

# Preliminary Results of NatHaLi-01: A First-In-Human Phase I/IIa Study of UCART20x22, a Dual Allogeneic CAR-T Cell Product Targeting CD20 and CD22, in Relapsed or Refractory (R/R) Non-Hodgkin Lymphoma (NHL)

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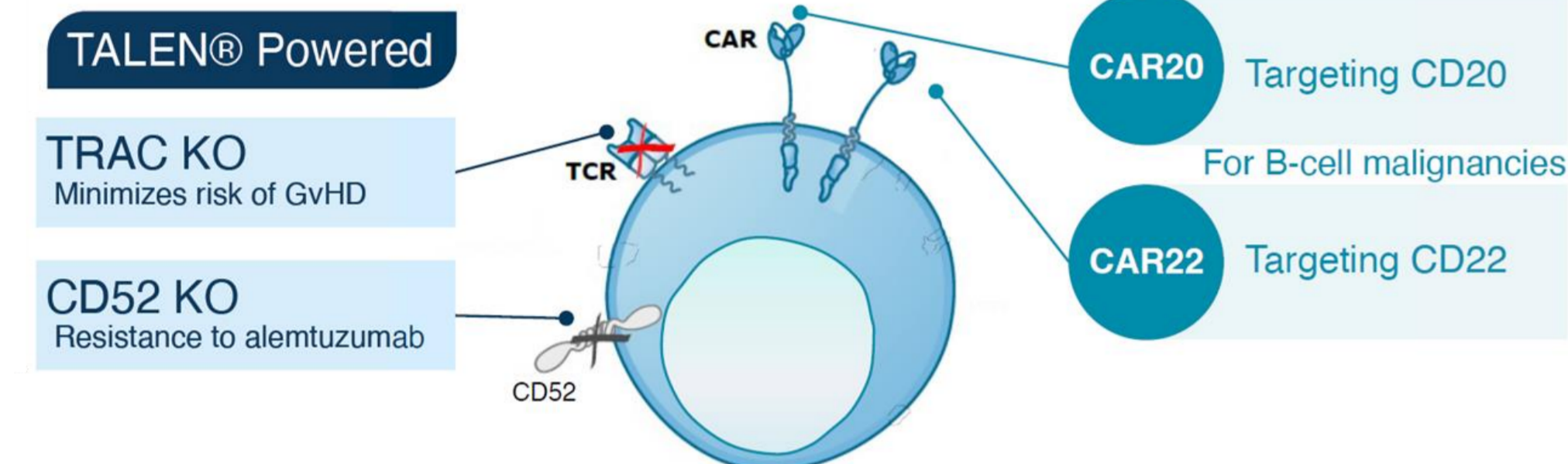
## #1 Introduction

- Autologous CD19-directed CAR T-cell therapies have revolutionized the treatment of R/R NHL, but up to approximately 50% of patients treated in the second or third line will ultimately fail these therapies.<sup>1-5</sup>
- Allogeneic chimeric antigen receptor (CAR) T-cell therapies targeting other antigens have the potential to provide benefit to these patients.
- UCART20x22 is the first allogeneic dual CAR T-cell therapy targeting CD20 and CD22 being tested in the clinic for R/R B-cell NHL and is manufactured by Collectis Biologics.

## #2 UCART20x22: Allogeneic "Off-the-Shelf" T-cell Product

### UCART20x22 (anti-CD20 and anti-CD22 scFv-41BB-CD3):

- Genetically modified allogeneic T-cell product manufactured from non-HLA-matched healthy donor cells
- CD20 and CD22 surface molecules are validated therapeutic targets in NHL



CAR, chimeric antigen receptor; GvHD, graft-vs-host disease; HLA, human leukocyte antigen; KO, knock out; LD, lymphodepletion; NHL, non-Hodgkin lymphoma; pts, patients; scFv, single-chain variable fragment; TCR, T-cell receptor; TRAC, T-cell receptor alpha constant.

## #3 Study Design (NCT05607420)

**Key inclusion criteria:**

- Age 18–80 years
- Mature B-cell NHL except CLL/SLL, Richter's from CLL/SLL, Burkitt's lymphoma, or Waldenstrom's macroglobulinemia
- Tumor positive for CD20 and/or CD22
- Received  $\geq 2$  prior lines including CD19 CART if eligible

**Primary objective:**

- Safety, tolerability, & MTD/TP2D of UCART20x22

**Additional objectives:**

- Investigator-assessed response by Lugano
- UCART20x22 expansion in PB
- Immune reconstitution

**Dose-escalation BOIN design • 2-4 pts/cohort**

**FCA LD regimen:**

- Fludarabine 30 mg/m<sup>2</sup> × 3d
- Cyclophosphamide 0.5 g/m<sup>2</sup> × 3d
- Alemtuzumab 60 mg total over 3 days

†Enrollment is ongoing. BOIN, Bayesian optimal interval; CART, chimeric antigen receptor T-cell therapy; DL, dose level; d, days; FCA, fludarabine + cyclophosphamide + alemtuzumab; LBCL, large B-cell lymphoma, LD, lymphodepletion; MTD, maximum tolerated dose; PB, peripheral blood; pts, patients; TP2D, recommended phase 2 dose.

## #4 Methods

- Primary endpoints are safety, tolerability, and determining the MTD/TP2D of UCART20x22. Additional endpoints include anti-lymphoma activity and expansion of UCART20x22.
- After FCA (fludarabine 30 mg/m<sup>2</sup> × 3 days, cyclophosphamide 0.5 g/m<sup>2</sup> × 3 days, CLLS52 [alemtuzumab] 60 mg total dose over 3 days) lymphodepletion, patients receive a single infusion of UCART20x22.

## #5 Baseline Characteristics

As of 28 July 2023, 3 patients received LD and were treated with UCART20x22

	Pt 1	Pt 2	Pt 3
Age	76	65	18
Sex	Female	Female	Female
NHL Subtype	DLBCL	Transformed FL	Transformed MZL
Genetic/Molecular	Double expressor (BCL2, MYC)	Triple-hit	NOTCH1, PLCG2, CCND3, XBP1
Antigen Present	CD20+/CD22 unknown	CD20+/CD22 unknown	CD20-/CD22+
Stage at Screening	IV	IV	IV
Number of Prior Therapies	2	4	8
Prior CD19 CART	None	Lisocabtagene maraleucel x2	Axicabtagene ciloleucel
ECOG	0	0	1
Baseline Deauville Score	4	5	5
Disease Status at Screening	Relapsed	Relapsed	Refractory

CART, chimeric antigen receptor T-cell therapy; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; LD, lymphodepletion; MZL, marginal zone lymphoma

## #6 Safety Summary

- No UCART20x22-related DLTs.
- No ICANS or GVHD was observed.
- One CLLS52-related DLT of bone marrow aplasia after Day 42 thought to be due to cumulative chemotherapy exposure in a patient with baseline grade 1/2 cytopenias and bone marrow hypocellularity at Screening.
- All patients experienced grade 1 or 2 CRS that resolved with treatment
  - Pt 1 had grade 1 CRS for 4 days and was treated with tocilizumab x3 and dexamethasone x1
  - Pt 2 had grade 2 CRS for 2 days and grade 1 CRS for 3 days managed with tocilizumab x3 and dexamethasone x1
  - Pt 3 had grade 1 CRS for 8 days and received tocilizumab x1

UCART20x22-Related Adverse Events (AE) by System Organ Class and Preferred Term

AE, n (%)	Any grade	Grade $\geq 3$
System Organ Class Preferred Term		
Patients with at least 1 UCART20x22-related AE	3 (100)	3 (100)
Immune system disorders	3 (100)	0
Cytokine release syndrome	3 (100)	0
Hypogammaglobulinemia	1 (33)	0
Nervous system disorders	1 (33)	0
Dizziness	1 (33)	0
Headache	1 (33)	0
General disorders and administration site conditions	1 (33)	0
Fatigue	1 (33)	0
Vascular disorders	1 (33)	0
Hypotension	1 (33)	0
Gastrointestinal disorders	1 (33)	0
Nausea	1 (33)	0
Musculoskeletal and connective tissue disorders	1 (33)	0
Pain in extremity	1 (33)	0
Skin and subcutaneous tissue disorders	1 (33)	0
Pruritus	1 (33)	0
Psychiatric disorders	1 (33)	0
Dyspnea	1 (33)	0
Blood and lymphatic system disorders	3 (100)	3 (100)
Anemia	3 (100)	3 (100)
Neutropenia	2 (67)	2 (67)
Thrombocytopenia	1 (33)	1 (33)
Pancytopenia	1 (33)	1 (33)
Febrile neutropenia	1 (33)	1 (33)
Investigations	1 (33)	0
Alanine aminotransferase increased	1 (33)	0
Aspartate aminotransferase increased	1 (33)	0
Blood alkaline phosphatase increased	1 (33)	0
Blood lactate dehydrogenase increased	1 (33)	0
Metabolism and nutrition disorders	3 (100)	0
Hyponatremia	2 (67)	0
Hypocalcemia	1 (33)	0
Hypophosphatemia	1 (33)	0

Treatment Emergent Serious Adverse Events (SAEs) by System Organ Class & Preferred Term

SAE, n (%)	Any grade	Grade $\geq 3$	Related to UCART20x22	Related to CLLS52
System Organ Class Preferred Term				
Blood and lymphatic system disorders	1 (33)	1 (33)		
Pancytopenia	1 (33)	1 (33)	Yes	Yes*
Infections and infestations	1 (33)	0		
Cytomegalovirus viremia	1 (33)	1 (33)	No	Yes
Pseudomonas sepsis	1 (33)	1 (33)	No	No
Nervous system disorders	1 (33)	0		
Neuralgia	1 (33)	0	No	No
Respiratory, thoracic, and mediastinal disorders	1 (33)	1 (33)		
Acute respiratory failure	1 (33)	1 (33)	No	No

\*DLT for CLLS52 thought to be due to cumulative chemotherapy exposure in a patient with baseline G1/2 cytopenias and bone marrow hypocellularity at Screening

## #7 Response

As of July 28, 2023, 3 patients were treated at dose level 1 and were evaluable for response:

- Pt 1 is a 76-year-old female with double-expressor DLBCL relapsed after R-CHOP, radiation therapy, and polatuzumab vedotin with bendamustine/rituximab who achieved a **partial metabolic response** at Day 28.
- Pt 2 is a 65-year-old female with triple-hit transformed follicular lymphoma previously treated with radiation therapy, bendamustine/rituximab, dose-adjusted R-EPOCH, and two lisocabtagene maraleucel treatments who achieved a **complete metabolic response** at Day 28.
- Pt 3 is an 18-year-old female with relapsed/refractory transformed marginal zone lymphoma who previously failed chemoimmunotherapy, venetoclax, ibrutinib, bendamustine/rituximab, axicabtagene ciloleucel, obinutuzumab, glofitamab, tafasitamab/lenalidomide, and an experimental epigenetic modifier who achieved a **complete metabolic response** at Day 28.

## #8 Translational Summary

- FCA lymphodepletion led to sustained suppression of endogenous T-cells for the duration of the treatment period, allowing for UCART20x22 expansion.
- Robust peripheral UCART20x22 expansion was observed in all three patients and correlated with CRS and changes in serum ferritin levels.
  - Expanding UCART20x22 cells are predominantly CD8+
- Serum cytokine/inflammatory marker levels increased prior to or during UCART20x22 peak expansion, with comparable results among all patients.
- Patient 3 exhibited low CD20 and high CD22 tumor expression at baseline.
- UCART20x22 cells were observed in day 9 post-treatment biopsy from patient 3.

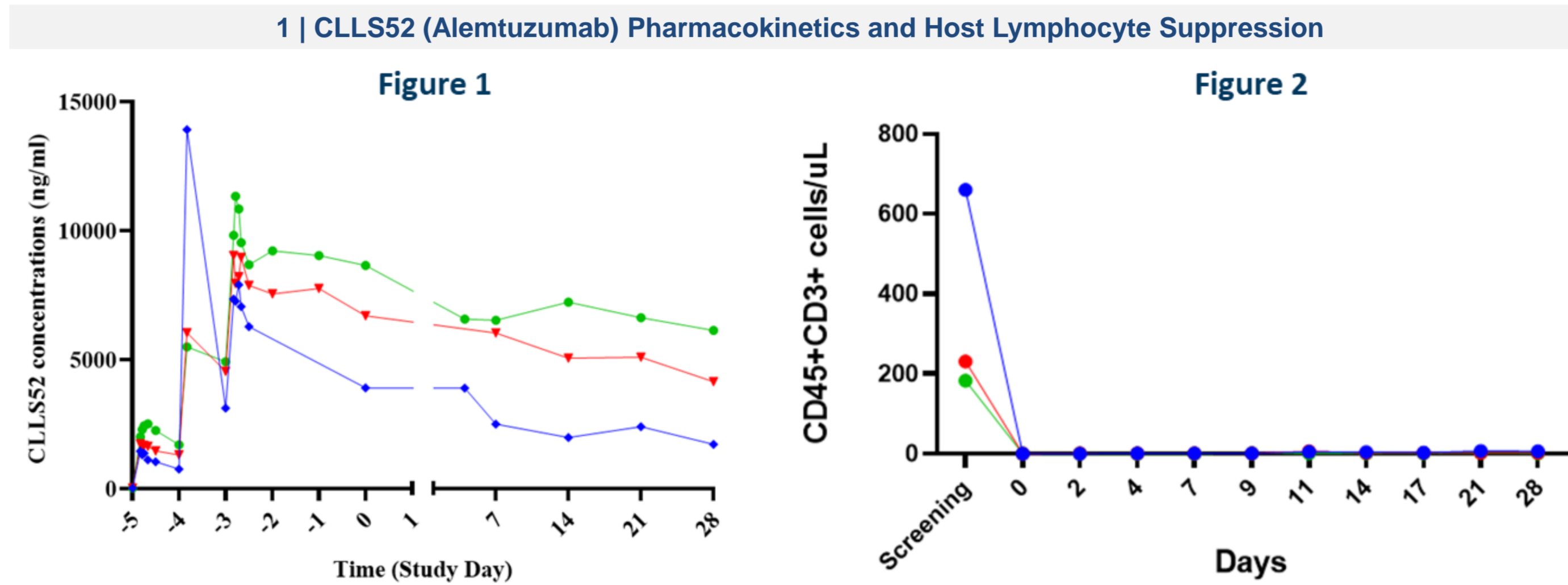
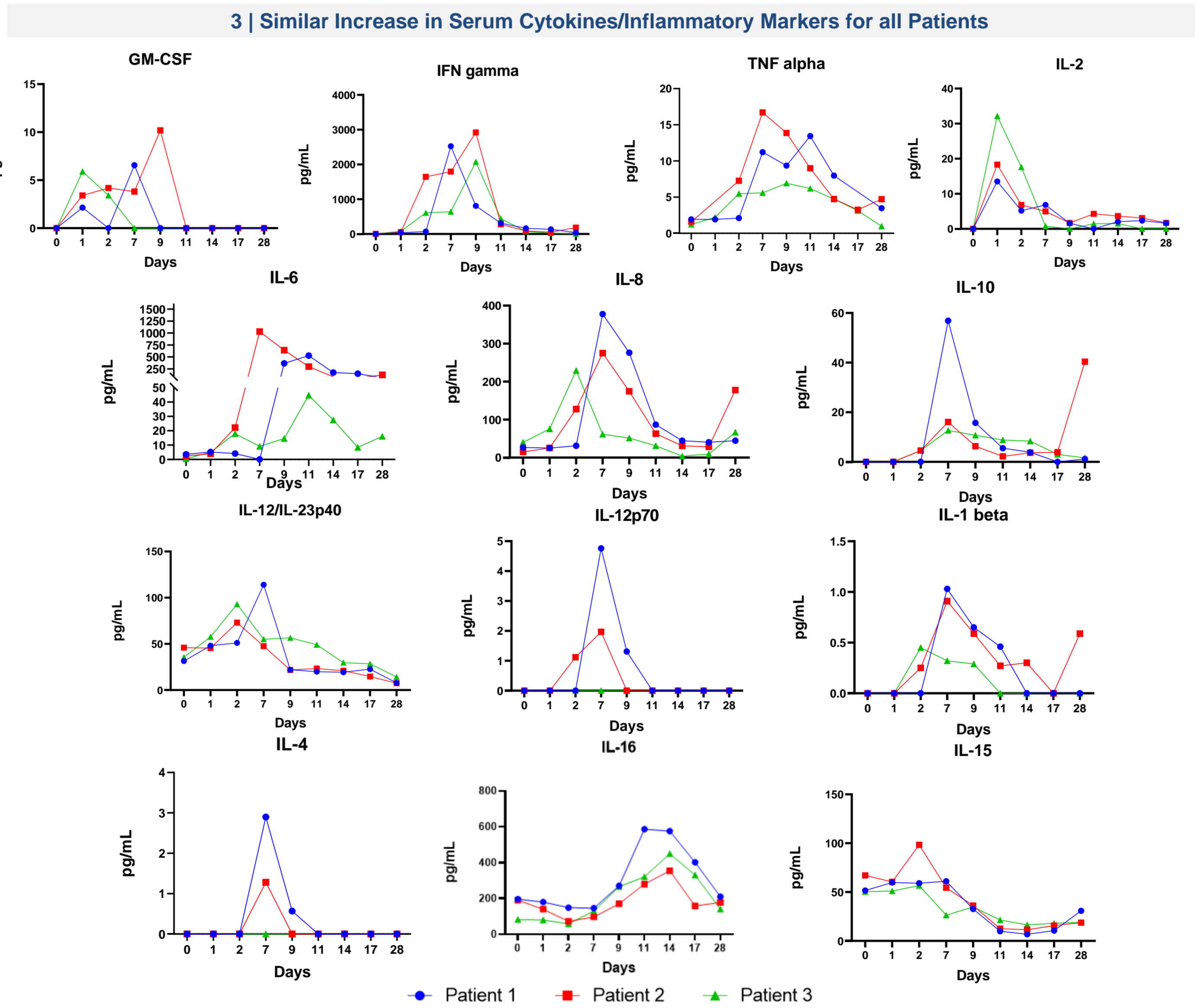


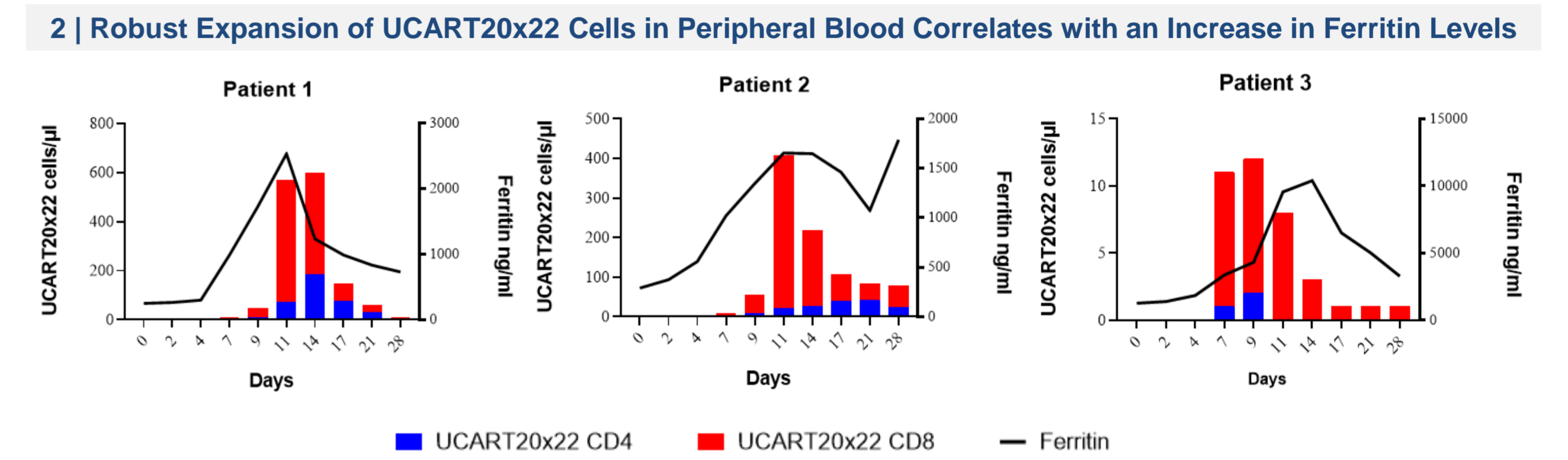
Figure 1 indicates that for all patients, the CLLS52 PK profiles are similar and consistent with literature results.<sup>6</sup> Concentrations increase with each dose administered with C<sub>max</sub> observed following the last dose, then concentrations decrease and were quantifiable at the last collected timepoint. Correlating with the CLLS52 PK profiles, Figure 2 shows adequate lymphodepletion for all patients until at least 28 days post-UCART20x22 administration.



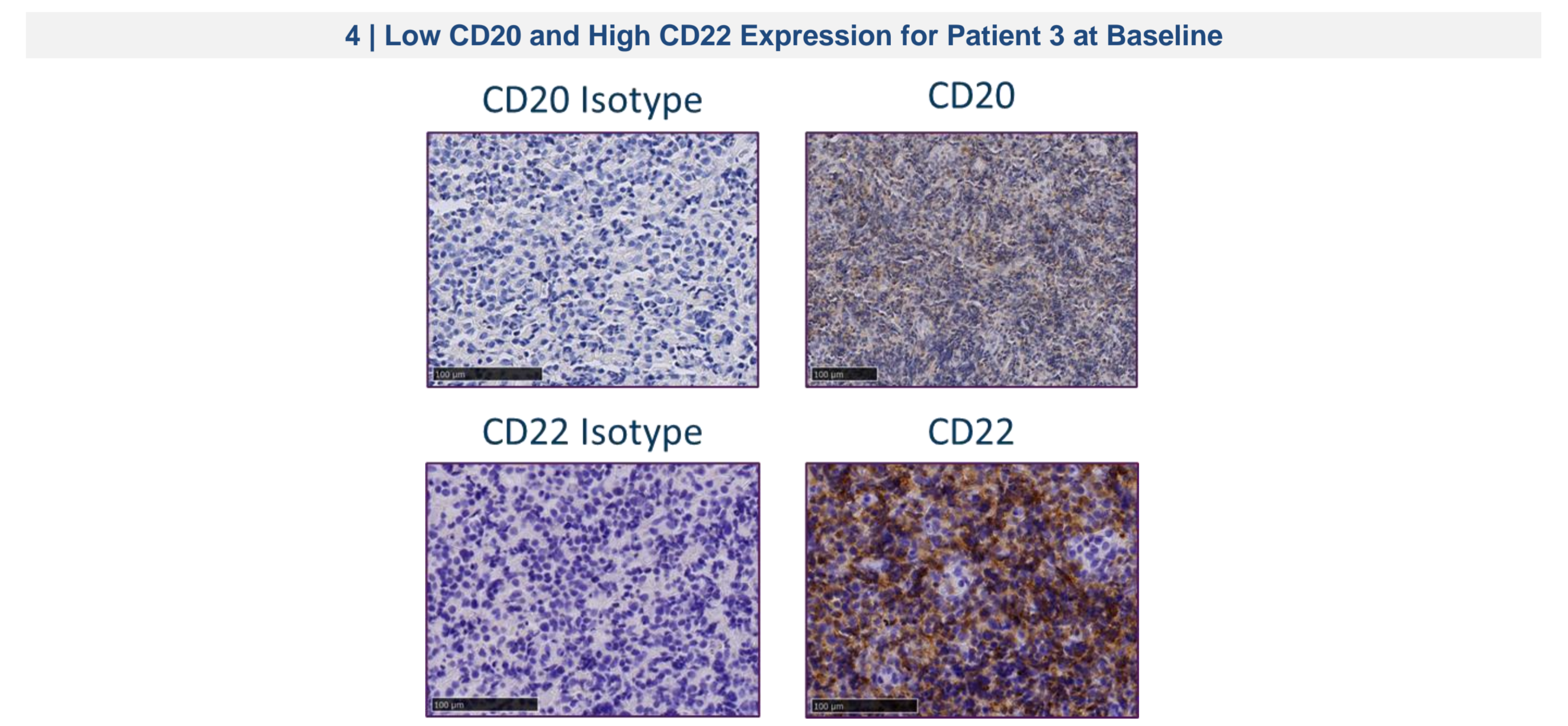
Cytokines were measured in serum using Meso Scale Discovery V-PLEX proinflammatory and cytokine panels. Peak levels were observed at initial expansion of UCART20x22 for GM-CSF, IFN $\gamma$ , TNF $\alpha$ , IL-1 $\beta$ , IL-2, IL-4, IL-8, IL-10, IL-12p40, IL-12p70, IL-15, and at peak expansion for IL-6 and IL-16.

## #9 Summary and Conclusions

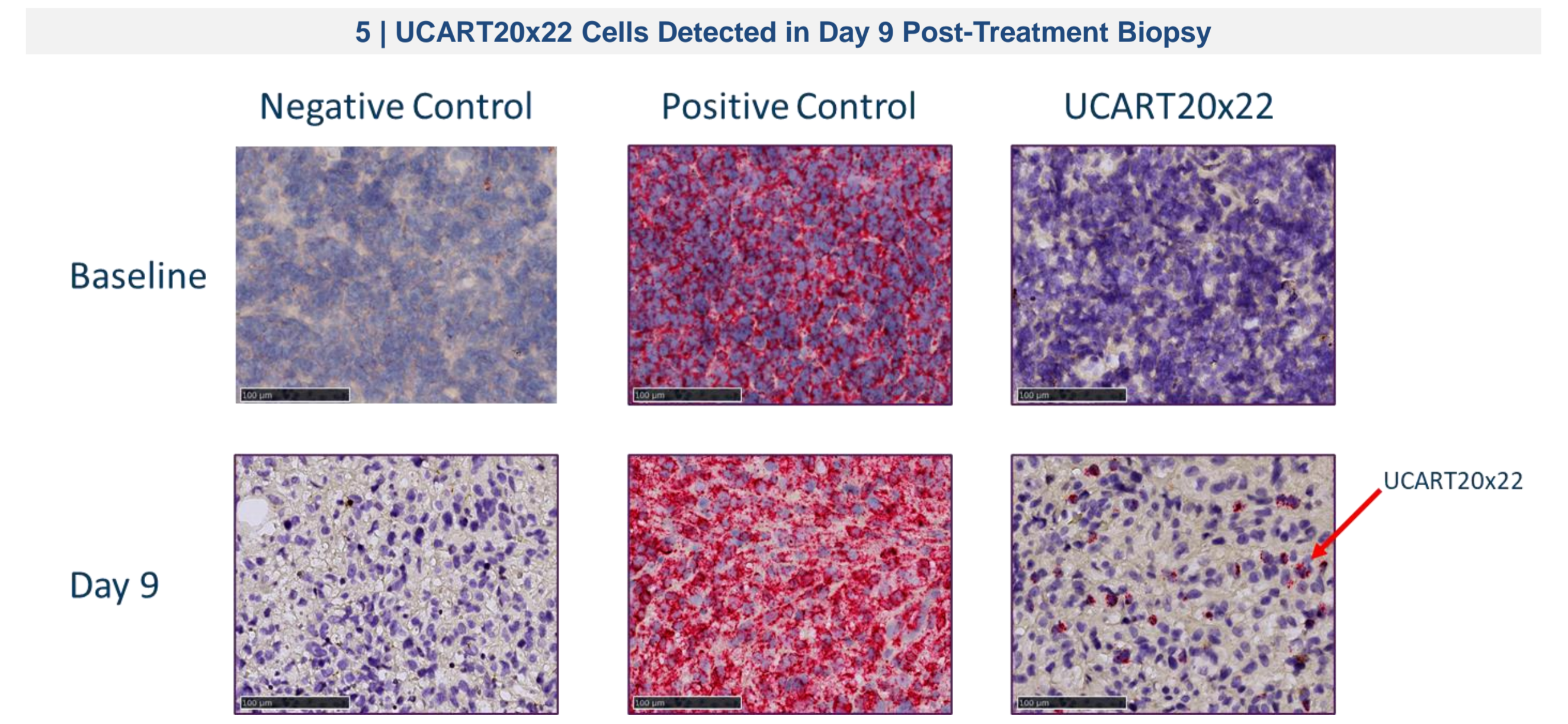
- UCART20x22 at dose level 1 (50 × 10<sup>6</sup> cells) is preliminarily safe and tolerable, with no grade  $\geq 3$  CRS, no ICANS, and no UCART20x22-related DLTs.
- All of the patients responded at the Day 28 disease assessment
  - 2 complete metabolic responses in patients who failed prior CAR19**
  - 1 partial metabolic response**
- UCART20x22 expansion was observed in all patients and associated with changes in inflammatory markers and cytokine levels.
- UCART20x22 was detected in one patient's post-treatment tumor biopsy.
- Overall, these data support the preliminary safety and efficacy of UCART20x22 in this R/R B-cell NHL population.
- The study is currently open and enrolling



UCART20x22 expansion was observed by flow cytometry in the peripheral blood in all patients, with peaks of ~600 cells/ $\mu$ L in Patient 1 at Day 14, ~400 cells/ $\mu$ L in Patient 2 at Day 11, and ~12 cells/ $\mu$ L in Patient 3 at Day 9, with predominantly CD8+ cells expanding.



CD20 and CD22 were measured by IHC (20X resolution) with the corresponding isotype negative control, which showed no staining



UCART20x22 cells were measured by RNAscope using a probe set specific for the UCART22 targeted sequence, at 20X magnification. No staining was observed with the negative control DapB (*Bacillus subtilis* strain SMY, a soil bacterium) in situ hybridization (ISH), strong staining with positive control UBC (ubiquitin C) ISH (red), UCART20x22 cells are detected by UCART22 ISH (Red), and hematoxylin counterstain (blue) nuclear staining.

## #10 References

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- For more information, please contact [clinicaltrials@collectis.com](mailto:clinicaltrials@collectis.com)