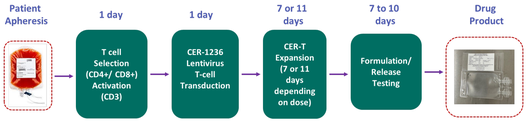
CER-1236 Chimeric Receptor Incorporates T cell Activation Domains and Pro-phagocytic Domains to Target TIM-4-L on Tumor Cells



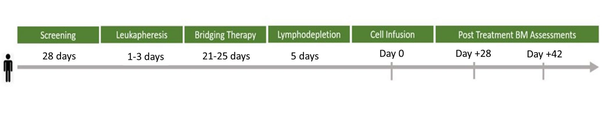
CER-1236 Eliminates Tumor cells using Cytotoxicity and Phagocytosis



CER-1236 T-cell Manufacturing Process Overview

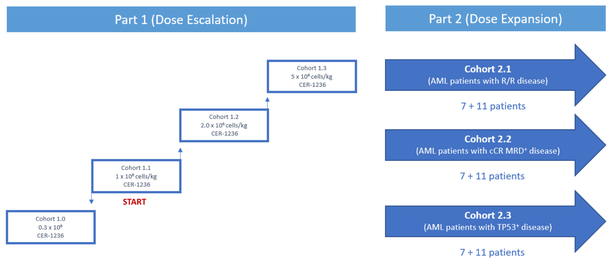


Production on the Miltenyi Prodigy allows for 21d vein-to-vein time



Methods

Trial Design



CertainT-1 Dose escalation and dose expansion trial design. Dose escalation will evaluate 3 doses using a BOIN dose escalation design. Anticipated dose levels are 1, 2, and 5e6 CER-1236+ T cells per kg.

Study Objectives

Primary	Secondary	Exploratory

Part 1:
• Evaluate the safety of CER-1236 by:
  • DLTs
  • TEAEs per CTCAE 5.0
  • CRS, ICANS, AEs of interest
Part 2:
• Estimate the rate of ORR and MRD negativity by:
  • CR, CRh, CRi
  • MRD negativity by flow cytometry
	Part 1:
	• Estimate the ORR, CR, cRD, and MRD negativity rates
	• Evaluate the PK and PD profile of CER-1236
	Part 2:
	• Evaluate the safety of CER-1236
	  • DLTs, TEAEs
	  • CRS, ICANS, AEs of interest
	  • 30- and 60-day mortality
	  • PK
	• Estimate OS and RFS
	• Estimate rate of transition to allo-SCT
		Part 1 & 2:
		• Determine manufacturing success rate
		• Study biomarkers of response and resistance

Inclusion Criteria	Exclusion Criteria
• Patient age >18 and <85 years • ALC >0.3x10^9/L prior to apheresis • ECOG status 0 to 1 • Fewer than 3 prior lines of therapy and 1 allo-SCT • Adequate renal and hepatic function • Must be candidate for allo-SCT with identified donor. • No more than cGVHD grade 1 • Confirmed diagnosis of de novo or secondary AML, or MDS/AML per ICC 2022 or WHO 2022 • Patients with R/R AML, OR • Patients with AML in composite CR (cCR, i.e., CR/CRi/CRh) and detectable, or persistent or recurrent MRD at >0.1% by multiparametric flow cytometry (local laboratory), OR • Patients with newly diagnosed TP53 mutated AML, or 'MDS/AML' per the International Consensus Classification 2022 and can be receiving standard of care therapy.	• Prior therapy with a permanently integrated, genetically modified cell product • APL (t15;17) or t(11;17)(q23;q21) • WBC count >10x10^9/L or peripheral or BM blasts >30% • Active and uncontrolled congestive heart failure • Prior use of any cytotoxic chemotherapy, targeted therapy, antibody-drug conjugates, radiation therapy, immunotherapy, or other investigational therapies within 2 weeks or 5 half-lives, whichever is shorter, prior to leukapheresis.

Dosing

Cohort Name	Dose Level	Dose of CER-1236⁺ cells (x10^6/kg)	Rationale
1.0	DL-1 (optional)	0.3	Fallback dose level in case DL1 exceeds MTD
1.1	DL1 (starting dose)	1.0	
1.1a	DL1a (optional)	1.5	If DL2 exceeds MTD
1.2	DL2	2.0	
1.2a	DL2a (optional)	3.5	If DL3 exceeds MTD
1.3	DL3	5.0	
1.3a	DL3a (optional)	10.0	If DL3 safe and data supports further escalation
1.4	DL4+	Based on data	If DL3a safe and data supports further escalation

Discussion

The first-in-human CertainT-1 trial will test a novel cell therapy, CER-1236, in relapsed and refractory AML patients at MD Anderson Cancer Center and other sites. CER-1236 targets a novel antigen, TIM-4-L, that is upregulated in AML and other malignancies but absent from healthy cells, and employs both cytotoxic and phagocytic mechanisms of killing. Safety and preliminary efficacy will be tested during dose escalation to determine the recommended phase 2 dose and understand other characteristics of CER-1236 cell therapy.

References and Acknowledgements

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