Lymphoma Tumor Board Cases

24th Multidisciplinary Management of Cancers: A Case-based Approach

ACCREDITATION
In support of improving patient care, i3 Health is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team. i3 Health designates this live activity for a maximum of *15 AMA PRA Category 1 Credit* ™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

INSTRUCTIONS TO RECEIVE CREDIT
An activity evaluation form has been distributed. To claim credit, you must turn in a completed and signed evaluation form at the conclusion of the program. Your certificate of attendance will be mailed or emailed to you in approximately 2 weeks for physicians.

UNAPPROVED USE DISCLOSURE
This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this activity do not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

DISCLAIMER
The information provided at this CME activity is for continuing education purposes only and is not meant to substitute for the independent medical/clinical judgment of a healthcare provider relative to diagnostic and treatment options of a specific patient's medical condition.

COMMERCIAL SUPPORT
None

Stanford Cancer Institute cancer.stanford.edu
Stanford MEDICINE
UCDAVIS HEALTH
UCSF COMPREHENSIVE CANCER CENTER
Helen Diller Family Comprehensive Cancer Center
ANCO Educating and Empowering the Northern California Cancer Community

24th Multidisciplinary Management of Cancers: A Case-based Approach

Panelists

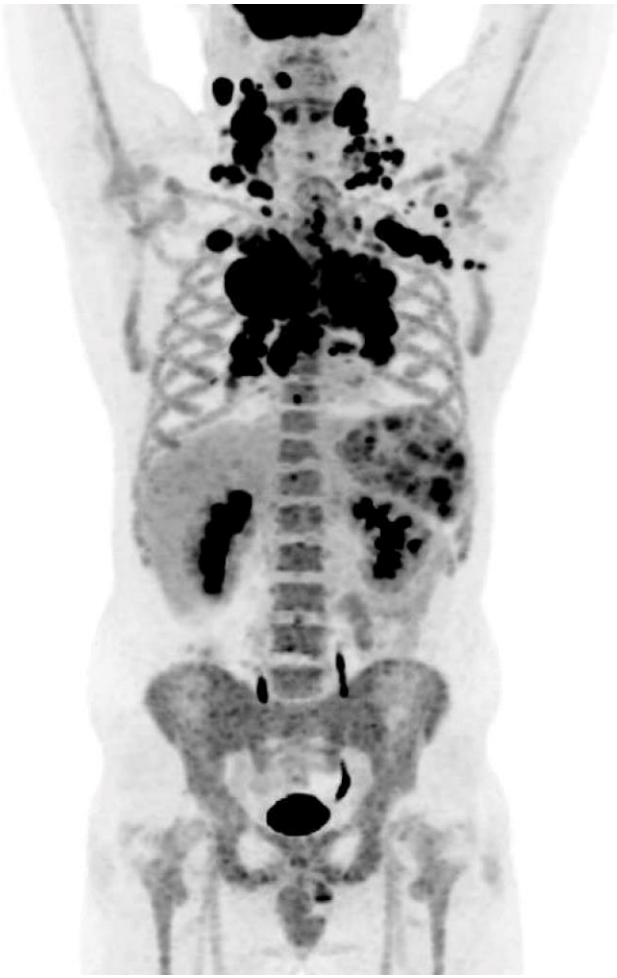
Charmalambos Andreadis, MD
Meryl Colton, MD
Ranjana Advani, MD
Wei Ai, MD
Neel Gupta, MD
Richard Hoppe, MD
Lisa Law, MD, TPMG
Michael Spinner, MD
Joseph Tuscano, MD

Disclosures

Full Name	Role	Type of Financial Relationship	Company Name
Charmalambos Andreadis, MD	Chair	Advisory Board or Panel	BMS, Kite/Gilead, Abbvie, Lilly, Epizyme, Astra Zeneca
Charmalambos Andreadis, MD	Chair	Grants/Research Support	Novartis, Roche, BMS, Merck, Genmab
Ranjana Advani, MD	Panel	Advisory Board or Panel	ADCT, Genentech/Roche, Beigene, Autolus
Wei Ai, MD	Panel	Advisory Board or Panel	Kyowa Kirin, Secura Bio
Wei Ai, MD	Panel	Consultant	Biomerieux
Neel Gupta, MD	Panel	Consultant	Corvus, Atara
Neel Gupta, MD	Panel	Advisory Board or Panel	ONO Pharmaceuticals
Michael Spinner, MD	Panel	Consultant	Kite/Gilead
Michael Spinner, MD	Panel	Advisory Board or Panel	ADC Therapeutics

Case #1

- 26-year-old man presents with cough, dyspnea, 20 lb weight loss, and R cervical LAD
- Chest X-ray → large anterior mediastinal mass
- CT neck/chest → extensive LAD in the bilateral neck, left axilla, mediastinum, and bilateral hilar nodes, the mediastinal mass measures 12 x 7 cm and encases the SVC
- Core biopsy of R cervical LN → large atypical cells positive for CD30, CD15, PAX5 (dim) and negative for CD20, CD3, EBER, and ALK in a mixed inflammatory background with prominent fibrosis, consistent with **classic Hodgkin lymphoma, nodular sclerosis type**
- PET-CT → hypermetabolic LAD in bilateral neck and chest with bulky mediastinal mass, numerous hypermetabolic splenic foci and bone lesions most prominent in spine
- Diagnosis → **Stage IVBX cHL, IPS 4** (male, stage IV, leukocytosis, low albumin)



Which regimen would you use to treat this patient with advanced stage Hodgkin lymphoma?

A. ABVD

B. BV-AVD

C. Nivo-AVD

D. Escalated BEACOPP

E. BrECADD

PET-adapted trials for advanced stage Hodgkin lymphoma

Trial	Population	Regimen (PET2- cohort)	N	PFS	Med f/u	Study conclusions	Reference
RATHL	Stage II*-IV	ABVD x 6 **ABVD x 2 → AVD x 4**	469 464	81% (7y) **79% (7y)**	7.3 years	De-escalation to AVD non-inferior	Luminari et al, JCO 2024
AHL LYSA	Stage IIB-IV	eBEACOPP x 6 **eBEACOPP x 2 → ABVD x 4**	413 361	86% (5y) **86% (5y)**	4.2 years	De-escalation to ABVD non-inferior	Casasnovas et al, *Lancet Oncol* 2019
GHSG HD18	Stage IIB-IV	eBEACOPP x 6-8 **eBEACOPP x 4**	508 505	91% (5y) **91% (5y)**	5.5 years	BEACOPP x 4 cycles non-inferior	Borchmann et al, *Lancet* 2017

Trials integrating novel agents into frontline therapy

ECHELON-1	Stage III-IV	ABVD x 6 **BV-AVD x 6**	670 664	75% (6y) **82% (6y)**	6 years	PFS & OS benefit with BV-AVD	Ansell et al, NEJM 2022
GHSG HD21	Stage IIB-IV	eBEACOPP x 4-6 **BrECADD x 4-6**	740 742	92% (3y) **95% (3y)**	3.3 years	BrECADD non-inferior	Borchmann et al, ASH 2023
SWOG S1826	Stage III-IV	BV-AVD x 6 **Nivo-AVD x 6**	487 489	86% (1y) **94% (1y)**	1 year	PFS benefit with Nivo-AVD	Herrera et al, ICML 2023

*Included stage II unfavorable risk patients

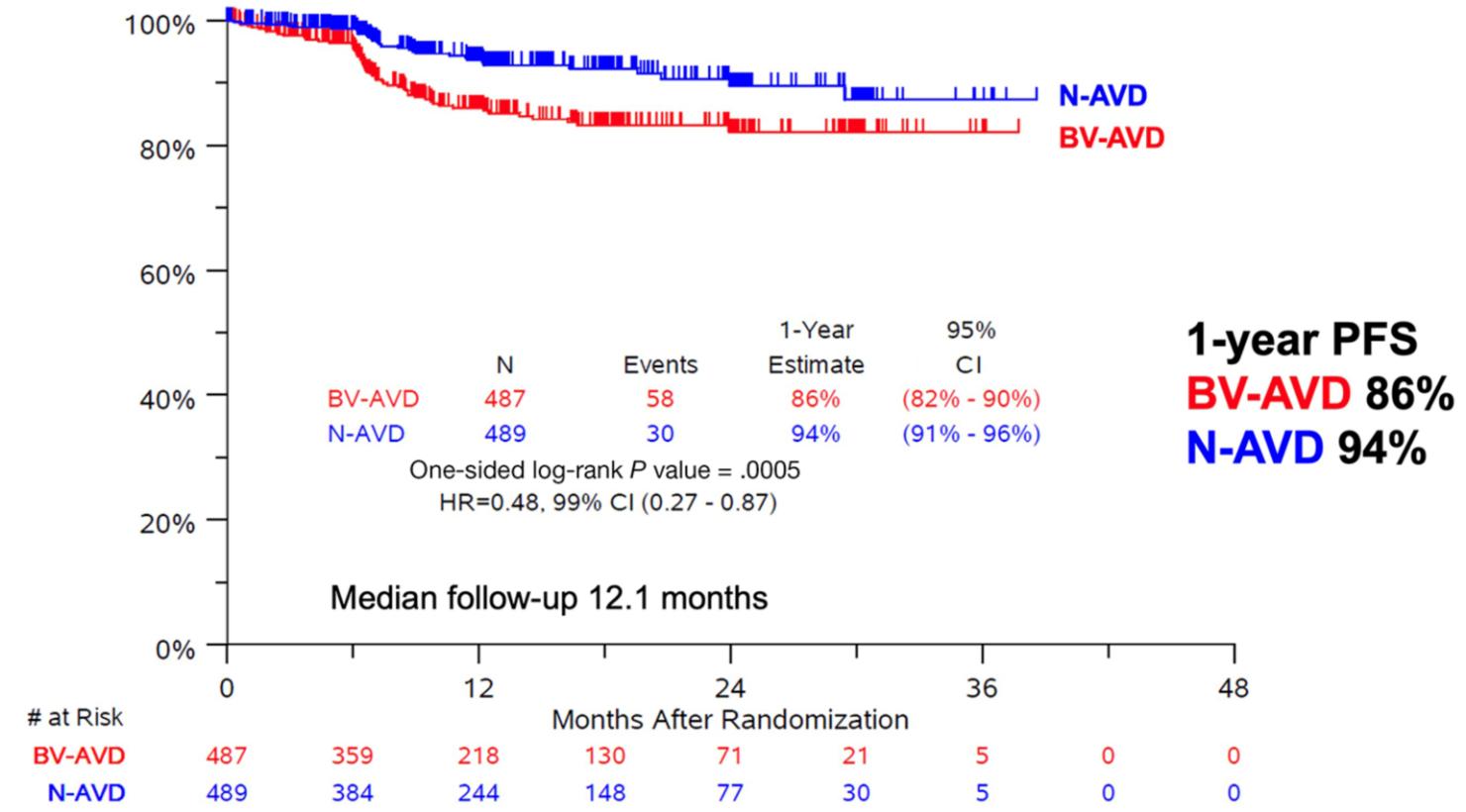
SWOG S1826 trial – Nivo-AVD vs BV-AVD for stage III-IV Hodgkin lymphoma[1]

Advantages of Nivo-AVD over BV-AVD:

- PFS benefit
- Less peripheral neuropathy
- G-CSF support not required
- Greater benefit in older adults >60[2]

Limitations/reservations:

- Short follow-up (1 year)
- Awaiting final manuscript
- Not currently FDA approved



[1] Herrera et al, ICML 2023 Plenary Abstract
[2] Rutherford et al, ASH 2023 Abstract #181

Case #1

- The patient is a classically trained violinist and concerned about the risk of peripheral neuropathy with brentuximab-based regimens
- He completes **6 cycles of nivo-AVD** with interim and EOT PET-CT showing **metabolic CR (Deauville 2)**
- 16 months in the future, the patient develops recurrent dyspnea and night sweats with repeat PET-CT showing a recurrent hypermetabolic mediastinal mass
- Biopsy of the mediastinal mass confirms **relapsed classic Hodgkin lymphoma**

Which of the following salvage regimens do you recommend?

A. ICE

B. BV + bendamustine

C. BV + nivolumab

D. Pembrolizumab + GVD

E. 36 Gy ISRT to the mediastinal mass

Traditional salvage chemotherapy regimens for relapsed/refractory Hodgkin lymphoma

Regimen	N	ORR	CR rate	PFS	Reference
ICE	65	85%	26%*	58% (3y)	Moskowitz et al, *Blood* 2001
DHAP	102	88%	21%*	59% (3y)	Josting et al, *Ann Oncol* 2002
GVD	91	70%	19%*	52% (4y)	Bartlett et al, *Ann Oncol* 2007
IGEV	91	81%	54%*	53% (3y)	Santoro et al, *Haematologica* 2007
ESHAP	82	67%	50%†	52 mo. (median)	Labrador et al, *Ann Hematol* 2014
BEGEV	58	83%	75%†	59% (5y)	Santoro et al, *J Clin Oncol* 2016

*CR rate assessed by CT

†CR rate assessed by PET

Novel salvage regimens incorporating BV and/or PD-1 inhibitors

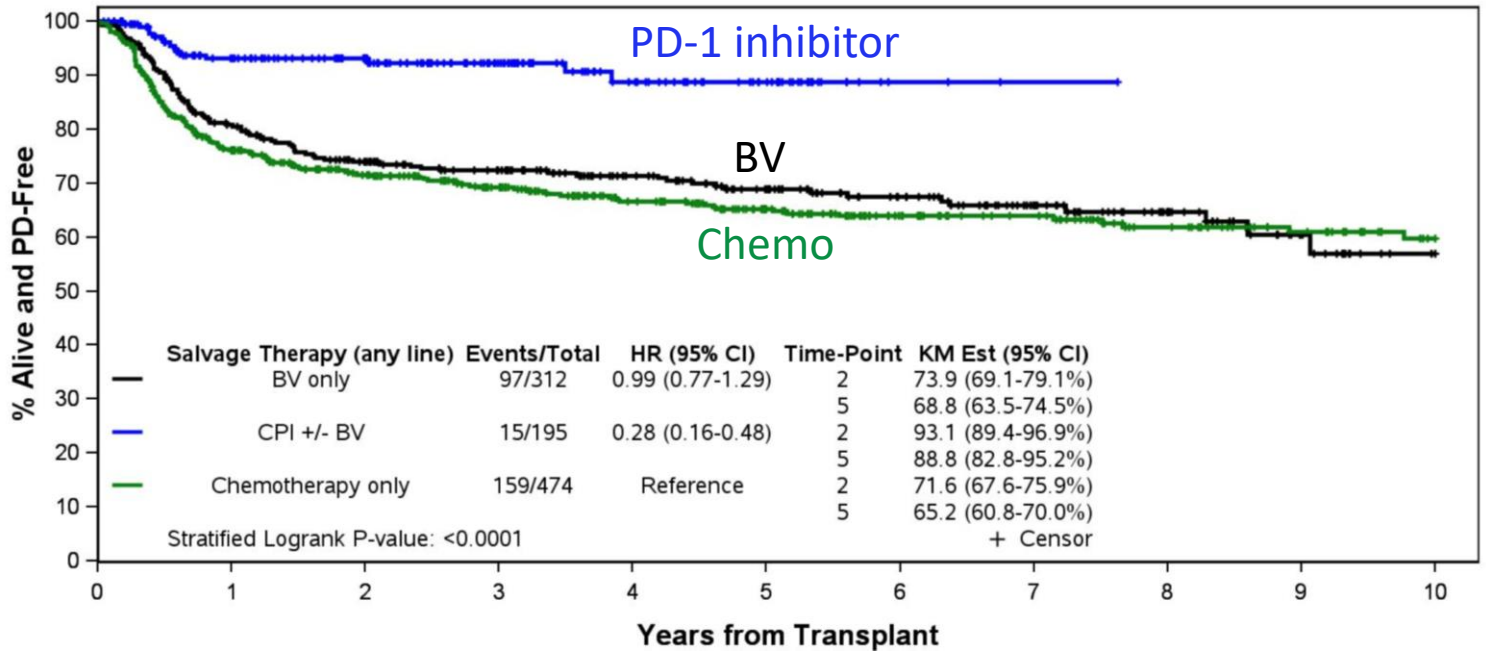
Regimen	Phase	N	CR Rate	PFS (All Patients)	PFS (AHCT Cohort)	Median Follow-Up
BV → augmented ICE	2	46	76%	82% (3 yrs)	82% (3 yrs)	20 mo.
BV + ICE	1/2	45	74%	80% (2 yrs)	NR	37 mo.
BV + DHAP	2	55	81%	74% (2 yrs)	NR	27 mo.
BV + ESHAP	1/2	66	70%	71% (2 yrs)	NR	27 mo.
BV + bendamustine	1/2	55	74%	63% (2 yrs)	70% (2 yrs)	21 mo.
Nivolumab + BV	1/2	93	67%	77% (3 yrs)	91% (3 yrs)	34 mo.
Nivolumab + ICE	2	37	91%	72% (2 yrs)	94% (2 yrs)	31 mo.
Pembrolizumab + ICE	2	42	87%	87% (2 yrs)	NR	24 mo.
Pembrolizumab + GVD	2	39	95%	100% (1 yr)	100% (1 yr)	14 mo.

Randall MP and Spinner MA. *Cancers* 2023

Comparison of salvage regimens prior to ASCT

- PD-1 inhibitor-based salvage regimens prior to ASCT improve PFS compared to BV or platinum-based chemotherapy in multiple large retrospective studies[1-3]

- PD-1 inhibitor-based salvage therapy prior to ASCT increases the risk of engraftment syndrome[4]



5-year PFS:

89%

69%

65%

[1] Spinner et al, *Blood* 2023
[2] Desai et al, *Am J Hematol* 2023
[3] Desai et al, ASH 2023 #182
[4] Taranto et al, ASH 2023 #3603

Case #1

- The patient receives **2 cycles of pembro-GVD,** achieving **metabolic CR (Deauville 1)**
- He undergoes Cytoxan mobilization, stem cell collection, and **ASCT with BEAM conditioning**
- On day +10 post-ASCT, he develops non-infectious fevers, diarrhea, and elevated AST/ALT coinciding with neutrophil engraftment. He is diagnosed with **engraftment syndrome**, which resolves with a short course of prednisone
- He is discharged on day +14 with excellent post-transplant recovery. He has mild **grade 1 peripheral sensory neuropathy** in his fingertips from prior chemotherapy

Do you recommend post-transplant maintenance or RT consolidation for this patient?

A. Yes, brentuximab maintenance x 16 cycles

B. Yes, pembrolizumab maintenance x 8 cycles

C. Yes, brentuximab + nivolumab maintenance x 8 cycles

D. Yes, consolidation with 30 Gy ISRT to the mediastinum

E. No maintenance or consolidation

Post-transplant maintenance or RT consolidation in high-risk patients

- **BV maintenance** improves PFS in patients at high risk for relapse after ASCT (phase 3 AETHERA trial)
  - AETHERA risk factors: primary refractory disease, early relapse <12 months, or extranodal disease at relapse
  - BV maintenance (up to 16 cycles) is FDA approved for patients with 1 or more AETHERA risk factors
  - BV maintenance has greater benefit for patients transplanted in PR than CR (Desai et al, ICML 2023)
- **PD-1 inhibitor maintenance** has encouraging outcomes in small phase 2 studies but not FDA approved

Maintenance regimen	Phase	Population	N	PFS	Reference
Brentuximab x 16 cycles	3	High risk per AETHERA	165	59% at 5 years	Moskowitz et al, *Blood* 2018
Pembrolizumab x 8 cycles	2	90% high risk per AETHERA	30	82% at 18 months	Armand et al, *Blood* 2019
BV + nivolumab x 8 cycles	2	High risk per AETHERA	59	94% at 18 months	Herrera et al, *Lancet Haematol* 2023

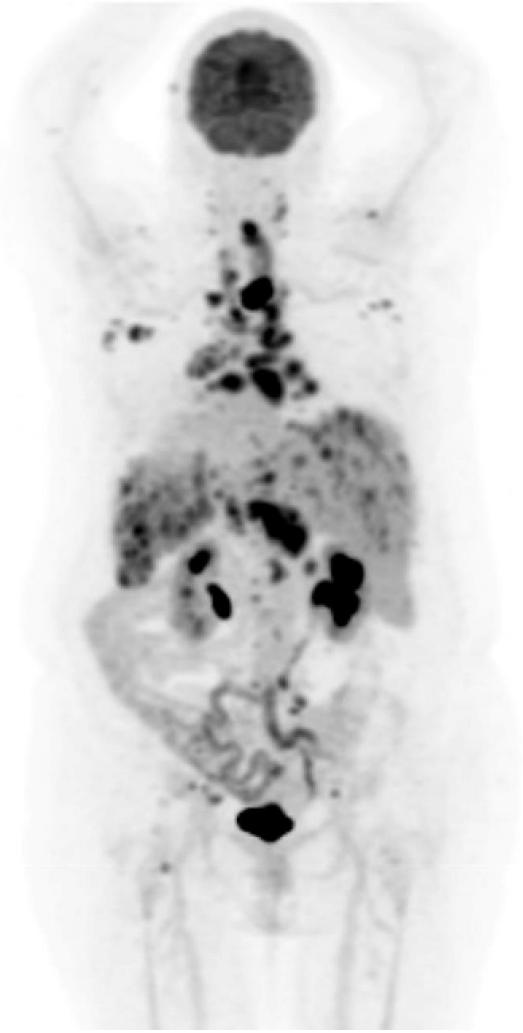
- **RT consolidation** may improve local control and PFS after ASCT based on retrospective studies
  - RT consolidation may be useful for patients with bulky disease or transplanted in PR (Wilke et al, IJROBP 2017)

Case #1 – Key Points

- Nivo-AVD improves PFS over BV-AVD in advanced stage Hodgkin lymphoma and has a better tolerability profile with less neuropathy and no need for G-CSF support
  - Longer follow-up is required to confirm durability
  - Awaiting publication of manuscript prior to FDA approval
- PD-1 inhibitor-based salvage regimens show promising PFS compared to BV or platinum-based regimens in multiple large retrospective studies
  - PD-1 inhibitors prior to ASCT may increase the risk of engraftment syndrome
  - Randomized phase 3 trial is planned to identify the optimal salvage regimen
- BV maintenance after ASCT improves PFS in high-risk patients; PD-1 inhibitor maintenance also appears promising in small studies and RT consolidation may be considered in select patients

Case #2

- 70-year-old woman was found to have a thyroid nodule on regular exam
- Thyroid FNA with atypical lymphocytes suspicious for lymphoid neoplasm
- PET/CT showed **extensive hypermetabolic adenopathy.** There are **hypo-enhancing foci** of hypermetabolism in the **spleen and liver,** and **skeleton**.
- Core biopsy of thyroid isthmus nodule showed **large B-cell lymphoma**. IHC positive for **CD20**, **CD10**, **MUM-1**, **BCL-6**, and **BCL-2**. Cells were negative for C-MYC and Cyclin D1. Ki-67 of 90%. EBER ISH negative. **FISH negative for C-MYC, BCL2, or BCL6 rearrangements**
- **ECOG 1. LDH wnl. EF >60%** on ECHO without other major comorbidities



Which regimen would you use to treat this patient with newly diagnosed GCB-DLBCL, non-double hit, with IPI 3?

A. R-CHOP

B. Pola-R-CHP

C. R-DA-EPOCH

D. R-mini-CHOP

ORIGINAL ARTICLE

Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma

Hervé Tilly, M.D., Franck Morschhauser, M.D., Ph.D., Laurie H. Sehn, M.D., M.P.H., Jonathan W. Friedberg, M.D., Marek Trněný, M.D., Jeff P. Sharman, M.D., Charles Herbaux, M.D., John M. Burke, M.D., Matthew Matasar, M.D., Shinya Rai, M.D., Ph.D., Koji Izutsu, M.D., Ph.D., Neha Mehta-Shah, M.D., et al.

Polatuzumab Vedotin

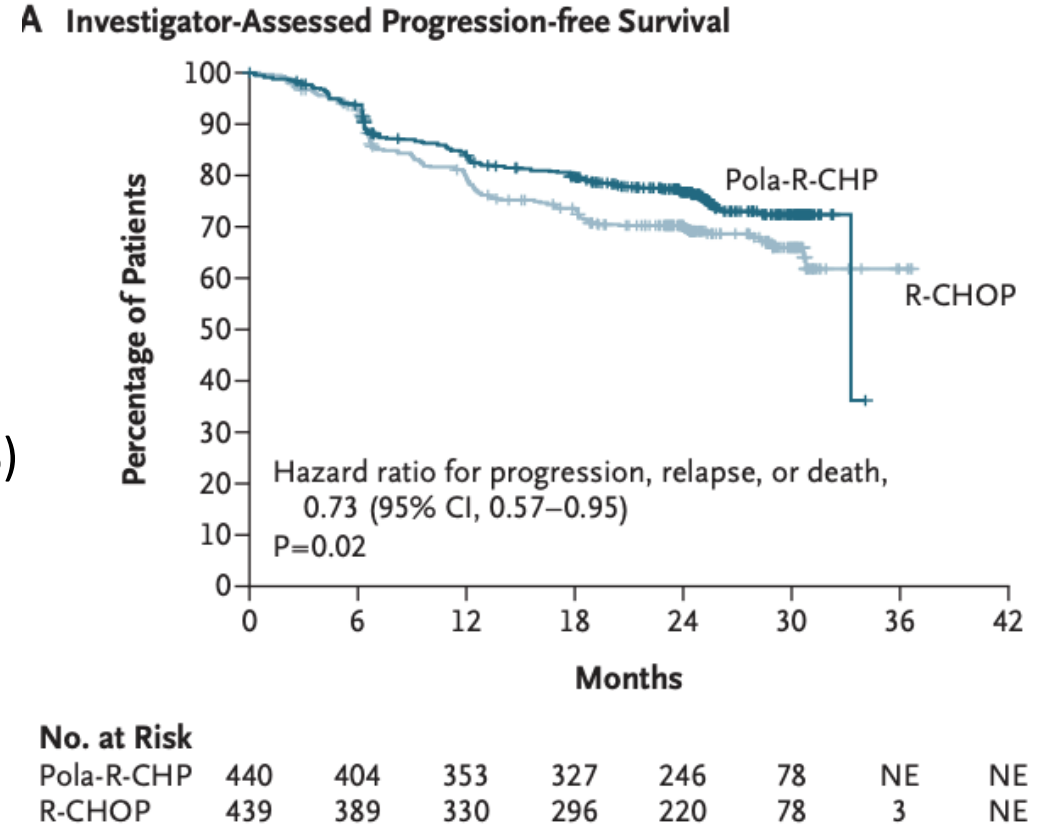
- Antibody drug conjugate that targets **CD79b**
- Approved April 2023 in the upfront setting

Efficacy

- Two-year PFS was **76.7%** (95% CI = 72.7%–80.8%) in the pola-R-CHP arm compared with **70.2%** (95% CI = 65.8%–74.6%) in the R-CHOP arm
- Subgroup analysis increased benefit in **non-GCB subtype**

Safety

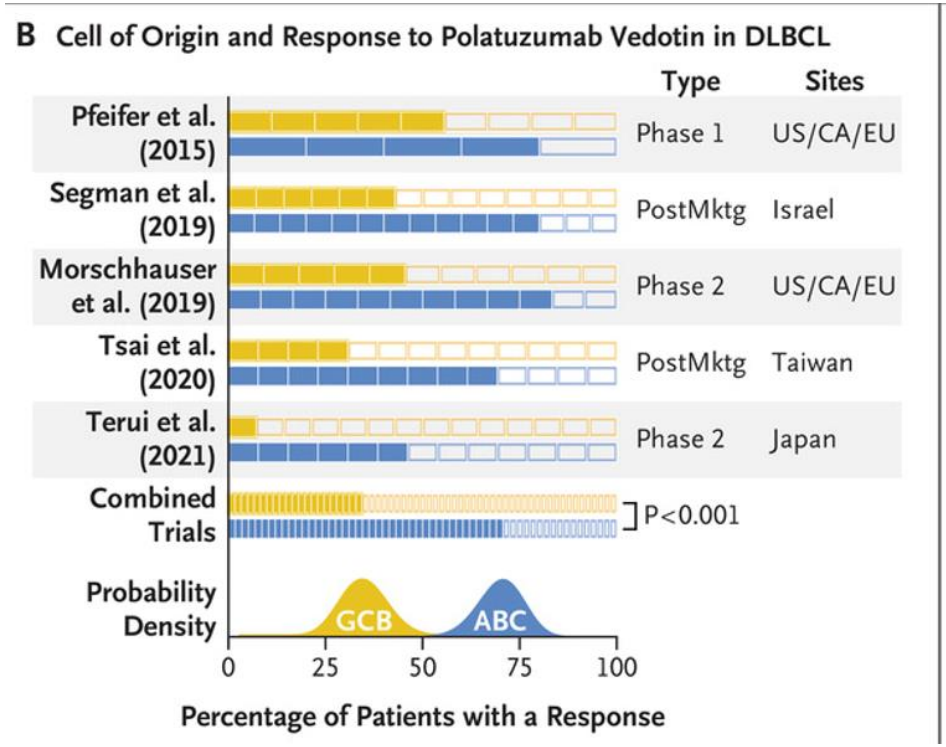
- Higher rates of neutropenic fever (13.8% vs 8%)
- No difference in peripheral neuropathy (1.6% vs 1%)

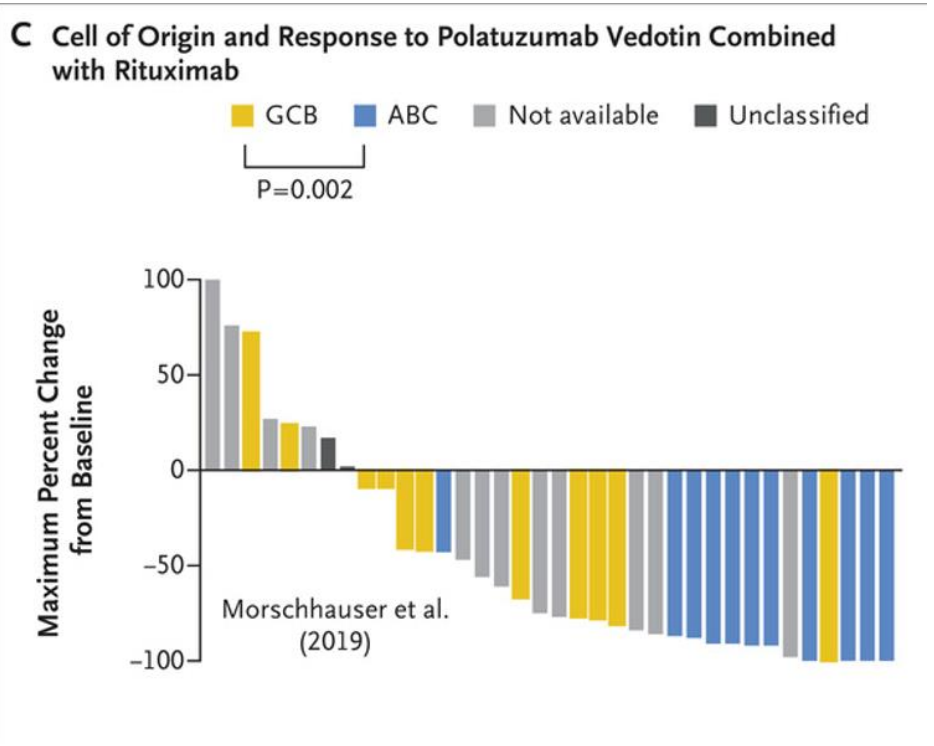


Tilly et al, 2022 *NEJM*

Stanford Cancer Institute cancer.stanford.edu | Stanford Medicine | UC DAVIS HEALTH | UCSF COMPREHENSIVE CANCER CENTER | Helen Diller Family Comprehensive Cancer Center | ANCO Educating and Empowering the Northern California Cancer Community

Early subgroup analysis showed increased benefit for non-GCB cell-of-origin

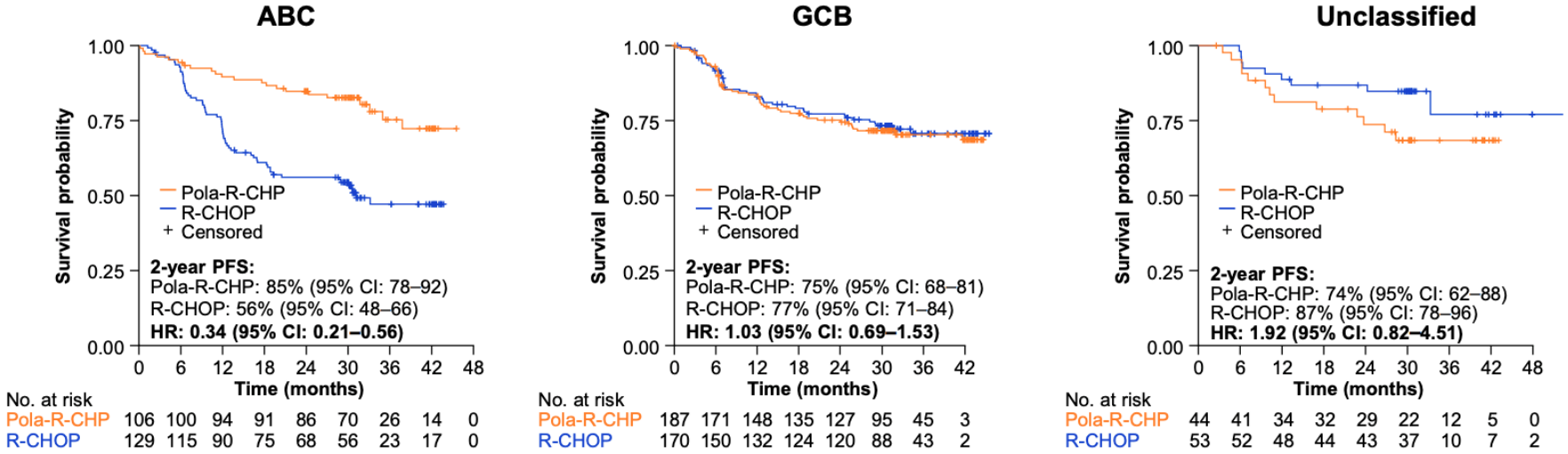




Palmer et al, 2023 *NEJM*
Tilly et al, 2022 *NEJM*
Russler-Germain, 2023 *Blood*

Further investigation reveals cell-of-origin might not be the whole story

Figure 1. Kaplan–Meier Estimates of Investigator-Assessed PFS* by COO Subgroup.

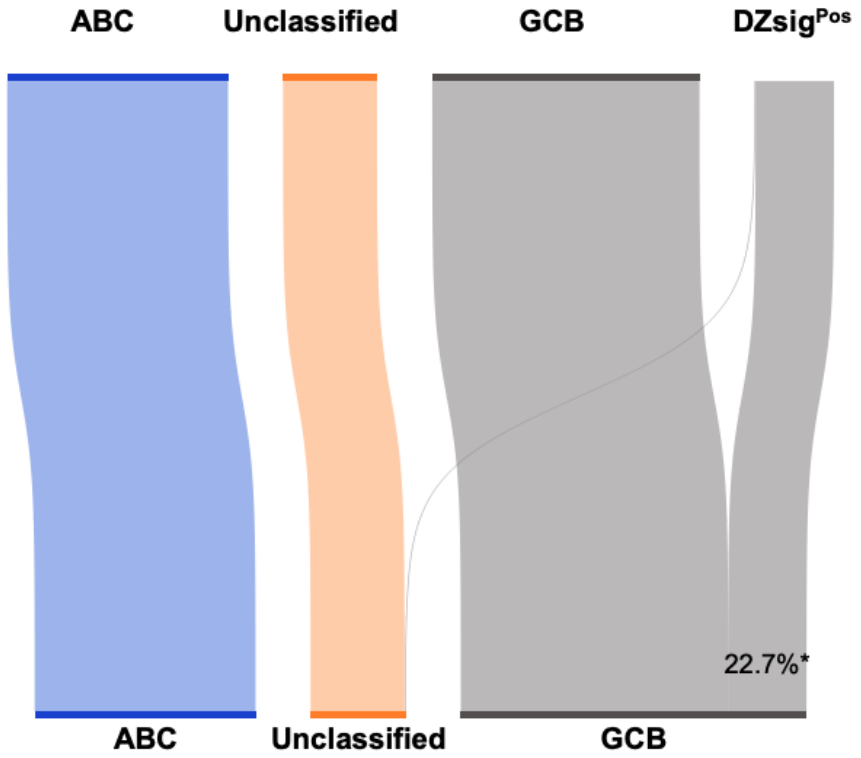


*Investigator-assessed disease progression and disease relapse or death from any cause were counted as events. Tick marks indicate censored data.

ABC, activated B cell; CI confidence interval; COO, cell of origin; GCB, germinal center B cell; HR, hazard ratio; PFS, progression-free survival.

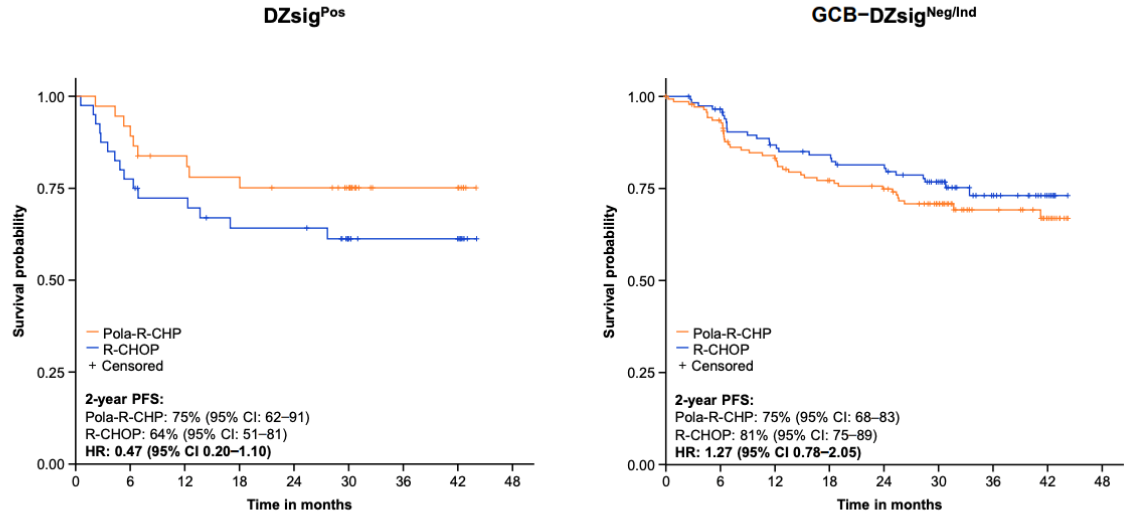
Morschhauser *et al*, P3000 *ASH 2023*

Molecular subtypes – deep zone signature – might also contribute to effectiveness of polatuzamab



*Proportion of GCB re-classified to DZsig^Pos

Figure 3. Kaplan–Meier estimates of investigator-assessed PFS* of DZsig groups by treatment arms.



Number at risk									
POLA−R−CHP	37	34	29	27	25	21	7	6	0
R−CHOP	40	31	27	23	23	14	10	9	0

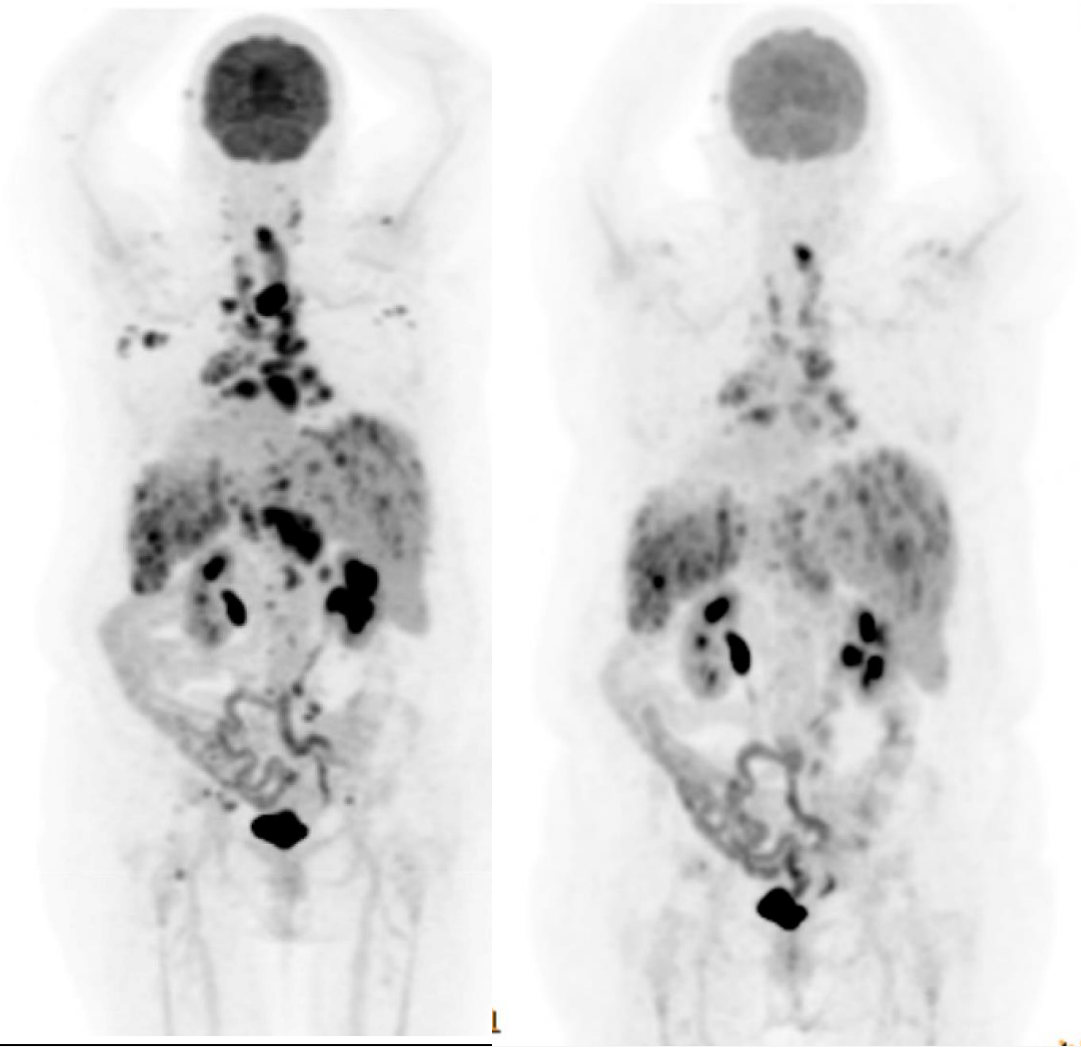
Number at risk									
POLA−R−CHP	141	129	111	100	95	68	34	24	0
R−CHOP	118	110	97	93	89	68	30	16	0

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

Morschhauser et al., P3000 *ASH 2023*

Case #2

- The patient received **6 cycles of Pola-R-CHP**
- End of treatment PET/CT showed **partial response, D4**



Which of the following salvage regimens do you recommend?

A. Platinum-based chemotherapy and plan to proceed to auto-HCT

B. Platinum-based chemotherapy and plan to proceed to allo-HCT

C. Referral for axicabtagene ciloleucel

D. Referral for tisagenlecleucel

E. Referral for lisocabtagene maraleucel

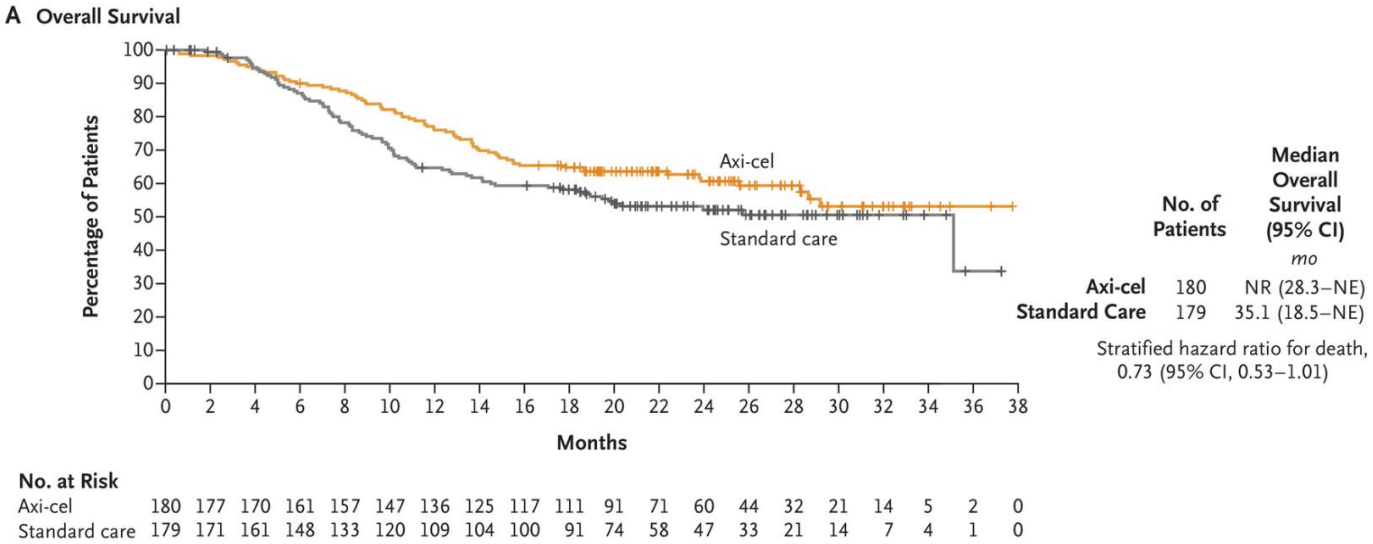
Choosing a CAR-T product in the second line

Product	2nd Line Trial	2nd signal	CR rate	PFS HR (95%CI)	CRS (≥ gr.3)	Neurotox (≥ gr.3)	Median days to manufacture	FDA approval 2nd line
Axicabtagene ciloleucel[1]	Zuma-7	CD28	65%	**0.49 (0.37, 0.65)**	92% (11%)	67% (32%)	30.4[4] (28.2-32.7)	✓
Lisocabtagene maraleucel[2]	TRANSFORM	4-1BB	66%	**0·41 (0.25, 0.66)**	42% (2%)	30% (10%)	35.9 (34.8-37)	✓
Tisagenlecleucel[3]	BELINDA	4-1BB	46%	1.07 (082, 1.4)	58% (12%)	21% (12%)	48.4 (42.9-55.9)	✗

1. Locke et al, *NEJM* 2022
2. Kamdar et al, *Lancet* 2022
3. Bishop et al, *NEJM* 2022
4. Locke et al, *Hemasphere* 2023

Axi-cel and Liso-cel show overall survival benefit in 2nd line

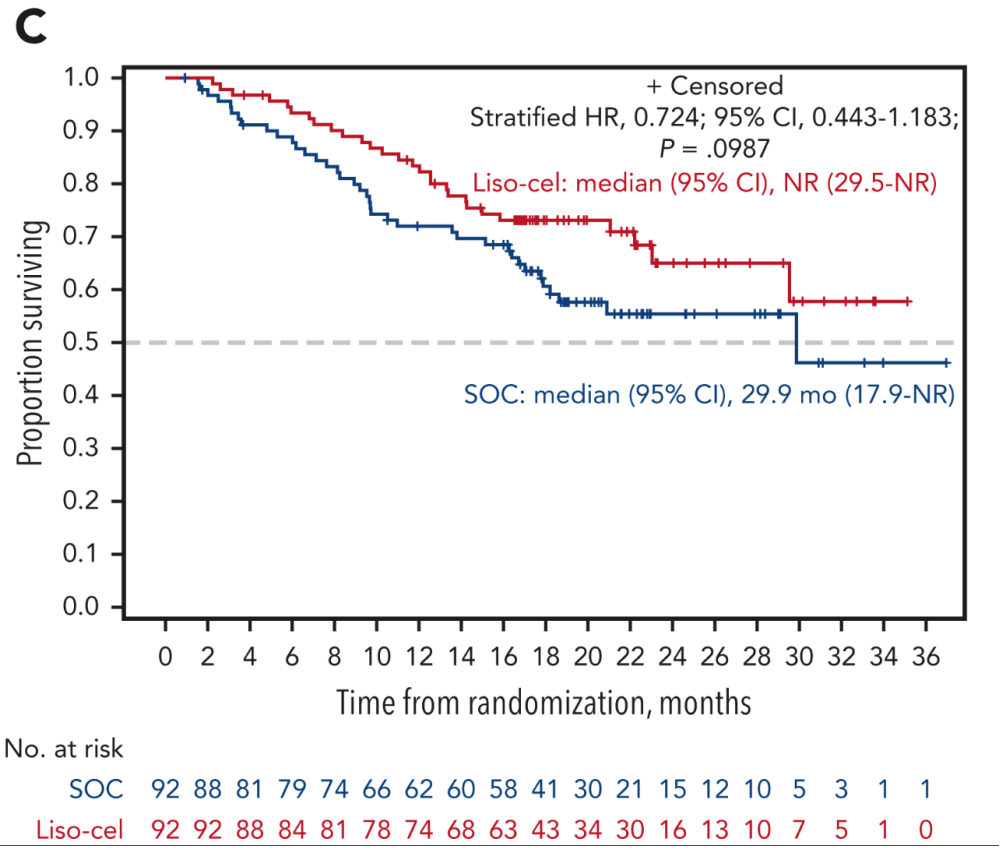
Axi-cel



	No. of Patients	Median Overall Survival (95% CI) mo
Axi-cel	180	NR (28.3–NE)
Standard Care	179	35.1 (18.5–NE)

Stratified hazard ratio for death, 0.73 (95% CI, 0.53–1.01)

Liso-cel



Locke et al, *NEJM* 2022
Abramson et al, Blood *2023*

Stanford Cancer Institute cancer.stanford.edu | Stanford MEDICINE | UCDAVIS HEALTH | UCSF COMPREHENSIVE CANCER CENTER | Helen Diller Family Comprehensive Cancer Center | ANCO Educating and Empowering the Northern California Cancer Community

2nd Line: Autologous transplant vs CAR-T in complete responders

Table-1: Selected baseline characteristics			
	CAR-T	auto-HCT	P-value
Age, years	64	59	0.14
Extra-nodal disease	58%	63%	0.37
Refractory disease to first-line	29%	20%	0.22
Prior lines of therapy, n	3	2	**<0.01**
Early treatment failure (within 12 months)	72%	58%	**0.02**
Elevated LDH before treatment	37%	31%	**0.04**
high-grade B-cell lymphoma with MYC and BCL2 or BCL6 rearrangement	14%	27%	**0.03**

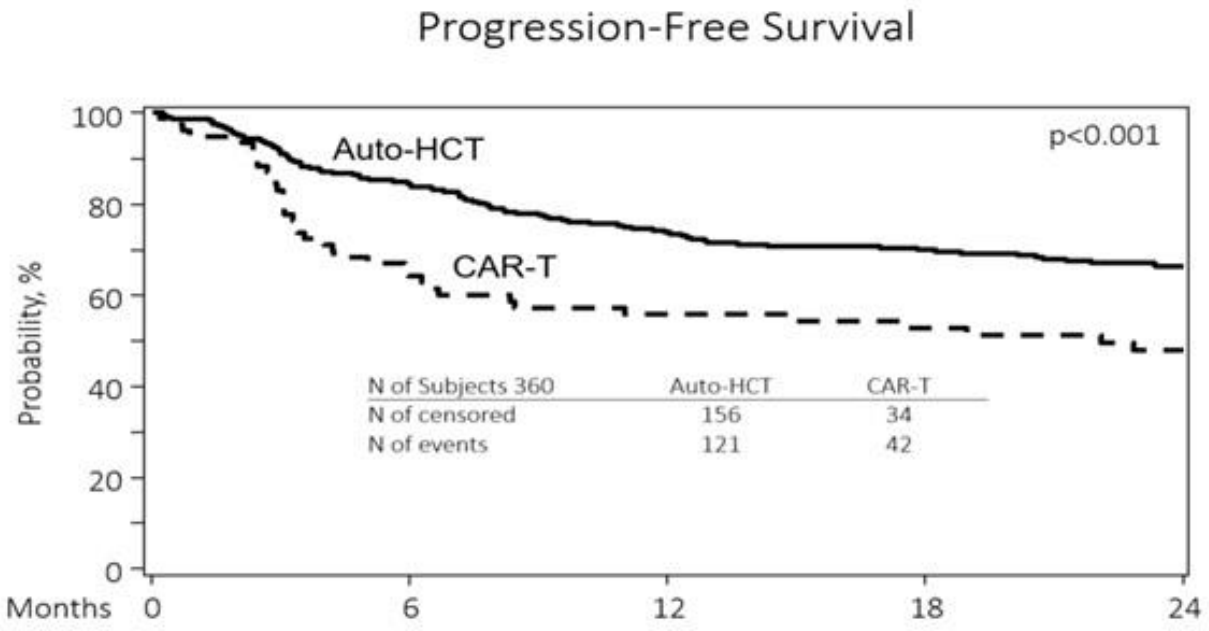


Figure-1: PFS in pts with LBCL who received auto-HCT vs. CAR-T while in CR

Shadman et al, Oral Presentation 781, *ASH 2023*

Case #2

- The decision was made to proceed to CAR-T **with Axi-cel (Yescarta)**
- She develops **Grade 1 CRS and Grade 1 ICANS** treated with tocilizumab and dexamethasone with resolution of symptoms
- PET/CT 90 days post CAR T shows **CR, D2**
- However, at 6 month follow up, she experiences new supraclavicular LAD and fevers. **Biopsy of SC LN reveals relapsed disease (CD19 positive, no rearrangements)**

Which of the following third line regimens do you recommend?

A. Tisagenlecleucel

B. Epcoritamab-bysps

C. Glofitamab-gxbms

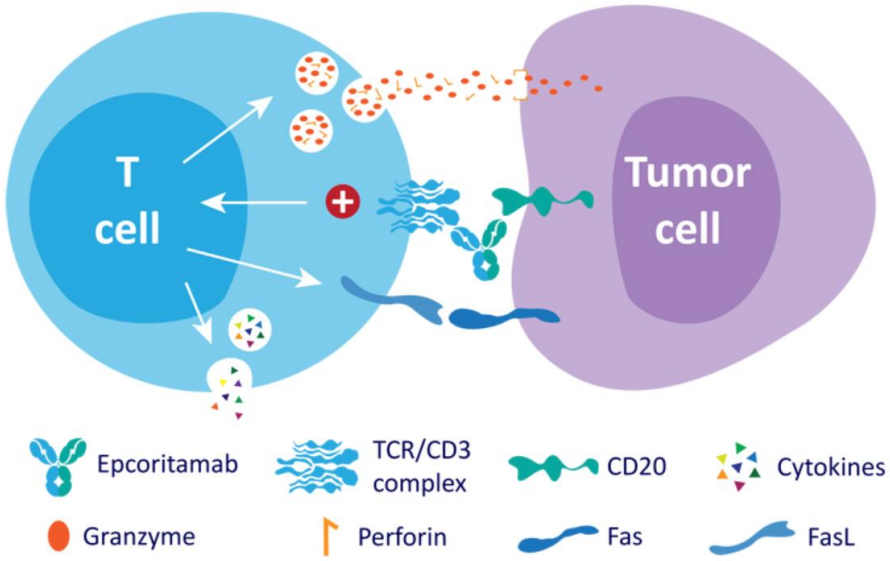
D. Loncastuximab tesirine-lpyl

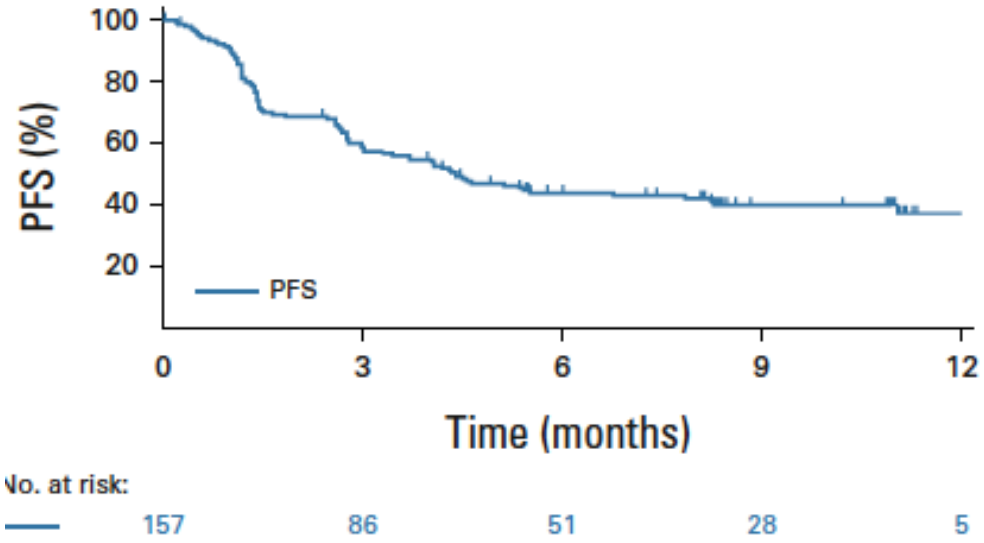
E. Tafasitamab - Lenalidomide

original reports

Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell–Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial

Catherine Thieblemont, MD, PhD[1]; Tycel Phillips, MD[2]; Herve Ghesquieres, MD, PhD[3]; Chan Y. Cheah, MBBS, DMSc[4,5]; Michael Roost Clausen, MD, PhD[6]; David Cunningham, MD[7]; Young Rok Do, MD, PhD[8]; Tatyana Feldman, MD[9]; Robin Gasiorowski, MBBS, PhD[10]; Wojciech Jurczak, MD, PhD[11]; Tae Min Kim, MD, PhD[12]; David John Lewis, MD[13]; Marjolein van der Poel, MD, PhD[14]; Michelle Limei Poon, MD[15]; Mariana Cota Stirner, MD, PhD[16]; Nurgul Kilavuz, MSc[17]; Christopher Chiu, PhD[17]; Menghui Chen, PhD[17]; Mariana Sacchi, MD[17]; Brian Elliott, MD[17]; Tahamtan Ahmadi, MD, PhD[17]; Martin Hutchings, MD, PhD[18]; and Pieternella J. Lugtenburg, MD, PhD[19]





AEs of special interest		
CRS[c]	78 (49.7)	4 (2.5)
ICANS[d]	10 (6.4)	1 (0.6)
Clinical tumor lysis syndrome	2 (1.3)	2 (1.3)

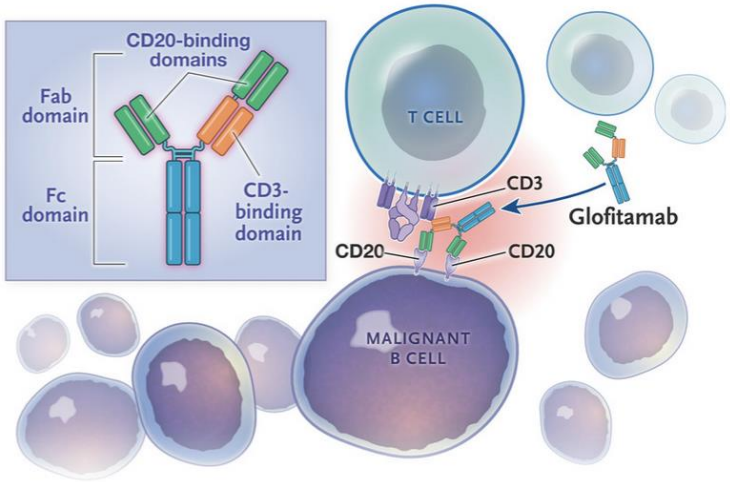
- ORR 63.1%
- CR 38.9%

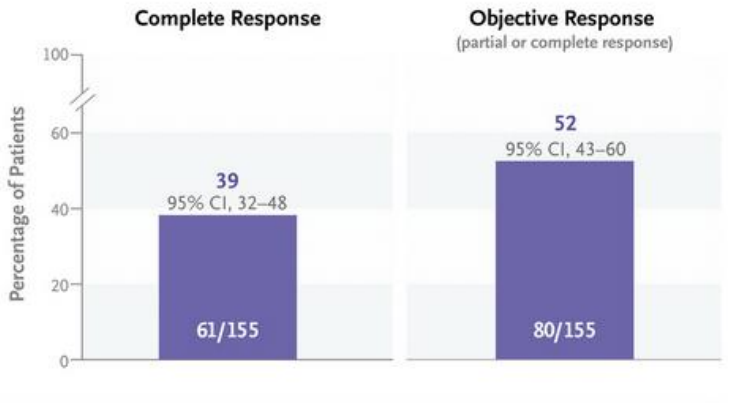
Thieblemont et al. JCO 2023 41(12): 22382247

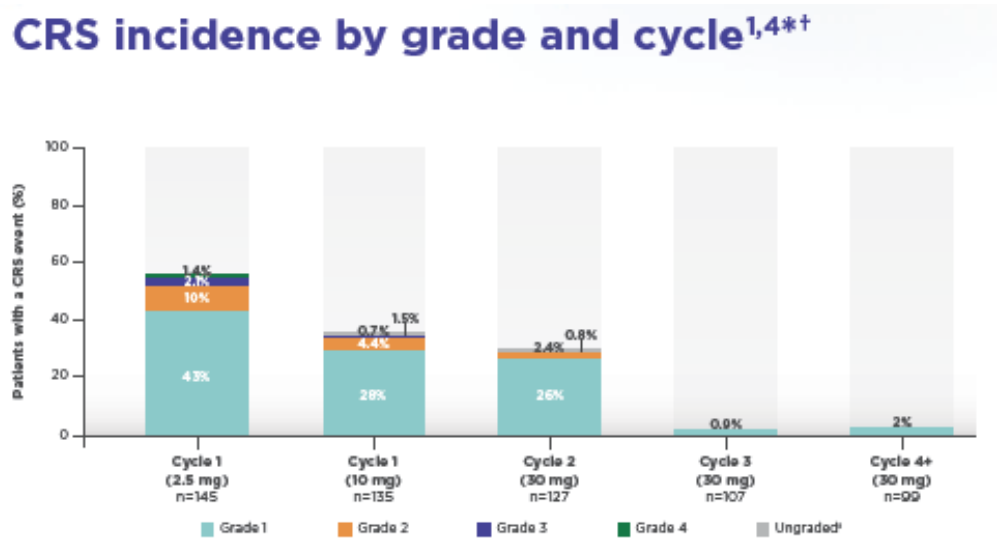
ORIGINAL ARTICLE

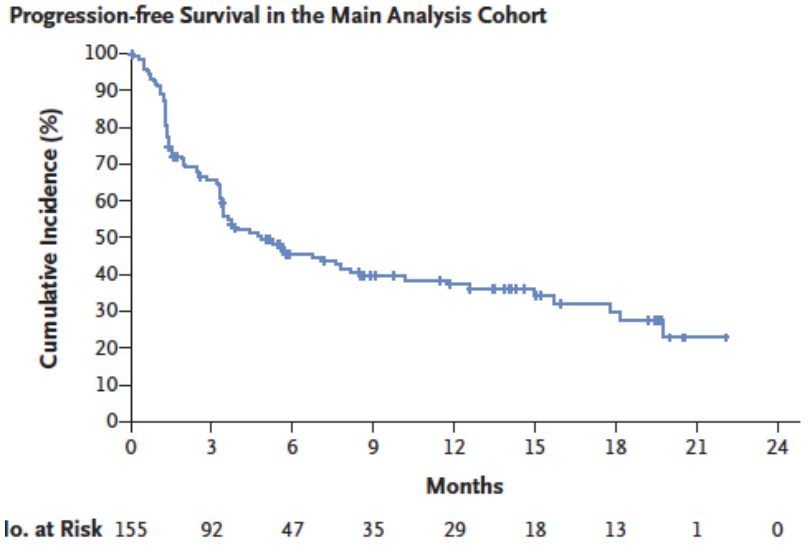
Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Michael J. Dickinson, M.B., B.S., D.Med.Sc., Carmelo Carlo-Stella, M.D., Franck Morschhauser, M.D., Ph.D., Emmanuel Bachy, M.D., Ph.D., Paolo Corradini, M.D., Gloria Iacoboni, M.D., Cyrus Khan, M.D., Tomasz Wróbel, M.D., Fritz Offner, M.D., Ph.D., Marek Trněný, M.D., Shang-Ju Wu, M.D., Ph.D., Guillaume Cartron, M.D., Ph.D., et al.









Dickenson et al, 2022 NEJM

Glofitamab Dosing Schedule

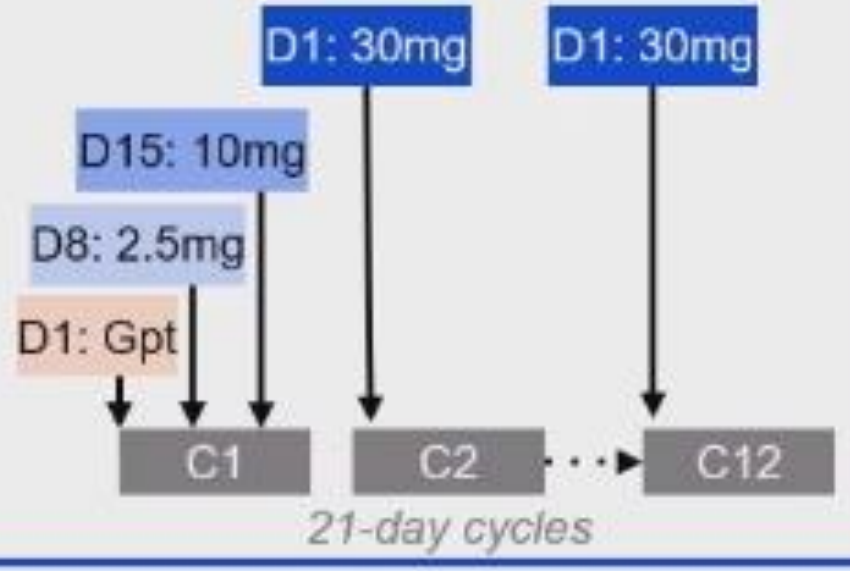
Glofitamab IV administration

Fixed-duration treatment:

- Up to 12 cycles (8.3 months)

CRS mitigation:

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



Hutchings et al, *ASH Oral Presentation 433* 2023

Evidence for Bispecifics in the Third Line

Bispecific	Patients (N)	Response rates	Survival outcomes	Rates of CRS	Rates of neurotoxicity	Treatment-related mortality
Epcoritamab (dose escalation)	68	ORR 68% (CR 45%) for LBCL	mPFS 9.1 mo	59% (no grade 3+)	6% (3% grade 3+)	0 patients
Epcoritamab (dose expansion)	157	ORR 63% (CR 39%) Prior CAR-T: ORR 54% (CR 34%)	mPFS 4.4 mo	50% (2.5% grade 3+)	6% (0.6% grade 3+)	9 patients (6%)
Glofitamab	154	ORR 52% (CR 39%) Prior CAR-T: CR 35%	mPFS 4.9 mo 1 y: PFS 37%, OS 50%	63% (4% grade 3+)	8% (3% grade 3+)	8 patients (5%)
Odronextamab	85	No prior CAR-T: ORR 53% (CR 53%)	mPFS 11.5 mo	54% (7% grade 3+)	12% (3% grade 3+)	7 patients (5%)

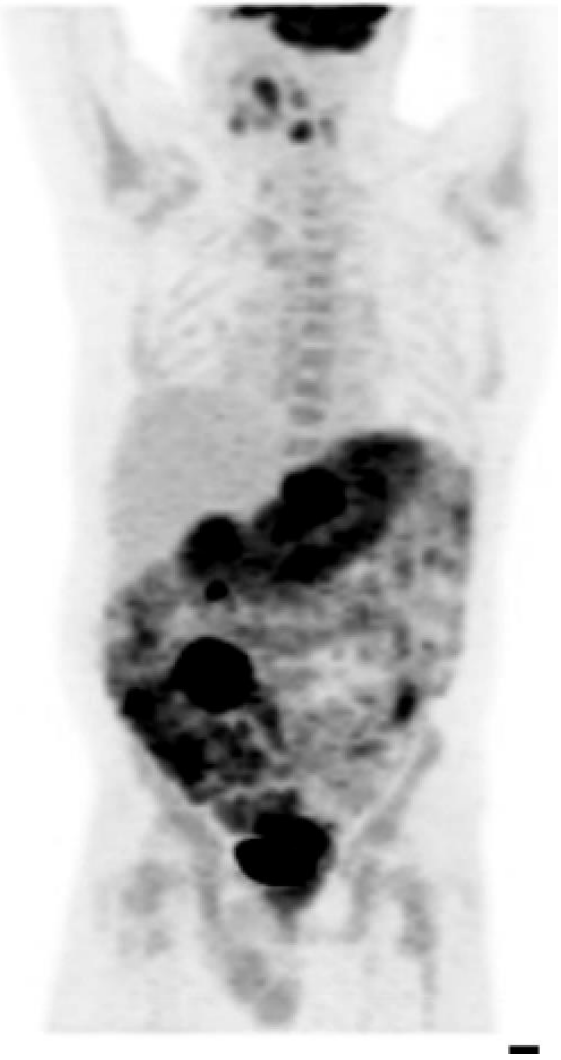
Major and Kamdar. *Am Soc Hematol Educ Program* 2023

Case #2 – Key Points

- R-Polatuzumab-CHP provides a PFS benefit in the frontline setting
  - Previous data suggested there is a greater benefit in non-GCB subtype DLBCL, but new data suggests there might be additional benefit for specific genetic subtypes
  - Future studies planned using bispecifics in the upfront setting
- Axi-cel and liso-cel are both FDA approved in the 2nd line relapsed setting
  - Axi-cel has fastest and most reliable manufacturing
  - Liso-cel has less CRS/ICANS and may be appropriate for older, frail patients
- Glofitimab and epcoritamab are bispecific antibodies approved for the treatment of relapsed/refractory DLBCL
  - These can be delivered off the shelf and outpatient
  - Manageable toxicity but require brief hospitalization during the first cycle

Case #3

- 44-year-old man who presents with 25 lb weight loss, diarrhea, and abdominal pain
- CT revealed: **mesenteric mass** in the right mid abdomen, at 3.7 x 3.2 cm, and severe, **diffuse wall thickening in the stomach**
- He subsequently had an upper endoscopy, which showed diffuse gastric fold thickening, with an erythematous and friable mucosa; there were multiple small clean-based ulcers
- The pathology showed **mantle cell lymphoma**. This was **Cyclin D1 positive, SOX11 positive, TP53 mutated, and had a Ki-67 score of 65%**



Which regimen would you use to treat this patient with newly diagnosed TP53 mutated mantle cell lymphoma?

A. Serial surveillance

B. NORDIC trial: Maxi-CHOP alternating with with R-HiDAC

C. Bendamustine + Rituximab followed by rituximab maintenance

D. LyMA regimen: RDHA + platinum x 4 cycles followed by auto transplant

E. Triangle regimen: Alternating R-CHOP with covalent BTKi/RDHA + platinum

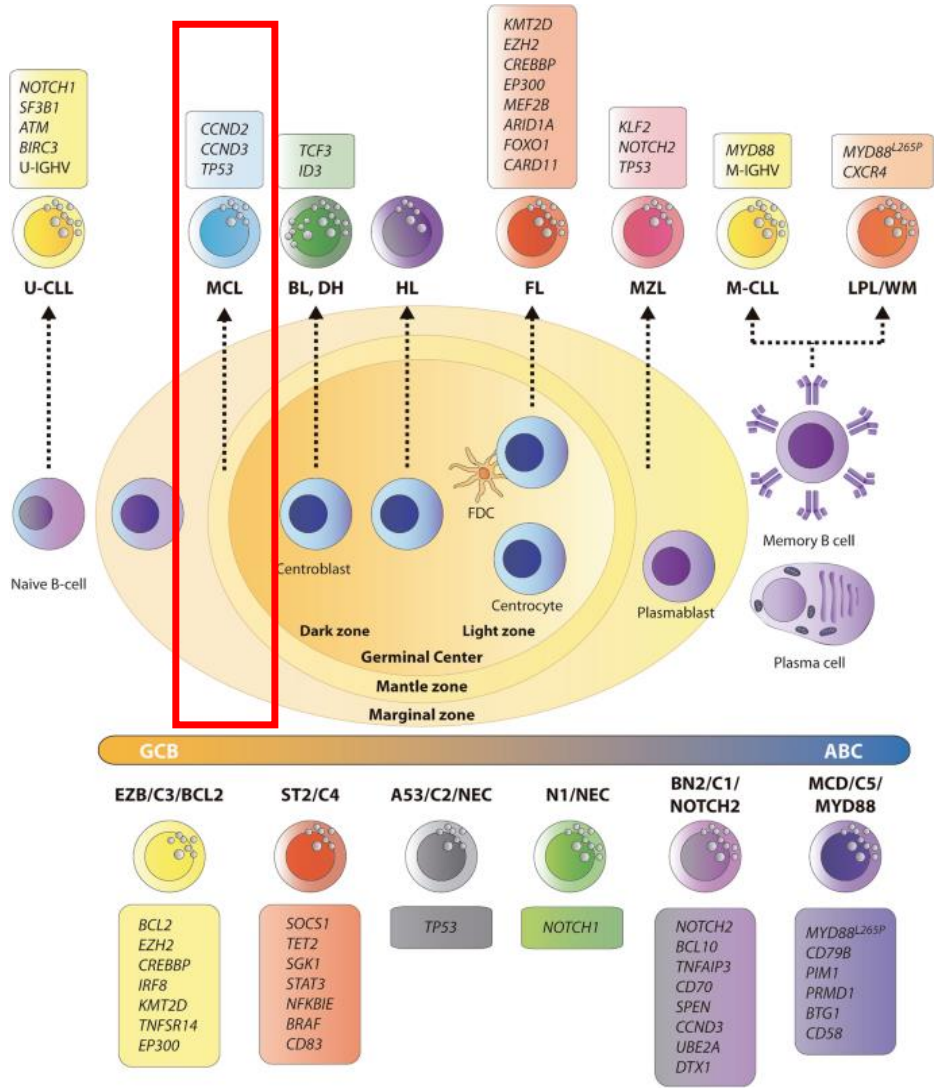
Mantle Cell Lymphoma

WHO Classification

Mantle cell lymphoma (MCL)	
Classical MCL	Mostly SOX11 (+) Unmutated/minimally mutated IGHV
Indolent leukemic non-nodal MCL[a]	Mostly SOX11 (–) Mutated IGHV
In situ mantle cell neoplasia	New name for in situ MCL, reflecting low clinical risk

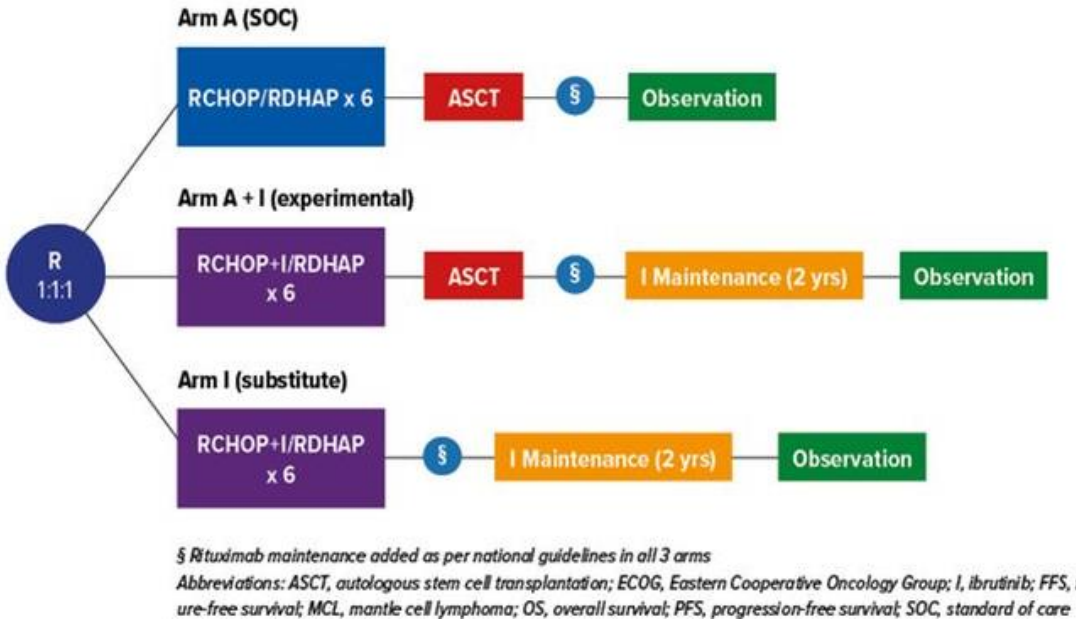
[a] Indolent leukemic non-nodal MCL with peripheral blood, bone marrow, and sometimes splenic involvement, may become more aggressive

ICC Classification



Regimens are Incorporating More non-Chemo Products

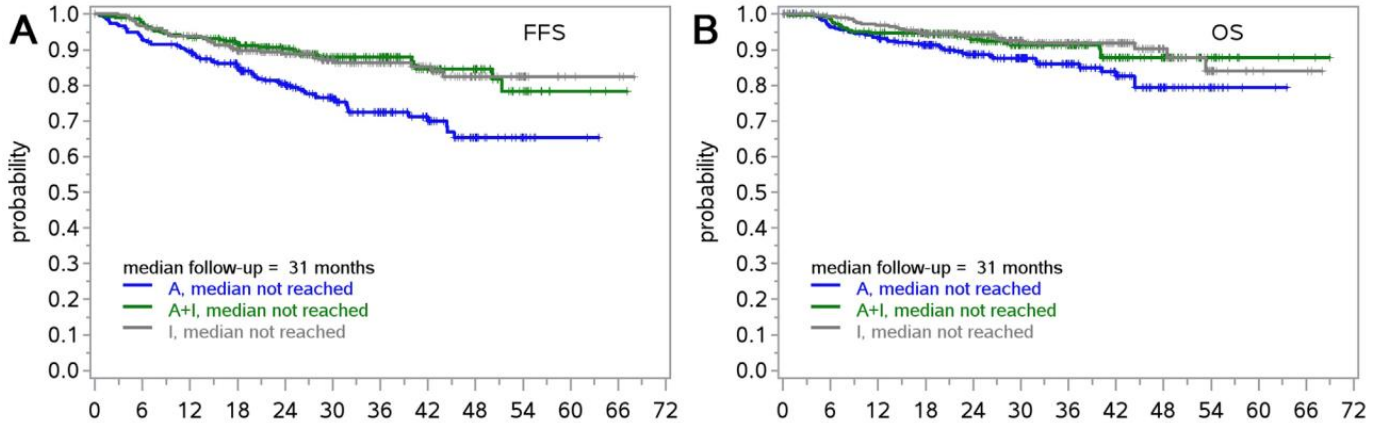
The Triangle Regimen



§ Rituximab maintenance added as per national guidelines in all 3 arms

Abbreviations: ASCT, autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; I, ibrutinib; FFS, failure-free survival; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression-free survival; SOC, standard of care

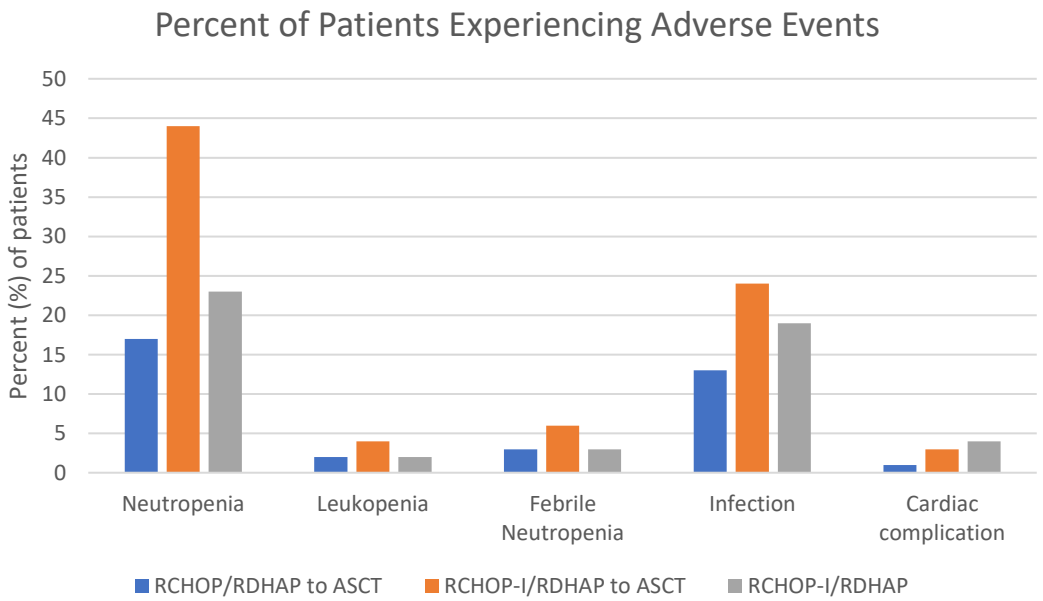
Figure 1A: FFS (primary outcome) and B: OS according to randomized trial arm A (R-CHOP/R-DHAP followed by ASCT), A+I (ibrutinib-R-CHOP/R-DHAP followed by ASCT and ibrutinib maintenance) and I (ibrutinib-R-CHOP/R-DHAP followed by ibrutinib maintenance)



Dreyling, et al, *Plenary Abstract ASH* 2023

The Triangle Regimen: Safety and Tolerability

- No significant differences in Grade 3–5 adverse events (AEs) between induction with R-CHOP/R-DHAP vs ibrutinib-R-CHOP/R-DHAP patient groups
- No significant differences in Grade 3–5 AEs between the two ASCT-containing arms (arm A and arm A + I)
- More Grade 3-5 AEs during maintenance in the ibrutinib-R-CHOP/DHAP + ASCT group

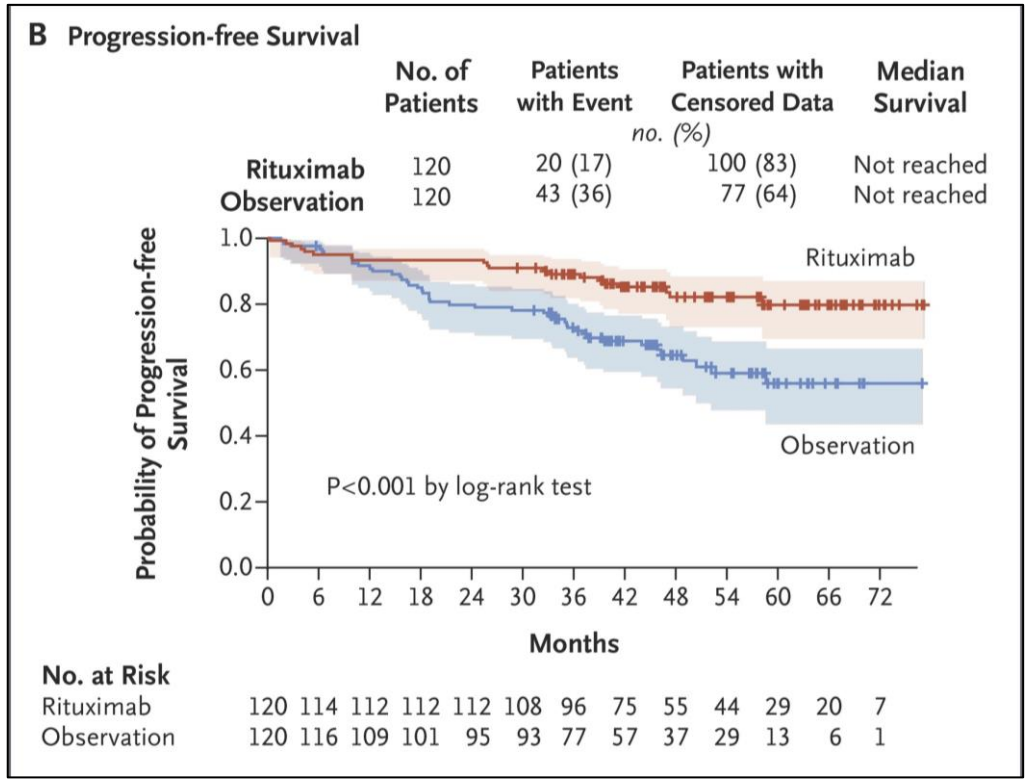


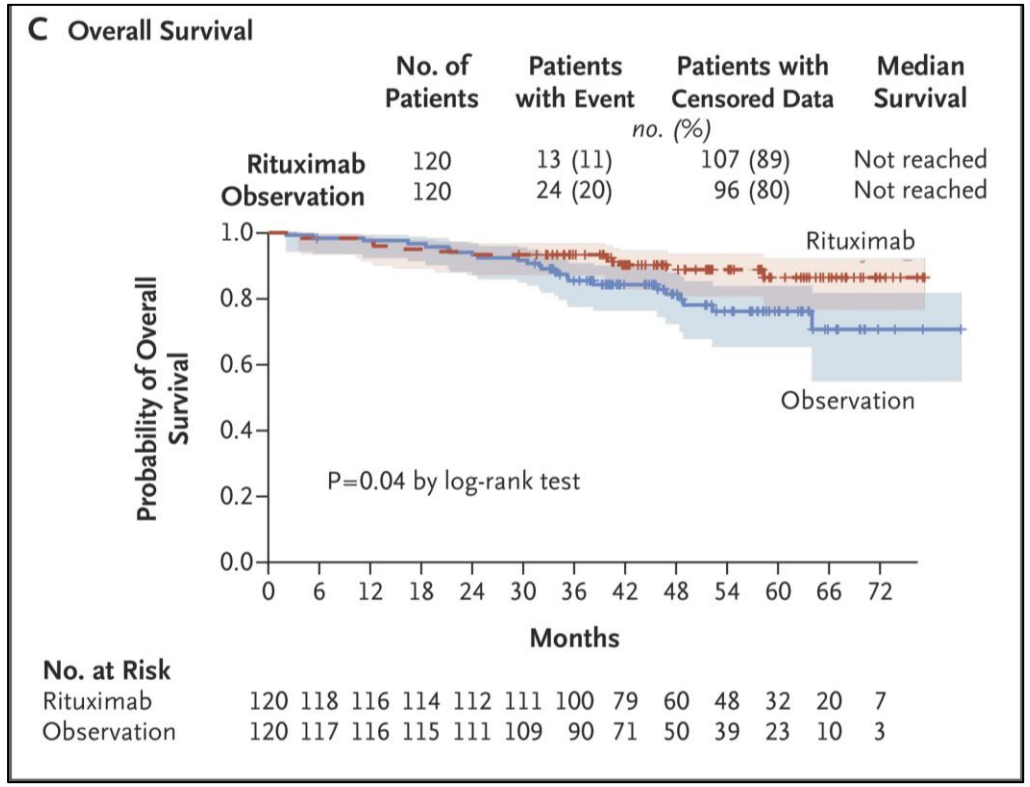
Dreyling et al, *Plenary Abstract ASH* 2023

ORIGINAL ARTICLE

Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma

Steven Le Gouill, M.D., Ph.D., Catherine Thieblemont, M.D., Ph.D., Lucie Oberic, M.D., Anne Moreau, M.D., Krimo Bouabdallah, M.D., Caroline Dartigeas, M.D., Gandhi Damaj, M.D., Ph.D., Thomas Gastinne, M.D., Vincent Ribrag, M.D., Ph.D., Pierre Feugier, M.D., Ph.D., Olivier Casasnovas, M.D., Hacène Zerazhi, M.D., et al., for the LYSA Group*





Gouill et al, *NEJM* 2017

Stanford Cancer Institute cancer.stanford.edu | Stanford MEDICINE | UCDAVIS HEALTH | UCSF COMPREHENSIVE CANCER CENTER | Helen Diller Family Comprehensive Cancer Center | ANCO Educating and Empowering the Northern California Cancer Community

Chemo-Free Regimens

Treatment	Outcome	Adverse Events	Reference
Lenalidomide + Rituximab	ORR: 92% 3-year PFS: 80%	Neutropenia (42%) Rash (29%)	Ruan et al, *NEJM* 2015
Venetoclax/lenalidomide/rituximab	ORR: 96%	Neutropenia (68%) Thrombocytopenia (50%)	Phillips et al, *JCO* 2021
Ibrutinib + Rituximab	ORR: 96% 3-year OFS: 87%	Grade 3 A fib (22%)	Jain et al, *JCO* 2022
Ibrutinib/Obinutuzumab/venetoclax	ORR: 85% 1-year PFS: 93%	Neutropenia (60%)	OASIS: Le Gouill, *Blood* 2021
Acalabrutinib/venetoclax/rituximab	ORR: 100% 1-year PFS: 89%	Diarrhea (62%) Headache (52%)	Wang et al, *Blood* 2021
Zanubrutinib + Rituximab	*In progress*	*In progress*	Dreyling et al, *Future Oncology* 2021

Case #3

- He was started on R-CHOP (Maxi-R-CHOP held out of **concern for TLS and GI perforation)**
- He was subsequently switched to **4 cycles of R-DHAOx, which he tolerated well**
- His best response was **PR, and presented with persistent symptoms**

How would you proceed?

A. BTKi monotherapy (acalabrutinib or zanubrutinib)

B. Rituximab + lenalidomide

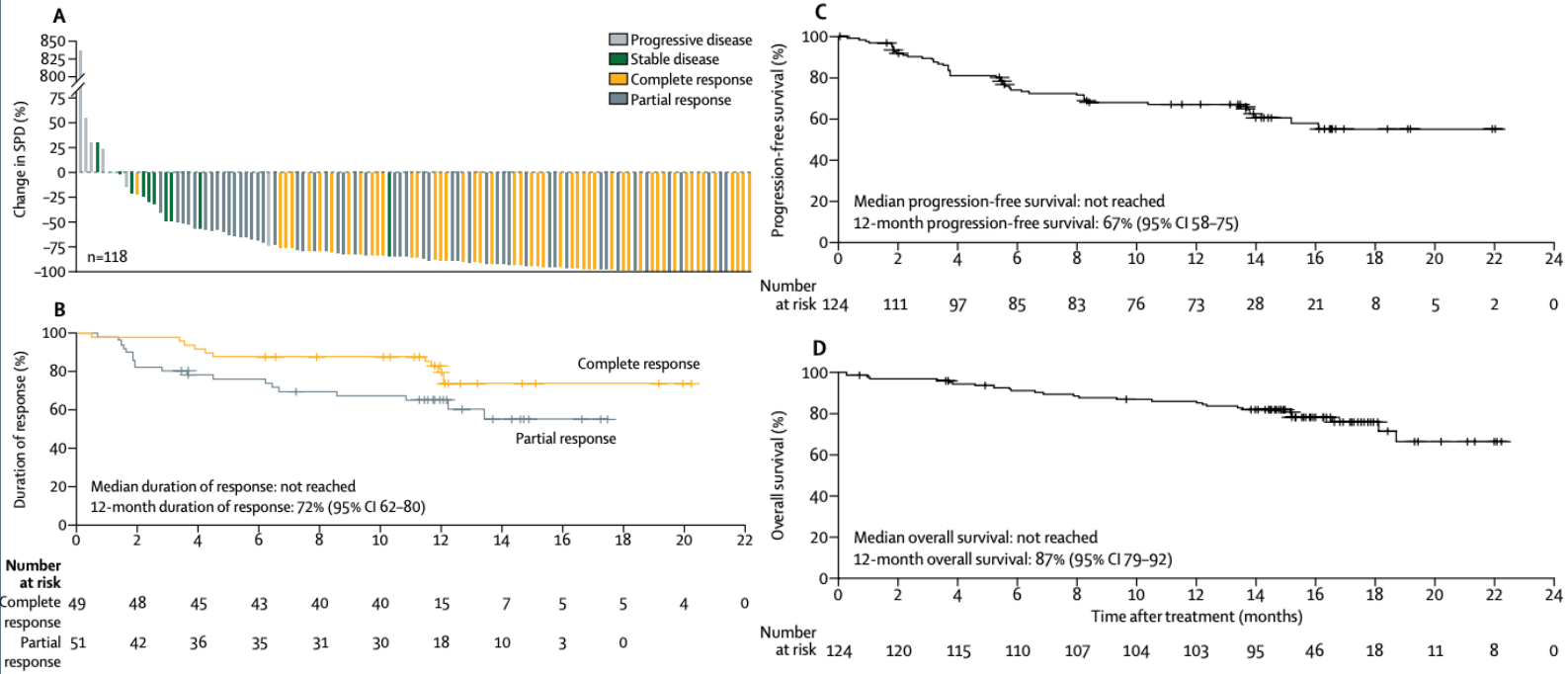
C. Ibrutinib + venetoclax

D. Gemcitabine + oxaliplatin + rituximab

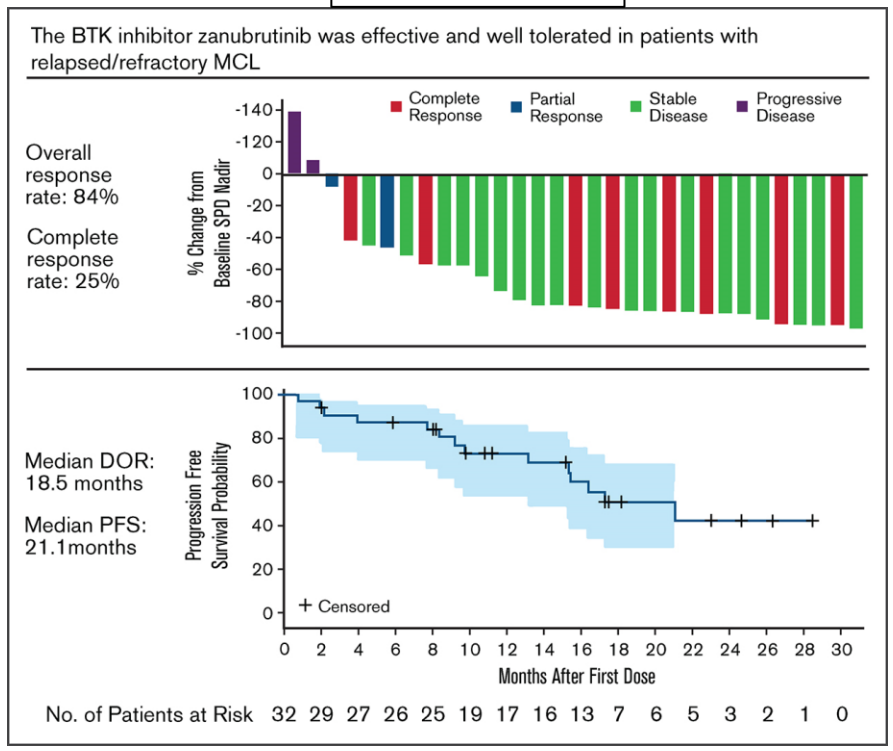
E. Brexucabtagene autoleucel

BTKi monotherapy in the relapsed/refractory setting

Acalabrutinib



Zanubrutinib



Wang et al, *Lancet* 2018
Song et al, *Clinical Cancer Research* 2020
Tam et al, *Blood Adv* 2021

Stanford Cancer Institute cancer.stanford.edu
Stanford MEDICINE
UCDAVIS HEALTH
UCSF COMPREHENSIVE CANCER CENTER
Helen Diller Family Comprehensive Cancer Center
ANCO Educating and Empowering the Northern California Cancer Community

NATIONAL ARCHIVES

FEDERAL REGISTER

The Daily Journal of the United States Government

Notice

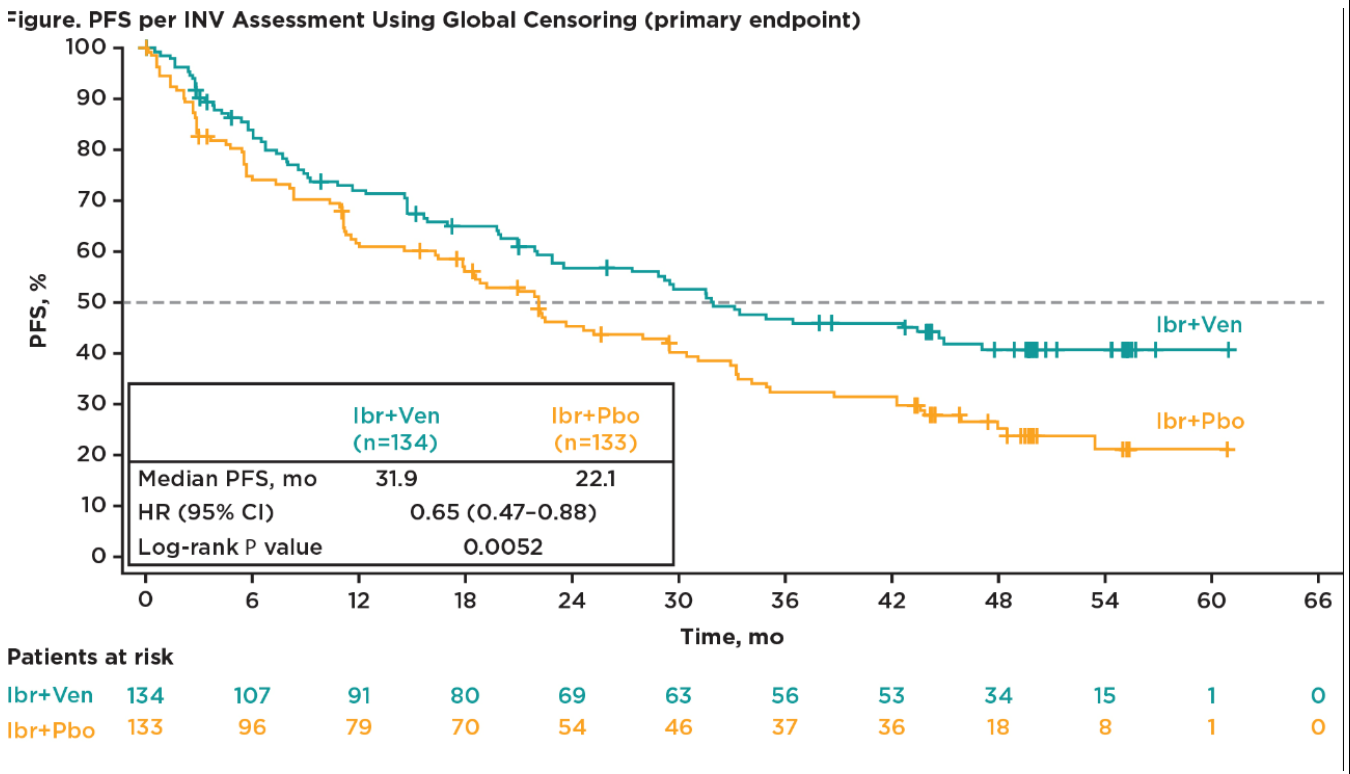
Pharmacyclics LLC.; Withdrawal of Approval of Indications for Mantle Cell Lymphoma and Marginal Zone Lymphoma for IMBRUVICA (ibrutinib) Capsules and Tablets

A Notice by the Food and Drug Administration on 12/18/2023

SYMPATICO

Combination Ibrutinib + Venetoclax

- Ibr+Ven combination had statistically significant improvement in **PFS** compared with Ibr+Placebo
- **CR** rates also significantly improved with Ibr+Ven
- **OS** was not significantly improved at this interim analysis
- The **safety** profile of Ibr+Ven was consistent with known AEs for each agent



Wang et al, Late Breaking Abstract-2, *ASH 2023*

Case #3

- Patient was treated with **zanubrutinib**
- After 2 cycles, he achieved a **PR**
- He had persistent GI bleeding

How would you proceed?

A. Continue zanubrutinib

B. Add venetoclax

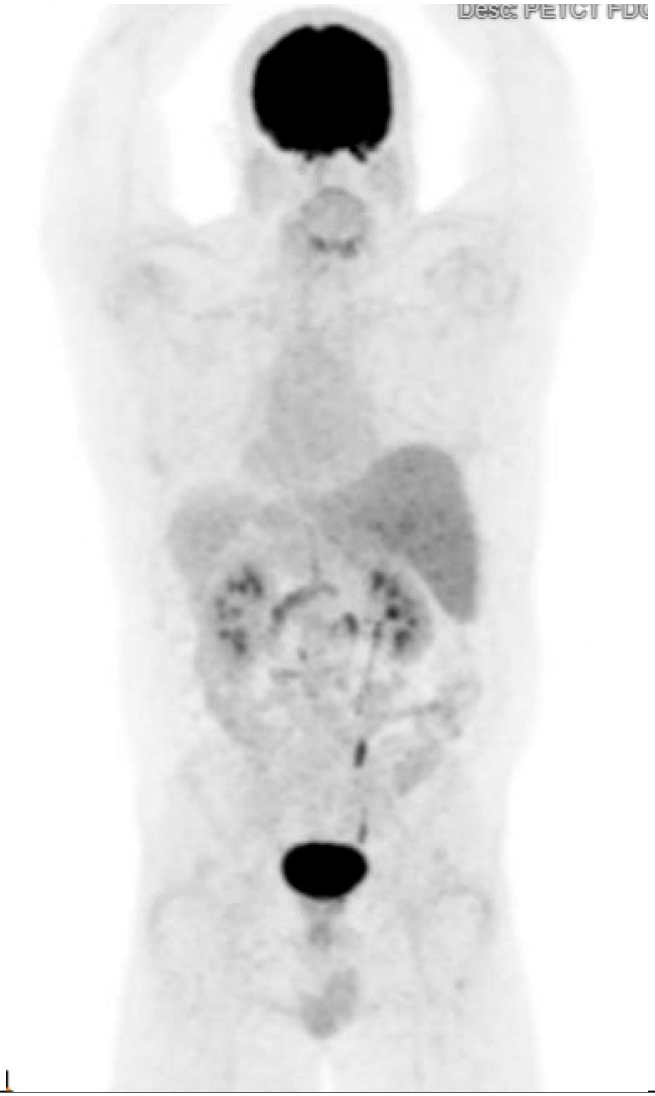
C. Switch to pirtobrutinib

D. Switch to rituximab + lenalidomide

E. Switch to brexucabtagene autoleucel

Case #3

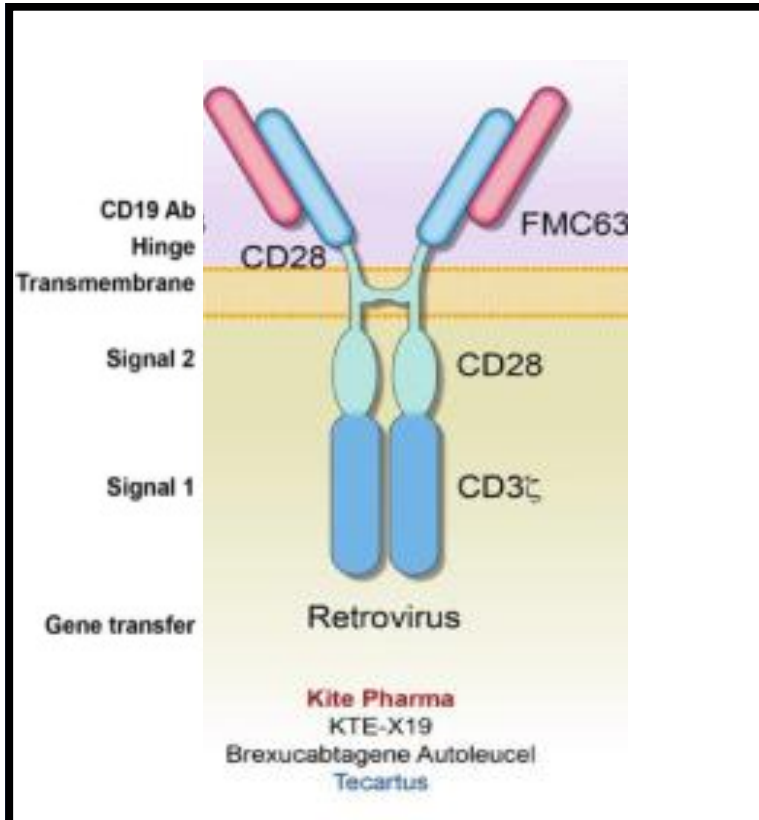
- Decision was made to treat with **brexucabtagene autoleucel**
- He has a **Deauville 2 CR** shown to the right
- He continues in CR nine months later

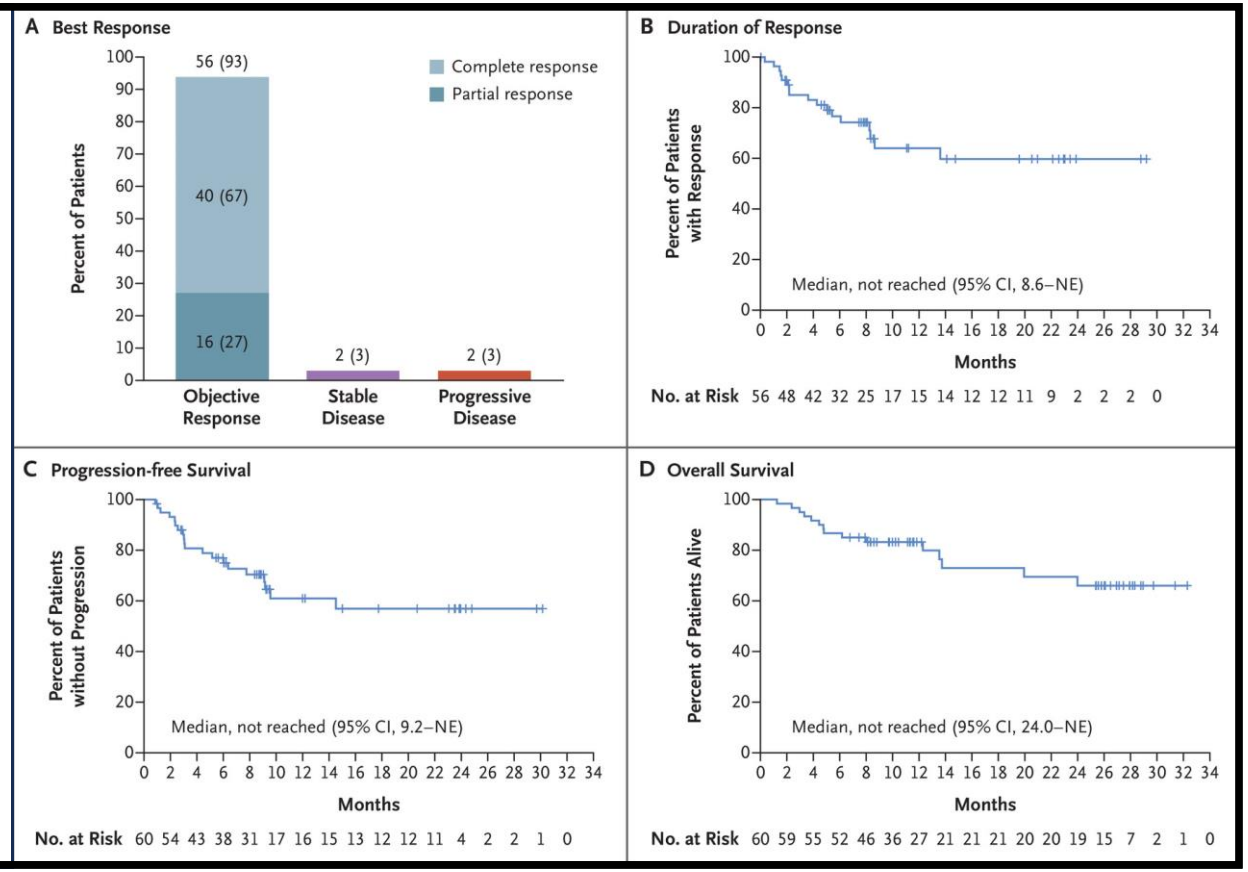


ORIGINAL ARTICLE

KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

Michael Wang, M.D., Javier Munoz, M.D., Andre Goy, M.D., Frederick L. Locke, M.D., Caron A. Jacobson, M.D., Brian T. Hill, M.D., Ph.D., John M. Timmerman, M.D., Houston Holmes, M.D., Samantha Jaglowski, M.D., Ian W. Flinn, M.D., Ph.D., Peter A. McSweeney, M.D., David B. Miklos, M.D., et al.

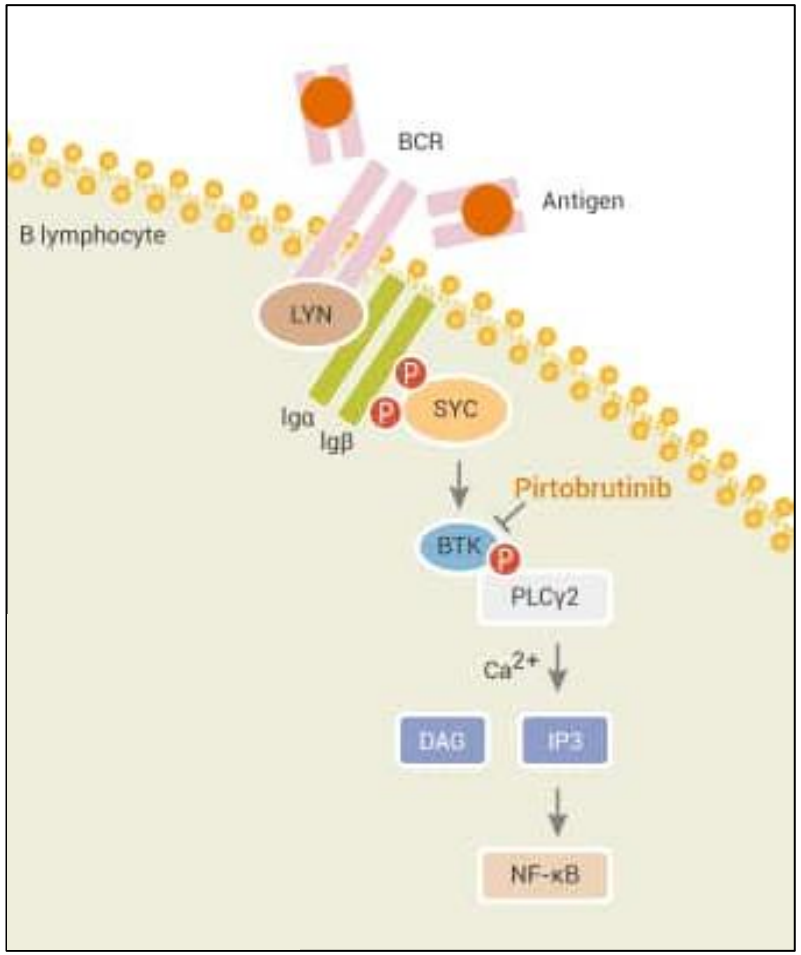




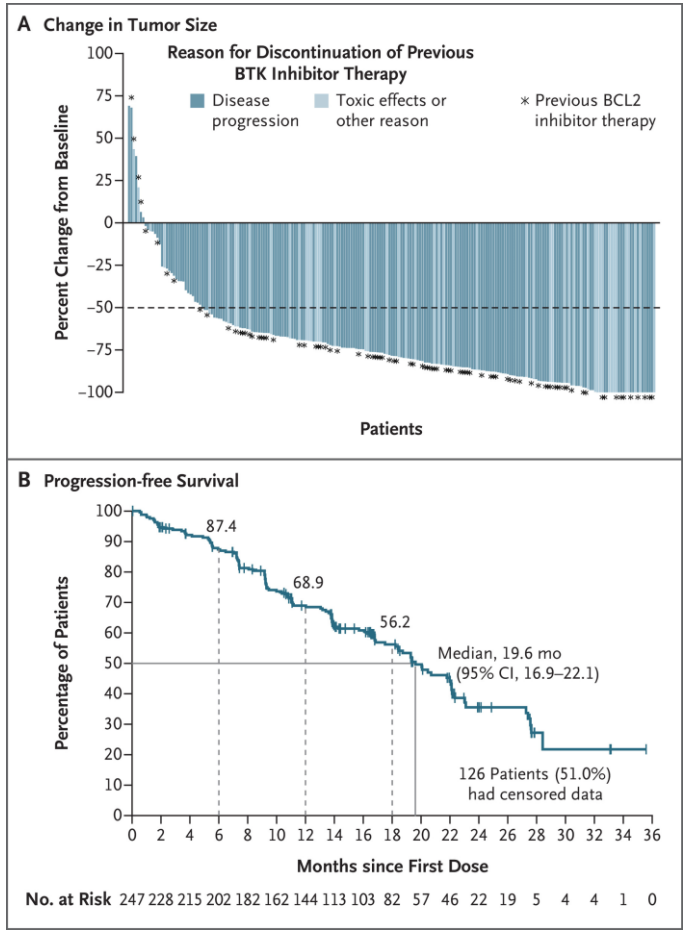
Wang et al, JCO 2023

Stanford Cancer Institute cancer.stanford.edu
Stanford MEDICINE
UCDAVIS HEALTH
UCSF COMPREHENSIVE CANCER CENTER
Helen Diller Family Comprehensive Cancer Center
ANCO Educating and Empowering the Northern California Cancer Community

Pirtobrutinib



- 120 patients with prior BTK inhibitor treatment received oral pirtobrutinib at 200 mg once daily until disease progression or unacceptable toxicity.
- ORR: 73.3% (67.3, 78.7)
- mPFS: 19.6 months
- Most common side effects:
  - Fatigue (29%)
  - Musculoskeletal pain (27%)
  - Diarrhea (19%)
  - Edema (18%)
  - Dyspnea (17%)

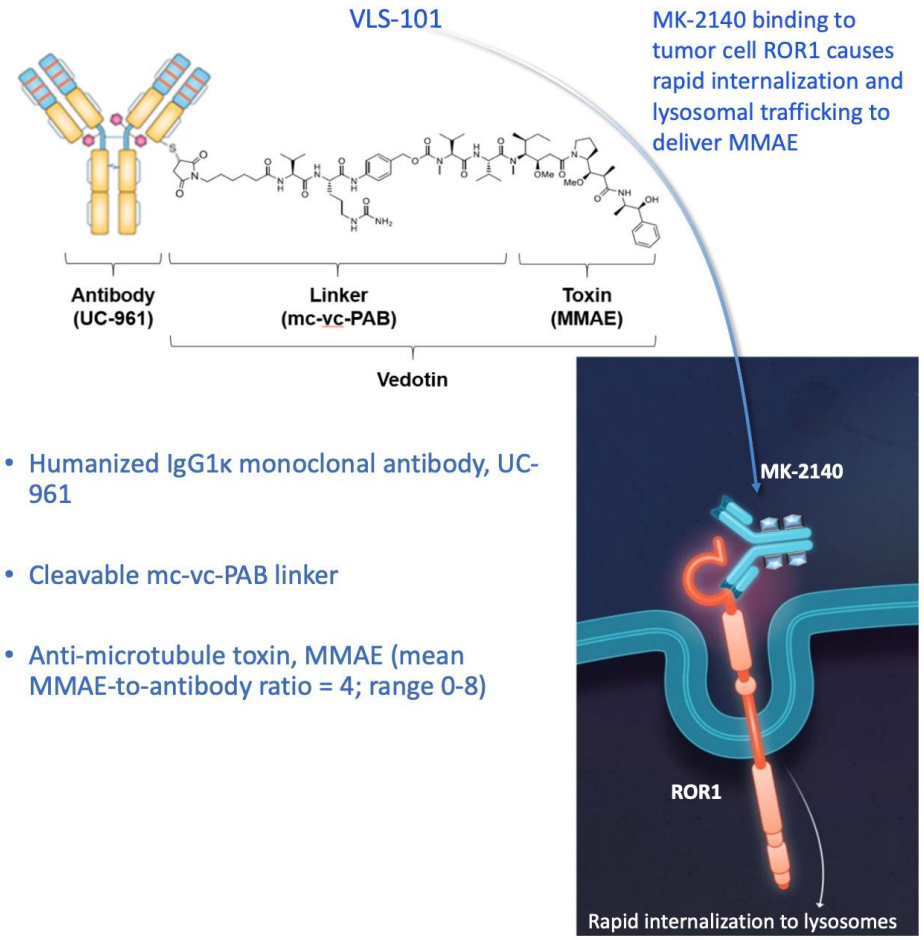


Mato et al, *NEJM* 2023

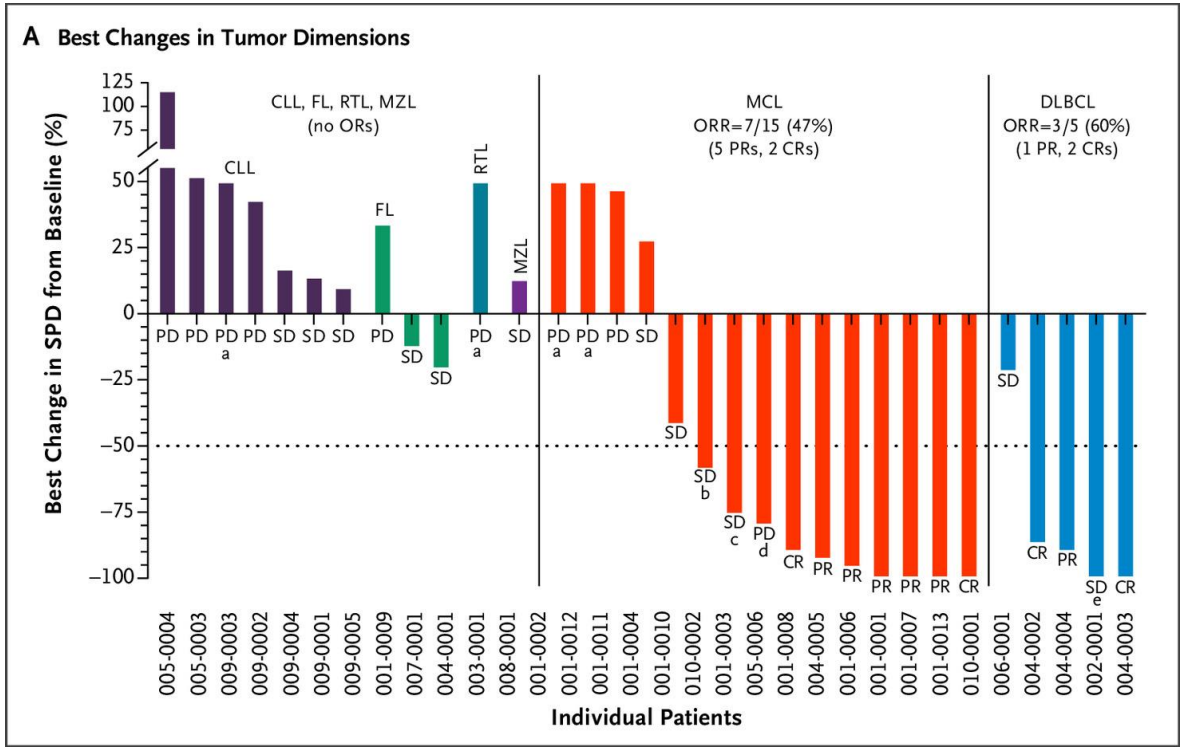
Stanford Cancer Institute cancer.stanford.edu | Stanford Medicine | UC DAVIS HEALTH | UCSF COMPREHENSIVE CANCER CENTER | Helen Diller Family Comprehensive Cancer Center | ANCO Educating and Empowering the Northern California Cancer Community

Other emerging therapies in the 3rd line setting

Zilovertamab vedotin



- Humanized IgG1κ monoclonal antibody, UC-961
- Cleavable mc-vc-PAB linker
- Anti-microtubule toxin, MMAE (mean MMAE-to-antibody ratio = 4; range 0-8)



Stanford Cancer Institute cancer.stanford.edu
Stanford MEDICINE
UCDAVIS HEALTH
UCSF Helen Diller Family Comprehensive Cancer Center
COMPREHENSIVE CANCER CENTER
ANCO Educating and Empowering the Northern California Cancer Community

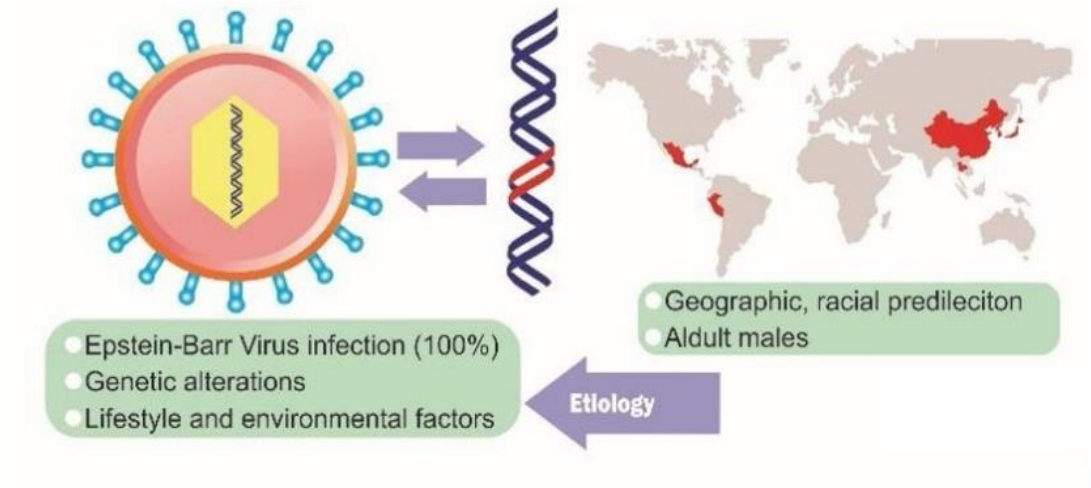
Case #3 – Key Points

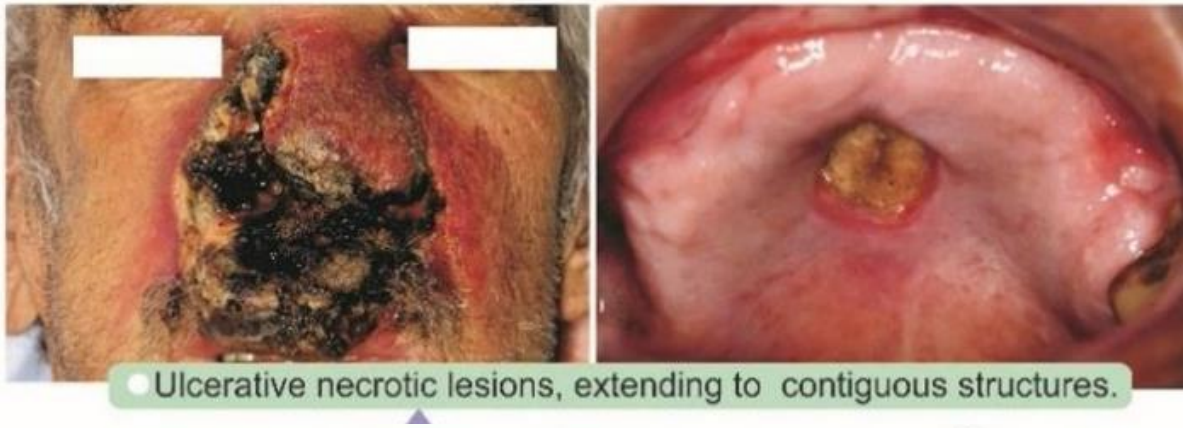
- Upfront therapy is evolving for mantle cell lymphoma, especially for patients who are TP53 mutated
  - Incorporating BTKi
  - Less cytoxic chemotherapy
- The role of transplant in the upfront setting is controversial
- Results from the SYMPATICO trial suggest combination venetoclax + BTKi therapy can yield a rapid response, if needed
- Many emerging therapies for third line
  - FDA-approved brexu-cel and pirtobrutinib
  - Other pipeline options include zilovertamab vedotin and bispecific antibodies

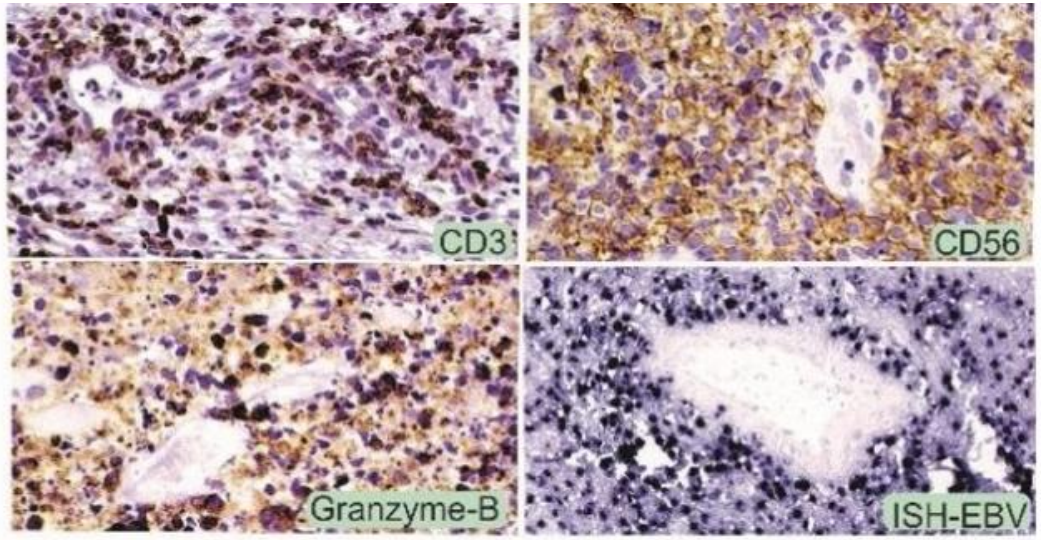
Case #4

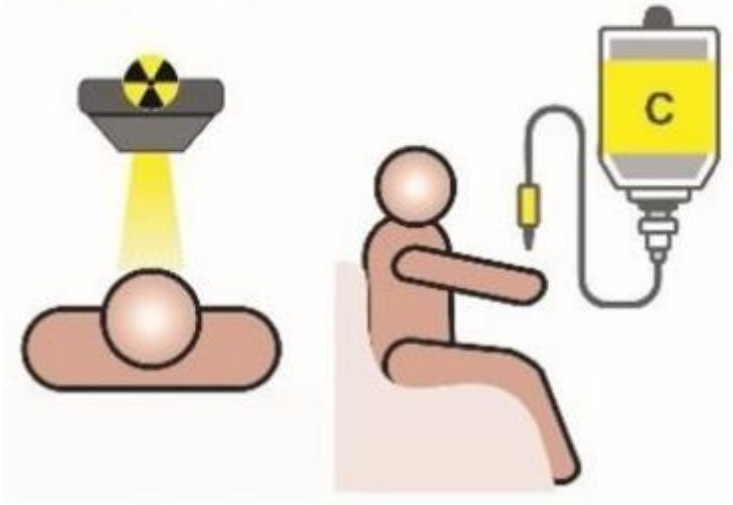
- 39-year-old previously healthy man presents with **60lb weight loss** over previous 5 months with associated night sweats/fevers
- He is found to have an **oropharyngeal mass with cervical LAD**
- Initially biopsies were inconclusive but repeat core biopsy revealed rare **EBV/CD56+ cells consistent with EBV+ extranodal NK/T cell lymphoma.** CD3, CD30, MUM1 positive, CD56, EBER positive. CD5 negative
- PET/CT revealed **stage IIE** disease
- Bone marrow biopsy shows no involvement

Extra nodal NK/T cell lymphoma, nasal type









Sanchez-Romero et al, *Critical review in oncology/hematology* 2021

Extra nodal NK/T cell lymphoma, nasal type

Prognostic Index of Natural Killer Lymphoma (PINK)	Prognostic Index of Natural Killer Cell Lymphoma with EBV DNA (PINK-E)
• Age > 60 years • Stage III or IV Disease • Distant Lymph-Node Involvement • Non-Nasal Type Disease	• Age > 60 years • Stage III or IV Disease • Distant Lymph-Node Involvement • Non-Nasal Type Disease • Epstein-Barr Virus DNA
Low Risk: 0 Risk Factors **Intermediate Risk**: 1 Risk Factors **High Risk**: 2 Risk Factors	**Low Risk**: 0-1 Risk Factors **Intermediate Risk**: 2 Risk Factors **High Risk**: ≥ 3 Risk Factors

Sanchez-Romero et al, *Critical review in oncology/hematology* 2021

How would you treat this patient with localized extra nodal NK/T cell lymphoma?

A. Combination RT + DeVIC

B. Modified SMILE

C. P-GEMOX +/- RT

D. DDGP +/- RT

E. Sandwich chemoradiation: GELAD x 2 cycles followed by RT x 2 cycles

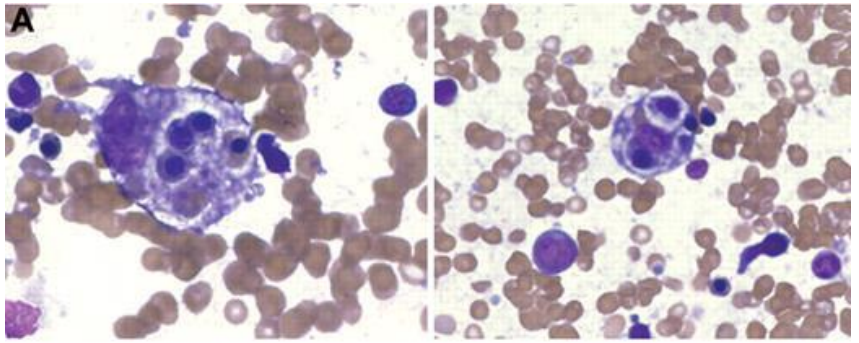
Case #4

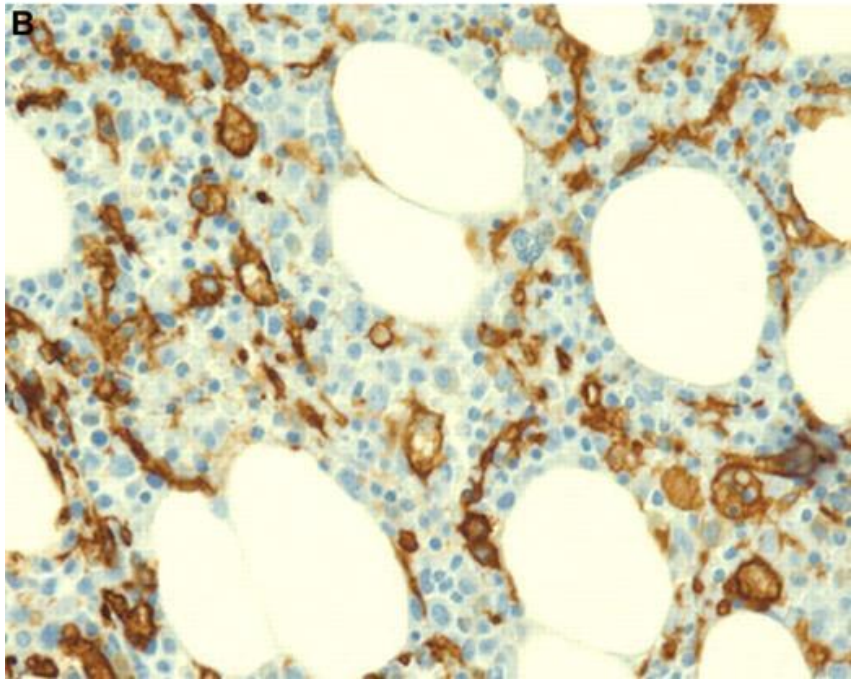
- He was treated with **DeVIC x 3 cycles + RT in 25 fractions**
- He was determined to be in **remission** by imaging and EBV quantitative PCR
- 1 month later, he was admitted to OSH for **fevers**, **pancytopenia**, **hepatosplenomegaly**, **transaminitis** with notable **ferritin 35,000** and **soluble IL2 1500** (nml range 158-623 U/mL)
- Bone marrow biopsy with **hemophagoctyosis** and no evidence of lymphoma

Hemophagocytic Lymphohistiocytosis

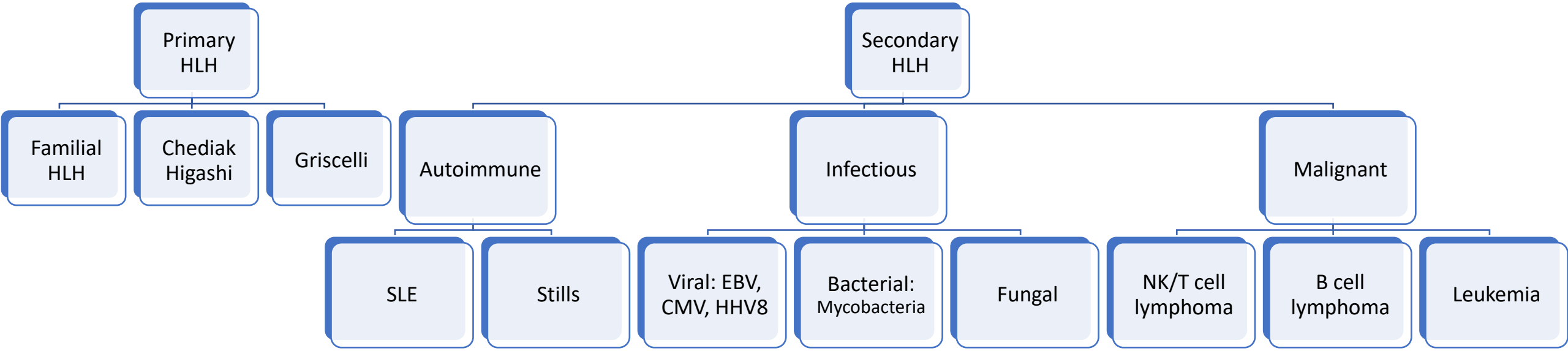
Diagnostic Criteria

A. Molecular diagnosis consistent with HLH: pathologic mutations of PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, or BIRC4
or
B. Five of the 8 criteria listed below are fulfilled:
1. Fever ≥ 38.5°C
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood)
Hemoglobin < 9 g/dL (in infants < 4 weeks: hemoglobin < 10 g/dL)
Platelets < 100×10^3/mL
Neutrophils < 1×10^3/mL
4. Hypertriglyceridemia (> 265 mg/dL) and/or hypofibrinogenemia (< 150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
6. Low or absent NK-cell activity
7. Ferritin > 500 ng/mL‡
8. Elevated sCD25 (α-chain of sIL-2 receptor)





Hemophagocytic Lymphohistiocytosis



Jordan et al. *Blood* 2011

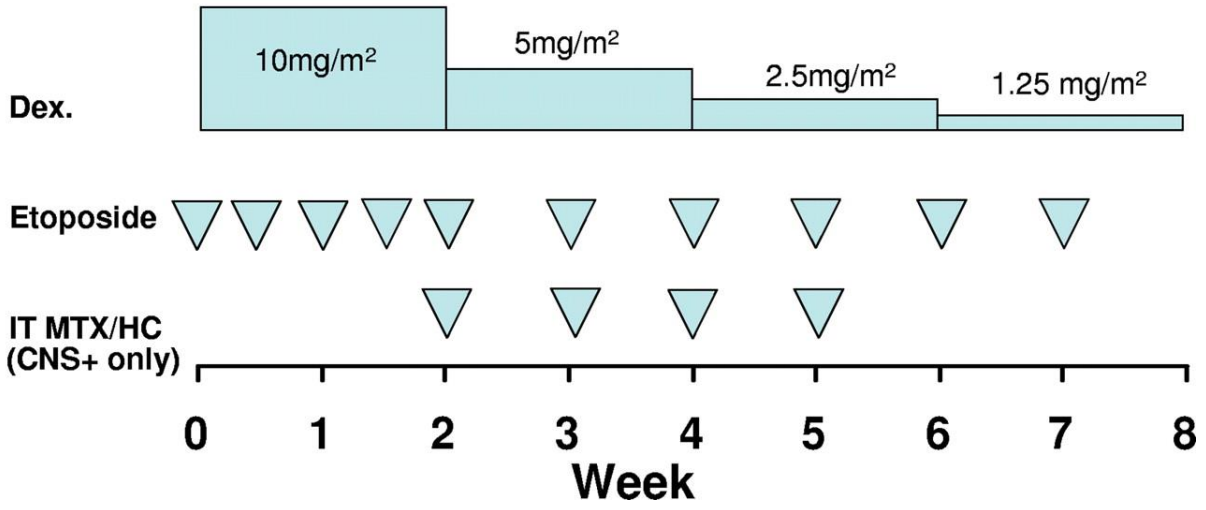
Targeted Genes to Test for Familial/Primary HLH

ADA	*AP3B1*	*AP3D1*	*BLOC1S6*	*CD27*
CD70	*CDC42*	*CORO1A*	*CTPS1*	*IFNAR2*
ITK	*LYST*	*MAGT1*	*MVK*	*NLRC4*
PRF1	*RAB27A*	*SH2D1A*	*SLC7A7*	*STX11*
	STXBP2	*UNC13D*	*XIAP*	

Jordan et al. *Blood* 2011

Hemophagocytic Lymphohistiocytosis (HLH)

HLH-94



HLH-2004

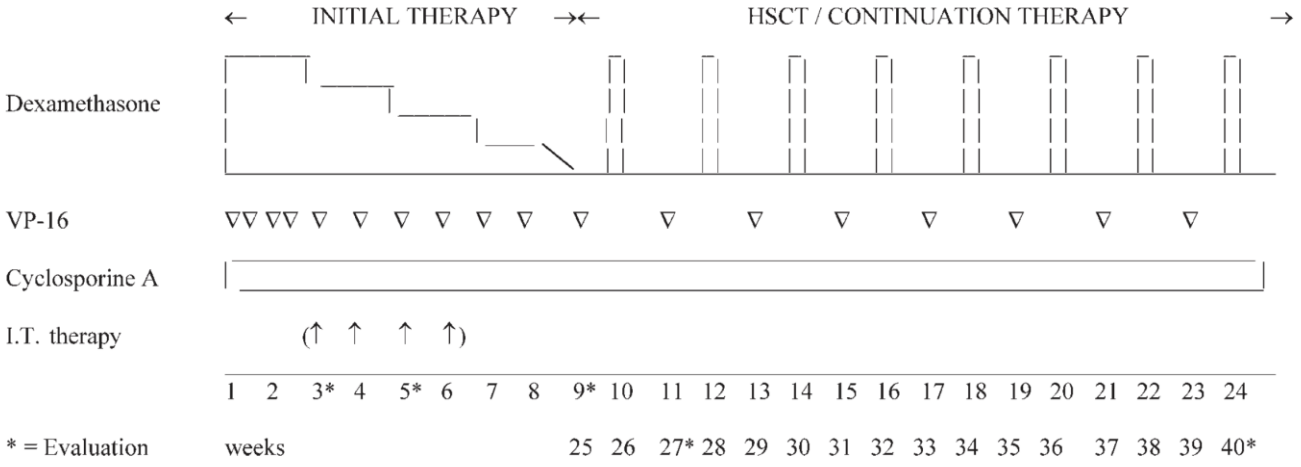


Fig. 2. Schematic treatment overview of the HLH-2004 protocol. For information on whether to start continuation therapy and perform stem-cell transplantation, see text and Figure 1. The complete protocol is available for request at www.histio.org/society/protocols. (VP-16 = etoposide, I.T. therapy = intrathecal methotrexate and corticosteroids, HSCT = hematopoietic stem cell transplantation.)

Henter et al, *Med Pediatr Oncol* 1997
Henter et al, *Pediatr Blood Cancer Pediatric blood & cancer* 2007

Case #4

- CT chest/abd/pelv: Few prominent loops of small bowel. Nondistended colon with liquid stool. Findings may represent early **enterocolitis** in appropriate clinical setting. PEG in place
- CT sinus: Bilateral maxillary sinus inflammatory changes which result in narrowing of the left ostiomeatal unit. Bilateral mastoid effusions
- **EBV PCR positive** at this time.
- He was started on **HLH-94 protocol**

Case #4

- After cycle 7 of etoposide, he presented to OSH for **neutropenic fever**
- **ANC: 310; Hgb: 6.5; Plts: 37**; **AST/ALT ~100**
- **Ferritin 17,000**
- **EBV viral load 2,577**
- Found to have colitis and ultimately transferred to UCSF for further management

How would you treat this patient?

A. PET/CT and repeat bone marrow biopsy to look for lymphoma recurrence

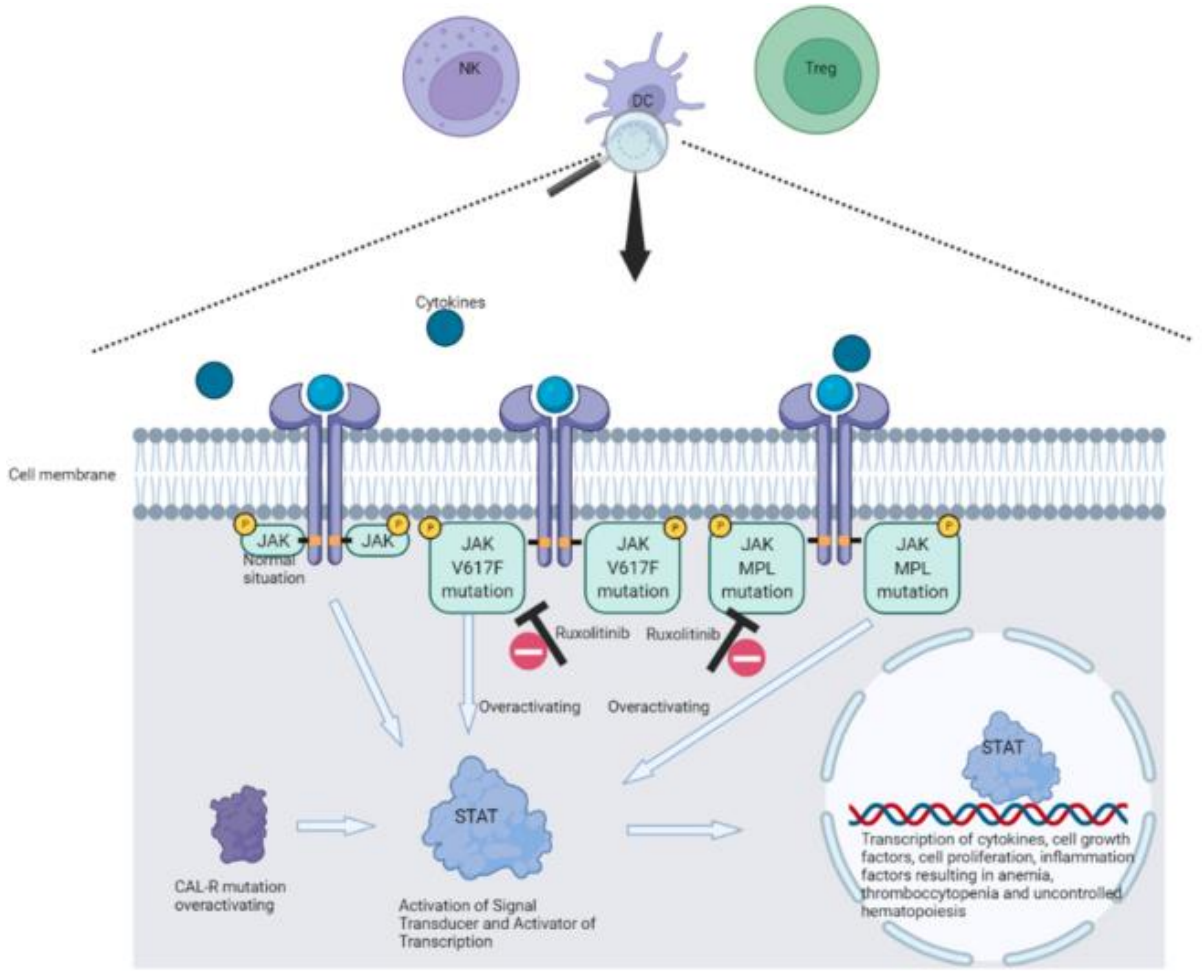
B. Perform genetic testing for primary HLH

C. Refer for allogeneic stem cell transplant

A. Add ruxolitinib

B. Add anakinra

Refractory HLH: Ruxolitinib



Lee and Logan. *Cancers*, 2023

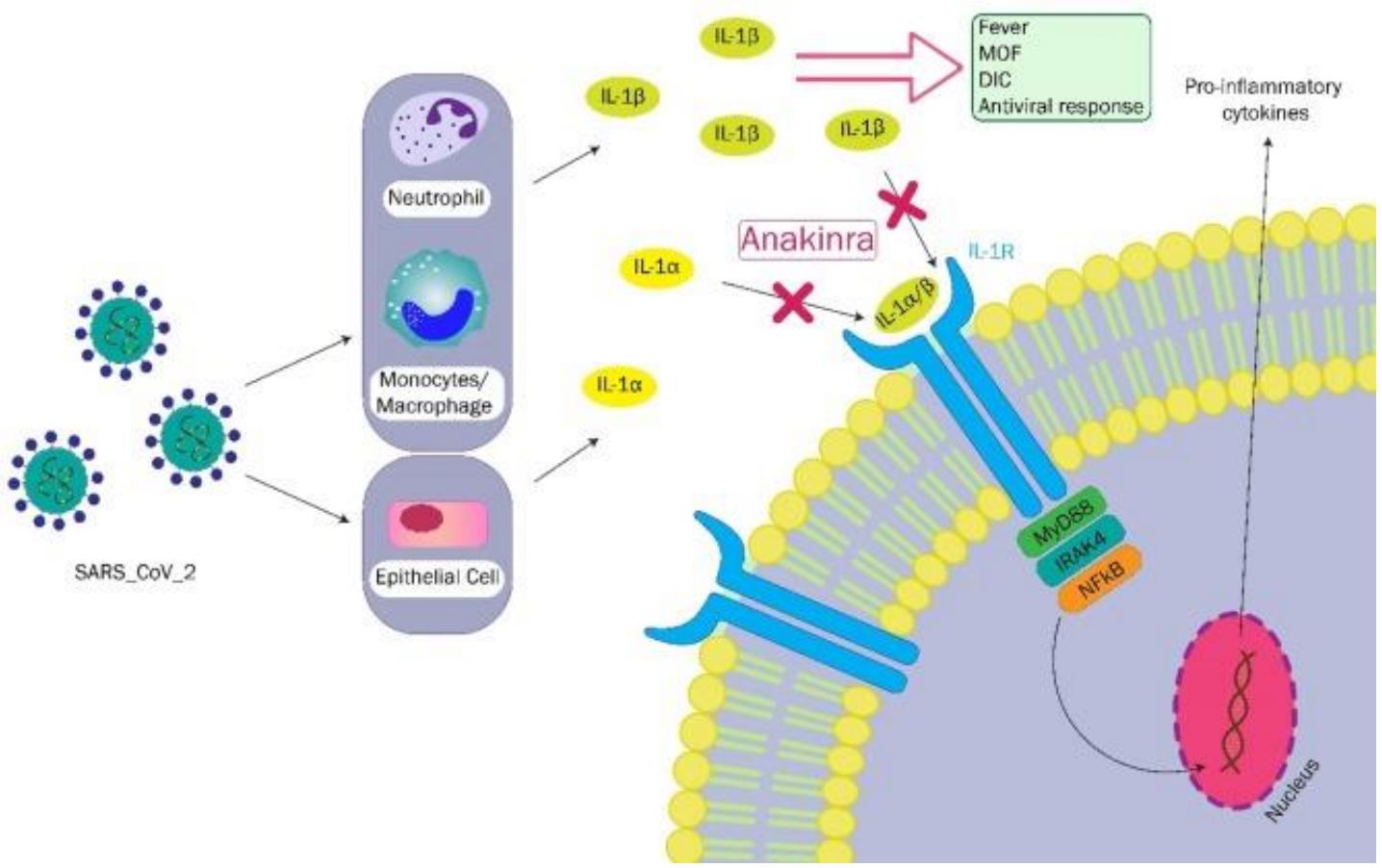
Refractory HLH: Ruxolitinib

Table 3. Publications on Ruxolitinib for the Treatment of Adults with mHLH.

Reference	N	Mean Age (Range)	HLH Type	New or R/R HLH	Target Rux Dose (BID)	Rux Duration	HLH Therapy	Response	OS * (f/u if Known)
Boonstra 2021 [84]	1	70	R/R Hodgkin; EBV viremia	New	15 mg	1.5 m	Rux	PR	100%
Hansen 2021 [85]	1	33	SPTL	R/R	15 mg	11 m	Dex/Etop –> Cy, Doxo, Vin, Pred –>Rux, Etop, IVIG +Alem	CR	100% (1 y)
Stalder 2023 [86]	6	52 y (34–72 y)	AML	New	10 mg	31–122 d	Dex, Etop, Rux, induction chemo	CR (83%), PR (17%)	33% (120 d)
Trantham 2020 [87]	2	66 y, 24 y	Suspected Hodgkin DLBCL	R/R	10 mg 15 mg	~6 m ~25 d	Dex/Etop –> Benda/Brentux –> Rux –> Alem/Anakinra R-EPOCH x3 –> R-CHOP x3 –> Rux, HD MTX, AraC, IT –> R-GCD –> R-ICE –> Alem/Dex	CR (100%)	0% (1 y, 14.5 m)
J Wang 2021 [88]	3	27 y, 28 y, 66 y	B cell lymphoma	R/R	10 mg	NR	HLH94 –> Rux, Doxo (lipo), Etop, Methylpred –> chemo –> HCT	NR	NR
H Wang 2020 [89]	2	24 y, 45 y	EBV+ NK cell leukemia Relapsed PTL	New	5 mg	~5 w	Dex/Etop, PLEX, Rux, Gem/Ox/Peg –> Pred Dex/Etop/Rux –> Gem/Ox/Peg	?CR (100%)	0% (~2 m?)
Zhou 2020 [90]	36	44.7 y (31–58 y)	Lymphoma	New	0.3 mg/kg daily	14 d	Dex/Etop/Rux/Doxo –> chemo	CR (28%), PR (56%)	39% (5 m)

Lee and Logan. *Cancers*, 2023

Refractory HLH: Anakinra



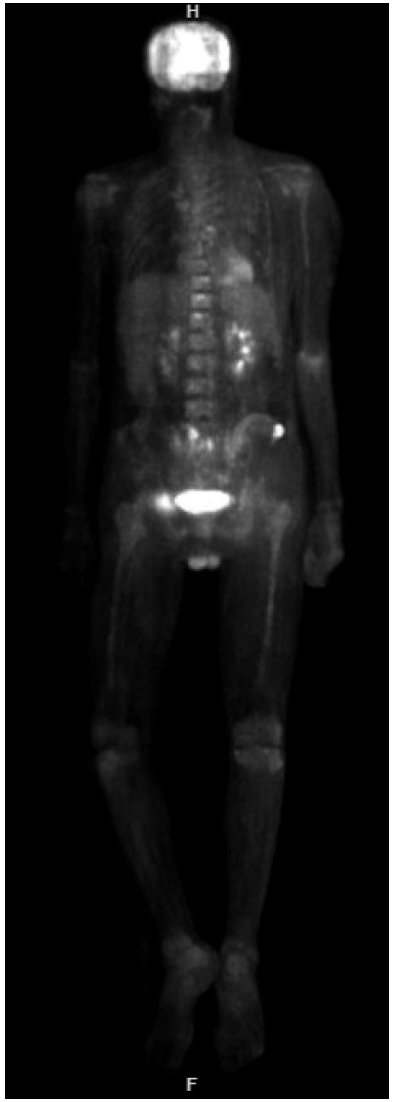
21 Case Reports:

- 10 patients first line therapy
- 5 patients as monotherapy
- Effective in 19/21 patients (90.5%)
- Fever resolution in 19 patients (90.5%) within a median of 1.0 day

Lee and Logan. *Cancers*, 2023
Bavarez *J Clin Med*, 2022

Case #4

- PET/CT revealed: **multiple sites of focal osseous hypermetabolism** in the pelvis and spine with variable degrees of confidence. **Deauville 5** if lymphoma
- Biopsy of bone lesion reveals **recurrent NK/T cell lymphoma**
- Bone marrow biopsy shows **NK/T cell involvement**



How would you treat this patient with recurrent stage IVE extra nodal NK/T cell lymphoma?

A. Modified SMILE

B. P-GEMOX +/- RT

C. Allo-HCT

D. Pembrolizumab or nivolumab

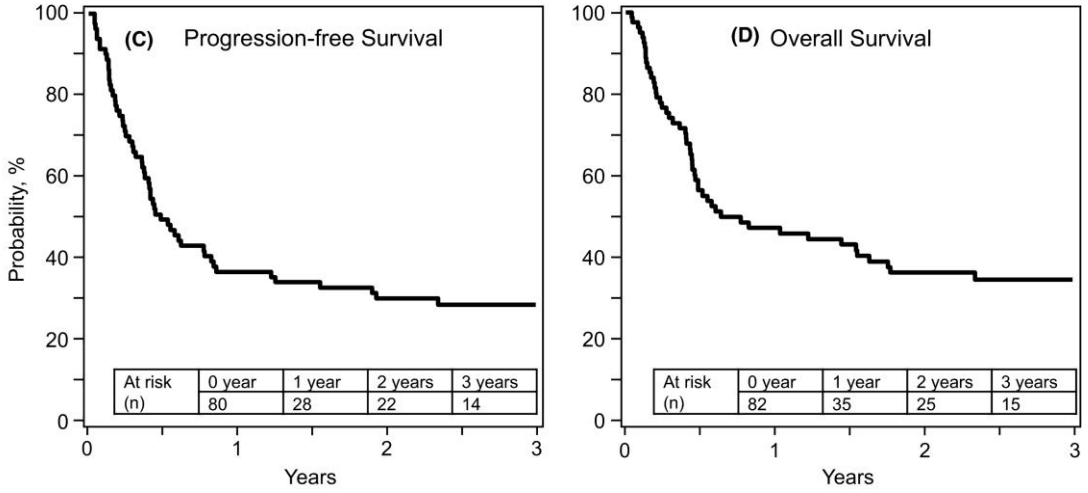
For advanced stage disease: combination chemotherapy with L-asparaginase is used

SMILE Regimen	L-Asparaginase / Methotrexate / Dexamethasone Regimen
In younger patients with better performance status	In older patients or those with lesser performance status
• Methotrexate 2 g/m^2 IV (6 hours) on Day 1 • Leucovorin 15 mg x4 IV or PO on Days 2, 3, 4 • Ifosfamide 1500 mg/m^2 IV on Days 2, 3, 4 • Mesna 300 mg/m^2 x3 IV on Days 2, 3, 4 • Dexamethasone 40 mg/day IV or PO on Days 2, 3, 4 • Etoposide 100 mg/m^2 IV on Days 2, 3, 4 • L-Asparaginase (*Escherichia coli*) 6000 U/m^2 IV on Days 8, 10, 12 ,14, 16, 18, 20 • G-CSF SubQ or IV starting on Day 6 until WBC > 5000/µL	• L-Asparaginase (*Escherichia coli*) 6000 U/m^2 IM on Days 2, 3, 6, and 8 • Methotrexate 3g/m^2 IV on Day 1 • Dexamethasone 40 mg x4 on Days 1, 2, 3, 4

There may be a role for allogenic stem cell transplant for patients who are chemo responsive

Kanate *et al*. 2018:

- 82 patients
- Included patients in CR (45%), PR (30%), or refractory disease (12%) at time of AlloHSCT.
- At median follow up of 36 months:
  - 3-Year PFS: 28%
  - 3-Year OS: 34%

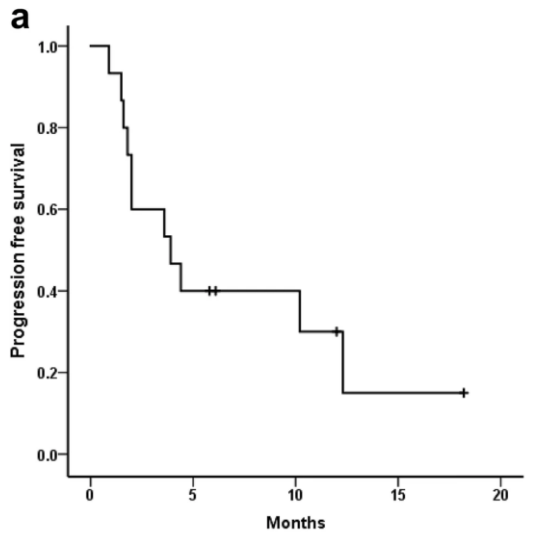


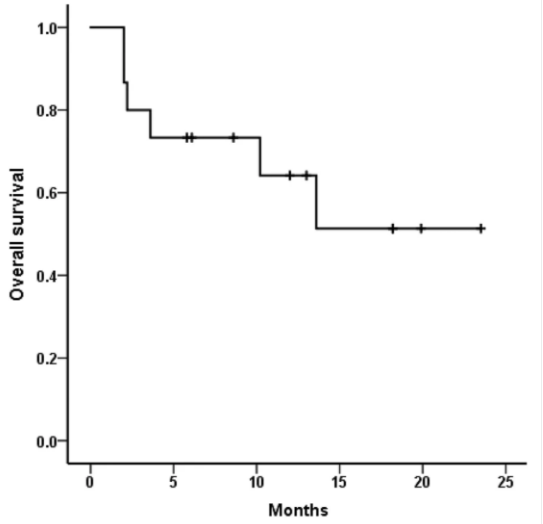
Kanate et al, *Br J Haematol* 2018

Novel CAR-T cell product for ENKTL

Baltaleucel-T (CMD-003): autologous EBV-specific T-Cell product

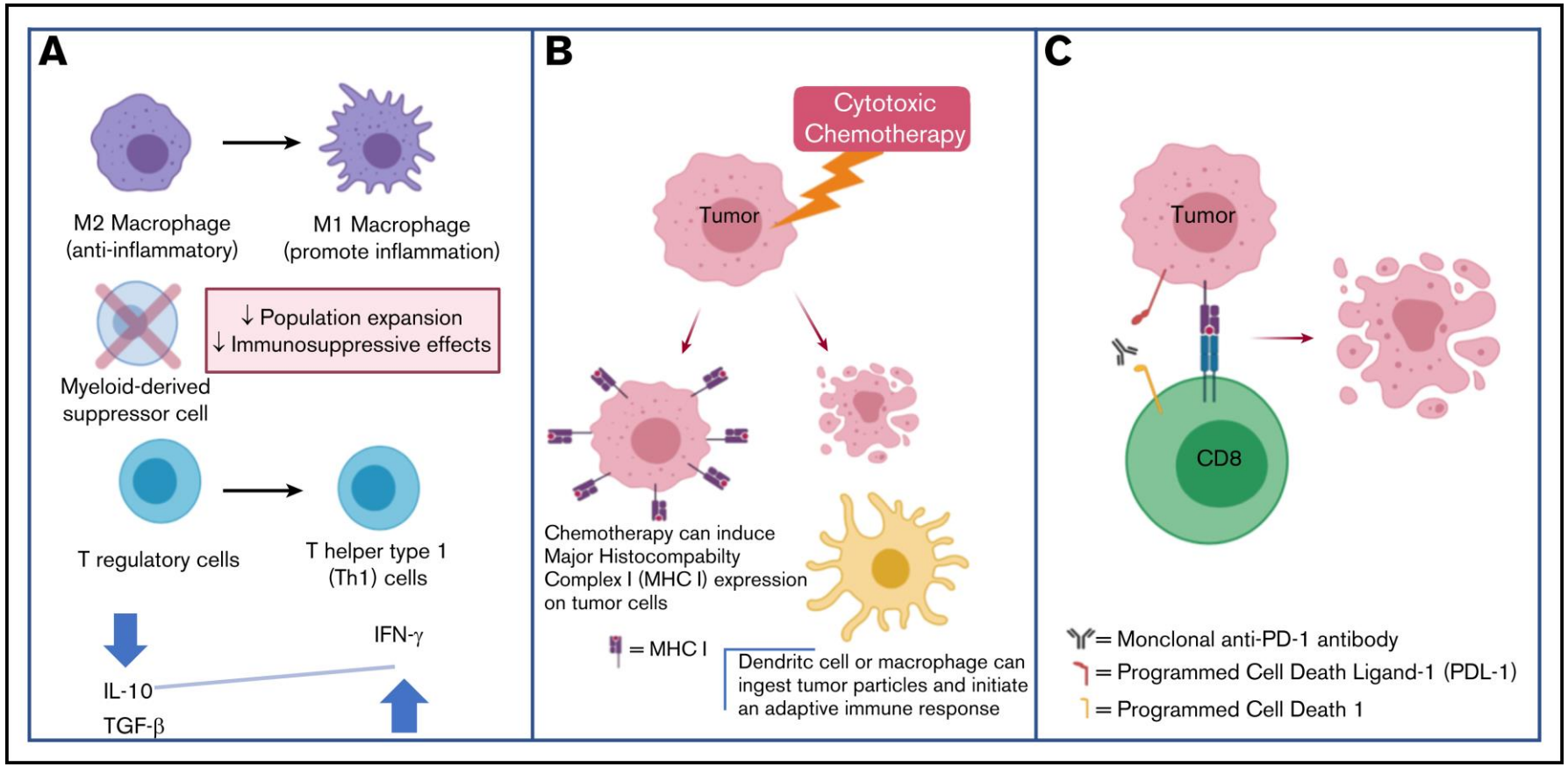
- Bridging chemotherapy allowed. All chemotherapy stopped 2 weeks prior to baltaleucel-T infusion.
- Two Cohorts:
  - Salvage: 10 of 15 patients with measurable disease on PET/CT
  - Adjuvant: 5 of 15 patients without measurable disease on PET/CT





Kim et al, Annals of Hematology 2021

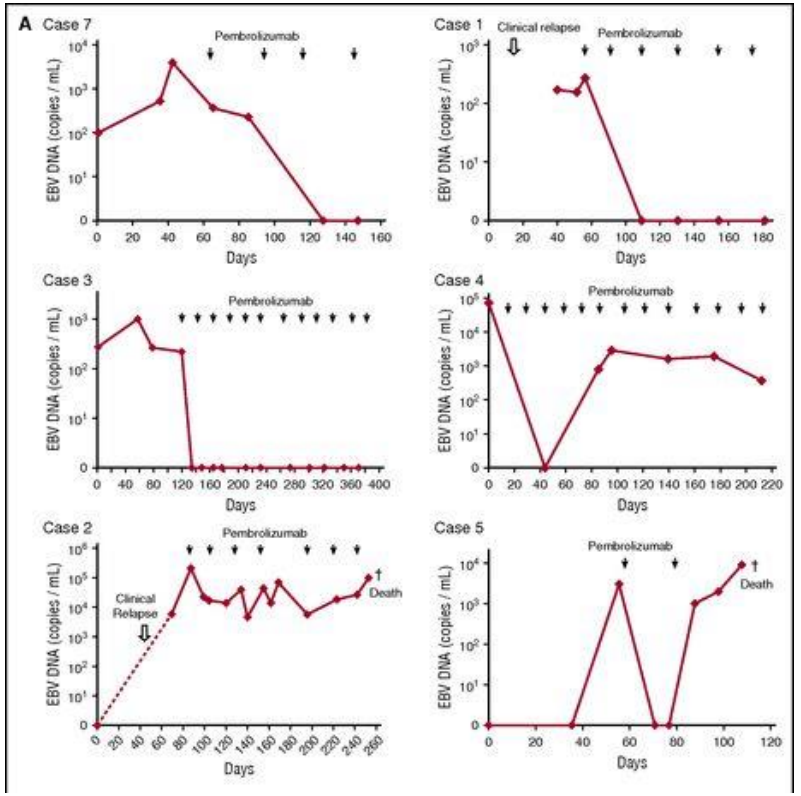
Check Point Inhibitors in ENKTL



Newalt, Blood Adv 2020

Check Point Inhibitors in ENKTL

- **Pembrolizumab**
  - 7 patients
  - Median of 7 cycles pembrolizumab administered.
  - All 7 patients achieved some type of objective response.
  - 2 patients achieved CR
  - 2 patients achieved clinical and radiologic CR,
    - 2 having molecular remission (undetectable EBV DNA).



Kwong et al, *Blood* 2017

Case #4: Conclusion

- The patient was started on **SMILE chemotherapy**
- His course was complicated by **neutropenic enterocolitis**
- Unfortunately, the patient had progressive fevers and encephalopathy and was transferred to the ICU for intubation
- He soon developed **DIC leading to renal failure and ultimately expired in the ICU**

Case #4 – Key Points

- Hemophagocytic Lymphohistiocytosis (HLH) is a clinical syndrome that is most often triggered by underlying malignancy and/or infection
  - Primary HLH is rare and genetic testing can be sent to aid in diagnosis
    - Primary HLH is treated with HLH-94 protocol
  - Secondary HLH is treated by treating the underlying cause
    - A thorough workup for lymphoma including PET/CT should always be performed
  - Primary HLH can be treated with HLH-94, but 50% of patients are refractory to treatment
    - Evidence is emerging for the use of ruxolitinib and anakinra in the refractory setting

Case #4 – Key Points

- NK/T cell lymphoma is an aggressive non-Hodgkin's lymphoma that can be treated with RT and chemotherapy in early stage
  - All patients should receive a PET/CT and bone marrow biopsy for appropriate staging
  - EBV viremia can be used to track MRD

- Transplant could be considered for patients achieving a CR

- Check point inhibitors can be used in the R/R setting