NOVEL STRATEGIES UNDER INVESTIGATION FOR PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Research To Practice I 2020 ASH annual meeting I Satellite symposium

Agenda

- Available efficacy and safety outcomes from studies evaluating novel BTKi/Bcl-2i combinations; ongoing Phase III studies
- Biologic rationale for and early efficacy and safety data with CD19-directed CAR T-cell therapy in patients with relapsed/refractory CLL
- Eligibility criteria for and primary and secondary endpoints of the Phase I/II TRANSCEND CLL 004 trial assessing lisocabtagene maraleucel in relapsed/refractory CLL; key findings in the overall trial population and among double-refractory patients
- Other ongoing studies evaluating CAR T-cell therapy in relapsed/refractory CLL
- Other promising agents and strategies under investigation in CLL
- 2 representative patient case discussions

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Novel BTKi/Bcl-2i combinations

- I+V trials:
  - CAPTIVATE Ph2 trial
    - MRD and fixed duration cohorts
  - CLARITY Ph2 trial

- Relapsed/refractory I+V trials
  - MDACC trial
  - Stanford/COH trial

- Ongoing Ph3 trials
  - Alliance: IO vs. IVO, age more than 70 yrs
  - ECOG-ACRIN: IO vs. IVO, age less than or equal to 70 yrs
  - UK FLAIR trial: I alone vs. [IR] vs. I+V x6 yrs vs. FCR

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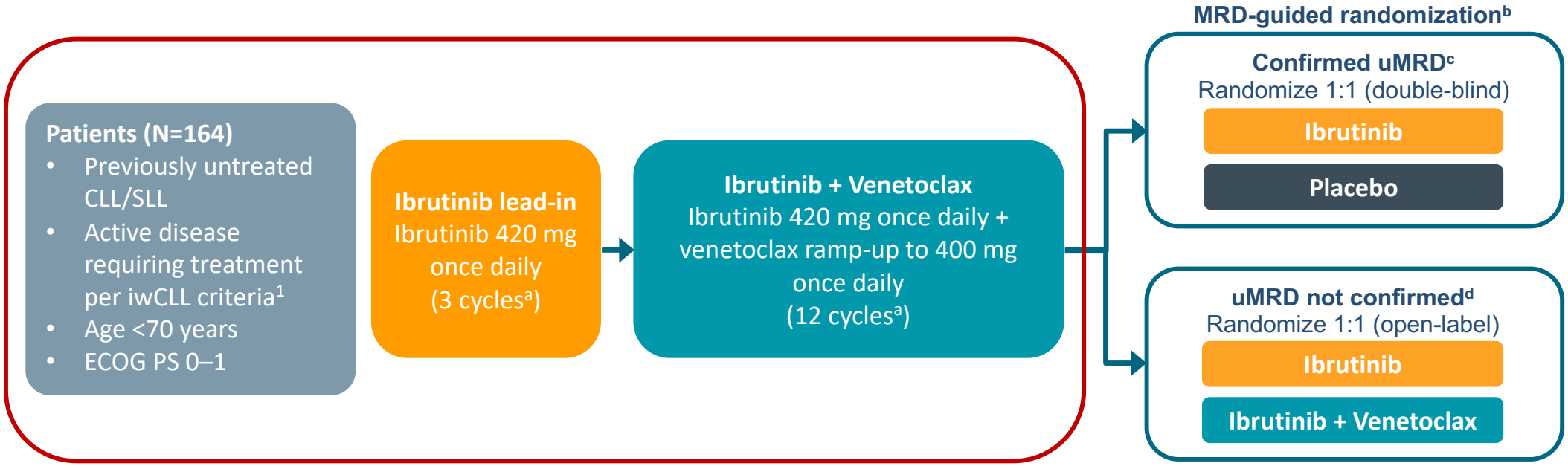
CAPTIVATE MRD Cohort: Study Design



- Results are presented for pre-randomization phase of the CAPTIVATE MRD cohort (N=164) with 12 cycles of ibrutinib + venetoclax prior to MRD-guided randomization
- Time-limited therapy with 12 cycles of ibrutinib + venetoclax to be evaluated in a separate fixed-duration cohort (N=159)

[a]1 cycle = 28 days; patients may have received 1 additional cycle while awaiting confirmation of undetectable MRD for randomization. [b]Stratified by IGHV mutation status. [c]Confirmed as having undetectable MRD ($<10^{-4}$ by 8-color flow cytometry) serially over at least 3 cycles in PB, and undetectable MRD in both PB and BM. [d]Defined as having detectable MRD or undetectable MRD not confirmed serially or not confirmed in both PB and BM.

1. Hallek M et al. *Blood*. 2008;111:5446-5456.

High Rates of Undetectable MRD Achieved in PB and BM With Up to 12 Cycles of I + V Combination

	Peripheral Blood n=163	Bone Marrow[a] n=155
Best response of undetectable MRD in evaluable patients[b] (95% CI)	**75%** (68–82)	**72%** (64–79)

- Rates of undetectable MRD in peripheral blood and bone marrow were highly concordant at Cycle 16 (91%)
- In the all-treated population (N=164), undetectable MRD was achieved in 75% of patients in peripheral blood and in 68% of patients in bone marrow with up to 12 cycles of combination
- Proportion of patients with undetectable MRD in peripheral blood increased over the 12 cycles of combination therapy
- At 15 months, 98% of patients were progression free with no deaths

[a]BM MRD assessment was scheduled after completion of 12 cycles of combination treatment.
[b]Patients with undetectable MRD at any postbaseline assessment; evaluable patients are those who had at least 1 MRD sample taken postbaseline.

EHA 2020, CAPTIVATE-MRD; Siddiqi et al.

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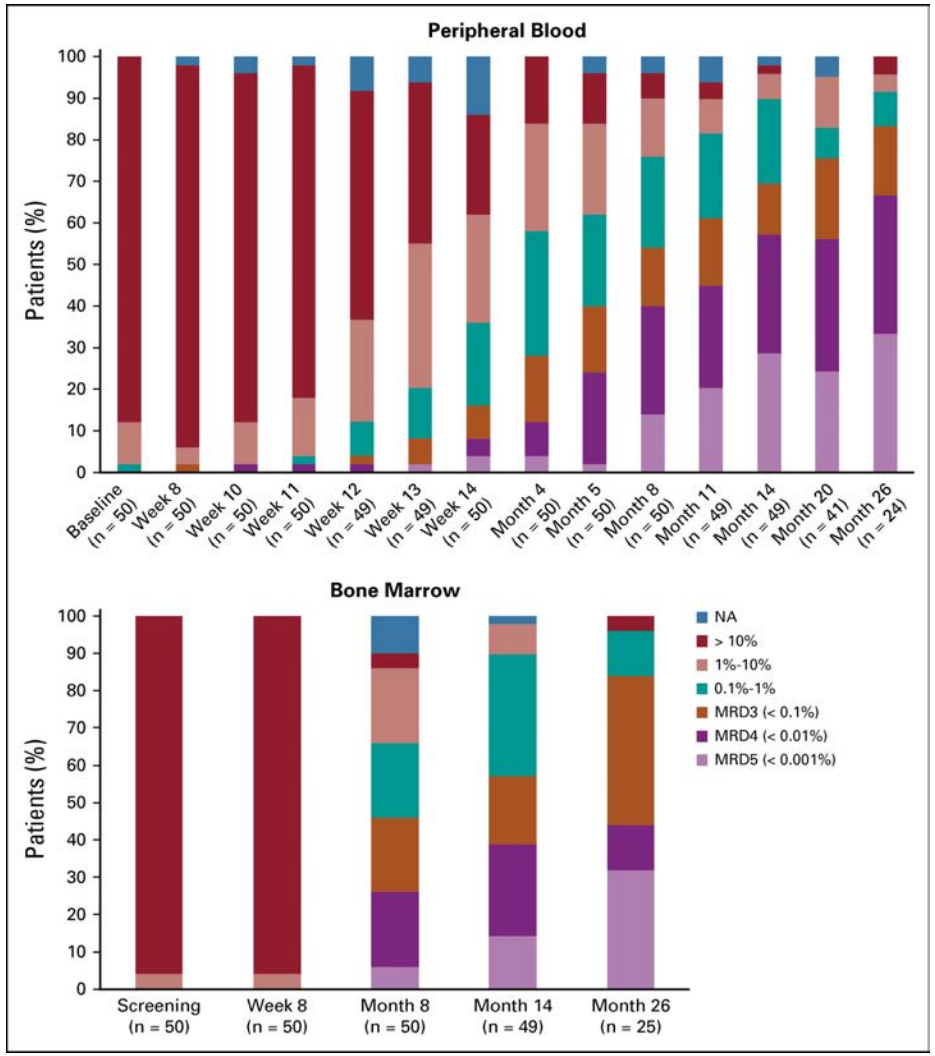
CLARITY Ph2 trial (up to 2 yrs of treatment)



Hillmen P, et al. J Clin Oncol 2019; 37:2722-2729

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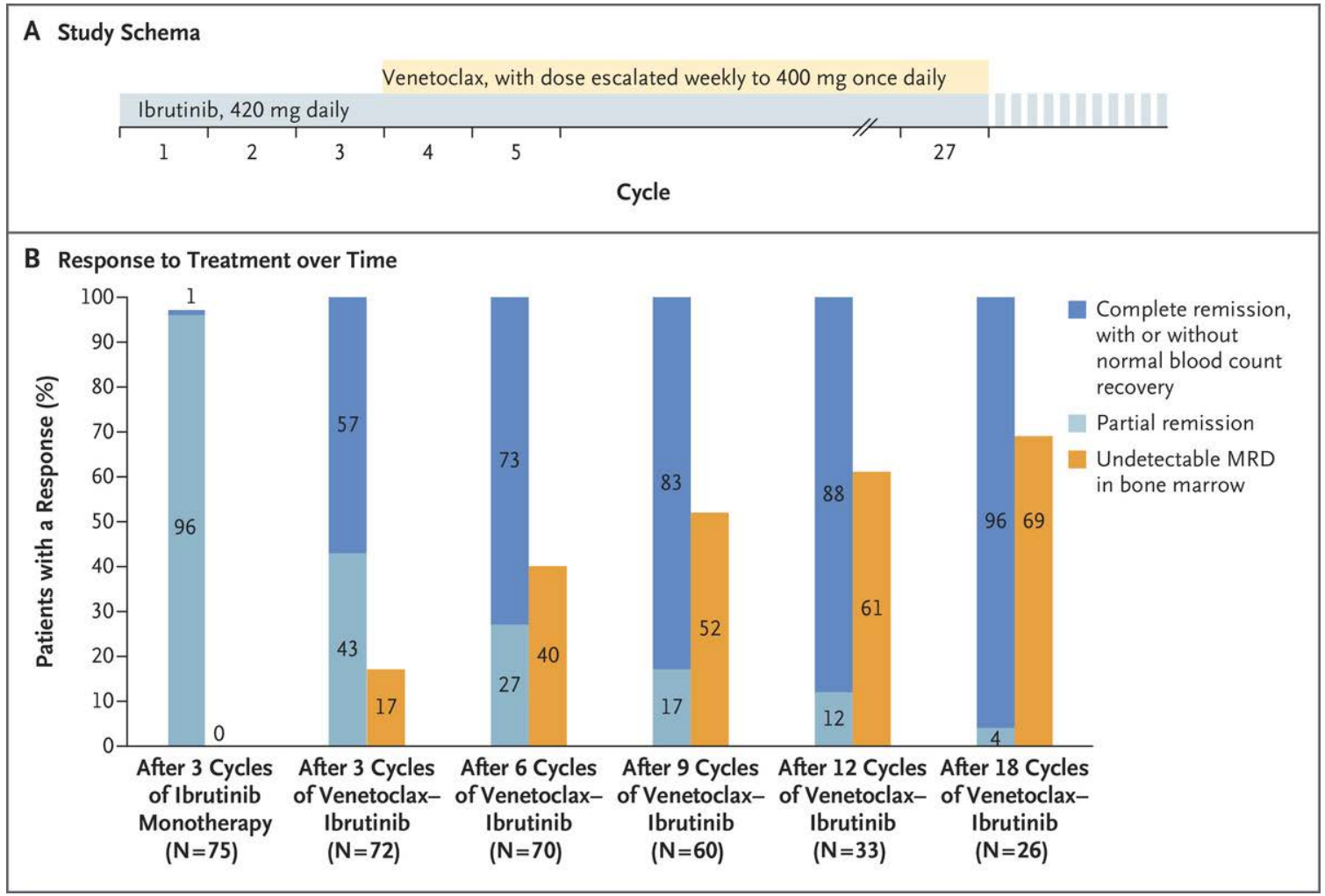
MDACC: IIT, Ph2, frontline high risk and older CLL pts, I+V for 24 cycles



N Jain et al. N Engl J Med 2019;380:2095-2103.

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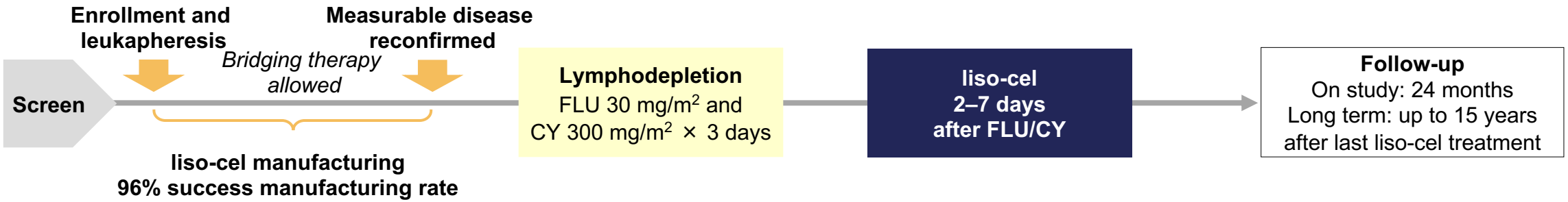
CAR T cell therapy in CLL

TRANSCEND CLL 004 Study Design



Key Eligibility

- Relapsed/refractory CLL/SLL
- Failed or ineligible for BTKi
- High-risk disease: failed ≥2 prior therapies
- Standard-risk disease: failed ≥3 prior therapies
- ECOG PS of 0–1

Dose Escalation: mTPI-2 Design

28-day DLT period

Primary Objectives

- Safety
- Determine recommended dose

Exploratory Objectives

- Antitumor activity
- Pharmacokinetic profile

Dose Level	Dose	Evaluable (N=23)
1	50 × 10^6 CAR+ T cells	9
2	100 × 10^6 CAR+ T cells	14

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Baseline Characteristics

	All Patients (N=23)
Age, years, median (range)	66 (49–79)
Male, n (%)	11 (48)
Time from diagnosis, months, median (range)	87.5 (30–209)
Bulky disease >5 cm, n (%)[a]	8 (35)
BALL risk score,[1] median (range)	2 (0–3)
SPD, cm², median (range)	25 (2–197)
LDH, U/L, median (range)	243 (119–634)
Received bridging therapy, n (%)	17 (74)
Stage, n (%)	
Rai stage III/IV	15 (65)
Binet stage C	16 (70)
High-risk features (any), n (%)	19 (83)
Del(17p)	8 (35)
TP53 mutation	14 (61)
Complex karyotype[b]	11 (48)
Lines of prior therapy, median (range)	5 (2–11)
Prior ibrutinib, n (%)	23 (100)
Ibrutinib refractory/relapsed, n (%)	21 (91)
BTKi progression and failed venetoclax,[c] n (%)	9 (39)

[a]Bulky disease defined as ≥1 lesion with longest diameter of >5 cm. [b]≥3 chromosomal aberrations. [c]Failed venetoclax defined as discontinuation due to PD or <PR after ≥3 months of therapy.
BTKi, Bruton tyrosine kinase inhibitor; LDH, lactate dehydrogenase; PD, progressive disease; PR, partial response; SPD, sum of the product of perpendicular diameters.
1. Soumerai JD, et al. *Lancet Haematol*. 2019;6:e366-e374.

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Baseline Characteristics

	All Patients (N=23)	Failed BTKi and Venetoclax (n=9)
Age, years, median (range)	66 (49–79)	68 (59–76)
Male, n (%)	11 (48)	4 (44)
Time from diagnosis, months, median (range)	87.5 (30–209)	145 (30–209)
Bulky disease >5 cm, n (%)[a]	8 (35)	4 (44)
BALL risk score,[1] median (range)	2 (0–3)	2 (0–3)
SPD, cm², median (range)	25 (2–197)	46 (2–197)
LDH, U/L, median (range)	243 (119–634)	245 (119–634)
Received bridging therapy, n (%)	17 (74)	7 (78)
Stage, n (%)		
Rai stage III/IV	15 (65)	7 (78)
Binet stage C	16 (70)	7 (78)
High-risk features (any), n (%)	19 (83)	8 (89)
Del(17p)	8 (35)	2 (22)
TP53 mutation	14 (61)	6 (67)
Complex karyotype[b]	11 (48)	3 (33)
Lines of prior therapy, median (range)	5 (2–11)	6 (5–10)
Prior ibrutinib, n (%)	23 (100)	9 (100)
Ibrutinib refractory/relapsed, n (%)	21 (91)	9 (100)
BTKi progression and failed venetoclax,[c] n (%)	9 (39)	9 (100)

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Incidence and Management of CRS and NEs

	All Patients (N=23)
CRS—any grade, n (%)	17 (74)
Median time to first onset, days (range)	4 (1–10)
Median duration of first event, days (range)	12 (2–50)
Grade 3, n (%)	2 (9)
NE[a]—any grade, n (%)	9 (39)
Median time to first onset, days (range)	4 (2–21)
Median duration of first event, days (range)	21 (6–56)
Grade ≥3,[b] n (%)	5 (22)
Any CRS or NE, n (%)	18 (78)
CRS only, n (%)	9 (39)
NE only, n (%)	1 (4)
Tocilizumab and/or steroid use	
Tocilizumab only	5 (22)
Steroids only	3 (13)
Both tocilizumab and steroids	9 (39)
Tocilizumab and/or steroid use	17 (74)

- No grade 5 CRS or NE occurred

[a]NEs are liso-cel related neurologic adverse events defined by the investigator; [b]NEs are not mutually exclusive; encephalopathy (n=3); aphasia (n=1); confusional state (n=1); muscular weakness (n=1); somnolence (n=1). BTKi, Bruton tyrosine kinase inhibitor; CRS, cytokine release syndrome; NE, neurological events; TEAEs, treatment-emergent adverse events.

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Incidence and Management of CRS and NEs

	All Patients (N=23)	Failed BTKi and Venetoclax (n=9)
CRS—any grade, n (%)	17 (74)	6 (67)
Median time to first onset, days (range)	4 (1–10)	1.5 (1–4)
Median duration of first event, days (range)	12 (2–50)	21 (6–50)
Grade 3, n (%)	2 (9)	1 (11)
NE[a]—any grade, n (%)	9 (39)	4 (44)
Median time to first onset, days (range)	4 (2–21)	6.5 (2–21)
Median duration of first event, days (range)	21 (6–56)	23.5 (6–49)
Grade ≥3,[a] n (%)	5 (22)	3 (33)
Any CRS or NE, n (%)	18 (78)	7 (78)
CRS only, n (%)	9 (39)	3 (33)
NE only, n (%)	1 (4)	1 (11)
Tocilizumab and/or steroid use		
Tocilizumab only	5 (22)	1 (11)
Steroids only	3 (13)	2 (22)
Both tocilizumab and steroids	9 (39)	3 (33)
Tocilizumab and/or steroid use	17 (74)	6 (67)

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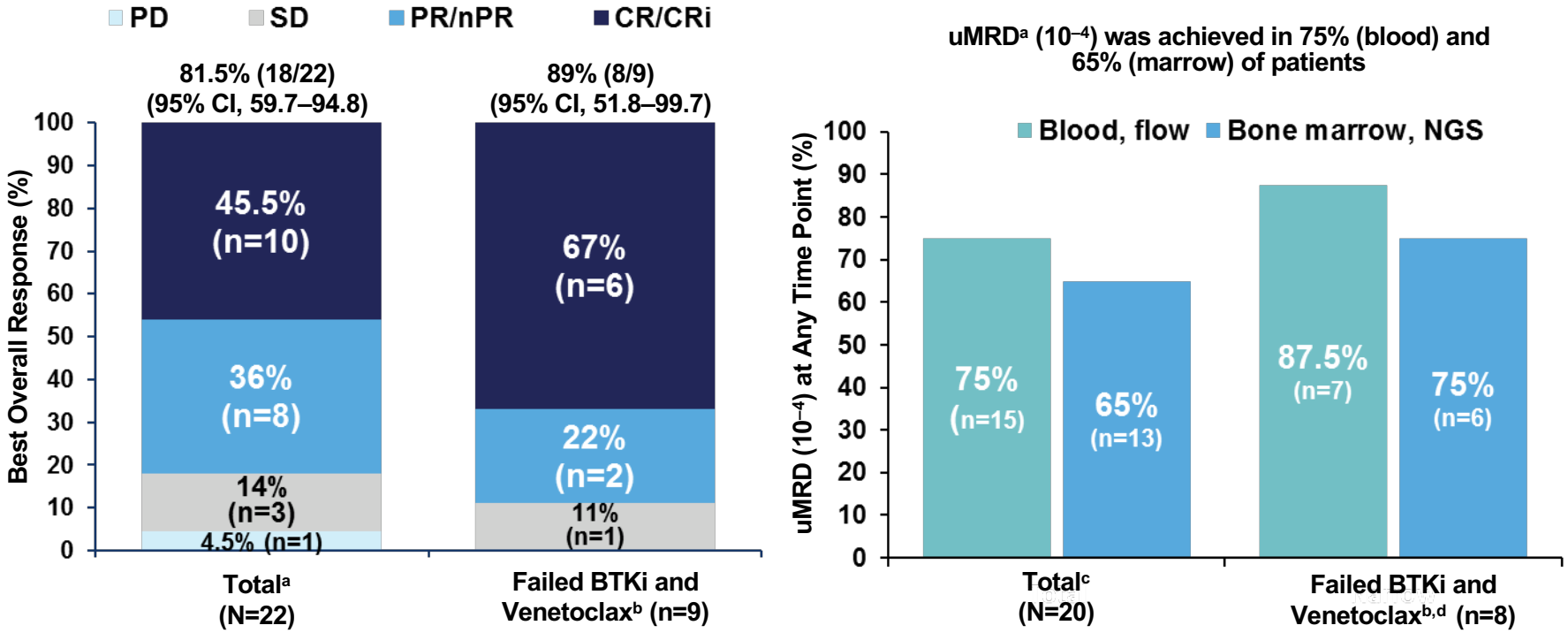
Best Overall Response and Undetectable MRD



Median study follow-up: 11 months

All percentages are rounded to whole numbers except those ending in .5. [a]Evaluable for response defined as having a pretreatment assessment and ≥1 postbaseline assessment. One patient was not evaluable for response. [b]Failed venetoclax defined as discontinuation due to PD or <PR after ≥3 months of therapy. [c]Evaluable for MRD was defined as patients with detectable MRD at baseline. Two patients were not evaluable for MRD. [d]One patient in this subset was not evaluable for MRD. BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; CR, complete response; CRi, complete response with incomplete blood count recovery; MRD, minimal residual disease; NGS, next-generation sequencing; nPR, nodular partial response; PD, progressive disease; PR, partial response; SD, stable disease; uMRD, undetectable minimal residual disease.

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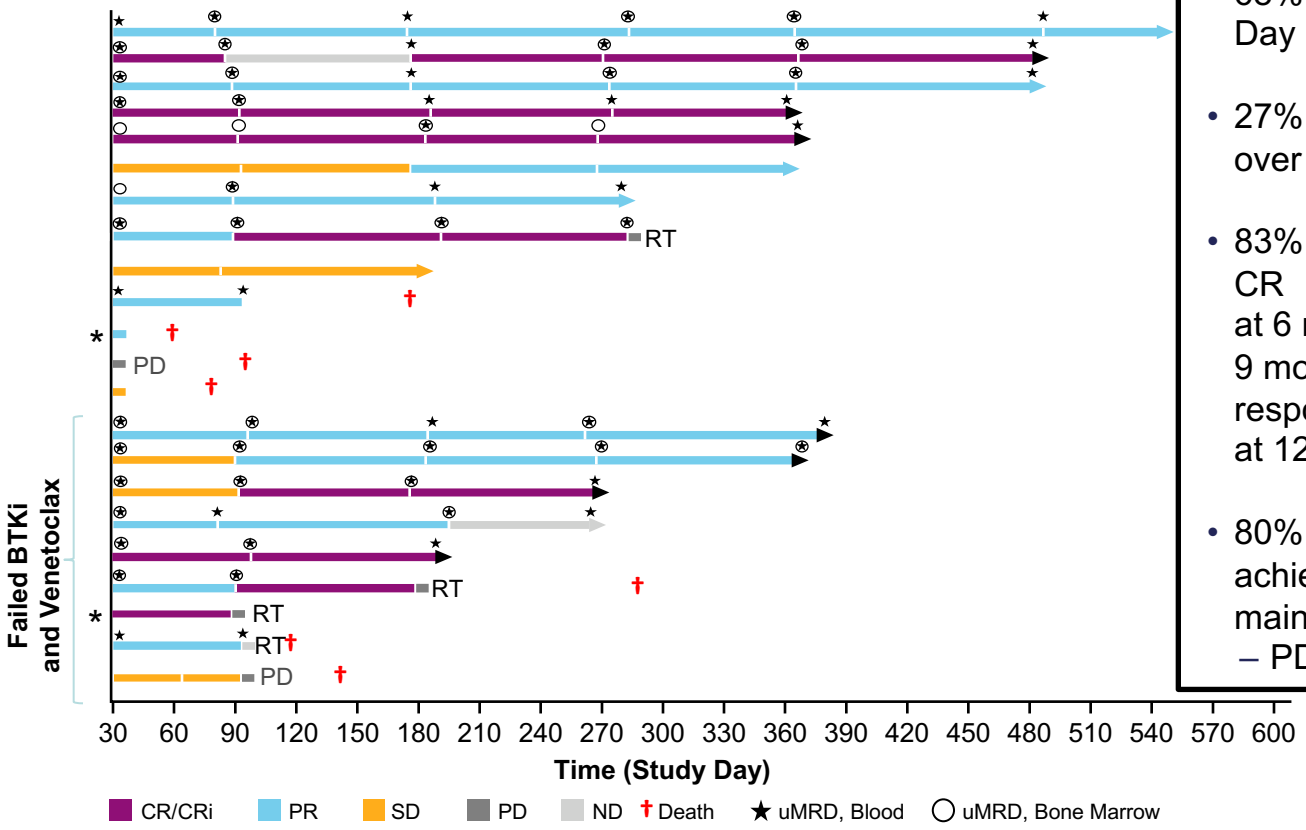
Individual Patient Response Assessments



- 68% (15/22) had a response by Day 30
- 27% (6/22) of responses deepened over time
- 83% (10/12) of patients with PR or CR
  at 6 months remain in response at 9 months, with 8 patients in response
  at 12 months or longer
- 80% (12/15) of patients who achieved uMRD in blood maintained their responses
  – PDs were all with RT

*MRD non-evaluable. There were 7 on-study deaths: 5 patients died from disease progression; 1 patient had grade 5 respiratory failure (DL1) unrelated to liso-cel treatment; 1 patient had septic shock, acute kidney injury, and pneumonia (DL2), unrelated to liso-cel treatment. No deaths occurred within the first 30 days. BTKi, Bruton tyrosine kinase inhibitor; CR, complete response; CRi, complete response with incomplete blood count recovery; DL, dose level; MRD, minimal residual disease; ND, not done; PD, progressive disease; PR, partial response; RT, Richter transformation; SD, stable disease; uMRD, undetectable MRD.

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Other ongoing CAR T-cell trials in CLL

- ZUMA-8 (axi-cel)
- JCAR014 + ibrutinib
- CTL019 + ibrutinib
- Novel CAR T targets like ROR1 and CD22
- Off-the-shelf CAR T-cell trials

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Patient 1: 67 yo man

- 67 yo Caucasian man seen in consultation on 9/18/17
- CLL/SLL diagnosed in 10/2006: high WBCs, ZAP70 pos, del13q, del11q, unmutated IGHV
- Rituximab+lenalidomide x7 (through 10/2008)
- At PD, high dose methylpred + ofatumumab x3
- Nodular PR then PD
- Ibrutinib (with rituximab initially) through 10/2015 when he developed blistering rash and stopped this drug
- Venetoclax started 3/2016 – PR initially but then PD (drug stopped 8/2017)
- High dose methylpred + obinutuzumab

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Patient 1 (cont.)

- Enrolled on liso-cel CAR T-cell trial
- Idelalisib controlled disease during cell manufacturing
- Received liso-cel cells on 1/31/18 after Flu/Cy lymphodepletion
- Complications included TLS, CRS, encephalopathy requiring ICU stay, CMV reactivation
- MRD positive remission at Day 30 that deepened to uMRD
- Remains in remission almost 3 years later

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Patient 2: 40 yo M

- 36 yo M with previously untreated CLL/SLL and del13q had rapid lymphocyte doubling time and progressing lymphadenopathy soon after diagnosis in 2016
- He consented to participate in the CAPTIVATE Ph2 trial and enrolled on the MRD cohort
- After 16 cycles of combination I+V therapy. He achieved MRD undetectable CR and was randomized to ibrutinib maintenance vs. placebo on 1/25/2018
- He remains on study on maintenance and has no toxicity

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Questions?