4th POSTGRADUATE

# CLL Conference

Bologna
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2023

Royal Hotel Carlton

**President:**
Pier Luigi Zinzani

# Is there already a role for CAR-T cell therapy in CLL?

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# Disclosures of Tanya Siddiqi, MD

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| AstraZeneca | | | | | X | X | |
| BMS | X | | | | X | X | |
| Beigene | | | | | X | X | |
| Abbvie | | | | | | X | |
| Gilead | | | | | | X | |

# High unmet need in R/R CLL/SLL after BTKi and venetoclax

- Outcomes remain poor for patients with R/R CLL/SLL who have relapsed after prior BTKi and venetoclax failure, with low CR/CRi rates of 0%—5% and short median OS[1—6]

- Real-world evidence indicates progressively worse outcomes as treatment options become exhausted[7]
  - Median time from dual discontinuation of BTKi and venetoclax to subsequent treatment failure or death was 5.6 months

- Effective therapies are needed for patients with CLL who have failed novel targeted therapies

1. Patel K, et al. *J Hematol Oncol* 2021;14:69; 2. Sedlarikova L, et al. *Front Oncol* 2020;10:894; 3. Lew TE, et al. *Blood Adv* 2021;5:4054—4058; 4. Jones J, et al. *Blood* 2016;128:637; 5. Mato AR, et al. *Clin Cancer Res* 2020;26:3589—3596; 6. VENCLEXTA® (venetoclax) [package insert]. North Chicago, IL: AbbVie Inc.; June 2022; 7. Mato AR, et al. *Clin Lymphoma Myeloma Leuk* 2023;23:57—67.

# Long-Term Remission of CLL with CAR T cells

- 2 advanced, chemotherapy-resistant CLL patients with the longest (10+ years) follow-up on any trial of CART19 cells
- Both patients had received five therapies before being treated at the University of Pennsylvania with autologous CART19 cells (tisagenlecleucel) cells in 2010
- Both patients have persistence of CAR-engineered T cells and both patients are still in remission as determined by flow cytometry and deep sequencing of IgH rearrangements for over 10 years

Melenhorst JJ, et al. Nature 2022; 602: 503-9

# CAR-T cells after failure of ibrutinib: JCAR014

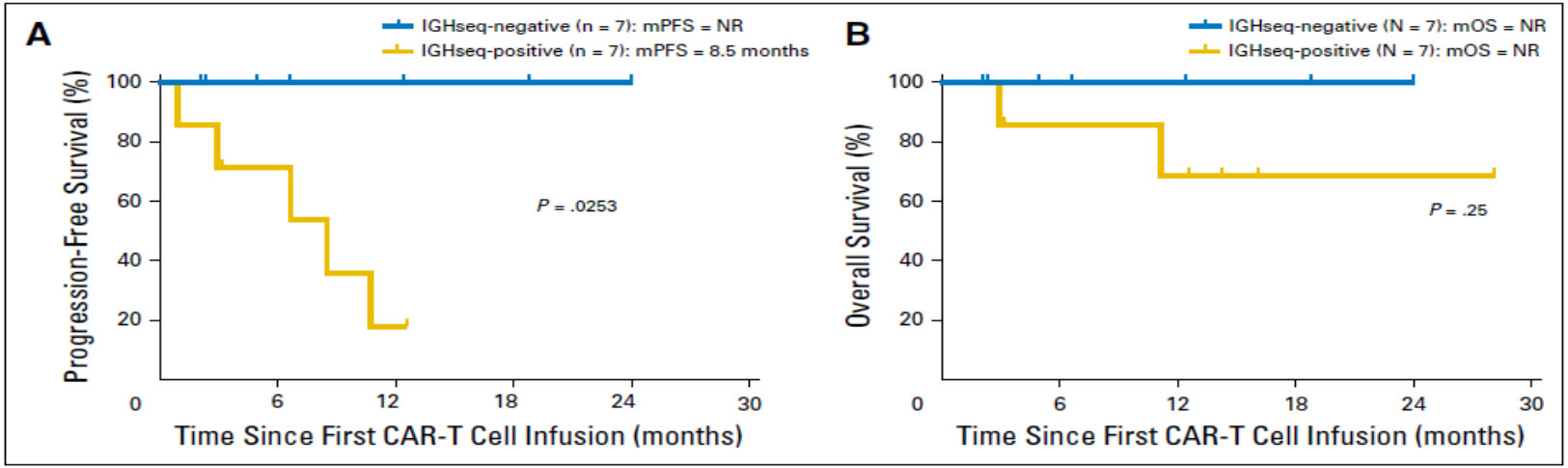


**Fig 4.** (A) Progression-free survival and (B) overall survival in patients who cleared disease from bone marrow 4 weeks after CAR-T cell infusion by flow cytometry and had no detectable malignant IGH copies (IGHseq-negative) compared with those who had detectable malignant IGH copies (IGHseq-positive). mOS, median OS; mPFS, median PFS; NR, not reached.

JCAR014 plus ibrutinib led to lower CRS severity and lower serum concentrations of CRS-associated cytokines despite equivalent in vivo CAR-T cell expansion

Turtle C, et al. JCO 2017; 35: 3010-20
Gauthier J, et al. Blood 2020; 135 (19): 1650–1660

# Lisocabtagene maraleucel in relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: primary analysis of the phase 1/2, single-arm, multicenter TRANSCEND CLL 004 study

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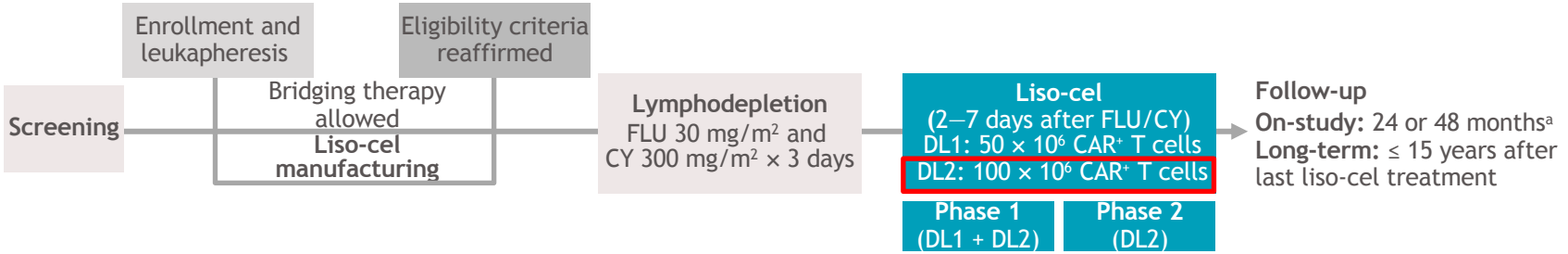
*ASCO 2023, ICML 2023, SOHO 2023*

# TRANSCEND CLL 004 study design: phase 1/2, open-label, multicenter study

ClinicalTrials.gov: NCT03331198




**Key patient eligibility criteria**

- Age ≥ 18 years
- R/R CLL/SLL with an indication for treatment
- Previously failed or ineligible for BTKi therapy
- Failure of ≥ 2 (high risk) or ≥ 3 (standard risk) lines of prior therapy
- ECOG PS ≤ 1
- Adequate bone marrow, organ, and cardiac function
- No Richter transformation nor active CNS involvement by malignancy

**Primary endpoint (PEAS at DL2)**

- CR/CRi rate per iwCLL 2018 by IRC assessment

**Key secondary endpoints (PEAS at DL2)**

- ORR, uMRD rate in blood

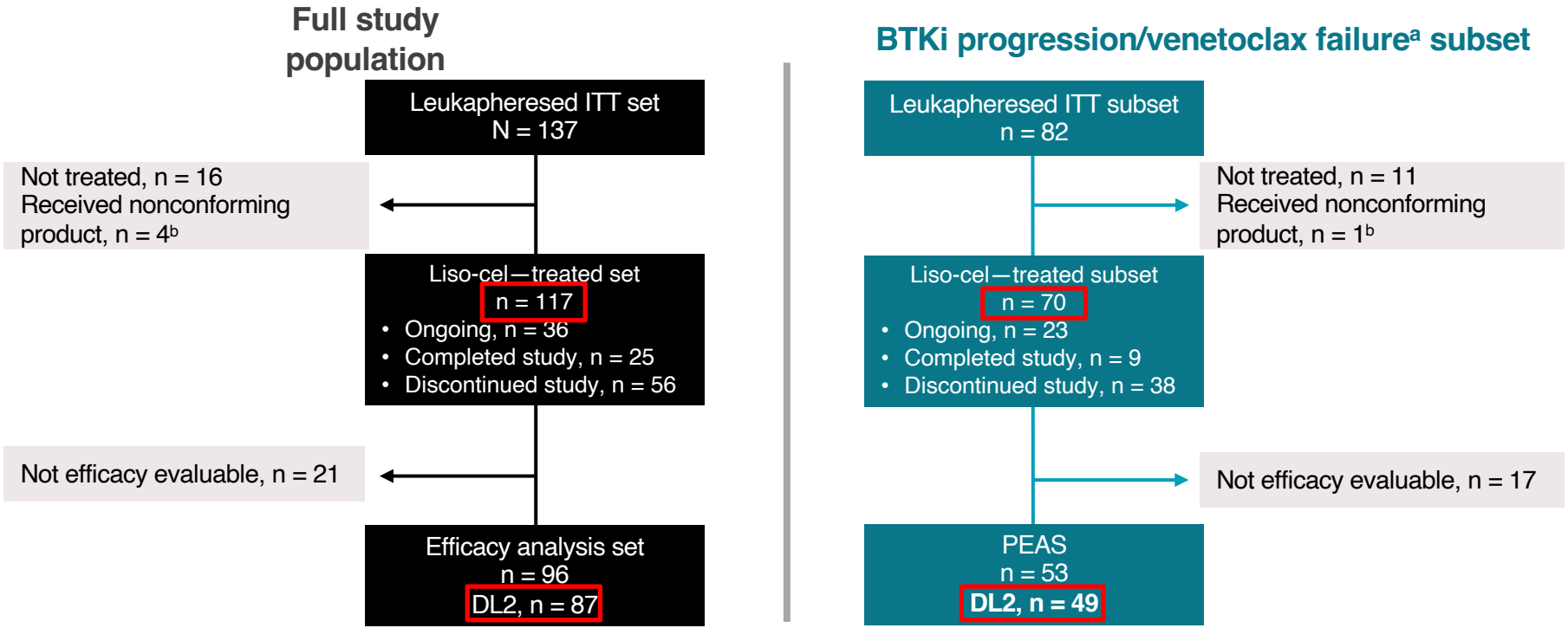
**Other secondary endpoints**

- DOR, DOCR, PFS, TTR, TTCR per IRC assessment, OS, uMRD CR rate in blood, and safety

- Primary and key secondary endpoints were tested in a prespecified subset of patients with BTKi progression and venetoclax failure (PEAS) at DL2 by the following hierarchy: CR/CRi rate ($H_0 \leq 5\%$), ORR ($H_0 \leq 40\%$), and uMRD rate in blood ($H_0 \leq 5\%$)

[a]Duration of follow-up was increased to 48 months in protocol amendment 5 (February 16, 2021). Patients still in ongoing response per iwCLL 2018 criteria after the 2-year follow-up were followed for safety, disease status, additional anticancer therapies, and survival for an additional 2 years or until progression.

# CONSORT diagram




[a]Venetoclax failure was defined as discontinuation of venetoclax due to disease progression or intolerability and met indications for further therapy per iwCLL 2018, or no objective response within 3 months of initiating venetoclax; [b]Nonconforming product was defined as any product wherein one of the CD8 or CD4 cell components did not meet one of the requirements to be considered liso-cel but was considered appropriate for infusion. ITT, intention to treat.

# Demographics and baseline characteristics

| Characteristic | Full study population (n = 117) | BTKi progression/venetoclax failure subset (n = 70) |
|---|---|---|
| **Median (range) age, y** | 65.0 (49—82) | 66.0 (49—78) |
| **Median (range) prior lines of systemic therapy** | 5 (2—12) | 5 (2—12) |
| **Bulky lymph nodes,[a] n (%)** | | |
| Yes | 52 (44) | 32 (46) |
| Unknown | 9 (8) | 8 (11) |
| **High-risk cytogenetics, n (%)** | 97 (83) | 60 (86) |
| **Prior BTKi, n (%)** | 117 (100) | 70 (100) |
| BTKi refractory[b] | 103 (88) | 70 (100) |
| BTKi relapsed[c] | 2 (2) | 0 |
| BTKi intolerant only | 12 (10) | 0 |
| **Prior venetoclax, n (%)** | 94 (80) | 70 (100) |
| Venetoclax refractory[b] | 89 (76) | 67 (96) |
| Venetoclax relapsed[c] | 0 | 0 |
| Venetoclax intolerant only | 4 (3) | 3 (4) |
| **Prior BTKi and venetoclax, n (%)** | 94 (80) | 70 (100) |
| BTKi progression/venetoclax failure,[d] n (%) | 70 (60) | 70 (100) |
| **Received bridging therapy, n (%)** | 89 (76) | 55 (79) |

[a]Defined as ≥ 1 lesion with the longest diameter of ≥ 5 cm; [b]Defined as no response or progression ≤ 6 months from last dose of therapy; [c]Defined as disease progression in a patient who previously had CR/CRi or PR/nPR for ≥ 6 months; [d]Including patients who progressed on a BTKi and met one of the following: (1) discontinued venetoclax due to disease progression or intolerability and patient's disease met indications for further therapy per iwCLL 2018, or (2) failed to achieve an objective response ≤ 3 months of initiating therapy. nPR, nodular partial response/remission.



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# Efficacy outcomes

| Efficacy | Full efficacy analysis population at DL2 (n = 87) | BTKi progression/venetoclax failure subset at DL2 (n = 49) |
|---|---|---|
| **Primary endpoint: IRC-assessed CR/CRi rate (95% CI) per iwCLL 2018, %** | 18 (11—28) | **18 (9—32); *P* = 0.0006[a]** |
| **Key secondary endpoints** | | |
| IRC-assessed ORR (95% CI), % | 47 (36—58) | 43 (29—58); *P* = 0.3931[a] |
| uMRD rate in blood (95% CI), % | 64 (53—74) | 63 (48—77)[b] |
| **Exploratory endpoint: uMRD rate in marrow (95% CI), %** | 59 (48—69) | 59 (44—73) |
| **Other secondary endpoints** | | |
| Best overall response, n (%) | | |
| CR/CRi | 16 (18) | 9 (18) |
| PR/nPR | 25 (29) | 12 (24) |
| SD | 34 (39) | 21 (43) |
| PD | 6 (7) | 4 (8) |
| Not evaluable | 6 (7) | 3 (6) |
| Median (range) time to first response, months | 1.5 (0.8—17.4) | 1.2 (0.8—17.4) |
| Median (range) time to first CR/CRi, months | 4.4 (1.1—17.9) | 3.0 (1.1—6.1) |

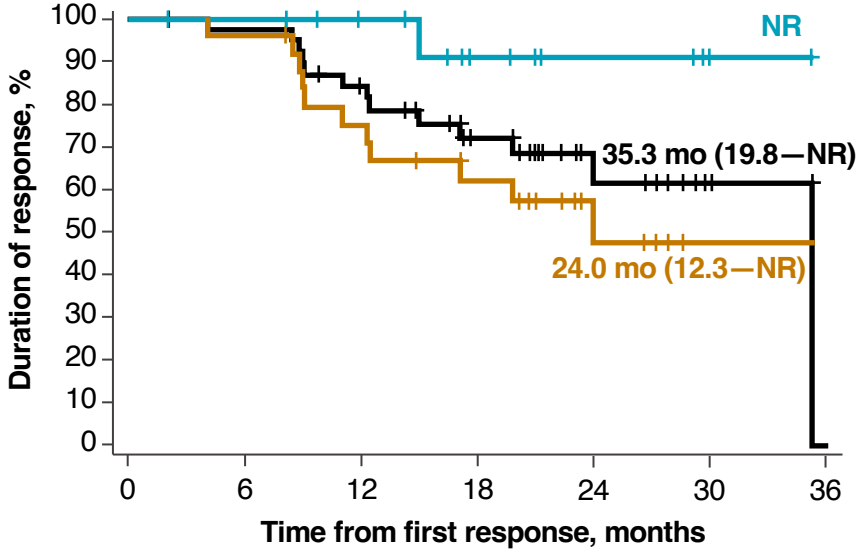
- **All MRD-evaluable responders were uMRD in blood and marrow** and 12 of 20 MRD-evaluable patients with SD were uMRD in blood; a majority of patients achieved uMRD by Day 30

[a]One-sided *P* value from binomial exact test ($H_0$ of CR/CRi ≤ 5%; $H_0$ of ORR ≤ 40%); [b]*P* value not presented for uMRD rate in blood ($H_0$ ≤ 5%) because the ORR hypothesis was not rejected at 1-sided 2.5% significance level. MRD, minimal residual disease; SD, stable disease.

# Duration of response by best overall response

**(A) Full study population at DL2 (n = 87)**

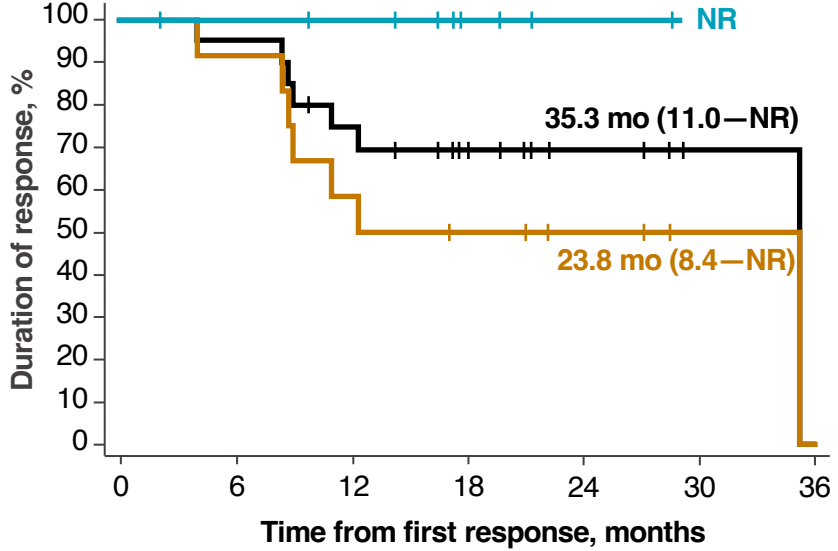
Median (95% CI) follow-up: 21.0 mo (17.5—26.6)




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| CR/CRi | 16 | 15 | 12 | 7 | 4 | 2 | 0 |
| PR/nPR | 25 | 24 | 18 | 13 | 5 | 1 | 0 |
| Responder | 41 | 39 | 30 | 20 | 9 | 3 | 0 |

**(B) BTKi progression/venetoclax failure subset at DL2 (n = 49)**

Median (95% CI) follow-up: 19.7 mo (16.5—27.2)




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 9 | 8 | 7 | 3 | 1 | 0 | 0 |
| | 12 | 11 | 7 | 5 | 3 | 1 | 0 |
| | 21 | 19 | 14 | 8 | 4 | 1 | 0 |

Data on Kaplan-Meier curves are expressed as median (95% CI, if available). NR, not reached.



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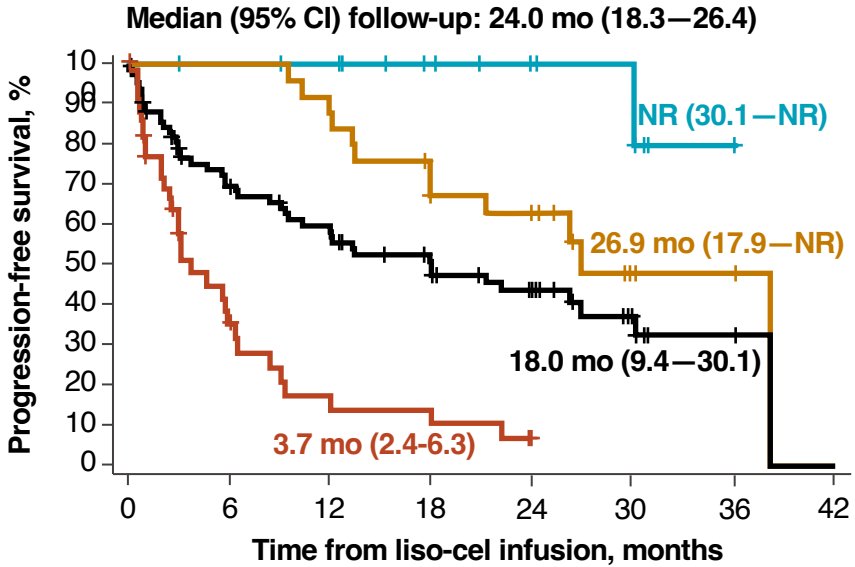
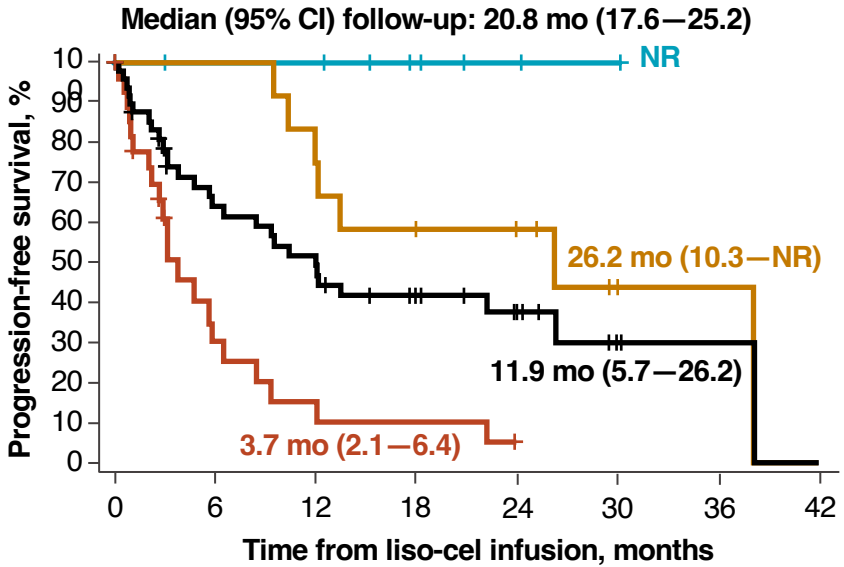
# Progression-free survival by best overall response

**(A) Full study population at DL2 (n = 87)**




| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| CR/CRi | 16 | 15 | 14 | 10 | 6 | 5 | 1 | 0 |
| PR/nPR | 25 | 25 | 22 | 15 | 11 | 3 | 2 | 0 |
| Nonresponder | 46 | 11 | 4 | 3 | 1 | 0 | 0 | 0 |
| Total | 87 | 51 | 40 | 28 | 18 | 8 | 3 | 0 |

**(B) BTKi progression/venetoclax failure subset at DL2 (n = 49)**

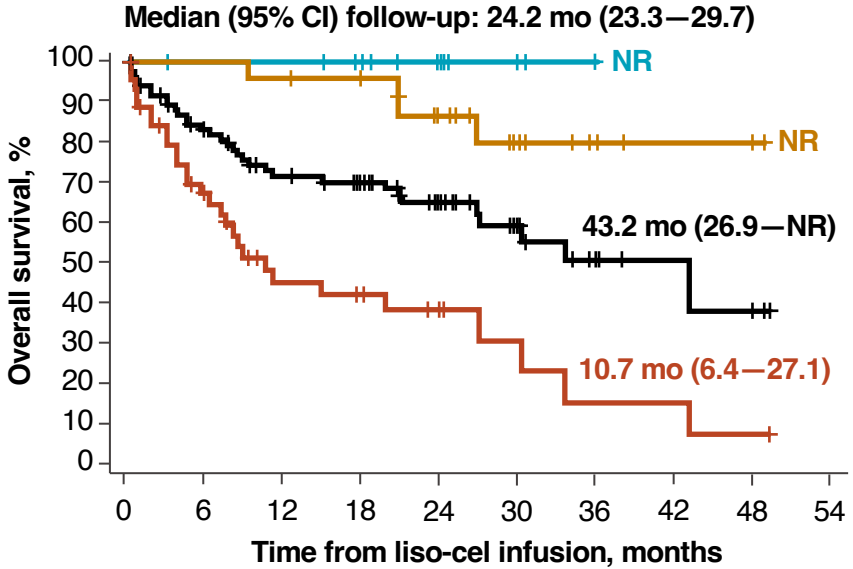



| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 9 | 8 | 8 | 5 | 2 | 1 | 0 | 0 |
| | 12 | 12 | 9 | 6 | 5 | 1 | 1 | 0 |
| | 28 | 6 | 2 | 2 | 0 | 0 | 0 | 0 |
| | 49 | 26 | 19 | 13 | 7 | 2 | 1 | 0 |

Data on Kaplan-Meier curves are expressed as median (95% CI, if available).

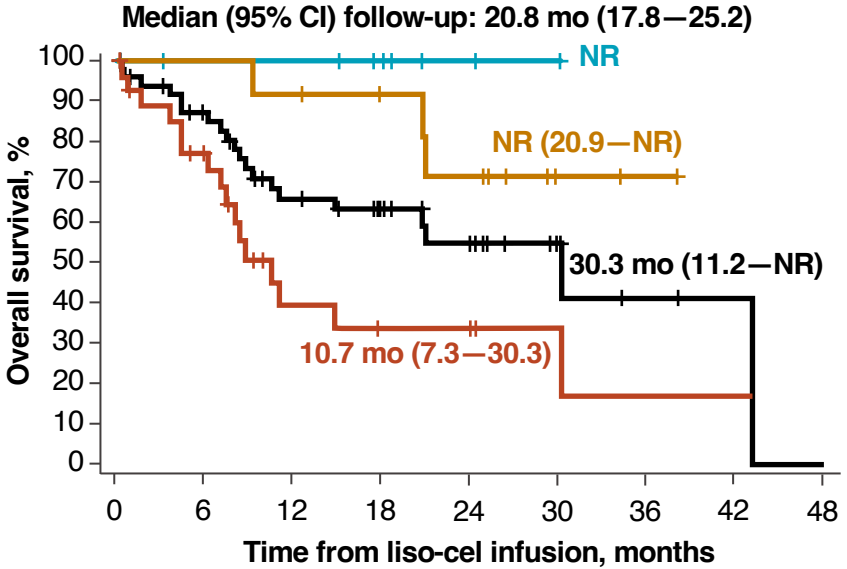
# Overall survival by best overall response

**(A) Full study population at DL2 (n = 87)**




| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| CR/CRi | 16 | 15 | 15 | 13 | 7 | 5 | 2 | 0 | 0 | 0 |
| PR/nPR | 25 | 25 | 24 | 21 | 16 | 9 | 5 | 2 | 2 | 0 |
| Nonresponder | 46 | 26 | 15 | 12 | 8 | 4 | 2 | 2 | 1 | 0 |
| Total | 87 | 66 | 54 | 46 | 31 | 18 | 9 | 4 | 3 | 0 |

**(B) BTKi progression/venetoclax failure subset at DL2 (n = 49)**




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 9 | 8 | 8 | 6 | 2 | 1 | 0 | 0 | 0 |
| 12 | 12 | 11 | 9 | 7 | 2 | 1 | 0 | 0 |
| 28 | 18 | 7 | 4 | 4 | 2 | 1 | 1 | 0 |
| 49 | 38 | 26 | 19 | 13 | 5 | 2 | 1 | 0 |

Data on Kaplan-Meier curves are expressed as median (95% CI, if available).



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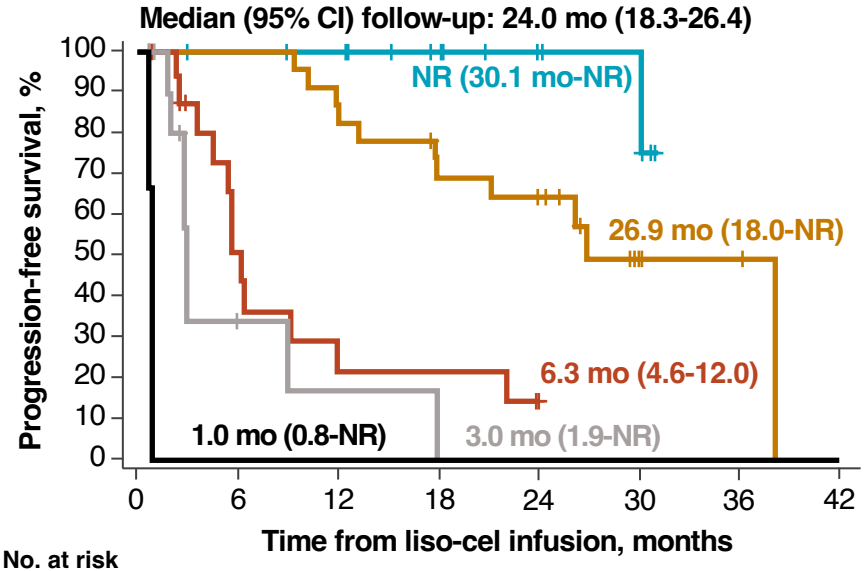
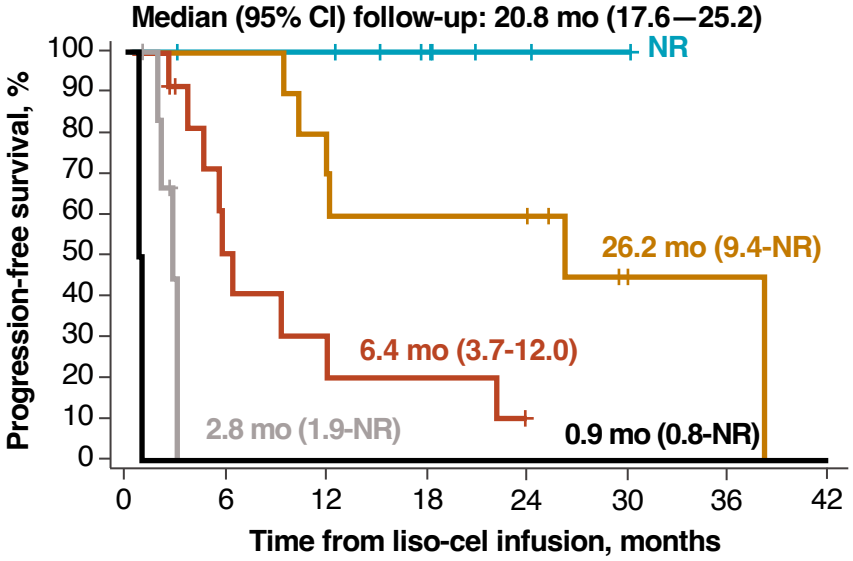
# PFS by BOR and MRD status in blood by next-generation sequencing at $10^{-4}$ sensitivity

**(A) Full study population at DL2 (n = 87)**




| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| CR/CRi uMRD | 15 | 14 | 13 | 9 | 5 | 4 | 0 | 0 |
| PR/nPR uMRD | 23 | 23 | 20 | 15 | 11 | 3 | 2 | 0 |
| SD uMRD | 18 | 7 | 3 | 3 | 1 | 0 | 0 | 0 |
| SD detectable MRD | 13 | 3 | 1 | 0 | 0 | 0 | 0 | 0 |
| PD detectable MRD | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**(B) BTKi progression/venetoclax failure subset at DL2 (n = 49)**




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| CR/CRi uMRD | 9 | 8 | 8 | 5 | 2 | 1 | 0 | 0 |
| PR/nPR uMRD | 10 | 10 | 7 | 6 | 5 | 1 | 1 | 0 |
| SD uMRD | 12 | 5 | 2 | 2 | 0 | 0 | 0 | 0 |
| SD detectable MRD | 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PD detectable MRD | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

- In exploratory analyses of PFS by uMRD in blood, median PFS of was around 26—27 months in patients with uMRD and < 3 months in those with detectable MRD in both population sets.

# Safety: TEAEs, AESIs, and management of CRS and NEs

- The most common grade ≥ 3 TEAEs (≥ 40%) were neutropenia (61%), anemia (52%), and thrombocytopenia (41%)

| Patients with CRS and NEs | Full study population (n = 117) |
|---|---|
| **CRS,[a] n (%)** | 99 (85) |
| Grade 1/2 | 43 (37)/46 (39) |
| Grade 3 | 10 (9) |
| Grade 4/5 | 0 |
| Median (range) time to onset/resolution, days | 4.0 (1—18)/6.0 (2—37) |
| **NE,[b] n (%)** | 53 (45) |
| Grade 1/2 | 13 (11)/18 (15) |
| Grade 3 | 21 (18) |
| Grade 4 | 1 (1) |
| Grade 5 | 0 |
| Median (range) time to onset/resolution, days | 7.0 (1—21)/7.0 (1—83) |

- 81 (69%) patients received tocilizumab and/or corticosteroids for management of CRS and/or NEs

| Other AESIs, n (%) | Full study population (n = 117) |
|---|---|
| **Prolonged cytopenia[c]** | 63 (54) |
| **Grade ≥ 3 infections[d]** | 20 (17) |
| **Hypogammaglobulinemia[e]** | 18 (15) |
| **Tumor lysis syndrome** | 13 (11) |
| **Second primary malignancy[e]** | 11 (9) |
| **Macrophage activation syndrome** | 4 (3) |

- 5 deaths due to TEAEs were reported
  - 4 considered unrelated to liso-cel by investigators (respiratory failure, sepsis, *Escherichia coli* infection, and invasive aspergillosis)
  - 1 considered related to liso-cel by investigators (macrophage activation syndrome)

[a]CRS was graded based on the Lee 2014 criteria; [b]NEs were defined as investigator-identified neurological AEs related to liso-cel; [c]Defined as grade ≥ 3 laboratory abnormalities of neutropenia, anemia, and/or thrombocytopenia at Day 30 after liso-cel infusion; [d]Includes grade ≥ 3 TEAEs from the infections and infestations (System Organ Class) by AE high-level group term; [e]AEs from the 90-day treatment-emergent period, posttreatment-emergent period, and long-term follow-up were included.

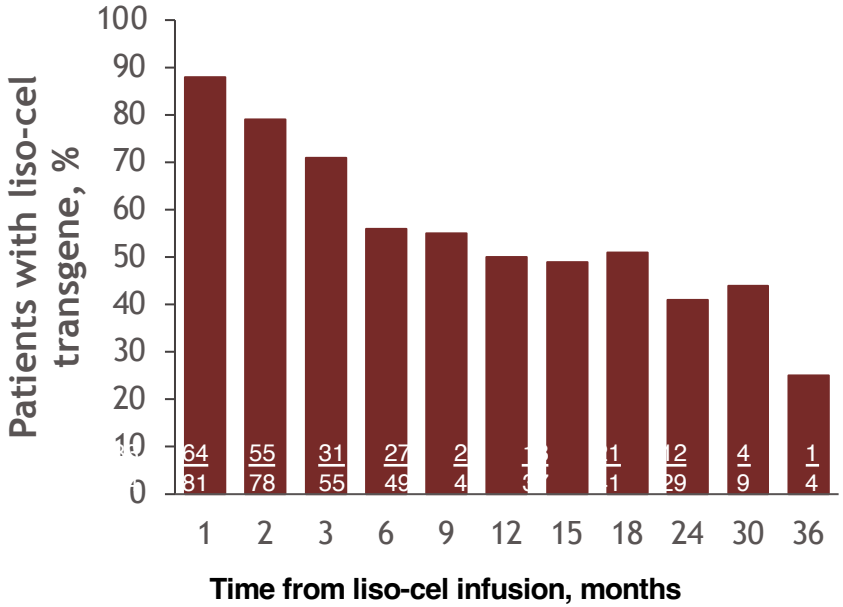
# Liso-cel cellular kinetics and persistence at DL2

## Liso-cel cellular kinetic parameters by qPCR

| | Cellular kinetic set at DL2 (n = 89) |
|---|---|
| **Median (IQR) $C_{max}$, copies/μg** | 79,338.0 (29,895.0—184,172.0) |
| **Median (IQR) $t_{max}$, days** | 14.0 (10.0—14.0) |
| **Median (IQR) $AUC_{(0-28d)}$, day*copies/μg** | 693,864.1 (221,422.7—1,765,580.9) |

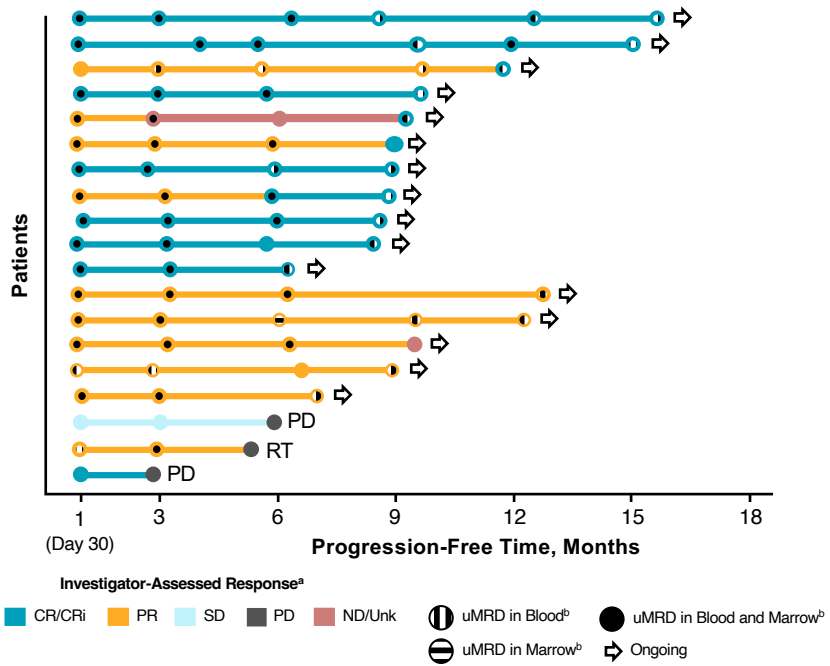
- Liso-cel exhibited rapid expansion with a median $t_{max}$ of 14 days after liso-cel
- Persistence of the liso-cel transgene was detected up to 36 months after liso-cel infusion in at least 1 of 4 evaluable patients

## Persistence of liso-cel in blood by qPCR at DL2[a]




[a]Data are number of patients with liso-cel persistence/number of patients with an available sample at the specific time point. Persistence was defined as a transgene count ≥ lower limit of detection (5 copies/reaction). Concentration values after the initiation of retreatment of liso-cel (including lymphodepletion) or after another anticancer treatment were excluded. $AUC_{(0-28d)}$, area under the curve from 0 to 28 days after infusion; $C_{max}$, maximum expansion; $t_{max}$, time to maximum expansion.

# Patient Responses at 10-month median followup – liso-cel + ibrutinib cohort



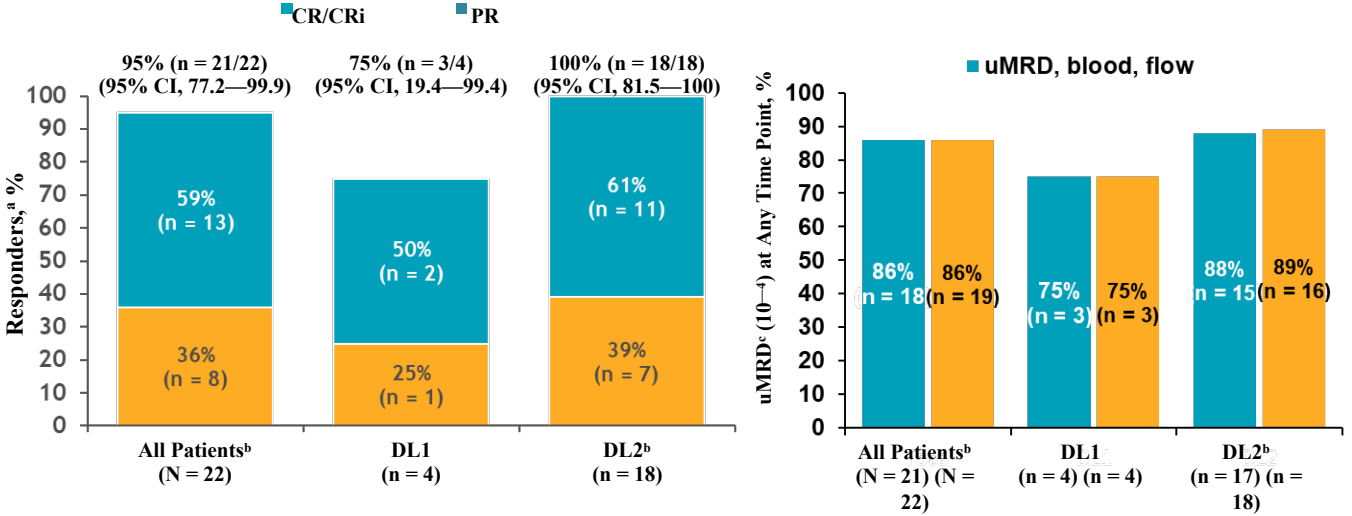

- All responders (n = 18/19) achieved a response by Day 30 after liso-cel
- Among 18 patients with ≥6 months of follow-up, 89% (n = 16/18) maintained or improved response from Day 30
- Of 17 patients who achieved uMRD in blood:
  - All achieved this response by Day 30
  - Only 1 later progressed due to Richter transformation (RT)

[a]Evaluated according to iwCLL 2018 criteria. [b]Assessed in blood by flow cytometry and/or in bone marrow by NGS. ND, not done; Unk, unknown.



Wierda W, et al. ASH annual mtg 2020

# Best Objective Response by iwCLL and uMRD (<$10^{-4}$) – liso-cel + ibrutinib cohort



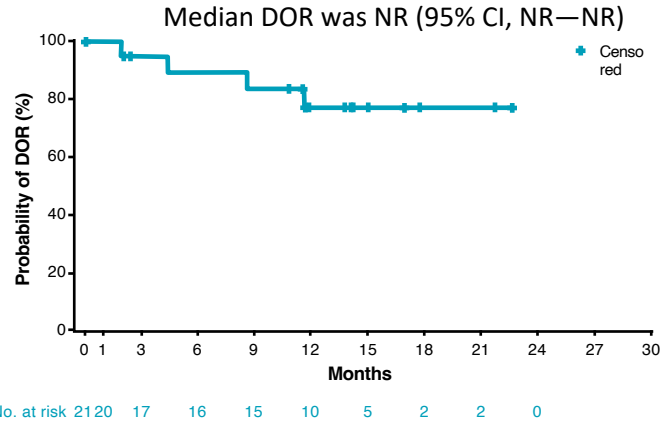

- No patients had PD during the first month after liso-cel
- One patient at DL1 had SD for 6 months but later progressed

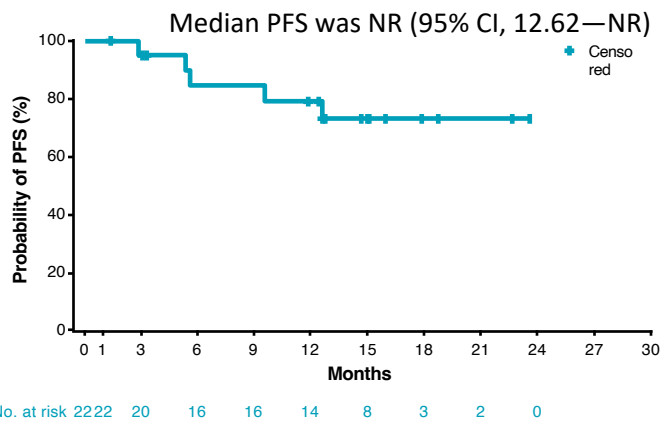
[a]Evaluated according to iwCLL 2018 criteria; [b]At the time of this data cut, 1 patient had only 11 days of follow-up after liso-cel infusion and was not yet evaluable for response; [c]Assessed in blood by flow cytometry and/or in bone marrow by NGS. CRi, CR with incomplete blood count recovery; NGS, next-generation sequencing.



Wierda W, et al. Virtual ICML 2021

# PFS and Duration of Response at 17-mo median followup – liso-cel + ibrutinib cohort



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# Conclusions

- TRANSCEND CLL 004 trial met its primary endpoint, with a CR/CRi rate of 18% in patients with R/R CLL/SLL after BTKi progression/venetoclax failure, which compares favorably with historical CR/CRi rates of 0%—5%[1—6]
- Liso-cel achieved high uMRD rates in both blood (63%) and marrow (59%)
- Efficacy outcomes were similar in the full study population (R/R CLL/SLL after prior BTKi), demonstrating a clinical benefit of liso-cel in this broader population
- Functional CAR T cells were successfully manufactured and demonstrated expansion and persistence in most patients
  - Higher liso-cel expansion was observed in responders and patients with uMRD
- The safety profile was manageable, with low rates of grade ≥ 3 CRS and NEs
- Overall, these results support liso-cel as a potential new treatment option for R/R CLL/SLL

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Thank you for your attention!

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