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Ruolo dell'emopoiesi clonale nei linfomi: may clonal hematopoiesis feed lymphoma?

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Disclosures

The young side of LYMPHOMA

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
BeOne						x	x

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Background - Diffuse large B-cell lymphoma (DLBCL)

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- Most common type of lymphoma worldwide.[1]
- Aggressive lymphoma.[1]
- Cure rate ~60-70% of patients after first-line treatment.[1]
- Divided into phenotypic subtypes based on cell of origin (COO): GCB, ABC, and unclassified.[2]
- Divided into molecular subtypes based on genetics.[3-5]
- Microenvironment is an important component of its biology.[6-7]

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[1] Sehn LH, Salles G., N Engl J Med. 2021; [2]Alizadeh A et al., Nature, 2000; [3]Chapuy et al., Nature Medicine, 2018; [4]Lacy SE, et al., Blood. 2020; [5]Wright GW, et al., Cancer Cell. 2020; [6]Kotlov N, et al., Cancer Discov. 2021; [7]Li X, et al., Cancer Cell. 2025

Background – Clonal Hematopoiesis (CH)

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- Clonal hematopoiesis is an age-associated expansion of somatically mutated blood cells.[1-3]
- Frequently involves mutations in *DNMT3A and TET2*[4]
- Associates with several disease phenotypes:
  - Founder clone of hematologic neoplasms, including myeloid malignancies and T-cell lymphomas [5-7]
  - Creates an inflammatory myeloid microenvironment that predisposes to chronic non-neoplastic diseases.[5,6]

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[1]Jaiswal et al., N Engl J Med, 2014; [2]Steensma et al., Blood, 2015; Genovese et al., [3]N Engl J Med, 2014; [4] Xie et al., Nat Med, 2014; [5]Jaiswal et al., N Engl J Med, 2017; [6]Jaiswal & Ebert, Science, 2019; [7]Cheng S, et al. Elife 2021

Objectives

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1. Determine the clinical impact of CH on disease progression in DLBCL patients;
2. Establish the correlation between CH and DLBCL genetics;
3. Evaluate at a single-cell level whether DLBCL cells contain CH mutations and whether the lymphoma microenvironment is enriched by CH-derived cells;
4. Investigate if CH promotes lymphoma *in vitro.*

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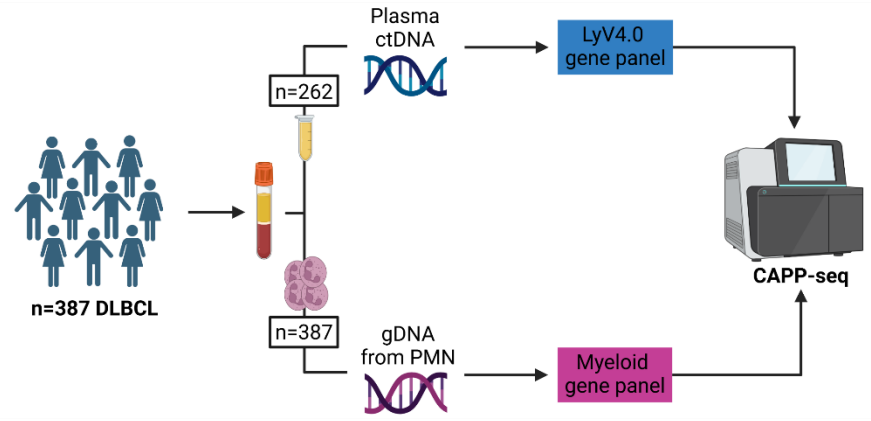
Objective 1

To assess the clinical impact of CH on disease progression in DLBCL patients

Results – Study cohort



Enrolled Patients
n = 387

CH Molecular Profiling
n = 387

Excluded *n = 125*
Sequenced with different Lymphoid Panel, *n = 125*

Excluded n = 80
SAKK38/19 screening failure, n = 80

NMF Lymphoid Clustering
n = 262

Baseline Clinical Characteristics
n = 307

Excluded *n = 124*
Unavailable survival data for SAKK38/19, *n = 124*

Survival analyses on IOSI-EMA003 Cohort
n = 183

Unpublished

Results – Landscape of CH in newly diagnosed DLBCL

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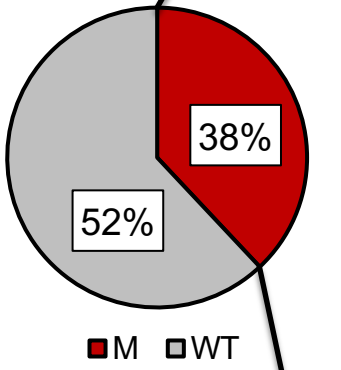

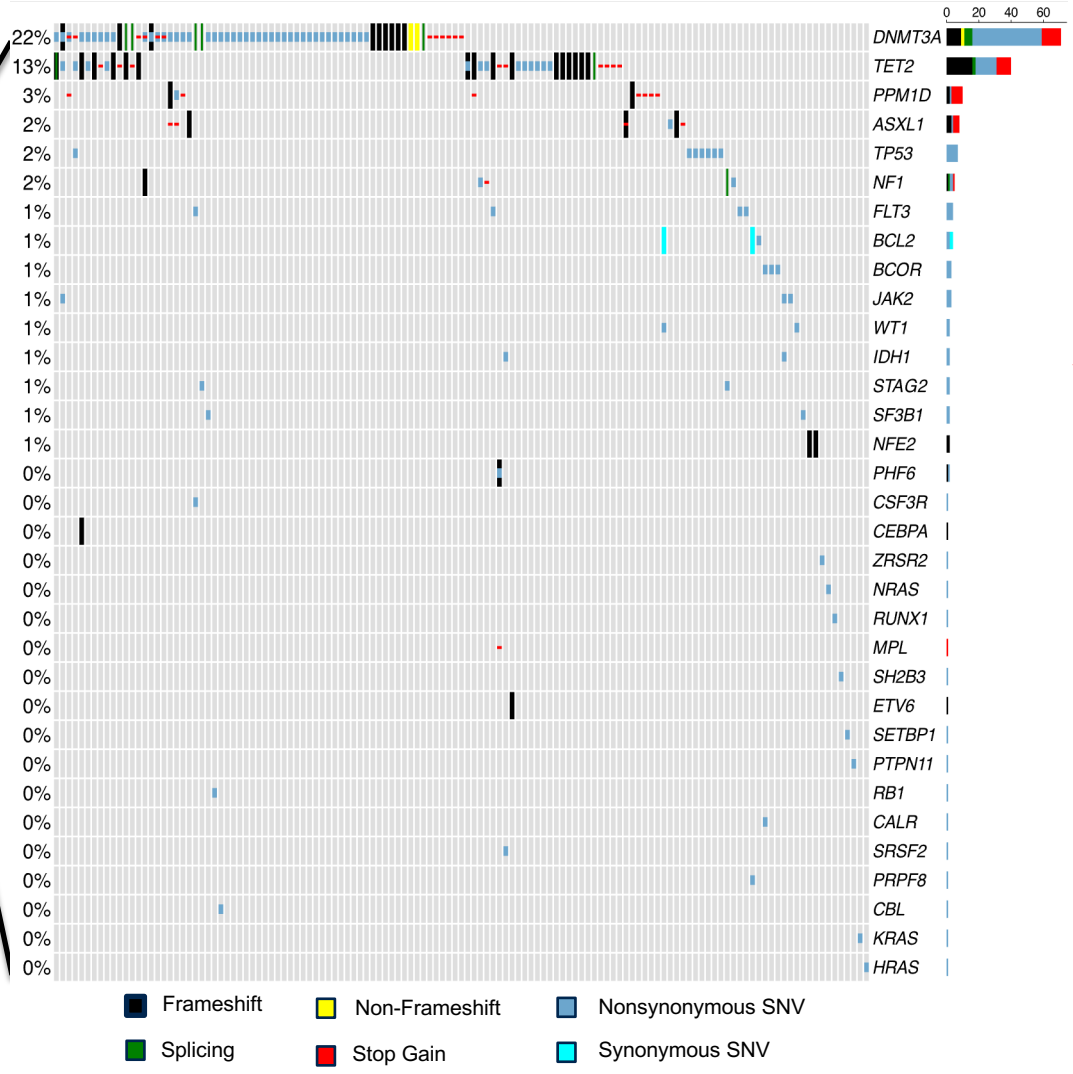

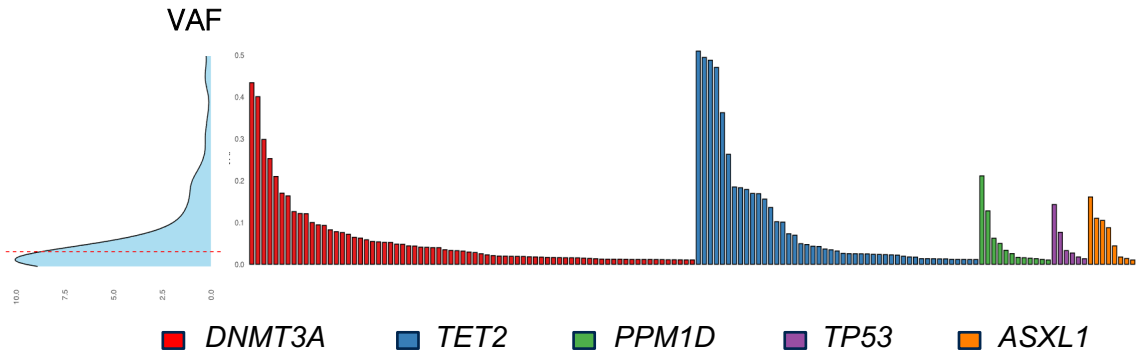

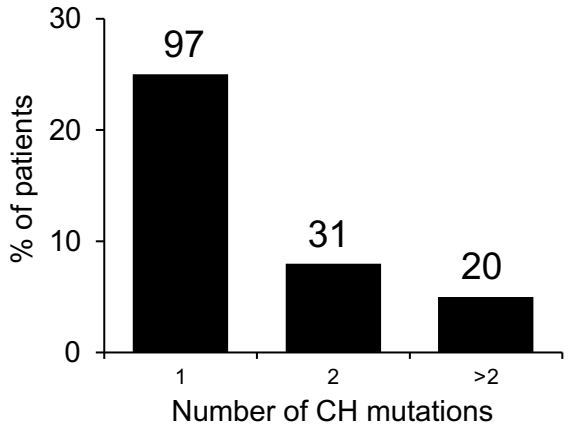

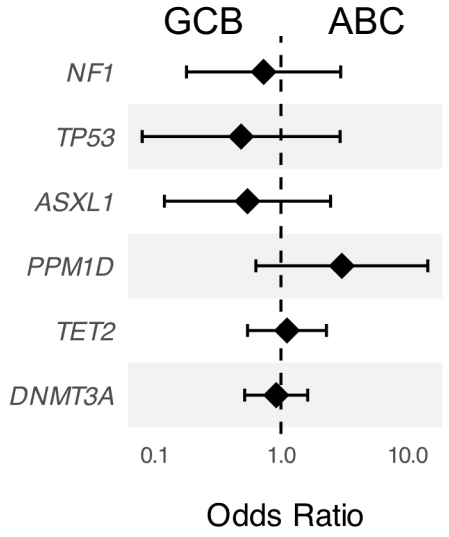

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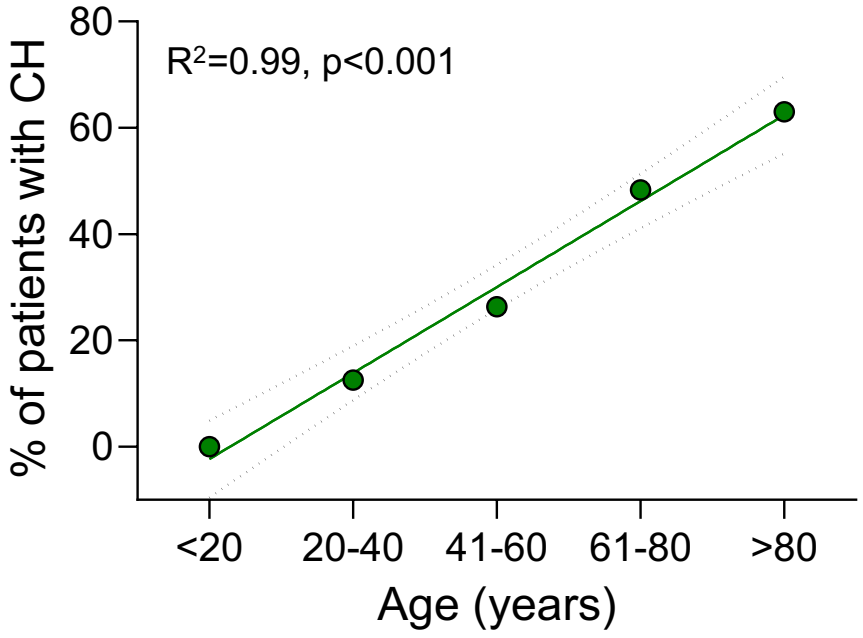
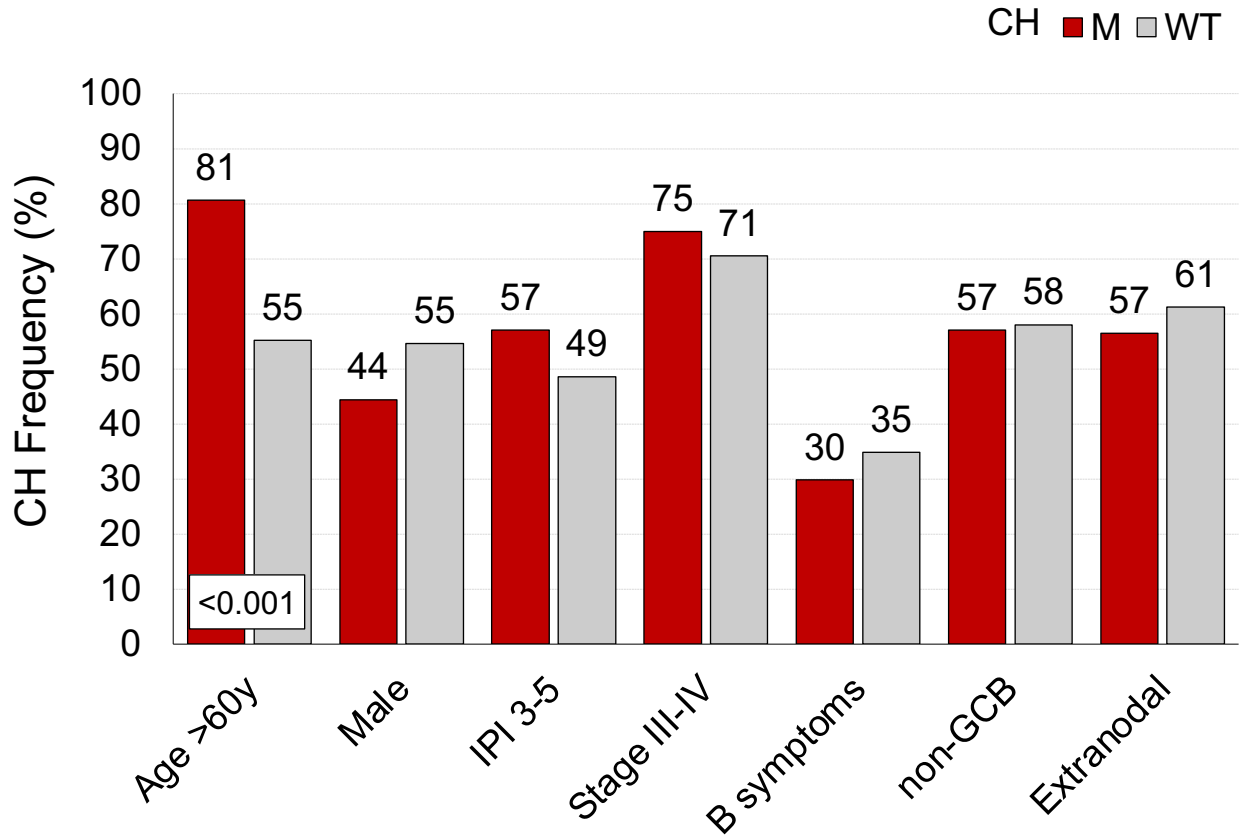
Results – Correlations between CH and patients' features





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Results – Impact of CH on cure rates of DLBCL

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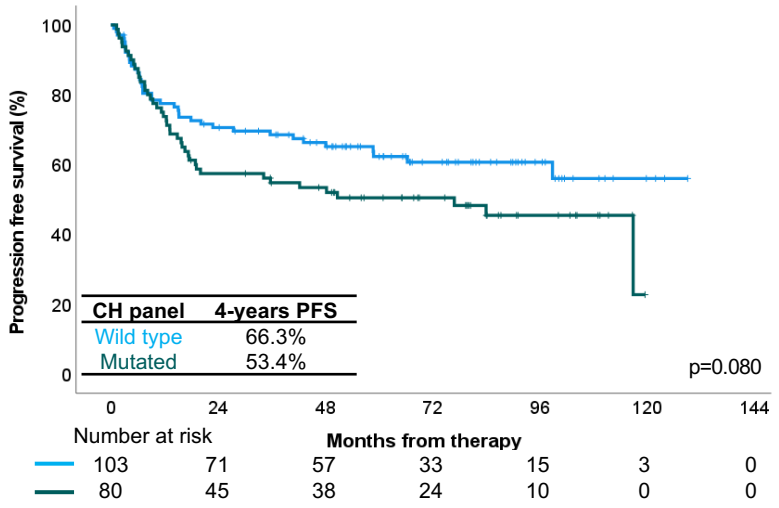
Progression-free survival

Median follow-up: 49.1 months (range, 0.66-129.1)

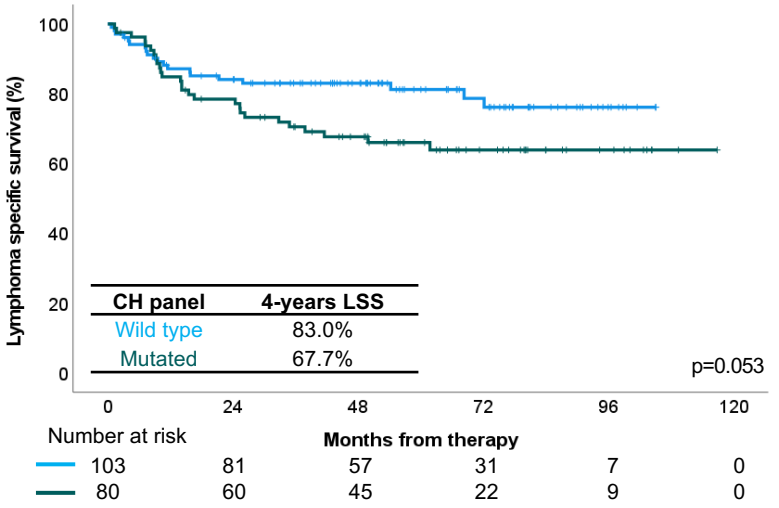


	HR	95% LCI	95% UCI	p
IPI				
Low risk	-	-	-	-
Low-Intermediate risk	2.946	1.285	6.750	0.011
High-Intermediate risk	2.875	1.280	6.459	0.011
High risk	5.321	2.414	11.728	<0.001
CH panel mutated	1.222	0.784	1.907	0.376

	HR	95% LCI	95% UCI	p
Age	1.021	1.004	1.039	0.017
CH panel mutated	1.296	0.831	2.021	0.252

Lymphoma-specific survival

Median follow-up: 50.1 months (range, 0.66-116.9)



	HR	95% LCI	95% UCI	p
IPI				
Low risk	-	-	-	-
Low-Intermediate risk	1.647	0.537	5.047	0.383
High-Intermediate risk	1.835	0.636	5.289	0.261
High risk	5.654	2.113	15.130	<0.001
CH panel mutated	1.381	0.766	2.490	0.284

	HR	95% LCI	95% UCI	p
Age	1.028	1.003	1.053	0.026
CH panel mutated	1.497	0.832	2.694	0.178

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Unpublished

Question for the audience

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Which of the following genes is most frequently mutated in patients with newly diagnosed DLBCL and clonal hematopoiesis?

A. TET2

B. DNMT3A

C. ASXL1

D. TP53

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Objective 2

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To assess the correlation between CH and DLBCL genetics

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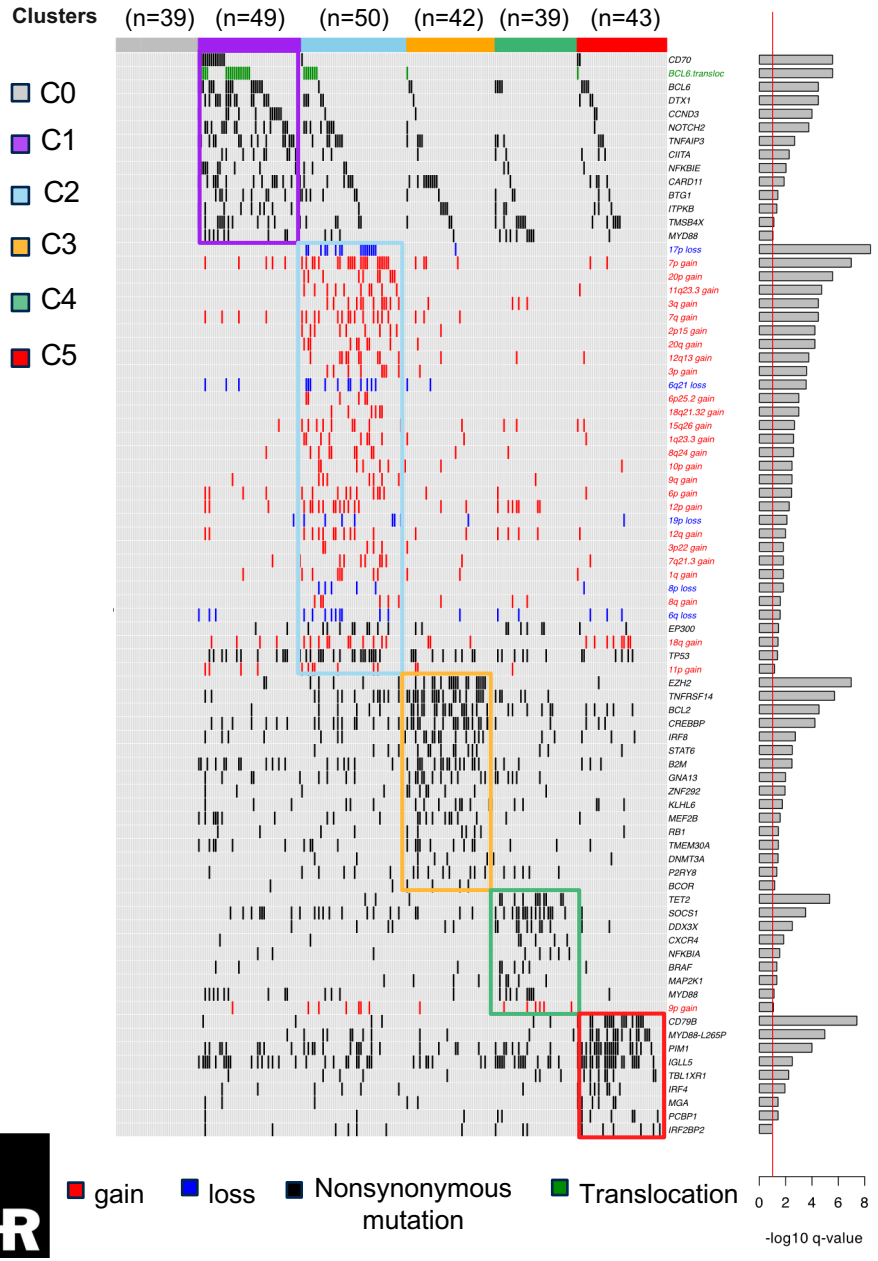
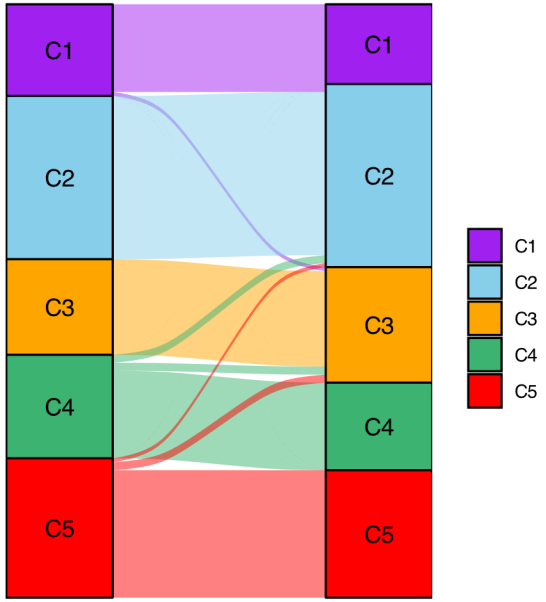
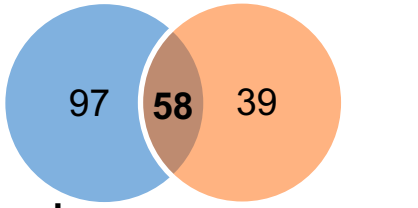
Results – DLBCL genetic subtypes and their association with CH



DLB*class*



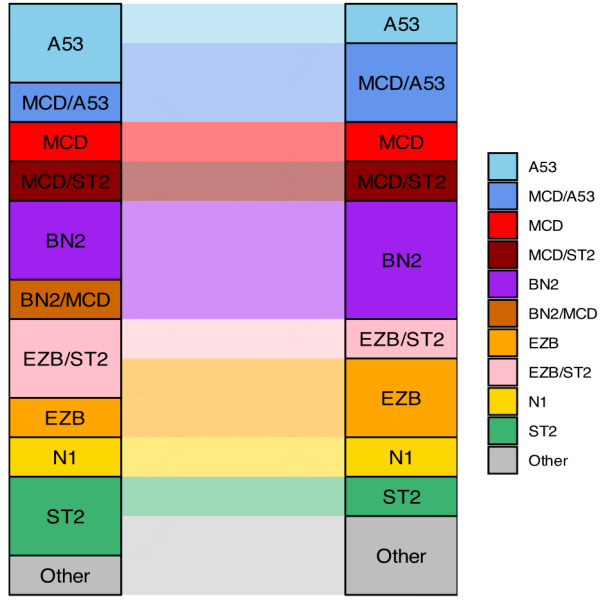
Expected Predicted



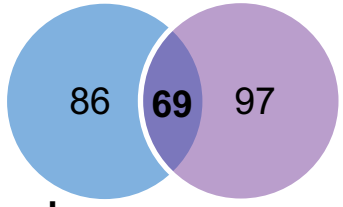
NGS-based Clustering

DLB*class*

LymphGen



Expected Predicted

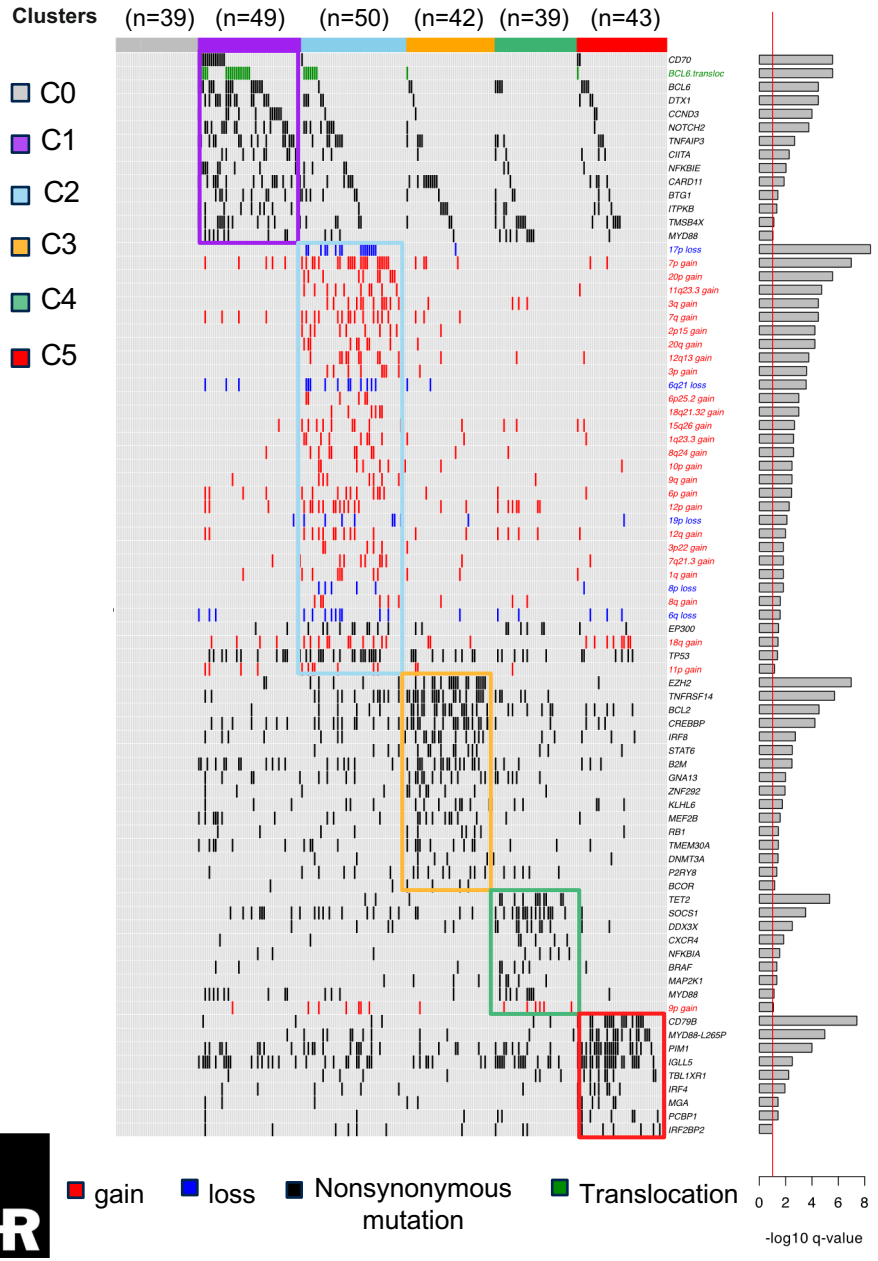


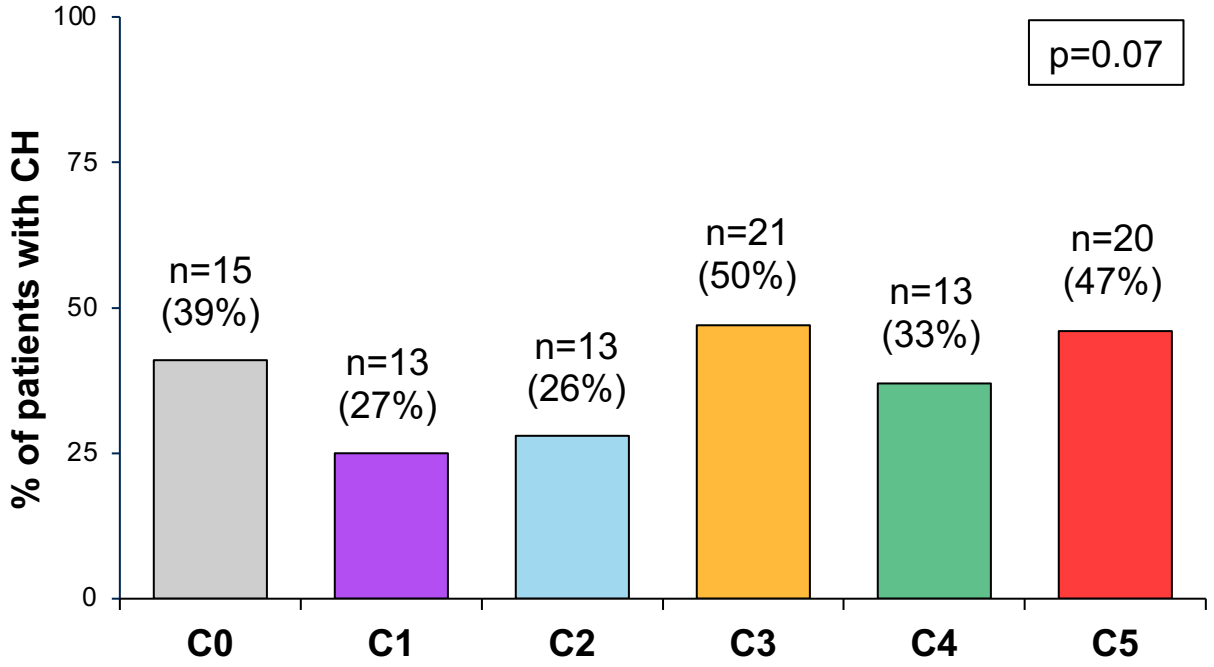
NGS-based Clustering

LymphGen

Unpublished

Results – DLBCL genetic subtypes and their association with CH





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Question for the audience

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Which method was used in this study to identify molecular subtypes of DLBCL??

A. Immunohistochemistry

B. Gene Expression Profiling (GEP)

C. Whole Genome Sequencing (WGS)

D. Targeted NGS panel

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Objective 3

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To investigate whether DLBCL cells contain CH mutations at a single-cell level

Results – Associations between CH and DLBCL Lymphomagenesis

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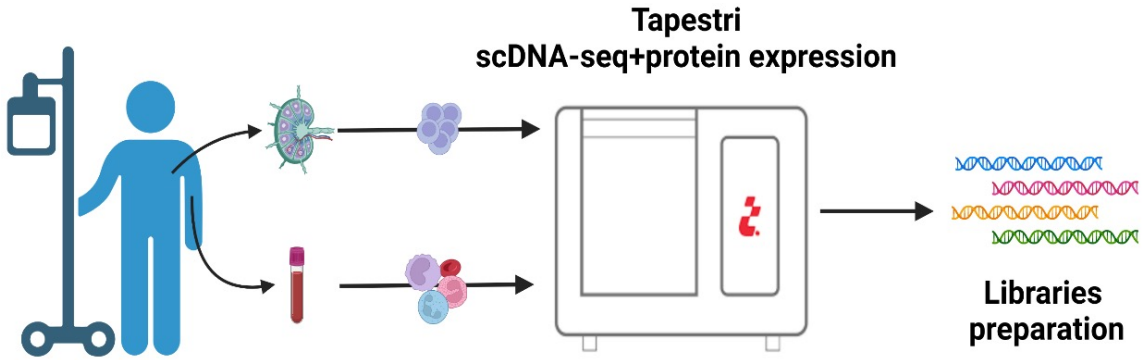
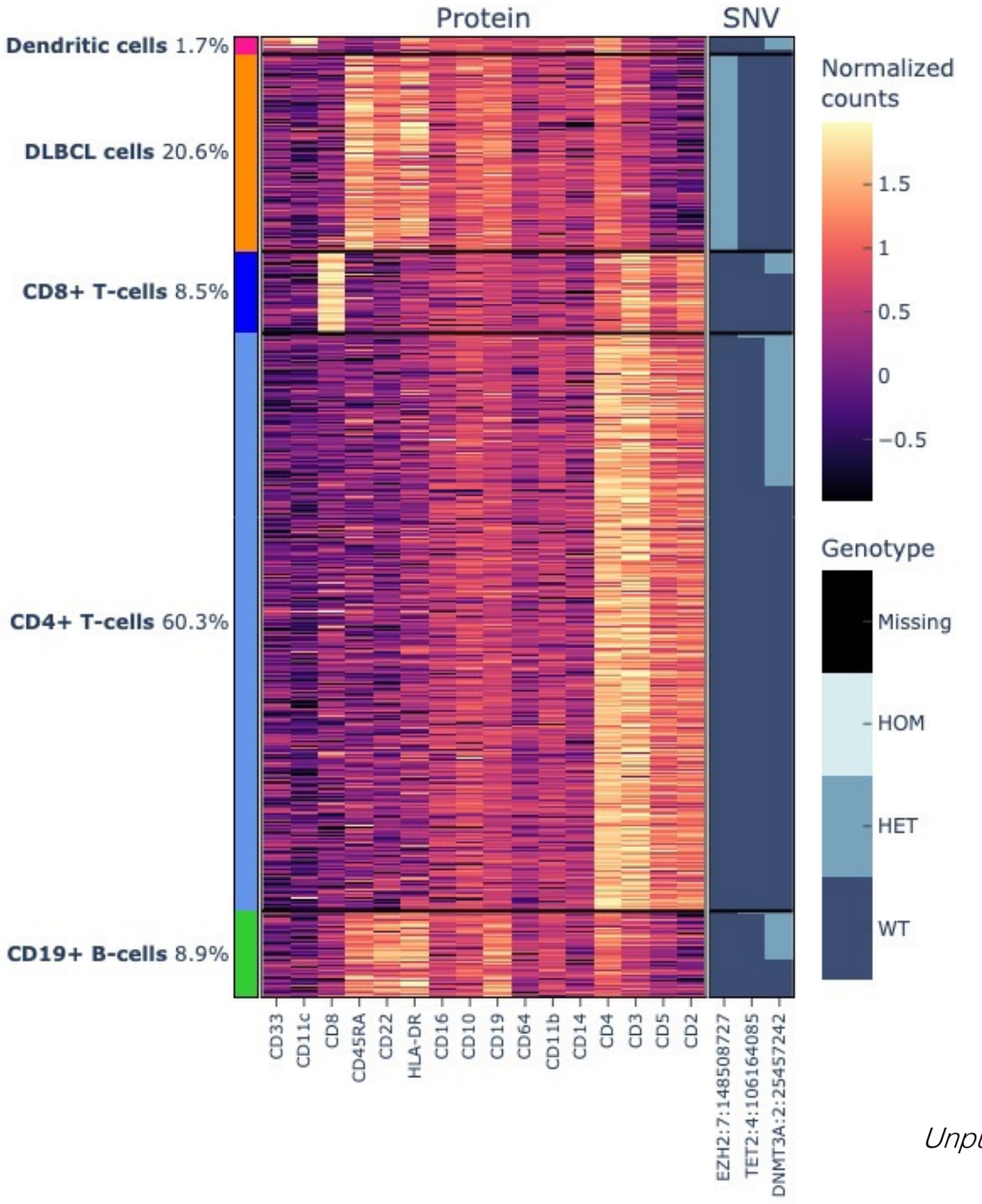


n=6 paired LN and BM/PB



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Objective 4

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To investigate if CH is enriched in the lymphoma microenvironment compared to peripheral blood

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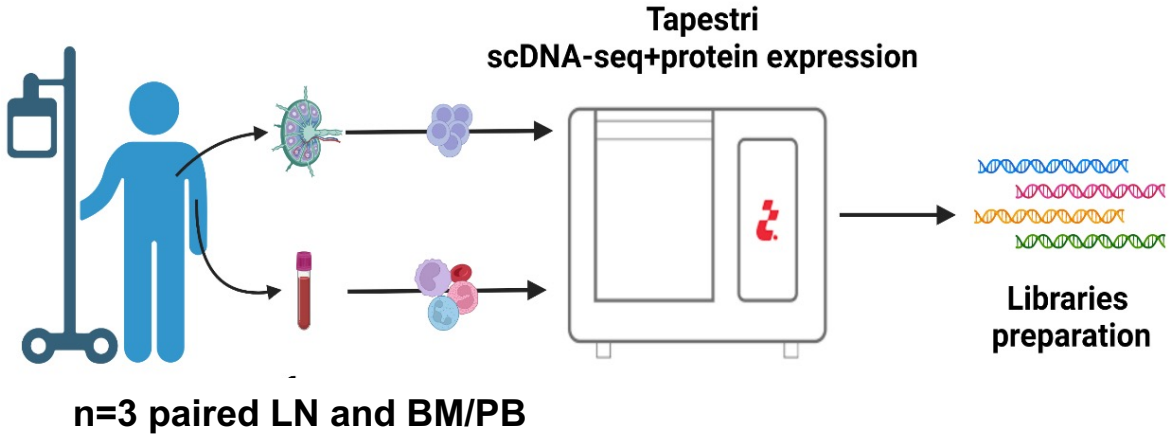
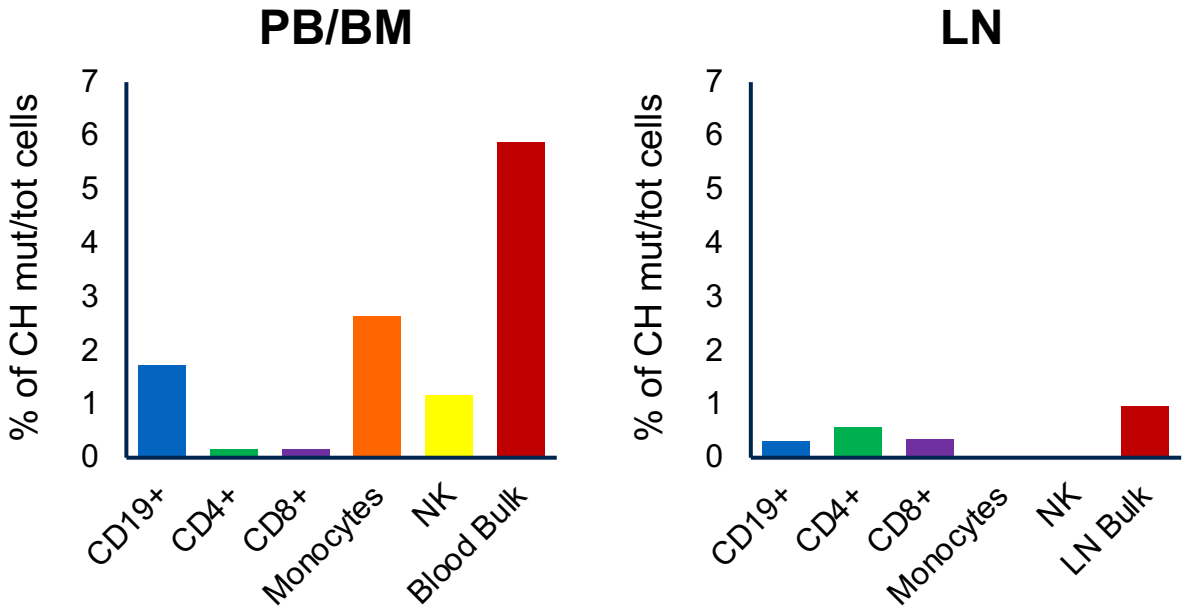
Results – Associations between CH and DLBCL microenvironment





CH-derived immune cells were not recruited into the tumor microenvironment to feed DLBCL cells

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Objective 5

The young side of LYMPHOMA

To investigate if CH promotes lymphoma *in vitro*

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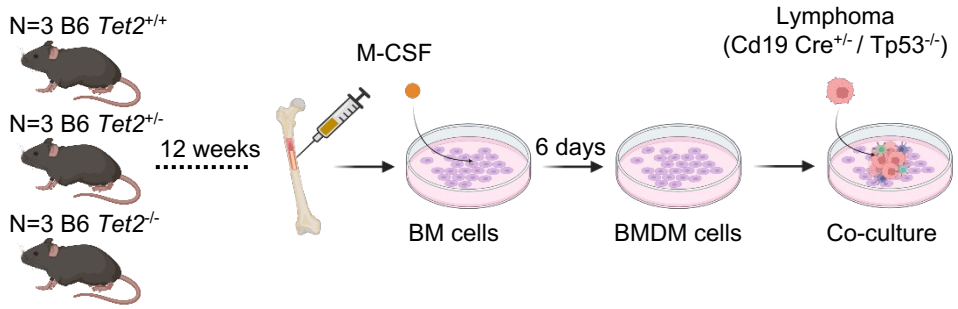
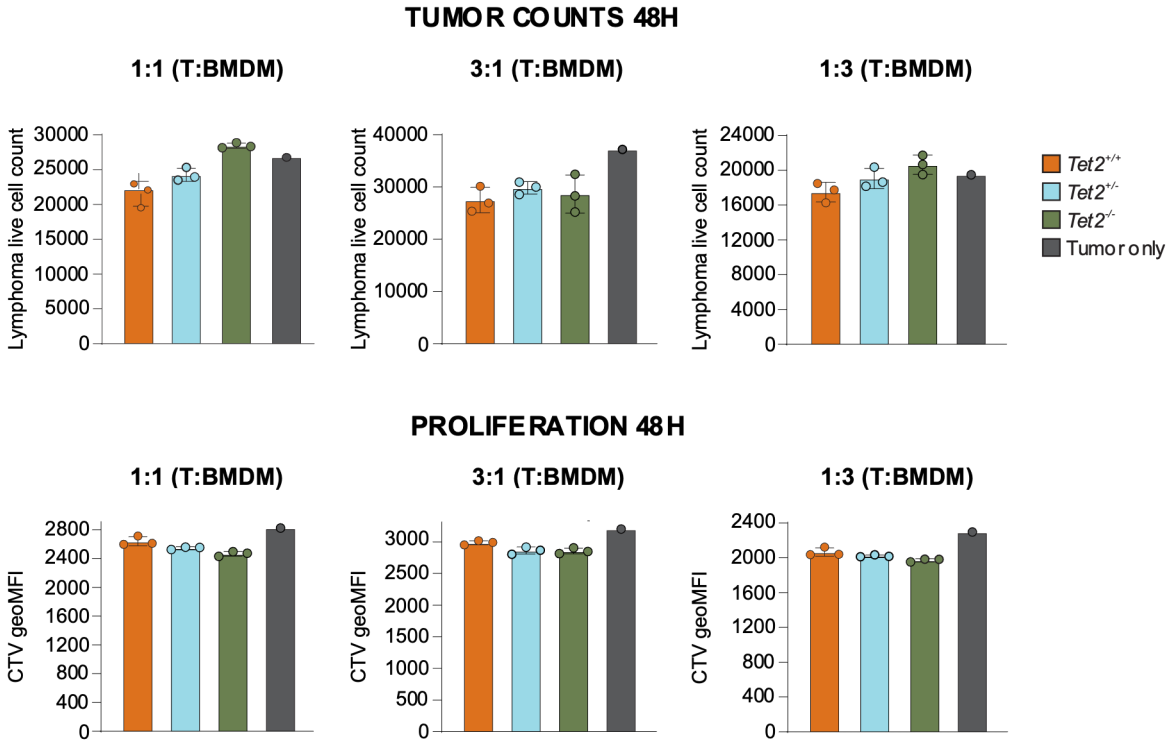
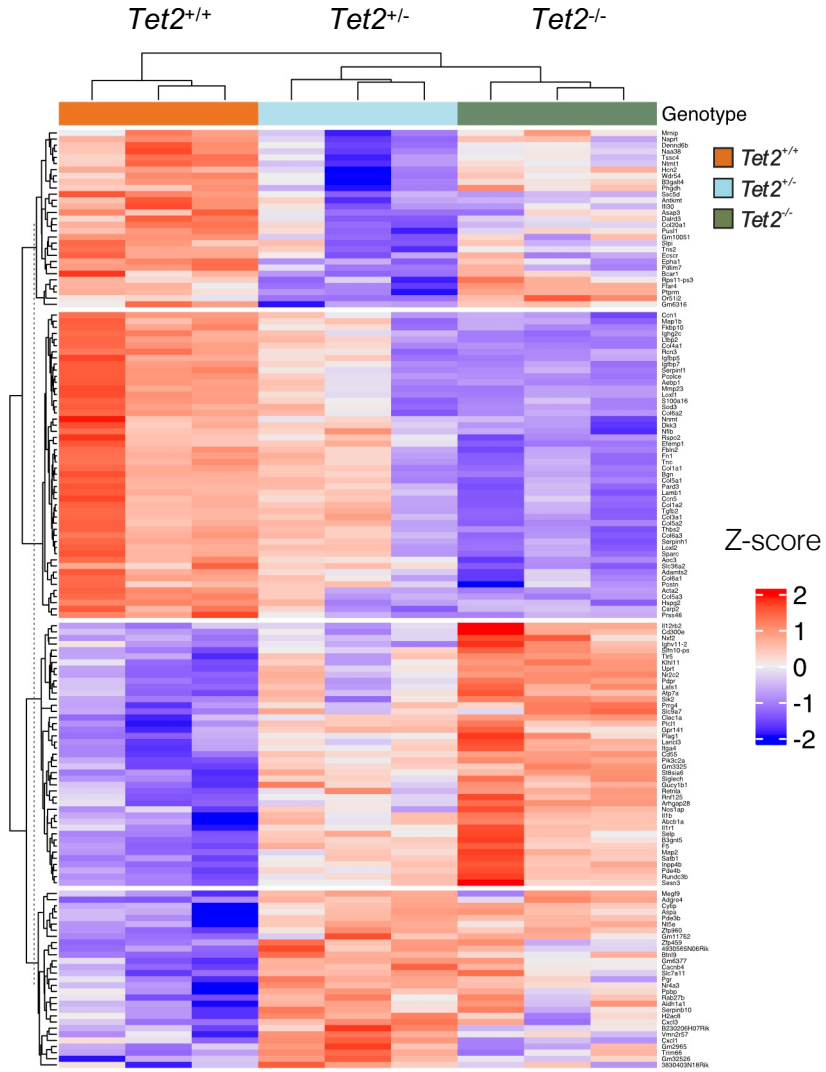
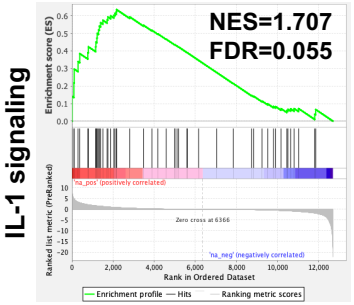
Results – Transcriptomic profiling of Tet2-mutant BMDM and functional impact on lymphoma









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Conclusion

The young side of LYMPHOMA

- PFS and LSS did not significantly differ between patients with and without CH after adjusting for age.
- CH mutations were not significantly associated with any specific molecular cluster of DLBCL.
- CH-associated mutations and lymphoma driver mutations were mutually exclusive.
- The tumor microenvironment showed no enrichment of CH-mutated cells compared to PB/BM.
- CH did not promote lymphoma growth *in vitro*

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Acknowledgment

Laboratory of Experimental Hematology
Simone Bocchetta
Alessio Bruscaggin
Adalgisa Condoluci
Gabriela Forestieri
Federico Jauk
Joyce Marques de Almeida
Deborah Piffaretti
Maria Cristina Pirosa
Flavio Pistolese
Matin Salehi
Lodovico Terzi di Bergamo
Davide Rossi

Università del Piemonte Orientale
Riccardo Moia
Mohammad Almasri
Prof. Gianluca Gaidano

Immune Mechanisms Lab
Hanif Javanmard Khameneh
Alessandro Zenobi
Prof. Greta Guarda

IOSI-EMA003
Investigators
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SAKK 38/19 trial
Steering committee
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Investigators