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GERENCIAMENTO
E PRODUÇÃO

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EVENTOS

Double-Refractory CLL: Cellular Therapy, Bispecific Antibodies, and Emerging Targets

Thursday May 14

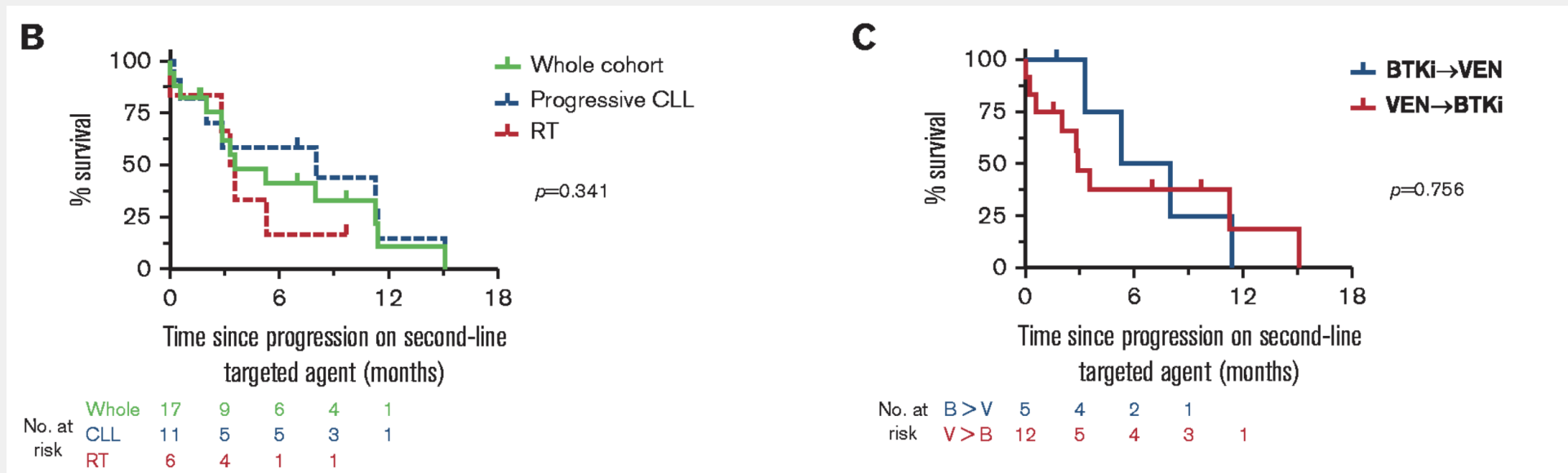
Catherine Coombs MD

Associate Clinical Professor
University of California Irvine



Double refractory CLL outcomes

- An early report showed bleak outcomes for patients who were sequentially resistant to both covalent BTKi and venetoclax
- High risk cohort with 88% with TP53 mutation or 17p deletion, 4 median prior lines of therapy



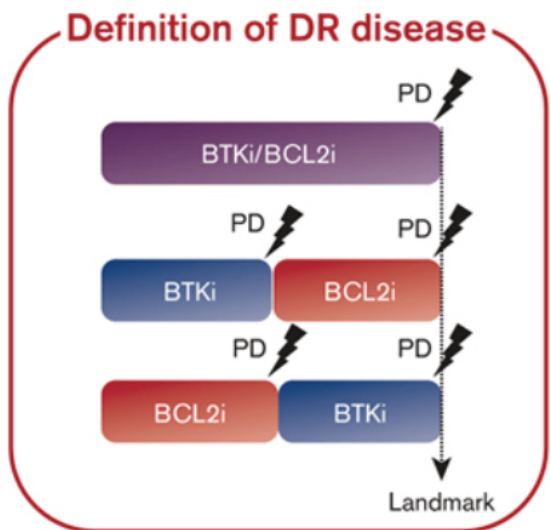
Outcomes of double-refractory CLL

- Authors defined double refractory (DR) CLL when progressive disease occurred during active treatment with a BTKi and a BCL2i
- 30 DR pts, and 65 DE patients included

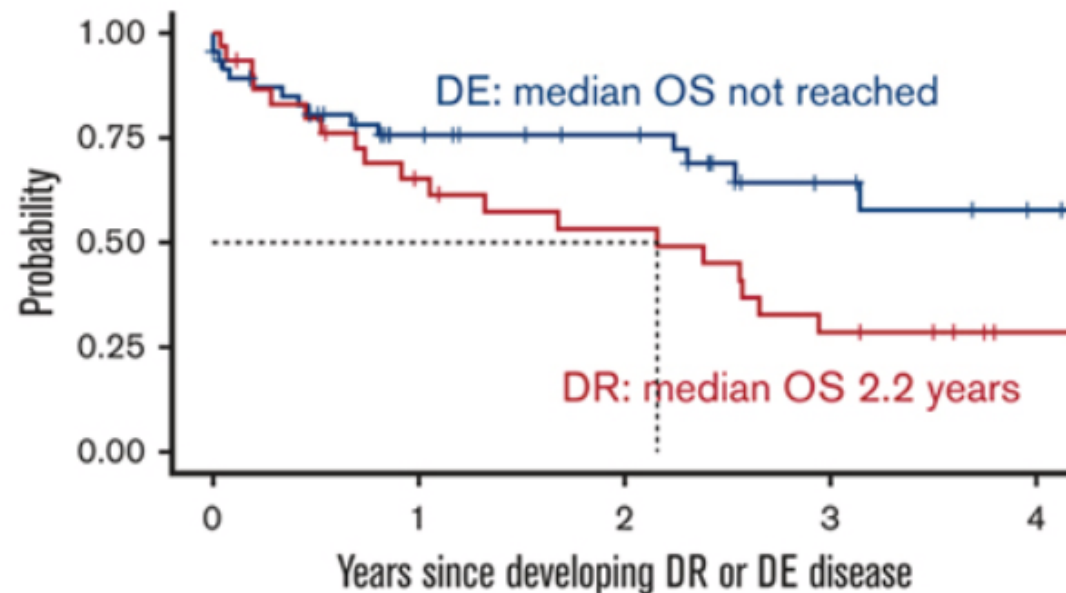
- **DR disease:** Progressive disease (PD) during active treatment with a BTKi and a BCL2i, given sequentially or in combination.

- **DE disease:** Exposed to both BTKi/BCL2i and stopped at least one of these agents due to reasons other than PD.

- **Landmark timepoint:** Last date of treatment with a BTKi or a BCL2i, whichever came later, for patients with DR or DE disease.



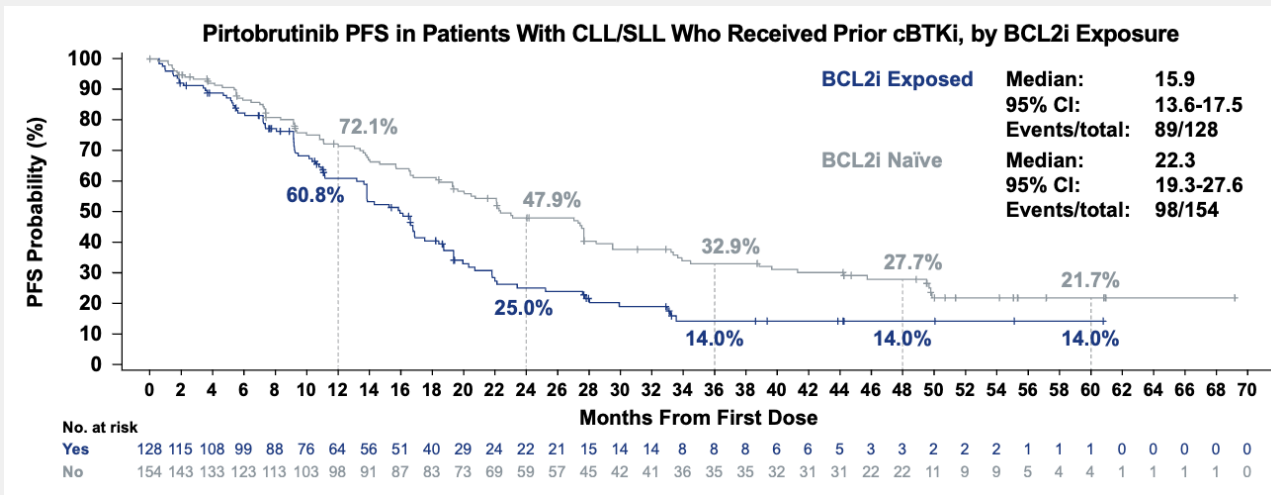
- Overall survival (OS) since the landmark timepoint



- 1.) Pirtobrutinib
- 2.) Lisocabtagene maraleucel (+/- ibrutinib)

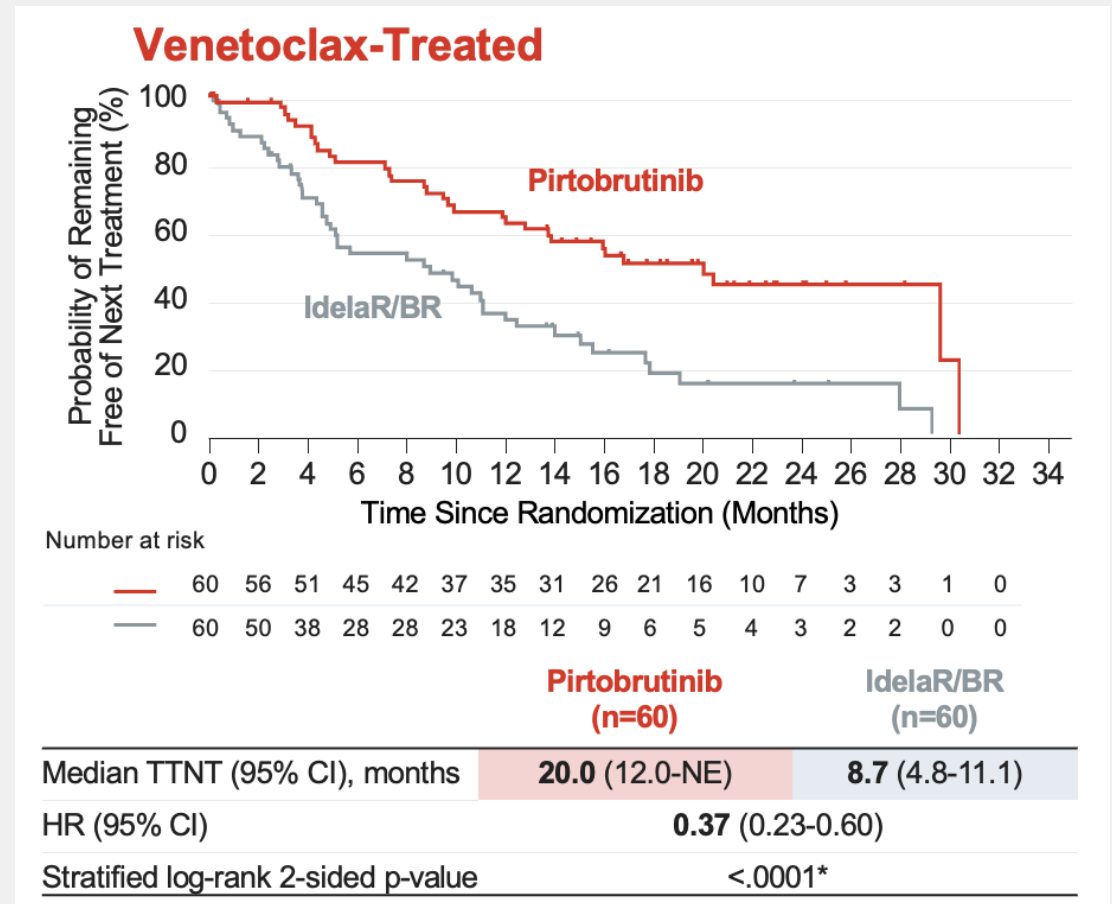
Should always consider clinical trial enrollment when available and patient is eligible

BRUIN phase 1/2 trial: PFS



Wierda W et al. ASH 2025

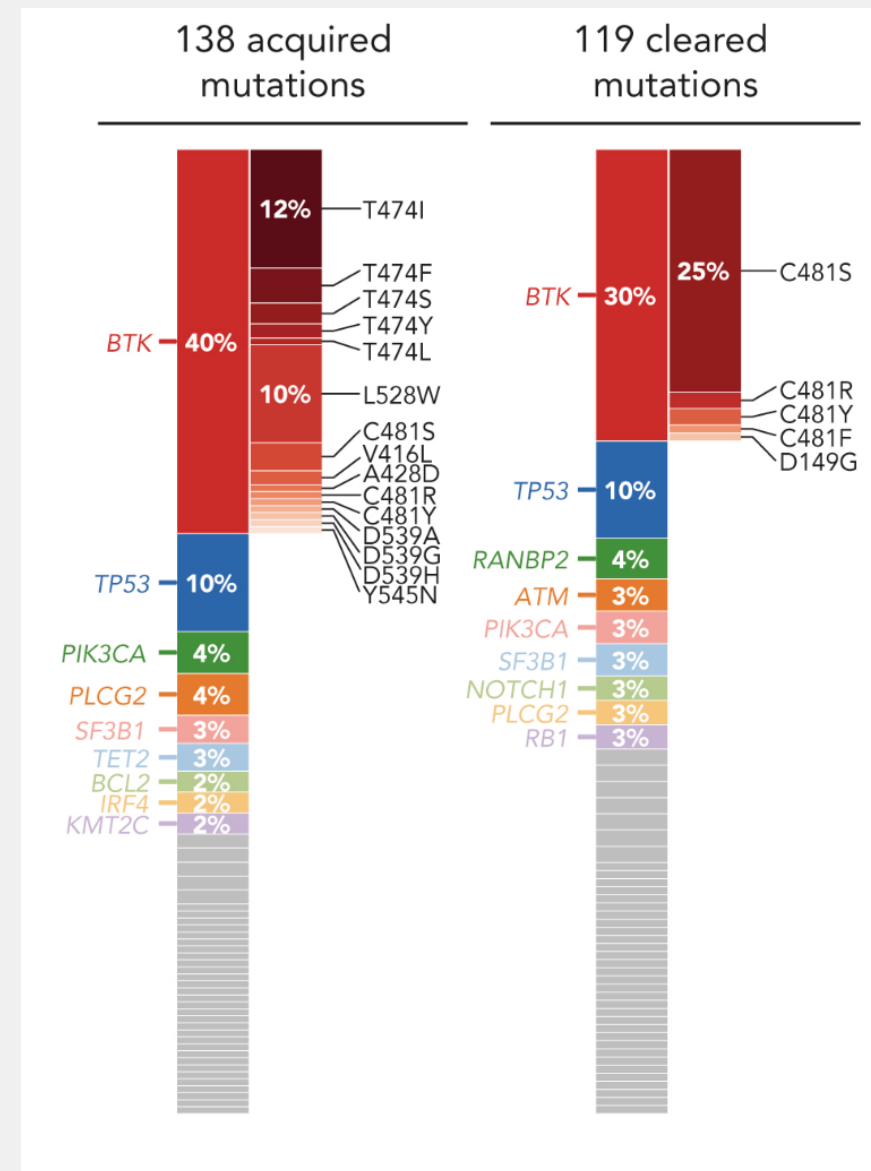
BRUIN CLL-321 trial: TTNT



Sharman J et al. JCO 2024

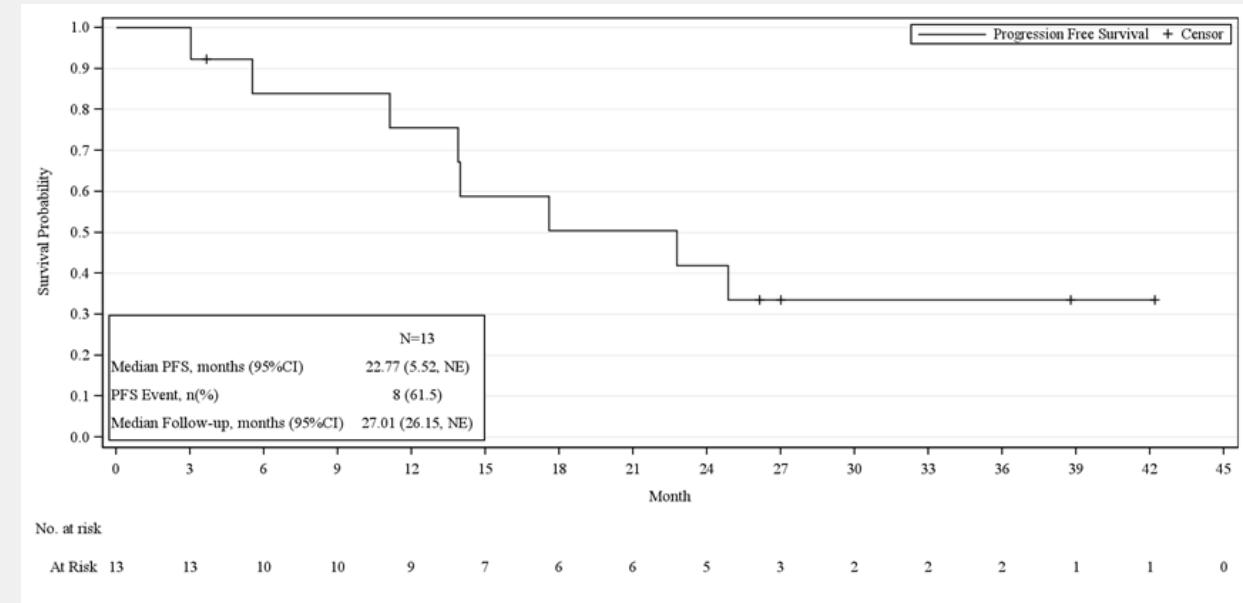
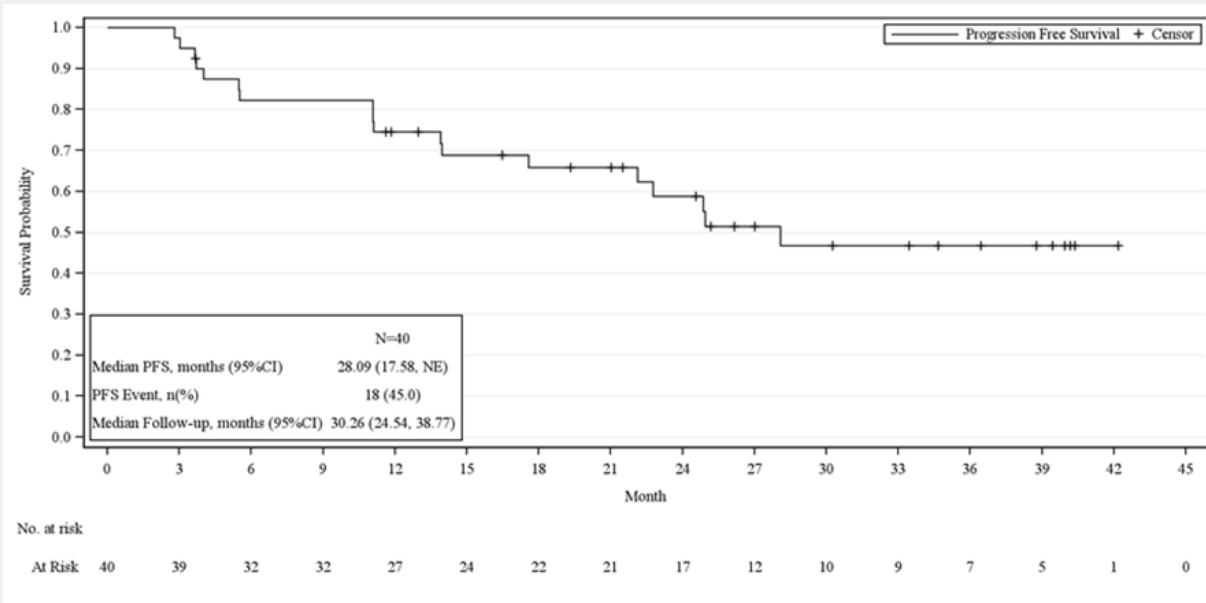
Pirtobrutinib resistance mechanisms

- Pirtobrutinib resistance mechanisms were examined in patients with pre and post treatment samples from BRUIN phase 1/2 trial
- A total of 55 acquired *BTK* mutations were detected in 39 patients, including gatekeeper mutations (T474I/F/S/Y/L, 26%), kinase-impaired L528W (16%), C481S/R/Y (5%), V416L (2%), and A428D (1%) and others proximal to the adenosine triphosphate-binding pocket, D539A/G/H (1%) and Y545N (1%).
- Decrease or complete clearance of *BTK* C481x was observed at PD in 36 of 43 patients (84%).
- Using a more sensitive assay, 37% (18/49) of acquired *BTK* mutations were detected at baseline at low allele frequency.

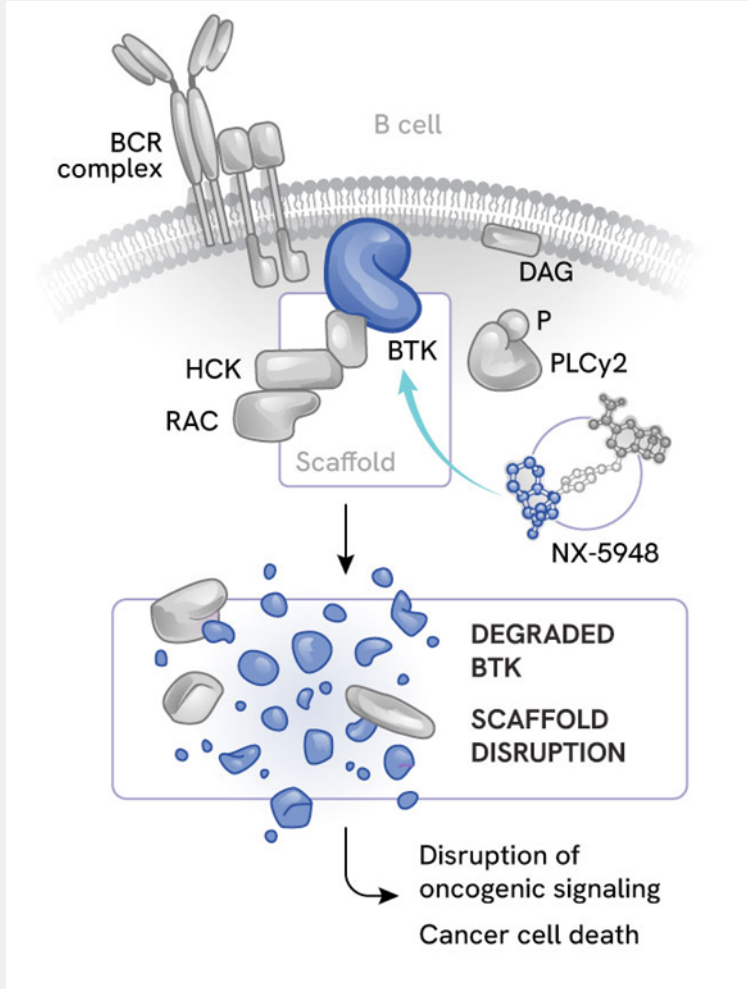


Rocbrutinib (LP-168)

- Rocbrutinib is a selective next-generation inhibitor of BTK that can irreversibly inhibit WT BTK, and reversibly inhibit C481 mutated BTK, with activity against known resistance mutations for ncBTKi
- No DLTs up to 300 mg dose
- 40 efficacy evaluable - 13 double-exposed pts treated, 4 triple-exposed

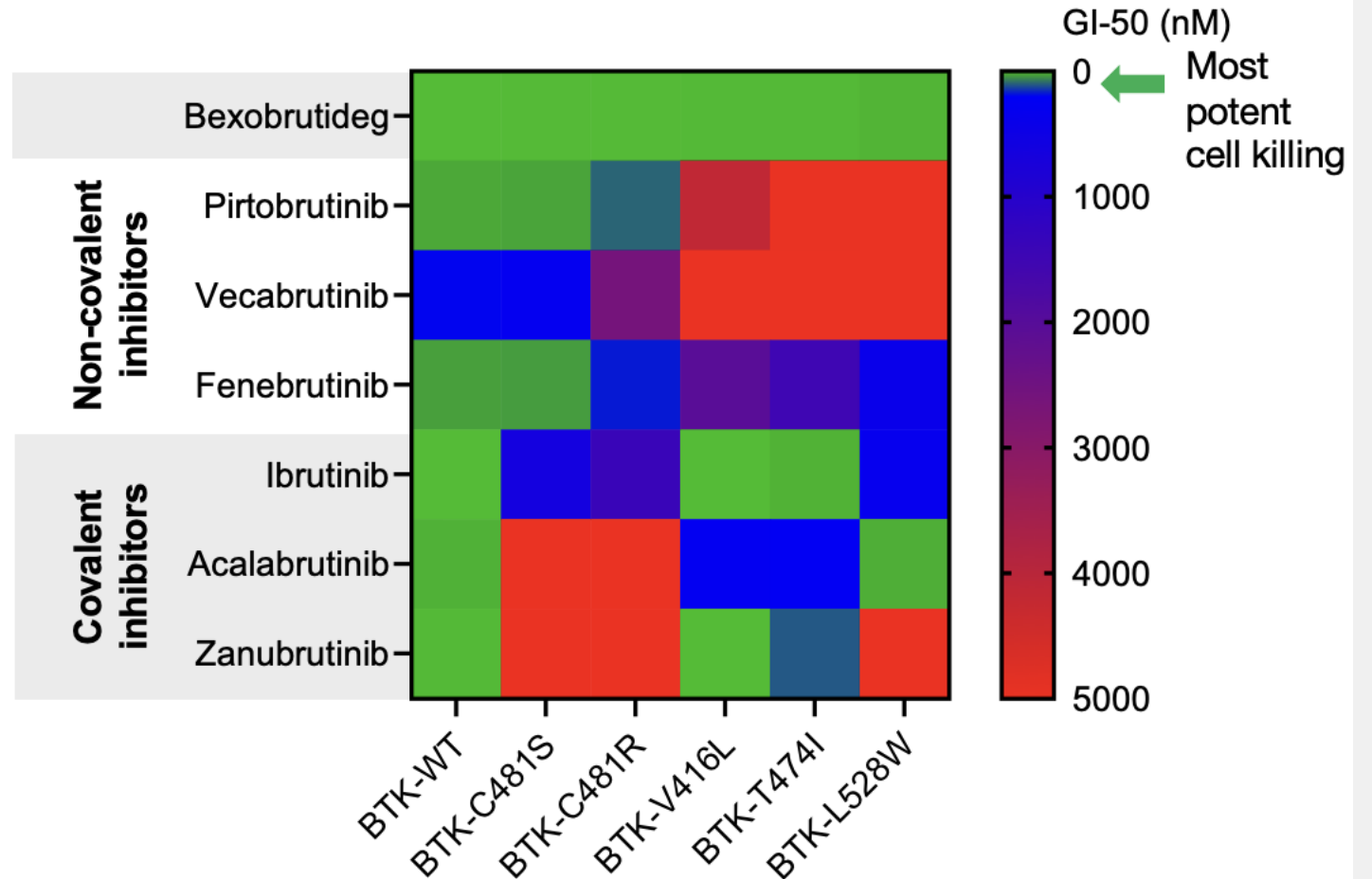


How to target BTK after resistance develops: BTK degraders



Omer Z et al ASH 2025

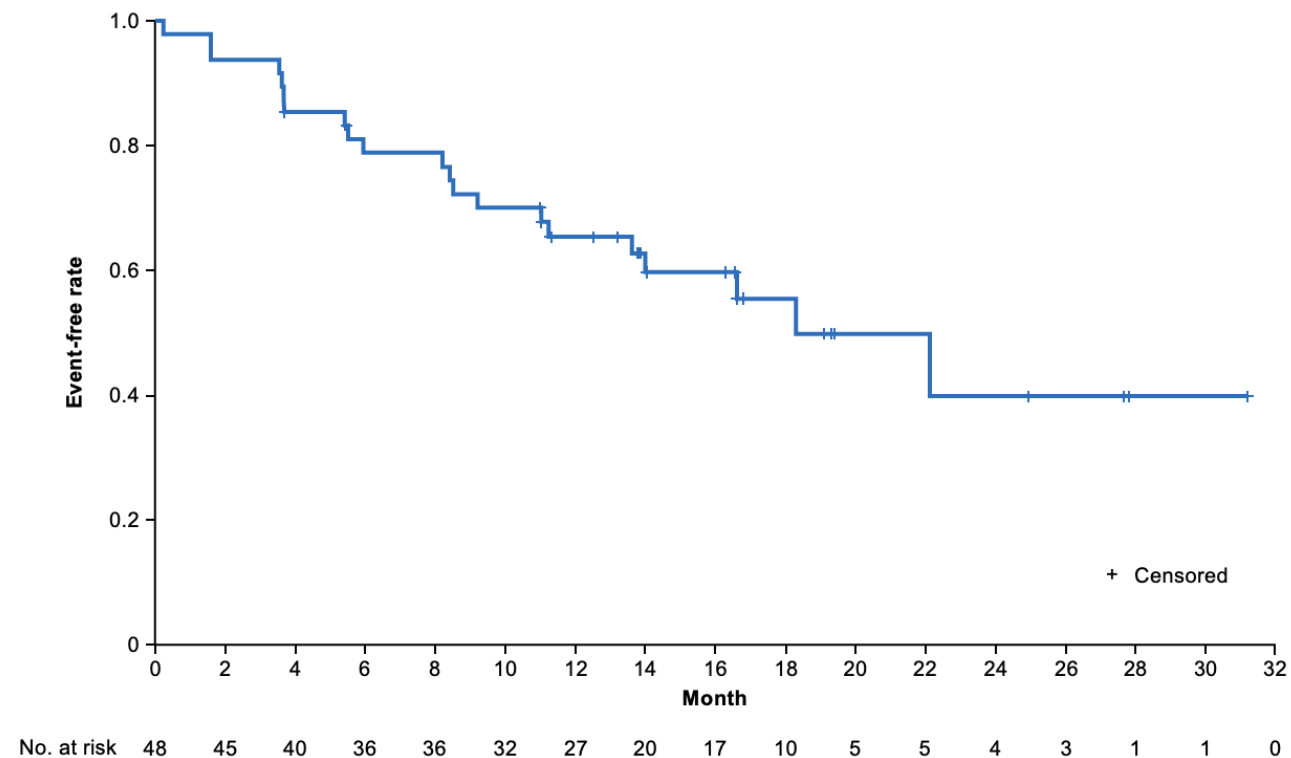
Bexobrutideg shows superior cell killing across mutations compared with BTK inhibitors*



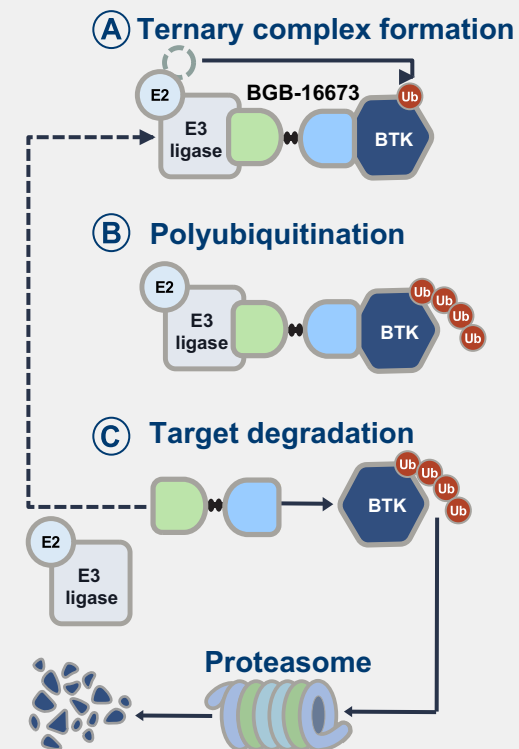
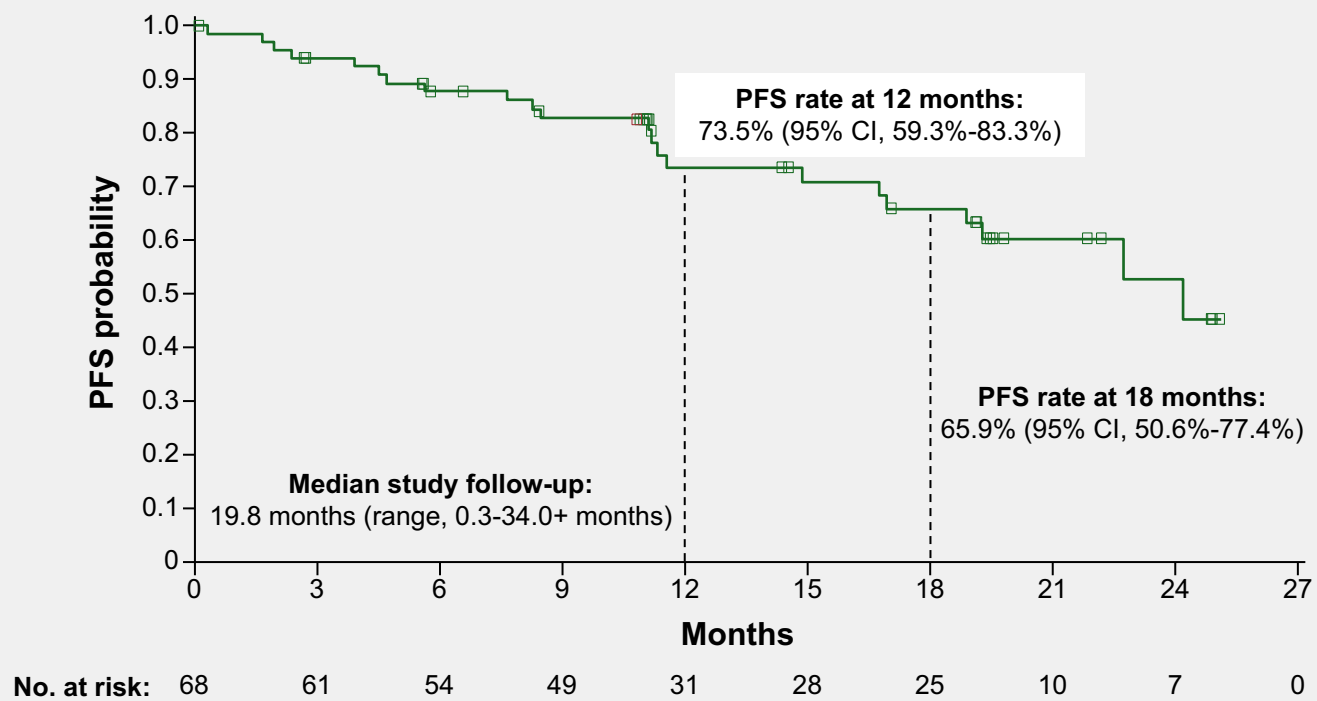
Bexobrutideg (formerly NX-5948)

- Phase 1a portion of trial, n=47 pts with CLL, ORR of 83%
 - 2 patients with CR (4.3%)
- Phase 1b looked at 200 mg vs 600 mg dose
 - 200 mg ORR 74%
 - 600 mg ORR 83%
 - 600 mg selected as RP2D
- 126 pts evaluable for safety with low afib, ~20% g3+ neutropenia, 6.3% discontinue for AE

Median PFS of 22.1 months in study population with longest follow-up



- CaDAnCe-101: Phase 1/2, Open-Label, Dose-Escalation/Expansion Study in R/R B-Cell Malignancies
- N= 68 CLL patients presented at ASH 2025, 4 median prior lines of therapy
- ORR= 85.3%
- Similar safety with neutropenia and pneumonia being g3/4 in 25% and 12% pts, respectively





The New York Times

A Cancer Treatment Makes Leukemia Vanish, but Creates More Mysteries

Two early recipients of CAR T immunotherapy were free of a blood cancer nearly a decade after receiving the therapy.

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A microscopic image showing numerous red blood cells, which are biconcave discs, scattered across a blue background. In the lower right quadrant, there is a cluster of green, spherical cells, likely representing the CAR-T cells mentioned in the article. The green cells have a textured, almost crystalline appearance.

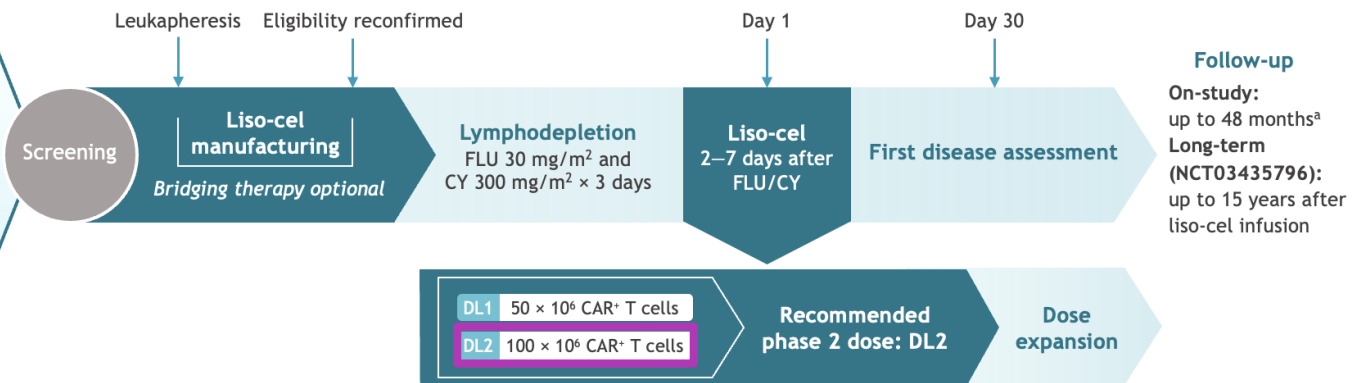
- CAR-T in CLL frequently leads to disappointing results for a variety of reasons
 - T-cell exhaustion phenotype
 - Immunosuppressive microenvironment
 - Poor manufacturing
 - Trials are in late line patients with many prior lines of therapy



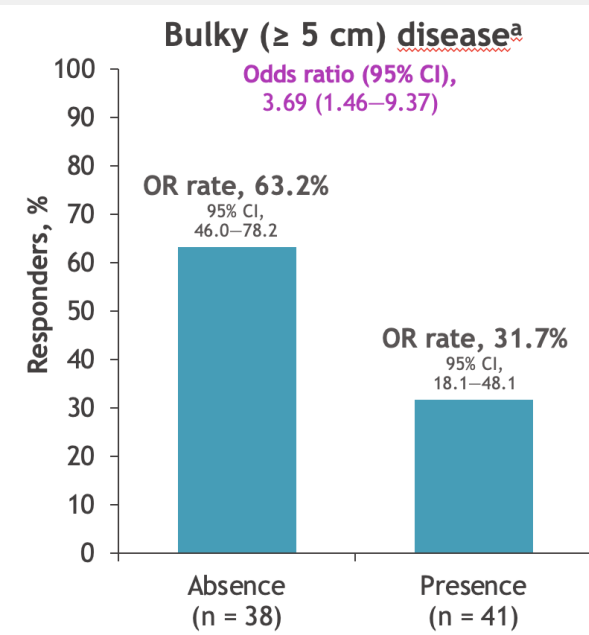
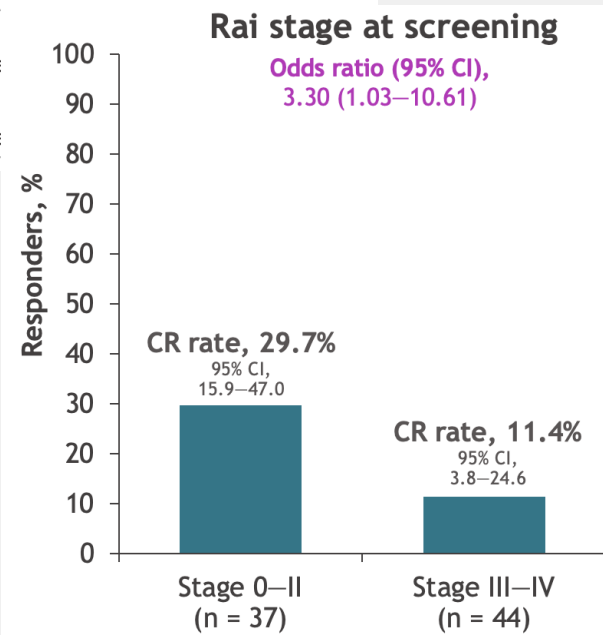
TRANSCEND CLL 004 trial

Key eligibility criteria

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

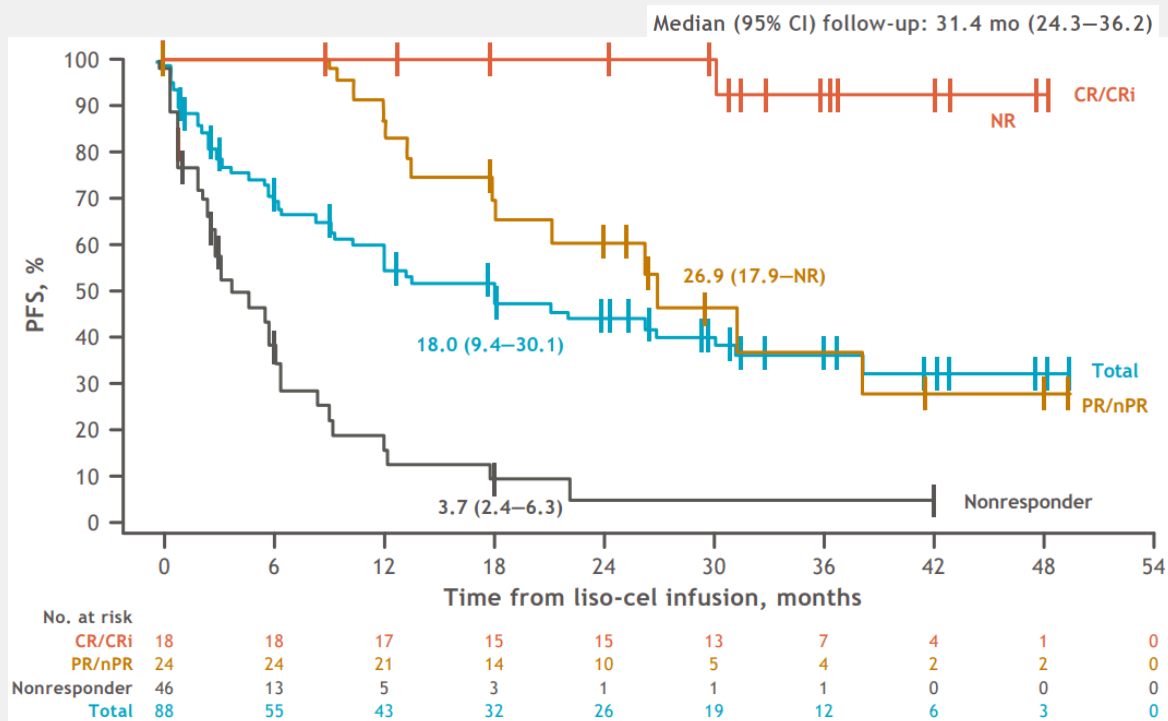


Primary analysis data cut: September 29, 2022		Full efficacy-evaluable set ^b at DL2 (n = 87)
Primary endpoint	CR/CRi rate	18% (95% CI, 11–28%)
Secondary endpoints	OR rate ^c	47% (95% CI, 36–58%)
	Median DOR	35.3 months (95% CI, 19.8–not reached)
	Median PFS	18.0 months (95% CI, 9.4–30.1)
	Median OS	43.2 months (95% CI, 26.9–not reached)

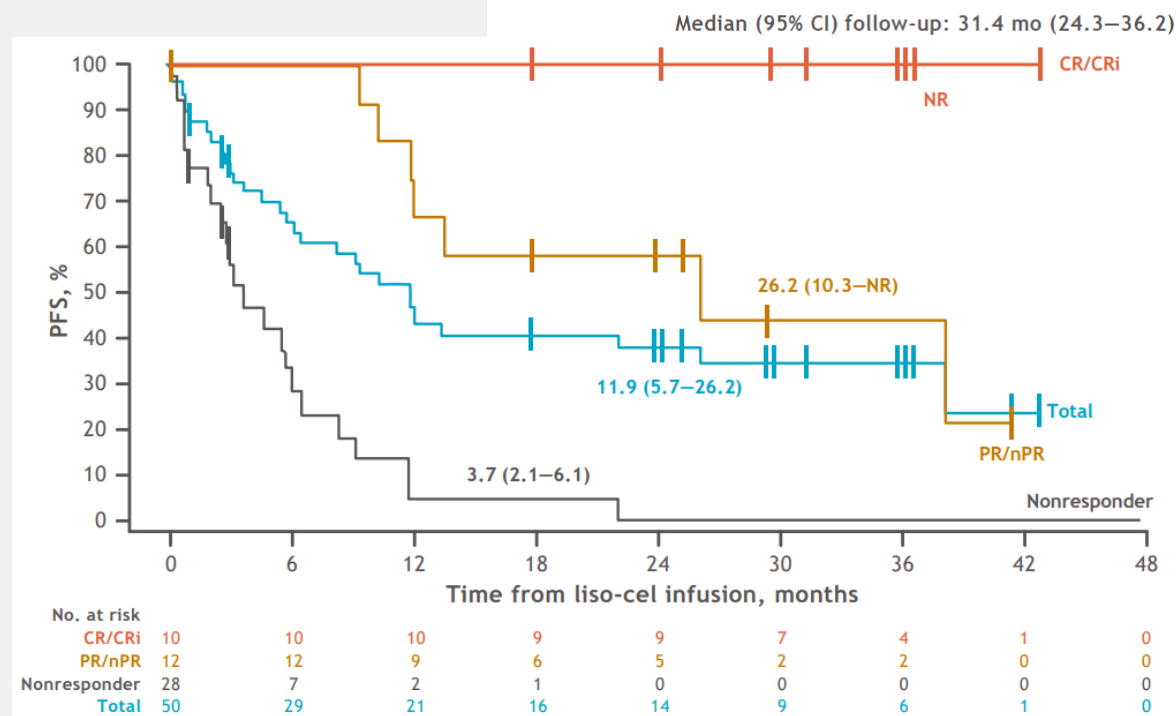


TRANSCEND CLL 004 PFS and Safety

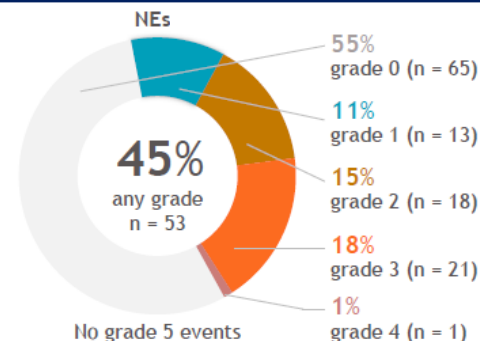
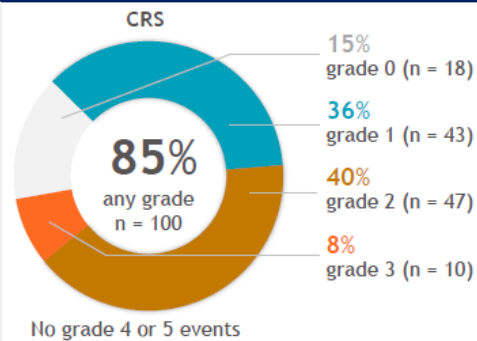
PFS in Full Population at DL2



PFS in PEAS at DL2



Cytokine Release Syndrome and Neurological Events



References: Siddiqi T, et al. Poster presented at ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA.

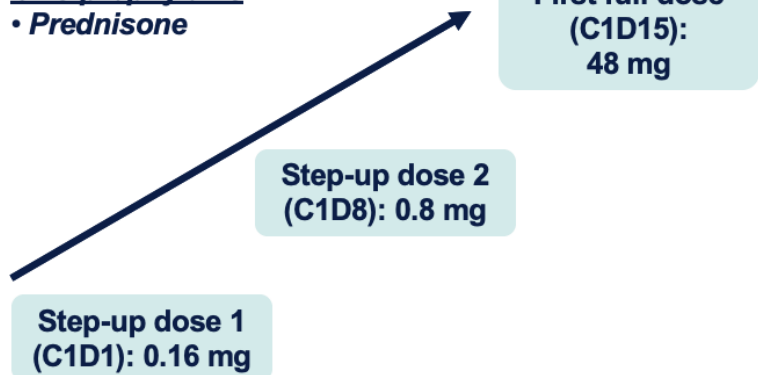
- 56 received ibr + liso-cel (DL1, n = 5; DL2, n = 51)
- At DL2, ORR was 86% (73.7-94.3), median (range) time to first response was 1.0 mo (0.9-6.0), and median DOR was 41.4 mo (23.3-not reached [NR]). CR/CRi rate (95% CI; primary endpoint) was 45%
- Median PFS and OS was 31.4 mo (20.1-NR) and NR (27.5-NR), respectively
- uMRD rate in blood and marrow was 86% (73.7-94.3) and 84% (71.4-93.0), respectively

- A total of 30 patients were included in the study, and 67% had deletion 17p or TP53 mutation.
- All patients had previous exposure to a covalent BTK inhibitor and a BCL-2 inhibitor.
- Patients had received a median of six prior lines of therapy, and 80% had previously been treated with chemotherapy.
- All patients have previously been treated with a covalent BTK inhibitor and a BCL2 inhibitor.
- 60% of patients were treated with pirtobrutinib as their last line of treatment before liso-cel.
- The overall response rate was 83%, and the complete response rate was 60%.
- Patients who had pirtobrutinib as their last line of therapy were more likely to achieve a complete response (72% vs 28%).
 - 18 patients had pirtobrutinib as last prior line of therapy
 - 12 stopped but 6 continued after liso-cel

Bispecific antibodies in CLL: EPCORE CLL-1

Expansion (EXP; N=23)

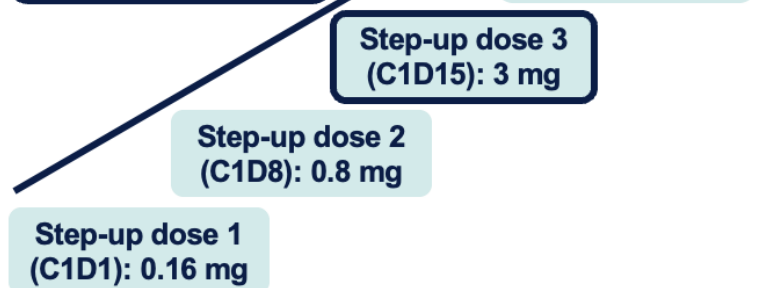
CRS prophylaxis
• Prednisone



Data cutoff: May 28, 2024
Median follow-up: 22.8 months

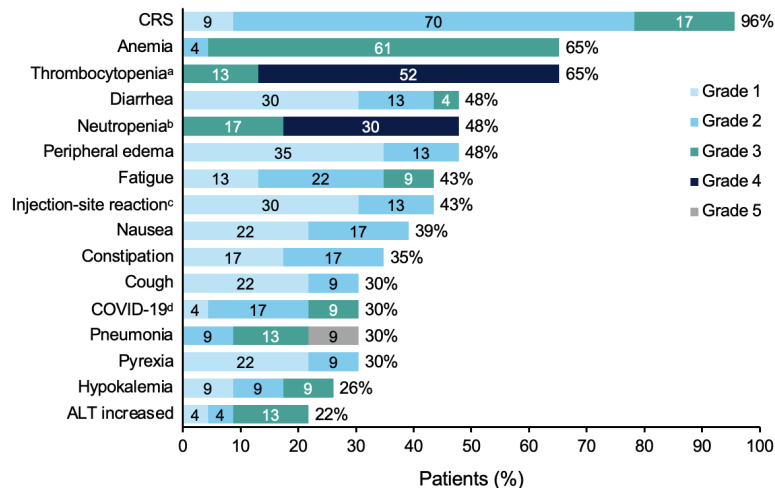
Cycle 1 Optimization (C1 OPT; N=17)

CRS prophylaxis
• Dexamethasone
• Adequate hydration

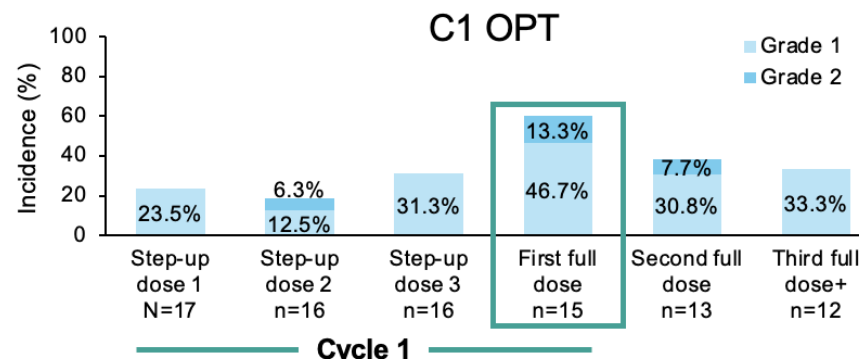
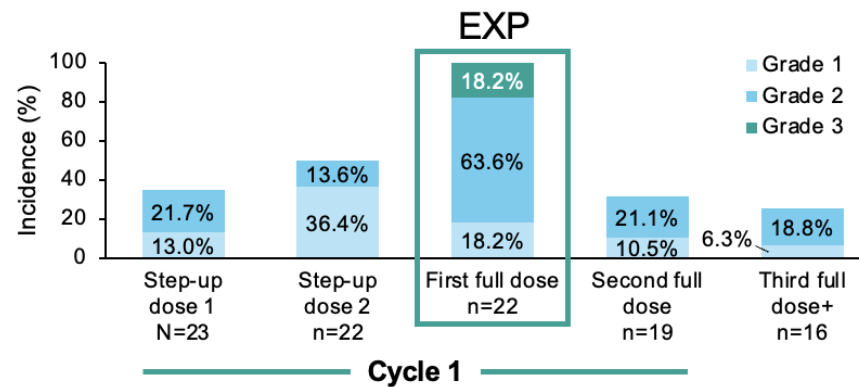


Data cutoff: May 28, 2024
Median follow-up: 2.9 months

Treatment-Emergent AEs (>20%) in EXP



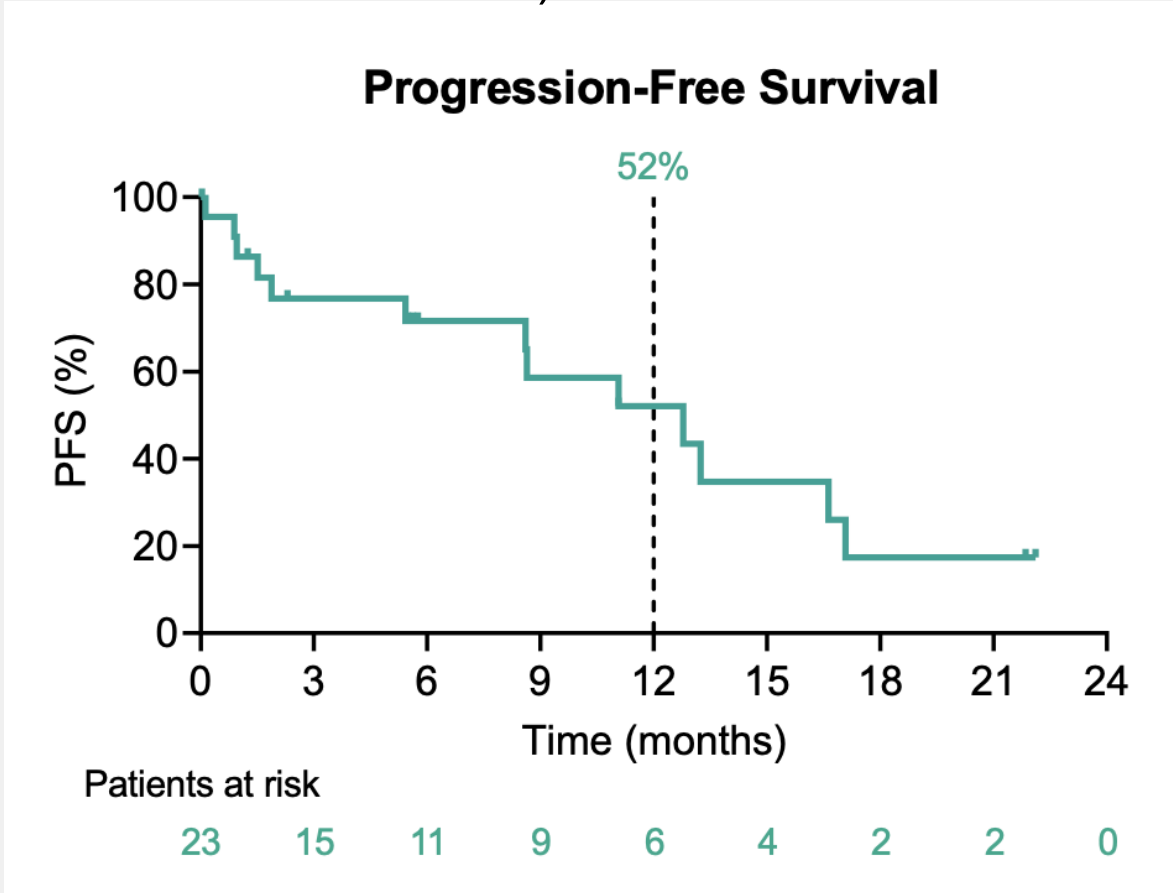
CRS Events by Dosing Period



Epcoritamab in CLL

- Enrolled pts had a median of 4 prior lines of therapy
- For EXP cohort, ORR was 61% with CR 39% (median f/u 22.8 months), median PFS 12.8 months
- For OPT cohort, ORR was 60% with CR 10% (median f/u of 2.9 months)

EXP MRD Negativity, n/n (%) ^c	uMRD4	uMRD6 ^d
Overall response ^b	9/12 (75)	8/12 (67)
Complete response	7/7 (100)	6/7 (86)
Partial response	2/5 (40)	2/5 (40)
Full analysis set	9/23 (39)	8/23 (35)





Transplantation and Cellular Therapy

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Guideline

Clinical Practice Recommendations on the Role Of Allogeneic Hematopoietic Cell Transplantation and Chimeric Antigen Receptor T-Cell Therapy in Patients With Chronic Lymphocytic Leukemia on Behalf of the American Society for Transplantation and Cellular Therapy



Mohamed A. Kharfan-Dabaja^{1,*}, Ambuj Kumar², Javier Pinilla-Ibarz³, Jennifer R. Brown⁴, Mazyar Shadman⁵, Farrukh T. Awan⁶, Saad S. Kenderian⁷, Tanya Siddiqi⁸, Jeremy S. Abramson⁹, Taha Al-Juhaishi¹⁰, Danielle M. Brander¹¹, Catherine C. Coombs¹², Richard R. Furman¹³, Nitin Jain¹⁴, Nadia Khan¹⁵, Nakhle S. Saba¹⁶, Jennifer M. Collins¹⁷, Amer Beitinjaneh¹⁸, Deborah M. Stephens¹⁹, Jennifer Woyach²⁰, Mehdi Hamadani²¹

Update to 2016 guidelines

A panel of 18 physicians with diverse expertise across different CLL treatment modalities and one methodologist participated in this effort. Any recommendation receiving 70% votes was considered a consensus.

	Treatment Setting*	Clinical Scenario	Proposed Treatment	Recommendation	Percentage Voting in Support of Recommendation
Responsive disease	Front-line consolidation	Objective response (CR/PR) to a covalent BTK inhibitor or a BCL2 inhibitor alone or in combination	Allo-HCT	Do not recommend	100%
			CAR T-cell therapy	Do not recommend	100%
	After 2 nd line therapy	CLL relapse after covalent BTK inhibitor, but objective response (CR/PR) to a BCL2 inhibitor	Allo-HCT	Do not recommend	94%
			CAR T-cell therapy	Do not recommend	83%
	After 2 nd line therapy	CLL relapse after a BCL2 inhibitor, but objective response (CR/PR) to a covalent BTK inhibitor	Allo-HCT	Do not recommend	94%
			CAR T-cell therapy	Do not recommend	94%
After 3 rd line therapy	CLL relapse after both a covalent BTK inhibitor and a BCL2 inhibitor and achieves at least a PR or better to a noncovalent BTK inhibitor†	Allo-HCT	Uncertain	56% in favor 44% against	
		CAR T-cell therapy	Recommend	78%	
Nonresponsive disease	After 2 nd line therapy	CLL relapse after a covalent BTK inhibitor and no response to a BCL2 inhibitor	Allo-HCT	Do not recommend	100%
			CAR T-cell therapy	Recommend	89%
	After 3 rd line therapy	CLL relapse after a covalent BTK inhibitors but no response to a BCL2 inhibitor and a noncovalent BTK inhibitor‡	Allo-HCT	Do not recommend	100%
			CAR T-cell therapy	Recommend	89%
	CAR T-cell failure	CLL patients with R/R disease after CAR T-cell therapy§	Allo-HCT	Recommend ¶	94%
Allo-HCT failure	R/R CLL after allo-HCT	CAR T-cell therapy	Recommend	89%	



- Phase 3 trial for rocbrutinib vs. pirtobrutinib (ROCKET-CLL)
- Registrational design trials for BTK degraders
 - Phase 2 DAYBreak CLL-201 (triple exposed single arm trial) for bexobrutideg (seeking accelerated approval) followed by confirmatory Phase 3 DAYBreak CLL-306 trial for bexobrutideg vs pirtobrutinib
 - CaDAnCe-302 compares BGB-16673 vs. investigator choice (idelaR, bendaR or venR retreatment)
 - CaDAnCe-304 compares BGB-16673 vs. pirtobrutinib

- Bispecifics: Epcoritamab is listed in NCCN as option in Richter's transformation but no approval pathway currently apparent in CLL (RT data, ORR 47.6%, Kater AP et al. Lancet Haem 2026)
 - Published data on mosunetuzumab in RT, ORR 40%, CR 20% (Lewis KL et al Blood Advances 2026),
 - Surovatamig (AZD0486) is a novel, fully human CD19xCD3 bispecific antibody actively being studied in CLL (previously presented data in DLBCL, follicular lymphoma)
 - SOUNDTRACK-E trial examines surovatamig in combination with other therapies (such as acalabrutinib) in patients with mature B-cell malignancies including CLL (NCT06564038)
 - SOUNDTRACK-C1 trial examines surovatamig as consolidation therapy in patients with unmutated IGHV

Thank you!

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