ASH-2021

Diffüz Büyük B Hücreli Lenfoma

Burhan Ferhanoğlu.

VKV Amerikan Hastanesi & Koç Üniversitesi

8 Ocak 2022

İçerik

1. R-CHOP vs Pola-R-CHP
2. Double-Hit Lenfoma (education)
3. DHL;Aliance;DA-EPOCH+Venetoclax
4. DHL;HOVON152;DA-EPOCH+ Nivo
5. CNS proflaksisinde yüksek doz MTX etkisiz mi?
6. Axicabtagene ciloleucel vs SCT
7. Lisocabtagene Maraleucel vs SCT
8. Tisalecleucel vs SCT (BELINDA)trial
9. Circulating tm DNA for non-invasive disease detection of patients with CNS lymphoma
10. CT monitoring and MRD assesment using NGS assay after frontline teratment of DLBCL

Empirical Development/Optimization of R-C

5y-OS	50%	60%	65-70%	>90% 70-80 70	
	1993	2002	2008	2019	2021

Optimal supportive care

CHOP → R-CHOP → 6 x R-CHOP → IPI 0 - 4x R-CHOP +2R; IPI all - 6 x R-CHOP; IPI 2/3 - 8 x R-CHOEP → pola + R-CHP; R-CHOP + XY

"failed"

Longer treatment (8 vs 6)
Dose-density (14 vs. 21)
Higher doses (Mega)
Early Transplant
Infusional applications
New CD20 antibodies

R-CHOP + X all comer designs
X = Bortezomib
X = Lenalidomide
X = Ibrutinib
X = other

LBA-1

The POLARIX Study: Polatuzumab Vedotin with Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (Pola-R-CHP) Versus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (R-CHOP) Therapy in Patients with Previously Untreated Diffuse Large B-Cell Lymphoma

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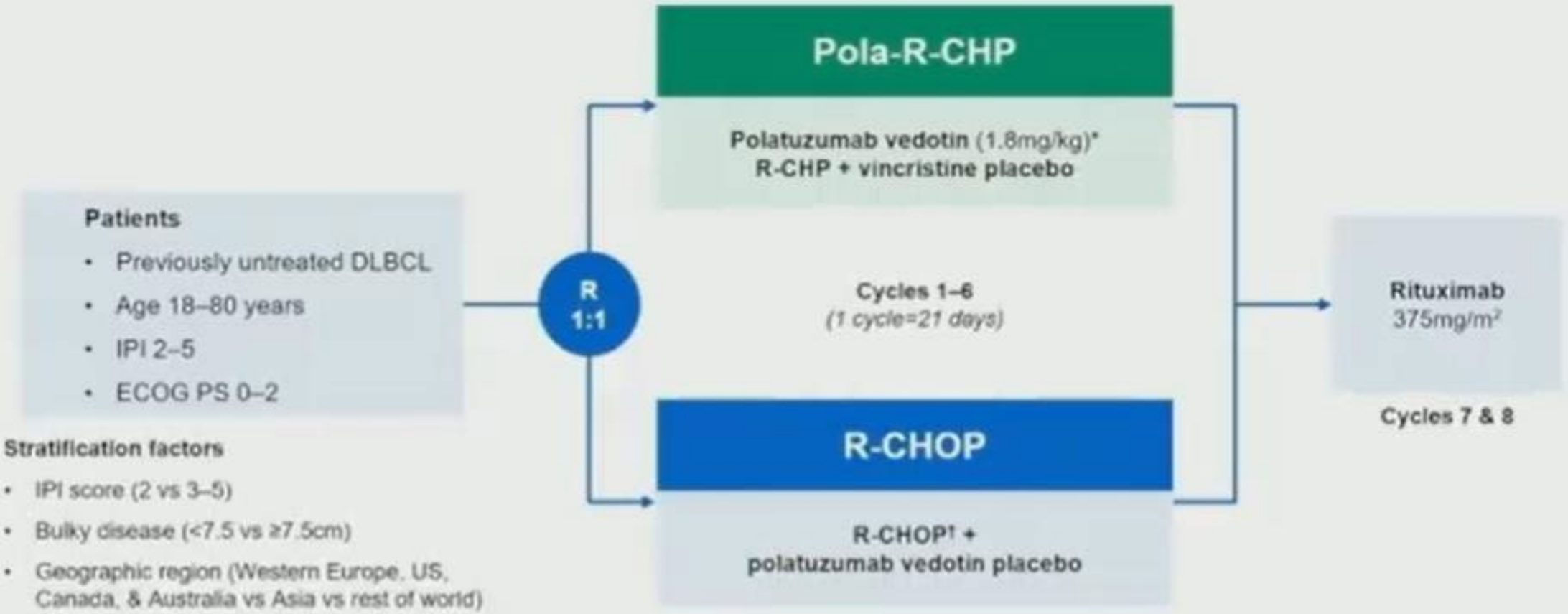
Late-Breaking Abstract Accepted as an Oral Presentation at the 63rd ASH Annual Meeting and Exposition, 11–14 December 2021

POLARIX: A randomized double-blinded study



*IV on Day 1. †R-CHOP: IV rituximab 375mg/m², cyclophosphamide 750mg/m², doxorubicin 50mg/m², and vincristine 1.4mg/m² (max. 2mg) on Day 1, plus oral prednisone 100mg once daily on Days 1–5.
IPI, International prognostic index; ECOG PS, Eastern Cooperative Oncology Group performance status; R, randomized

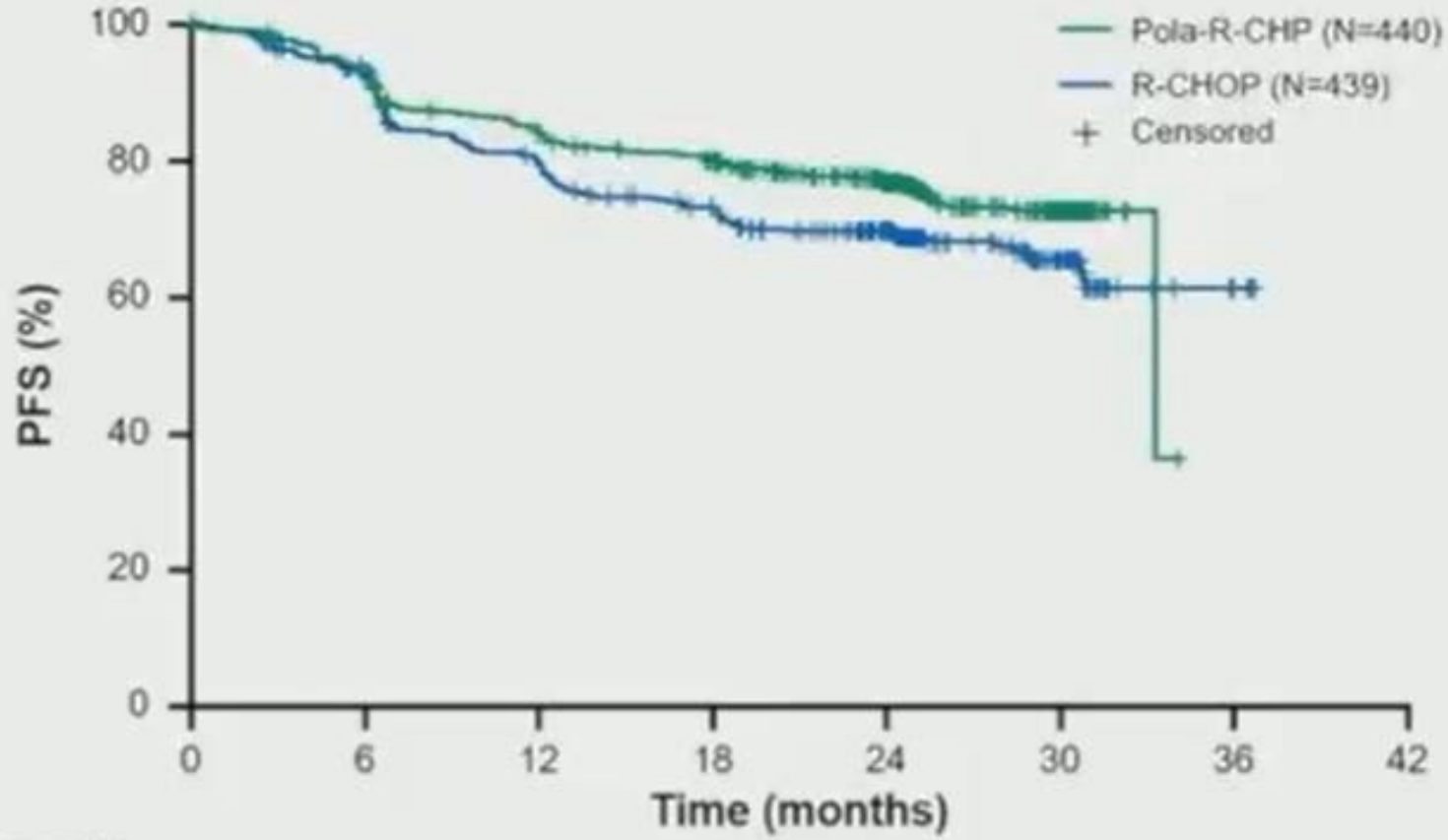
Baseline characteristics

ITT population		Pola-R-CHP (N=440)	R-CHOP (N=439)
Age	Median (range), years	65.0 (19–80)	66.0 (19–80)
Sex, n (%)	Male	239 (54)	234 (53)
ECOG PS, n (%)	0–1	374 (85)	363 (83)
	2	66 (15)	75 (17)
Bulky disease (≥7.5cm), n (%)	Present	193 (44)	192 (44)
Elevated LDH, n (%)	Yes	291 (66)	284 (65)
Time from diagnosis to treatment initiation	Median, days	26	27
Ann Arbor Stage, n (%)	III–IV	393 (89)	387 (88)
Extranodal sites, n (%)	≥2	213 (48)	213 (49)
IPI score, n (%)	2	167 (38)	167 (38)
	3–5	273 (62)	272 (62)
Cell-of-origin, (%)*	ABC	102 (31)	119 (35)
	GCB	184 (56)	168 (50)
	Unclassified	44 (13)	51 (15)
MYC/BCL2 expression, n (%)*	Double expression	139 (38)	151 (41)
MYC/BCL2/BCL6 rearrangement, n (%)*	Double-/triple-hit	26 (8)	19 (6)

*In the Pola-R-CHP and R-CHOP groups, respectively, the numbers of patients evaluable for cell-of-origin were 330 and 338, with IHC for MYC/BCL2 expression were 362 and 366, and with FISH for *MYC/BCL2/BCL6* rearrangements were 331 and 334.
ABC, activated B-cell; FISH, fluorescence in situ hybridization; GCB, germinal center B-cell; LDH, lactate dehydrogenase.

Primary endpoint: Progression-free survival

Pola-R-CHP significantly improved PFS versus R-CHOP



No. of patients at risk

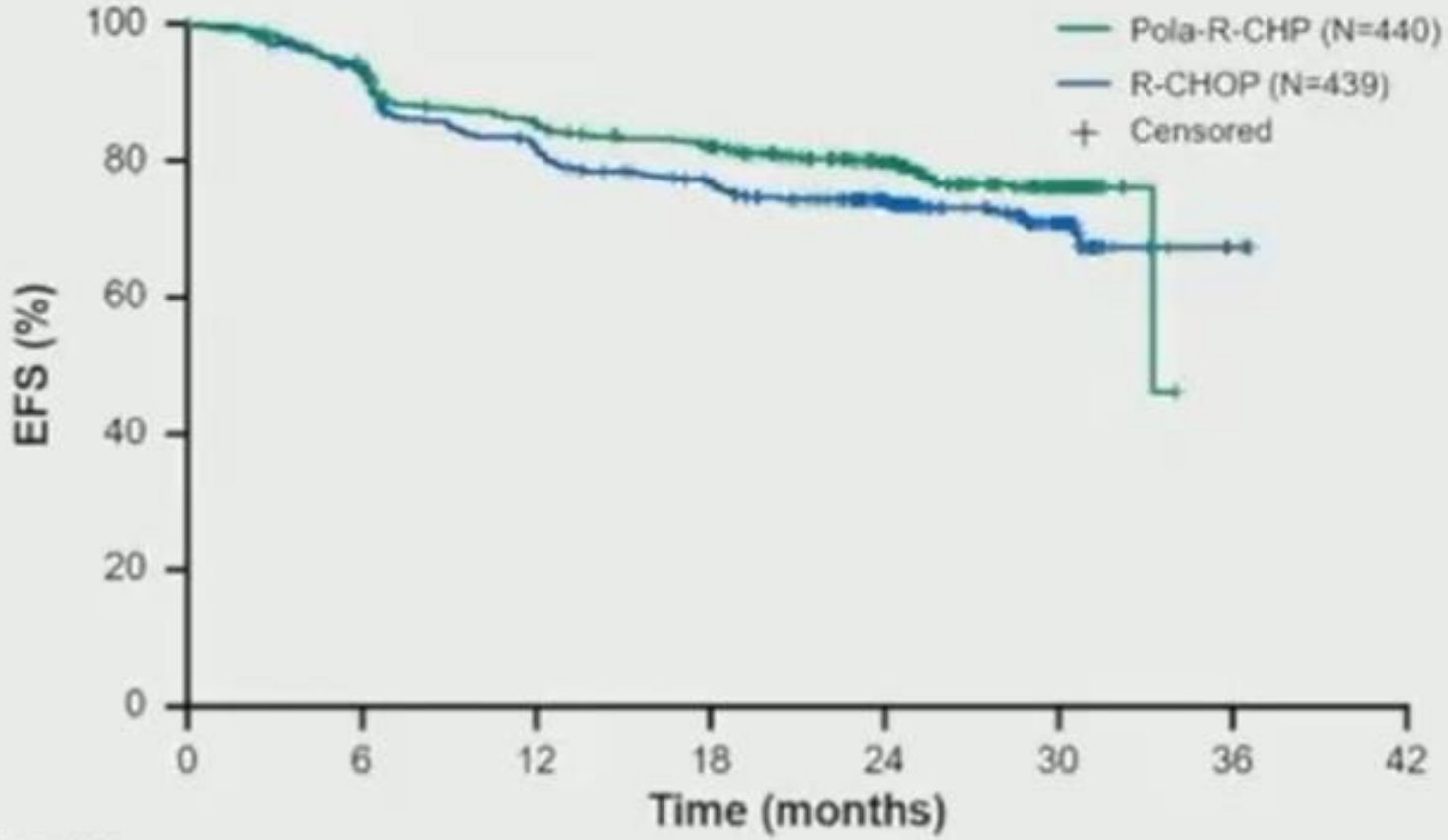
Pola-R-CHP*	440	404	353	327	246	78	NE	NE
R-CHOP	439	385	330	298	220	78	3	NE

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.
NE, not evaluable.

HR 0.73 (P<0.02)
95% CI: 0.57, 0.95

- Pola-R-CHP demonstrated a **27% reduction 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%**)

Event-free survival

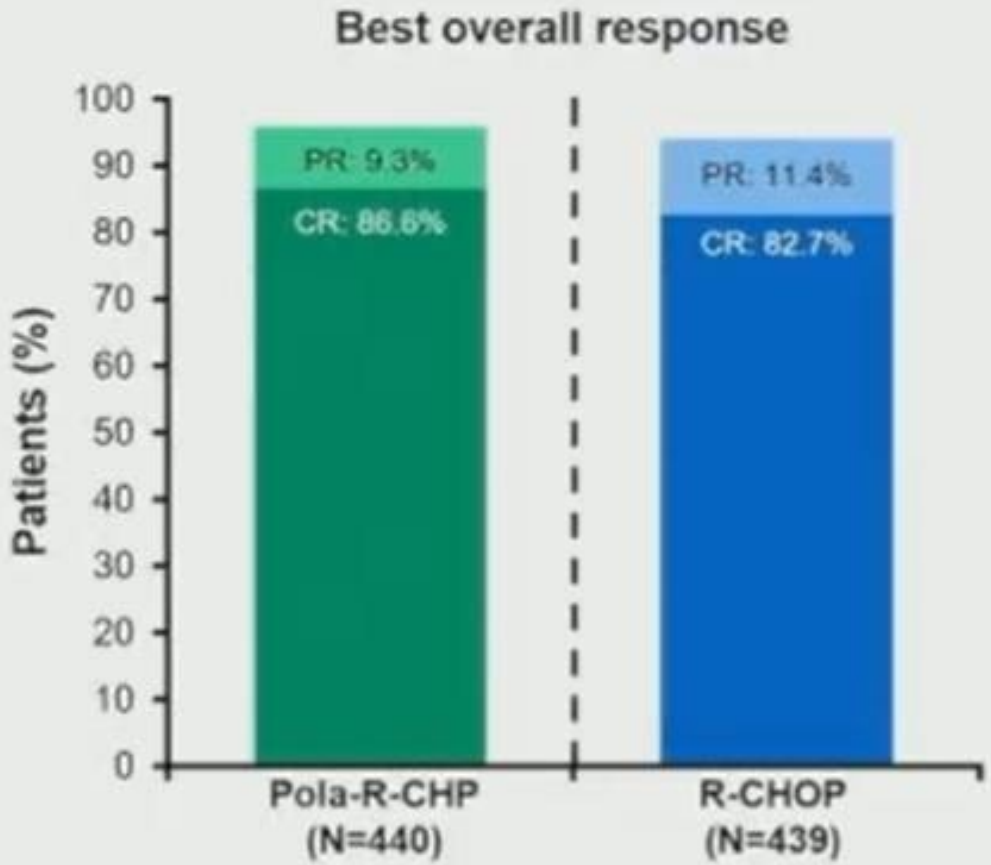


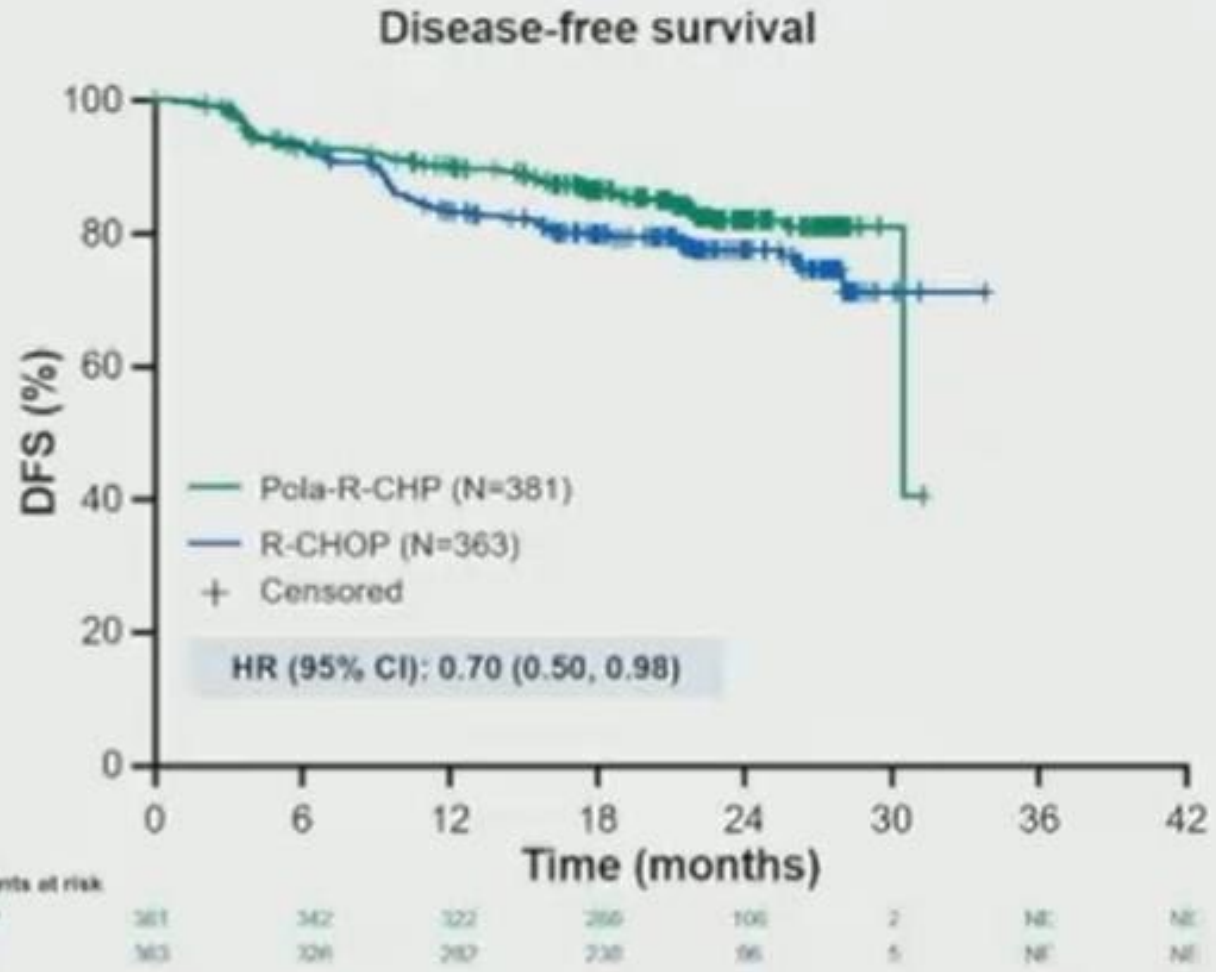
HR 0.75 (P=0.02)
95% CI: 0.58, 0.96

No. of patients at risk								
Pola-R-CHP[a]	440	402	346	323	243	79	NE	NE
R-CHOP[b]	439	386	327	294	218	78	3	NE

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.
EFS, event-free survival.

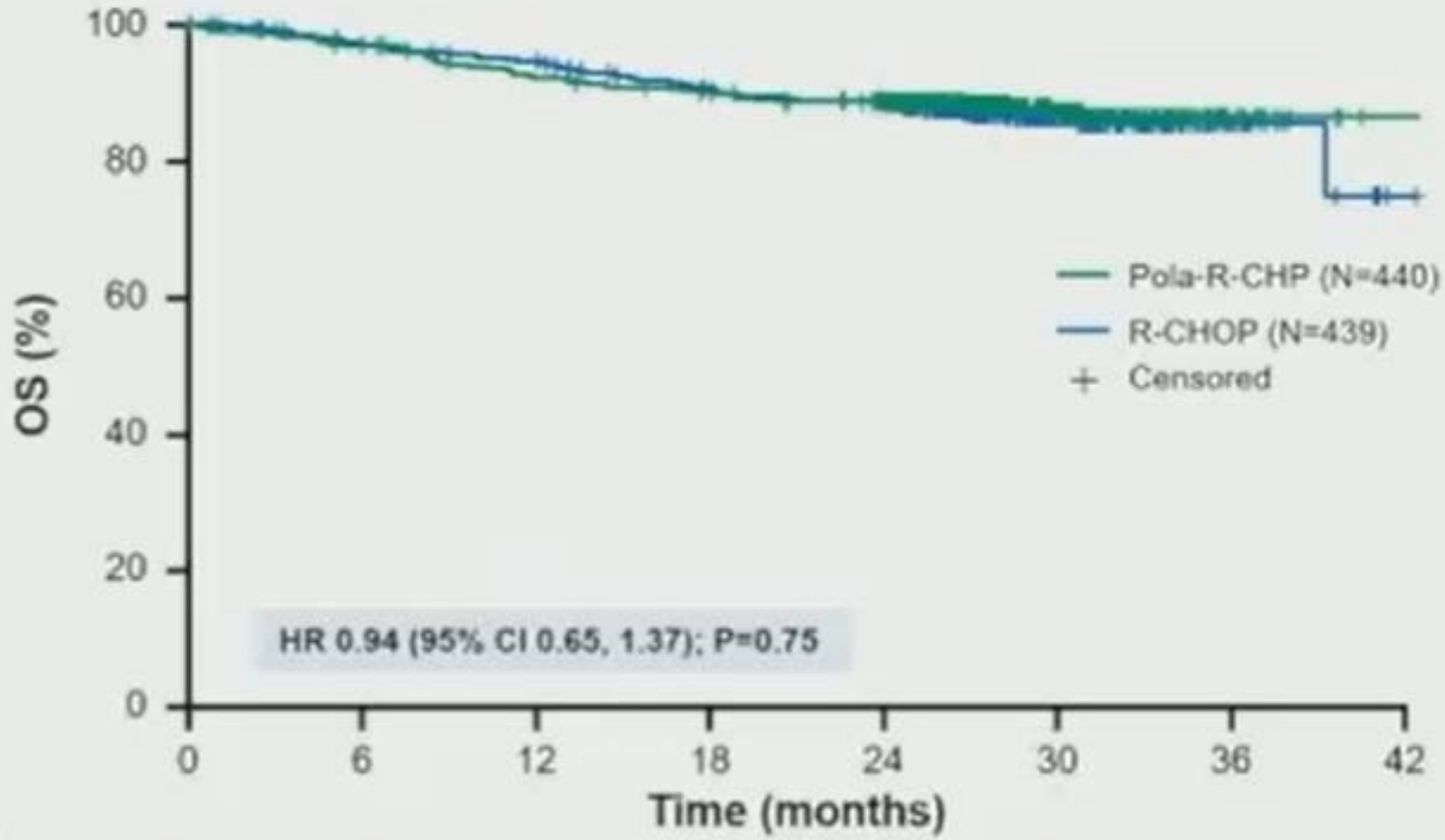
Response rates and disease-free survival





ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up. Disease-free survival (DFS) defined as the time from the date of the first occurrence of a documented complete response to the date of progression, relapse, or death from any cause for the subgroup of patients with a best overall response of CR.

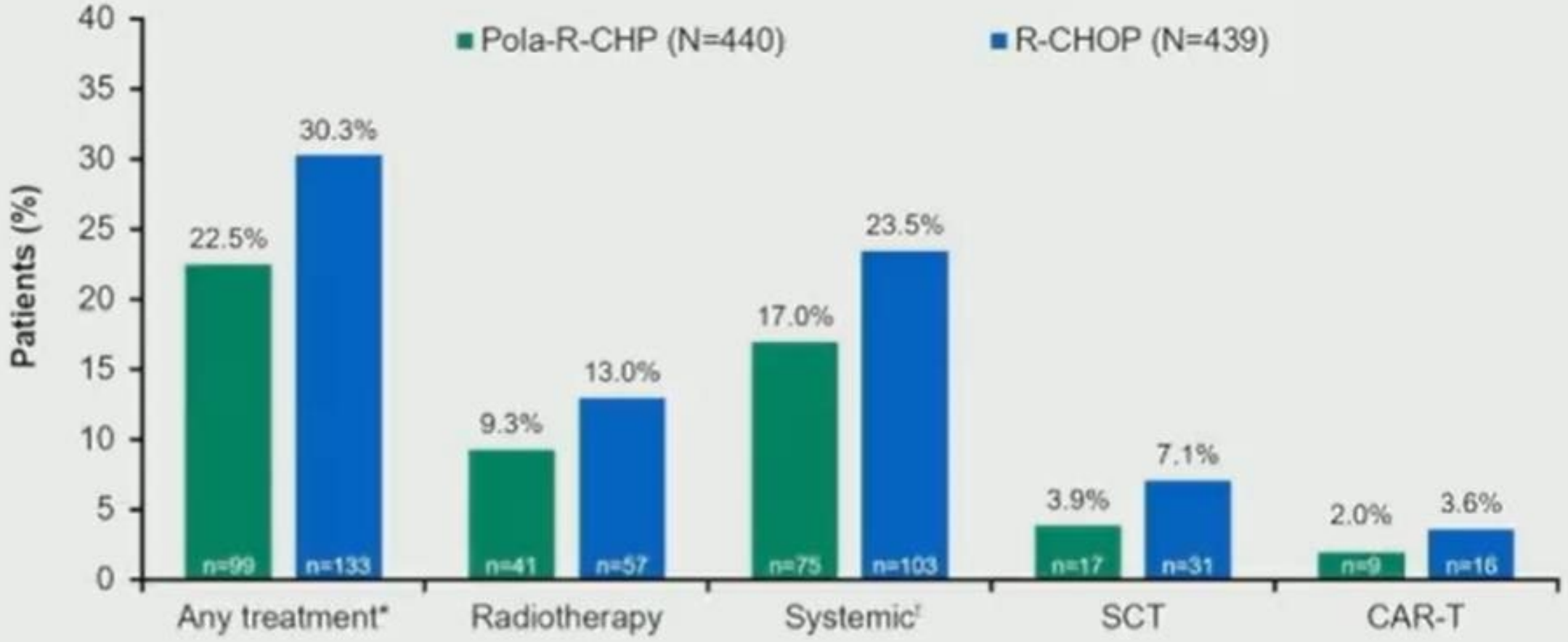
Overall survival



No. of patients at risk								
Pola-R-CHP	440	423	397	384	362	149	15	1
R-CHOP	439	414	401	378	355	132	20	1

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.

Patients receiving subsequent treatments



Data cut-off: June 28, 2021. *Subsequent lymphoma treatment was defined as non-protocol anti-lymphoma therapy; †Includes any monotherapy, multi-drug, or cell-based regimen.
CAR-T, chimeric antigen receptor T-cell therapy; SCT, stem cell transplant

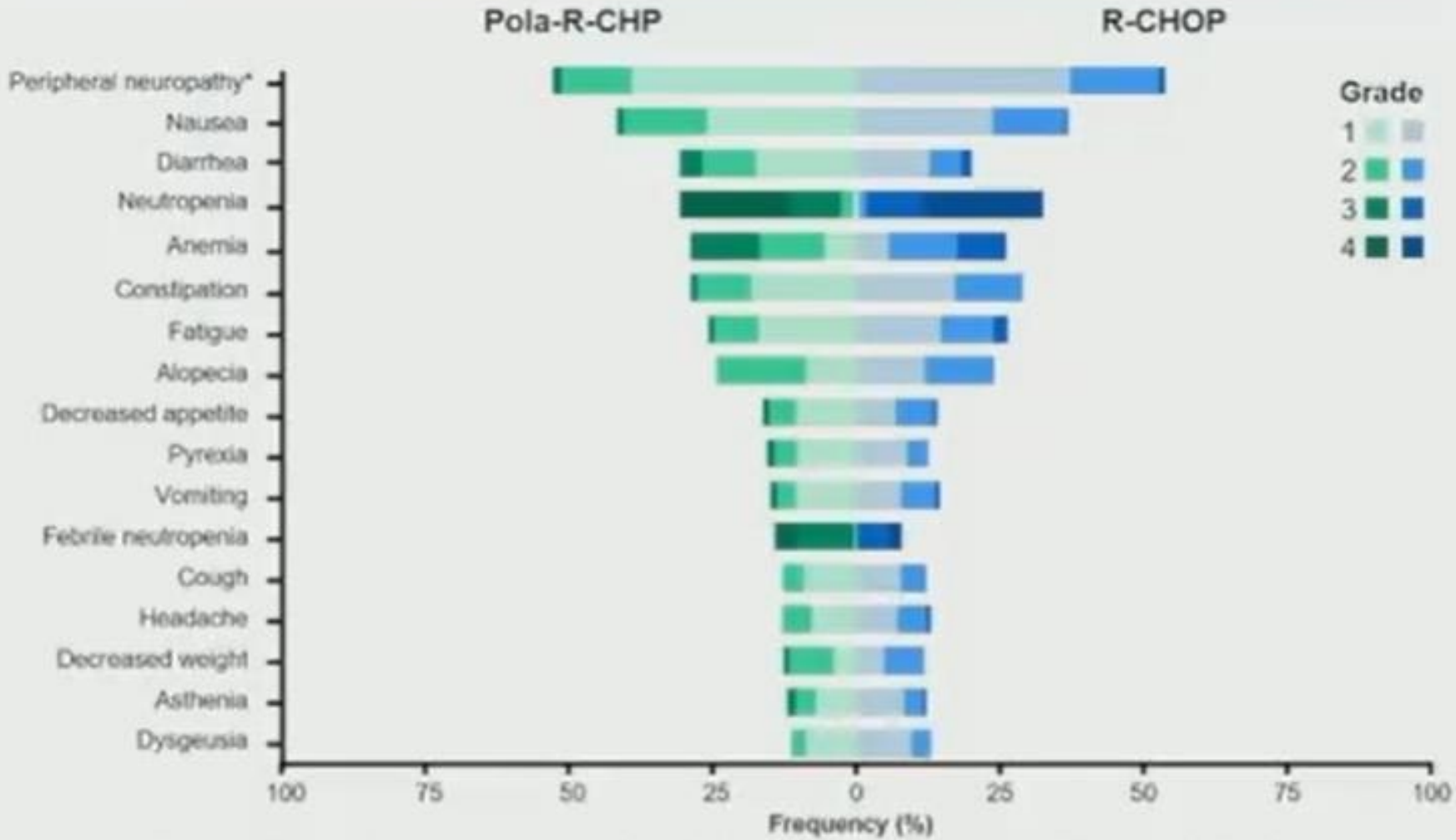
Safety summary

Safety profiles were similar with Pola-R-CHP and R-CHOP

n (%)	Pola-R-CHP (N=435)	R-CHOP (N=438)
Any-grade adverse events	426 (97.9)	431 (98.4)
Grade 3–4	251 (57.7)	252 (57.5)
Grade 5	13 (3.0)	10 (2.3)
Serious adverse events	148 (34.0)	134 (30.6)
Adverse events leading to:		
Discontinuation of any study drug	27 (6.2)	29 (6.6)
Polatuzumab vedotin / vincristine	19 (4.4)	22 (5.0)
Dose reduction of any study drug	40 (9.2)	57 (13.0)

Data cut-off: June 28, 2021.

Common adverse events



Data cut-off: June 28, 2021. Adverse events are Medical Dictionary for Regulatory Activities version 24.0 preferred terms; shown are all-grade adverse events occurring in ≥12% of patients in any treatment arm. *Peripheral neuropathy is defined by standard organ class group of preferred terms.

Conclusions

Pola-R-CHP significantly prolongs PFS compared with R-CHOP (HR 0.73) in patients with intermediate- and high-risk previously untreated DLBCL

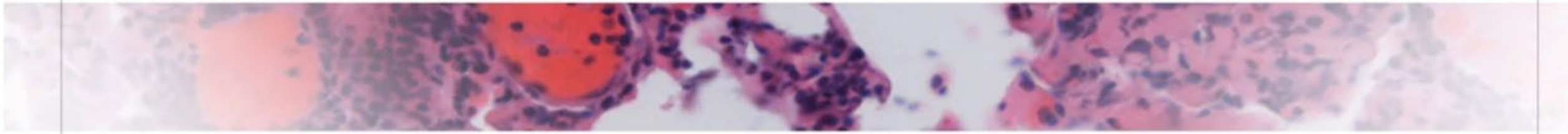
The **safety profiles** of Pola-R-CHP and R-CHOP were **comparable**

Exploratory analyses are ongoing with regards to various subgroups and other prognostic classification systems

These results **support the use of Pola-R-CHP** in the initial management of patients with DLBCL

American Society *of* Hematology

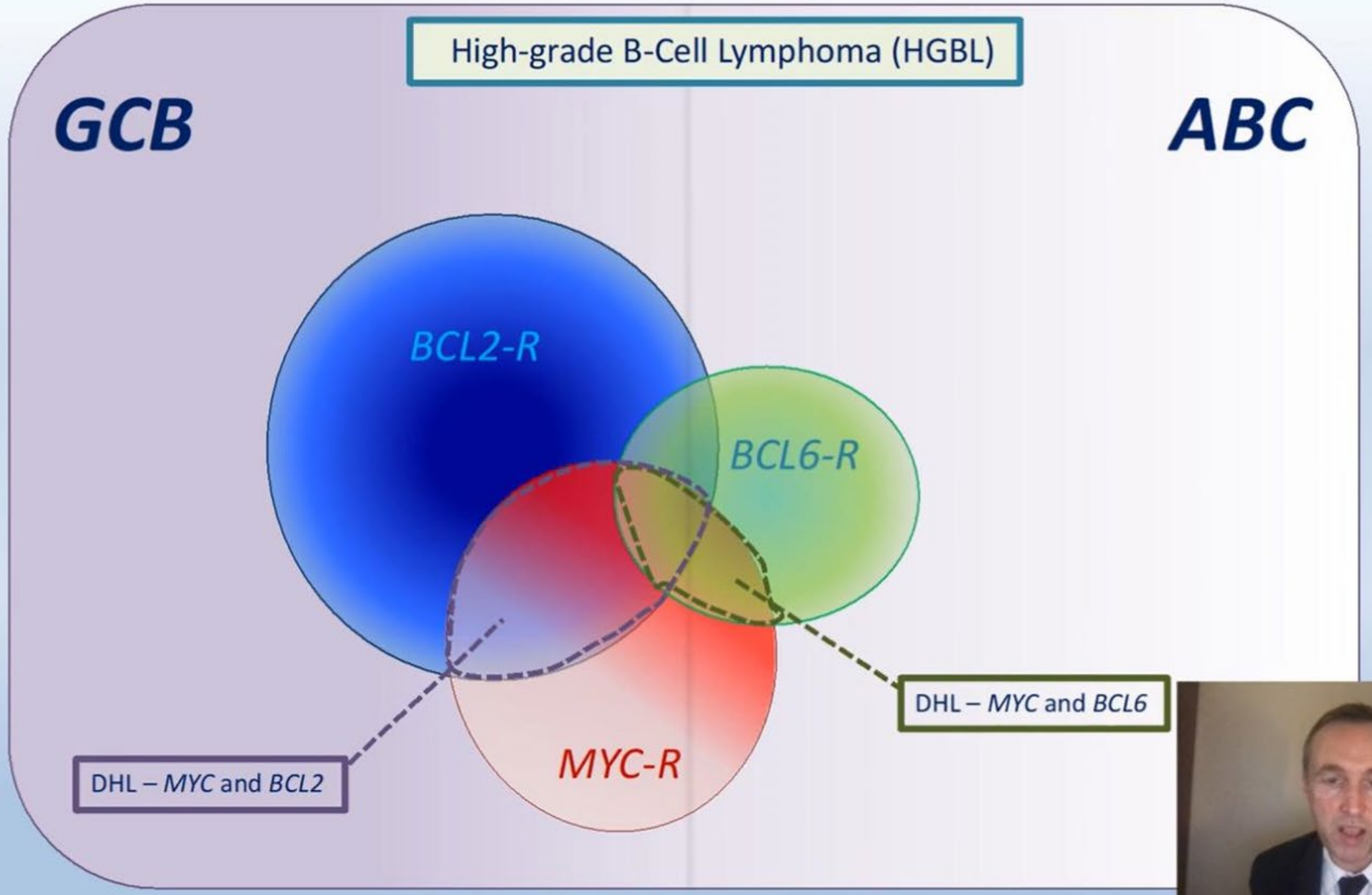
Helping hematologists conquer blood diseases worldwide

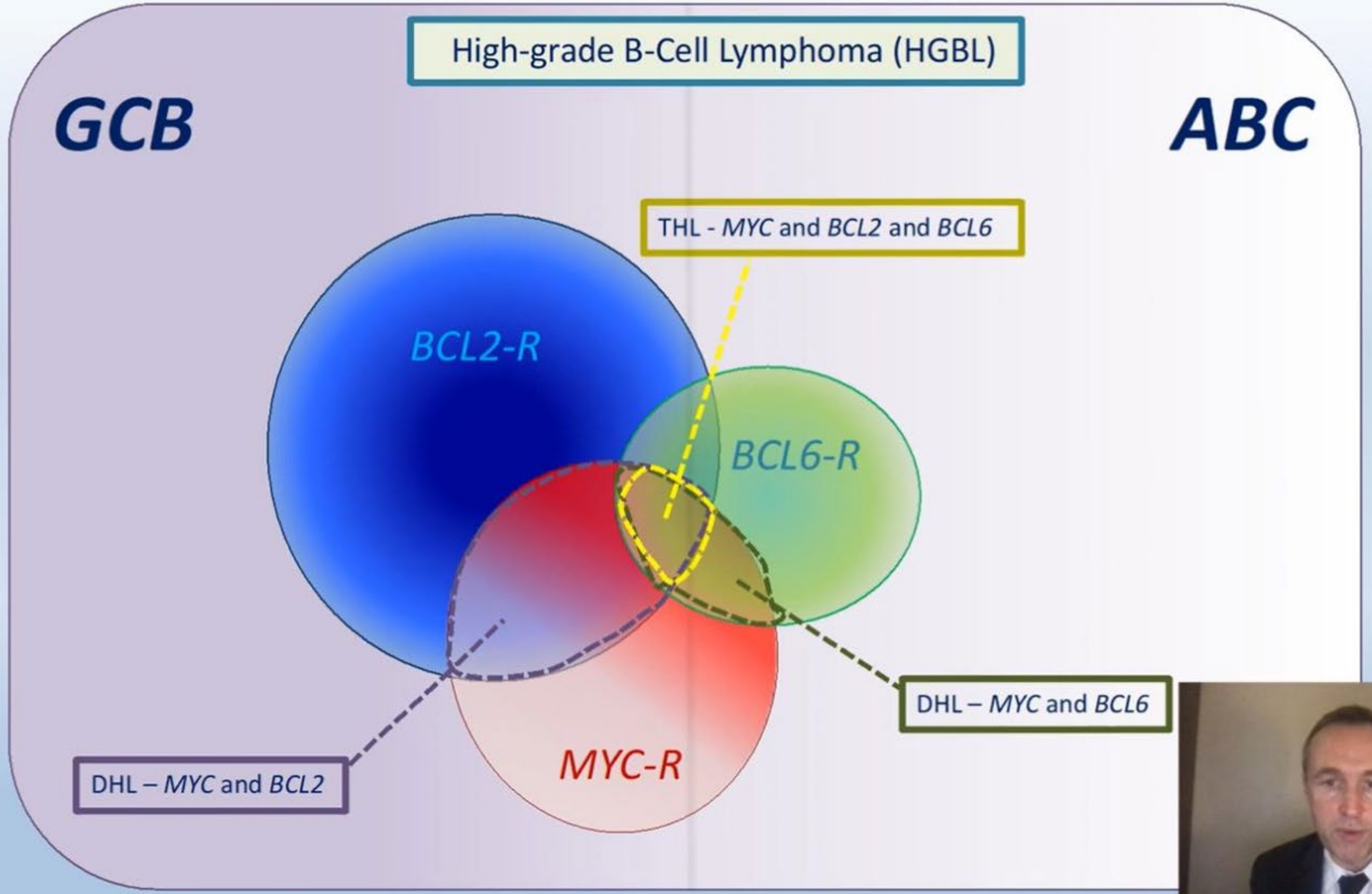


Double-Hit lymphoma – Optimizing therapy

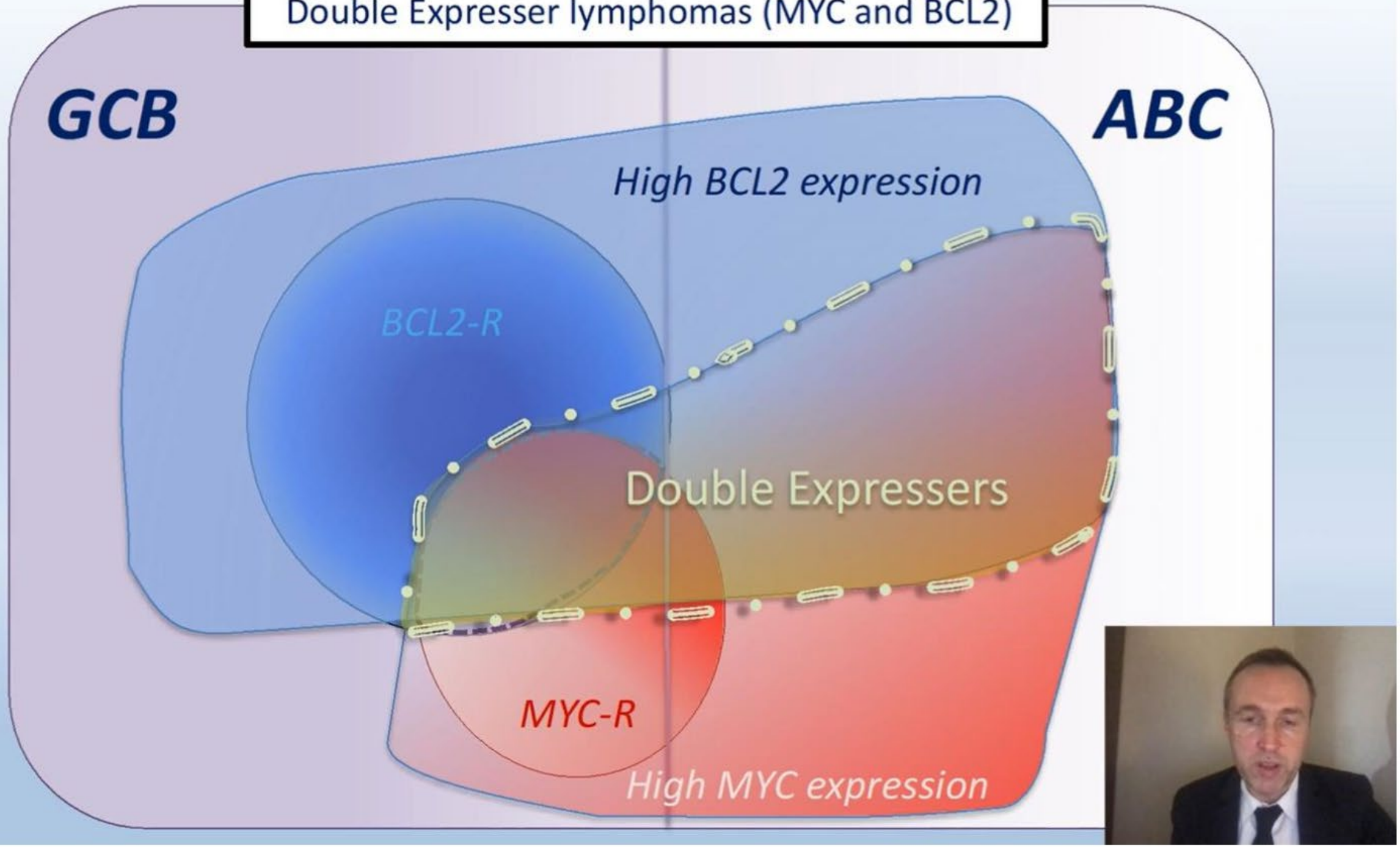
Kieron Dunleavy
Director of Hematology
Lombardi Cancer Center
Professor of Medicine
Georgetown University
Washington DC

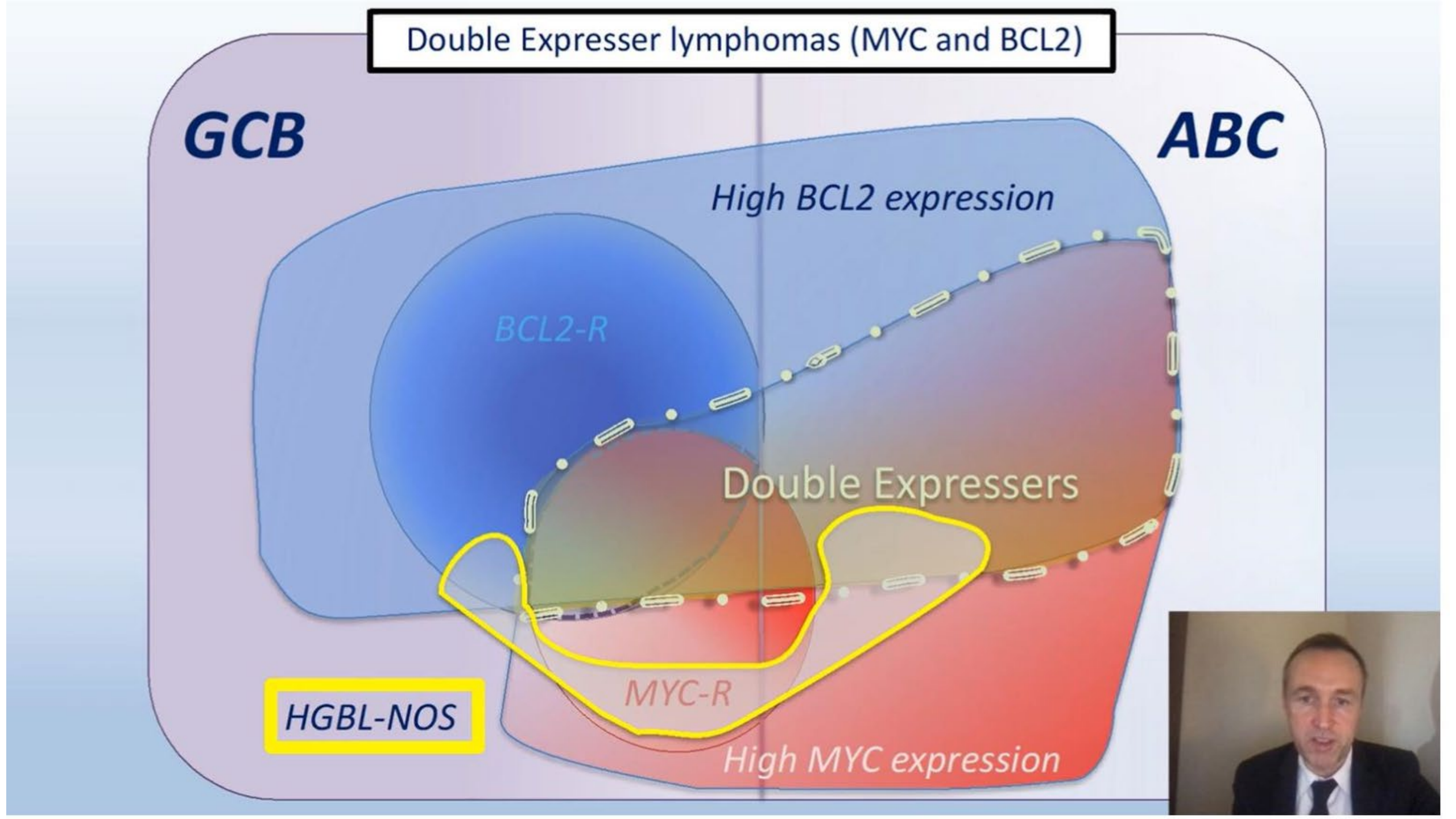
Georgetown | Lombardi
COMPREHENSIVE CANCER CENTER


High-grade B-Cell Lymphoma (HGBL)
GCB
ABC
BCL2-R
BCL6-R
MYC-R
DHL – MYC and BCL6
DHL – MYC and BCL2

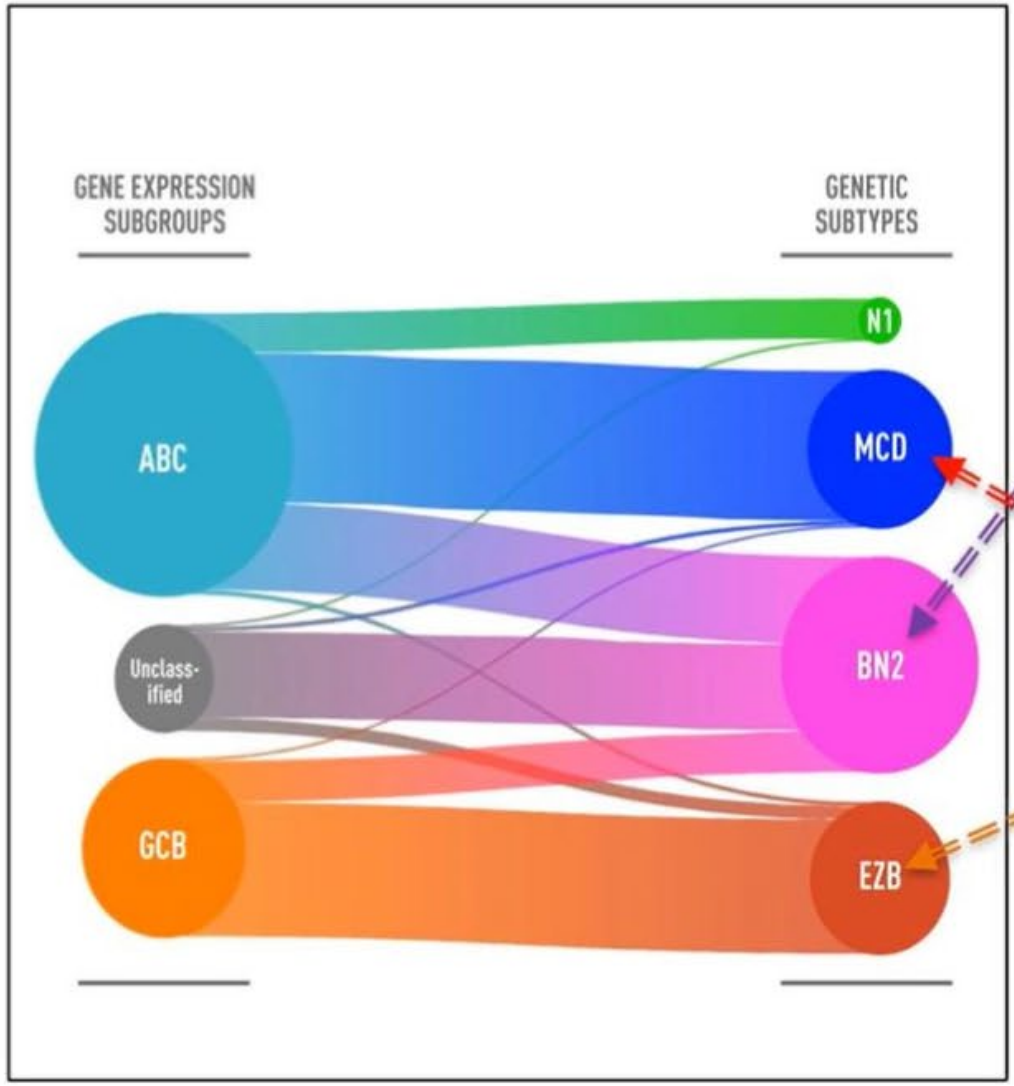

High-grade B-Cell Lymphoma (HGBL)
GCB
ABC
THL - MYC and BCL2 and BCL6
BCL2-R
BCL6-R
MYC-R
DHL – MYC and BCL6
DHL – MYC and BCL2

Double Expresser lymphomas (MYC and BCL2)




Double Expresser lymphomas (MYC and BCL2)
GCB
ABC
High BCL2 expression
BCL2-R
Double Expressers
MYC-R
HGBL-NOS
High MYC expression

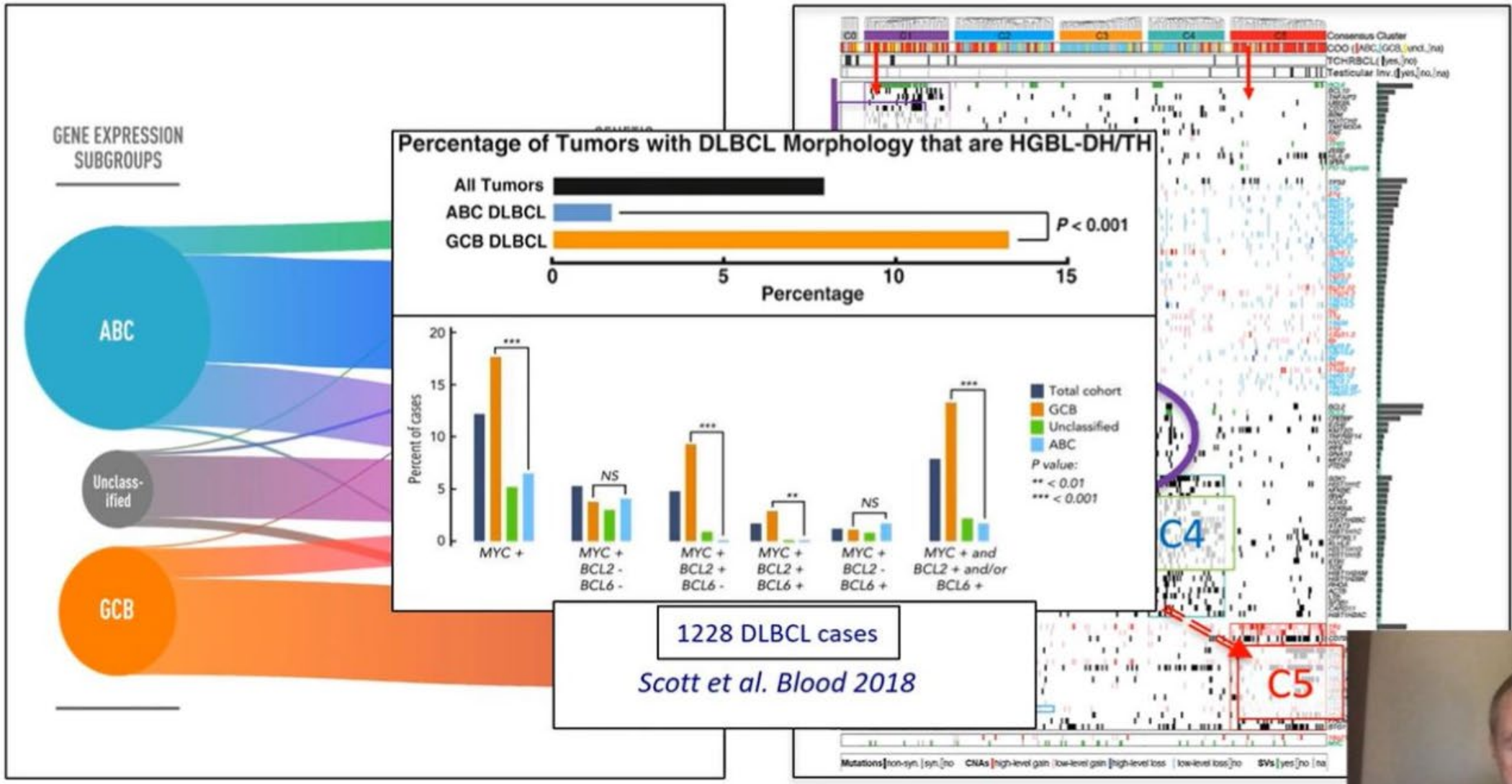
Genetic Subtypes of DLBCL



Wright et al. Cancer Cell 2020

Chapuy et al. Nature Medi

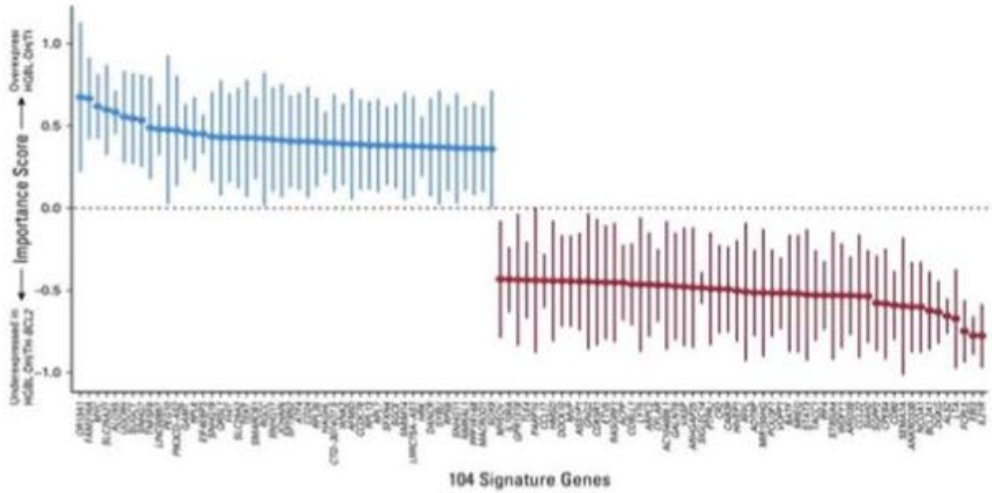
Genetic Subtypes of DLBCL

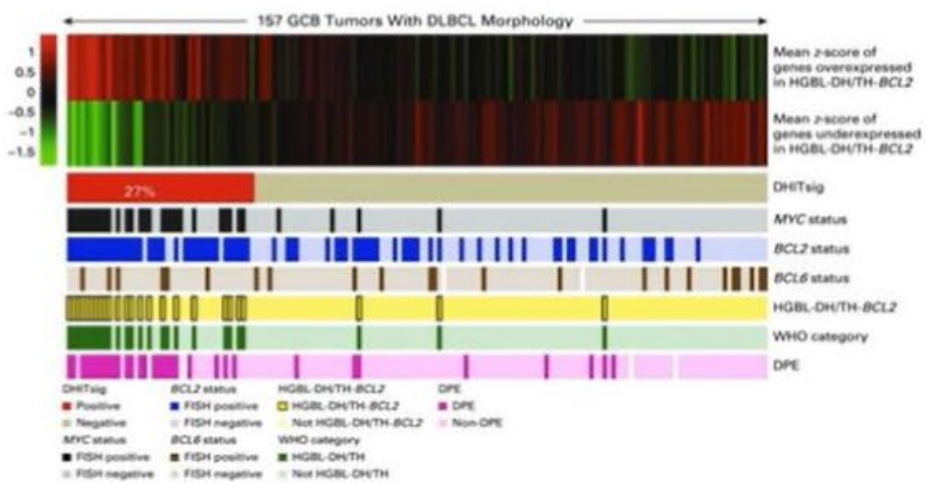


Wright et al. Cancer Cell 2020

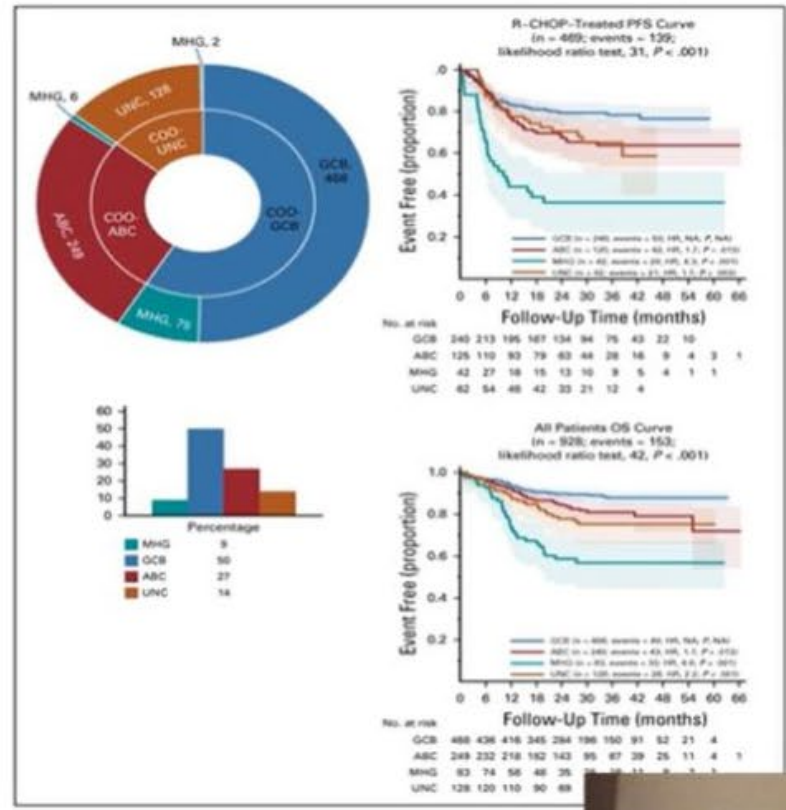
Chapuy et al. Nature Medi

‘Double-Hit’ and Molecular HG signatures





Ennishi et al. JCO 2019



928 cases

Sha et al. JCO

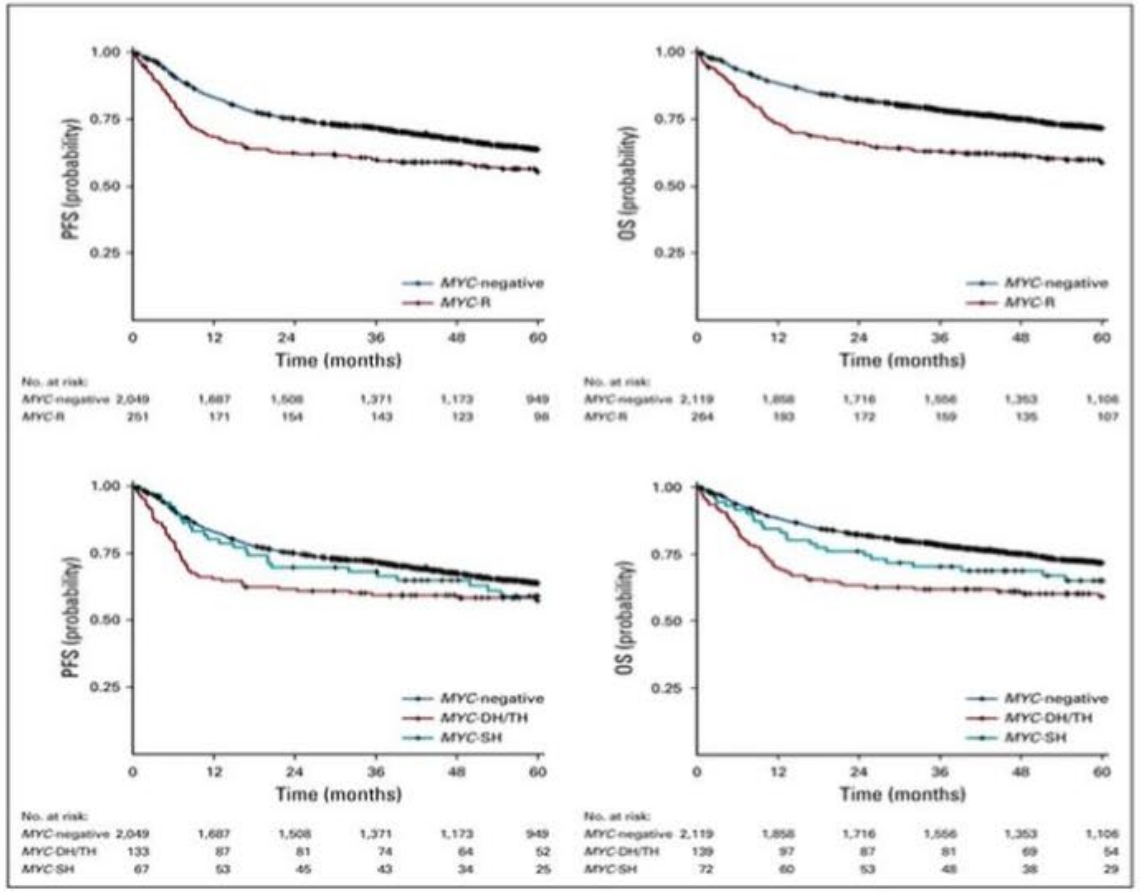
Optimal Approach to High Grade B-Cell Lymphoma

Study	N	Patient population/Study	Treatment	Outcome
Rosenwald et al. [13]	2383: (MYC-R in 11%)	DLBCL/HGBL Retrospective analysis of prospective and patient registry studies	R-CHOP	MYC-R was associated with shorted PFS and OS; Neg. prognostic impact of MYC-R only with BCL2 and/or BCL6 and an IG partner
Dunleavy et al. [14]	53	MYC-R Aggressive B-cell lymphoma. Prospective, single-arm, multicenter trial	DA-EPOCH-R	4-year EFS and OS were 71% and 77%; No difference for SH versus DH/THL
Chamuleau et al. [28]	82	MYC-R DLBCL. Prospective single-arm multicenter trial	R-CHOP + lenalidomide	2-year EFS and OS were 63% and 73%
Leppa et al. [16]	139	DLBCL. High IPI score/high-risk cohort. 12% had DHL. Prospective, single arm, multicenter trial.	Dose-dense chemo (MTX/R-CHOEP-14, ARA C	5-year FFS and OS were 74% and 83%. No significant worse outcome for DHL group.
McMillan et al. [15]	111	DLBCL. IPI 3-5. 12% had HGBL. Prospective study.	R-CODOX-M/R-IVAC	2-year PFS and OS were 68% and 76%. No worse outcome for HGBL.
Laude et al.[17]	160	All patients had HGBL. Retrospective study.	R-CHOP versus intensive chemotherapy	At 32 months, 2 and 4-year PFS were 40% and 28% for R-CHOP; 57% and 52% f therapy.

Prognostic Significance of *MYC* rearrangement

2383 patients
MYC-R in 264 (11%)
Received R-CHOP

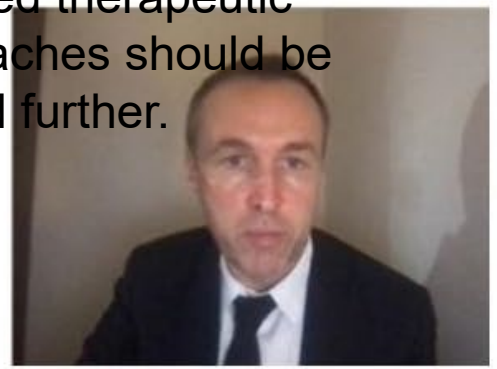
Lunenburg Lymphoma Biomarker Consortium



Rosenwald et al. JCO 2019

CONCLUSION

The negative prognostic impact of *MYC*-R in DLBCL is largely observed in patients with *MYC* double hit/triple-hit disease in which *MYC* is translocated to an IG partner, and this effect is restricted to the first 2 years after diagnosis. Our results suggest that diagnostic strategies should be adopted to identify this high-risk cohort, and risk-adjusted therapeutic approaches should be refined further.



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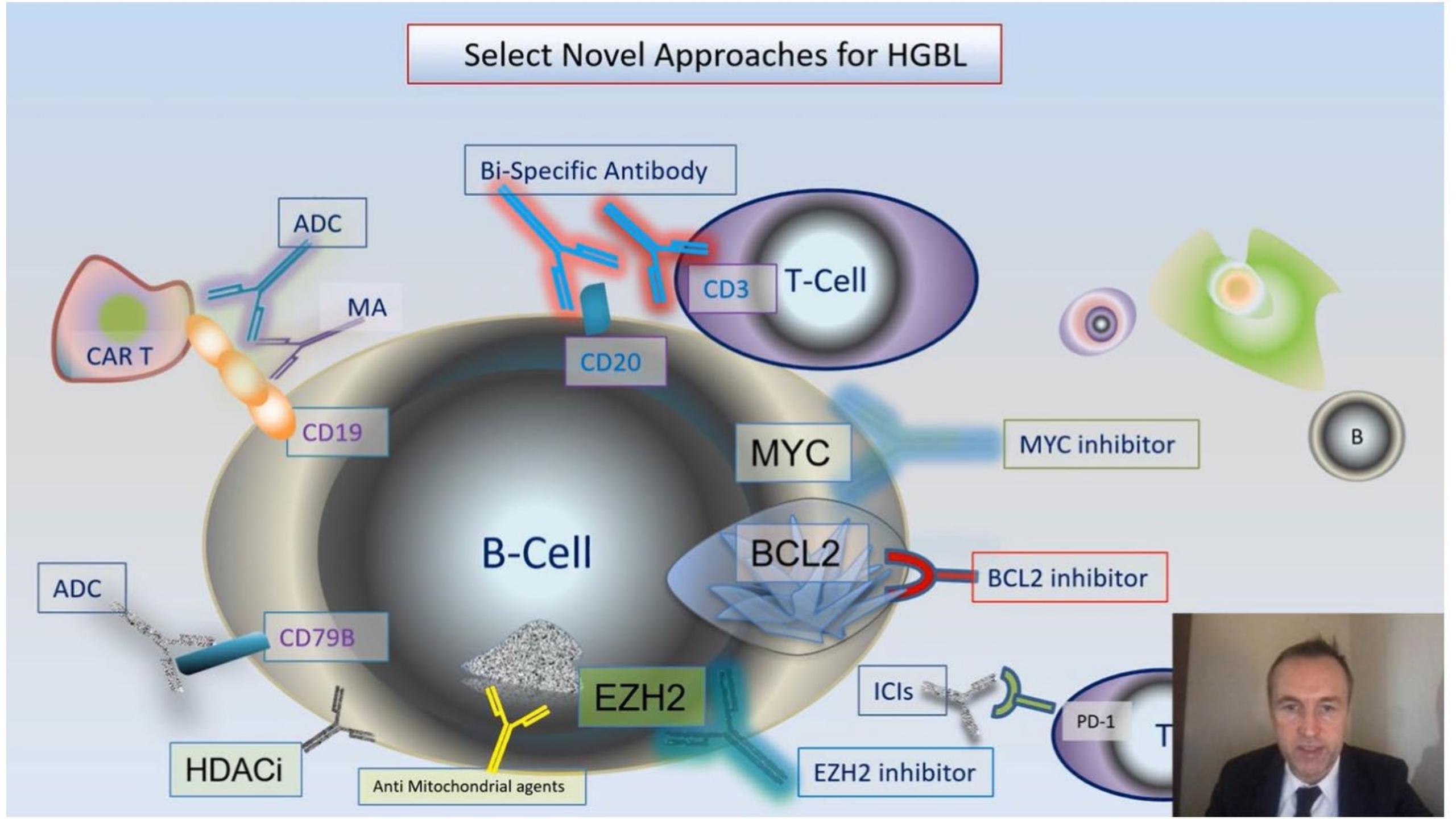
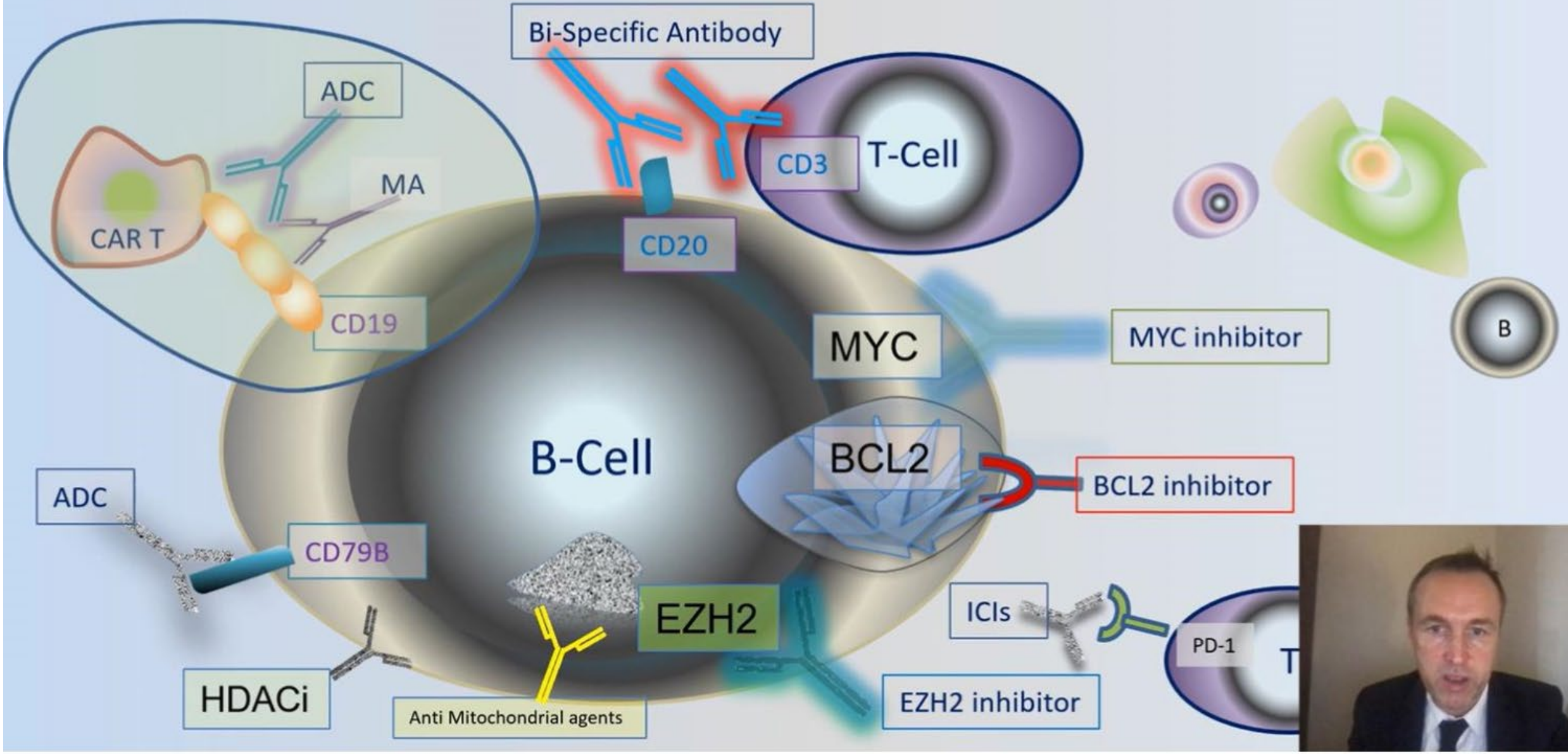
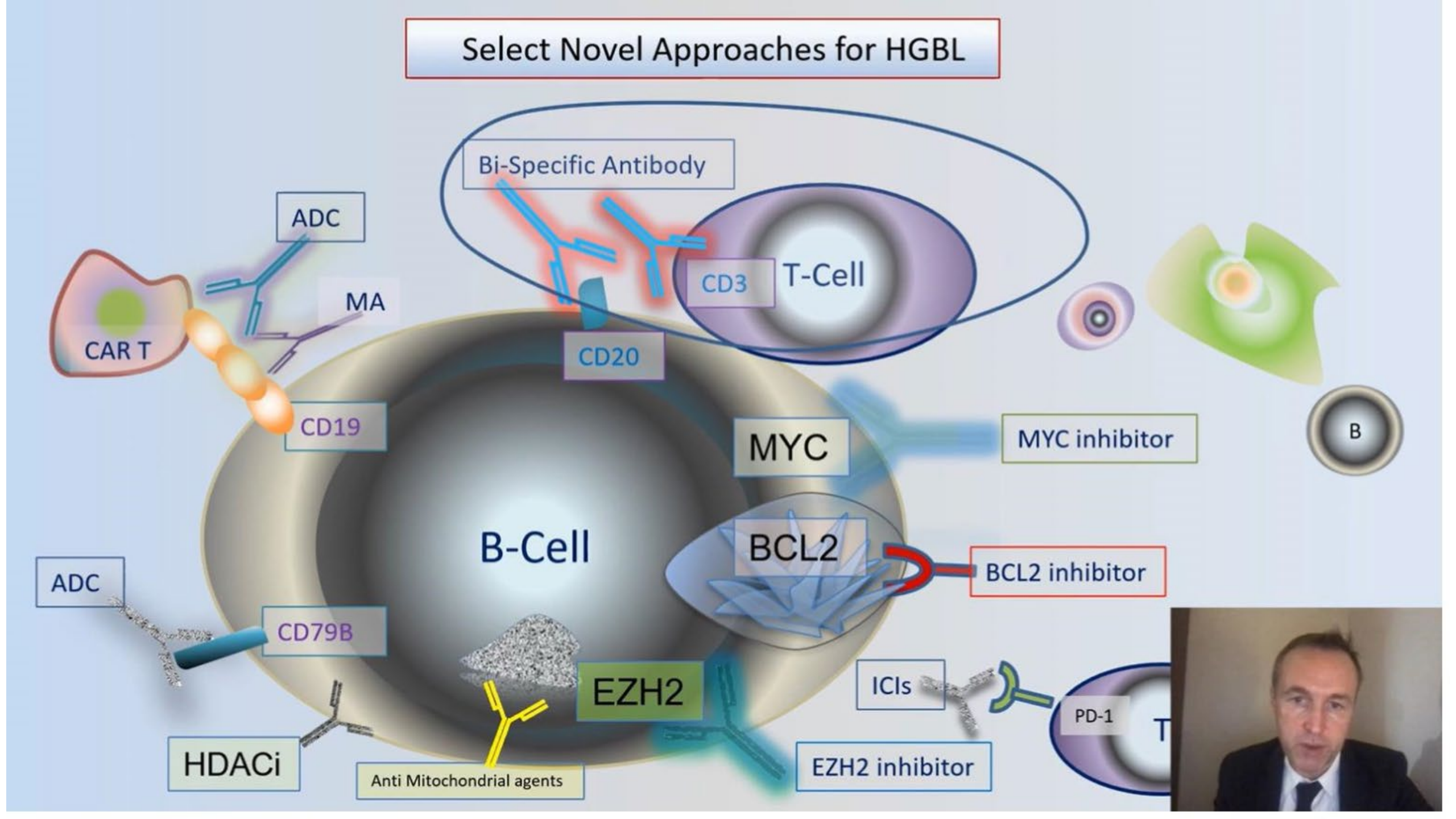
Approach to Relapsed/Refractory HGBL

Select Novel Approaches for HGBL

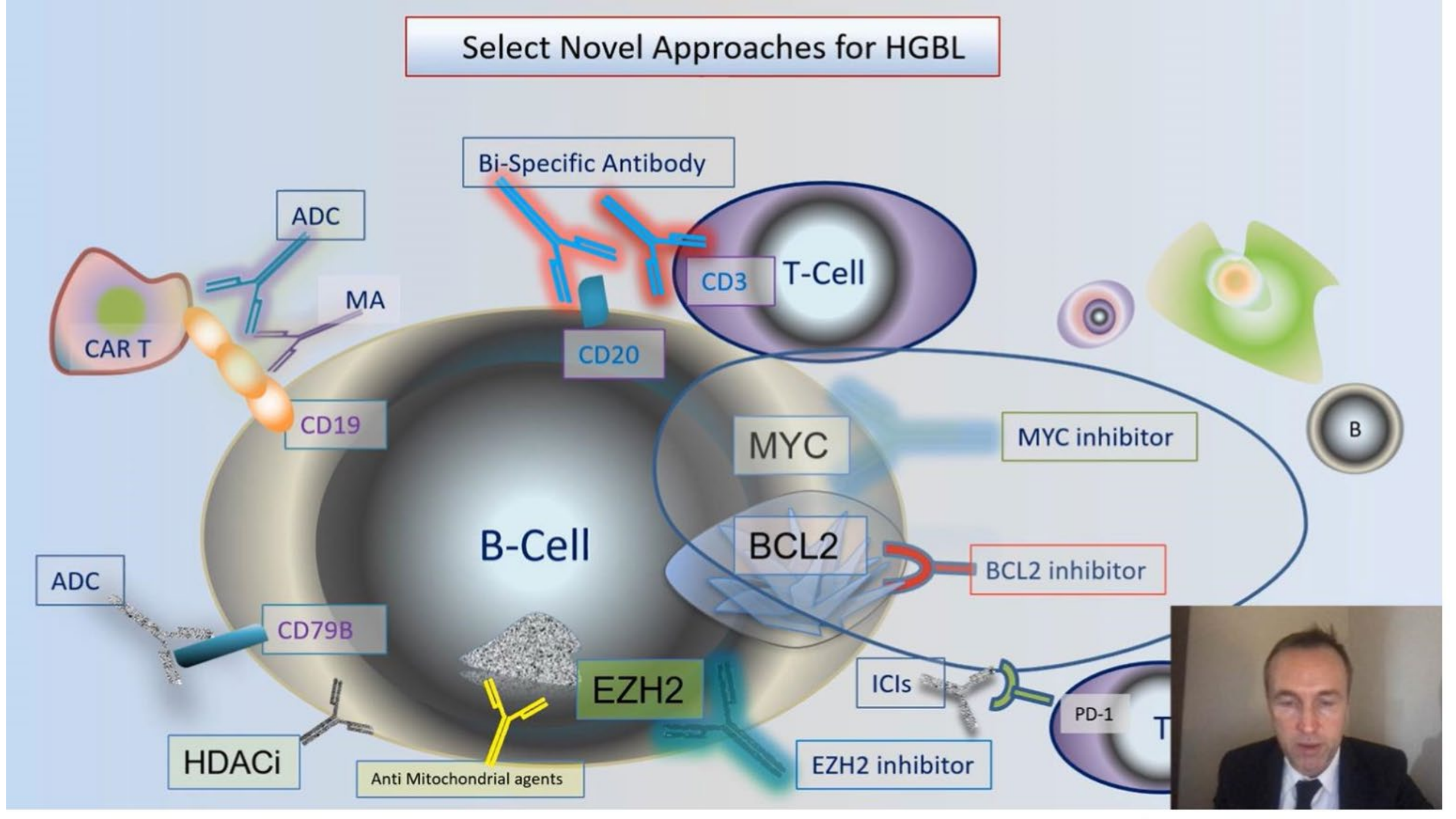


Select Novel Approaches for HGBL

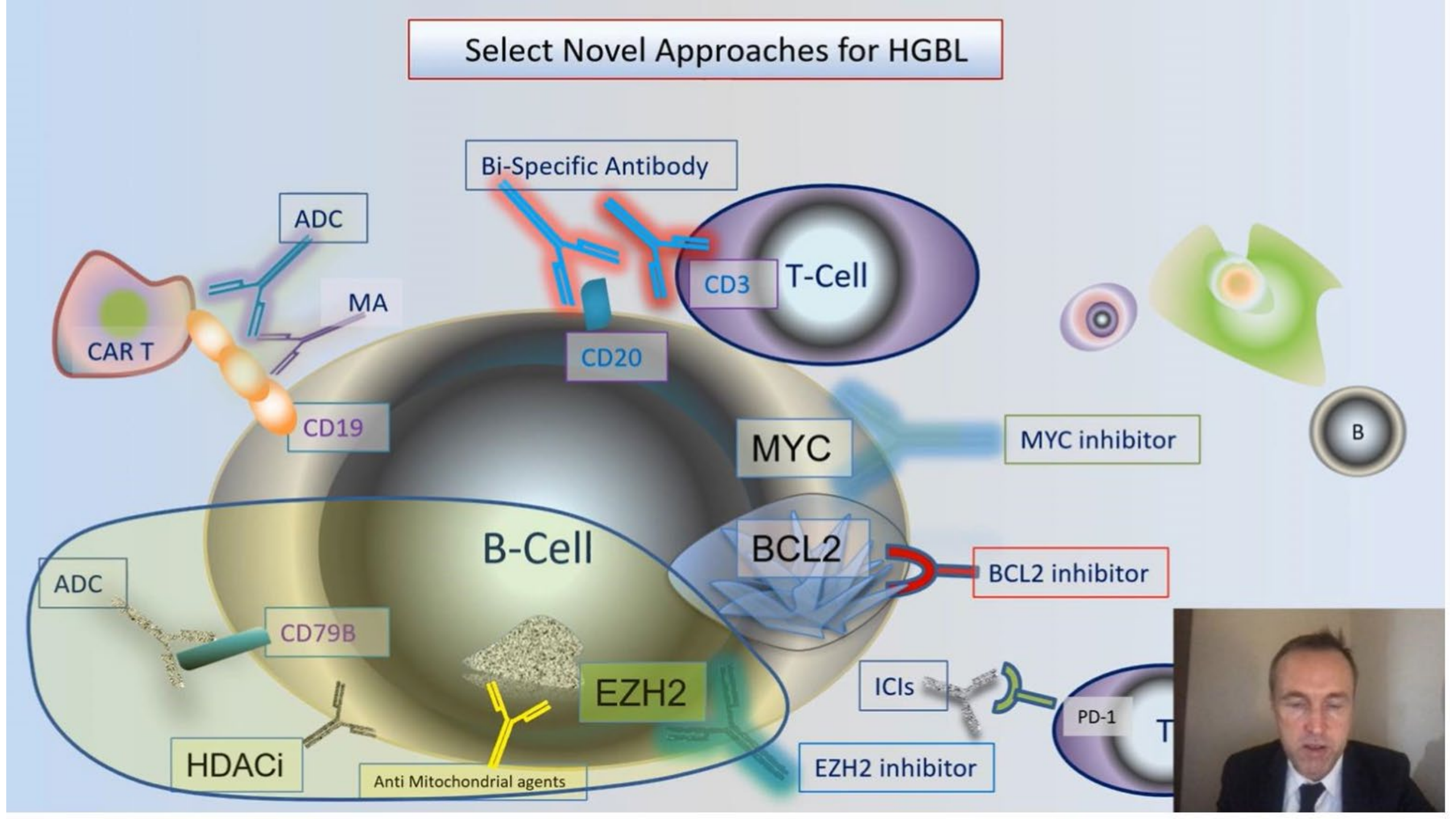


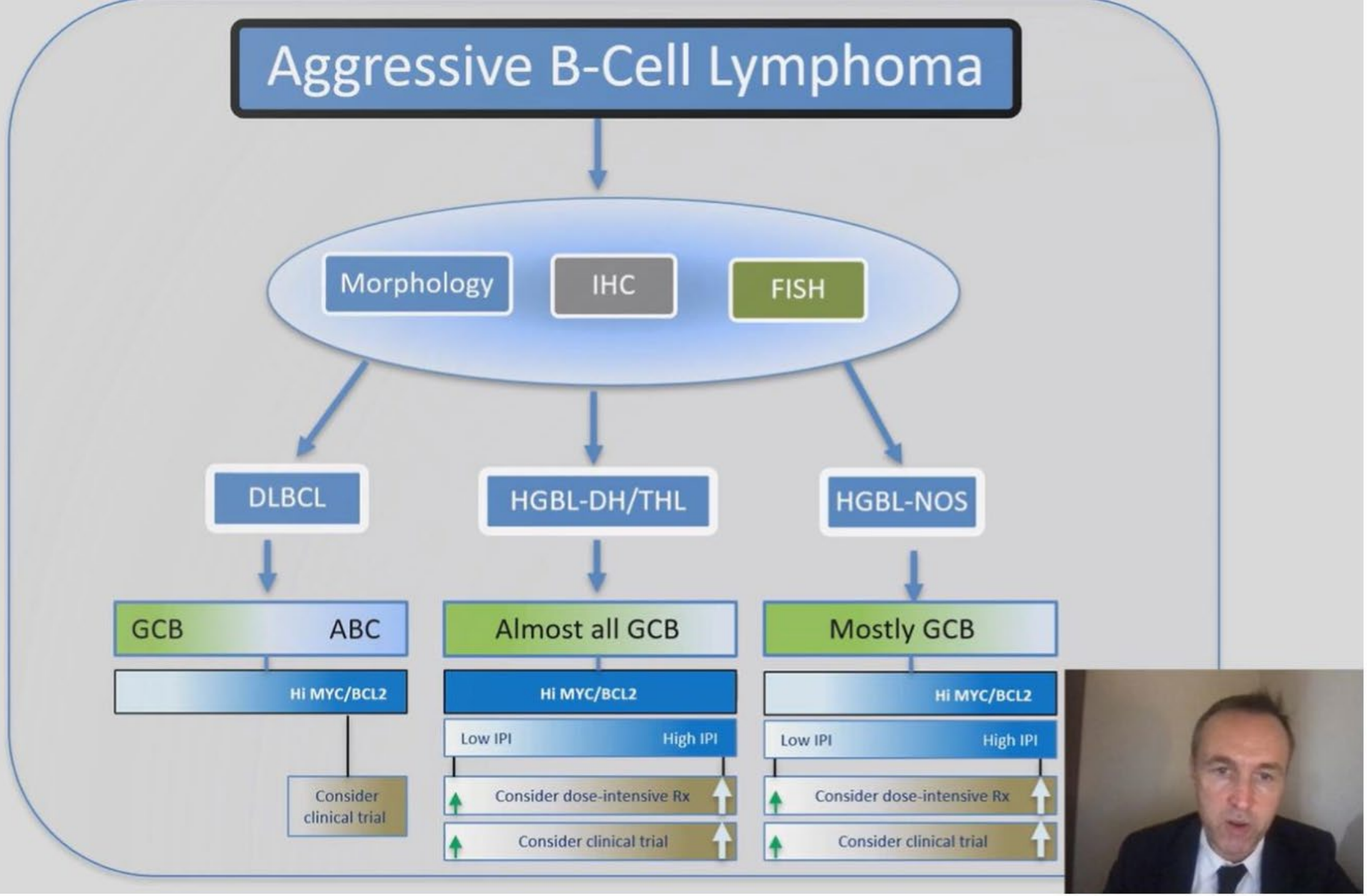

Select Novel Approaches for HGBL
Bi-Specific Antibody
ADC
CD3
T-Cell
MA
CAR T
CD20
CD19
MYC
MYC inhibitor
B
B-Cell
BCL2
BCL2 inhibitor
ADC
CD79B
EZH2
ICIs
PD-1
HDACi
Anti Mitochondrial agents
EZH2 inhibitor

Select Novel Approaches for HGBL



Select Novel Approaches for HGBL




Aggressive B-Cell Lymphoma
Morphology
IHC
FISH
DLBCL
HGBL-DH/THL
HGBL-NOS
GCB
ABC
Hi MYC/BCL2
Consider clinical trial
Almost all GCB
Hi MYC/BCL2
Low IPI
High IPI
Consider dose-intensive Rx
Consider clinical trial
Mostly GCB
Hi MYC/BCL2
Low IPI
High IPI
Consider dose-intensive Rx
Consider clinical trial

Alliance 051701: Randomized Phase II/III Study of DA-EPOCH-R ± Venetoclax in Patients With Previously Untreated Double-Hit Lymphoma

CCO Independent Conference Coverage Highlights*

of the *2021 ASH Annual Meeting, December 11-14, 2021*

Atlanta, Georgia

*CCO is an independent medical education company that provides state-of-the-art medical information to healthcare professionals through conference coverage and other educational programs.

Provided by Clinical Care Options, LLC

This program is supported by educational grants from AbbVie; AstraZeneca; Daiichi Sankyo, Inc.; GlaxoSmithKline; Incyte Corporation; Jazz Pharmaceuticals; Merck Sharp & Dohme Corp.; and Novartis Pharmaceuticals Corporation.

Alliance 051701: DHL Cohort Study Design

- Randomized, open-label phase II/III trial in cohort of patients with DHL (data cutoff: July 8, 2021)
  - DA-EPOCH-R + venetoclax safety signal led to early closure, data release on December 2, 2020

Adults with DHL,*
ECOG PS ≤2;
adequate organ function;
no known CNS involvement;
no uncontrolled HIV, HBV, HCV;
receipt of steroids, radiation, or single cycle of CT prior to enrolment allowed
(N = 73†)

DA-EPOCH-R +
Venetoclax 600 mg/day on
Days 4-8 of cycle 1; Days 1-5 of cycles 2-6
(n = 37)

DA-EPOCH-R
(n = 36)

Continue until PD, unacceptable toxicity or completion of 6 cycles

Follow-up for 10 yr or until death

Primary endpoint: PFS (phase II)

Abramson. ASH 2021. Abstr 523. NCT03984448.

Alliance 051701: Baseline Characteristics

Characteristic	DA-EPOCH-R + Venetoclax (n = 36)	DA-EPOCH-R (n = 30)
Median age, yr (range)	65 (41-80)	66 (37-79)
Female, n (%)	17 (47)	13 (43)
White, n (%)	33 (97)	26 (93)
Prior chemotherapy cycle, n (%)	20 (56)	18 (60)
Ann Arbor stage, n (%)		
▪ I/II	5 (14)	4 (13)
▪ III/IV	31 (86)	26 (87)
Elevated LDH, n (%)	22 (61)	16 (53)
IPI, n (%)		
▪ Low/low intermediate	13 (36)	11 (37)
▪ High intermediate/high	23 (64)	19 (63)
FISH abnormality, n (%)		
▪ *MYC/BCL2*	22 (63)	20 (67)
▪ *MYC/BCL6*	4 (12)	0
▪ *MYC/BCL2/BCL6*	9 (26)	10 (33)

Abramson. ASH 2021. Abstr 523.

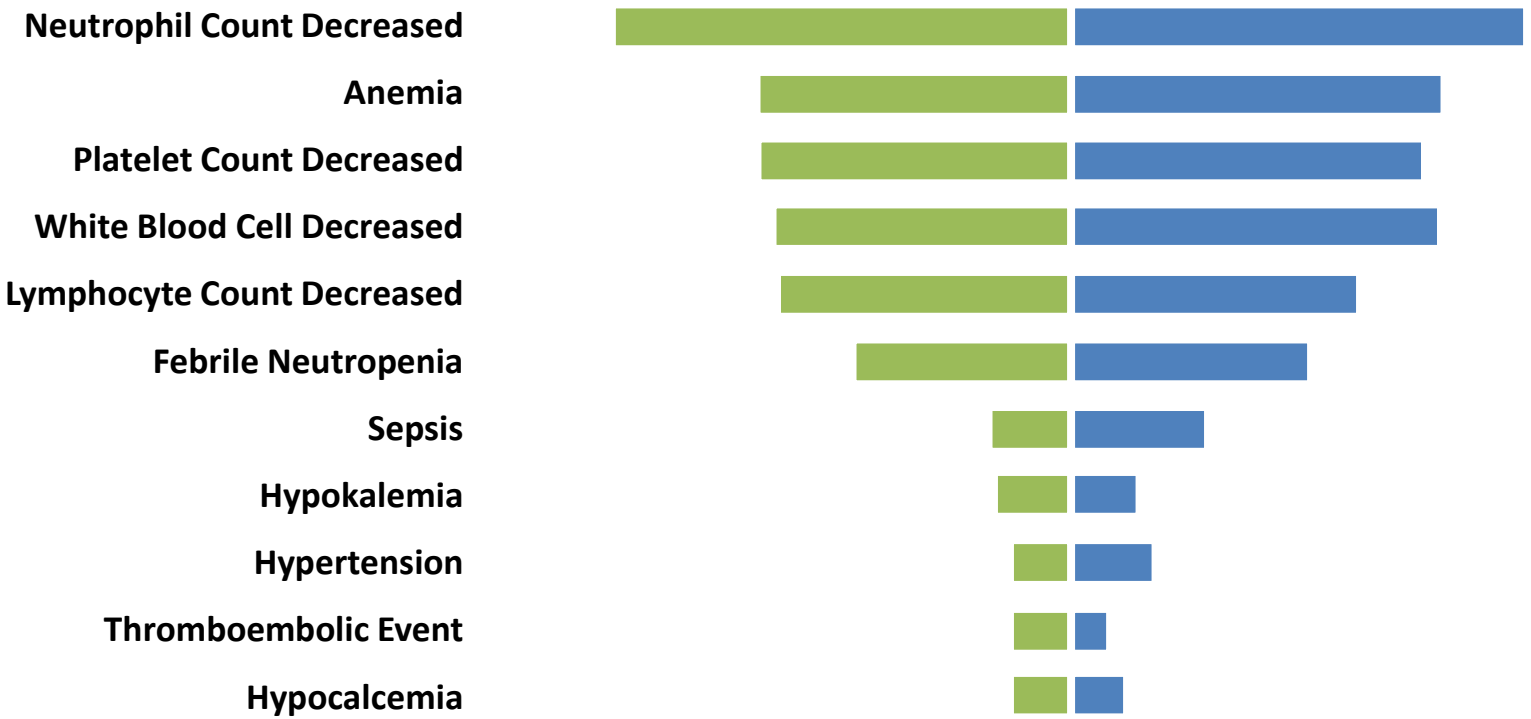
Slide credit: clinicaloptions.com

Alliance 051701: Treatment Administered

Parameter	DA-EPOCH-R + Venetoclax (n = 35)	DA-EPOCH-R (n = 30)
Completed treatment, n (%)	17 (49)	21 (70)
Median number of cycles, n (IQR)	6 (3-6)	6 (5-6)
Dose reduction for any agent/venetoclax, n (%)	21 (60)/12 (34)	19 (63)
Dose omission for any agent/venetoclax, n (%)	10 (29)/9 (26)	3 (10)
Dose delay for any agent/venetoclax, n (%)	5 (14)/3 (9)	5 (17)
DA-EPOCH-R dose escalation, n (%)	8 (22)	21 (70)
DA-EPOCH-R dose reduction by 1 level, n (%)	13 (36)	5 (17)
DA-EPOCH-R dose reduction by 2 levels, n (%)	5 (14)	2 (7)

Abramson. ASH 2021. Abstr 523.

Alliance 051701: Safety

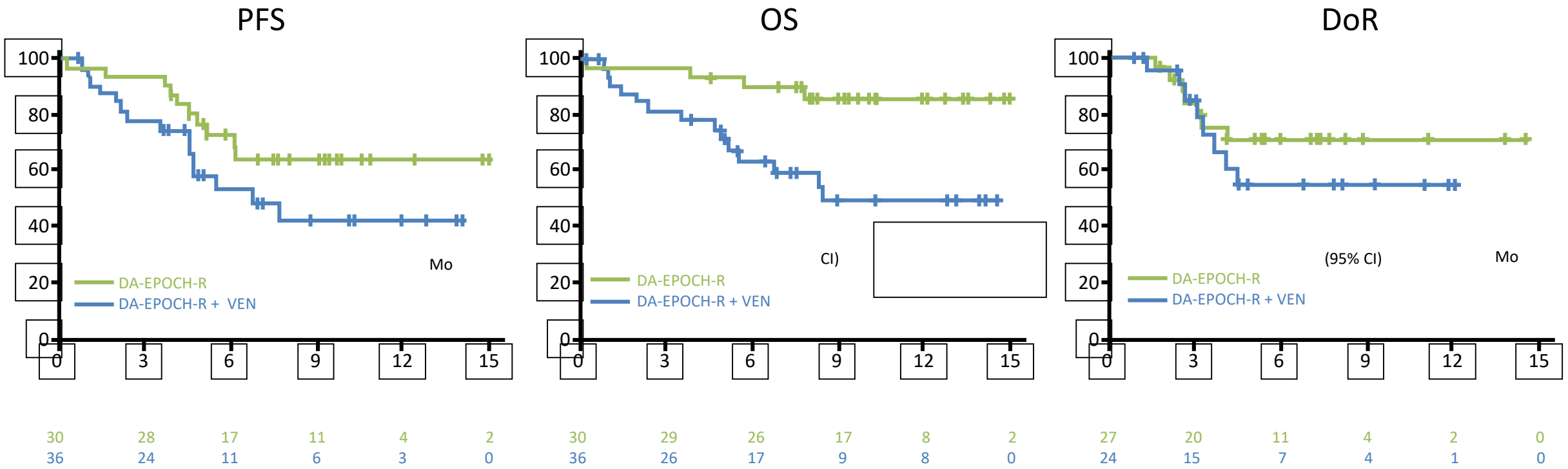


- Grade 5 AEs on or ≤30 days after treatment: 3.3% (1/30) with DA-EPOCH-R* vs 17.1% (6/35) with **DA-EPOCH-R plus venetoclax†**

1 each, dyspnea, sepsis. †n = 5, sepsis; n = 2, cardiac arrest; n = 1 each, lung infection, hypoxia, COVID-19.

Abramson. ASH 2021. Abstr 523. Reproduced with permission.

Alliance 051701: Efficacy Outcomes



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Alliance 051701: Conclusions

- In Alliance 051701, the addition of venetoclax to DA-EPOCH-R was associated with excess treatment-related toxicity and mortality, triggering early closure of the DHL cohort
- However, investigators concluded that DA-EPOCH-R performed well as a control arm with limited follow-up
  - Furthermore, study demonstrated feasibility of conducting prospective cooperative group trials in setting of DHL
- Dual expressing lymphoma cohort receiving R-CHOP ± venetoclax of Alliance 051701 has completed phase II accrual

Abramson. ASH 2021. Abstr 523.

HOVON-152 Phase II Trial

Jonge et al. ASH 2021 Abstract #1414

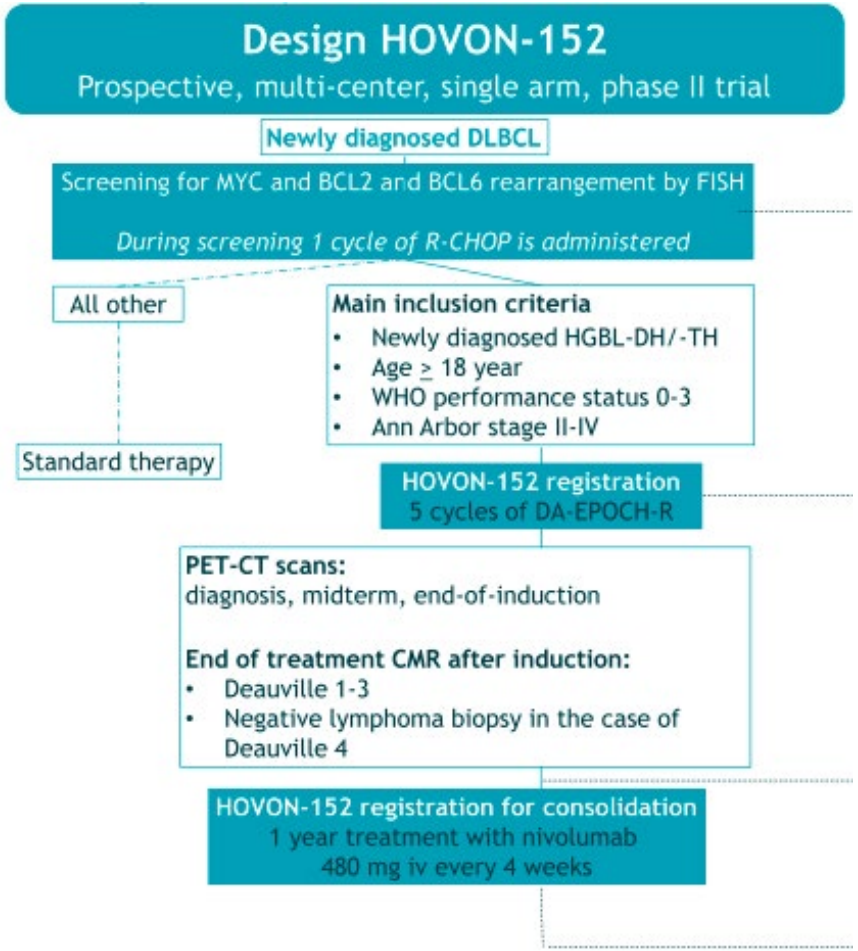
HGBCL with MYC and/or BCL6 rearrangements treated ith DA-EPOCH-R induction and Nivolumab consolidation

HOVON152 - Background

- Prognosis is poor in DH/TH lymphoma with R-CHOP
- OS improvement is not proven with DA-EPOCH-R
- Tumors overexpressing MYC may be susceptible for immune checkpoint inhibitors (CI)
- Rationale for CI after reaching CMR to improve tumor immune surveillance for MRD

Jonge et al. ASH 2021 Abstract #1414

HOVON152 - Objectives & Design



Total (no, %)	33	(100%)
Sex (no, %)		
Male	20	(61%)
Female	13	(39%)
Age (years)		
Median (IQR)	61	53-66
WHO performance status (no, %)		
0	19	(58%)
1	11	(33%)
2	3	(9%)
Ann Arbor Stage (no, %)		
II	4	(12%)
III	7	(21%)
IV	22	(67%)
International Prognostic Index score (no, %)		
0-1	7	(21%)
2	13	(39%)
3	10	(30%)
4-5	3	(9%)
Time from diagnosis to start treatment (days)		
Median (IQR)	9	8-22
Pathology central review Morphology (no, %)		
DLBCL	25	(76%)
Blastoid/intermediate	5	(15%)
Insufficient tissue quality for morphological assessment	3	(9%)
Pathology central review Rearrangements (no, %)		
DH (BCL2)	25	(76%)
DH (BCL6)	3	(9%)
TH	5	(15%)

- Improve of 12-months DFS with nivolumab consolidation from 70% to 85% in patients with CMR
- Evaluate CMR rates, OS and Safety
- Explore biomarkers of response

Jonge et al. ASH 2021 Abstract #1414

HOVON152 - Results & Conclusion

Enrollment
From 2018 to 2021,
69 of 97 patients have been enrolled
33 patients were included for interim analysis

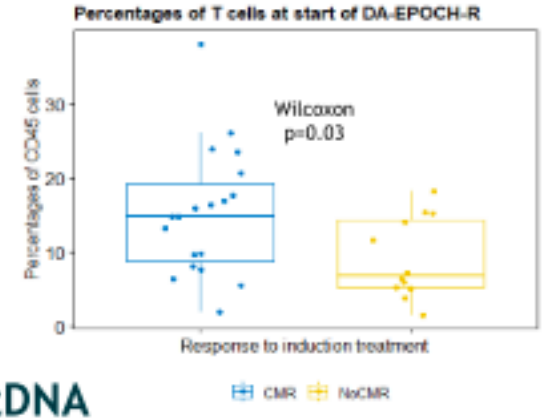
Toxicities during DA-EPOCH-R
Grade 5 AE (sepsis): 1 patient (3%)
Grade 4 AE: 9 patients (27%)
Grade 3 AE: 9 patients (27%)

Neurotoxicity led to dose adjustments or discontinuation of vincristine in 52% of the patients. In an amendment the vincristine dose was capped at 2 mg/cycle.

CMR achievement
20/33 patients reached CMR (61%; 95% CI 42-77%) and continued with Nivolumab consolidation
11/33 patients did not reach CMR (33%)
2/33 patients went off protocol due to progression

Toxicities during Nivolumab
Grade 4 AE: 1 patients
Grade 3 AE: 2 patients

- **T cells**



- **ctDNA**

N= 16 ctDNA analysis possible

10/16 patients achieved CMR

9/10 CMR patients were MRD neg at midterm
1/10 CMR patient was MRD pos at midterm and relapsed shortly after

6/16 patients did not achieve CMR
4 patients were MRD positive

N= 12 no clone detectable for monitoring

- 61% of patients achieve CMR with DA-EPOCH-R
  - Toxicity mainly due to neurotoxicity
  - 1 death due to sepsis (3%)
- Nivolumab consolidation is safe
  - Only one patient went off protocol due to colitis
- Ct-DNA based MRD negativity at midterm and higher T cell percentages after 1 cycle of R-CHOP.

Jonge et al. ASH 2021 Abstract #1414

American Society of Hematology
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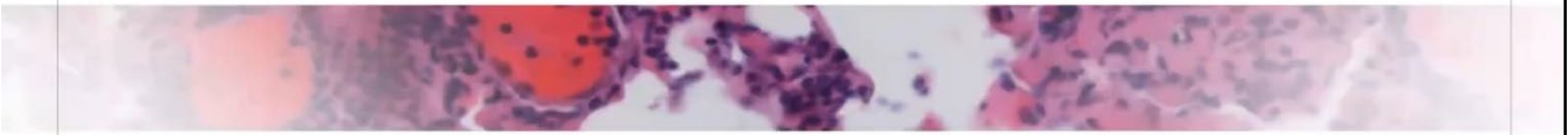


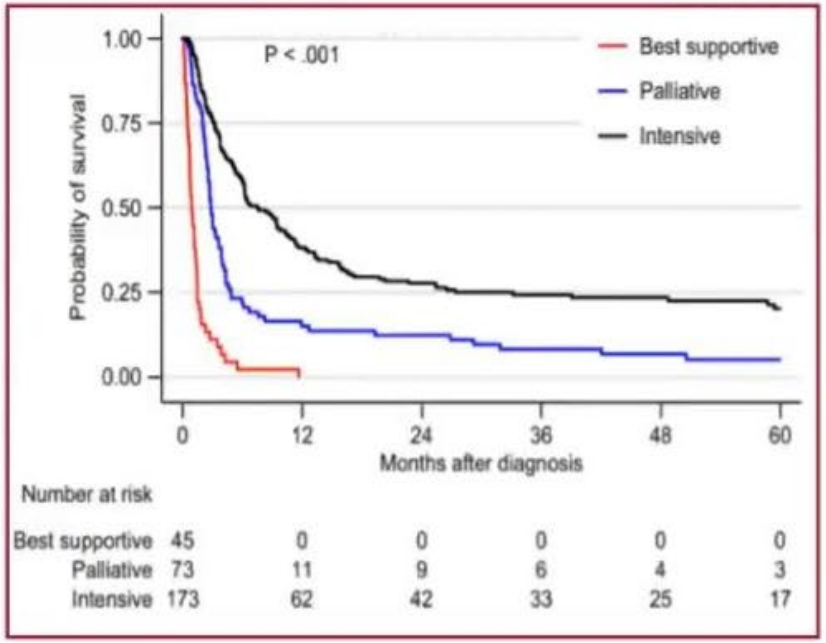
High-Dose Methotrexate is Not Associated with Reduction in CNS Relapse in Patients with Aggressive B-Cell Lymphoma: an International Retrospective Study of 2300 High-Risk Patients

K Lewis, L Jakobsen, D Villa, S Bobillo, K Smedby, K Savage, TA Eyre, K Cwynarski, P Caporn, J Van Zyl, M Klanova, M Trněny, R Puckrin, D Stewart, M Bishton, C Fox, A Tun, G Thanarajasingam, F Djebbari, E Joffe, S Eloranta, S Harrysson, L Sehn, S Maliske, K Poonsombudlert, X Guo, G Hapgood, K Manos, E Hawkes, J Khwaja, A Minson, M Dickinson, A Øvlisen, G Gregory, M Gilbertson, I Streit, H Scott, M Ku, S de Mel, KY Yong, L Xin, M Mokoonlall, D Talaulikar, N McVilly, A Johnston, M Brunner, P Pophali, M Maurer, TC El-Galaly*, CY Cheah*

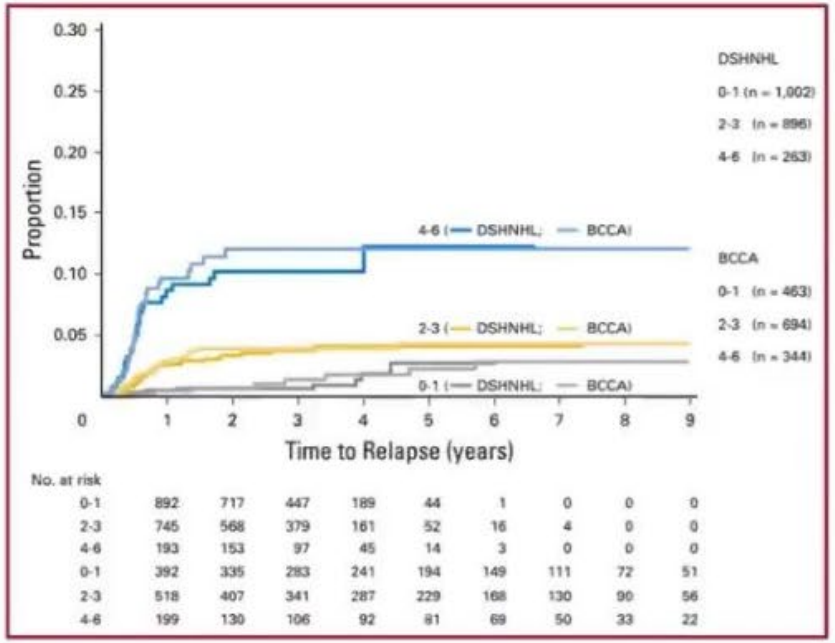
*joint senior author

Background

- Central Nervous System relapse (CNS relapse) is an uncommon but devastating complication of aggressive B-cell lymphoma



Survival after CNS relapse[1]



CNS relapse risk by CNS-IPI[2]

[1] El Galaly *et al*, *Eur J* Can 2017, [2]Schmitz *et al*, *JCO* 2016

Aim

- To determine whether systemic methotrexate is effective at preventing CNS relapse in patients with aggressive B-cell lymphoma and high risk of CNS relapse according to currently used risk classifications

Methods

- Multicentre, retrospective study, 21 sites
- Chart/registry review - consecutively diagnosed patients 2000-2020.

- To detect reduction in CNS relapse rate from 10% to 5%, α 0.05
  → 1300 patients (650 no HD-MTX; 650 HD-MTX)

Definitions

- HD-MTX = at least one cycle of intravenous methotrexate at any dose

- R-CHOP-like therapy = R-CHOP, R-CEOP, G-CHOP.

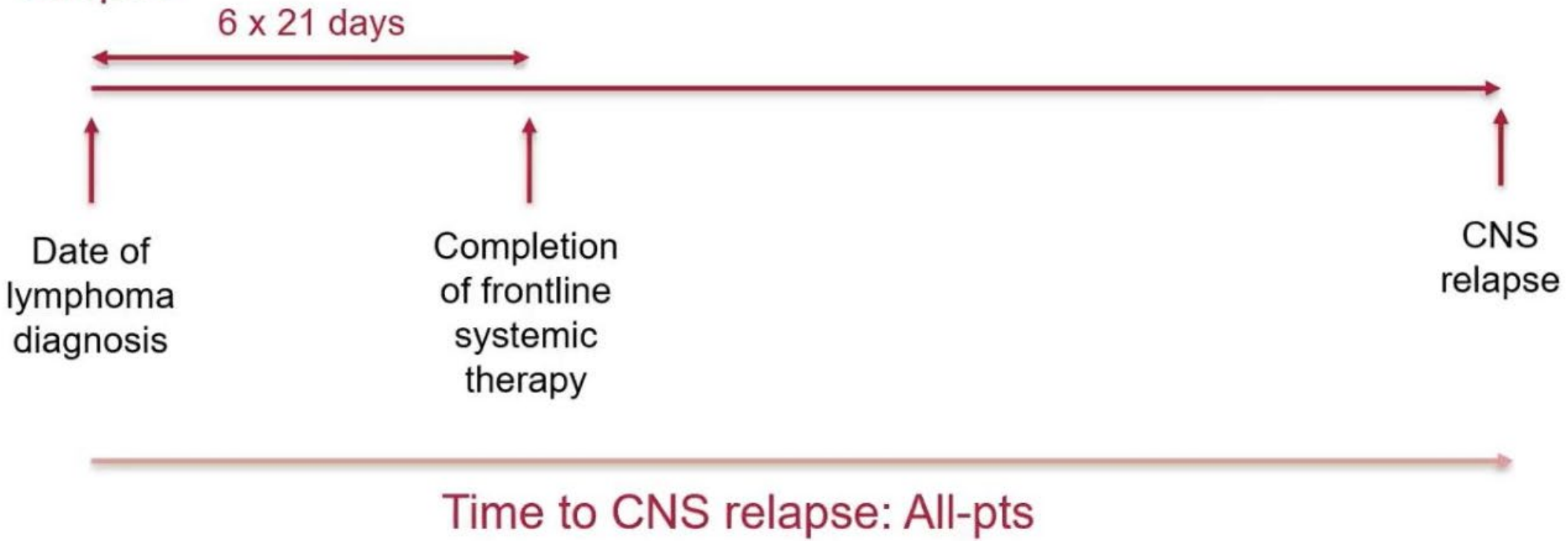
Eligibility criteria

Inclusion	Exclusion
• DLBCL with CNS-IPI 4-6 OR • HGBL with rearrangements of *MYC* + *BCL2* and/or *BCL6* OR • Primary breast/testicular DLBCL • 18-80 years • Curative intent anti-CD20 based chemoimmunotherapy • Biopsy proven transformed indolent B-NHL (treatment naïve) • HIV associated DLBCL	• CNS involvement by lymphoma at diagnosis* • PMBCL • Transformed NLPHD • PTLD • Clinical suspicion high grade transformation of low grade lymphoma • Previously treated transformed indolent lymphoma

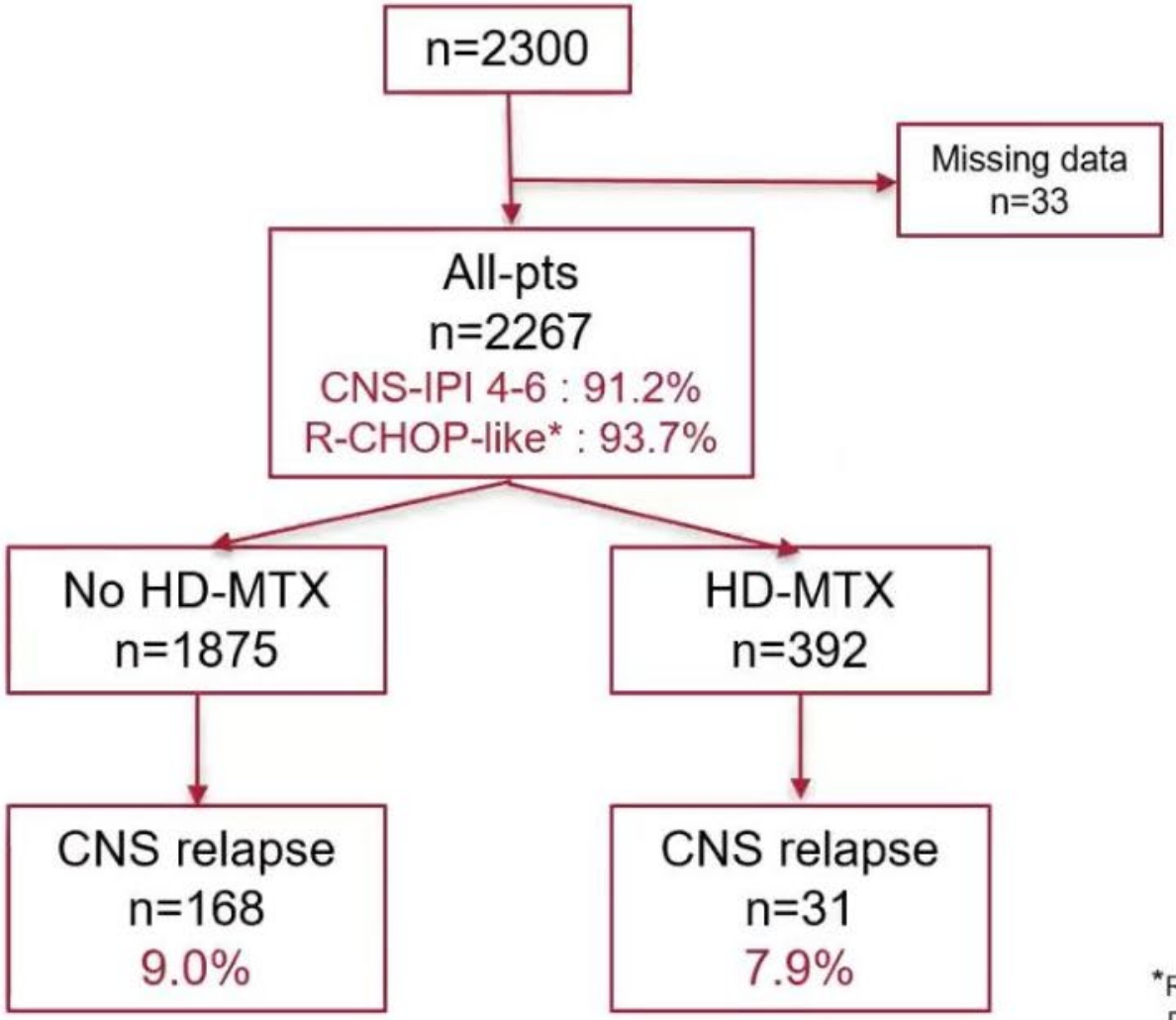
* Investigations to rule out CNS involvement not required for enrolment

Methods

- CNS relapse events were included if present as a feature of first lymphoma relapse



Results – All-pts (n=2267)



Median follow up :
5.8 years (0.0-19.1)

*R-CHOP-like = R-CHOP, G-CHOP, R-CEOP.
Remaining 6.3% received DA-EPOCH-R.

Baseline demographics

Factor	All-pts (n=2267)	
n (%)	No HD-MTX (n=1875)	HD-MTX (n=392)
Diagnosis		
-DLBCL	1751 (93.4)	352 (89.8)
-HGBL with (MYC/BCL2/BCL6)	124 (6.6)	40 (10.2)
Age, median (range)	68 (18-80)	65 (19-80)
Age group, n(%)		
-18-60 years	334 (17.8)	109 (27.8)
-61-80 years	1541 (82.2)	283 (72.2)
Sex, n(%)		
-Male	978 (52.2)	237(60.5)
-Female	897 (47.8)	155 (39.5)
Stage, n(%)		
-I-II	65 (3.5)	4 (1.0)
-III-IV	1810 (96.5)	388 (99.0)
ECOG, n(%)		
-0-1	659 (35.3)	226 (58.1)
2-4	1208 (64.7)	163 (41.9)
B-symptoms, n(%)	1019 (55.2)	219 (56.4)
LDH elevated, n(%)	1664 (89.5)	346 (88.9)
Extranodal sites, n(%)		
-0-1	565 (30.1)	57 (14.5)
-≥2	1309 (69.9)	335 (85.5)

Baseline characteristics

Factor	All-pts (n=2300)		CR-pts (n=1455)	
n (%)	No HD-MTX (n=1890)	HD-MTX (n=410)	No HD-MTX (n=1171)	HD-MTX (n=284)
Diagnosis -DLBCL -HGBL with (MYC plus BCL2/BCL6)*	1768 (93.5) 122 (6.5)	370 (90.2) 40 (9.8)	1103 (94.2) 68 (5.8)	257 (90.5) 27 (9.5)
Age, median (range)	68 (18-80)	65 (19-80)	68 (18-80)	65 (19-80)
Age group, n(%) -18-60 years -61-80 years	353 (18.7) 1537 (81.3)	125 (30.5) 285 (69.5)	219 (18.7) 952 (81.3)	80 (28.2) 204 (71.8)
Sex, n(%) -Male -Female	992 (52.5) 898 (47.5)	246 (60.0) 164 (40.0)	588 (50.2) 583 (49.8)	167 (58.8) 117 (41.2)
Stage, n(%) -I-II -III-IV	71 (3.8) 1819 (96.2)	13 (3.2) 397 (96.8)	61 (5.2) 1110 (94.8)	10 (3.5) 274 (96.5)
ECOG, n(%) -0-1 2-4	679 (36.1) 1202 (63.9)	245 (60.2) 162 (39.8)	486 (41.8) 678 (58.2)	179 (63.5) 103 (36.5)
B-symptoms, n(%)	1007 (54.1)	219 (53.9)	560 (48.4)	136 (48.4)
LDH elevated n(%)	1648 (87.9)	351 (86.5)	989 (84.8)	236 (83.7)
Extranodal sites, n(%) -0-1 -≥2	465 (24.6) 1425 (75.4)	67 (16.3) 343 (83.7)	298 (25.4) 873 (74.6)	45 (15.8) 239 (84.2)

Figure 1

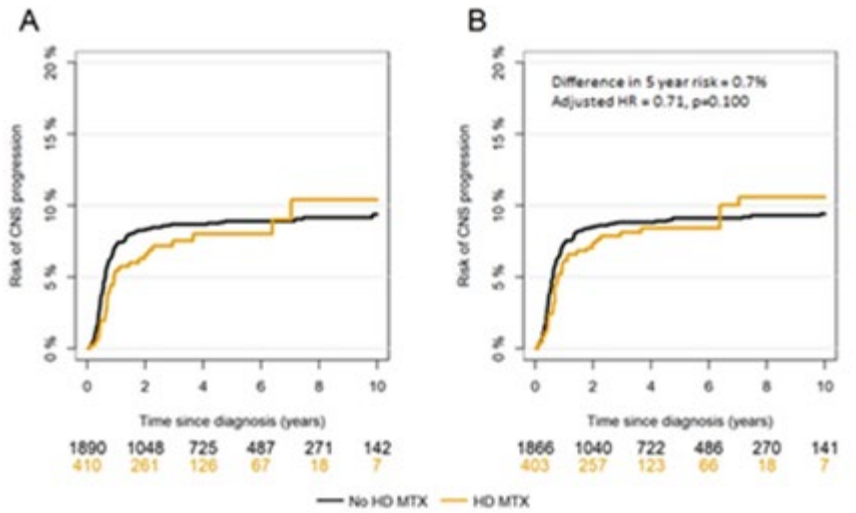


Figure 2

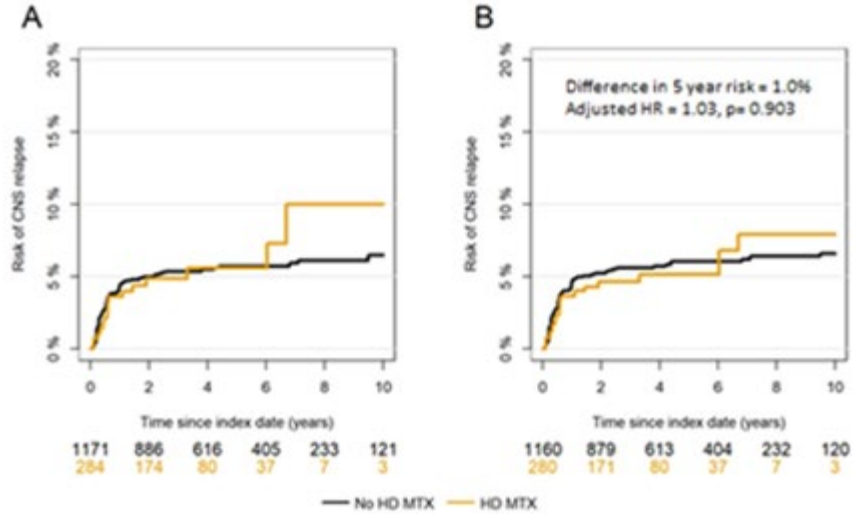


Figure 1: Cumulative incidence of CNS relapse All-pts; A = crude, B = adjusted for LDH, age, extranodal sites, renal/adrenal involvement, ECOG performance status.

Figure 2: Cumulative incidence of CNS relapse CR-pts; A = crude, B = adjusted for LDH, age, extranodal sites, renal/adrenal involvement, ECOG performance status.

All-pts: Disease and treatment characteristics

Factor	No HD-MTX n=1875	HD-MTX n=392	p-value
HGBL with rearrangements of *MYC* + *BCL2* and/or *BCL6*, n (%)	124 (6.6)	40 (10.2)	0.018
Treatment, n(%)			0.303
R-CHOP-like*	1762 (94.0)	363 (92.6)	
DA-EPOCH-R	113 (6.0)	29 (7.4)	
Number of extranodal sites, n(%)			<0.001
0-1	565 (30.1)	57 (14.5)	
2	739 (39.4)	164 (41.8)	
3	343 (18.3)	90 (23.0)	
4	134 (7.2)	54 (13.8)	
>4	93 (5.0)	27 (6.9)	
High-risk extranodal site, n (%)			
Renal	287 (15.3)	107 (27.3)	<0.001
Adrenal	112 (6.0)	44 (11.2)	<0.001
Testicular	38 (3.9)	25 (10.6)	<0.001
Breast	23 (1.2)	9 (2.3)	0.104
CNS baseline assessment, n (%)			<0.001
Nil specific	960 (51.2)	181 (46.2)	
MRI or CT brain	50 (2.7)	27 (6.9)	
CSF analysis	291 (15.5)	119 (30.4)	
MRI/CT brain and CSF analysis	64 (3.4)	42 (10.7)	
Unknown	510 (27.2)	23 (5.9)	
CNS prophylaxis received, n (%)			N/A
None	1447 (77.2)	-	
Intrathecal MTX	428 (22.8)	-	
HD-MTX	-	254 (64.8)	
Intrathecal + HD-MTX	-	138 (35.2)	

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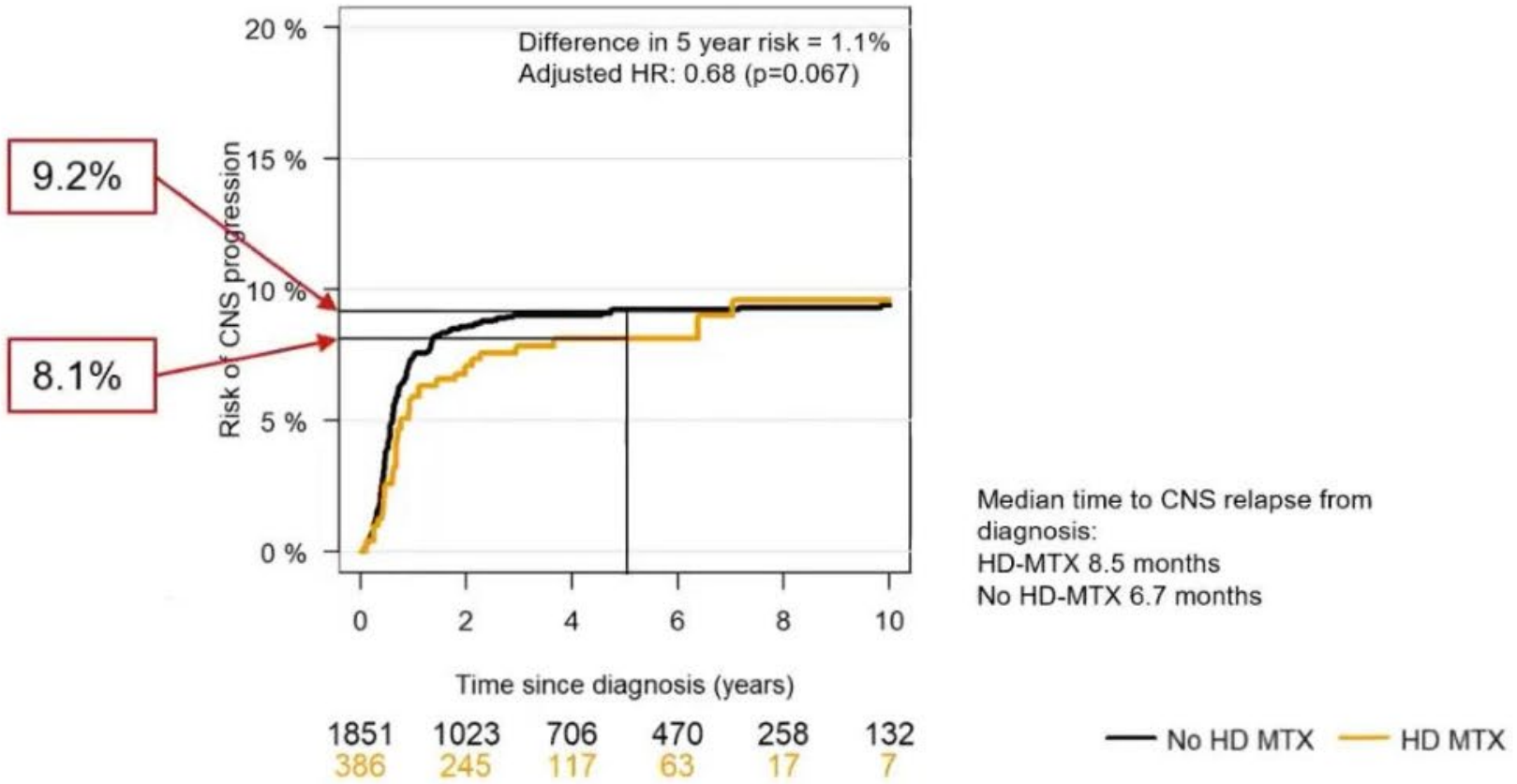
None	1447 (77.2)	-	
Intrathecal MTX	428 (22.8)	-	
HD-MTX	-	254 (64.8)	
Intrathecal + HD-MTX	-	138 (35.2)	

≥3 : 43.7% vs 30.5%

High risk : 51.4% vs 26.4%

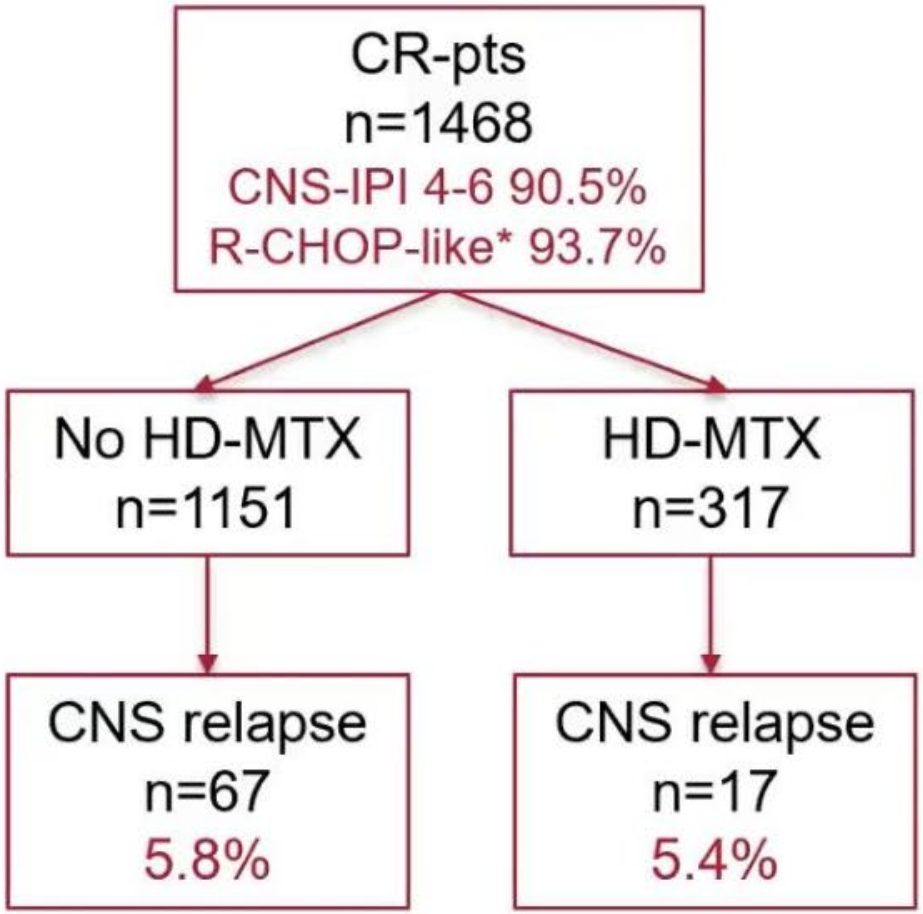
Cumulative incidence of CNS relapse: All-pts (n=2267)



Median time to CNS relapse from diagnosis:
HD-MTX 8.5 months
No HD-MTX 6.7 months

Cumulative incidence of CNS relapse All-pts: adjusted for LDH, age, extranodal sites, renal/adrenal involvement, ECOG performance status.

Results – CR-pts (n=1468)



Median follow up =
5.4 years (0.0-18.7)

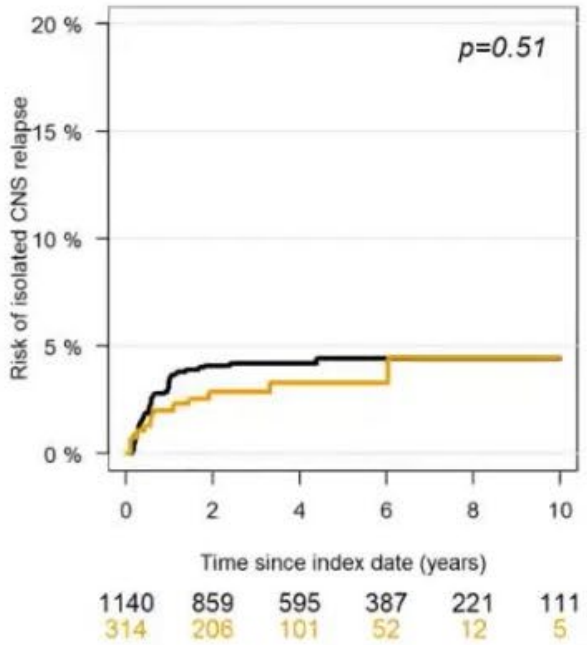
*R-CHOP-like = R-CHOP, G-CHOP, R-CEOP.
Remaining 6.3% received DA-EPOCH-R.

Exploratory subgroup analyses

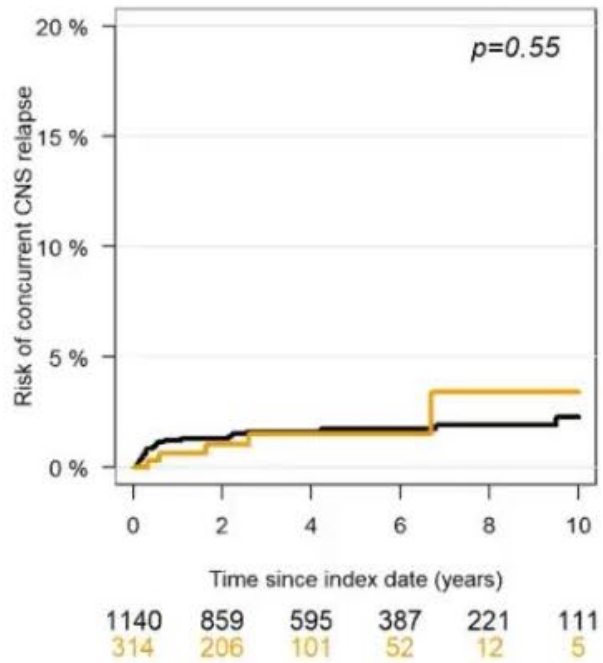
- We performed subgroup analyses to explore the impact of HD-MTX according to:
  - HD-MTX dose ($\geq 3 g/m^2$ vs $< 3 g/m^2$)
  - Number of extranodal sites
  - Specific extranodal site involvement
  - CNS-IPI score
  - Histological diagnosis
  - Presence of isolated CNS relapse vs systemic/synchronous CNS relapse
  - HD-MTX infusion schedule
  - Concurrent use of intrathecal therapy

Isolated CNS vs CNS/systemic relapse

Isolated CNS relapse



Synchronous CNS/systemic relapse

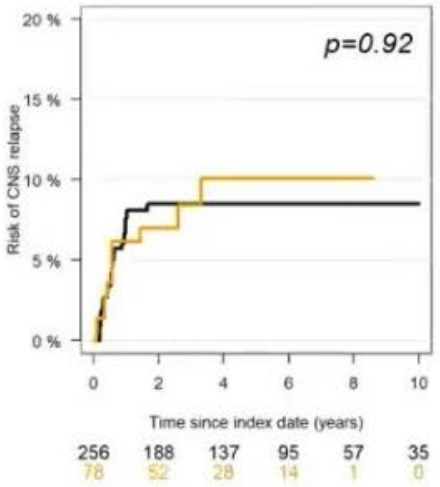


No HD MTX — HD MTX

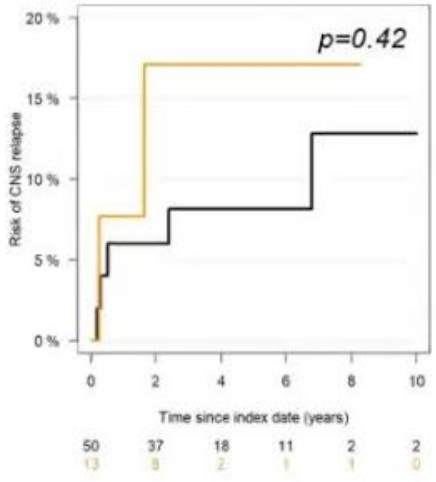
*Isolated CNS relapse = CNS relapse without systemic lymphoma relapse within 28 days.
**Synchronous CNS/systemic relapse = CNS relapse occurring within 28 days of systemic lymphoma relapse.

CNS-IPI score

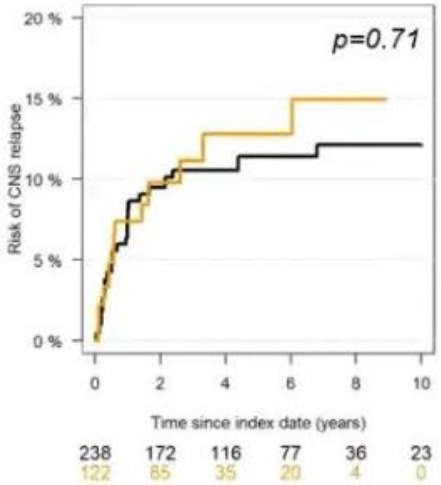
CNS-IPI = 5



CNS-IPI = 6



CNS-IPI = 6 + extras*

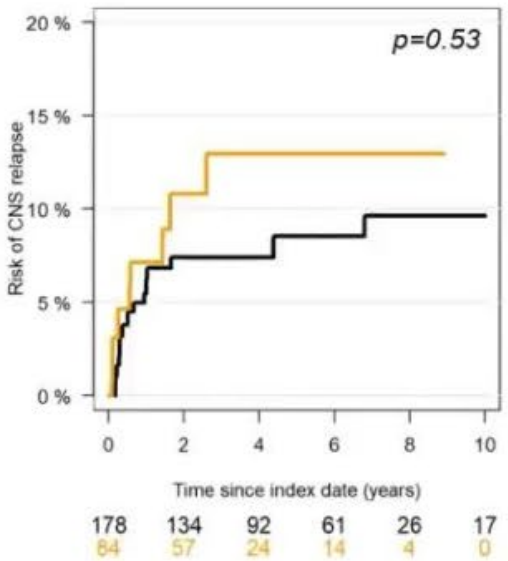


No HD MTX HD MTX

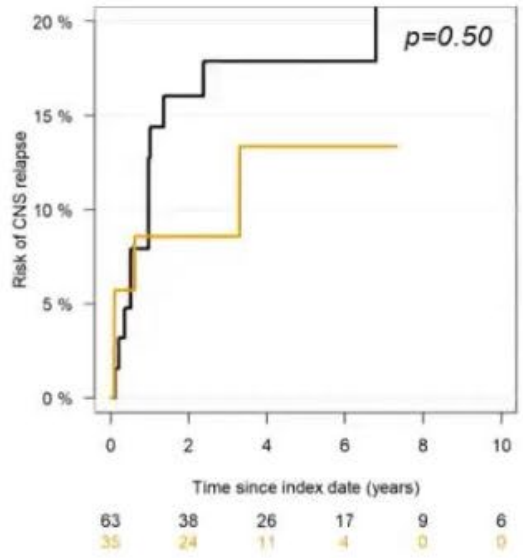
*extras = patients with specific high risk extranodal sites (testis, breast, renal, adrenal)

High-risk extranodal sites

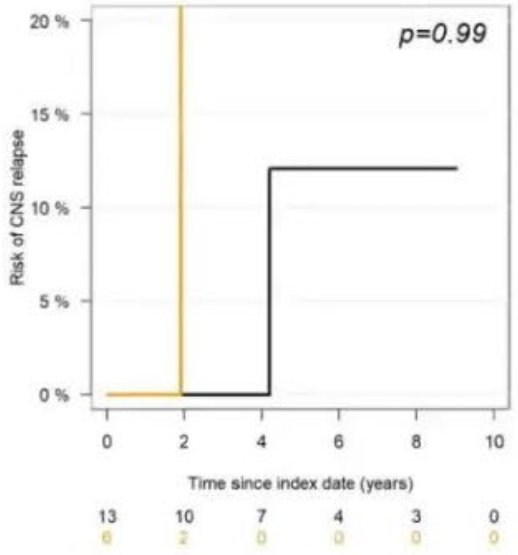
Renal



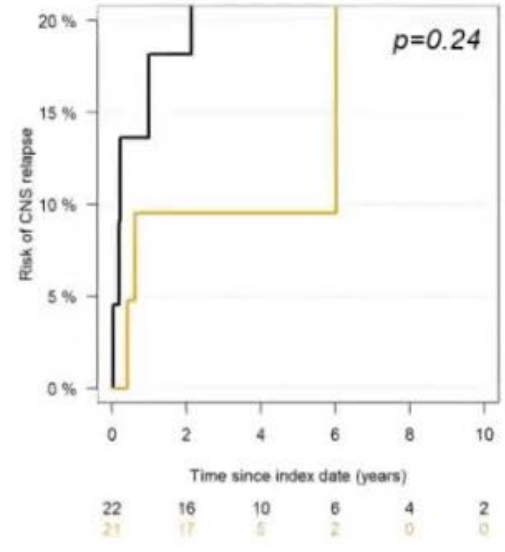
Adrenal



Breast



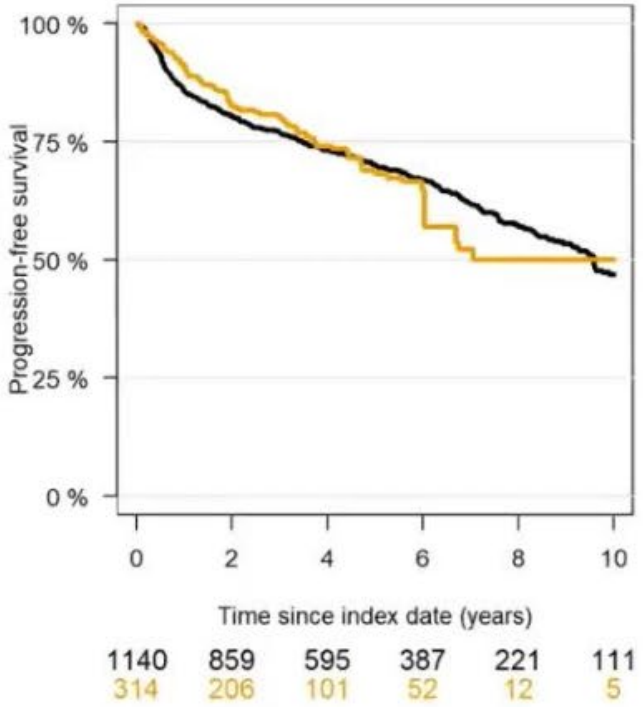
Testicular



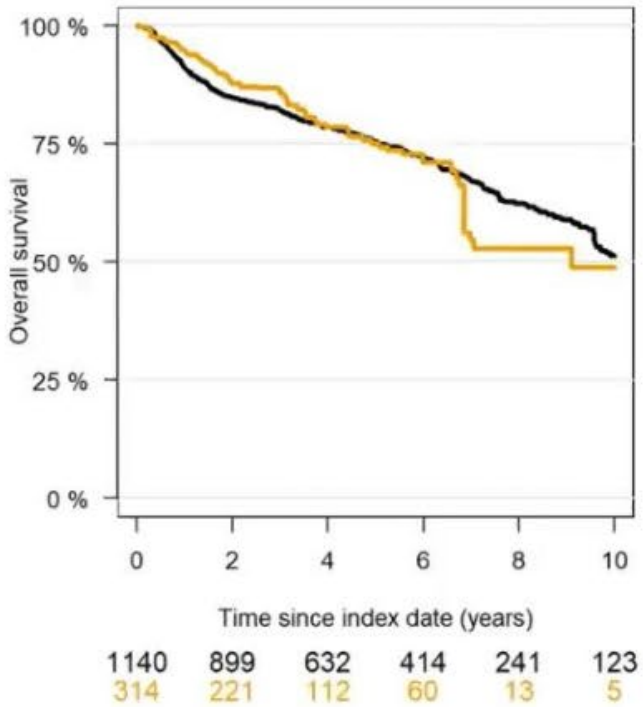
No HD MTX HD MTX

Progression free and overall survival – CR-pts

PFS



OS



Conclusions

- In the largest study to date investigating efficacy of HD-MTX in reducing CNS relapse in high-risk patients,HD-MTX was not associated with reduction in CNS relapse:
  - Overall
  - For patients in CR at completion of frontline therapy
  - In any high-risk subgroup

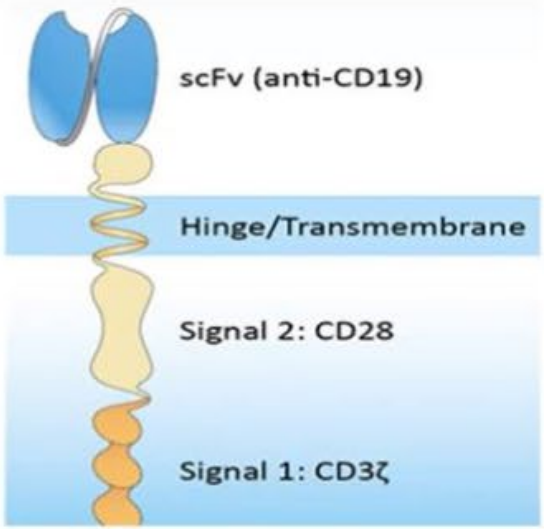
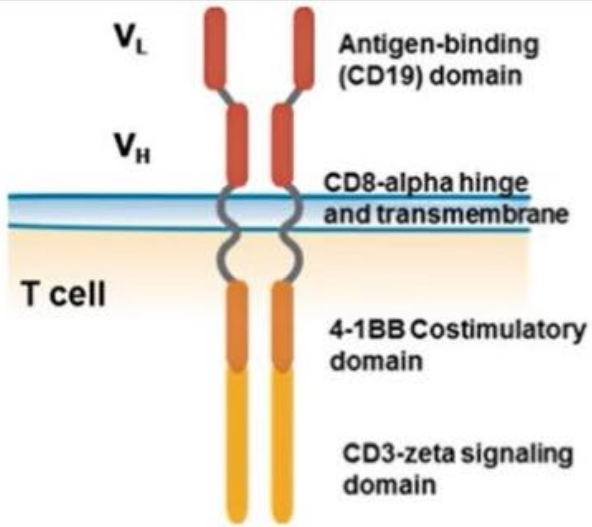
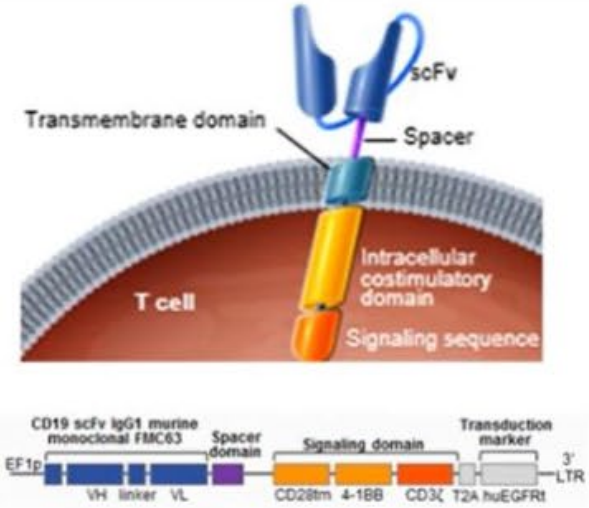
SINGLE-ROUTE CNS PROPHYLAXIS FOR AGGRESSIVE NON-HODGKIN LYMPHOMAS: REAL-WORLD OUTCOMES FROM 21 US ACADEMIC INSTITUTIONS

Orellana-Noia VM[1,2], Reed DR[2,3], McCook AA[4], Sen JM[5], Barlow CM[2], Malecek M-K[6], Watkins M[6], Kahl BS[6], Spinner MA[7], Advani R[7], Voorhees TJ[8,9], Snow A[8], Grover NS[8], Ayers A[1], Romancik JT[1], Liu Y[10], Huntington SF[10], Chavez JC[11], Saeed H[11], Lazaryan A[11], Raghunathan V[12, 13], Spurgeon SE[12], Ollila TA[14], Del Prete C[14], Olszewski AJ[14], Ayers EC[2,15], Landsburg DJ[15], Echalier B[16], Lee J[16], Kamdar M[16], Caimi PF[28, 18], Fu T[19], Liu J[19], David KA[19], Alharthy H[20], Law J[21], Karmali R[22], Shah H[23], Stephens DM[23], Major A[24], Rojek AE[24], Smith SM[24], Yellala A[25], Kallam A[25], Nakhoda S[26], Khan N[26], Sohail MA[18], Hill BT[18], Barrett-Campbell O[27], Lansigan F[27], Switchenko J[4], Cohen JB[1], Portell CA[2]

KEY POINTS:

1. In a large multicenter analysis of adult DLBCL patients, route of CNS prophylaxis did not affect CNS relapse rates
2. Testicular involvement, non-GCB subtype, and high extranodal burden predicted increased CNS risk despite MTX-based prophylaxis by either route.

FDA Approved CD19 CARTs in R/R DLBCL

Axicabtagene ciloleucel (Yescarta; axi-cel)	Tisagenlecleucel (Kymriah; tisa-cel)	Lisocabtagene Maraleucel (Breyanzi; liso-cel)
ZUMA-1	JULIET	TRANSCEND
		
CD28-CD3ζ	41BB-CD3ζ	41BB-CD3ζ
Duration of follow-up: 4 years	Duration of follow-up: 40.3 mo	Duration of follow-up: 18.8 mo
Locke FL, et al. *Lancet Oncol*. 2019;20(1): 31-42.	Schuster S, et al. *N Engl J Med* 2019;380:45-56.	Abramson JS, et al. *Lancet* 2020; 396: 839–52

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Helping hematologists conquer blood diseases worldwide

Start Your Engines: CAR T-cells Challenge Therapeutic Paradigm for Relapsed/Refractory Aggressive B-cell Lymphomas

Introduction to *Primary Analysis of ZUMA-7: A Phase 3 Randomized Trial of Axicabtagene Ciloleucel (AxiCel) Versus Standard-of-Care Therapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma*

Alex F. Herrera, MD
Associate Professor
Division of Lymphoma, Department of Hematology and Hematopoietic Cell Transplantation
City of Hope

Relapsed/Refractory Aggressive B-cell Lymphoma

- ~1/3 of pts with aggressive B-NHL
- Standard treatment is:
  - Salvage/2L chemo-immunotherapy
  - Autologous stem cell transplantation (ASCT) for chemosensitive pts
- ASCT cures about half of pts

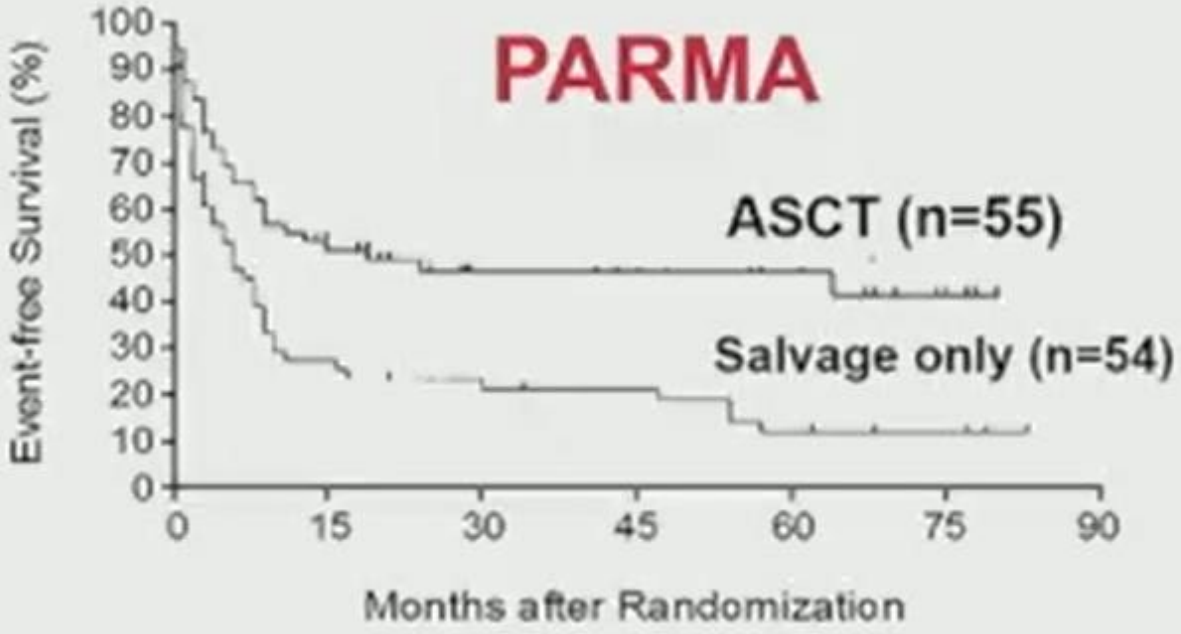


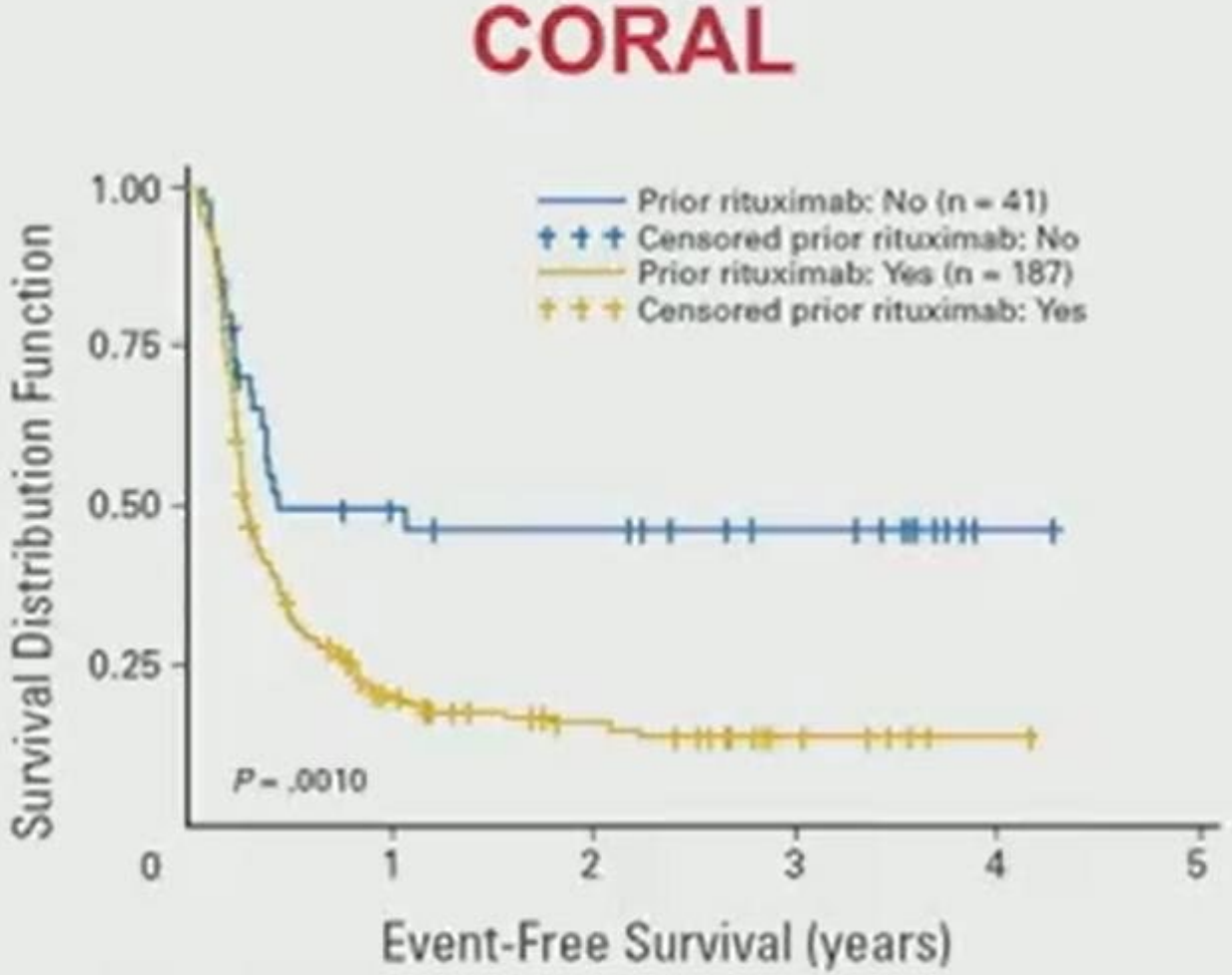
Figure 1. Kaplan–Meier Curves for Event-free Survival of Patients in the Transplantation and Conventional-Treatment Groups.

Philip et al. *NEJM*. 1995.

Early relapse after R-CHOP → dismal outcomes

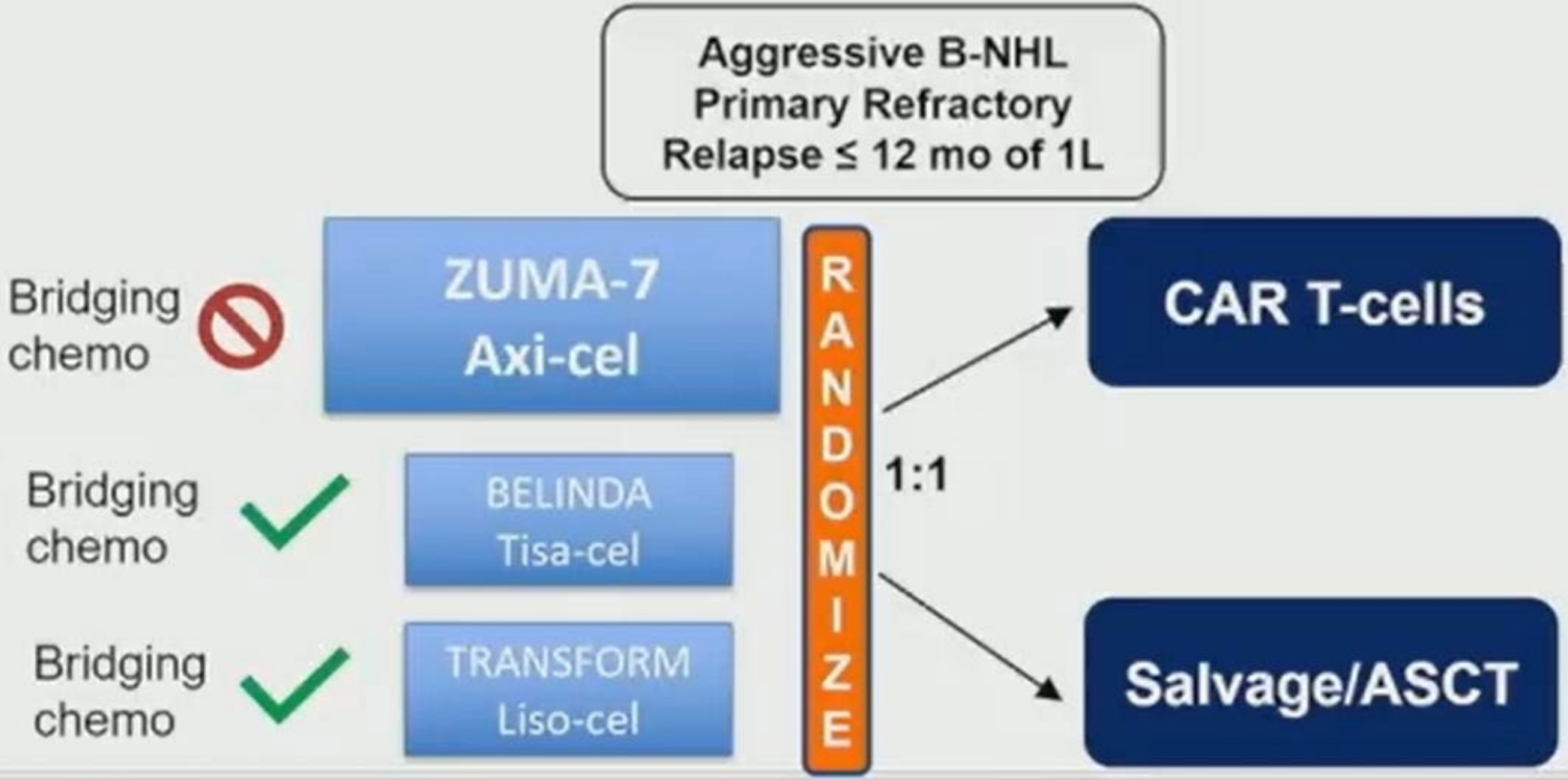
1° refractory/early relapse after prior rituximab

- 2L salvage intent-to-transplant outcomes:
  - ORR 46%
  - 3y EFS 20%
  - 3y OS 39%



Gisselbrecht et al. *JCO* 2010

ZUMA-7: Uncharted Territory

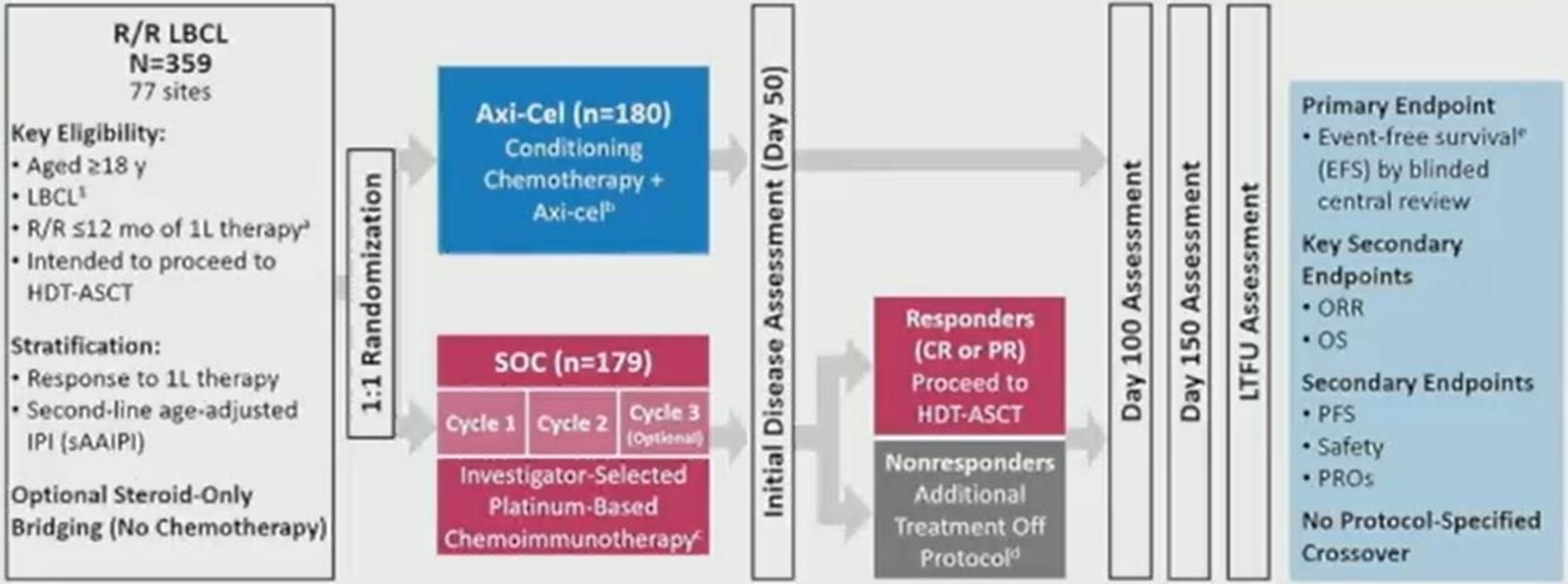


Primary Analysis of ZUMA-7: a Phase 3 Randomized Trial of Axicabtagene Ciloleucel versus Standard-of-Care Therapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma

Frederick L. Locke, MD[1]; David B. Miklos, MD, PhD[2]; Caron A. Jacobson, MD, MMSc[3]; Miguel-Angel Perales, MD[4]; Marie José Kersten MD, PhD[5]; Olalekan O. Oluwole, MBBS, MPH[6]; Armin Ghobadi, MD[7]; Aaron P. Rapoport, MD[8]; Joseph P. McGuirk, DO[9]; John M. Pagel, MD, PhD[10]; Javier Muñoz, MD, MS, MBA, FACP[11]; Umar Farooq, MD[12]; Tom van Meerten, MD, PhD[13]; Patrick M. Reagan, MD[14]; Anna Sureda, MD, PhD[15]; Ian W. Flinn, MD, PhD[16]; Peter Vandenberghe, MD, PhD[17]; Kevin W. Song, MD, FRCPC[18]; Michael Dickinson, MBBS, D Med Sci, FRACP, FRCPA[19]; Monique C. Minnema, MD, PhD[20]; Peter A. Riedell, MD[21]; Lori A. Leslie, MD[22]; Sridhar Chaganti, MD[23]; Yin Yang, MS, MD[24]; Simone Filosto, PhD[24]; Marco Schupp, MD[24]; Christina To, MD[24]; Paul Cheng, MD, PhD[24]; Leo I. Gordon, MD[25]; and Jason R. Westin, MD, MS, FACP[26], on behalf of all ZUMA-7 investigators and contributing Kite members

[1]Moffitt Cancer Center, Tampa, FL, USA; [2]Stanford University School of Medicine, Stanford, CA, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [5]Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands, on behalf of HOVON/LLPC; [6]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [7]Washington University School of Medicine, St Louis, MO, USA; [8]The Marlene and Stewart Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD, USA; [9]University of Kansas Cancer Center, Kansas City, KS, USA; [10]Swedish Cancer Institute, Seattle, WA, USA; [11]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [12]University of Iowa, Iowa City, IA, USA; [13]University Medical Center Groningen, Groningen, Netherlands, on behalf of HOVON/LLPC; [14]University of Rochester School of Medicine, Rochester, NY, USA; [15]Hematology Department, Institut Català d'Oncologia-Hospitalet, IDIBELL, Universitat de Barcelona, Barcelona, Spain; [16]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; [17]University Hospitals Leuven, Leuven, Belgium; [18]Division of Hematology, University of British Columbia and Leukemia/BMT Program of BC, Vancouver General Hospital, Vancouver, BC, Canada; [19]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and the University of Melbourne, Melbourne, Victoria, Australia; [20]UMC, University of Utrecht, The Netherlands, on behalf of HOVON/LLPC; [21]The University of Chicago Medical Center, Chicago, IL, USA; [22]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA; [23]Centre for Clinical Haematology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; [24]Kite, a Gilead Company, Santa Monica, CA, USA; [25]Northwestern University Feinberg School of Medicine and the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA; and [26]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

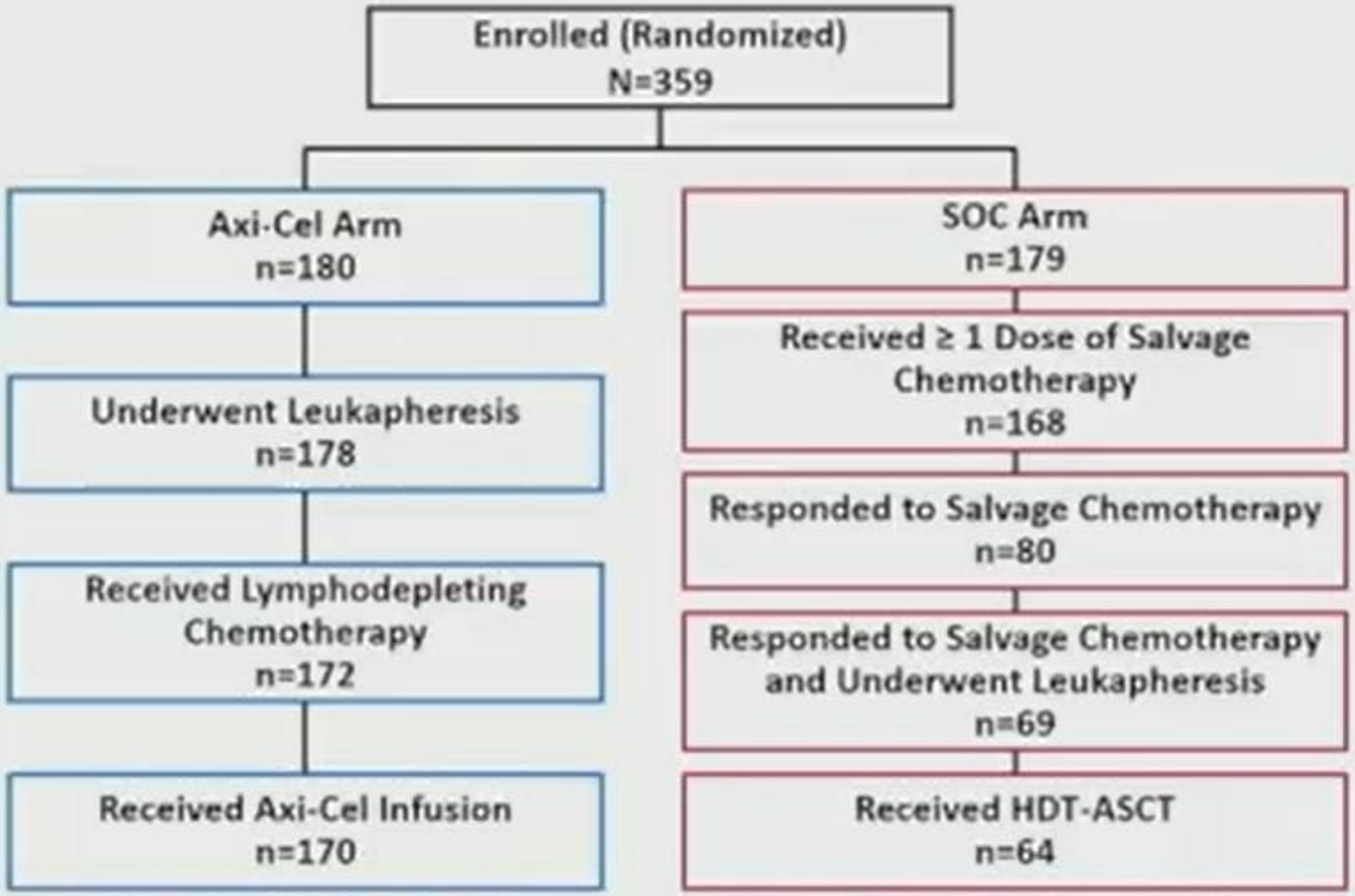
ZUMA-7 Study Schema and Endpoints: Axi-Cel Versus SOC as Second-Line Therapy in Patients With R/R LBCL



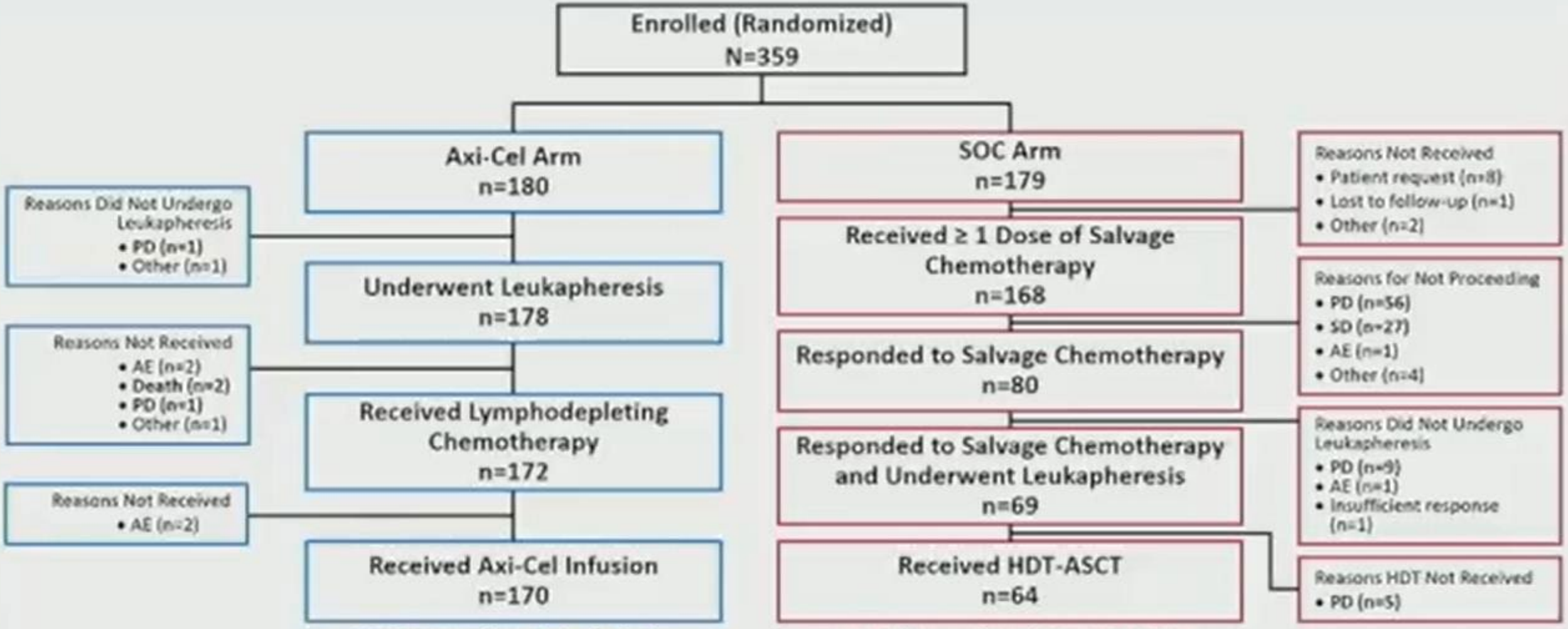
[a] Refractory disease was defined as no CR to 1L therapy; relapsed disease was defined as CR followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy. [b] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m²/day) and fludarabine (30 mg/m²/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2×10^6 CAR T cells/kg). [c] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. [d] 56% of patients received subsequent cellular immunotherapy. [e] EFS was defined as time from randomization to the earliest date of disease progression per Lugano Classification,[2] commencement of new lymphoma therapy, or death from any cause.

1. Swerdlow SH, et al. *Blood*. 2016;127:2375-2390. 2. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

Patient Disposition: Nearly 3× as Many Axi-Cel Patients Received Definitive Therapy Versus SOC Patients



Patient Disposition: Nearly 3× as Many Axi-Cel Patients Received Definitive Therapy Versus SOC Patients

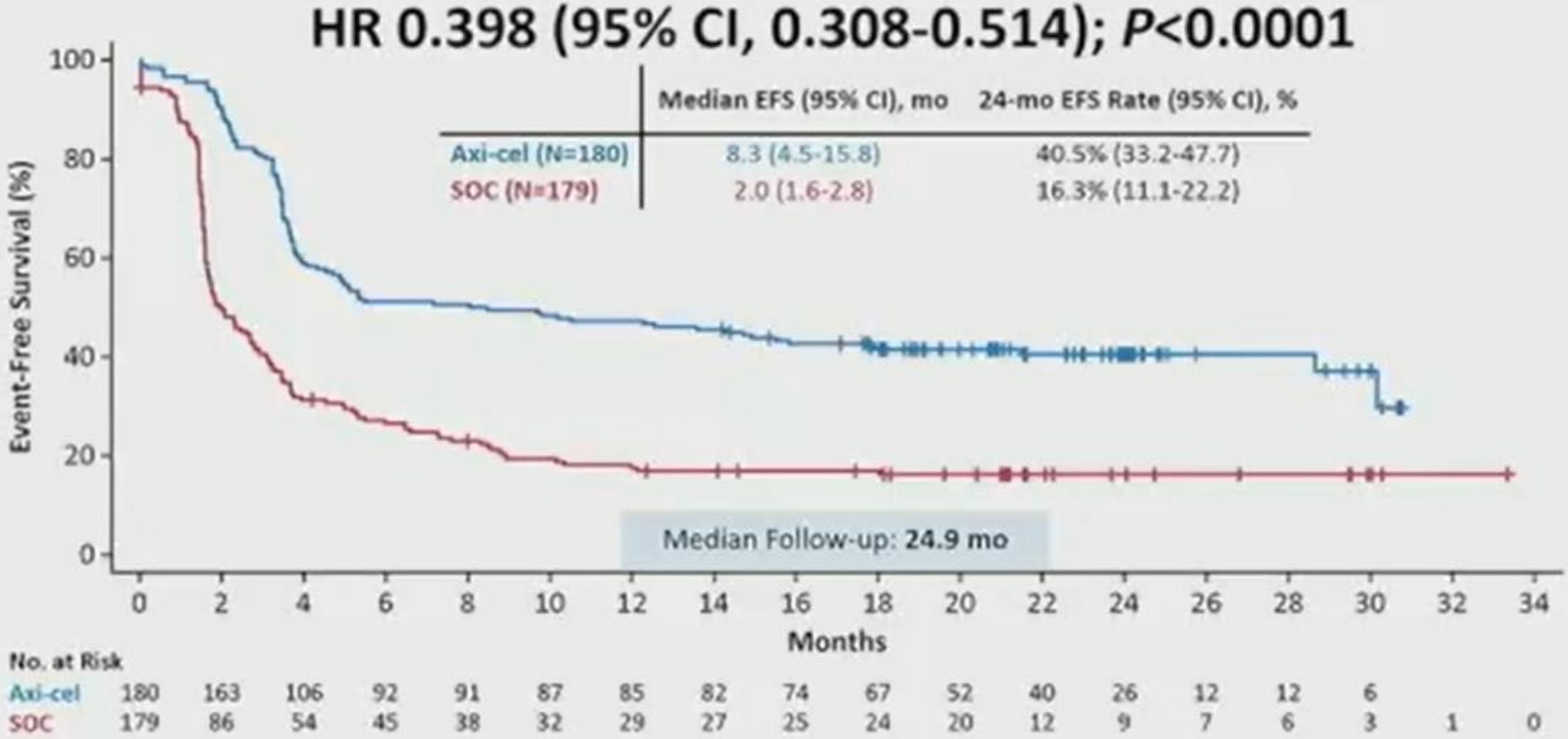


Baseline Characteristics Were Generally Balanced Between the Axi-Cel and SOC Arm

Characteristic	Axi-Cel n=180	SOC n=179	Overall N=359
Median age (range), years	58 (21-80)	60 (26-81)	59 (21-81)
≥65 years, n (%)	51 (28)	58 (32)	109 (30)
Disease stage III-IV, n (%)	139 (77)	146 (82)	285 (79)
sAAIPI of 2-3[a], n (%)	82 (46)	79 (44)	161 (45)
Response to 1L therapy[a], n (%)			
Primary refractory	133 (74)	131 (73)	264 (74)
Relapse ≤12 mo of 1L therapy	47 (26)	48 (27)	95 (26)
Prognostic marker per central laboratory, n (%)			
HGBL (including double-/triple-hit)	31 (17)	25 (14)	56 (16)
Double expressor lymphoma	57 (32)	62 (35)	119 (33)
MYC rearrangement	15 (8)	7 (4)	22 (6)
Elevated LDH level[b]	101 (56)	94 (53)	195 (54)

[a] As reported by investigator at the time of randomization. [b] Lactate dehydrogenase level greater than upper limit of normal per local laboratory reference range.

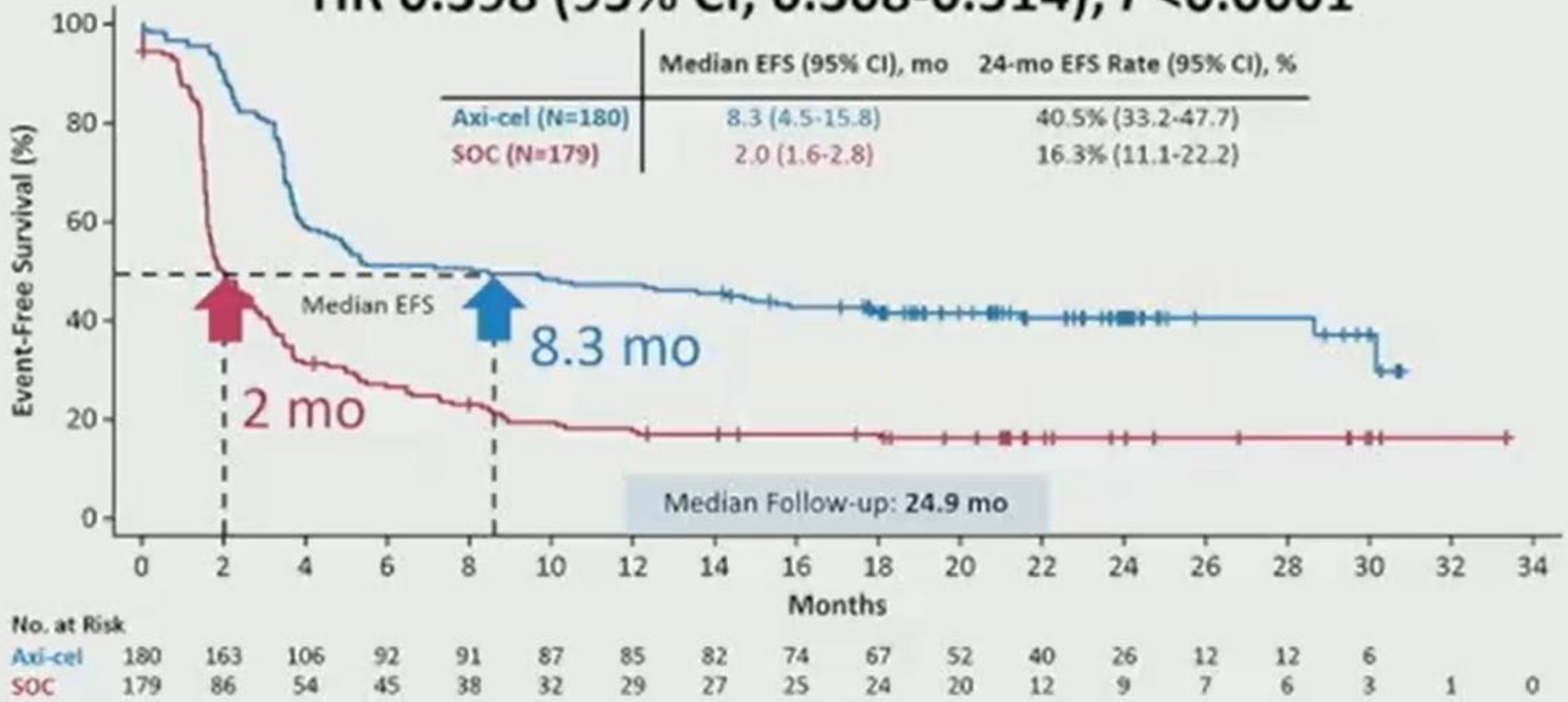
Primary EFS Endpoint: Axi-Cel Is Superior to SOC



Primary EFS Endpoint: Axi-Cel Is Superior to SOC

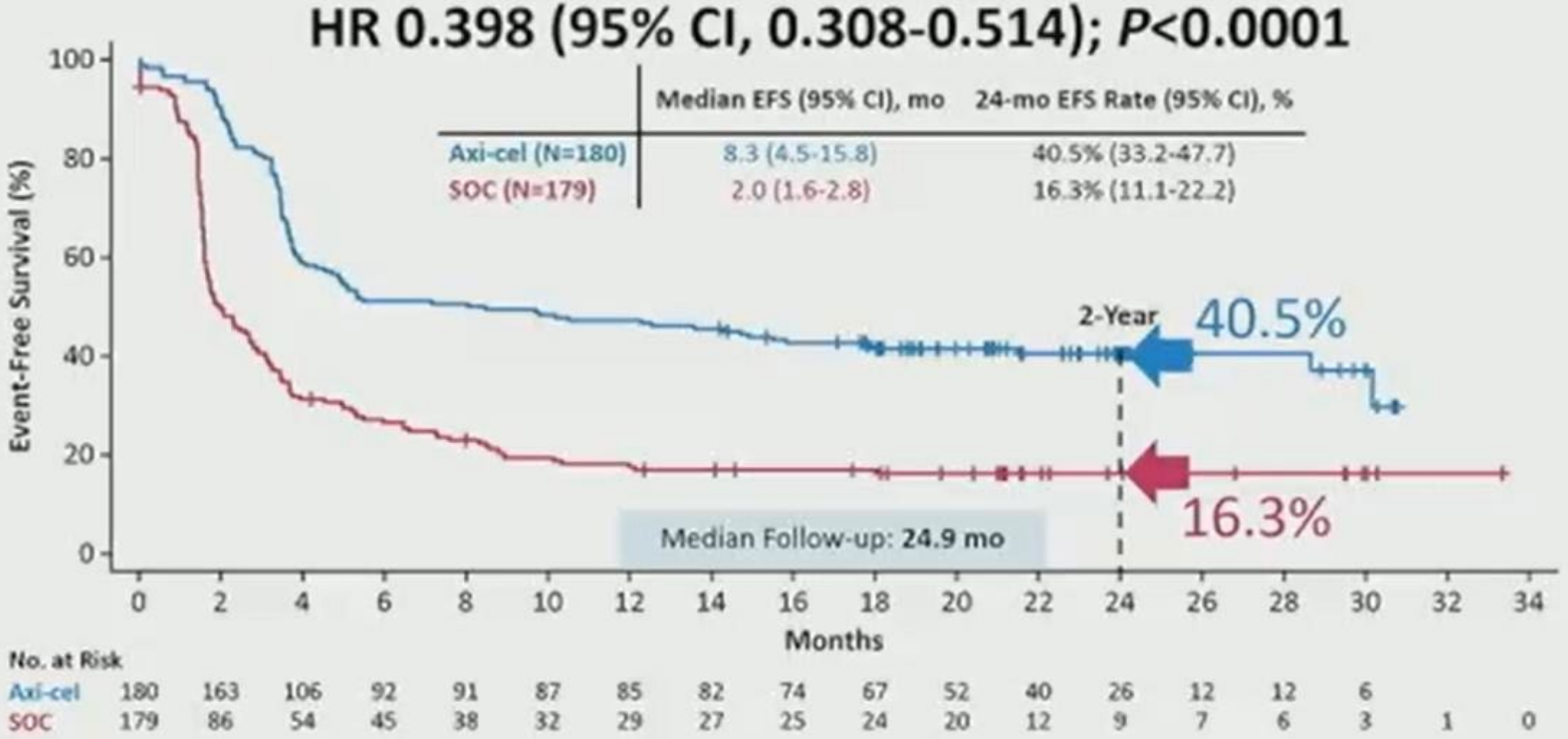
HR 0.398 (95% CI, 0.308-0.514); *P*<0.0001

	Median EFS (95% CI), mo	24-mo EFS Rate (95% CI), %
Axi-cel (N=180)	8.3 (4.5-15.8)	40.5% (33.2-47.7)
SOC (N=179)	2.0 (1.6-2.8)	16.3% (11.1-22.2)



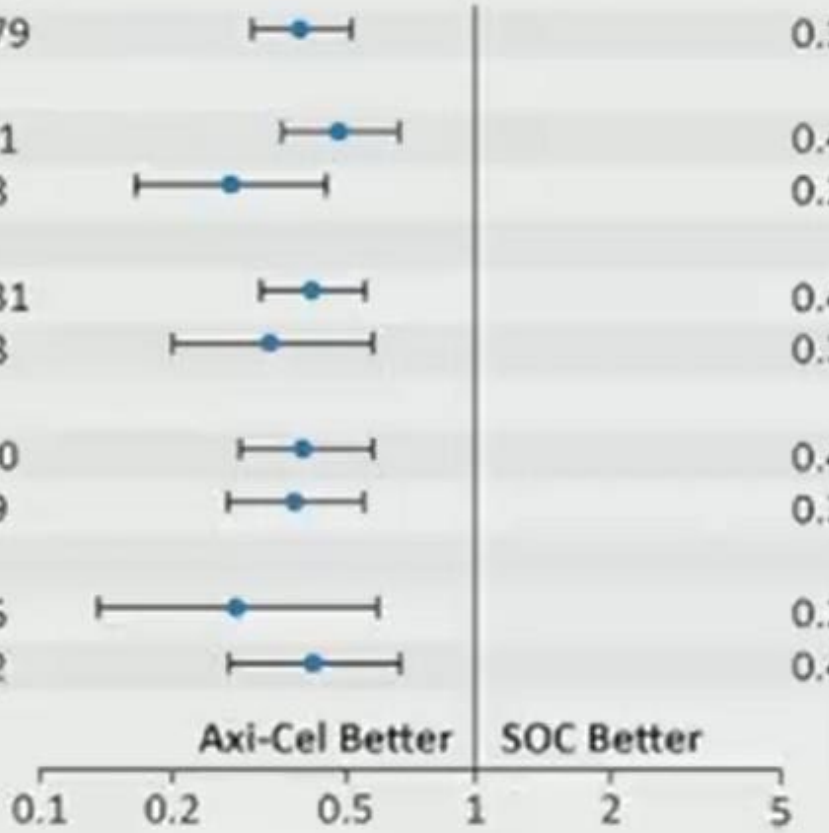
No. at Risk																	
Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6	
SOC	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

Primary EFS Endpoint: Axi-Cel Is Superior to SOC

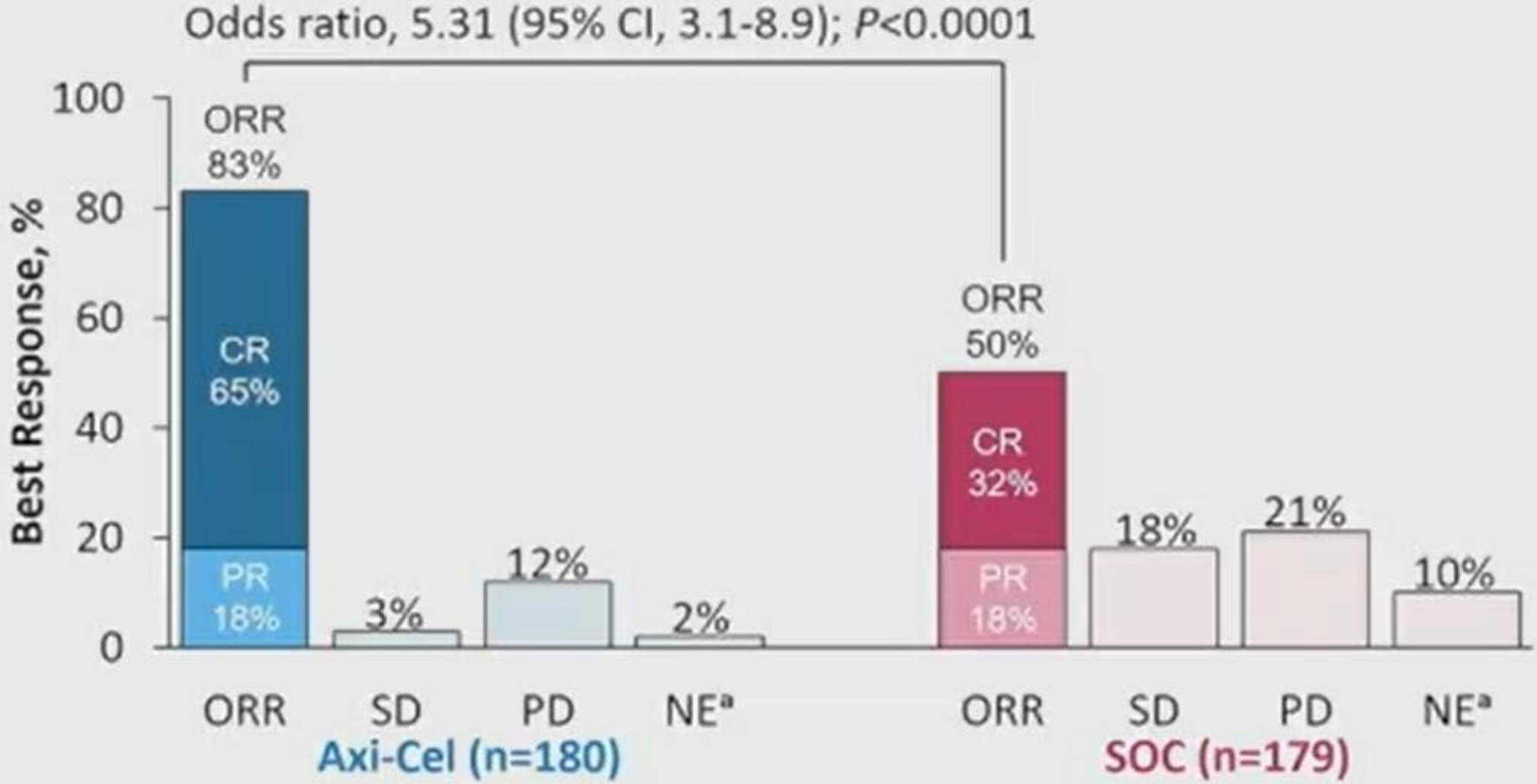


EFS Improvements With Axi-Cel Versus SOC Were Consistent Among Key Patient Subgroups

	Axi-Cel EFS Event/N	SOC EFS Event/N	HR (95% CI)
Overall	108/180	144/179	0.398 (0.308-0.514)
Age, years			
<65	81/129	96/121	0.490 (0.361-0.666)
≥65	27/51	48/58	0.276 (0.164-0.465)
Response to 1L therapy at randomization			
Primary refractory	85/133	106/131	0.426 (0.319-0.570)
Relapse ≤12 months of 1L therapy	23/47	38/48	0.342 (0.202-0.579)
sAAIPI			
0-1	54/98	73/100	0.407 (0.285-0.582)
2-3	54/82	71/79	0.388 (0.269-0.561)
Prognostic marker per central laboratory			
HGBL-double/triple hit	15/31	21/25	0.285 (0.137-0.593)
Double expressor lymphoma	35/57	50/62	0.424 (0.268-0.671)

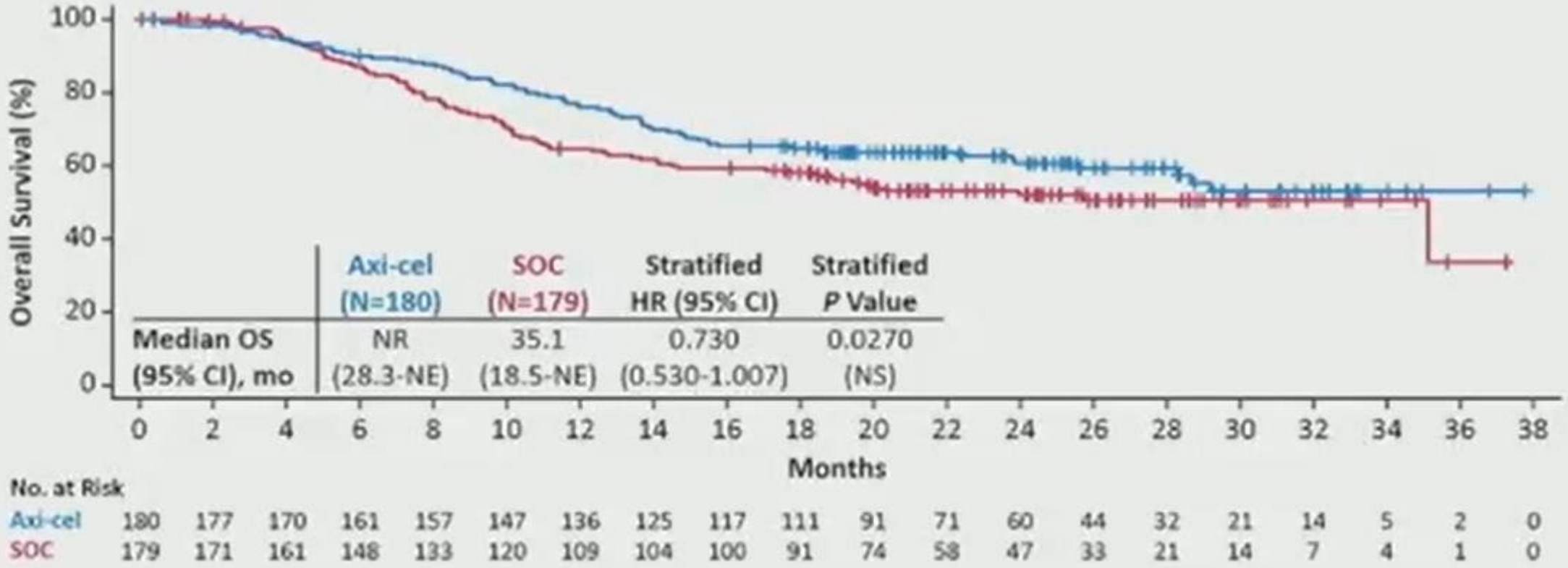


ORR Was Significantly Higher in Axi-Cel Versus SOC Patients



[a]Not evaluable (NE): In the axi-cel arm, response assessments were not done for 4 patients. In the SOC arm, there were 4 patients with undefined disease and 14 who did not have response assessments done.

Median OS, Evaluated as an Interim Analysis, Was Not Reached for Axi-Cel Versus 35.1 Months for SOC



- 56% of SOC patients received subsequent cellular immunotherapy (off protocol)
- Preplanned sensitivity analysis[a] suggests an OS benefit, likely confounded by SOC treatment switching

[a] Analysis utilized the validated and commonly used Rank Preserving Structural Failure Time model, which preserves randomization as described by Robins and Tsiatis (*Commun Stat Theory Methods*. 1991;2609-2631) and revealed the difference in treatment effect if SOC patients did not receive subsequent cellular immunotherapy. Stratified hazard ratio was 0.580 (95% CI, 0.416-0.809).

Safety Profile of Axi-Cel Was Manageable and Consistent With Previous Studies in Refractory LBCL[1,2]

Adverse Events, n (%)[a]	Axi-Cel n=170		SOC n=168	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	**170 (100)**	**155 (91)**	**168 (100)**	**140 (83)**
Pyrexia	158 (93)	15 (9)	43 (26)	1 (1)
Neutropenia[b]	121 (71)	118 (69)	70 (42)	69 (41)
Hypotension	75 (44)	19 (11)	25 (15)	5 (3)
Fatigue	71 (42)	11 (6)	87 (52)	4 (2)
Anemia	71 (42)	51 (30)	91 (54)	65 (39)
Diarrhea	71 (42)	4 (2)	66 (39)	7 (4)
Headache	70 (41)	5 (3)	43 (26)	2 (1)
Nausea	69 (41)	3 (2)	116 (69)	9 (5)
Sinus tachycardia	58 (34)	3 (2)	17 (10)	1 (1)
Leukopenia[c]	55 (32)	50 (29)	43 (26)	37 (22)
Any serious AE	**85 (50)**	**72 (42)**	**77 (46)**	**67 (40)**

Reason for Death	Axi-Cel n=170	SOC n=168
Progressive disease, n (%)	47 (28)	64 (38)
Grade 5 AE during protocol-specified reporting period, n (%)	7 (4)[d]	2 (1)[e]
Definitive therapy-related mortality, n/N (%)	1/170 (1)[f]	2/64 (3)[e]

1. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531-2544. 2. Locke FL, et al. *Blood*. 2017;130:2826.

[a] Included are any adverse events of any grade occurring in ≥20% of patients in either the axi-cel or SOC arm. [b] Combined preferred terms of neutropenia and neutrophil count decreased. [c] Combined preferred terms of leukopenia and white blood cell count decreased. [d] COVID-19 (n=2) and lung adenocarcinoma, myocardial infarction, progressive multifocal leukoencephalopathy, sepsis, and hepatitis B reactivation (n=1 each). [e] Cardiac arrest and acute respiratory distress syndrome (n=1 each). [f] Hepatitis B reactivation.

Grade ≥3 CRS and Neurologic Events Were Generally Consistent With Third-Line Treatment of Patients[1]

CRS Parameter	Axi-Cel n=170
CRS, n (%)[a]	
Any grade	157 (92)
Grade ≥3	11 (6)
Grade 5	0
Most common any-grade symptoms, n/n (%)	
Pyrexia	155/157 (99)
Hypotension	68/157 (43)
Sinus tachycardia	49/157 (31)
AE management[d], n (%)	
Tocilizumab	111 (65)
Corticosteroids	40 (24)
Vasopressors	11 (6)
Median time to onset, days	3
Median duration of events, days	7

Neurologic Event Parameter	Axi-cel n=170	SOC n=168
Neurologic events, n (%)[b]		
Any grade	102 (60)	33 (20)[c]
Grade ≥3	36 (21)	1 (1)
Grade 5	0	0
Most common any-grade symptoms, n (%)		
Tremor	44 (26)	1 (1)
Confusional state	40 (24)	4 (2)
Aphasia	36 (21)	0
AE management[d], n (%)		
Corticosteroids	54 (32)	-
Median time to onset, days	7	23
Median duration of events, days	9	23

1. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531-2544. 2. Lee DW, et al. *Blood*. 2014;124:188-195. 3. Topp MS, et al. *Lancet Oncol*. 2015;16:57-66.

[a] CRS was graded according to Lee et al.[2] [b] Neurologic events were identified per prespecified search list based on methods used in the blinatumomab registrational study.[3] Neurologic events were graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. [c] Other preferred terms reported in the SOC arm (in ≤2 patients) included somnolence, agitation, hypoesthesia, lethargy, depressed level of consciousness, cognitive disorder, memory impairment, bradyphrenia, taste disorder, hallucination, hallucination visual, nystagmus, head discomfort, and neuralgia. [d] Toxicity management followed ZUMA-1 pivotal arms.

Conclusions

- ZUMA-7 is the first randomized CAR T-cell trial and has 24.9 months median follow-up
- ZUMA-7 met its primary EFS endpoint, demonstrating statistically significant and clinically meaningful improvement in efficacy with axi-cel versus second-line SOC in R/R LBCL
- Axi-cel showed superiority over SOC

>4-fold greater median EFS	2.5-fold greater 2-year EFS	33% higher ORR	Double the CR rate	EFS improvements across key subgroups

- Nearly 3× the number of patients in the axi-cel arm received definitive therapy versus the SOC arm
- Axi-cel had a manageable safety profile that was consistent with previous studies[1,2]
- Paradigm shift: Axi-cel should be the new standard for patients with second-line R/R LBCL

1. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531-2544. 2. Locke FL, et al. *Blood*. 2017;130:2826.

Lisocabtagene Maraleucel, a CD19-Directed Chimeric Antigen Receptor T Cell Therapy, Versus Standard of Care with Salvage Chemotherapy Followed by Autologous Stem Cell Transplantation as Second-Line Treatment in Patients with Relapsed or Refractory Large B-Cell Lymphoma: Results from the Randomized Phase 3 TRANSFORM Study

Manali Kamdar,[1] Scott R. Solomon,[2] Jon Arnason,[3] Patrick B. Johnston,[4] Bertram Glass,[5] Veronika Bachanova,[6] Sami Ibrahimi,[7] Stephan Mielke,[8] Pim Mutsaers,[9] Francisco Hernandez-Ilizaliturri,[10] Koji Izutsu,[11] Franck Morschhauser,[12] Matthew Lunning,[13] David G. Maloney,[14] Alessandro Crotta,[15] Sandrine Montheard,[15] Alessandro Previtali,[15] Lara Stepan,[16] Ken Ogasawara,[16] Timothy Mack,[16] Jeremy S. Abramson[17]

[1]University of Colorado Cancer Center, Aurora, CO, USA; [2]Northside Hospital Cancer Institute, Atlanta, GA, USA; [3]Beth Israel Deaconess Medical Center, Boston, MA, USA; [4]Mayo Clinic, Rochester, MN, USA; [5]Helios Klinikum Berlin-Buch, Berlin, Germany; [6]University of Minnesota, Minneapolis, MN, USA; [7]University of Oklahoma Stephenson Cancer Center, Oklahoma City, OK, USA; [8]Center of Allogeneic Stem Cell Transplantation and Cellular Therapy (CAST), Karolinska Institutet and University Hospital, Stockholm, Sweden; [9]Erasmus University Medical Center, Rotterdam, The Netherlands, on behalf of HOVON/LLPC; [10]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [11]National Cancer Center Hospital, Tokyo, Japan; [12]Université de Lille, Centre Hospitalier Universitaire de Lille, ULR 7365, GRITA – Groupe de Recherche sur les formes Injectables et les Technologies Associées, Lille, France; [13]University of Nebraska Medical Center, Omaha, NE, USA; [14]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [15]Celgene, a Bristol-Myers Squibb Company, Boudry, Switzerland; [16]Bristol Myers Squibb, Princeton, NJ, USA; [17]Massachusetts General Hospital Cancer Center, Boston, MA, USA

LBA #6

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Tisagenlecleucel vs Standard of Care as Second-Line Therapy of Primary Refractory or Relapsed Aggressive B-Cell Non-Hodgkin Lymphoma: Analysis of the Phase III BELINDA Study

Michael R. Bishop,[1] Michael Dickinson[2], Duncan Purtill[3], Pere Barba[4], Armando Santoro[5], Nada Hamad[6], Koji Kato[7], Anna Sureda[8], Richard Greil[9], Catherine Thieblemont[10], Franck Morschhauser[11], Martin Janz[12], Ian Flinn[13], Werner Rabitsch[14], Yok Lam Kwong[15], Marie José Kersten[16], Monique C. Minnema[17], Harald Holte[18], Esther Hian Li Chan[19], Joaquin Martinez-Lopez[20], Antonia M.S. Mueller[21], Richard T. Maziarz[22], Joseph P. McGuirk[23], Emmanuel Bachy[24], Steven Le Gouill[25,A], Martin Dreyling[26], Hideo Hatigae[27], David Bond[28], Charalambos Andreadis[29], Peter McSweeney[13], Mohamed Kharfan-Dabaja[30], Simon Newsome[31], Evgeny Degtyarev[31], Christopher del Corral[32], Giovanna Andreola[33], Aisha Masood[32], Stephen J. Schuster[33], Ulrich Jaeger[34], Peter Borchmann[35,*], Jason R. Westin[36,*]

[1]The David and Ellis Jacobs Center for Cellular Therapy, University of Chicago, Chicago, IL, USA; [2]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC, Australia; [3]Fiona Stanley Hospital, Murdoch, WA, Australia; [4]Hospital Universitari Vall d'Hebron and Universitat Autònoma de Barcelona, Barcelona, Spain; [5]Department of Biomedical Sciences, Humanitas University and IRCCS Humanitas Research Hospital-Humanitas Cancer Center, Milan, Italy; [6]Department of Haematology, St Vincent's Hospital Sydney, Australia and St Vincent's Clinical School, Sydney, University of New South Wales, Australia; [7]Hematology, Oncology, and Cardiovascular Medicine, Kyushu University Hospital, Fukuoka, Japan; [8]Clinical Hematology Department, Institut Català d'Oncologia – Hospitalet de Llobregat, Barcelona, Spain; [9]3rd Medical Department, Paracelsus Medical University, Salzburg Cancer Research Institute-CCCIT, and Cancer Cluster Salzburg, Salzburg, Austria; [10]AP-HP, Hemato-Oncologie, Hôpital Saint Louis, Paris, France; [11]Centre Hospitalier Universitaire de Lille, Lille, France; [12]Hematology, Oncology and Tumorimmunology, Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany; [13]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [14]Internal Medicine I, Staff Unit, Vienna General Hospital-Medical University of Vienna, Vienna, Austria; [15]Department of Medicine, Queen Mary Hospital, Hong Kong, China; [16]Department of Oncology, Oslo University Hospital, Oslo, Norway and KG Jebsen Center for B-cell Malignancies, Oslo, Norway; [17]National University Cancer Institute Singapore, Singapore; [18]Hematology Department, Hospital 12 de Octubre, Complutense University, 3+12, CIBO, Madrid, Spain; [19]Department of Medical Oncology and Hematology, University Hospital, Zurich, Switzerland; [20]Center for Hematological Malignancies, Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; [21]Division of Hematologic Malignancies and Cellular Therapeutics, The University of Kansas Cancer Center, Westwood, KS, USA; [22]Hospices Civils de Lyon and Université Claude Bernard Lyon 1, Lyon, France; [23]CRCINA, INSERM and Nantes Medical University, Nantes, France; [24]Medizinische Klinik III, LMU Klinikum, Munich, Germany; [25]Ohio State University Hospital, Sendai, Japan; [26]The Ohio State University, Columbus, OH, USA; [27]Fabian Order Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [28]Division of Hematology, Oncology and Blood and Marrow Transplantation and Cellular Therapy Program, Mayo Clinic, Jacksonville, FL, USA; [29]Novartis Pharma AG, Basel, Switzerland; [30]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [31]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [32]Clinical Division of Hematology and Hemostaseology, Department of Medicine I, Vienna General Hospital – Medical University of Vienna, Vienna, Austria; [33]Clinic I for Internal Medicine, University Hospital Cologne, Cologne, Germany; [34]Department of Lymphoma & Myeloma, M D Anderson Cancer Center, Houston, TX, USA; *Dr. Borchmann and Dr. Westin are co-senior authors; [A]At the time of the present work, now affiliated with Institut Curie, Paris, France.

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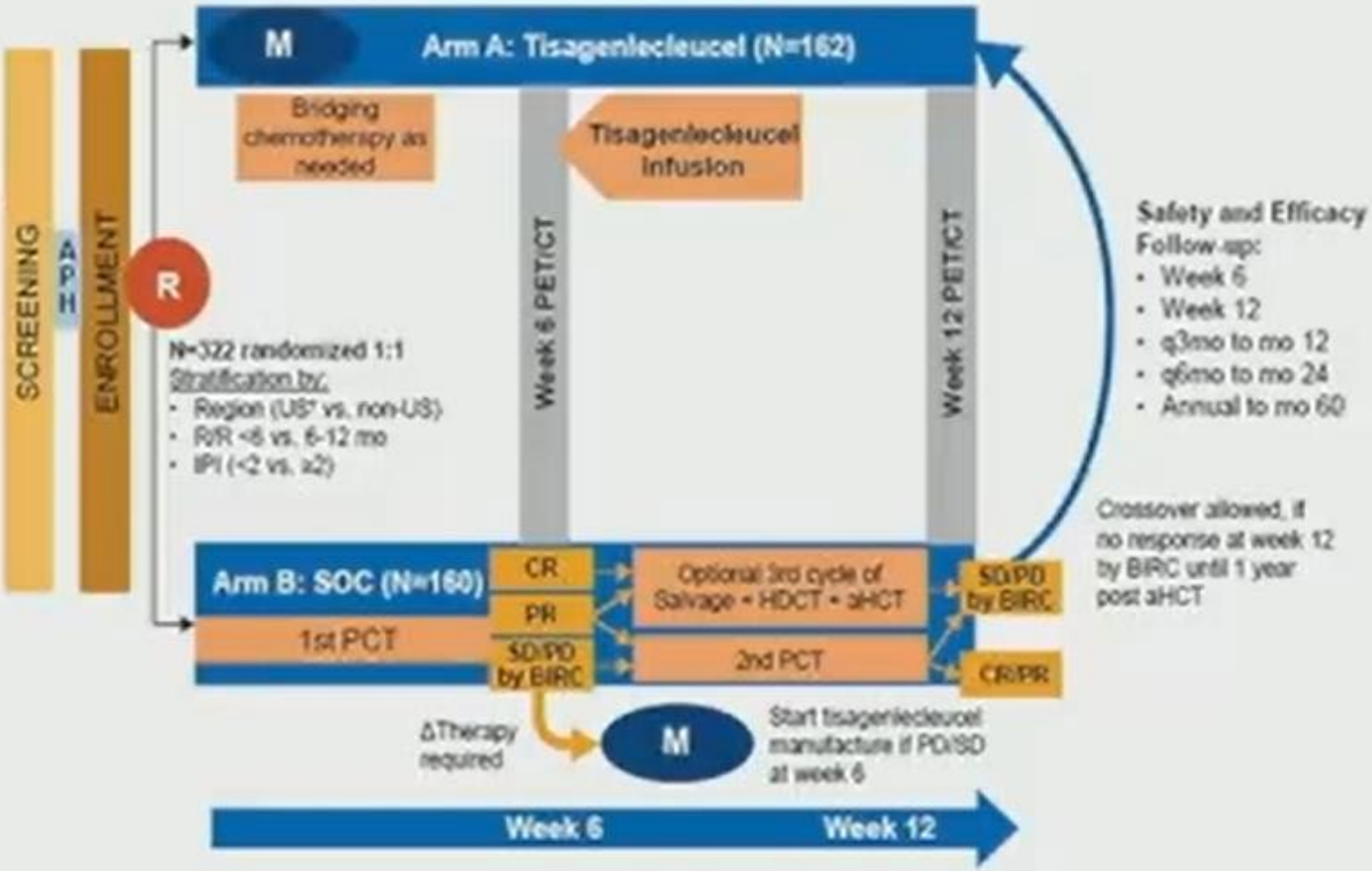
Presented at the 2021 ASH Annual Meeting, 11-14 December, 2021, Georgia World Congress Center – Atlanta, GA

BELINDA Study Design

Key eligibility criteria:

- ≥18 years-old
- Histologically-confirmed aNHL r/r within 12 months of first-line treatment
- autoHCT eligible
- ECOG PS 0-1



Data cutoff: May 6, 2021

Primary Endpoint:
Event-free Survival
EFS Event:
- **SD/PD by BIRC at/after week 12 ± 1 week**
- **Death at any time**

Secondary Endpoints:
- ORR: Best overall response at/after week 12
- Safety
- Cellular kinetics

aHCT, autologous hematopoietic cell transplantation; aNHL, aggressive non-Hodgkin lymphoma; APH, leukapheresis; BIRC, blinded independent review committee; CR, complete response; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HDCT, high-dose chemotherapy; IPI, International Prognostic Index; M, manufacturing; ORR, overall response rate; OS, overall survival; PCT, platinum-based immunochemotherapy; PD, progressive disease; PET, positron emission tomography; PR, partial response; q3mo, every 3 months; q6mo, every 6 months; R, randomization; SD, stable disease; SOC, standard of care; US, United States.

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Baseline Demographic and Disease Characteristics

	Tisagenlecleucel Arm (N=162)	SOC Arm (N=160)
Age ≥65 yr – no. (%)	54 (33.3)	46 (28.8)
Sex, M – no. (%)	103 (63.6)	98 (61.3)
Region – no. (%)		
US†	48 (29.6)	47 (29.4)
Race		
White	128 (79.0)	128 (80.0)
Asian	20 (12.3)	22 (13.8)
Black or African American	8 (4.9)	3 (1.9)
Other/Unknown	6 (3.7)	7 (4.4)
Ethnicity Hispanic or Latino	12 (7.4)	13 (8.1)
Disease subtypes – no. (%)		
DLBCL-NOS	101 (62.3)	112 (70.0)
HGBL with *MYC* and *BCL2* and/or *BCL6*	32 (19.8)	19 (11.9)
HGBL-NOS	7 (4.3)	8 (5.0)
PMBCL	12 (7.4)	13 (8.1)
FL grade 3B	5 (3.1)	1 (0.6)
Other	5 (3.1)	7 (4.4)
Remission duration – no. (%)		
Refractory	107 (66.0)	107 (66.9)
Relapsed <6 mo	30 (18.5)	32 (20.0)
Relapsed 6-12 mo	25 (15.4)	21 (13.1)
ECOG performance status 1 – no. (%)	70 (43.2)	65 (40.6)
IPI ≥2 – no. (%)*	106 (65.4)	92 (57.5)
Stage at time of study entry – no. (%)		
I/IE and II/II E/II Bulky	55 (34.0)	62 (38.8)
III and IV	107 (66.0)	98 (61.3)
Median time since initial diagnosis to randomization, median mo (Q1-Q3)	8.4 (6.8-11.1)	8.2 (5.9-11.4)
Median time since most recent relapse/PD to randomization, median mo (Q1-Q3)	1.4 (0.9-2.2)	1.1 (0.8-1.8)

*The imbalance in IPI, despite being a stratification factor, is due to incorrect data entry in the IRT system at the time of randomization. †North America was a stratification factor, and all enrolled patients in this group were from the US. Refractory: Patients who did not achieve CR on first-line therapy to current lymphoma. Relapsed: Patients who had CR on first-line therapy to current lymphoma and relapsed prior to the study. DLBCL diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; NOS, not otherwise specified; PD, progressive disease; PMBCL, primary mediastinal B-cell lymphoma; SOC, standard of care; US, United States.

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Sex, M – no. (%)	103 (63.6)	98 (61.3)
Region – no. (%)		
US[1]	48 (29.6)	47 (29.4)
Race		
White	128 (79.0)	128 (80.0)
Asian	20 (12.3)	22 (13.8)
Black or African American	8 (4.9)	3 (1.9)
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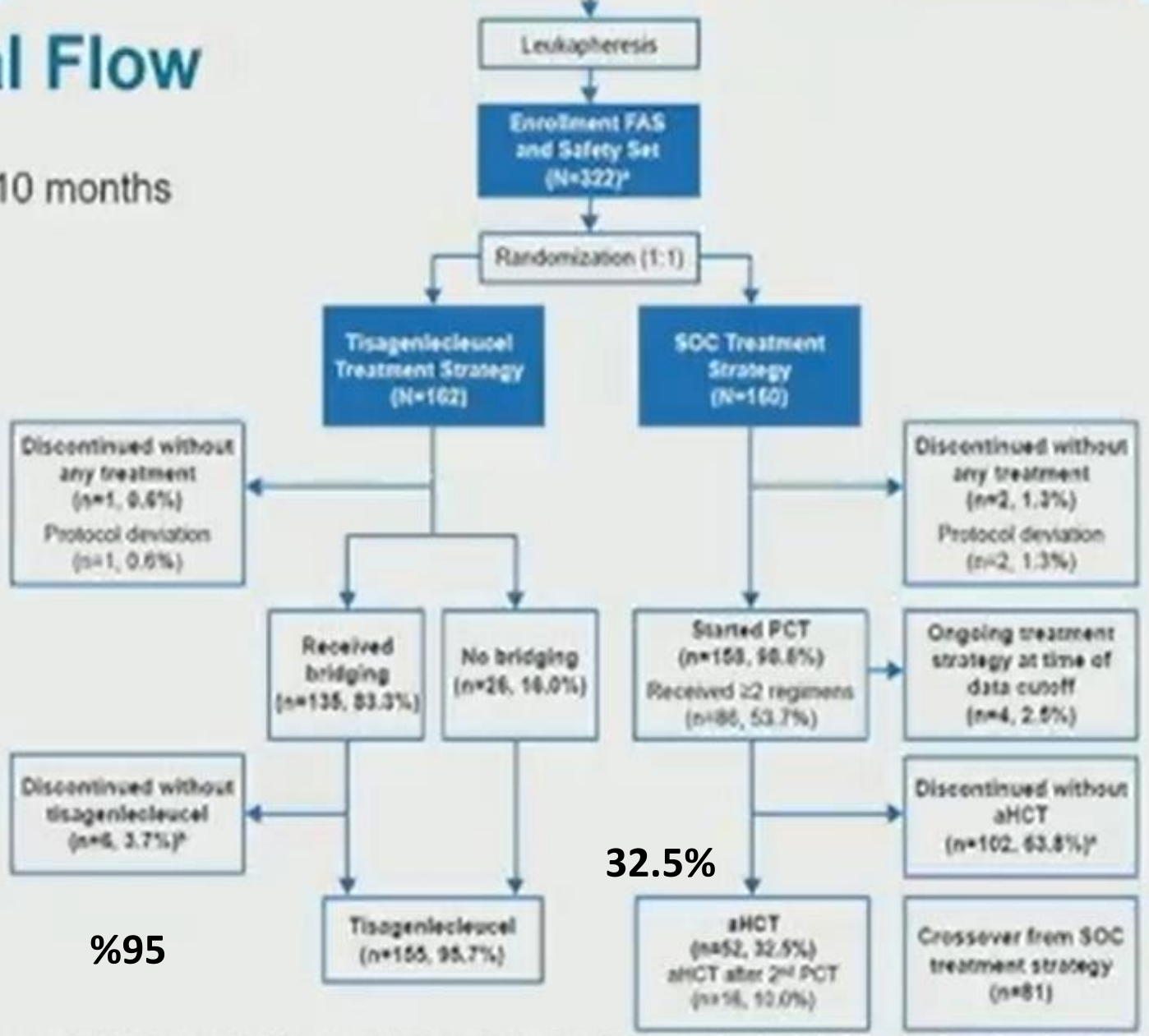
Patient Trial Flow

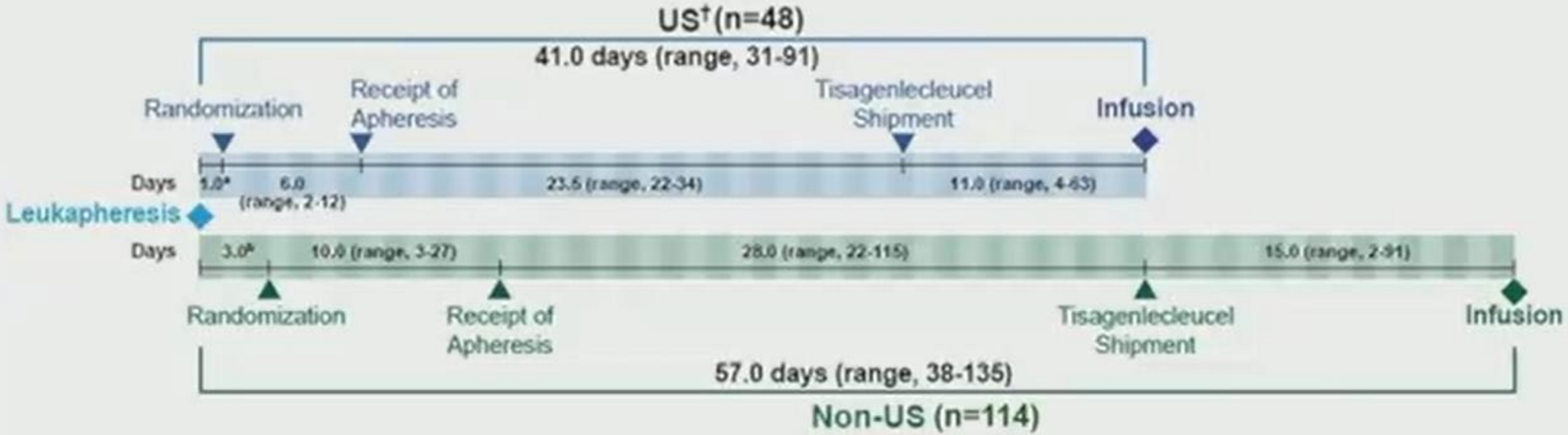
- Median follow-up: 10 months (range, 2.9-23.2)



aFAS and safety sets used to compare efficacy and safety between the 2 treatment strategies during the safety comparison period, defined as from day of randomization to the earlier of 56 days after last dose of study treatment or start date of new anticancer therapy. bReasons for discontinuation without tisagenlecleucel infusion include physician decision (n=2, 1.2%), PD (n=2, 1.2%), Manufacturing issue (n=1, 0.6%), and patient decision (n=1, 0.6%). cReasons for discontinuation without aHCT include PD (n=76, 47.5%), physician decision (n=14, 8.8%), death (n=7, 4.4%), patient decision (n=2, 1.3%), technical problems (n=2, 1.3%), and protocol deviation (n=1, 0.6%). aHCT, autologous hematopoietic cell transplantation; FAS, full analysis set; PCT, platinum-based immunochemotherapy; SOC, standard of care.

Time to Tisagenlecleucel Infusion

- Median time to infusion for all patients on the Tisagenlecleucel arm was 52 days (range, 31-135)



†North America was a stratification factor, and all enrolled patients in this group were from the United States (US).
[a]range, 1-6 days, [b]range, 1-17 days

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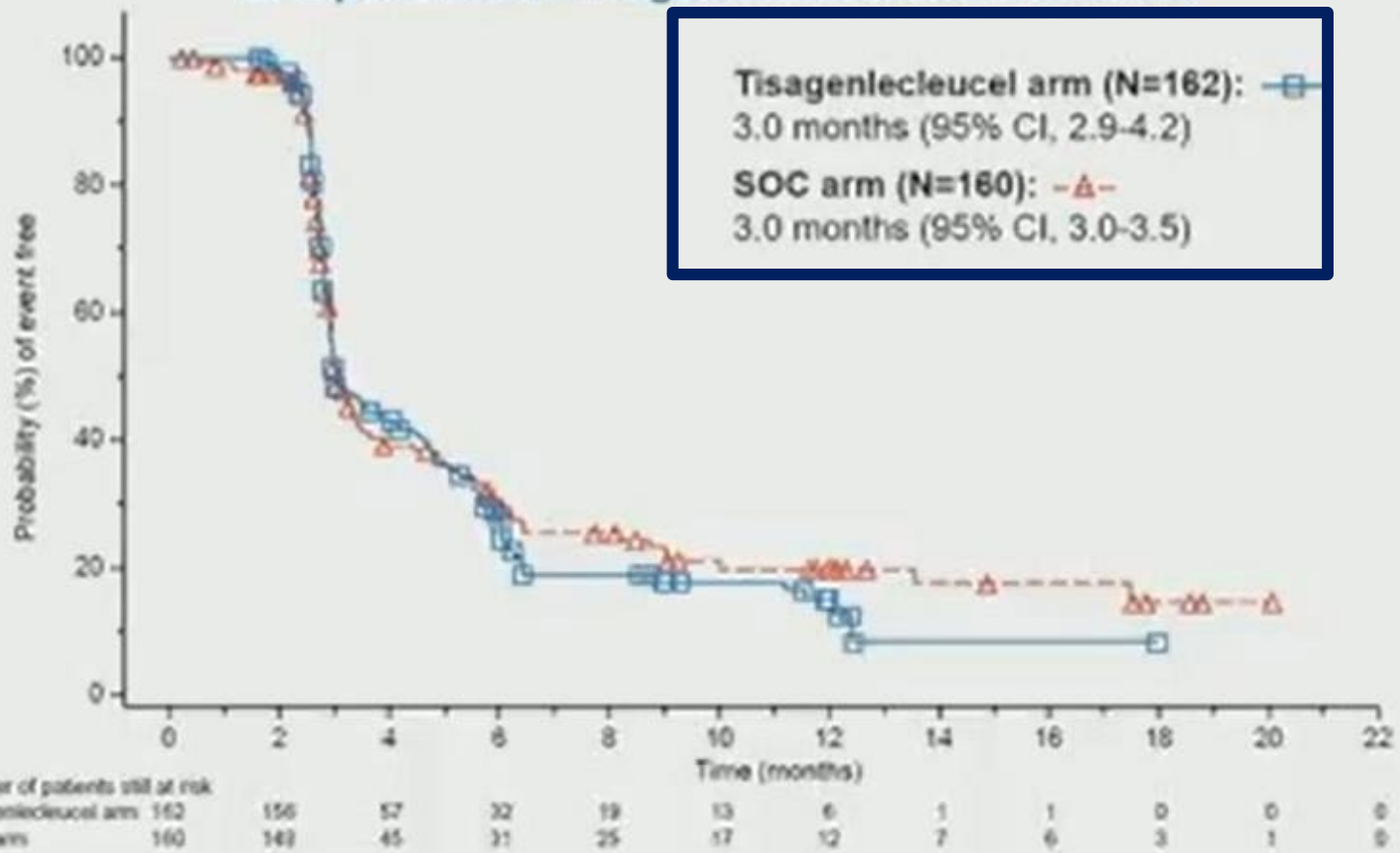
No Difference in EFS Between Treatment Arms

EFS per BIRC in Tisagenlecleucel and SOC Arms



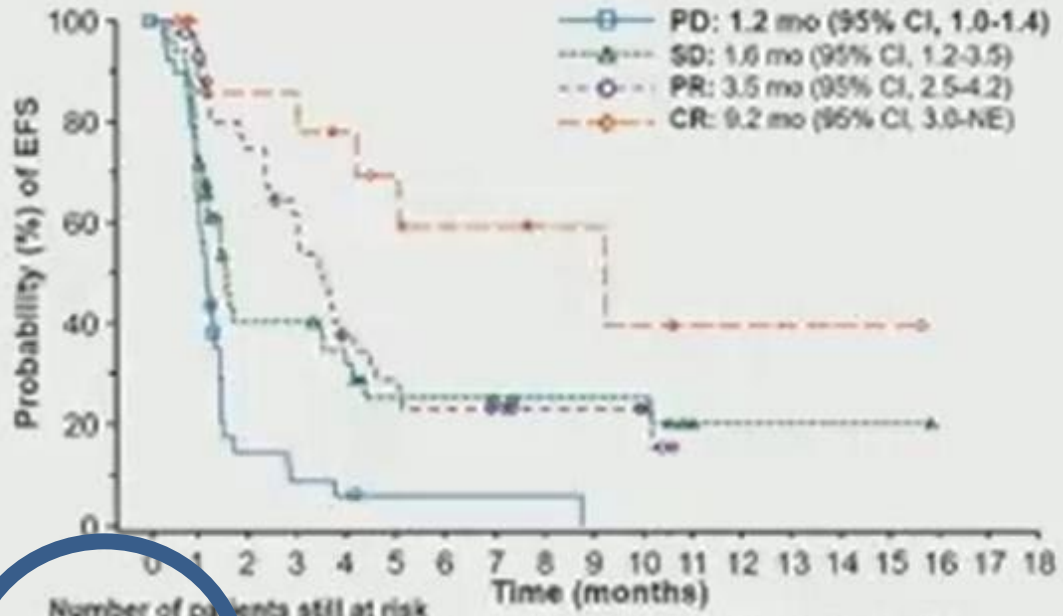
- EFS[a] was not significantly different between treatment arms
  - Primary analysis: Stratified unadjusted HR: 1.07 (95% CI, 0.82-1.40, p[b]=0.69)
  - Supportive analysis: Stratified adjusted[c] HR: 0.95 (95% CI, 0.72-1.25)
  - 6 patients responded to tisagenlecleucel infusion, but were captured as an EFS event due to SD/PD before or soon after infusion[d]

[a]EFS events defined as PD/SD after day 71 or death at any time. [b]p-value derived from 1-sided stratified log-rank test. [c]Adjusted for for potential imbalances in patient characteristics with pre-specified covariates of age, sex, race, ECOG performance status, histological subgroup, disease stage, and disease subtype. [d]Stratified adjusted HR accounting for delayed responses in both arms yield HR of 0.84 (95% CI: 0.63, 1.12).

BIRC, blinded independent review committee; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; OS, overall survival; PD, progressive disease; SD, stable disease; SOC, standard of care.

EFS by Pre-infusion Response Status and Disease Diagnosis in the Tisagenlecleucel Arm

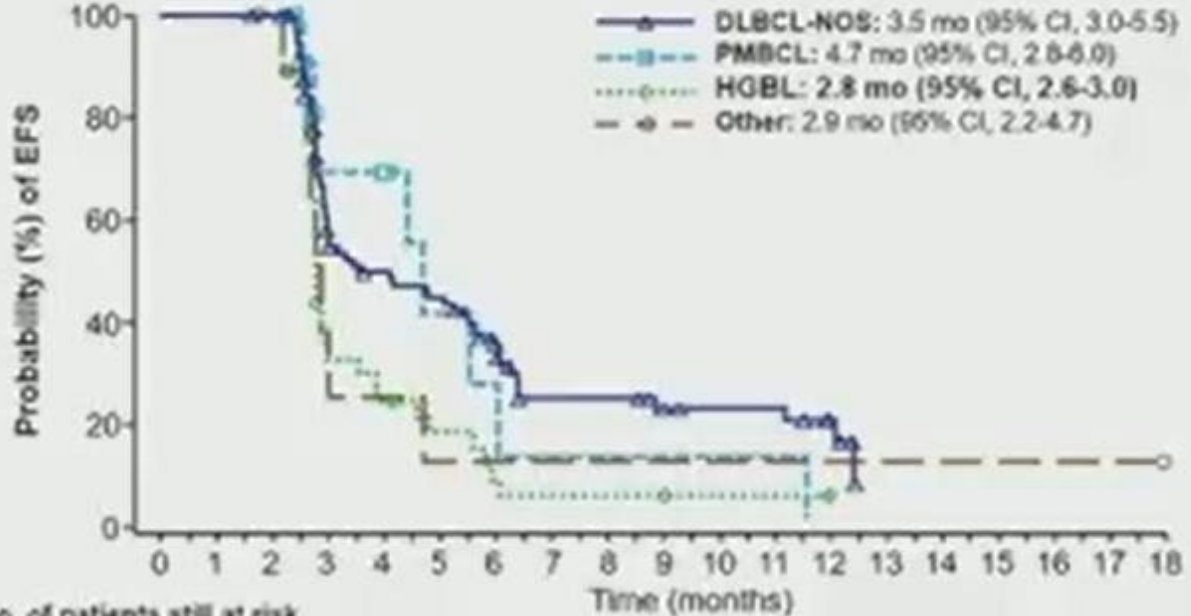
EFS[a] by per BIRC Response Status Pre-infusion



Number of patients still at risk

PD	41	25	5	3	2	1	1	1	1	0	0	0	0	0	0	0	0
SD	56	37	5	15	11	7	7	6	5	5	5	2	1	1	1	1	0
PR	42	39	9	23	13	10	8	7	5	5	3	0	0	0	0	0	0
CR	17	12	11	11	9	7	5	5	3	3	2	1	1	1	1	1	0

EFS per BIRC by Disease Diagnosis[b]



No. of patients still at risk

DLBCL NOS	101	101	99	49	40	36	28	15	15	12	10	10	5	0	0	0	0	0	0
PMBCL	12	12	12	6	6	3	2	1	1	1	1	1	0	0	0	0	0	0	0
HBGL	39	39	36	12	9	6	3	2	2	2	1	1	0	0	0	0	0	0	0
Other	10	10	9	3	2	1	1	1	1	1	1	1	1	1	1	1	1	1	0

[a]Time is relative to date of tisagenlecleucel infusion. Median time from pre-infusion disease assessment to infusion was 10 days (range, 2-57; Q1-Q3, 8-15). [b]EFS events defined as PD/SD after day 71 from randomization or death at any time.

BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; DLBCL NOS, diffuse large B-cell lymphoma not otherwise specified; EFS, event-free survival; HGBL, high-grade B-cell lymphoma; mEFS, modified event-free survival; NE, not estimable; PD, progressive disease; PMBCL, primary mediastinal B-cell lymphoma; PR, partial response; SD, stable disease; SOC, standard of care.

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ORR at Week 6 and Best Overall Response

	Week 6 Assessment[a] (Response to PCT)		Best Overall Response (at/after Week 12 Assessment)[b]	
	Tisagenlecleucel Arm (N=162)	SOC Arm (N=160)	Tisagenlecleucel Arm (N=162)	SOC Arm (N=160)
ORR				
CR+PR – no. (%) 95% CI	62 (38.3) (30.8-46.2)	86 (53.8) (45.7-61.7)	75 (46.3) (38.4-54.3)	68 (42.5) (34.7-50.6)
Best Overall Response – no. (%)				
CR	18 (11.1)	31 (19.4)	46 (28.4)	44 (27.5)
PR	44 (27.2)	55 (34.4)	29 (17.9)	24 (15.0)
SD	48 (29.6)	46 (28.8)	19 (11.7)	22 (13.8)
PD	42 (25.9)	22 (13.8)	50 (30.9)	46 (28.8)
UNK	10 (6.2)	6 (3.8)	18 (11.1)	24 (15.0)

[a]Prior to tisagenlecleucel infusion as per protocol. Week 6 assessment considered as the earliest assessment on or after day 29 and on or before the earliest of day 70 or new anticancer therapy date and per protocol reflected last disease assessment prior to infusion in the tisagenlecleucel arm and disease status after first PCT in the SOC arm. [b]After tisagenlecleucel infusion as per protocol. BOR considers efficacy assessments on or after day 71 and until SD/PD or start of new therapy. Six patients in the tisagenlecleucel arm and 1 patient in the SOC arm responded after initial SD/PD and without starting a new therapy, but were considered nonresponders for ORR as defined per protocol.

BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; mBOR, modified best overall response; mORR, modified overall response rate; ORR, overall response rate; PCT, platinum-based immunochemotherapy; PD, progressive disease; PR, partial response; SD, stable disease; SOC, standard of care; UNK, unknown.

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	Week 6 Assessment[a] (Response to PCT)		Best Overall Response (at/after Week 12 Assessment)[b]	
	Tisagenlecleucel Arm (N=162)	SOC Arm (N=160)	Tisagenlecleucel Arm (N=162)	SOC Arm (N=160)
ORR				
CR+PR – no. (%)	62 (38.3)	86 (53.8)	75 (46.3)	68 (42.5)
95% CI	(30.8-46.2)	(45.7-61.7)	(38.4-54.3)	(34.7-50.6)
Best Overall Response – no. (%)				
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ORR				
CR+PR – no. (%)	62 (38.3)	86 (53.8)	75 (46.3)	68 (42.5)
95% CI	(30.8-46.2)	(45.7-61.7)	(38.4-54.3)	(34.7-50.6)
Best Overall Response – no. (%)				
CR	18 (11.1)	31 (19.4)	46 (28.4)	44 (27.5)
PR	44 (27.2)	55 (34.4)	29 (17.9)	24 (15.0)
SD	48 (29.6)	46 (28.8)	19 (11.7)	22 (13.8)
PD	42 (25.9)	22 (13.8)	50 (30.9)	46 (28.8)
UNK	10 (6.2)	6 (3.8)	18 (11.1)	24 (15.0)

[a]Prior to tisagenlecleucel infusion as per protocol. Week 6 assessment considered as the earliest assessment on or after day 29 and on or before the earliest of day 70 or new anticancer therapy date and per protocol reflected last disease assessment prior to infusion in the tisagenlecleucel arm and disease status after first PCT in the SOC arm. [b]After tisagenlecleucel infusion as per protocol. BOR considers efficacy assessments on or after day 71 and until SD/PD or start of new therapy. Six patients in the tisagenlecleucel arm and 1 patient in the SOC arm responded after initial SD/PD and without starting a new therapy, but were considered nonresponders for ORR as defined per protocol.

BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; mBOR, modified best overall response; mORR, modified overall response rate; ORR, overall response rate; PCT, platinum-based immunochemotherapy; PD, progressive disease; PR, partial response; SD, stable disease; SOC, standard of care; UNK, unknown.

Presented at the 2021 ASH Annual Meeting, 11-14 December, 2021, Georgia World Congress Center - Atlanta, GA

Conclusions

- EFS was not significantly different between tisagenlecleucel and SOC treatment strategies in patients with aggressive NHL that was refractory or relapsed early after first-line therapy
- Our findings suggest the importance of preventing PD prior to infusion
  - A higher proportion of patients had PD at week 6, prior to CAR T-cell infusion, in the tisagenlecleucel arm
- Effective bridging prior to CAR T-cell infusion and a shorter time to infusion for this chemotherapy-refractory patient population could be critical to improve outcomes
- Insights from this randomized Phase III study should help guide optimal use of CAR T-cells in patients with r/r aggressive NHL requiring second-line therapy and design of future CAR-T trials

CAR, chimeric antigen receptor; EFS, event-free survival; NHL, non-Hodgkin lymphoma; PD, progressive disease; r/r, refractory or relapsed; SOC, standard of care.

Presented at the 2021 ASH Annual Meeting, 11-14 December, 2021, Georgia World Congress Center - Atlanta, GA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma

M.R. Bishop, M. Dickinson, D. Purtill, P. Barba, A. Santoro, N. Hamad, K. Kato, A. Sureda, R. Greil, C. Thieblemont, F. Morschhauser, M. Janz, I. Flinn, W. Rabitsch, Y.-L. Kwong, M.-J. Kersten, M.C. Minnema, H. Holte, E.H.L. Chan, J. Martinez-Lopez, A.M.S. Müller, R.T. Maziarz, J.P. McGuirk, E. Bachy, S. Le Gouill, M. Dreyling, H. Harigae, D. Bond, C. Andreadis, P. McSweeney, M. Kharfan-Dabaja, S. Newsome, E. Degtyarev, R. Awasthi, C. del Corral, G. Andreola, A. Masood, S.J. Schuster, U. Jäger, P. Borchmann, and J.R. Westin

Profiling of Circulating Tumor DNA for Noninvasive Disease Detection, Risk Stratification, and MRD Monitoring in Patients with CNS Lymphoma

Mutter JA*, Alig S*, Lauer EM, Esfahani MS, Mitschke J, Kurtz DM, Kühn J, Bleul S, Olsen M, Liu CL, Jin MC, Macaulay CW, Neidert NN, Volk T, Rauer S, Heiland DH, Finke J, Duyster J, Wehrle J, Prinz M, Illerhaus G, Reinacher PC, Schorb E, Diehn M, Alizadeh AA, Scherer F

63rd ASH Annual Meeting, Plenary Session, 12/12/2021

Central nervous system lymphoma

Central nervous system lymphoma (CNSL)
Major clinical challenges

Poor prognosis after relapse / progression

Heterogeneous outcomes following methotrexate-based treatment

Tools for accurate risk stratification and prediction of outcomes are lacking

Ferreri AJM et al., *Lancet Haematol*, 2016
Illerhaus G et al., *Lancet Haematol* , 2016
Grommes C et al., *J Clin Oncol*, 2017
Holdhoff M et al., *Onco Targets Ther*, 2020

Diagnosis relies on invasive procedures

Often inconclusive due to inaccurate tissue targeting

Associated with peri- and postoperative morbidity and mortality

Air EL et al., *J Neurosurg*, 2009
Manoj N et al., *J Neurosci Rural Pract*, 2014
Malone H et al., *World Neurosurg*, 2015

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Central nervous system lymphoma

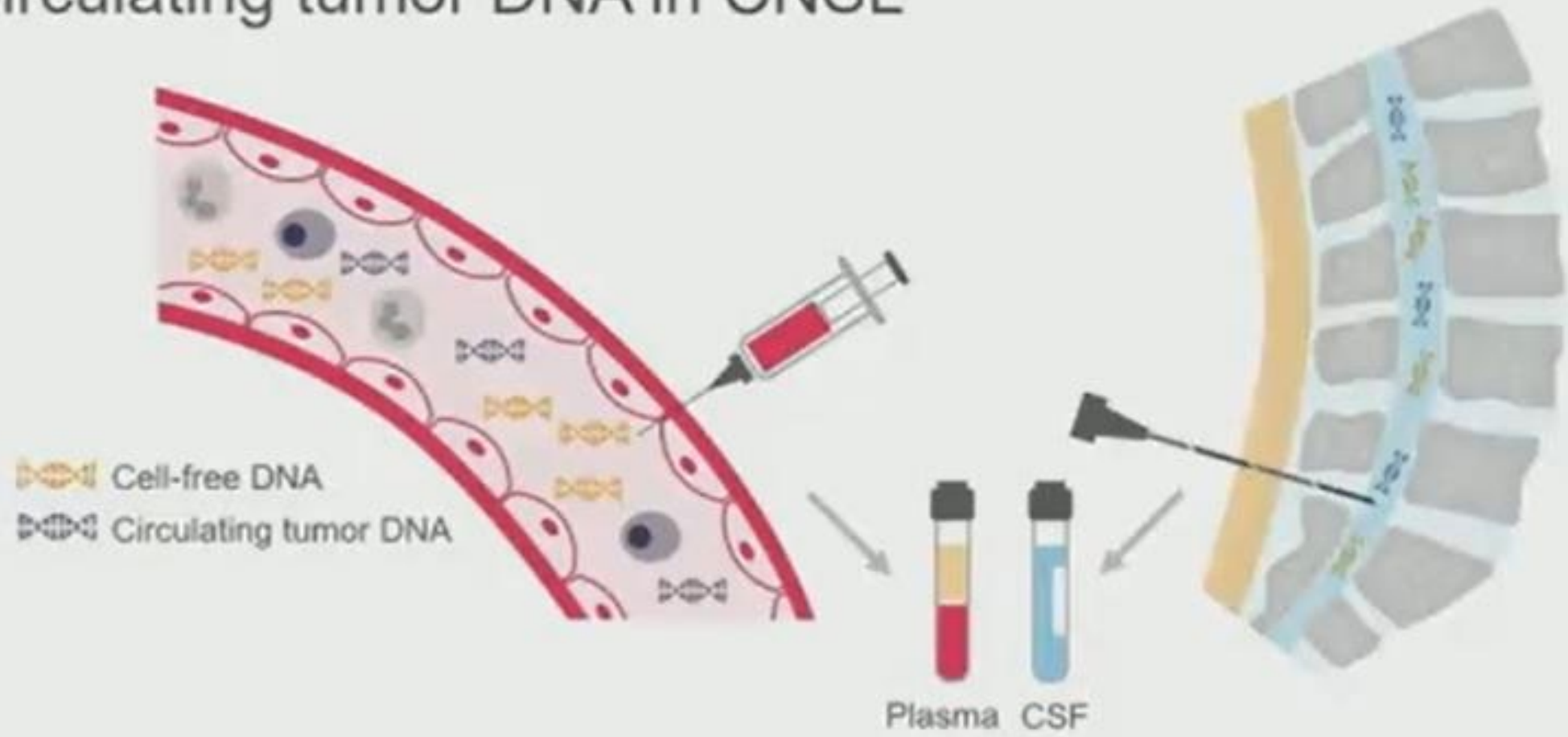
Central nervous system lymphoma (CNSL)
Major clinical challenges

Poor prognosis after relapse / progression	Diagnosis relies on invasive procedures
Heterogeneous outcomes following methotrexate-based treatment Tools for accurate risk stratification and prediction of outcomes are lacking	Often inconclusive due to inaccurate tissue targeting Associated with peri- and postoperative morbidity and mortality

Unmet need for innovative biomarkers that facilitate

1) Identification of patients at high risk for relapse / progression
2) Biopsy-free diagnosis of CNSL

Circulating tumor DNA in CNSL



Limitations of ctDNA detection in CNSL

- Extremely low ctDNA concentrations in plasma
- Low detection rates in plasma (0-32%) by NGS
- Limited applicability of single gene assays (*MYD88* ^{L265P})

Yoon et al., *Cancer Res Treat*, 2021
Montesinos-Rongen M et al., *J Mol Diagn*, 2020
Hattori K et al., *Cancer Science*, 2018
Fontanilles M et al., *Oncotarget*, 2017

Methods

CAPP-Seq

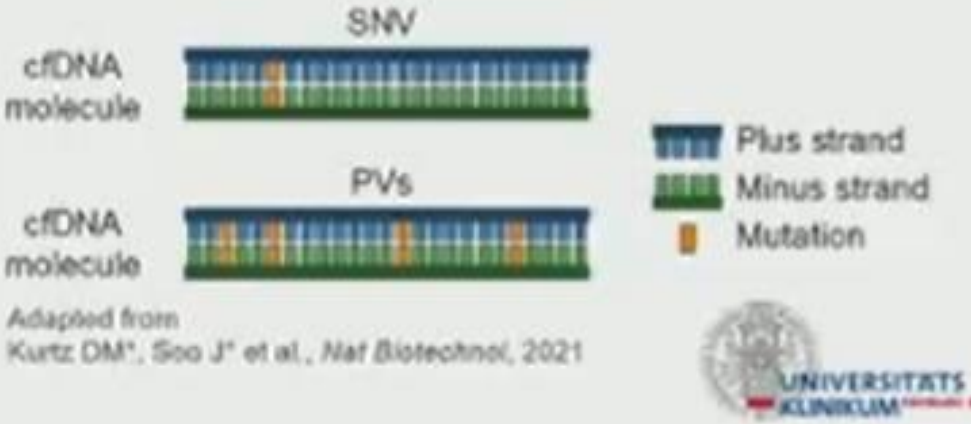
- Targeted capture high-throughput sequencing technology
- Sequencing panel: 199 kb, capturing 580 genetic regions

→ **Genotyping** of gDNA in tumor and ctDNA in CSF and plasma

PhasED-seq

- Utilizes phased variants (PVs) that occur within a typical cfDNA molecule
- Ultrasensitive detection of ctDNA (~1:2,000,000 = 0.00005%)

→ **Monitoring** of ctDNA in plasma and CSF



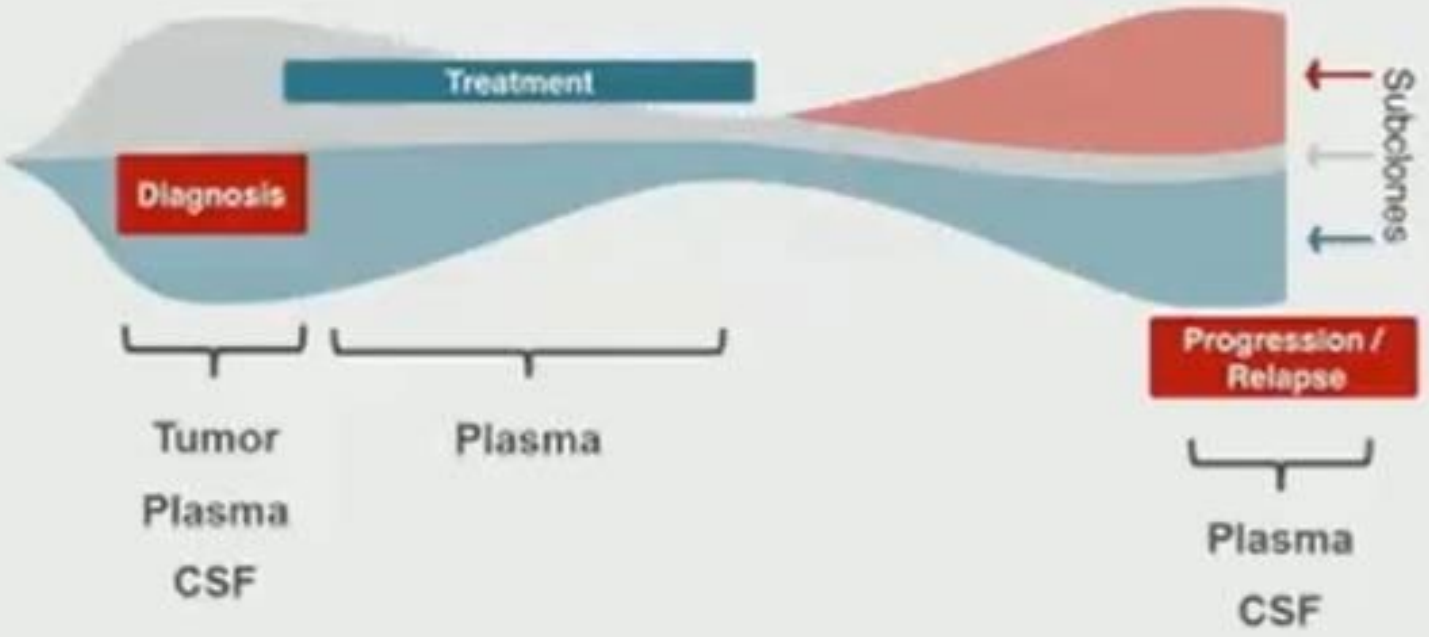
Adapted from
Kurtz DM*, Soo J* et al., *Nat Biotechnol*, 2021

Kurtz DM*, Soo J* et al., *Nat Biotechnol*, 2021
Kurtz DM*, Scherer F* et al., *J Clin Oncol*, 2018
Newman AM*, Lovejoy AF*, Klass DM* et al., *Nat Biotechnol*, 2016
Scherer F*, Kurtz DM*, Newman AM* et al., *Sci Transl Med*, 2016
Newman AM et al., *Nat Med*, 2014

Study cohort (Freiburg University)

Patient cohort (n = 67)*	
Median age (years)	65
Gender, n (%)	
Female	30 (44.8)
Male	37 (55.2)
Diagnosis, n (%)	
PCNSL	55 (82.1)
Isolated SCNSL (iSCLC)	12 (17.9)
Histology, n (%)	
DLBCL	65 (97)
CLL	1 (1.5)
CD38+ LBCL	1 (1.5)
Treatment strategy, n (%)	
Curative-intent	52 (77.6)
Palliative	10 (14.9)
NA	5 (7.5)
Surgical procedure, n (%)	
Biopsy	57 (85.1)
Complete resection	2 (3.0)
Partial resection	4 (6.0)
NA	4 (6.0)
MSKCC score, n (%)	
1	1 (1.5)
2	39 (58.2)
3	19 (28.4)
NA	8 (11.9)

* Patients with tumor and at least one plasma sample



Non-CNSL brain tumors n = 44

Healthy controls n = 24

Total samples: 270

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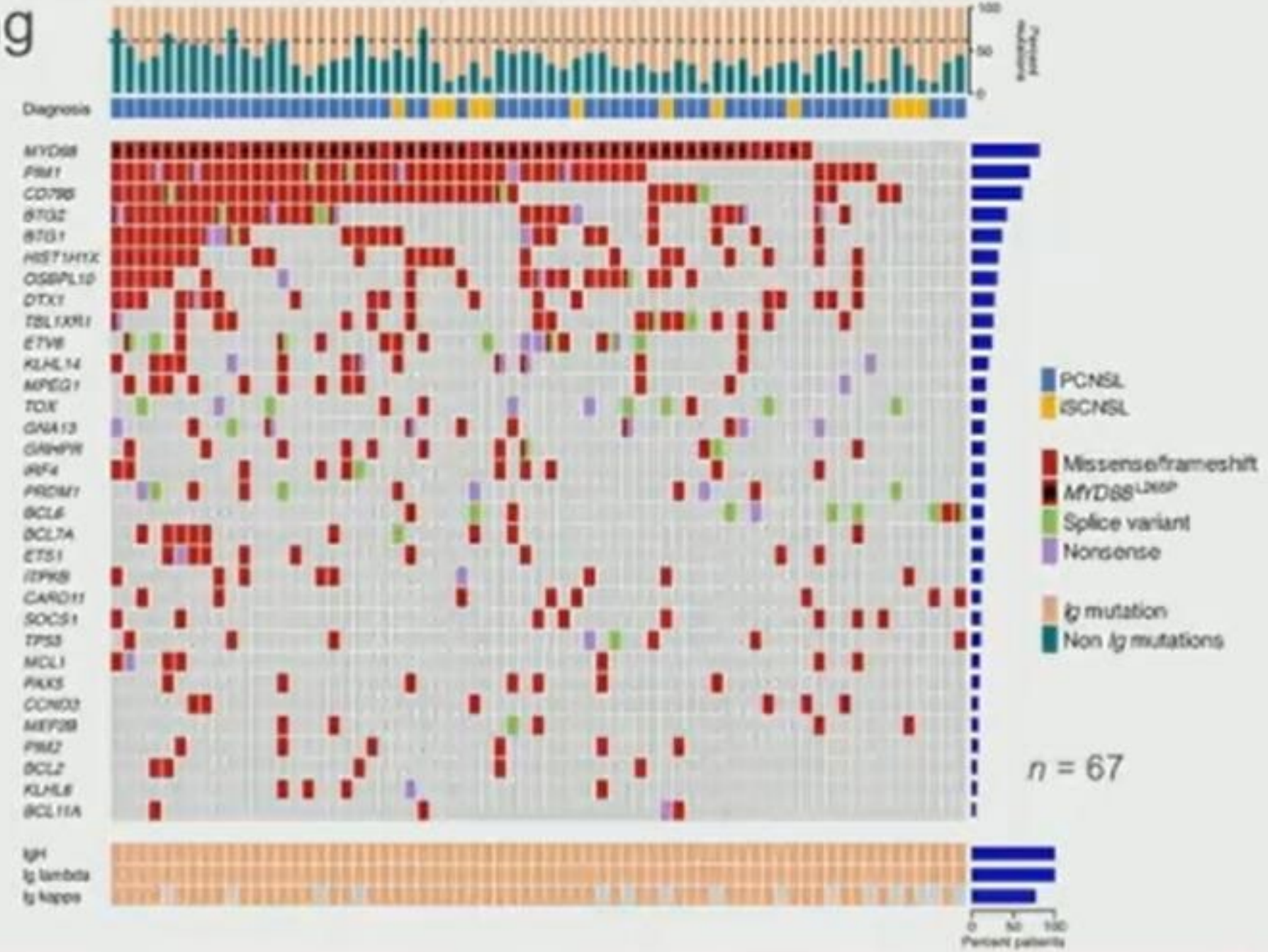
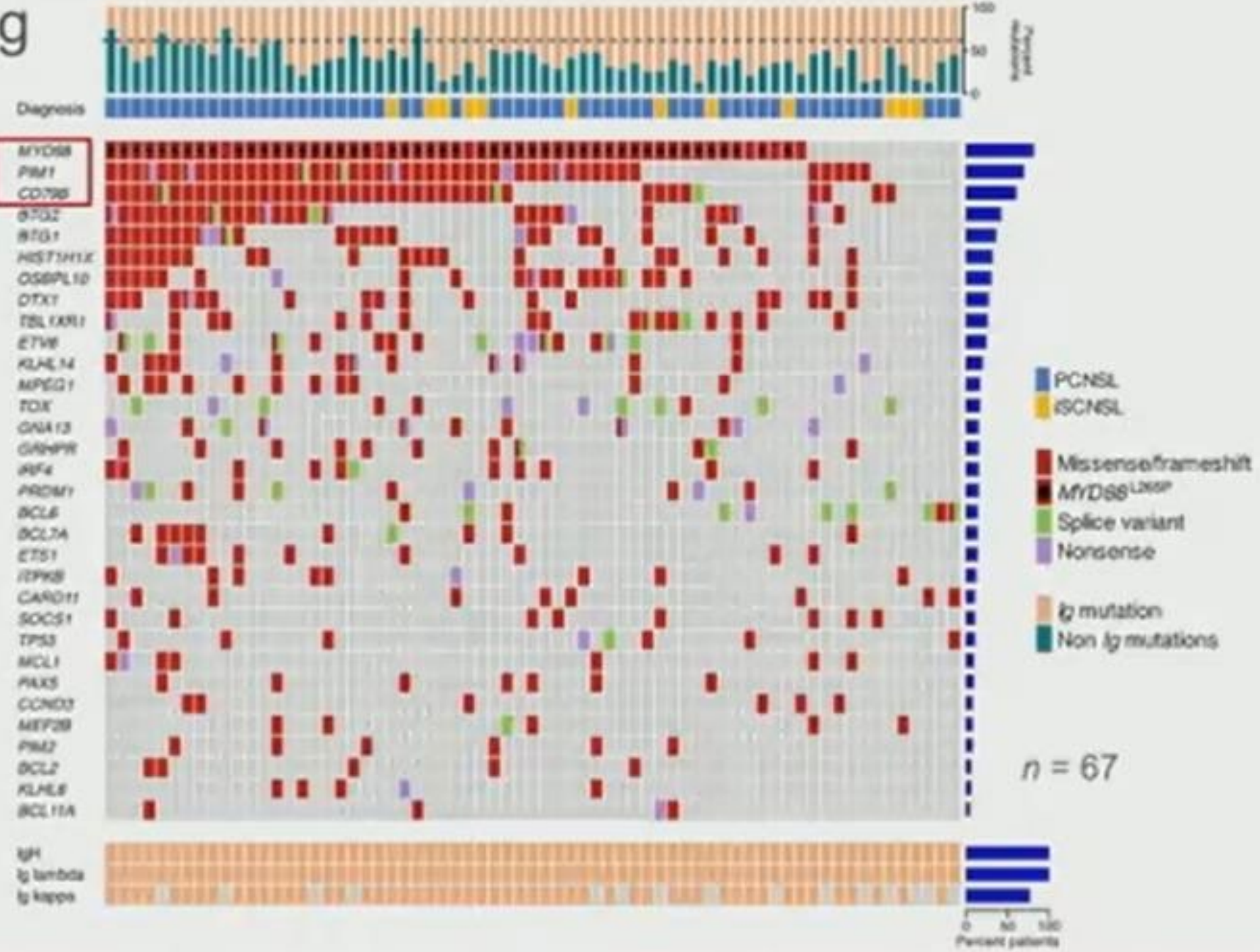
Tumor genotyping



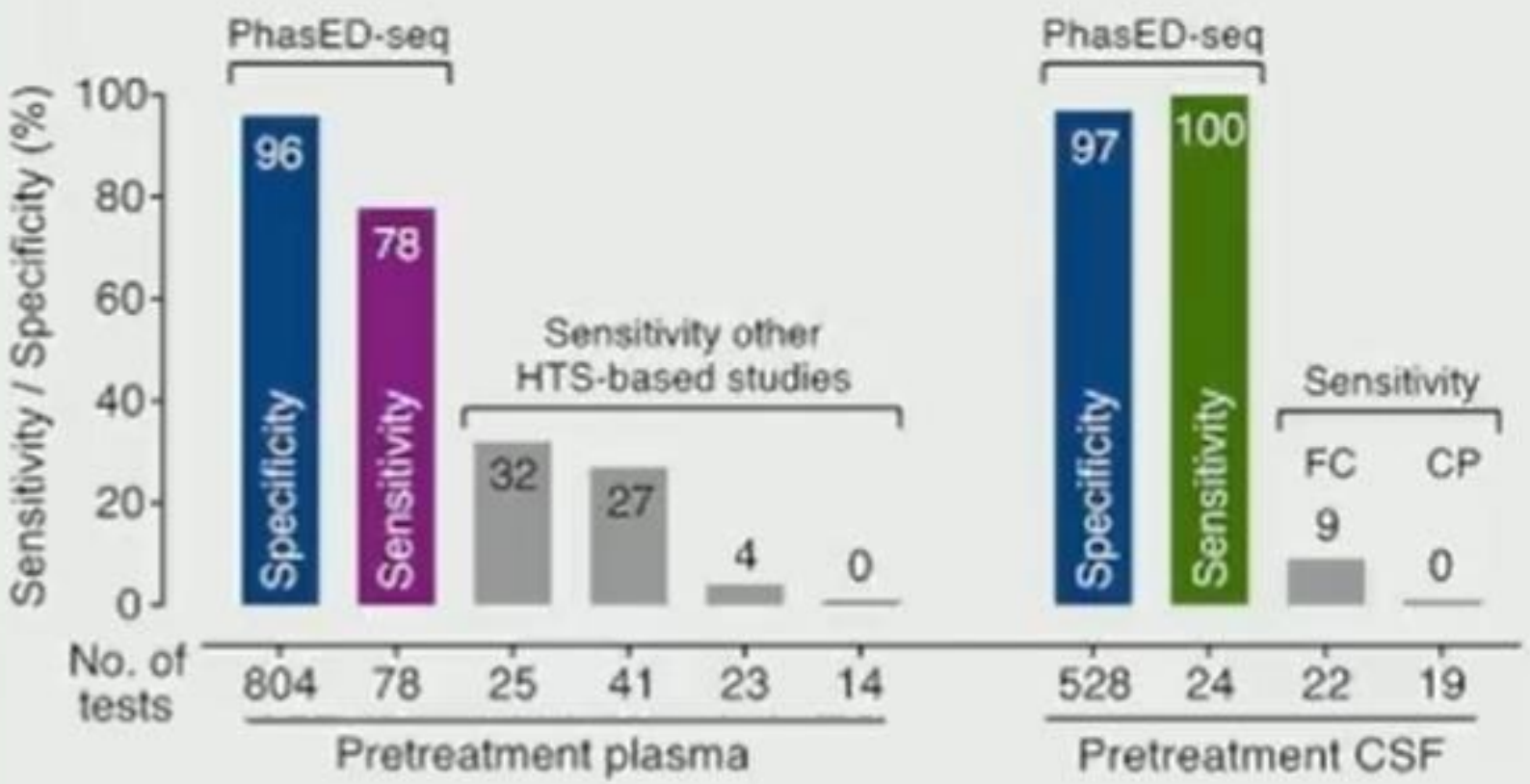
Tumor genotyping

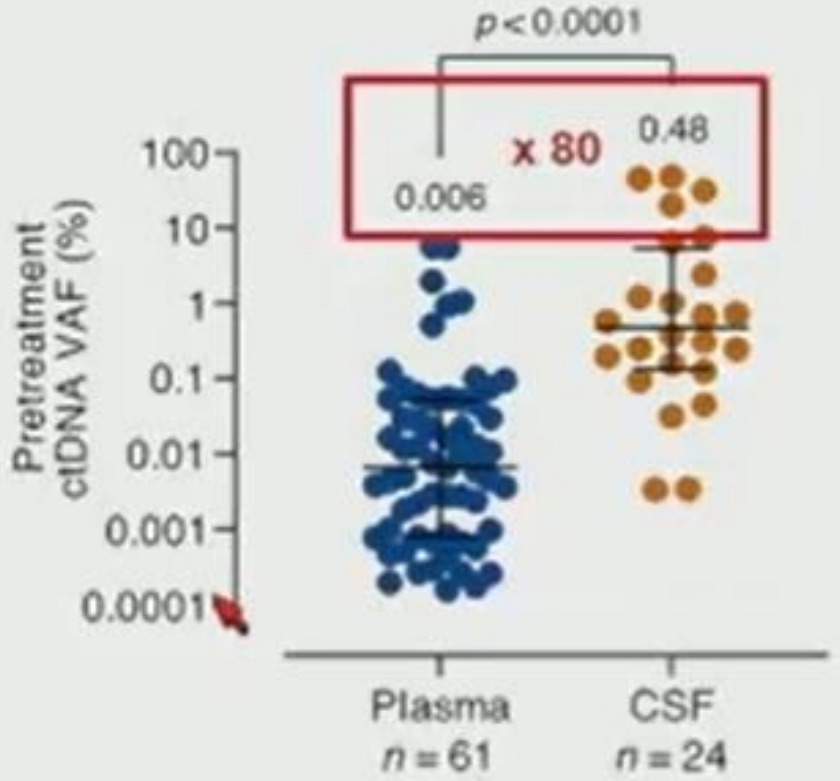
MYD88 L265P
73% of patients



Median number of mutations per patient: 288

Improved tumor-informed ctDNA detection in CNSL





Yoon et al., *Cancer Res Treat*, 2021
Montesinos-Rongen M et al., *J Mol Diagn*, 2020
Hattori K et al., *Cancer Science*, 2018
Fontanilles M et al., *Oncotarget*, 2017

FC = Flow cytometry
CP = Cytopathology

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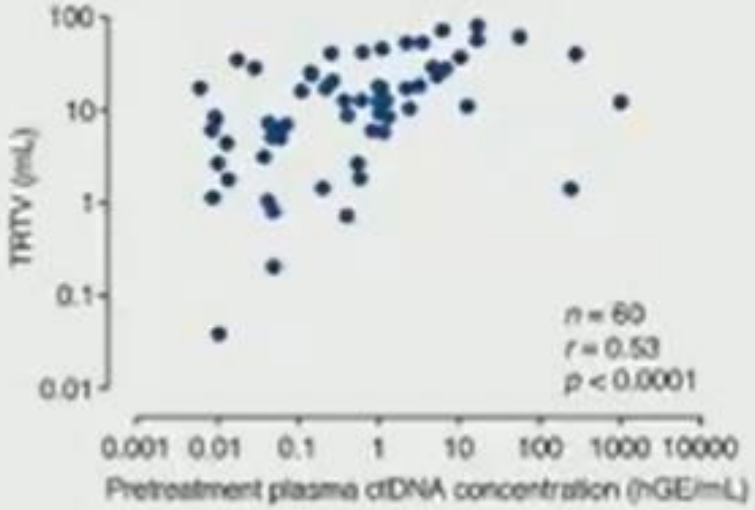
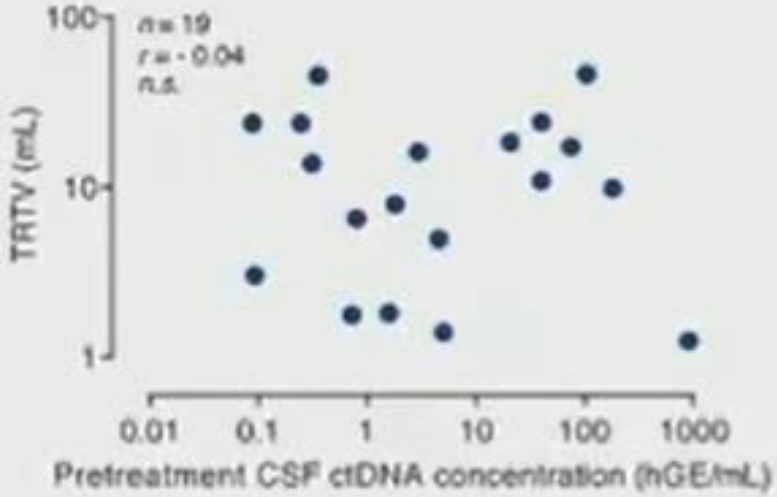
Association of pretreatment ctDNA with radiographic features

Plasma

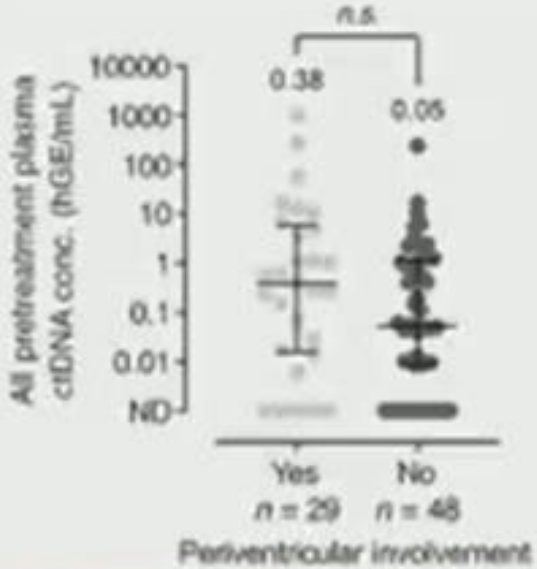
CSF

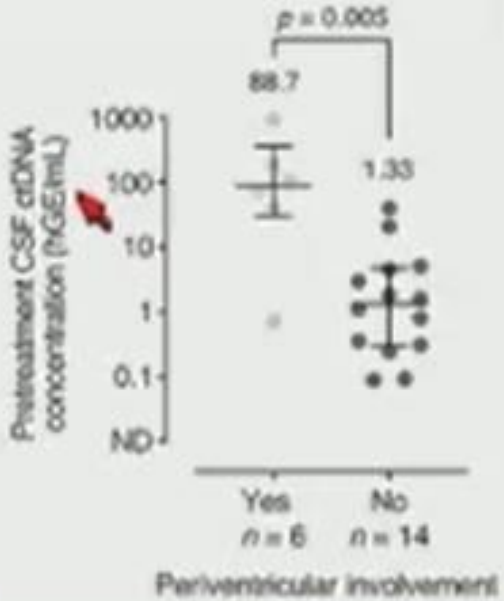
Total radiographic tumor volume (TRTV)



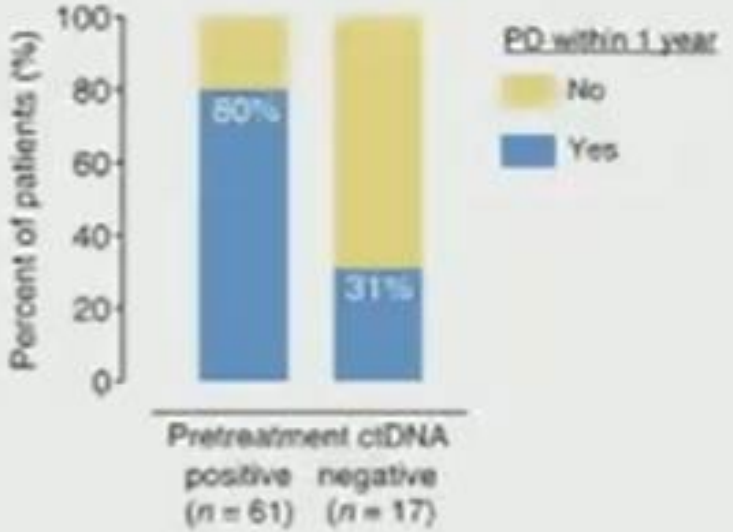


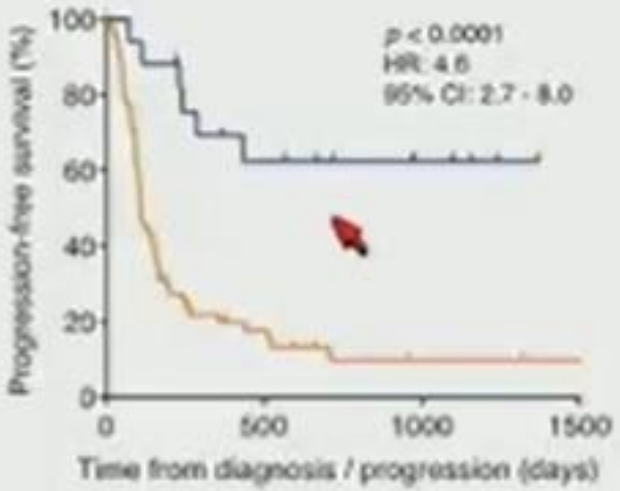
Periventricular involvement

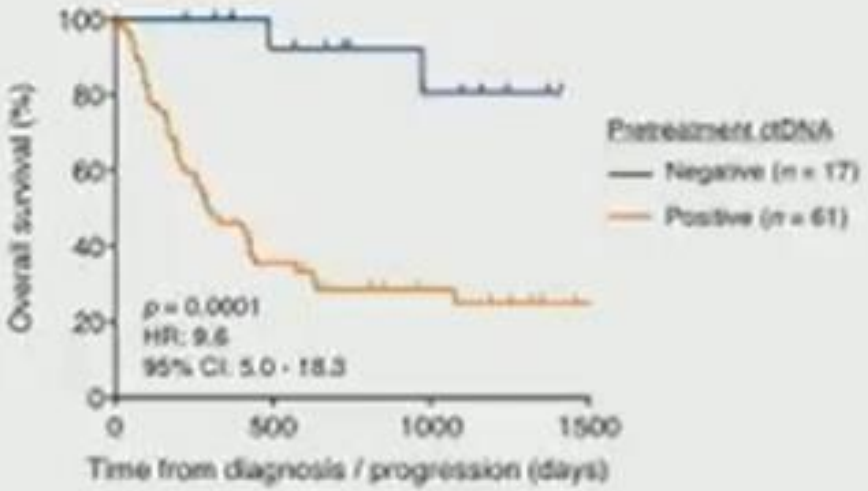


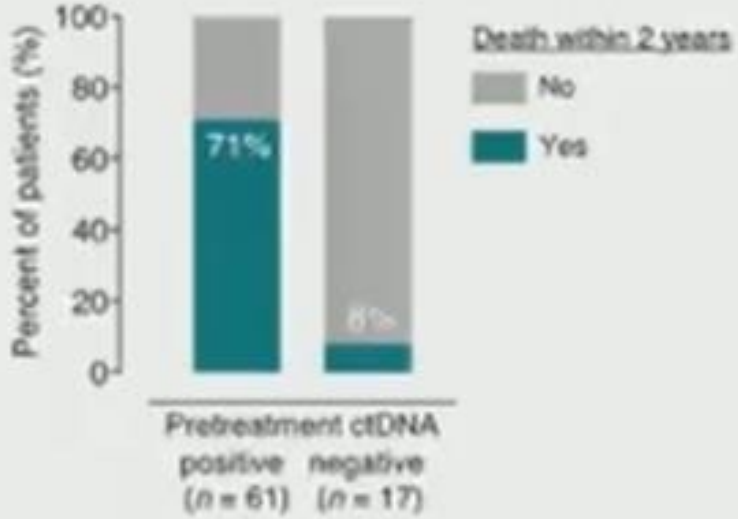


Pretreatment plasma ctDNA as a prognostic biomarker









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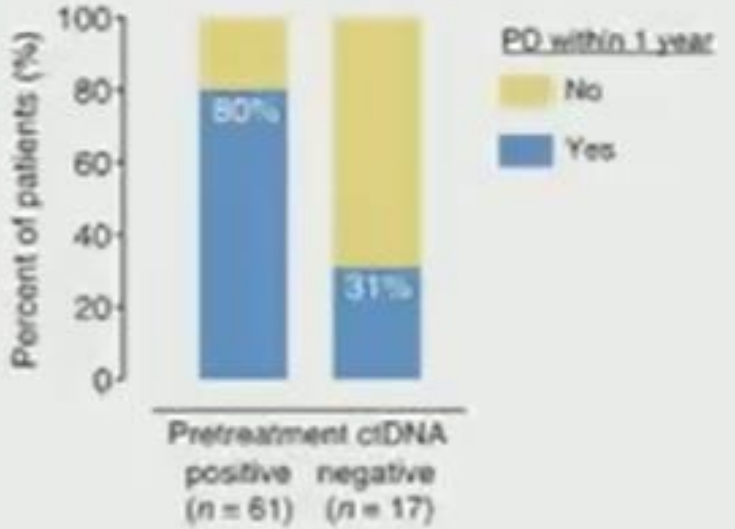
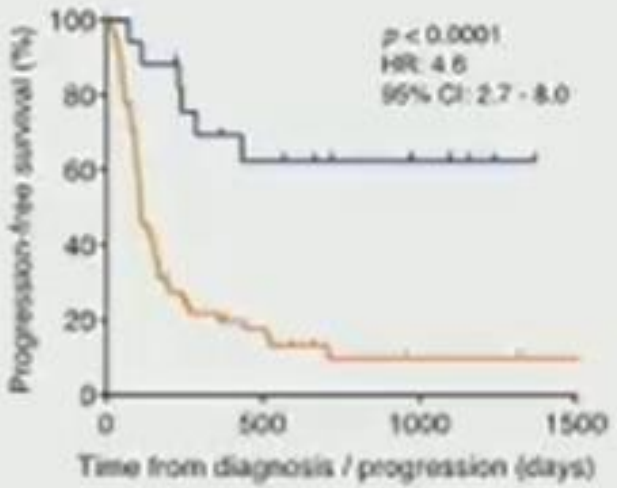
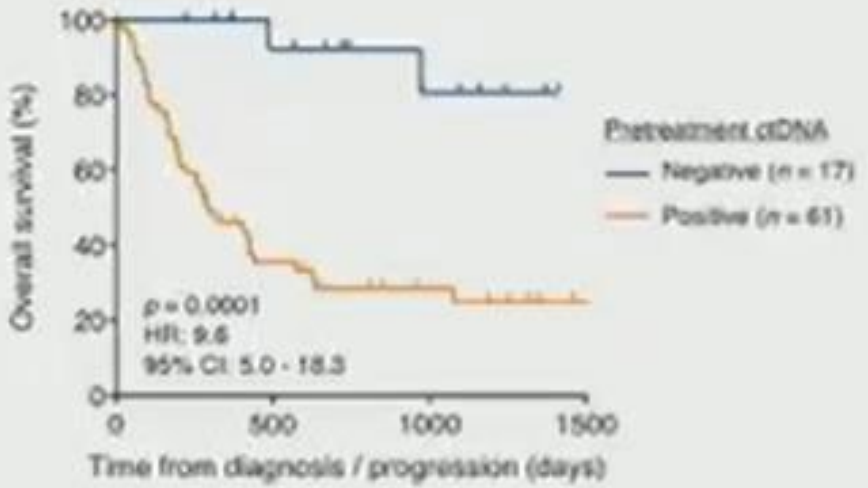
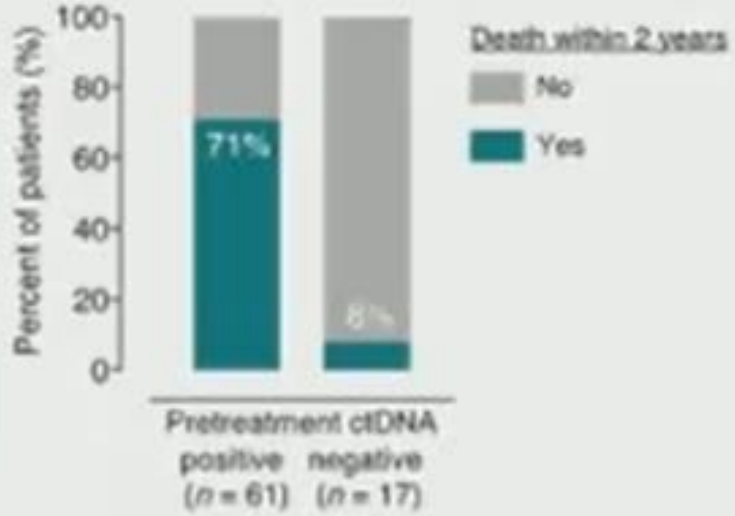
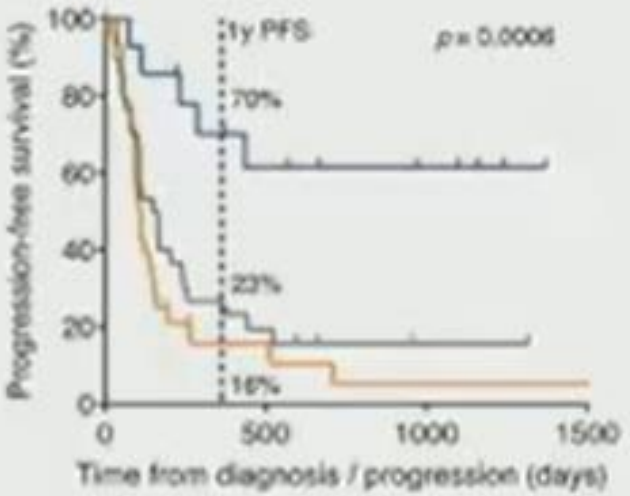
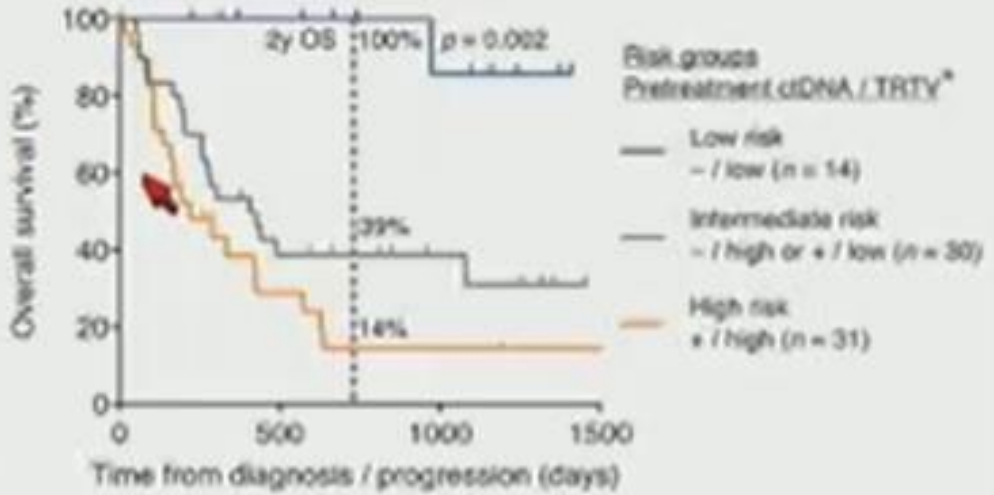






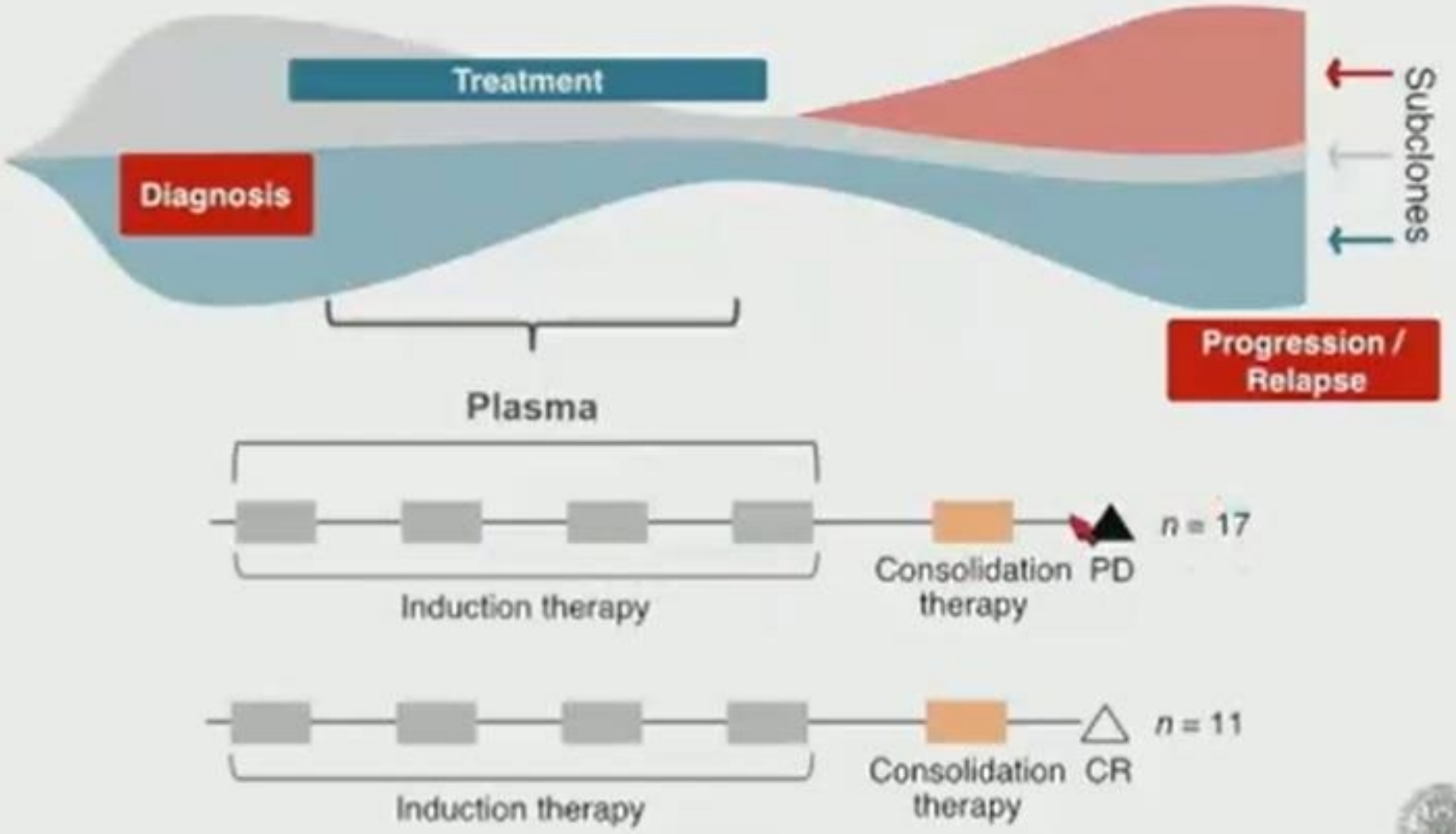




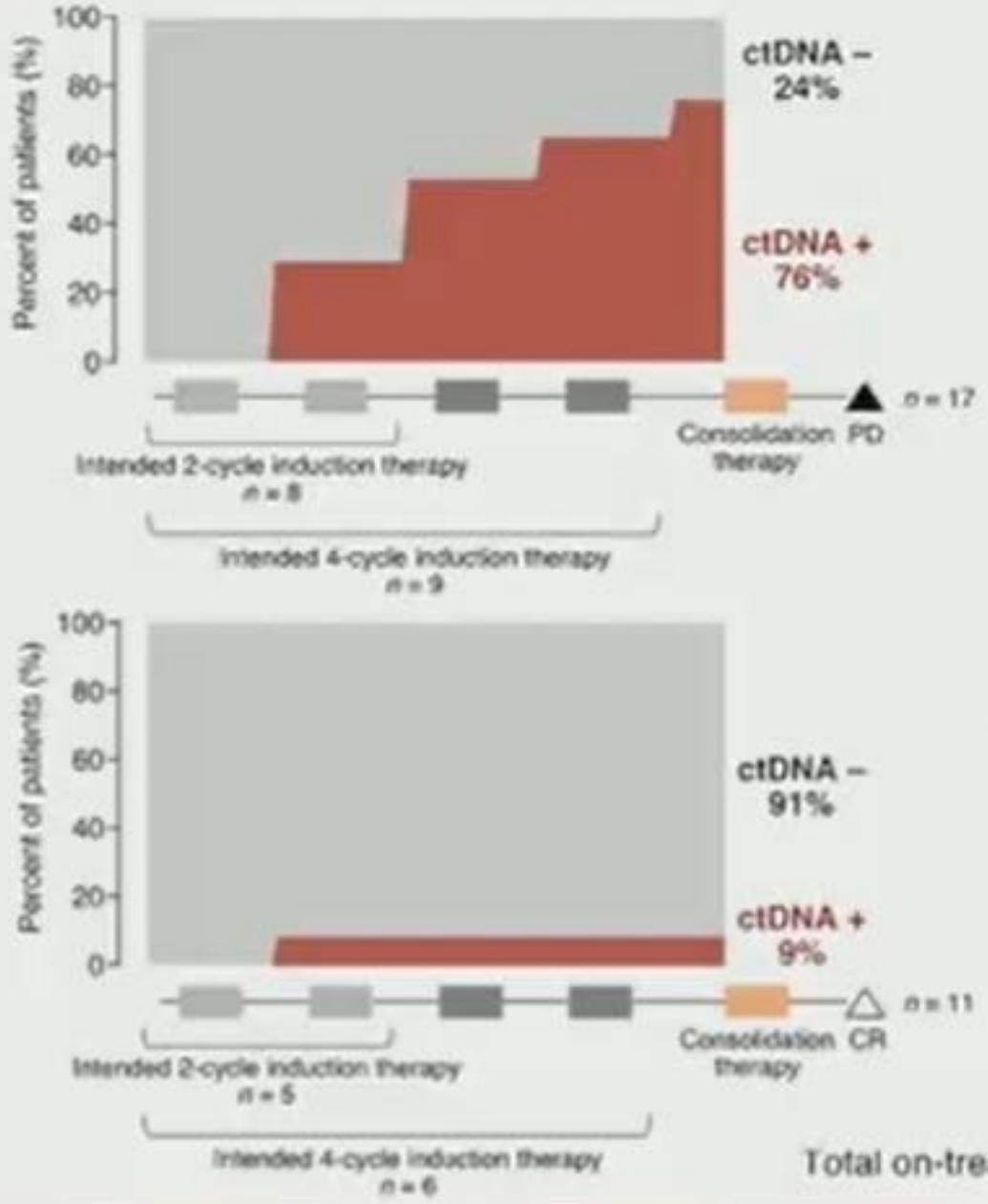


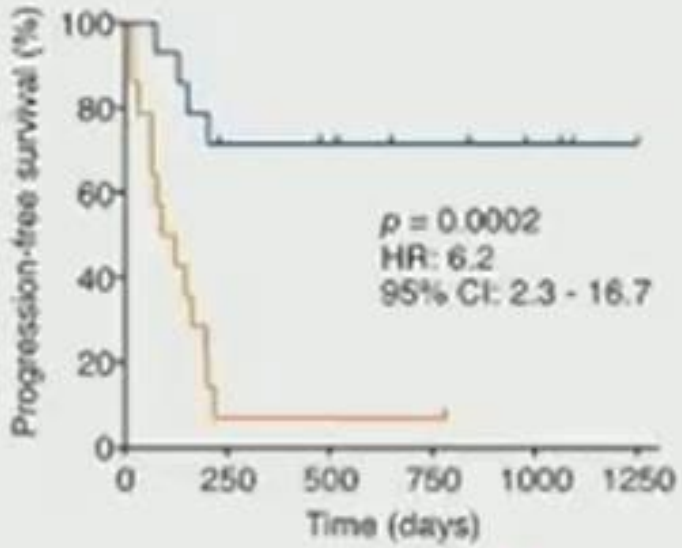
*Tabouret E et al., *Neuro Oncol*, 2017

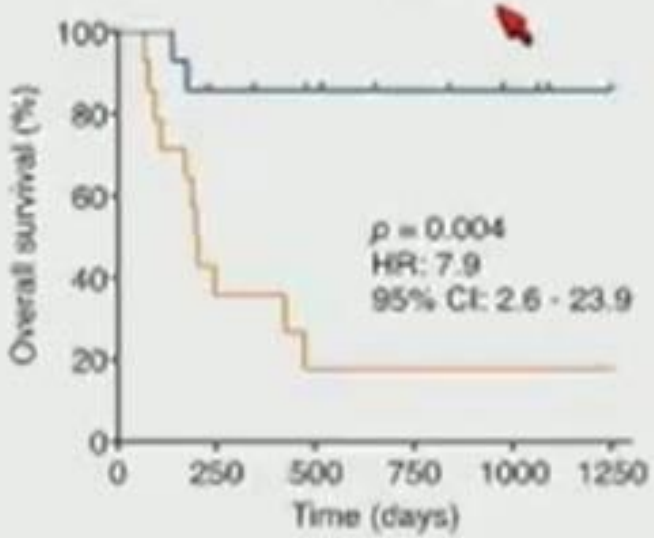
On-treatment plasma ctDNA as a prognostic biomarker



On-treatment plasma ctDNA as a prognostic biomarker







ctDNA status during induction therapy

- Negative (n = 14)
- Positive (n = 14)

Total on-treatment plasma samples: n = 49

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Biopsy-free CNSL classification

CNSL vs. Non-CNSL (other primary brain tumors or brain metastases)

- Different treatment strategies
- Suboptimal discriminatory capacity of radiographic imaging
- Mutational landscapes are fundamentally different

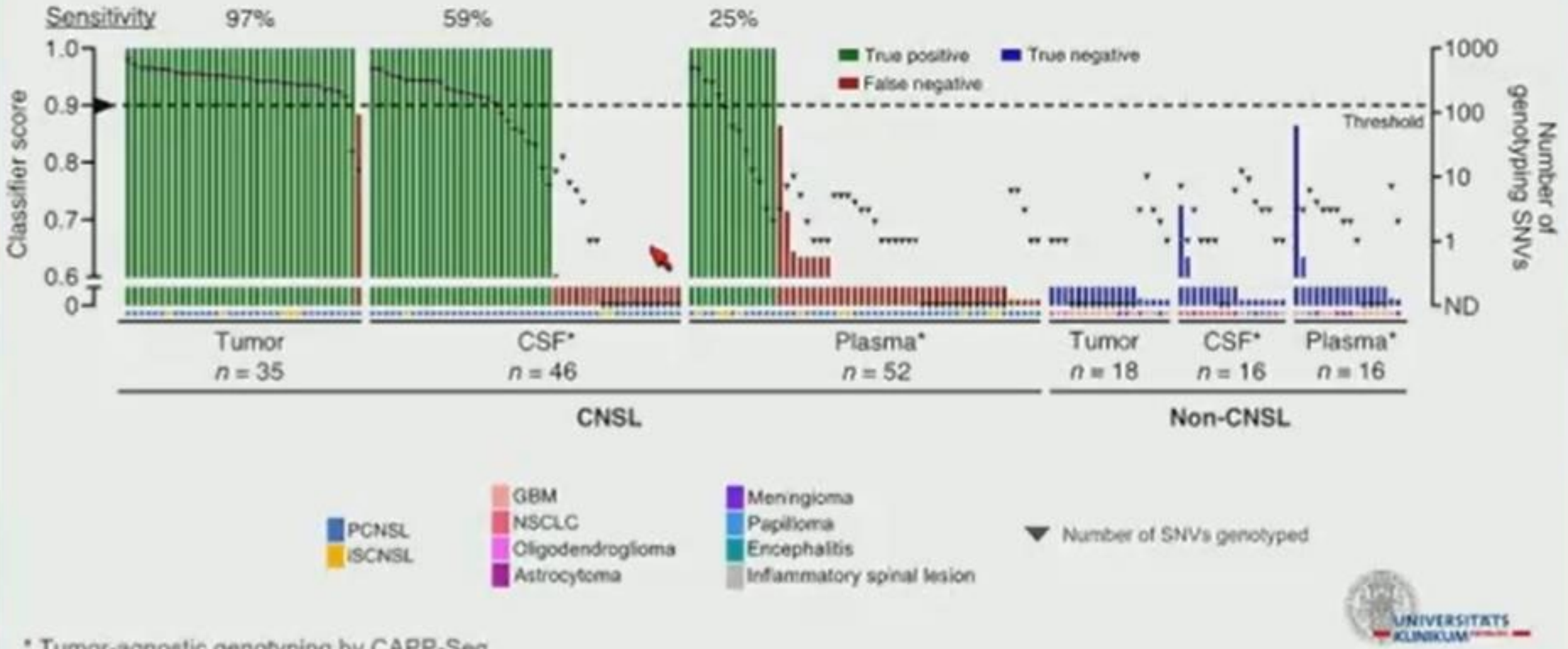
Hypothesis: CNSL can be diagnosed without surgical procedure based on ctDNA mutational profiles in CSF or plasma

Methodology

- Training cohort: Mutational data from 30 CNSL tumors (this study) and 2647 Non-CNSL tumors (public datasets)
- Approach: **Ensemble of Empirical Bayesian Models** to define a **Classifier score**
- Independent validation cohort: Tumor-agnostic genotyping by CAPP-Seq:
  - CNSL (35 tumors, 46 CSF, 52 plasma)
  - Non-CNSL (18 tumors, 16 CSF, 16 plasma)

Biopsy-free CNSL classification

Independent validation cohort: total of 183 samples



* Tumor-agnostic genotyping by CAPP-Seq

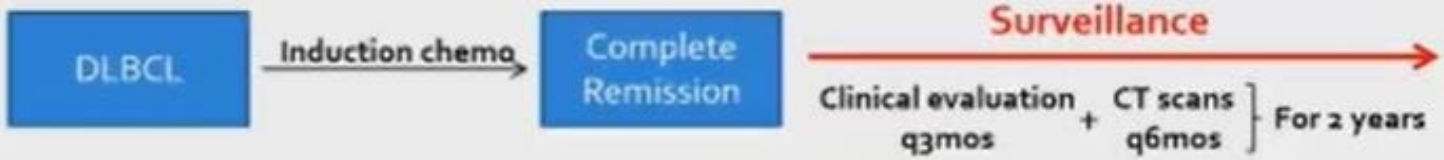
Memorial Sloan Kettering Cancer Center

A Prospective Multicenter Study of Minimal Residual Disease Assessment Using a Next-Generation Immunosequencing Assay and CT Monitoring for Surveillance after Frontline Treatment in Diffuse Large B-Cell Lymphoma

Anita Kumar MD, Jason R. Westin MD, Stephen J. Schuster MD, Grzegorz S. Nowakowski MD, Izidore S. Lossos MD, Allison Jacob, Ashlee Joseph, Leana Laraque, Venkat Seshan PhD, Shreya Vemuri, Andrew D. Zelenetz MD PhD

Background

Standard Surveillance Strategy in DLBCL:



- Diffuse large B-cell lymphoma (DLBCL) is frequently curable after frontline therapy, however, relapses can occur after achievement of a PET-negative complete remission (CR).
- Early radiographic detection of relapse may be associated with improved outcomes
- Controversy exists regarding the utility of post-therapy surveillance imaging:
  - Patient anxiety
  - Radiation exposure
  - False-positive results
  - Cost
  - Unclear survival benefit

Choosing Wisely®
An initiative of the ABIM Foundation

"Limit use of surveillance CT imaging in pts in CR from aggressive NHL"

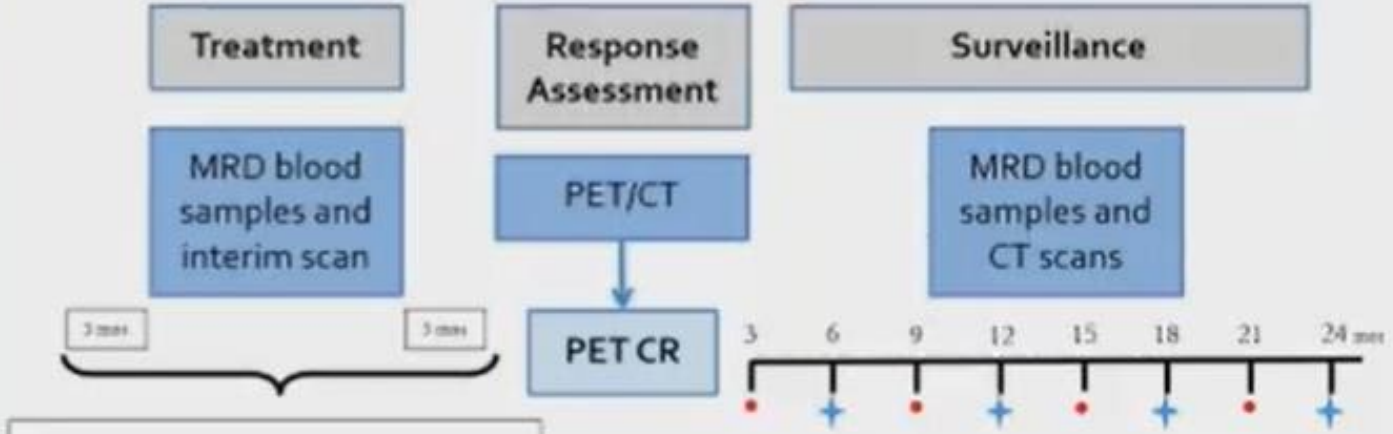
Thompson JCO 2014

Study Design: prospective, multicenter, non-therapeutic

Primary endpoint: determine the test characteristics (sensitivity, specificity, NPV, PPV) of the immunosequencing MRD assay

Key Eligibility Criteria:

- ≥ 18 years
- De novo DLBCL or HGBCL (including PMBL, TCRBCL, etc)
- Receive 1st line multi-agent chemotherapy (RCHOP, clinical trial, can include RT or HDT/ASCR)
- Required baseline test specimen to identify tumor-specific clonotype
- Transformed disease from antecedent or simultaneous indolent lymphoma not eligible



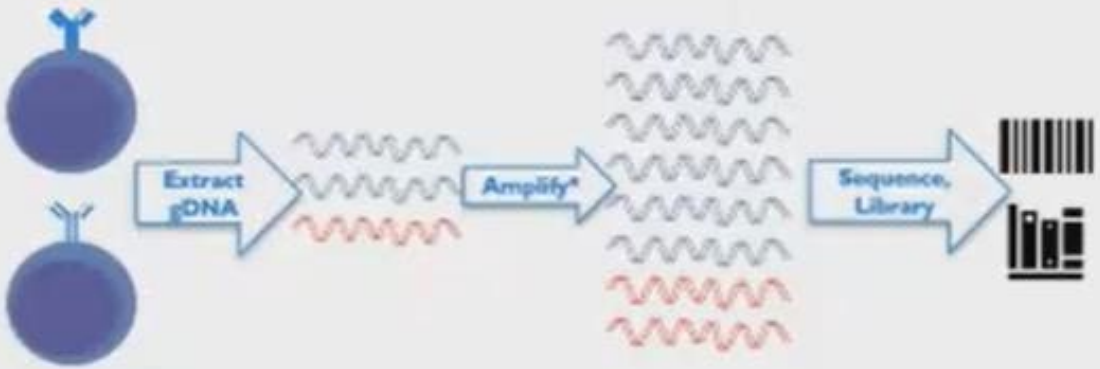
Time window for enrollment:
Pre-treatment (≤3 mos prior to chemotx start), during treatment, or post-treatment (≤4 months from chemotherapy end)

Peripheral blood MRD samples collected in 2 K2EDTA tubes

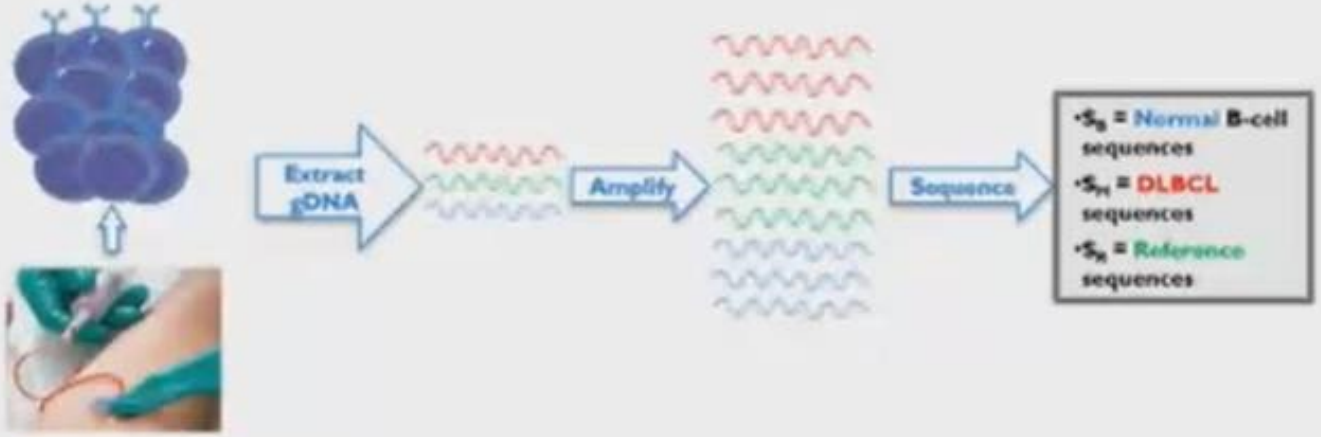
SHIP at AMBIENT TEMPERATUE TO ADAPTIVE BIOTECHNOLOGIES ON DAY OF SAMPLING AND SUBSEQUENTLY PROCESSED at ADAPTIVE

MRD Methodology: clonoSEQ® Adaptive Biotechnologies

Baseline biopsy: ID tumor specific clonotype(s)



Peripheral blood: quantify presence of tumor-associated sequences ("MRD")



- B-cells have unique marker of clonality as a result of variable, diversity, and joining (VDJ) gene segments in immunoglobulin gene
- Identify and track rearrangements of IgH-VDJ, IgH-DJ , Igkappa, Iglambda and translocations in Bcl1/2-IgH

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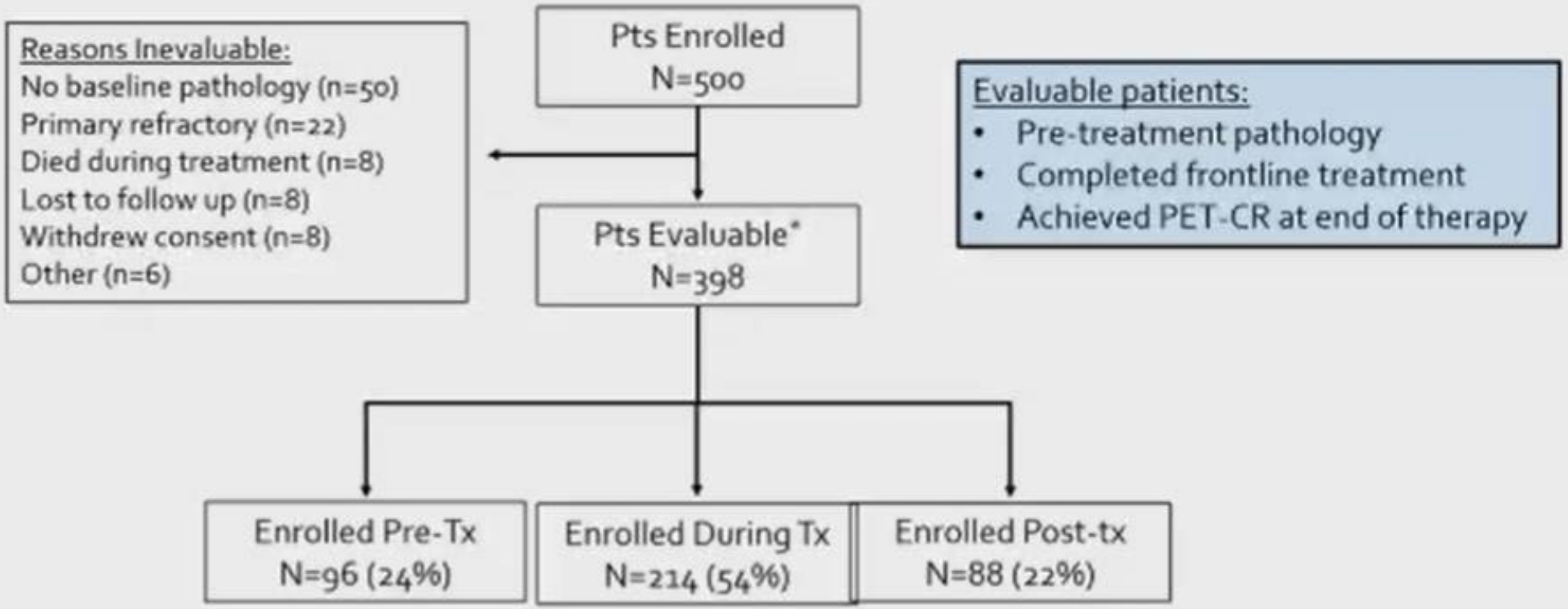
Patient Flow Chart



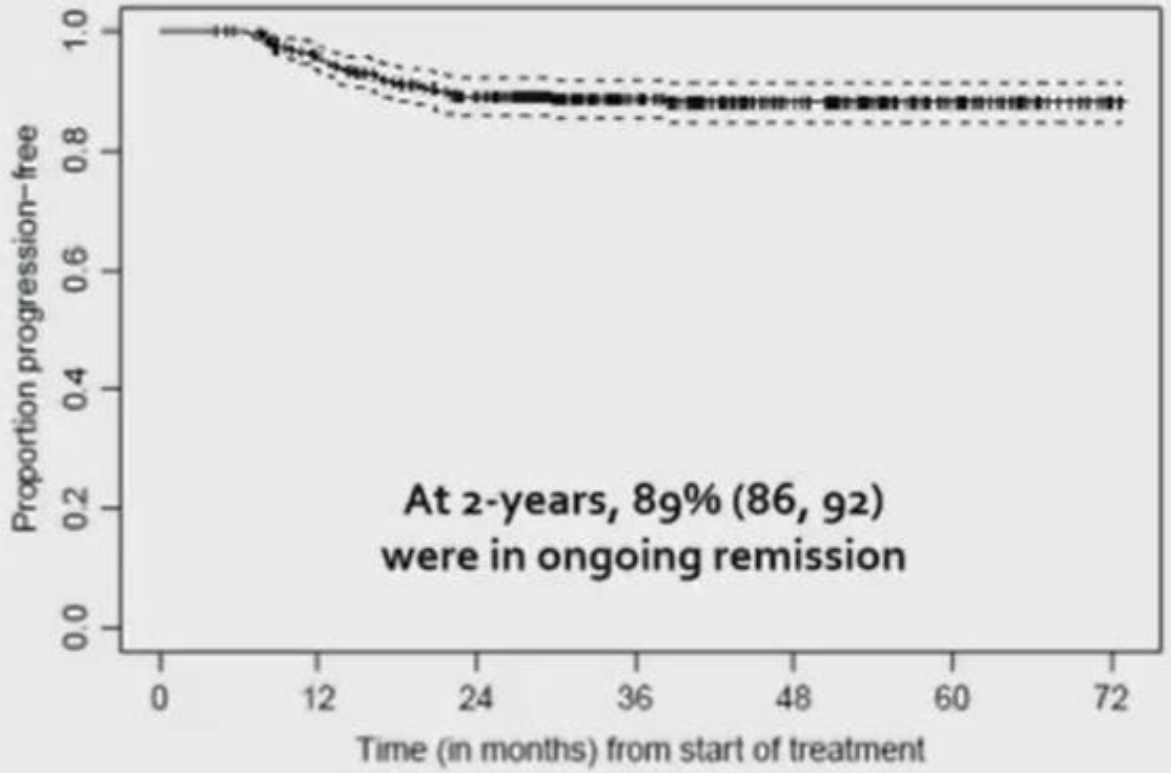
Memoria
Cancer C

Baseline Patient Characteristics (n=398)

Characteristic	N(%)
Site of Enrollment	
Memorial Sloan Kettering	221 (55%)
MD Anderson Cancer Center	55 (14%)
University of Pennsylvania	54 (13%)
Mayo Clinic	42 (11%)
University of Miami	26 (7%)
Age in years, median (range)	62 (19-95)
Male, n (%)	229 (58)
Diagnosis	
DLBCL, NOS	345 (86%)
Primary Mediastinal B-cell Lymphoma	25 (6%)
High Grade B-cell Lymphoma	20 (5%)
T-cell Rich B-cell Lymphoma	5 (1%)
Other (transformed indolent B-cell NHL)	3 (1%)

Characteristic	N(%)
Stage	
I/II	155 (39)
III/IV	203 (61)
R-IPI Score	
Very good (0)	53 (13)
Good (1-2)	184 (46)
Poor (3-5)	161 (40)
Treatments	
RCHOP x 6 cycles	146 (36%)
REPOCH x 6 cycles	82 (20%)
Clinical trial	59 (15%)
RCHOP + RT	36 (10%)
Other RCHOP variations	75 (19%)

Duration of complete response



Median follow up 34 months

Relapses, n=43

How was relapse detected?	
Clinical symptoms alone	4 (9%)
Evaluation by oncologist alone	0 (0%)
Surveillance imaging alone	19 (44%)
Imaging - *and* - clinical symptoms and/or evaluation by oncologist	20 (47%)

In 44% of patients, relapse was detected using surveillance imaging (typically CT CAP) in an otherwise asymptomatic, clinically well patient

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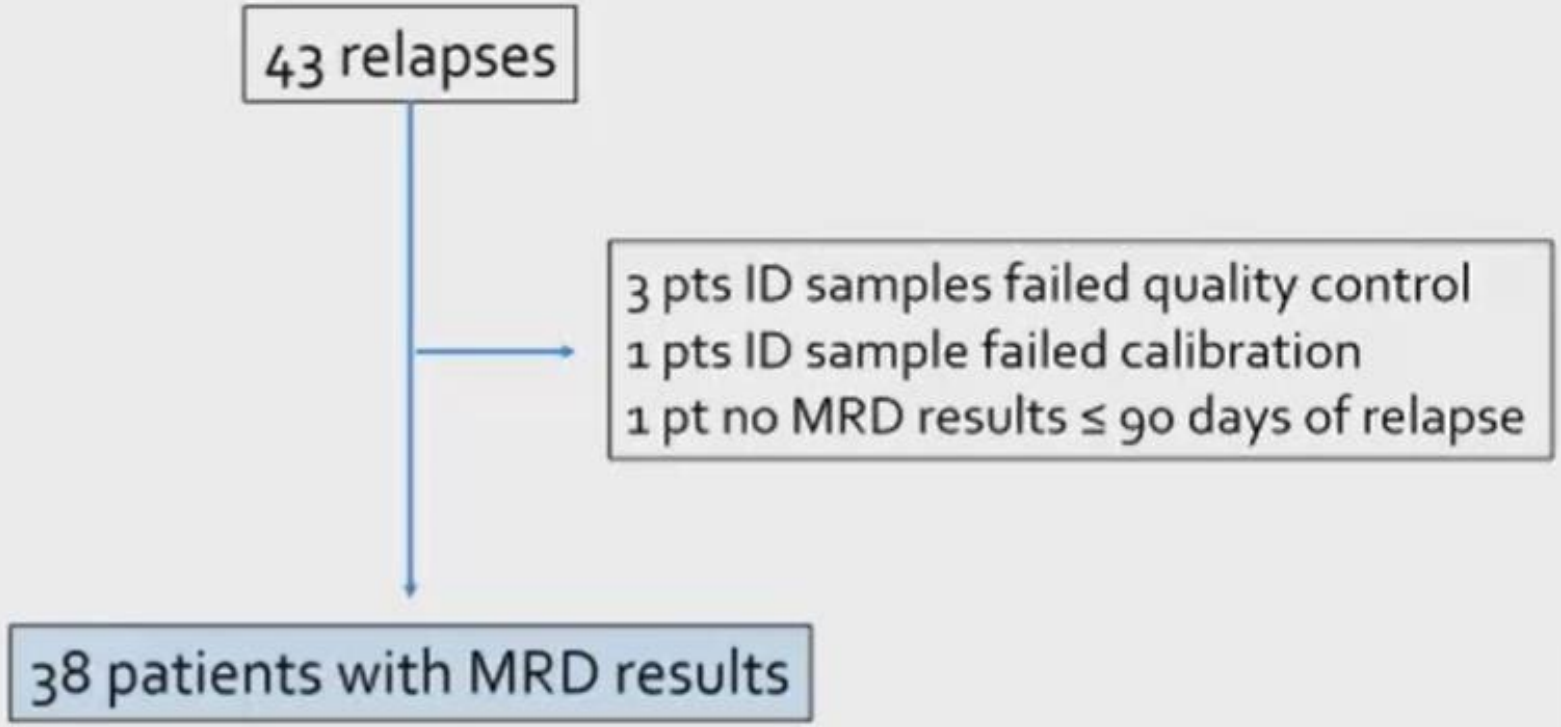
MRD Analysis—Evaluable Relapsed pts



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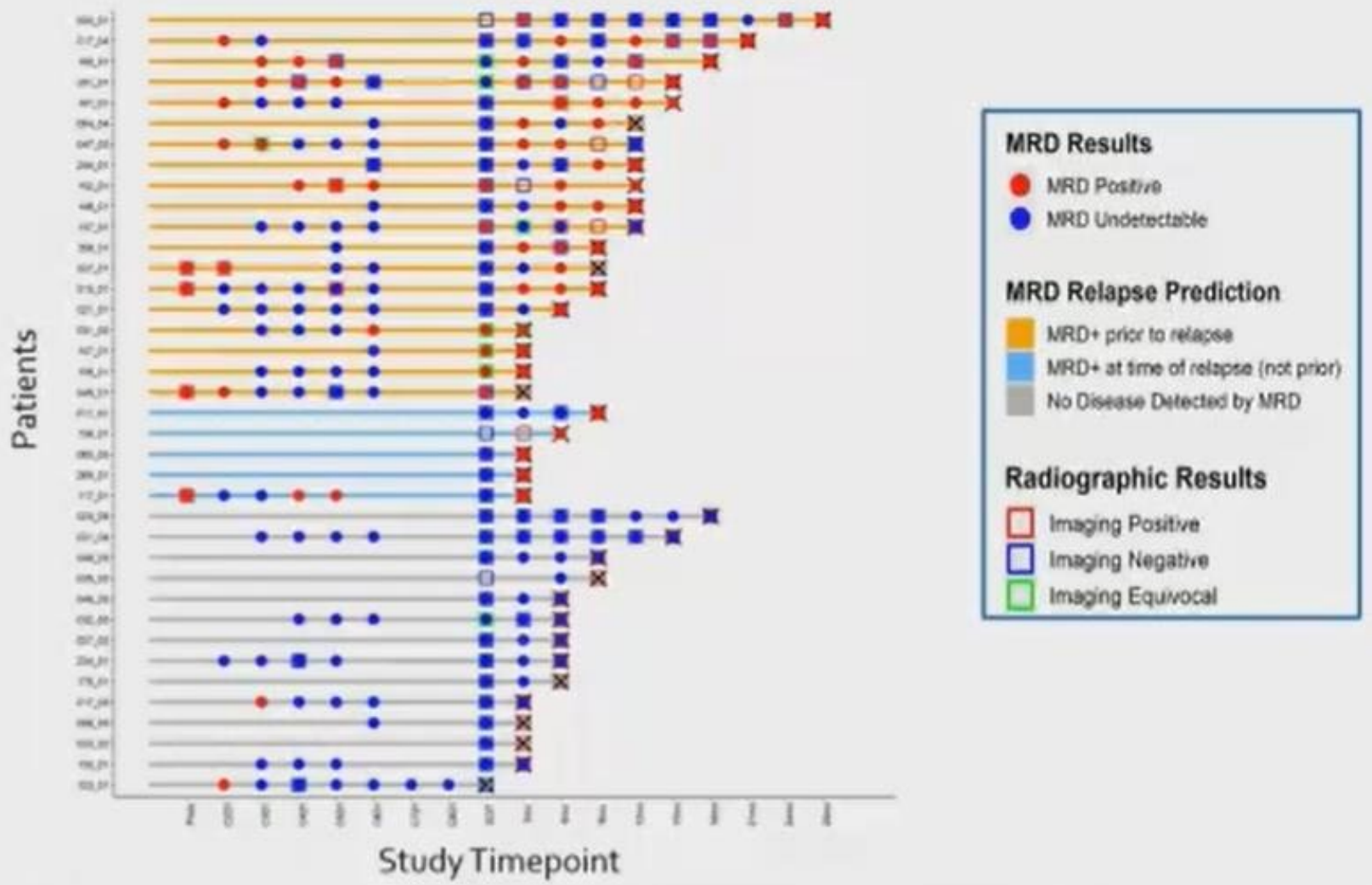
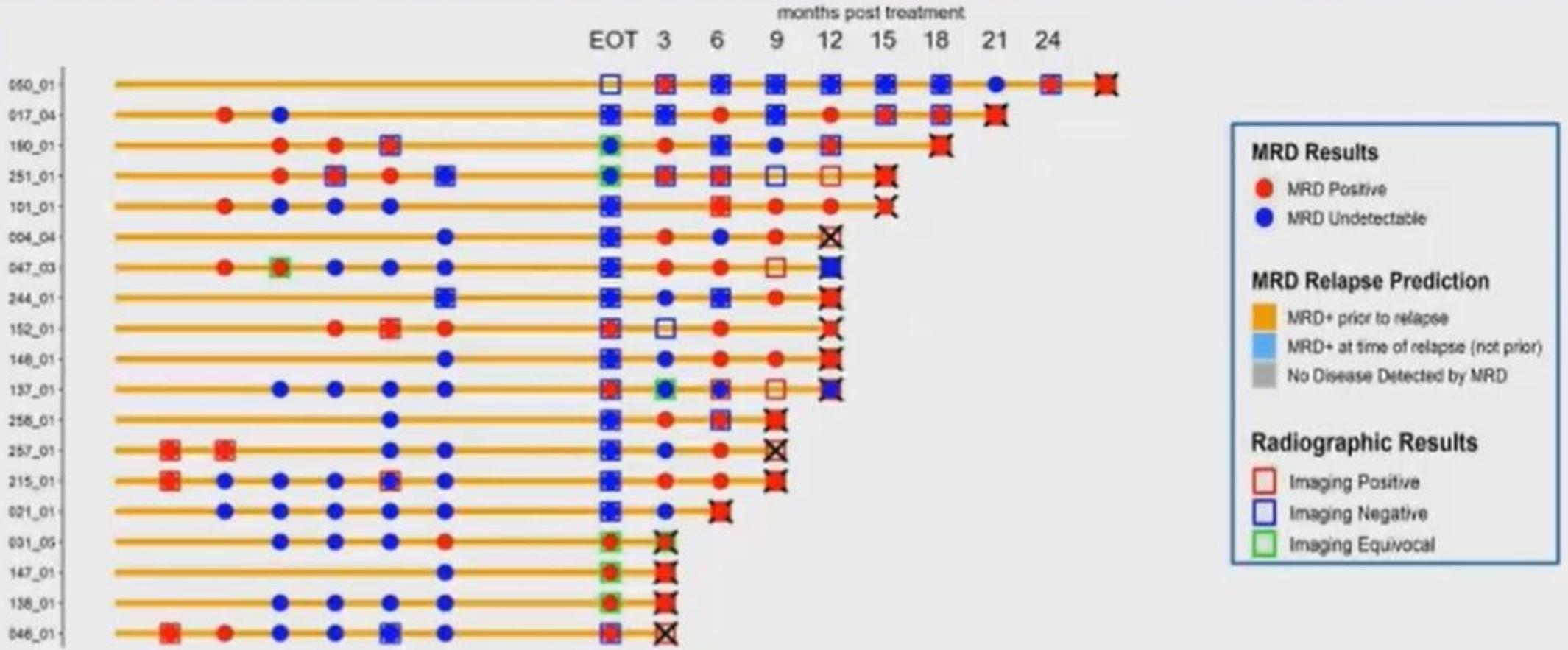
MRD Analysis—Evaluable Relapsed Patients, PBMC and plasma

Swimmer's Plot
N=38

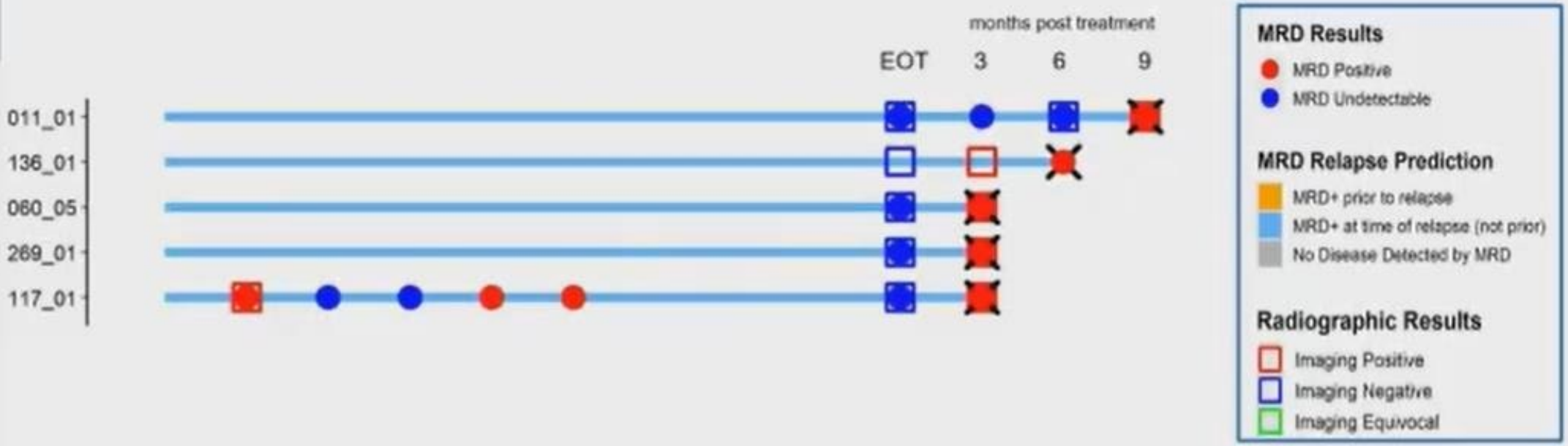


MRD Analysis—Evaluable Relapsed Patients



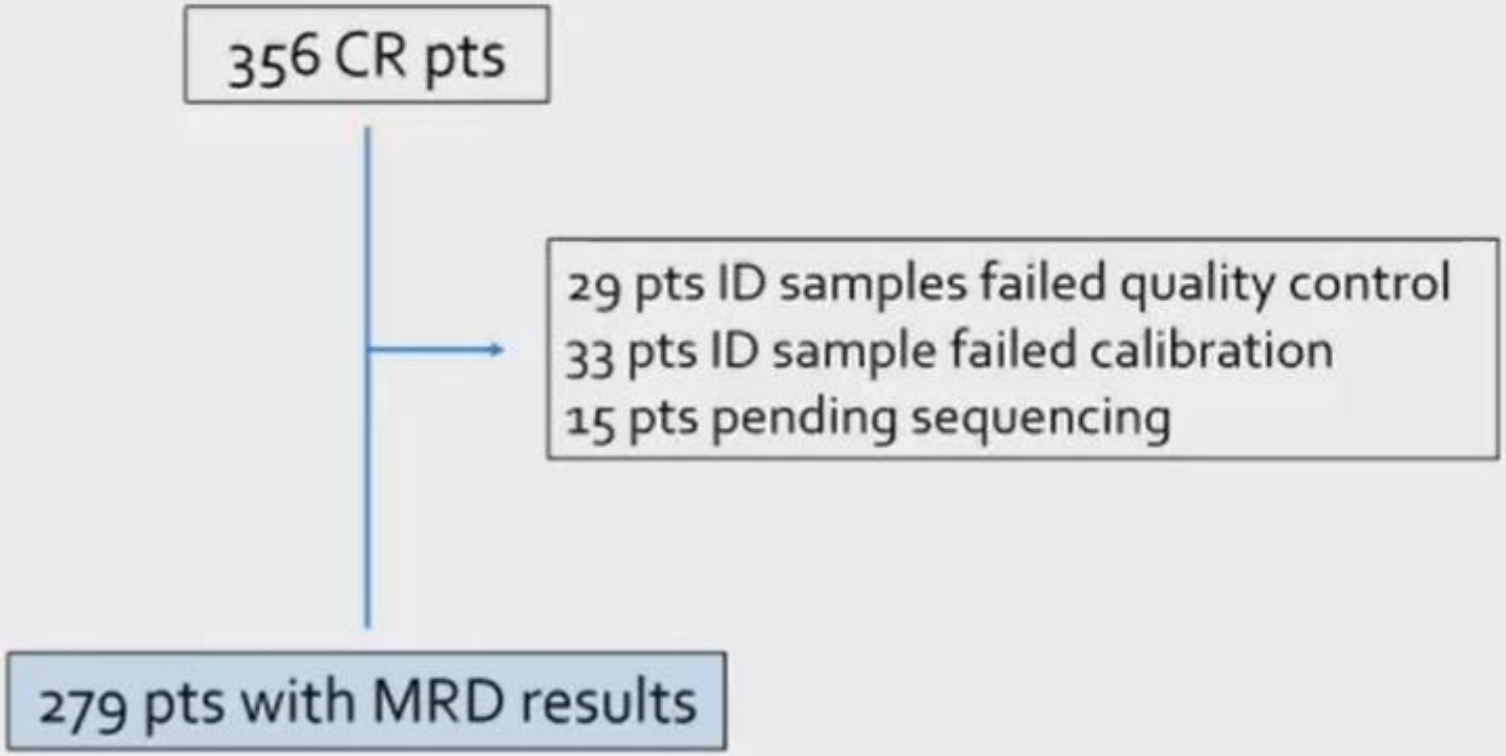
19 pts MRD positive prior to clinical relapse
Median anticipation 3 months (range 0-24 months)

MRD Analysis—Evaluable Relapsed Patients



5 pts MRD positive at the time of clinical relapse

MRD Analysis—Evaluable CR pts



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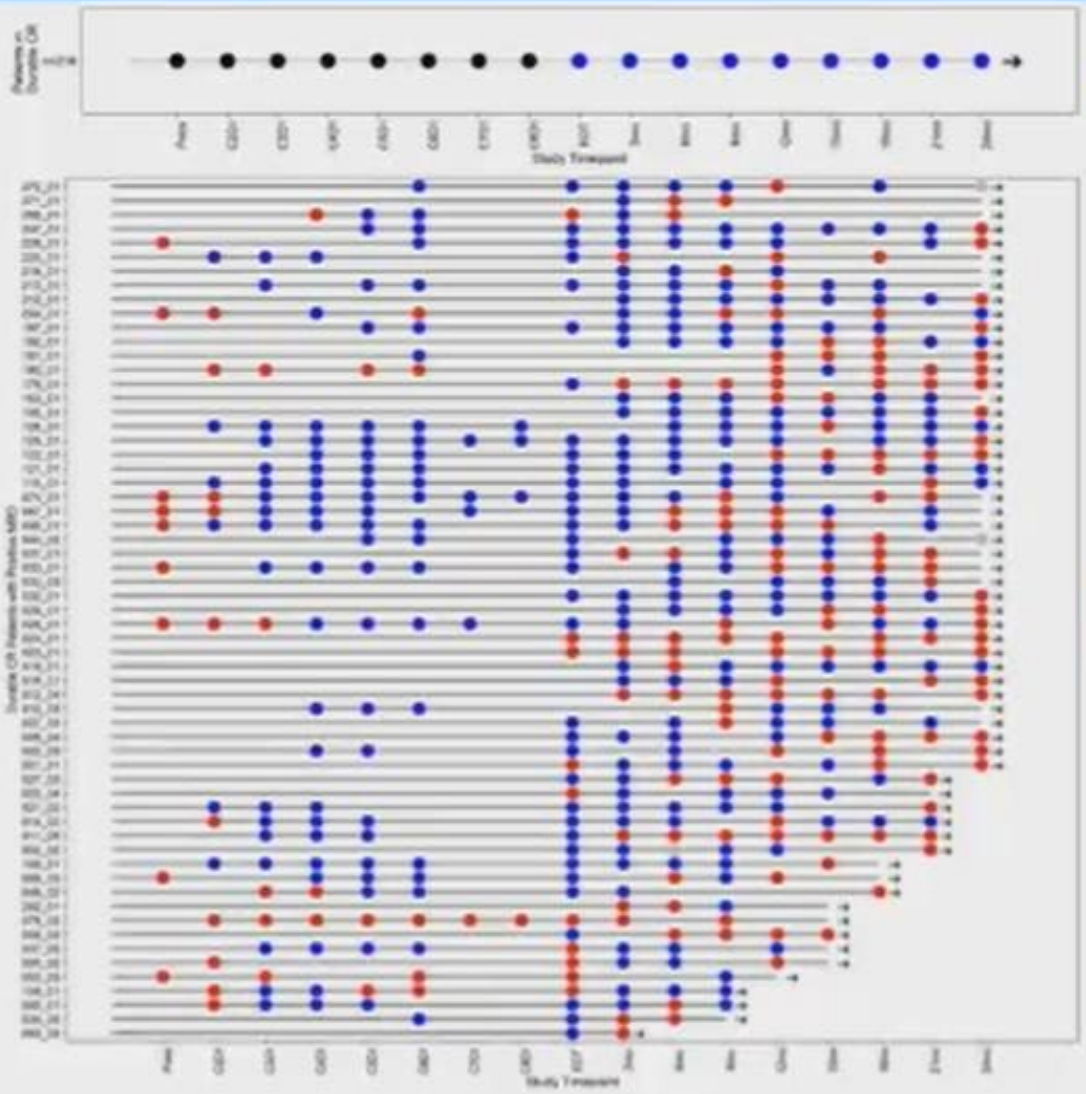
CR pts MRD results, N=279, PBMC and plasma



Undetectable MRD during durable CR, N=218 (78%)

MRD positive during durable CR, N=61 (22%)

Any positive in PBMC or plasma

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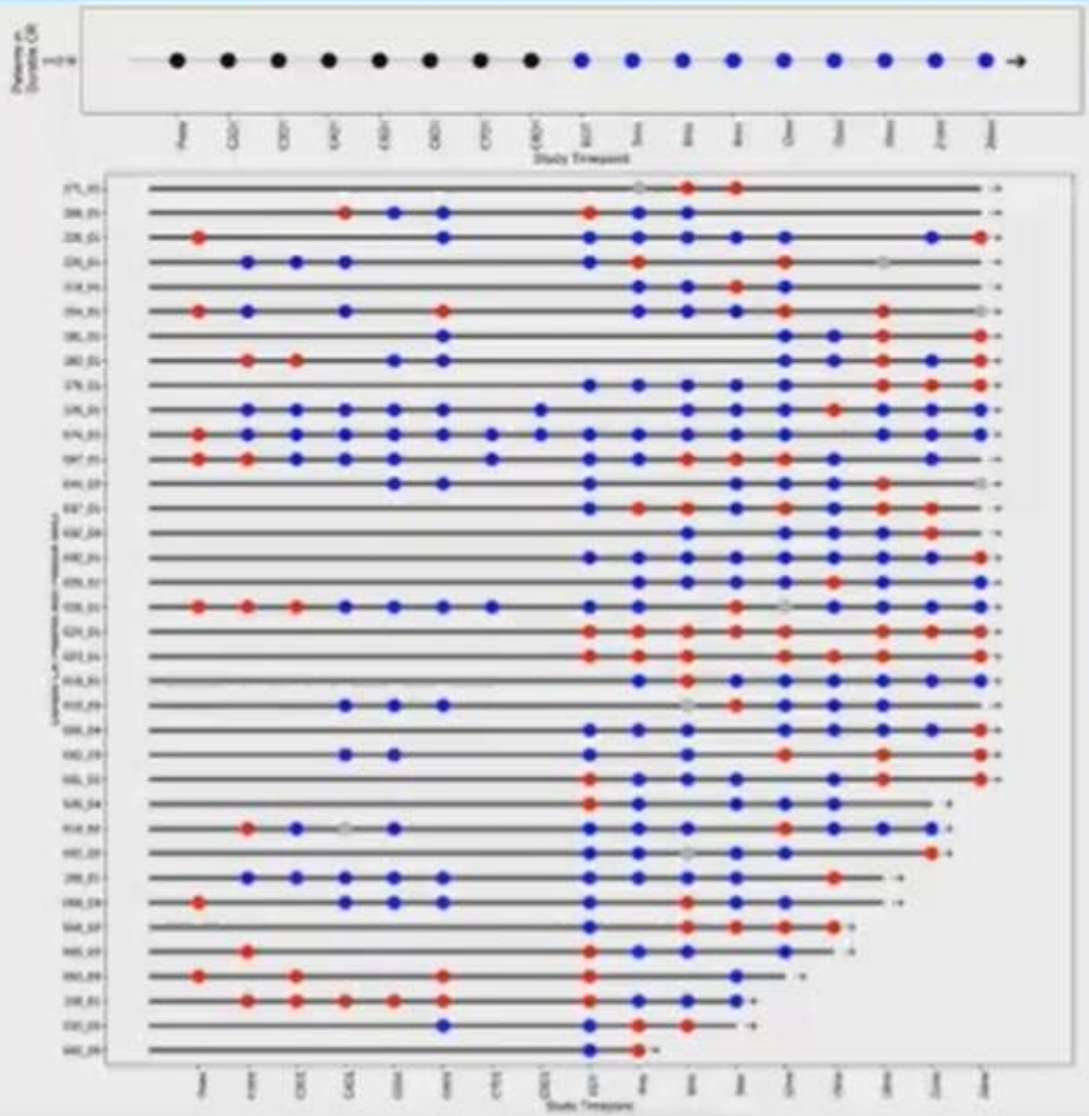
CR pts MRD results, N=279, plasma



Undetectable MRD during durable CR, N= 243 (87%)

MRD positive during durable CR, N=36 (13%)

Any positive in plasma compartment

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Summary of test characteristics

Test characteristics at the patient level:

Compartment	Sensitivity	Specificity	Positive predictive value	Negative predictive value
PBMC and Plasma	63% (24/38)	78% (218/279)	28% (24/85)	94% (218/232)
Plasma	58% (22/38)	87% (243/279)	38% (22/58)	94% (243/259)
PBMC	53% (20/38)	83% (231/279)	29% (20/68)	93% (231/249)

Cellular compartment – peripheral blood mononuclear cells
Acellular compartment – plasma

Plasma MRD detection had improved sensitivity and specificity compared with circulating cells

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Conclusions

- DLBCL patients treated in modern era (2015-to date) have overall excellent outcomes after achieving an EOT PET-CR

- The first prospective data with standard follow up schedule to describe how relapses are detected in DLBCL.
  - Retrospective data has reported low rate of asymptomatic relapse detection
  - **A substantial proportion (44%) of clinical relapses were detected radiographically in asymptomatic patients in our study, supporting the value of CT surveillance imaging in DLBCL, particularly for pts with advanced stage or high-risk disease.**
  - Given increased number of therapies in rel/ref DLBCL (i.e., CART), early detection may have higher likelihood of translating into an overall survival benefit

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Conclusions

- MRD assessment using an immunosequencing MRD assay had suboptimal sensitivity in the post-treatment surveillance setting in DLBCL
  - The results may be related to:
    - The very limited amount of circulating DNA in PET-CR patients
    - Degradation of ctDNA collected in EDTA tubes and processed at variable timepoints
- Plasma MRD detection had improved sensitivity and specificity compared with circulating cells
- Further investigation of false positive results are ongoing

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Özet

1. Pola-R-CHP ‘nin ilk seçenek tedavide yer alması için maliyet analizi önemli bir parametre
2. Double-Hit Lenfoma: hala IPI, FISH analiz sonucu elde edilinceye kadar önemli bir parametre. IPI düşük hastada R-CHOP, yüksek hastada DA-EPOCH ile tedaviye başlanmalı ve nihai sonuca göre tedavi modifiye edilmelidir. DH in FISH ile sınırlı olmadığı, DH signature ün önemi…
3. CNS proflaksisinde yüksek doz MTX konusu prospektif çalışmalarla desteklenmedikçe standart yaklaşım değişmemeli.
4. CAR-T cell e ulaşma giderek daha zorunlu hale gelmekte.CAR-T ye erken evrede tedavi gereksinimi artmakta. Primer refrakter/ erken nüks hastada CAR-T standart tedavi seçeneğidir. Kurtarma rejimine yanıtsız hastalarda da CAR-T düşünülmeli. CAR-T teknolojisine daha kolay ulaşılmalı.
5. Remisyonda DBBHL da CT ile hastalık takibi yeniden gündeme gelmiş durumda
6. cf-DNA non-invaziv hastalık tanı, prognoz ve takibinde giderek yer alacaktır. Alt-yapıda molekuler genetik ile ortak çalışma önem kazanmakta.

ASH 2021 sonrası

Diffuse Büyük B Hücreli Lenfoma güncellemesi

Burhan Ferhanoğlu.

VKV Amerikan Hastanesi

8 Ocak 2022