Safety and Efficacy of UCART22 in Heavily Pretreated Patients with Relapsed or Refractory CD22+ B-Cell Acute Lymphoblastic Leukemia (B-ALL): Results from the Phase 1 BALLI-01 Trial

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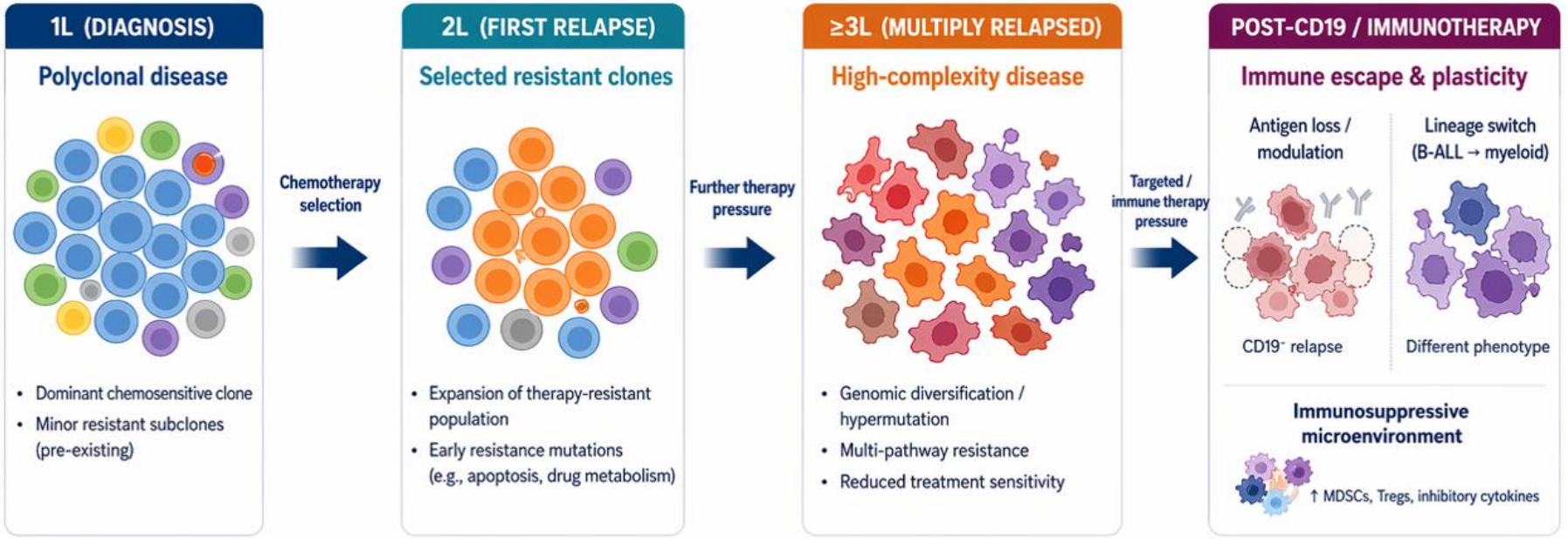
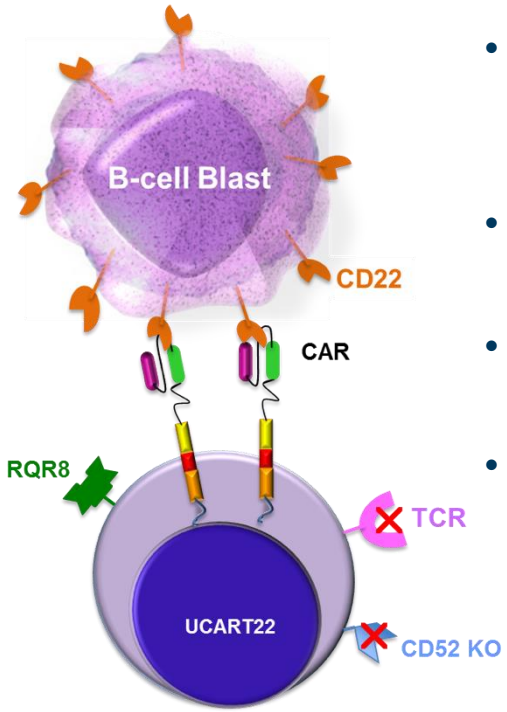
Background: 3L and Beyond B-ALL

- B-cell Acute Lymphoblastic Leukemia (B-ALL) in the third-line (3L) setting and beyond represents an area of significant unmet clinical need
  - Highly aggressive disease biology
  - Enriched for resistance mutations
  - Lack of standard-of-care treatments
- Few patients in late line become eligible for potentially curative allogeneic stem cell transplant
- CD22 remains a viable target in R/R B-ALL



UCART22: Allogeneic CD22 CAR T

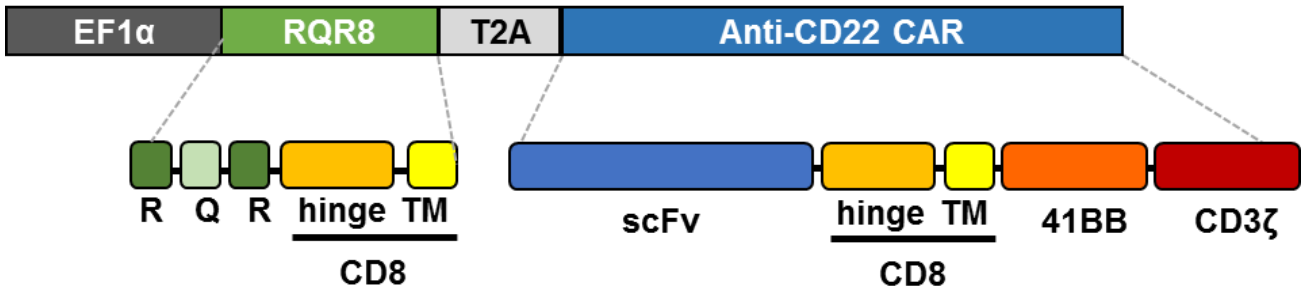


- CD22 CAR expression to redirect T-cells to tumor antigens
- Rituximab mimotope (RQR8)

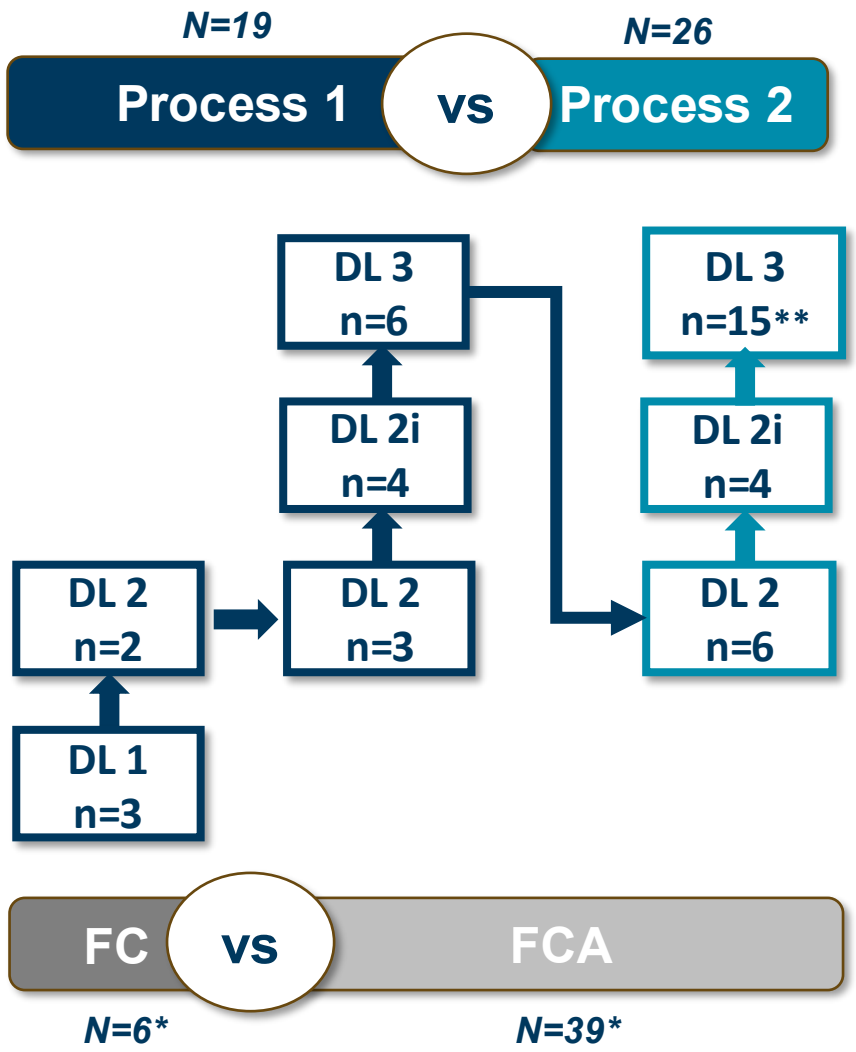
Lentiviral vector

- TRAC disruption using TALEN® to eliminate TCR from the cell surface and avoid GvHD
- CD52 disruption using TALEN® to eliminate sensitivity to the lymphodepletion agent alemtuzumab

mRNA electroporation



BALLI-01 Study Design



UCART22 Dose Level:
DL1: 1×10^5 cells/kg
DL2: 1×10^6 cells/kg
DL2i: 2.5×10^6 cells/kg
DL3: 5×10^6 cells/kg

Process 1 (P1): manufactured by external CDMO
Process 2 (P2): manufactured by Cellectis

2 lymphodepletion schedules were assessed

- **FC:** Fludarabine (F), 30 mg/m^2/d for 4 days
  Cyclophosphamide (C), 1 g/m^2/d for 3 days
- **FCA:** Fludarabine (F), 30 mg/m^2/d for 3 days
  Cyclophosphamide (C), 500 mg/m^2/d for 3 days
  Alemtuzumab (A), IV, 60 mg total (flat dose) over 3 days

** low alemtuzumab weight-based dose was assessed in 5 patients in a sub-study

- **FCA-W:** Fludarabine (F), 30 mg/m^2/d for 3 days
  Cyclophosphamide (C), 500 mg/m^2/d for 3 days
  Alemtuzumab (A), IV, 0.7 mg/kg capped at 48 mg over 3 days

*1 Patient from both FC (P1) and FCA (P2) cohorts did not receive UCART22 (due to infections)

BALLI-01 Phase Study Design

Key Inclusion Criteria

- Age 15-70 years, adequate organ function (for sub study age ≤ 50)
- ECOG PS ≤1
- Measurable or evaluable disease in the BM of at least 0.01% blasts or non-CNS extramedullary disease (for alemtuzumab weight-based sub study ≥5% marrow blasts)
- % of B-ALL blast expressing CD22 >70%
- ≥2 prior lines

Key Objectives

- To assess the safety of UCART22 and alemtuzumab
- To define the RP2D of UCART22
- To assess the response
- To define the need for alemtuzumab in LD regimen
- To assess alemtuzumab PK

Exploratory Objectives

- To assess UCART22 expansion and persistence
- To assess MRD status in responders

Baseline Demographic and Clinical Characteristics (N=45)

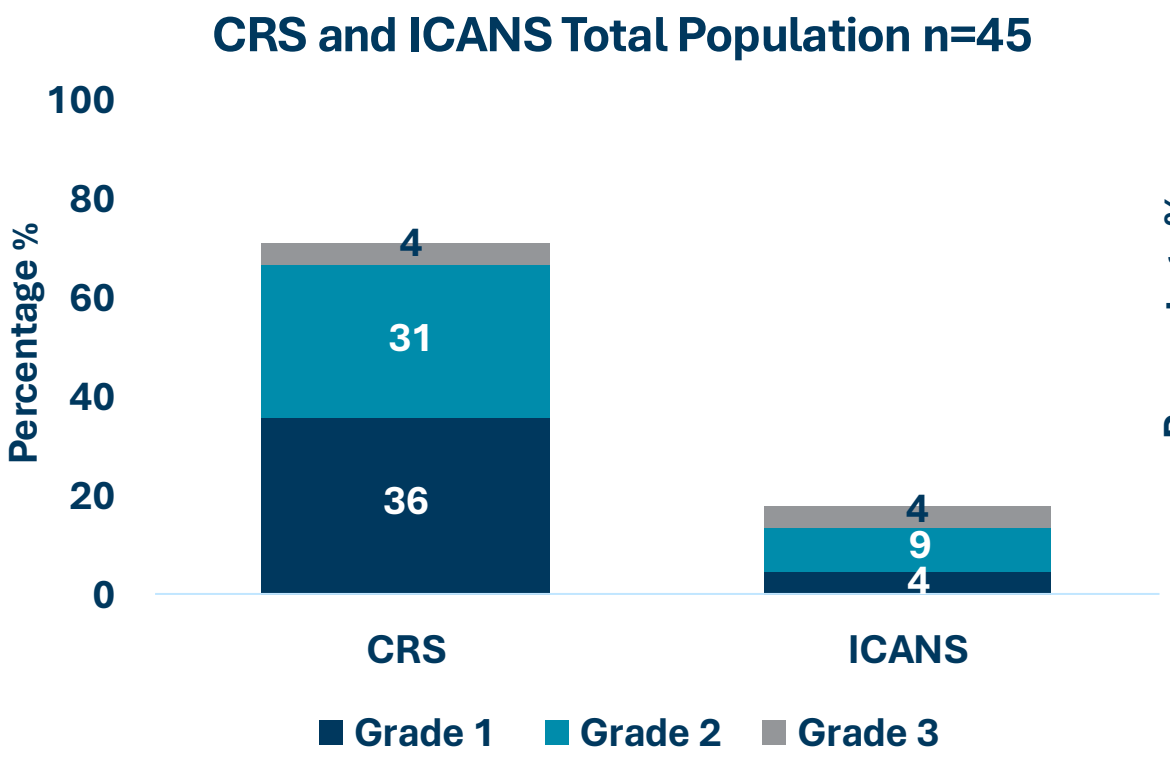
Summary	P1 n=19	P2 n=26	TOTAL N=45
Age (yrs), median (range)	**28.5 (17-61)**	**28 (16-68)**	**28 (16-68)**
Sex			
Male, n (%)	11 (55)	14 (56)	25 (55.6)
Female, n (%)	8 (42)	12 (46)	20 (44.4)
ECOG			
ECOG 0, n (%)	6 (30)	8 (32)	14 (31.1)
ECOG 1, n (%)	13 (68)	15 (58)	28 (62.2)
ECOG missing, n (%)	0 (0)	3 (12)	3 (6.7)
Ph+ B-ALL	1 (5)	3 (12)	4 (9)
Number of prior treatments, median (range)	**3 (2-6)**	**4 (2-11)**	**4 (2-11)**
Prior HSCT, n (%)	8 (42)	13 (50)	21 (46.7)
Prior blinatumomab, n (%)	12 (63)	25 (96)	37 (82.2)
Prior inotuzumab, n (%)	10 (50)	14 (56)	24 (53.3)
Prior CD19 CAR T-cell therapy, n (%)	8 (42)	15 (57)	23 (51.1)
BM blasts % at screening, median (range)	**41.2 (1-99)**	**71 (1-98)**	**64 (1-99)**
BM blasts <5%, n (%)	3 (15%)	1 (4%)	4 (9%)

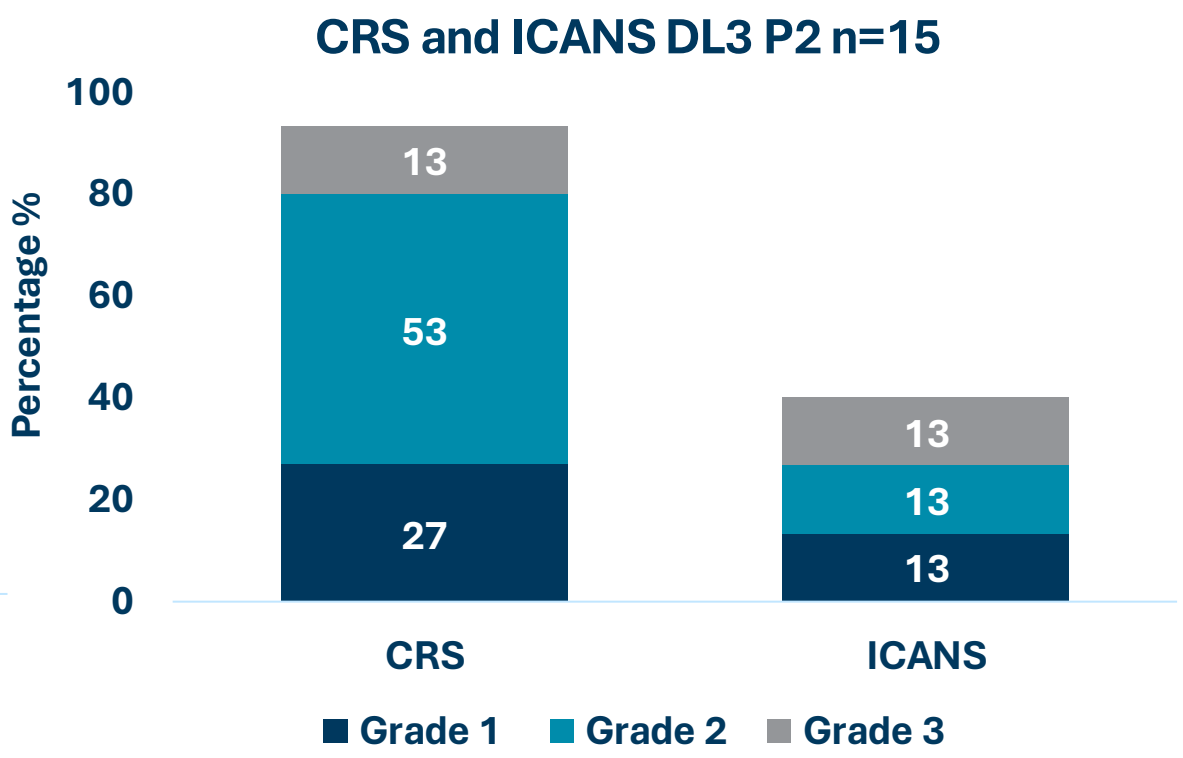
Baseline Demographic and Clinical Characteristics DL3 Cohort (P2), n=15

	DL3 P2 n=15 (%)	Target Phase 2 population, (age ≤50) n=12 (%)	
		Main study n=7 (%)	**Sub-Study** Alemtuzumab weight-based dosing n=5 (%)
Age (yrs), median (range)	**28 (16-66)**	**23 (16-30)**	**39 (23-45)**
Sex			
Male, n (%)	7 (46.7)	3 (42.9)	2 (40)
Female, n (%)	8 (53.3)	4 (57.1)	3 (60)
ECOG			
0, n (%)	5 (33.3)	4 (57.1)	0 (0)
1, n (%)	9 (60)	2 (28.6)	5 (100)
missing, n (%)	1 (6.7)	1 (14.3)	0 (0)
Number of prior treatments, median (range)	**5 (2-11)**	**5 (4-6)**	**5 (3-11)**
Prior HSCT, n (%)	6 (40)	3 (42.9)	3 (60)
Prior blinatumomab, n (%)	14 (93.3)	7 (100)	4 (80)
Prior inotuzumab, n (%)	8 (53.3)	3 (42.9)	3 (60)
Prior CD19 CAR T-cell therapy, n (%)	7 (46.7)	3 (42.9)	3 (60)
BM Blasts % at screening, median (range)	**66.6 (14-98)**	**62.5 (14-72.8)**	**79.9 (50-98)**

* 3 patients out of 15 in DL3 P2 were >50 years old

Low Incidence of Grade ≥3 CRS and ICANS





- No grade 4 or 5 CRS or ICANS
- Median time to onset from UCART22 infusion, median (range)
  - CRS: onset 4 days (1-22) / duration: 2.5 days
  - ICANS: onset 3.5 days (1-12) / duration: 2 days

ICANS: Immune effector cell-associated neurotoxicity syndrome
CRS: Cytokine release syndrome

UCART22 | Related SAEs

SAE	Cohort	Grade	# of events
Cytokine release syndrome	DL3	3	2
	DL2	2	1
Graft versus host disease in skin	DL2i	2	1
Hemophagocytic lymphohistiocytosis	DL3	4	1
Hydrocephalus	DL2	3	1
Immune effector cell-associated neurotoxicity syndrome	DL3	3	2
Multiple organ dysfunction syndrome*	DL3	5	1
Platelet count decreased	DL2	4	1
Sepsis	DL2	5	1
Total	**11 events in 8 subjects**		

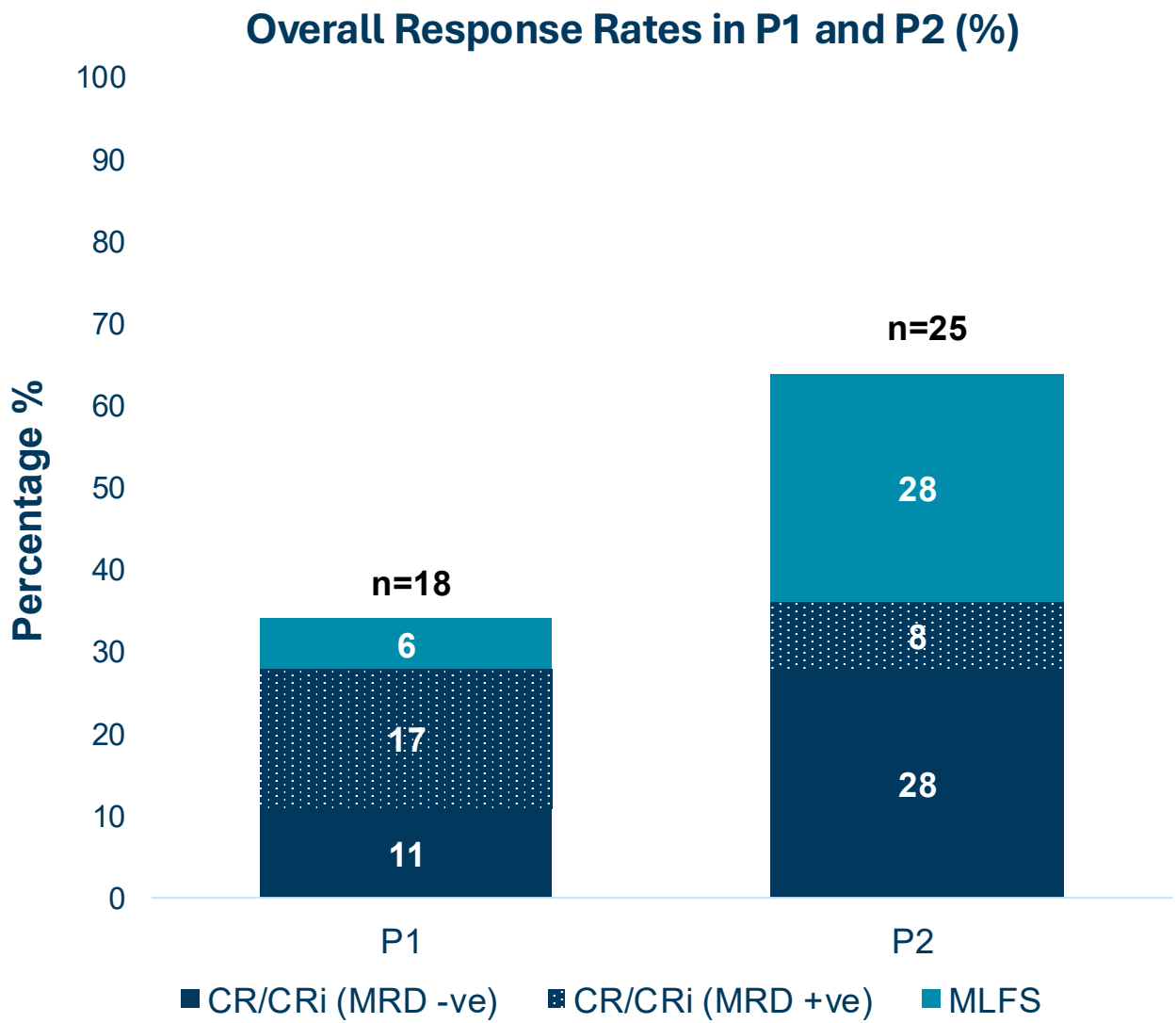
- **Dose Limiting Toxicity**

SAE: Serious Adverse Event – SAEs and related only.

Infections & Viral reactivations

Bacterial infections Grade ≥ 3	N of patients	Related to LD	Related to UCART22
Total	**9**	**4**	**-**
Local infections (cystitis, cellulitis, perineal, orbital)	5	3	-
Bacteremia	4	-	1
Fungal infections Grade ≥ 3			
Total (aspergillosis, tracheitis, sinusitis)	**6**	**2**	-
Grade 5	5	1 (aspergillus)	-
Viral infections/reactivations			
Total	**20**	**13**	-
CMV infections (grade 1 and 2)	4	4	-
ADV infections (grade 1 and 2)	2	2	-
Herpes/reactivations (grade 1-3)	6	4	-
Other viral infections (grade 1 and 2)	8	3	-
Viremia (PCR)	**23**	-	-
CMV HHV6	9 14	-	-
Sepsis/Septic shock Grade ≥ 3			
Total	**12**	**3**	**1**
Bacterial	2	-	-
Agent not defined	10	3	1
Grade 5	**3**	1	1

Higher Response Rates in P2



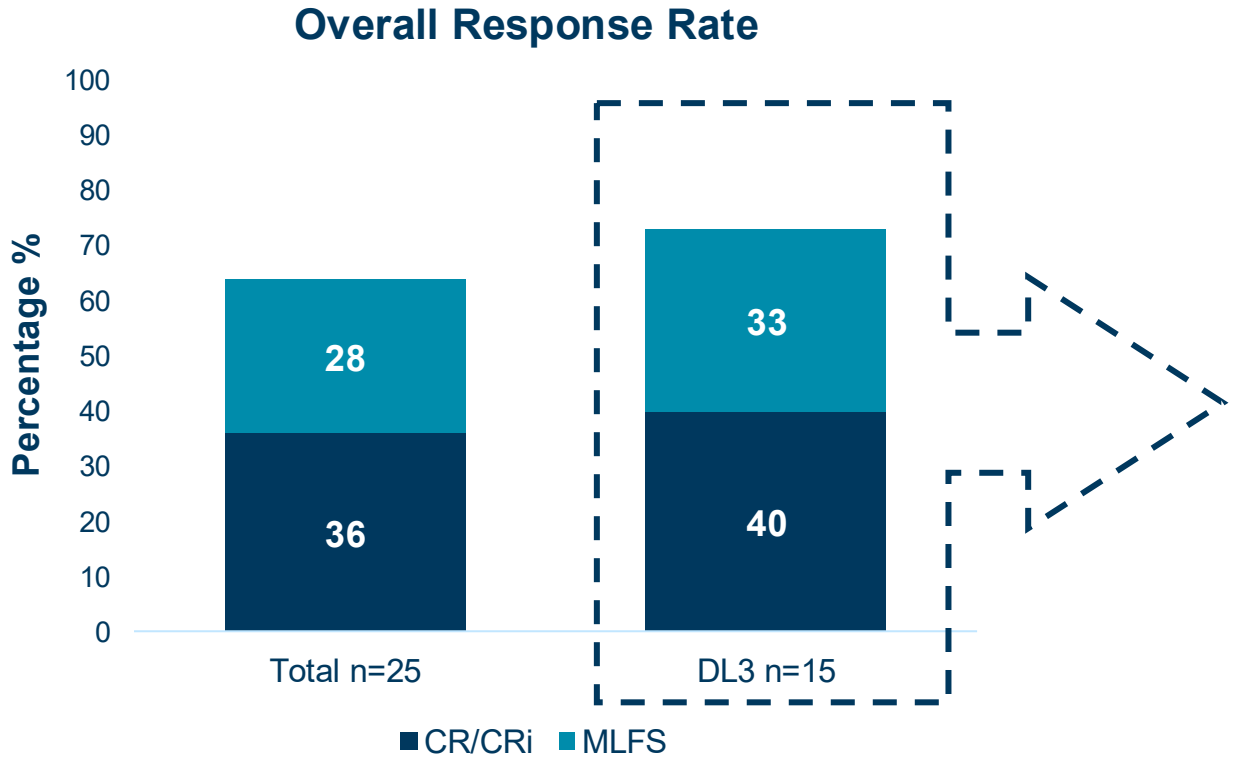
P1 manufactured by external CDMO
P2 manufactured Internally

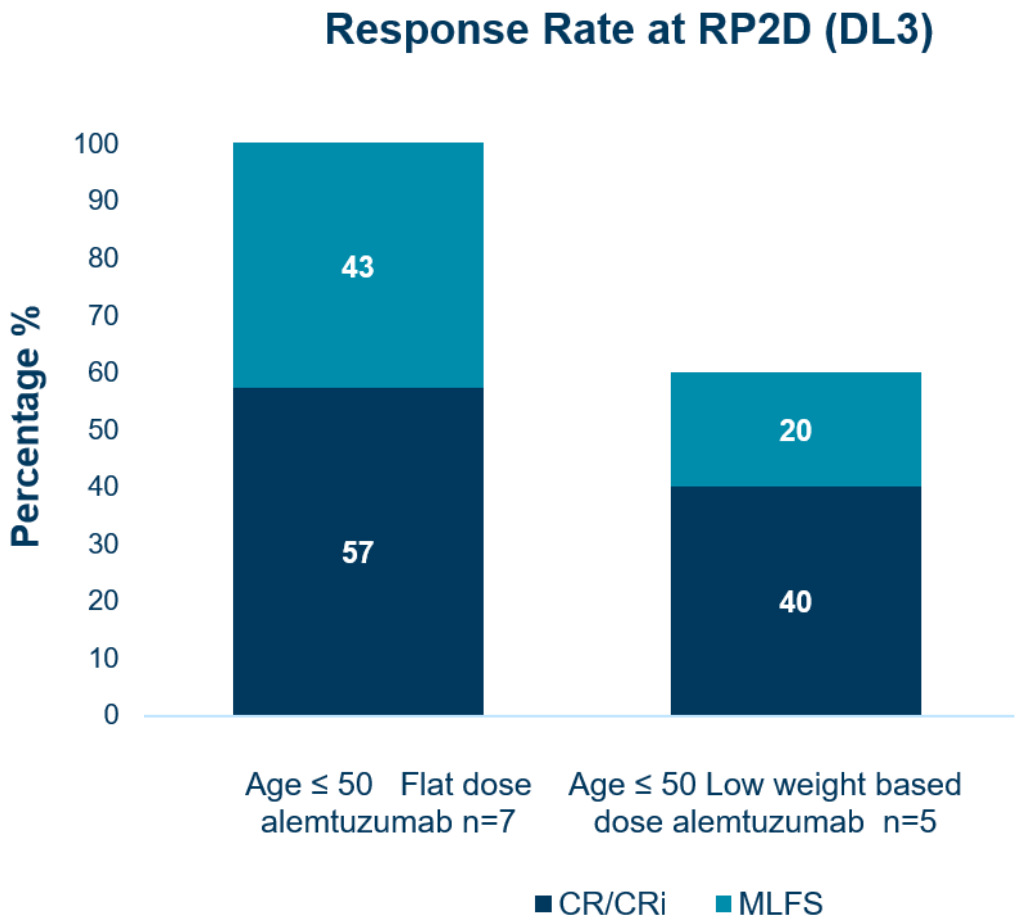
- **36%** of P2 achieved **CR/CRi**
  - **P2: 78%** of CR/CRi achieved **MRD neg (flow)**

CR/CRi - Complete remission/complete remission with incomplete hematologic recovery
MLFS - Morphologic leukemia-free state

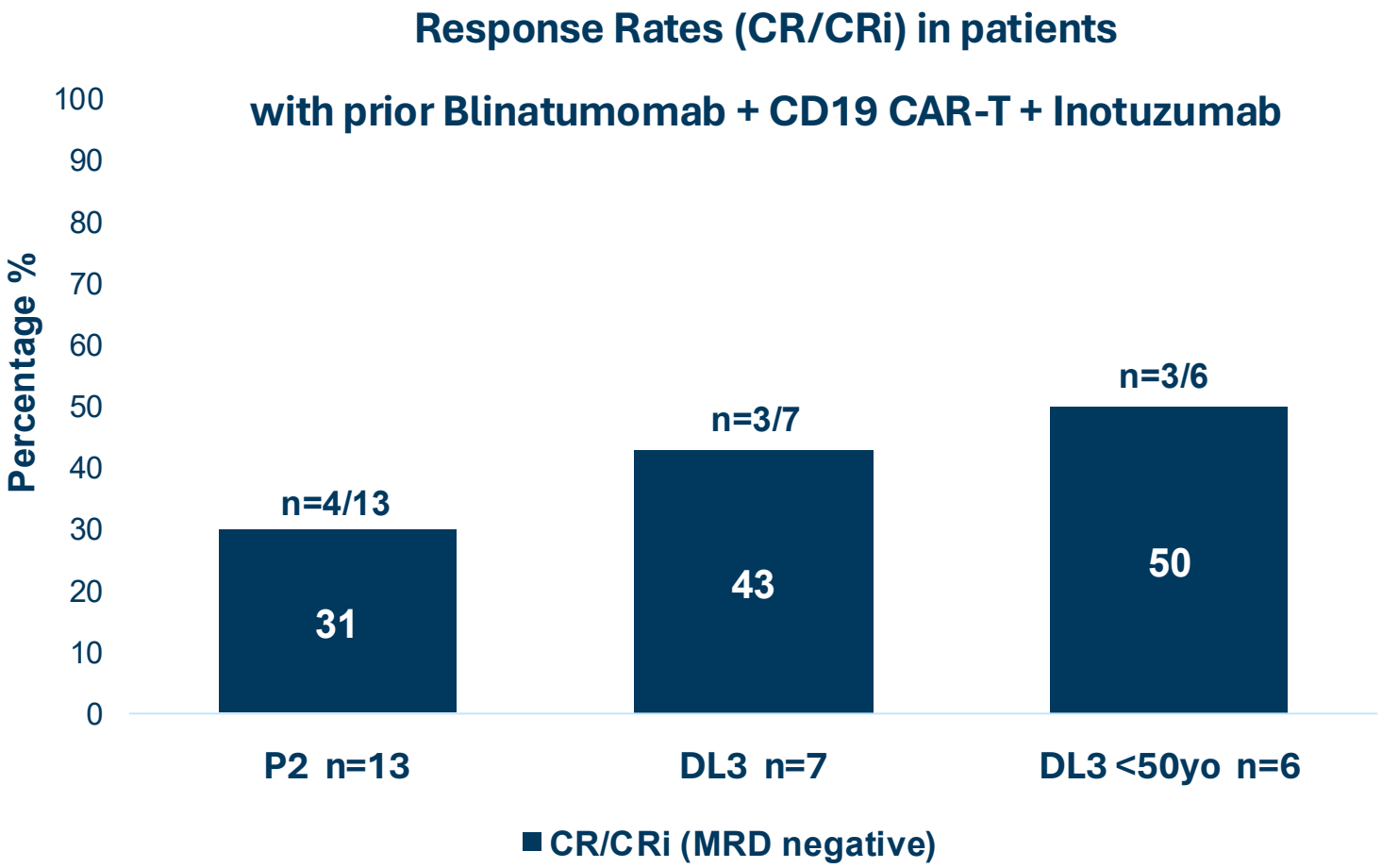
Higher Response Rates at P2 Dose Level 3

- Low weight-based dose of alemtuzumab evaluated in advance of Phase 2 dose optimization
- Required for Project Optimus





Clinically meaningful CR/CRi Rates in P2 Patients Prior Exposed to Targeted Therapies Blinatumomab + CD19 CAR-T + Inotuzumab



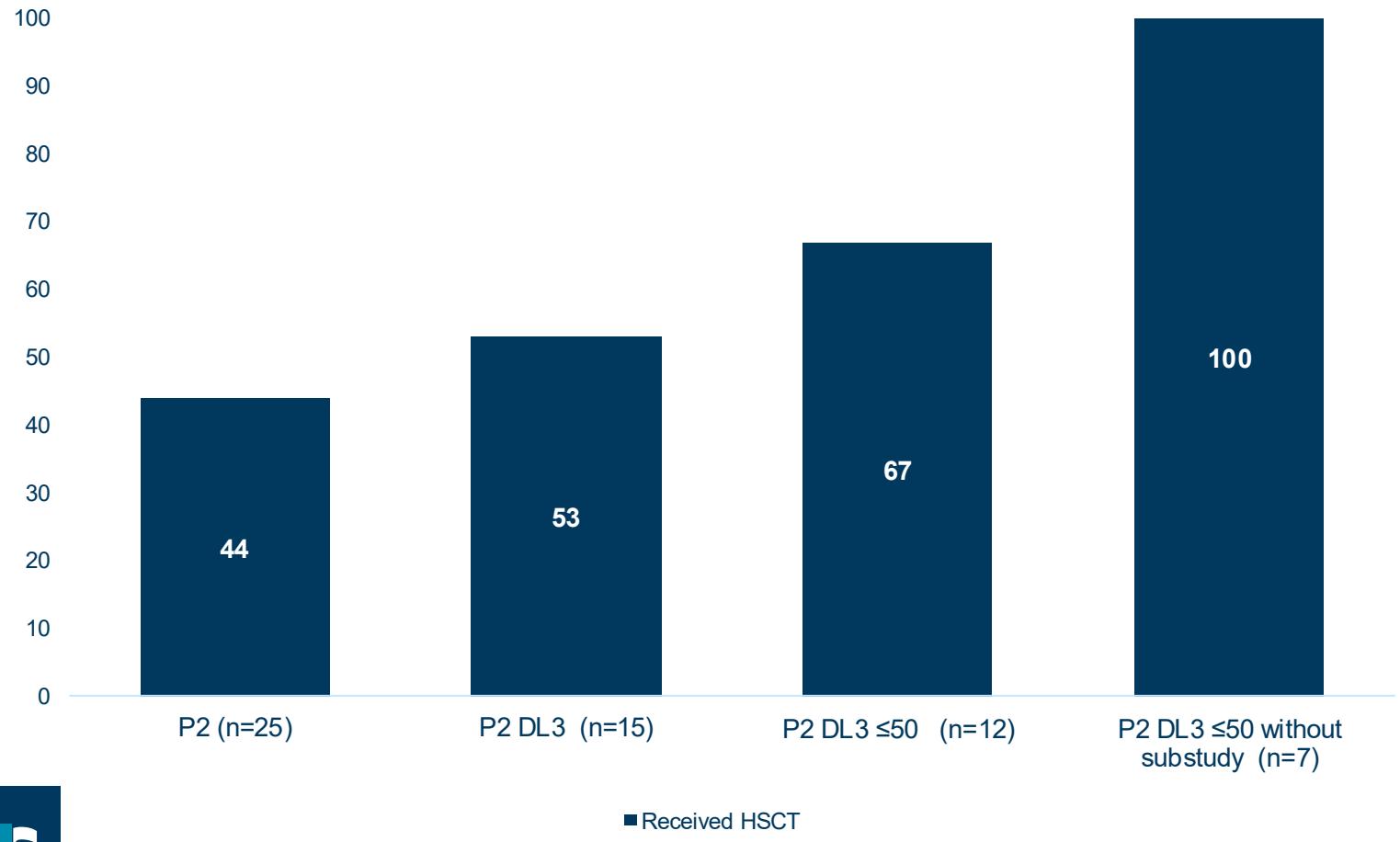
Patient characteristics (n=13)

- Age, median [range]: 26 years [17-66]
- Number of prior therapies, median [range]: 5 [3-9]
- BM blasts at screening, % [range]: 67 [1-98]
- Prior HSCT, number of patients (%): 7 (54)

13/25 patients in P2 had previous received prior blinatumomab, CD19 CAR T, and inotuzumab

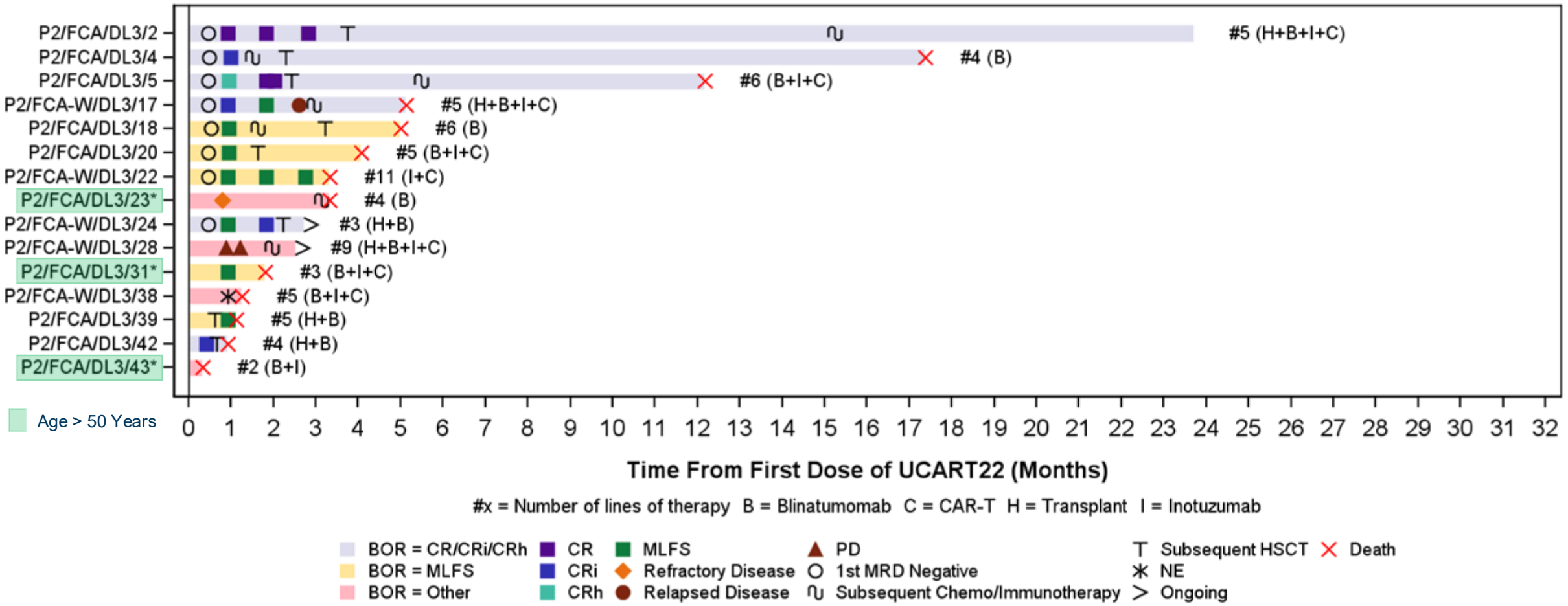
Subjects Received Transplant post UCART22 (P2)

Subjects who received HSCT (%)

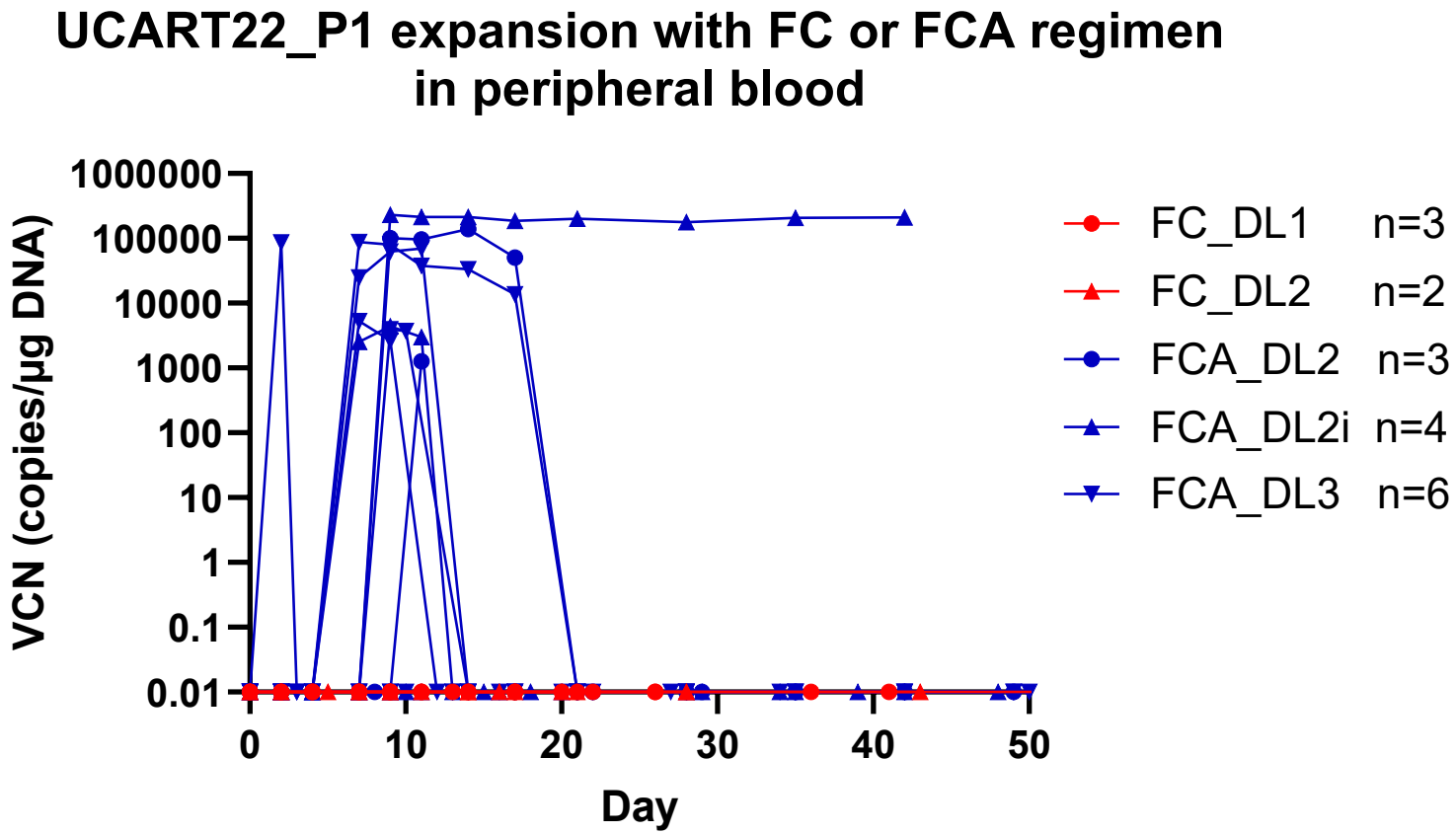


- Decision for transplant was at the discretion of the treating physician
- Transplant was not a predefined trial endpoint
- Sub study investigated a low weight-based dose of alemtuzumab
- Target phase 2 LD regimen includes a higher dose of alemtuzumab

DL3 – P2 Subjects Swimmer Plot



UCART22-P1 – confirmed expansion with FCA but not FC LD regimen

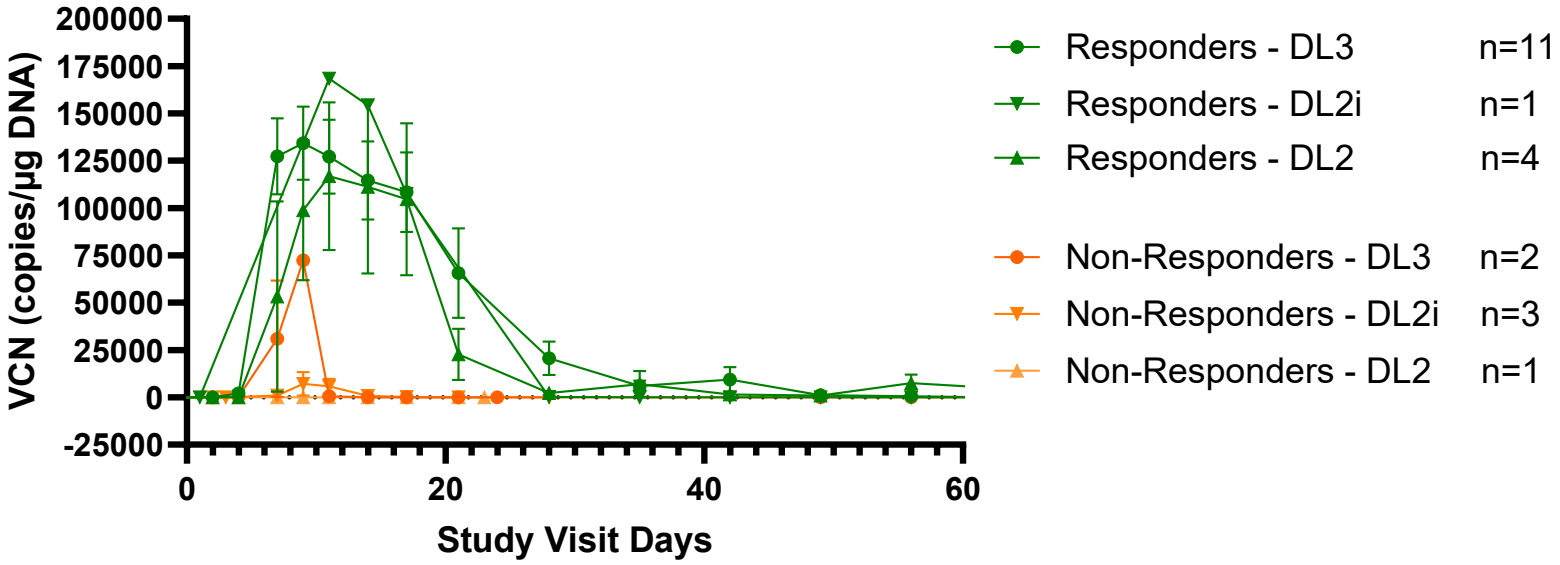


- FC Lymphodepletion regimen: no expansion
- FCA Lymphodepletion regimen: overall 60% expansion at DL2, DL2i and DL3

LD: Lymphodepletion

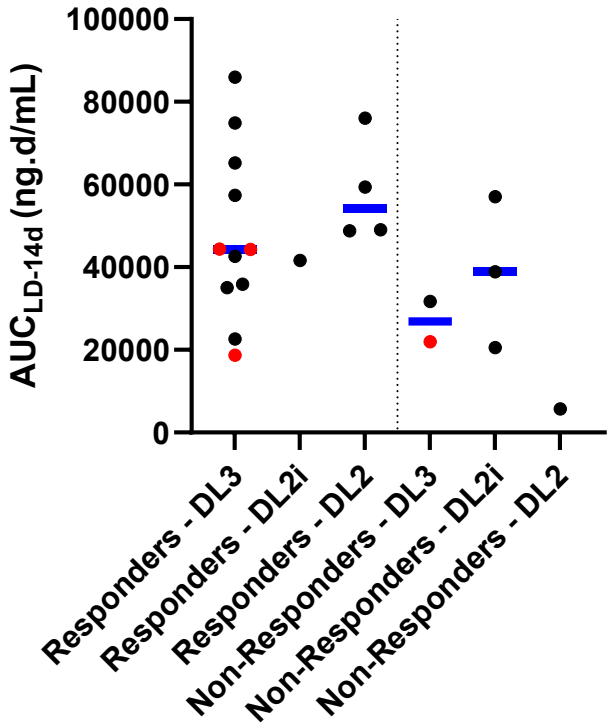
UCART22-P2 Expansion and Alemtuzumab Exposure by Response

UCART22-P2 expansion in peripheral blood by dose level (DL)



Responders = CR/CRi/MLFS
Mean ± SEM

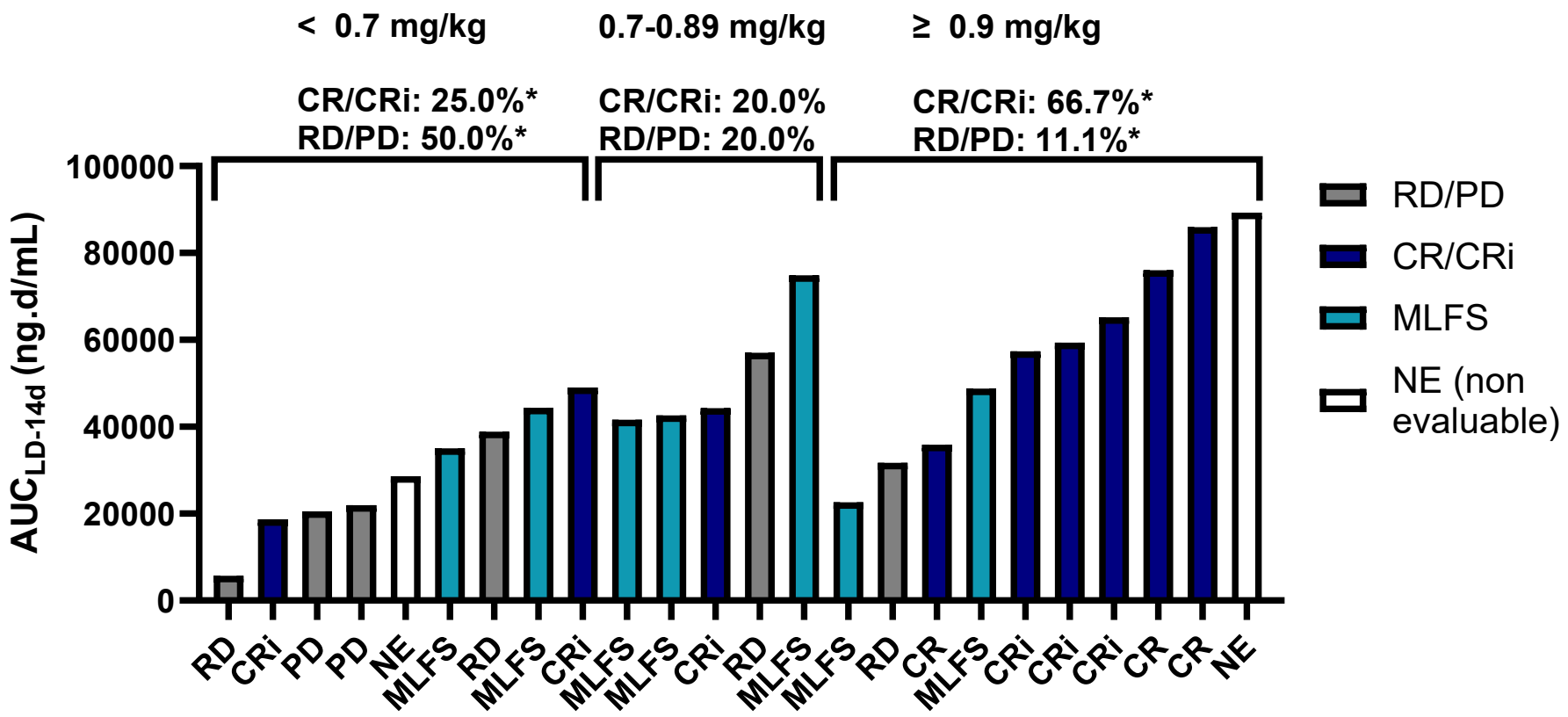
UCART22-P2 Alemtuzumab exposure per DL



- Non-responders had low or no UCART22-P2 expansion
- Majority of non-responders had low alemtuzumab exposure

• data points for patients in low ALZ weight-based dosing cohort in red

Alemtuzumab-Exposure Response Data Guides Weight-Based Dosing Thresholds (P2)

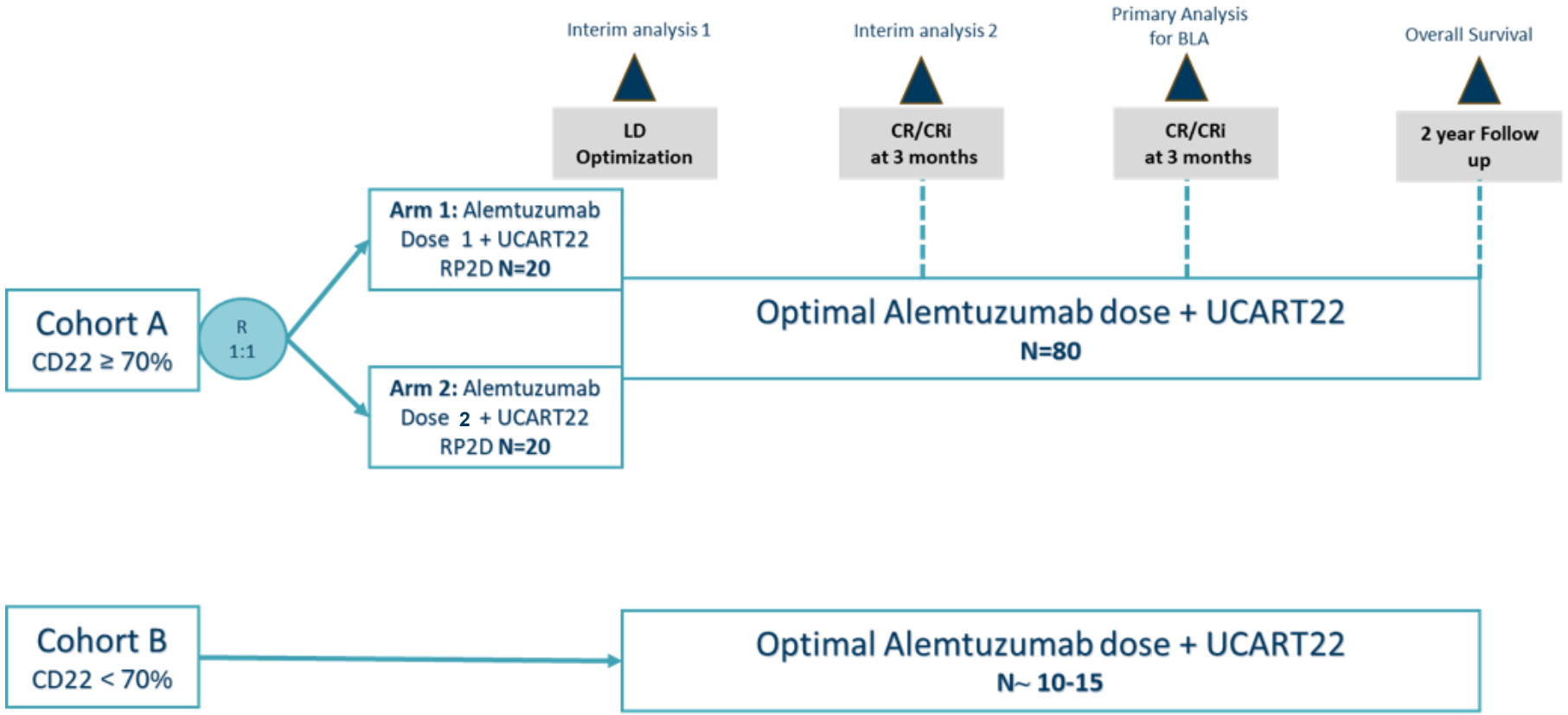


*non evaluable subjects excluded from calculation

Exposure–response relationship suggests:

- **<0.7 mg/kg** → might lead to less efficacy
- **≥0.9 mg/kg** → increased likelihood of achieving **CR/CRi**

Pivotal Phase 2 : Study Design



Key Inclusion Criteria

- Age 12- 50 years
- R/R disease after ≥2 lines
- BM of at least 5% blasts
- Prior CD19 CAR-T unless subject unable to receive

Primary Endpoints

CR/CRi within 3 months

Secondary Endpoints

- Transplant eligibility
- MRD negativity (within 3 months)
- DoR
- EFS, OS (12 months)
- QoL

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LD: Lymphodepletion; RP2D: Recommended Phase 2 Dose

Conclusions from the Phase 1 Study

- UCART22 led to low rates of grade ≥3 CRS and ICANS
  - One DLT occurred during Phase 1 – Dose Escalation
- In a very heavily pre-treated patient population with a median of 5 prior lines of therapy, clinically meaningful CR/CRi rates were achieved
- RP2D of UCART22 defined at 5 x 10^6 cells/kg (with a maximum of 400 x10^6 cells)
- FCA LD regimen promotes optimal UCART22 expansion
  - Higher alemtuzumab exposure is associated with deeper responses and increased UCART22 persistence
- UCART22 at RP2D allowed majority of target Ph2 patient population to proceed to allogeneic transplant
- Phase 2 Pivotal study now on-going with sites in Europe and North America

LD: Lymphodepletion; RP2D: Recommended Phase 2 Dose

Pivotal Phase 2 Study Now Enrolling

75 planned study centers in North America and Europe

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- For questions or comments, please contact Dr. Nitin Jain: njain@mdanderson.org
- For more information, please contact clinicaltrials@cellectis.com