



Case 3: A Rare Case within a Rare Case and its Molecular Implications

Monthly Multi-Institutional Hematopathology
Interesting Case Conference

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PGY-5, Hematopathology fellow
3/11/26

Outline

- **Clinical Presentation**
 - **Biopsies**
 - **Molecular Results**
 - **Final Diagnosis**
 - **Discussion**
 - **Follow-up**
 - **Take Home Messages**
-
- **Nothing to disclose**

Clinical Presentation

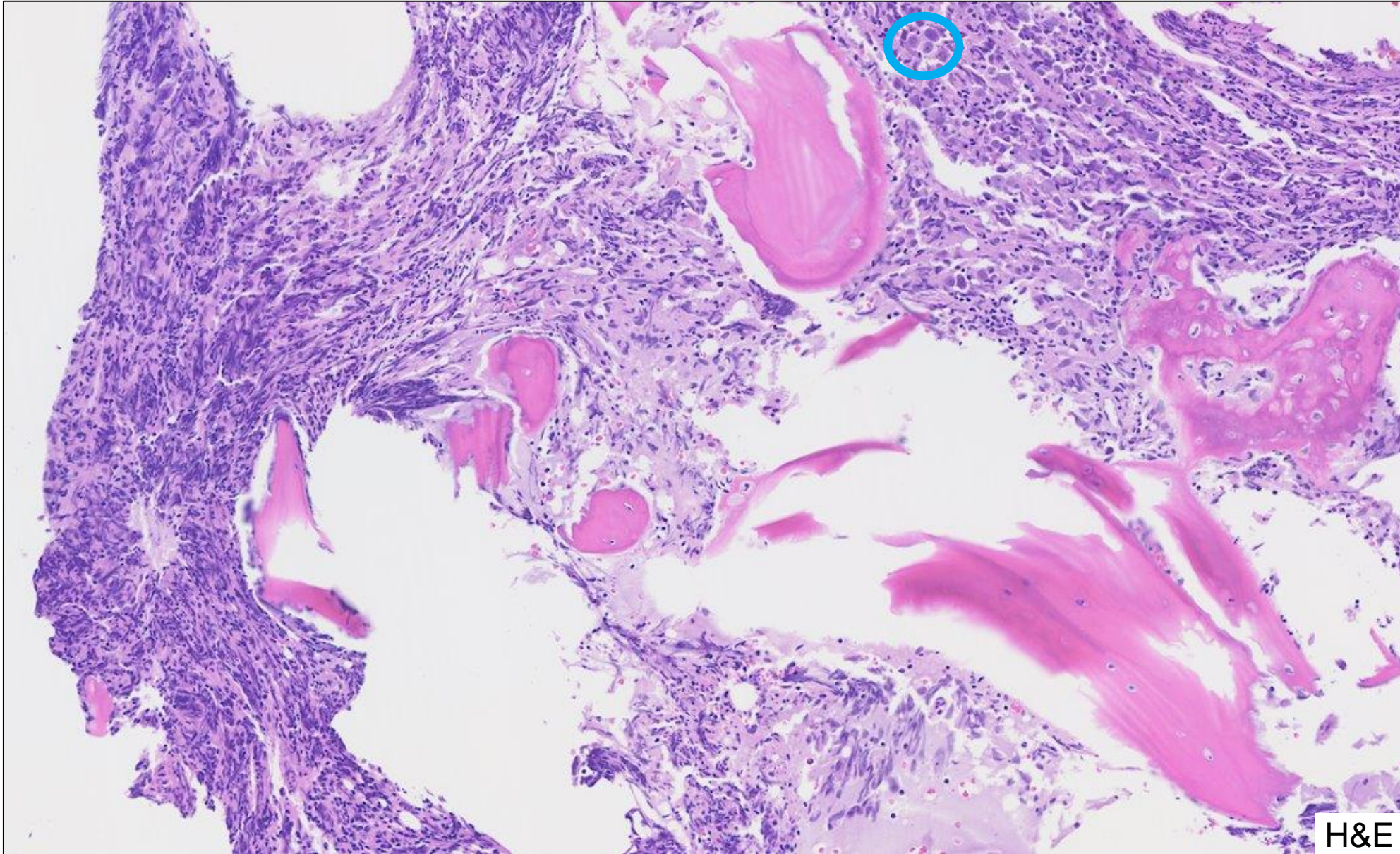
- A 69-year-old man
 - History of prostate cancer s/p prostatectomy and longstanding history of JAK2+ myeloproliferative neoplasm (MPN) on hydroxyurea (diagnosed at an outside hospital, no molecular reports available).
 - Presenting with weight loss and severe hip pain for >4 weeks.
- Imaging CT and MRI: Isolated lytic bone changes at the sacroiliac junction.



CBC		Ref. Range
White blood cell count	11.8 K/uL	4.5 - 11.0 x10E3/uL
Hemoglobin	12.9 g/dL	13.9 - 16.3 g/dL
Platelet count	714 K/uL	150 - 450 x10E3/uL

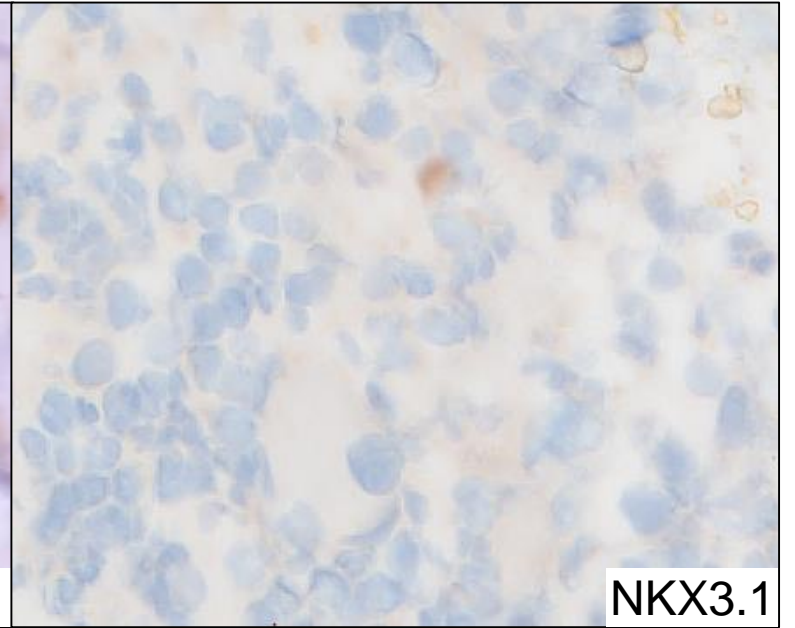
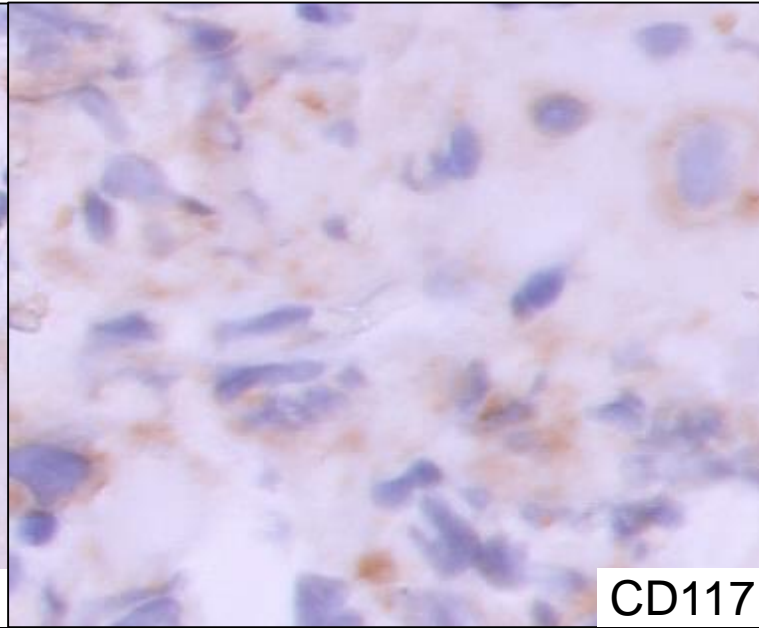
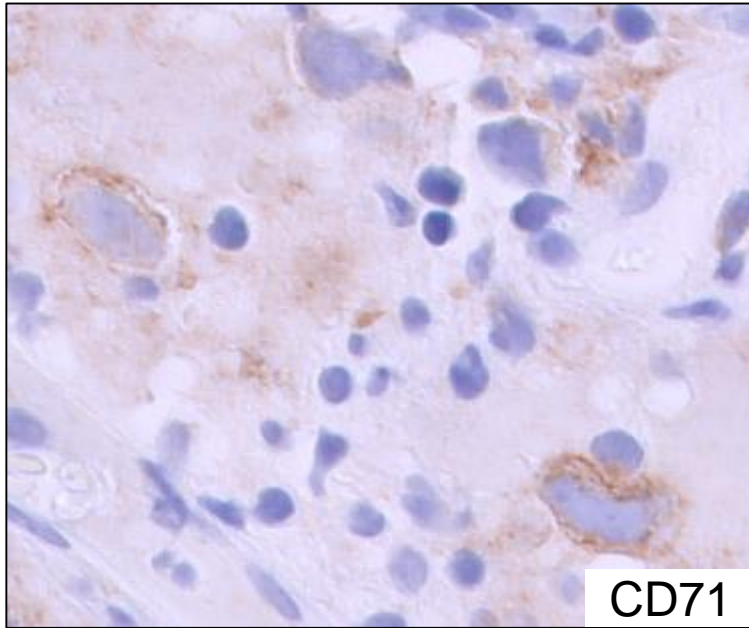
Differential %		Ref. Range %
Neutrophils	74.3	40.0 - 78.0
Lymphocytes	14.3	15.0 - 50.0
Monocytes	6.6	2.0 - 11.0
Eosinophils	2.7	0.0 - 5.0
Basophils	0.8	0.0 - 1.0

First Biopsy – Left Posterior High Iliac Bone

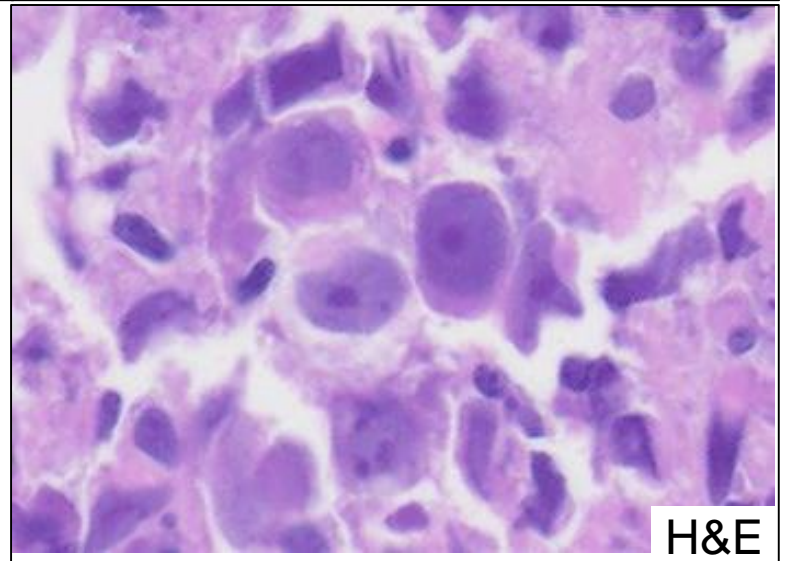


H&E

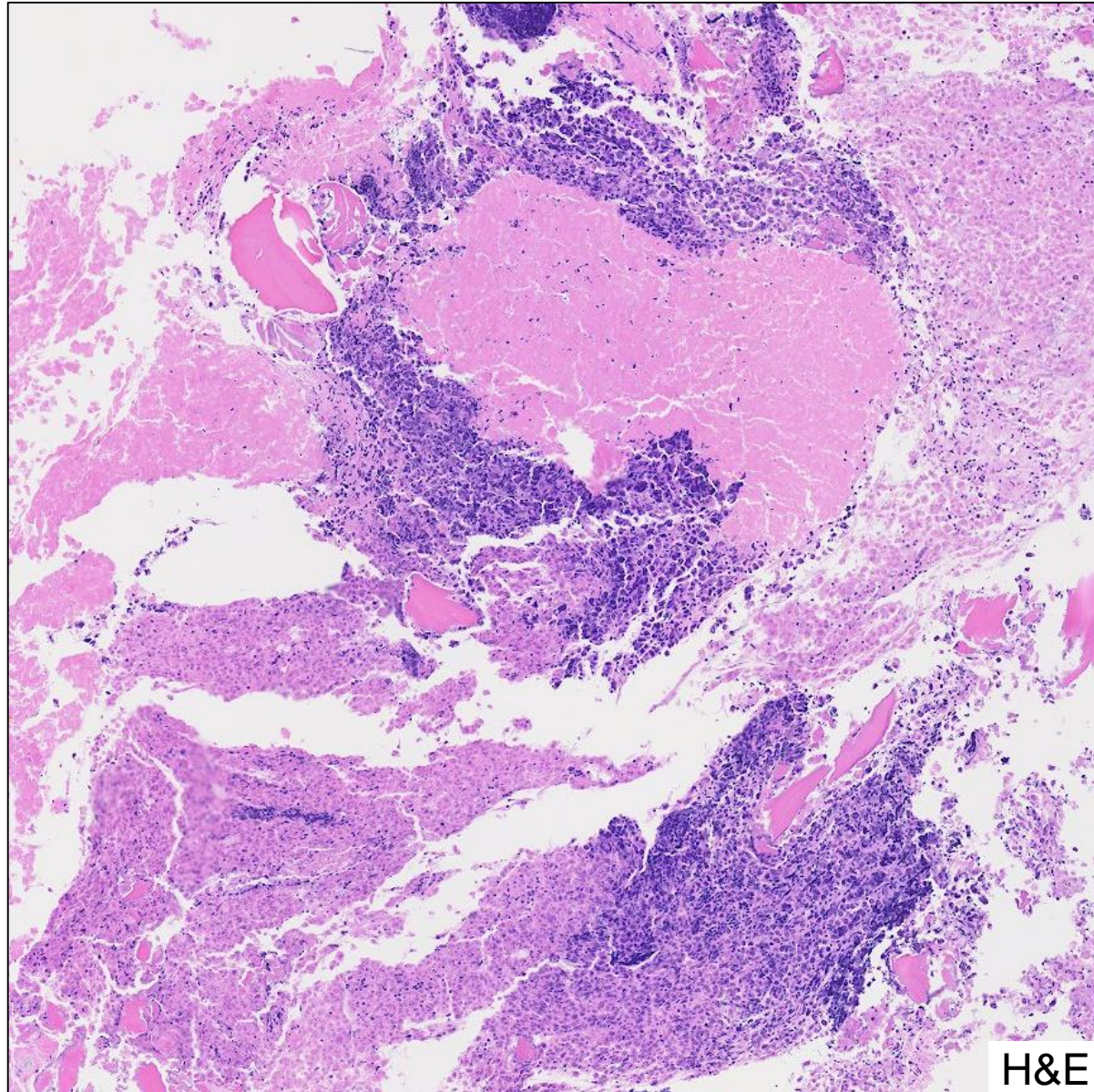
First Biopsy



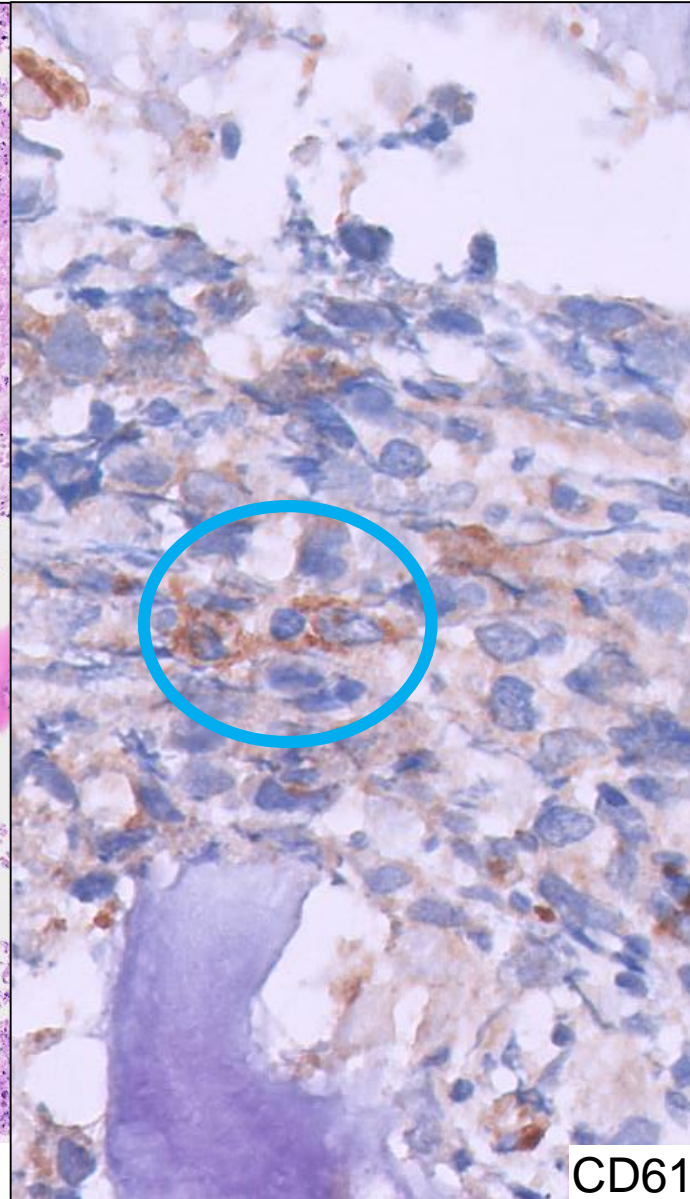
- **FRAGMENTED WITH SIGNIFICANTLY CRUSHED CELLULAR ELEMENTS.**
- **SMALL FOCAL AREAS SHOW INFILTRATION BY LARGE ATYPICAL CELLS.**



Second Biopsy – Lesion At Posterior Left Ilium

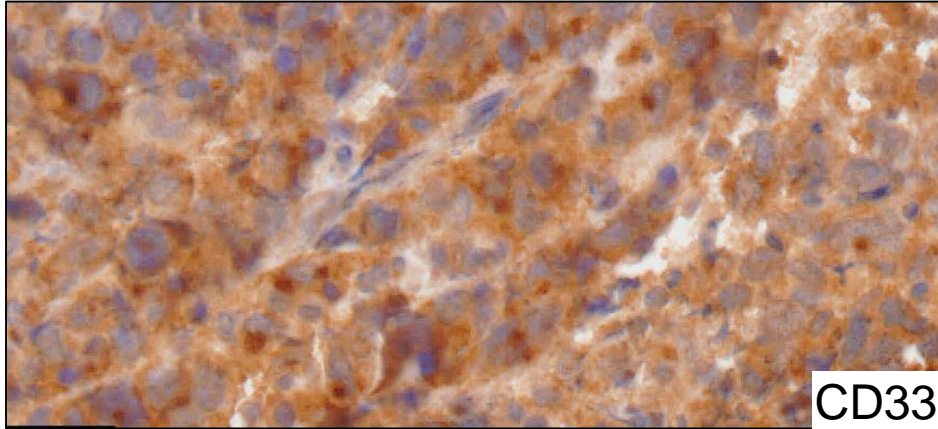
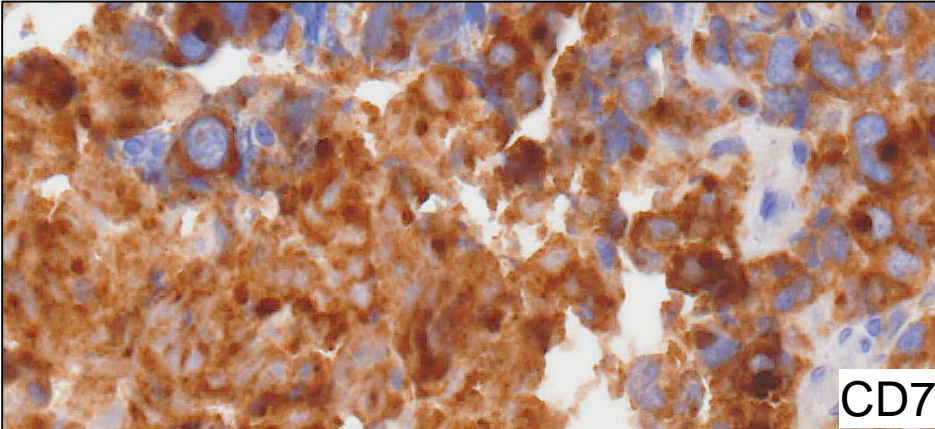
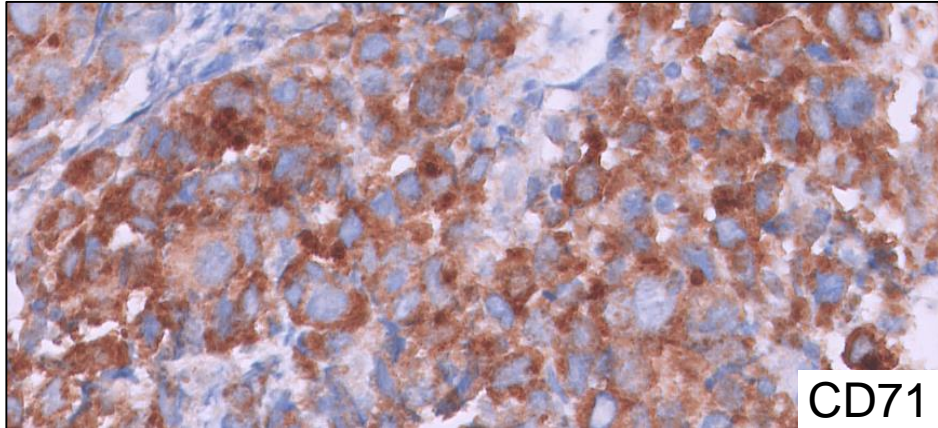
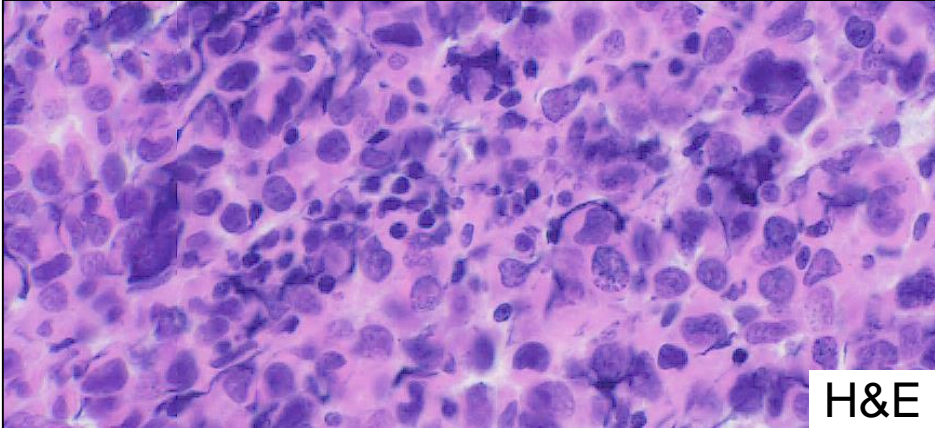


H&E



CD61

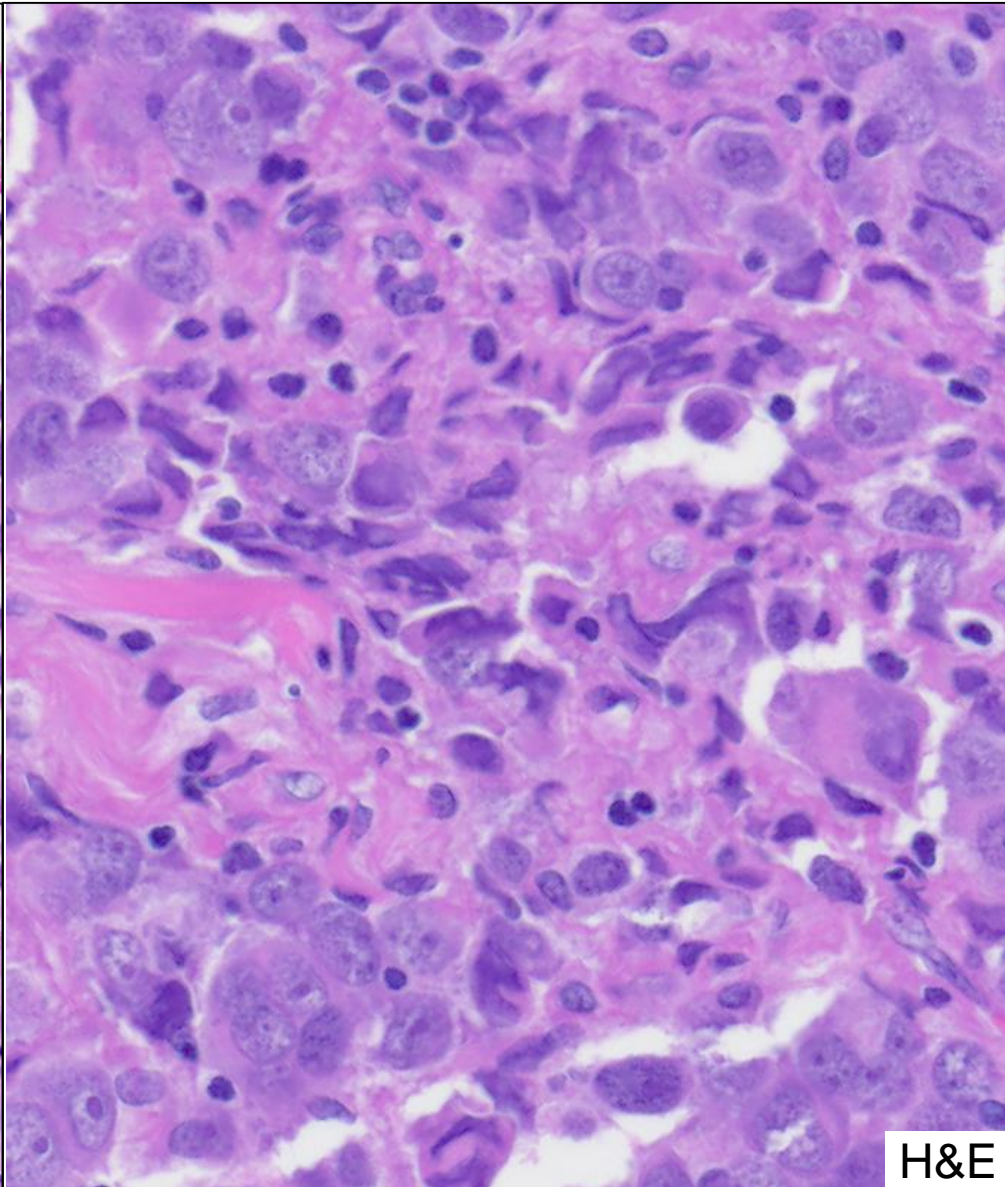
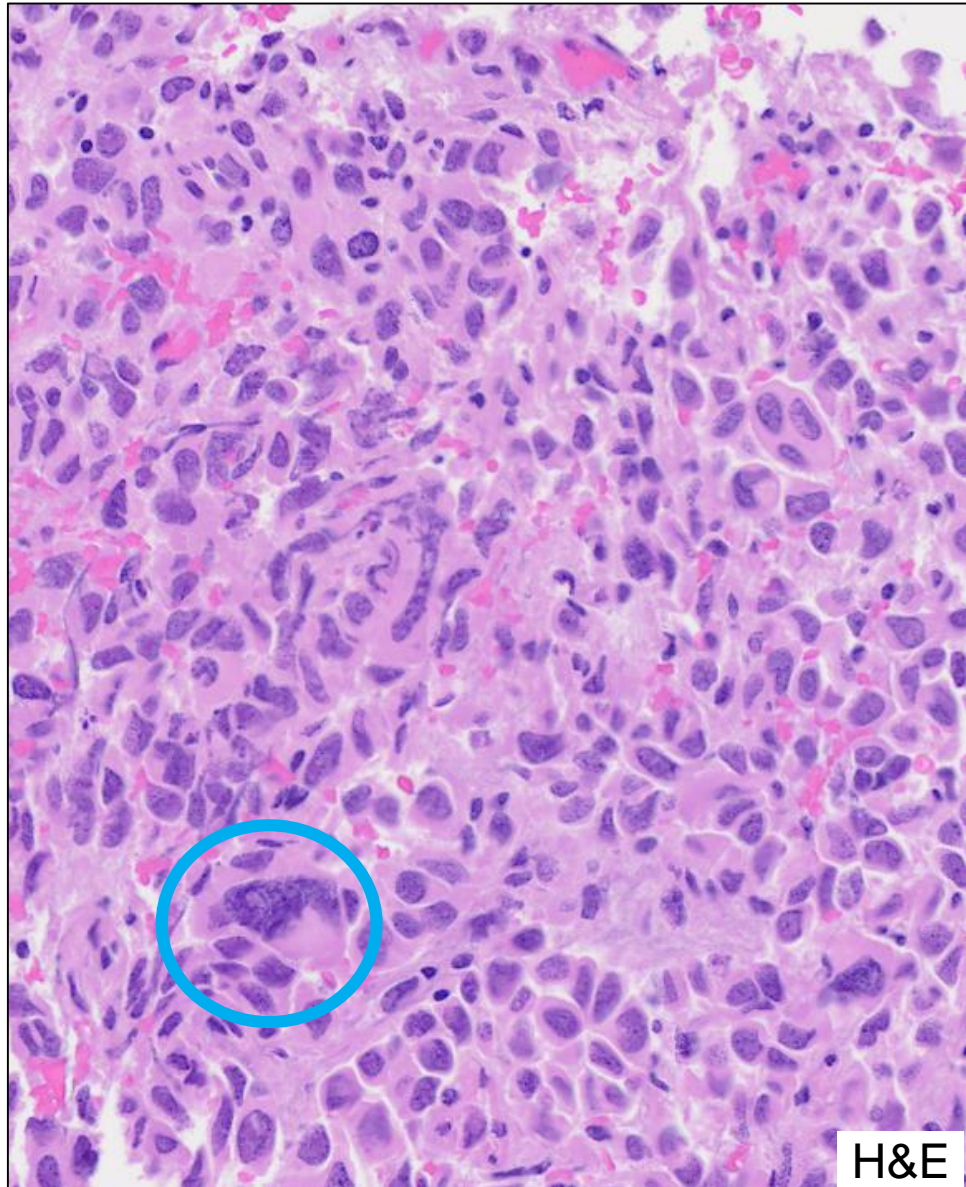
Second Biopsy – Lesion At Posterior Left Ilium



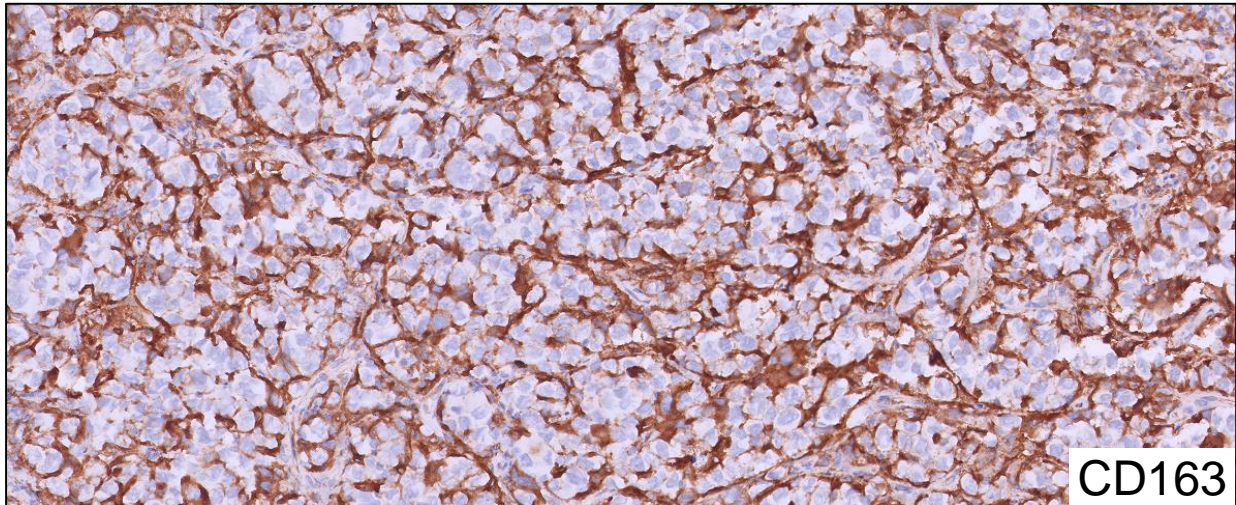
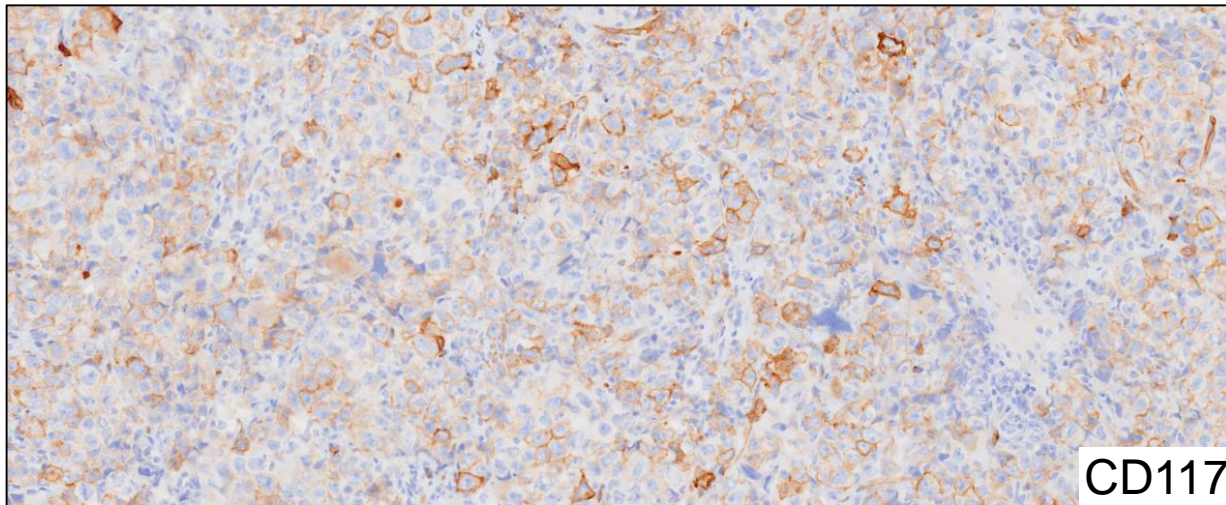
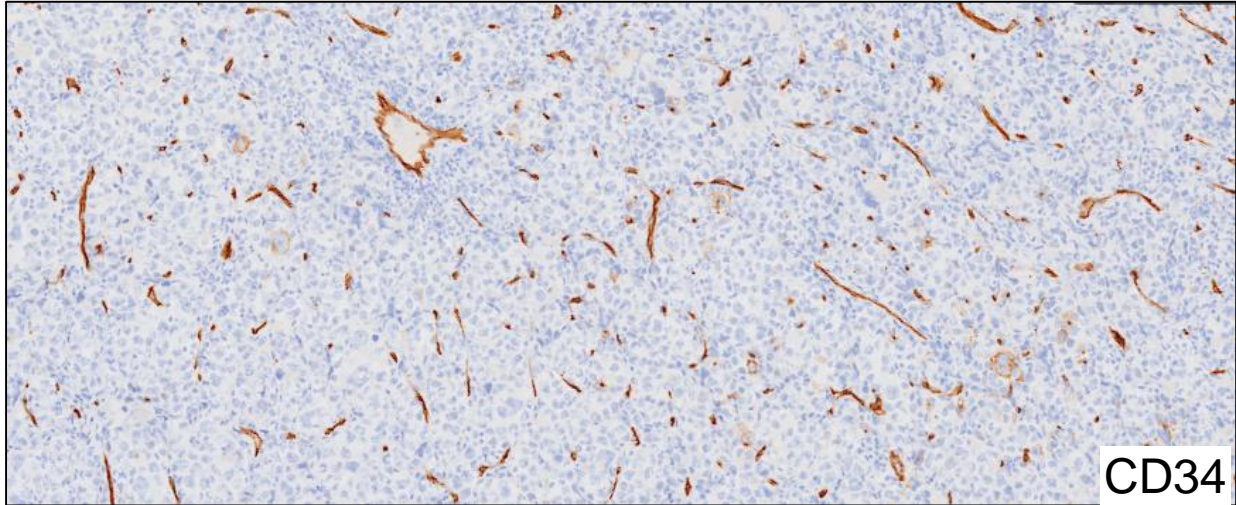
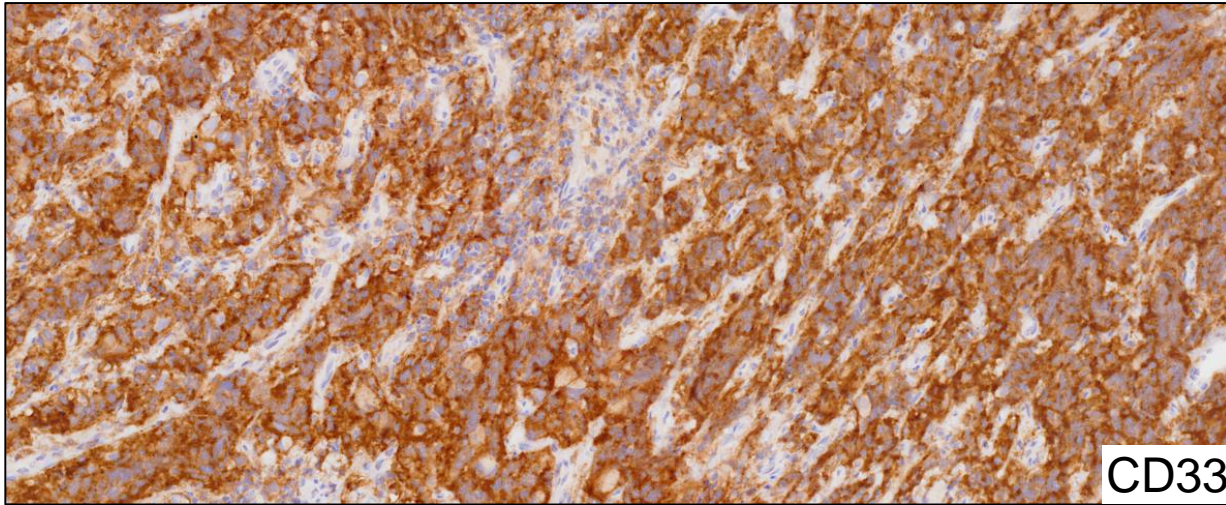
POSITIVE	NEGATIVE
CD43 (partial)	CD45
CD33	CD34
CD71	CD117
CD7	TdT
P53 (variable)	CD68
	CD56
	MUM1
	AE1/AE3
	NKX3.1

AGGRESSIVE HEMATOLYMPHOID NEOPLASM WITH EXTENSIVE NECROSIS.

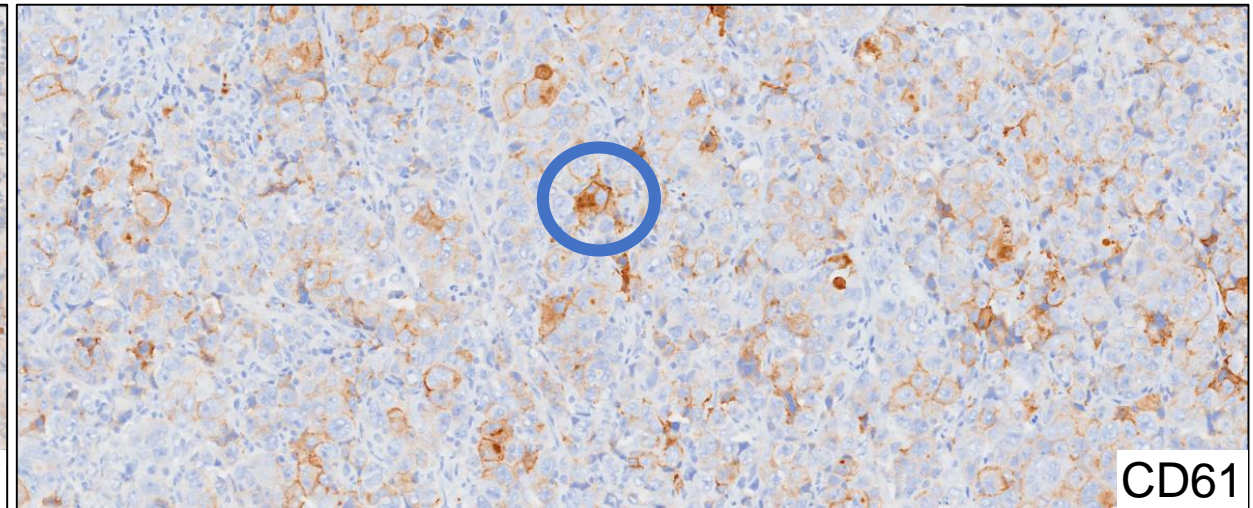
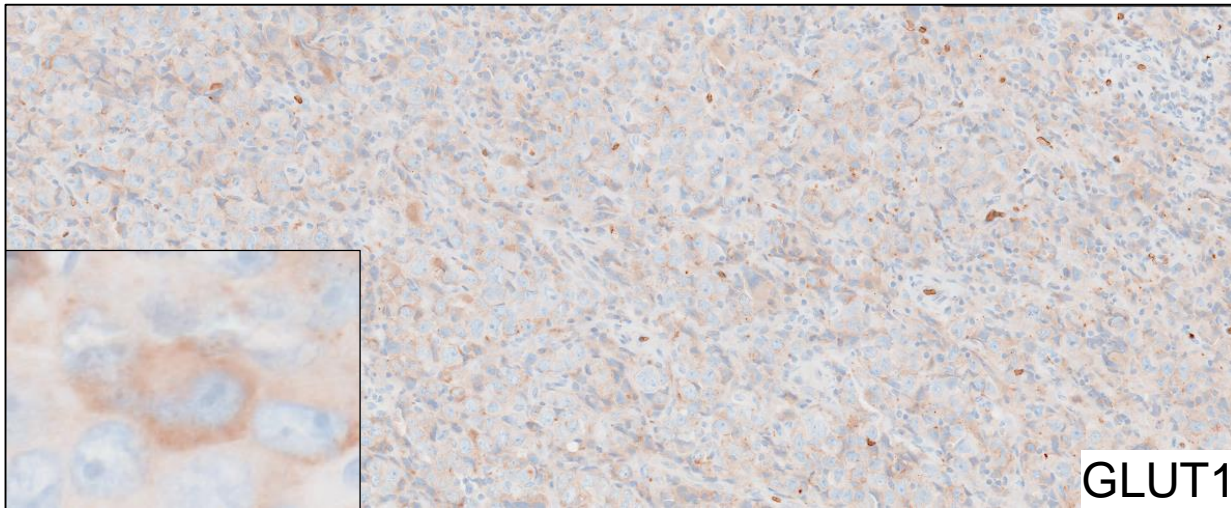
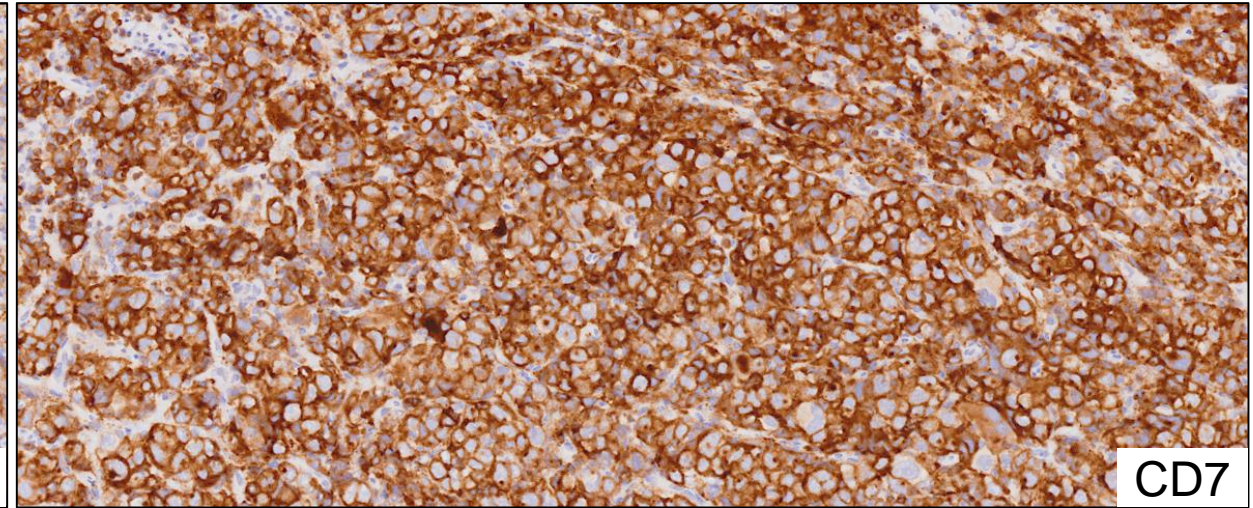
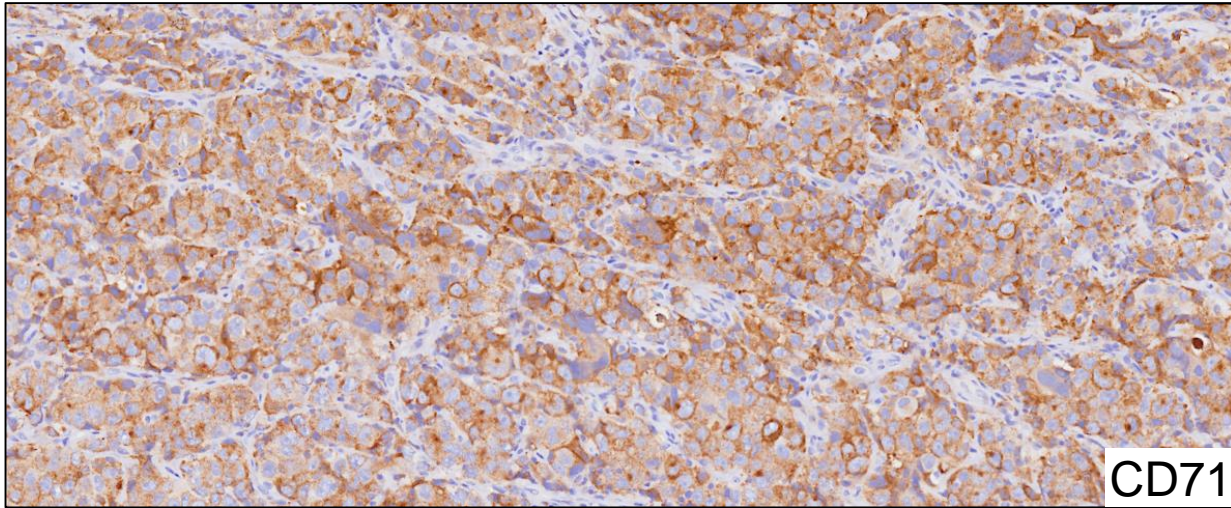
Third Biopsy - Left Iliac Lesion



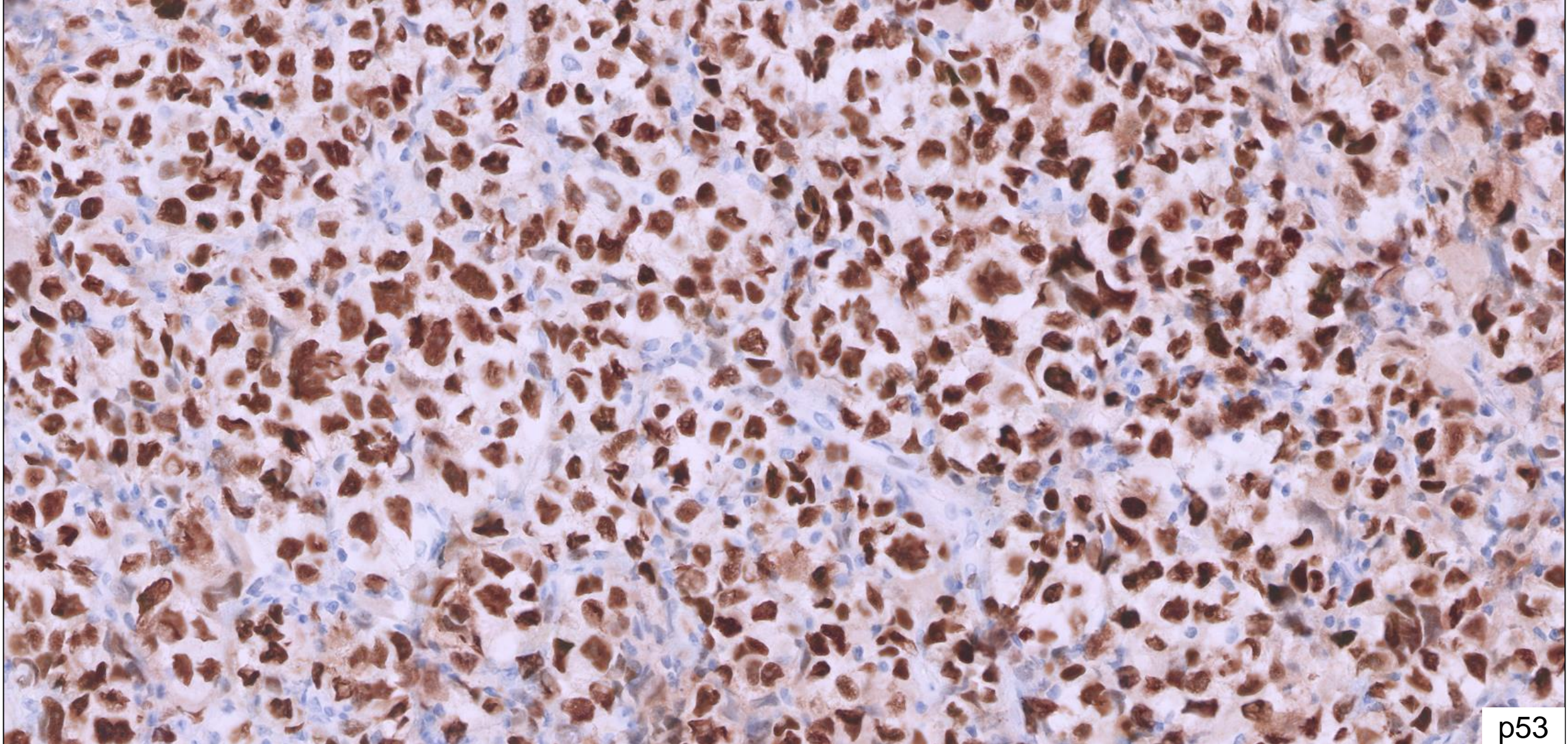
Third Biopsy



Third Biopsy



Third Biopsy



p53

Final Diagnosis

POSITIVE	NEGATIVE
CD45	CD34
CD43	MPO
p53	CD3
CD71	CD20
GLUT-1 (weak)	TdT
CD61 (subset)	CD30
CD33	MUM1
CD117 (subset)	SOX11
CD7	ALK1
INI1 retained	CD163

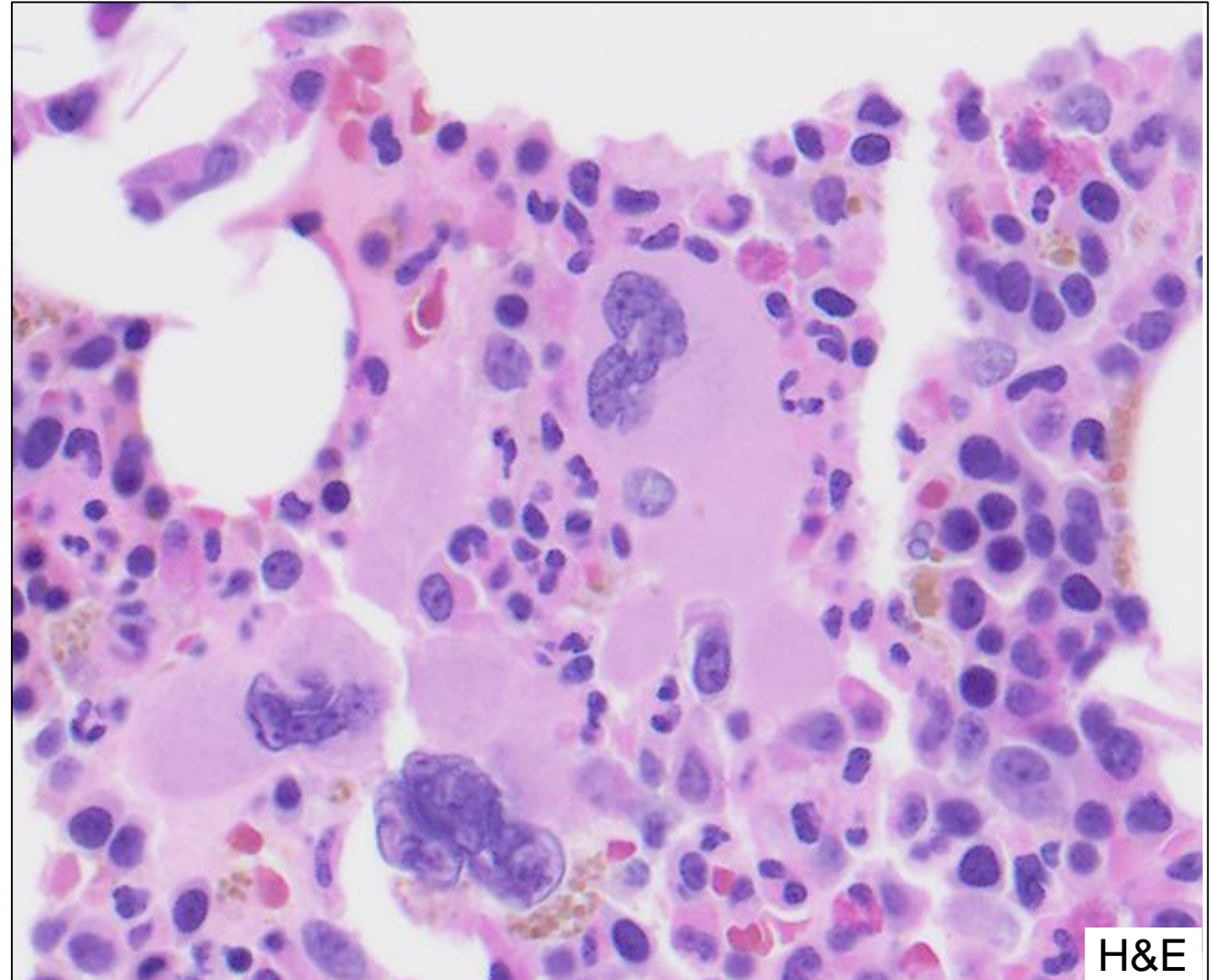
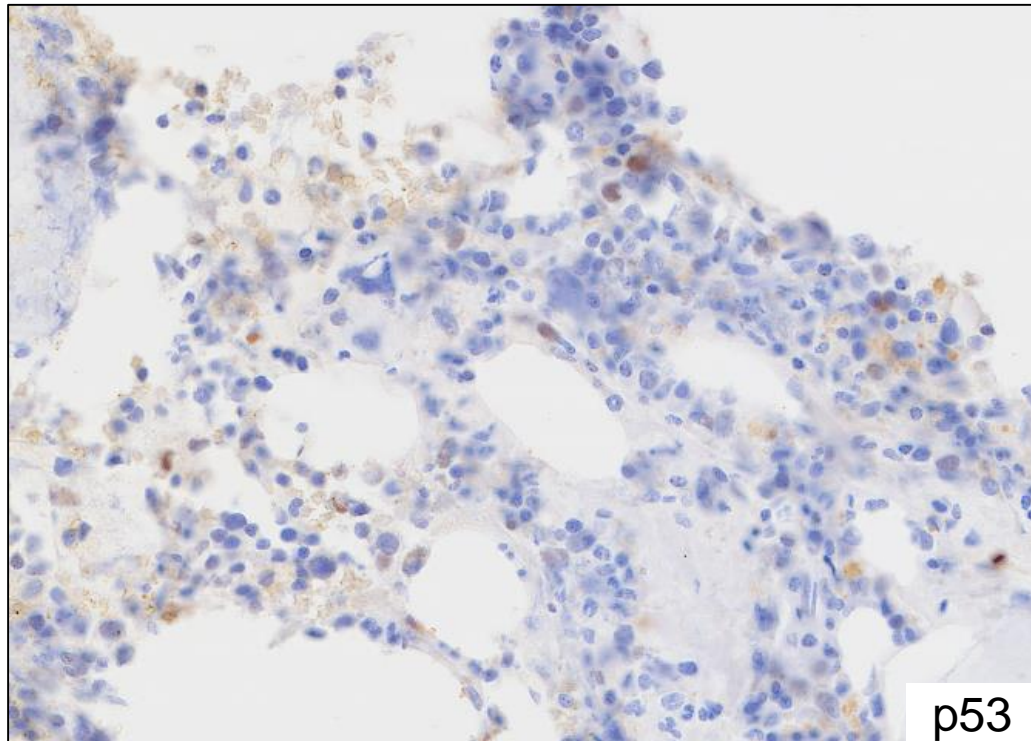
- HIGH GRADE MYELOID NEOPLASM WITH P53 OVEREXPRESSION.
- The expression of CD71 and GLUT1 raises the possibility of erythroblastic sarcoma.

Molecular Results - FoundationOne Heme Next Generation Sequencing

MUTATION	VAF
<i>JAK2</i> V617F	34.6%
<i>TP53</i> Y234S	33.5%
<i>TP53</i> P152R	35%
<i>SF3B1</i> K666N	1%

Bone Marrow

- PERSISTENT MYELOPROLIFERATIVE NEOPLASM.
- NORMOCELLULAR MARROW (~40%) FOR AGE
- Karyotype performed on the marrow: 46, XY
- Cytogenetics: No clonal rearrangements



Erythroblastic Sarcoma / Acute Erythroid Leukemia

- WHO HAEM-5 - Acute erythroid leukemia
 - Rare, aggressive subtype of AML with neoplastic proliferation of erythroid cells.
 - High prevalence of *TP53* alterations - 65% of detected *TP53* mutations were biallelic inactivation (NGS).
- ICC - Pure erythroid leukemia; most cases classified as AML with mutated *TP53*.

	Pediatric ES (n=11)	Adult ES (n=36)
Other associated myeloid neoplasms	0/11	25/36
<i>TP53</i> mutations	0/10	17/19 (89%)
<i>JAK2</i> mutations	2/10 (<i>JAK2</i> variants of uncertain significance)	3/19 (<i>JAK2</i> V617F)

- Median overall survival of three months.

Erythroblastic Sarcoma / Acute Erythroid Leukemia

Summary of the key immunostains and molecular genetic data^a

Immunostain or molecular characteristic	Adult ES (our cohort)	Pediatric ES			Total ES
		Our cohort	Literature	Total	
CD43	20/22	9/9	8/8	17/17	37/39
CD45	11/29	3/10	1/9	4/19	15/48 ^b
CD34	0/33	0/10	1/9	1/19	0/52
CD36	3/3	3/3	4/4	7/7	10/10
CD71	33/33	10/10	6/6	16/16	49/49
CD117	24/33	9/10	6/8	15/18	39/51
E-Cad	30/31	4/6	4/7	8/13	38/44
GLUT1	8/8	4/4	0/0	4/4	12/12
CD235a	16/22	3/6	5/6	8/12	24/34
Hemoglobin A	5/10	3/3	2/3	5/6	10/16
P53	21/24	3/9 ^c	0/1	3/10	24/34
Complex karyotype without -17	7/17	3/6	3/6	6/12	13/29
Complex karyotype with -17	8/17	2/6	0/6	2/12	10/29
TP53 mutation	17/19	0/4	0/6	0/10	17/29

Adult and pediatric cases share similar morphology and immunophenotype, however, with distinct molecular profiles.

Acute Myeloid Leukemia with Both Erythroid and Megakaryocytic Differentiation

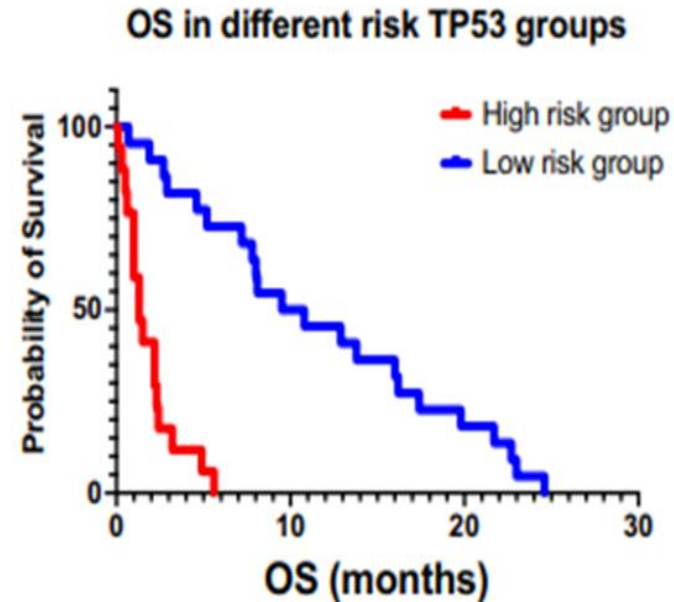
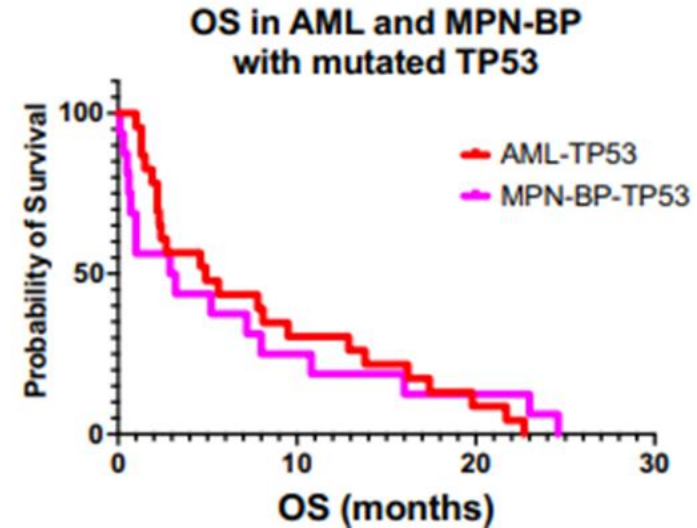
- Liu et al, three patients with AML demonstrating co-expression of:
 - Erythroid markers (at least two): CD71, glycophorin A, CD117, E-cadherin
 - Megakaryocytic markers: CD61, Von Willebrand factor, CD42b

	Liu et al	Literature review	
	Adult Cases (n=3)	Adult Cases (n=6)	Pediatric Cases (n=2)
Complex Karyotype	2/3	5/5	0/2
<i>TP53</i> mutation	3/3	3/3	0/1
<i>JAK2</i> V617F mutation	1/3	2/3	0/1

- Adult cases showed cytogenetic and / or mutational profiles associated with poor prognosis.
- Likely derives from leukemic transformation of megakaryocyte-erythroid precursors (MEP).

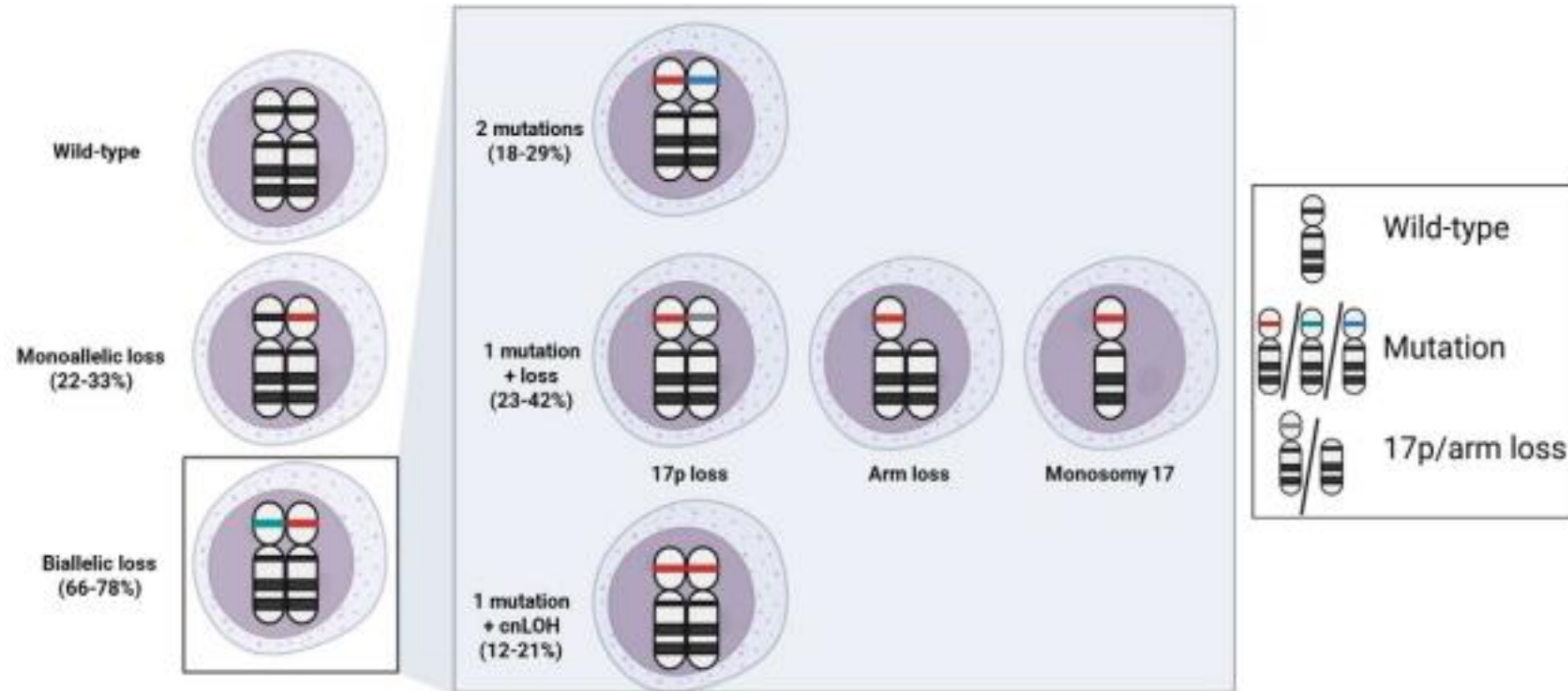
TP53-Mutated AML and Blast Phase MPN: Distinct Mutation Leads to Poorer Prognosis

<i>TP53</i> mutations	OS (Months)
Intron 4	1.3
Exon 5	1.0
Exon 6	16.2
Exon 7	7.9
OD	2.3

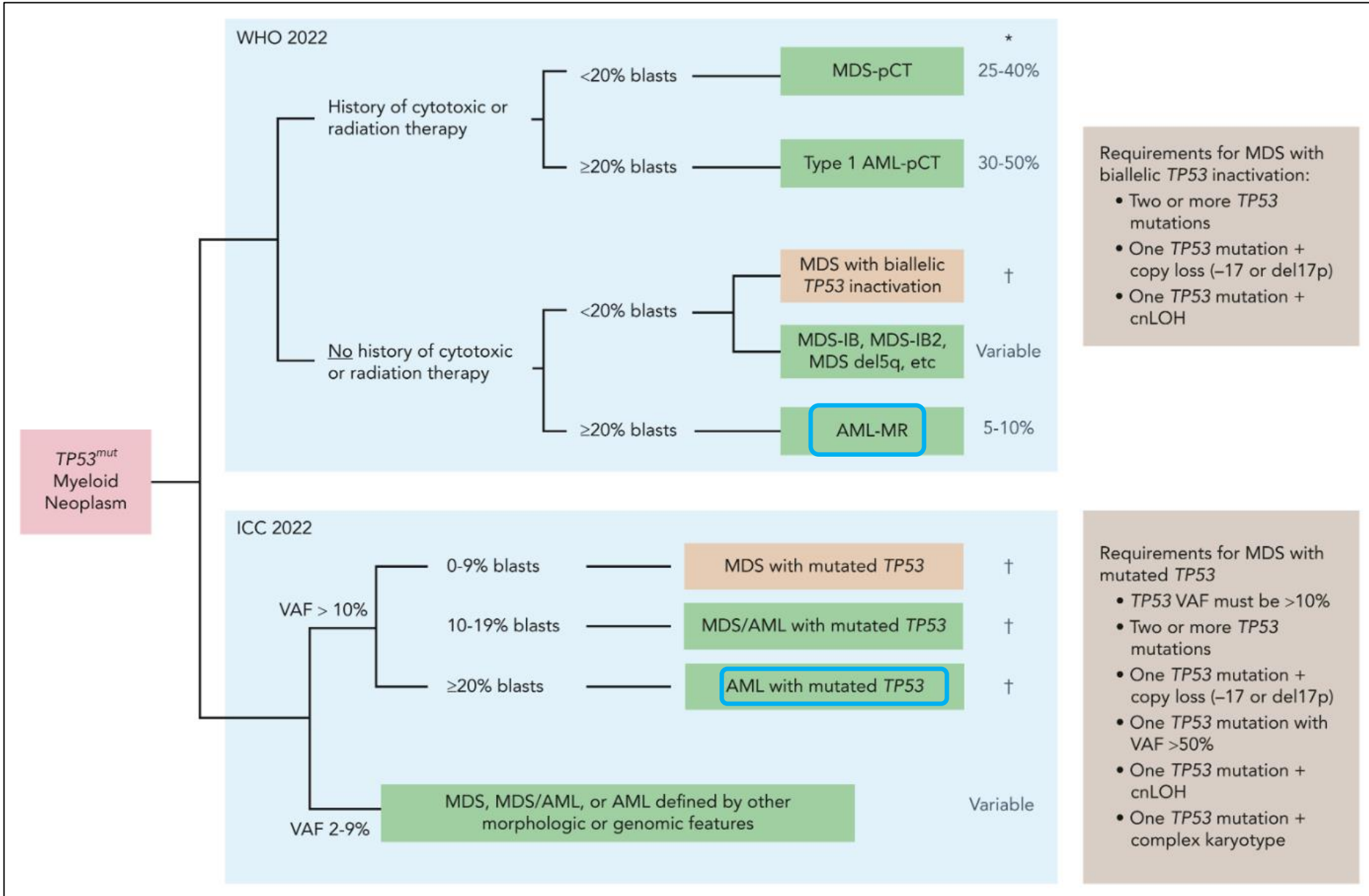


TP53- "Guardian of the genome"

- Transcription factor regulating cell proliferation, DNA stability and repair, and cell cycle arrest and apoptosis.
- *TP53* alteration – most prevalent abnormality in human cancers, but less frequent in myeloid neoplasms.
 - ~10-14% in de novo MDS/AML
 - ~33-37% in therapy related myeloid neoplasms.



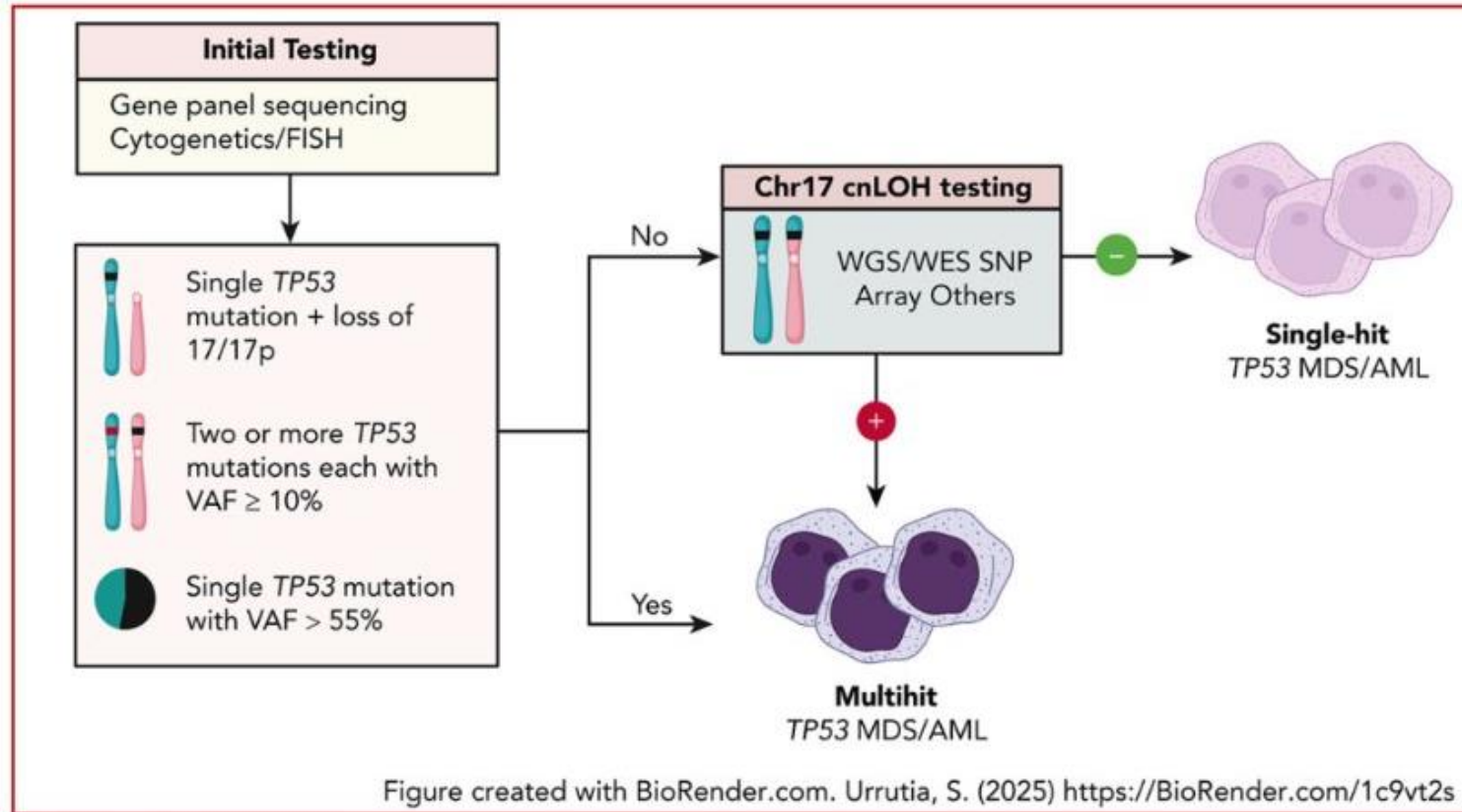
TP53 in WHO-HAEM5 and ICC



Critical components

1. Allelic status
2. Variant allele frequency
3. Complex karyotype

Testing for *TP53*

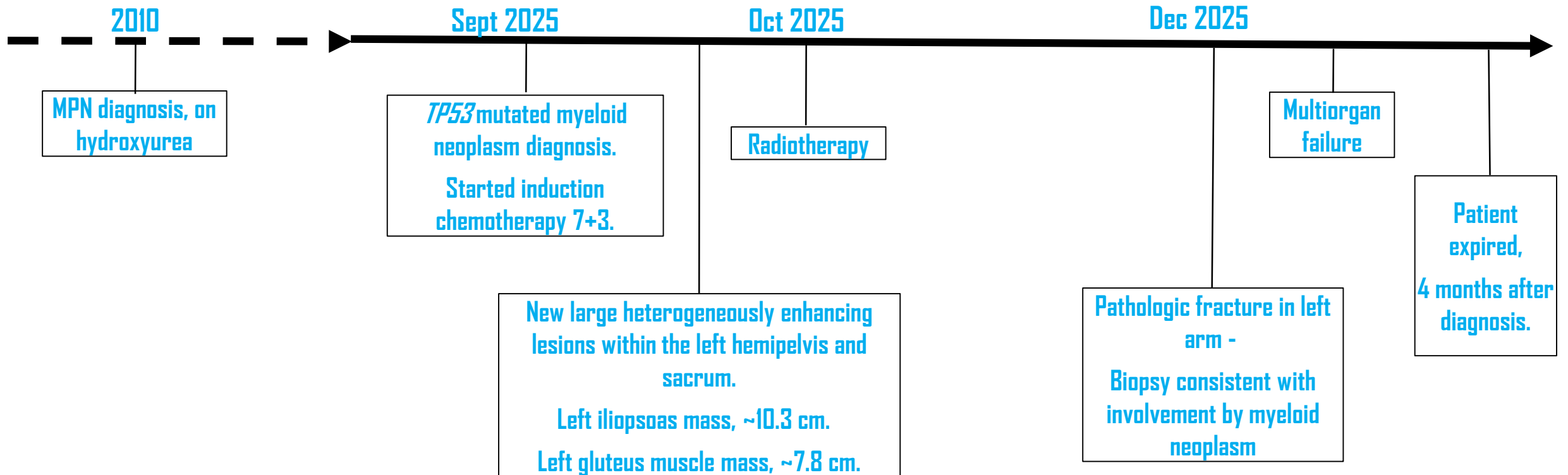


Conclusion: In *TP53* mutant myeloid neoplasms, copy-neutral loss of heterozygosity (cnLOH) accurately determines allelic status, making clinical testing for this event warranted.

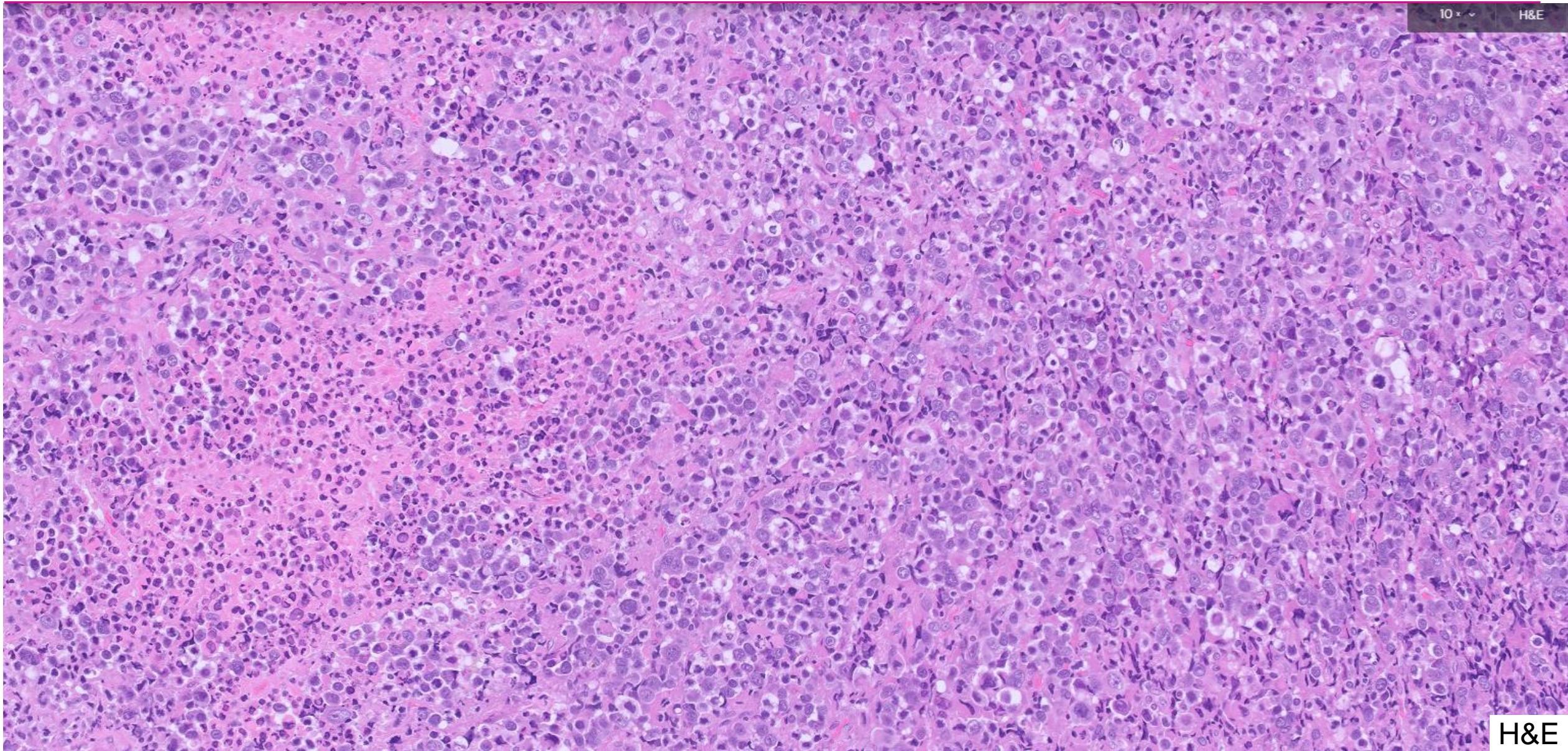
Urrutia et al. DOI: 10.1182/*blood*.2025029691



Follow up

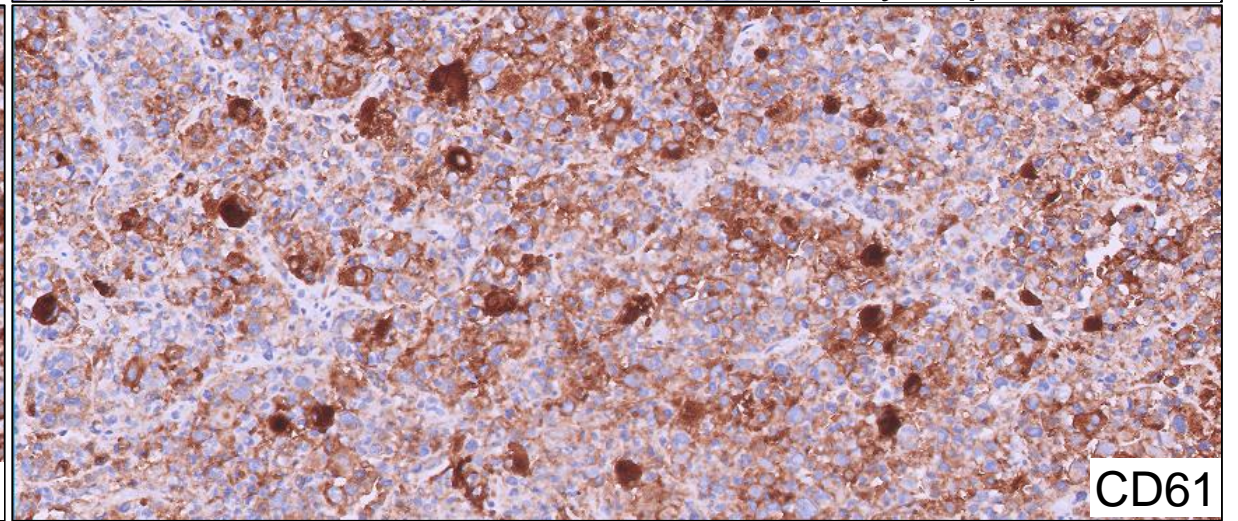
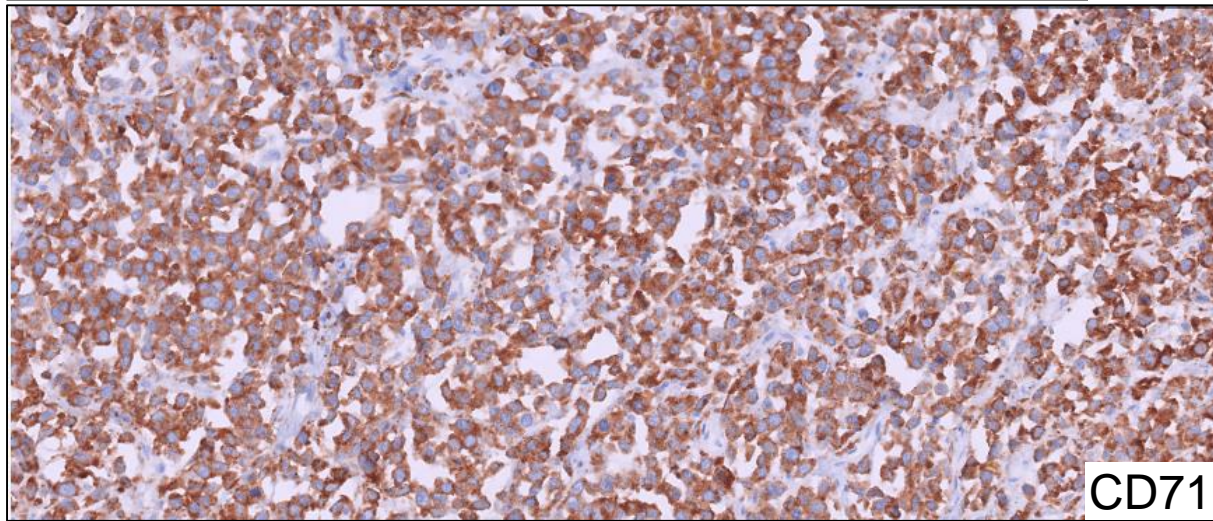
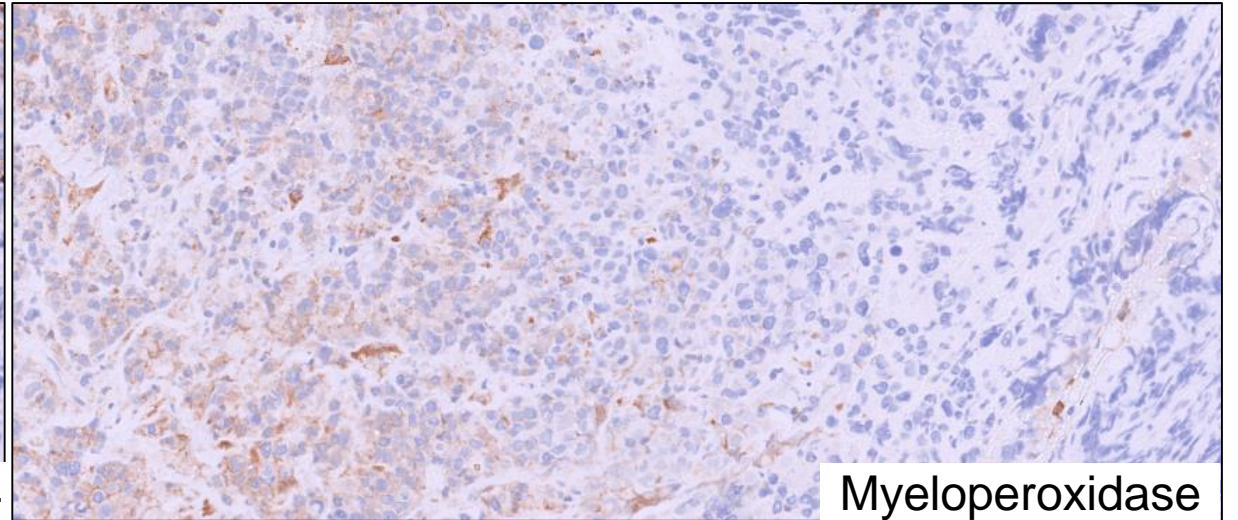
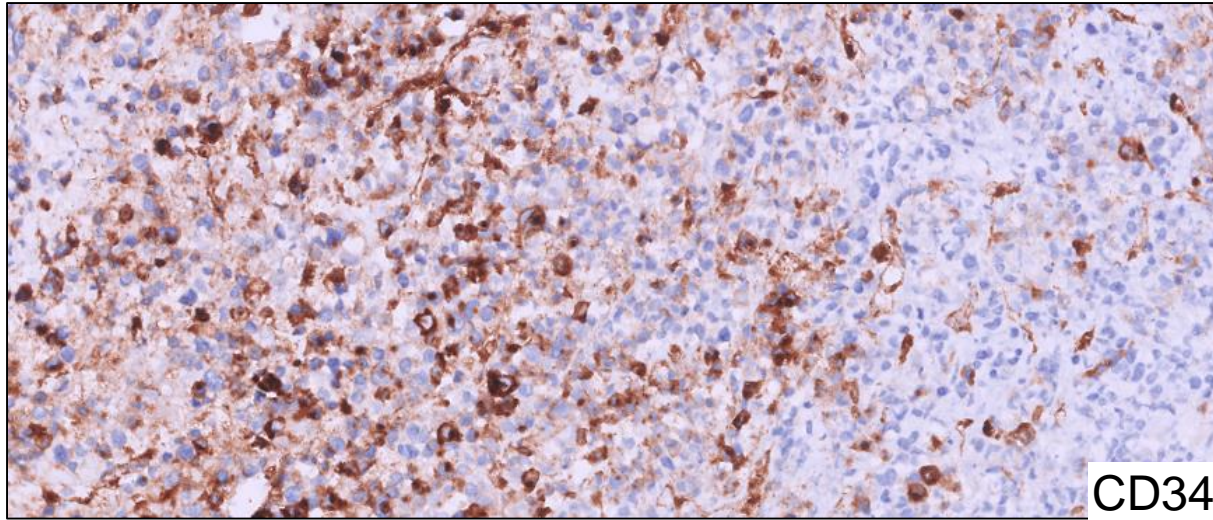


Fourth Biopsy – Left Proximal Humerus Lesion

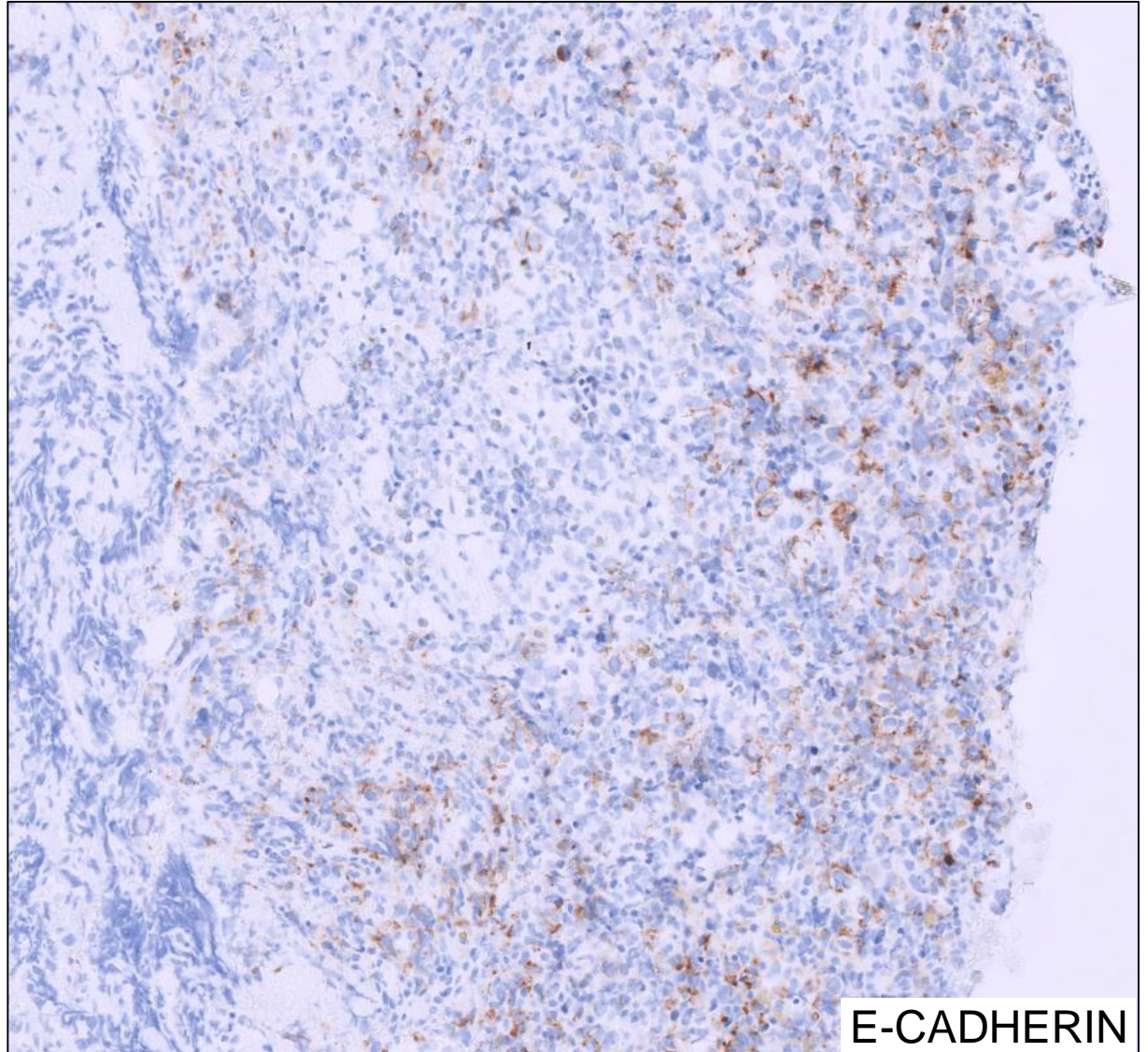
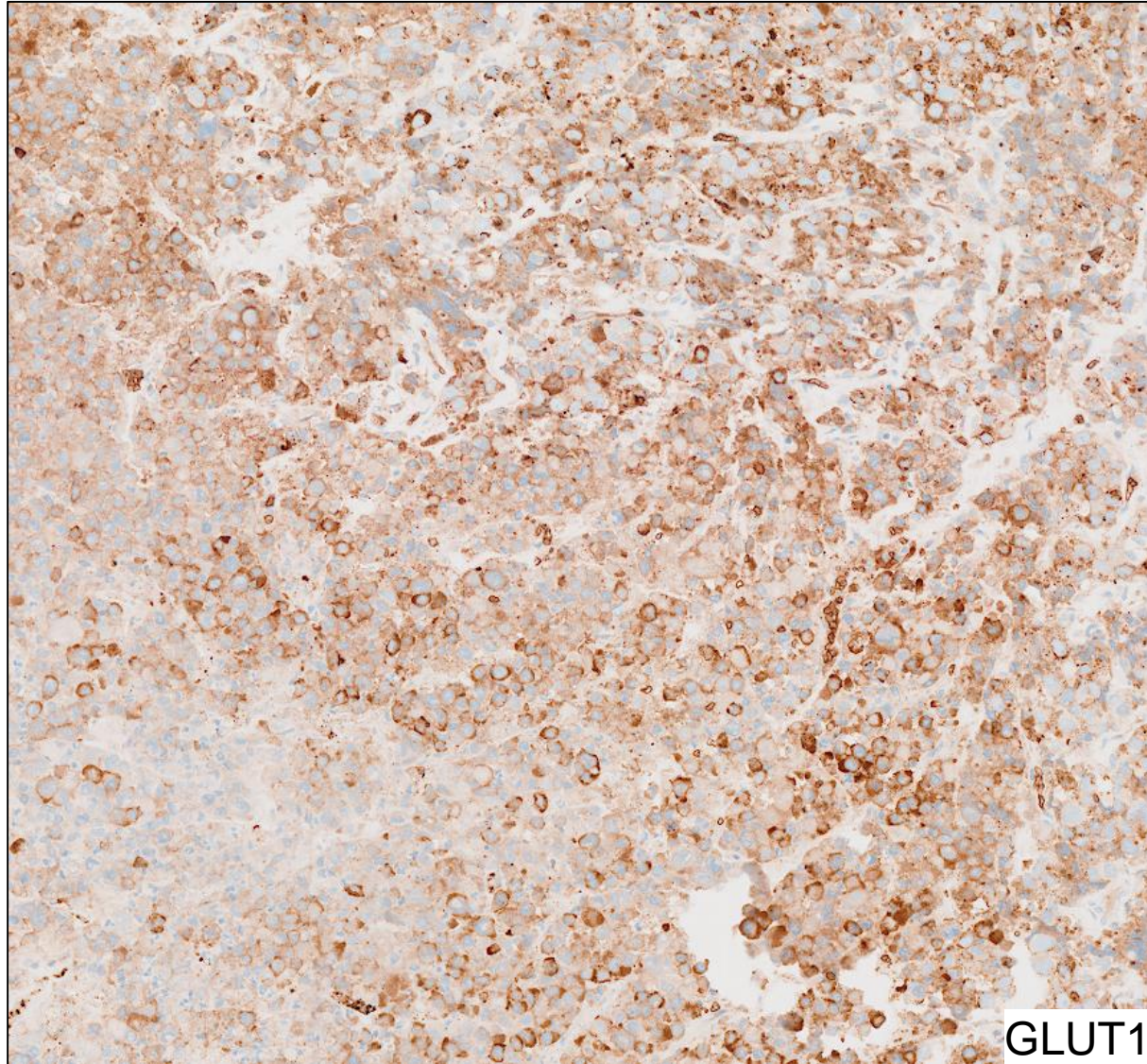


H&E

Fourth Biopsy



Fourth Biopsy



Fourth Biopsy

POSITIVE	NEGATIVE
CD45	CD3
CD43	CD20
p53	PAX5
CD71	CD19
CD34 (partial)	CD68
CD61	Glycophorin A
CD33	
MPO (equivocal)	
CD7	
INI1 retained	
Lysozyme (weakly positive)	
GLUT1	
E-cadherin (focal)	

- MYELOID NEOPLASM WITH MUTATED *TP53*; CONSISTENT WITH PROGRESSION OF PATIENT'S MPN
- THE TUMOR SHOWS DIFFERENTIATION ALONG:
 - ERYTHROID LINEAGE
 - MEGAKARYOCYTIC LINEAGE

Take Home Messages

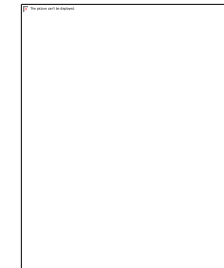
- Critical components of *TP53* evaluation for classification in myeloid neoplasms:
 - Allelic status
 - Variant allele frequency
 - Complex karyotype
- Specific mutations within *TP53* may be associated with poorer outcomes.
- Adult versus pediatric erythroblastic sarcoma / acute erythroid leukemia show distinct molecular profiles.
- "In a world full of carcinogens, be someone's (WILD TYPE) *p53*."

References

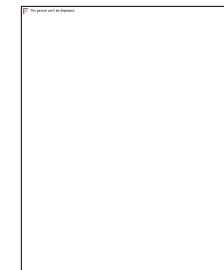
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Additional Material



Findings Indicate *TP53* Alterations Play a Significant Role in Myeloproliferative Neoplasm Disease Progression

- During the 66th American Society of Hematology Annual Meeting and Exposition, **Shivani Handa, MD**, of the Division of Hematology at The Ohio State University Wexner Medical Center in Columbus, presented findings showing that *TP53* alterations (*TP53+*) have a stronger association with overall survival (OS) and risk of leukemic progression in patients with myeloproliferative neoplasms (MPN) than previously validated high-molecular risk (HMR) mutations used in the MIPSS70v.2 scoring system.
- The retrospective study included 74 total patients (median age = 61; 60% male) with *TP53+* MPN (40 single-hit *TP53+*, 34 multi-hit *TP53+*). Most patients (78%; 37/40 single-hit, 21/34 multi-hit) had detectable *TP53+* before transformation to MPN-accelerated/blast phase (AP/BP).
- VAF greater than 36% was identified as the optimal cut-point associated with the highest risk of transformation ($p=0.002$). “As expected, the risk continues to increase with higher VAF levels; every 10% increase in VAF was associated with a 16% increase in the risk of evolution,” Dr. Handa said.
- Additionally, patients with multi-hit *TP53+* had a significantly higher incidence of transformation to MPN-AP/BP than single-hit patients (64.7% vs. 17.5%; $p=0.0015$). When compared with patients with HMR mutations, the multi-hit but not single-hit *TP53+* cohort had a significantly higher risk of transformation to MPN-AP/BP ($p=0.00354$).
- “Patients who were in the chronic phase only transformed to acute leukemia when they acquired that second hit. However, when it comes to patients with myelofibrosis, single-hit *TP53+* — especially with a high VAF between 40% to 50% — can be a risk factor for transformation to leukemia,” Dr. Handa said. **She recommends “testing all patients with newly diagnosed MPN at baseline and then retesting at regular intervals to potentially intervene prior to leukemic transformation.”**
- “One could argue that these patients should be included under the same umbrella of *TP53* myeloid neoplasms, and then hopefully they can be included in future clinical trials that are designed for *TP53* mutated MDS or acute myeloid leukemia, where currently patients with MPN are not included.”
- **Reference**
- Handa S, Riazat-Kesh Y, Marcellino B, et al. [TP53 alterations confer increased risk of leukemic transformation and worse survival as compared to high molecular risk mutations in patients with myeloproliferative neoplasms](#). Abstract 243. Presented at the 66th American Society of Hematology Annual Meeting and Exposition; December 7, 2024; San Diego, California.

Table 3.. **Advantages and limitations of methods to determine TP53 cnLOH**

Method	Resolution (kb)	Sensitivity* (%)	Advantages	Limitations	TAT (d)	Reference
WGS	1	~10	Detects CNA, SV, and SNV data	High cost and specialized interpretation	5-10	20
CMA	20-50	10-15	Detects CNA data	Does not detect translocations; unable to detect different clones	5-14	60
OGM	5-50	10-15	Detects CNA and SV data	High cost, limited clinical experience, and specialized interpretation	3-7	57
WES	1	5-10	Detects CNA, SV, and SNV data	High cost and does not include noncoding sequences	5-14	60

CMA, chromosomal microarray; CNA, copy number abnormalities; kb, kilobase; OGM, optical genome mapping; SV, structural variants (eg, translocations, inversion, etc); TAT, turnaround time; WES, whole exome sequencing.

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For cnLOH.