

Multi-Institutional Lymphoma Hematology Symposium

The Changing Landscape of Follicular Lymphoma

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Spasso Italian Grill, 34 S. Front Street, Philadelphia

Prof. Stephen J. Schuster's Disclosures

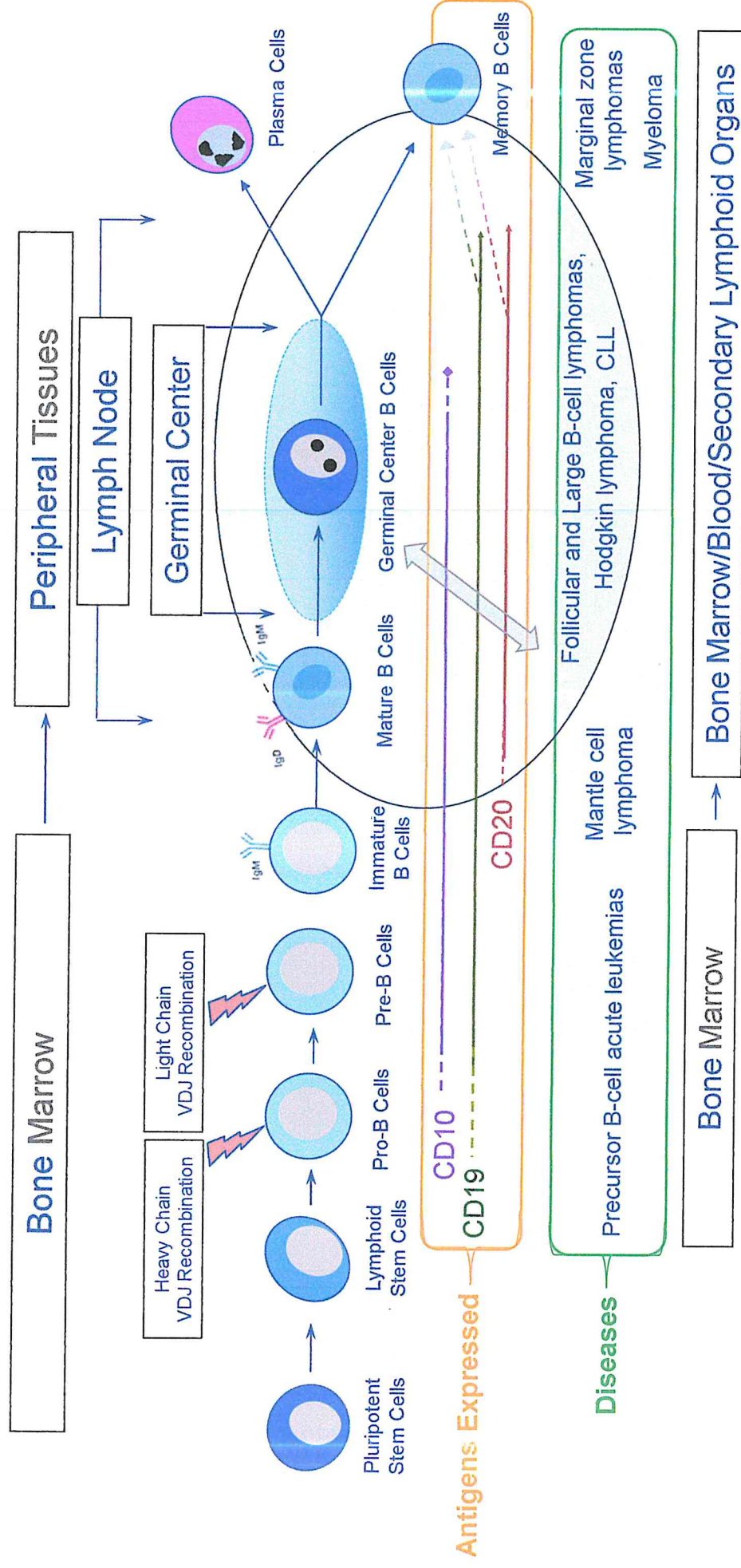
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie						X	
ADC Therapeutics						X	
AstraZeneca			X			X	
BeiGene						X	
BioNTech			X				
BMS						X	
Caribou Bio			X			X	
Genentech/Roche	X					X	
Genmab	X		X			X	
Janssen						X	
Novartis	X		X			X	
Vittoria Bio							X

The Changing Landscape on Follicular Lymphoma

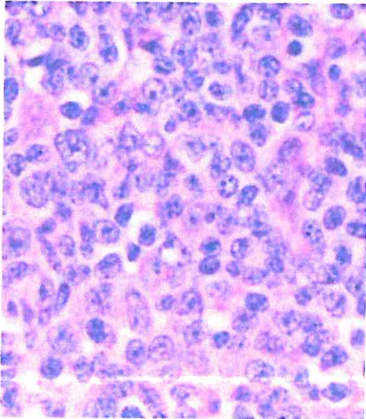
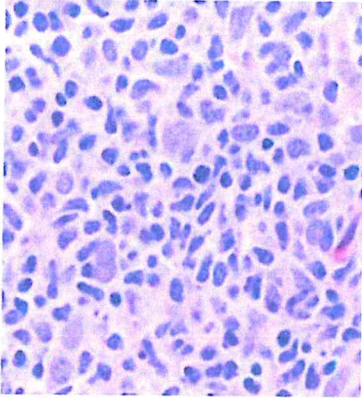
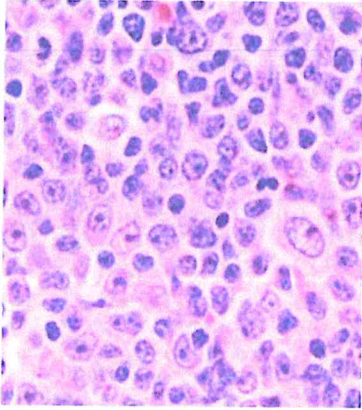
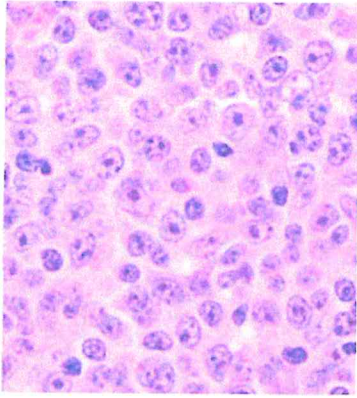
Overview

- **Follicular lymphoma background**
 - Biology
 - Classification
 - Natural history
 - Indications for and approaches to therapy
- **Third and later line therapies**
 - *Bispecific antibodies (BsAbs)*
 - Mosunetuzumab
 - Epcoritamab
 - *CAR T cells (CAR-T)*
 - Axicabtagene ciloleucel
 - Tisagenlecleucel
 - Lisocabtagene maraleucel

Normal B Cell Development and Related B-Cell Malignancies



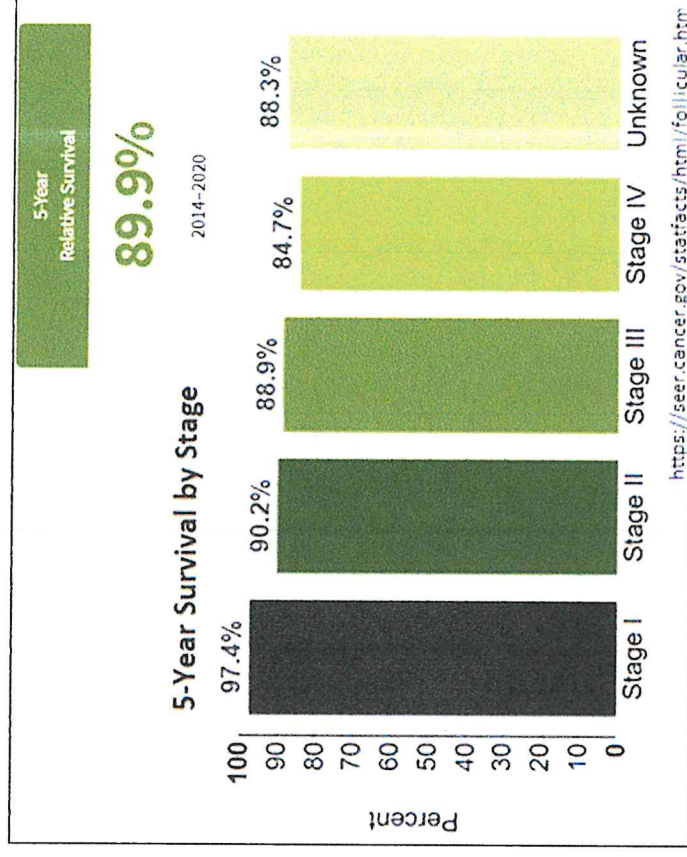
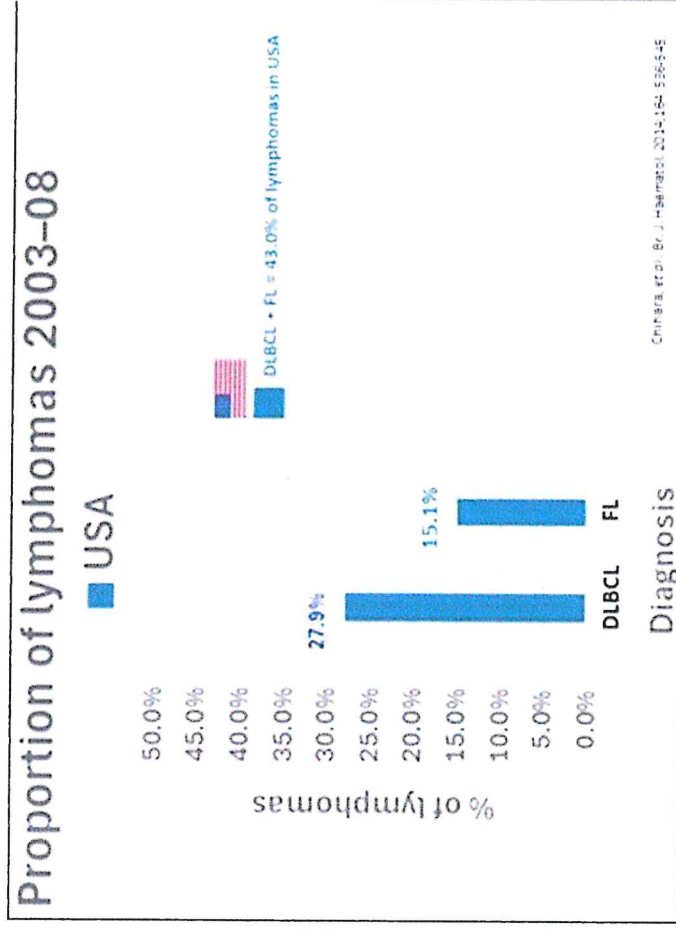
Follicular Lymphoma: Classification

The International Consensus Classification (ICC) of Mature Lymphoid Neoplasms (2022)		WHO Classification of Hematolymphoid Tumors: Lymphoid Neoplasms (2024; 5th edition)	
Mature B-cell lymphomas		Mature B-cell lymphomas	
- Follicular Lymphoma (FL) grades 1, 2, 3A - FL grade 3B - Not Included - In situ follicular neoplasia - Duodenal-type follicular lymphoma - Pediatric-type follicular lymphoma		<i>Follicular lymphoma</i> - Classic FL (cFL) - Follicular large B-cell lymphoma (FLBCL) - Follicular lymphoma with unusual cytological features (ucFL) - In situ follicular B-cell neoplasm - Duodenal-type follicular lymphoma - Pediatric-type follicular lymphoma	
BCL2-R negative, CD23-positive follicle center lymphoma		FL with predominantly diffuse growth pattern (dFL)	
FL, Grade 1 0-5 centroblasts per HPF  FL, Grade 2 6-15 centroblasts per HPF  FL, Grade, 3a >15 centroblasts per HPF  FL, Grade 3b > 15 centroblasts per HPF with solid sheets of centroblasts 			

Follicular Lymphoma: Natural History

- Incidence and Survival

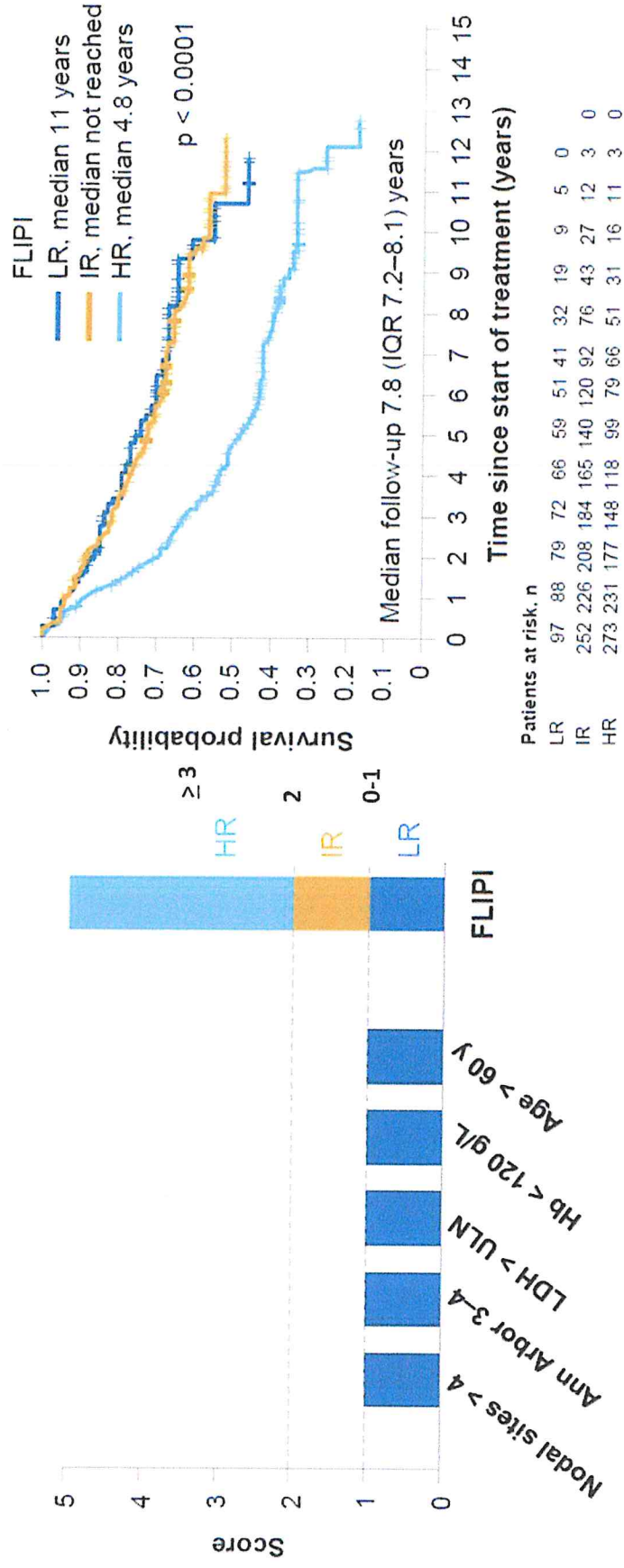
- Follicular lymphoma is the 2nd most common lymphoma in the USA (if excluding CLL)
- USA: ~ 15,000 new cases of follicular lymphoma are diagnosed annually¹



¹<https://www.lls.org/research/follicular-lymphoma-fl>

Follicular Lymphoma: Natural History

- Follicular Lymphoma International Prognostic Index (FLIPI)
- Useful for prognosis *before* therapy



LR, low risk; IR, intermediate risk. HR, high risk

Buske C, et al. Blood. 2006;108:1504-8.
 Pastore A, et al. Lancet Oncol. 2015;16:1111-22.
 Solal-Celigny P, et al. Blood 2004;104:1258-65.

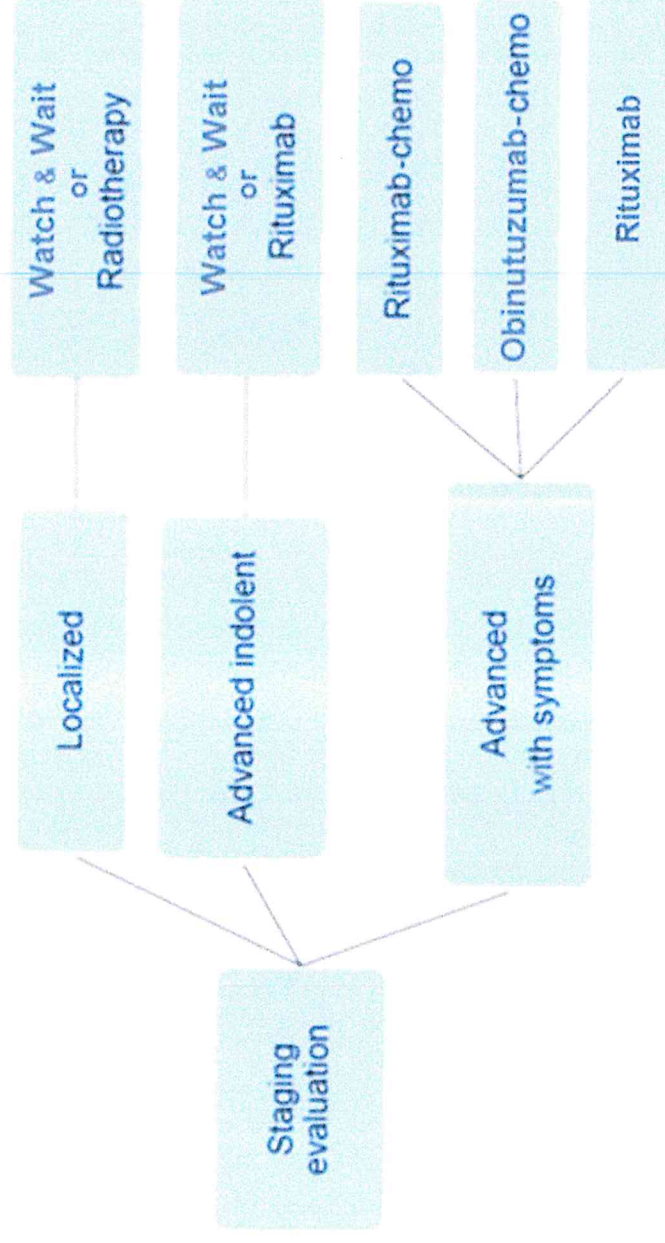
Follicular Lymphoma: Indications for Treatment

Reasonable considerations for initiating treatment	
B symptoms	>38 °C, fever of undetermined origin, night sweating, weight loss without reason >10% within 6 months
Abnormal signs	Lymphoma-related, symptomatic enlargement of liver or spleen; pleural effusion; ascites fluid
Organ injury	Lymphoma causing organ dysfunction
Cytopenias	Anemia, thrombocytopenia, and /or neutropenia
Bulky disease	Diameters of at least 3 tumors ≥5 cm or diameter of one tumor ≥7 cm
Tumor progression	Tumor enlarged by 20% - 30% over 2 to 3 months, or enlarged by 50% within 6 months

GELF criteria ¹ (Groupe d'Etude des Lymphomes Folliculaires)	BNLI criteria ² (British National Lymphoma Investigation)
High tumour bulk defined by either • Tumour > 7 cm • 3 nodes in 3 distinct areas each > 3 cm • Symptomatic splenic enlargement • Organ compression • Ascites or pleural effusion	Rapid disease progression in the preceding 3 months
Presence of systemic symptoms	Life-threatening organ involvement
Serum LDH or β2-microglobulin above normal values	Renal or liver infiltration
	Bone lesions
	Systemic symptoms or pruritus
	Hb < 10 g/dL or WBC < 3.0 × 10 ⁹ /L or platelet count < 100 × 10 ⁹ /L: related to marrow involvement

¹Brice P, et al. J Clin Oncol. 1997;15:1110-7; ²Ardeshna KM, et al. Lancet. 2003;362:516-22.

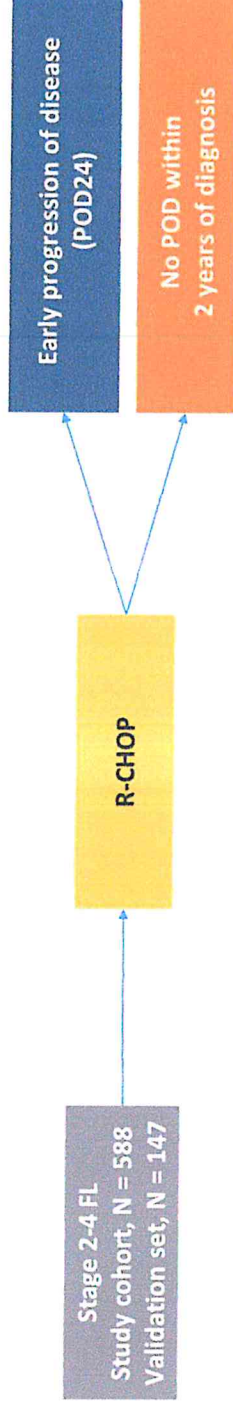
Follicular Lymphoma: General Approaches to First-Line Therapy



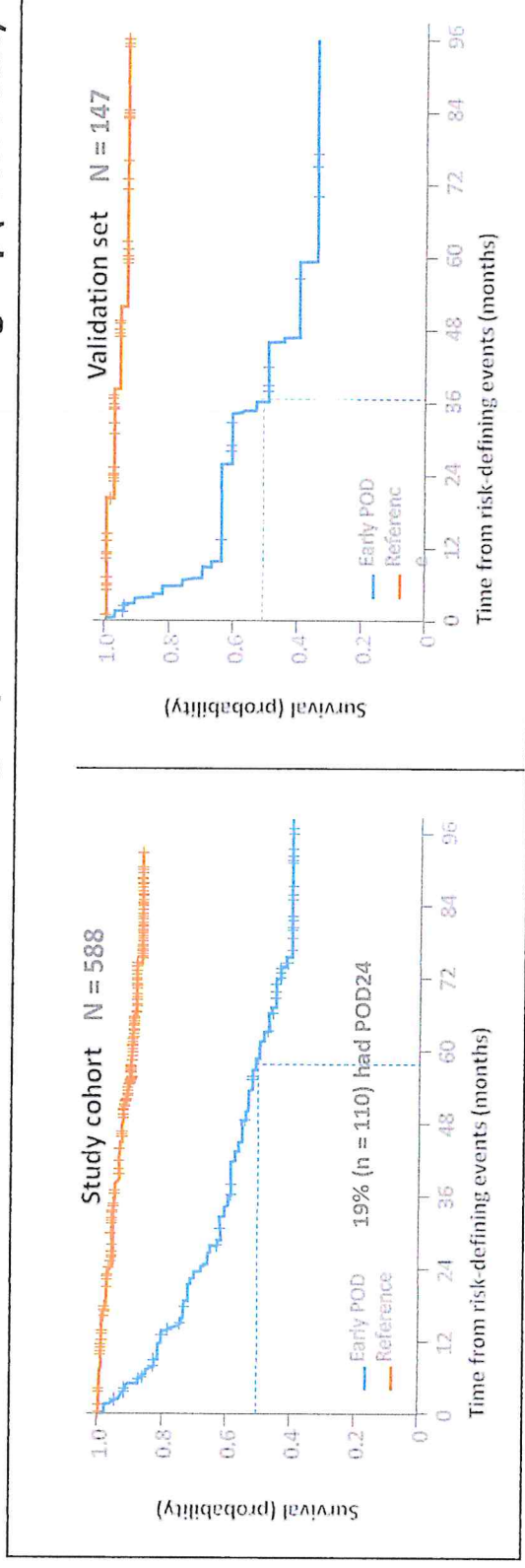
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Relapse after 1st-Line Therapy of Follicular Lymphoma: Prognosis

- POD24: Useful for prognosis *after* therapy



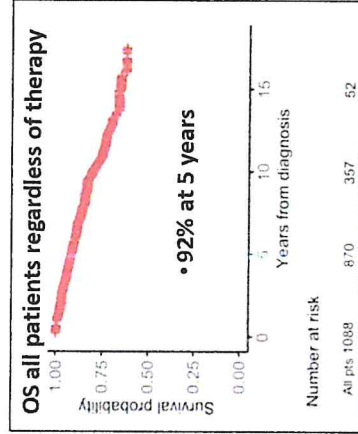
5-year overall survival was lower in the POD24 group than in the reference group (~50% v 90%)



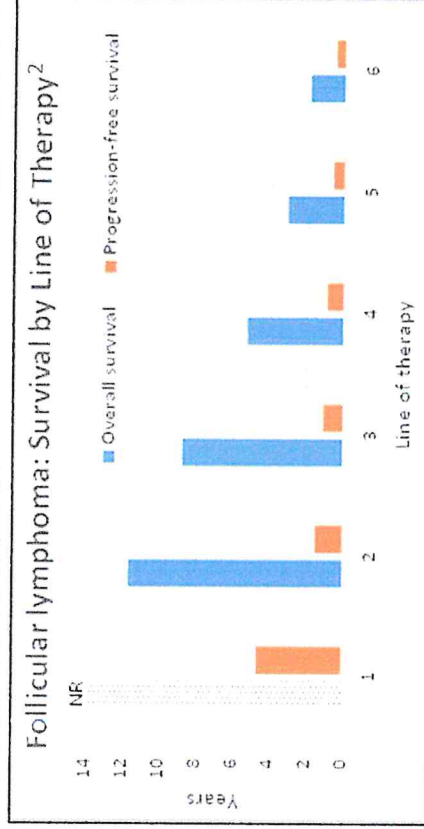
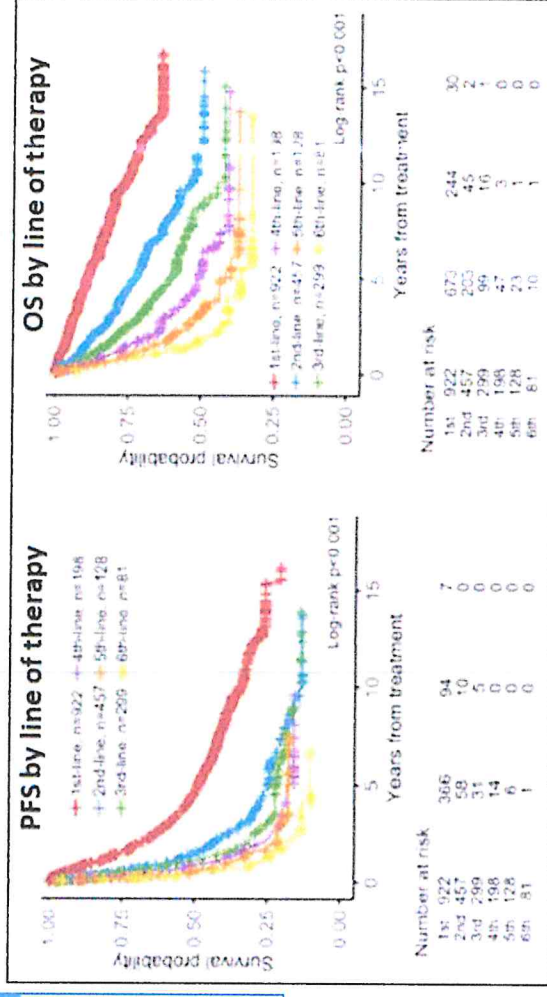
POD24, patients with progression of disease within 2 years or less of diagnosis.

Follicular Lymphoma: Relapse and Survival by Line(s) of Therapy

- Single institution (MSKCC), retrospective study, 1998 - 2009 (*post-rituximab/pre-CAR T era*)¹
- N = 1,088 patients with FL, grade 1-3A; 922 patients required treatment
- *Survival calculated from time of diagnosis or from time of treatment initiation*



Line of therapy	PFS (median, years)	OS (median, years)
1	4.7	not reached
2	1.5	11.7
3	1.1	8.8
4	0.9	5.3
5	0.6	3.1
6	0.5	1.9



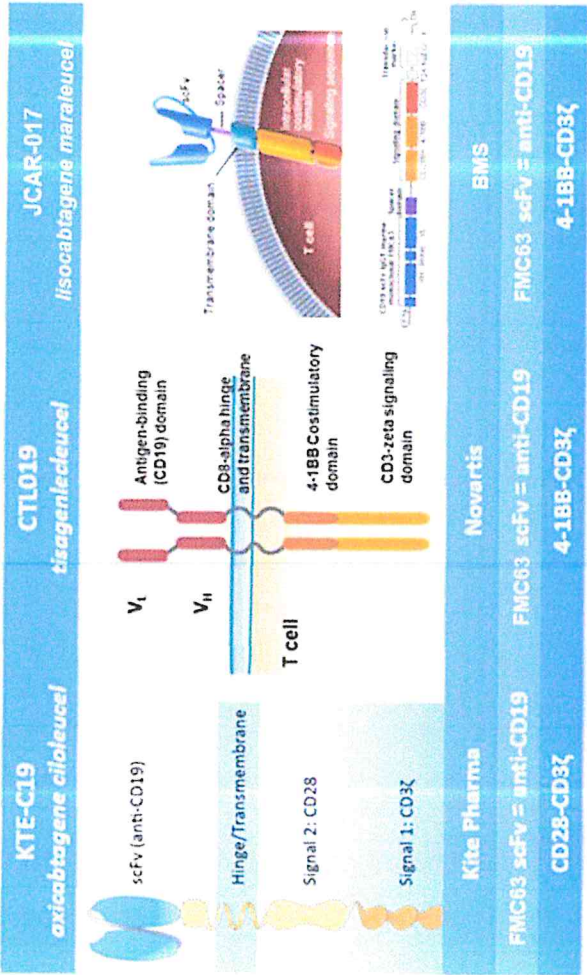
¹Batlevi, et al. Blood Cancer J. 2020;10:74.

²adapted from Batlevi, et al.

Relapsed/Refractory Follicular Lymphoma: CAR-T cells

- Three CD19-directed CAR-T products for $\geq 3^{\text{rd}}$ -line therapy of FL

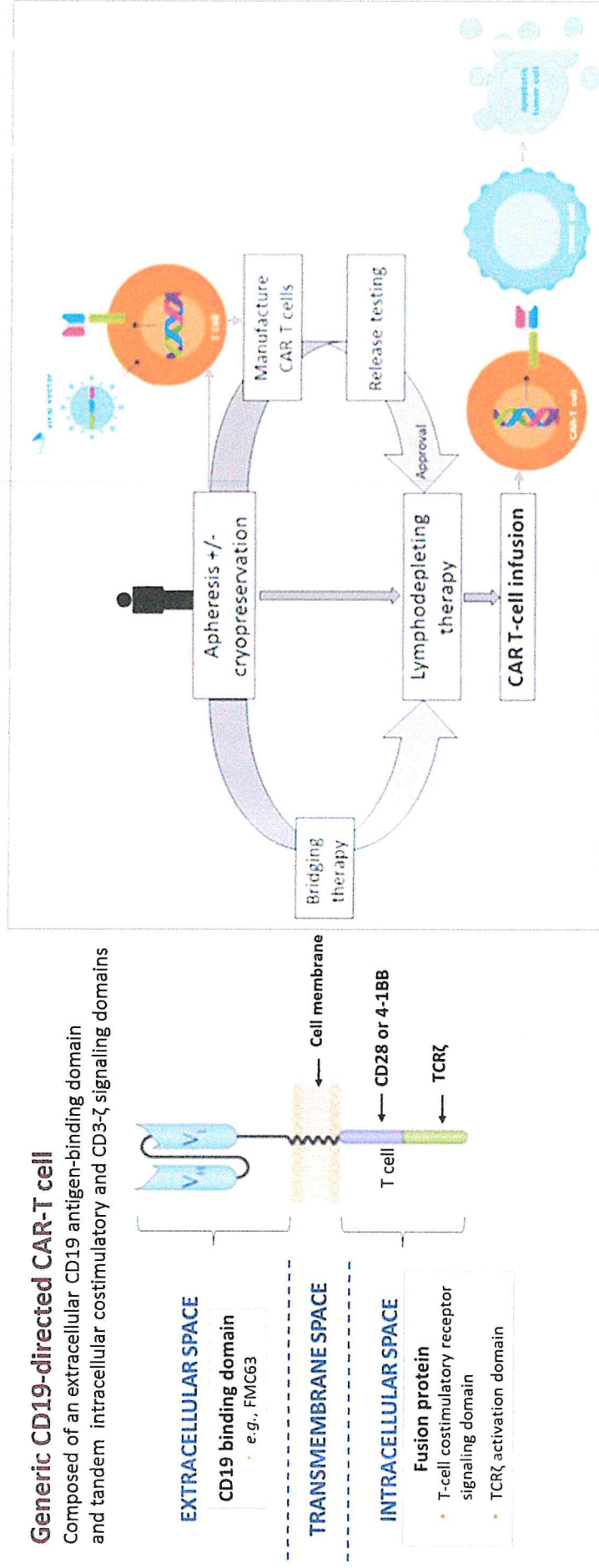
CAR-T Products and Indications	FDA Approved
Axicabtagene ciloleucel • $\geq 3^{\text{rd}}$ line therapy of r/r FL	2021
Tisagenlecleucel • $\geq 3^{\text{rd}}$ line therapy of r/r FL	2022
Lisocabtagene maraleucel • $\geq 3^{\text{rd}}$ line therapy of r/r FL	2024



- Efficacy: efficacy appears similar
- Toxicities: similar
- Manufacturing and Logistics: somewhat different

Relapsed/Refractory Follicular Lymphoma: CAR-T Therapies

- CAR-T Cells: Structure, MOA, & Clinical Application



Requires: 1) Apheresis

2) Manufacturing

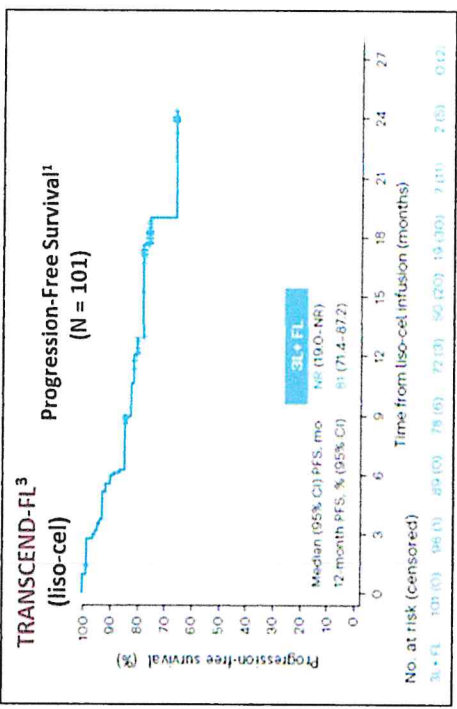
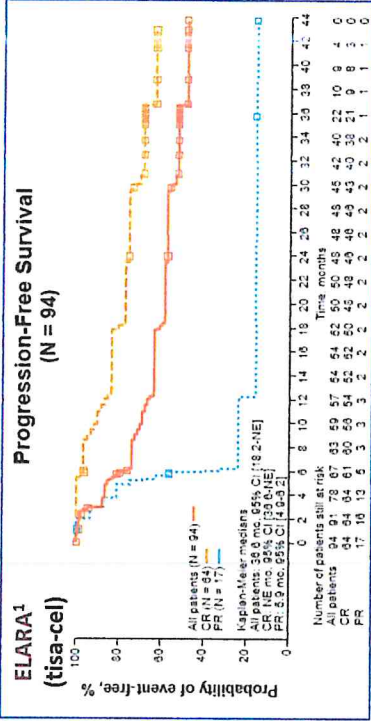
3) Lymphodepletion chemotherapy

MOA, mechanism of action; TCR, T-cell receptor

CAR-T for ≥ 3rd-Line Therapy of R/R Follicular Lymphoma

Product	Tisagenlecleucel	Axicabtagene ciloleucel	Lisocabtagene maraleucel
Trial	ELARA ¹	ZUMA-5 ²	TRANSCEND-FL ³
Design	Phase II	Phase II	Phase II
Patients, N	N = 94	N = 127	N = 101
Median prior therapies	4	3	3
Median follow-up, months (mo)	30 mo	42 mo	18 mo
ORR	86%	94%	97%
CRR	69%	79%	94%
median PFS	37 mo	40 mo	NR @ 18 mo
12-month PFS rate	67%	79%	81%
24-month PFS rate	57%	--	--
36-month PFS rate	53%	54%	--
Any grade CRS/NT	48%/37%	78%/56%	58%/15%
Grade ≥ 3 CRS	0%	7%	1%
Grade ≥ 3 NT	3%	15%	2%

Compare PFS rates with 12- and 24-month PFS rates of 37% and 26% for similar follicular lymphoma patients before CAR-T or BsAb⁴

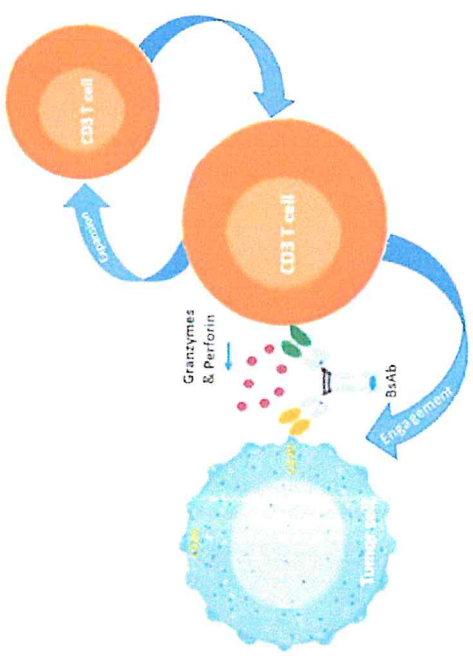


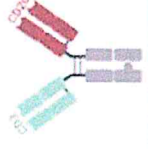
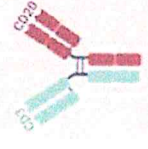
r/r, relapsed/refractory; FL, follicular lymphoma; ORR, overall response rate; CRR, complete response rate; PFS, progression free survival; NR, not reached; mo, months; CRS, cytokine release syndrome; NT, neurotoxicity; d, day

¹Schuster, et al. ASH 2023; Abstract #601 (oral); ²Neelapu, et al. Blood 2024;143(6):496-506; ³Morschhauser, et al. ICML 2023; ⁴Salles G, et al. Blood Adv. 2022;6(225):5835-5842.

Bispecific Antibodies for $\geq 3^{\text{rd}}$ -Line Therapy of R/R Follicular Lymphoma

- Bispecific Antibodies (BsAbs)



Bi-Specific Antibody	Targets	Design	Ig Fragment Formats	Ref.
mosunetuzumab	CD20 x CD3		- humanized mouse heterodimeric IgG1-based antibody - monovalent CD20 and monovalent CD3ε binding - modified Fc devoid of FcγR and complement binding - CD20 binding moiety from rituximab	1
epcoritamab	CD20 x CD3		- humanized mouse IgG1-based heterodimeric antibody - monovalent CD20 and monovalent CD3 binding - IgG1 Fc modified to minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield - CD20 binding moiety from ofatumumab	2

BsAb Products and Indications	FDA Approved	MHLW Approved
Epcoritamab, 1:1 ($\alpha\text{CD20}:\alpha\text{CD3}$) • $\geq 3^{\text{rd}}$ line therapy of r/r FL grades 1-3A	Jun 2024	Feb 2025
Mosunetuzumab, 1:1 ($\alpha\text{CD20}:\alpha\text{CD3}$) • $\geq 3^{\text{rd}}$ line therapy of r/r FL grades 1-3A	Dec 2022	Dec 2024

¹Schuster SJ, et al. ASH 2019, Plenary Abstract 6; ²Hutchings M, et al. ASH 2020, Abstract 406

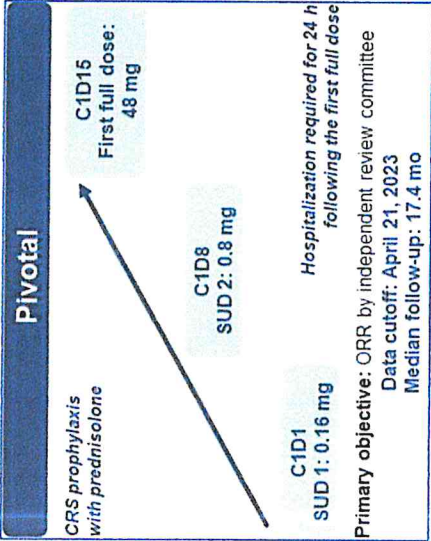
Relapsed/Refractory Follicular Lymphoma: Bispecific Antibodies

- Epcoritamab, a CD20/CD3 BsAb

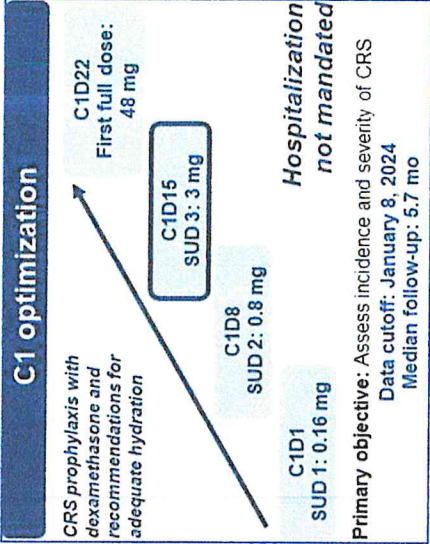
- EPCORE NHL-1: Epcoritamab in Relapsed or Refractory (r/r) Follicular Lymphoma (FL) after ≥ 2 lines of therapy
Pivotal trial and Cycle (C) 1 Optimization (OPT) Cohorts (≥ 3rd-Line Therapy)

EPCORE NHL-1: **Pivotal r/r FL Cohort**, after ≥2 prior therapies²

EPCORE NHL-1: **C1 OPT Cohort r/r FL**, after ≥2 prior therapies¹



- Key inclusion criteria**
- R/R CD20⁺ FL grade 1–3A
 - ECOG PS 0–2
 - ≥2 prior lines of therapy, including ≥1 with an anti-CD20 mAb
 - Prior treatment with an alkylating agent or lenalidomide
 - FDG-avid by PET/CT
 - Prior CAR T allowed



Cycle	Day	Dose
C1	1	SUD 1 0.16 mg
	8	SUD2 0.8 mg
	15	Full 48 mg
	22	48 mg
C2, C3	1, 8, 15, 22	48 mg
C4-C9	1, 15	48 mg
C10 and every 28 D	1	48 mg

Cycle	Day	Dose
C1	1	SUD 1 0.16 mg
	8	SUD2 0.8 mg
	15	SUD3 3 mg
	22	Full 48 mg
C2, C3	1, 8, 15, 22	48 mg
C4-C9	1, 15	48 mg
C10 and every 28 D	1	48 mg

C, cycle; D, day; SUD, step-up dose; OPT, optimization

¹Vose, J *et al.*, ASCO 2024; Abstract 7015; ²Linton KM, *et al.* ASH 2023; Abstract 1655.

Epcoritamab for ≥ 3rd-Line Therapy of R/R Follicular Lymphoma: Summary

- EPCORE NHL-1: Pivotal r/r FL Cohort, after ≥2 prior therapies
C1 OPT Cohort r/r FL, after ≥2 prior therapies

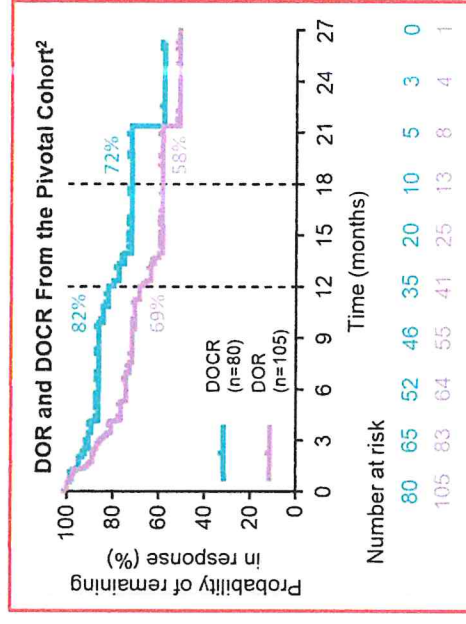
Patient Characteristics

Demographics	Pivotal Cohort N=128	C1 OPT N=86
Median age, y (range)	65 (39–84)	63.5 (33–90)
Male, n (%)	79 (62)	49 (57)
Ann Arbor stage, n (%)		
III–IV	109 (85)	79 (92)
FLIPI, n (%)		
3–5	78 (61)	44 (51)
Median # prior therapies (range)	3 (2–9)	2 (2–9)
≥3 prior lines, n (%)	81 (63)	41 (48)
≥4 prior lines, n (%)	40 (31)	17 (20)
POD24 (any 1L), n (%)	67 (52)	42 (49)
Double refractory, n (%)	90 (70)	54 (63)
Primary refractory, n (%)	69 (54)	38 (44)
Refractory ¹ to last prior systemic therapy, n (%)	88 (69)	49 (57)

Outcomes (Pivotal Cohort)

Best Overall Response, n (%)	N=128
Overall response rate	105 (82)
Complete response	80 (63)
Partial response	25 (20)
Median follow-up, months (range)	17.4 mo (0.2–30.1)

Adverse events of special interest		
Trial	Pivotal ¹	C1 OPT ²
Any grade CRS/NT	66%/6%	49%/0
Grade ≥ 3 CRS	2%	0
Grade ≥ 3 NT	0	0



Epcoritamab exposure	Pivotal Cohort N=128	C1 OPT N=86
Median follow-up, mo (range)	17.4 (0.2 to 30.1)	5.7 (0.4–11.8)
Median number of cycles initiated (range)	8 (1–33)	5 (1–12)
Median duration of treatment, mo (range)	8.3 (0.03–30)	3.8 (0.3–11.8)
Ongoing treatment, n (%)	47 (37)	64 (74)
Discontinued treatment, n (%)	81 (63)	22 (26)

DOCR, duration of complete response; DOR, duration of response; OS, overall survival; PFS, progression-free survival, W, week; C, cycle; CRS, cytokine release syndrome; NT, neurologic toxicity

¹Vose, *J et al.*, ASCO 2024; Abstract 7015; ²Linton KM, *et al.* ASH 2023; Abstract 1655.

Mosunetuzumab for $\geq 3^{\text{rd}}$ -Line Therapy of R/R Follicular Lymphoma

- Pivotal Trial Study Design

Key inclusion criteria

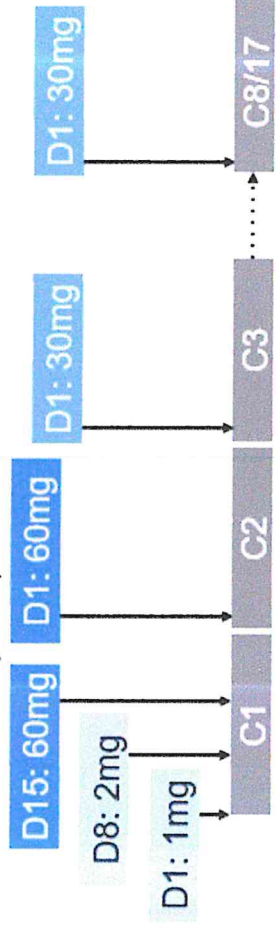
- R/R FL Grade 1–3a
- ≥ 2 prior therapies including an anti-CD20 antibody and an alkylator
- ECOG PS 0–1

Endpoints

- Primary: CR rate* as best response
- Secondary: CR rate (INV-assessed), ORR,[†] DOR,[†] DOCR,[†] PFS,[†] OS, and safety

Mosunetuzumab administration

- IV administration in 21-day cycles with C1 SUD
- Fixed-duration treatment: 8 cycles if CR after C8 or 17 cycles if PR/SD after C8
- No mandatory hospitalization



*By independent review committee (IRC); [†]ORR, DOR, DOCR, PFS were assessed by IRC and investigators.

C, cycle; D, day; DOCR, duration of complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; SUD, step-up dosing

Mosunetuzumab for $\geq 3^{\text{rd}}$ -Line Therapy of R/R Follicular Lymphoma: Summary

- Mosunetuzumab administered for fixed duration in 21-day cycles (CR, 8 cycles; PR, 17 cycles)
 - Step-up dosing in C1 (C1, day 1: 1 mg; C1, day 8: 2 mg; C1, day 15: 60 mg); C2, day 1: 60 mg; C3, day 1 and onward: 30 mg

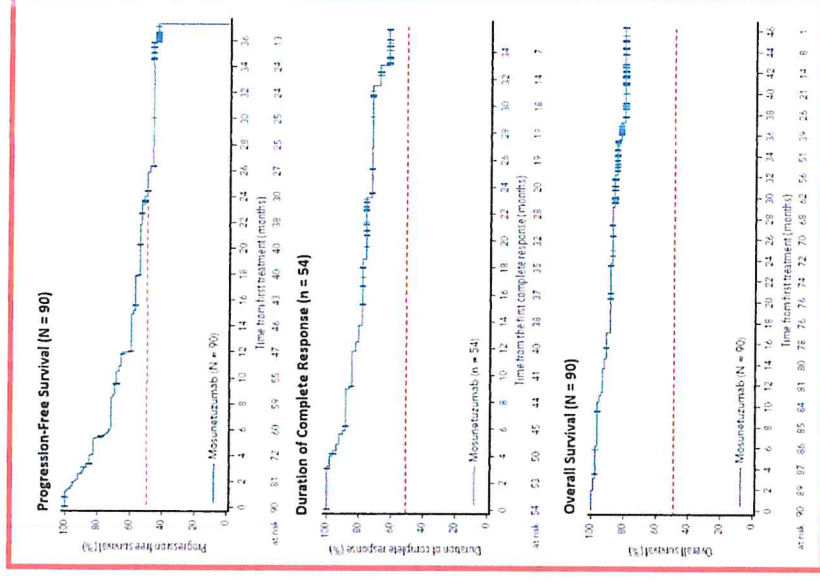
Patient Characteristics

Demographics	N = 90
Median age, years (range)	60 (29 - 90)
Male, n (%)	55 (61.1)
Ann Arbor stage, n (%)	
III-IV	69 (76.7%)
Median # prior therapies (range)	3 (2 - 10)
2 prior lines, n (%)	35 (38.9)
≥ 3 prior lines, n (%)	55 (61.1)
Prior ASCT, n (%)	28 (31.1)
Prior CAR-T	3 (3.3)
POD24, n (%)	47 (52.2)
Double refractory, n (%)	48 (53.3)
Refractory to anti-CD20, n (%)	71 (78.9)
Refractory to last prior, n (%)	62 (68.9)

Results

Product	Mosunetuzumab
Design	Pivotal Phase I/II ¹
Patients, N	N = 90
Median prior therapies	3
Median follow-up, months	37.4 mo
ORR	78%
CRR	60%
median PFS, months	24 mo
36-month PFS rate	43%
median DOR, months	36 mo
30-month DOR rate	57%
median DOCR, months	not reached
30-month DOCR rate	72%
median OS, months	NR
36-month OS rate	82%
Adverse Events of Special Interest	
Any grade CRS/NT	44%/1%
Grade ≥ 3 CRS	2%
Grade ≥ 3 NT	0%

KM Survival Estimates



r/r, relapsed/refractory; FL, follicular lymphoma; ORR, overall response rate;
CRR, complete response rate; DOCR, duration of complete response;
DOR, duration of response; OS, overall survival; PFS, progression-free survival,
CRS, cytokine release syndrome; NT, neurologic toxicity

“CAR-T versus BsAb?”



“How do we choose?”

Targeting CD20 with BsAb after prior CD19-directed CAR-T

Case History

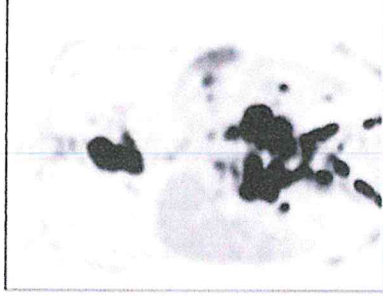
- 58-year old woman with relapsed/refractory FL
- 8 lines of systemic treatment prior to mosunetuzumab
- CR post CAR-T lasted 26 months

Treatment History

Start	Treatment
October 2009	Rituxan monotherapy x 4 doses
November 2009	Rituxan maintenance
April 2011	Rituxan/bendamustine x 6 cycles
June 2014	Lenalidomide/ Rituxan
July 2014	R-CHOP x 6 cycles
November 2014	Day 0 BCV auto PBSCT
September 2015	CAR T-cell infusion (CTL019)
December 2017	Pembrolizumab (3 cycles)
February 2018	Idelalisib (discontinued for rash)
May 2018	Copanlisib
September 2018	BTCT4465A (mosunetuzumab) x 8 cycles

- achieved a CR after 3 cycles of mosunetuzumab

Day -12 (baseline)



After cycle 3 mosunetuzumab



CAR transgene PCR: ≤ 50 copies/ μ g DNA

380 copies/ μ g DNA

- Patient has been off mosunetuzumab for **6 years** in CR

Exploratory biomarkers

- Expansion of lymphocytes (including residual CAR-T cells) observed in some patients following treatment
- In patients with prior CAR-T therapy, response to mosunetuzumab observed **with or without** CAR-T expansion

Targeting CD20 with BsAb before CD19-directed CAR-T

- *anti-CD19 CAR-T therapy in a patient with mixed response to mosunetuzumab*

Case History

- 31-year-old man with refractory follicular lymphoma, grade 1-2/3, stage IV (50% marrow involvement) with missense variants in CREBBP and in TP53 on NGS
- 3 lines of systemic therapy failed before receiving mosunetuzumab
- Rapidly progressing lymphoma with urgent need for therapy

Treatment History

August 2017

CHOP x 6 cycles + R maintenance: PR with PD 3 months post R-CHOP

May 2018

R-ICE x 2 cycles: PR

July 2018

R-DHAP x 2 cycles: PR

August 2018

R-DHAP cycle 3 with unsuccessful stem cell collection

March 2019

mosunetuzumab: PD after cycle 4 (cervical lymph nodes only)

July 2019

low-dose radiation to neck (200 cGy x 2 doses)

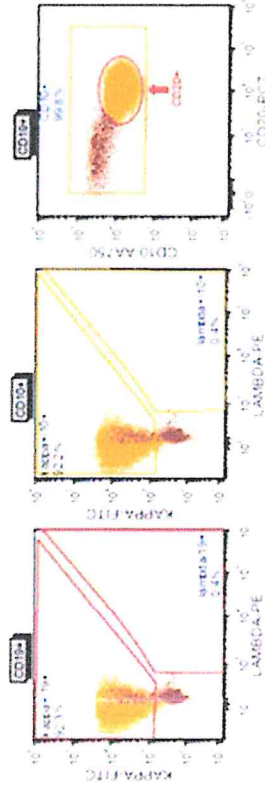
August 2019

CAR-T infusion

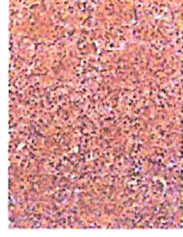
Targeting CD20 with BsAb before CD19-directed CAR-T

- *anti-CD19 CAR-T therapy in a patient with mixed response to mosunetuzumab*

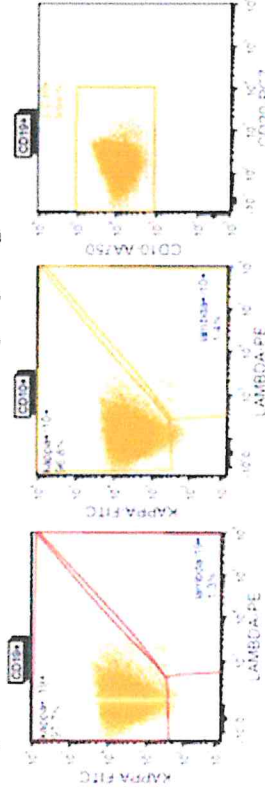
Pre-mosunetuzumab: baseline CD20 and CD19 co-expression



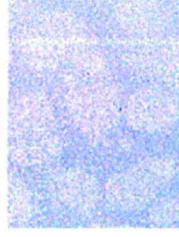
CD20 (L26*) stain



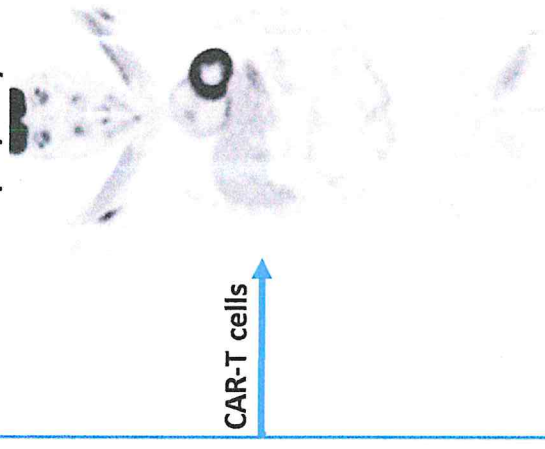
After 4 cycles of mosunetuzumab:
response in all lesions except progression in neck with CD20 loss



CD20 (L26) stain



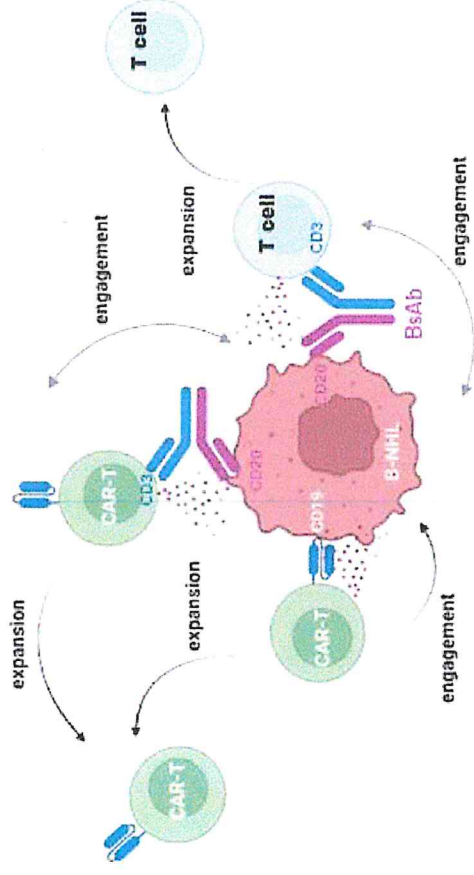
CD19-CAR-T cells
(Day 102)



CAR-T cells

The patient has maintained a complete response at **5+ years** post CAR-T

“CAR-T versus BsAb?”

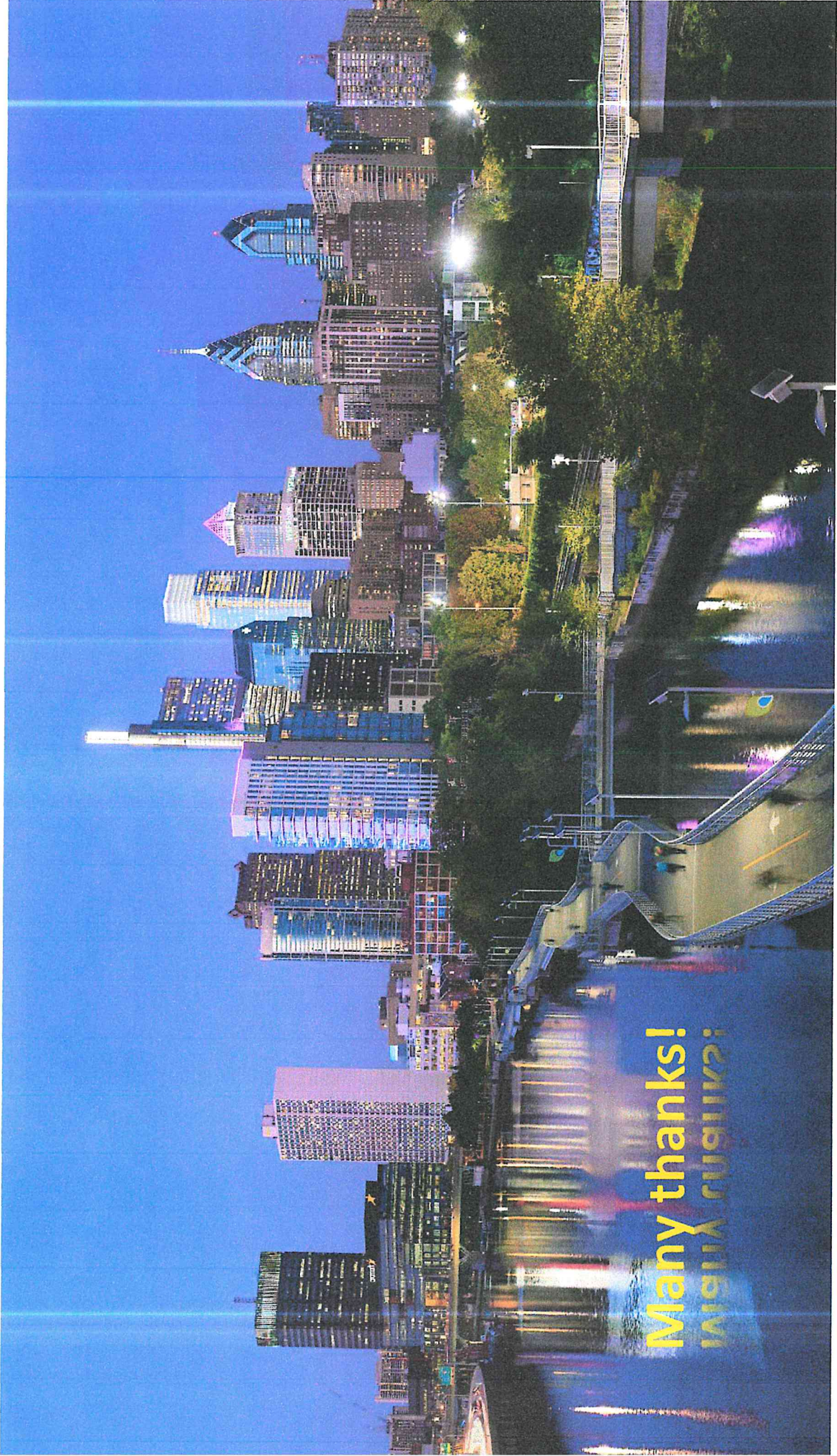


“Maybe we should work together?”

Multi-Institutional Lymphoma Hematology Symposium

Conclusions:

- 1) Both CD19-directed CAR-T cell therapies and CD20/CD3-directed bispecific antibody therapies improve outcomes for patients with relapsed/refractory follicular lymphoma as third or later therapy compared to older therapeutic approaches
- 2) Choosing between CAR-T and BsAb therapy or sequencing these T cell-mediated therapies depends on the specific clinical situation; for example, the urgency of initiating treatment and tumor antigen expression, etc.



Many thanks!
MIAHUI RUSHIK?



Patient Case Presentation: NGS as a Diagnostic Tool

Zachary Frosch, MD, MSHP

Assistant Professor

Department of Hematology/Oncology

Cancer Prevention and Control

Fox Chase Cancer Center



Objectives

- 1) Demonstrate the role molecular testing can play in lymphoma diagnosis
- 2) Illustrate the predictive value of molecular testing in lymphoma therapy

Presentation

- 78 year old woman
- Previously healthy and active – helped maintain her small farm
- Presents with 2 months of:
 - Fatigue
 - Weakness
 - High fevers (>103)
 - 15 lb weight loss
 - Bilateral joint pain and swelling in the hands

Presentation

- Multiple courses of antibiotics with her primary provider without persistent improvement
- Ultimately led to ED presentation

Workup Prior to Presentation to Your Office

- CT of the Chest, Abdomen and Pelvis
 - 1-2cm lymphadenopathy at multiple sites
 - Spleen 13cm
- Selected Lab Testing:
 - Broad infectious workup negative except for + IgM and IgG for toxoplasmosis
 - ANA and RF negative
 - ESR 82
 - WBC 7.1, hgb 9.3, platelets 337
 - Creatine and AST/ALT/Tbili WNL
- Core needle biopsy of axillary node:
 - Small sample consistent with benign reactive lymphoid tissue and no evidence of lymphoma

PET/CT Results

- Multisite lymphadenopathy up to 2.5cm Lymph nodes
- SUV range 3-7
- Diffusely increased uptake in the spleen without focal lesions

Initial Excisional Lymph Node Biopsy

- Axillary LN biopsy:
 - Preserved nodal architecture, enlarged secondary follicles
 - Interfollicular regions with increased high endothelial venules and small to intermediate sized lymphocytes with small aggregates of histiocytes

Initial Excisional Lymph Node Biopsy

- Axillary LN biopsy:
- Read as: Reactive node with features of toxoplasma lymphadenitis

Initial Excisional Lymph Node Biopsy

- Axillary LN biopsy:
- TCR gamma/beta rearrangement positive, IGH negative
- Tandem flow cytometry was negative

Initial Excisional Lymph Node Biopsy

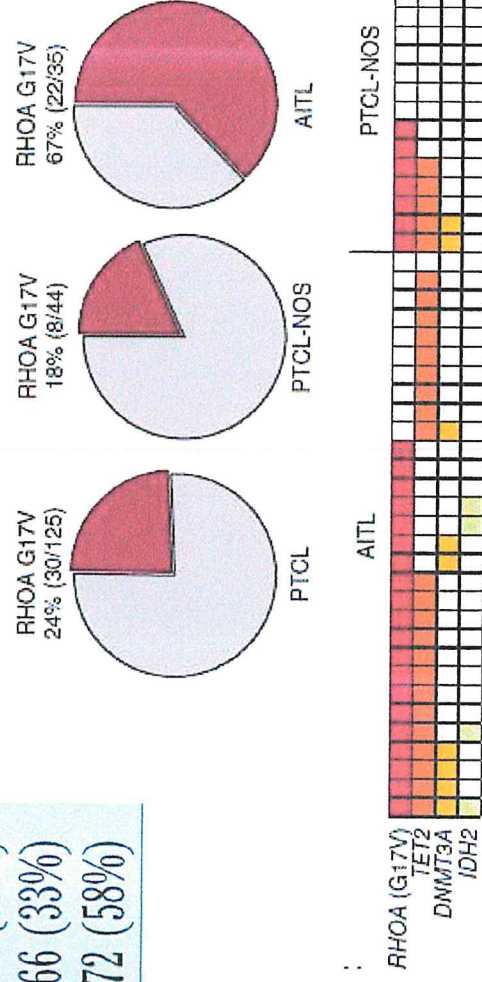
- Addendums:
 - Spirochete staining and toxoplasma staining negative
 - Remainder of infectious staining negative
 - CXCL13, ICOS, PD1 (follicular helper T cell markers) negative
 - No cytogenetic abnormalities on a microarray

More From her Excisional Lymph Node Biopsy

- NGS shows:
 - Tier 2 mutation in RhoaA (G17V)
 - Tier 2 mutation in TET2
- Diagnosis amended to Nodal T Follicular Helper Cell Lymphoma, Angioimmunoblastic Type

Recurrent Genetic Alterations in AITL

AITL	
Mutations (%)	
<i>TET2</i>	31/64 (48%)
<i>DNMT3A</i>	19/64 (30%)
<i>IDH2</i>	22/66 (33%)
<i>RHOA</i> (G17V)	42/72 (58%)

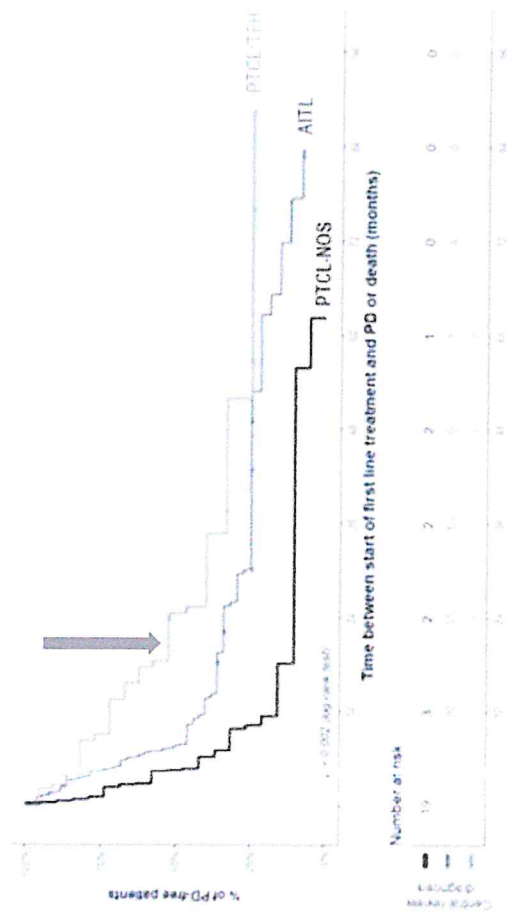


Dobay MP, Lemonnier F, Missiaglia E, et al. Integrative clinicopathological and molecular analyses of angioimmunoblastic T-cell lymphoma and other nodal lymphomas of follicular helper T-cell origin. *Haematologica*. Apr 2017;102(4):e148-e151.

Palomero T, Couronne L, Khiabanian H, et al. Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. *Nat Genet*. Feb 2014;46(2):166-70.

AITL and TFH

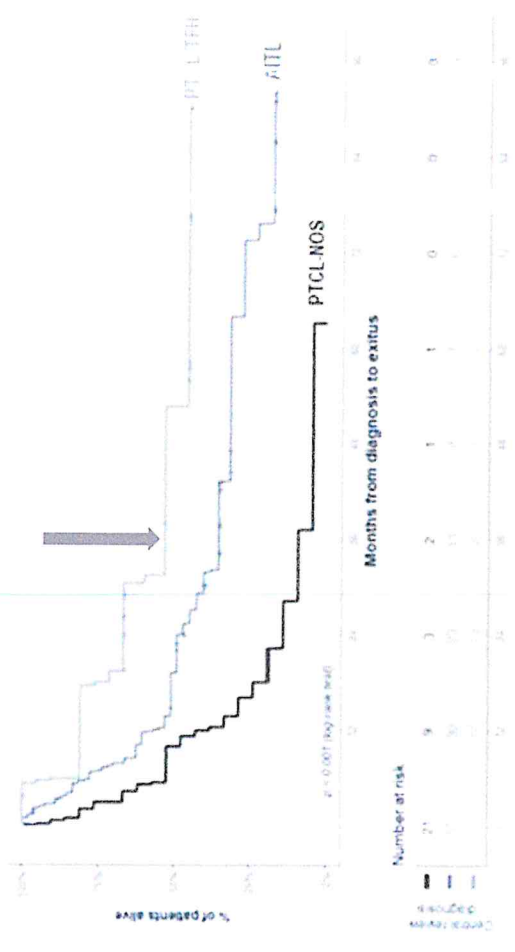
(A) Progression-free survival



Progression-free survival (PFS)¹

	PTCL-NOS	AITL	PTCL-TFH	All	p-value ²
Events, n (%)	19 (100.00%)	42 (82.4%)	14 (63.6%)	75 (81.5%)	
Median PFS, months (95% CI) ¹	4.6 (1.9-7.3)	7.8 (5.8-11.8)	24.6 (15.2-34.1)	9.2 (5.5-13.0)	0.002

(B) Overall survival

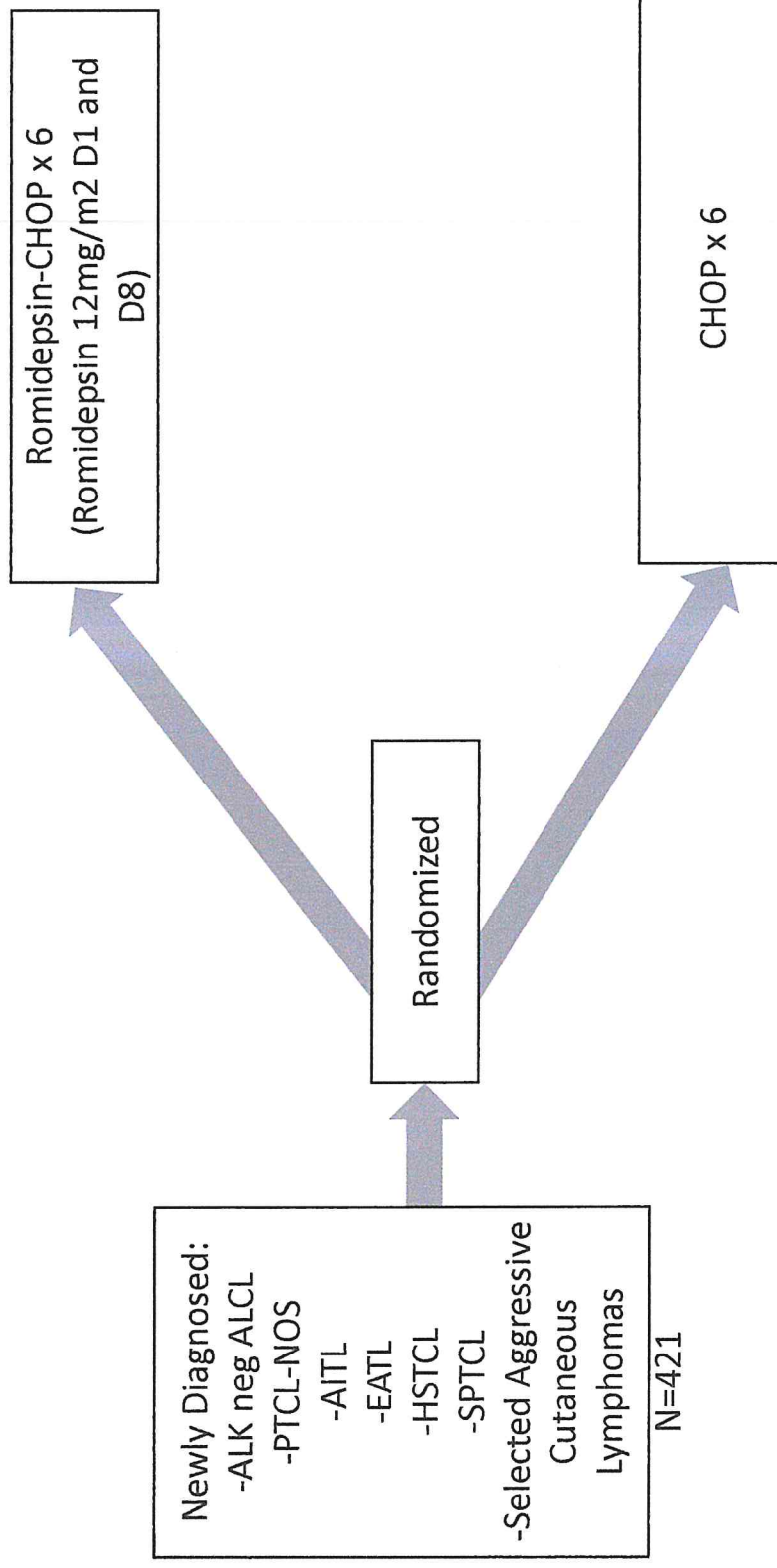


Overall survival (OS)¹

	PTCL-NOS	AITL	PTCL-TFH	All	p-value ²
Events, n (%)	21 (100.00%)	37 (67.3%)	10 (43.5%)	68 (68.7%)	
Median OS, months (95% CI) ¹	10.0 (0.9-19.2)	19.3 (4.2-34.4)	52.6 (NE) ¹	18.1 (3.2-27.9)	<0.001

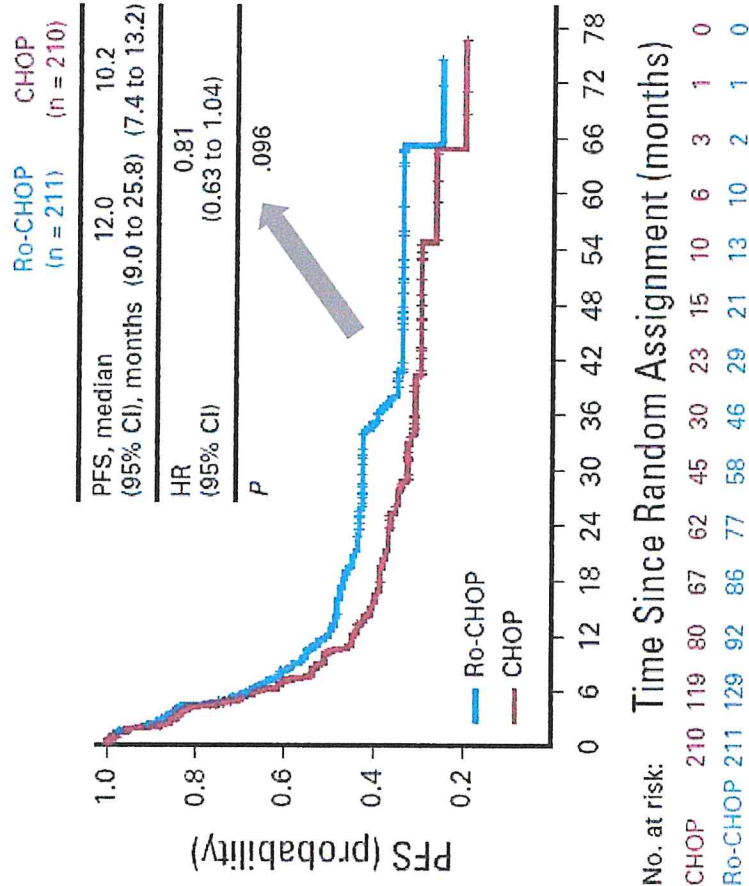
Garcia-Sancho B/H 2023

Ro-CHOP

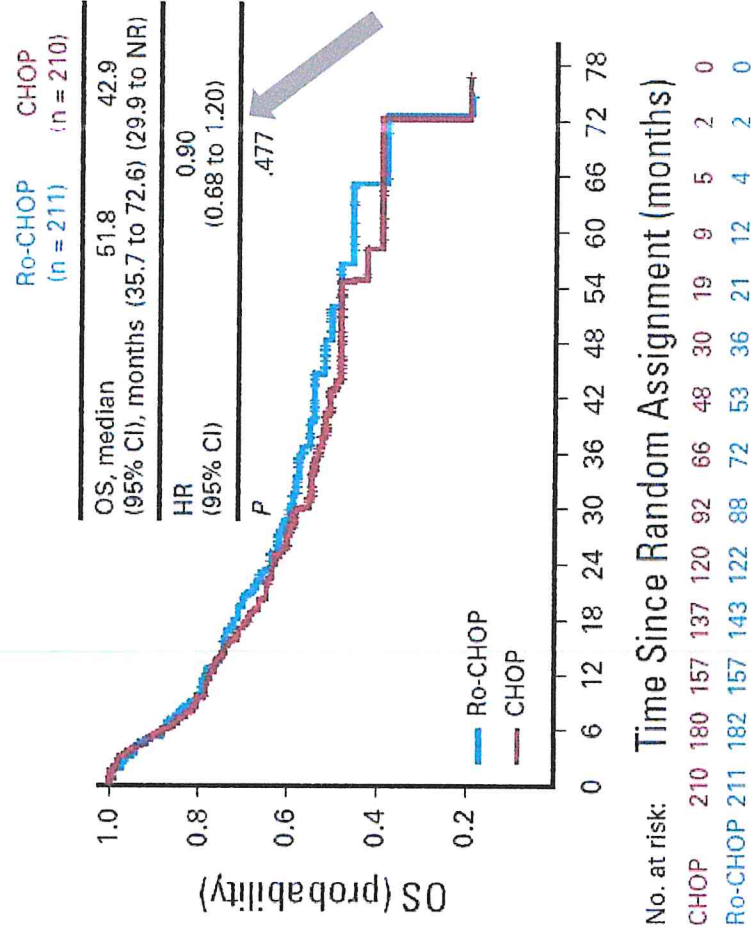


Ro-CHOP

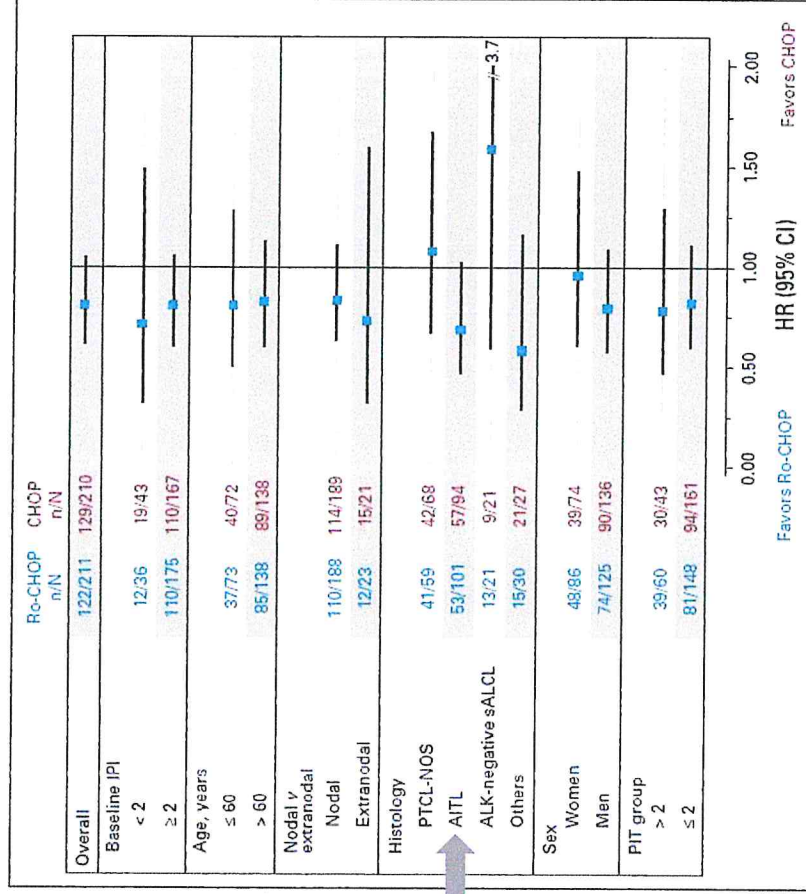
A



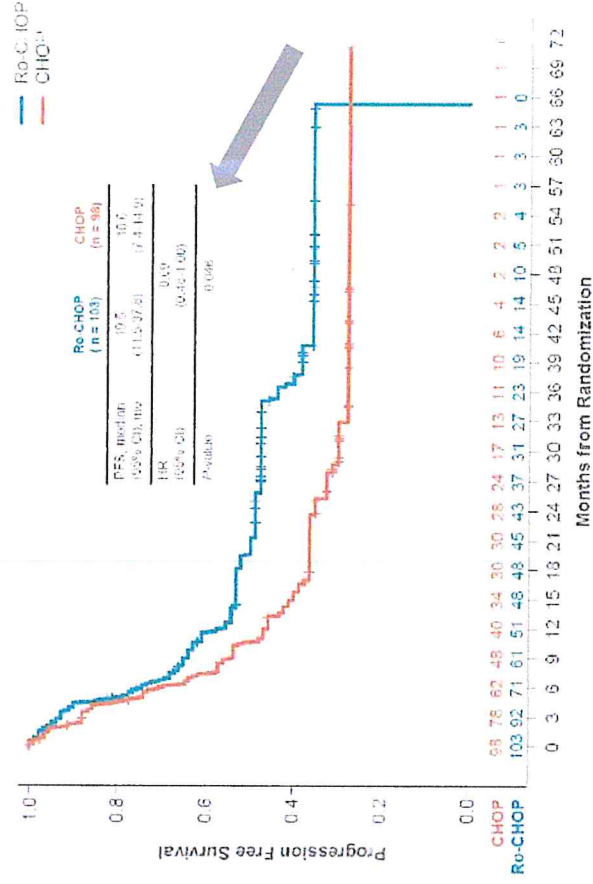
B



Ro-CHOP: Missed Opportunity?



Supplemental figure 3. PFS according to treatment arm in the centrally confirmed AITL and related IFH PTCL histological subgroup



What About in More Common Lymphomas?

Cell of Origin in Diffuse Large B-Cell Lymphoma

Regular Article

LYMPHOID NEOPLASIA

DLBclass: a probabilistic molecular classifier to guide clinical investigation and practice in diffuse large B-cell lymphoma

Chapuy B, Wood T, Stewart C, et al. DLBclass: a probabilistic molecular classifier to guide clinical investigation and practice in diffuse large B-cell lymphoma. *Blood*. May 1 2025;145(18):2041-2055.

THE NEW ENGLAND JOURNAL of MEDICINE

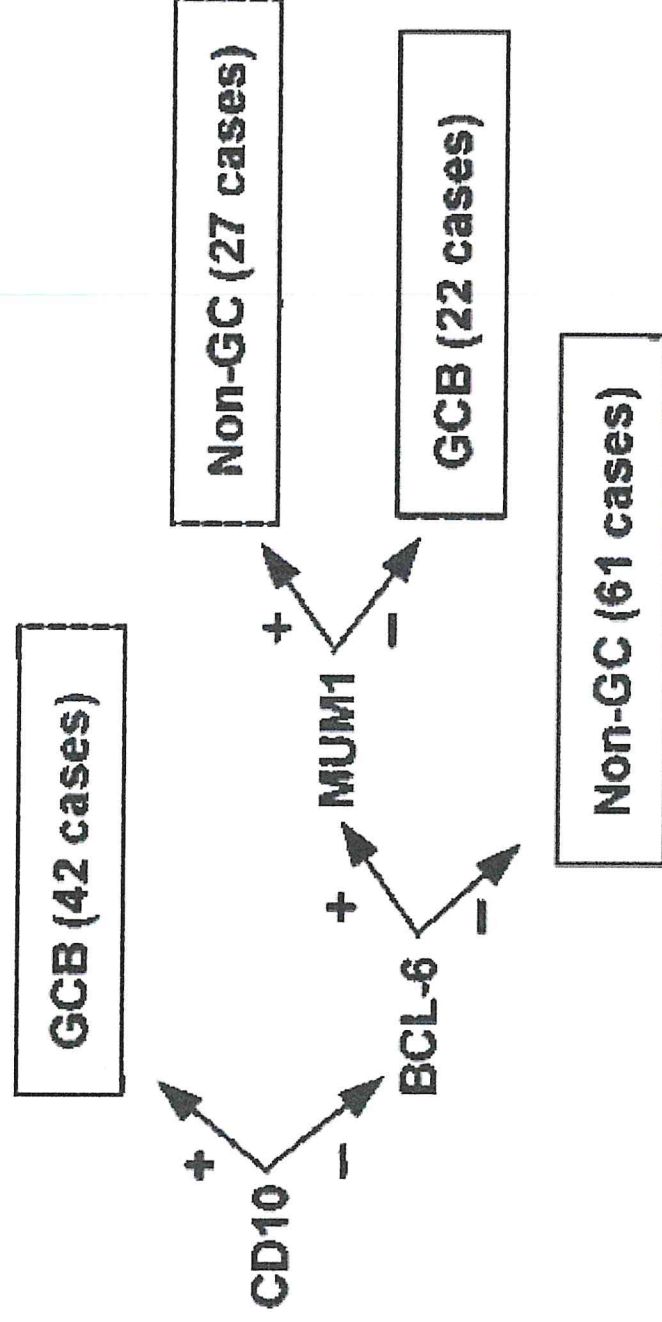
ORIGINAL ARTICLE

Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma

R. Schmitz, G.W. Wright, D.W. Huang, C.A. Johnson, J.D. Phelan, J.Q. Wang, S. Roulland, M. Kasbekar, R.M. Young, A.L. Shaffer, D.J. Hodson, W. Xiao, X. Yu, Y. Yang, H. Zhao, W. Xu, X. Liu, B. Zhou, W. Du, W.C. Chan, E.S. Jaffe, R.D. Gascoyne, J.M. Connors, E. Campo, A. Lopez-Guillermo, A. Rosenwald, G. Ott, J. Delabie, L.M. Rimsza, K. Tay Kuang Wei, A.D. Zelenetz, J.P. Leonard, N.L. Bartlett, B. Tran, J. Shetty, Y. Zhao, D.R. Soppet, S. Pittaluga, W.H. Wilson, and L.M. Staudt

Schmitz R, Wright GW, Huang DW, et al. Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. *New England Journal of Medicine*. 2018;378(15):1396-1407.

Hans Algorithm



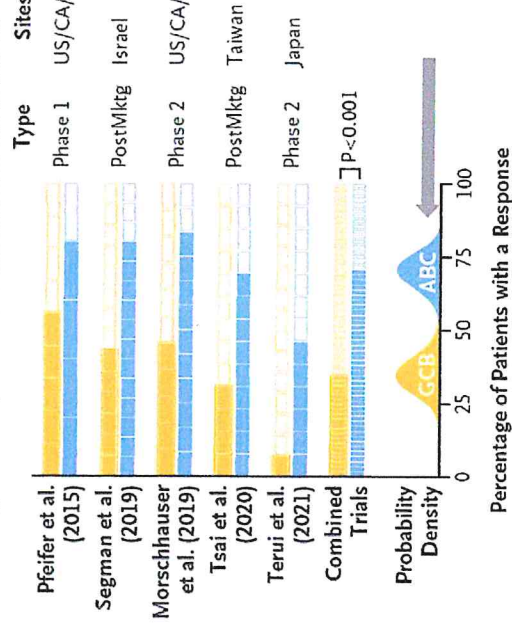
Hans CP. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004;103(1):275-282.

POLARIX and Other Trials by Cell of Origin

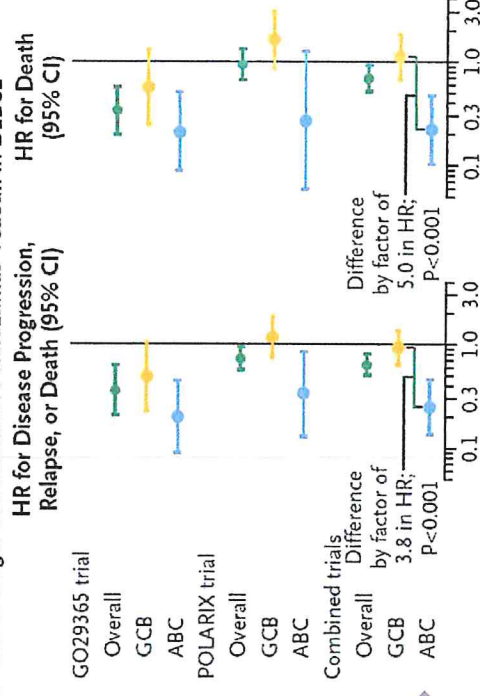
Baseline Risk Factors	Pola-R-CHP (N=440)		R-CHOP (N=439)		Hazard Ratio	95% Wald CI	Pola-R-CHP Better		R-CHOP Better	
	Total N	n	2-year Rate	n			2-year Rate	n		
Cell-of-origin	352	184	75.1	168	1.0	(0.7 to 1.5)	76.9	168		
	221	102	83.9	119	0.4	(0.2 to 0.6)	58.8	119		
	95	44	73.0	51	1.9	(0.8 to 4.5)	86.2	51		
	211	110	73.8	101	0.7	(0.4 to 1.2)	64.3	101		
Unclassified										
Unknown										

Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. *N Engl J Med*. Jan 27 2022;386(4):351-363

B Cell of Origin and Response to Polatuzumab Vedotin in DLBCL



D Cell of Origin and Benefit of Polatuzumab Vedotin in DLBCL



Palmer AC, Kurtz DM, Alizadeh AA. Cell-of-Origin Subtypes and Therapeutic Benefit from Polatuzumab Vedotin. *N Engl J Med*. Aug 24 2023;389(8):764-766.

Take Home Points

- Molecular testing plays an increasingly important role in lymphoma, both diagnostically and therapeutically
- NGS may be helpful in certain difficult diagnostic situations, this is just an illustrative example
- Our traditional pathologic/diagnostic categories contain heterogeneity – not just true in follicular T-cell lymphomas

Questions/Discussion?



SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

Update in Classic Hodgkin Lymphoma (cHL)

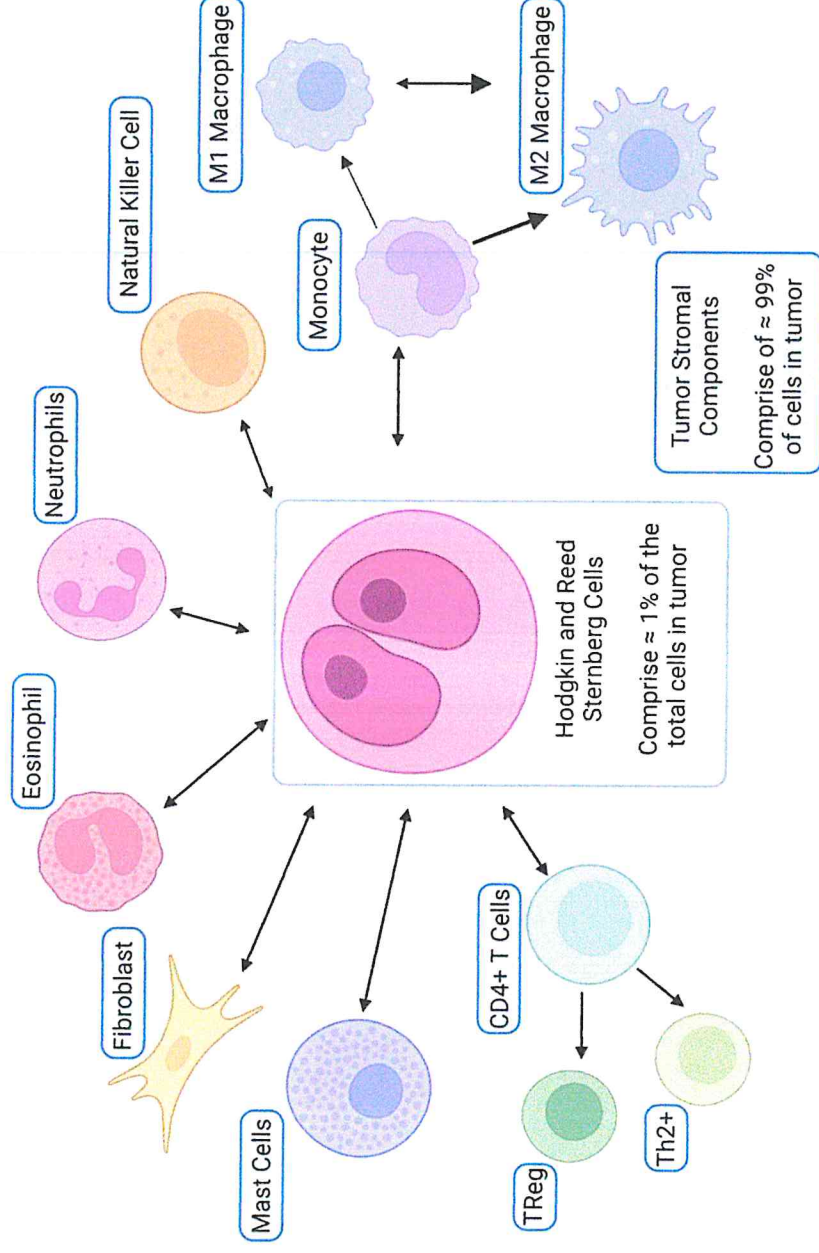
Ubaldo Martinez Outschoorn, MD
Professor of Medical Oncology

9/25/2025

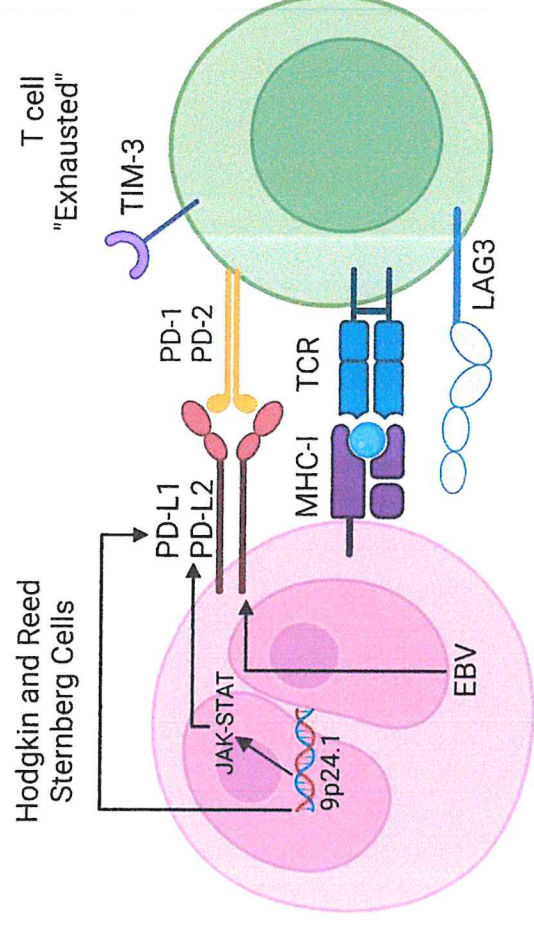
Outline

- Histology and Markers
- Complications of Therapy
- Management
 - Early Favorable
 - Early Unfavorable
 - Advanced Stage
 - Relapsed/Refractory
- PET/CT and Metabolism
- Circulating DNA

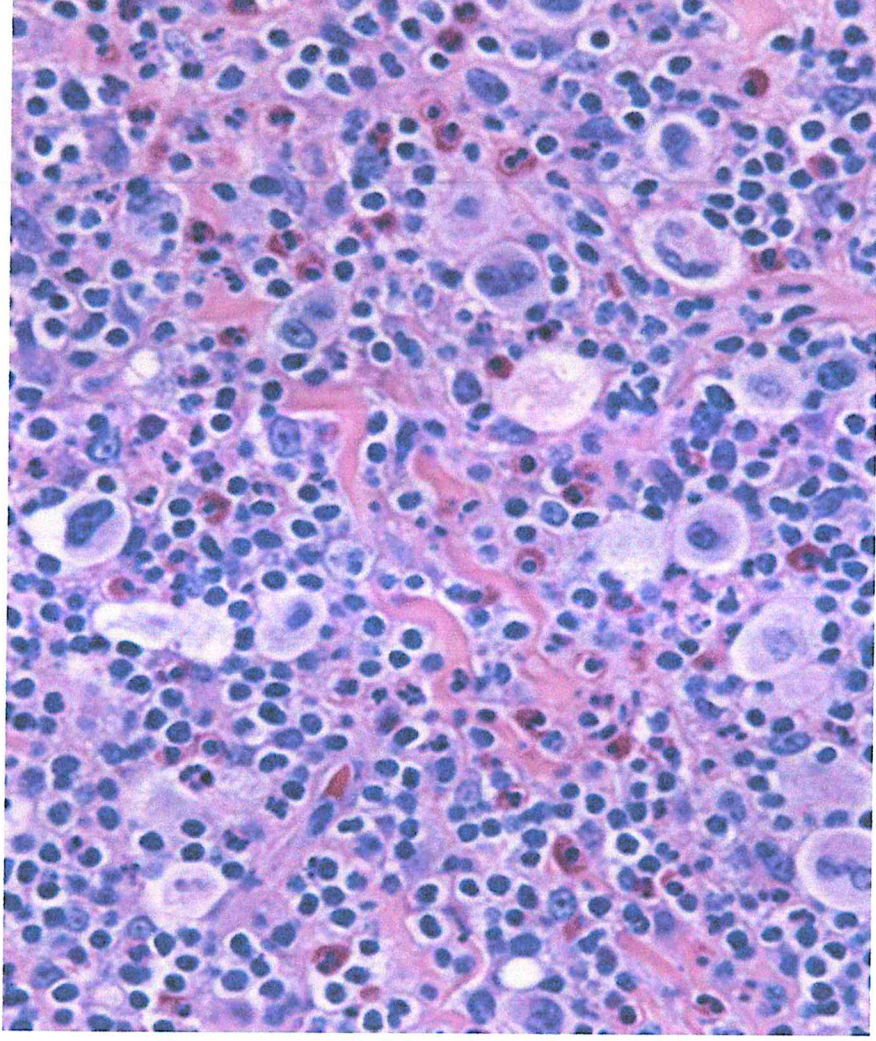
TME of Classic Hodgkin Lymphoma



HRS and T Cell Interactions



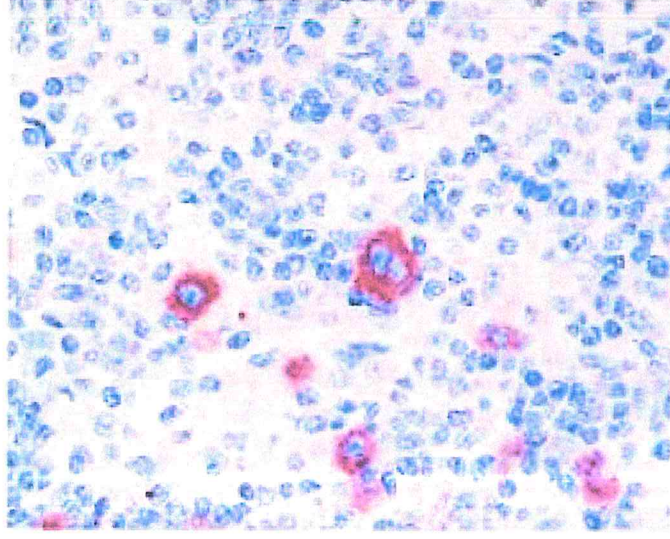
Tumor Histology in Classic Hodgkin Lymphoma



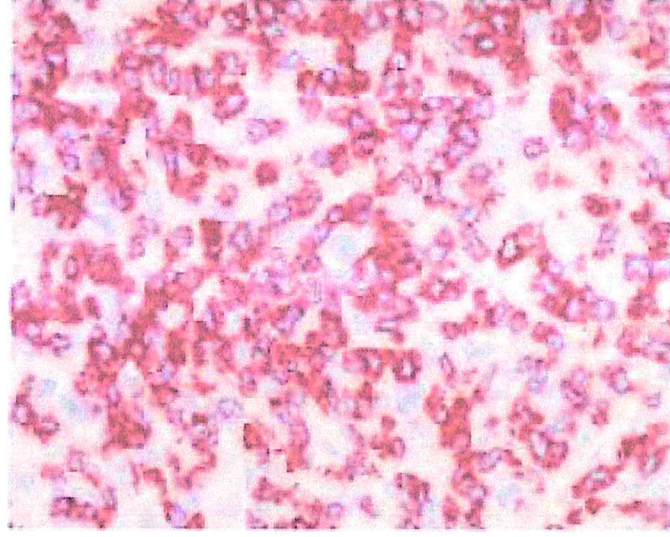
Mikkilineni L, et al. Semin Oncol. 2017;44(3):218-225

Pathologic Characterization of Classic Hodgkin Lymphoma

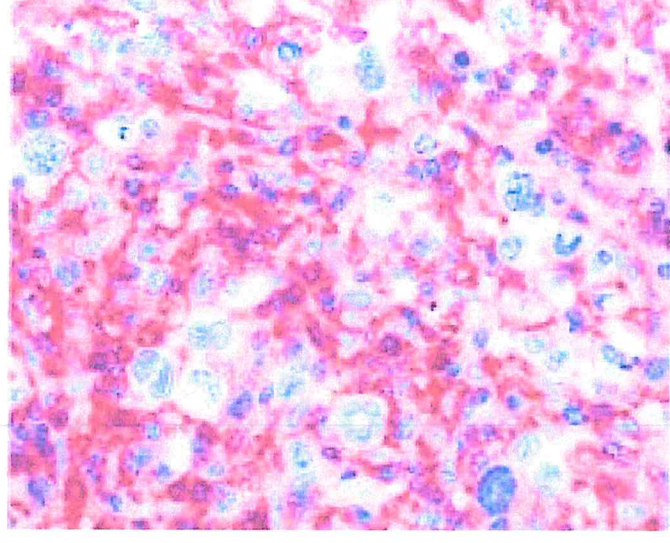
CD30



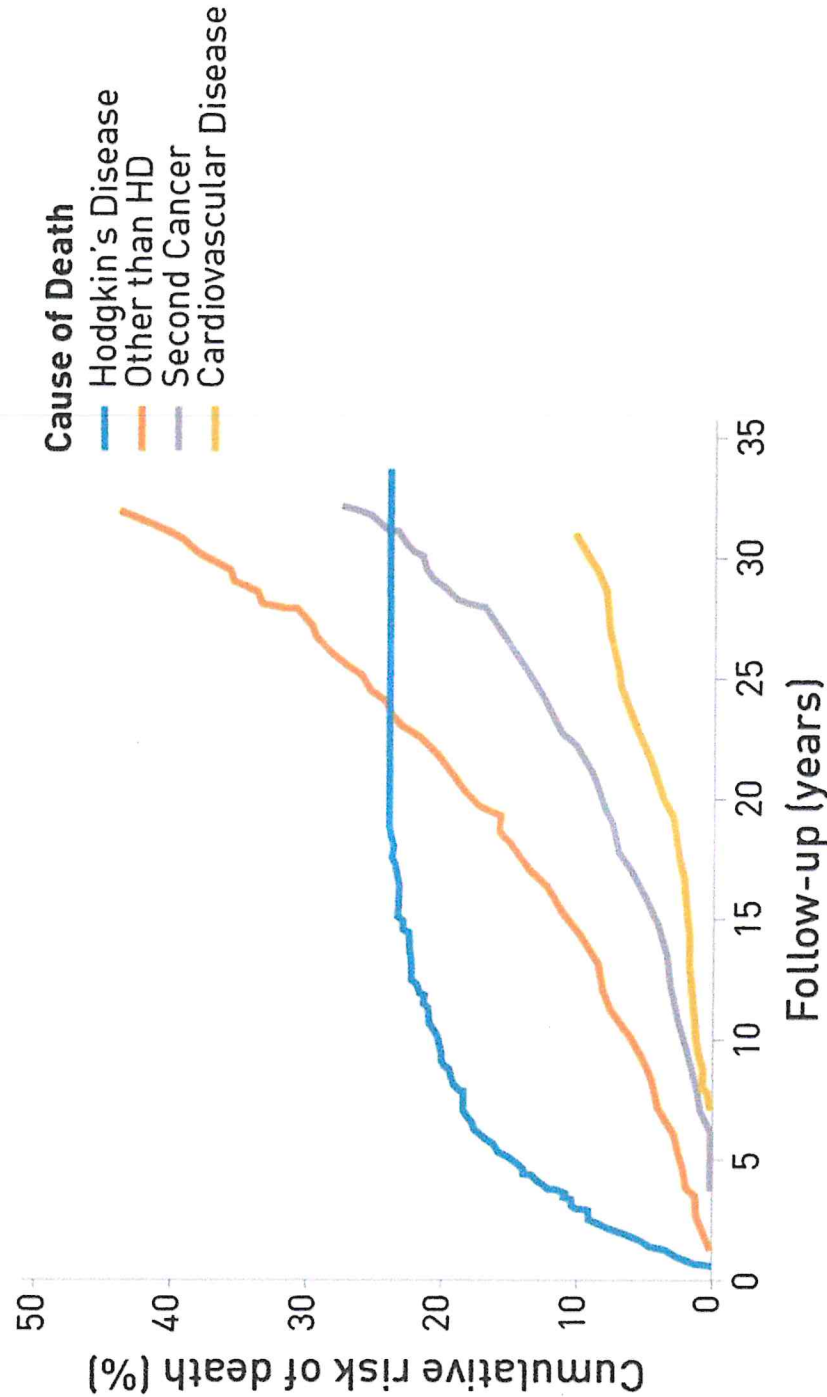
CD3



CD45

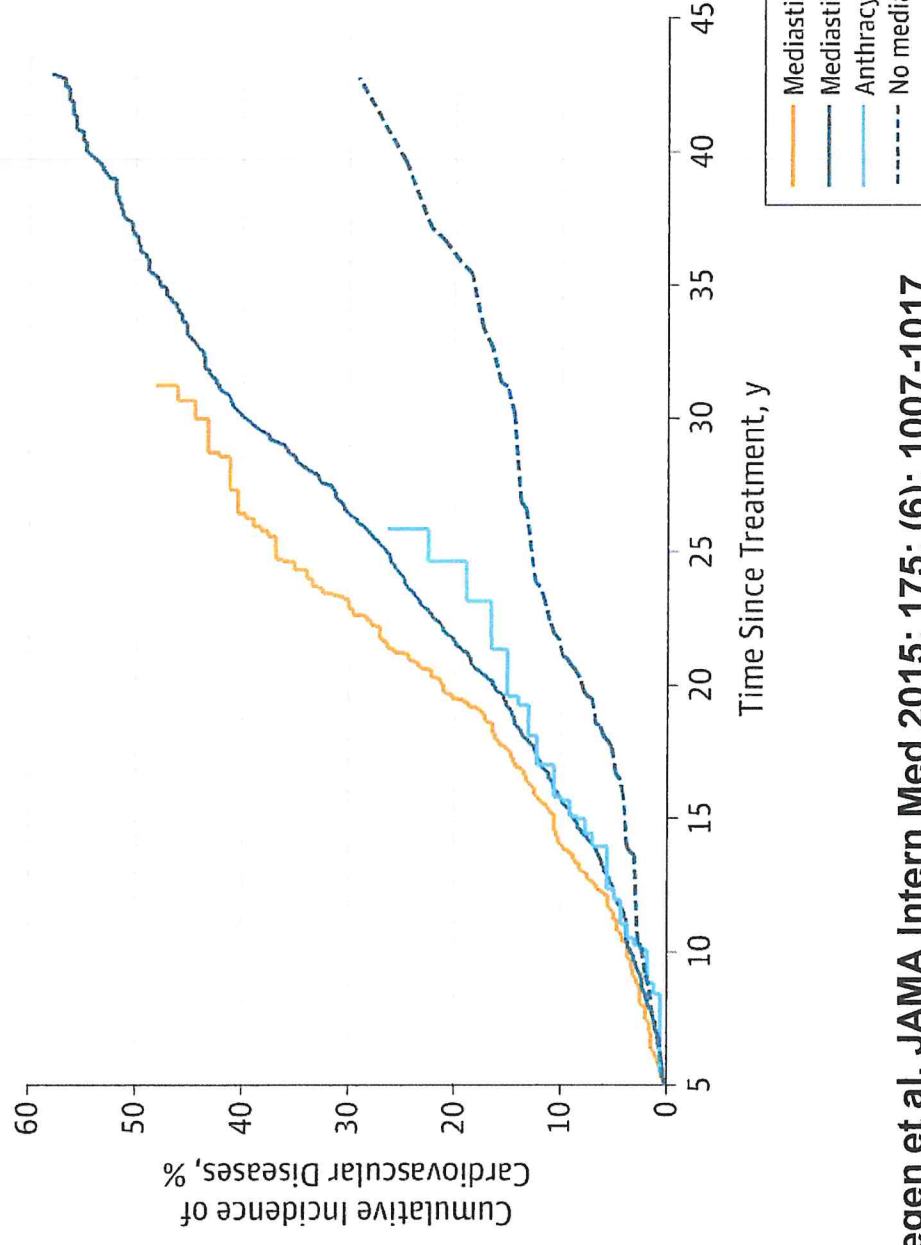


Late Complications of Therapy of Classic Hodgkin Lymphoma



Aleman BM et al. *J Clin Oncol*. 2003;21(18):3431-3439.

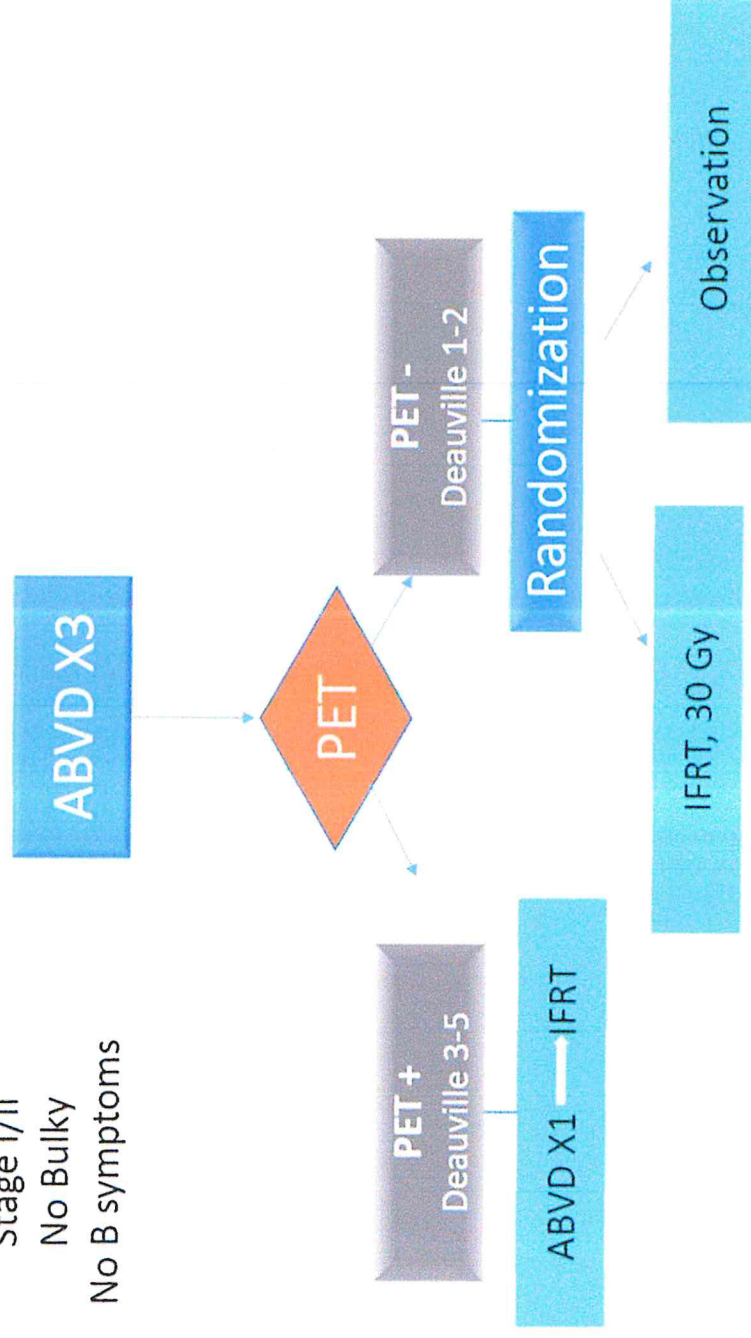
Cumulative incidence of cardiovascular disease by cHL treatment



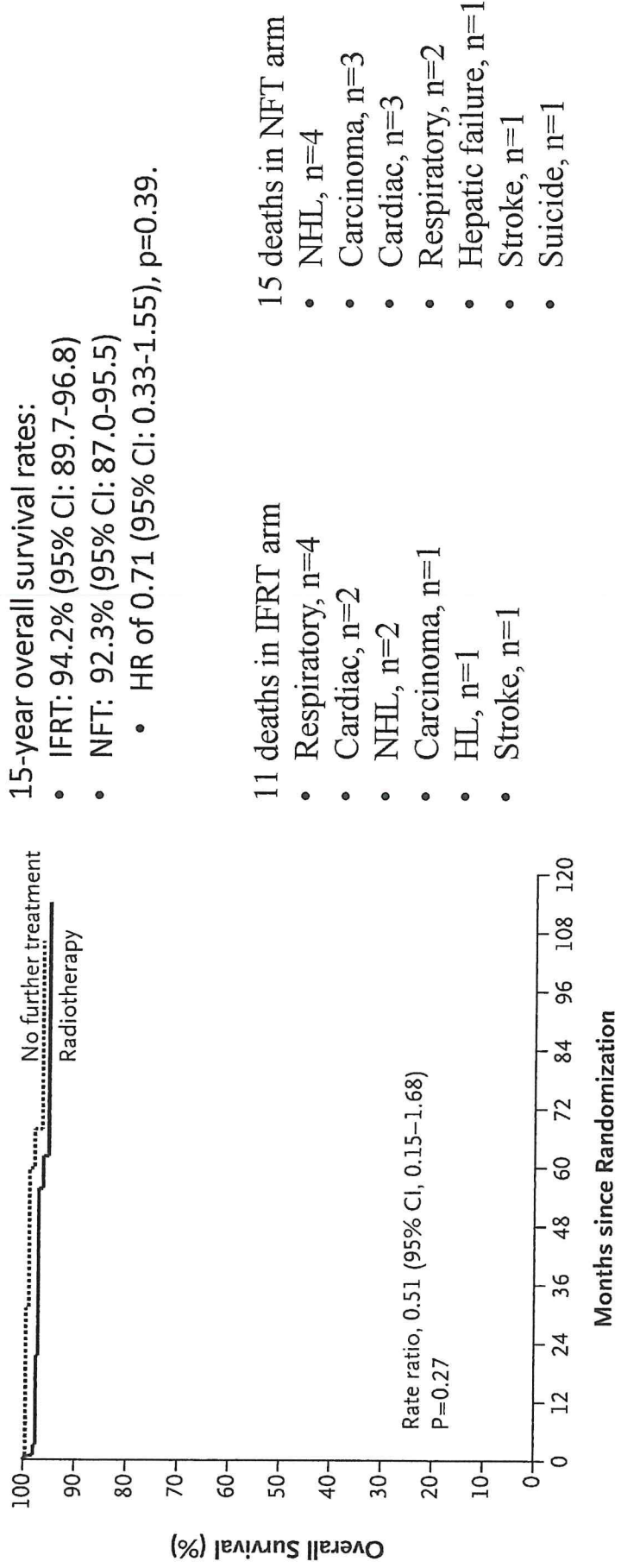
Van Nimwegen et al. JAMA Intern Med 2015; 175; (6): 1007-1017

UK NCRI Rapid Trial

Stage I/II
No Bulky
No B symptoms



Rapid Trial-Early Stage IA/IIA Favorable cHL

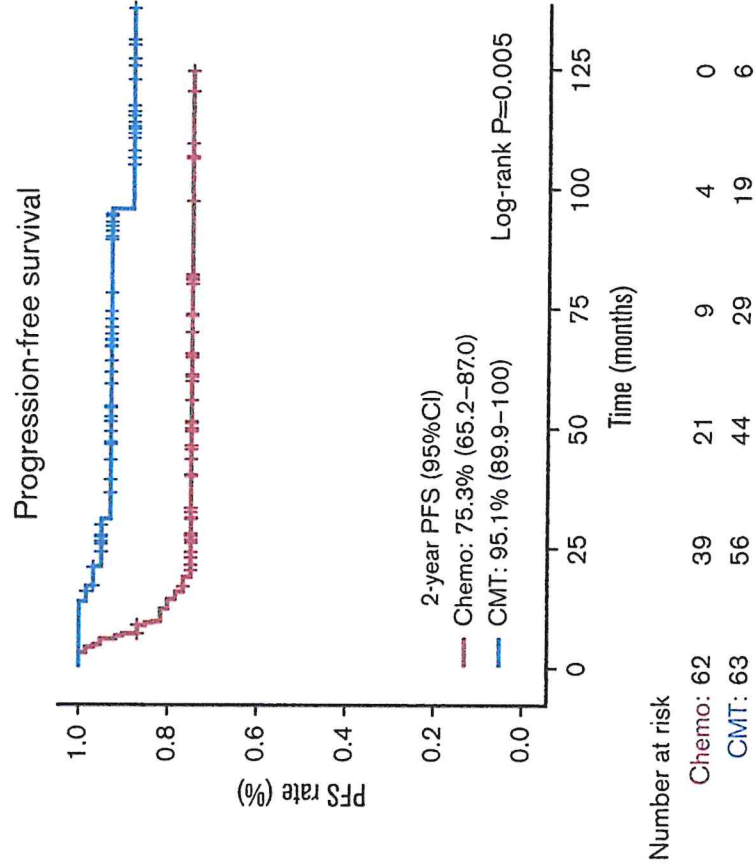


15-year overall survival rates:

- IFRT: 94.2% (95% CI: 89.7-96.8)
- NFT: 92.3% (95% CI: 87.0-95.5)
 - HR of 0.71 (95% CI: 0.33-1.55), p=0.39.

No. at Risk	209	200	191	175	139	103	60	34	13	2	0
Radiotherapy	211	204	196	167	140	97	56	18	6	0	0
No further treatment											

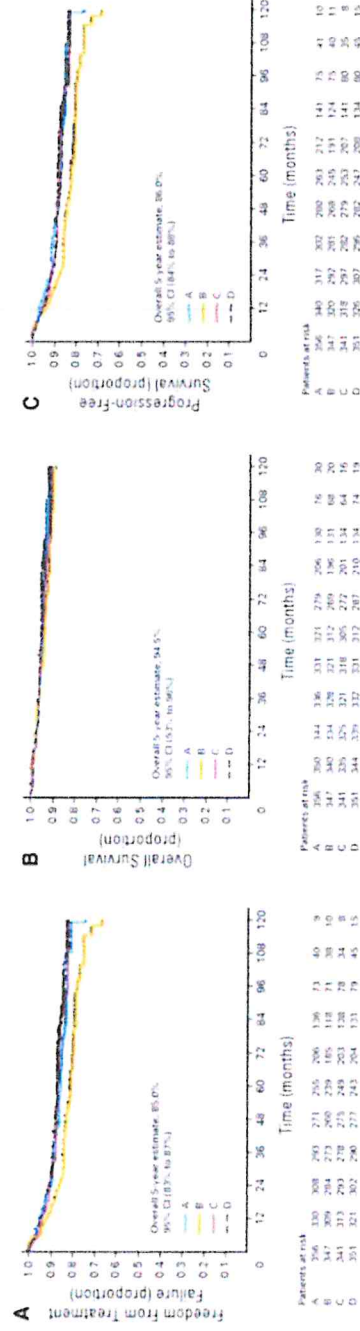
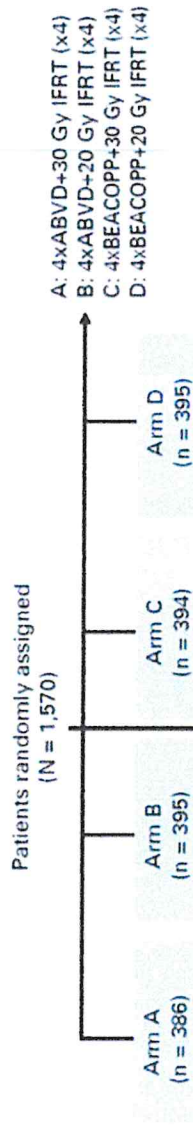
Mayo Clinic Experience of combined modality therapy (CMT) versus ChemoRx for early-stage Classic Hodgkin Lymphoma



- In the real-world setting, CMT improved outcomes for patients with PET2-positive and unfavorable disease.
- Similar to clinical trials, favorable, non-bulky, and PET2-negative subgroups had comparable survival outcomes with chemotherapy alone.

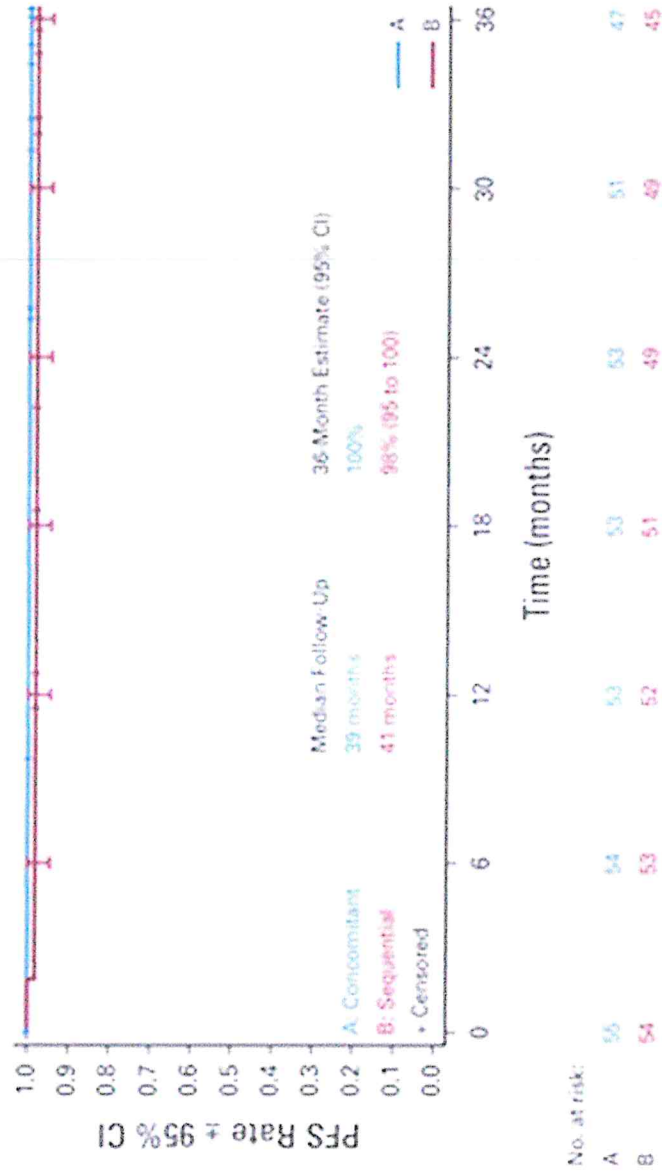
Chohan K, et al. Blood Adv, 2022

Unfavorable ESHL GHSG HD11 trial



ABVD X 4 followed by 30 Gy IFRT is adequate

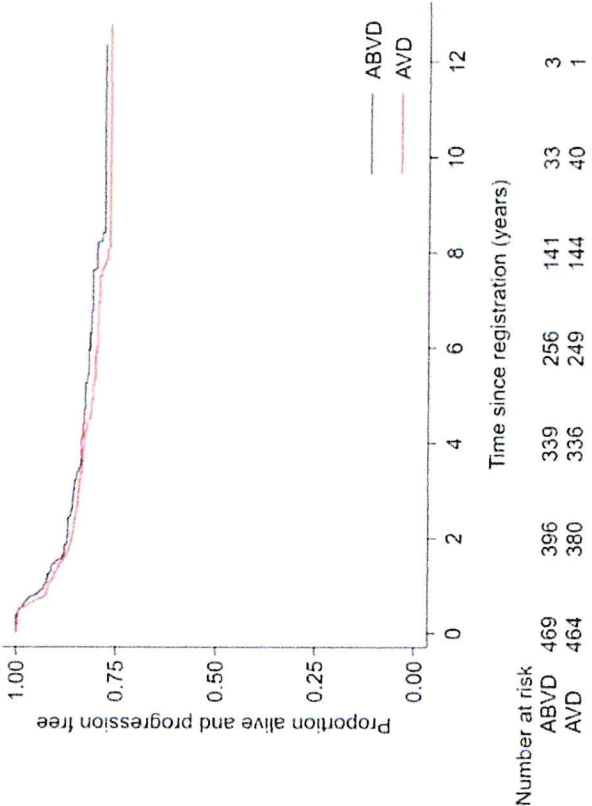
GHSG NIVAHL Trial of Nivolumab and AVD in Early –Stage Unfavorable Hodgkin Lymphoma



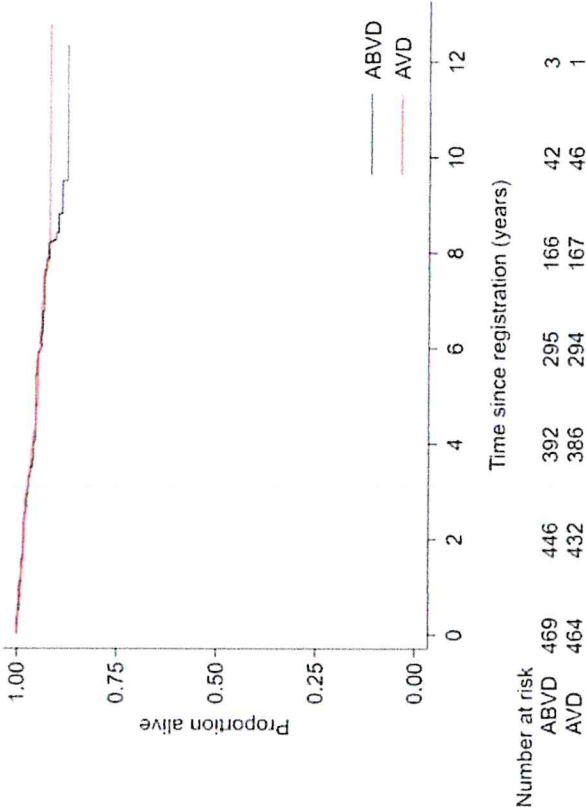
Bröckelmann P, et al. JCO 2023

RATHL Long Term Follow-up

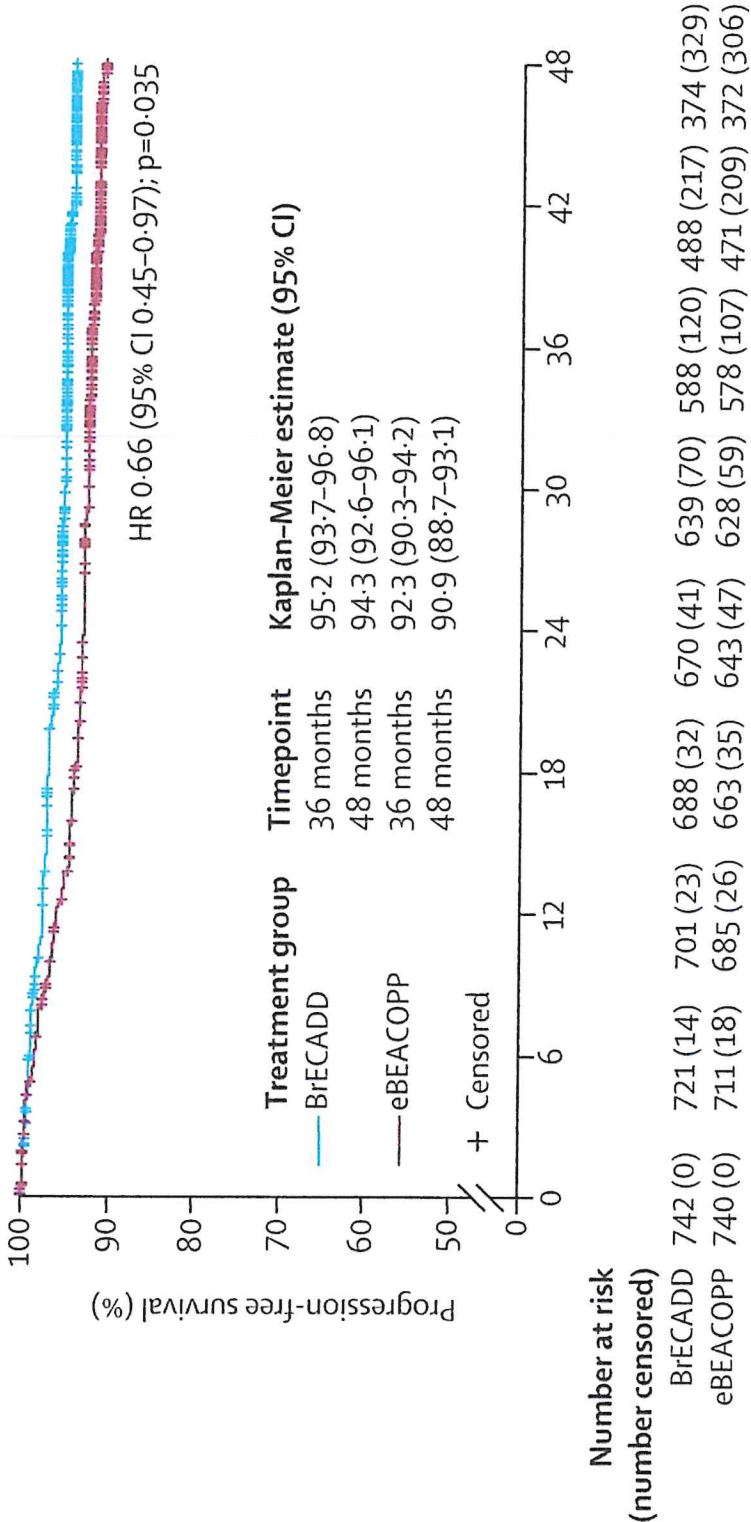
PFS of PET-negative pts



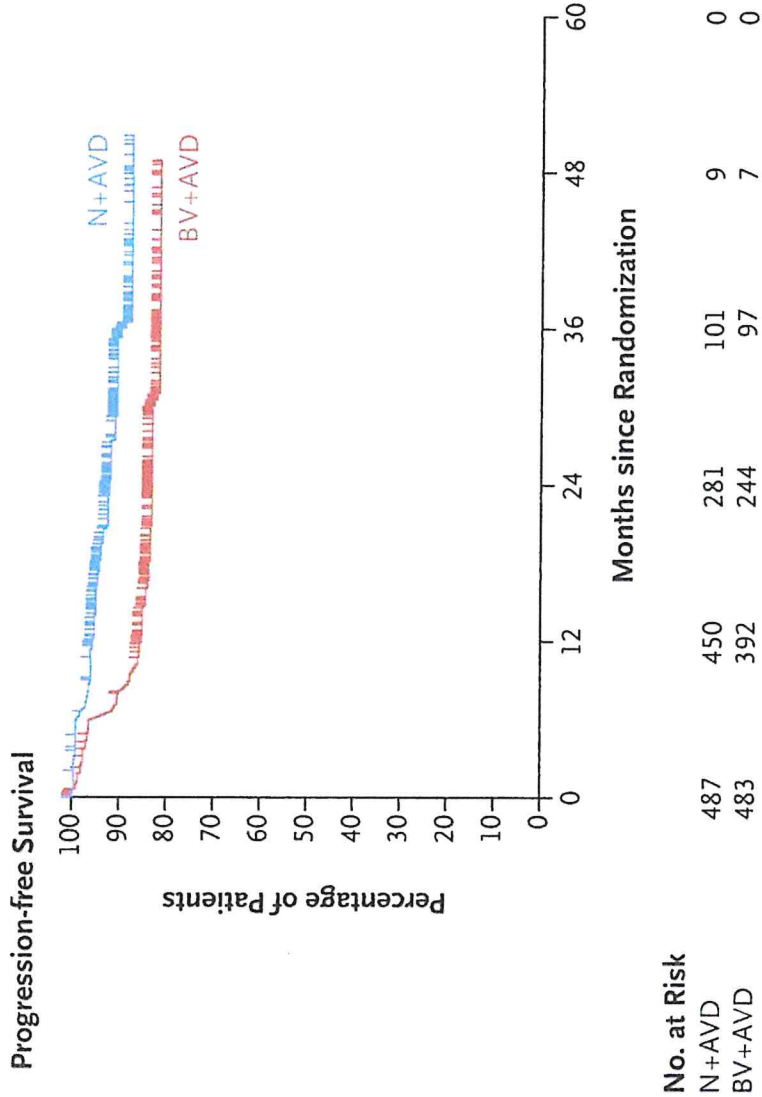
OS of PET-negative pts



GHSG HD21: BrECADD versus eBEACOPP in Advanced cHL



S1826: Nivolumab+AVD in Advanced cHL



Disease Progression or Death	no. of patients	2-Year Estimate for Progression-free Survival (95% CI)	
		percent	percent
N+AVD	41	92 (89–94)	
BV+AVD	81	83 (79–86)	
Hazard ratio, 0.45 (95% CI, 0.30–0.65)			

Herrera, et al. N Engl J Med 2024; 392:1379-1389

S1826-Nivolumab+AVD in Older Patients

Better tolerated and Improved PFS

Figure: Progression-Free Survival for Patients Aged ≥60 years Enrolled on S1826.

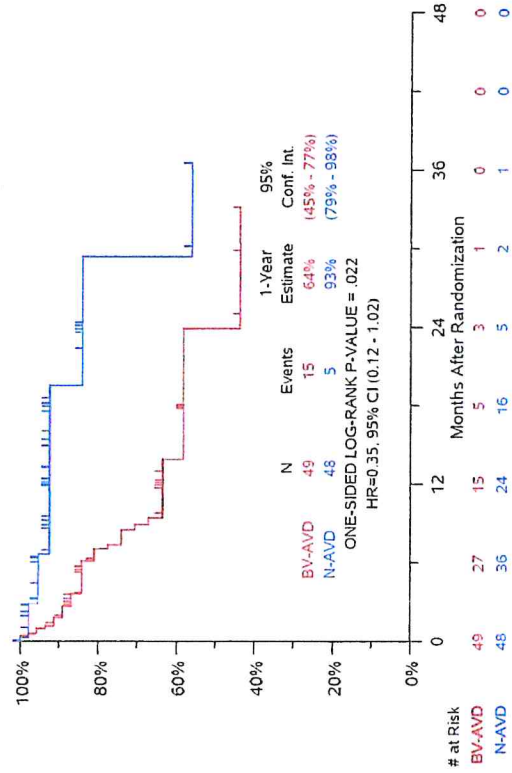


Table: Key Adverse Events by Treatment Arm (Any Grade and Grade ≥3).

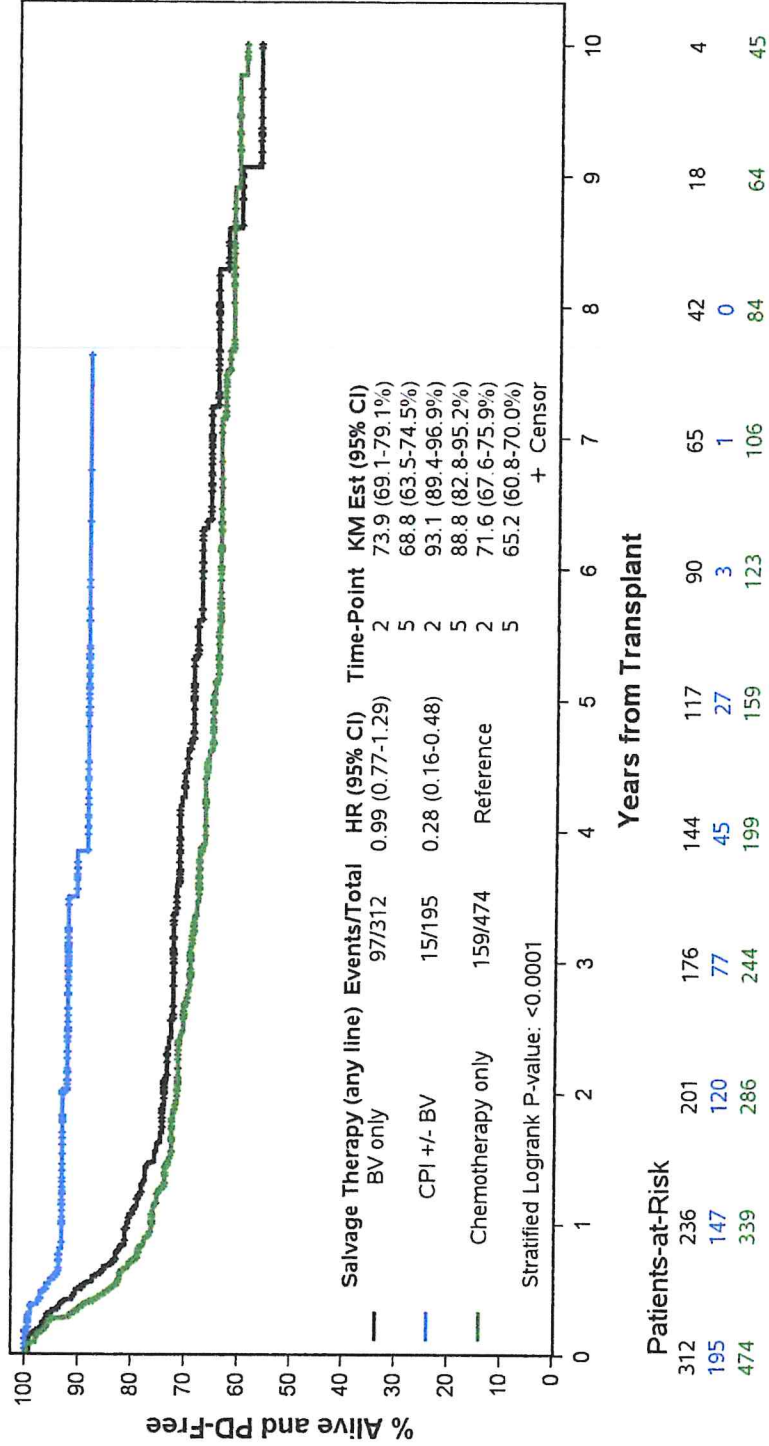
Adverse Event	N-AVD (N=48)		Bv-AVD (N=47)		p-value ³	N-AVD (N=48)		Bv-AVD (N=47)		p-value ³
	Any	Grade	Any	Grade		Any	Grade	Any	Grade	
Febrile neutropenia	6 (13%)		9 (19%)		0.42	6 (13%)		9 (19%)		0.42
Sepsis	3 (6%)		10 (21%)		0.04	3 (6%)		10 (21%)		0.04
Infections and infestations	9 (19%)		16 (34%)		0.11	3 (6%)		10 (21%)		0.04
Peripheral sensory neuropathy ¹	15 (31%)		31 (66%)		0.001	1 (2%)		5 (11%)		0.11
Peripheral motor neuropathy ²	4 (8%)		7 (15%)		0.36	0 (0%)		1 (2%)		0.49

¹Peripheral sensory neuropathy by grade (gr): for N-AVD, gr 1: 21%, gr 2: 8%, and gr 3: 2%; for Bv-AVD, gr 1: 17%, gr 2: 38%, and gr 3: 11%.

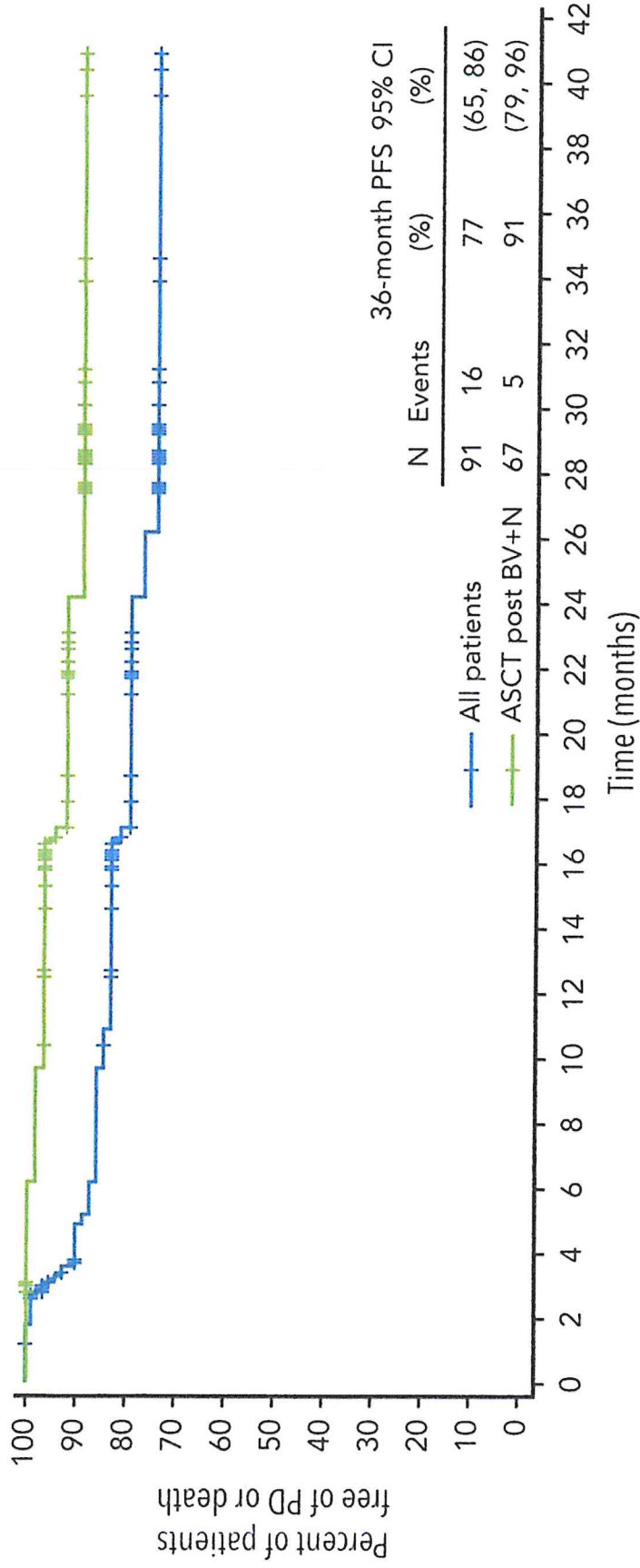
²Peripheral motor neuropathy by gr: for N-AVD, gr 1: 8%; for Bv-AVD gr 1: 6%, gr 2: 6%, and gr 3: 2%.

³Two-sided Fisher's Exact Test

CPI before Autologous Stem Cell Transplant Improves Outcomes in R/R HL



BV+Nivo in R/R HL: 3-year study results

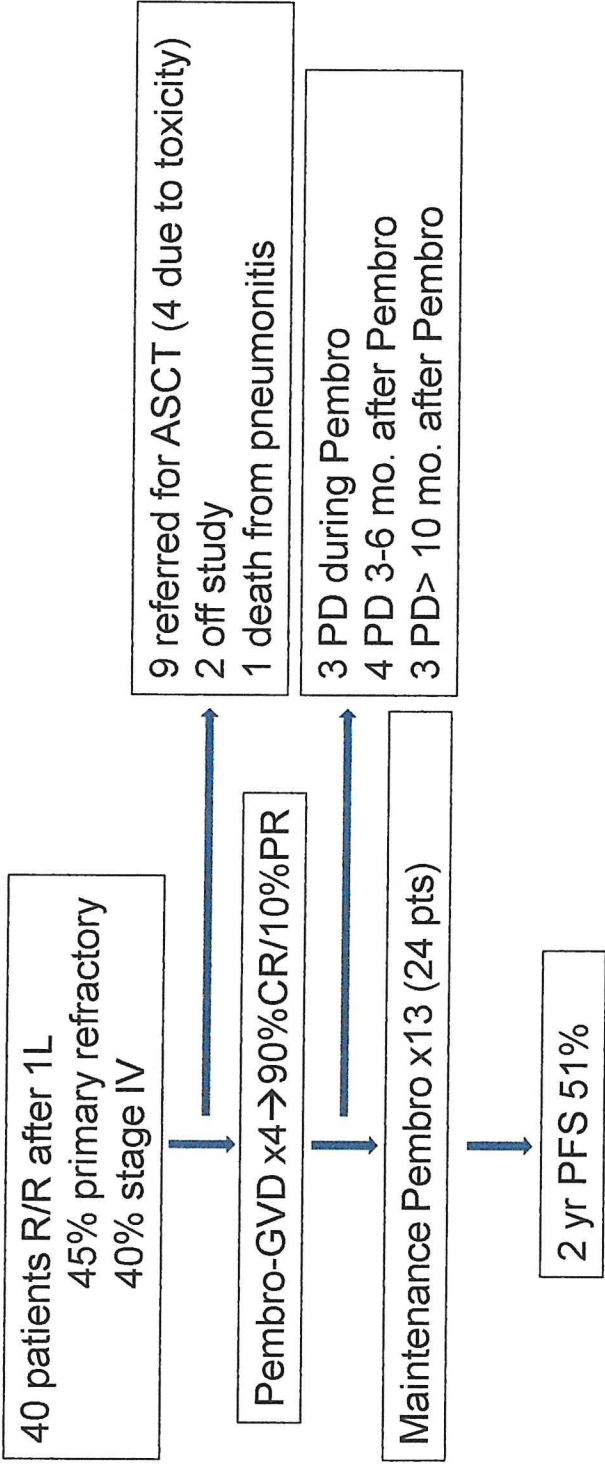


N at Risk (Events)

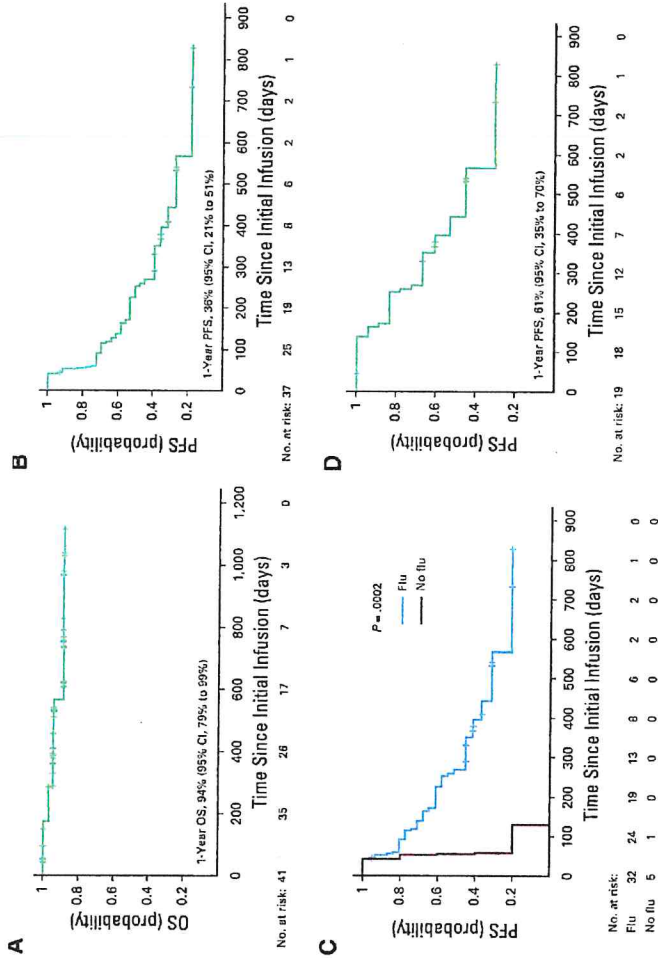
All patients	91(0)	89(1)	65(8)	63(10)	62(11)	61(12)	58(13)	56(13)	51(13)	39(15)	38(15)	34(15)	30(15)	29(16)	24(17)	8(17)	5(17)	4(17)	3(17)	2(17)	0(17)
Per-protocol ASCT	67(0)	67(0)	61(0)	61(0)	60(1)	59(2)	57(2)	55(2)	50(2)	38(4)	37(4)	33(4)	29(4)	28(5)	24(5)	8(5)	5(5)	4(5)	3(5)	2(5)	0(5)

Advani R, et al. Blood, 2021

Pembro maintenance instead of ASCT after Pembro-GVD



CD30 directed CAR T for relapse post-transplant in cHL

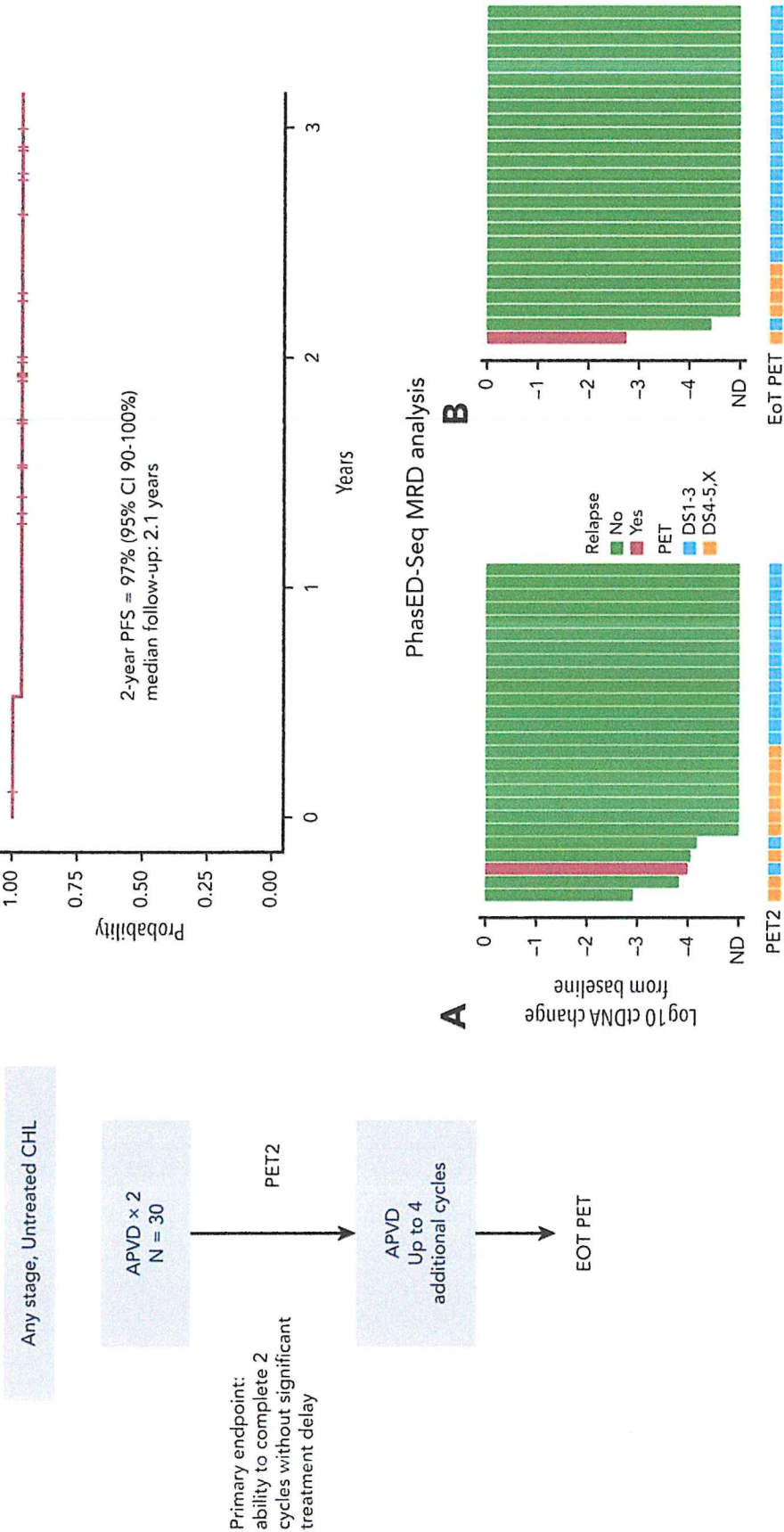


Ramos C, et al. J Clin Oncol. 2020;38(32):3794-3804

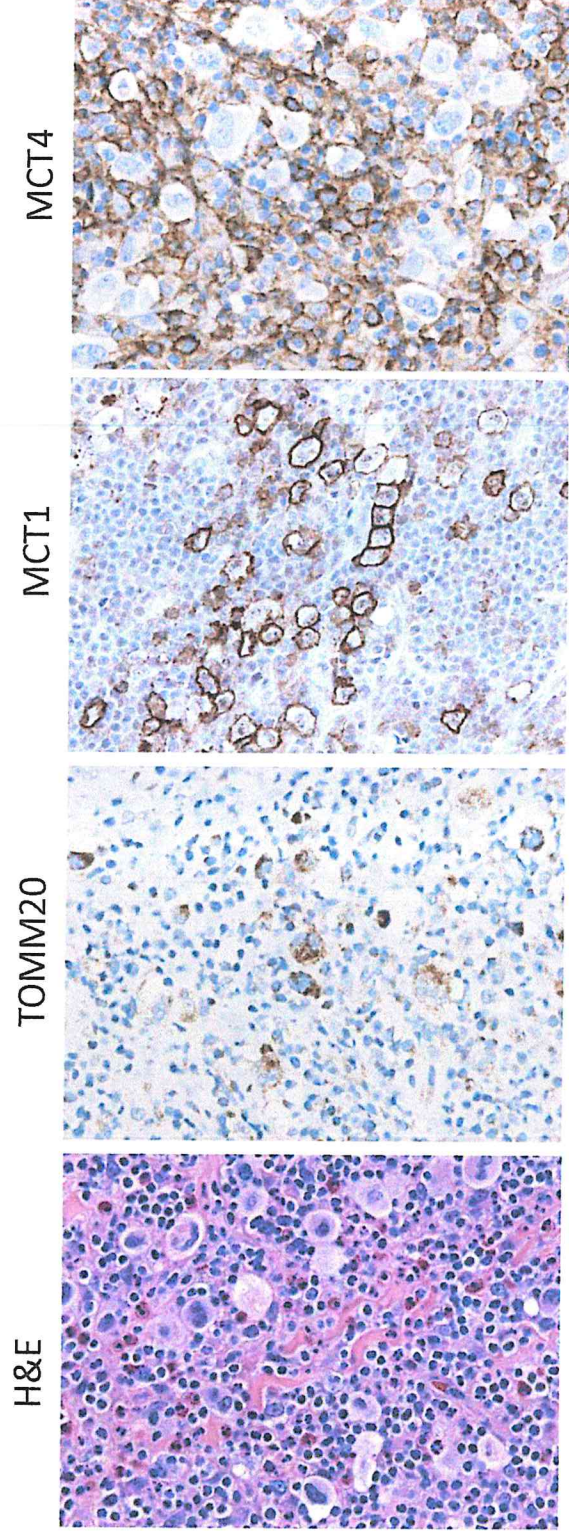
Unknowns in R/R cHL

- Do all patients with relapsed cHL need an autoSCT?
 - BV/nivo+/-RT
 - Pembro-GVDx4→pembro x 13
- What is the role of consolidation therapy? RT if not previously given? BV? CPLs?
- What is the best salvage regimen for patients who fail frontline Nivo-AVD?

Concurrent Pembrolizumab with AVD (APVD) in untreated HL



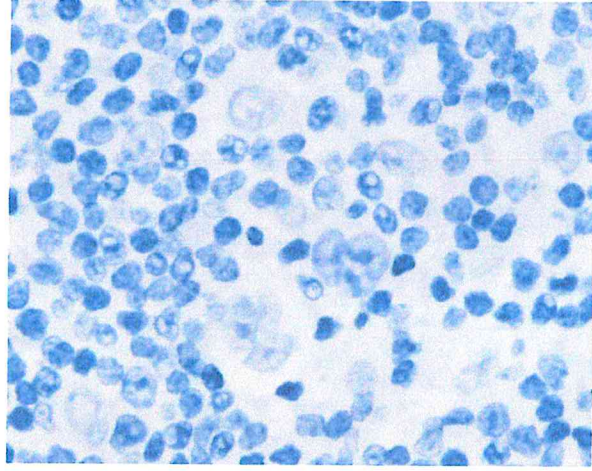
Metabolic Compartments in Hodgkin Lymphoma



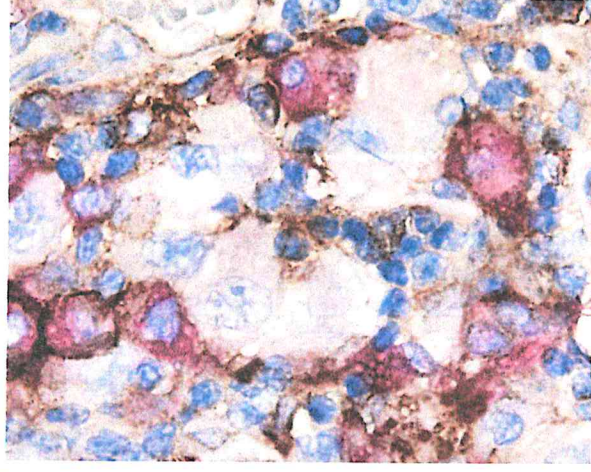
Mikkilineni L, et al. Semin Oncol. 2017;44(3):218-225

Metabolic Compartments in Hodgkin Lymphoma

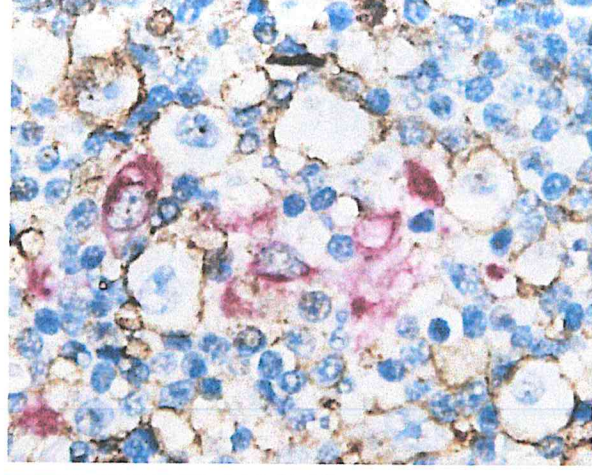
Negative Control



MCT4(brown) + CD68(red)

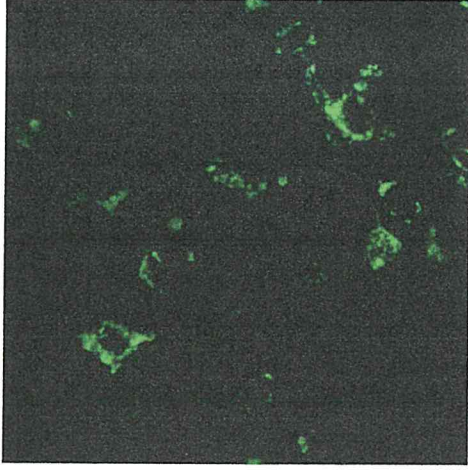


MCT1(brown) + CD68(red)

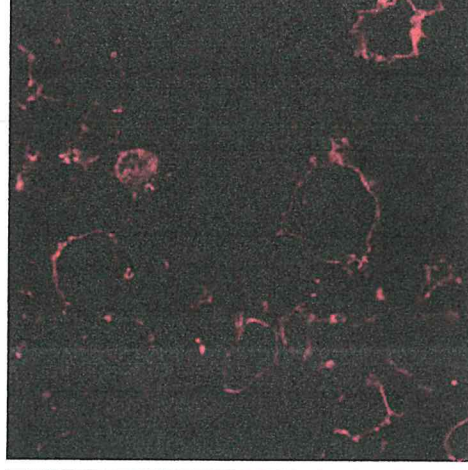


Metabolic Compartments in Hodgkin Lymphoma

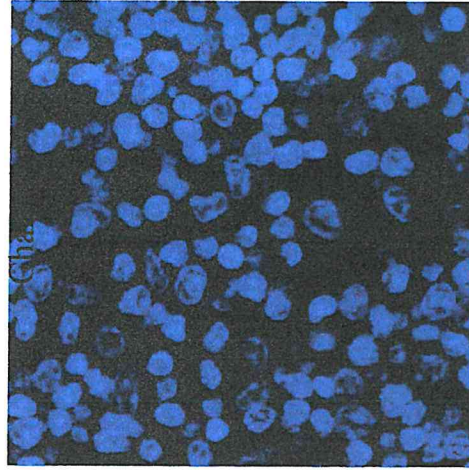
CD68-Green Channel



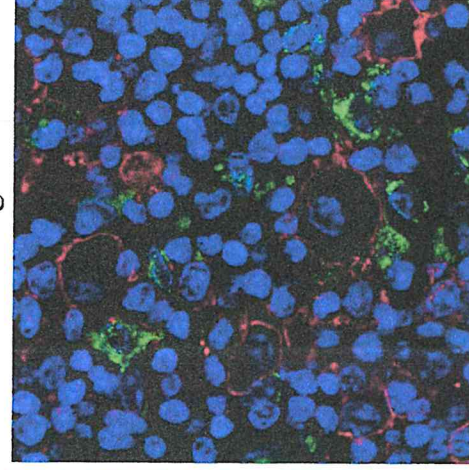
MCT1-Red Channel



Nuclei-Blue

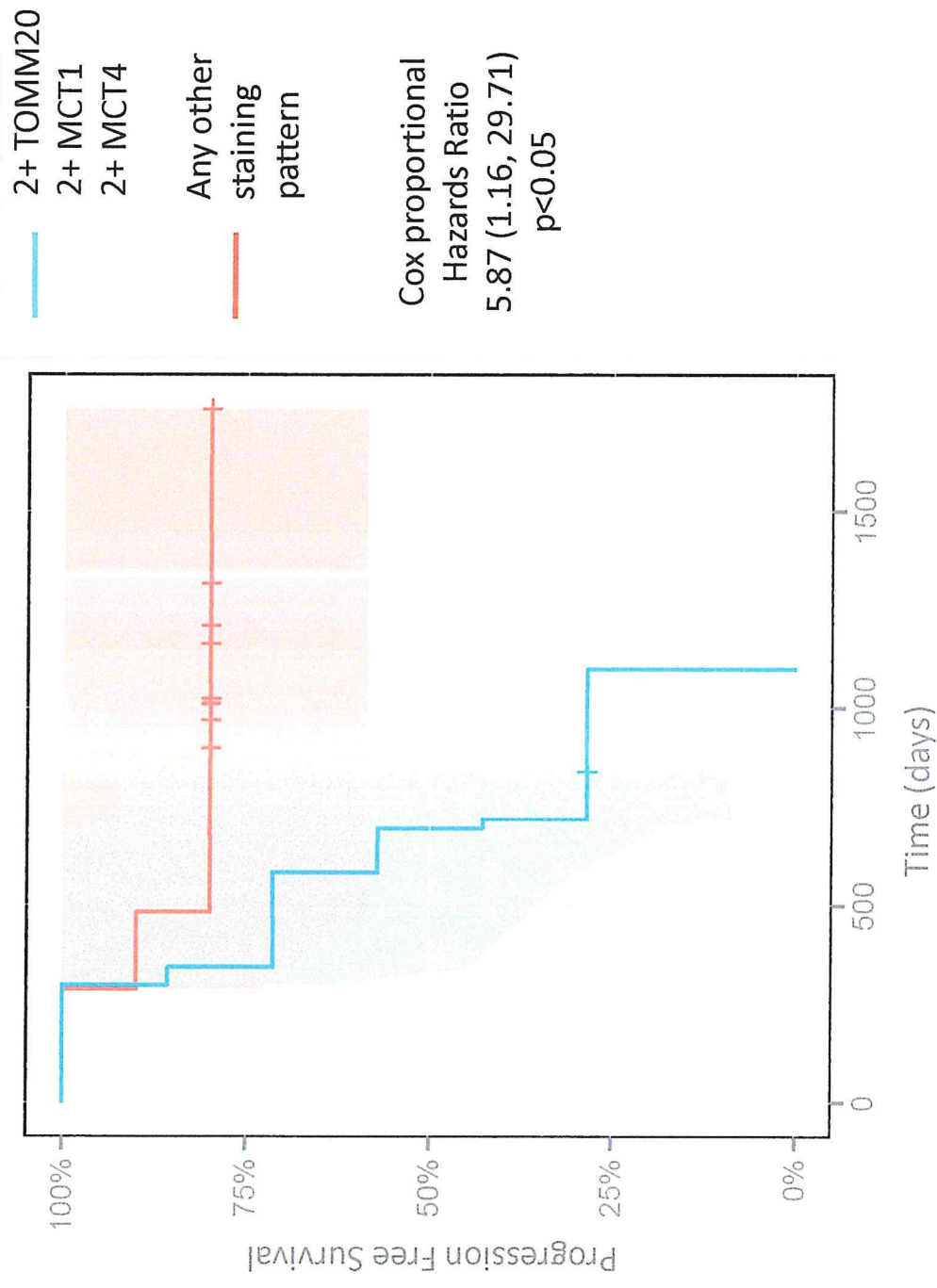


Merge



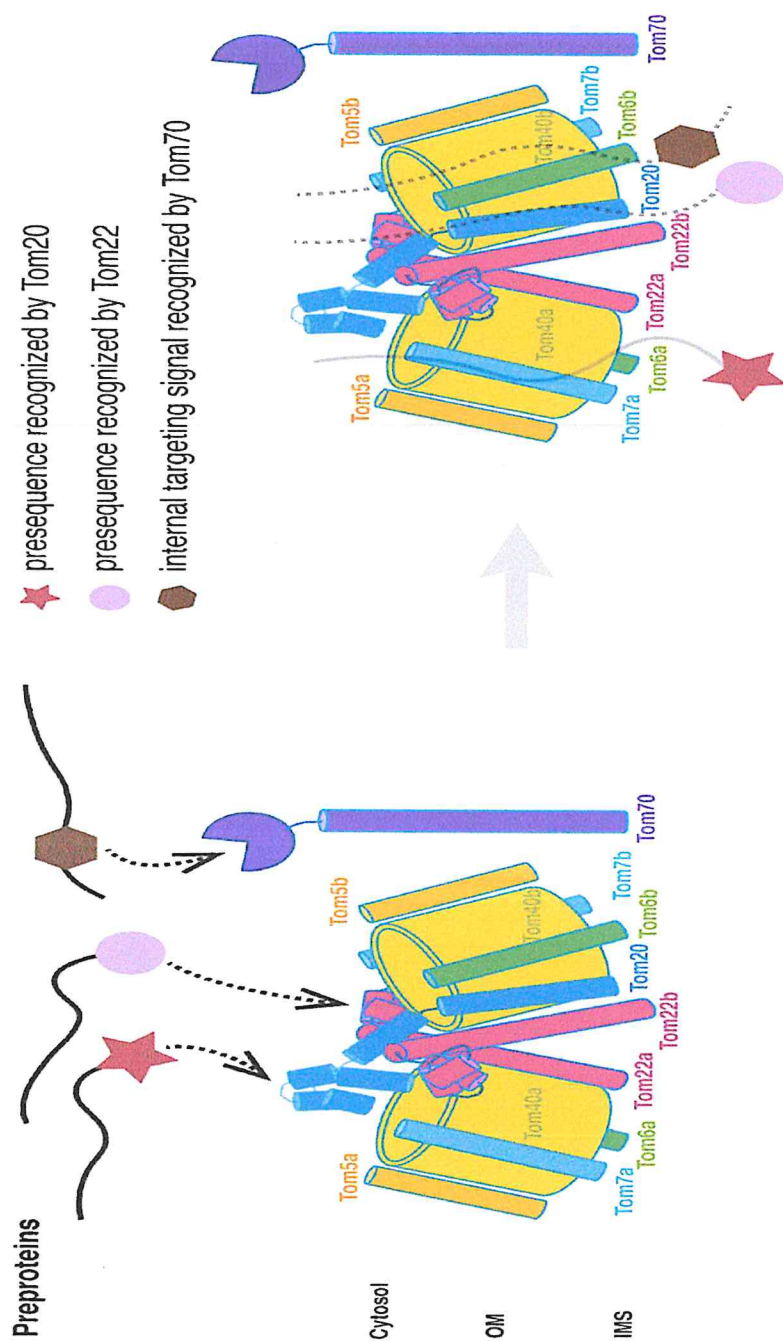
Mikkilineni L, et al. Semin Oncol. 2017;44(3):218-225

TOMM20, MCT1 and MCT4 staining and Progression Free Survival in Hodgkin Lymphoma

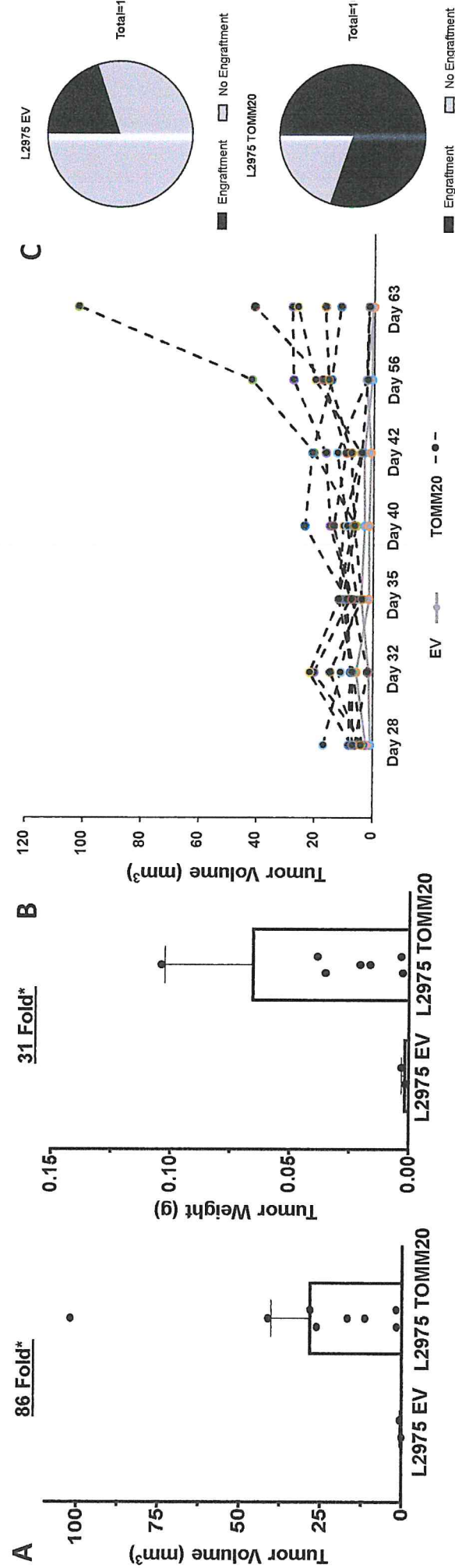


Mikkilineni L, et al. Semin Oncol. 2017;44(3):218-225

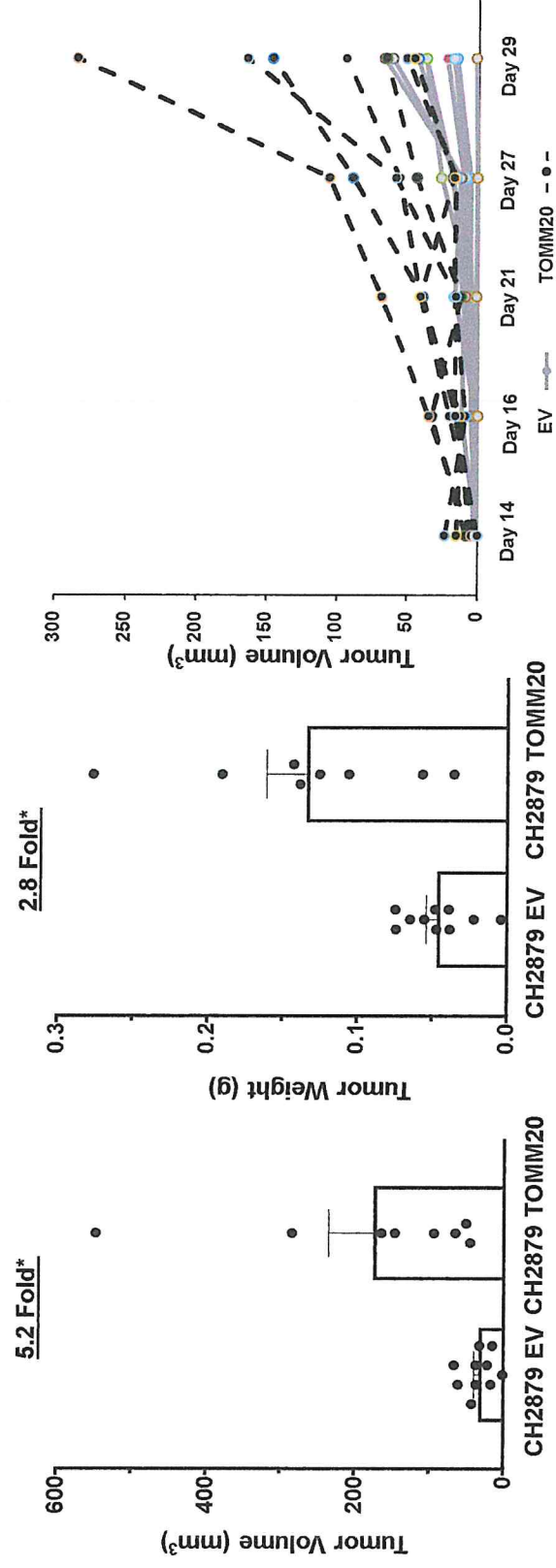
Transporter subunits of the Outer Mitochondrial Membrane



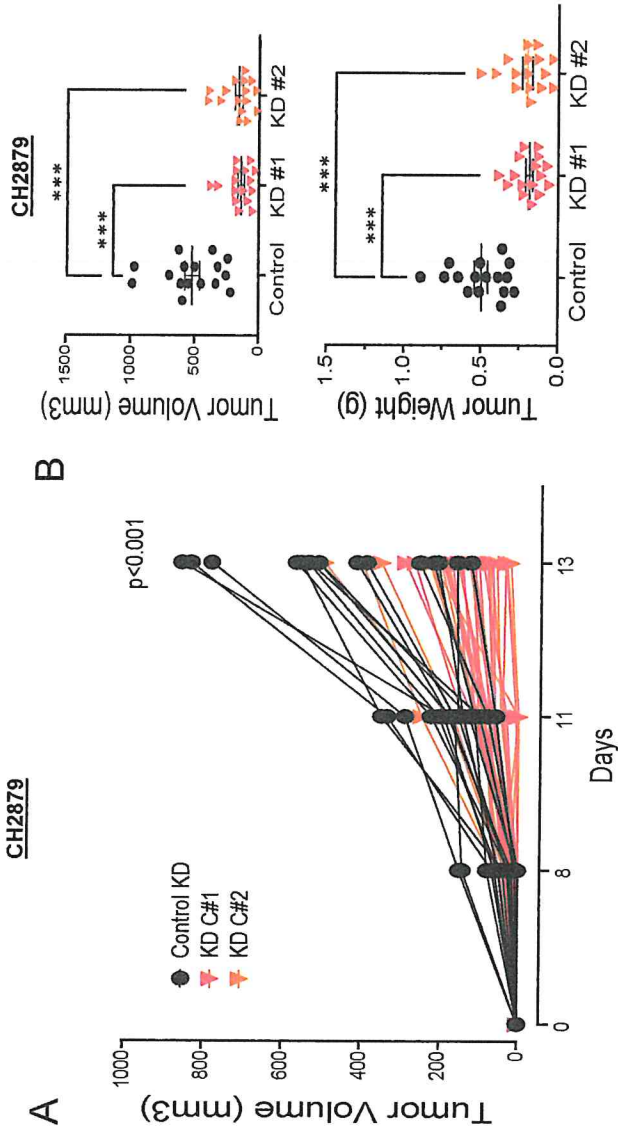
TOMM20 promotes tumor growth and engraftment



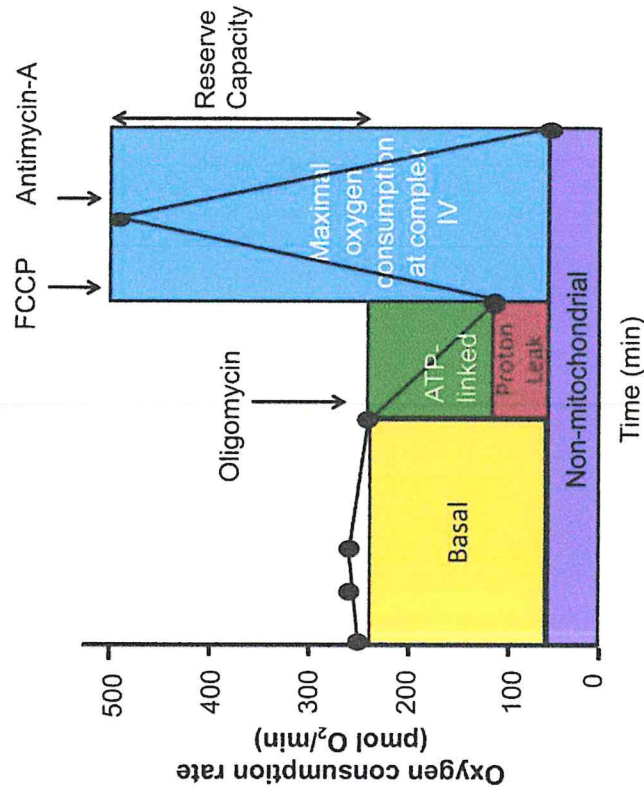
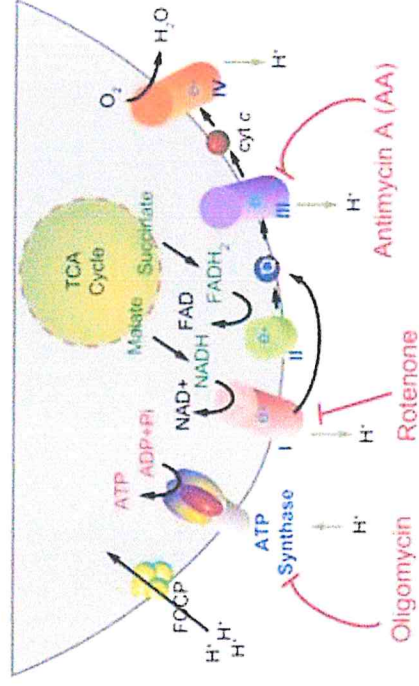
TOMM20 induces tumor growth



TOMM20 knockdown reduces tumor growth



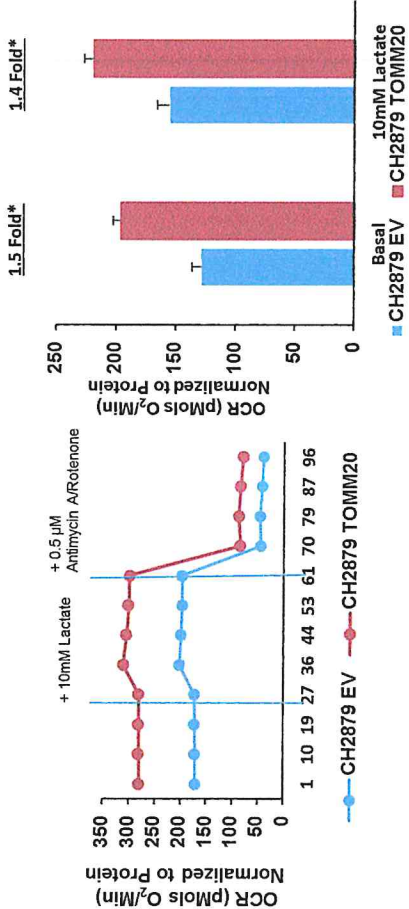
Cellular Mitochondrial Bioenergetic Profile



Cancer Cell. 2012 Oct 16;22(4):547-60

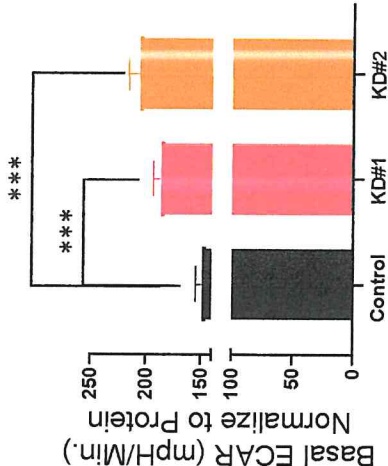
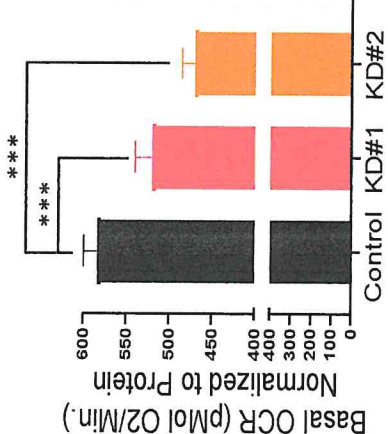
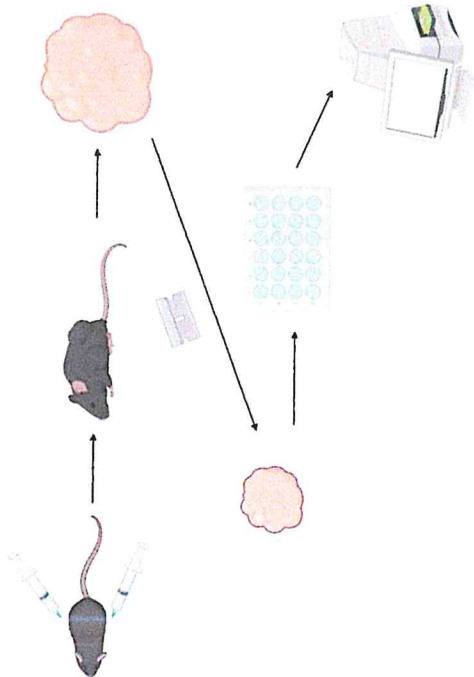
Biol Chem 2012 Dec;393(12):1485-1512.

Effect of TOMM20 on Oxygen Consumption

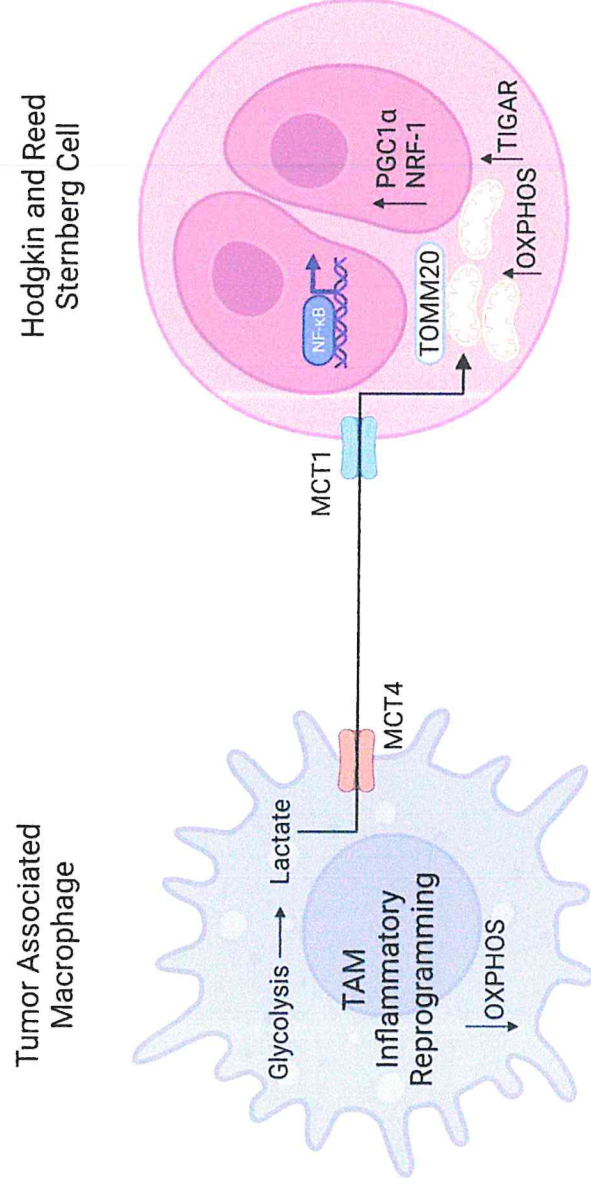


TOMM20 knockdown reduces oxygen consumption in tumor microtissues

CH2879

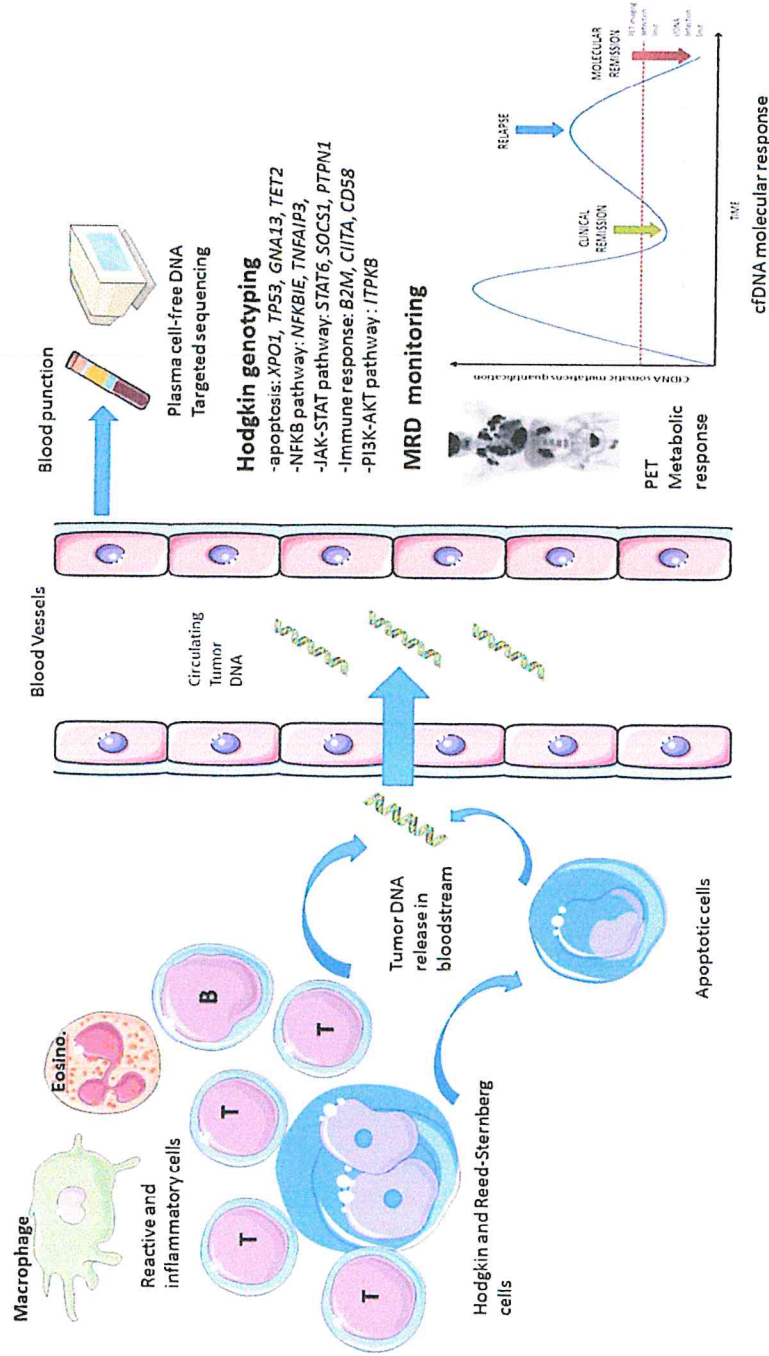


Metabolic Coupling in Hodgkin Lymphoma

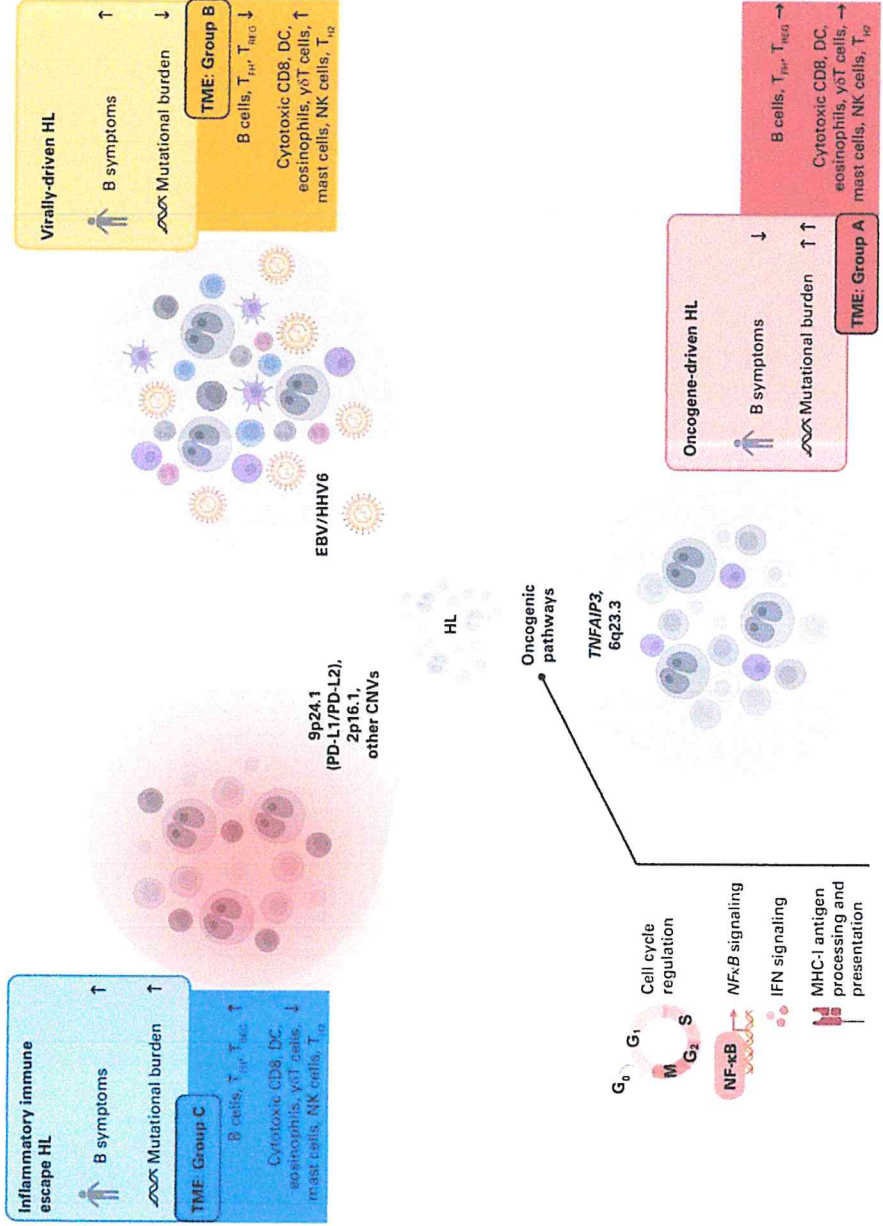


Masel R, et al. Best Pract Res Clin Haematol. 2023 Dec;36(4):101514

Circulating DNA in cHL for genotyping and response-adapted therapy

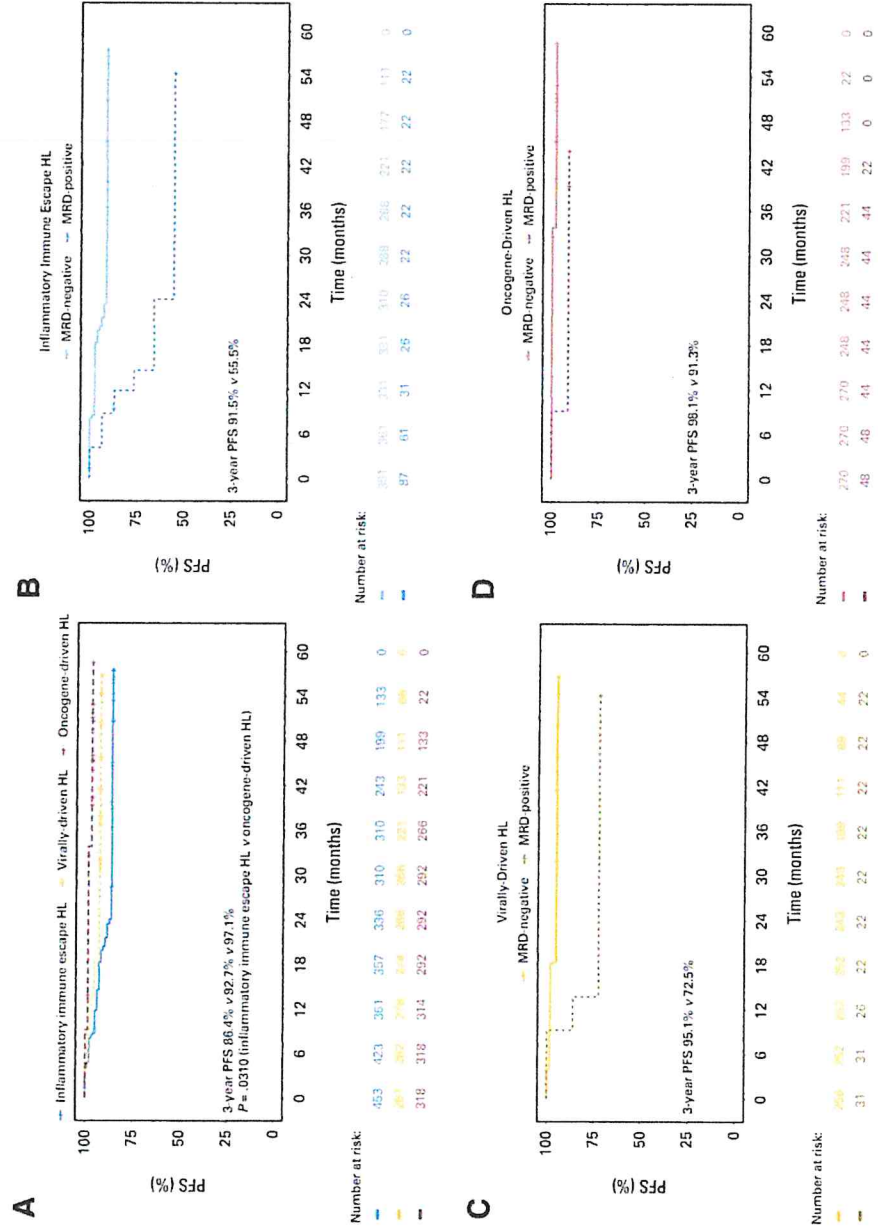


Circulating DNA Molecular Classification of HL



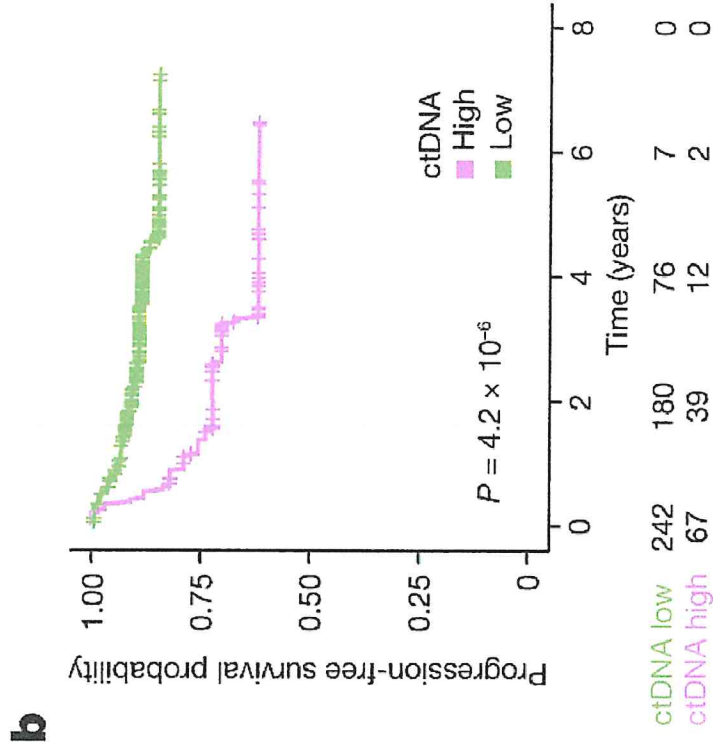
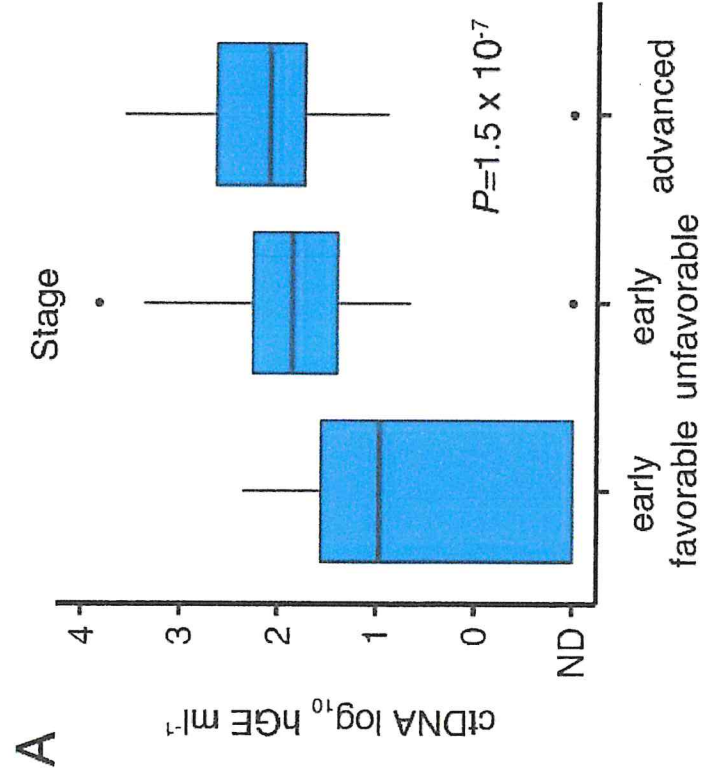
Heger J, et al. JCO 2024; 09-30

Circulating DNA Molecular Classification of HL



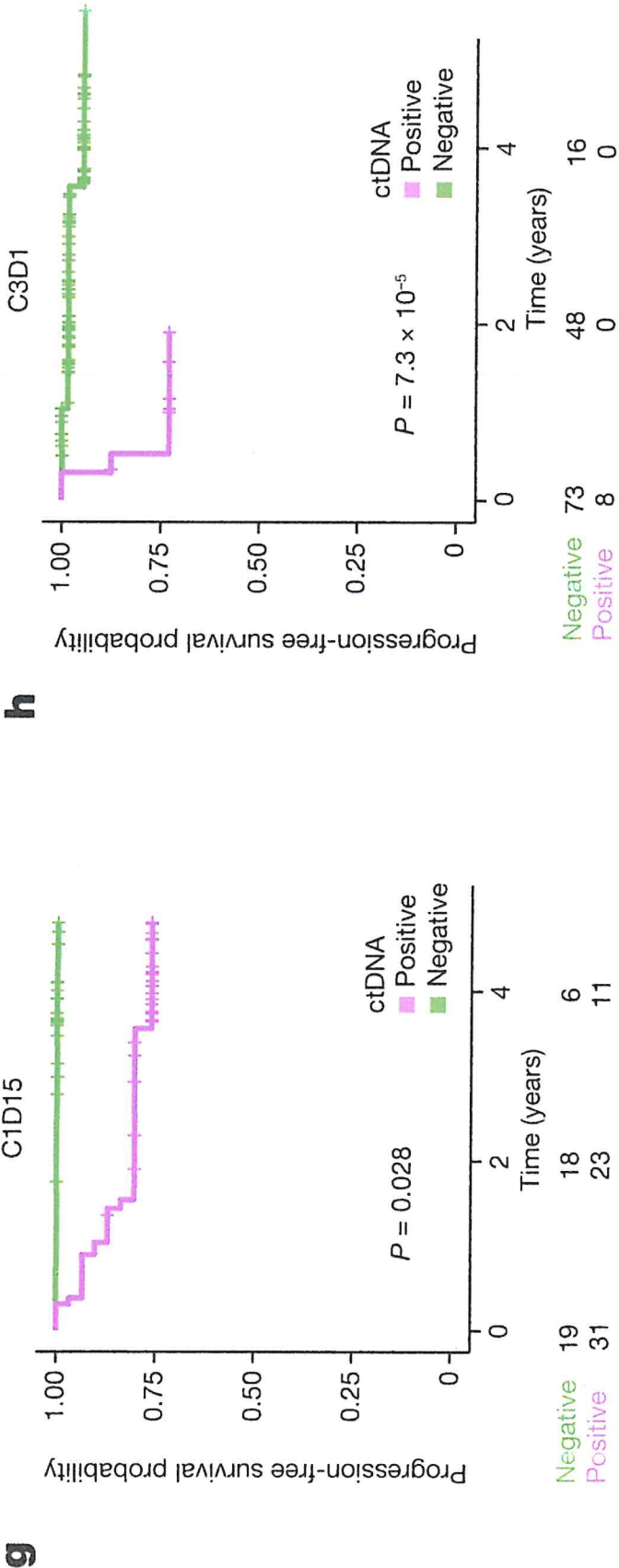
Heger J, et al. JCO 2024; 09-30

Circulating tumor DNA is prognostic in cHL



Alig S, et al. Nature 2024; 625:778-787

Circulating tumor DNA is prognostic in cHL



Conclusions

- Frontline therapy is evolving: to include new agents particularly CPI
 - Early stage:
 - Many patients can avoid RT
 - Incorporation of BV or CPI
 - Advanced stage
 - Nivo-AVD>BV-AVD>ABVD
- Salvage regimens incorporating CPI are highly effective.
 - Is this still true after CPI containing frontline therapy?
- Can we identify a subset of relapsed patients who do not need an autoSCT?
 - Low risk features (late relapse, eligible for radiation)
 - Rapid, deep response to salvage therapy
- Circulating tumor DNA is prognostic.