The young side of
LYMPHOMA

gli under 40 a confronto

Verona, Centro Congressi Camera di Commercio
26-27 settembre 2025

Ruolo della re-biopsy: aspetti clinici

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Ematologia, Istituto Tumori “Giovanni Paolo II”, Bari, Italy

Disclosures of Name Surname

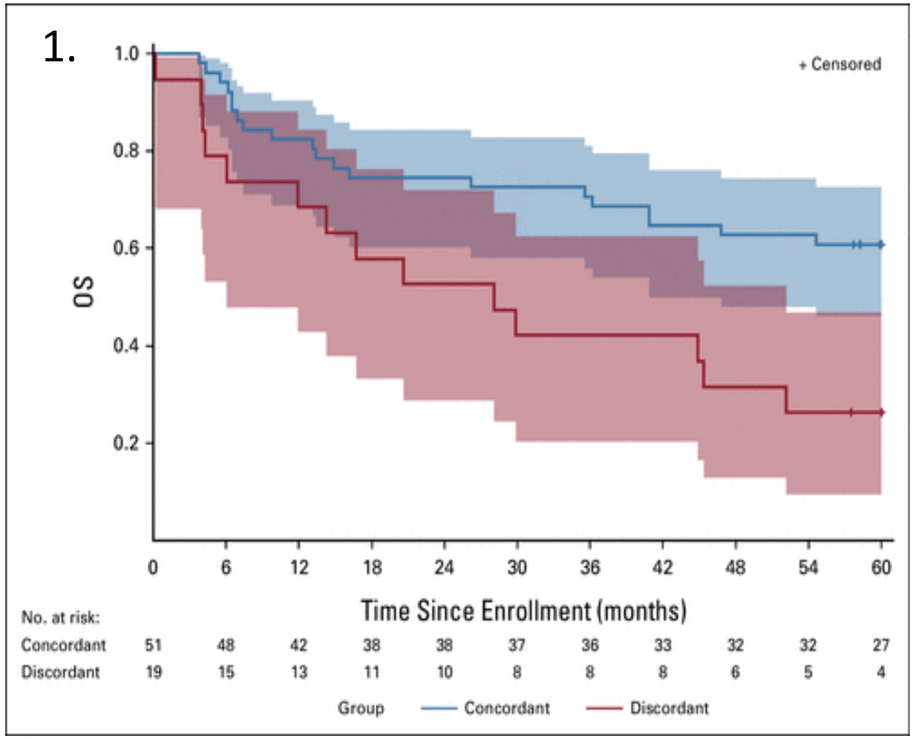
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					X		X
BeONE					X		X
J&J					X		X
Eli Lilly							X
Menarini					X		
Novartis	X						
Takeda					X	X	X

AGENDA

1. Importance of accurate diagnosis and disease monitoring
2. Rationale and clinical indications for rebiopsy
3. Practical Considerations
4. Emerging Technologies and Future Directions
5. Summary and Conclusions

Importance of accurate diagnosis and disease monitoring

1.

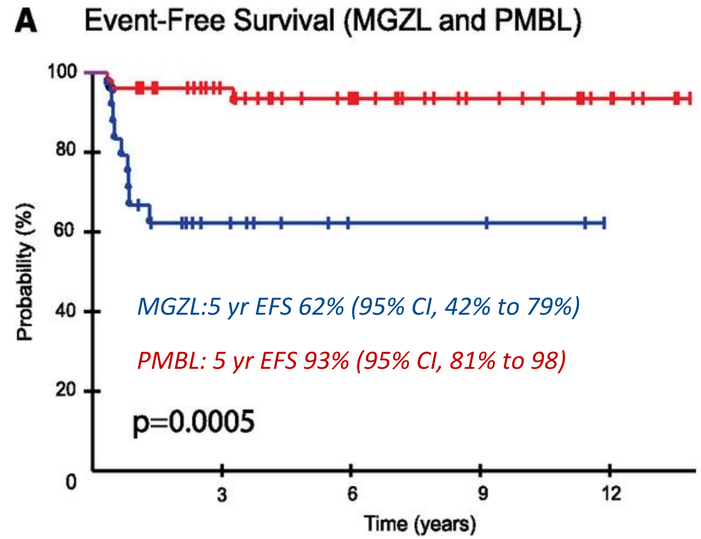


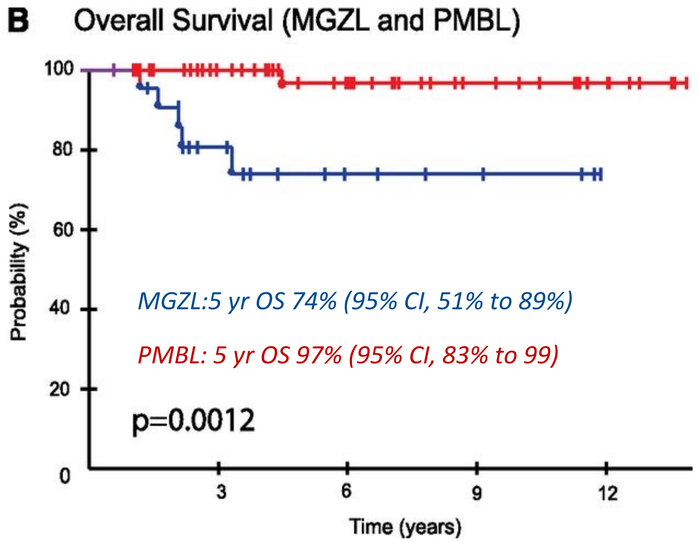
1. Kaplan-Meier survival estimate for patients with concordant versus discordant pathologic diagnosis after MGH review with number of patients at risk and 95% confidence limits. Massachusetts General Hospital. ***Chipidza et al., JCO Glob Oncol, 2021***

2. Kaplan-Meier plots of EFS and OS of MGZL and PMBL. ***Wyndham et al., Blood, 2014***

3. Kaplan-Meier plots of OS of PTCLs and HL.
ICML 2025, poster 388 Luminari et al.
Ansel et al., N Engl J Med, 2022

2.





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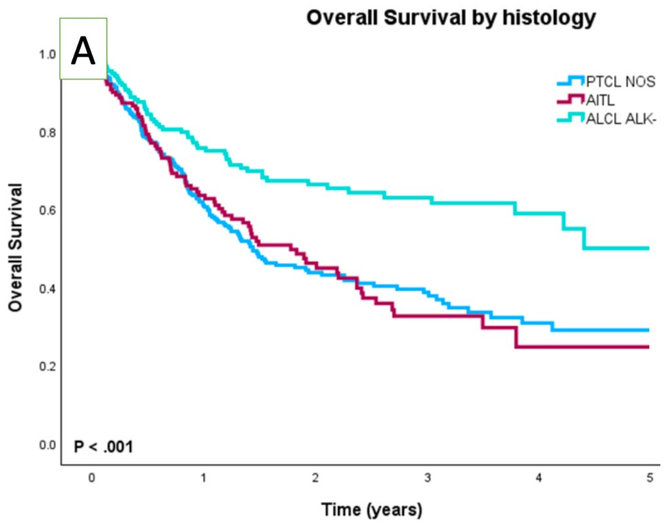

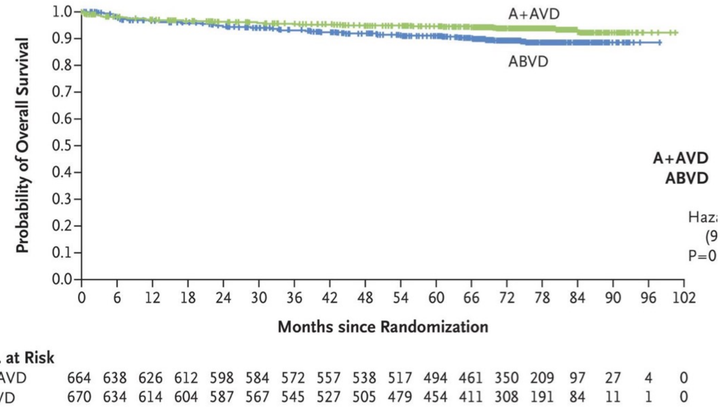

Rationale and clinical indications for re-biopsy

1. Heterogeneity and evolution of lymphoma at molecular and histologic levels
2. Limitations of initial biopsy and diagnosis
3. Changes in disease biology over time due to therapy or progression
4. Need for updated tissue diagnosis to guide treatment decisions
5. Suspected disease relapse or progression
6. Transformation to a more aggressive lymphoma subtype (e.g., FL to DLBCL, Richter)
7. Discrepant clinical or imaging findings
8. Assessment before initiating novel therapies (e.g., CAR-T, targeted agents)
9. Evaluation of resistance mechanisms post-therapy

Heterogeneity and evolution of lymphoma at molecular and histologic levels

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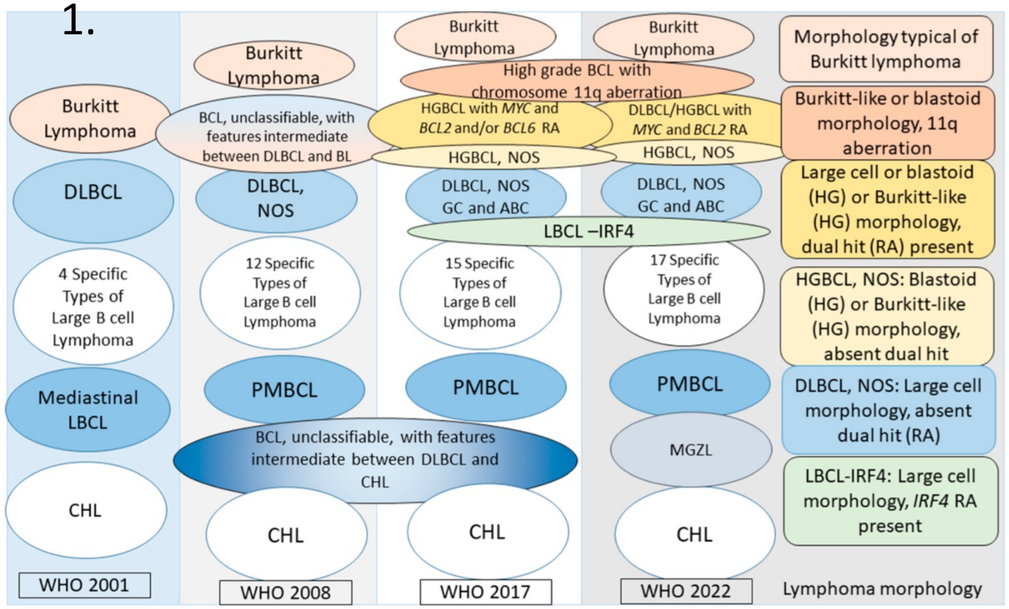

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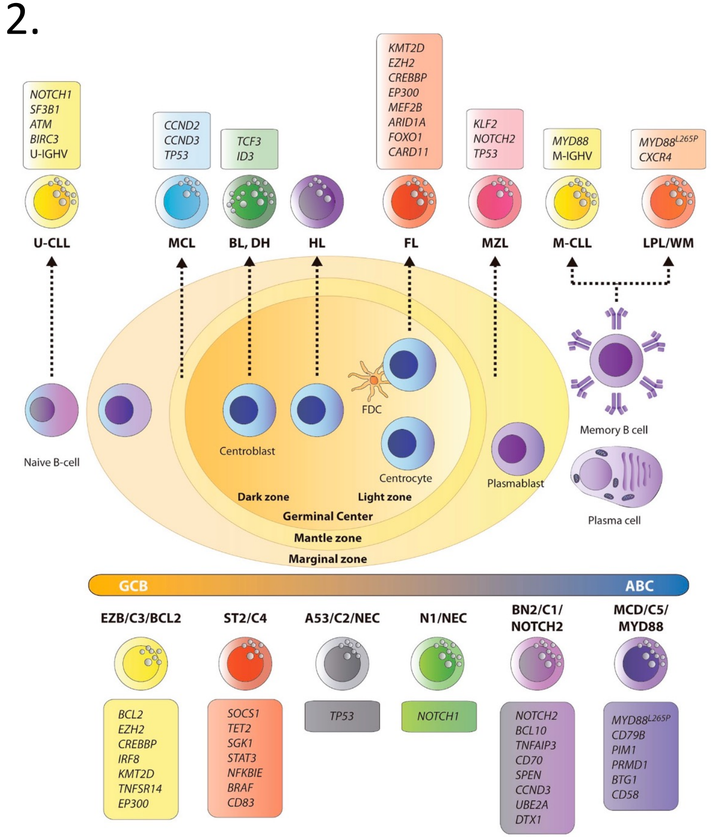

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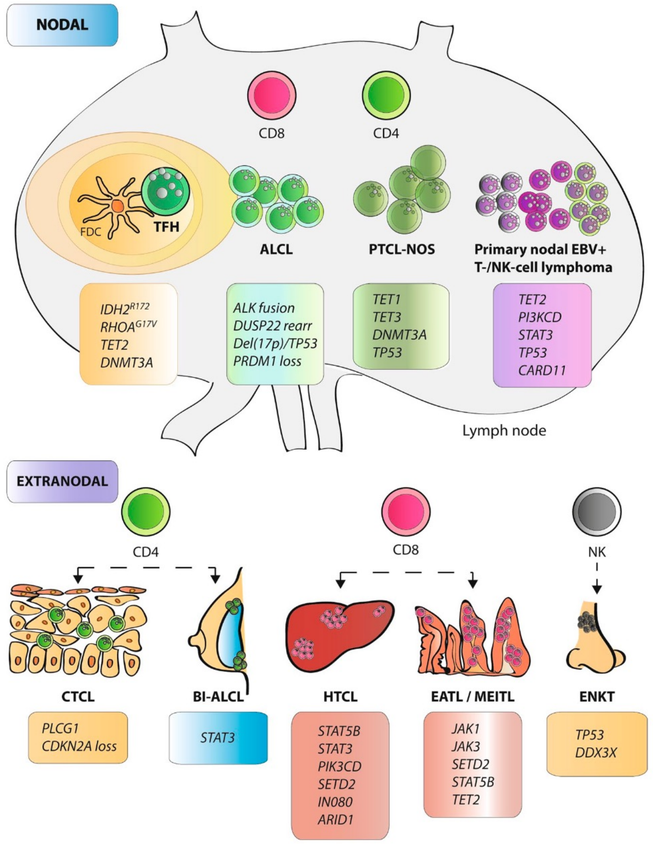

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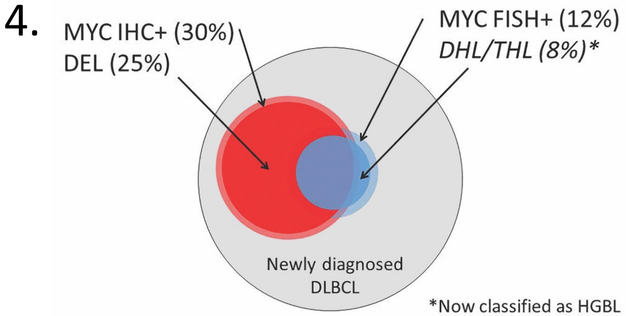
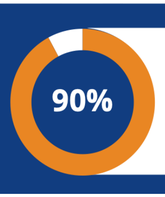




They are histologically classified as Hodgkin or non-Hodgkin lymphoma (NHL), with NHL accounting for 90% of cases

1. R. Kansal et al, *Lymphatics* 2023, *1*(2), 155-219
2. Sánchez-Beato et al, Clinical and Translational Oncology (2024) 26:1043–1062
3. Sánchez-Beato et al, Clinical and Translational Oncology (2024) 26:1043–1062
4. Daniel J. Landsburg, MD, and Brad S. Kahl, MD, https://dailynews.ascopubs.org/do/exploiting-molecular-heterogeneity-aggressive-b-cell-lymphomas-develop-effective-new

Summary of genetic alterations in B/T-cell lymphomas and their clinical utility

B-cell Lymphoma		Genetic alterations	Clinical significance
Burkitt Lymphoma (BL)	EBV +	***MYC rear.***, *MYC* aSHM, *CDKN2A*, *DDX3X*	DIAGNOSTIC
		TP53	PROGNOSTIC
	EBV -	***MYC* rear.**, ***TCF3*, *ID3***, *CDKN2A*, *DDX3X*	DIAGNOSTIC
		TP53	PROGNOSTIC
Hodgkin Lymphoma (HL)		*XPO1*, *EP300*, *CREBBP*, *TP53*, *B2M*, *NFKBIE*, *TNFAIP3*, *STAT3*, *STAT6*, *PTPN1*, *ITPKB*, *GNA13*, *ARID1A*, *KTM2D*, *IGLL5*, *CSFR2B*, *BTK*	FUTURE
Diffuse large B-cell lymphoma, not otherwise specified (DLBCL-NOS)		***NOTCH2*, *BCL10*, *TNFAIP3*, *UBE2A*, *CD70*, *CCND3*, *DTX1*, *BCL2*, *EZH2*, *CREBBP*, *TNFRSF14*, *KMT2D*, *IRF8*, *EP300*, *GNA13*, *MYD88*, *CD79B*, *PIM1*, *PIM2*, *PRDM1*, *BTG1*, *CD58*, *NOTCH1*, *SGK1*, *SOCS1*, *TET2*, *STAT3*, *TP53*; *MYC* rear., *BCL2* rearr., *BCL6* rear**	DIAGNOSTIC/PROGNOSTIC
Large B-cell lymphoma with IRF4 rearrangement		***IRF4* rear**, *IRF4*, *CARD11*, *MYD88*, *CD79B*	DIAGNOSTIC
Large B-cell lymphoma with 11q aberration		**11q aberration**, *GNA13*	DIAGNOSTIC
High grade B-cell lymphoma (HGBCL)	HGBCL-DH-*BCL2*	***MYC* rear.**, ***BCL2* rear.**, *BCL2*, *KMT2D*, *CREBBP*, *TNFRS14*, *EZH2*	DIAGNOSTIC/PROGNOSTIC
	HGBCL-DH-*BCL6*	***MYC* rear.**, ***BCL6* rear**	DIAGNOSTIC
	HGBCL-NOS	*MYD88*, *CD79B*, *TBL1XR1*, *TP53*, *KMT2D*	DIAGNOSTIC

Sánchez-Beato et al, Clin and Transl Oncology (2024)

Summary of genetic alterations in B/T-cell lymphomas and their clinical utility

B-cell Lymphoma		Genetic alterations	Clinical significance
Chronic lymphocytic leukemia (CLL)		**IGVH SHM, Del(17p)/*TP53*, Del(11q),** Del(13q), trisomy 12**, *NOTCH1, SF3B1, ATM, BIRC3,*** *NFKBIE, EGR2, MYD88, XPO1, CHD2*	DIAGNOSTIC/PROGNOSTIC
		BTK, PLCG2, BCL2, TP53, *CARD11*	PREDICTIVE
Lymphoplasmacytic lymphoma (LPL)		***MYD88^{L265P}#, CXCR4***	DIAGNOSTIC/PROGNOSTIC/PREDICTIVE
Marginal zone lymphoma (MZL)	Spleenic MZL	***KLF2***, ***NOTCH2***, ***TP53***, *NOTCH1, MLL2, ARID1A, SIN3A, TNFAIP3, MYD88, CARD11*, **trisomies *3*, *18***, Del(7q)	DIAGNOSTIC
	Nodal MZL	***KLF2, NOTCH2,*** *KMT2D, PTPRP,* **trisomies *3, 18***, *7, 12*	DIAGNOSTIC
	Extranodal MZL	**trisomies 3, 18, 12, T(11;18)#,** T(1;14), T(3;14), T(14;18) (IGH::MALT1)*; TNFAIP3, CD79A, CD79B, CARD11, BIRC3, TRAF3, TNFRSF11A*	DIAGNOSTIC/PROGNOSTIC (m7-FLIPI)/ THERAPY
Follicular lymphoma (FL)	FL	**T(14;18); *KMT2D, EZH2*#, CREBBP#, EP300#, MEF2B#, ARID1A#, FOXO1#, CARD11#***	DIAGNOSIS/PROGNOSTIC$^{\#}$/THERAPY*
		NOTCH2, DTX1, UBE2A, HIST1H1E, MYC, TP53, CCND3, GNA13, S1PR2, P2RY8, POU2AF1, CDKN2A/B loss	PROGNOSTIC (HT)
	Diffuse FL	***TNFRSF14, STAT6, CREBBP,*** *EZH2*	DIAGNOSTIC
	Pediatric TFL	*TNFRSF14, MAP2K1*	DIAGNOSTIC
	Duodenal type FL	*TNFRSF14, CREBBP, EZH2*	DIAGNOSTIC
Mantle cell lymphoma (MCL)		**T(11;14), *CCND2* and *CCND3* rearr**	DIAGNOSTIC
		IGVH SHM, Del(17p)/*TP53*, *ATM, NOTCH1/2, KMT2D*	PROGNOSTIC
		Del(17p)/*TP53*, *BIRC3, TRAF2, NSD2, CARD11*	PREDICTIVE

Sánchez-Beato et al, Clin and Transl Oncology (2024)

T-cell Lymphoma		Genetic alterations	Clinical significance
Follicular helper T-cell lymphoma (TFH)	Angioimmunoblastic (AITL) Follicular type Not otherwise specified (NOS)	***IDH2^{R172}, RHOA^{G17V}, TET2, DNMT3A$,*** *VAV1, CD28, ICOS, FYN* and *LCK* rearr	DIAGNOSTIC/PREDICTIVE$^{\$}$
Anaplastic large cell lymphoma (ALCL)	ALK-positive	**ALK fusion,** *NOTCH1**	DIAGNOSTIC/THERAPY*
	ALK-negative	***DUSP22* rearr#,** *JAK1, JAK3, STAT3*	DIAGNOSTIC/PROGNOSTIC$^{\#}$/PREDICTIVE
		Del(17p)/*TP53*, *TP63* rearr., *PRDM1* loss	PROGNOSTIC
Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)	PTCL-TBX21 PTCL-GATA3	***TET1, TET3, DNMT3A*** ***TP53#,*** *PRDM1, CDKN2A/B, RB1* and *PTEN* loss, *STAT3 and MYC* gain	DIAGNOSTIC/PROGNOSTIC$^{\#}$
Primary nodal EBV-positive T-/NK-cell lymphoma		*TET2, PI3KCD, STAT3, TP53, CARD11*	DIAGNOSTIC
Cutaneous T-cell lymphoma (CTCL)		***PLCG1,*** *NFATC2, NFAT5, ZEB1, PRKCQ, RHOA, VAV1, PREX2, CTCF, ARID1A, TRRAP*	DIAGNOSTIC
Hepatosplenic T-cell lymphoma (HTCL)		***STAT5B, STAT3, PIK3CD, SETD2, IN080, ARID1;*** Loss of *7p,* amplification of *7q*	DIAGNOSTIC
Breast implant-associated ALCL		***STAT3,*** *JAK1, JAK3, DNMT3, TP53*	DIAGNOSTIC
Extranodal NK/T-cell lymphoma (ENKT), nasal type		***TP53#, DDX3X#,*** Del*(6q), STAT3, JAK3, STAT5B*	PROGNOSTIC$^{\#}$

Sánchez-Beato et al, Clin and Transl Oncology (2024)

Why Re-Biopsy? The Clinical Rationale

Key Clinical Questions to Address	Answer, example
Is it a true relapse?	**Imaging (PET/CT scans):** - show metabolic activity, **BUT NOT** always definitively differentiate between lymphoma, inflammation, false-positive or other conditions (e.g., sarcoidosis) -biopsy provides a **definitive histological confirmation**.
Has the lymphoma subtype changed?	- particularly important for **indolent lymphomas** (FL) - transform into a **more aggressive** subtype (DLBCL). - **"histologic transformation"** requires a completely **different** and more intensive treatment **approach**
Has the molecular and genetic profile evolved?	- lymphoma's **biology may change** over time - **new mutations or genetic alterations** may emerge - **affect** prognosis and treatment options.

Clinical Scenarios for Re-Biopsy

Scenario 1:
Suspected Relapse/Progression

- A patient on follow-up or after completing therapy shows new or growing lesions on a physical exam or imaging (PET/CT, CT scan)
- Crucial when imaging findings are equivocal or a different diagnosis is in the differential.

Scenario 2:
Histologic Transformation

- Patient with indolent lymphoma (FL, MZL) has a sudden change in clinical course:
  - ✓ Rapidly enlarging l/nodes or masses
  - ✓ Development of B-symptoms
  - ✓ Elevated serum LDH…

A re-biopsy is mandatory

Scenario 3:
Refractory Disease

- A patient is not responding to therapy
- Re-biopsy can help to identify resistance mechanisms or lymphoma's biology that may guide the selection of a new, more effective therapy…?
- Another diagnosis (different lymphoma subtype…)

QUESTIONABLE

Articles

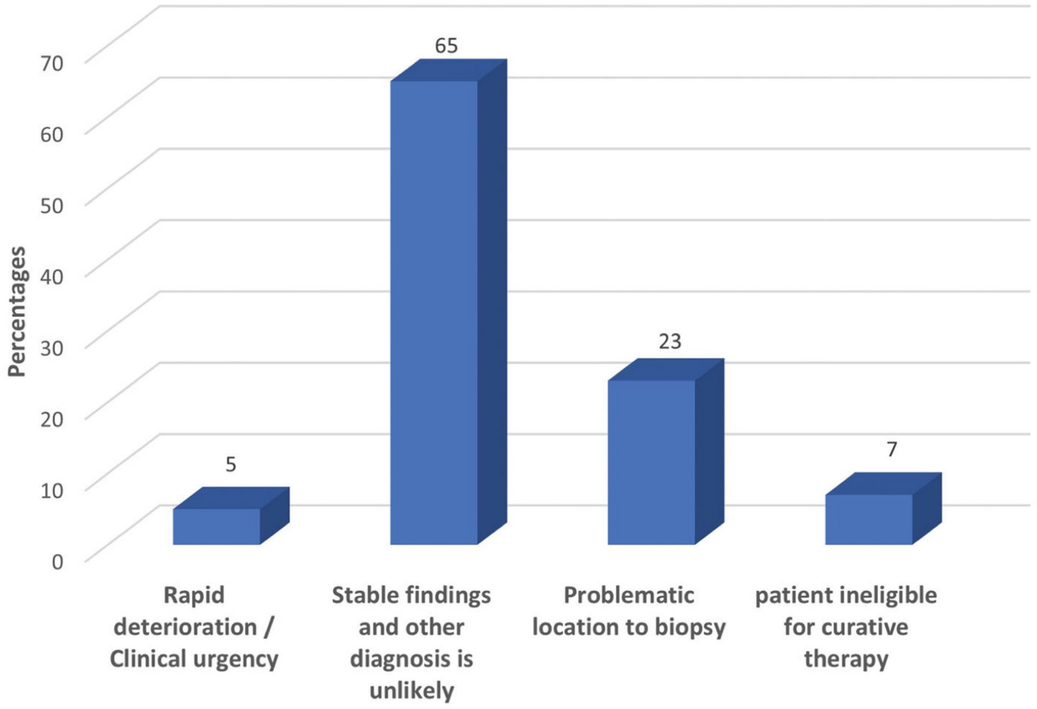
Repeat biopsy in relapsed or refractory diffuse large B cell lymphoma: a nationwide survey and retrospective study

Tamar Berger, Karyn Revital Geiger, Moshe Yeshurun, Anat Gafter-Gvili, Tzippy Shochat, Ronit Gurion, Pia Raanani & Oren Pasvolsky ...show less

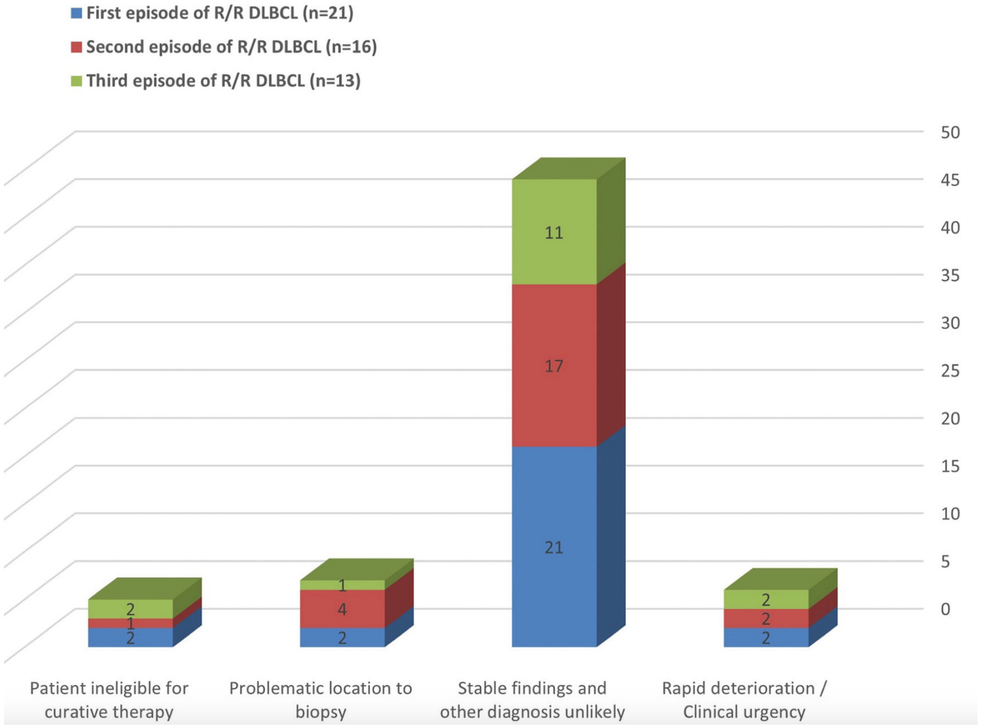
Pages 2461-2468 | Received 02 Apr 2022, Accepted 18 May 2022, Published online: 28 May 2022

Leukemia & Lymphoma

- **A two-part study:** a nationwide case-vignette survey
- **64 participating** physicians opted **not to re-biopsy** in at least one scenario, more often in refractory cases.
- In the **retrospective part**, 116 R/R aNHL cases among 61 pts were identified
- **Re-biopsy not performed in 72%** more in refractory - mostly due to low likelihood of alternative diagnoses or problematic location for biopsy.



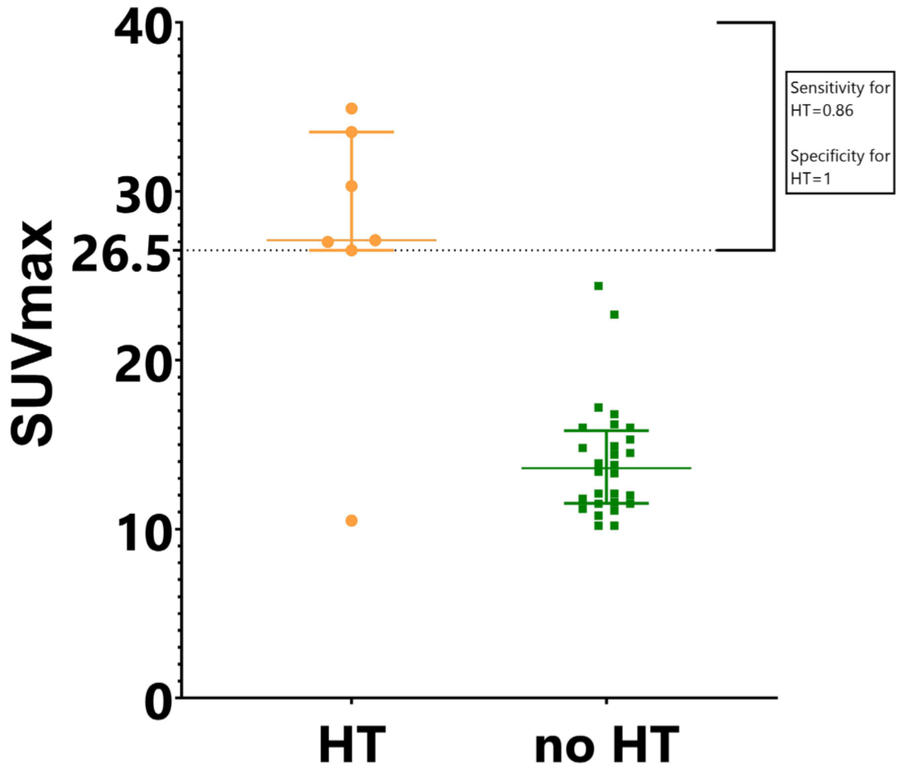
Reasons for avoiding a biopsy in suspected R/R disease



Reasons for avoiding a biopsy in R/R DLBCL – stratified by line of therapy

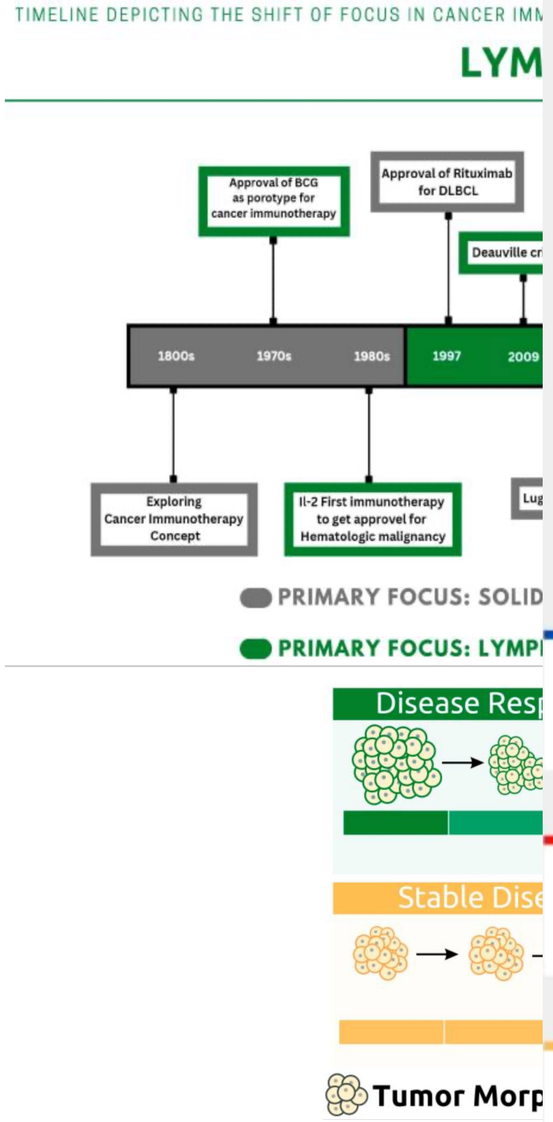
PET/CT-guided re-biopsy may find clinically unsuspicious transformation of FL

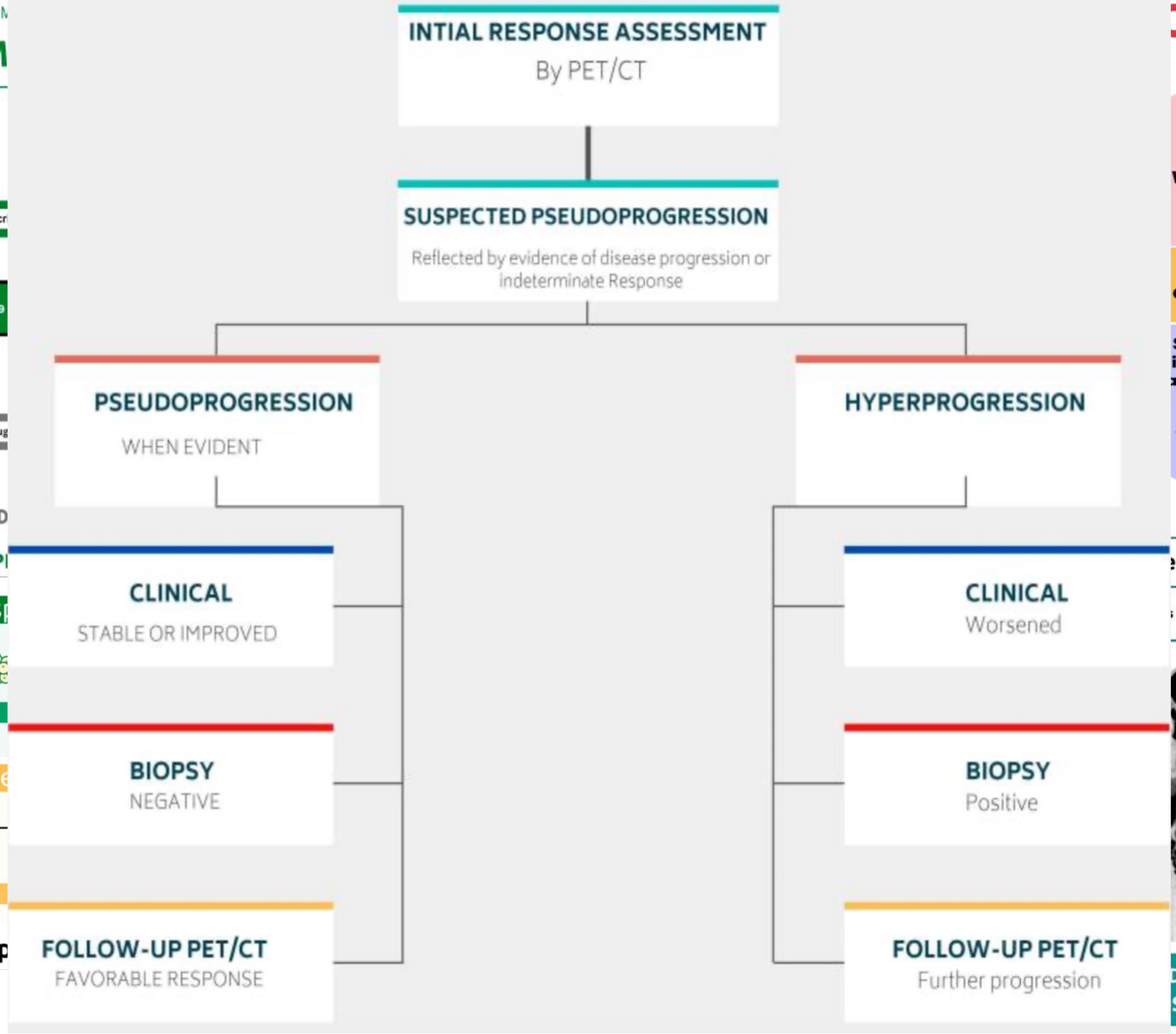
- **Retrospective study**
- Pts who had undergone **PET/CT** during primary diagnosis or relapse of **FL between 2010 and 2020**
- The **diagnosis changed** from an indolent disease to a transformed lymphoma **in >10% (7/63)**
- The **HT risk** associated with high **SUVmax (>10)** was **24%** (7 of 29 performed biopsies)
- 4 out of these 7 pts with verified HT had **NO previous clinical suspicion of transformation**

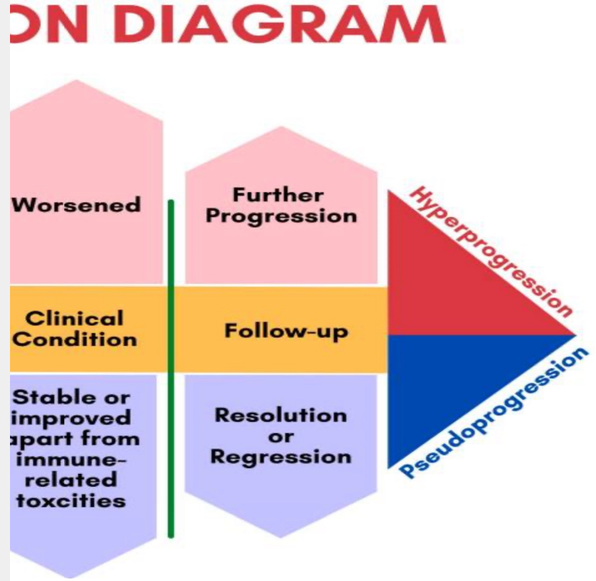


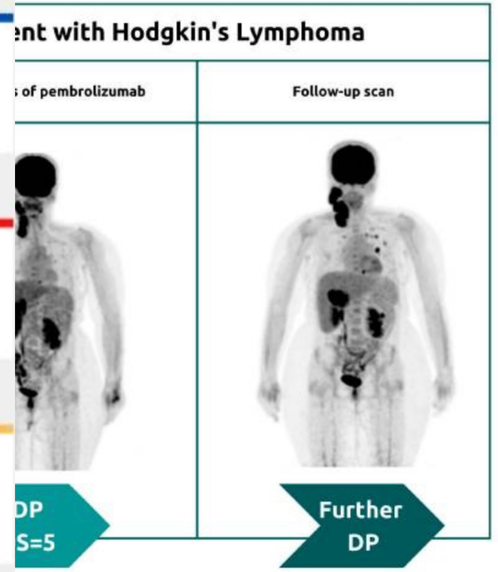
A comparison of individual SUVmax values between pts with HT vs no HT, with the sensitivity and specificity for HT of the threshold 26.5. The graph includes patients with SUVmax <10 and a new biopsy

Rajamäki et al., Cancer Medicine, 2022









Mansour et al, Cancers 2023

Therapeutic Implications of Re-Biopsy

Re-biopsy findings have a direct impact on patient management by guiding subsequent therapeutic decisions

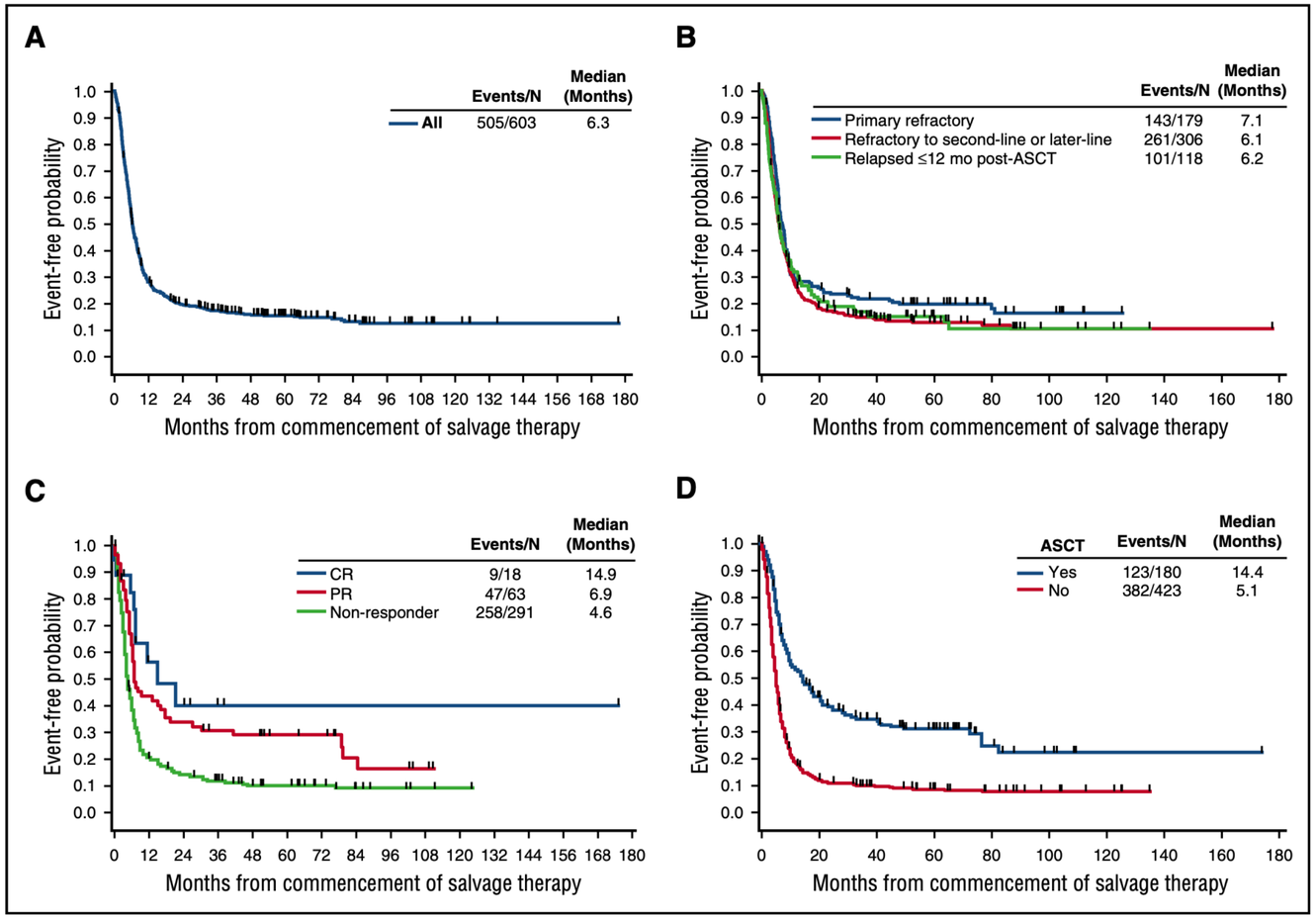
Personalized Treatment Planning:

- **Histologic Transformation:**
  - ➢ indolent to aggressive lymphoma
  - ➢ change to an intensive regimen
- **Molecular Profiling:**
  - ➢ new mutations or markers

Prognostic Value:

- patient risk-stratification
- disease course
- possible treatment options

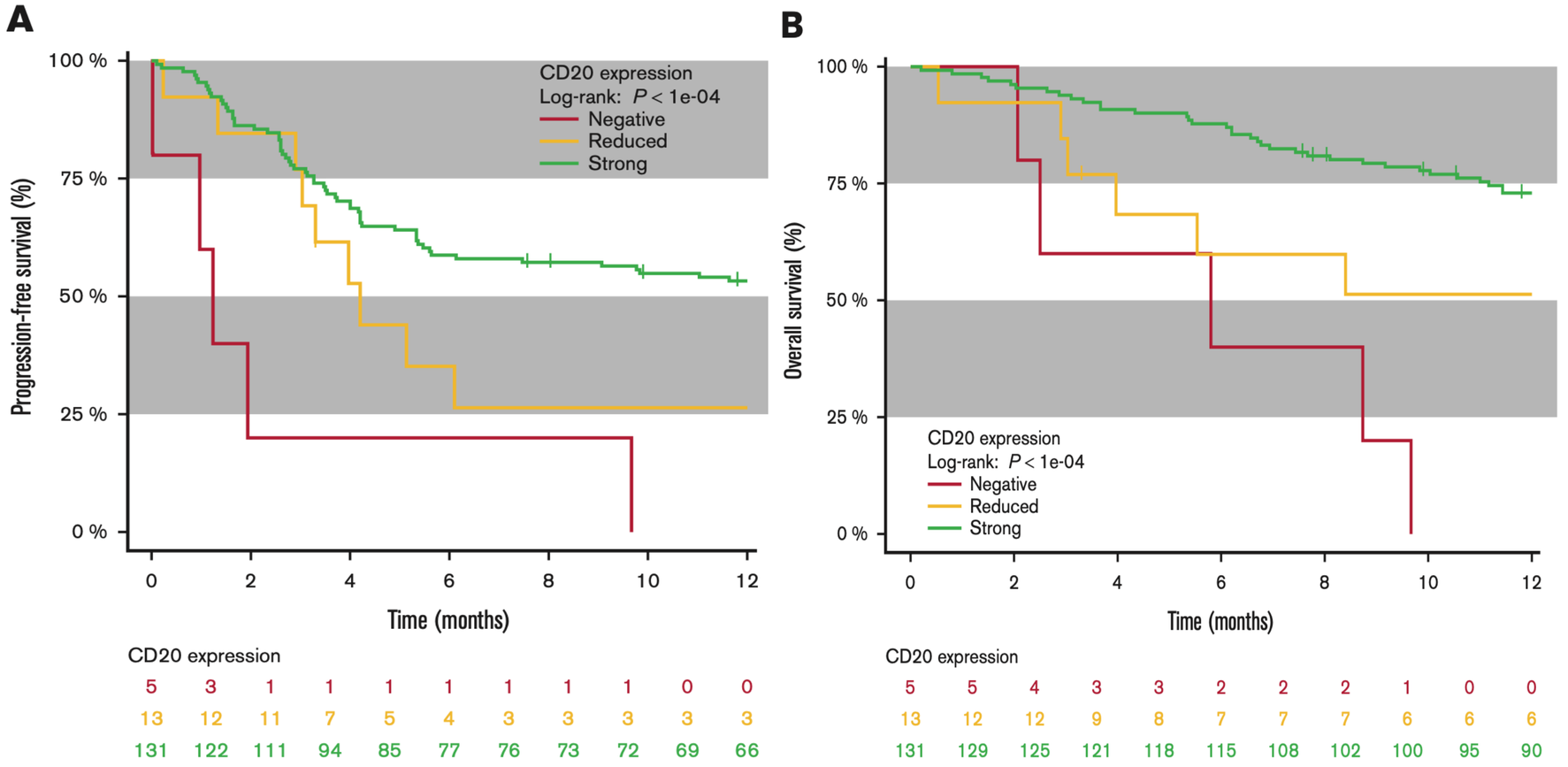
SCHOLAR-1 STUDY IN REFRACTORY DLBCL



Crump et al., BLOOD, 2017

OS from commencement of salvage therapy. Shown for the (A) overall population, B) refractory subgroups, (C) tumor response, and (D) post- refractory transplantation status

Reduced CD20 expression yields inferior survival in patients with B-cell lymphoma treated with CD20×CD3 antibodies



- 3 Danish centers
- Pts received CD20×CD3 bispecifics
- Period 2017 -2024 in phase 1/2 trials
- 148 pretreatment and 60 post-treatment samples

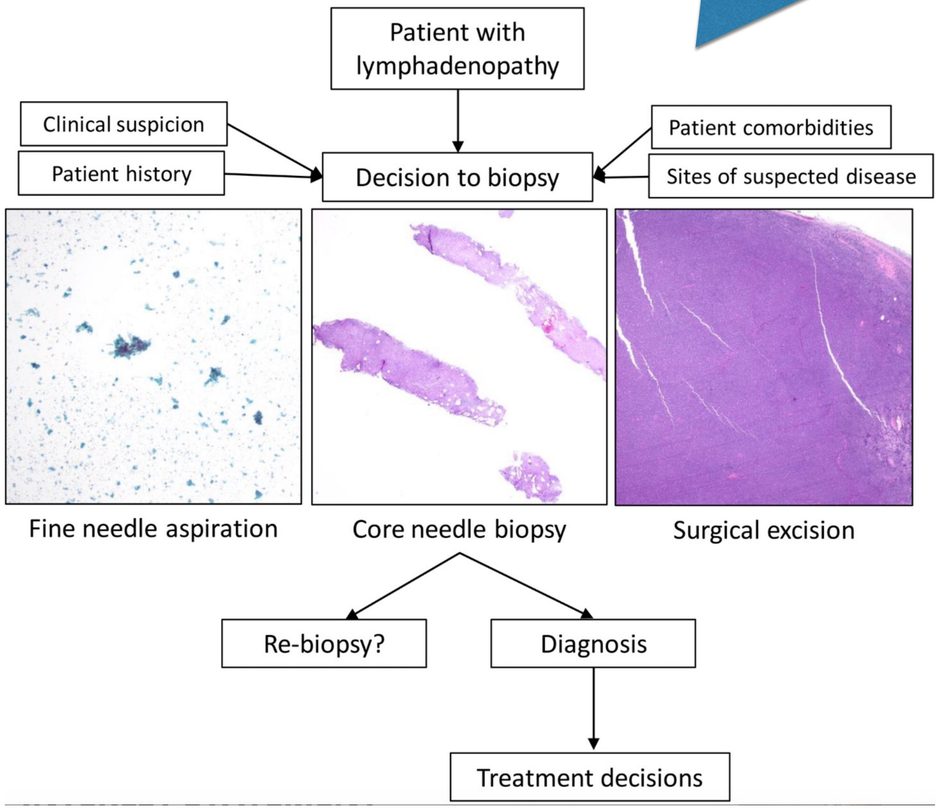
Survival in strong, reduced, and negative immunohistochemical expression of CD20. (A) PFS of patients with either strong, reduced, or negative IHC expression of CD20 antigen. (B) OS of patients with either strong, reduced, or negative IHC expression of CD20 antigen.

Kyvsgaard, Blood 2025

Challenges and Considerations in Re-Biopsy

1.

Even among hematopathologists, the frequency of misdiagnosis of lymphoma is approximately 9.6%



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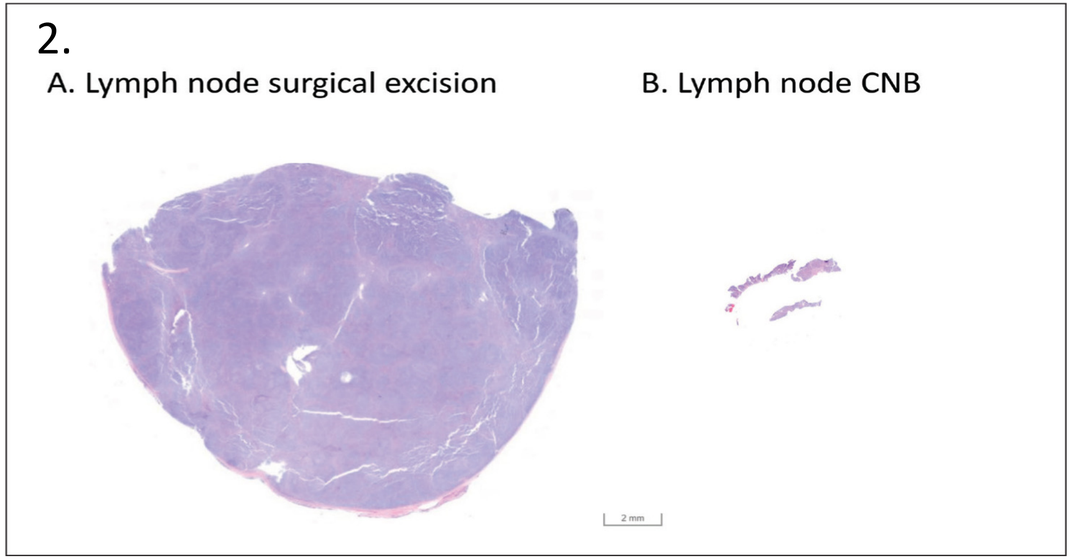

Size Matters in Lymphoma Diagnosis Tissue Biopsy

1. Invasiveness and Risk:
Tissue biopsy is an invasive procedure with potential risks, including bleeding and infection.

2. Adequacy of Tissue:
A core needle biopsy may not always provide enough tissue for all necessary tests.

3. Logistical Challenges:
Re-biopsy can delay the initiation of salvage therapy.

1. Fitzpatrick et al, Cytopathology, 2024
2. Hasserjian, The Hematologist, 2023

Emerging Technologies: The Rise of Liquid Biopsy

Advantages of Liquid Biopsy:

- Minimally invasive and can be easily repeated for longitudinal monitoring.
- Can provide a more comprehensive view of tumor heterogeneity.

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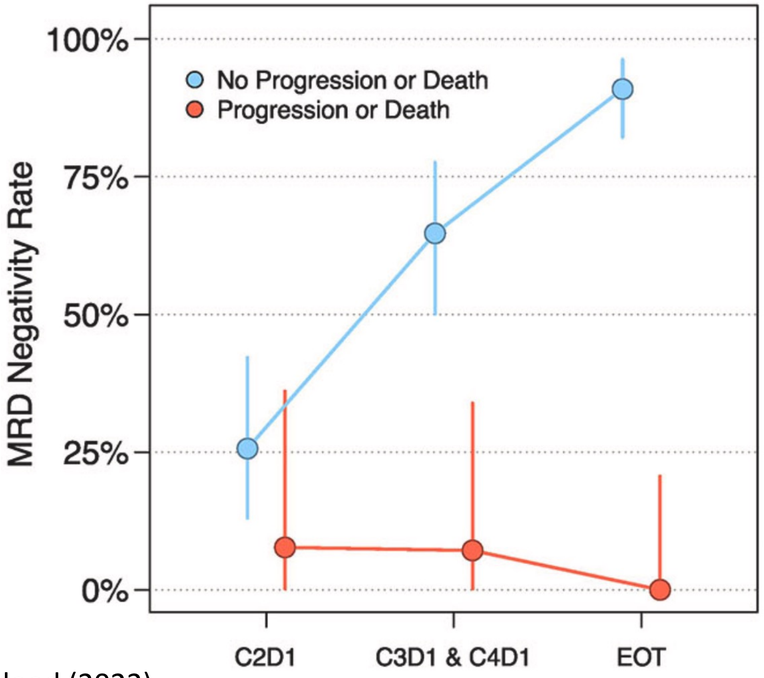
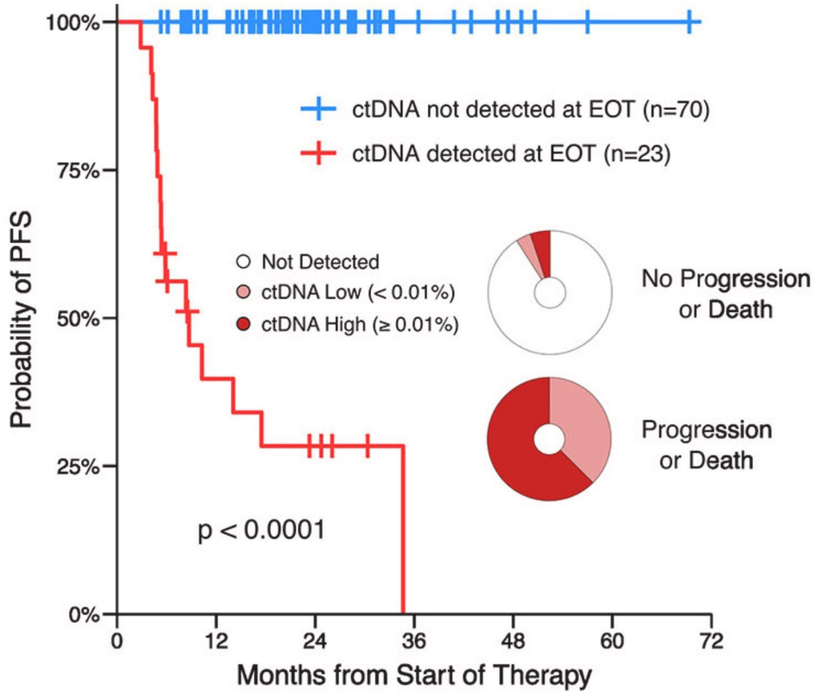


Roschewski et al., Blood (2022)

Current Role and Future Potential:

- Used to monitor treatment response and detect minimal residual disease (MRD).
- Complementary tool; not a replacement for tissue biopsy

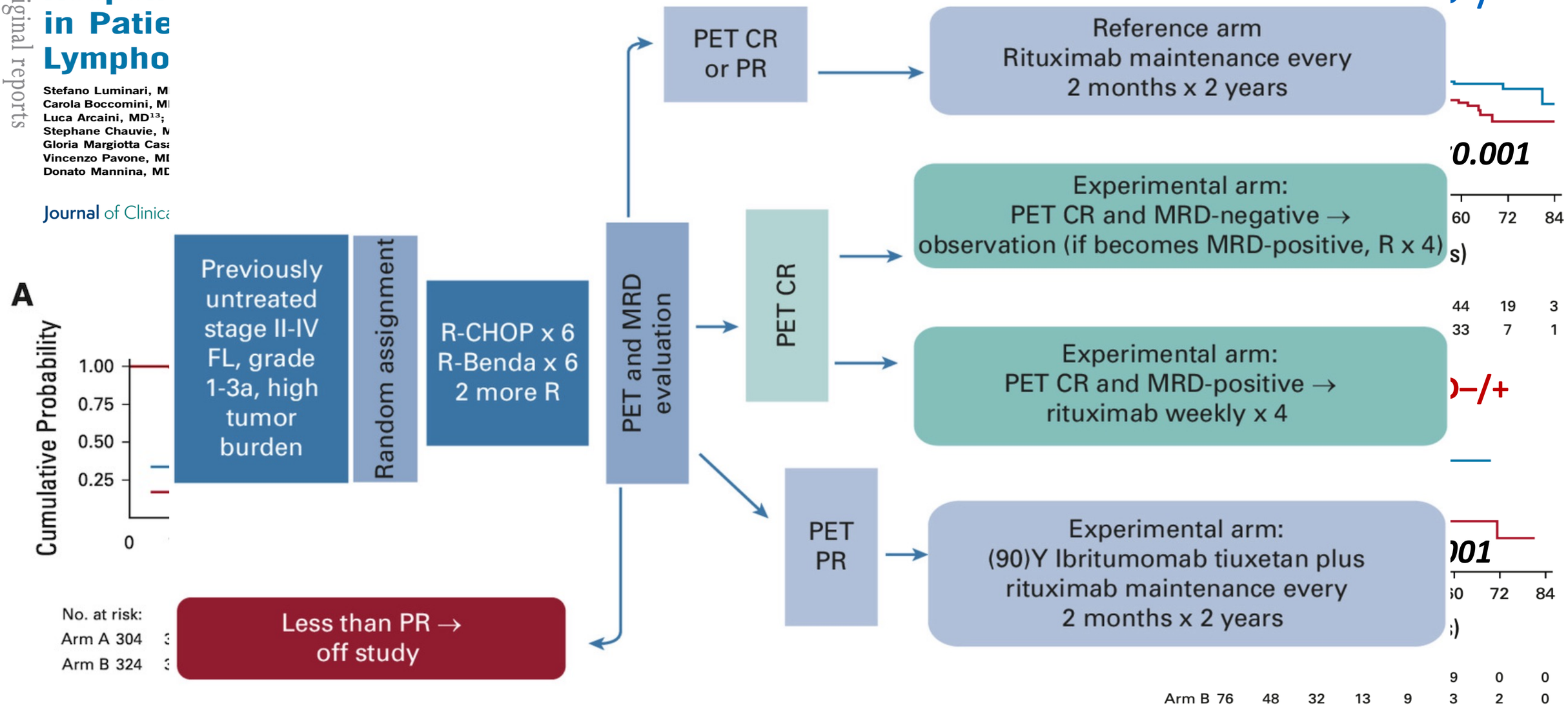


original reports

Respons-Adapted Postinduction Strategy
in Patie
Lympho

Stefano Luminari, M
Carola Boccomini, M
Luca Arcaini, MD[13];
Stephane Chauvie, M
Gloria Margiotta Casa
Vincenzo Pavone, MI
Donato Mannina, MD

Journal of Clinica



OR PET EOT repositivized during follow-up

Conclusions: *A Balanced Approach*

1. Tissue re-biopsy remains a cornerstone of care in specific situations for patients with relapsed or refractory lymphoma.

- Histological confirmation of relapse.
- Detection of histologic transformation.
- Guidance for therapeutic decisions based on updated molecular and genetic profiles

2. A collaborative, multidisciplinary approach is essential.

3. The future of lymphoma management will likely involve a synergistic approach

- tissue biopsies provide definitive diagnosis
- liquid biopsies: dynamic, real-time tool for monitoring and guiding treatment