AMELI-01:Preliminary Results from A Phase I Trial of UCART123v1.2, an Anti-CD123 Allogeneic CAR-T Cell Product, in Adult Patients with Relapsed or Refractory (R/R) CD123+ Acute Myeloid Leukemia

David A. Sallman[1], Daniel J. DeAngelo[2], Naveen Pemmaraju[3], Shira Dinner[4], Saar Gill[5], Rebecca Olin[6], Eunice S. Wang[7], Marina Konopleva[3], Eileen Stark[8], Ana Korngold[8], Asifa Haider[8], Kate Backhouse[8], Carolyn Figliola[8], Daniel J. Lee[8], Kathryn Newhall[8], Mark G. Frattini[8], Carrie Brownstein[8], Gail J. Roboz[9]

[1]H. Lee Moffitt Cancer Center, [2]Dana-Farber Cancer Institute, [3]MD Anderson Cancer Center, [4]Northwestern Medical Center, [5]University of Pennsylvania Perelman School of Medicine, [6]University of California San Francisco, [7]Roswell Park Comprehensive Cancer Center, [8]Cellectis, Inc., and [9]Weill Cornell Medical College

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Background and Introduction

- It is estimated that 20,050 new cases and 11,540 deaths related to AML will occur in the US in 2022

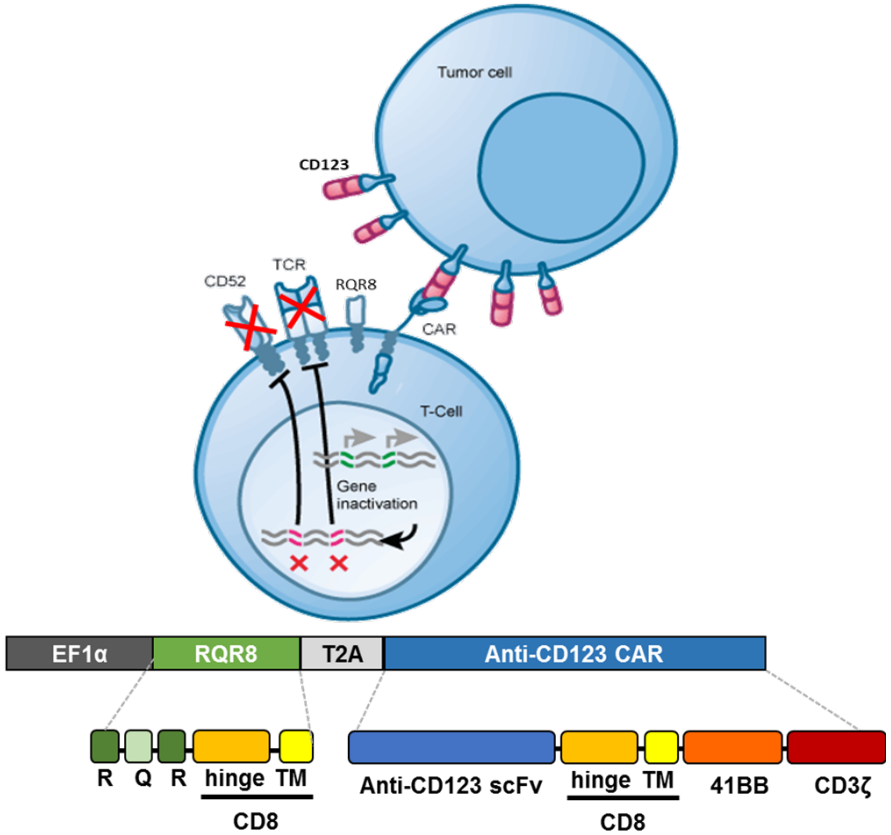
- Outcomes for patients with R/R AML remain poor, with response rates <30% and an expected 5-year overall survival of <15%

- AMELI-01 (NCT03190278) is a phase I, open-label, dose-escalation trial evaluating the safety, tolerability, expansion, and preliminary activity of UCART123v1.2 given at escalating doses after LD with fludarabine and cyclophosphamide (FC) or FC with alemtuzumab (FCA) in patients with R/R CD123+ AML

UCART123v1.2: Allogeneic “Off-the-Shelf” T-cell Product

UCART123v1.2 (anti-CD123 scFv-41BB-CD3ζ):

- CD123 is a validated therapeutic target in AML
- Genetically modified allogeneic T-cell product manufactured from non-HLA–matched healthy donor cells
- *TRAC* disrupted using TALEN® to eliminate TCRαβ from the cell surface and reduce risk of GvHD
- *CD52* disrupted using TALEN® to eliminate sensitivity to LD with alemtuzumab



AML, acute myeloid leukemia; CAR, chimeric antigen receptor; GvHD, graft-vs-host disease; HLA, human leukocyte antigen; LD, lymphodepletion; pts, patients; scFv, single-chain variable fragment; TCR, T-cell receptor; TRAC, T-cell receptor alpha constant; TALEN ®, Transcription Activator-Like Effector Nuclease.

AMELI-01 Study Design

Key inclusion criteria

- Relapsed or primary refractory AML (≥5% bone marrow blasts)
- Blasts expressing CD123
- PS of ≤1 and adequate organ function

Primary objective

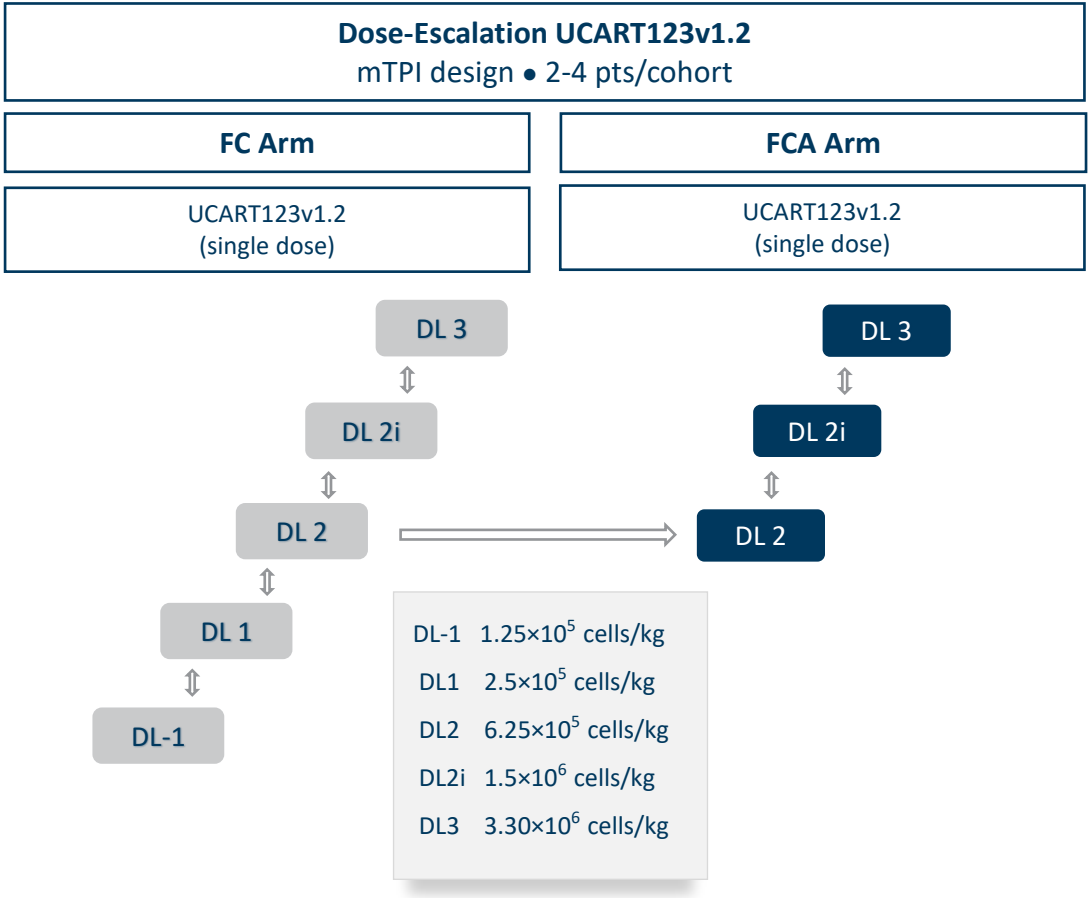
- Safety, tolerability, & MTD/RP2D of UCART123v1.2

Additional objectives

- Investigator-assessed response
- UCART123v1.2 expansion, trafficking, persistence in PB and BM
- Immune reconstitution

LD regimens:

- **FC:** Fludarabine 30 mg/m²x 4d + Cyclophosphamide 750 mg/m² x 3d
- **FCA:** Fludarabine 30 mg/m²x 4d + Cyclophosphamide 750 mg/m² x 3d + Alemtuzumab 12 mg/day x 4d



Baseline Characteristics

Characteristic	Total (N = 18*)
Age, median (range), years	57 (18-64)
Female, n (%)	8 (44)
ECOG PS 1, n (%)	17 (94)
ELN 2017 Classification, n (%)	
Adverse risk	14 (78)
Intermediate risk	3 (17)
Median baseline bone marrow blasts % (range)	37 (0-88)
Number of prior treatments, median (range)	4 (3-9)
Prior HSCT, n (%)	9 (50)
Cytogenetic and Molecular Abnormalities, n (%)	
TP53	6 (33)
FLT3-ITD	2 (11)
ASXL1	3 (17)
RUNX1	2 (11)
MECOM (EVI1)	2 (11)
MLL/KMT2A	1 (6)
Monosomal karyotype	3 (17)

*17 of the 18 pts who received LD with FC or FCA were treated with UCART123v1.2.
ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European Leukemia Net; FC, fludarabine + cyclophosphamide; FCA, FC + alemtuzumab; HSCT, hematopoietic stem cell transplantation; LD, lymphodepletion.

UCART123v1.2 - Related TEAEs (FC + FCA)

TEAE, n	FC		FCA		FC + FCA	
	FC Total [n=8] DL1=2; DL2=3; DL2i=2; DL3=1		FCA Total [n=9] DL2=8; DL2i=1		All patients N=17*	
	Any grade	Gr ≥3	Any grade	Gr ≥3	Any grade	Gr ≥3
CRS	8	2	9	2 ✿	**17**	**4**
HLH	1	1	1	0	**2**	**1**
ICANS	1	1	1	0	**2**	**1**
ALT increased	4	1	1	1	**5**	**2**
AST increased	4	1	1	1	**5**	**1**
Blood fibrinogen decreased	0	0	2	0	**2**	**0**
DIC	0	0	1	0	**1**	**0**
Confused state	1	0	1	0	**2**	**0**
Fatigue	2	0	0	0	**2**	**0**
Acute kidney injury	0	0	1	1	**1**	**1**
Bacterial infection	0	0	1	1	**1**	**1**
INR increased	0	0	1	1	**1**	**1**
Lymphocyte count decreased	0	0	1	1	**1**	**1**
Pulmonary edema	0	0	1	1	**1**	**1**
Sinus bradycardia	1	1	0	0	**1**	**1**
Vasogenic cerebral edema	1	1	0	0	**1**	**1**

DL, dose level; FC, fludarabine + cyclophosphamide; FCA, FC + alemtuzumab; GvHD, graft-vs-host disease; TEAE, treatment-emergent adverse event.; CRS, cytokine release syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell associated neurotoxicity syndrome; DIS, disseminated intravascular coagulopathy; INR, international normalized ratio

*As of Oct. 10, 2022, 18 patients received LD, 17 received UCART123v1.2

✿ 2 Grade 5 events related to CRS

UCART123v1.2 - Serious TEAEs (All Cause – FC + FCA)

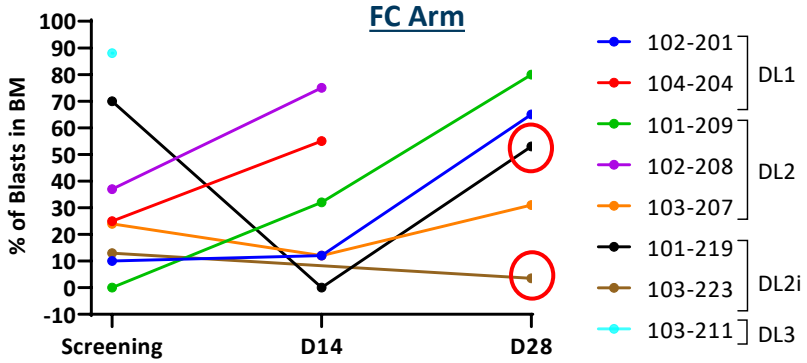
Serious TEAE, n (%)	FC		FCA		FC + FCA	
	FC Total [n=8] DL1=2; DL2=3; DL2i=2; DL3=1		FCA Total [n=9] DL2=8; DL2i=1		**Total patients N=17***	
	Any grade	Gr ≥3	Any grade	Gr ≥3	**Any grade**	**Gr ≥3**
CRS	3	2	2	2 ✿	**5**	**4**
ICANS	1	1	0	0	**1**	**1**
Pneumonia	1	1	1	1	**2**	**2**
Pneumonia fungal	2	2	0	0	**2**	**2**
Febrile neutropenia	0	0	1	1	**1**	**1**
Fungemia	0	0	1	1	**1**	**1**
Hemorrhage intracranial	0	0	1	1	**1**	**1**
Large intestinal hemorrhage	1	1	0	0	**1**	**1**
Pericardial effusion	1	1	0	0	**1**	**1**
Septic shock	1	1	0	0	**1**	**1**

DL, dose level; FC, fludarabine + cyclophosphamide; FCA, FC + alemtuzumab; TEAE, treatment-emergent adverse event; CRS, cytokine release syndrome; ICANS, immune effector cell associated neurotoxicity syndrome

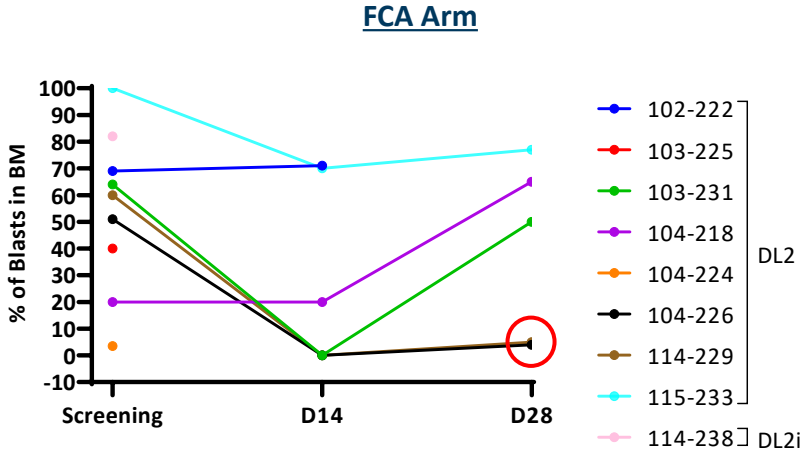
* As of Oct. 10, 2022, 18 patients received LD, 17 received UCART123v1.2

✿ 2 Grade 5 events related to CRS

Anti-Leukemic Activity Observed in 4/17 Patients at DL2 and Above



- FC arm
  - Patient **101-219** (DL2i): SD
  - Patient **103-223** (DL2i): MLFS

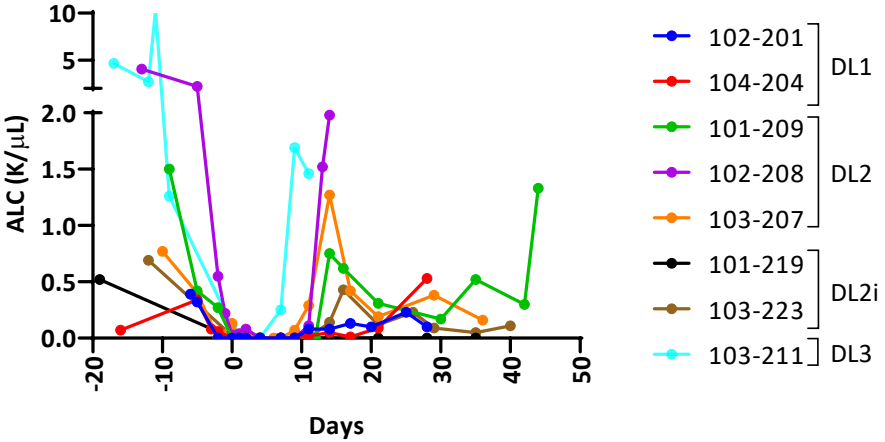


- FCA arm
  - Patient **114-229** (DL2): SD
    - Achieved greater than 90% BM blast reduction (60% to 5%) at D28
  - Patient **104-226** (DL2): MRD negative CR
    - Achieved CRi at D28 followed by MRD negative CR at D56

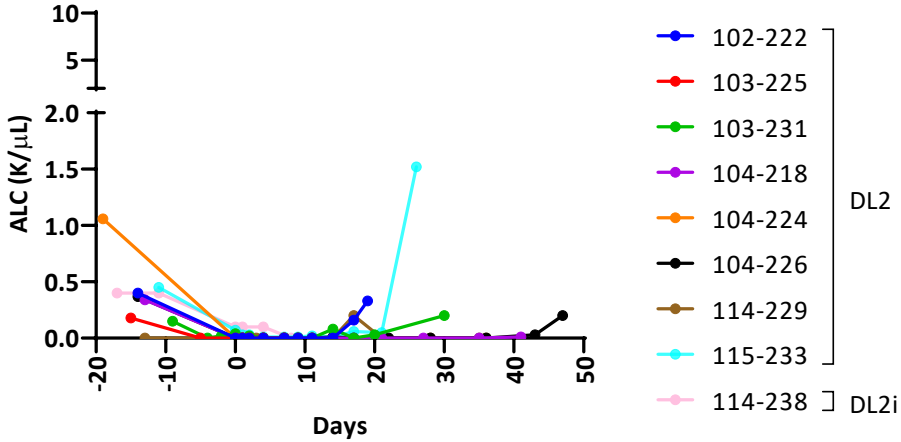
Addition of Alemtuzumab Results in Prolonged Lymphodepletion

Absolute Lymphocyte Counts

FC Arm

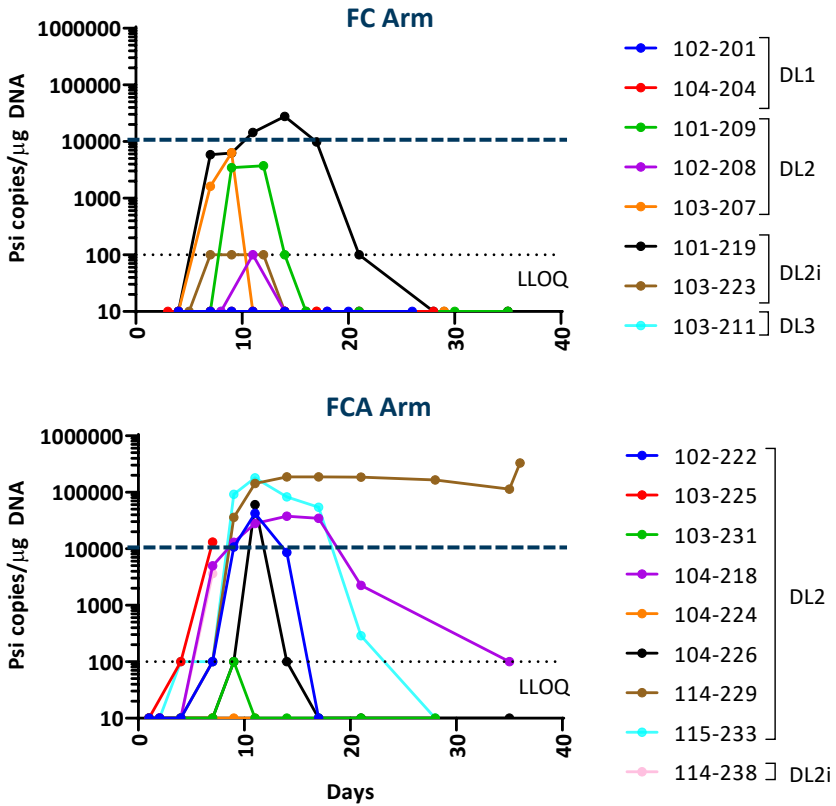


FCA Arm

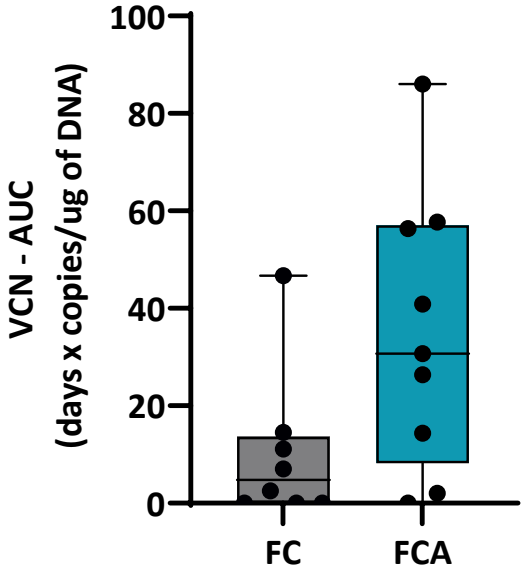


Addition of Alemtuzumab Results in Increased UCART123v1.2 Expansion

UCART123 Cell Expansion in WB by VCN

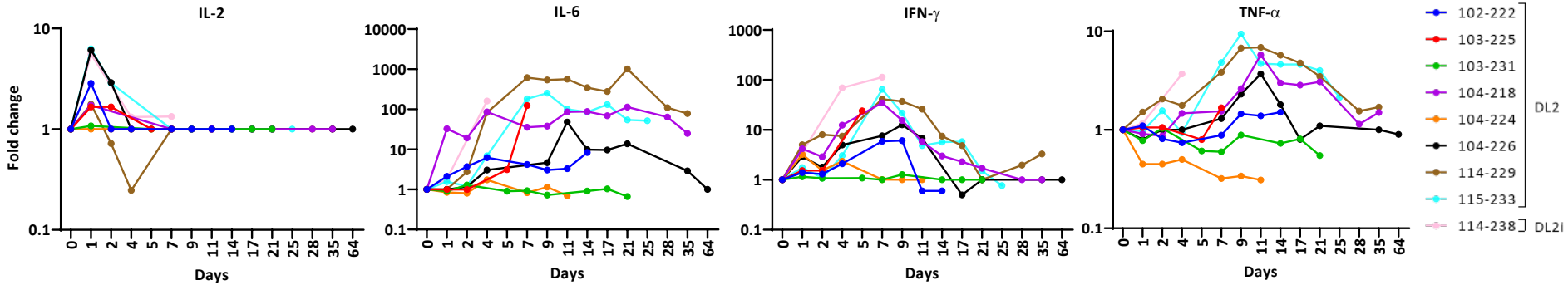


VCN AUC(0-28days)

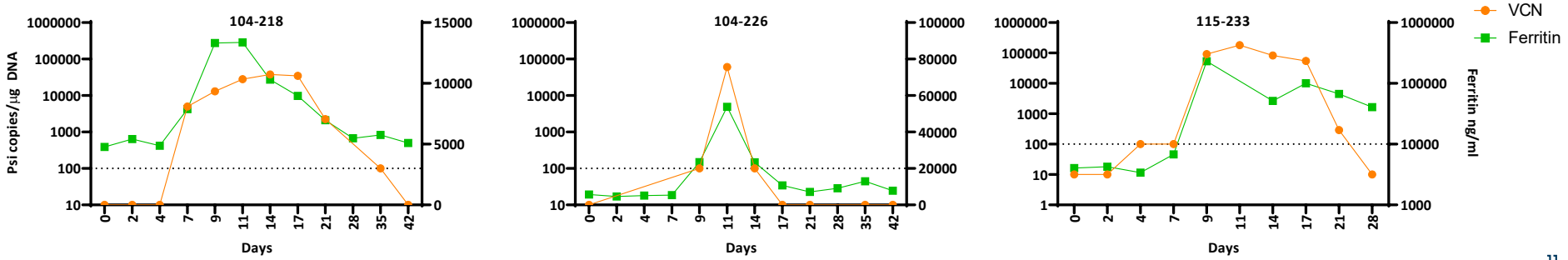


Cytokine Secretion and Ferritin Levels Correlated with UCART123v1.2 Cell Expansion

Cytokine Profile of All Patients from FCA Arm



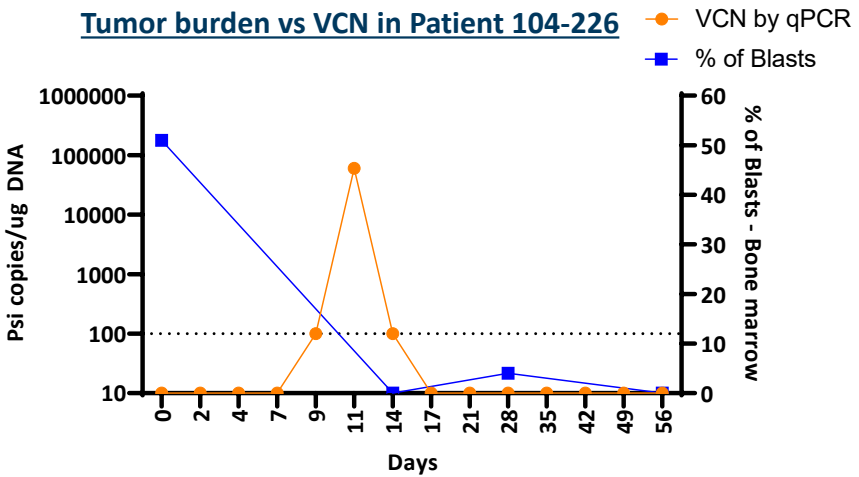
Ferritin vs VCN in Select Patients from FCA Arm



Patient 104-226 Achieved a Durable MRD Negative CR

Clinical Characteristics	
Age, Race, Sex	64 year old white female
ECOG	1
ELN 2017 Classification; WHO Classification	Adverse risk; AML with myelodysplasia-related changes
Cytogenetic and Molecular Abnormalities	45,XX,-7,t(10;12)(q24;p13)[5]; IDH1, EZH2
Number of prior treatments	5 - including allogeneic HSCT 2016
Past Medical History	MDS, 2011; Focal nodular hyperplasia of the liver, 2016

Response Summary	BM Biopsy Blast %	BM Aspirate Blast %	MRD	ELN Response
Screening Day -14	51%	Not done		
Day 14	0%	Not done		
Day 28	3.8%	4%	Pos 0.6%	CRi
Day 56	2.8%	0%	Neg	CR
Day 84	0%	0%	Neg	CR
FU 1, Day 181	2%	0%	Neg	CR
FU 2, Day 270	1%	0%	Neg	CR
FU 3, Day 365	0%	0%	Neg	CR

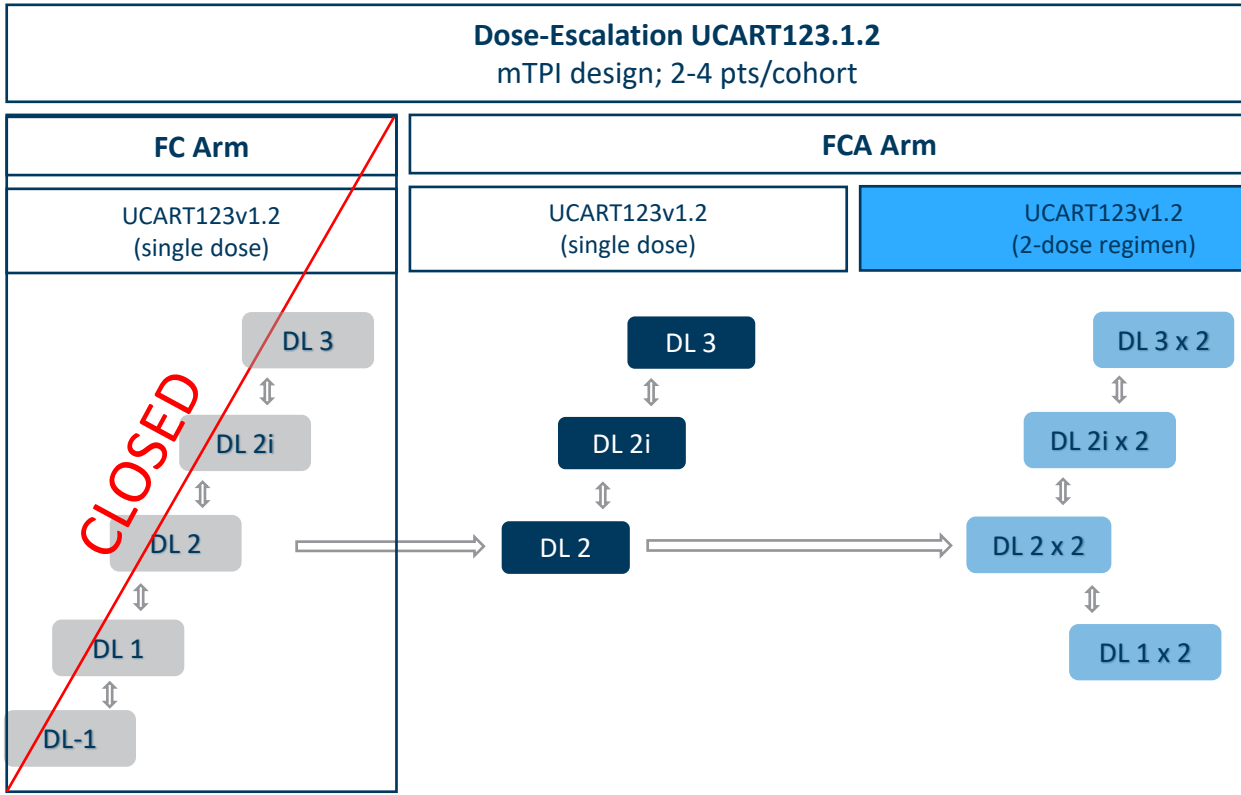


MDS myelodysplastic syndrome; HSCT Hemopoietic stem cell transplant; MRD minimal residual disease; CRi compete response with incomplete hematologic recovery; CR complete response

Translational Data From Patient 104-226 and Others Supports Use of a Two-Dose Regimen of UCART123v1.2

- UCART123v1.2 expansion correlates with reduction in tumor burden at DL2 (6.25×10^5 cells/kg) but at this dose, UCART123v1.2 cell function is not sufficient for sustained anti-leukemic activity in all patients
- A second dose would then be given to allow for additional UCART123v1.2 expansion and clinical activity after 10-14 days without the use of additional lymphodepletion
- The second peak of expansion in the setting of reduced disease burden should be safe and allow for clearance of residual disease
- The 2-dose regimen will initiate at DL2, a dose that has already been administered and cleared for safety as a single dose, and incorporate the use of prophylactic tocilizumab

AMELI-01 Amended Protocol with Two-Dose Regimen Design



UCART123.v1.2	
DL-1	1.25×10^5 cells/kg
DL1	2.5×10^5 cells/kg
DL2	6.25×10^5 cells/kg
DL2i	1.5×10^6 cells/kg
DL3	3.30×10^6 cells/kg

Conclusions

- Adding alemtuzumab to the FC regimen was associated with improved LD and significantly higher UCART123v1.2 cell expansion, which correlated with improved activity and cytokine profiles
  - ➢ One patient in the DL2 FCA arm achieved >90% blast reduction at Day 28
  - ➢ One patient in the DL2 FCA arm achieved a long term durable MRD negative CR (now past 12 months)
- Overall, these data support further study of UCART123v1.2 after FCA LD in pts with R/R AML
- Based on observed UCART123v1.2 expansion patterns and cytokine profiles, the study will be enrolling patients in the FCA 2-dose regimen arm

Acknowledgments

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- For questions or comments, please contact Dr. David A. Sallman: David.Sallman@moffitt.org
- For more information, please contact clinicaltrials@cellectis.com

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