Multi-Institutional Hematopathology Interesting Case Conference

Case 3

Nisha Patel, D.O.

02/25/2026

National Institutes of Health
Clinical Center

Clinical Presentation

A ~20 y/o patient with relapsed/refractory

B-lymphoblastic leukemia (CRLF2-rearranged)

was referred to our institution for

CD19/CD22 CAR T-cell therapy.

Disease Course

Baseline Pre CAR T-cell Therapy:

- Bone Marrow (Day -1): Involved by B-ALL (~40% of marrow cellularity)
- PET/CT: Evidence of extramedullary disease

Day +21:

- Bone Marrow: No morphologic or immunophenotypic evidence of B-ALL

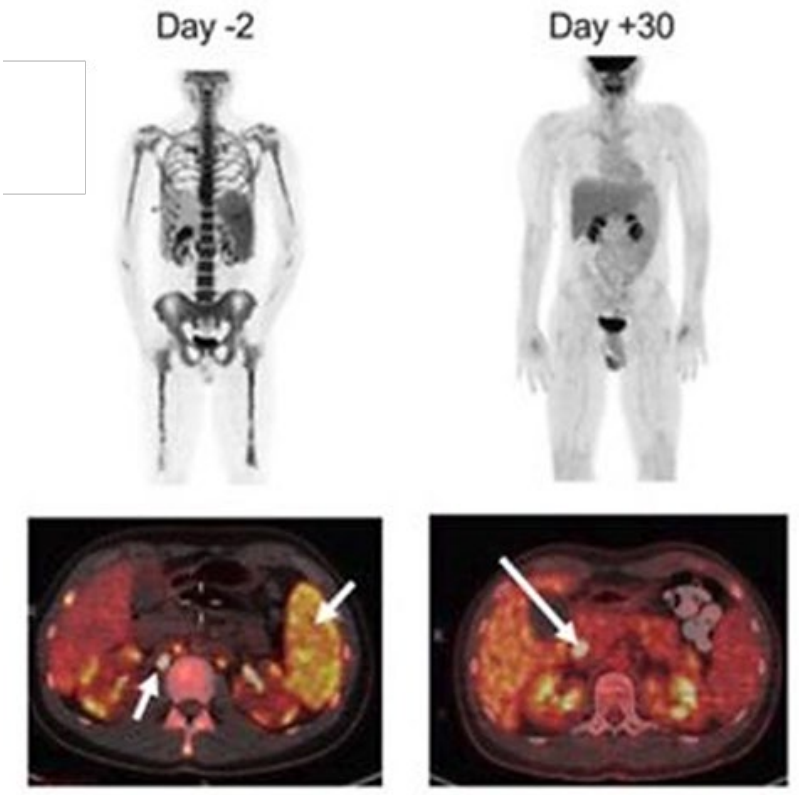
In Interim…..

PET/CT:

- Resolved FDG uptake of bone marrow, spleen, right kidney, and retroperitoneal nodes.
- **New focal increased uptake at the region of pancreatic head**
- **Peripheral NGS: Re-emergence of clone**

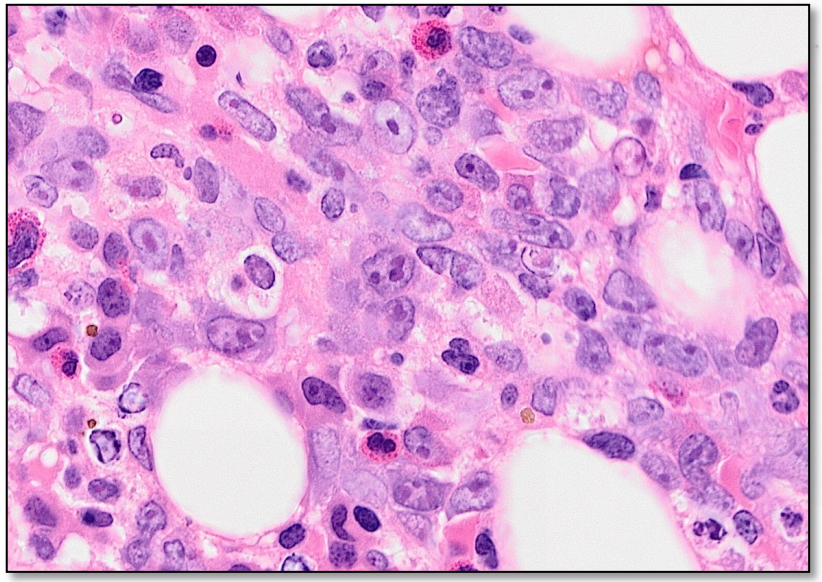
Day +48

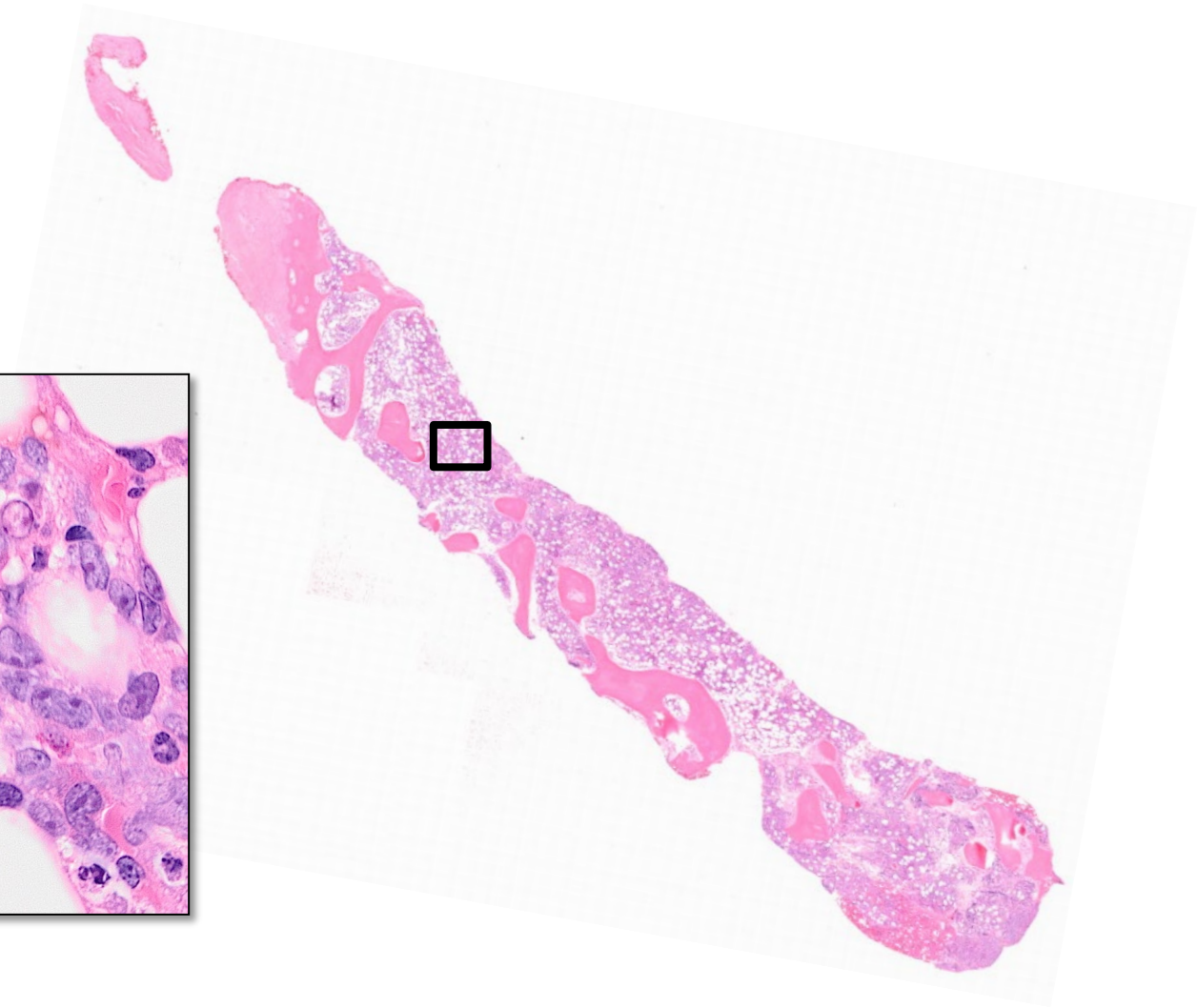
- Bone Marrow: **(PROVIDED CASE 3)**



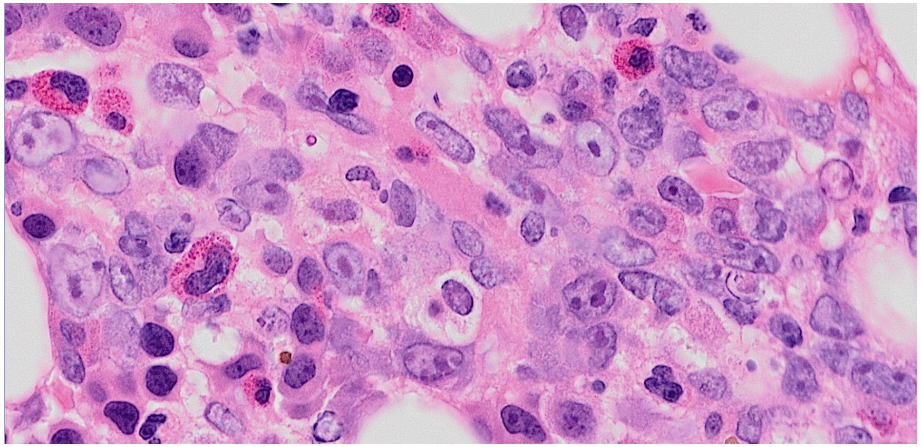
PMID: 39461880

Pre- CAR T-cell therapy (Day -1): B-lymphoblastic leukemia (B-ALL)

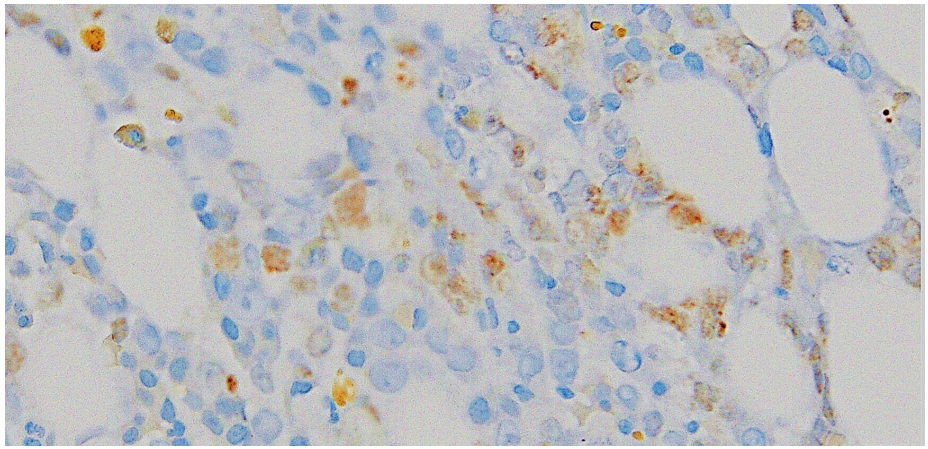




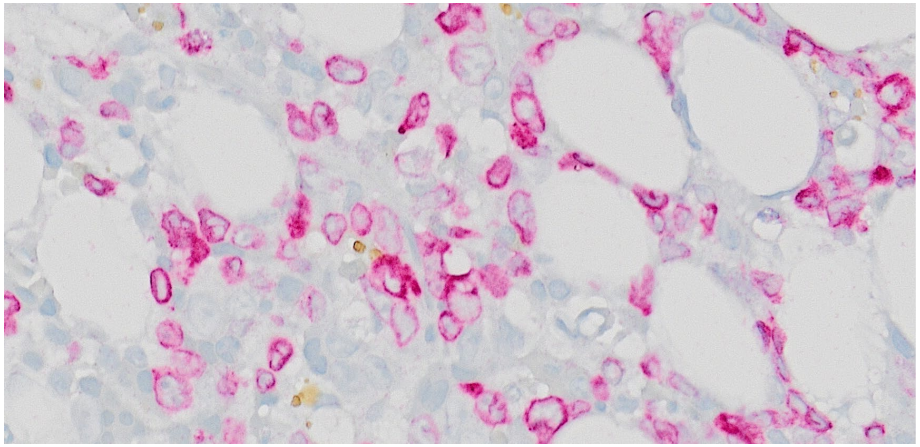
Pre- CAR T-cell therapy (Day -1): B-lymphoblastic leukemia (B-ALL)



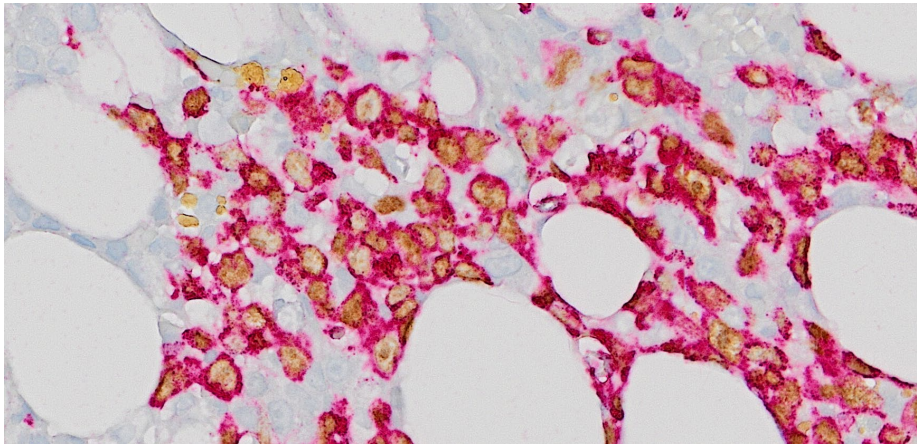
H&E



TdT

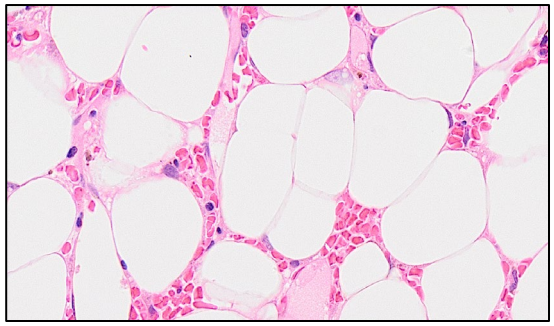


CD79a

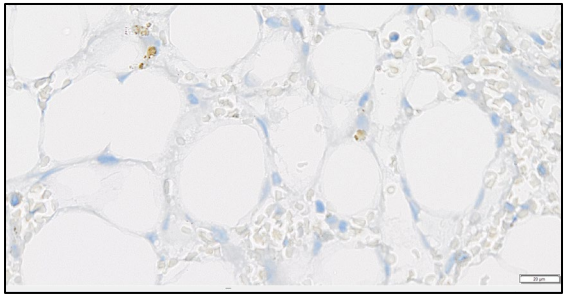


PAX5/CD10 dual stain

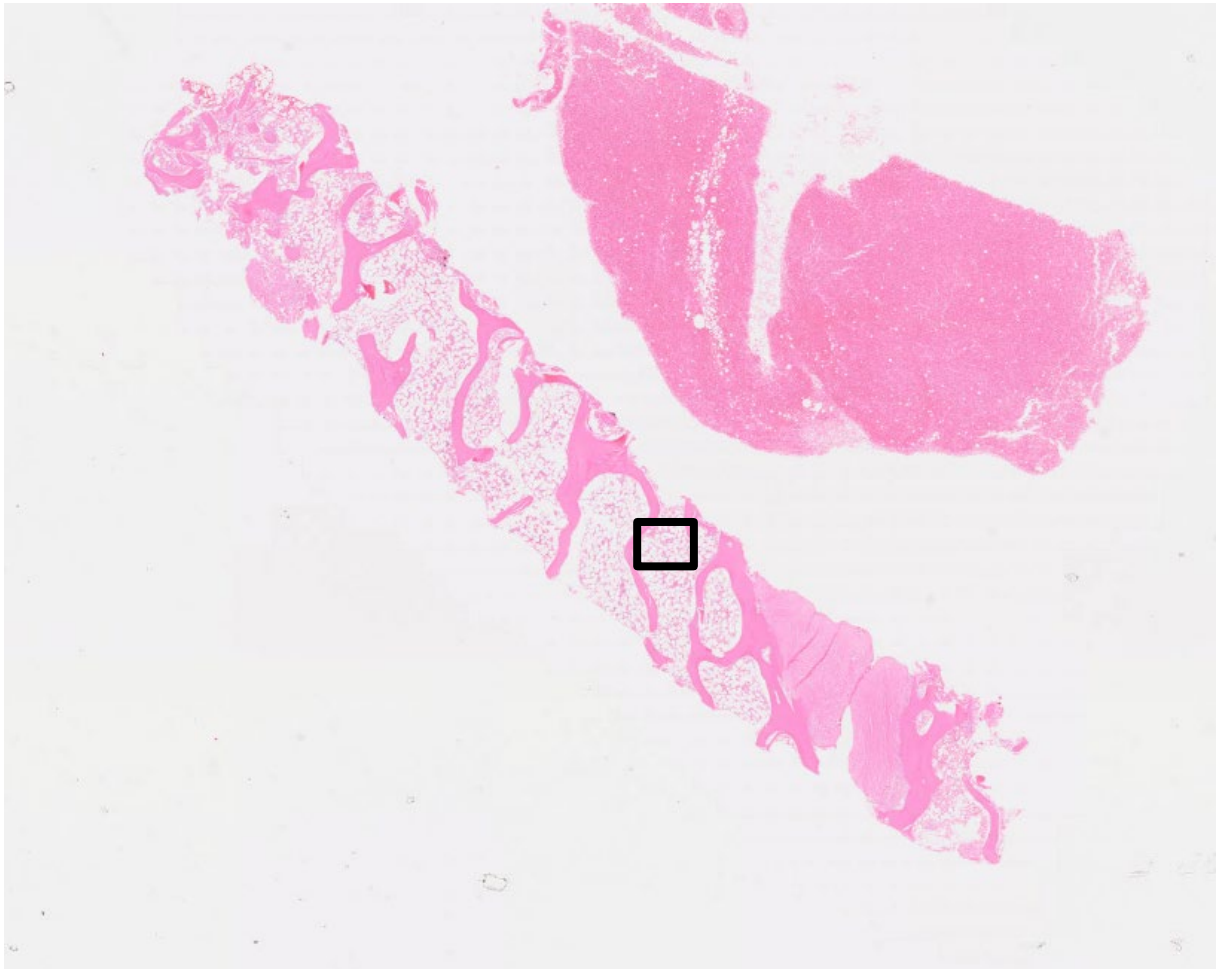
Post Therapy Marrow (Day +21):



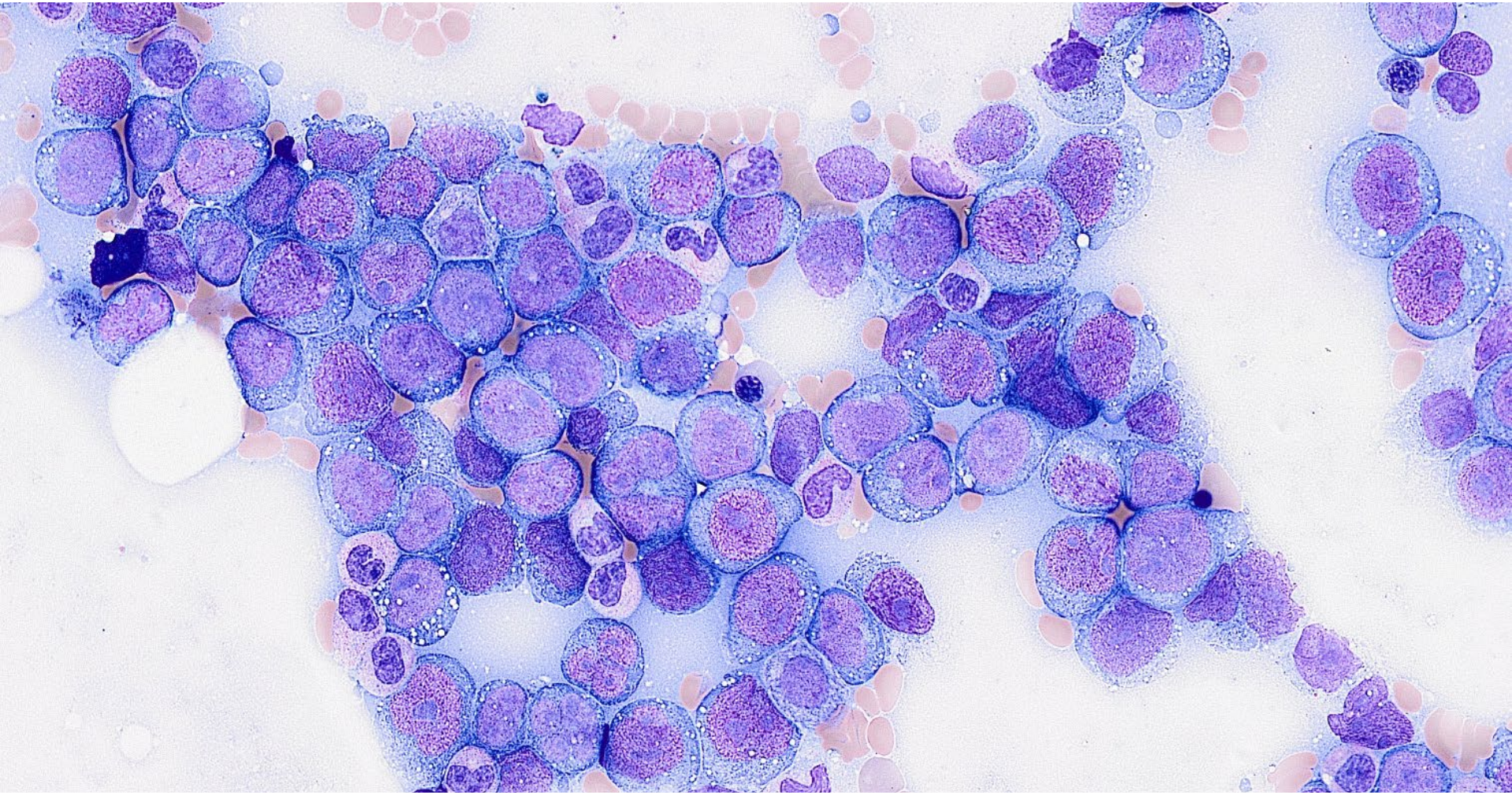
H&E



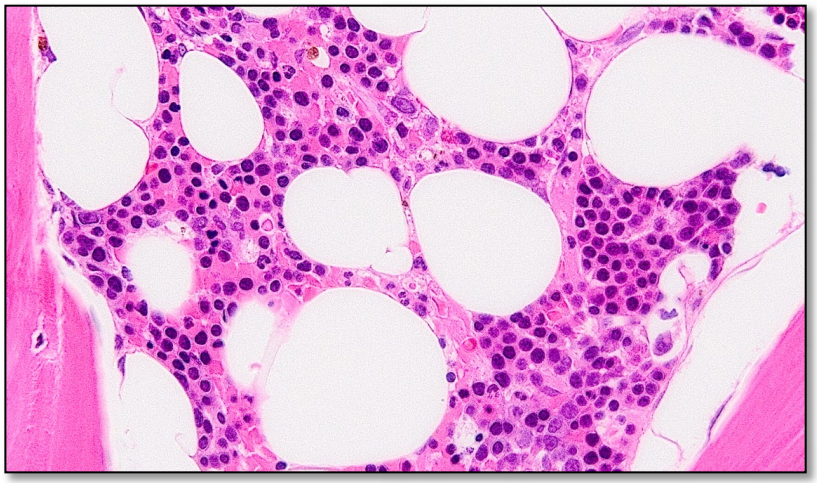
CD79a



Post Therapy Marrow (Day +48)

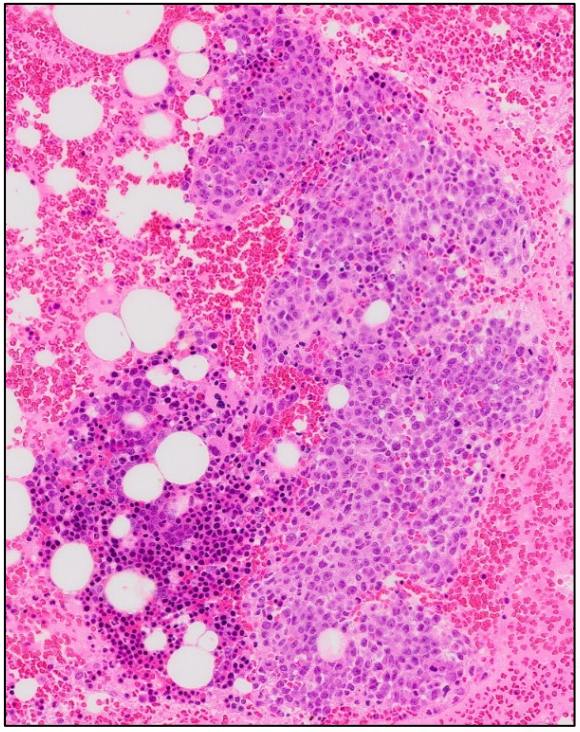


Post Therapy Marrow (Day +48)

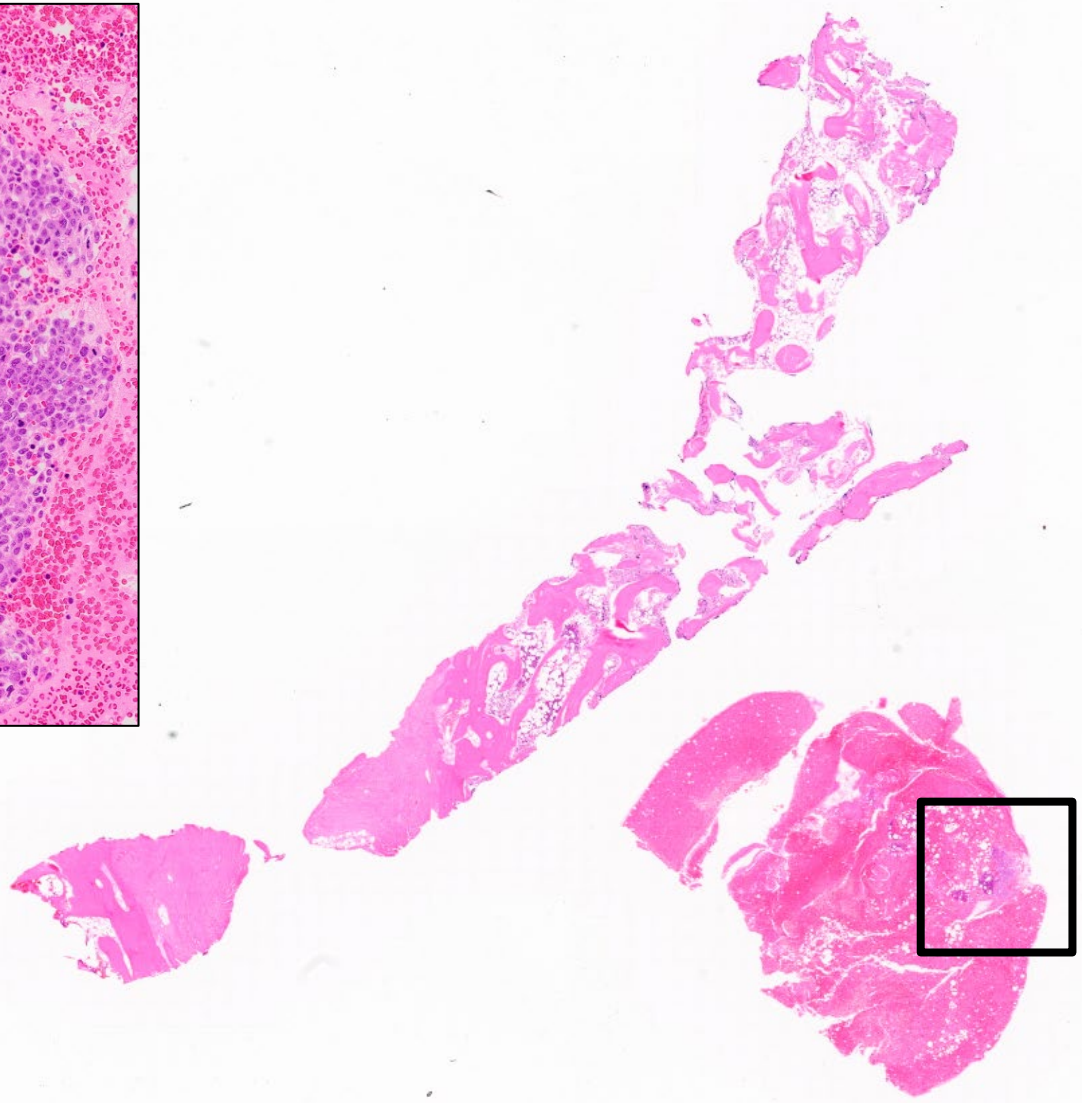


Marrow Biopsy

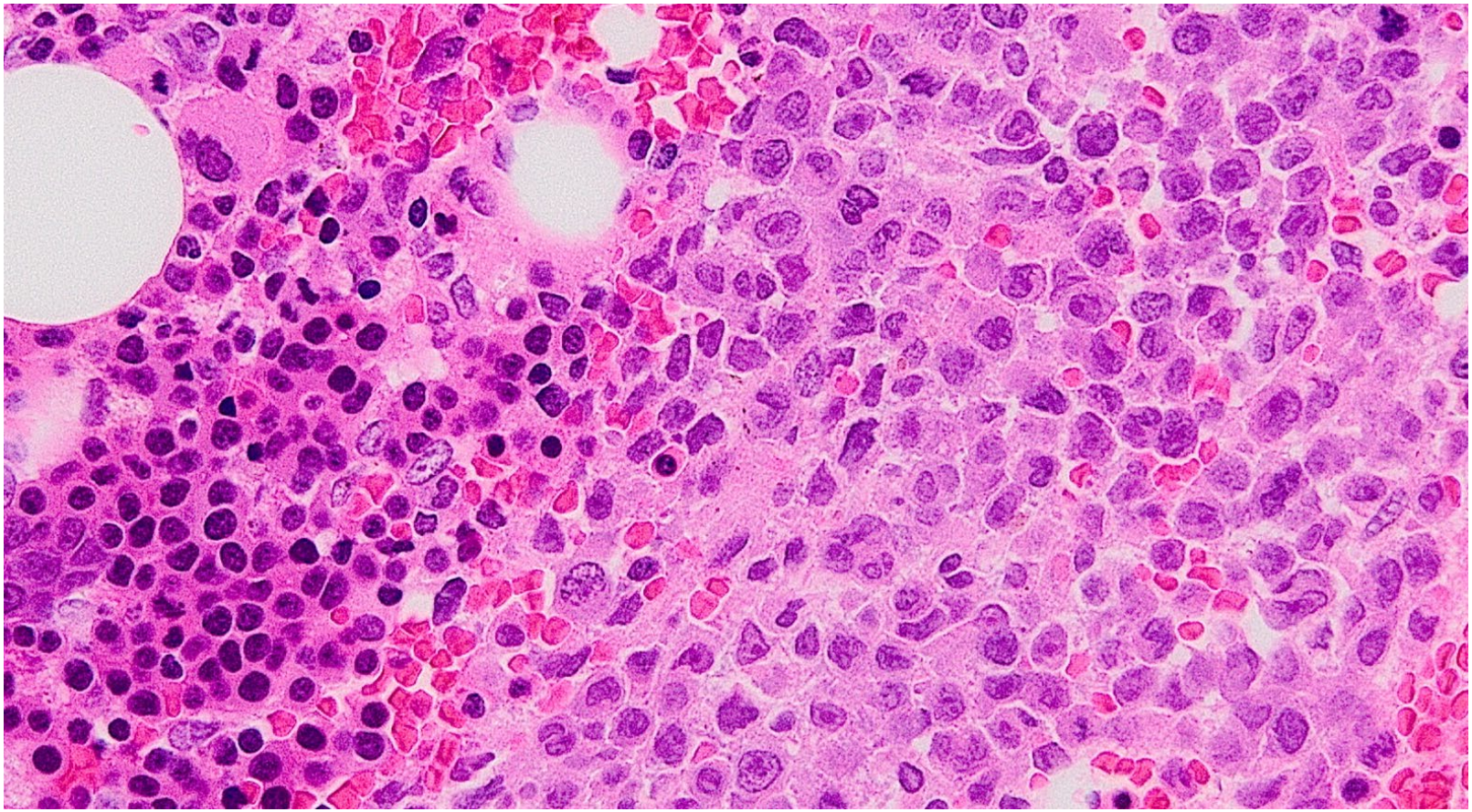
Post Therapy Marrow (Day +48)



Marrow Aspirate
(Clot)

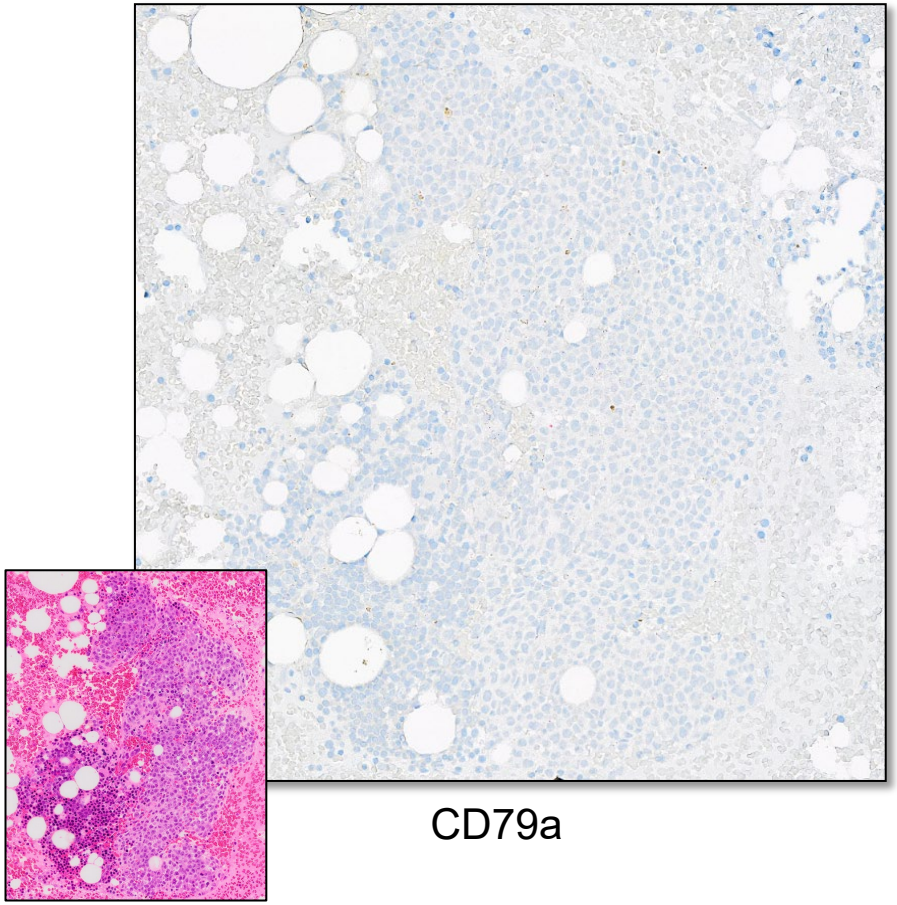


Post Therapy Marrow (Day +48)

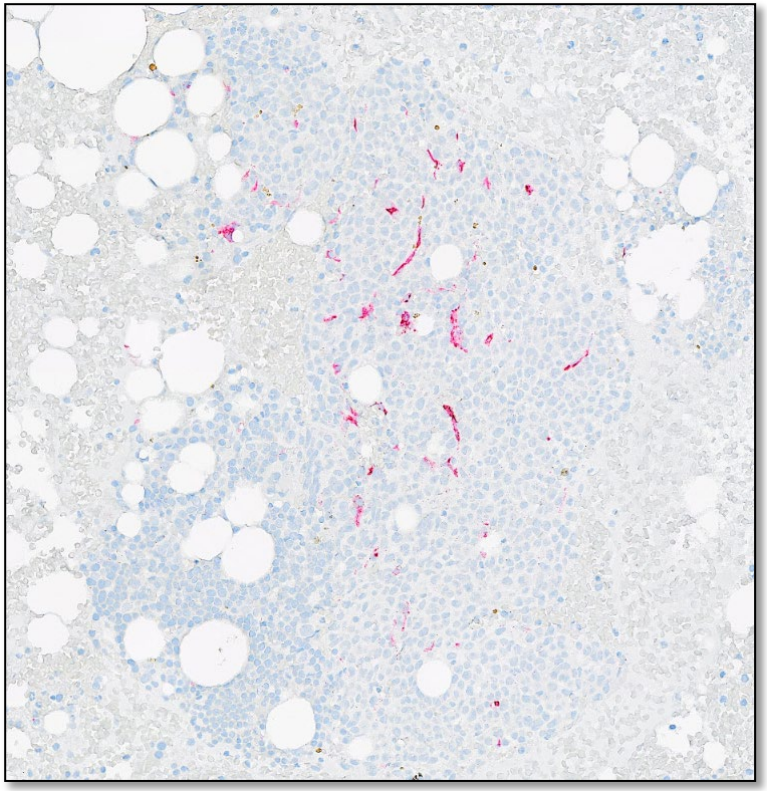


Marrow Aspirate
(Clot)

Post Therapy Marrow (Day +48)

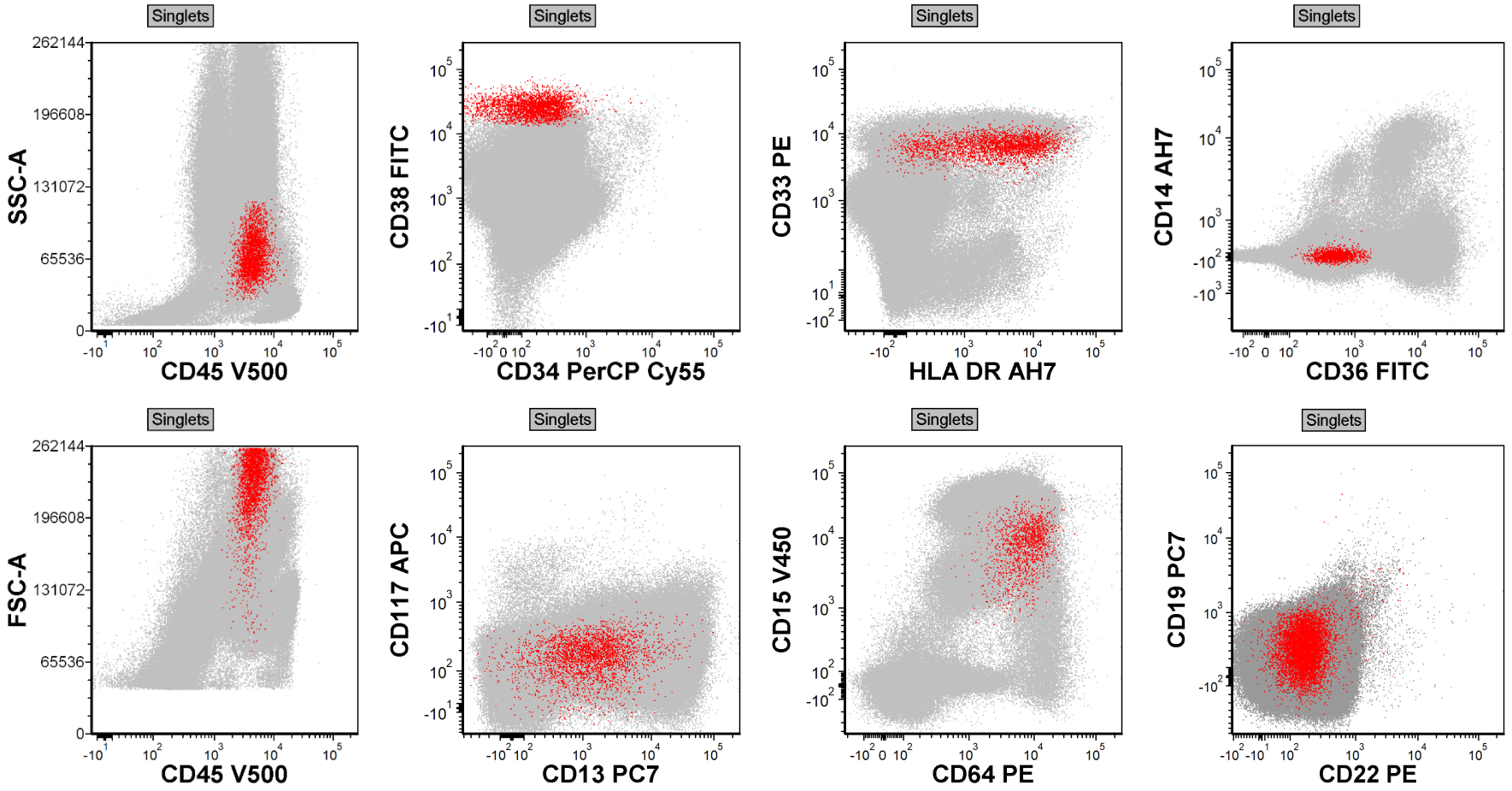


CD79a



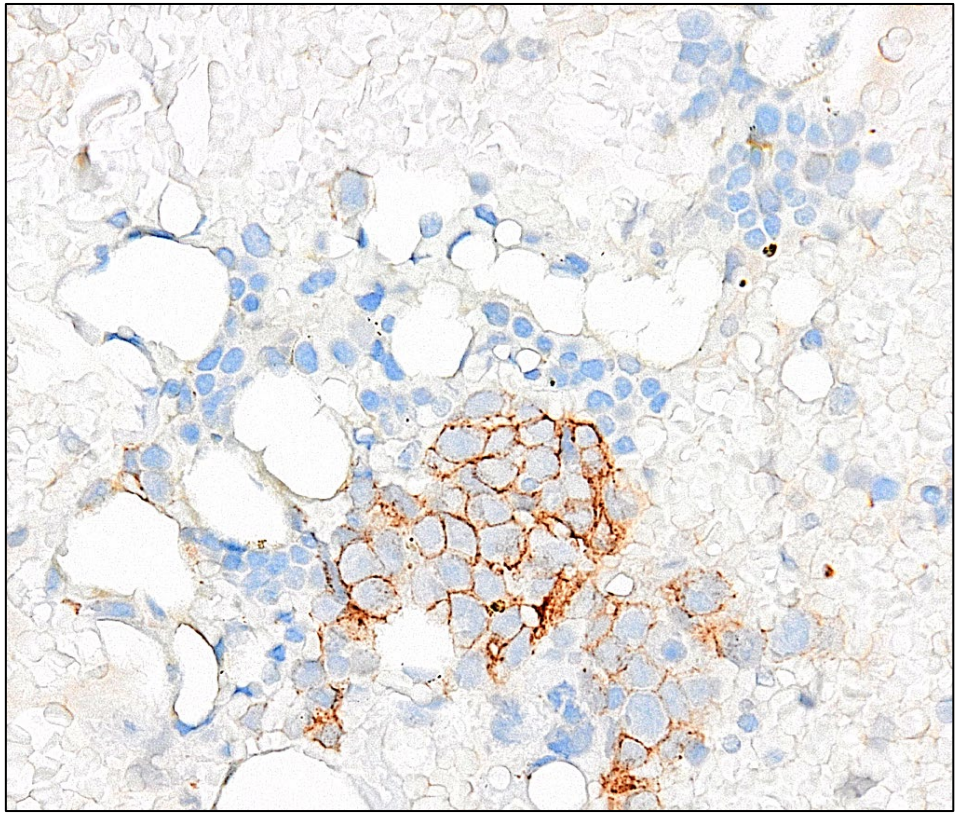
CD34

Post Therapy Marrow (Day +48)

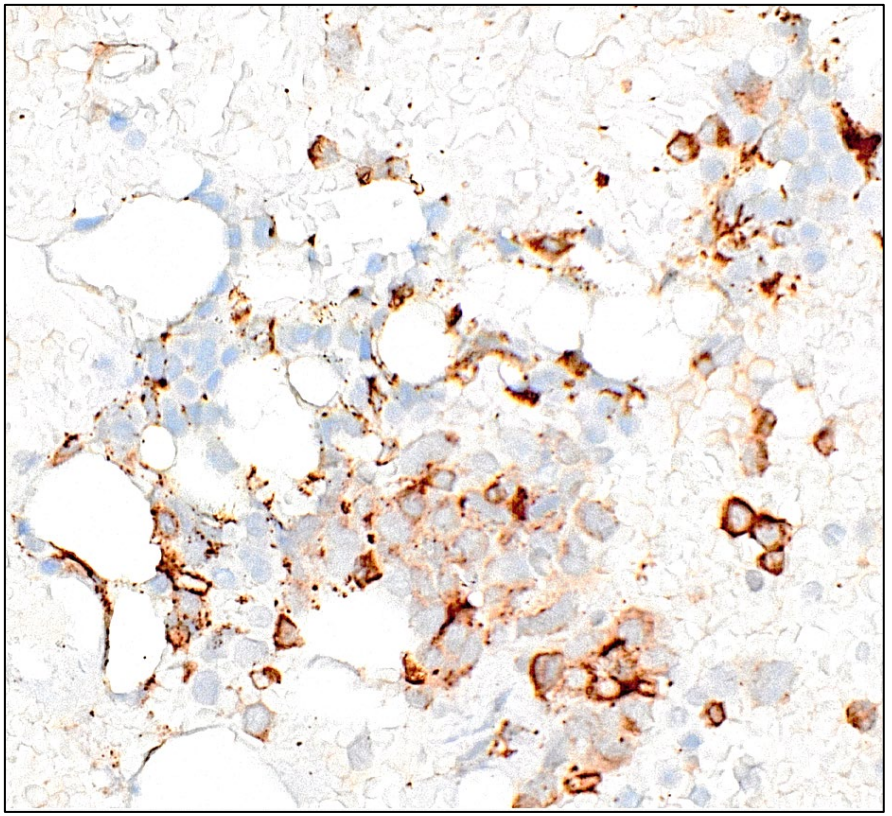


Images/Workup courtesy of
Dr. Hao-Wei Wang and Dr. Constance Yuan

Post Therapy Marrow (Day +48)



CD38



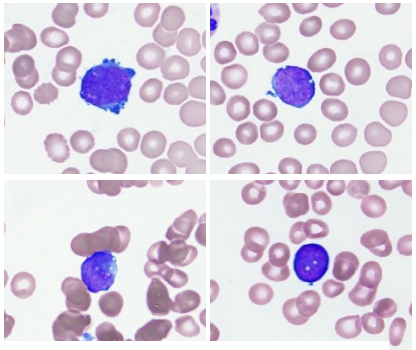
CD68

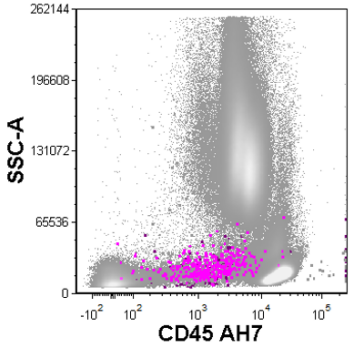
Diagnosis: Acute Myeloid Leukemia (Monocytic Leukemia)

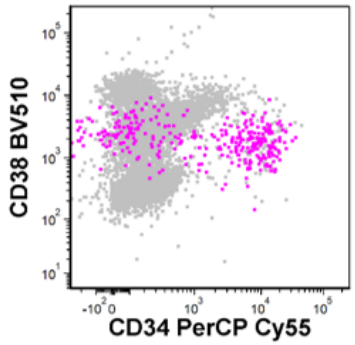
Pre-Therapy

B-Lymphoblastic Leukemia	
Markers	Expression
CD10	Positive
CD13	Dim/variable
CD19	Positive
CD20	Positive
CD24	Positive
CD33	Positive
CD34	Partial
CD38	Positive (moderate)
CD45	Dim to Negative

*Review: No definitive evidence of population of interest by flow cytometry



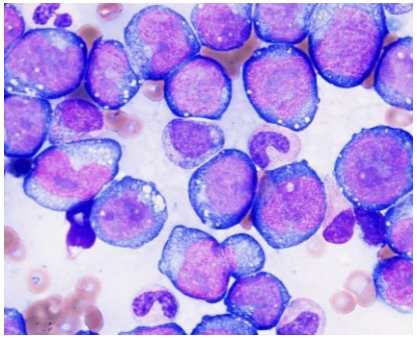


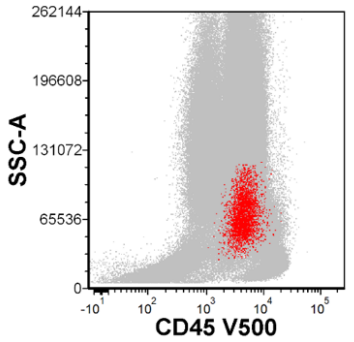


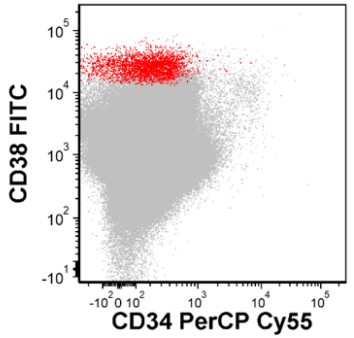
Post-Therapy

Population of Interest	
Markers	Expression
CD13	Dim/variable
CD14	Negative
CD33	Bright
CD34	Negative
CD38	Positive (Bright)
CD45	Moderate to bright
CD64	Positive
CD117	Negative
HLADR	Variably positive

*Negative for B-cell and T-cell markers







NIH National Institutes of Health
Clinical Center

Genetic Studies

Initial cytogenetic/molecular findings at B-ALL diagnosis

- IGH::CRLF2 fusion
- JAK2 and PTPN11 mutations
- ClonoSeq: Three dominant B-cell Igκ sequences, two dominant T-cell receptor gamma (TCRG) sequences, and one dominant T-cell receptor beta (TCRB) sequence

Cytogenetic/molecular findings at acute myeloid leukemia diagnosis

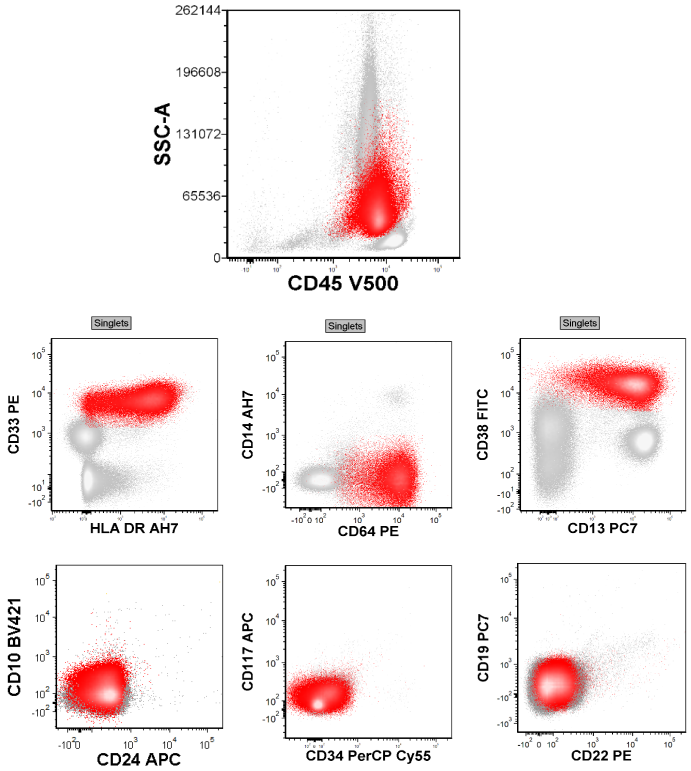
- CRLF2 fusion not detected by FISH
- Retained JAK2 and PTPN11 mutations
- Retained ClonoSeq profile: three dominant B-cell Igκ sequences, two dominant T-cell receptor gamma (TCRG) sequences, and one dominant T-cell receptor beta (TCRB) sequence

Lineage Switch

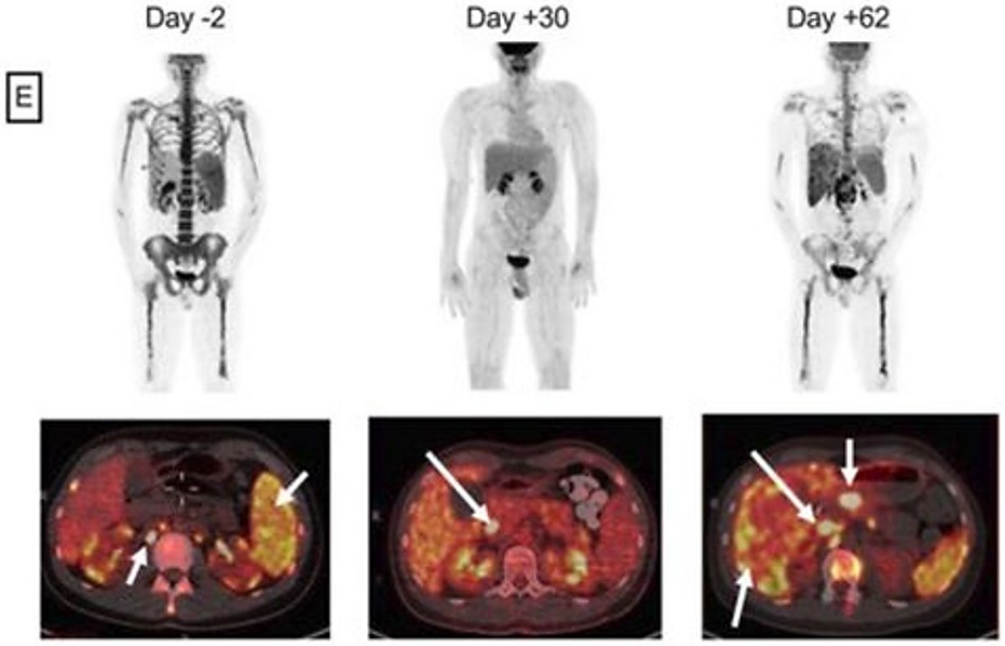
- Lineage switch refers to the phenotypic transformation of one leukemia lineage to another with retention of baseline genetics
- Mechanism of Post-Immunotherapy Relapse
- B-ALL lineage Switch Post Immunotherapy has been described with other genetic abnormalities:
  - BCR-ABL1 fusion
  - KMT2A (MLL1) rearrangement
  - DUX4 rearrangement
  - ZNF384 rearrangement
  - PAX5 alteration

Follow-up

Day +64 Peripheral Blood Flow Cytometry



Images/Workup courtesy of
Dr. Constance Yuan and Dr. Hao-Wei Wang



PMID: 39461880

Project EVOLVE

Large international collaborative retrospective study that systematically characterized post-immunotherapy lineage switch

75 LS cases

- B-ALL → AML: 53 cases (≈70.7%).
- B-ALL → (MPAL)/(ALAL): 17 cases (≈22.7%).
- T-ALL → AML: 5 cases (≈ 6.7%)

Timing: median of 1.5 months (range: 0-36.5 months) after immunotherapy (~81% occurred within first 6 months of most proximal immunotherapy).

Outcomes: Poor. The median overall survival after LS diagnosis ~4.8 months.

PMID: 40193715

Discussion Points

- Awareness of Lineage Switch
- Restrictions of flow cytometry
- Multimodal approach
- Sampling (focal lesions)

Acknowledgement

- **Our Patients**

- DLM Hematology
  - Drs. Raul Braylan, Katherine Calvo, Irina Maric, and Alina Dulau-Florea

- NCI Laboratory of Pathology
  - Drs. Constance Yuan & Hao-Wei Wang

- Mariela Monreal, Flow Cytometry Analyst

- DLM/NCI Laboratory Staff

- Clinical Team, Radiology, Molecular/Genetic Services

References

- Silbert SK, Scanlon S, Wang HW, et al. *CRLF2*-rearranged B-cell ALL with extramedullary lineage switch to AML following CD19-targeted therapy. *J Immunother Cancer*. 2024;12(10):e009499. Published 2024 Oct 26. doi:10.1136/jitc-2024-009499. PMID: 39461880

- Silbert SK, Rankin AW, Hoang CN, et al. Project EVOLVE: an international analysis of postimmunotherapy lineage switch, an emergent form of relapse in leukemia. Blood. 2025;146(4):437-455. doi:10.1182/blood.2024026655 PMID 40193715

- Goodlad JR, Xiao W, Amador C, et al. Phenotypic and genotypic infidelity in B-lineage neoplasms, including transdifferentiation following targeted therapy: Report from the 2021 SH/EAHP Workshop. *Am J Clin Pathol*. 2023;159(6):538-553. doi:10.1093/ajcp/aqad035 PMID: 37085149.