23rd INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

APRIL 10-11, 2026

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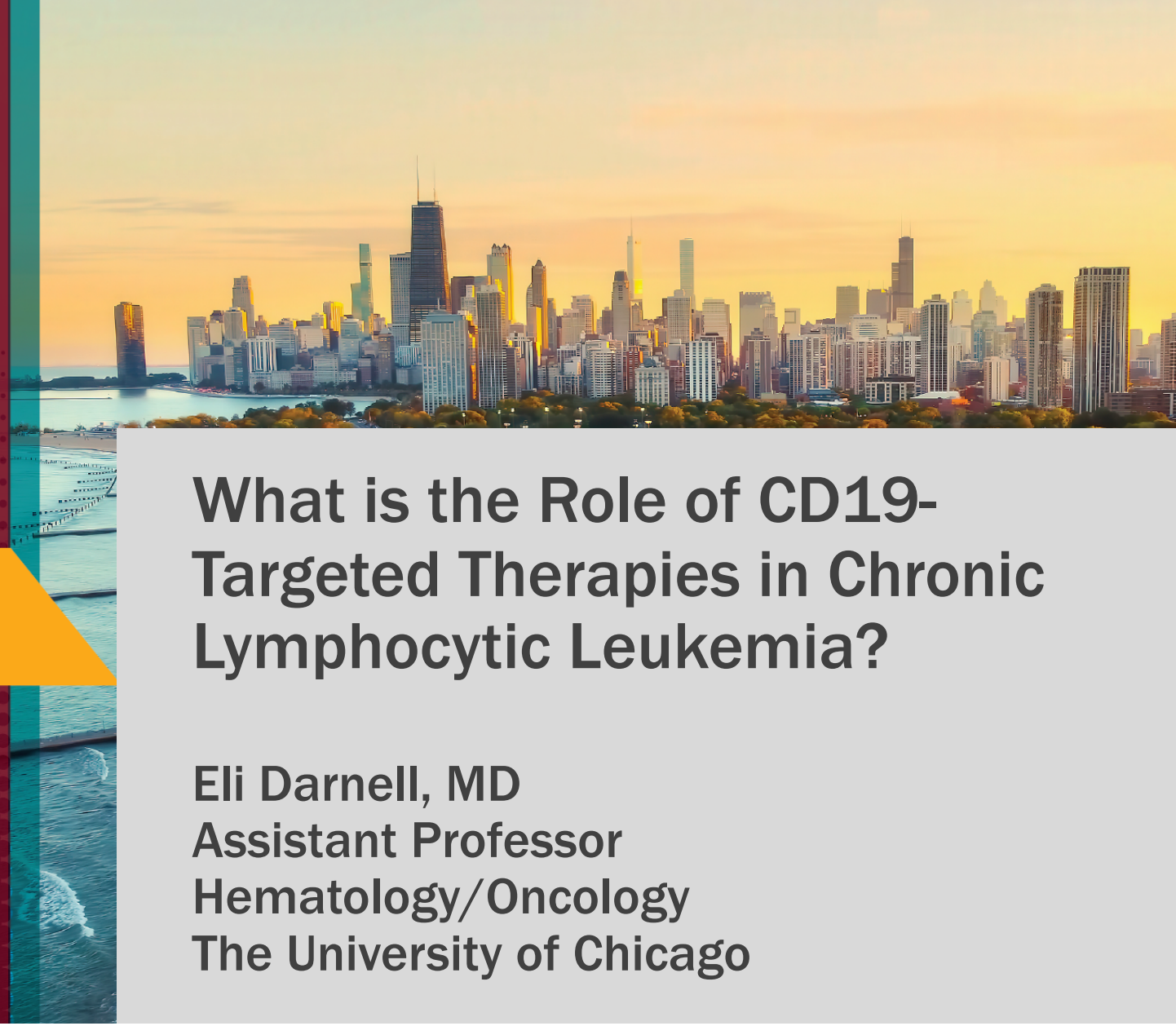

What is the Role of CD19-Targeted Therapies in Chronic Lymphocytic Leukemia?

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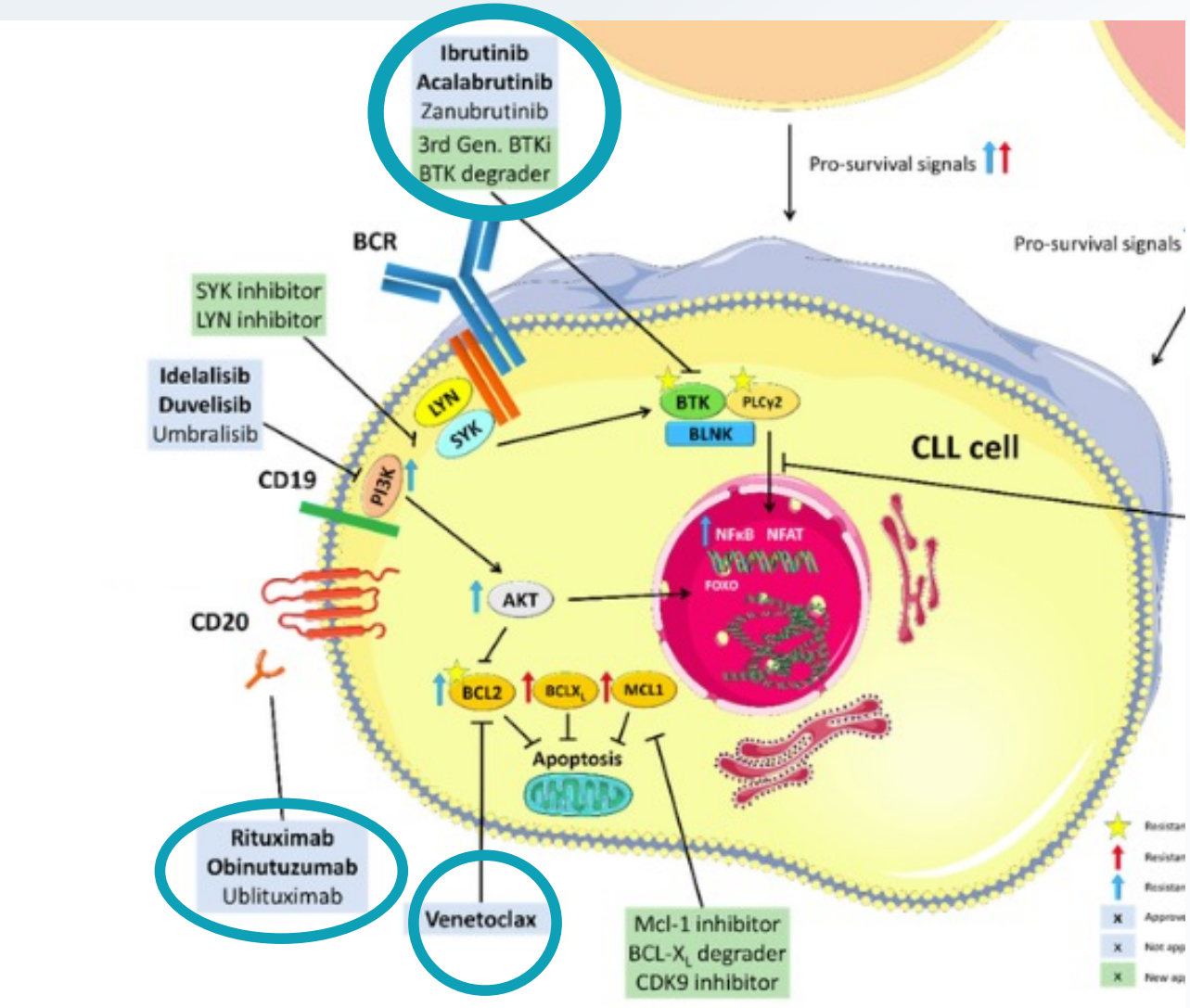
Disclosures

- Inventor on a patent related to CD19 CAR T-cell therapy held by MGH
- Discussing investigational and/or off label use of therapeutics

What is the role for CD19-directed therapy in CLL?



CLL Immunophenotype

CD19+

CD5+

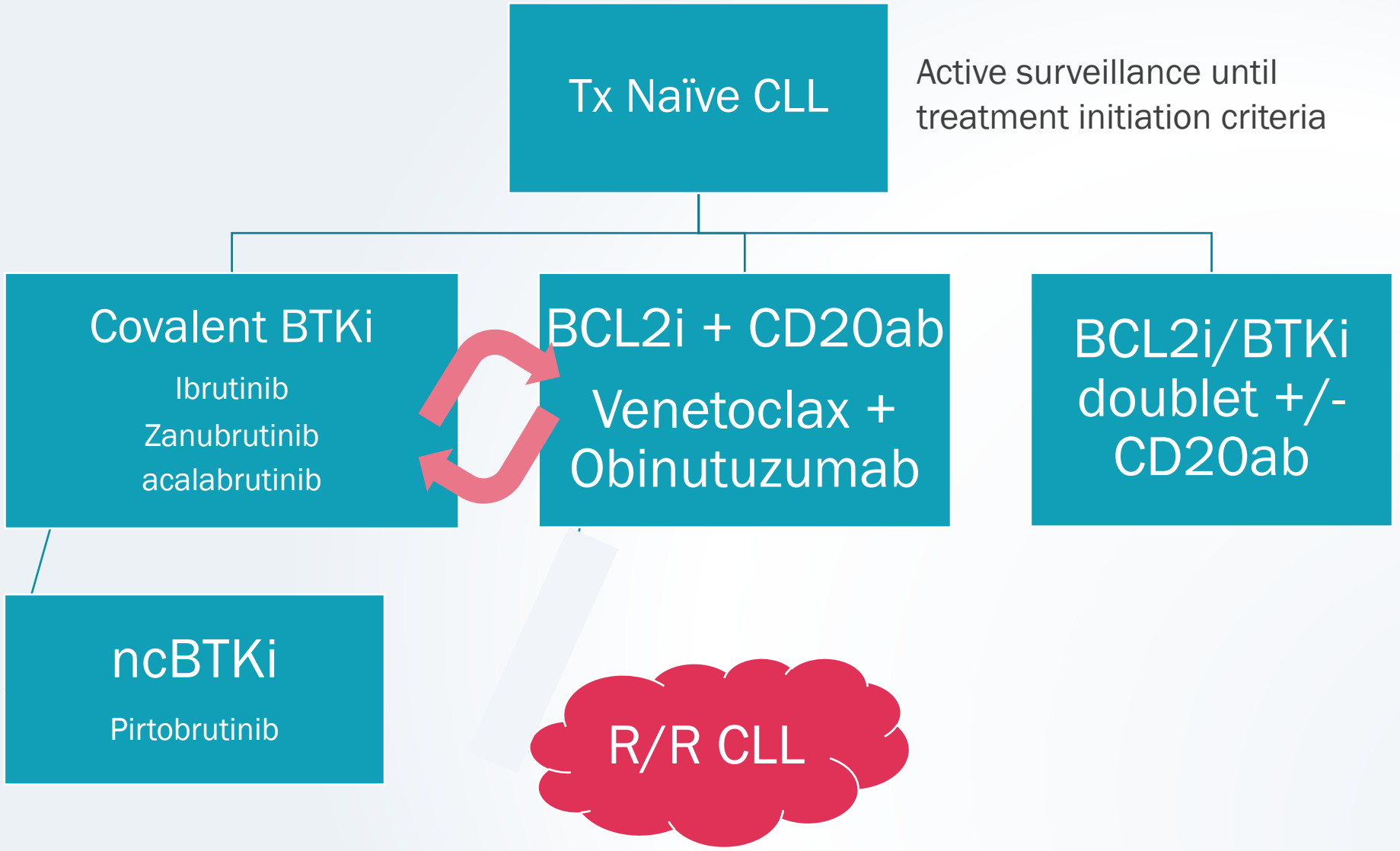
CD20 dim

CD23+

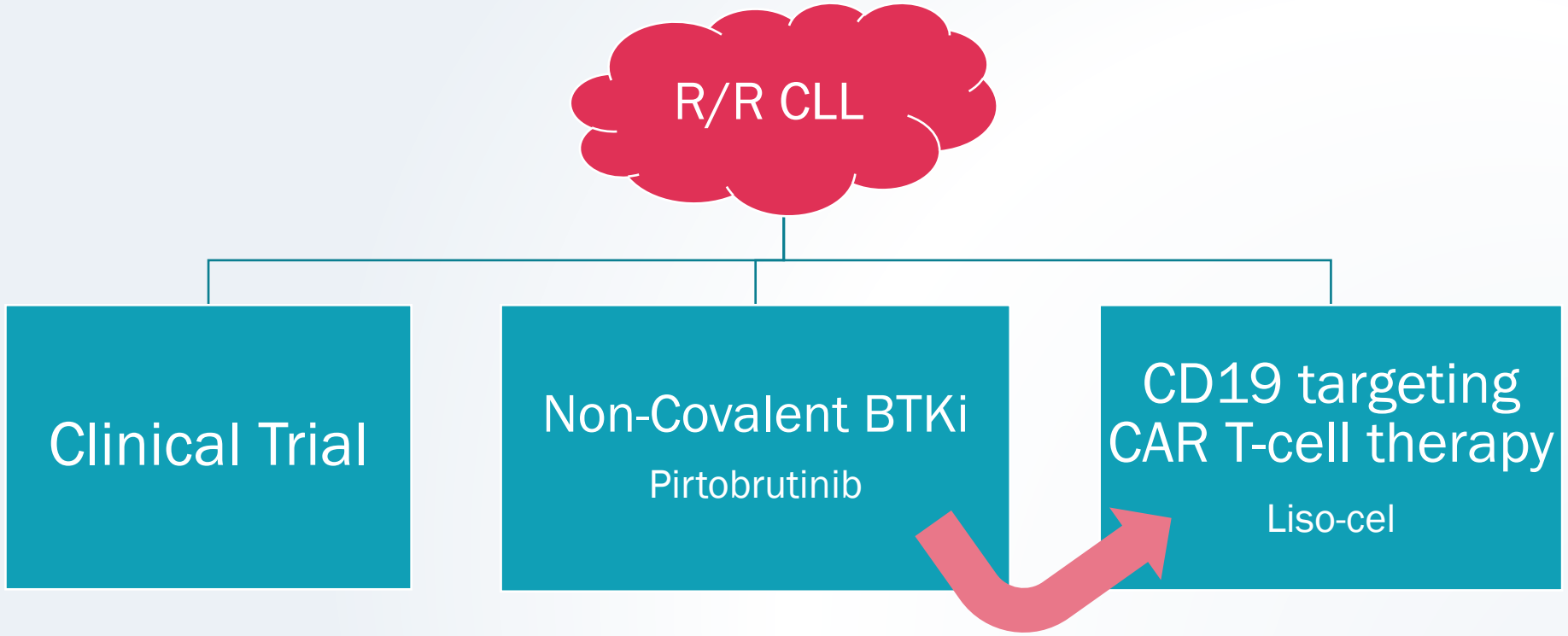
CD200+

Furstenau et al, Cancers 2021, *13*(6), 1336; https://doi.org/10.3390/cancers13061336

CLL: Treatment Paradigm



CLL: R/R “Double-Exposed” Treatment Paradigm



TRANSCEND CLL 004

- Multicenter single-arm phase I-II study of lisocabtagene maraleucel, a CD19 targeting autologous CAR T—cell product, in r/r CLL
- Eligibility: ≥2 lines of prior therapy including BTKi. PEAS required BCL2i and BTKi
- DL1 (phase I) DL2 (phase II), PEAS: subset with BTKi/BCL2i failure

	Full population*		BTK inhibitor progression and venetoclax failure subset*	
	DL2 (n=108)	Total (n=117)	DL2 (n=66)	Total (n=70)
(Continued from previous page)				
Previous therapy				
Previous BTK inhibitor	108 (100%)	117 (100%)	66 (100%)	70 (100%)
BTK inhibitor refractory†	95 (88%)	103 (88%)	66 (100%)	70 (100%)
BTK inhibitor relapsed‡	1 (<1%)	2 (2%)	0	0
BTK inhibitor intolerant only	12 (11%)	12 (10%)	0	0
Previous venetoclax	89 (82%)	94 (80%)	66 (100%)	70 (100%)
Venetoclax refractory†	84 (78%)	89 (76%)	63 (95%)	67 (96%)
Venetoclax relapsed‡	0	0	0	0
Venetoclax intolerant only	4 (4%)	4 (3%)	3 (5%)	3 (4%)
Previous BTK inhibitor and venetoclax	89 (82%)	94 (80%)	66 (100%)	70 (100%)
BTK inhibitor progression and venetoclax failure§	66 (61%)	70 (60%)	66 (100%)	70 (100%)
Previous chemoimmunotherapy	93 (86%)	101 (86%)	58 (88%)	62 (89%)
Previous HSCT	6 (6%)	7 (6%)	6 (9%)	7 (10%)
Previous PI3K inhibitor	28 (26%)	29 (25%)	21 (32%)	22 (31%)
Received bridging therapy	84 (78%)	89 (76%)	53 (80%)	55 (79%)
Time from diagnosis to liso-cel infusion, months	132·5 (83·9–178·2)	128·9 (82·8–172·7)	143·1 (85·1–186·3)	138·5 (84·1–182·9)

Siddiqi, Jordan Gauthier, Saad S. Kenderian, Danielle M. Brander, Kathleen Dorritie, Jacob D. Soumerai, Peter A. Riedell, Nirav N. Shah, Rajneesh Nath, Charalambos Andreadis, Daniel A. Ermann, Shuo Ma, Tatyana Feldman, Scott R. Solomon, Stephen J. Schuster, Sherilyn A. Tuazon, Serena K. Perna, San-San Ou, Neha Rane, Eniko Papp, Yizhe Chen, William G. Wierda; Lisocabtagene Maraleucel (liso-cel) in Patients (pts) with Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): Updated Follow-up of Transcend CLL 004. *Blood* 2024; 144 (Supplement 1): 4633

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TRANSCEND CLL 004: Safety

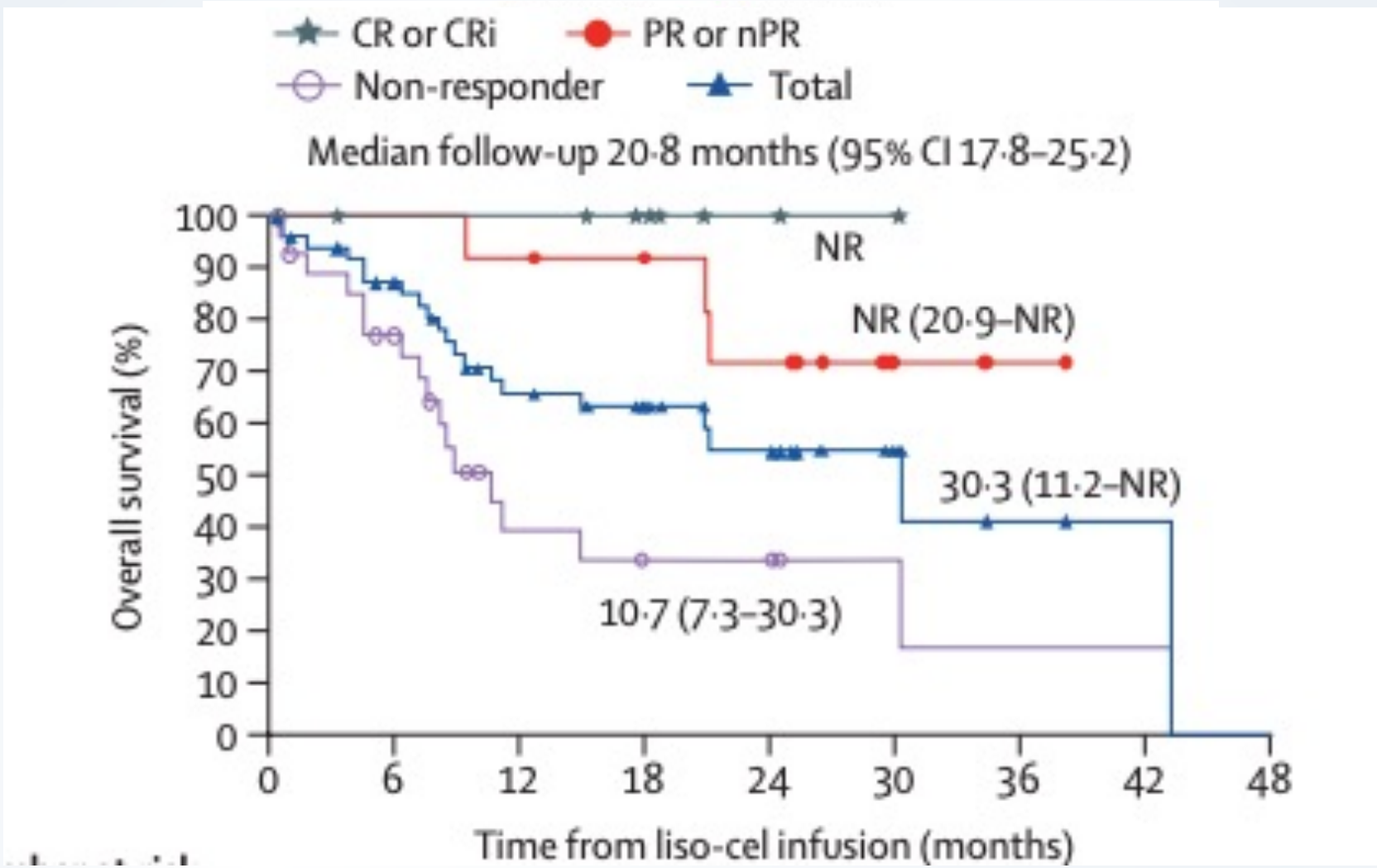
	Any grade	Grade 3	Grade 4	Grade 5
Any treatment-emergent adverse event	117 (100%)	18 (15%)	85 (73%)	5 (4%)*
Cytokine release syndrome	99 (85%)	10 (9%)	0	0
Anaemia	78 (67%)	61 (52%)	0	0
Neutropenia	72 (62%)	11 (9%)	60 (51%)	0
Thrombocytopenia	58 (50%)	14 (12%)	34 (29%)	0
Fatigue	40 (34%)	7 (6%)	0	0
Nausea	39 (33%)	0	0	0
Diarrhoea	34 (29%)	1 (1%)	0	0
Headache	34 (29%)	1 (1%)	0	0
Leukopenia	34 (29%)	3 (3%)	28 (24%)	0
Hypokalaemia	32 (27%)	2 (2%)	0	0
Pyrexia	32 (27%)	1 (1%)	0	0
Confusional state	31 (26%)	11 (9%)	0	0
Hypocalcaemia	30 (26%)	5 (4%)	0	0
Constipation	29 (25%)	0	0	0
Decreased appetite	29 (25%)	4 (3%)	0	0
Dizziness	29 (25%)	0	0	0
Hypophosphataemia	28 (24%)	14 (12%)	2 (2%)	0
Tremor	28 (24%)	2 (2%)	0	0
Lymphopenia	24 (21%)	7 (6%)	16 (14%)	0
Hypomagnesaemia	24 (21%)	0	0	0
Decreased blood fibrinogen	23 (20%)	6 (5%)	0	0
Hyperglycaemia	23 (20%)	10 (9%)	2 (2%)	0

	Full population (n=117)
Patients with cytokine release syndrome	
Any grade	99 (85%)
Grade 1	43 (37%)
Grade 2	46 (39%)
Grade 3	10 (9%)
Grade 4	0
Grade 5	0
Time to cytokine release syndrome onset, days*	4 (1–7)
Time to cytokine release syndrome resolution, days*	6 (4–11)
Patients with neurological events†	
Any grade	53 (45%)
Grade 1	13 (11%)
Grade 2	18 (15%)
Grade 3	21 (18%)
Grade 4	1 (1%)
Grade 5	0
Time to neurological event onset, days*	7 (4–11)
Time to neurological event resolution, days*	7 (4–16)

Siddiqi, Jordan Gauthier, Saad S. Kenderian, Danielle M. Brander, Kathleen Dorritie, Jacob D. Soumerai, Peter A. Riedell, Nirav N. Shah, Rajneesh Nath, Charalambos Andreadis, Daniel A. Ermann, Shuo Ma, Tatyana Feldman, Scott R. Solomon, Stephen J. Schuster, Sherilyn A. Tuazon, Serena K. Perna, San-San Ou, Neha Rane, Eniko Papp, Yizhe Chen, William G. Wierda; Lisocabtagene Maraleucel (liso-cel) in Patients (pts) with Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): Updated Follow-up of Transcend CLL 004. *Blood* 2024; 144 (Supplement 1): 4633

TRANSCEND CLL 004: Outcomes

- ORR (DL2 full population) 47% ORR (PEAS) 43%
- CRR 18% for both full (DL2) and PEAS
- Median DOR 35.3mo



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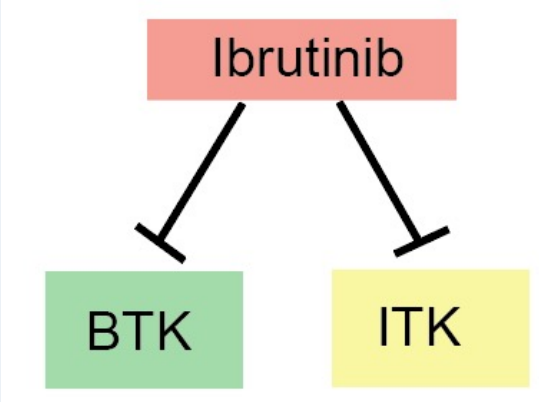
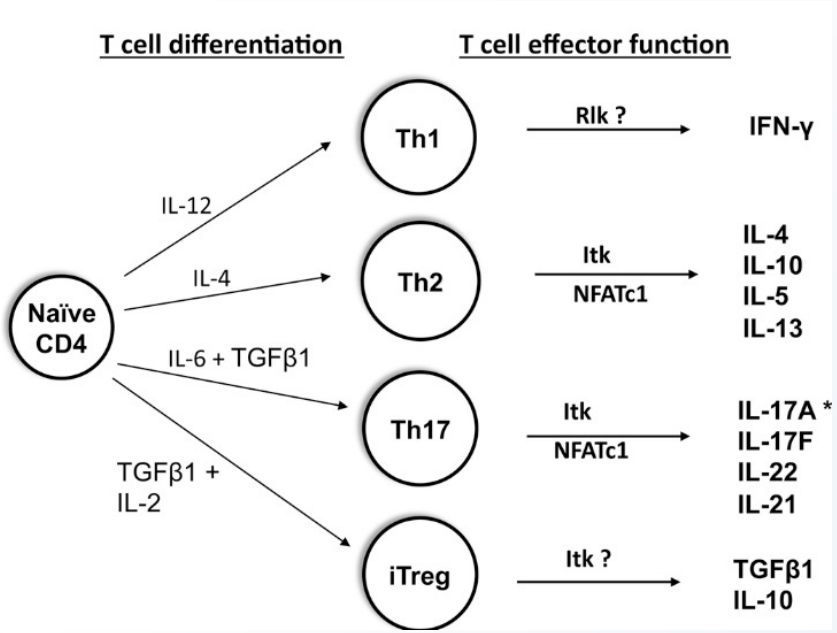
CD19 CAR T-cell Therapy, a potential curative option?

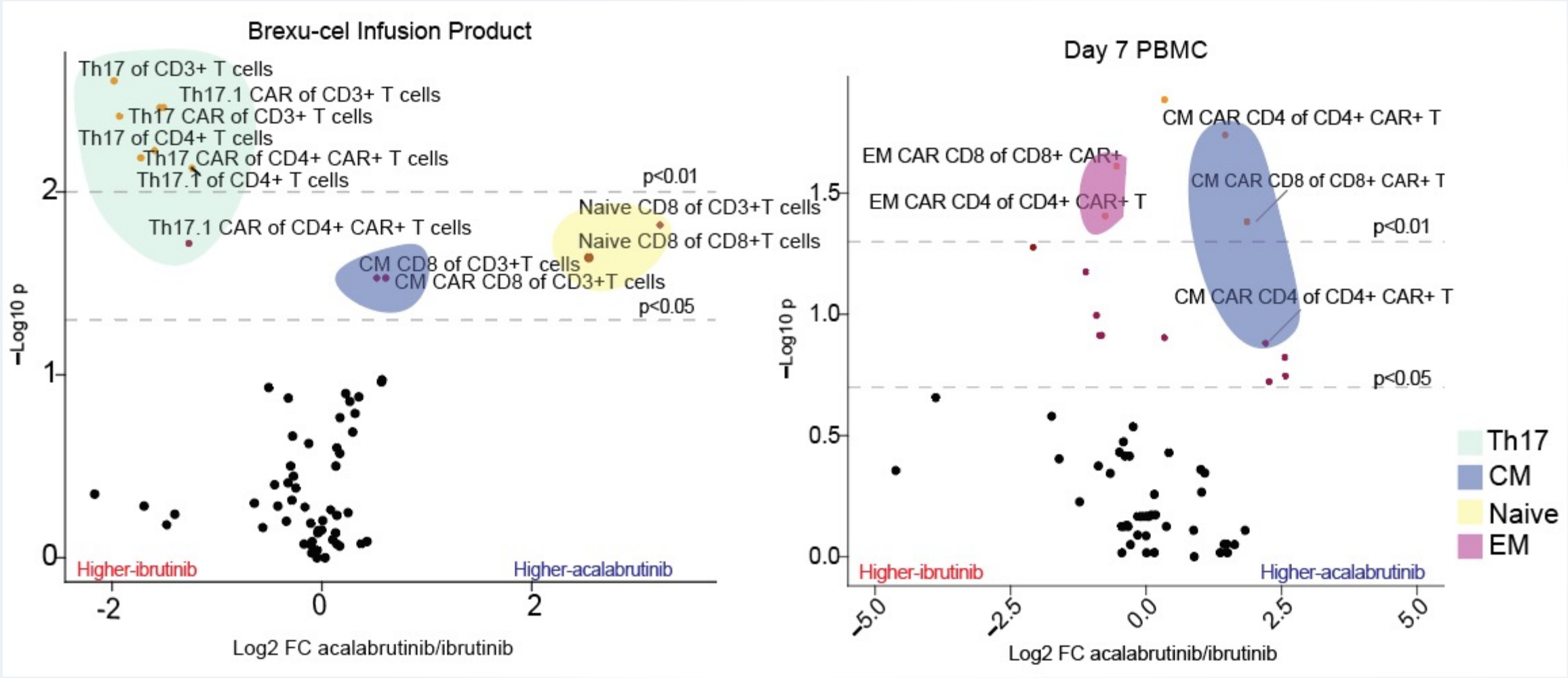
- ORR is limited compared to other B-cell malignancies, but DOR can be long in those achieving CR
- CLL patients with ≥1 year PFS to CD19 CAR T (n=34) had 5-year PFS 57.1%, no relapses observed if progression free after 4 years.
  - **Concluded CD19 CART is curative in a subset of CLL patients. Efforts to understand factors leading to long responders and increase ORR in CLL ongoing**





Benjamin F. Frost, Noelle Frey, Elizabeth O. Hexner, Stephen J. Schuster, Sunita D. Nasta, Alison W Loren, Jakub Svoboda, Daniel J. Landsburg, Bruce Levine, Joseph A. Fraietta, J. Joseph Melenhorst, Elizabeth Veloso, Wei-Ting Hwang, Carl H. June, David L. Porter, Saar Gill; Curing CLL: Long-Term Outcomes of Chronic Lymphocytic Leukemia Patients with at Least One Year of Response to CART-19 Therapy. *Blood* 2024; 144 (Supplement 1): 588. doi: https://doi.org/10.1182/blood-2024-204197

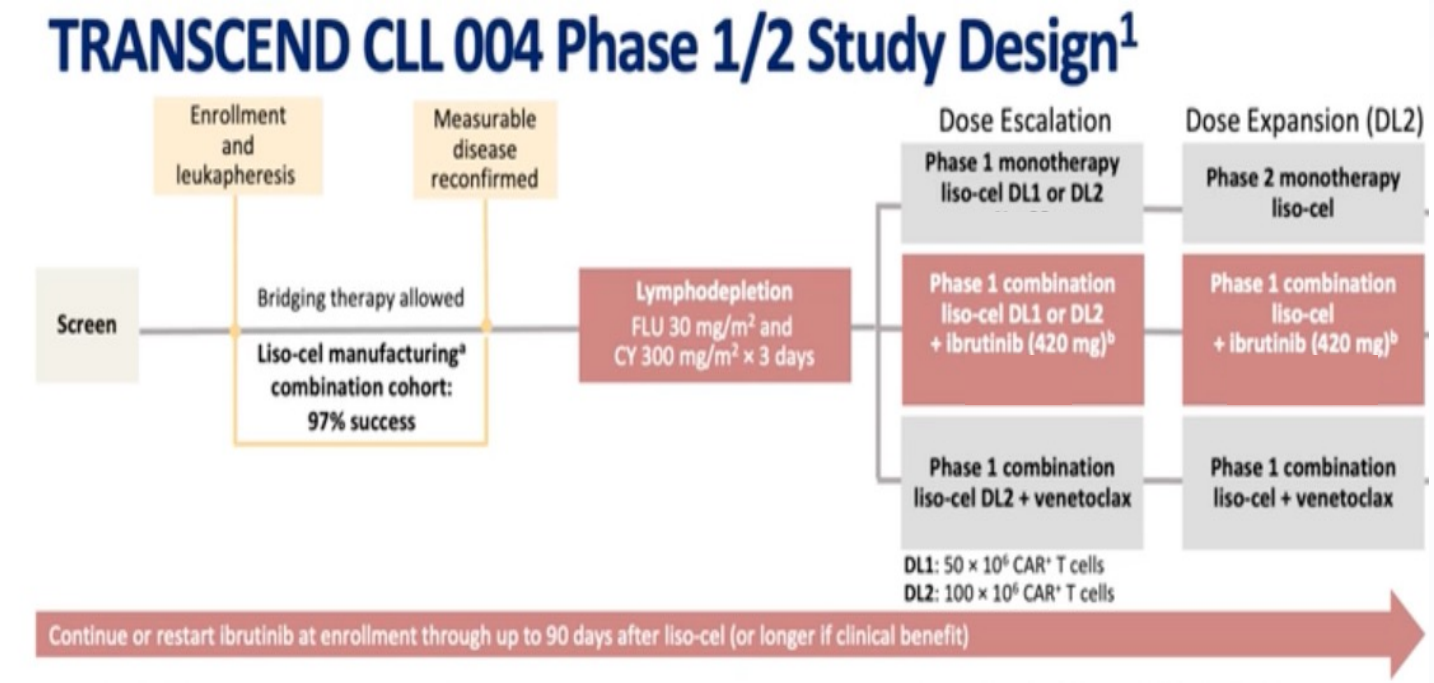
Can BTKi improve CD19 CAR T therapy? A look at ZUMA2 (MCL)



Darnell et al, Blood Advances 2026

Eli P. Darnell, Kathleen M. E. Gallagher, Justyna Kanska, Irene Scarfò, Gabriela Balderrama-Gutierrez, Trisha R. Berger, Justin Budka, David J. Bozym, Tarinee Huang, Rhine Shen, Mark B. Leick, Marcela V. Maus; Ibrutinib exposure correlates with improved efficacy of CAR T cells in patients with mantle cell lymphoma. *Blood Adv* 2026; 10 (4): 1023–1034. doi: https://doi.org/10.1182/bloodadvances.2025018137

Can BTKi improve CD19 CAR T therapy?



TRANSCEND CLL 004

	Liso-cel monotherapy	Liso-cel +ibrutinib
n (DL2)	108	51
G3+ CRS	9%	4%
G3+ NE	19%	11%
ORR	47%	86%
CRR	18%	45%
DOR (mo)	35.3	41.4

Wierda et al, ASH, 2024

Liso-cel + ibrutinib added into CLL NCCN guidelines based on these data

William G. Wierda, Kathleen Dorritie, Jordan Gauthier, Rajneesh Nath, Thomas J. Kipps, Peter A. Riedell, Herbert A. Eradat, Saad S. Kenderian, Mohamed A. Kharfan-Dabaja, Nirav N. Shah, Scott R. Solomon, Daniel A. Ermann, Jon E. Arnason, Abhinav Deol, Tatyana Feldman, Charalambos Andreadis, Monalisa Ghosh, Shuo Ma, Stephen J. Schuster, Usama Gergis, Julie M. Vose, Jacob D. Soumerai, Koen van Besien, Sherilyn A. Tuazon, Serena K. Perna, San-San Ou, Neha Rane, Eniko Papp, Yizhe Chen, Tanya Siddiqi; Lisocabtagene Maraleucel (liso-cel) Combined with Ibrutinib (ibr) for Patients (pts) with Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): Primary Results from the Open-Label, Phase 1/2 Transcend CLL 004 Study. *Blood* 2024; 144 (Supplement 1): 887. doi: https://doi.org/10.1182/blood-2024-200339

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CLL: Special circumstances for CD19 directed therapy

Richter Transformation

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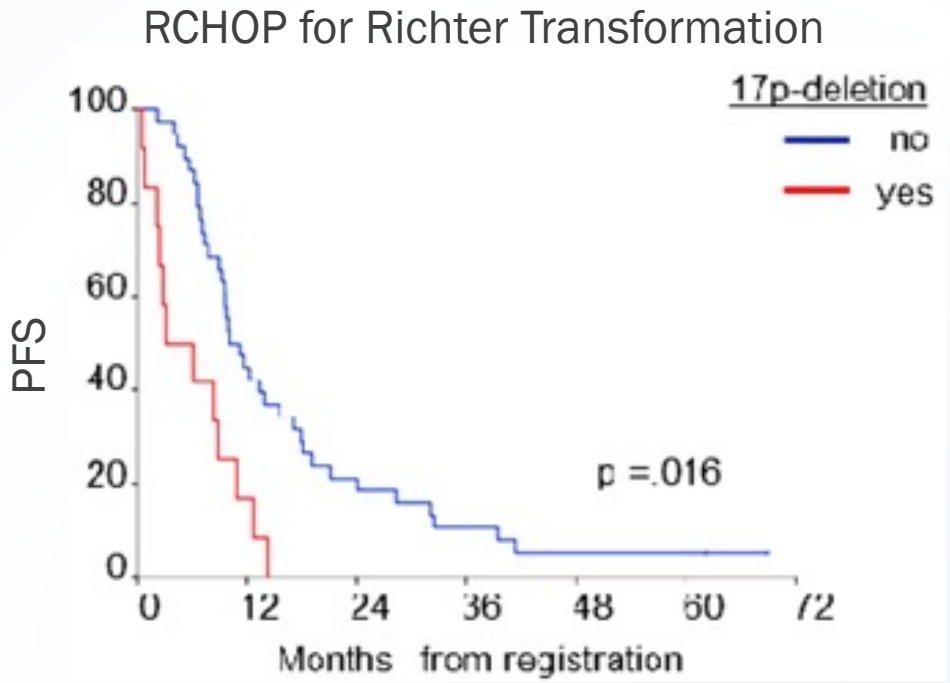
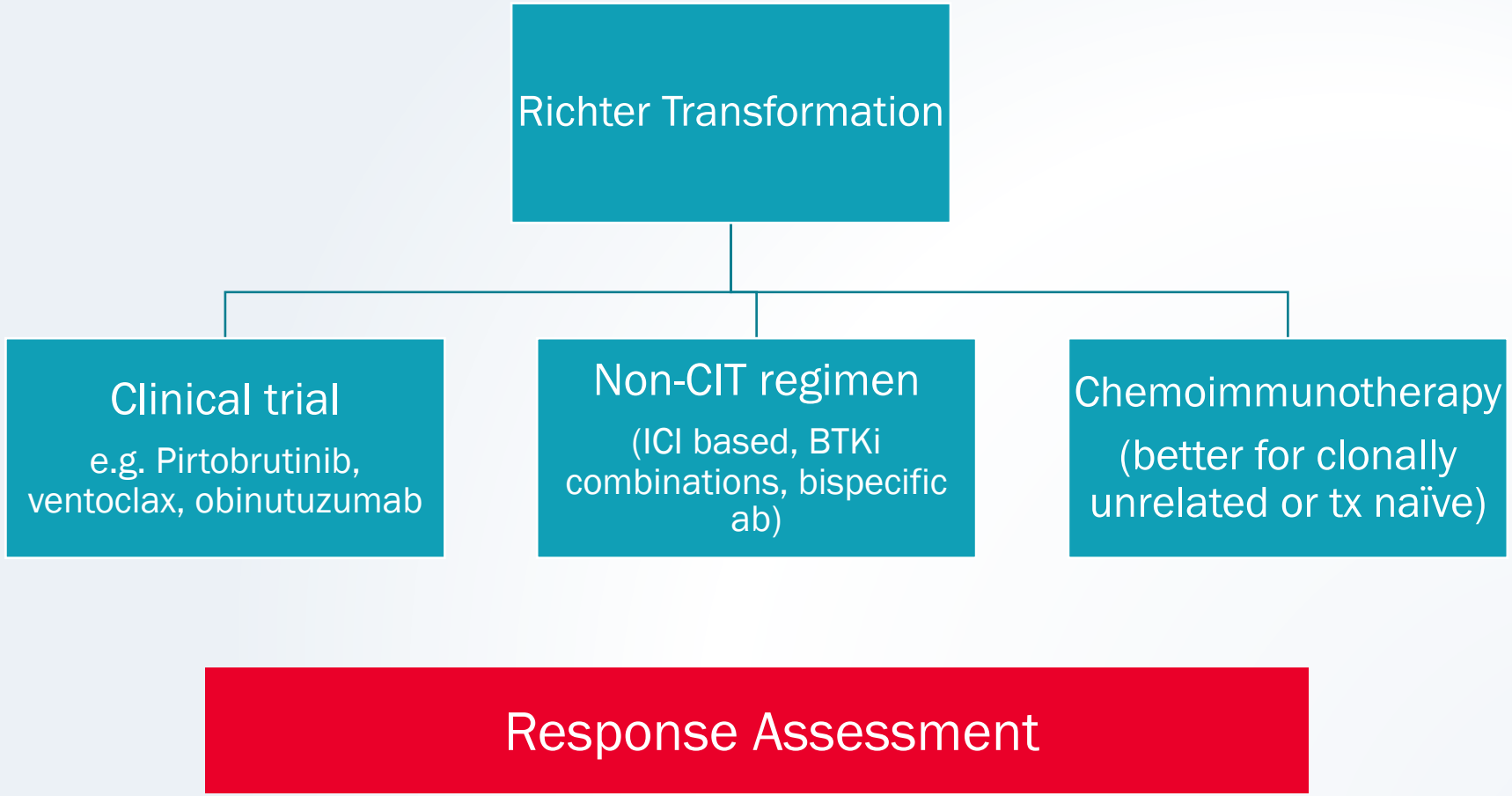
Richter Transformation: The role of CAR T-cell Therapy

- Richter transformation 2-10% lifetime incidence in patients with CLL
- 70-80% of DLBCL Richters is clonally related (IGHV) to underlying CLL
- Significant enrichment (>50%) for poor-risk molecular profiles (e.g. TP53 mutant, 17p del)
- Outcomes with CIT are poor

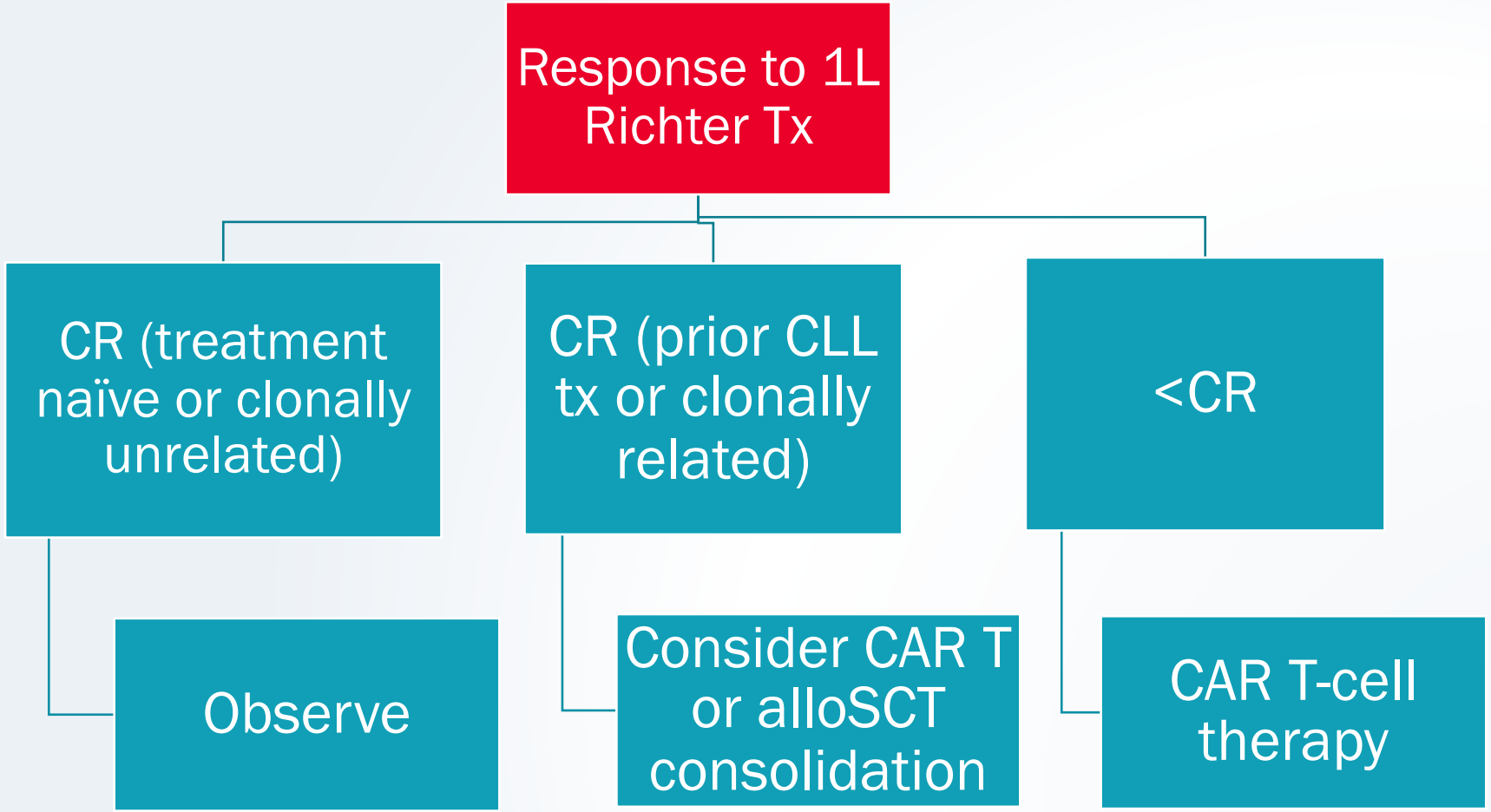


Langerbeins, P., Busch, R., Anheier, N., Dürig, J., Bergmann, M., Goebeler, M.-E., Hurtz, H.-J., Stauch, M.B., Stilgenbauer, S., Döhner, H., Fink, A.-M., Cramer, P., Fischer, K., Wendtner, C.-M., Hallek, M. and Eichhorst, B. (2014), Poor efficacy and tolerability of R-CHOP in relapsed/refractory chronic lymphocytic leukemia and Richter transformation. Am. J. Hematol., 89: E239-E243. https://doi.org/10.1002/ajh.23841

Richter Transformation: The role of CAR T-cell Therapy



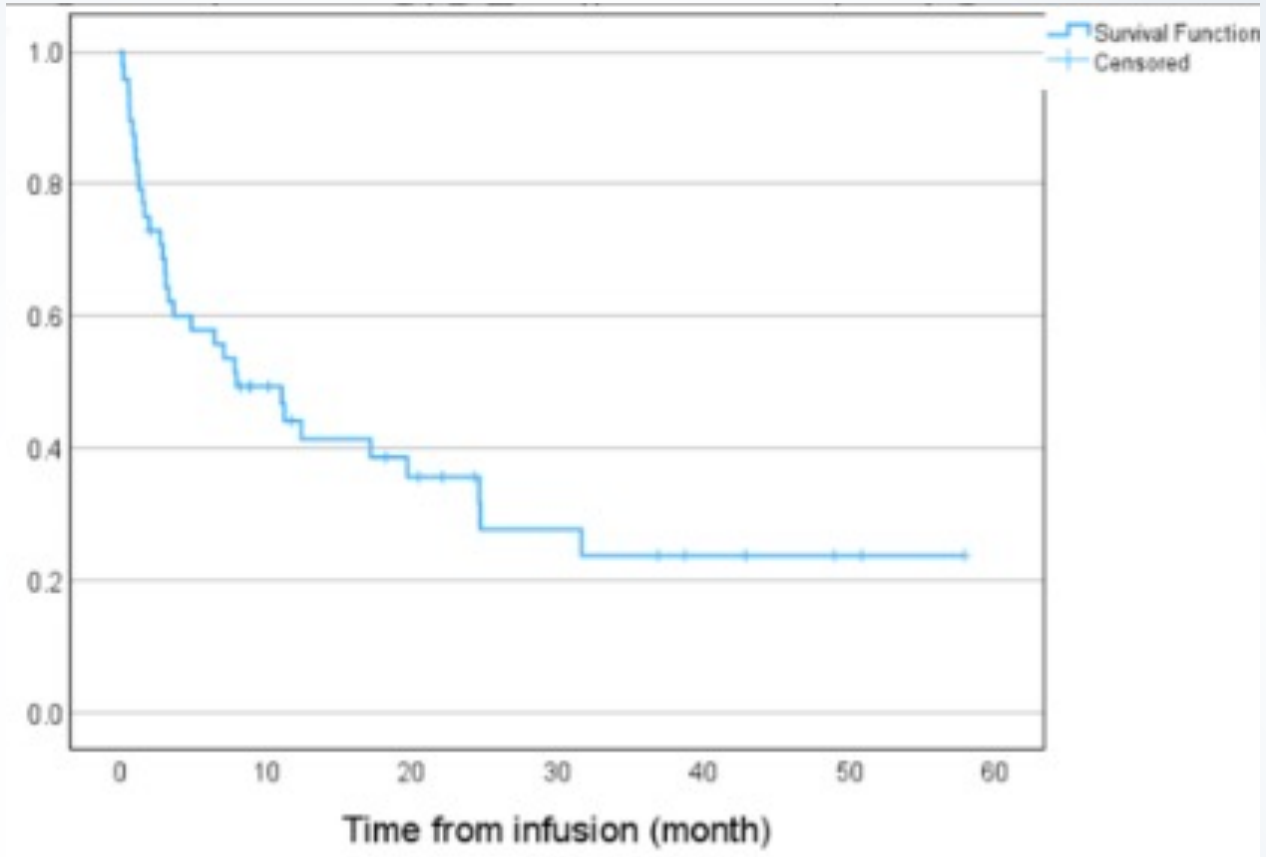
Richter Transformation: The role of CAR T-cell Therapy



Richter Transformation: The role of CAR T-cell Therapy

Retrospective multicenter study (2025) by European research initiative in CLL (ERIC) of RT treated with CD19 CAR T-cell therapy (n=54)

- ORR 65%, CRR 50% (3 months)
- 12-month PFS 41%, median 8mo
- Median OS 14.4mo
- Median PFS for CR 31.6mo, OS not reached for this group



Number at risk		6m	12m	18m	24m	30m	36m
	N=48	20	6	2	1	2	1

O.Beyar-Katz, O.Benjamini, J.Delgado, et al., "CD19 CAR T-Cell Therapy in Richter Transformation: A Multicentre Retrospective Analysis by the European Research Initiative on Chronic Lymphocytic Leukaemia," Journal of Cellular and Molecular Medicine29, no. 20 (2025): e70841, https://doi.org/10.1111/jcmm.70841.

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CLL: Special circumstances for CD19 directed therapy

Investigational CD19 agents in CLL

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Experimental and Off-label CD19-targeting Therapies in CLL

- Tafasitamab (CD19 monoclonal ab)
  - *Pongas et al ASH 2025: Phase II MRD guided tafasitamab + Zanubrutinib 1L CLL. ORR 85% CRR 25%*
- Loncastuximab Tesirine (CD19 ADC)
  - *Phase I study of loncastuximab + acalabrutinib enrolling*
- CD19 Bispecific antibodies
  - *Anticipated CLL/SLL studies with this therapeutic drug class*

Takeaways

What are the current CD19 targeting therapies in CLL?

- Currently, CD19 CAR T-cell therapies (liso-cel the only FDA approved CAR) are the only SOC CD19 targeting class of therapy for CLL
- Other CD19 therapies (ADC, bispecifics) under investigation

When should we deploy CD19 CAR T cell therapy in CLL?

- R/R disease, 3L+ after exposure to BTKi and BCL2i.
- Richter transformation: consider CAR T consolidation/salvage

Limitations of CD19 CAR T-cell products in CLL?

- ORR for CAR T as monotherapy in r/r CLL is modest compared to other B cell malignancies
- However, CR is often durable and potentially curative
- Potential to improve responses with combinatorial approaches (BTKi)