Case discussion: Sequencing therapies

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March 2024

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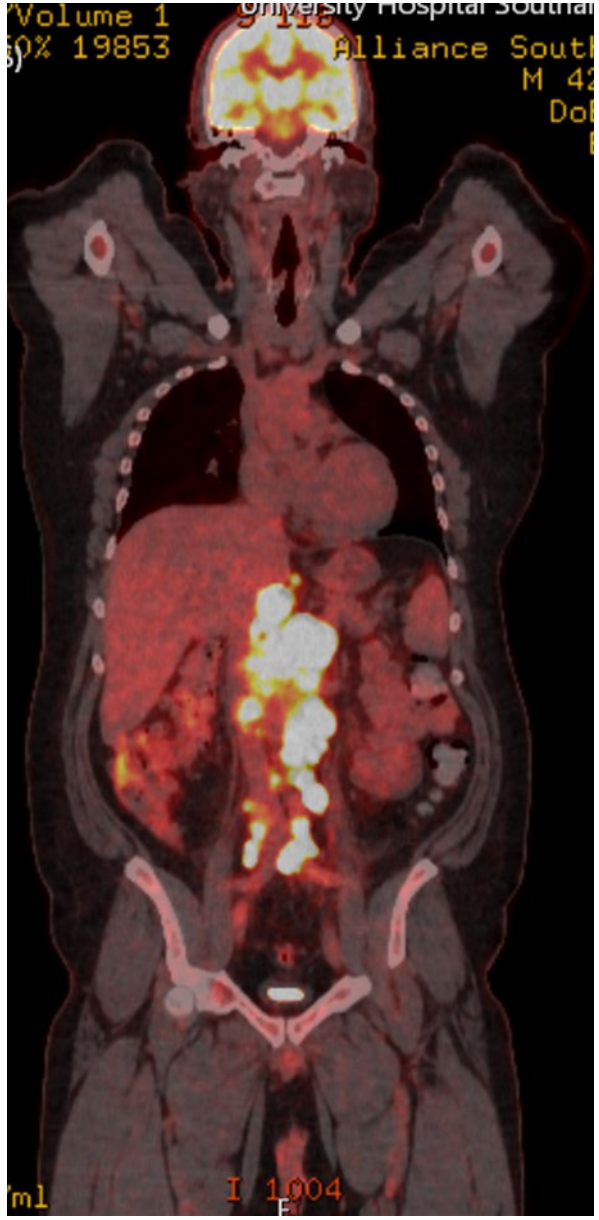
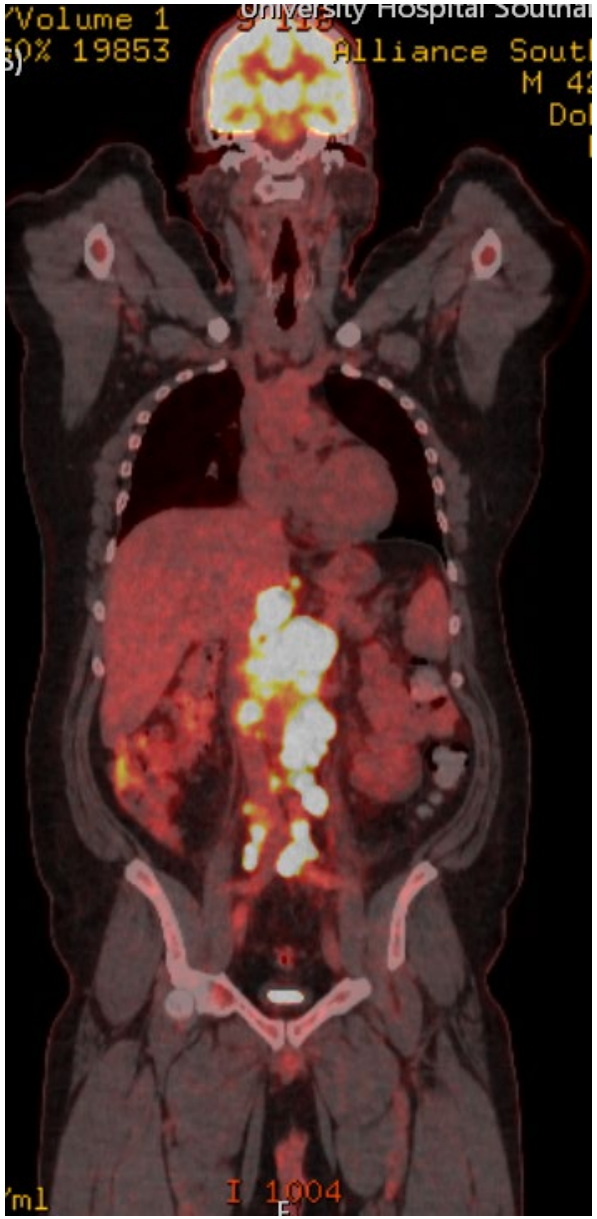
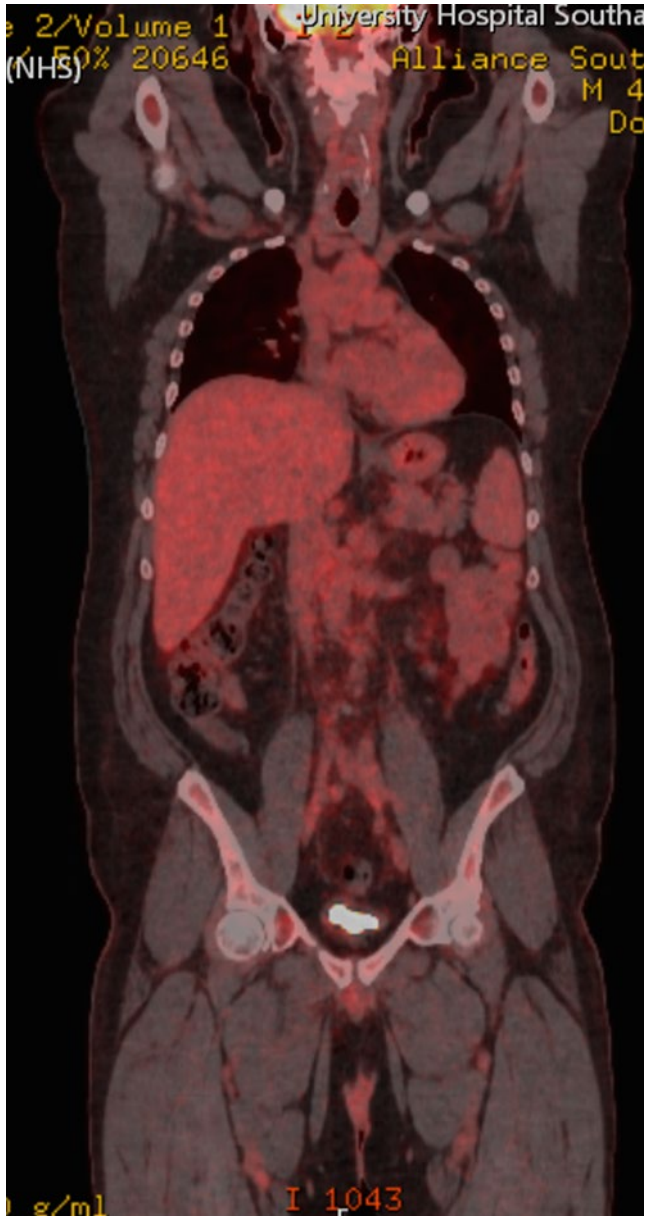
47 year old male

Feb 2017:

- Pharmacist. Presents with abdominal pain, weight loss and night sweats
- CT: Para aortic lymphadenopathy and mesentery. Spleen homogenous, 16cm. Mediastinal and hilar lymph nodes. Pulmonary lesions
- FBC: Mild normochromic normocytic anaemia
- Biochemistry: LDH 2243 (upper limit of normal 420). Normal renal functions
- IVB DLBCL (NOS) GC phenotype. Ki67 80-90%
- *MYC*-R and *BCL2*-R: DHL
- IPI 3/5.







DA EPOCH-R

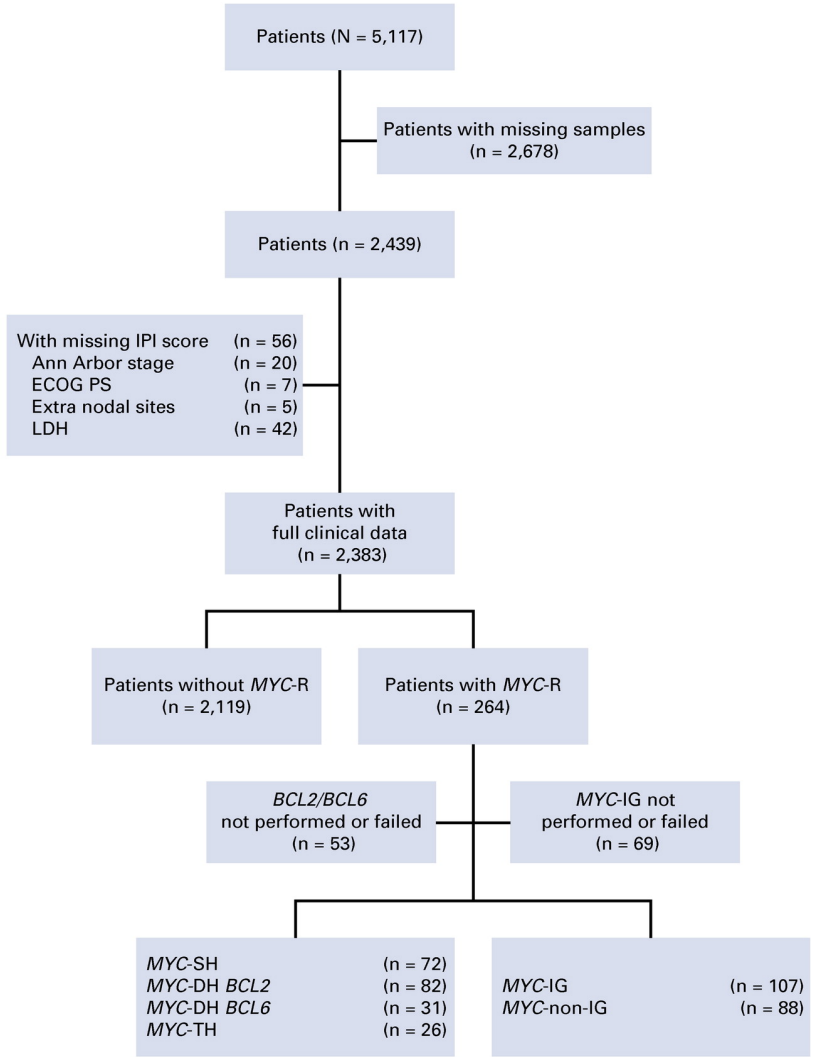
Interim PET (April 2017)

DS=2 [complete metabolic response]

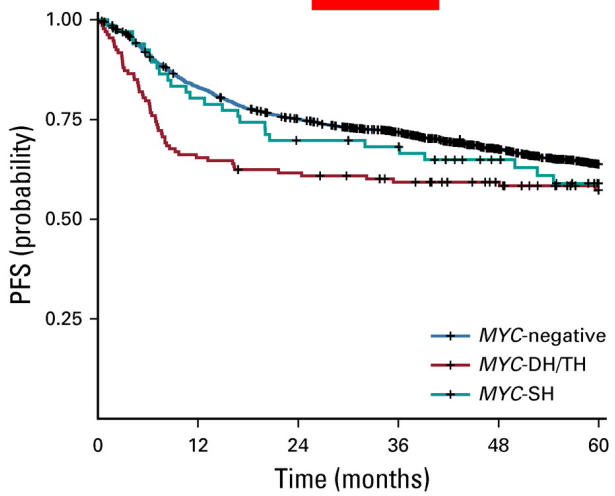
Grade 1 sensory peripheral neuropathy after cycle 2. Declined escalation of agents [vincristine not escalated in DA-EPOCH-R]

[decision]

FISH and DLBCL prognosis



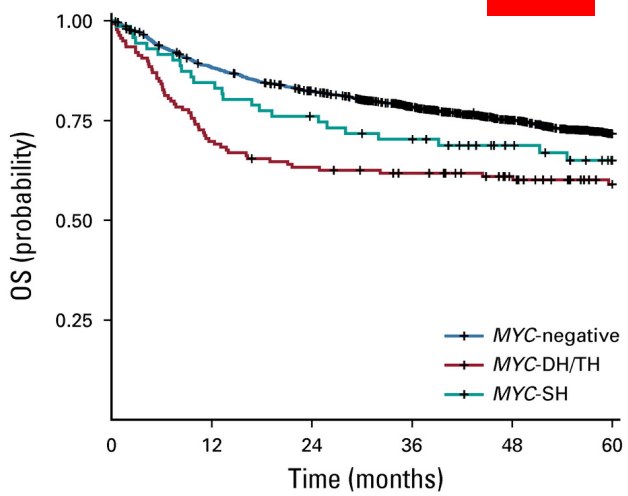
PFS



No. at risk:

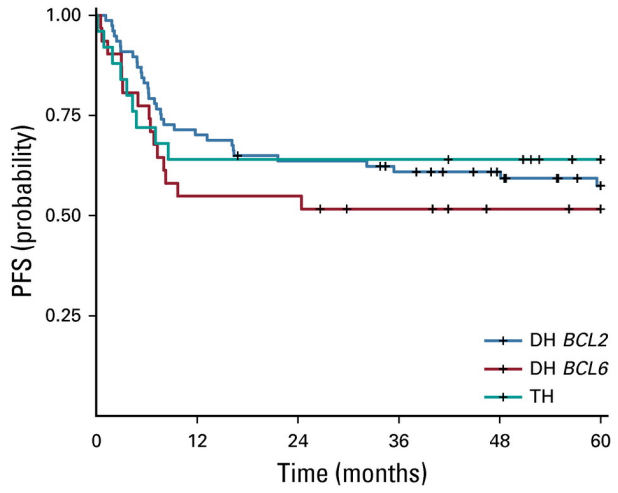
MYC-negative	2,049	1,687	1,508	1,371	1,173	949
MYC-DH/TH	133	87	81	74	64	52
MYC-SH	67	53	45	43	34	25

OS



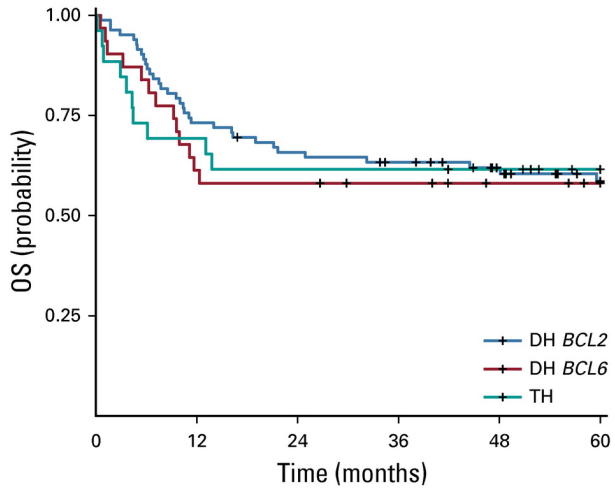
No. at risk:

MYC-negative	2,119	1,858	1,716	1,556	1,353	1,106
MYC-DH/TH	139	97	87	81	69	54
MYC-SH	72	60	53	48	38	29



No. at risk:

DH *BCL2*	77	54	48	44	38	31
DH *BCL6*	31	17	17	14	11	10
TH	25	16	16	16	15	11



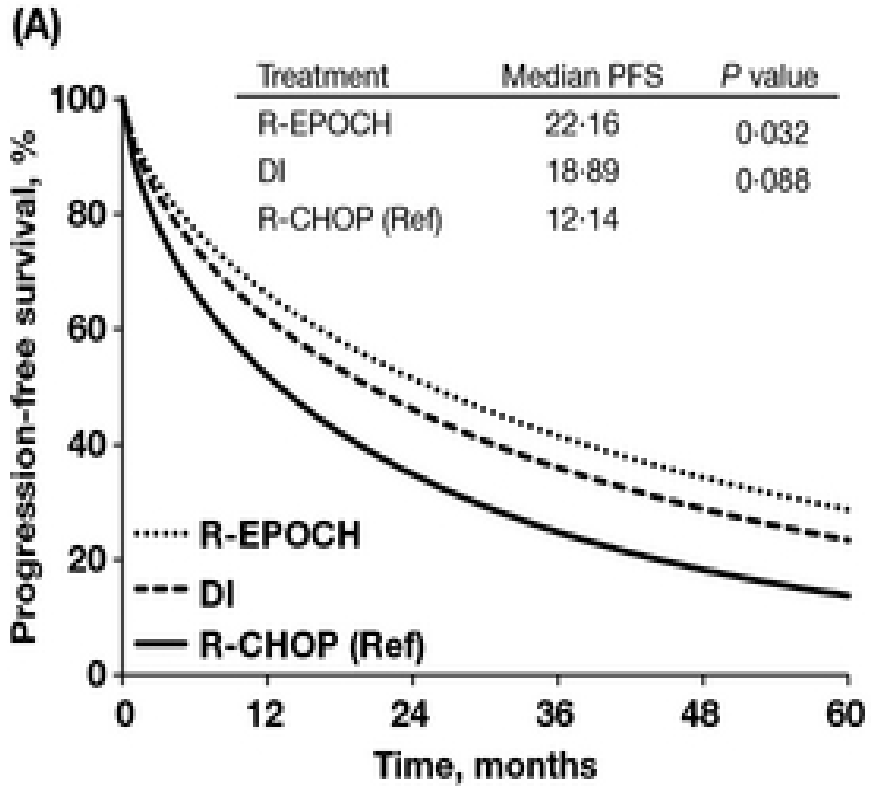
No. at risk:

DH *BCL2*	82	60	53	49	41	32
DH *BCL6*	31	19	18	16	13	11
TH	26	18	16	16	15	11

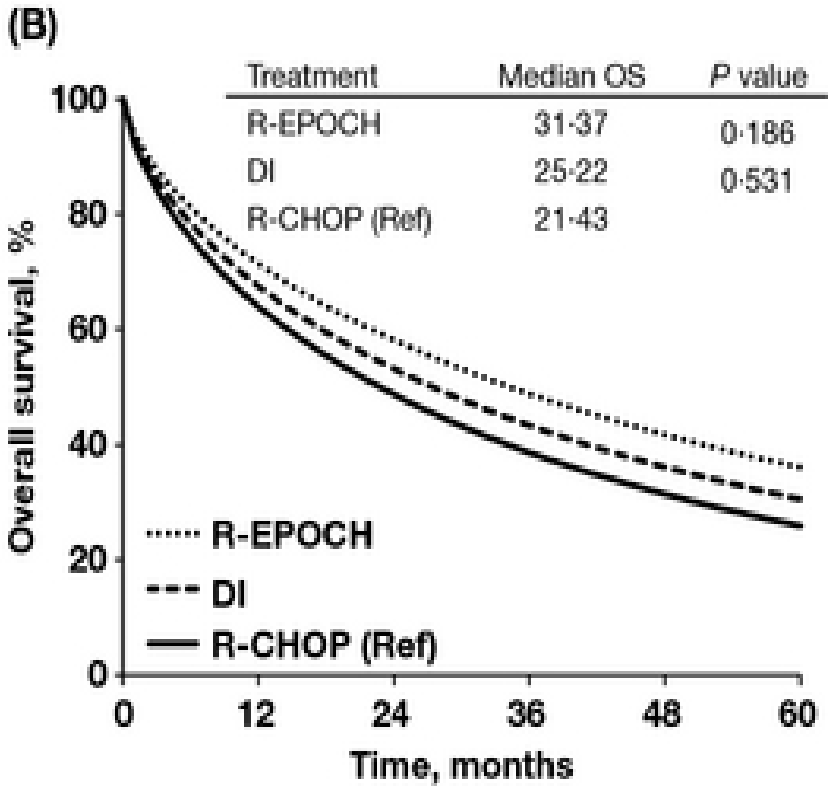
Rosenwald et al JCO 2019 on behalf of the LLBC

Meta-analysis (Howlett et al. BJH 2015)

394 patients (11 studies)
R-CHOP =180; DA-EPOC-R=91; DI=123

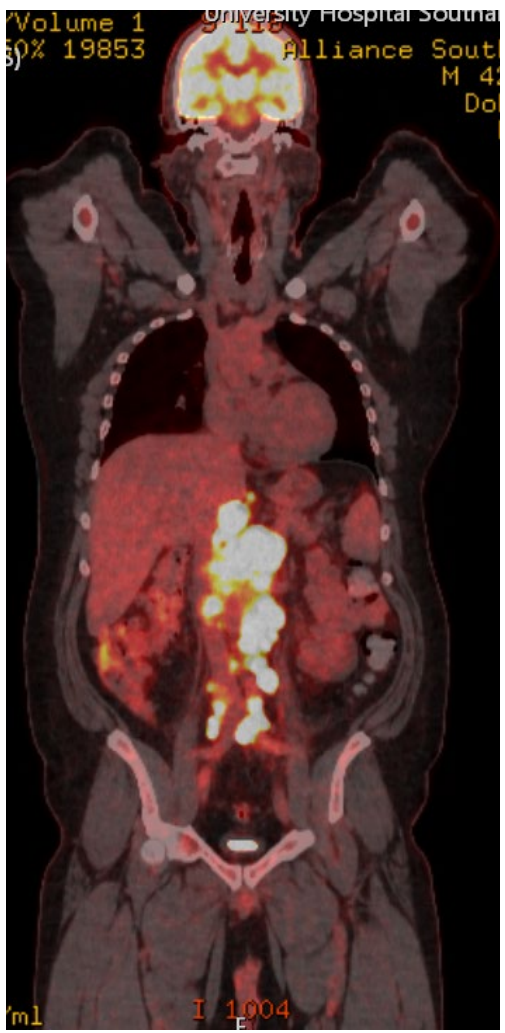


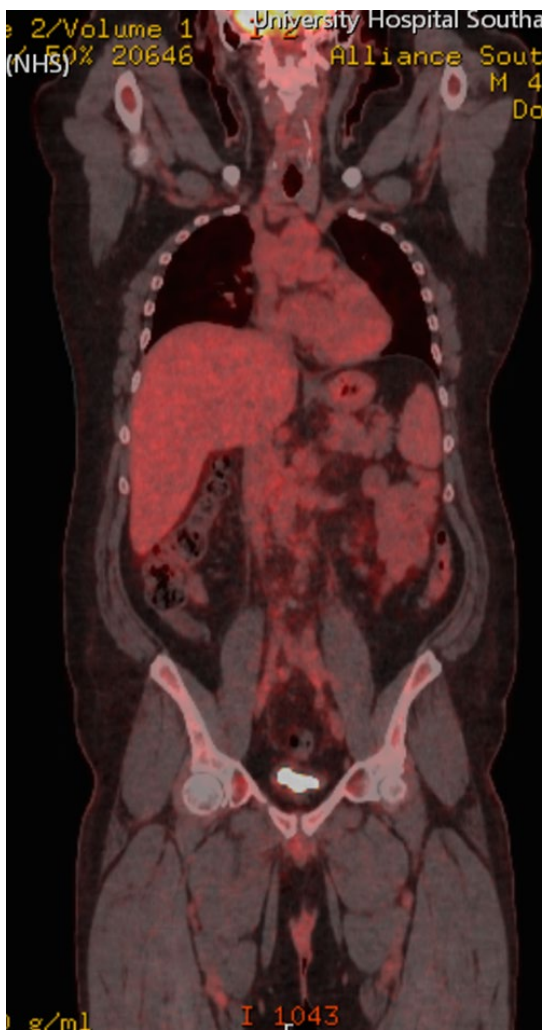
PFS

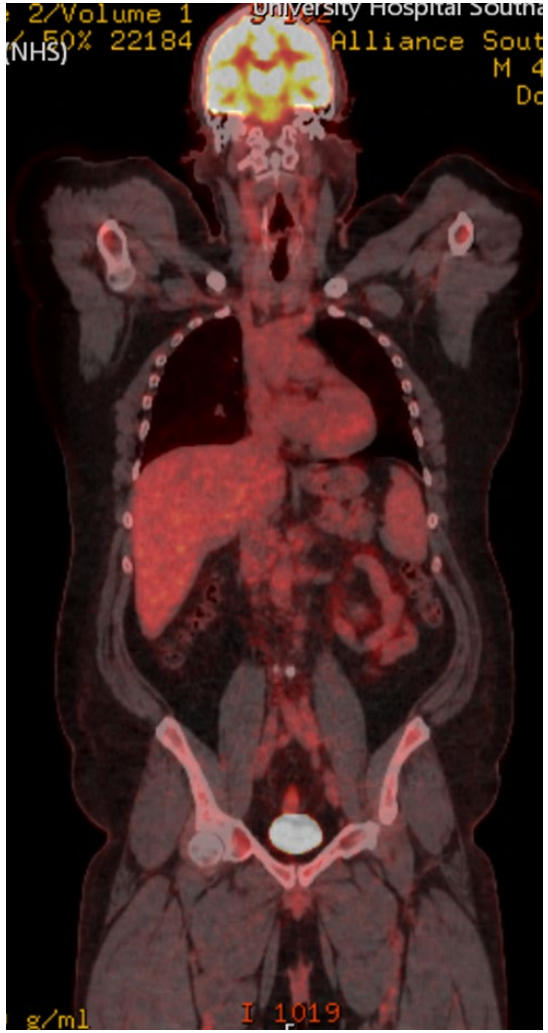


OS

- Only 2 of 11 studies provided IPD
- No clarity in baseline prognostic variables
- 40% of data from congress reports with no formal publication
- No stratification according to transplantation consolidation







Baseline

Interim
DA-EPOCH-R #2

EOT
DA-EPOCH-R #6

EOT (Jun 2017)

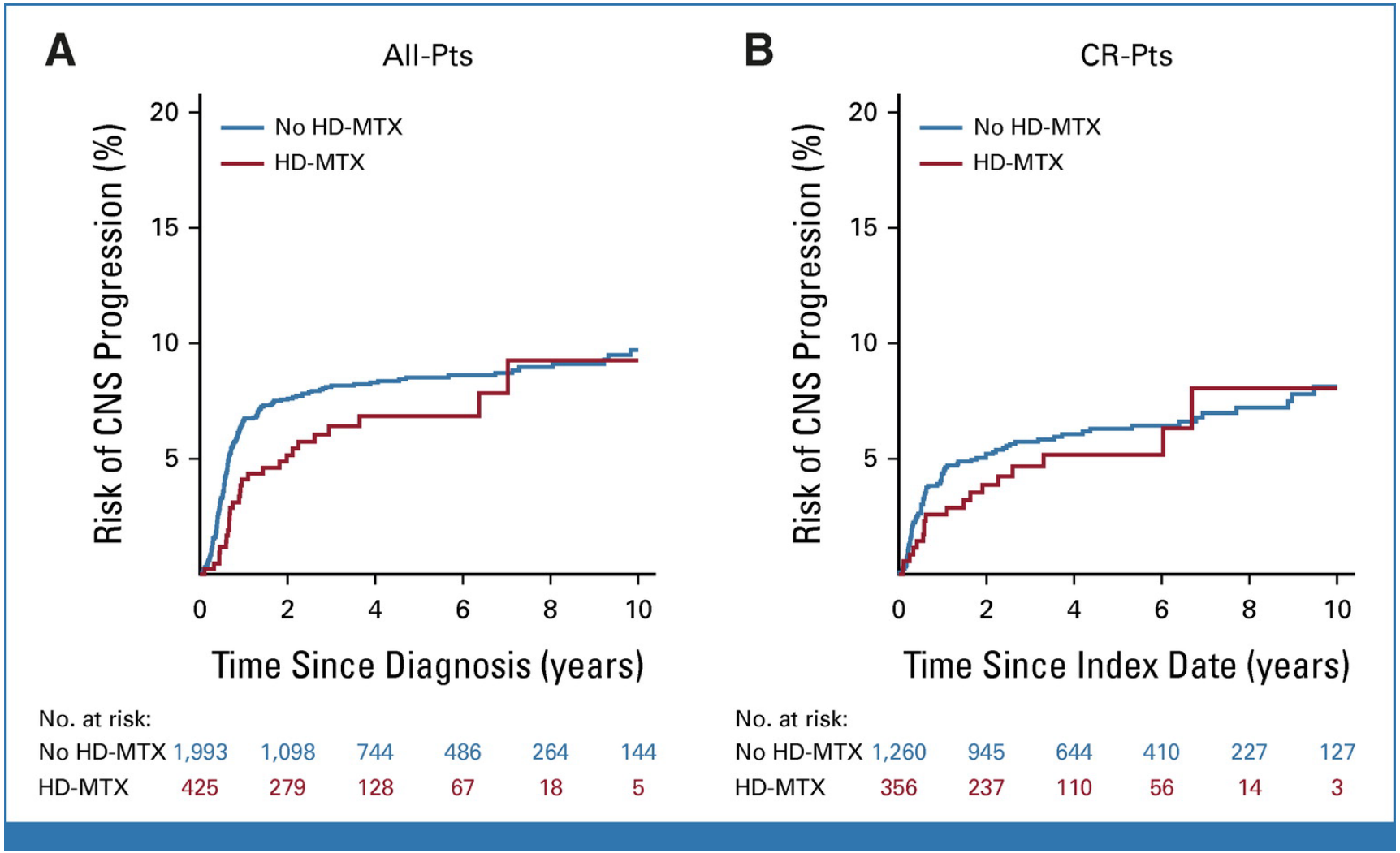
CMR

Given IV MTX prophylaxis x2

[decision]

Large retrospective cohort: Anthracycline/rituximab(n>2500; 1600 in CR)

5-year cumulative CNS progression risk was 7.4% (95% CI, 5.9 to 8.9)



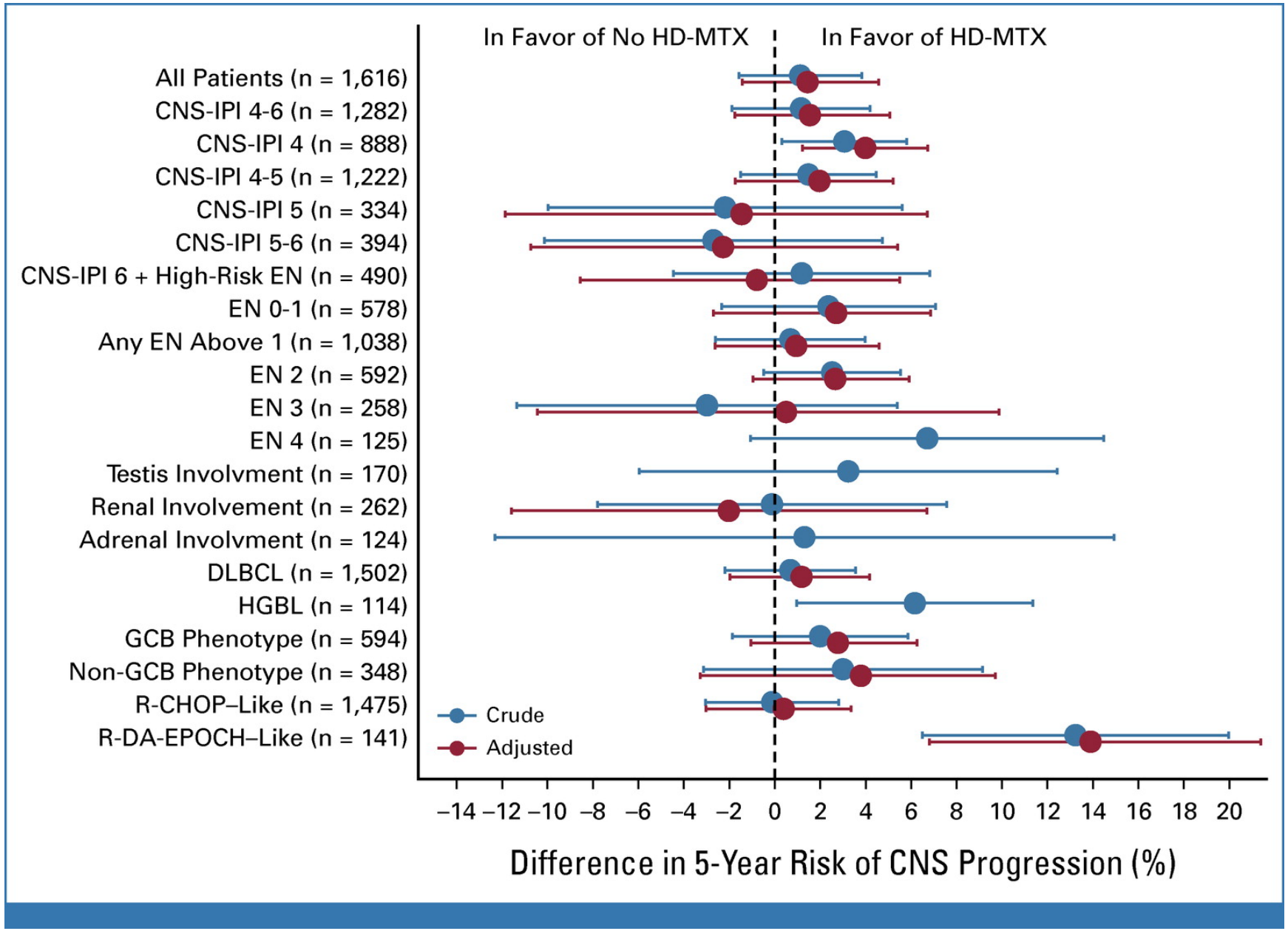
- no difference

in 5-year adjusted risk of CNS progression between HD-MTX and no HD-MTX groups; 5.0% versus 6.5% (adjusted risk difference, 1.4% [95% CI, –1.5 to 4.1]

- absolute risk reduction of 1.6% with HD-MTX,

63 patients would need to be treated to prevent one CNS progression event over 5 years

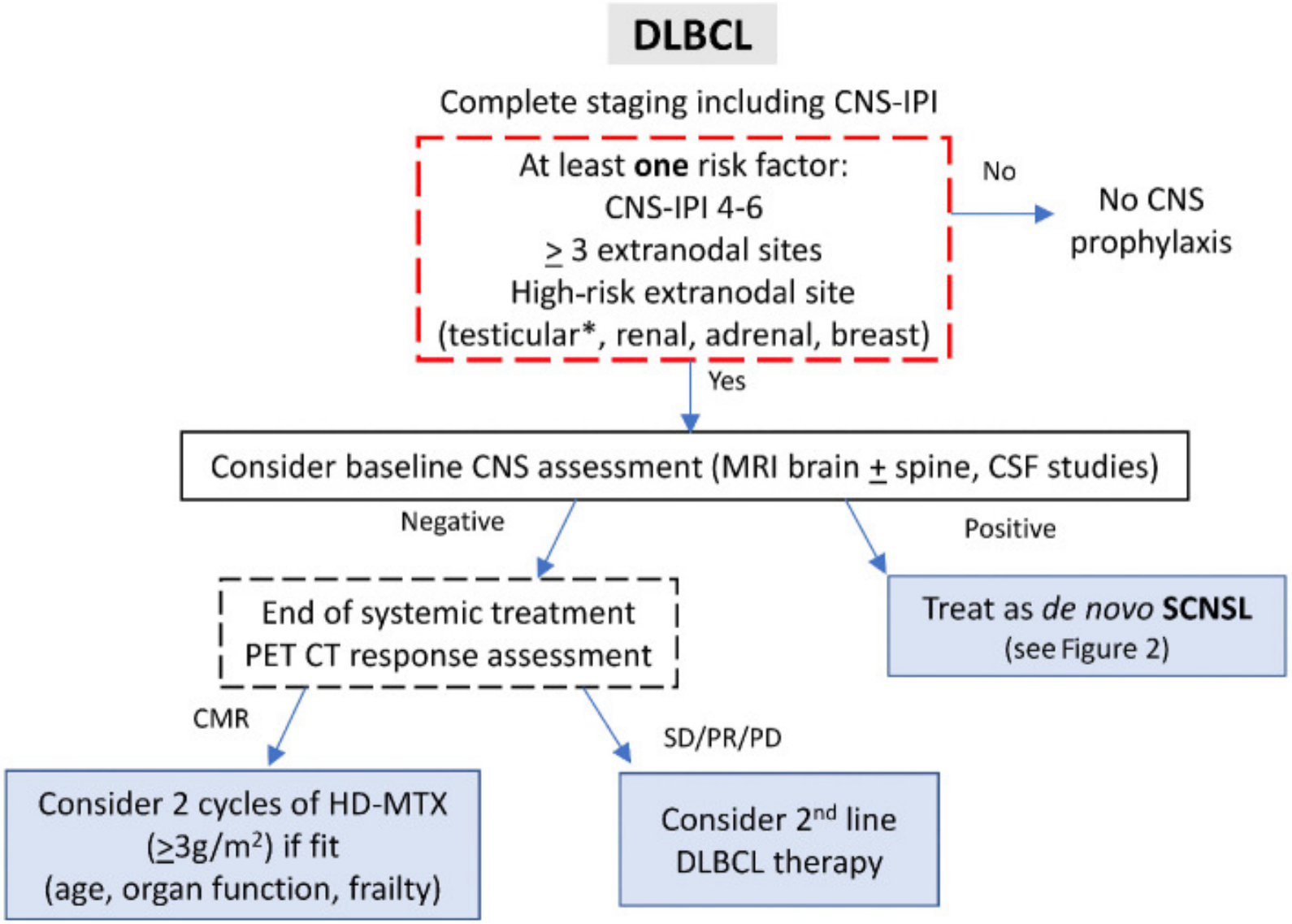
Lewis et al. JCO 2023



No significant impact of HD-MTX observed in high-risk subgroups. All underpowered to draw definitive conclusions regarding the efficacy of HD-MTX in specific high-risk clinical scenarios

Lewis et al. JCO 2023

Our approach to preventing CNS disease



47 year old male

- Feb 2017: IVB DLBCL (NOS) non-GC no *MYC*-R.
  IPI 3/5

  R-CHOP x6 and IV MTX to CMR

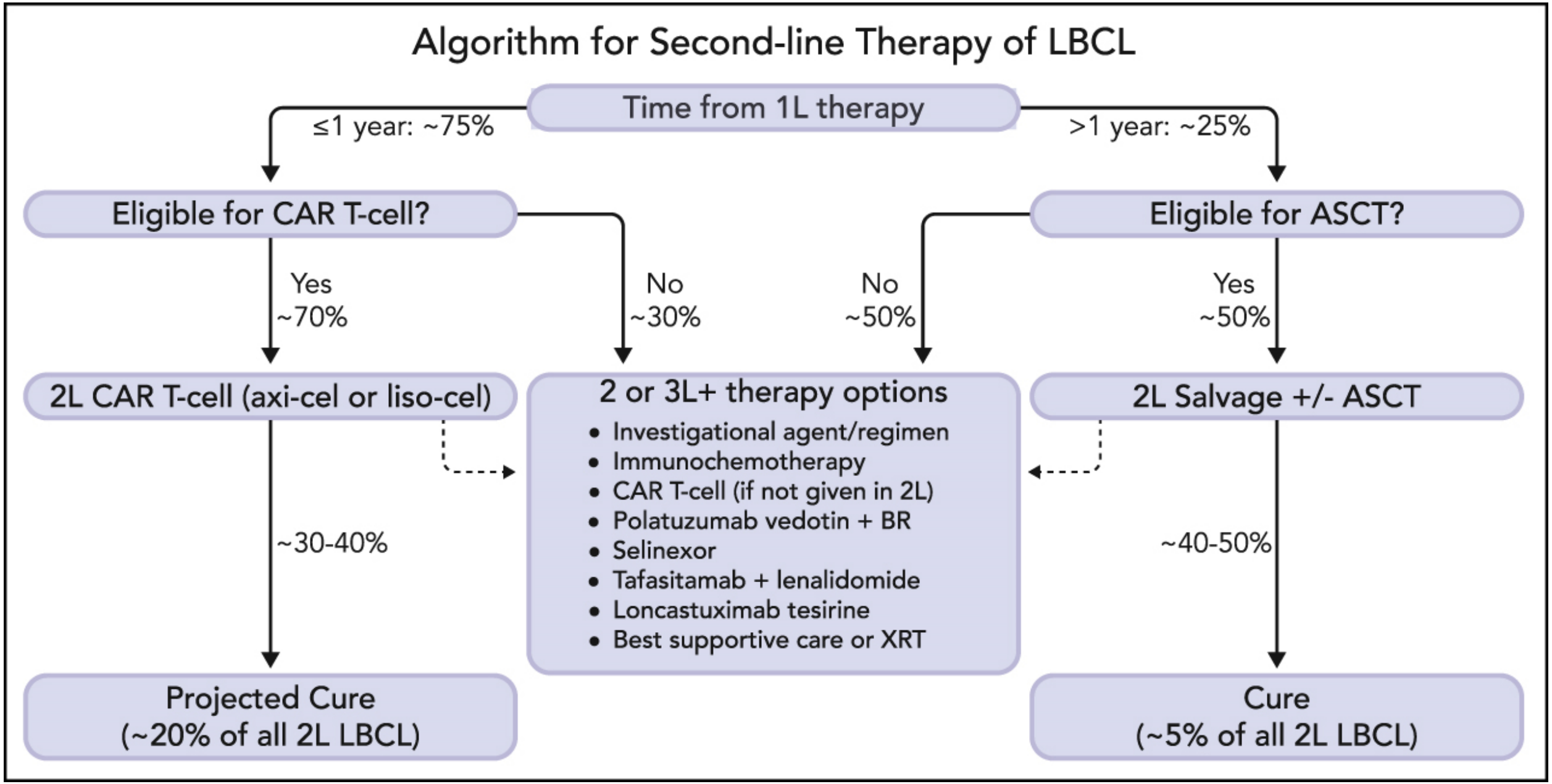
April 2018 disease recurrence.

- R-ICE x3 to metabolic complete response.

  High-dose chemotherapy (BEAM) and peripheral blood progenitor cell rescue August 2018

  [in second CR]

  [decision today in light of current data]



Westin and Sehn 2022

47 year old male

- Feb 2017: IVB DLBCL (NOS) non-GC no *MYC*-R. IPI 3/5

  R-CHOP x6 and IV MTX to CMR

- April 2018 disease recurrence. R-ICE x3 to metabolic complete response.

  High-dose chemotherapy (BEAM) and peripheral blood progenitor cell rescue August 2018

- November 2019 disease recurrence treated with CAR-T cell therapy (Axi-cel: December 2019) to complete response. Grade 2 CRS and grade 1 ICANS

47 year old male

- August 2020 disease progression

  Bone marrow some dysplastic change and infiltration

  Reduction with pembrolizumab to mixed response.

47 year old male

- August 2020 disease progression

  Bone marrow some dysplastic change and infiltration

  Reduction with pembrolizumab to mixed response.

  Rituximab, bendamustine and polatuzumab to CMR

[Decision: what next, if any]

47 year old male

- August 2020 disease progression

  Bone marrow some dysplastic change and infiltration

  Reduction with pembrolizumab to mixed response.

  Rituximab, bendamustine and polatuzumab to CMR

- Consolidation November 2021 with 9/10 HLA matched unrelated donor sibling allogeneic transplant.

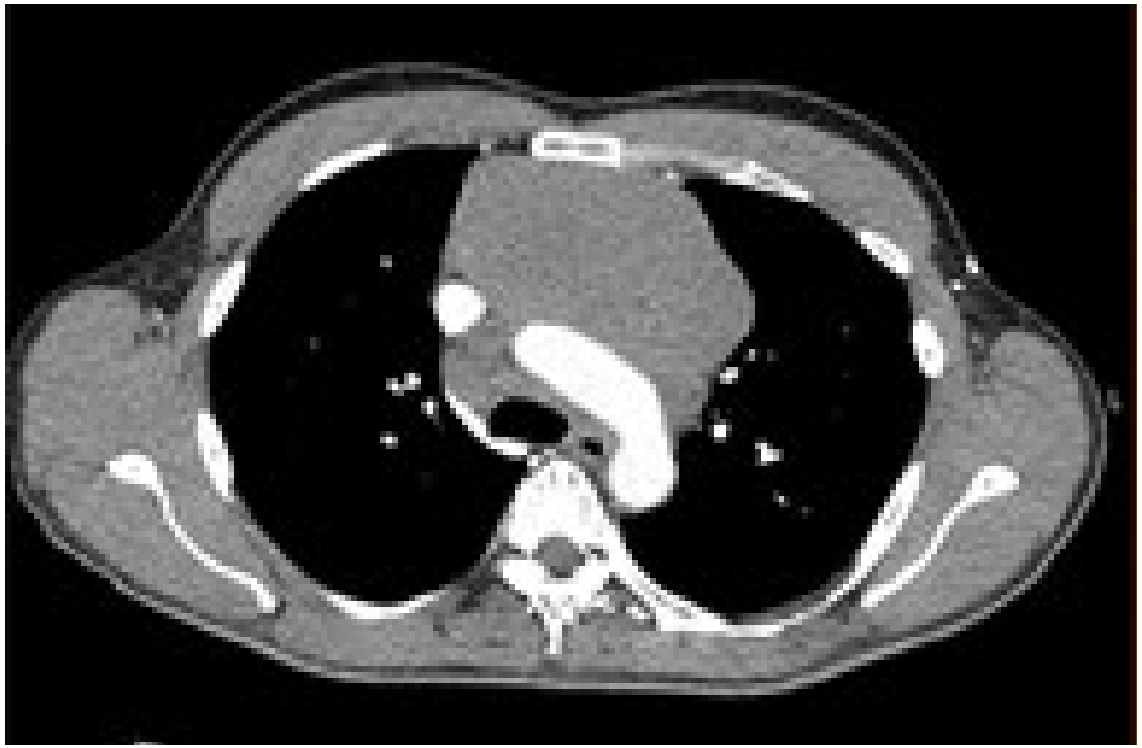
  Largely uncomplicated. Grade 1 aGVHD and asymptomatic CMV reactivation

May 2023

Disease progression

Large mediastinal mass, bilateral cervical and retroperitoneal LN

Biopsy: High-grade B-cell lymphoma (*MYC*/*BCL2*)



June 2023

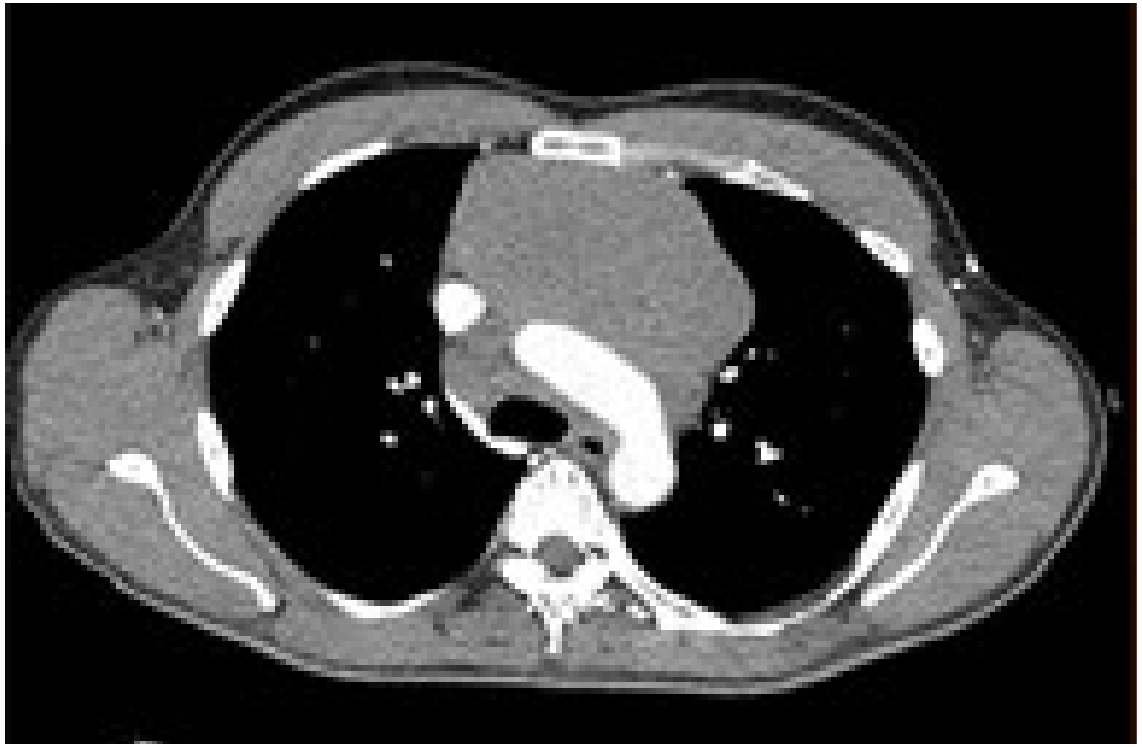
Disease progression

Large mediastinal mass, bilateral cervical and retroperitoneal LN

Biopsy: High-grade B-cell lymphoma (*MYC*/*BCL2*)

Emergency palliative RT to mediastinum for immediate relief of SVCO

[decision: Should we stop?]



Glofitamab

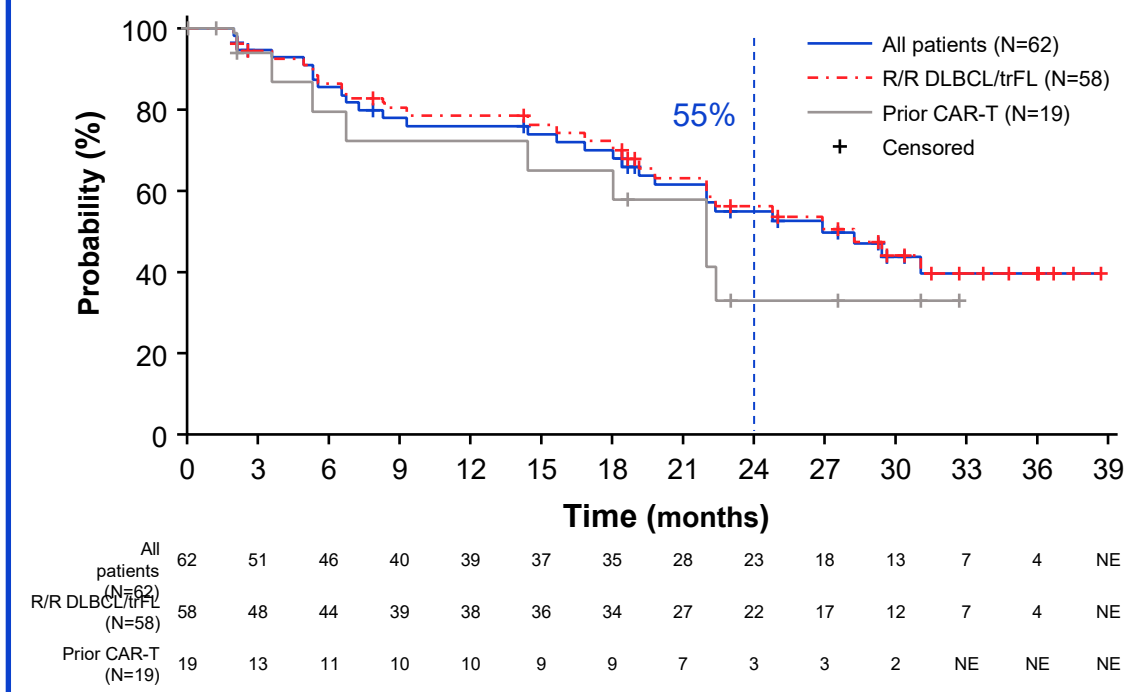
Grade 2 CRS on first full dose

One dose tocilizumab given and dexamethasone for 36 hours

Response rates and DoCR

	All patients (N=155)*	R/R DLBCL/ trFL (N=132)[1†‡]	Prior CAR-T (N=52)†
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]	74 (56) [47.2–64.7]	26 (50) [35.8–64.2]
CR rate, n (%) [95% CI]	62 (40) [32.2–48.2]	58 (44) [35.3–52.8]	19 (37) [23.6–51.0]
Median DoCR, months (95% CI)	26.9 (19.8–NR)	28.3 (19.8–NR)	22.0 (6.7–NR)
24-month DoCR, % (95% CI)	55.0 (41.1–68.8)	56.2 (41.9–70.4)	33.1 (7.2–59.0)
Median CR follow-up, months (range)	29.6 (0–39)	29.6 (0–39)	23.0 (0–33)
Ongoing CRs, n/N (%)	34/62 (55)	32/58 (55)	10/19 (53)

DoCR by IRC



- Median time on study: 32.1 months (range: 0–43)

With 32 months median follow-up, glofitamab showed high response rates and durable remissions across subgroups

*Intent-to-treat population (DLBCL, trFL, HGBCL, and PMBCL); †Patients in this subgroup had similar baseline characteristics to the overall population; ‡Primary efficacy population reported in the glofitamab USPI, all patients received at least one dose of glofitamab. CI, confidence interval; NE, not estimable; NR, not reached; USPI, United States prescribing information.

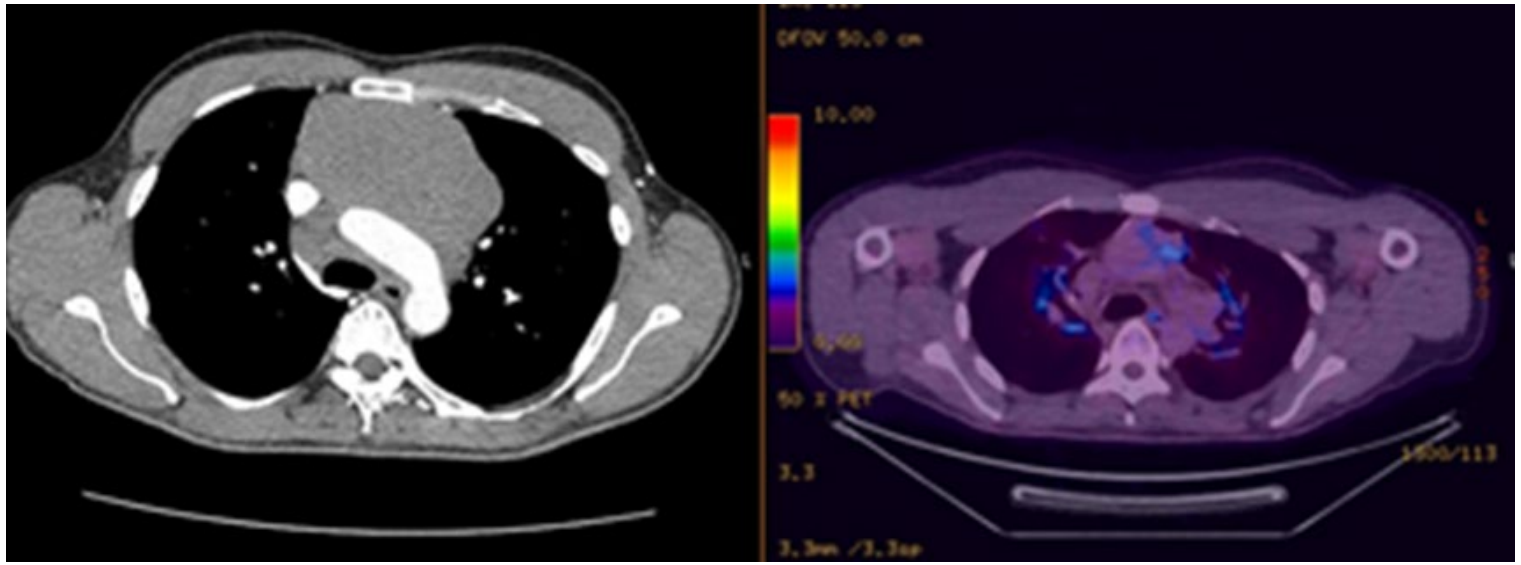
1. COLUMVI USPI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761309s000lbl.pdf

Glofitamab

Grade 2 CRS on first full dose

One dose tocilizumab given and dexamethasone for 36 hours

Cycle 3 achieved CMR



RSV November 2023.

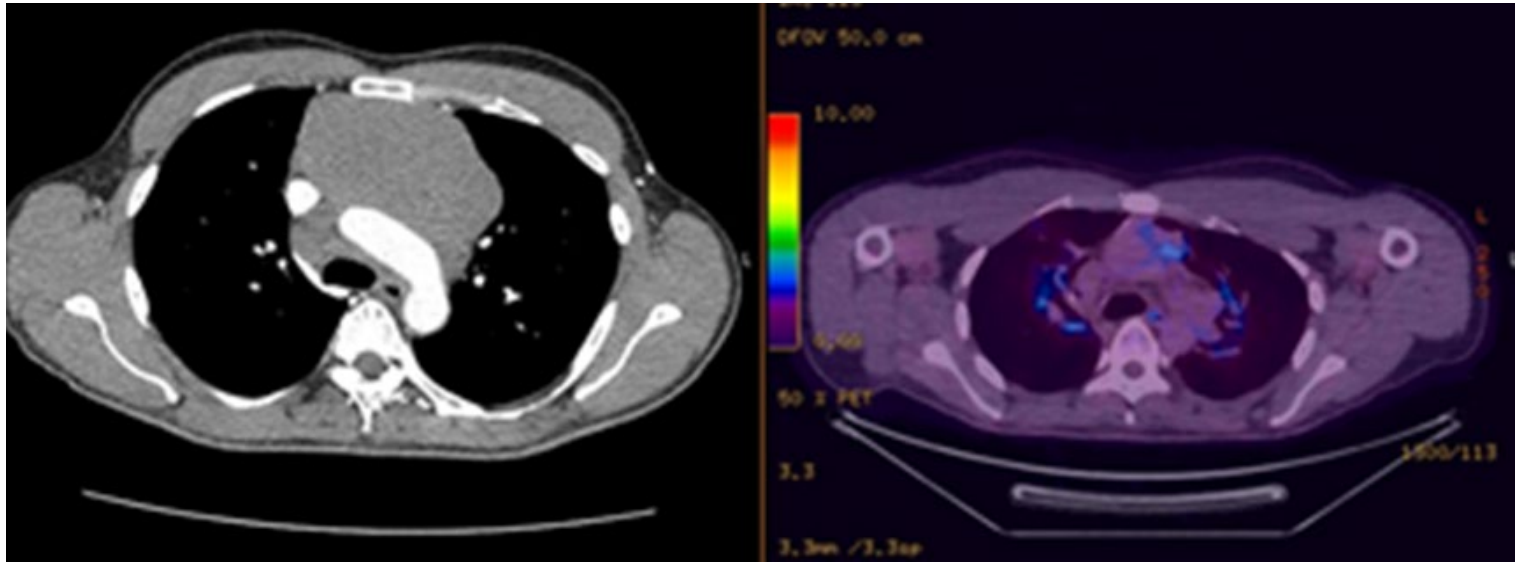
Hypogammaglobulinemia: IVIg replacement Nov 2023

Glofitamab

Grade 2 CRS on first full dose

One dose tocilizumab given and dexamethasone for 36 hours

Cycle 3 achieved CMR



RSV September 2023.

Hypogammaglobulinemia: IVIg replacement Nov 2023

Reduced CD4 absent CD19+ B-cells in PB

October recurrent chest infections: Bronchiectasis diagnosed. Declined further therapy after

Feb 2024

Disease progression. RP mass [6 cm maximal]

[decision: Should we stop?]

Role of loncastuximab [CD19 expression]

Biopsy CD19 negative

Feb 2024

Disease progression.

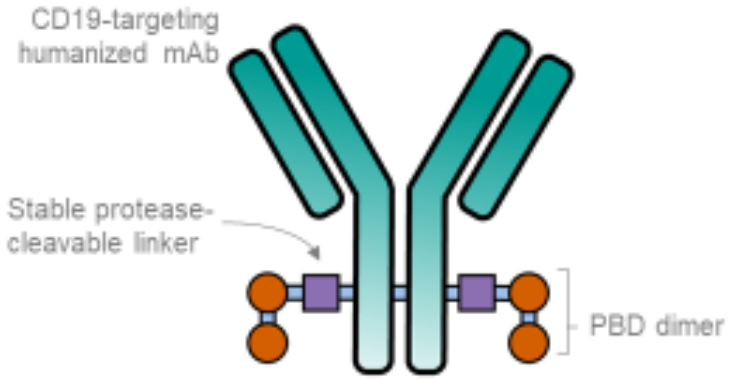
RP mass [6 cm maximal]

[decision: Should we stop?]

Role of loncastuximab [CD19 expression]

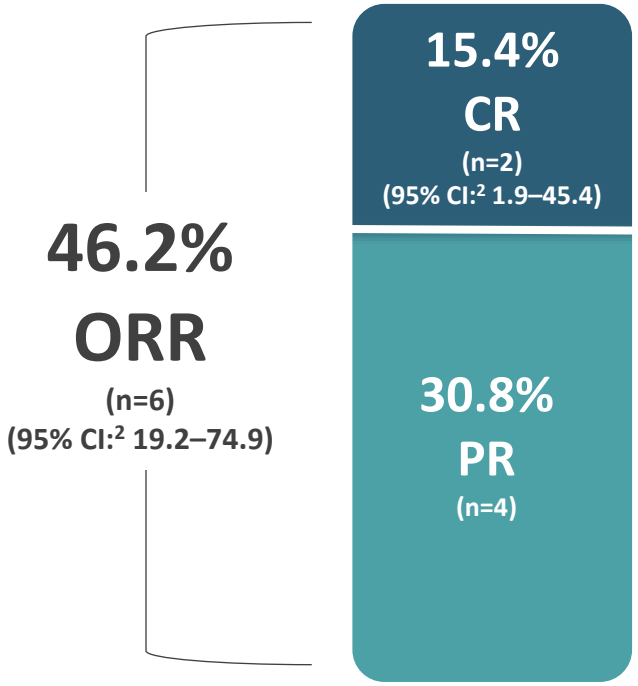
Loncastuximab Teserine

- Loncastuximab tesirine is an ADC targeting CD19, which is expressed exclusively on the surface of B cells[2,3]
- The payload is a small molecule PBD dimer and alkylating agent[3]
  - The PBD dimer binds to the DNA minor groove and forms highly cytotoxic DNA interstrand crosslinks, inducing tumor cell death



Efficacy in patients who previously received CAR-T[1]

After a median follow-up of 8 months, 13 patients received a median of 2 cycles of Lonca (range 1–9)



Median DOR: 8 months
(95% CI: 103 days–NR)

Response to Lonca, based on independent review, was seen in 6/13 (46.2%) patients already treated with CAR-T

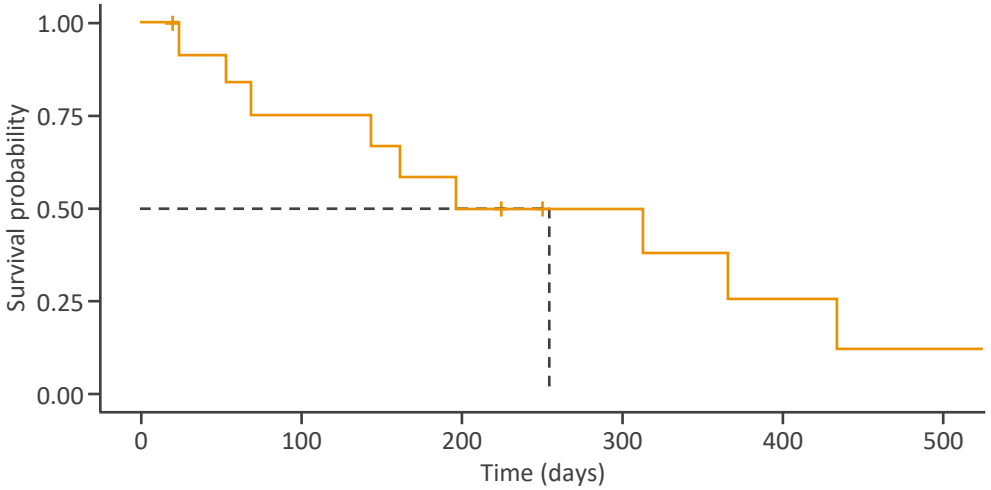
Of these, 5 had previously presented response to CAR-T and the sixth patient had prolonged, stable disease for > 1 year after CAR-T

While limited by its small sample size, the response rates observed in this high-risk population are comparable to those observed in other patient subsets

CAR, chimeric antigen receptor; CI, confidence interval; CR, complete response; DOR, duration of response; Lonca, loncastuximab tesirine; NR, not reached; ORR, overall response rate; PR, partial response.
1. Caimi et al. *Clin Lymphoma Myeloma Leuk* 2022 **2.** Data on file.

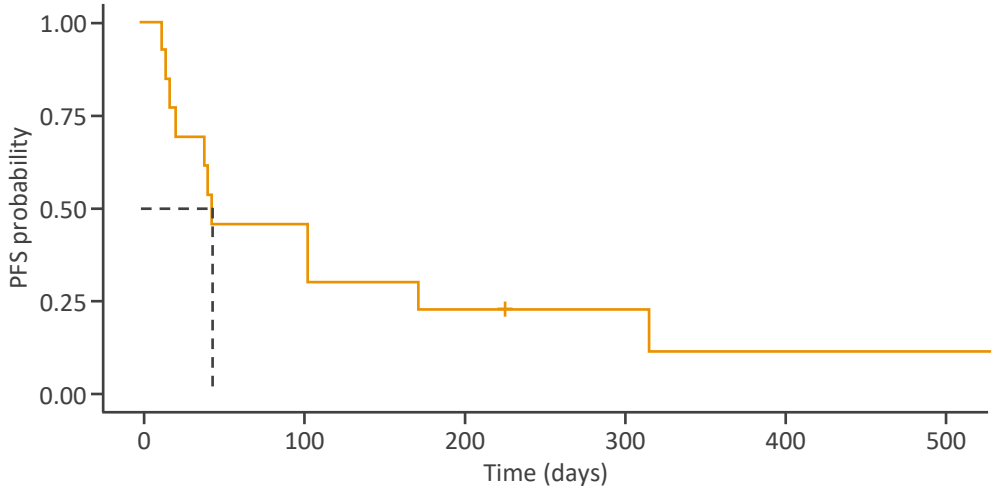
OS and PFS in patients failing previous CAR-T therapy[1]

Overall survival (N=13)



Median OS after Lonca: **8.2 months**
(95% CI: 144d–NR)

Progression-free survival (N=13)



Median PFS after Lonca: **1.4 months**
(95% CI: 21d–NR)

This analysis is only exploratory and data have to be interpreted with caution due to the low numbers.
CAR, chimeric antigen receptor; CI, confidence interval; d, days; Lonca, loncastuximab tesirine; NR, not reached; OS, overall survival; PFS, progression-free survival.
1. Caimi et al. *Clin Lymphoma Myeloma Leuk* 2022.

Feb 2024

Disease progression. RP mass [6 cm maximal]

[decision: Should we stop?]

Role of loncastuximab [CD19 expression]

Biopsy CD19 negative

Requests supportive care

The many challenges

- Initial therapy for DHL [now HGBCL (MYC/BCL2)]
- CNS directed therapy
- Optimal treatment early failure
- Post CAR-T relapsed
- Still a role for allo
- Sequencing of bispecifics
- Toxicity of B-cell aplasia
- Loss of CD19 antigen
- Parallel planning