How to sequence non-CAR T-cell therapy for relapsed/refractory DLBCL

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Overview

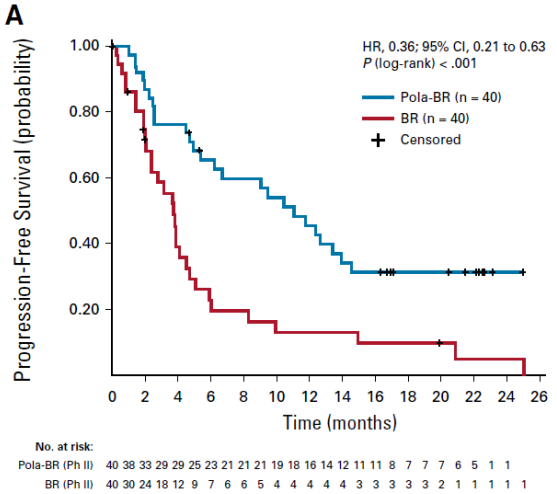
- Recently FDA-approved therapies for R/R DLBCL
  - Polatuzumab vedotin (+rituximab/bendamustine) (June 2019)
  - Selinexor (June 2020)
  - Tafasitamab (+lenalidomide) (July 2020)
  - Loncastuximab teserine (April 2021)

- Sequencing of therapies
  - Line of therapy (2^{nd} vs 3^{rd} and beyond)
  - Candidacy for cellular therapies (CART19, ASCT)
  - Other factors – disease progression rate, patient preference

Polatuzumab vedotin

- MOA: anti-CD79B ADC linked to MMAE
- Design: phase 2 randomized (pola-BR vs BR), n=40 each arm
- Inclusion criteria: non-transformed DLBCL, ≥1 line prior therapy, ASCT ineligible
- Dosing: IV q3 weeks x6 cycles
- Toxicity: cytopenias, infection, low-grade PN (pola)

Outcome	Pola-BR	BR
ORR	45%	17.5%
CRR	40%	17.5%
mPFS	9.5 mo	3.7 mo
mDOR	12.6 mo	7.7 mo
mOS	12.4 mo	4.7 mo

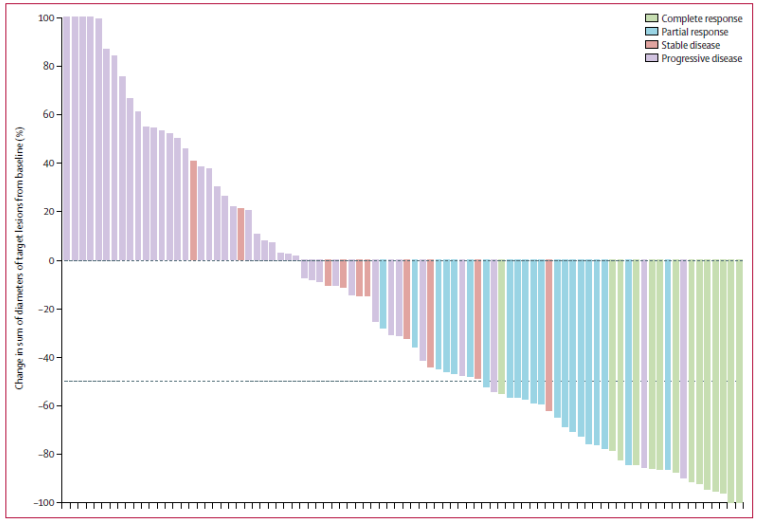


J Clin Oncol. 2020 Jan 10;38(2):155-165

Selinexor

- MOA: selective inhibitor of XPO1-mediated nuclear export
- Design: phase 2, n=127 (SADAL)
- Inclusion criteria: DLBCL (incl transformed), 2-5 lines prior therapy, ASCT ineligible, 60-98 days since last lymphoma therapy
- Dosing: PO 60 mg or 100 mg twice weekly (100 mg dose discontinued)
- Toxicity: cytopenias (thrombocytopenia), fatigue, nausea

Outcome	All pts
ORR	28%
CRR	12%
mPFS	2.6 mo
mDOR	9.3 mo
mOS	9.1mo

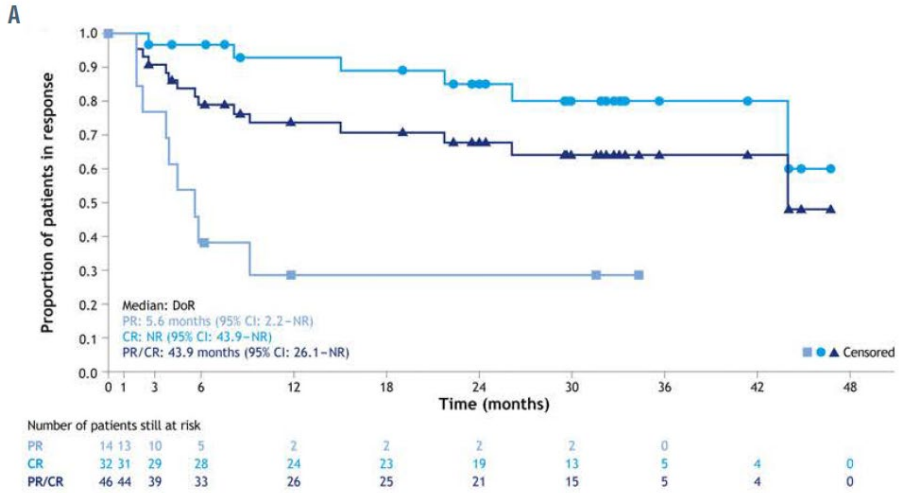


Lancet Haematol. 2020 Jul;7(7):e511-e522

Tafasitamab

- MOA: FC-enhanced humanized anti-CD19 mAb
- Design: phase 2 combination with lenalidomide, n=81 (L-MIND)
- Inclusion criteria: DLBCL (incl transformed), 1-3 lines prior therapy, ASCT ineligible, non-DHL, non-primary refractory
- Dosing: tafa: IV qwk x4 mo then q2wk until progression, len 25 mg d1-21 x12 mo
- Toxicity: cytopenias, infection, rash, diarrhea

Outcome	All pts
ORR	60%
CRR	43%
mPFS	11.6 mo
mDOR	43.9 mo
mOS	33.5 mo

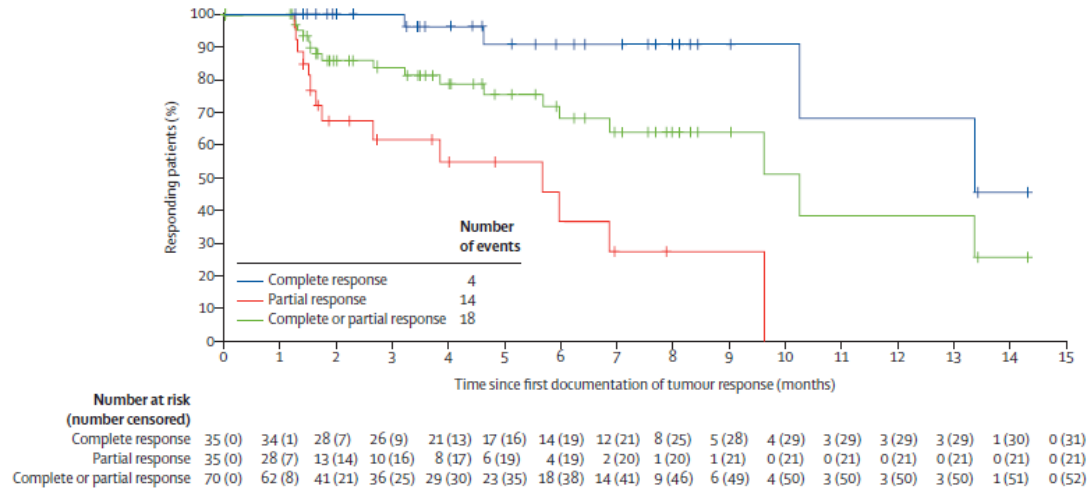


Lancet Oncol. 2020 Jul;21(7):978-988.
Haematologica. 2021 Sep 1;106(9):2417-2426

Loncastuximab teserine

- MOA: anti-CD19 ADC linked to SG3199
- Design: phase 2, n=145 (LOTIS-2)
- Inclusion criteria: DLBCL (incl transformed), ≥2 lines prior therapy
- Dosing: IV q3wk dosing x1 year (higher dose for C1-2)
- Toxicity: cytopenias, GI, edema, elevated LFTs (including GGT)

Outcome	All pts
ORR	48%
CRR	24%
mPFS	4.9 mo
mDOR	10.3 mo
mOS	9.9 mo



Number at risk (number censored)																
Complete response	35 (0)	34 (1)	28 (7)	26 (9)	21 (13)	17 (16)	14 (19)	12 (21)	8 (25)	5 (28)	4 (29)	3 (29)	3 (29)	3 (29)	1 (30)	0 (31)
Partial response	35 (0)	28 (7)	13 (14)	10 (16)	8 (17)	6 (19)	4 (19)	2 (20)	1 (20)	1 (21)	0 (21)	0 (21)	0 (21)	0 (21)	0 (21)	0 (21)
Complete or partial response	70 (0)	62 (8)	41 (21)	36 (25)	29 (30)	23 (35)	18 (38)	14 (41)	9 (46)	6 (49)	4 (50)	3 (50)	3 (50)	3 (50)	1 (51)	0 (52)

Lancet Oncol. 2021 Jun;22(6):790-800.

Summary – R/R DLBCL therapies

Agent	Prior therapy	Relevant exclusion criteria	ORR	CRR	Median PFS	Median OS	Median DOR
Polatuzumab (+bendamustine /rituximab)	≥ 1 line	Transformed indolent lymphoma	45%	40%	9.5 months	12.4 months	12.6 months
Selinexor	2-5 lines	Treatment within prior 60-98 days	28%	12%	2.6 months	9.1 months	9.3 months
Tafasitamab (+lenalidomide)	1-3 lines	DHL, primary refractory	58%	40%	11.6 months	33.5 months	43.9 months
Loncastuximab	≥ 2 lines		48%	24%	4.9 months	9.9 months	10.3 months

Summary – R/R DLBCL therapies (continued)

Agent	Median time to response	ORR ≥3rd line setting	ORR d novo/
Polatuzumab (+bendamustine /rituximab)	NR	50%	45%/N
Selinexor	2 months	28%	24%/3
Tafasitamab (+lenalidomide)	2 months	50%	~58%/
Loncastuximab	1.5 months	48%	49%/4

- Design: retrospective, n=50
- Inclusion: R/R DLBCL/HGBL, bridging tx prior to CART19
- Dosing: 48% pola monotherapy, 30% benda

Outcome	All pts
mClinresp	21.5 d
mRadresp	64 d
mEarlresp	22 d

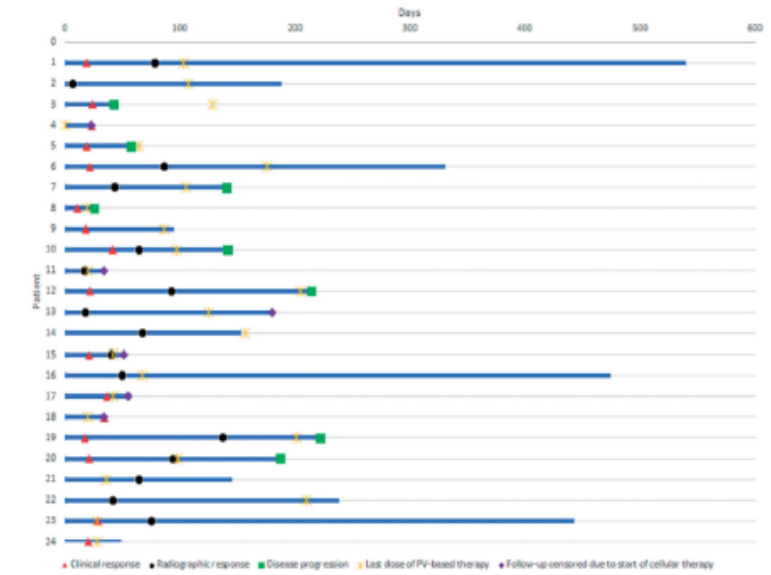


Figure 1. Treatment and response durations in responding patients.

Leuk Lymphoma. 2022 Jan;63(1):243-246

CD19 expression/CD19-targeted therapy response following CD19-directed antibodies

Tafasitamab

- Case series of 8 lymph node biopsies taken from patients with progression on tafa-len treated on L-MIND
  - All had CD19 expression by IHC
  - 3/8 <85 days post-last dose of tafa (window of potential residual exposure)

- Case series of 2 patients with serial lymph node biopsies after progression on tafa-len who received CART19
  - Patient #1 – CD19 expression negative on days 4, 14, 26 but positive on day 32. NE for CART19 response
  - Patient #2 - CD19 expression negative on day 7, positive on day 25. Response to CART19

Loncastuximab

- 15 patients treated on LOTIS-2 received subsequent CART19 therapy
  - 7/15 achieved response
  - 6/15 achieved CR
  - No mention of CD19 expression

Leuk Lymphoma. 2022 Feb;63(2):468-472

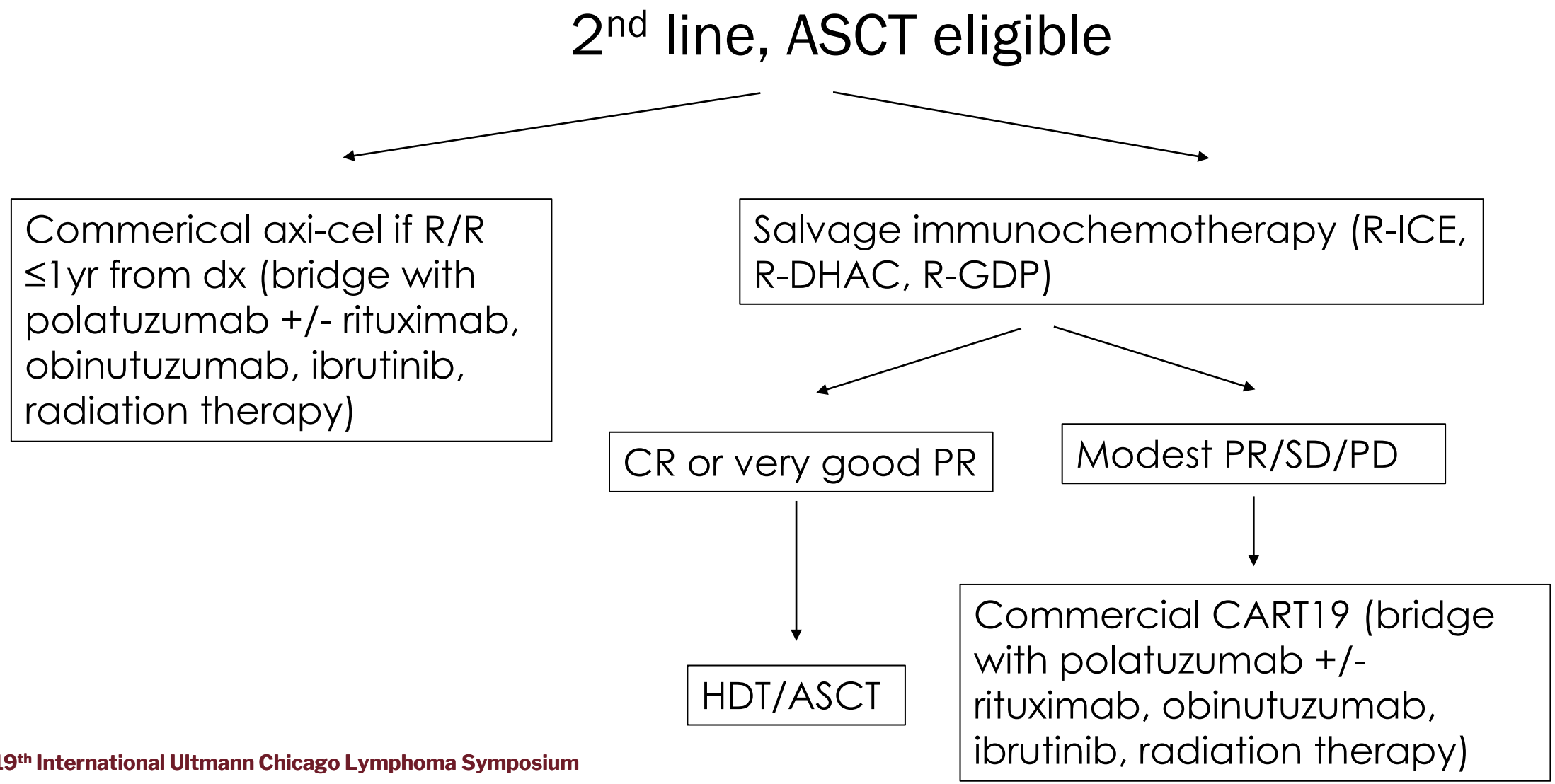
Leuk Lymphoma. 2022 Mar;63(3):751-754

Sequencing of R/R DLBCL therapies

- Patient “buckets”
  - 2nd line, ASCT eligible
  - 2nd line, non-ASCT eligible, CART19 eligible
  - 2nd line, non-ASCT/non-CART19 eligible
  - ≥3rd line, CART19 eligible
  - ≥3rd line, non-CART19 eligible

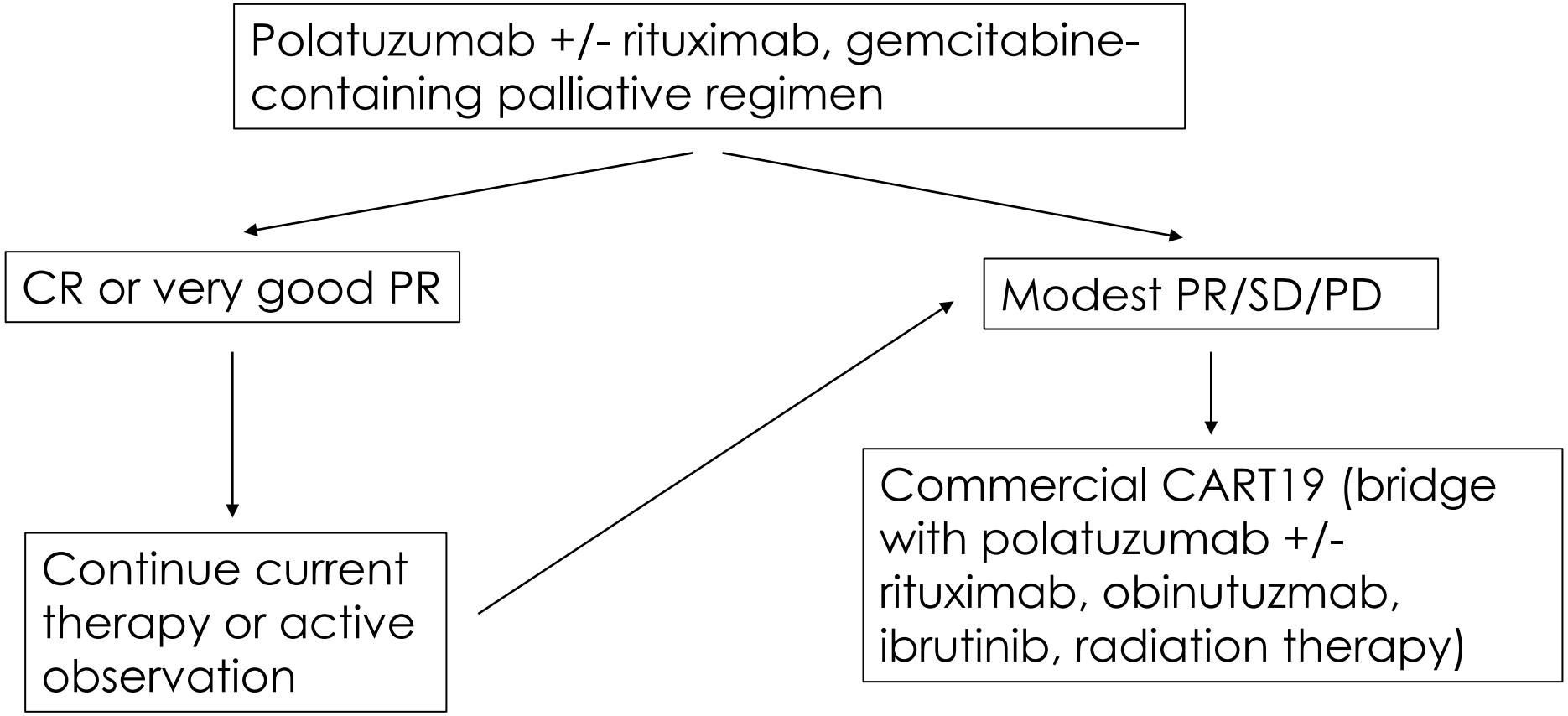
- Patient factors
  - Comorbidities
  - Toxicity from prior therapy
  - Preference for IV and/or oral therapy
  - Willingness to travel to infusion center

Sequencing of R/R DLBCL therapies



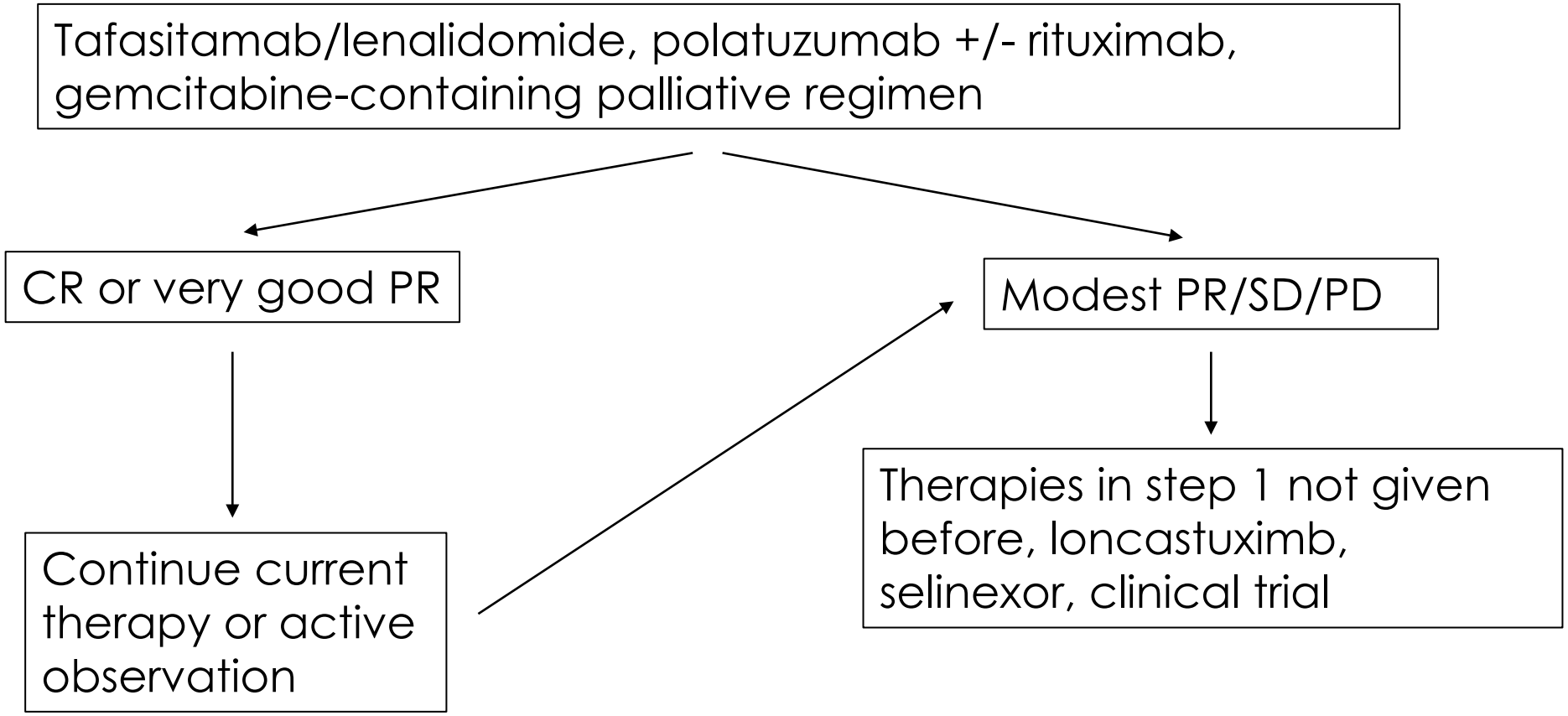
Sequencing of R/R DLBCL therapies

2nd line, non-ASCT eligible, CART19 eligible



Sequencing of R/R DLBCL therapies

2nd line, non-ASCT/non-CART19 eligible



Sequencing of R/R DLBCL therapies

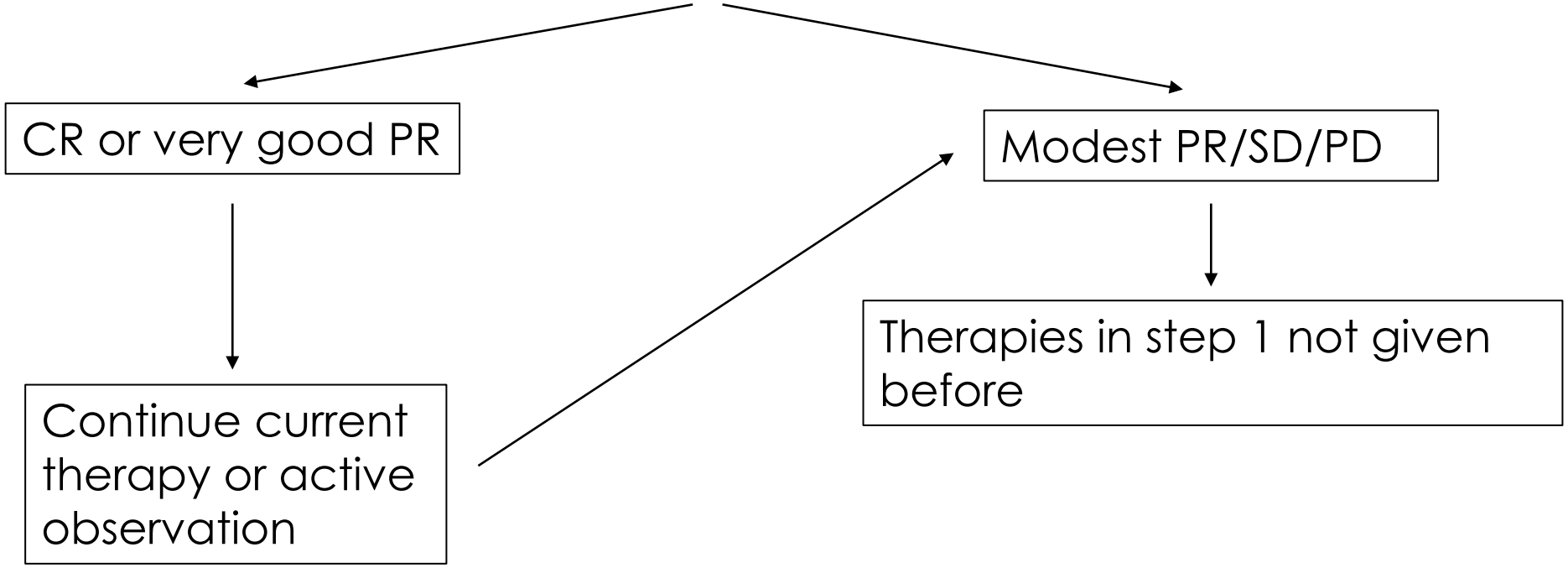
≥3rd line, CART19 eligible

Commercial CART19 (bridge with polatuzumab +/- rituximab, obinutuzmab, ibrutinib, radiation therapy)

Sequencing of R/R DLBCL therapies

≥3rd line, non-CART19 eligible

Tafasitamab/lenalidomide (CD19+), polatuzumab +/- rituximab, loncastuximab (CD19+), selinexor, gemcitabine-containing palliative regimen, salvage immunochemotherapy (if ASCT candidate and not previously received), clinical trial



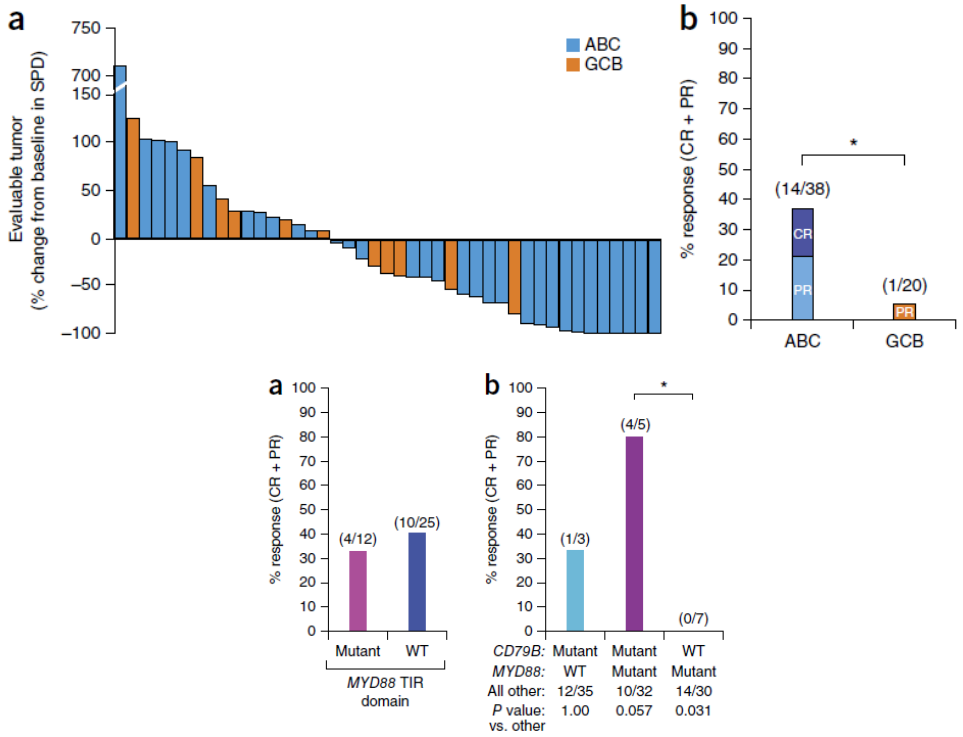
Conclusions

- Recently FDA-approved therapies for R/R DLBCL are efficacious and tolerable
- No optimal standard sequencing of therapies for all patients
- Consider individual patient factors
  - Eligible for CART19 – consider avoiding prior use of CD19-directed therapies
  - Post-CART19 – test for CD19 expression prior to using CD19-directed therapies
  - Rapid disease progression – polatuzumab, cytotoxic chemo
  - Willing to receive frequent infusion therapy – tafasitamab/lenalidomide
  - Oral therapy only - selinexor

Non-FDA-approved R/R DLBCL therapies

Ibrutinib

- MOA: BTK inhibitor
- Design: phase 2, n=80, dose 560 mg daily



Obintuzumab

- MOA: type II glycoengineered anti-CD20 mAb
- Design: phase 2, n=25 R/R DLBCL (GAUGUIN)

Table 2. Response Rates

	400/400 mg (n = 21)		1,600/800 mg (n = 19)		Total (N = 40)	
Responders	No. of Patients	%	No. of Patients	%	No. of Patients	%
DLBCL subset						
No. of patients	10		15		25	
ETR	3	30	4	27	7	28
CR/CRu	1	10	0	0	1	4
BOR	3	30	5	33	8	32
CR/CRu	1	10	3	20	4	16

Nat Med. 2015 Aug;21(8):922-6.

J Clin Oncol. 2013 Aug 10;31(23):2912-9.

ARS Question

- When should CD19-directed therapies be used for a R/R DLBCL patient relative to treatment with CART19

A. Before CART19
B. After CART19
C. After CART only if tumor cells express CD19
D. Never
E. A and B
F. A and C