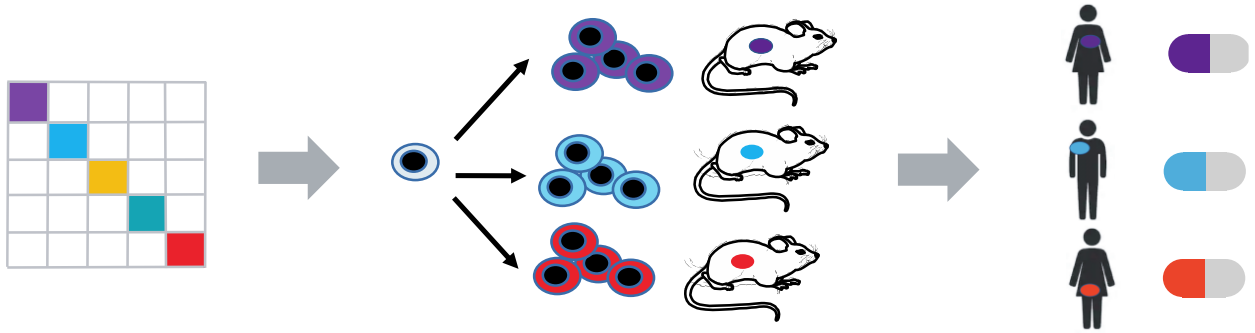
CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

DGHO
JAHRESTAGUNG
Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie
www.jahrestagung-haematologie-onkologie.com
2023 13.–16. Okt. Hamburg

GLA German Lymphoma Alliance

DGHO2023: Aggressive NHL Update

Molecular getriebene Therapien: Ready for Prime Time?



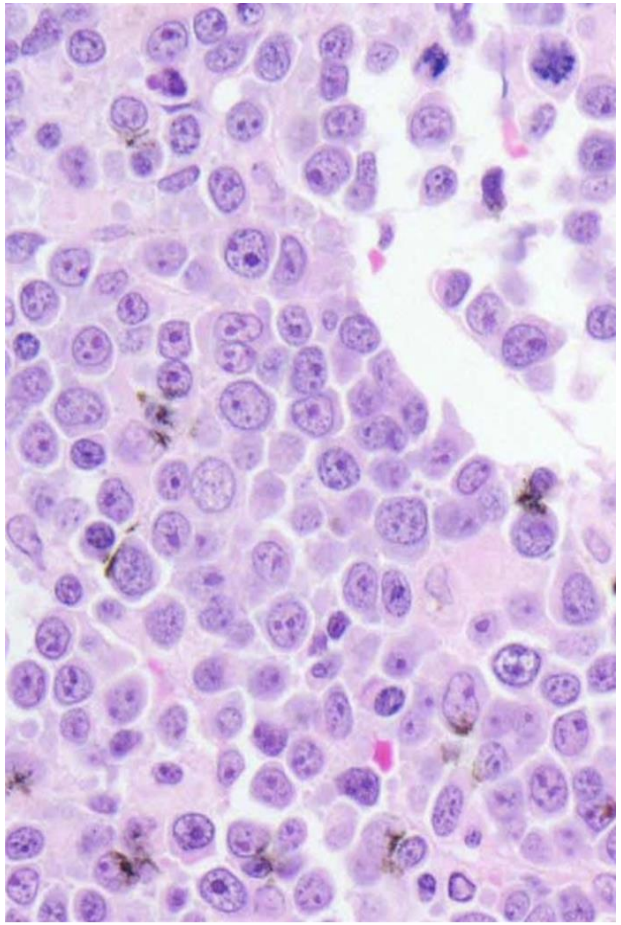
Björn Chapuy
Charité, University Medical Center Berlin

16. Oktober 2023

Disclosures of Prof. Dr. Björn Chapuy

- I have the following financial relationships to disclose:
  - *Research support from* Gilead Sciences:
    Gilead Oncology Award Winner 2021 (with S. Dietrich)
    Gilead Oncology Award Winner 2018
  - *Honoraria for*
    invited talks BMS, Astra Zeneca, Gilead, Roche, Incyte, Sandoz, AbbVie, Sobi, Ono KML, ars tempi
    advisory boards Regeneron, Roche, ADC, Incyte, BMS, AbbVie, Sobi
  - *Patents* I hold several patents on molecular subtyping of large B-cell lymphoma

Diffuse Large B-cell Lymphoma (DLBCL)

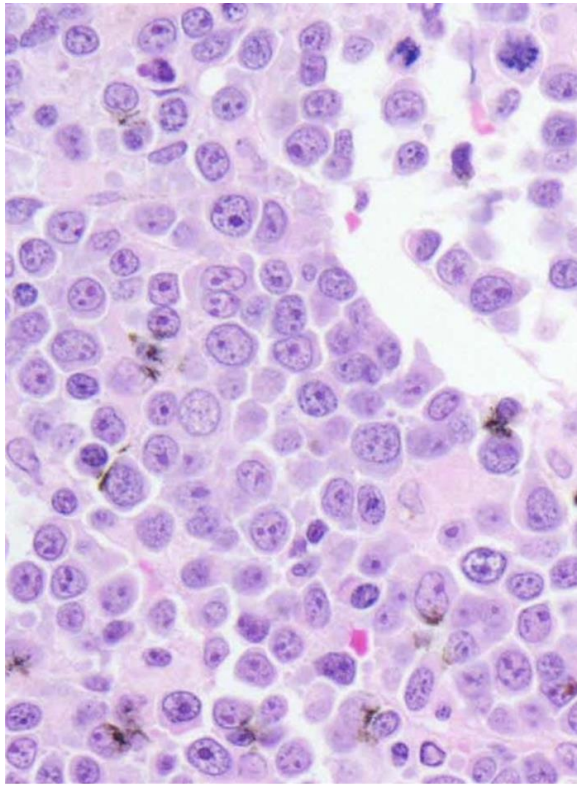


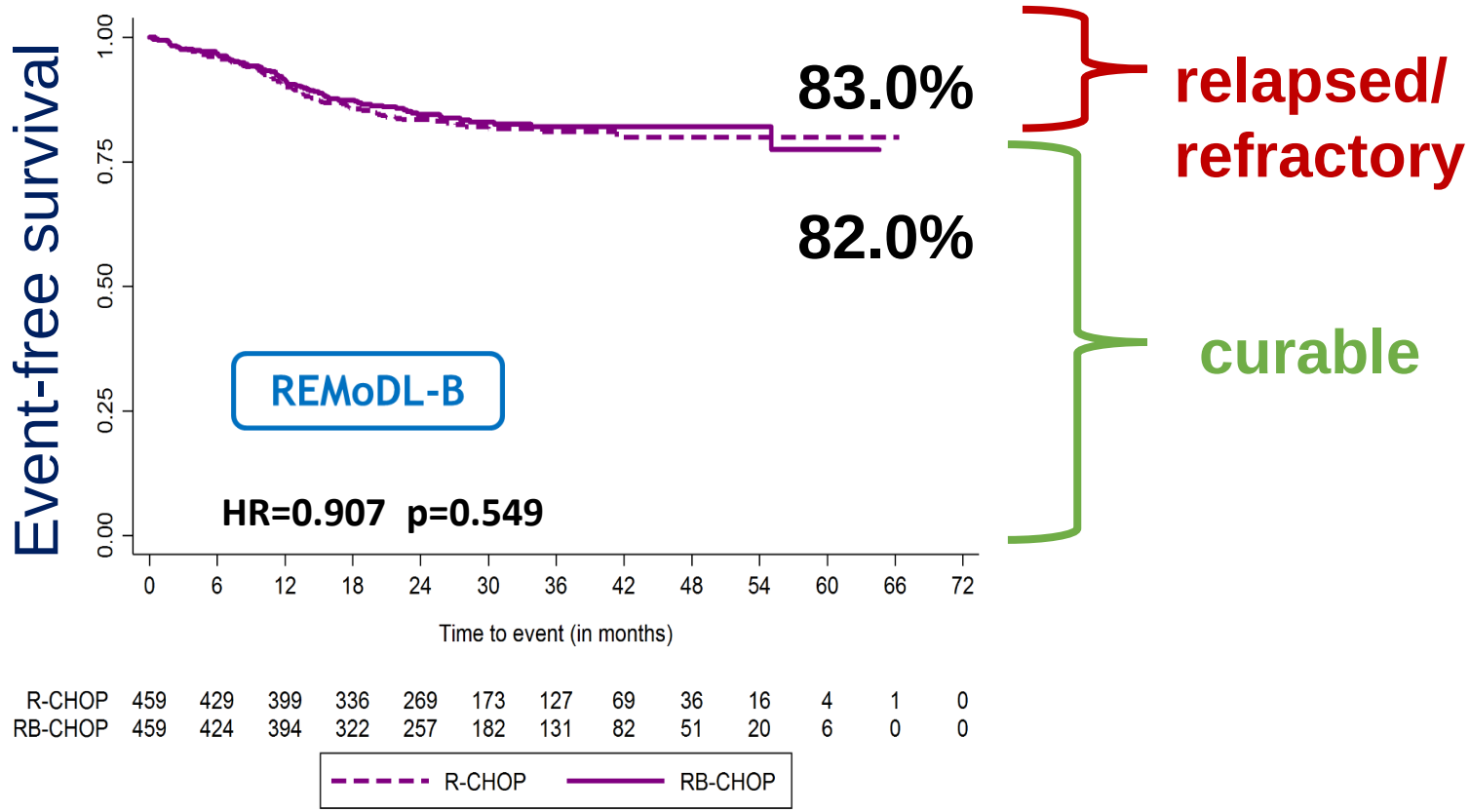
- Most common aggressive Non-Hodgkin lymphoma in adults.
- Arises from antigen-exposed germinal center B-cells.
- Molecular heterogenous disease with recognized transcriptionally subtypes with distinct functional characteristics.
- Genetically-defined DLBCL subtypes recently discovered.

➔Despite a more granular picture on the molecular insights of DLBCL have the perspectives of patients over the last 20 years only marginally.

DLBCL

One disease, one treatment?



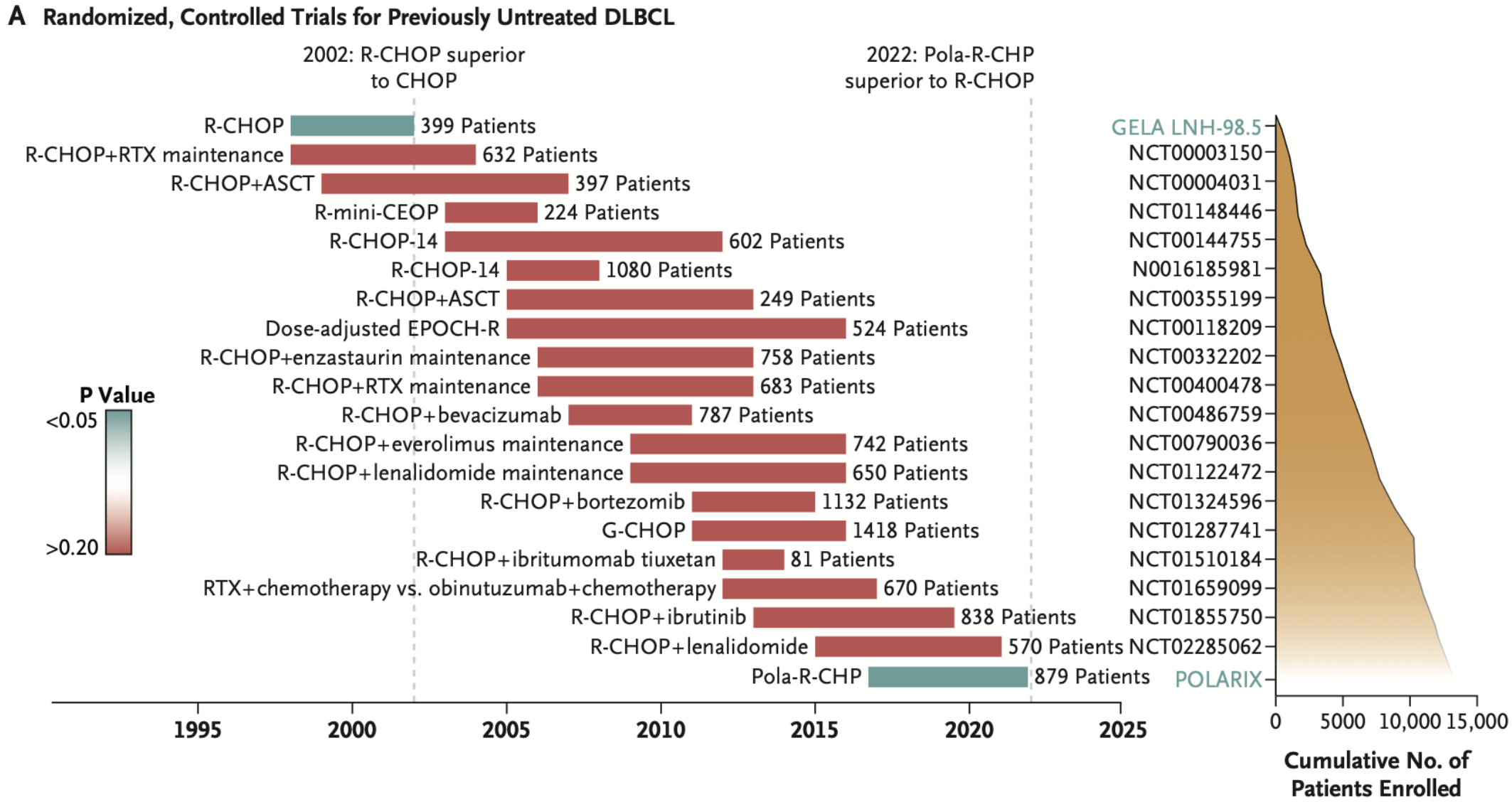


➔ R-CHOP-like treatments is the established standard since decades.

https://imagebank.hematology.org/image/1811

Davies ICML 2017

Empirical Optimization of R-CHOP - Not a Success Story

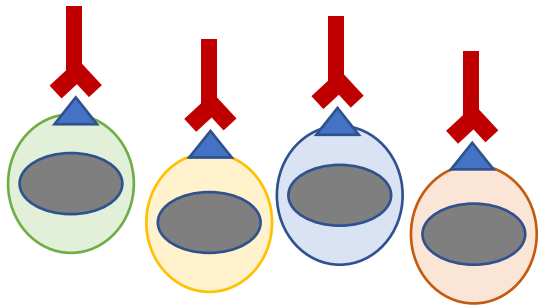


Palmer et al NEJM 2023

Current Strategies Towards Precision Medicine in Lymphoma

Molecular agnostic

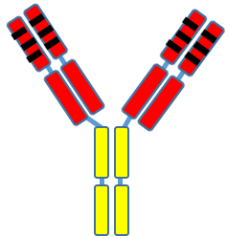
“All comer” Studies
Nowadays mainly targeting surface epitopes



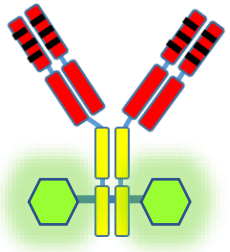
Armory of Lymphoma Treatment - New Bullets on the “Horizon”

Targeting Surface Epitopes

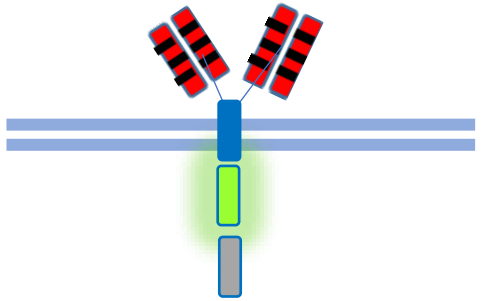
Chemo



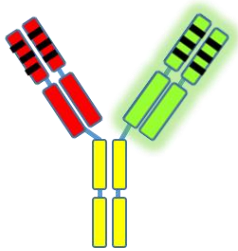
Antibodies



Antibody Drug Conjugats



CAR T-Cells & „friends

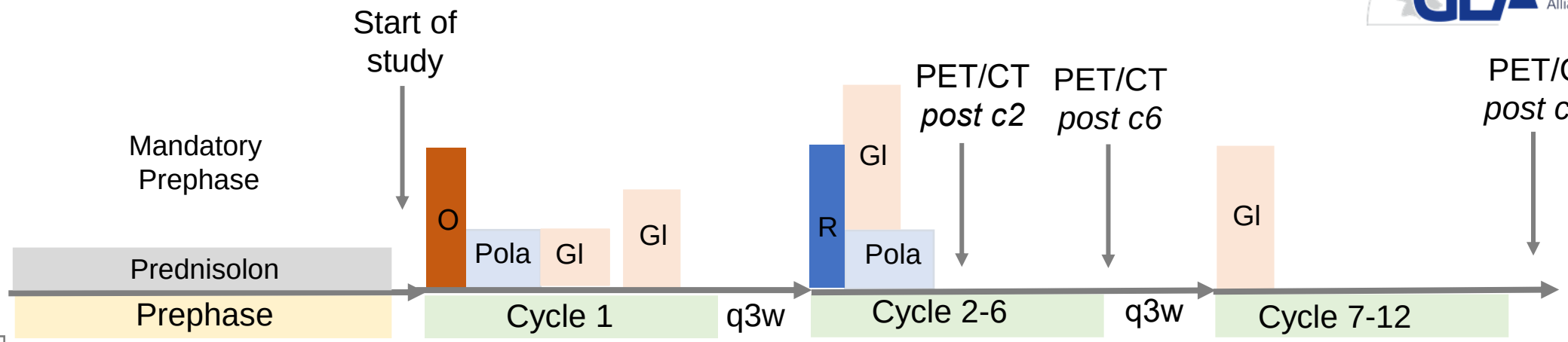


bispecific Antibodies

Empirical Strategy

- Combine as single agents or smart combinations in all-comer trials
- Biomarkers and understanding of molecular heterogeneity often only if primary end point is failed

Chemolight R-PolaGlo for 1L Pat Ineligible for R-CHOP-based Therapies



R Rituximab
O Obinotuzumab
Pola Polatuzumab
Gl Glofitamab

Debulking

D1-D5: Prednisolon 100mg
Can have started before enrollment

Polatuzumab + Glofitamab step-up dosing

D1: Obinutuzumab 1000mg
D2: Polatuzumab 1.8mg/kg
D8: Glofitamab 2.5mg
D15 Glofitamab 10mg

Pola + Glo target dose

D1: Rituximab 375mg/m^2
D1: Polatuzumab 1.8mg/kg
D2: Glofitamab 30mg

Glo target dose consolidation

D1: Glofitamab 30mg

Inclusion criteria

- All fit pats >79yo, or
- Pat non fit pat not eligible for R-CHOP-like therapies

Study Design and End Points

One arm, multicentric Phase II in Germany/Austria
80 patients (30 centers – 24 Germany/6 Austria)
Primary end point
- 1y PFS rate

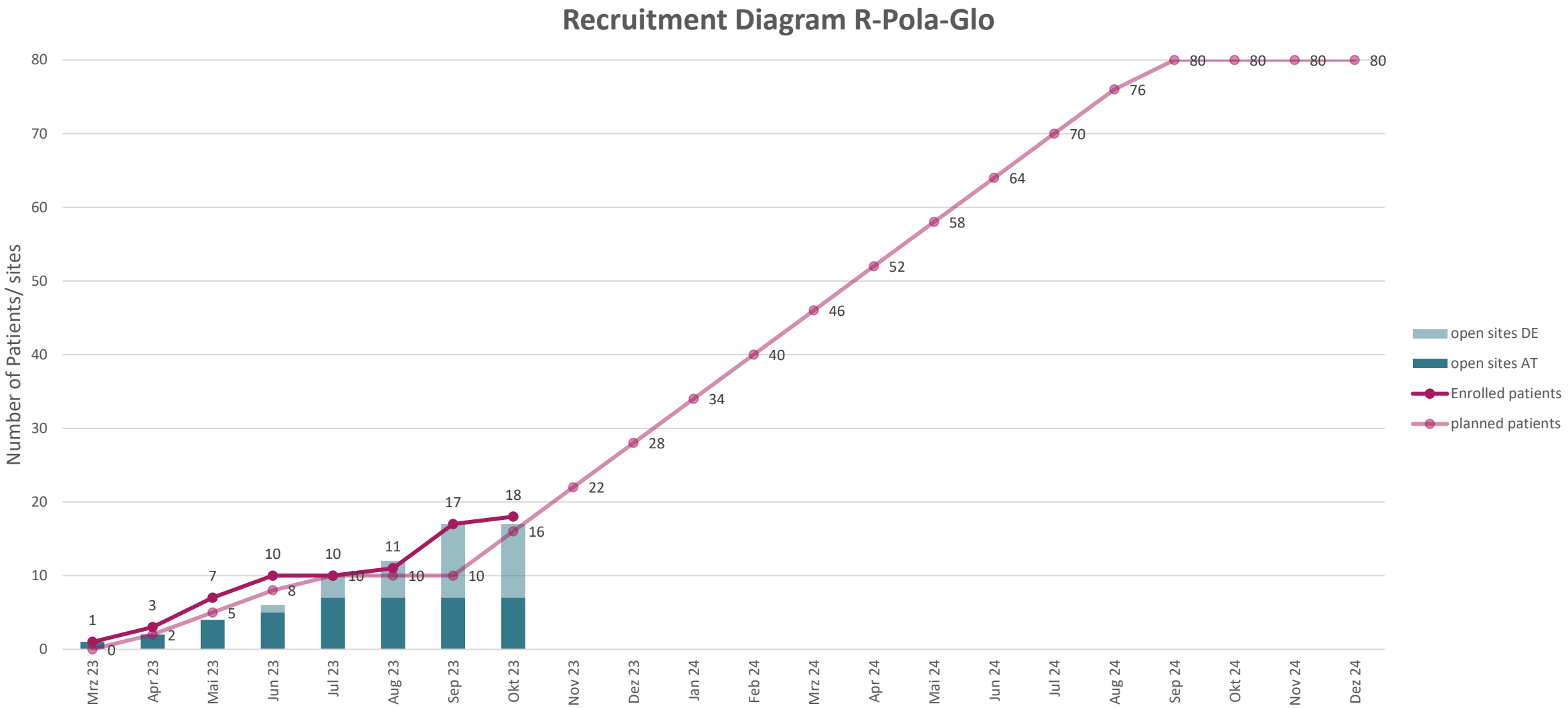
Secondary end points
- Efficacy (EFS, OS, DOR, rate of mCR after cycle 6, Conversion rate in maintenece)
- Feasibility and Toxicities (SAE,AE, Adherence)
- Explorative (QoL and PET/ctDNA related MRD)

Correlative Studies

- Baseline proteogenomic molecular studies incl. COO, MYC/BCL2 Status, genetic subtypes, TME characterization
- Dynamic response assessment with liquid biopsy before, after each cycle and as f/u and correlation to PET/CT-based imaging
- Assessment of T-cell clones/T-cell diversity and MHC peptide loading

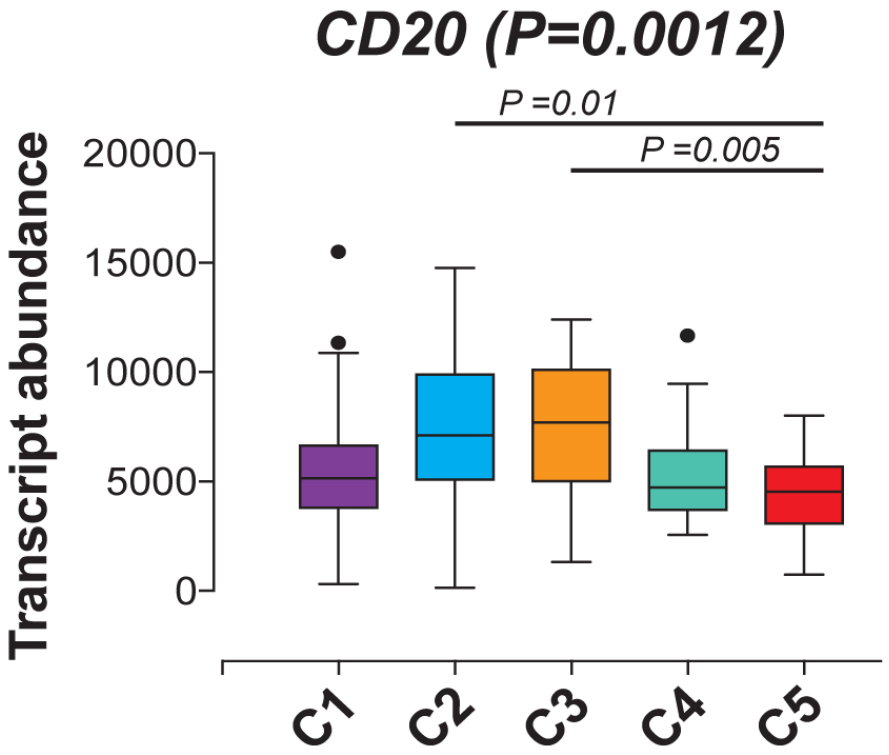
Responsible PIs: B. Chapuy for the GLA and R. Greil for the AGMT

Recruitment of R-Pola-Glo



THANK YOU!

Heterogenous Abundance of CD20 in Genetic C1-C5 DLBCL Subtypes

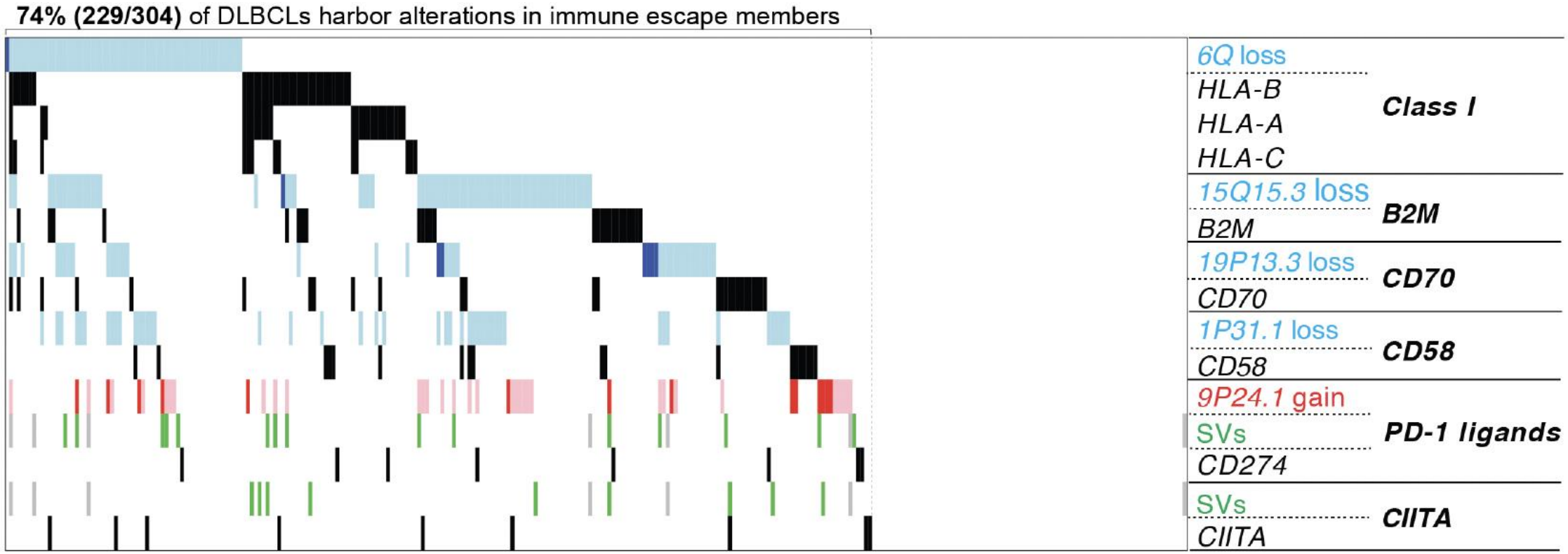


- CD20 transcript abundance is significantly different in genetically defined subtypes

➔ Highlights that epitope density varies for so called “agnostic” therapies

Chapuy Nat Med; 2018; 24(5):679-690

Frequent Genetic Bases of Immune Escape Pathways in Untreated DLBCL



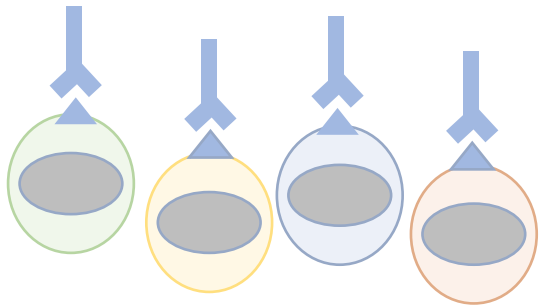
➔ 2/3 of DLBCL patients have genetic alterations in a potent immune escape pathways

Chapuy Nat Med; 2018; 24(5):679-690

Current Strategies Towards Precision Medicine in Lymphoma

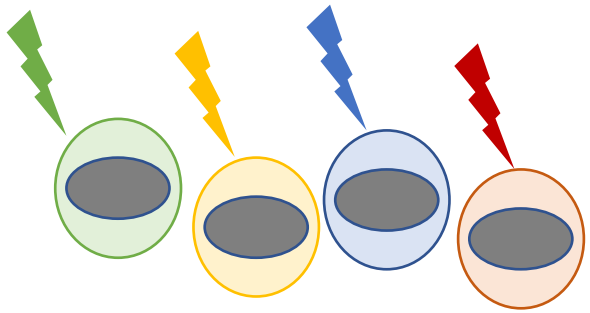
Molecular agnostic

"All comer" Studies
Nowadays mainly targeting surface epitopes

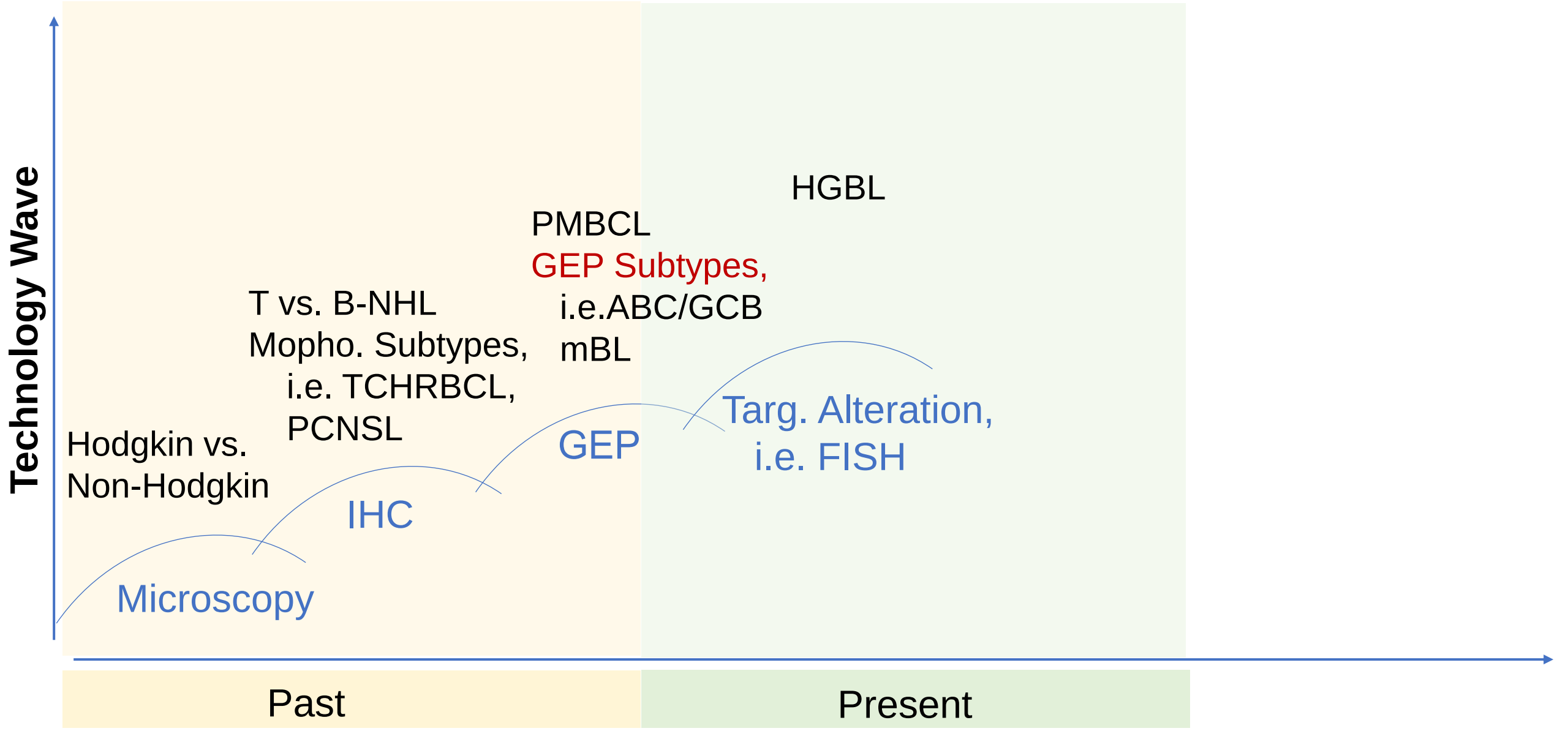


Molecular-driven

Understanding Molecular Heterogeneity
&
Targeting Actionable Alterations

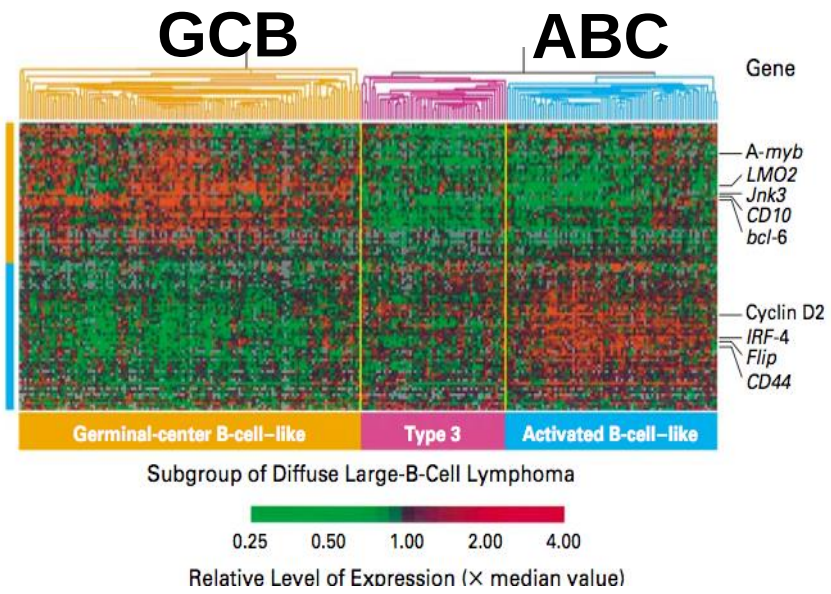


Evolving Molecular Heterogeneity with Technology



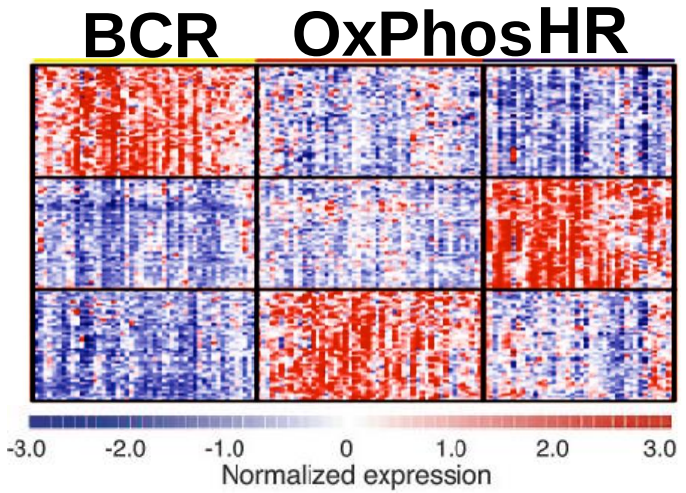
Transcriptional Heterogeneity in DLBCL

Cell of origin



Alizadeh et al, Nature 2000
Rosenwald et al, NEJM 2002
Lenz et al NEJM 2008
Lenz and Staudt NEJM 2010

Consensus Clusters

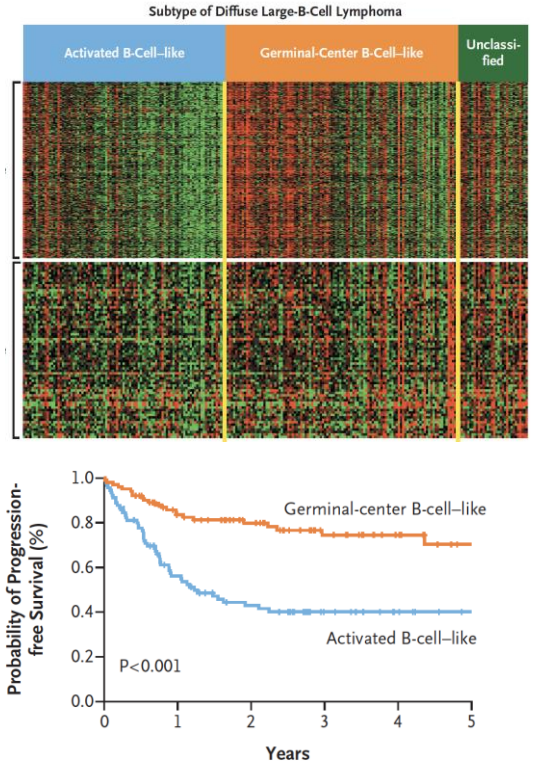


Monti et al, Blood 2005
Chen et al, Cancer Cell 2012
Caro et al, Cancer Cell 2013

- Transcriptionally defined disease subtypes highlight specific aspects of DLBCL biology, suggest cancer cell dependencies and identify rational therapeutic targets.

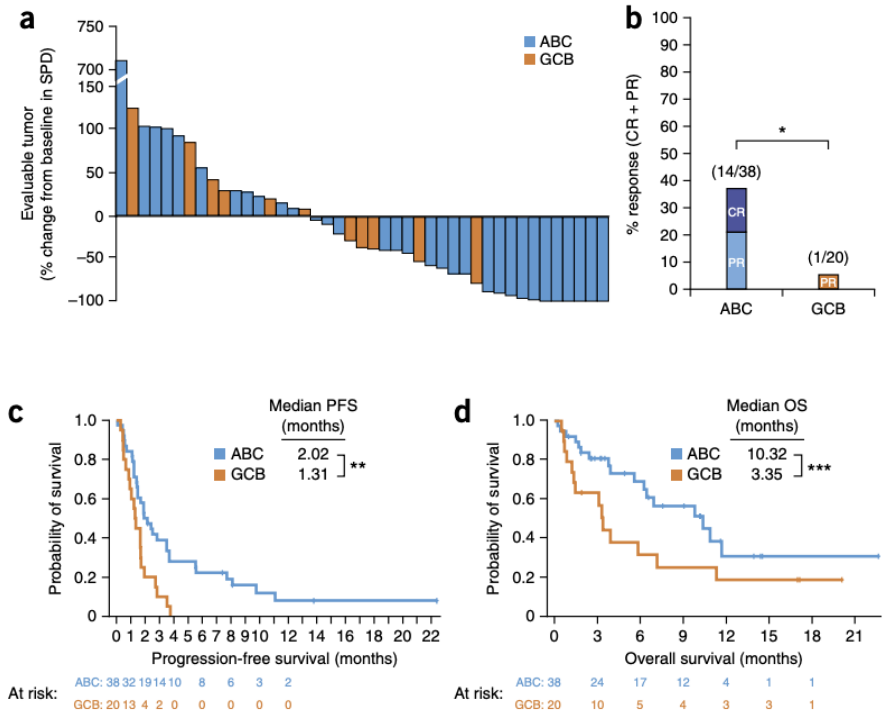
Targeting ABC-type DLBCL

Transcriptional Heterogeneity of DLBCL



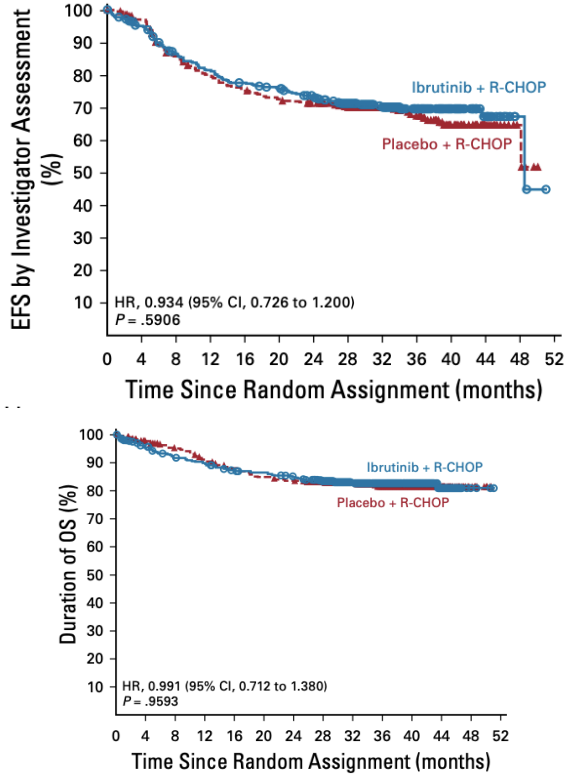
Lenz et al. *N Engl J Med* 2008;359:2313-23

Vulnerability of ABC to BTK Inhibition



Wilson et al. *Nat Med.* 2015; 21, 922–926.

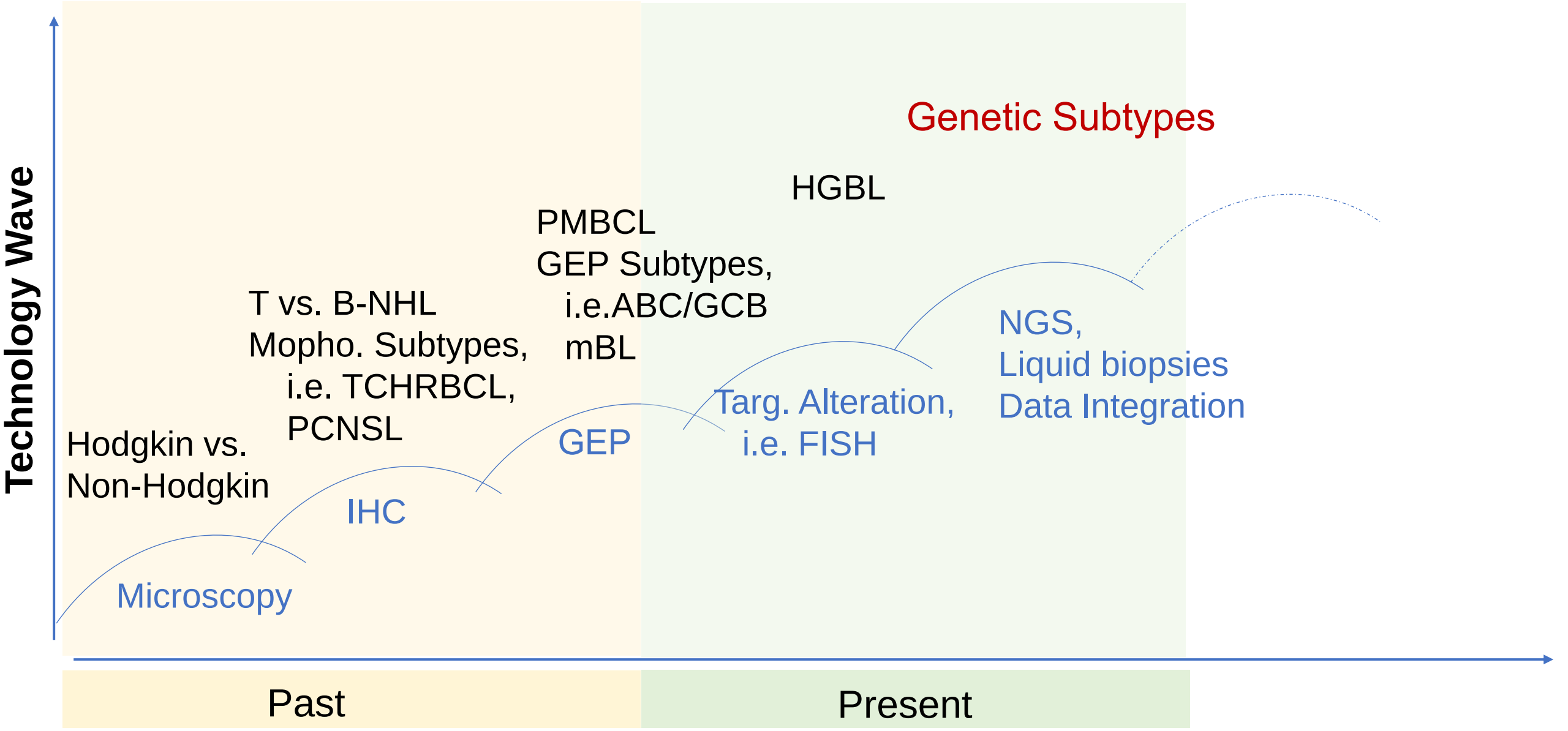
Phase III Trial Failed End Point



Younes et al. *JCO.* 2019; 20;37(15):1285-1295.

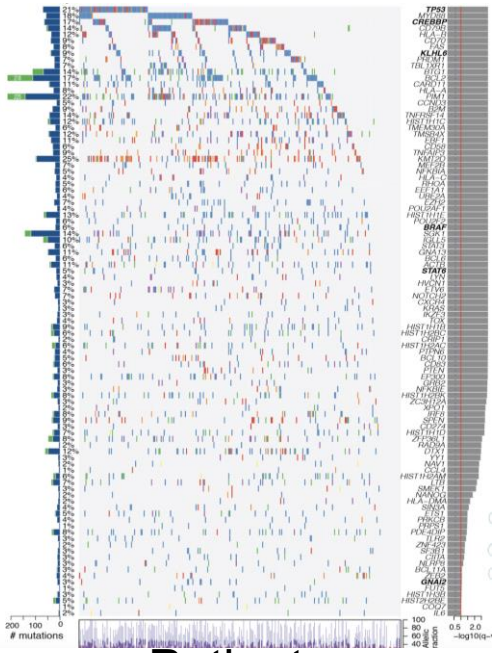
➔ Suggested that there is additional molecular heterogeneity

Evolving Molecular Heterogeneity with Technology

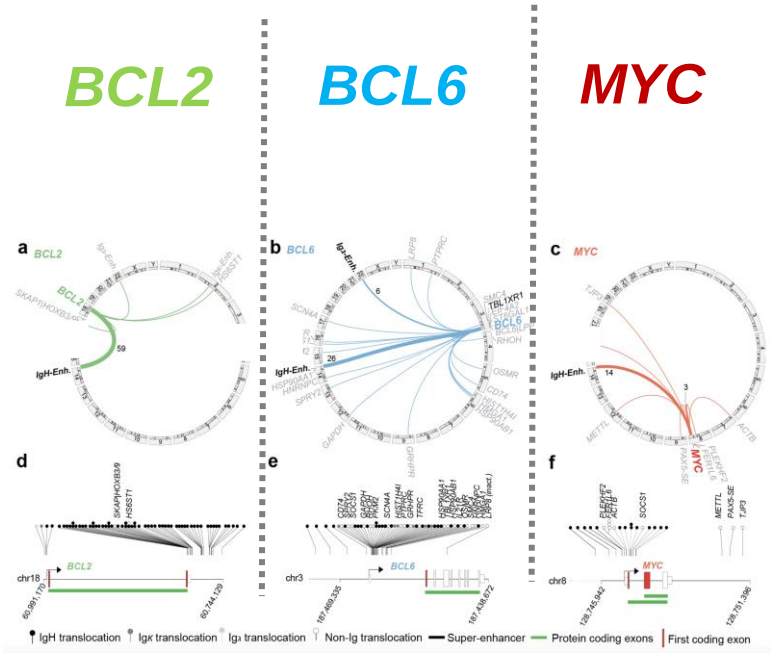


Comprehensive Genomic Analysis of Primary DLBCL

Mutations



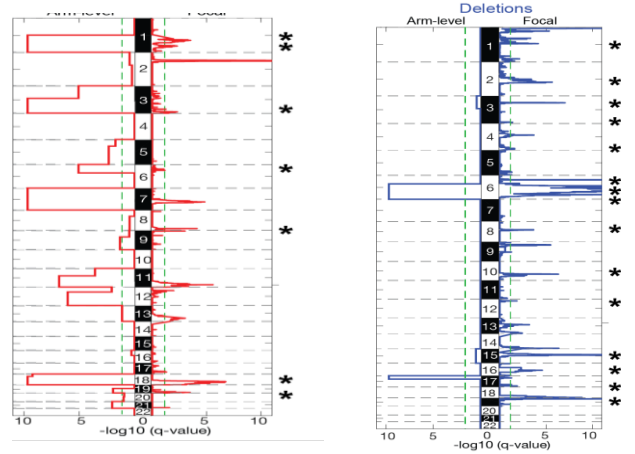
SVs



SCNAs

Amplifications **Deletions**

Arm-level Focal Arm-level Focal



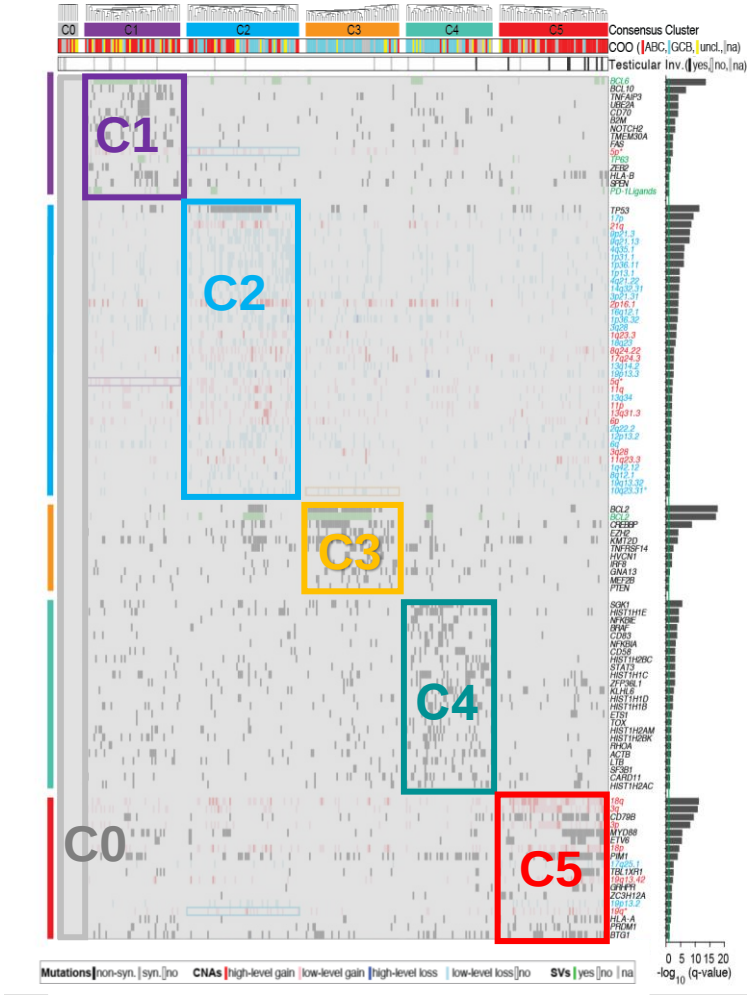
* Significantly mutated genes within SCNAs

- Integration of recurrent mutations, somatic copy number alterations (SCNAs) and structural variants (SVs) in newly diagnosed DLBCLs.
- Median # of genetic driver alterations is 17 (1-48)

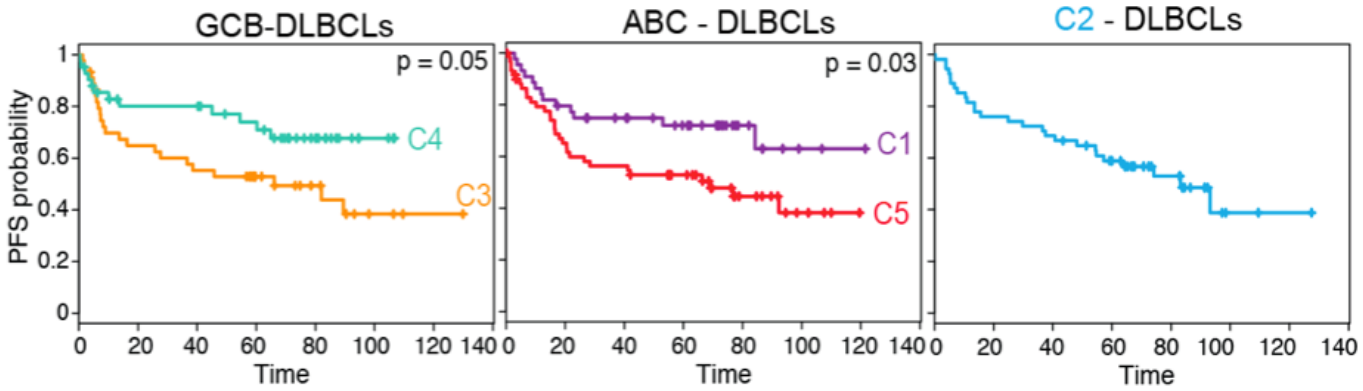
GOAL: Define DLBCL genetic substructure

Genetic Signatures Predictive for Outcome Independent of the IPI

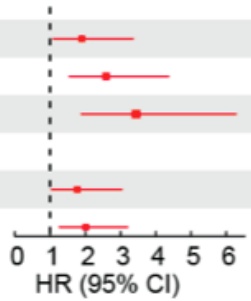
Genetically-distinct DLBCLs



Predictive for Outcome



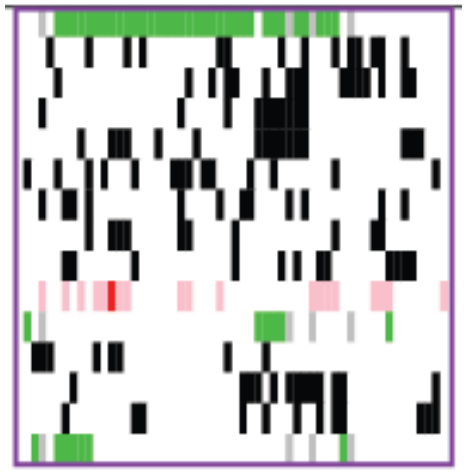
	Term	N	HR	p-value
IPI	Low	88	Reference	–
	Low-int.	56	1.90	0.027
	High-int.	74	2.59	< 0.001
	High	34	3.44	< 0.001
Clusters	C0/C1/C4	94	Reference	–
	C2	53	1.77	0.039
	C3/C5	105	2.01	0.003

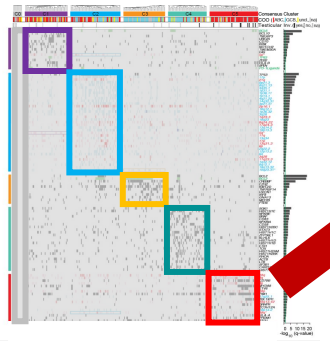


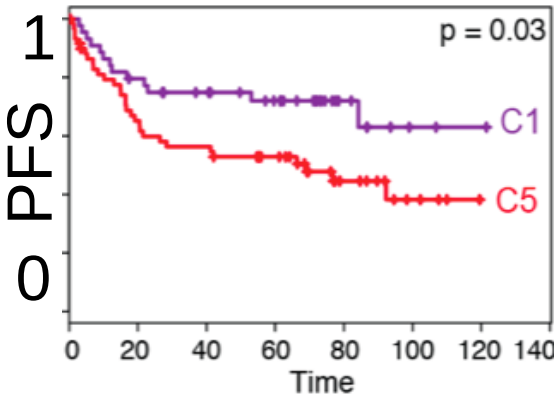
Chapuy, Stewart, Dunford et al. *Nat Med;* 2018; 24(5):679-690

Genetically Distinct ABC-enriched DLBCLs

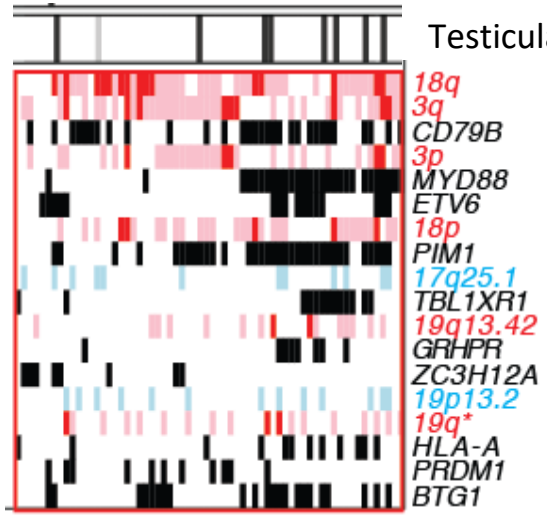
C1 DLBCLs







C5 DLBCLs



- Mutations as previously described in marginal zone lymphoma **(MZL)**[1-4]
- *BCL6* SVs associated with **transformed MZL**[5]
- **Favorable** outcomes

➔ **20%** of DLBCLs occultly transformed **MZL ?**

- 18q/*BCL2* gain with concurrent mutations in *MYD88*^{L265P}/*CD79B*
- Resembled genetic sign. of **PCNSL and PTL**[6] and **other extranodal lymphoma**[7]
- **8/9 DLBCL with testicular involvement**
- **Unfavorable** outcome

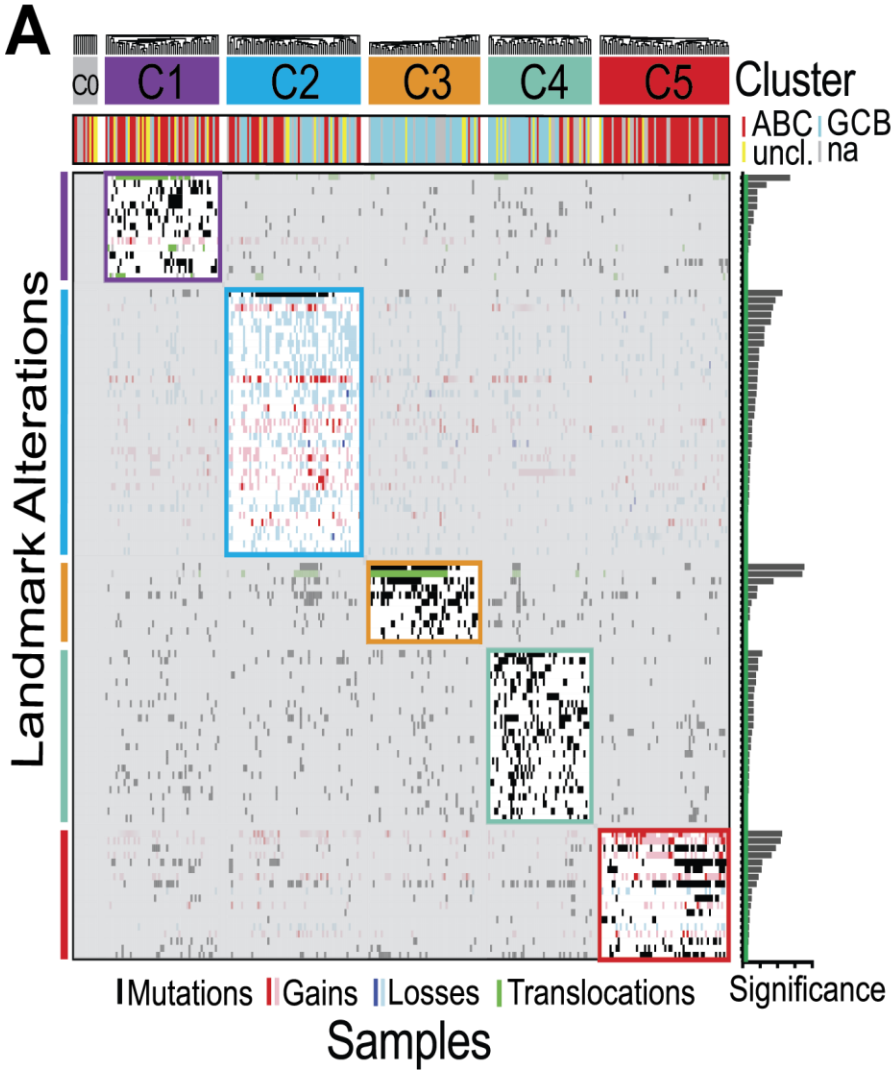
➔ Coordinate genetic signature associated with extranodal tropism.

[1] *Zhang et al., Nat. Gen 1999*
[2] *Rossi et al., JEM 2012*
[3] *Kiel et al., JEM 2012*
[4] *Spina et al., Blood 2016*
[5] *Flossbach et al., Int J Cancer 2011*
[6] *Chapuy, Roemer et al., Blood 2016*
[7] *Wright et al Cancer Cell 2020*

Chapuy, Stewart, Dunford et al. Nat Med; 2018
Wienand and Chapuy. *Hem Oncol* 2021

Genetically-distinct DLBCLs and their Associated Features

A



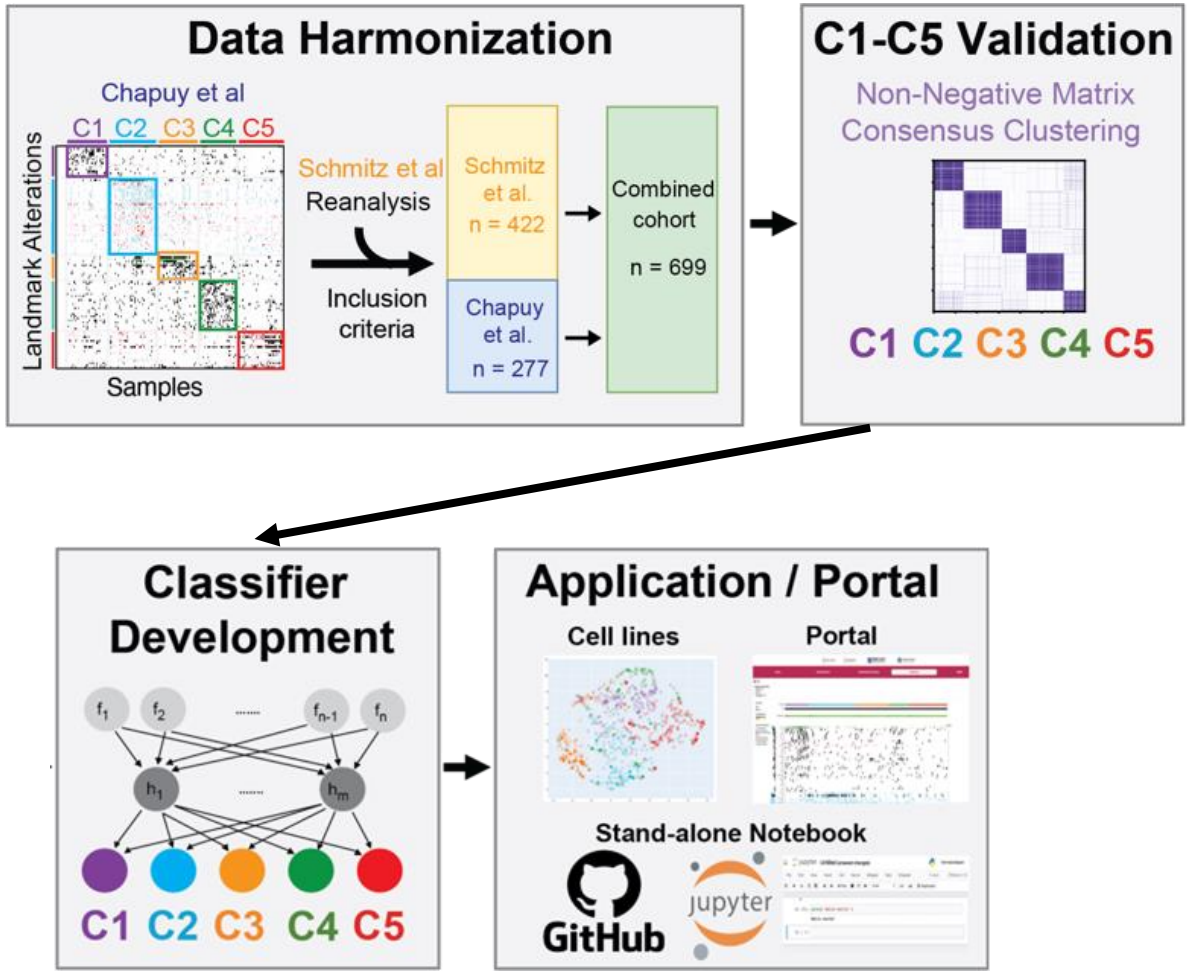
B

Genetic Subtype *DFCI*	Genetic Subtype *NCI*	Key Features	Transcriptional Subtype	Prognosis
C1	BN2	*BCL6* and NOTCH2- and NF-κB and immune escape pathway alterations; occulty transfomed MZL	ABC	Favorable
C2	(A53 / TP53)	Biallelic inactivation of *TP53*, 9p21.3/*CDKN2A;* genomic instablity	ABC/GCB independent	Steady rate of progression
C3	EZB	*BCL2* SVs, inactivating *PTEN* alterations and alterations of epigenetic enzymes	GCB	Unfavorable
C4	ST2	BCR/PI3K-, JAK/STAT-, RAS-pathway and histone alterations	GCB	Favorable
C5	MCD	*BCL2* copy gain, activating *MYD88* and *CD79B* mutations; extranodal tropism	ABC	Unfavorable

DLBclass

Wienand and Chapuy, ICML 2021

Molecular Classificator for DLB*class*



DLBclass

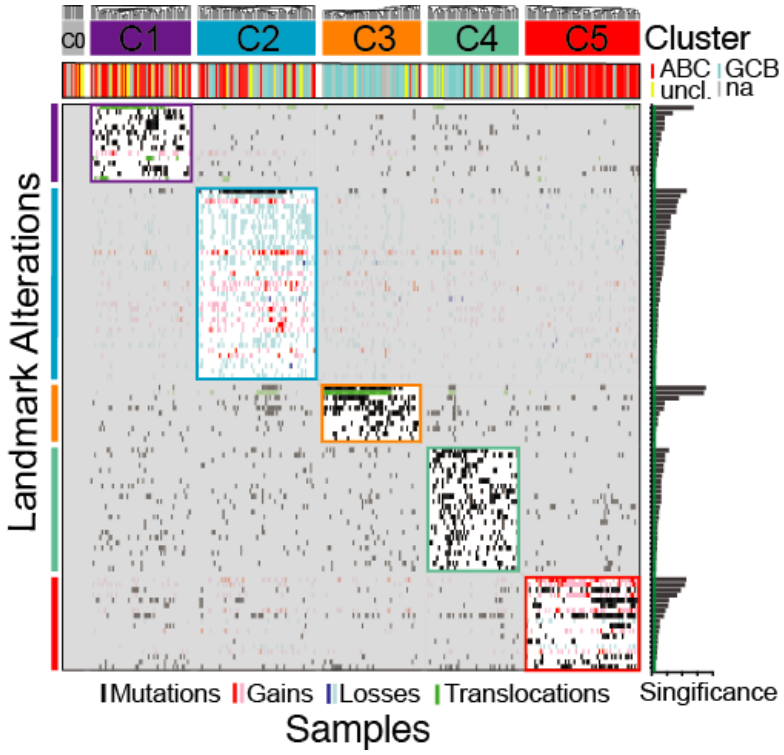
Properties

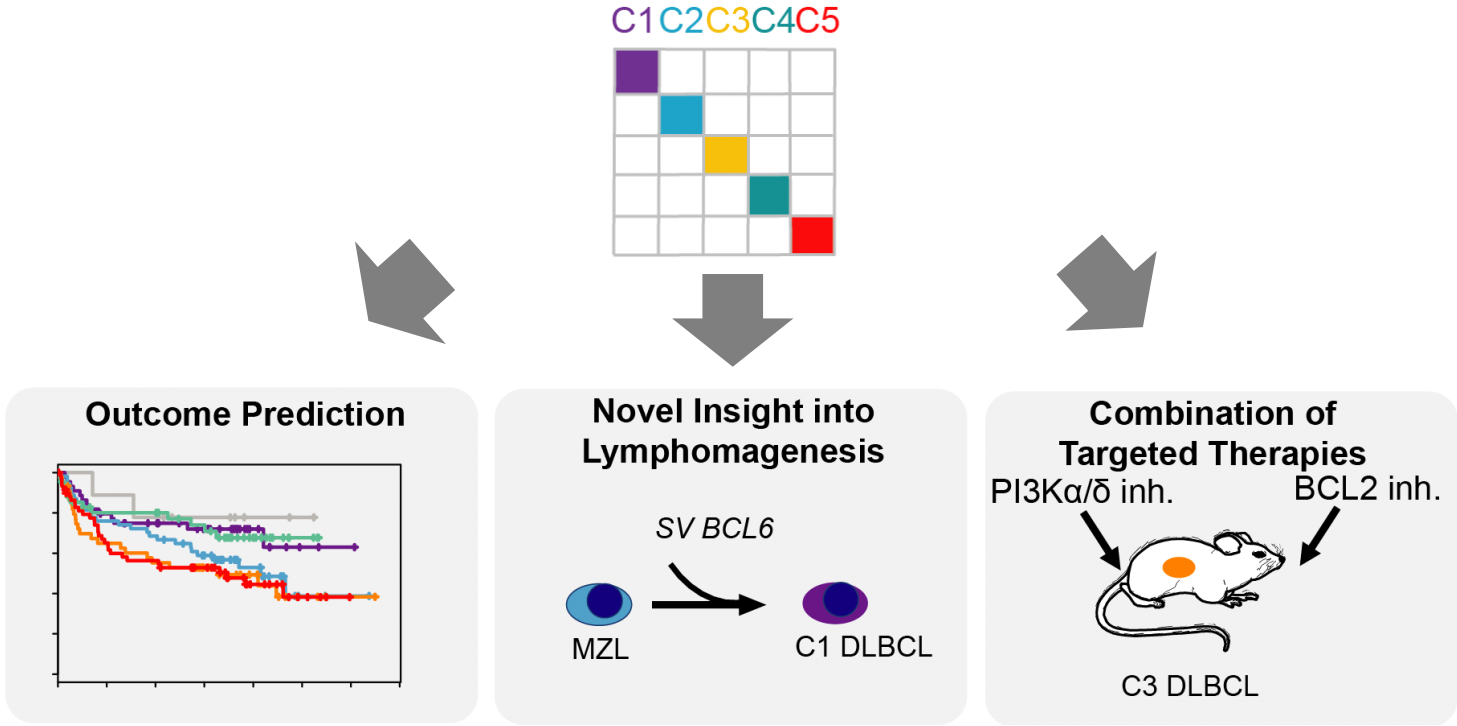
- Robust classification of single cases
- Output: C1-C5, probabilistic
- "easy-to-use" online tool

- Accurate identification of the C1-C5 DLBCL subtypes in newly diagnosed patients possible.
- Necessity for clinical translation.

Chapuy, Stewart, Wood, et al. in preparation

Genetically Distinct DLBCL Subtypes

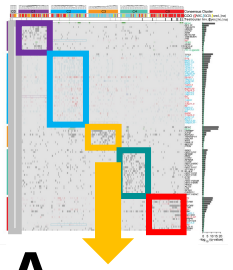




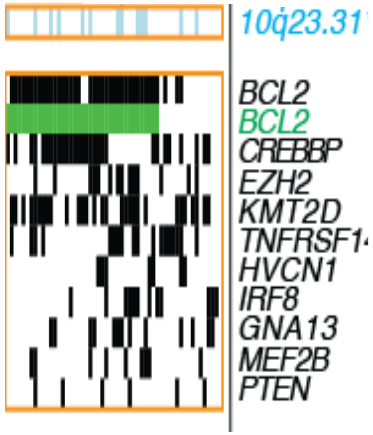
➔ Genetically-defined DLBCL subsets (C1-C5) predict different outcomes, provide novel insights into lymphomagenesis and suggest certain combinations of targeted therapies.

Chapuy, Stewart, Dunford, et al. Nat Med 2018 *Bojarczuk et al. Blood 2019* *Bojarczuk and Chapuy, EHA Educational 2019*

Roadmap to Targeted Combination Therapies – PI3Kαδ/BCL2 Inhibition in C3 DLBCLs



A



C3 DLBCLs

- Co-targeting of PI3Kad and BCL2 is highly synergistic in genetically-defined pre-clinical DLBCL models.

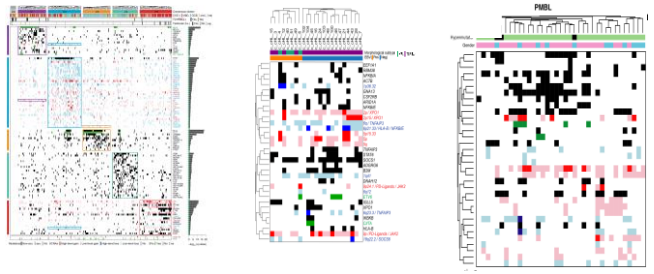
➔ Proof of concept that genetically-defined clusters provide a roadmap for rational (pre)clinical therapies

Bojarczuk K et al., Blood 2018

Molecular Lymphoma Board

~800 primary lymphoma

DLBCL CHL PMBL



Genomic Signature

Public DBs

Molekular Tumorboard Onkopus

Prediction of single- and combination therapies

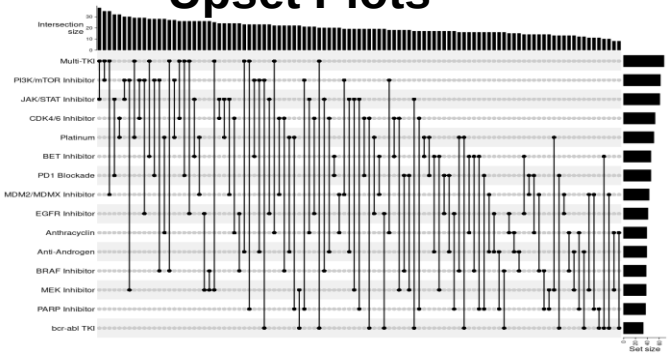
SNV
CNV
Fusions

GDKD
CIViC
TARGET

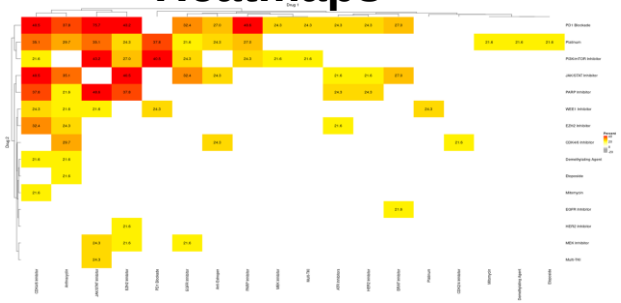
Classification of therapy and evidence level

	Approved	Clinical	Preclinical
Same Cancer	A1	A2	A3
Other Cancer	B1	B2	B3

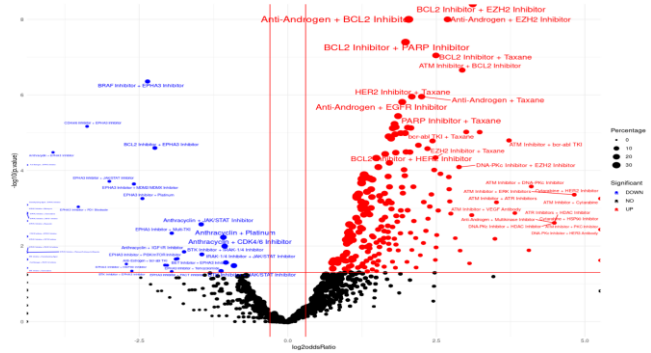
Upset Plots



Heatmaps



Vulcano Plots

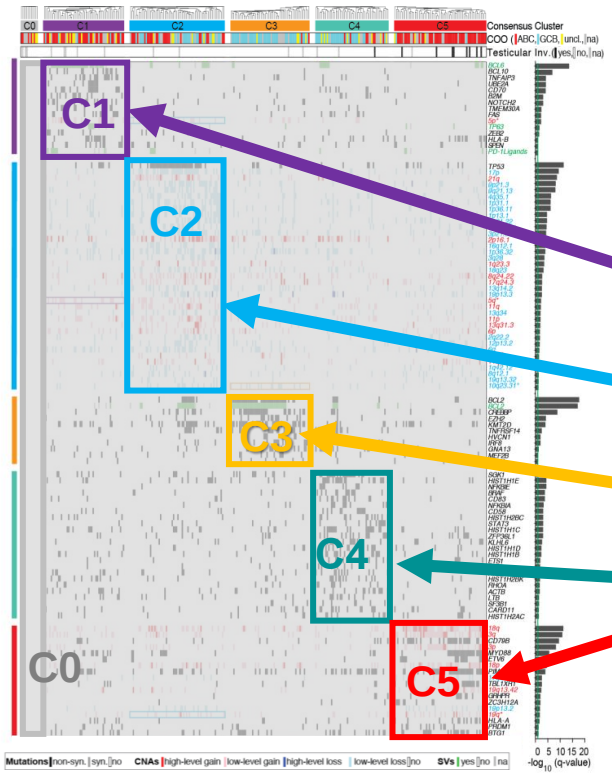


➔ Testable hypotheses are currently being evaluated in the wet-lab

In collaboration mit T. Beißbarth (UMG) und dem CADS Program des BIH

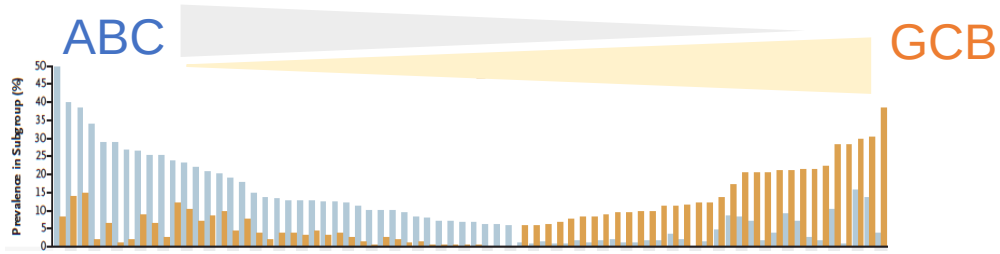
Genetic DLBCL Classifications

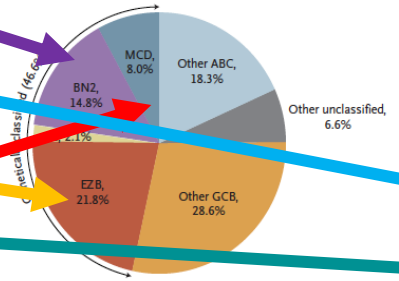
DLBclass



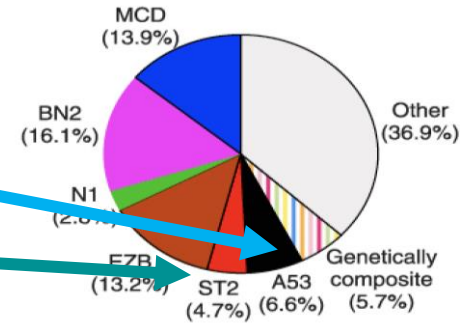
Chapuy, Stewart, Dunford, et al. *Nat. Med.* 2018

LymphGen





Schmitz, Wright, Huang, Johnson, et al. *NEJM* 2018



Wright et al. *Cancer Cell* 2020

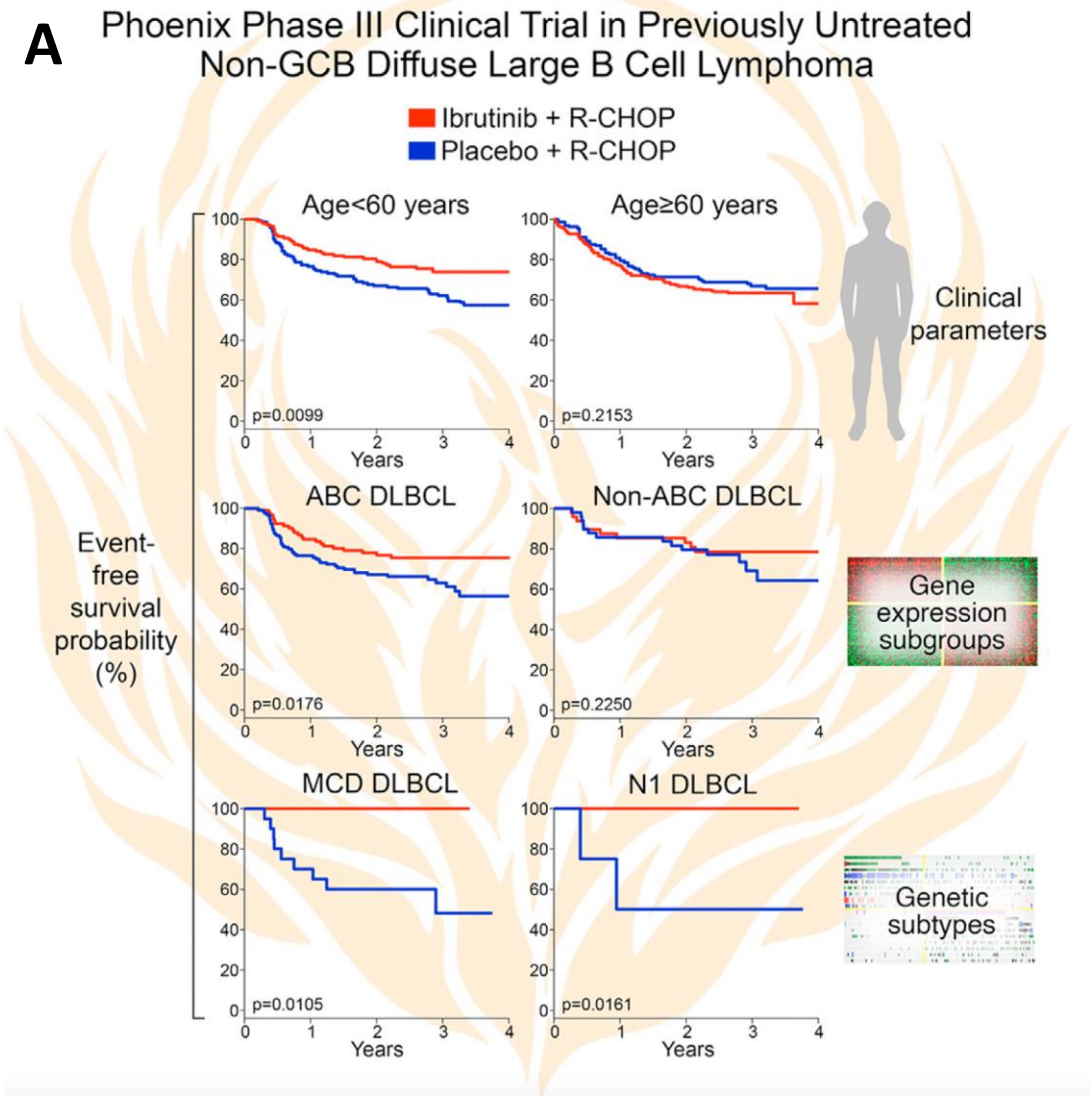
➔ DLBCL is genetically a heterogeneous disease with multiple genetic subtypes.

➔ Major subtypes have been validated using targeted approaches[1].

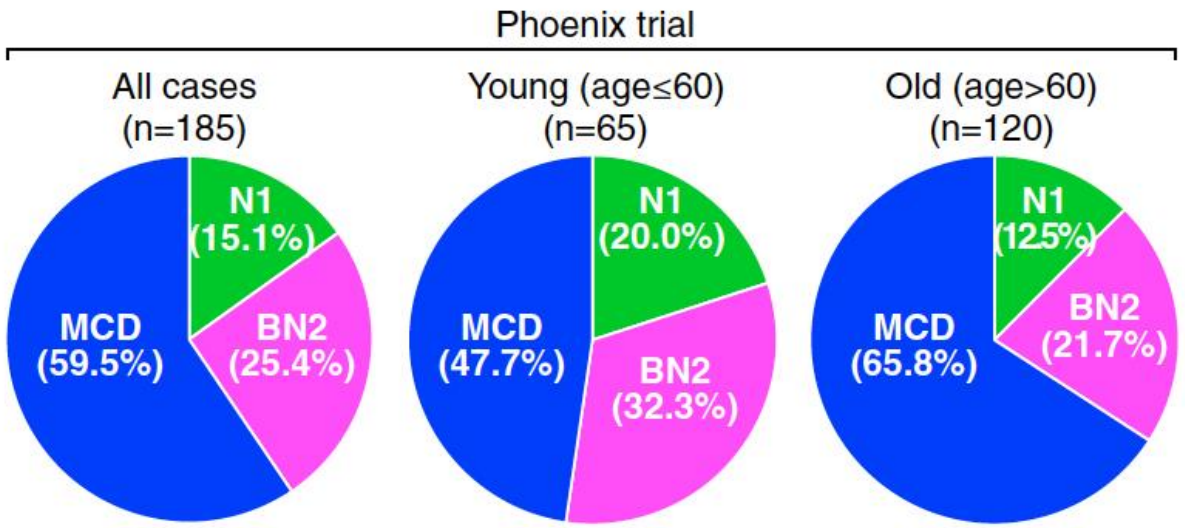
[1] Lacy et al *Blood* 2020

Effect of Ibrutinib with R-CHOP Chemotherapy in Genetic Subtypes of DLBCL

A



B

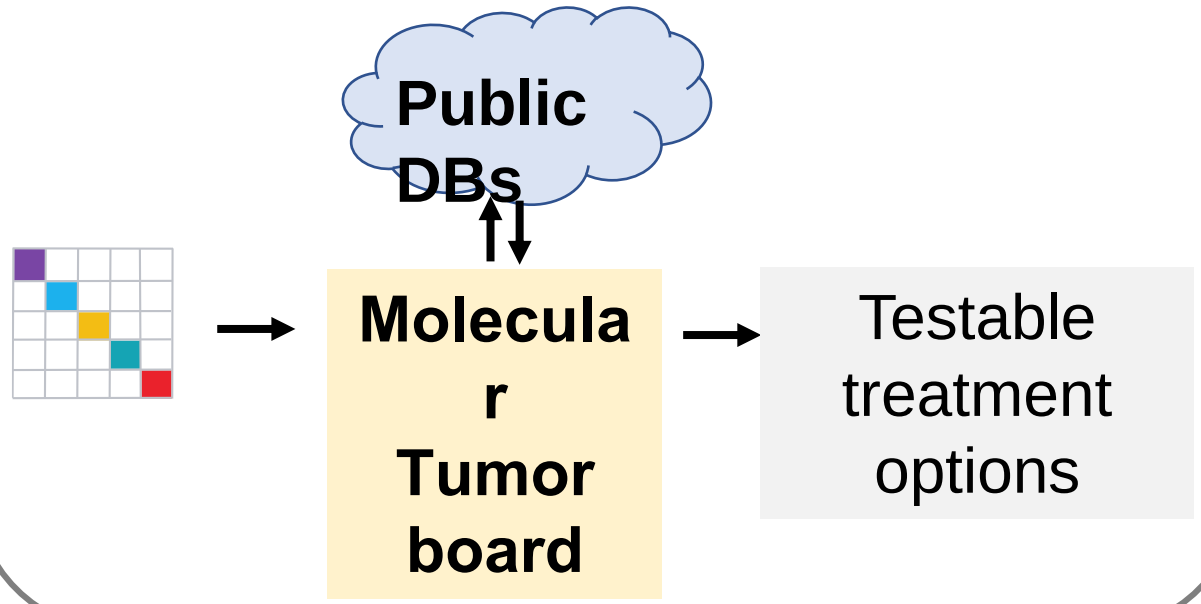


- BTK inhibitor ibrutinib plus R-CHOP is effective in younger patients with ABC DLBCL
- Patients with the MCD and N1 subtypes have 100% survival with ibrutinib plus R-CHOP

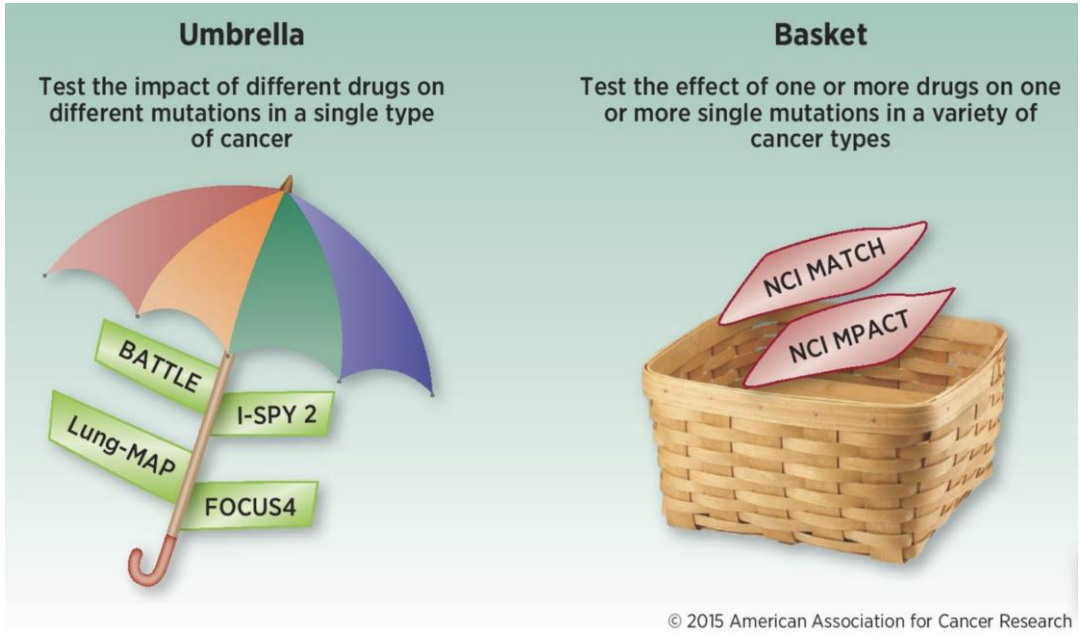
Wilson et al *Cancer Cell* 2021

Change in Patient Management and Trial Culture

Molecular Tumor Boards



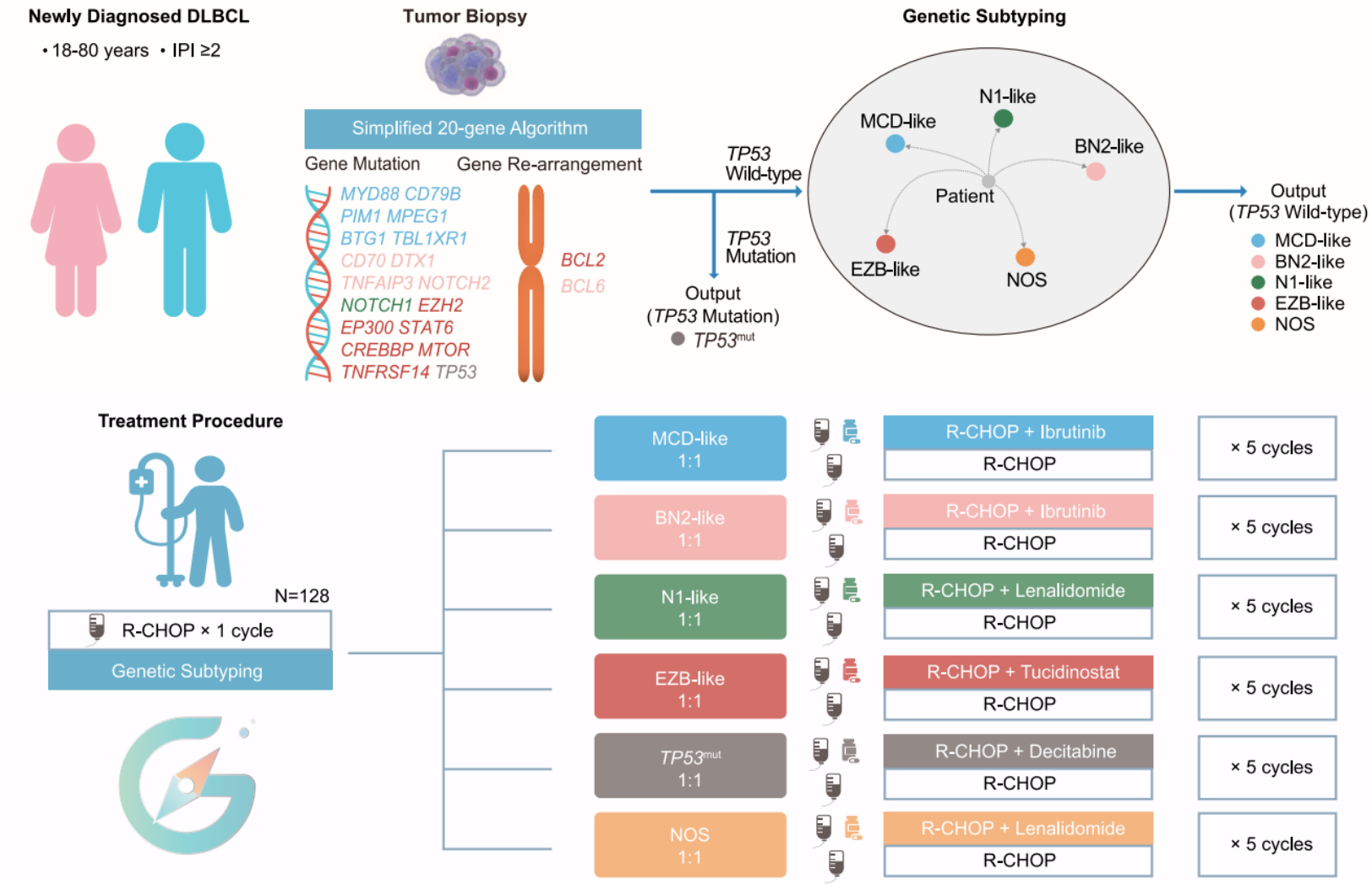
All Comer Trials become problematic



➔ Complex biology demands molecularly trained physician and clinically trained biologists/computational biologists

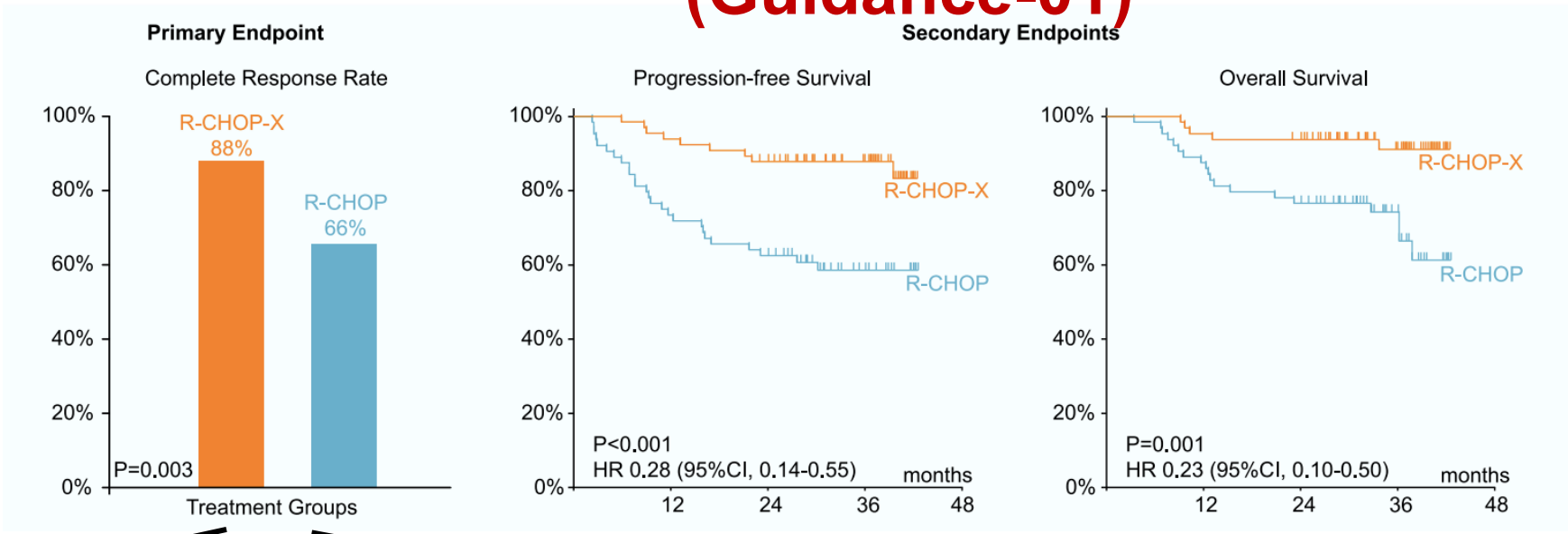
➔ Need to rethink clinical trial designs

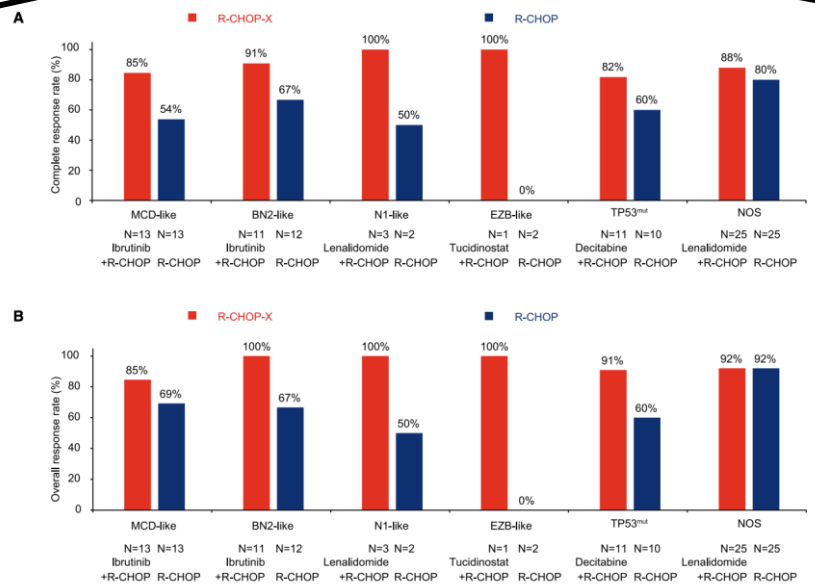
Biomarker-guided Targeted Therapy in DLBCL – R-CHOP+X (Guidance-01)



Zhang et al Cancer Cell 2023

Biomarker-guided Targeted Therapy in DLBCL – R-CHOP+X (Guidance-01)

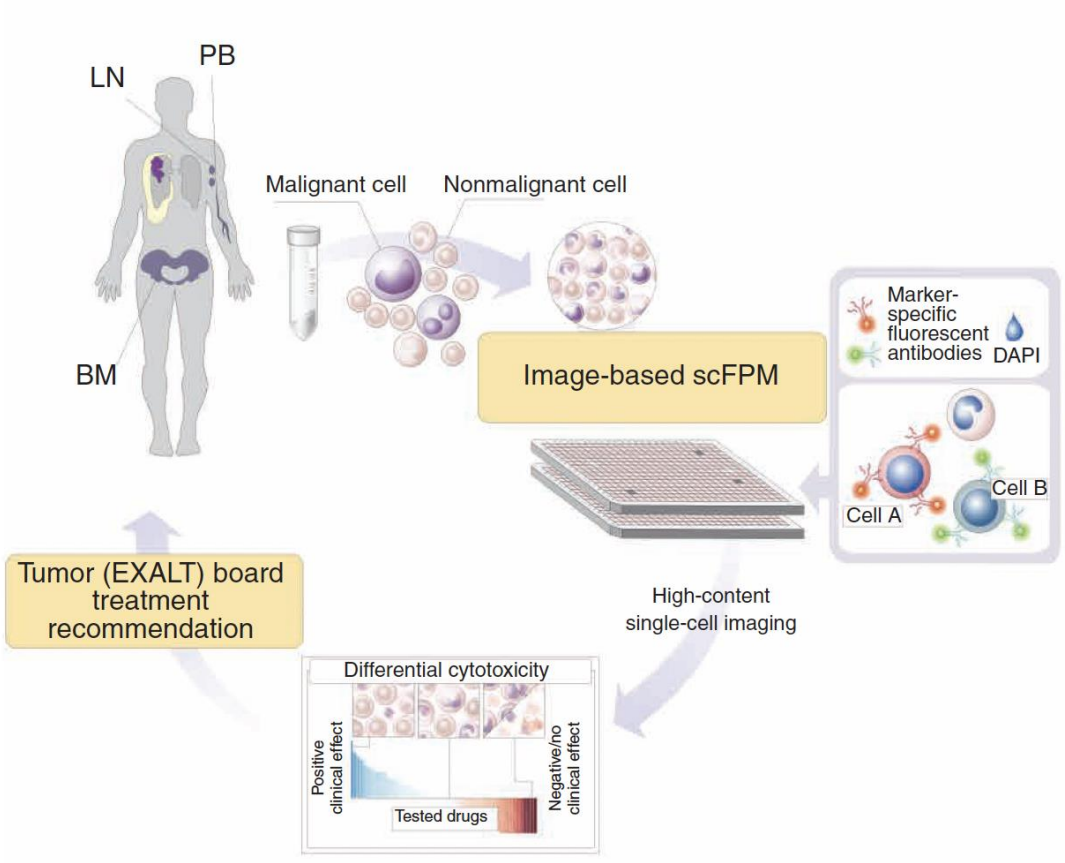


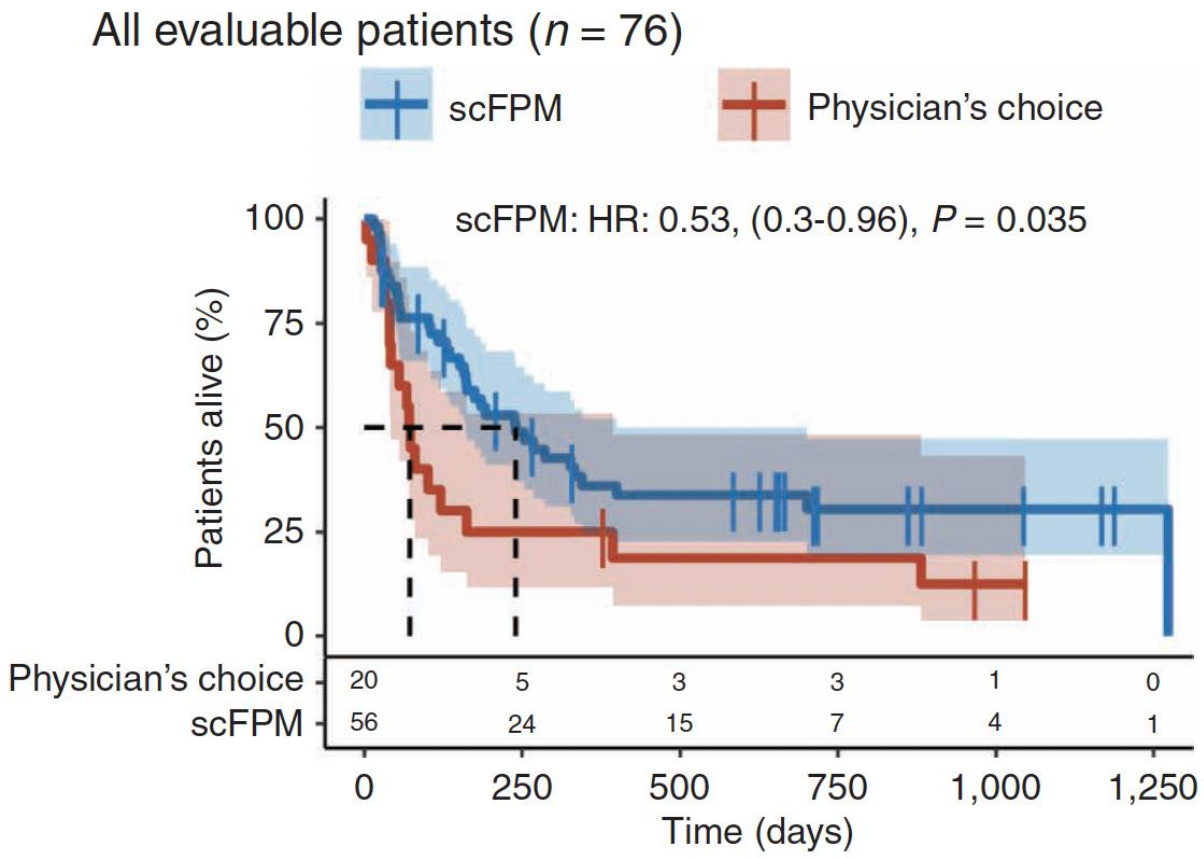


- ➔ Promising preliminary data
- ➔ Provides insights into feasibility of biomarker driven trials
- ➔ Cave: small numbers

Zhang et al Cancer Cell 2023

EXALT TRIAL[1] – Proof of concept functional informed n of 1 trial in hematology



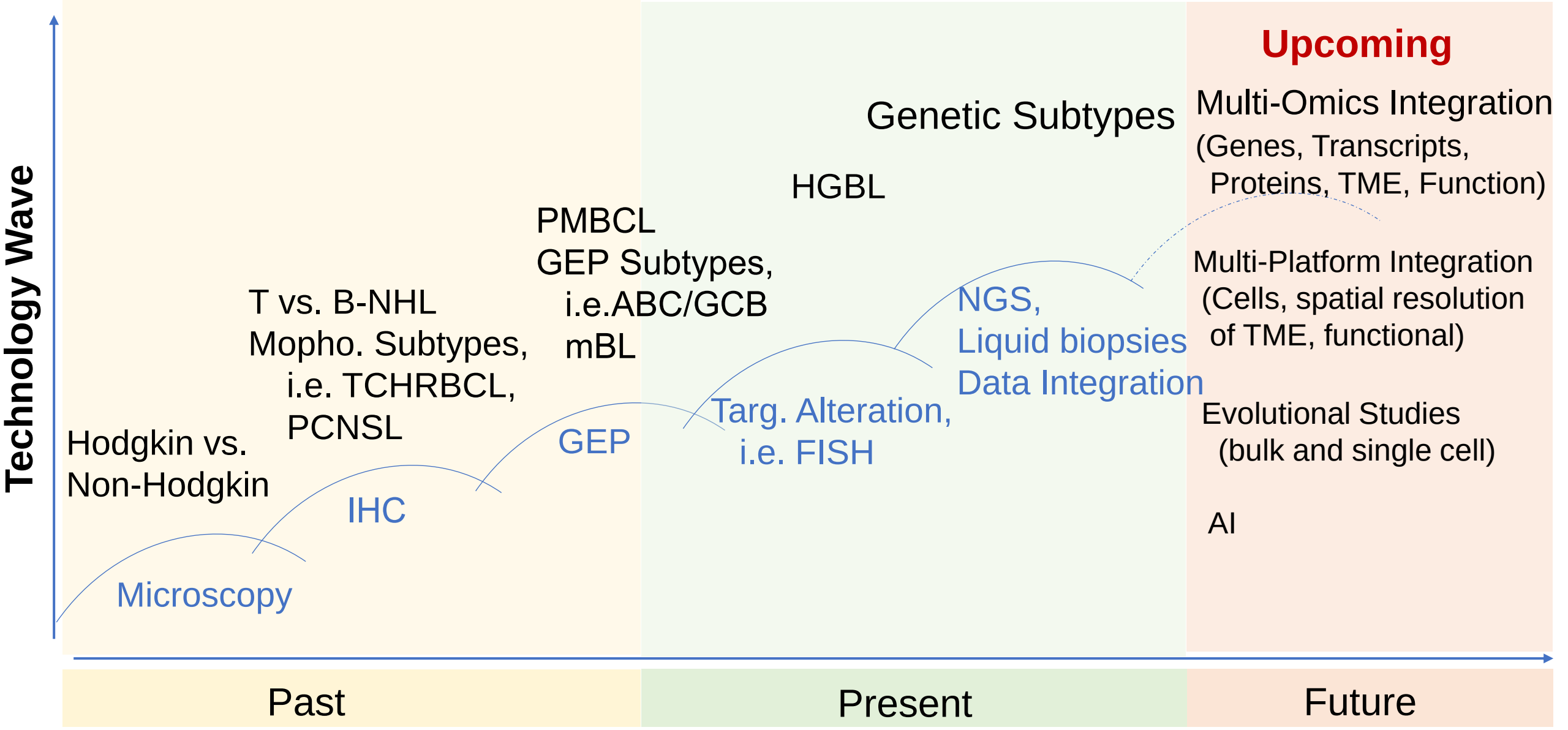


➔ Ex vivo drug screen to generate functional signatures.

➔ Non-intervential SMARTtrial demonstrate feasibility in aggressive hematological diseases[2]

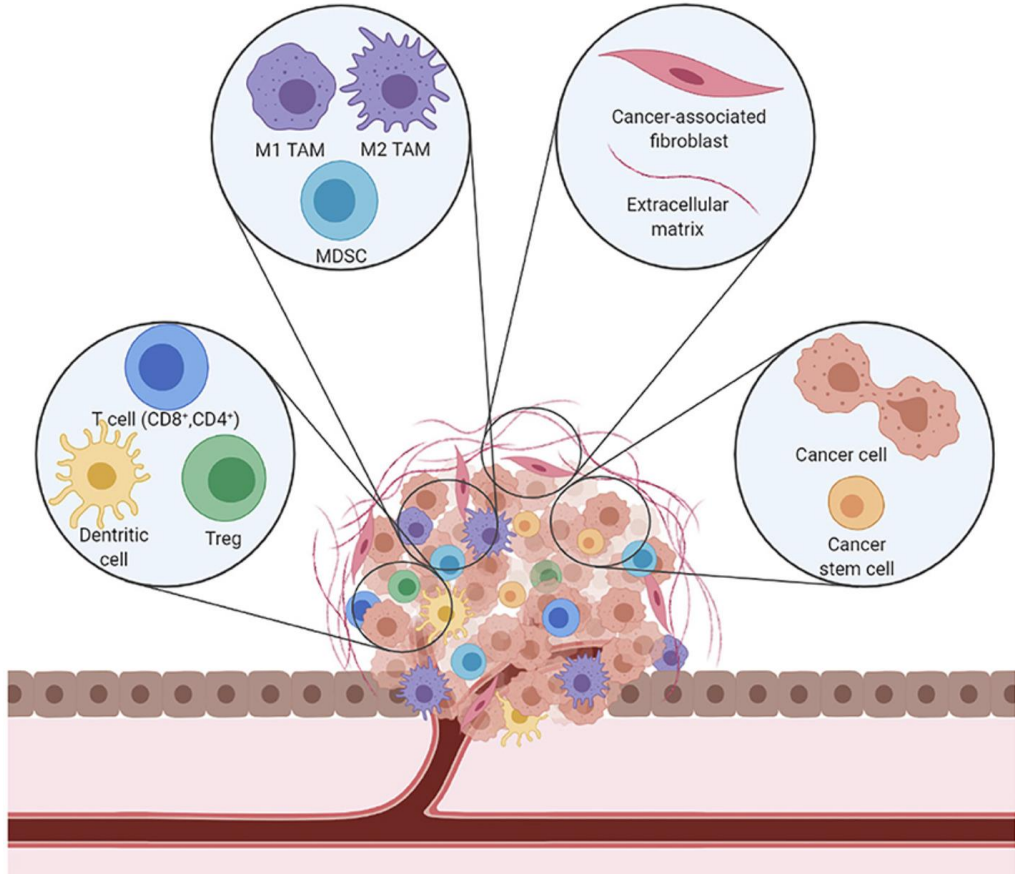
1 Kornauth, Pemovska, Vladimer et al *Cancer Discovery* 2022; 2 Liebers et al Nat Cancer 2023

Evolving Molecular Heterogeneity with Technology



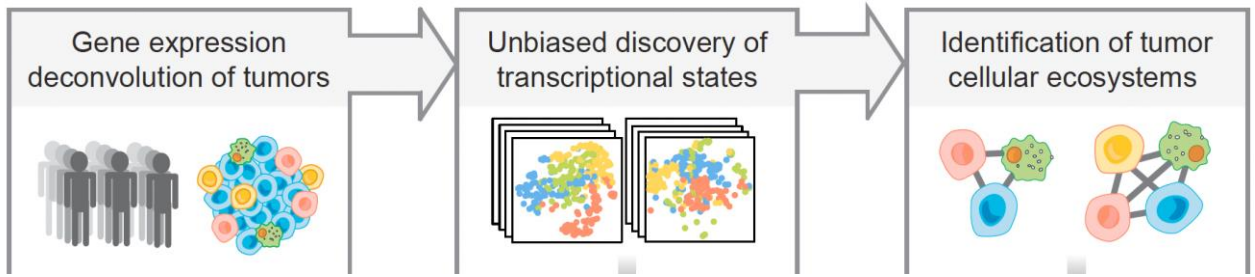
Beyond the Lymphoma Cell - Tumor as Organs

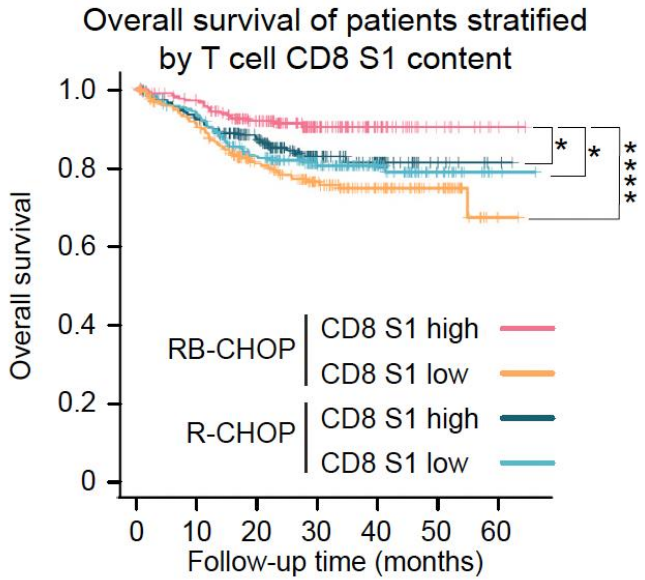
Lymphoma Microenvironment



Benavente et al *Front in Oncol* 2020

"DLBCL Ecosystems"





Steen, Luca et al *Cancer Cell* 2021

➔ Different lymphoma microenvironment signatures exists that might be relevant for treatment?

Dufva, Pölönen et al *Cancer Cell* 2020; Kotlov et al Cancer Discovery 2021; Steen, Luca et al *Cancer Cell* 2021; Ye et al *Cell Rep* 2022

Utility of Molecular Classifiers

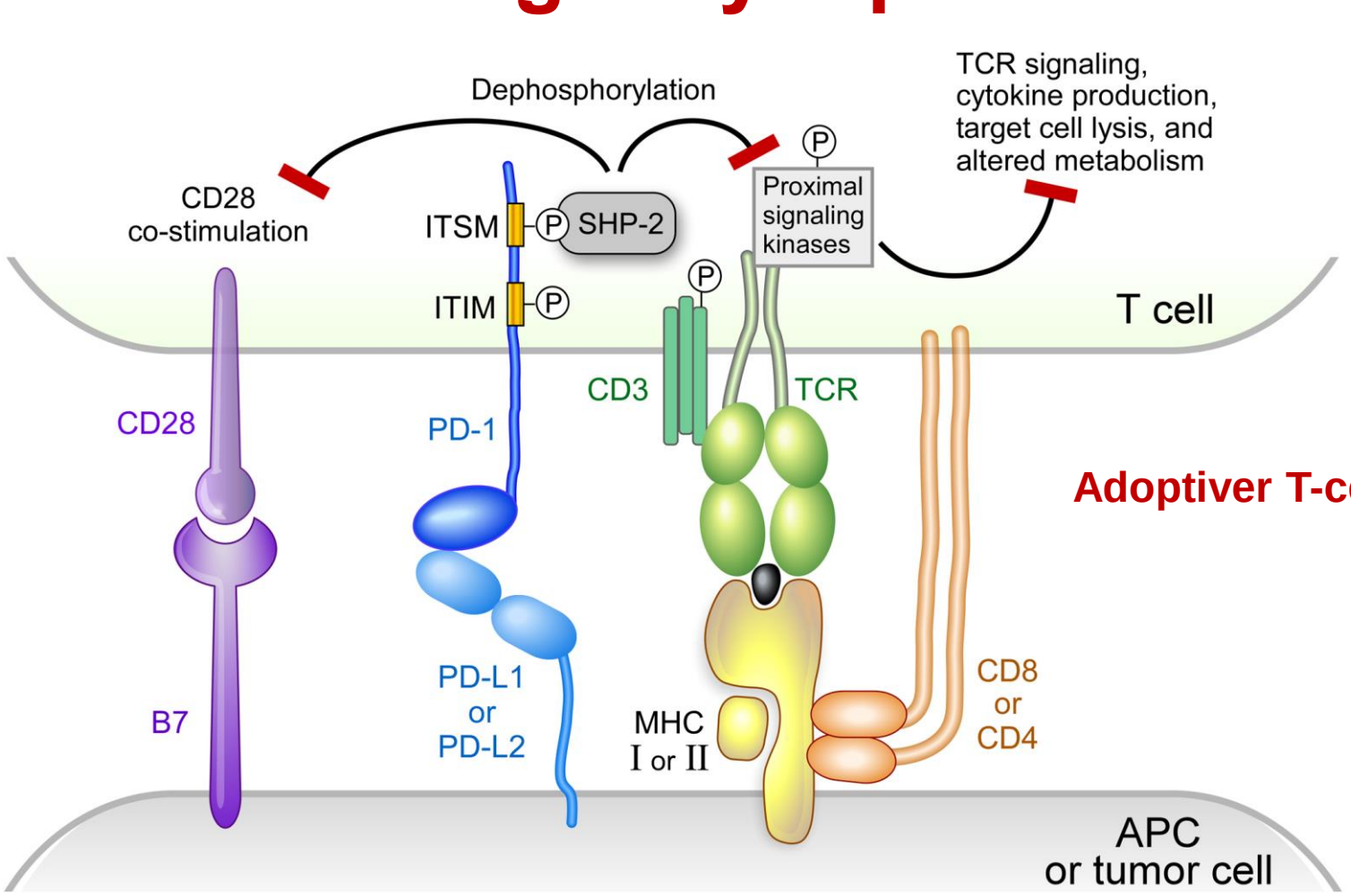
Goals	Can Molecular Classifiers help?
• Improve accuracy of diagnosis	**Yes**
• Identify relevant molecular subtypes (= biologically meaningful)	**Yes**
• Develop prognostic models for standard treatments	**Yes**
• Stratify patients for targeted treatments (personalized treatments)	**Very Likley**

➔ Adding genetic classification into the routine pathology diagnostic workflow **will soon be useful** to capture the full spectrum of molecular heterogeneity

➔ **Without precision diagnostics no precision treatment!**

Weigert and Chapuy, *Onkologe 2019*

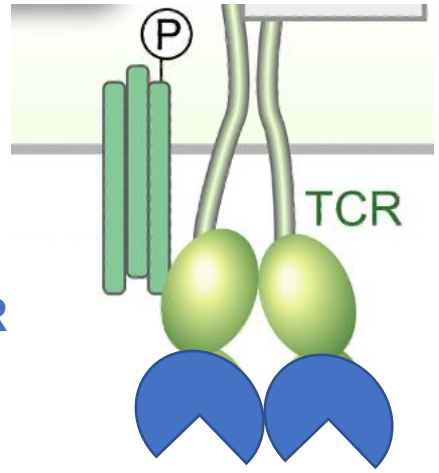
Immunologic Synapse – T-cell Activation



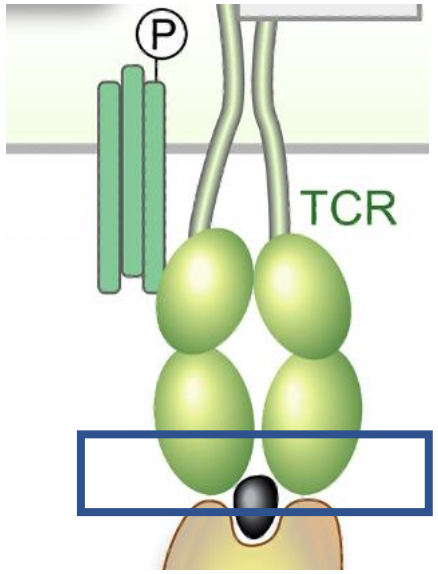
Modified from Baumeister *et al.* 2016; *Annu. Rev. Immunol.* 34:539-73

Adoptiver T-cell Transfer

CAR



TCR



Off-the-shelf TCRs in Development

Precision immunotherapy with a *MyD88 L265P* specific TCR für R/R lymphoma

Preclinical development

Clinical development

Isolation

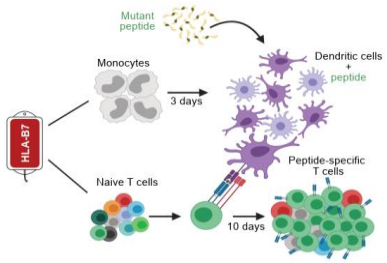
In vitro efficacy / safety testing

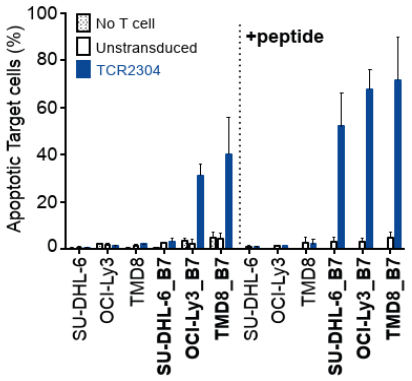
In vivo testing

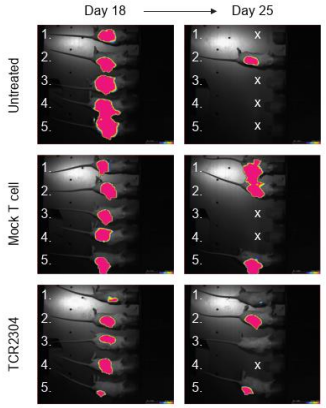
Manufacturing (Prodigy)

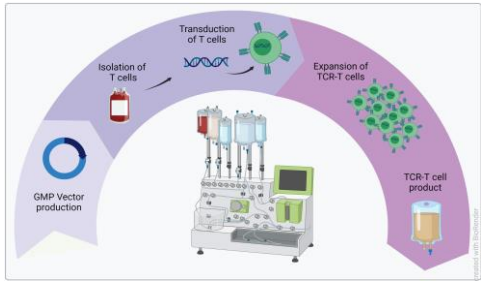
NCT Multicenter Trial

Human, HLA-matched









Auto-TCR-T-cells retroviral transduction

Charité-SCF

Berlin

Heidelberg

Würzburg

GLA

BMBF funding

First-patient-in Q1/2024

International PCT-application PCT/EP2020/051405, Cinar et al., JITC 2021

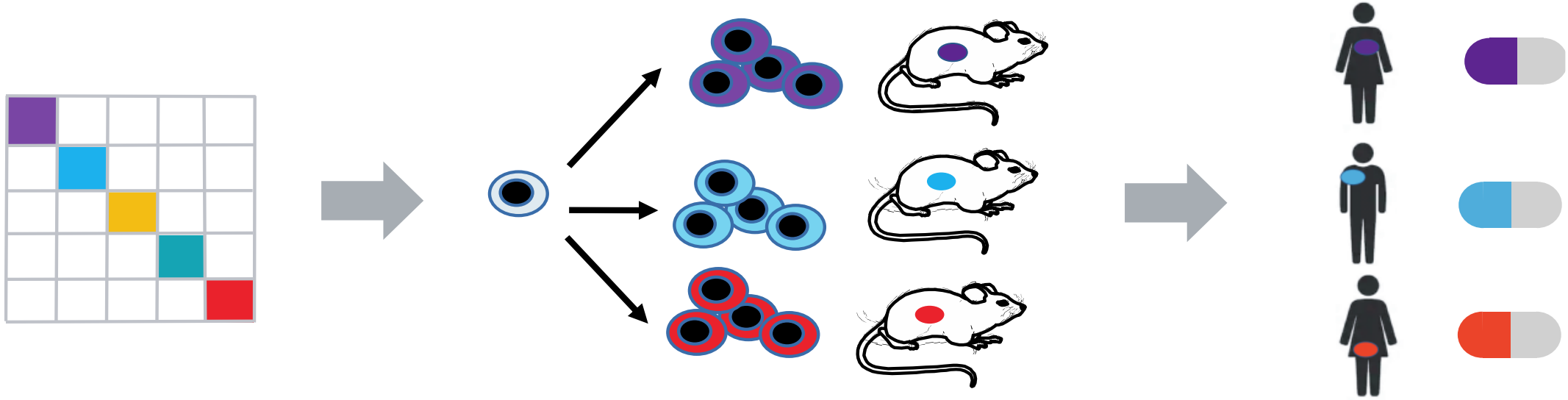
Antonia Busse

From Risk-Adapted to Biological-Informed Lymphoma Therapies

Identify Actionable Molecular Signatures

Exploit Associated Survival Pathways

Develop Rational Therapies and Biomarkers



Interested?

Contact bjoern.chapuy@charite.de

More Info https://go.umg.eu/ag-chapuy

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Hiring now! Open Positions for:
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S.

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M. Maulhardt
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D. Böckle

PhD

L. Ohlmeier
D. Joopi
A. Sinningen

MTAs

M. Schulz
V. Grewe

More Info https://go.umg.eu/ag-chapuy

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Thank you for your attention!

Looking forward to your questions?