Immunotherapy Treatment for Leukemia – Chronic Lymphocytic Leukemia

Adam Kittai, MD, MBA

Associate Professor

Director, CLL Program, Perlmutter Cancer Center

Director, Lymphoma Program, Perlmutter Cancer Center-LI

Disclosures:

Name of Company	Research support	Consultant	Scientific Advisory Board	Other
Abbvie		x	x	
AstraZeneca	x	x	x	Speaker Honoraria
Eli Lilly				Speaker Honoraria
Galapagos		x	x	
Genmab			x	
Janssen				Speaker Honoraria
Pfizer			x	

Agenda:

1. **Anti-CD20 Monoclonal Antibodies**
2. **Chimeric Antigen Receptor T-cell Therapy (CAR-T)**

   What is it

   When to use it

   How well does it work

   What are the toxicities and long-term efficacy
3. **Bispecific Antibodies**

   What is it

   When to use it

   How well does it work

   What are the toxicities and long-term efficacy

Anti-CD20 Monoclonal Antibodies

Anti-CD20 Antibodies

1. **Target the “CD20” outside of B-cells**

2. **Often used agents;**

   Obinutuzumab - Favored

   Rituximab

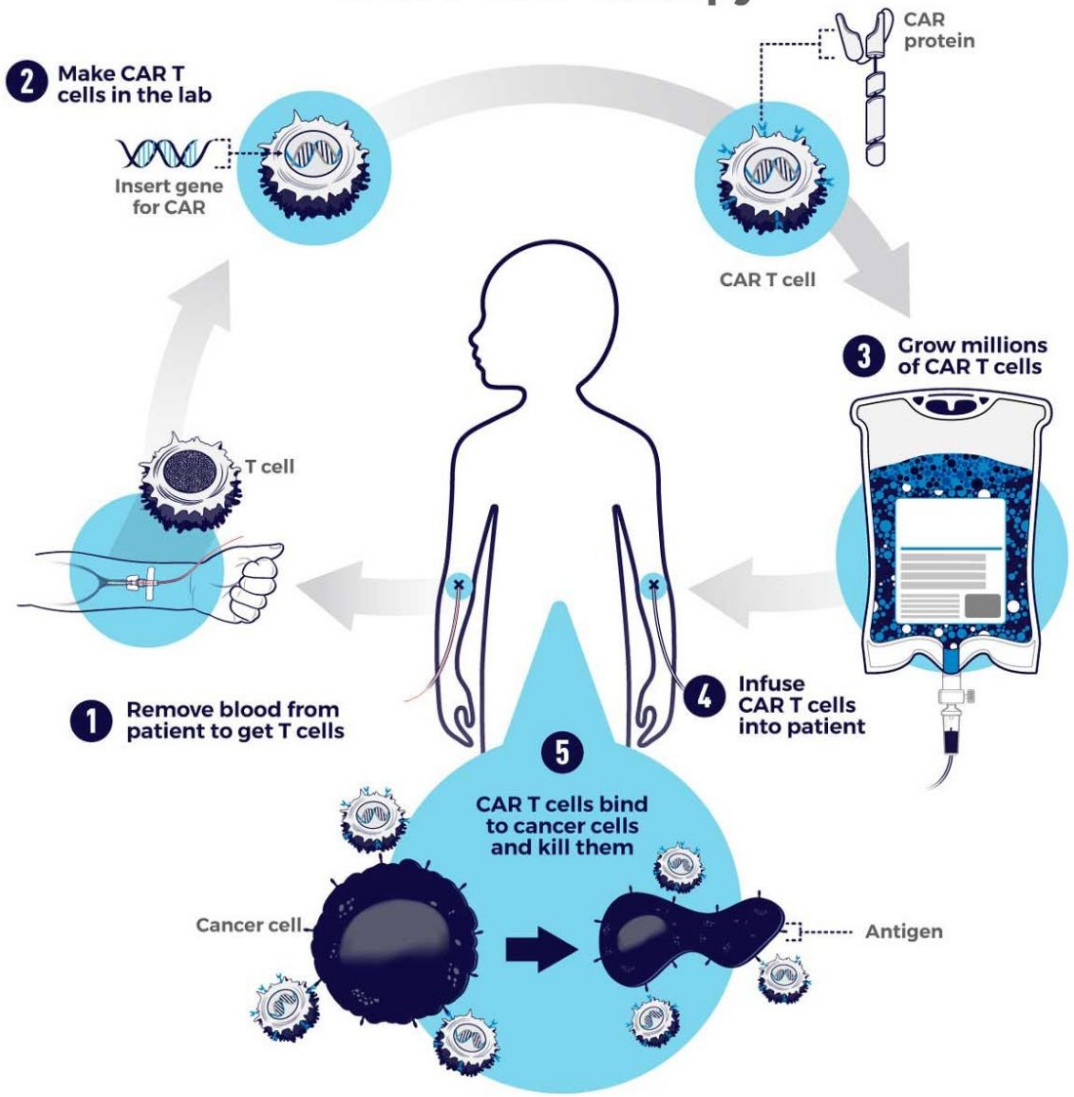
3. **Usually used in combination;**

   Venetoclax + Obinutuzumab or Rituximab

   Acalabrutinib + Obinutuzumab

CAR-T for CLL

CAR T-Cell Therapy



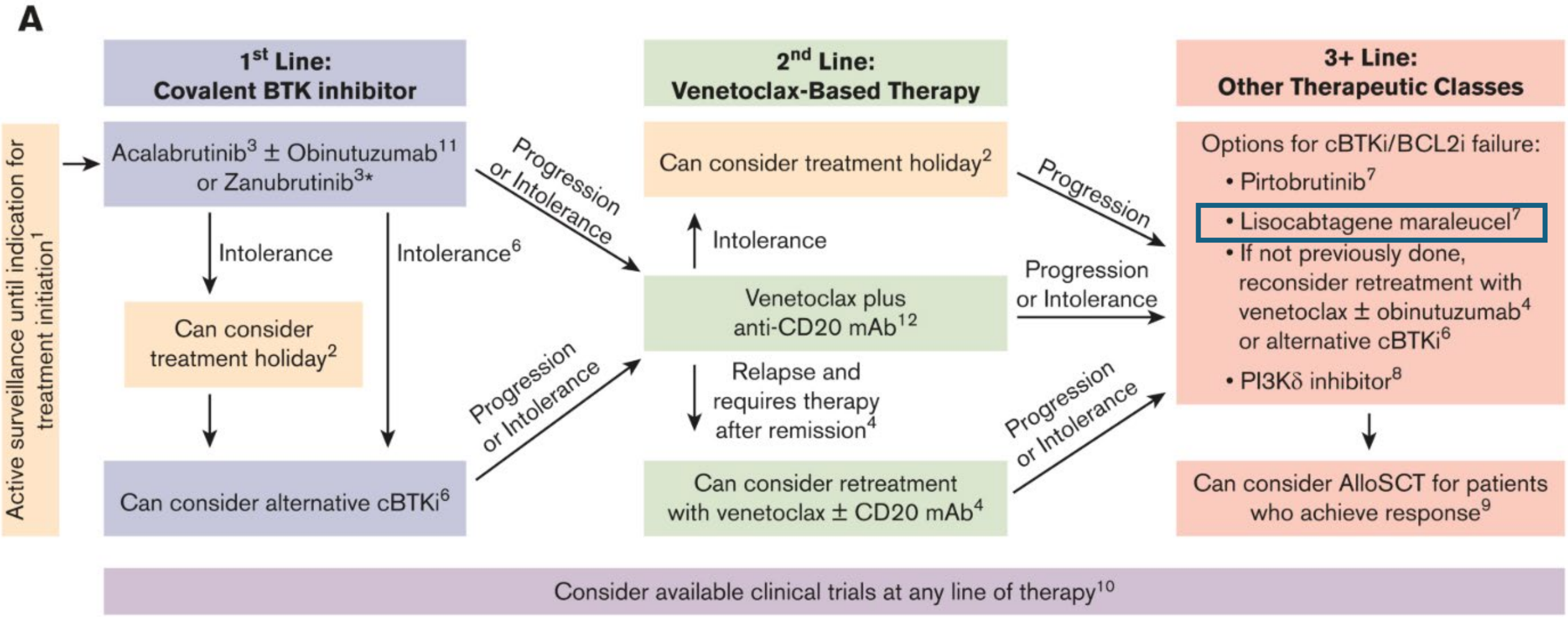
CAR T-cell therapy is a type of treatment in which a patient's T cells are genetically engineered in the laboratory so they will bind to specific proteins (antigens) on cancer cells and kill them. **(1)** A patient's T cells are removed from their blood. Then, **(2)** the gene for a special receptor called a chimeric antigen receptor (CAR) is inserted into the T cells in the laboratory. The gene encodes the engineered CAR protein that is expressed on the surface of the patient's T cells, creating a CAR T cell. **(3)** Millions of CAR T cells are grown in the laboratory. **(4)** They are then given to the patient by intravenous infusion. **(5)** The CAR T cells bind to antigens on the cancer cells and kill them.

cancer.gov

NCCN Guidelines

THERAPY FOR RELAPSED OR REFRACTORY DISEASE AFTER PRIOR cBTKi-BASED AND BCL2i-CONTAINING REGIMENS[e,f]	
Preferred • Chimeric antigen receptor (CAR) T-cell therapy ▸ Lisocabtagene maraleucel (CD19-directed)[dd] ± Ibrutinib[j] • ncBTKi-based regimen: ▸ Pirtobrutinib (continuous) (category 1) (if not previously given)	**Other Recommended** • PI3Ki-based regimens ▸ Duvelisib ▸ Idelalisib[bb] ± Rituximab • FC + Rituximab[s,t,**] • Lenalidomide[cc] ± Rituximab • Obinutuzumab • Alemtuzumab[dd] ± Rituximab (with del(17p)/*TP53* mutation) • Bendamustine[p] + Rituximab[q,**] (category 2B for patients ≥65 y or patients <65 y with significant comorbidities) • HDMP + anti-CD20 mAb[o] (category 2A with del[17p]; category 2B without del[17p])

** Not recommended for CLL/SLL with del(17p)/*TP53* mutation.



Soumerai et al Blood Advances 2025

Before I would even consider CAR-T for CLL

Patients would usually have received:

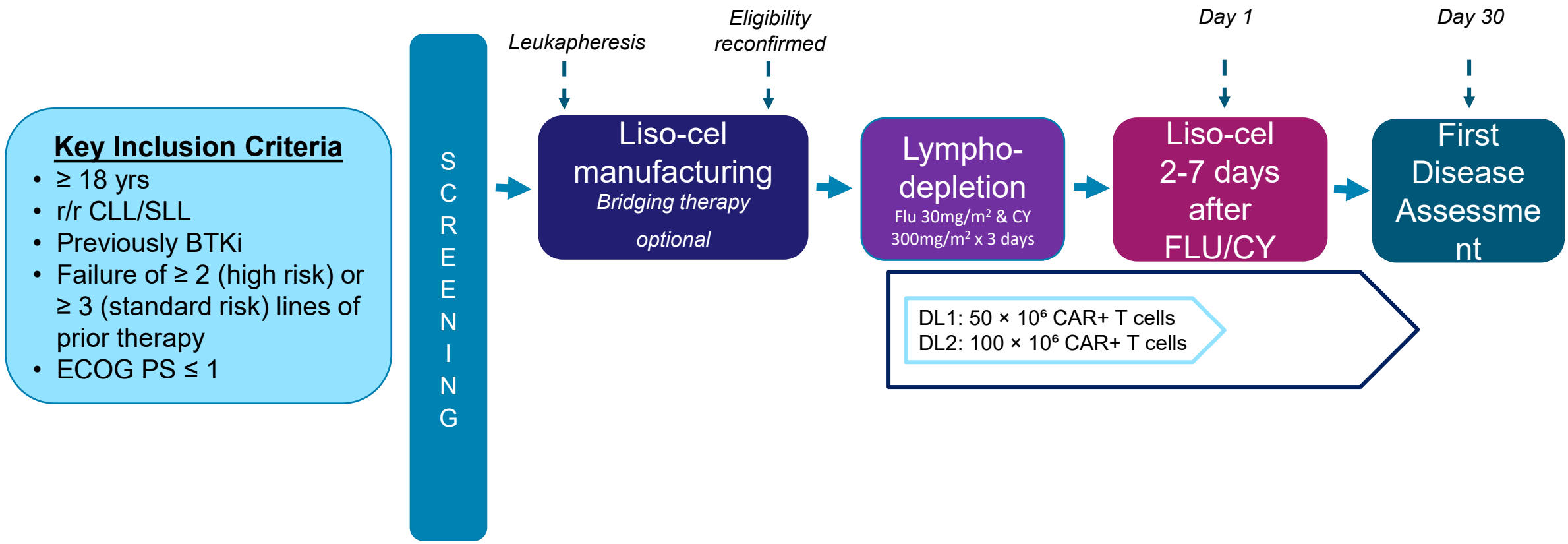
Venetoclax-based regimen

Covalent BTK inhibitor – Ibrutinib, Acalabrutinib, Zanubrutinib

Non-Covalent BTK inhibitor - Pirtobrutinib

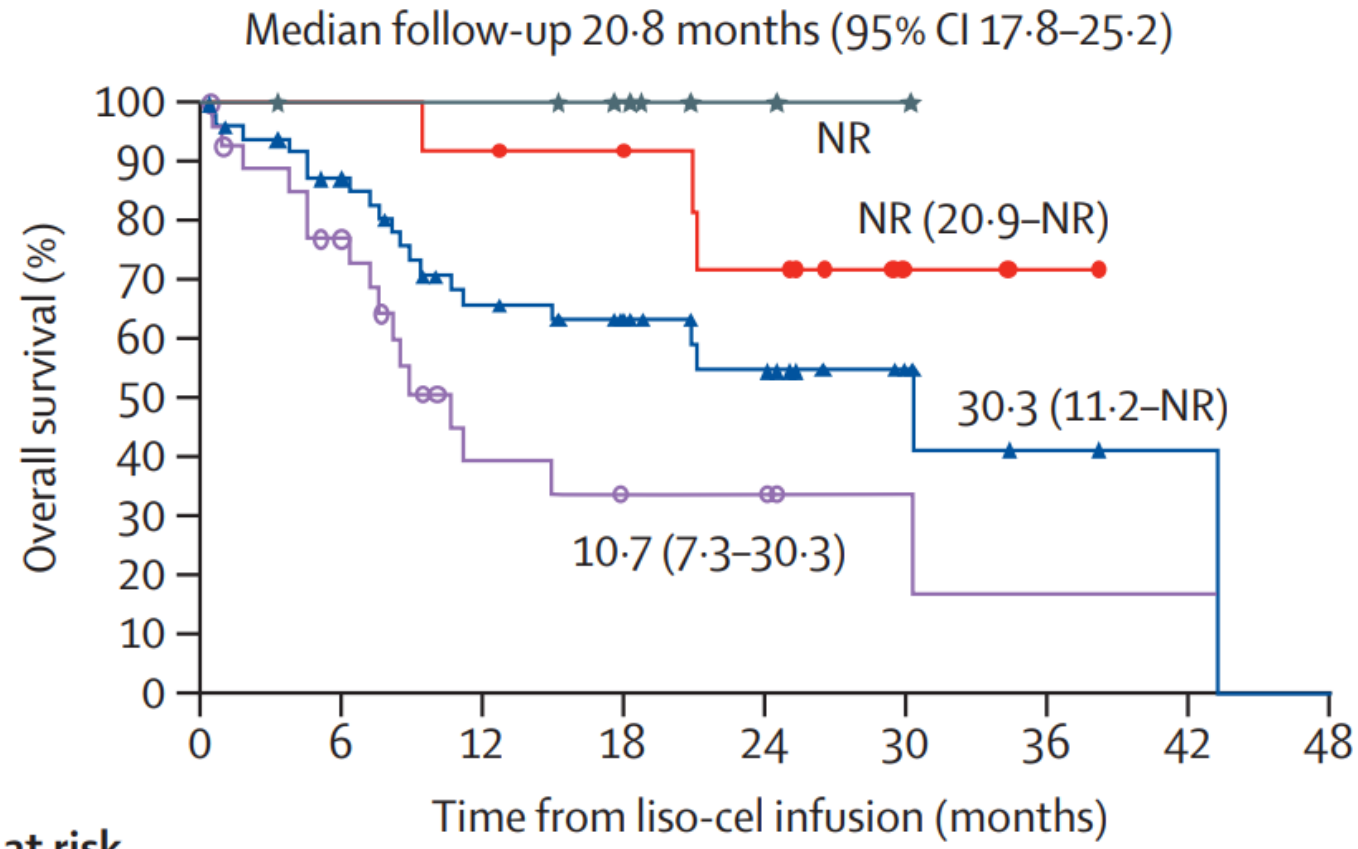
An anti-CD20 Antibody – Obinutuzumab – A type of immunotherapy

TRANSCEND CLL004: Study Design



References: Siddiqi T, et al. *Lancet*. 2023;402(10402):641-654.

TRANSCEND-004 – Liso-cel for RR CLL



Number at risk

CR or CRi	9	8	8	6	2	1	0	0	0
PR or nPR	12	12	11	9	7	2	1	0	0
Non-responder	28	18	7	4	4	2	1	1	0
Total	49	38	26	19	13	5	2	1	0

Siddiqi T et al Lancet 2023

Liso-Cel + Ibrutinib Cohort – TRANSCEND CLL-004

Patient Characteristics		DL2 + Ibr (n=51)	Liso-cel + Ibr (n=56)
Median age (range), years		65 (44-77)	65 (44-77)
Median prior LOT (range), n		5 (1-13)	5 (1-13)
≤3 prior LOT, n (%)		19 (37)	20 (36)
Prior therapy, n (%)	BTKi	51 (100)	56 (100)
	Ven	39 (76)	42 (75)
	BTKi and Ven	39 (76)	42 (75)
	BTKi PD/Ven failure[a]	28 (55)	31 (55)
High-risk cytogenetics, n (%)	Overall	50 (98)	55 (98)
	del(17p)	23 (45)	25 (45)
	Mutated TP53	23 (45)	24 (43)
	Unmutated IGHV	37 (73)	39 (70)
	Complex karyotype[b]	25 (49)	29 (52)

Wierda et al ASH 2024. Abstract 887.

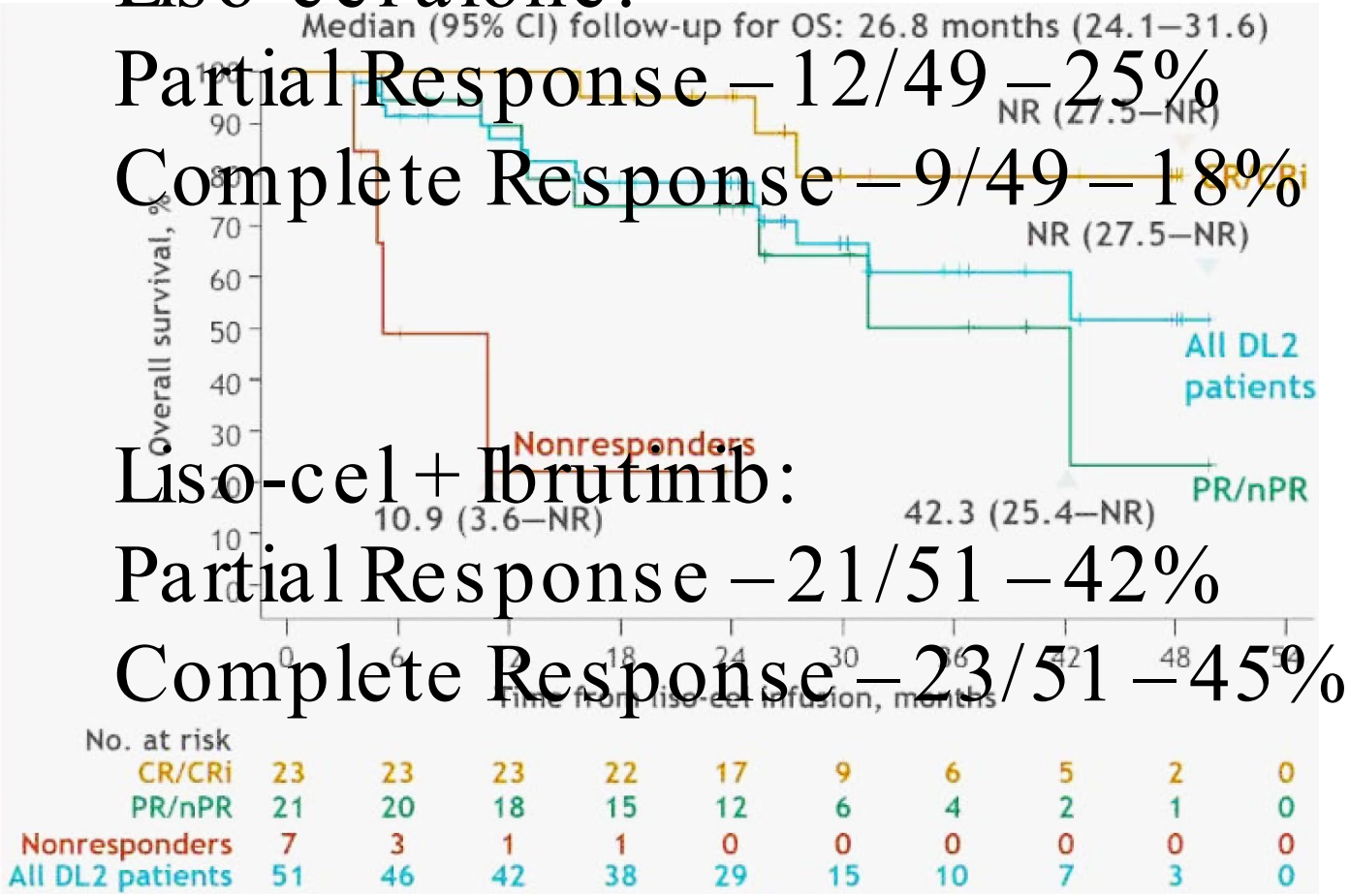
PFS and OS of Ibrutinib + Liso-cel

Treatment

- Median Ibr exposure (in the total combination-treated set)
  - 34 days (range, 15-188) before Liso-cel
  - 95 days (range, 6-1517) after Liso-cel

Liso-cel alone:
Partial Response – 12/49 – 25%
Complete Response – 9/49 – 18%

Liso-cel + Ibrutinib:
Partial Response – 21/51 – 42%
Complete Response – 23/51 – 45%



Wierda et al ASH 2024. Abstract 887.

Toxicity

Cytokine Release Syndrome (CRS)

- High Fevers
- Hypotension
- Caused by T-cell activation
- ~3 day onset

Neurotoxicity (ICANS)

- Worsening confusion over time
- ~5 day onset

TRANSCEND CLL004: CRS, Neurologic Events, AEs of Special Interest

	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)
Other adverse events of special interest	
Prolonged cytopenia‡	63 (54%)
Grade ≥3 infections§	20 (17%)
Hypogammaglobulinaemia¶	18 (15%)
Tumour lysis syndrome	13 (11%)
Second primary malignancy‖	11 (9%)
Macrophage activation syndrome**	4 (3%)

Most common treatment-emergent AEs (any grade)

- Anemia: 78 (67%)
- Neutropenia: 72 (62%)
- Thrombocytopenia: 58 (50%)
- Fatigue: 40 (34%)

References: Siddiqi T, et al. *Lancet*. 2023;402(10402):641-654.

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Pros and Cons of CAR T-Cell therapy

Pros

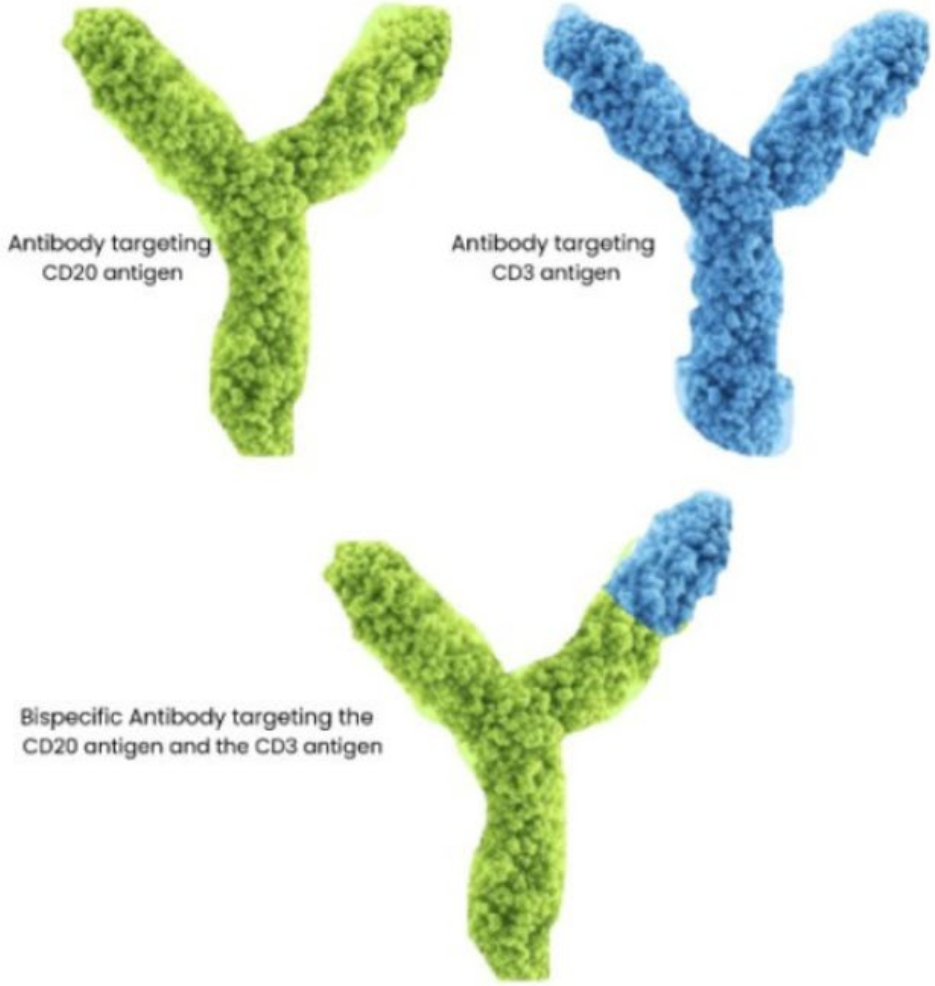
- Durable responses for patients who obtain a complete response
- Works in patients with high-risk CLL
- One-time therapy

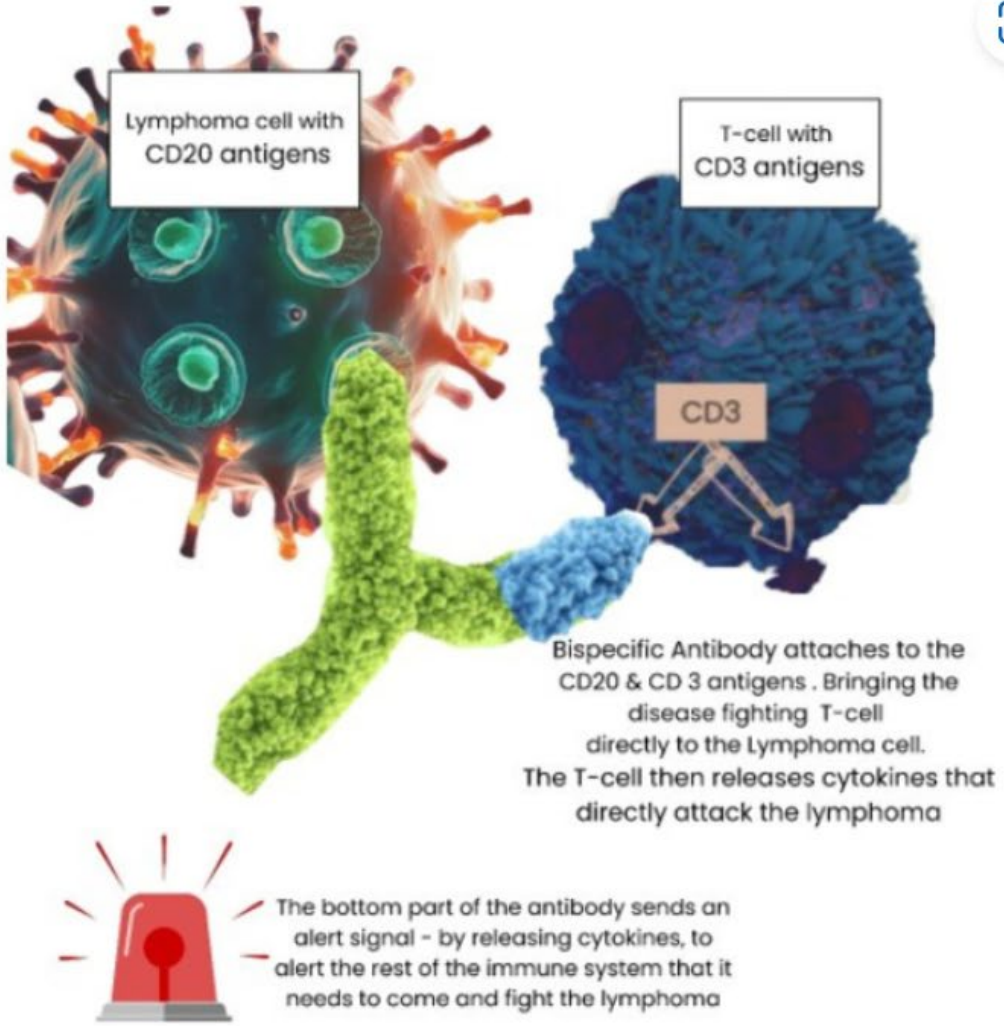
Cons

- Significant cost
- Toxicity
- Manufacturing time ~3 weeks
- Need to increase complete response rate
- Inpatient administration

Bispecific antibodies for CLL

Bispecific Antibodies





Picture courtesy of
Health Literacy Now (2025)

Bispecific Antibodies

- Epcoritamab
- Glofitamab
- Mosunetuzumab
- All target the “CD20” protein on the outside of CLL cells
  - Similar to rituximab or obinutuzumab in what it targets

Epcoritamab Data

Cycle[a]	Day	Dose of EPKINLY	
Cycle 1	1	Step-up dose 1	0.16 mg
	8	Step-up dose 2	0.8 mg
	15	Step-up dose 3	3 mg
	22	First full dose	48 mg
Cycles 2 and 3	1, 8, 15 and 22	48 mg	
Cycles 4 to 9	1 and 15	48 mg	
Cycle 10 and beyond	1	48 mg	

[a] Cycle = 28 days

- Total Patients = 40
- Median Follow-up 22.8 months
- 4 prior lines of therapy
- All pts had prior BTKi
- ORR was 61% and CR rate was 39%
- Time to response - 2.0 months
- Median progression-free survival - 12.8 months
- Median OS was not reached
- CRS - 71% G1, 12% G2
- No ICANS

Pros and Cons of Bispecific Antibodies

Pros

- Off-the-shelf
- Novel mechanism of action
- Better tolerated
- Outpatient administration

Cons

- Not available yet
- Has to be given often
- Long-term data not available
- Need to increase efficacy

Conclusions

- CAR-T is currently approved
  - Use in combination with a BTKi
  - Use after prior BTKi and Venetoclax
- More work needs to be done focusing on safety of CAR-T

- Bispecific antibodies are not approved for CLL
  - Studies currently underway
  - Will be a long time for approval
  - Seem to mitigate risk, and maintain efficacy

Thank you