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INDY HEME REVIEW 2024: ADVANCES IN AGGRESSIVE B- AND T-CELL LYMPHOMAS

Sonali M. Smith, MD FASCO
Elwood V. Jensen Professor of Medicine
Chief, Section of Hematology/Oncology
Co-Leader, Cancer Service Line
The University of Chicago

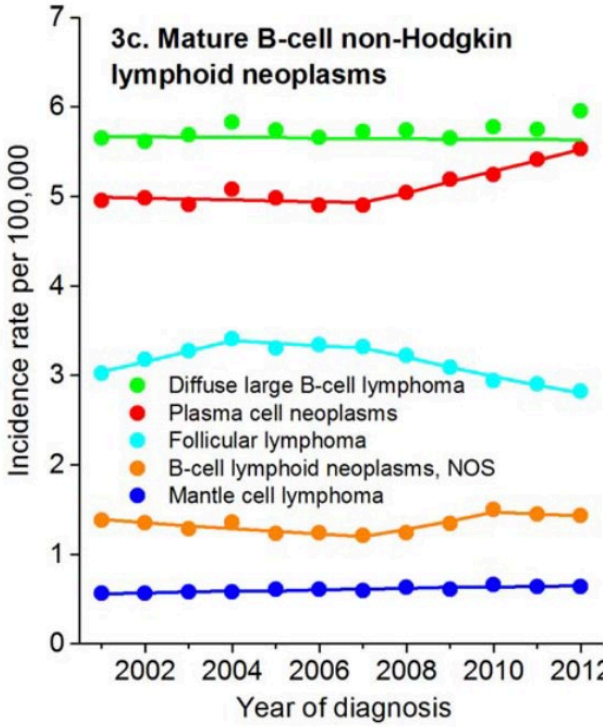
Disclosures

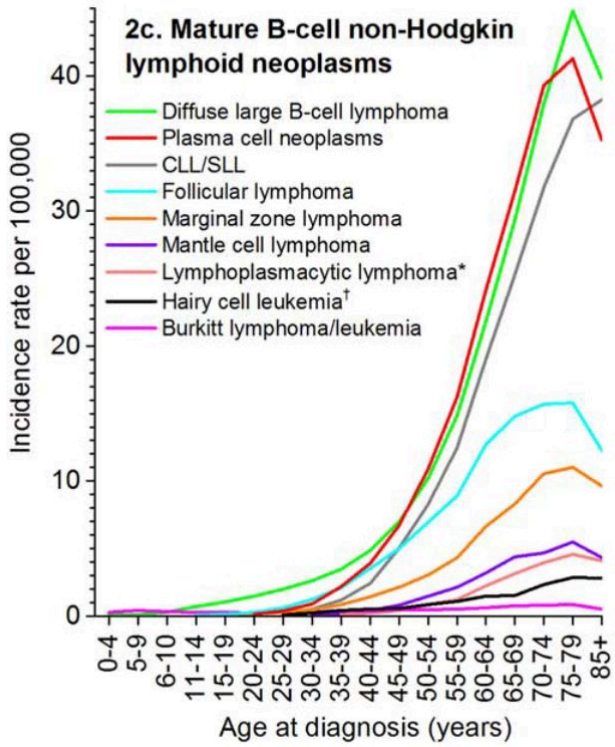
- Consulting in past 24 months:
  - Ono Pharmaceuticals
  - Gilead
  - BMS
  - Genmab
- Spouse is employed by Caris Life Sciences
- I may discuss approved agents in unapproved settings and unapproved agents in development. I will disclose when this is the case.

DLBCL in context

Goal of treatment is CURE

- DLBCL is the most common lymphoid cancer
- ~27K new/year in US
- Increases with age
- Occurs in all age groups





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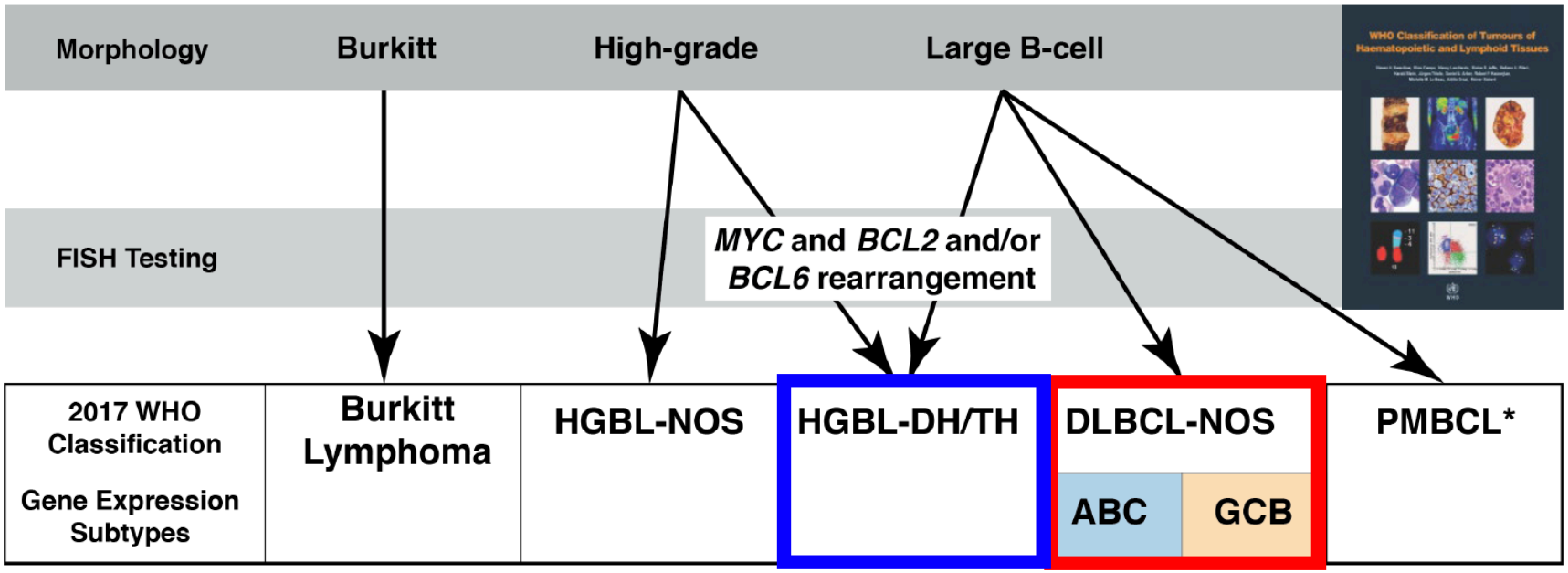
Teras CA Cancer J Clin 2016 Nov 12;66(6):443-459

Heterogeneity of aggressive B-cell lymphomas



HGBL-NOS: high-grade B-cell lymphoma NOS
HGBL-DH/TH: high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements
PMBCL: Primary mediastinal B-cell lymphoma

Swerdlow et al WHO revised 4th Edition 2017

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Slide adapted from Laurie Sehn

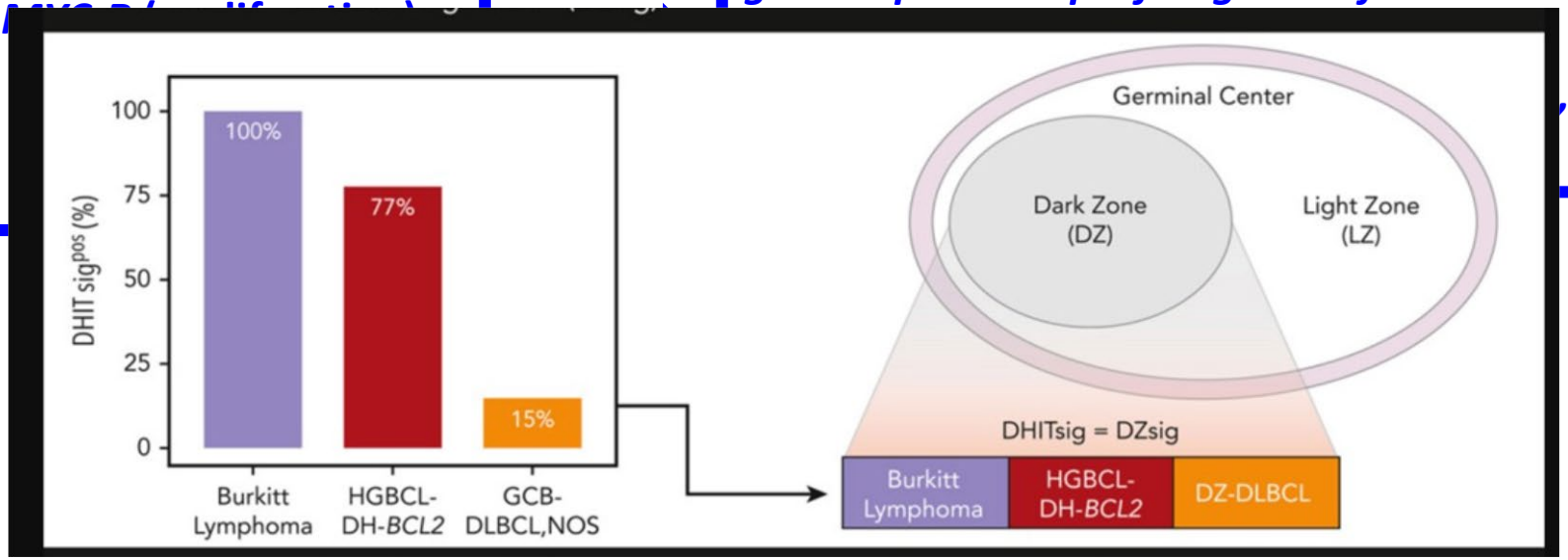
“Double hit lymphoma”: a diagnosis in evolution

Double hit lymphoma

DZsig+

DHITsig+

gene expression profiling identifies tumors



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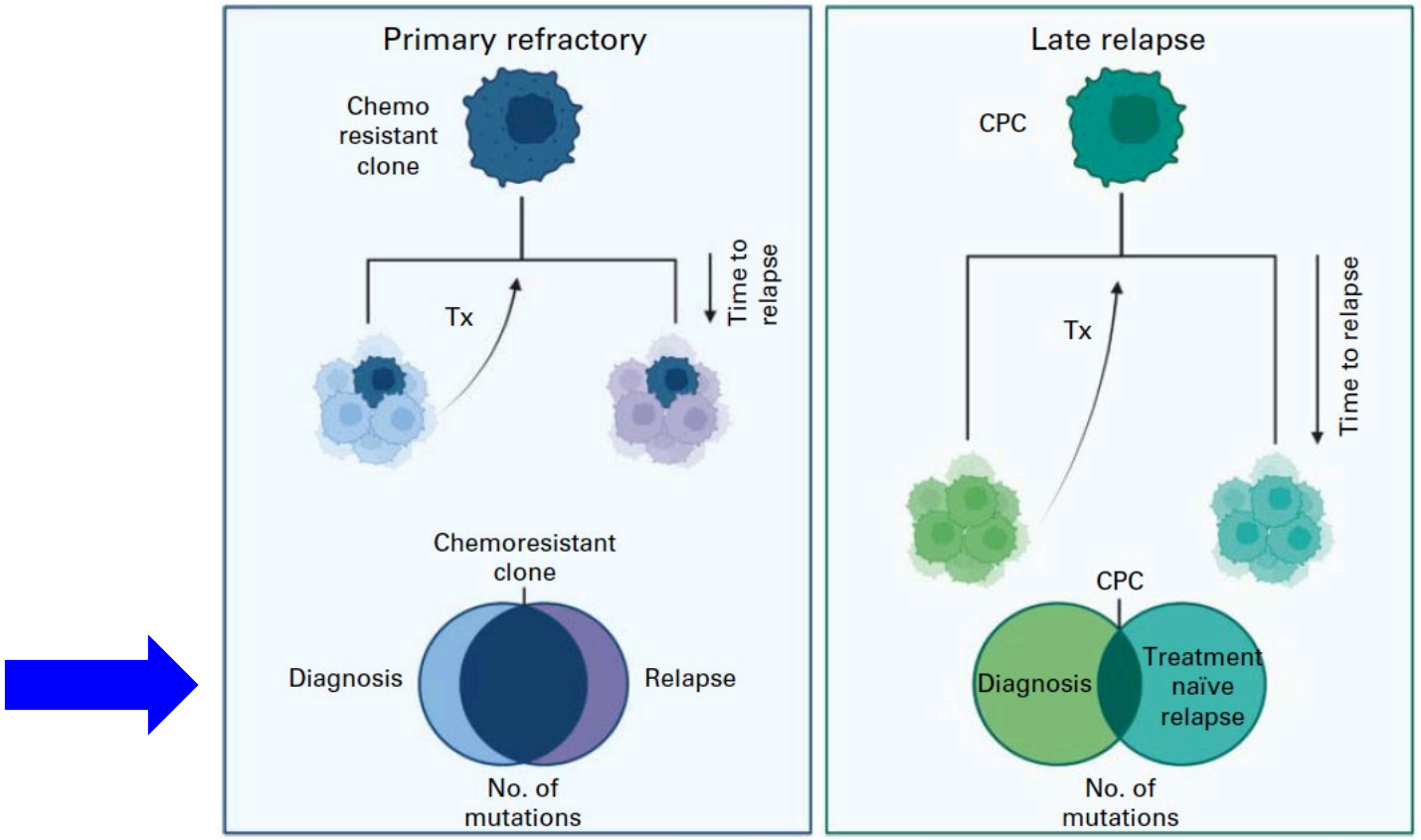
Hilton Blood 2019 Oct 31;134(18):1528-1532
Alduaij Blood Volume 141, Issue 20, 18 May 2023, Pages 2493-2507

Biology of rel/ref DLBCL may differ based on time to relapse



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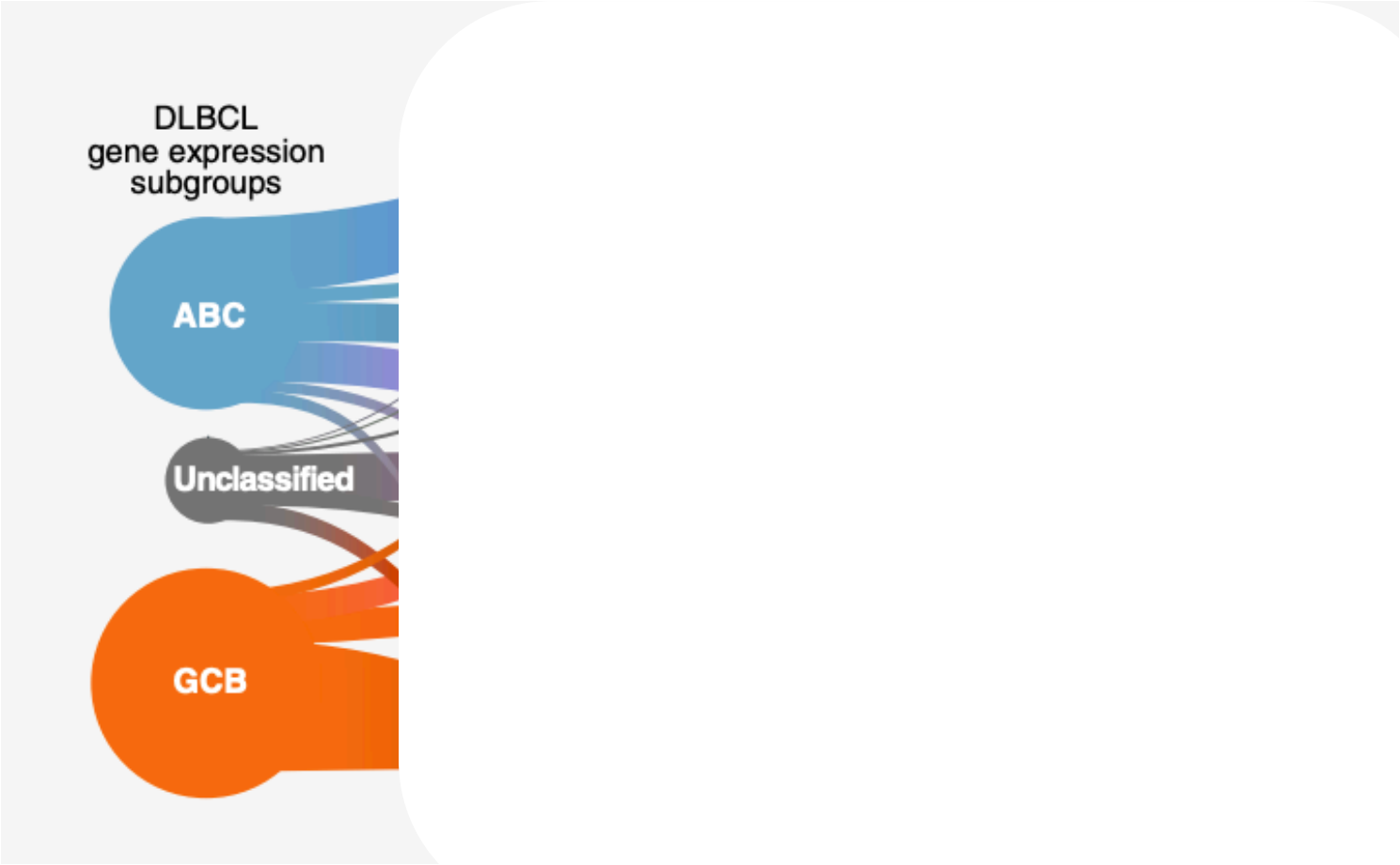
Hilton J Clin Oncol 2023; 41:4164-4177

Rethinking biologic heterogeneity in DLBCL



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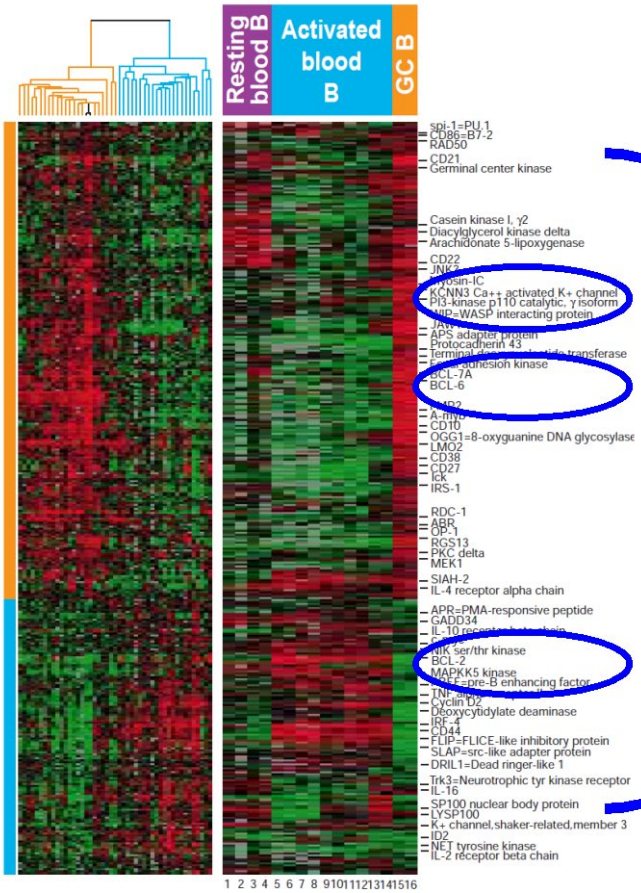
Wright Cancer Cell 2020 Apr 13;37(4):551-568.e14

Cell-of-origin (COO) has not succeeded as a *predictive* tool in DLBCL



PI3K

BCL6

BCR signaling

SYK

…and MANY more

Majority of COO-directed trials are NEGATIVE (PHOENIX, PYRAMID, ROBUST)

Putative targets may differ between GC and non-GC DLBCL

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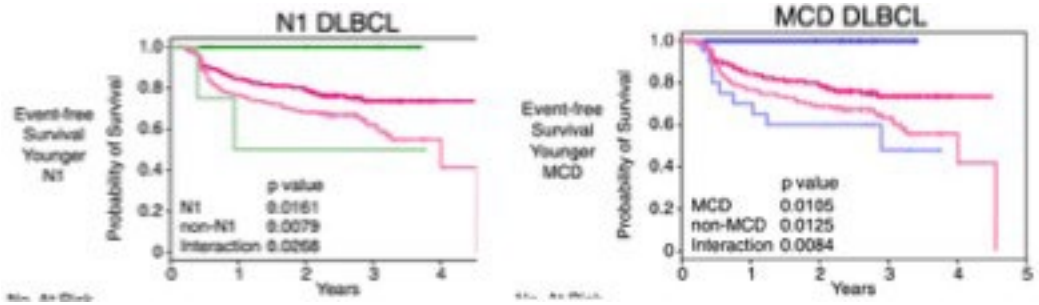
Monti Blood. 2005 Mar 1;105(5):1851-61; Alizadeh Nature. 2000 Feb 3;403(6769):503-11

Revisiting the "negative" PHOENIX Trial: R-CHOP +/- ibrutinib

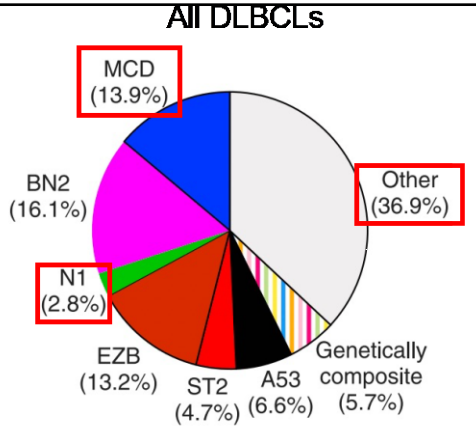
- R-CHOP + ibrutinib failed to improve survival for non-GCB DLBCLs in the phase III PHOENIX trial
  - Toxicity
  - Gap between Dx and Tx
  - **Underlying heterogeneity**

- Retrospective analysis - MCD and N1 DLBCLs benefit from R-CHOP + ibrutinib
  - MCD : *MYD88*^{L265P} and *CD79B* mutations
  - N1 : *NOTCH1* mutations



Can we identify a more easily translatable biomarker for BTKi in DLBCL?

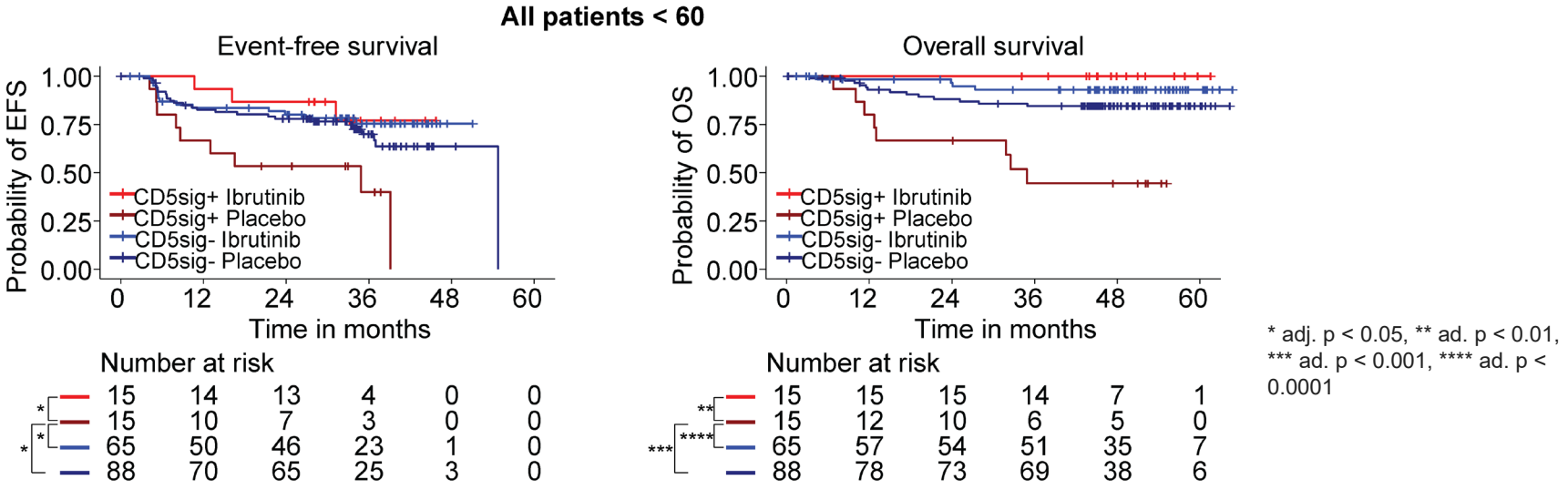
1. Complex methodology
   - Uses WES + CNA + FISH (+ GEP)
2. MCDs and N1s make up < 20-30% of non-GCB DLBCL
3. 40-70% of non-GCB DLBCLs are genetically unclassified
   - These patients also benefit from R-CHOP + ibrutinib



Sehn N Engl J Med. 2021 Mar 4;384(9):842-858; Wilson Cancer Cell. 2021 Dec 13;39(12):1643-1653.e3

CD5sig+ DLBCLs exhibit a selective survival advantage with ibrutinib + R-CHOP

- CD5 is a marker of B cell activation
- Enriched for non-GCB cell of origin
- Enriched for *MYD88* and *CD79B* mutations
- Clear positive and negative IHC staining
- Ubiquitously expressed on BTKi-responsive cancers like CLL and MCL



* adj. p < 0.05, ** ad. p < 0.01, *** ad. p < 0.001, **** ad. p < 0.0001

Cooper J Clin Oncol 2023 Dec 11:JCO2301574.

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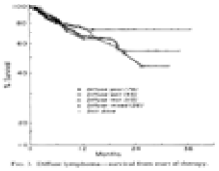
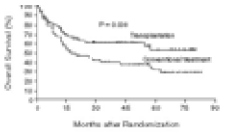
LBCL Treatment

Major milestones in DLBCL Treatment

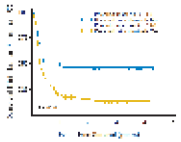
CHOP leads to cure in 54% of pts





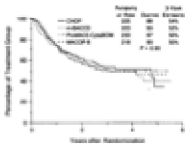
HDC/ABMT in 2L chemosensitive disease has 53% long-term survival

HDC/ASCT benefits fewer patients (~15-40% with long-term survival)

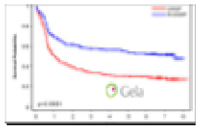


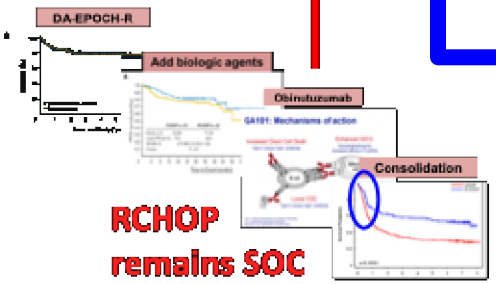
1976 | 1993 | 1995 | 2002 | 2010 | 2017

CHOP as effective and less toxic than intensive regimens



Rituximab plus CHOP improves OS





RCHOP remains SOC

November 2017: axi-cel is approved for 3L+ DLBCL followed soon by tisa-cel and liso-cel

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Major milestones in DLBCL Treatment

Axi-cel for 3L+ DLBCL

Pola-BR for RR DLBCL

Liso-cel for 3L+ DLBCL
Lonca-T for RR DLBCL

2017 2018 2019 2020 2021 2022

Tisa-cel for 3L+ DLBCL

Selinexor for RR DLBCL
Tafa-len for RR DLBCL

Axi-cel and Liso-cel for 2L+ DLBCL

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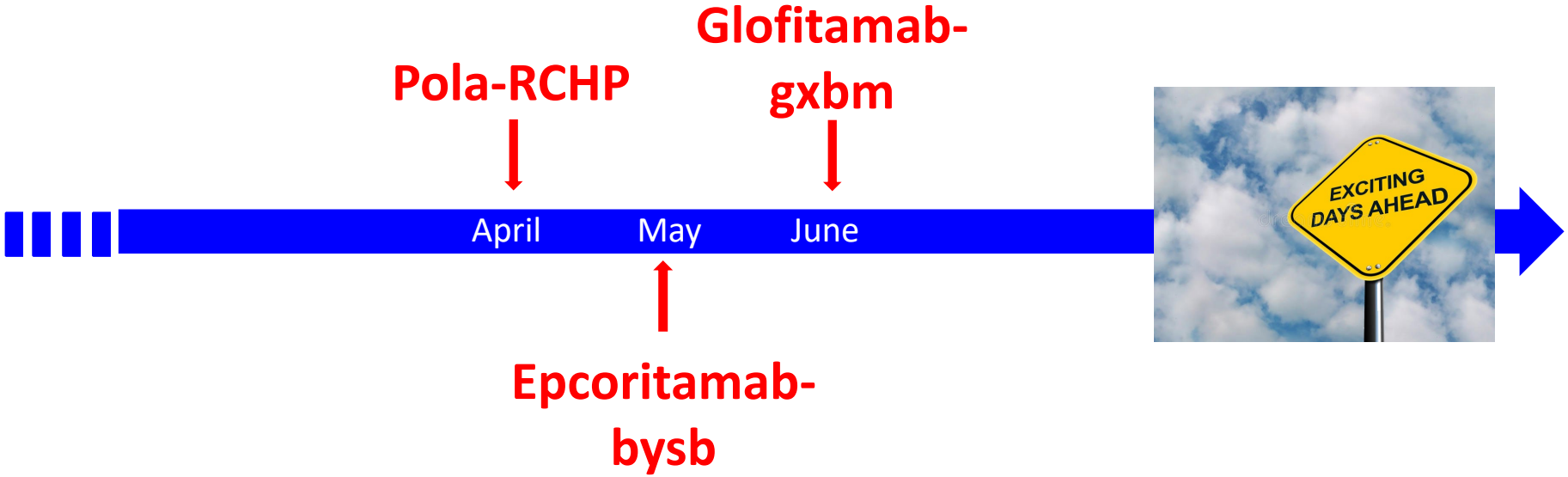
Major milestones in DLBCL Treatment: 2023 Updates



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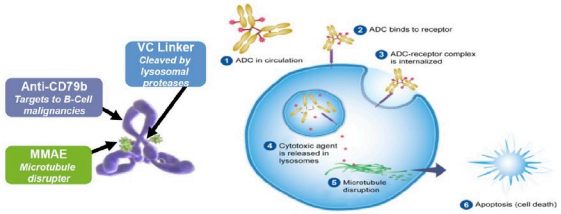
POLARIX: a randomized double blind phase 3 trial

- Microtubule inhibitor MMAE conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker



Patients

- Previously untreated DLBCL
- Age 18–80 years
- IPI 2–5
- ECOG PS 0–2

Stratification factors

- IPI score (2 vs 3–5)
- Bulky disease (<7.5 vs ≥7.5cm)
- Geographic region (Western Europe, US, Canada, & Australia vs Asia vs rest of world)

R 1:1

Pola-R-CHP

Polatuzumab vedotin (1.8mg/kg)*
R-CHP + vincristine placebo

Cycles 1–6
(1 cycle=21 days)

R-CHOP

R-CHOP† +
polatuzumab vedotin placebo

Rituximab
375mg/m²

Cycles 7 & 8

PRIMARY ENDPT: PFS
Med f/u 28.2m

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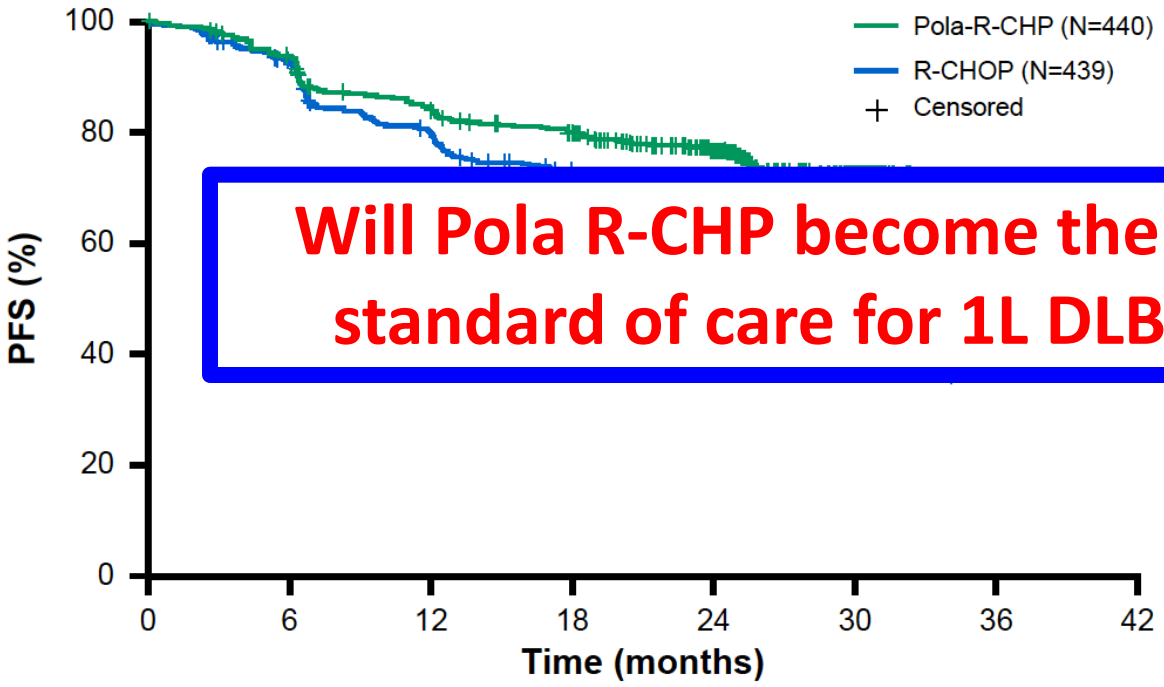
Tilly N Engl J Med. 2022 Jan 27;386(4):351-363

POLARIX: primary endpoint was met



Will Pola R-CHP become the new standard of care for 1L DLBCL?

HR 0.73 (P<0.02)
l: 0.57, 0.95

HP demonstrated a **27%**
n in the relative risk of disease progression, relapse, or death versus R-CHOP

- **24-month PFS:**
  76.7% with Pola-R-CHP versus
  70.2% with R-CHOP (**Δ=6.5%**)

No. of patients at risk								
Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

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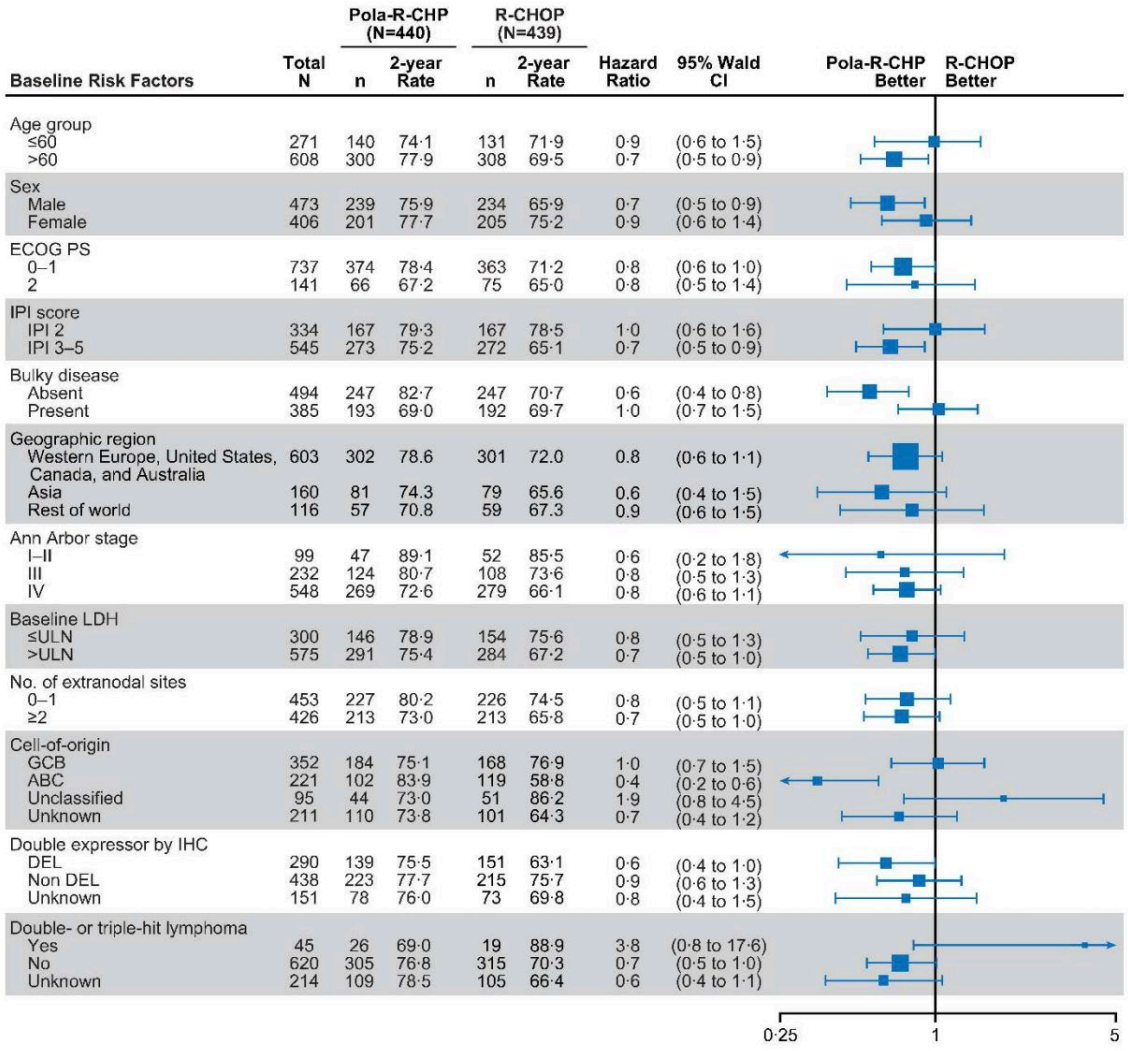
No difference in overall survival

Tilly N Engl J Med. 2022 Jan 27;386(4):351-363

POLARIX Subgroup Analysis

Pola-RCHP better for

- Older pts
- PS 0-1
- Non-bulky disease
- ABC subtype
- No DHL/THL



Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)
Asia	160	81	74.3	79	65.6	0.6	(0·4 to 1·5)
Rest of world	116	57	70.8	59	67.3	0.9	(0·6 to 1·5)
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·8)
III	232	124	80·7	108	73·6	0·8	(0·5 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)

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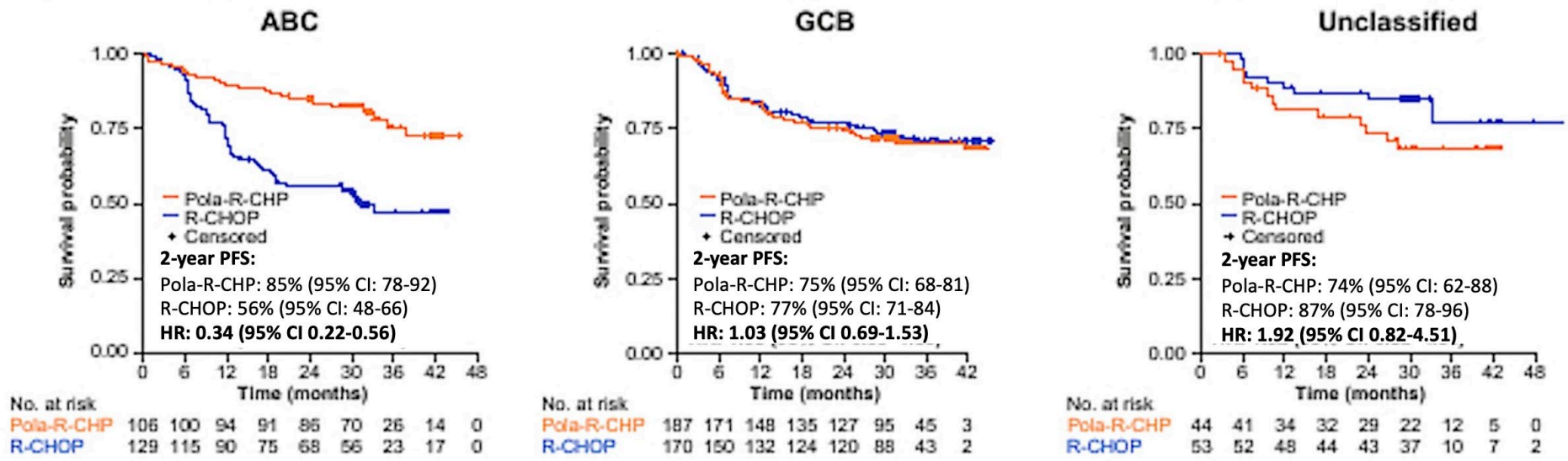
Tilly N Engl J Med. 2022 Jan 27;386(4):351-363

Pola-RCHP vs RCHOP by cell of origin



*Investigator-assessed disease progression and disease relapse or death from any cause were counted as events. Tick marks indicate censored data.
ABC, activated B cell; CI confidence interval; COO, cell of origin; GCB, germinal center B cell; HR, hazard ratio; PFS, progression-free survival.

Should cell-of-origin influence treatment selection in TN DLBCL?

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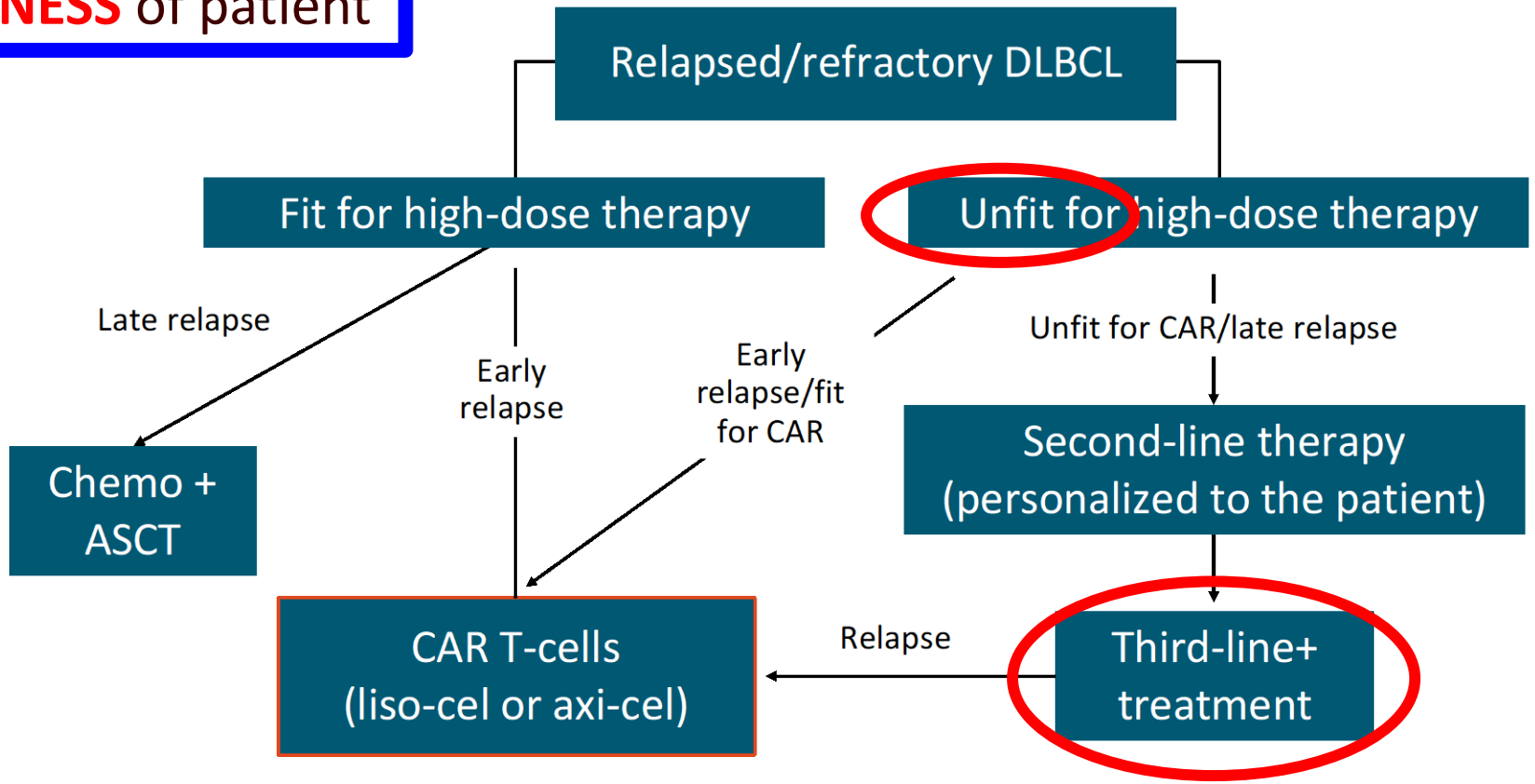
Morchauser ASH 2023, abstract 3000

A new algorithm for rel/ref LBCL

TIMING of relapse
FITNESS of patient



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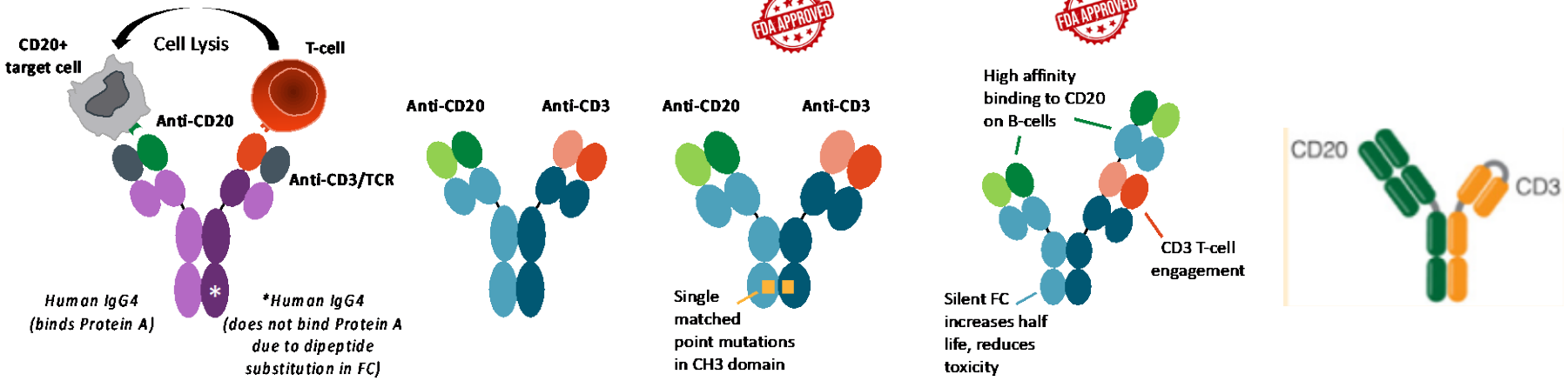
Slide courtesy of Michael Bishop

CD20xCD3 bispecific antibodies in DLBCL



Clinicaloptions.com*

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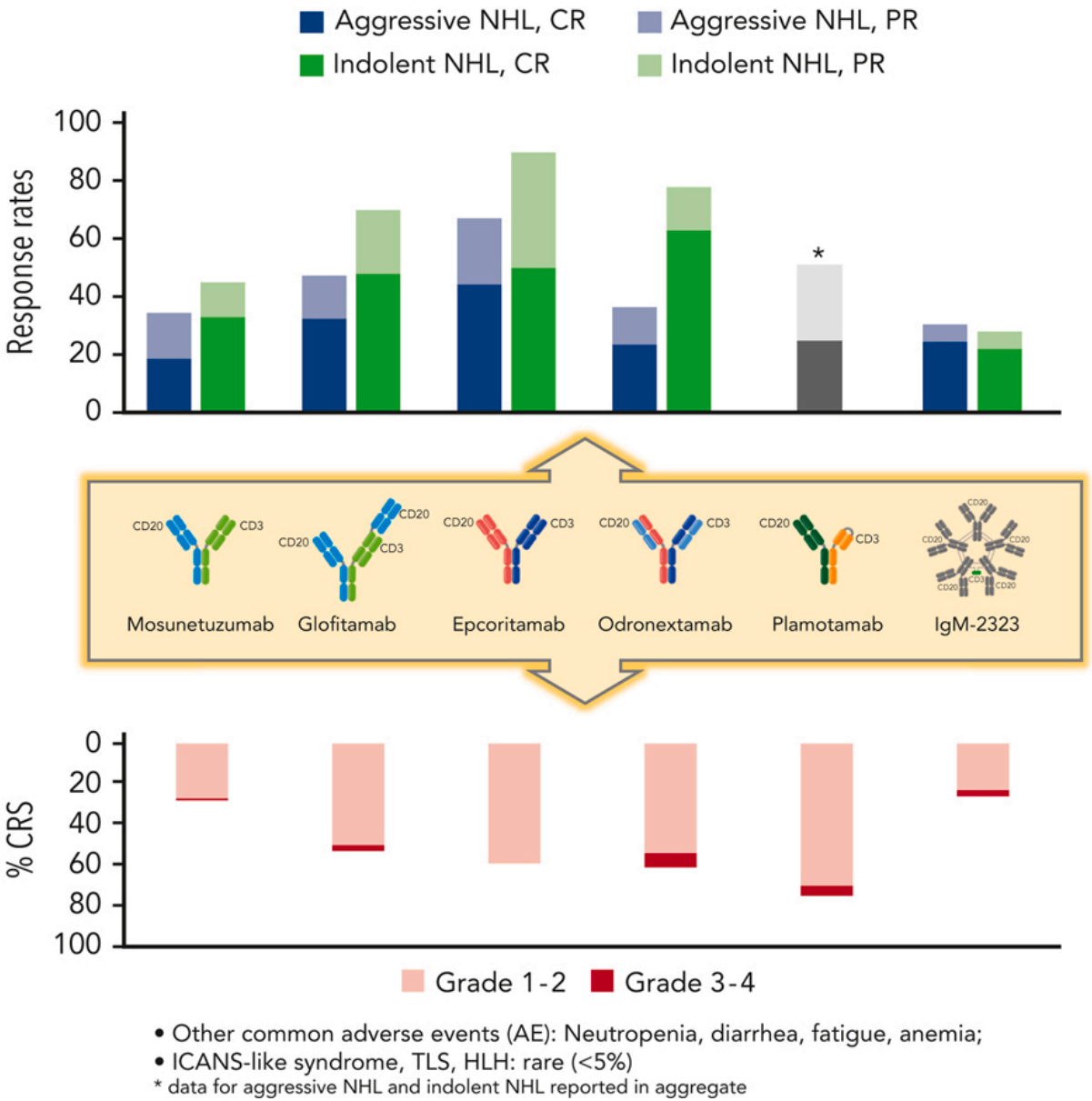
Castaneda-Puglianni. Drugs Context. 2021;10:2021. Bannerji. ASH 2020. Abstr 42. Budde. ASH 2018. Abstr 399. Hutchings. Lancet. 2021;398:1157. Engelberts. eBioMedicine. 2020;52:102625. Hutchings. JCO. 2021;39:1959.

Major themes:

1. CRS is in first cycle (5h to 5d)
2. ICANS is less common



- Other common adverse events (AE): Neutropenia, diarrhea, fatigue, anemia;
- ICANS-like syndrome, TLS, HLH: rare (<5%)

* data for aggressive NHL and indolent NHL reported in aggregate

Falchi Blood (2023) 141 (5): 467–480

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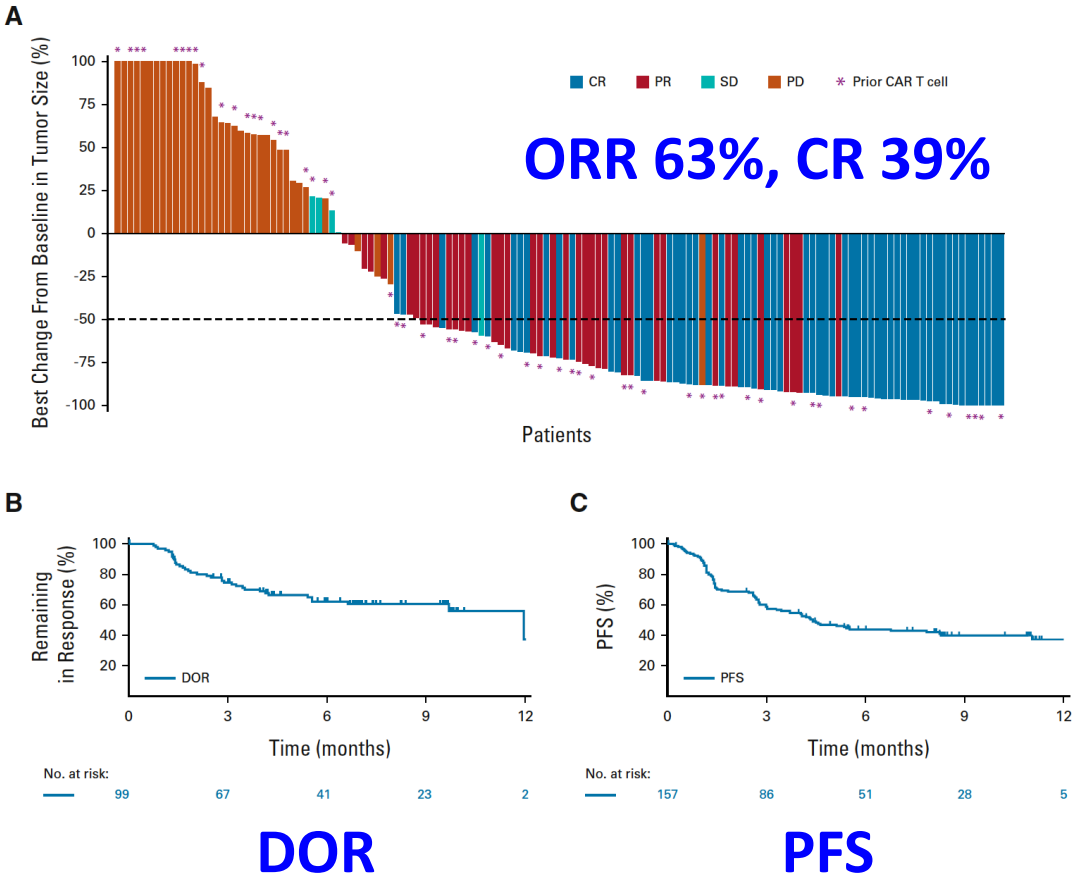
Subcutaneous epcoritamab in rel/ref DLBCL (phase I/II trial)



DOR **PFS**

- ~76% refractory to at least 2 lines of treatment
- ~40% with prior CAR-T
- 75% of prior CAR-T recipients progressed within 6 months

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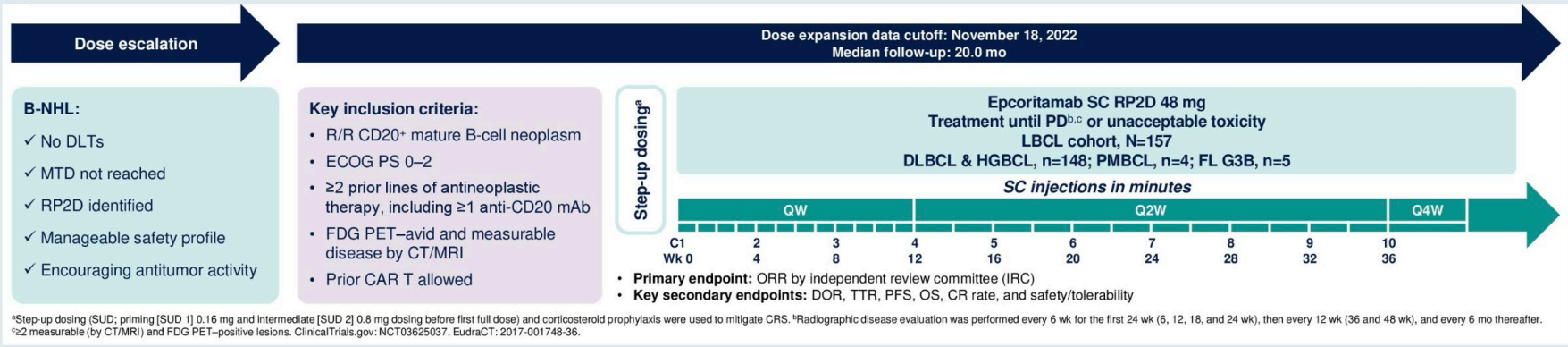
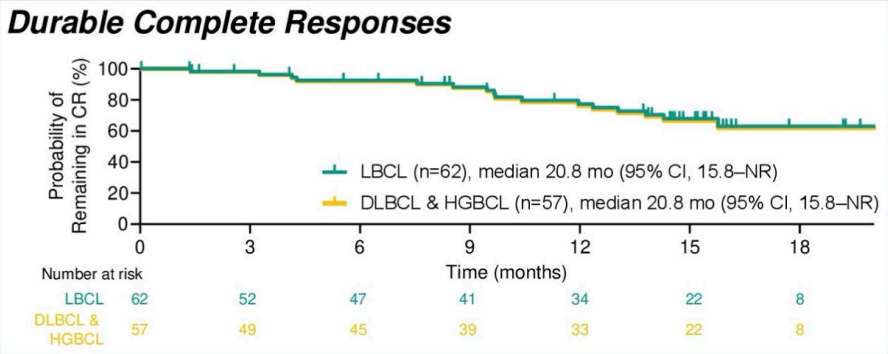
Thieblemont Journal of Clinical Oncology 41, no. 12 (April 20, 2023) 2238-2247.

Epcoritamab SC in aggressive B-cell lymphoma (med f/u 20m)





Best Overall Response, n (%)	DLBCL & HGBCL, n=148[a]	LBCL, N=157[a]
Overall response	90 (61) [95% CI, 53–69]	99 (63) [95% CI, 55–71]
Complete response	57 (39) [95% CI, 31–47]	62 (39) [95% CI, 32–48]
Partial response	33 (22)	37 (24)
Stable disease	5 (3)	5 (3)
Progressive disease	37 (25)	37 (24)

Based on IRC per Lugano criteria. [a]16 patients were not evaluable.

- The most common AE was CRS in 51% of patients (mostly grade 1-2), followed by neutropenia in 25% of patients.

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Karimi ASCO 2023 abstr 7525

Glofitamab Study Design: phase II

Pivotal single-arm Phase II study in patients with R/R LBCL and ≥2 prior therapies

Key inclusion criteria

- DLBCL NOS, HGBCL, transformed FL, or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including:
  - Anti-CD20 antibody
  - Anthracycline

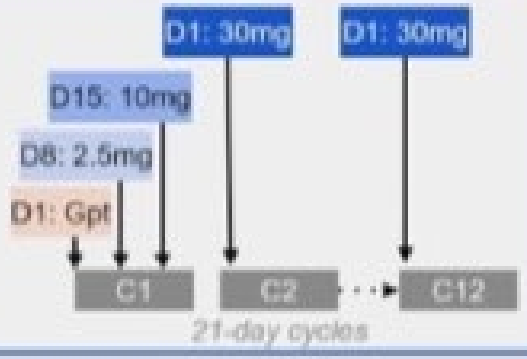
Glofitamab IV administration

Fixed-duration treatment:

- Up to 12 cycles (8.3 months)

CRS mitigation:

- Obinutuzumab IV pre-treatment (1000mg)
- C1 step-up dosing
- Monitoring after first glofitamab dose (2.5mg)



Endpoints

- **Primary**: CR (best response) rate by IRC*
- **Key secondary**: ORR,† DoR,† DoCR,† PFS, and OS

Intravenous infusion

Fixed duration (12 cycles)

Obinutuzumab pre-treatment

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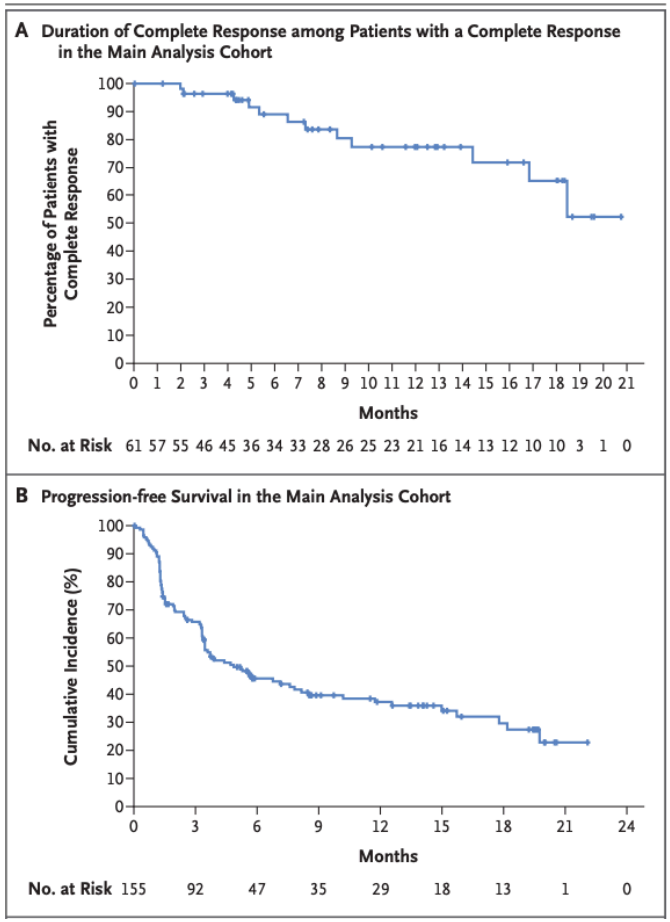
Dickinson December 15, 2022 N Engl J Med 2022; 387:2220-2231

Glofitamab in rel/ref DLBCL (phase I/II trial)



- ~86% refractory to most recent therapy
- ~30% with prior CAR-T

- **RESULTS**:
  - 39% CR
  - DOR > 18m
  - DOR for CR is not reached

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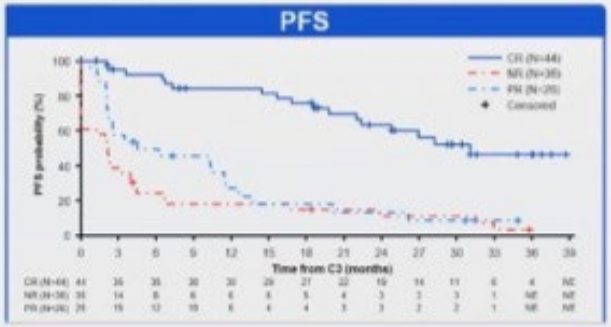
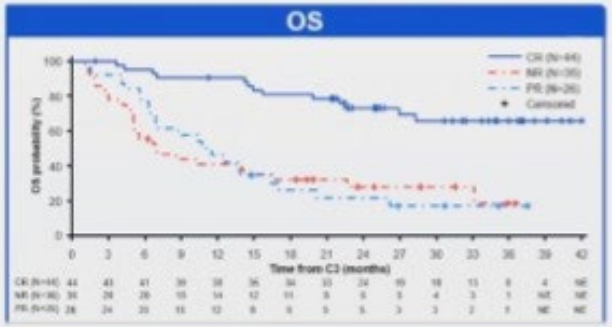
Dickinson December 15, 2022 N Engl J Med 2022; 387:2220-2231

Glofitamab phase II (32m follow up)

- Med PFS 31m
- CR matters

Landmark analysis by response at Cycle 3



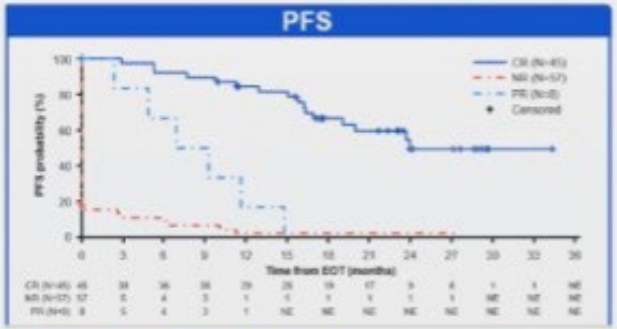


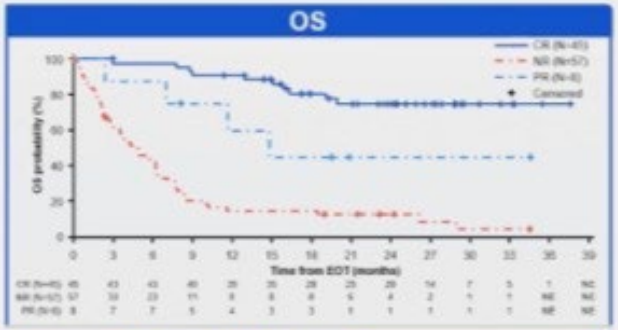
Landmark PFS from C3 in patients with CR at C3*	N=44
Median PFS, months (95% CI)	31.1 (22.4–NE)
24-month PFS rate, % (95% CI)	63.5 (47.5–79.6)

Landmark OS from C3 in patients with CR at C3*	N=44
Median OS, months (95% CI)	NE (NE)
24-month OS rate, % (95% CI)	73.4 (59.9–87.0)

A high proportion of patients with a CR at C3 remained progression-free and alive after 24 months

Landmark analysis by response at EOT





Landmark PFS from EOT in patients with CR at EOT*	N=45
Median PFS, months (95% CI)	24.0 (19.1–NE)
18-month PFS rate, % (95% CI)	66.6 (51.0–82.2)

Landmark OS from EOT in patients with CR at EOT*	N=45
Median OS, months (95% CI)	NE (NE)
18-month OS rate, % (95% CI)	80.7 (68.6–92.8)

Majority of patients with a CR at EOT remained progression-free and alive at 18 months after EOT

*KM estimates.
EOT, end-of-treatment; NR, no response.

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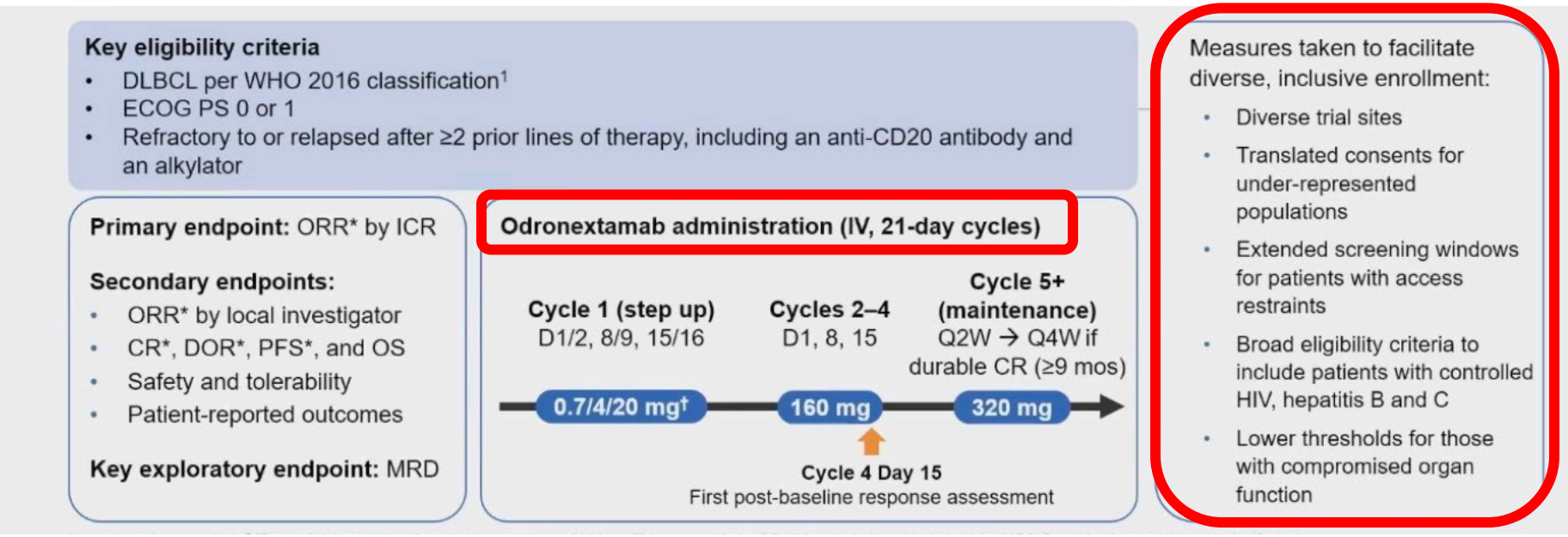
Odronextamab: phase II trial in rel/ref DLBCL (ELM-2)



- Med age 67y (range, 24-88)
- 24% ≥ 75y
- Prior tx 2 (range, 2-8)
- 86% refractory to last line of treatment

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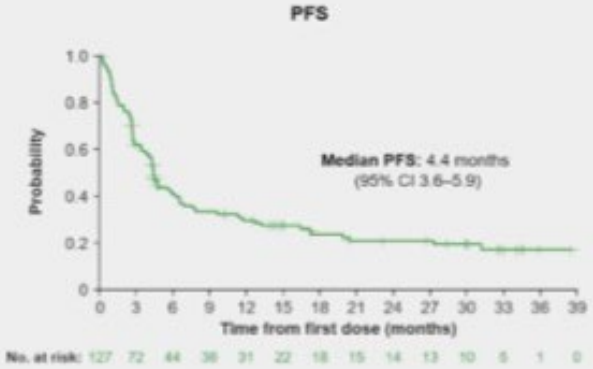
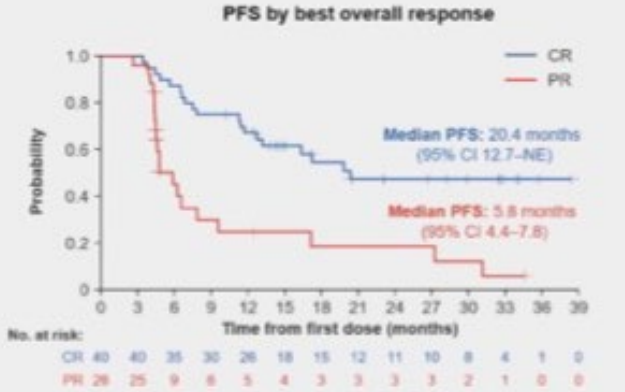
Ayyapan ASH oral presentation Abstr #436 2023

Odronextamab PFS and OS

ELM-2: Progression-free survival

- Median PFS was 20.4 months in complete responders versus 5.8 months in partial responders



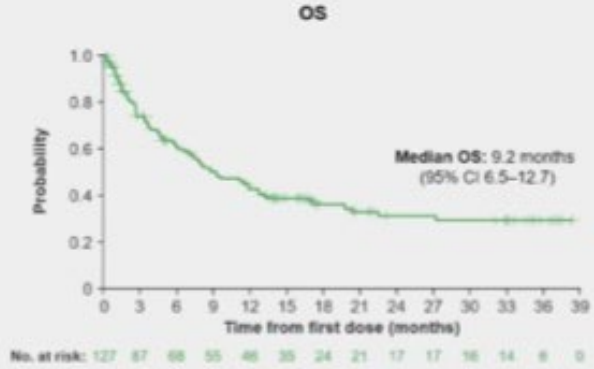


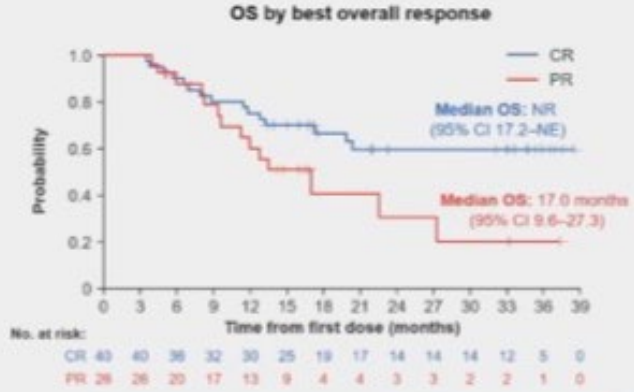
	N=127
12-month PFS rate, % (95% CI)	29.6 (21.5–38.2)
24-month PFS rate, % (95% CI)	21.1 (13.7–29.7)

	CR (n=40)	PR (n=26)
12-month PFS rate, % (95% CI)	67.2 (50.3–79.5)	25.2 (9.5–44.7)
24-month PFS rate, % (95% CI)	47.5 (29.9–63.1)	18.9 (5.4–38.6)

ELM-2: Overall survival

- Median OS was not reached in complete responders versus 17.0 months in partial responders





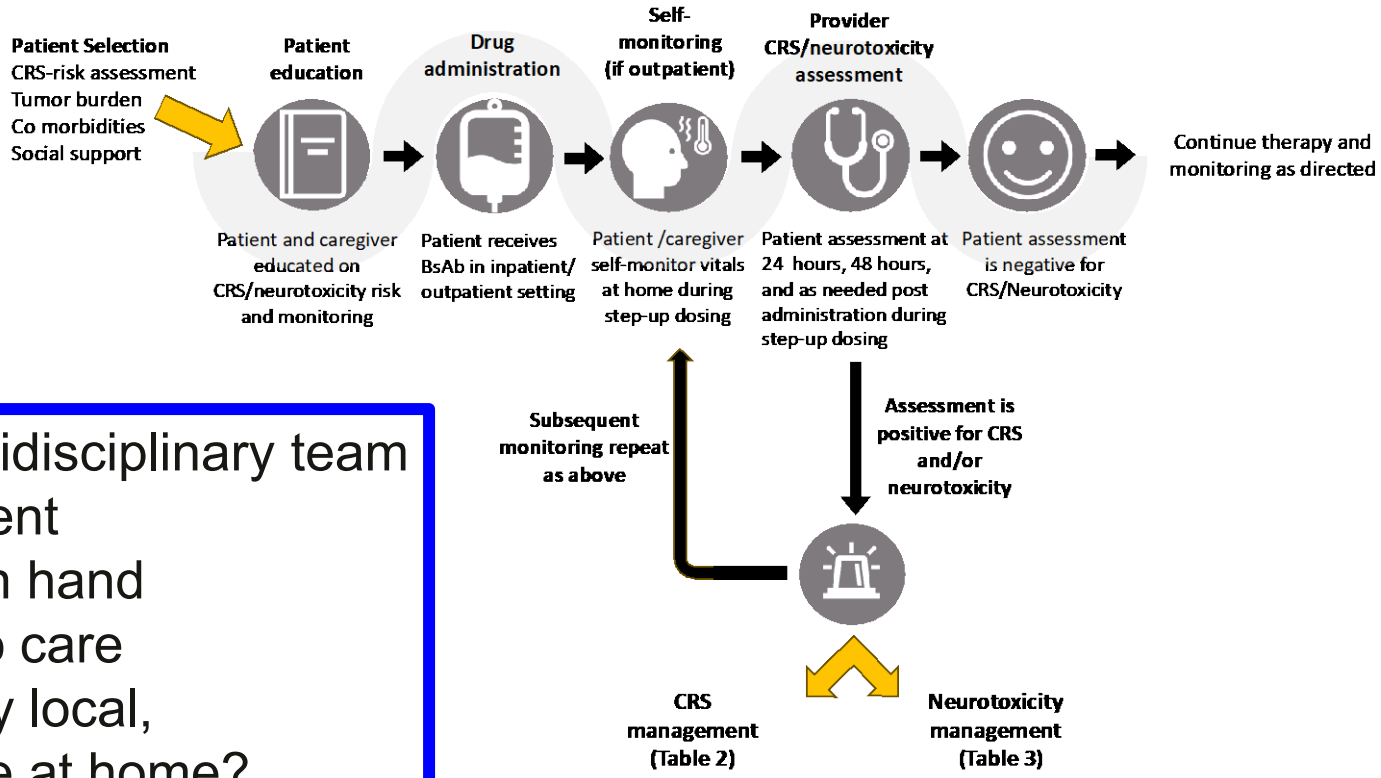
	N=127
12-month OS rate, % (95% CI)	42.9 (33.7–51.8)
24-month OS rate, % (95% CI)	31.6 (22.4–41.1)

	CR (n=40)	PR (n=26)
12-month OS rate, % (95% CI)	75.0 (58.5–85.7)	60.2 (37.2–77.0)
24-month OS rate, % (95% CI)	59.6 (41.7–73.7)	30.5 (9.3–55.3)

Data cut-off date: August 19, 2023.
CI, confidence interval; CR, complete response; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response.

Ayyapan ASH oral presentation
Abstr #436 2023

Can bispecifics be safely delivered in community settings? YES***



- Educated multidisciplinary team
- Educated patient
- Tocilizumab on hand
- 24-7 access to care
- Caregiver, stay local, dexamethasone at home?

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Crombie, et al., Consensus Recommendations on the Management of Toxicity Associated with CD3xCD20 Bispecific Antibody Therapy (Blood, in press 2024)

CAR-T vs. Bispecifics vs. Other regimens in LBCL

Bispecifics

- Off the shelf
- Lower CRS
- Need for longer treatment

CAR-T

- Requires manufacturing
- Higher CRS, ICANS
- "one and done"

Other regimens:

- Unknown curative potential, often indefinite treatment
- Easily available
- Examples: Tafa-len, Lonca-T, Pola-BR (or pola-R), Selinexor

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Trials available via NCTN/NCORP in rel/ref LBCL

S2207: RP2 in rel/ref LBCL

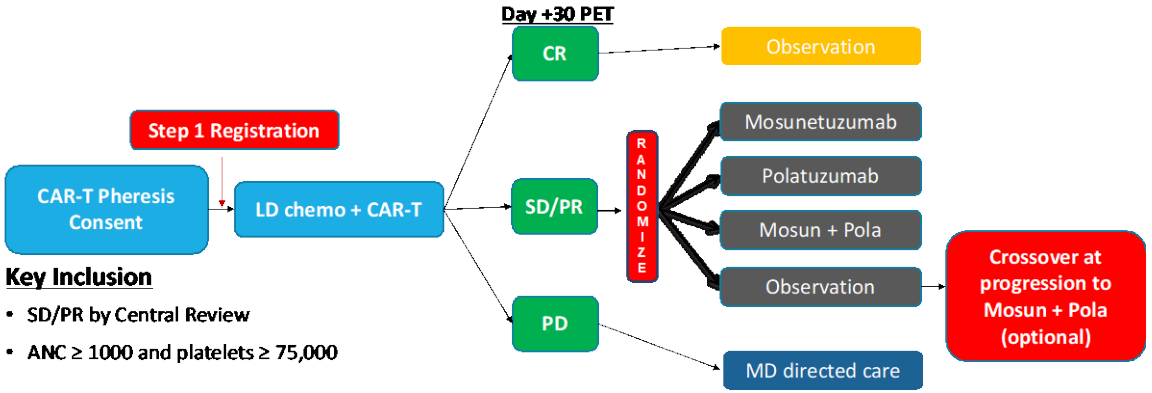
Rel/ref LBCL
- COO
- Rel vs. ref

Tafa-len

Tafa-len + taz

Tafa-len + zanu

S2114: post-CAR-T optimization



Key Inclusion
- SD/PR by Central Review
- ANC ≥ 1000 and platelets ≥ 75,000

Stratification
- SD vs PR on Day +30 PET
- CAR-T receipt as 2nd line vs ≥ 3rd line

Primary Objective: Compare 1 year PFS 25.0% (observation) vs 50.0% (consolidation) → **120 patients (30 per arm)**

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www.clinicaltrials.gov

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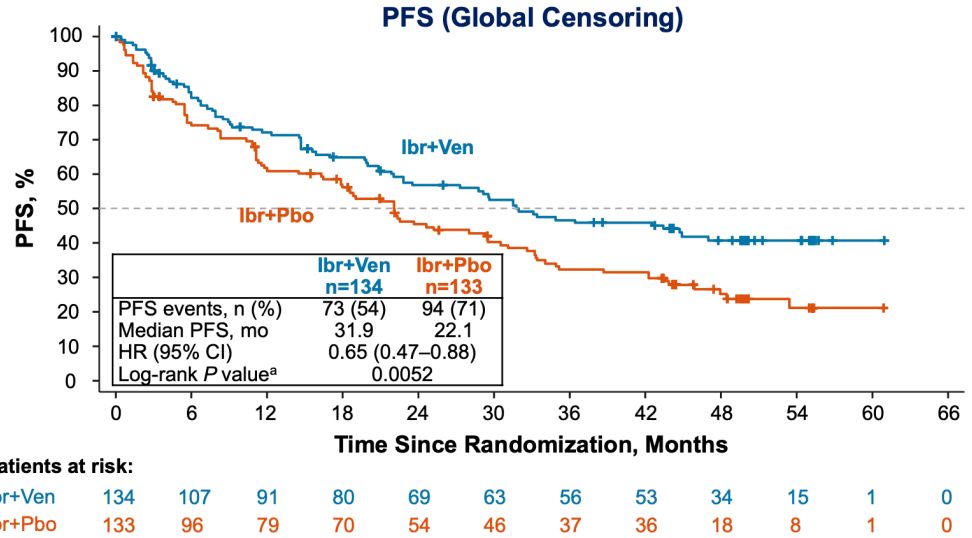
Mantle cell lymphoma

SYMPATICO: RP3 ibr-ven vs. ibr-pbo x 24m→ibr maintenance

Primary Endpoint: Investigator-Assessed PFS Was Significantly Improved With Ibrutinib + Venetoclax Versus Ibrutinib + Placebo



Median PFS, mo	Global Censoring[b]				US FDA Censoring[c]			
	Ibr+Ven n=134	Ibr+Pbo n=133	HR (95% CI)	Log-rank *P* value[a]	Ibr+Ven n=134	Ibr+Pbo n=133	HR (95% CI)	Log-rank *P* value[a]
Investigator assessment	31.9	22.1	0.65 (0.47–0.88)	0.0052	42.6	22.1	0.60 (0.44–0.83)	0.0021
IRC assessment	31.8	20.9	0.67 (0.49–0.91)	0.0108	43.5	22.1	0.63 (0.45–0.87)	0.0057

No unexpected toxicity

No sig diff in OS (?trend)

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ASH 2023;Abstract LBA-2

Acalabrutinib monotherapy in rel/ref MCL (n=124)

Pt Characteristics:

Med age 68y

37.1% bulky

21% blastoid morphology

Ki67 > 50% in 25% of pts

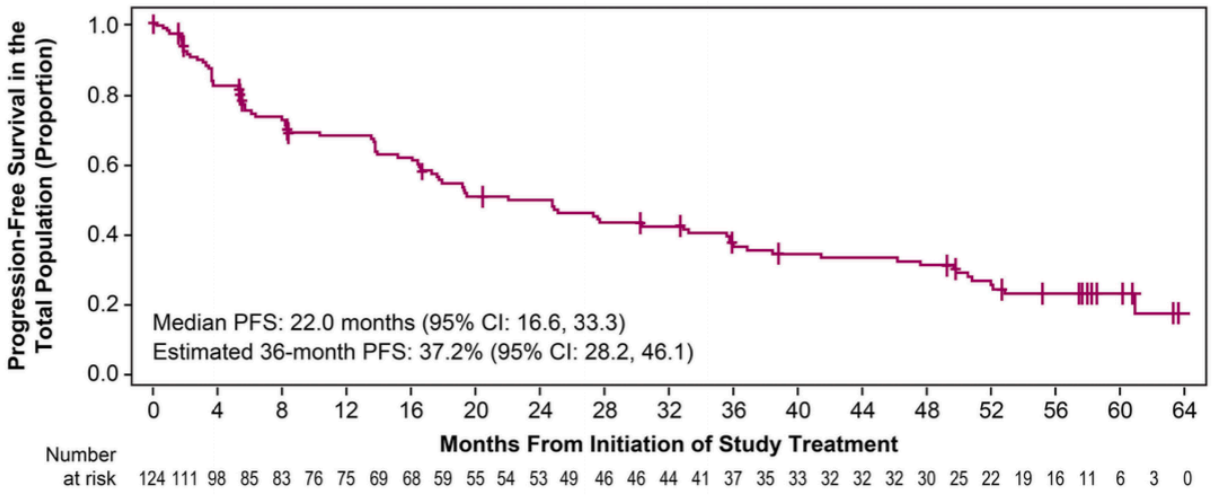
Results:

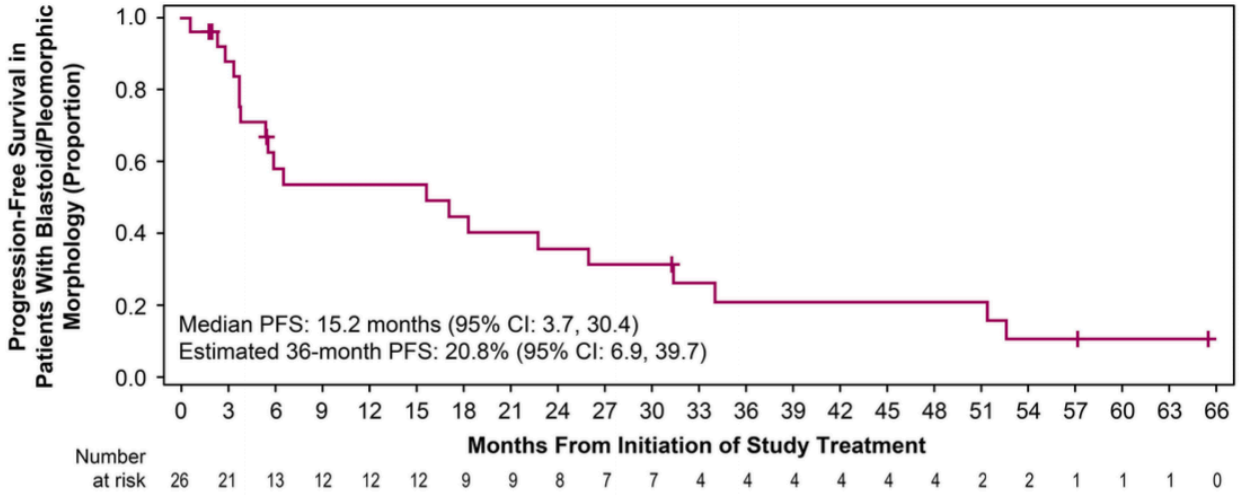
ORR 81%

CR 47.6%

DoR 28m

Low risk and CR pts had the best outcomes





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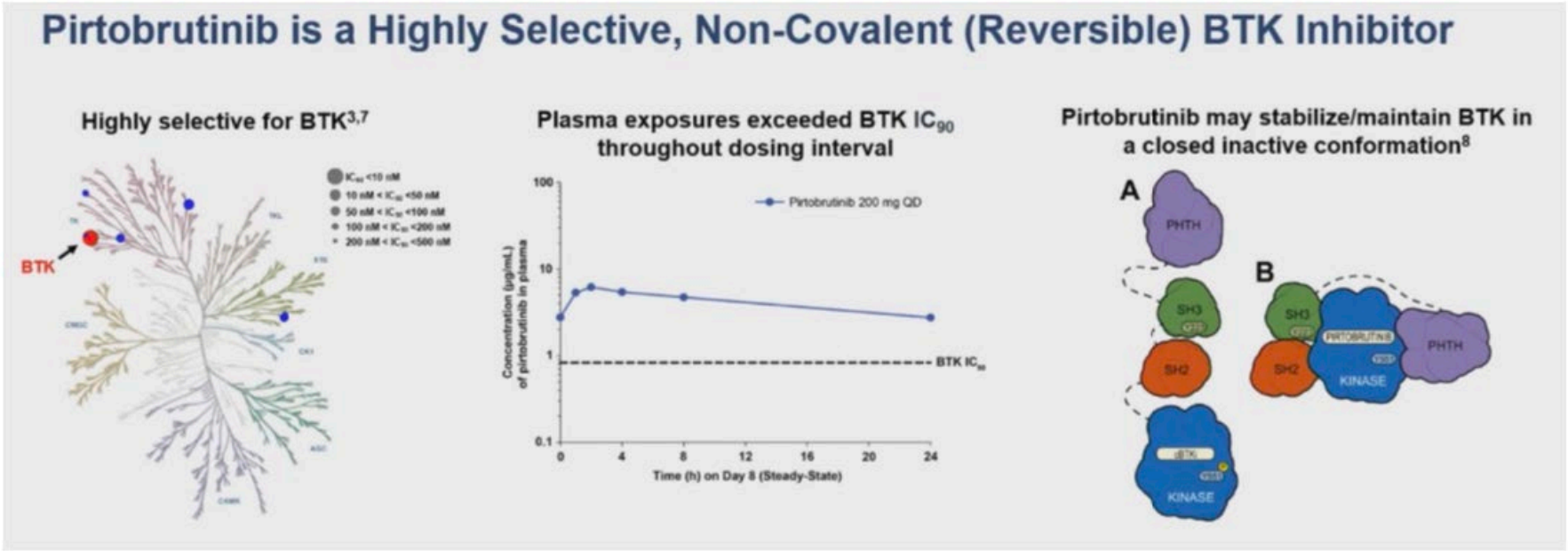
Le Gouill Haematologica 2024;109(1):343-50.

BRUIN Phase I/II trial of pirtobrutinib monotherapy (MCL cohort=166, with 14 naïve to prior BTKi)



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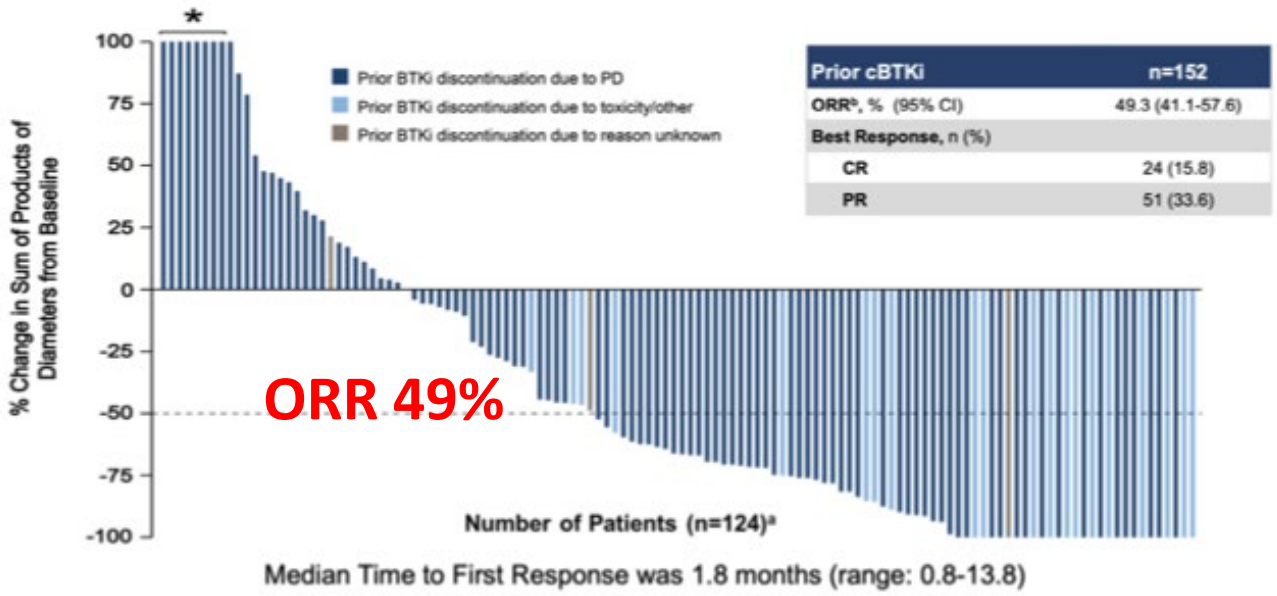
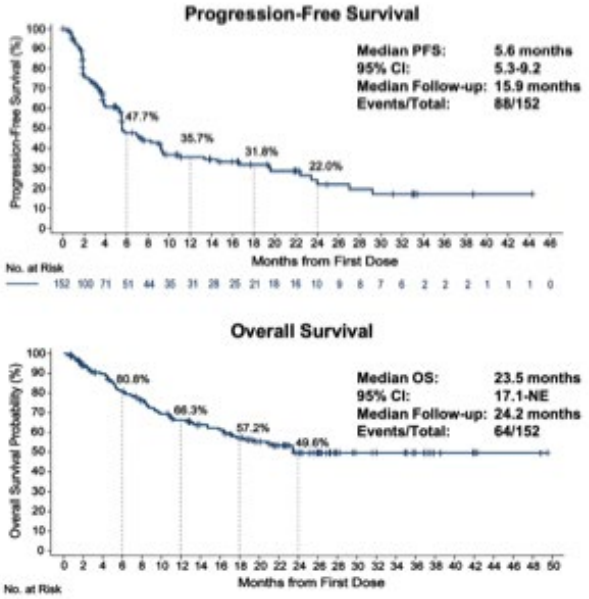
Cohen ASH 2023;Abstract 981.

Pirtobrutinib in rel/ref MCL



Prior cBTKi	n=152
ORR[b], % (95% CI)	49.3 (41.1-57.6)
Best Response, n (%)	
CR	24 (15.8)
PR	51 (33.6)

Med DoR 21m



Cohen ASH 2023;Abstract 981.

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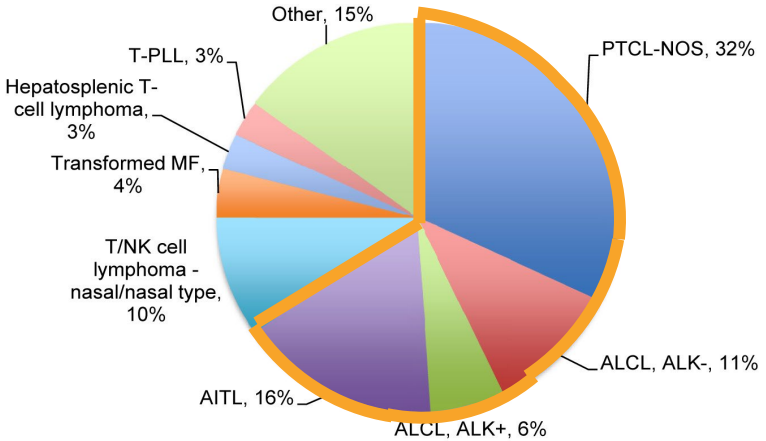
Advances in T-cell Lymphomas

T-NHL: rare, heterogeneous, chemoresistant

- PTCL:
  - 7% of all non-Hodgkin lymphomas
  - 19 entities with varied clinical and pathologic presentations
  - Median Age at Diagnosis: 65y
- Treatment strategies derived from aggressive B-cell lymphomas
- Different histologies have unique biology



ALCL
- CD30 positive
- ALK+ or ALK-
- Large anaplastic cells

AITL/Nodal PTCL with TFH features/Follicular T-cell lymphoma
- 2 of the following: BCL6, CD10, PD1, CXCL13, ICOS

PTCL NOS
- Grab bag term

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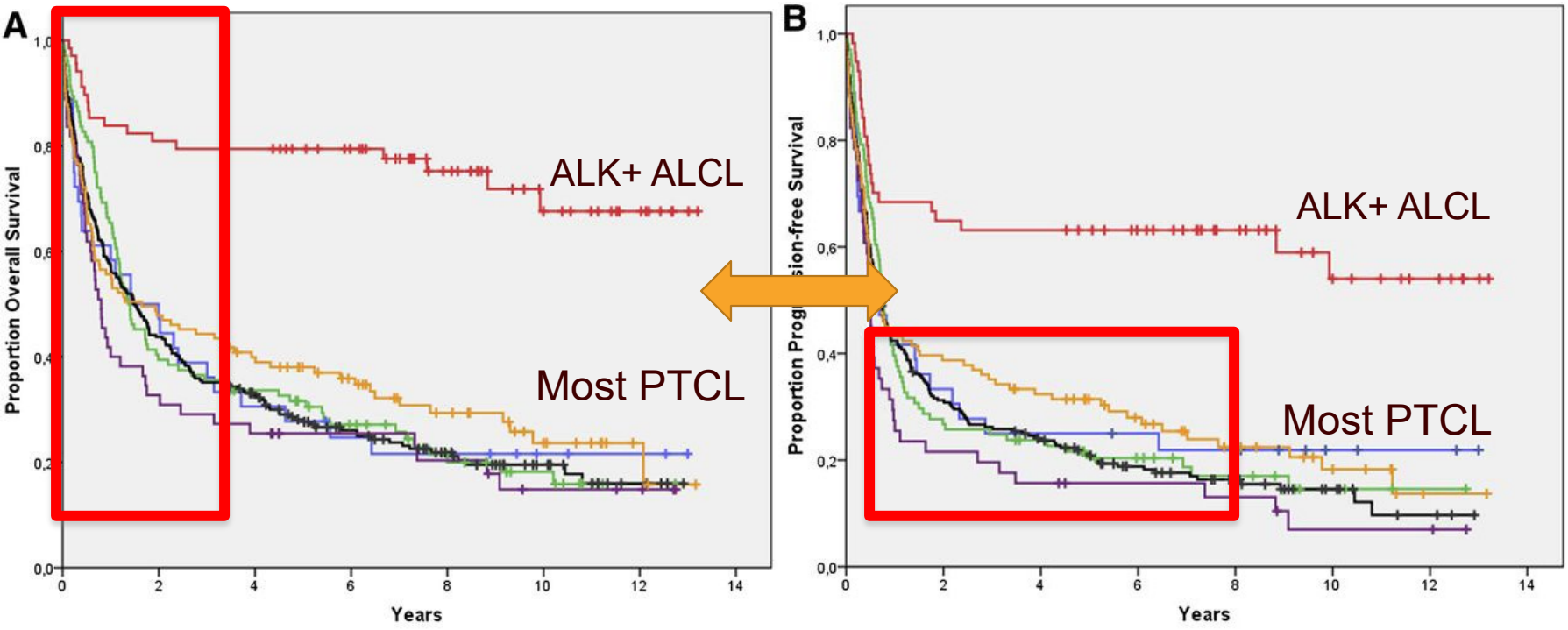
Slide courtesy of Neha Mehta-Shah

Hsi et al. Clin Lymph Myel Leukemia 2017

Expected outcomes with PTCL: Swedish National Registry

Overall Survival

Progression Free Survival



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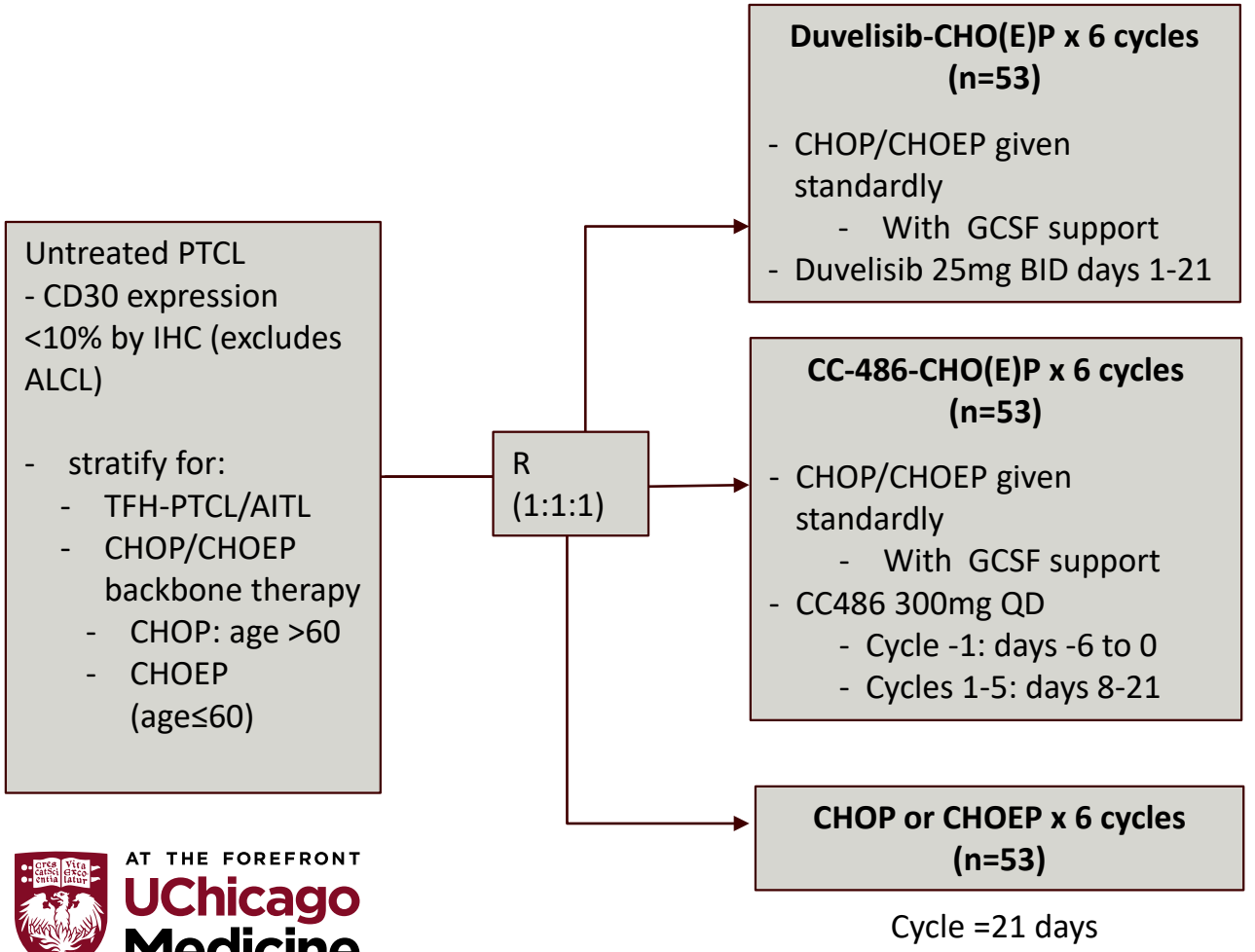
Ellin F et al. Blood 2014;124:1570-1577

A051902: A randomized phase II study of duvelisib or 5-azacitidine in addition to CHOP or CHOEP in comparison to CHOP/CHOEP



- Primary Objective:
  - To compare the PET CR rate of duvelisib or 5-azacitidine in combination with CHOP/CHOEP compared to CHOP/CHOEP
- Primary Endpoint:
  - 25% difference PET CR rate
- Correlative Studies:
  - Monitoring MRD
    - Alizadeh
  - Gene Expression Profiling and Custom Capture Sequencing
    - Dave
  - Patient Reported Outcomes
    - Thanarajasingam
  - PET/CT Evaluation
    - Schoder and Wright

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NCCN Guidelines for rel/ref T-NHL: laundry list of options

SECOND-LINE AND SUBSEQUENT THERAPY (NO INTENTION TO PROCEED TO TRANSPLANT)

Preferred regimens (regimens in alphabetical order)
- Clinical trial
- Belinostat
- Brentuximab vedotin for CD30+ PTCL[e,h]
- Duvelisib[j]
- Pralatrexate
- Romidepsin

Other recommended regimens (alphabetical order by category)
- Single agents
  - Alemtuzumab[k]
  - Bendamustine[e]
  - Cyclophosphamide and/or etoposide (IV or PO)
  - Gemcitabine
  - Lenalidomide[e]
  - RT[l]
  - Bortezomib[m] (category 2B)
  - Ruxolitinib (category 2B)
- Combination regimen
  - Brentuximab vedotin and bendamustine for CD30+ PTCL[e,h] (category 2B)

SECOND-LINE AND SUBSEQUENT THERAPY (NO INTENTION TO PROCEED TO TRANSPLANT)

Preferred regimens (regimens in alphabetical order)
- Clinical trial
- Belinostat
- Brentuximab vedotin for CD30+ AITL[e,h]
- Duvelisib[j]
- Romidepsin

Other recommended regimens (alphabetical order by category)
- Single agents
  - Alemtuzumab[k]
  - Azacitidine (PO/IV/SC)[p]
  - Bendamustine[e]
  - Cyclophosphamide and/or etoposide (IV or PO)
  - Cyclosporine[n]
  - Gemcitabine
  - Lenalidomide[e]
  - Pralatrexate[o]
  - RT[l]
  - Bortezomib[m] (category 2B)
  - Ruxolitinib (category 2B)
- Combination regimen
  - Brentuximab vedotin and bendamustine for CD30+ PTCL[e,h] (category 2B)

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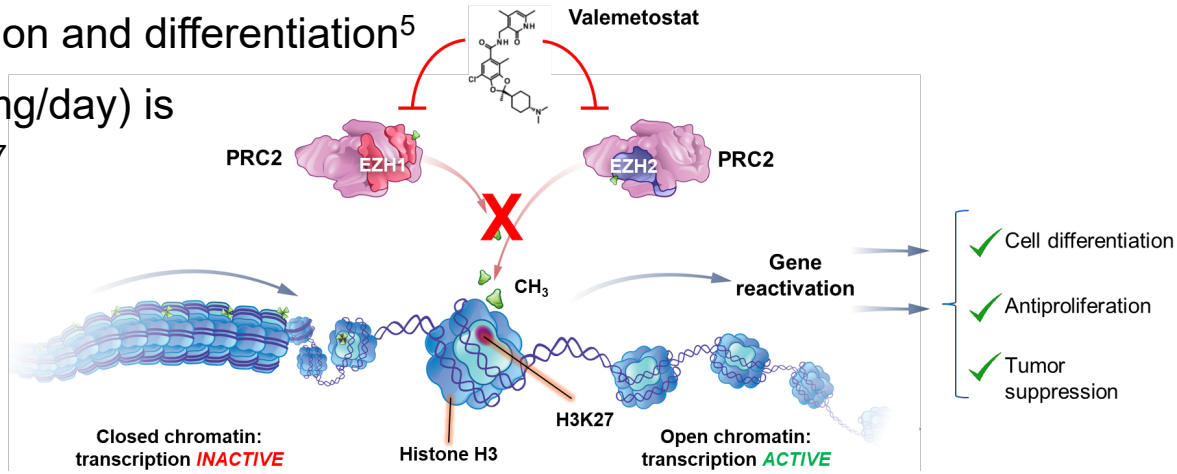
https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf

Efficacy and Safety of Valemetostat Monotherapy in Patients With Relapsed or Refractory Peripheral T-Cell Lymphomas: Primary Results of the Phase 2 VALENTINE-PTCL01 Study

- EZH2 overexpression drives the development and progression of many types of cancer, including PTCL[4]
  - *EZH2* mutations are rare in PTCL
- Valemetostat tosylate is a novel, potent, and **selective dual inhibitor of EZH2 and EZH1**
  - Valemetostat prevents H3K27me3, thereby increasing the expression of genes silenced by H3K27me3, including genes associated with the regulation of cell proliferation and differentiation[5]
- Valemetostat monotherapy (200 mg/day) is approved in Japan for R/R ATLL[6,7]



ATLL, adult T-cell leukemia/lymphoma; EZH, enhancer of zeste homolog; H3K27me3, tri-methylation of lysine 27 on histone H3 protein; NHL, non-Hodgkin lymphoma; OS, overall survival; PFS, progression-free survival; PRC2, polycomb repressive complex 2; PTCL, peripheral T-cell lymphoma; R/R, relapsed/refractory.

1. Vose J, et al. *J Clin Oncol* 2008;26:4124–4130. 2. Ling L, et al. *Br J Haematol* 2017;178:772–780. 3. Sibon D, et al. *Cancers* 2022;14:2332. 4. Herviou L, et al. *Oncotarget* 2016;7:2284–2296. 5. Yamagishi M, et al. *Cell Rep* 2019;29:2321–2337.e7. 6. EZHARMIA® (valemetostat tosilate). [package insert]. Tokyo, Japan: Daiichi Sankyo; 2022. 7. Izutsu K, et al. *Blood* 2023;141:1159–1168.

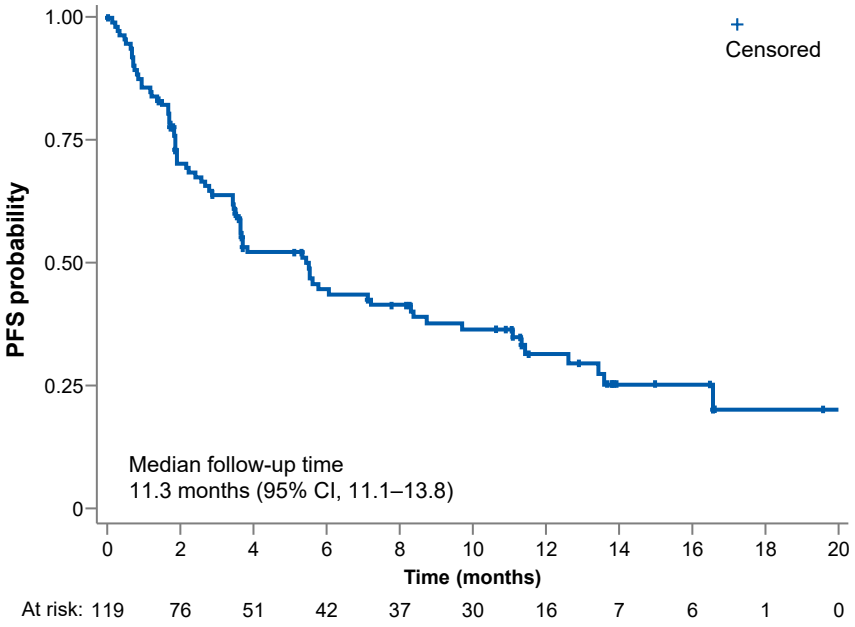
Horwitz SM, et al. ASH 2023 #302

Progression-Free Survival and Overall Survival (n=133)

Valemetostat 200mg qd until intolerance or progression

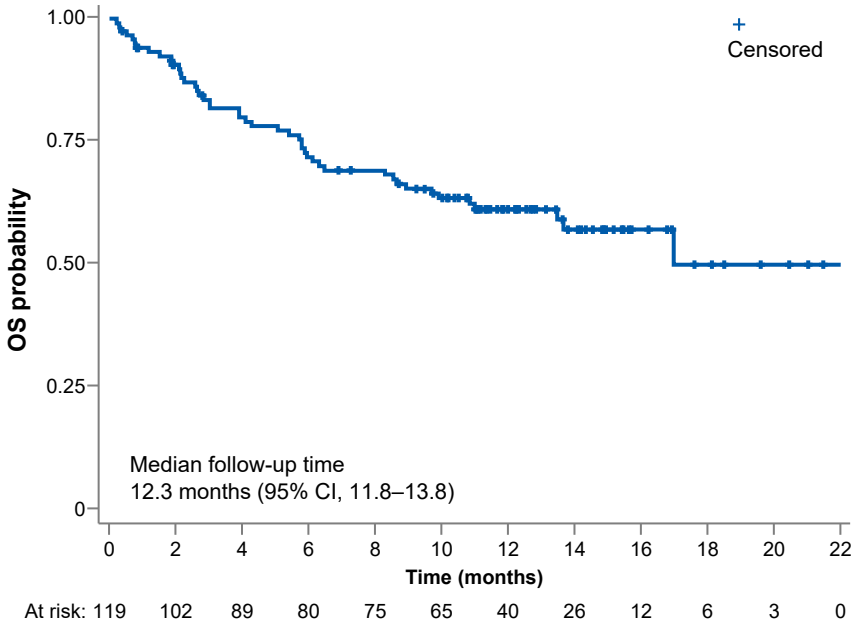
PFS[a]

Median 5.5 months (95% CI, 3.5–8.3)
(N = 119)



OS

Median 17 months (95% CI, 13.5 months to NE)
(N = 119)

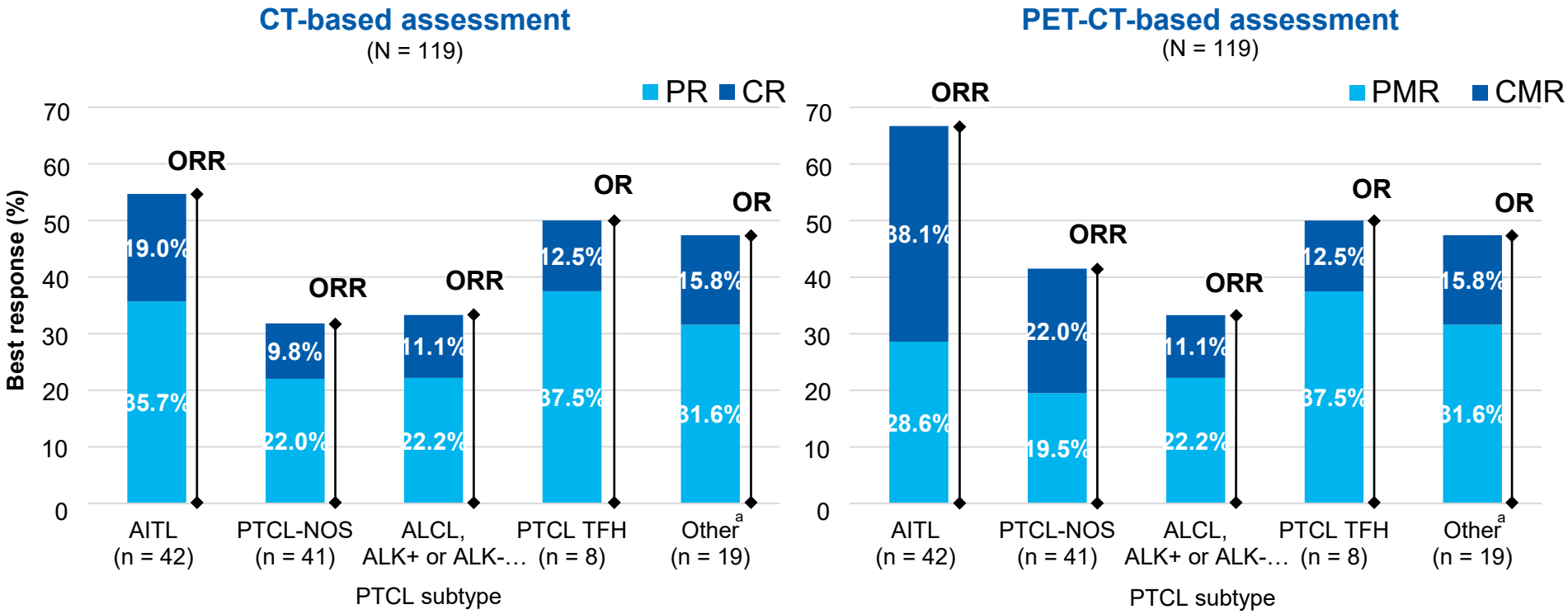


Data cutoff: May 5, 2023.
[a] PFS evaluated by BICR CT-based assessment.

Horwitz SM, et al. ASH 2023 #302

Clinical Response by PTCL Subtype

Responses were observed across all PTCL subtypes



Data cutoff: May 5, 2023.

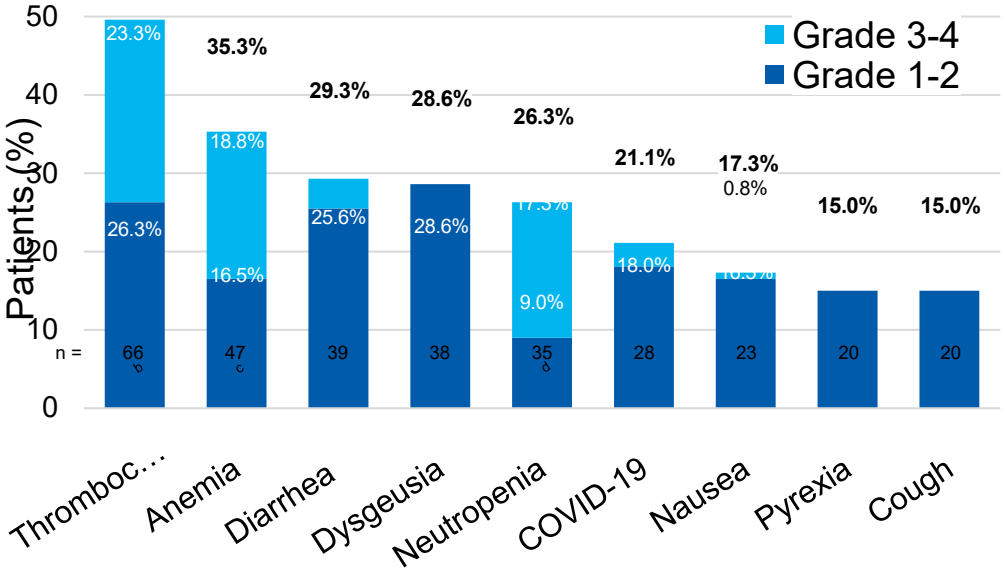
[a] Other TCLs include 3 patients with FTL, 1 with PCGTL, 1 with CD8+ PCAECTCL, 1 with MEITL, and 13 with other eligible, but undetermined PTCL subtypes.

TTR ~8 weeks

Horwitz SM, et al. ASH 2023 #302

VALENTINE PTCL01: valemetostat 200mg/d in rel/ref PTCL

- Cytopenias were common, and were manageable with dose modifications and/or supportive therapies such as transfusions and G-CSF
  - Thrombocytopenia was the most frequent any grade (49.6%) and grade ≥ 3 (23.3%) TEAE
  - The median time to first onset of platelet count < 50×10^9/L was 18 days from the first dose and the median time to recovery was 12 days
- 2 patients developed secondary AML and discontinued treatment



TEAEs leading to dose modifications[a] (N = 133)

Preferred term	Treatment discontinuation %	Dose reduction %	Dose interruption %
Any TEAE	**9.8**	**15.8**	**49.6**
Thrombocytopenia[b]	2.3	5.3	16.5
Anemia[c]	0	3.8	9.8
COVID-19	0	1.5	8.3
Neutropenia[d]	0	2.3	5.3

Data cutoff: May 5, 2023.
[a] TEAEs included that led to treatment interruption in ≥ 5% of patients. [b] Thrombocytopenia includes platelet count decrease. [c] Anemia includes hemoglobin decrease, and red blood cell count decrease.
[d] Neutropenia includes neutrophil count decrease.
AML, acute myeloid leukemia; G-CSF, granulocyte colony stimulating factor.

Horwitz SM, et al. ASH 2023 #302

JACKPOT8: phase II pivotal trial of selective JAK1 inhibitor golidocitinib (AZD4205) in rel/ref PTCL

- Golidocitinib: oral agent, highly selective for JAK1 (>200X selectivity over JAK2, JAK3, TYK2
- Prior phase I trial with favorable safety profile
- Treatment schema: 150mg/d until progression (n=104; 88 evaluable)

Tumor Response	n = 88
ORR, n (%)	39 (44.3)
Overall response, n (%)	
Complete response	21 (23.9)
Partial response	18 (20.5)
Stable disease	17 (19.3)
Progressive disease	20 (22.7)
Not evaluable	12 (13.6)

The most common (incidence >10%) Grade≥3 TRAEs included thrombocytopenia, leukopenia, neutropenia and lymphocytopenia

Song ASH Abstract 2023 #305

JACKPOT8 Subgroup analysis

Subgroup	ORR n/N (%)	95% CI [a]
Overall	39/88 (44.3)	(33.7, 55.3)
Age Group		
<65	27/61 (44.3)	(31.5, 57.6)
≥65	12/27 (44.4)	(25.5, 64.7)
Sex		
Female	18/31 (58.1)	(39.1, 75.5)
Male	21/57 (36.8)	(24.4, 50.7)
Geographical Region		
Asia: China and S. Korea	37/83 (44.6)	(33.7, 55.9)
Non-Asia: United States and Australia	2/5 (40.0)	(5.3, 85.3)
Prior Systemic Therapy		
<2	6/24 (25.0)	(9.8, 46.7)
≥2	33/64 (51.6)	(38.7, 64.2)
Prior HDAC Inhibitor Therapy		
Yes	24/44 (54.5)	(38.8, 69.6)
No	15/44 (34.1)	(20.5, 49.9)
Prior CD30 Targeted Therapy		
Yes	4/9 (44.4)	(13.7, 78.8)
No	35/79 (44.3)	(33.1, 55.9)
Histology Subtype by Central Pathology Review		
PTCL-not otherwise specified (PTCL, NOS)	23/50 (46.0)	(31.8, 60.7)
Angioimmunoblastic T-cell lymphoma (AITL)	9/16 (56.3)	(29.9, 80.2)
Anaplastic large-cell lymphoma (ALCL)	1/10 (10.0)	(0.3, 44.5)
Natural killer/T-cell lymphoma (NK/TCL)	2/3 (66.7)	(9.4, 99.2)
Others	4/9 (44.4)	(13.7, 78.8)
Bone Marrow Involvement at Baseline by Biopsy		
Yes	9/19 (47.4)	(24.4, 71.1)
No	30/69 (43.5)	(31.6, 56.0)
ECOG Performance Status at Baseline		
0	17/40 (42.5)	(27.0, 59.1)
≥1	22/48 (45.8)	(31.4, 60.8)
LDH Elevation at Baseline		
Yes	14/46 (30.4)	(17.7, 45.8)
No	25/42 (59.5)	(43.3, 74.4)

Tumor responses observed across all PTCL subtypes, all subgroups irrespective of age, sex, ECOG score, BM involvement, LDH levels, and prior anti-lymphoma therapies.

Song ASH Abstract 2023 #305

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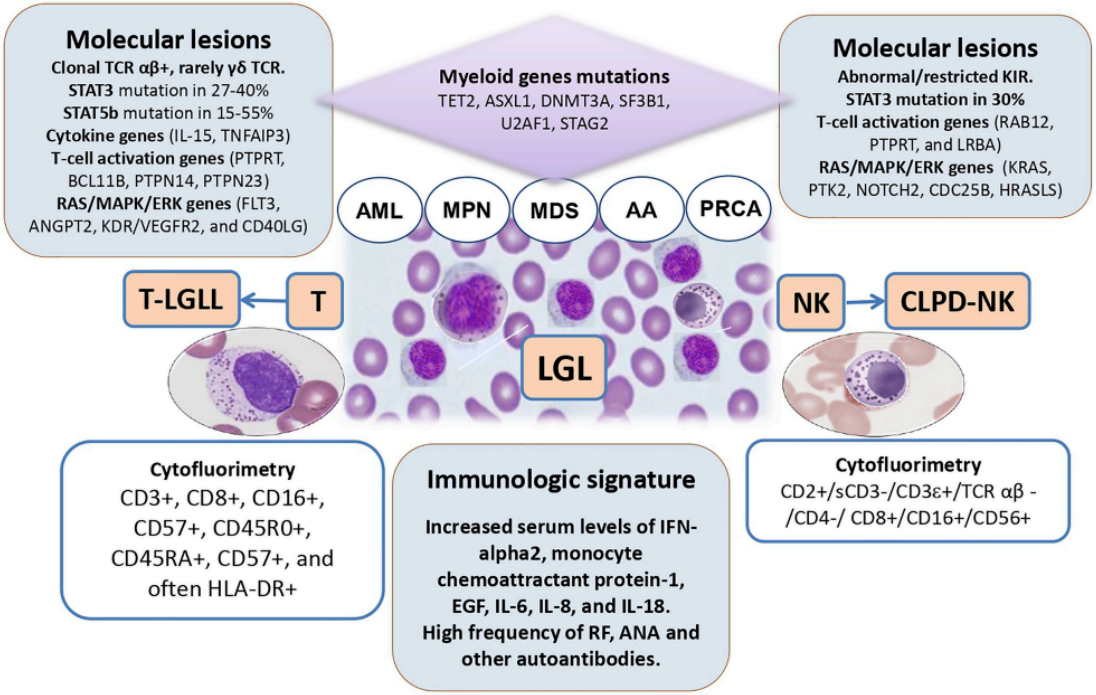


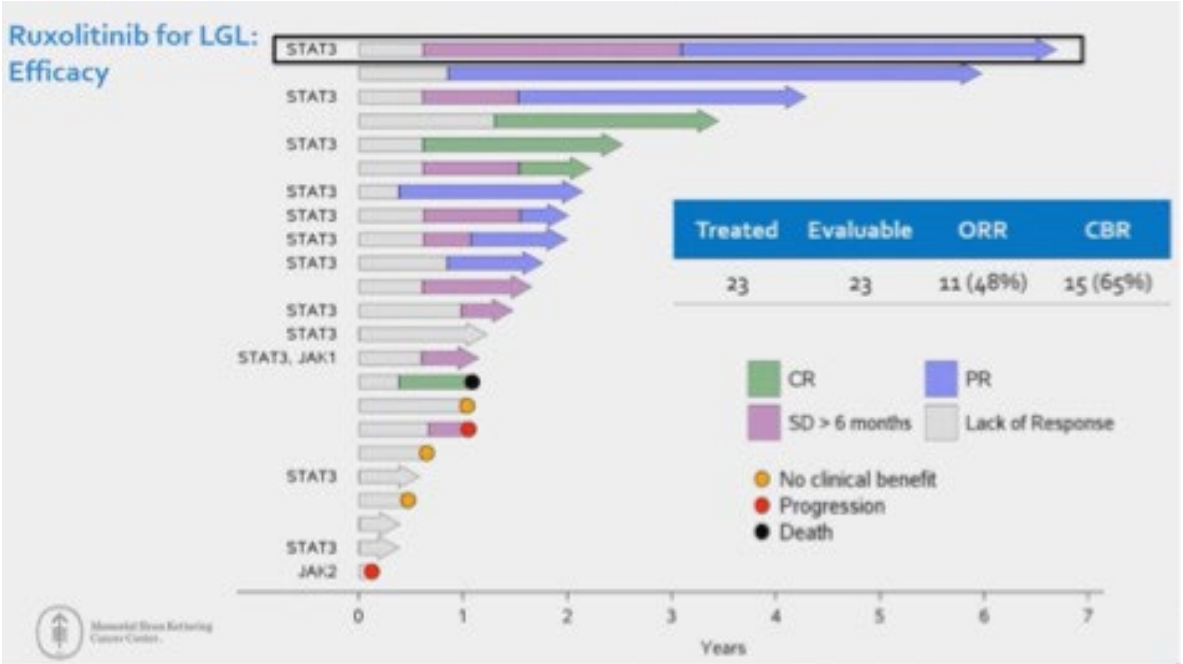
T-LGL Background

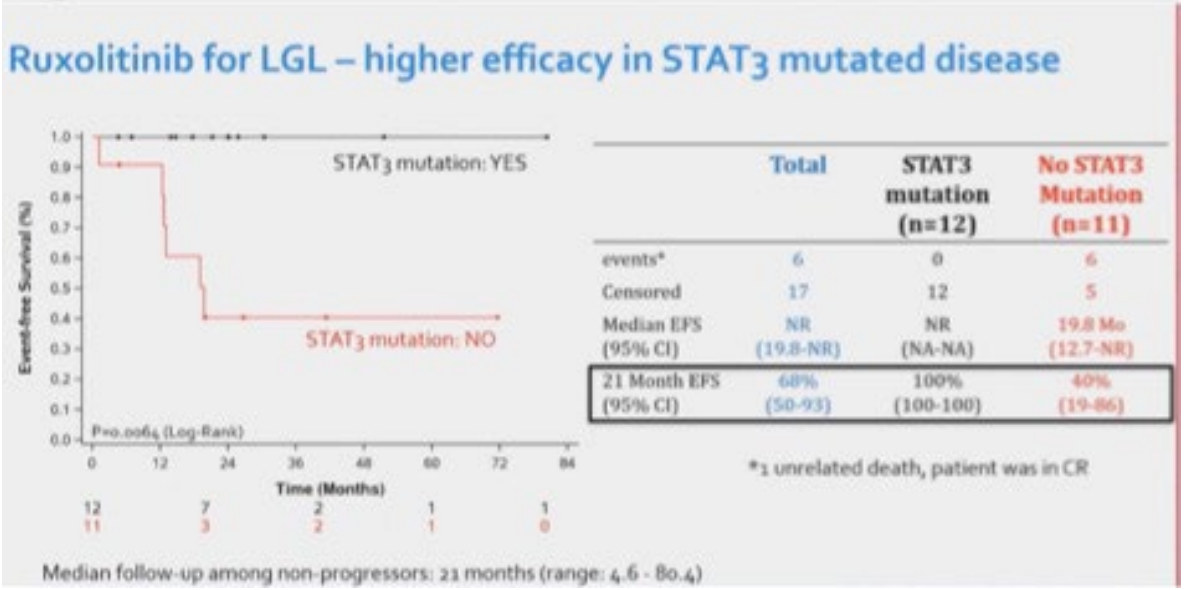
- Rare disease with ~1000 new cases/year
- T-LGL and NK-LGL characterized by clonal expansion of LGL cells resistant to cell death and associated with
  - Neutropenia, anemia, less commonly thrombocytopenia
  - Autoimmune phenomenon
- Constitutive activation of JAK/STAT pathway
- Frequent gain of function STAT3 mutations
- Treatments: methotrexate, cyclophosphamide, cyclosporine
  - Responses typically 50% with response duration 20-70m

[1]Lamy T, Moignet A, Loughran TP, Jr. LGL leukemia: from pathogenesis to treatment. Blood. 2017;129(9):1082-1094
[2]Magnano L, Rivero A, Matutes E. Large Granular Lymphocytic Leukemia: Current State of Diagnosis, Pathogenesis and Treatment. Current Oncology Reports. 2022/05/01 2022;24(5):633-644.

Fattizzo Front. Oncol., 01 October 2021 Sec. Cancer Immunity and Immunotherapy Volume 11 - 2021

Phase II trial of ruxolitinib monotherapy in rel/ref T-LGL (n=23)





*STAT3 mut mediate resistance!! So, why should ruxolitinib work?

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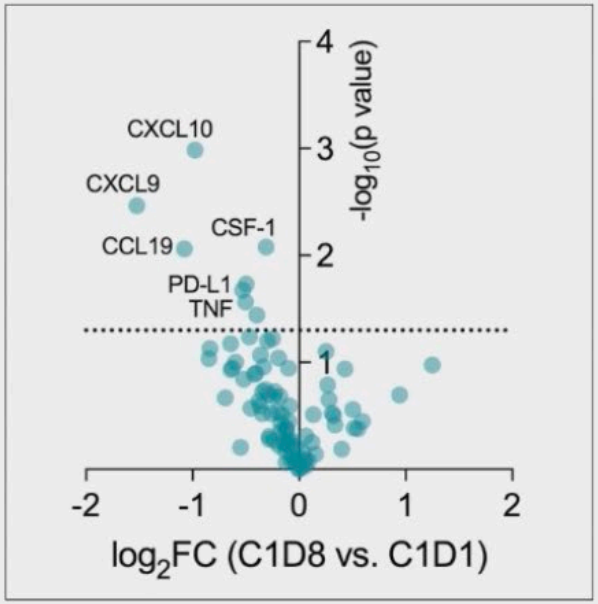
Moskowitz Blood (2023) 142 (Supplement 1): 183.

Ruxolitinib decreases myeloid cell inflammation in T-LGL

- Ruxolitinib treatment was associated with decreased production of several **myeloid-derived chemokines** (CXCL9, CXCL10, CCL19) in responders:
  - CXCL9 negatively regulates hematopoiesis (Lu et al, ***Cell Res*** 2008)
  - CXCL10 and CCL19 have known roles in lymphoid cell homing
  - Do myeloid cell-derived chemokines recruit inflammatory cells to the bone marrow?

➢ **Ruxolitinib reverses myelosuppression by inhibiting myeloid cells' inflammatory effect?**



Decrease in soluble mediators of inflammation in responders

Decrease in JAK/STAT expressing myeloid cells was associated with response

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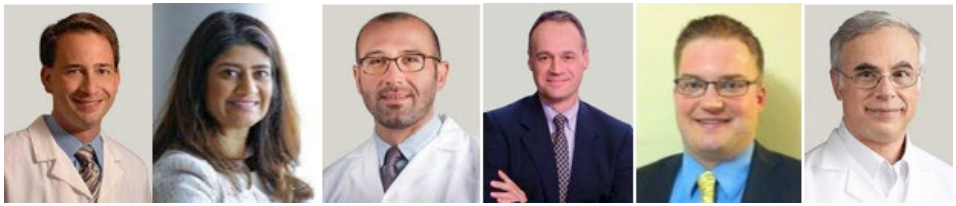
Moskowitz Blood (2023) 142 (Supplement 1): 183.

Summary

- **DLBCL**
  - Three new approvals in 2023
  - Integration of bispecific agents is next
  - Advances in biology may direct treatment
- **MCL**
  - Non-covalent BTKi are on the horizon
- **T-NHL**
  - Much work remains to be done
  - Targeted approaches will be key to reversing poor outcomes

THANK YOU

Opening 2027



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UChicago Medicine

LYMPHOMA PROGRAM:
The University of Chicago
cancer@uchospitals.edu