Update on Novel Therapies in Relapsed Mantle Cell Lymphoma

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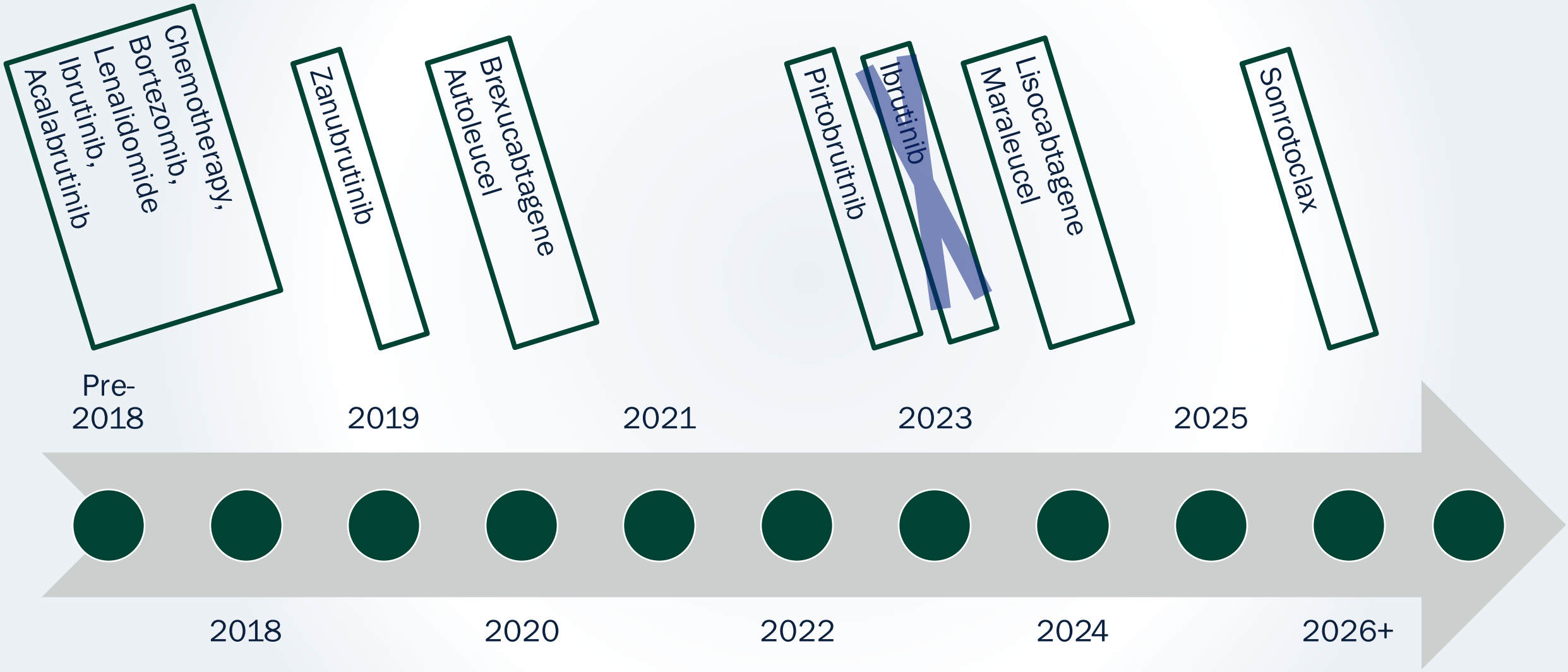
DDHO 2026

Evolution of Approved Treatments for Relapsed/Refractory MCL



Recent and Upcoming Therapies in Rel/Ref MCL

Targeted Therapies

- BTK inhibitors
  - Pirtobrutinib
- BCL2 inhibitors
  - Sonrotoclax
- *ROR1-directed therapies*

Cellular Therapies

- Brexucabtagene autoleucel
- Lisocabtagene maraleucel

Immunotherapies

- *Glofitamab*

Important Considerations:
- Many combinations under investigation
- Updates to front-line management impact rel/ref approaches

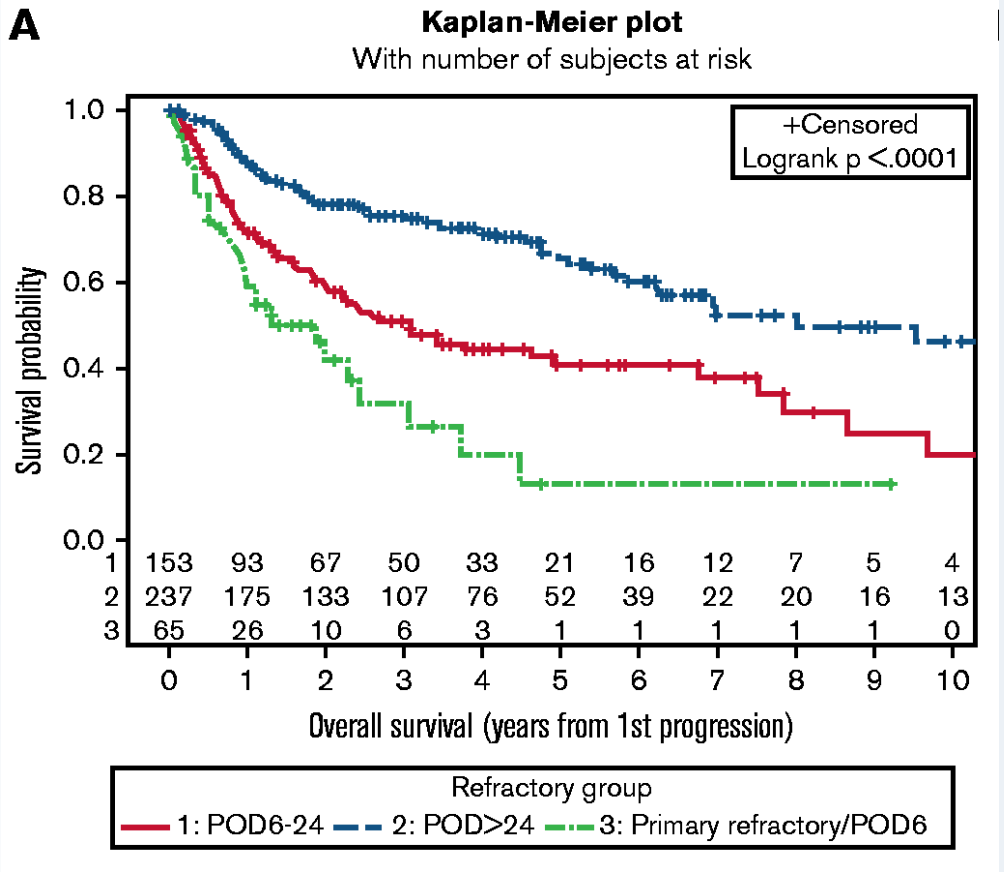
My Current Thought Process

1) Are any of the following present?
   a) Prior BTKi during induction
   b) Presence of TP53 mutation
   c) Early Recurrence (ie, < 24 months)

2) Is the patient a CAR-T Candidate? Allo transplant?
   a) Age < 80 (generally)
   b) Social support and manageable comorbidities

3) Are there clinical trial options?

Post-relapse OS based on time to recurrence



Bond et al, Blood Adv 2022

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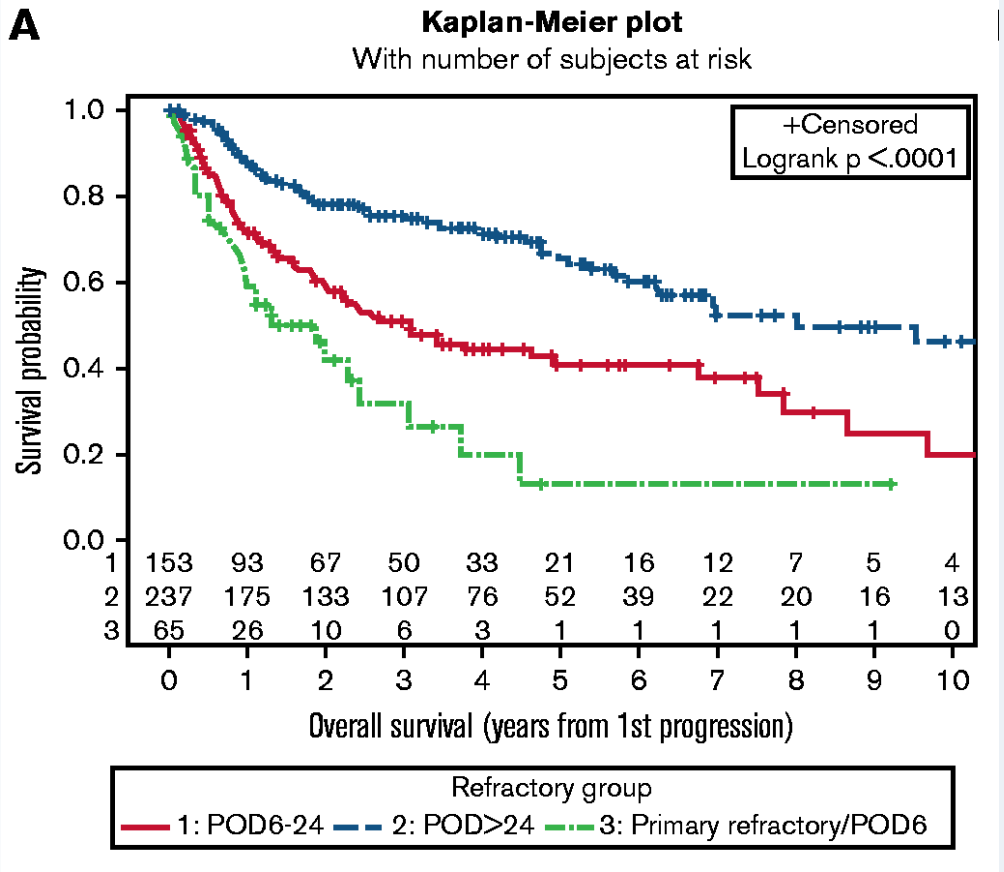
This is NOT CLL – Relapsed MCL is often aggressive

Post-relapse OS based on time to recurrence



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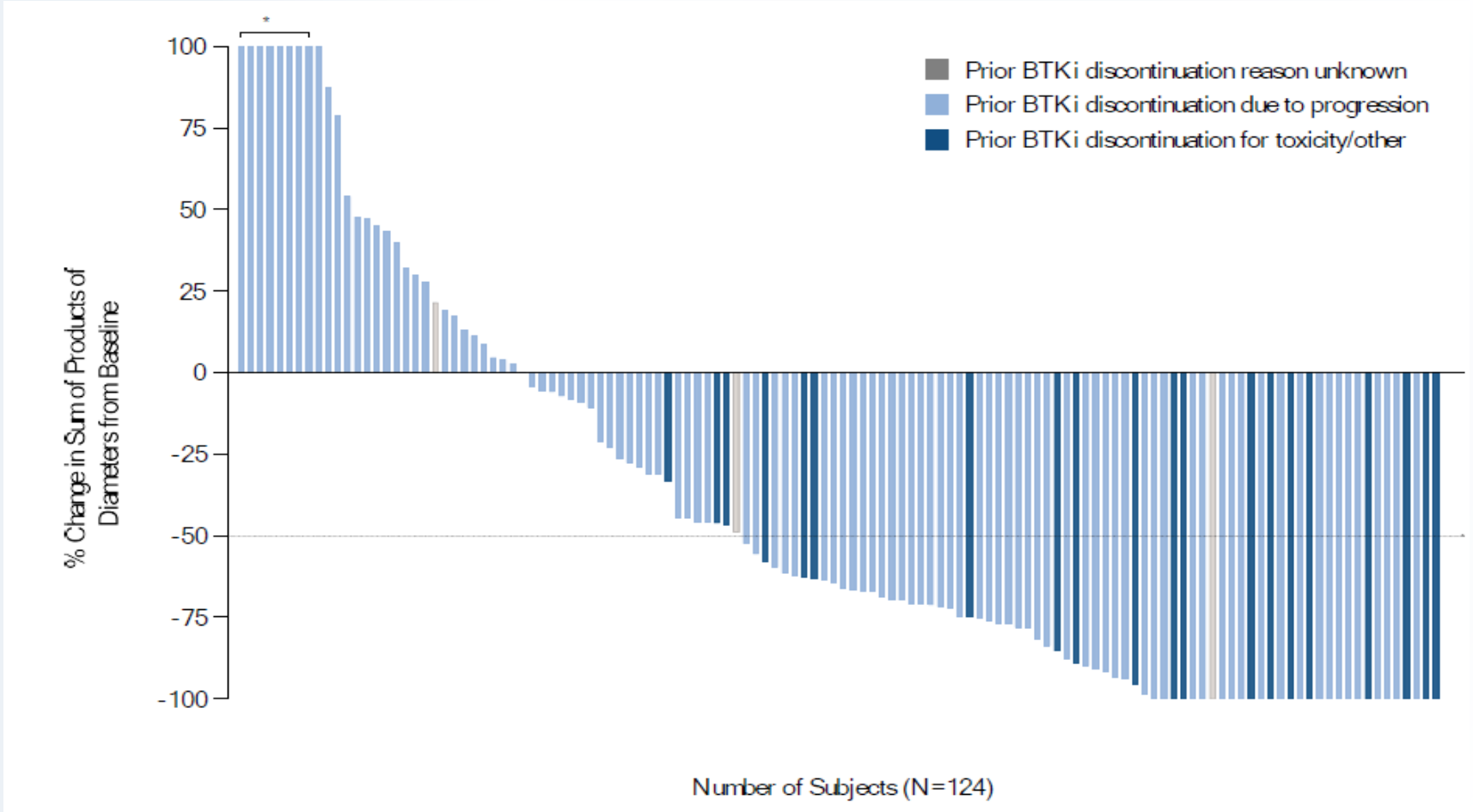
Pirtobrutinib – non-Covalent BTK inhibitor



Prior cBTKi	n=152
ORR[b], % (95% CI)	49.3 (41.1-57.6)
Best Response, n (%)	
CR	24 (15.8)
PR	51 (33.6)

Wang et al, ASH 2025 Annual Meeting

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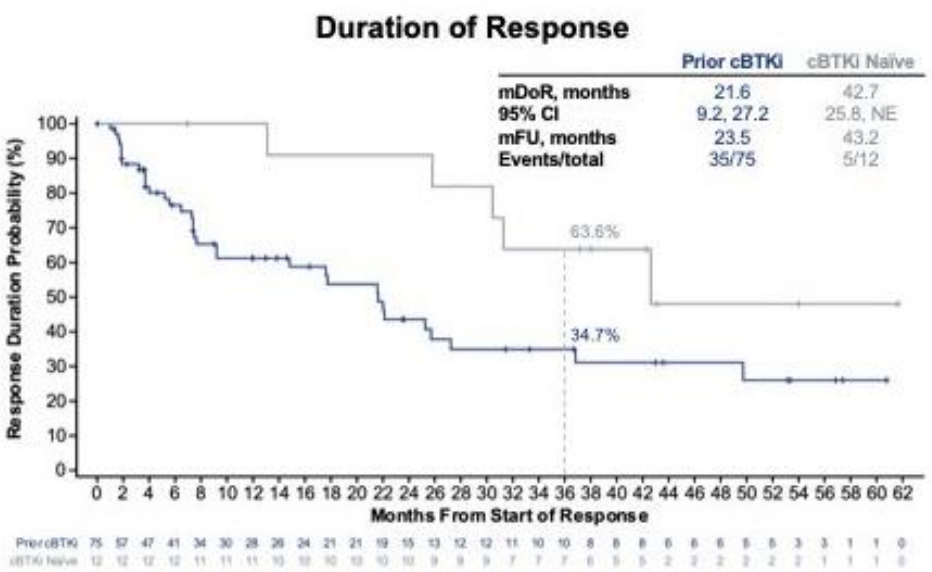
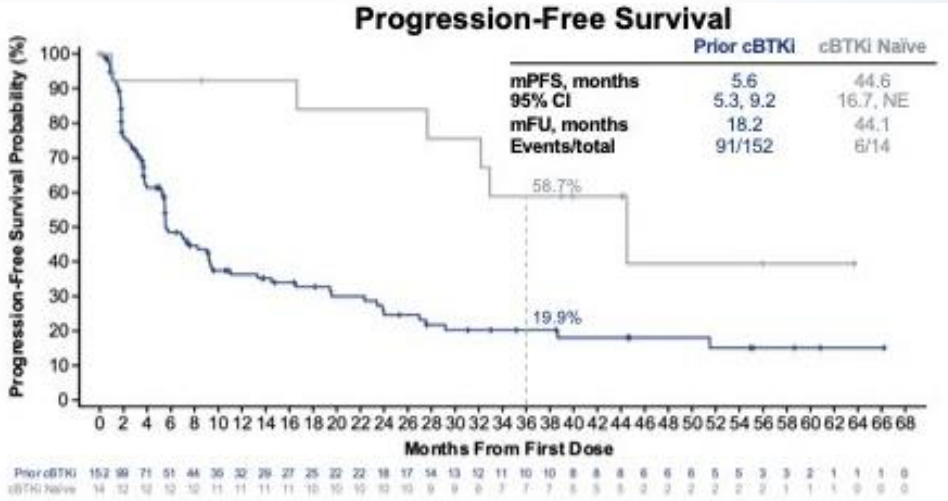
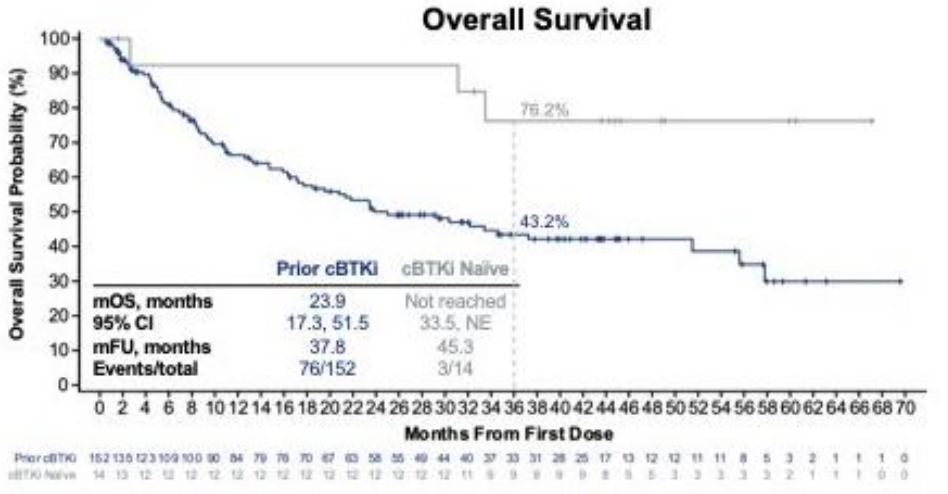


Outcome by Reason of Discontinuation From Prior BTKi

	PD	Toxicity/Other
mDoR, months	14.8	25.3
95% CI	4.0, 27.2	7.5, NE
mPFS, months	5.5	27.0
95% CI	3.8, 7.4	9.3, NE
mOS, months	18.5	57.8
95% CI	11.3, 33.5	32.2, NE





Wang et al, ASH 2025 Annual Meeting

New BCL2 Inhibitor – Sonrotoclax (BGB-11417-201)

Eligibility criteria

- Age ≥18 years
- Histologically-confirmed MCL per WHO 2016 classification
- ≥1 line of anti-CD20-based therapy and ≥1 BTK inhibitor
- ECOG PS of 0-2
- No prior BCL2 inhibitor treatment

Study design

Parts 1A + 1B dose escalation and safety expansion

Target dose 2:
320 mg QD (n=12)

Target dose 1:
160 mg QD (n=10)

Safety expansion: up to 2 cohorts at select sonrotoclax target dose levels n≤12 per cohort (including part 1A)

Part 1 endpoints

- Primary: DLTs (part 1A), TEAEs, SAEs, AEs leading to discontinuation, TLS events
- Secondary: preliminary antitumor activity

Part 2 efficacy expansion

Sonrotoclax at RP2D[a] until PD
n=103

Part 2 endpoints

- Primary: ORR by IRC (Lugano 2014)
- Secondary: ORR by INV, DOR by IRC and INV, PFS by IRC and INV, TTR by IRC and INV, HR-QOL, OS, safety

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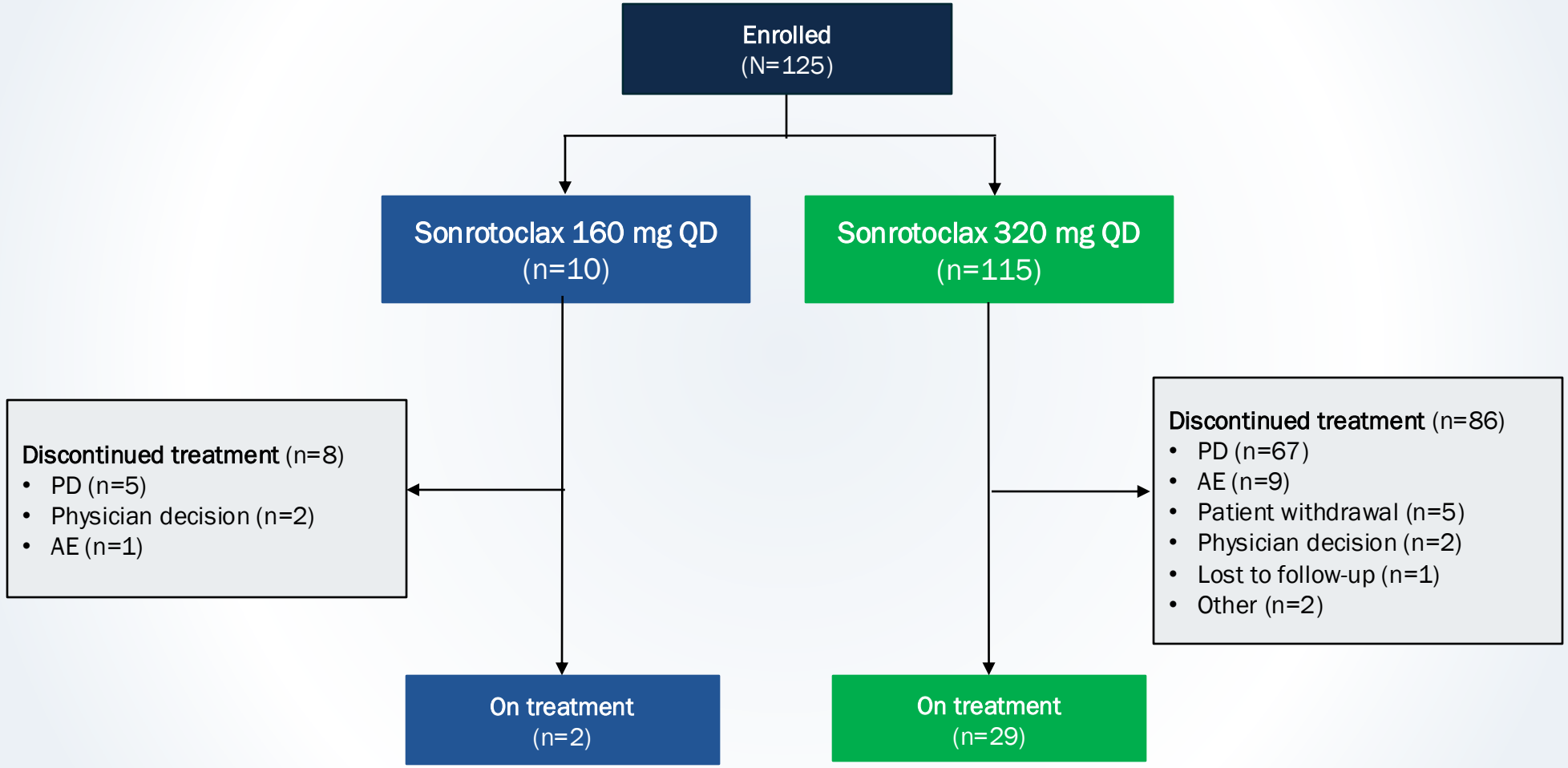
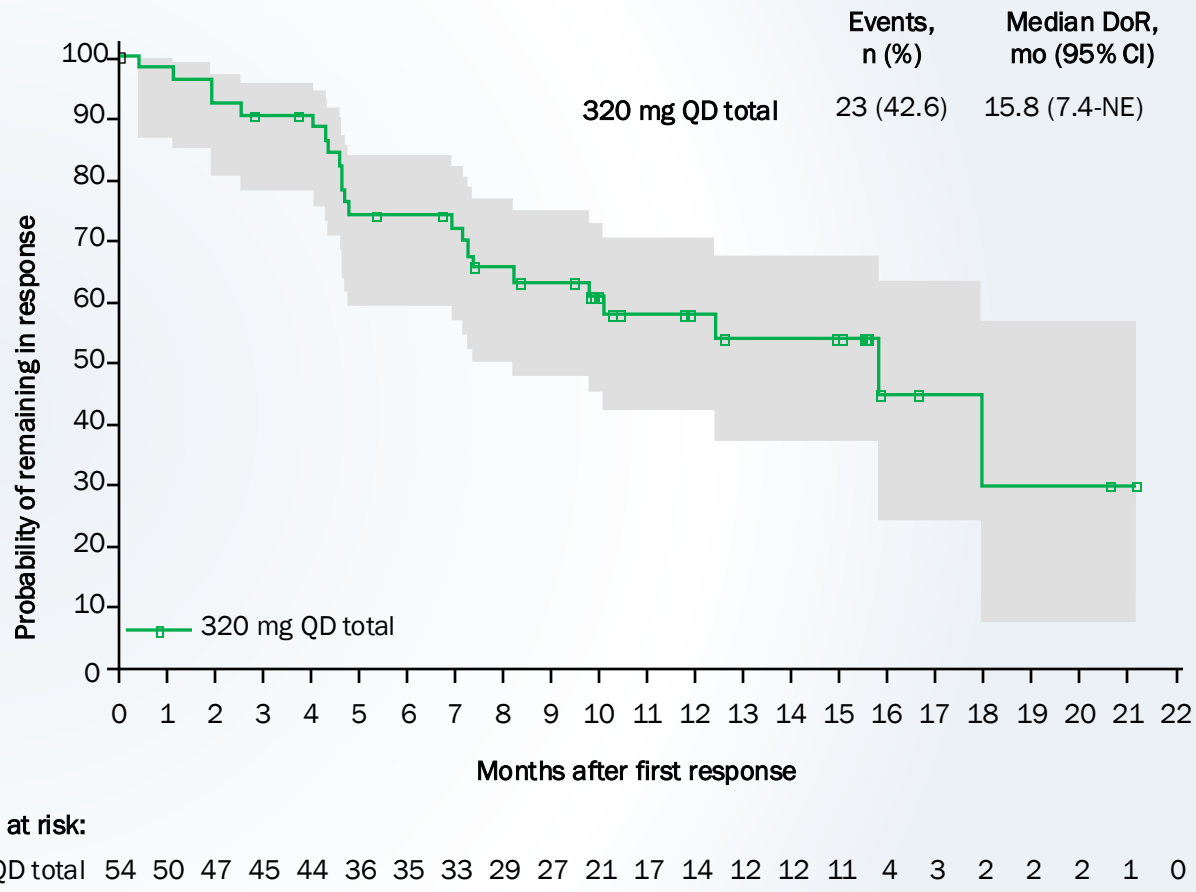


Wang et al, 2025 ASH Annual Meeting

Sonrotoclax in MCL: Response rate and Duration of Response

	Part 2: Sonrotoclax 320 mg (n=103)	
Parameters	**IRC-assessed**	**INV-assessed**
ORR, n (%)	54 (52.4)	49 (47.6)
95% CI, %	42.4-62.4	37.6-57.6
1-sided *P* value	<.0001	N/A
CR rate, n (%)	16 (15.5)	23 (22.3)
95% CI, %	9.1-24.0	14.7-31.6
TTR, median (range), months	1.9 (1.6-6.2)	1.9 (1.6-4.0)



Wang et al, 2025 ASH Annual Meeting

Sonrotocolax Safety Profile

8 Patients with TLS Events

Most common grade 3+ AEs:
- Cytopenias
- Infections

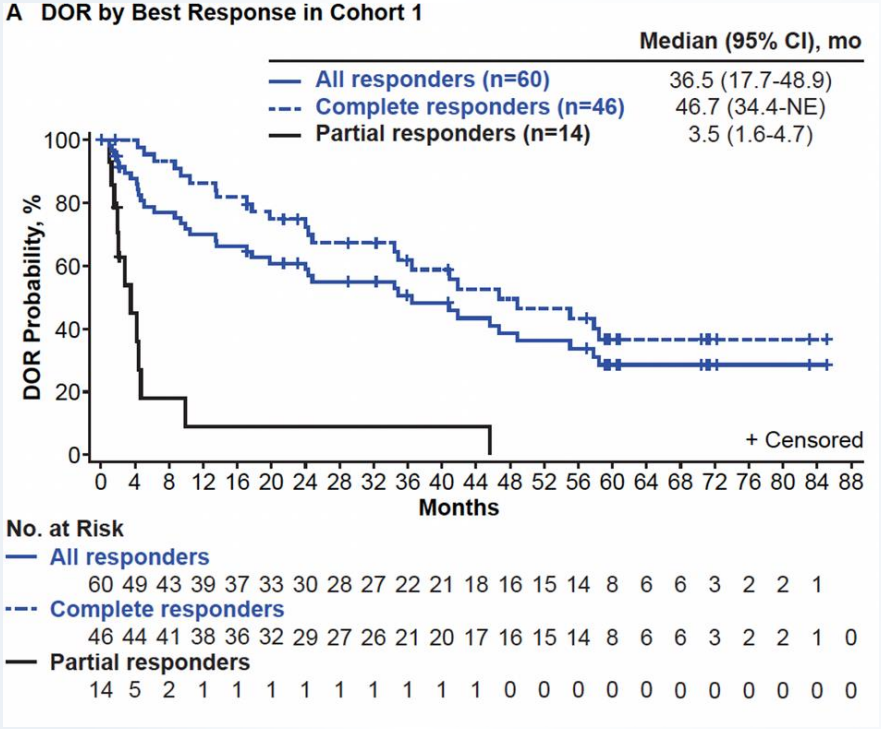
FDA Accelerated Approval May 13, 2026:
Adults with relapsed/refractory MCL who have received at least 2 lines of prior therapy, including a BTKi.

Patients, n (%)	Sonrotoclax 320 mg (n=115)	
	Any grade	Grade ≥3
Neutropenia[a]	41 (35.7)	22 (19.1)
Thrombocytopenia[b]	28 (24.3)	11 (9.6)
Anemia[c]	28 (24.3)	9 (7.8)
White blood cell count decreased	25 (21.7)	3 (2.6)
Hyperuricemia	22 (19.1)	0
Hypokalemia	20 (17.4)	0
Pneumonia	18 (15.7)	12 (10.4)
Diarrhea	16 (13.9)	5 (4.3)
AST increased	14 (12.2)	1 (0.9)
ALT increased	12 (10.4)	0
Constipation	12 (10.4)	0
Lymphopenia[d]	12 (10.4)	7 (6.1)
Select TEAEs by category/AE/SOC		
Infections (SOC)	45 (39.1)	19 (16.5)
Febrile neutropenia	2 (1.7)	2 (1.7)
TLS (AE)	8 (7.0)	8 (7.0)

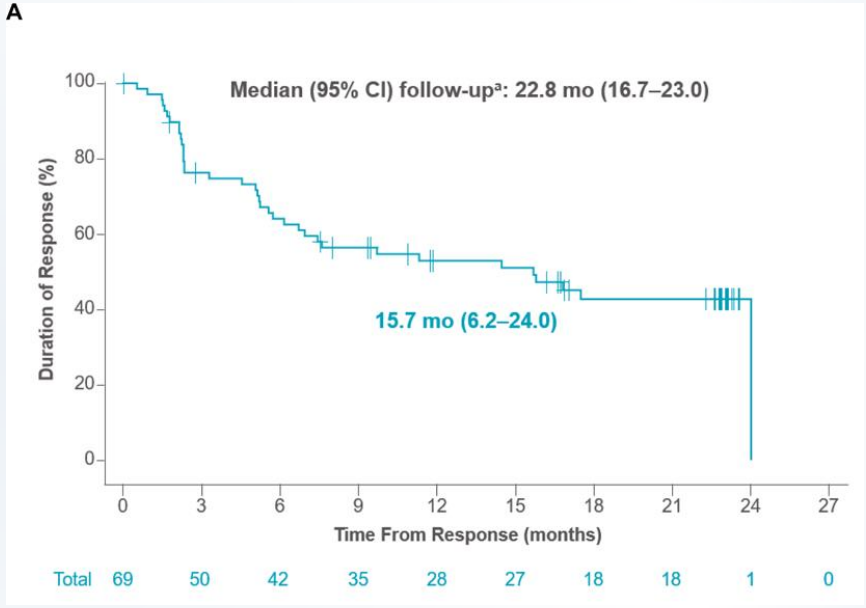
Wang et al, 2026 ASH Annual Meeting

Survival Outcomes with Approved CAR-T Products

Brexucabtagene Autoleucel – ZUMA2

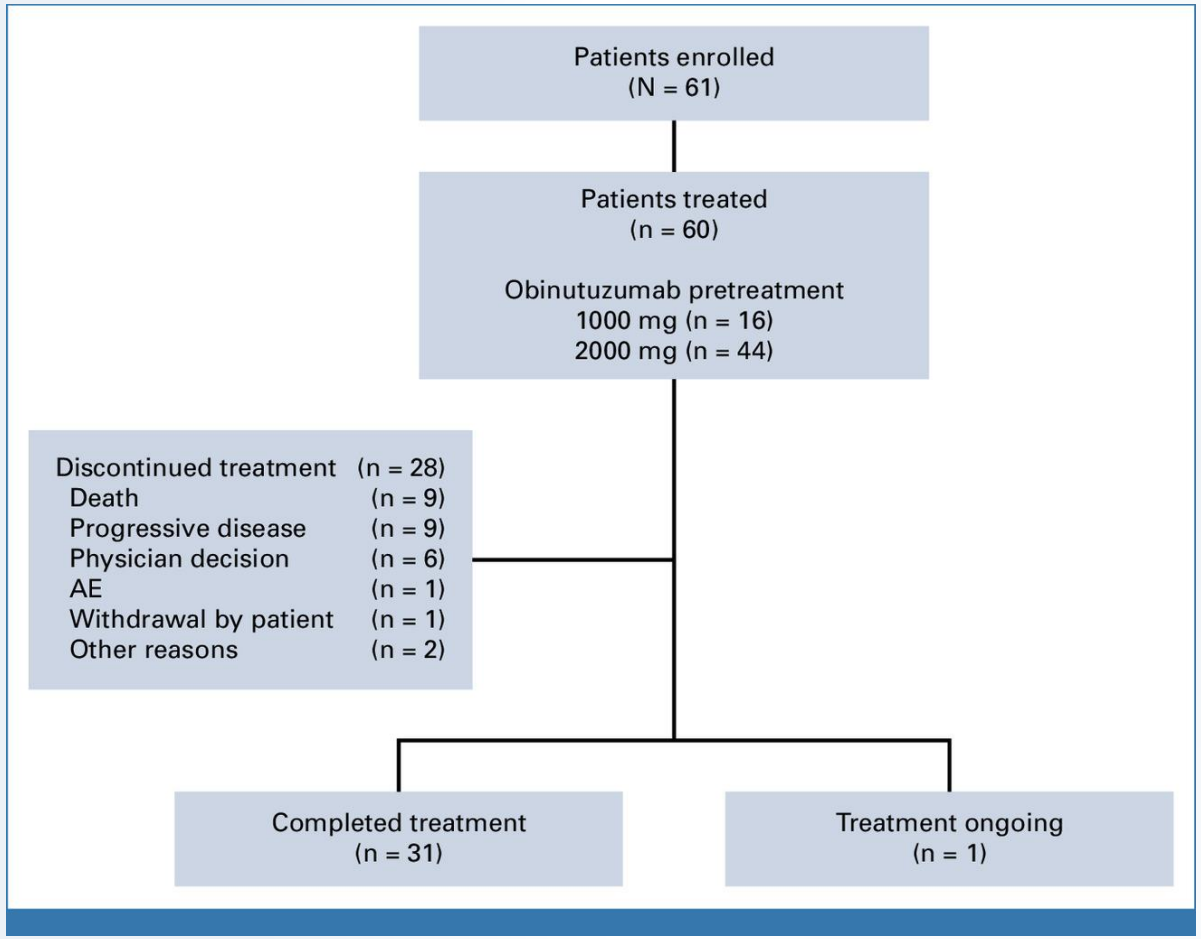


Lisocabtagene Autoleucel - TRANSCEND



Munoz, J Hematol & Oncol, 2026; Wang et al, J Clin Oncol 2024

Glofitamab is Active in R/R MCL



	Prior BTKi	No Prior BTKi	All Patients
CR Rate	22 (71%)	25 (86%)	47 (78%
PR Rate	1 (3.2%)	3 (10.3%)	4 (6.7%)
ORR	23 (74%)	28 (97%)	51 (85%)
Median PFS	8.6 mo	-	16.8 mo
Median DoCR	12.6 mo	-	15.4 mo
Median DoR	12.6 mo	-	16.2 mo

Phillips et al, J Clin Oncol 2025

Glofitamab is Active in R/R MCL, But.....

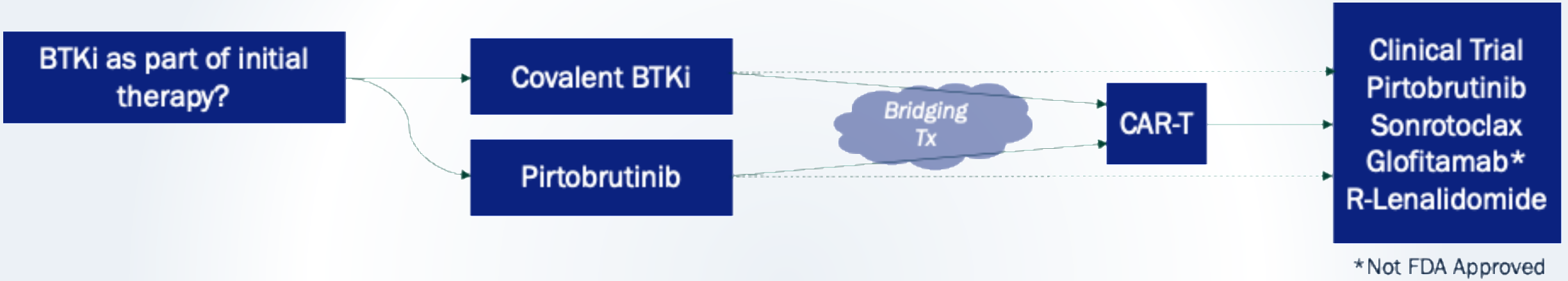
Cytokine Release Syndrome	All Patients
Any CRS	42 (70%)
Grade 3+ CRS	7 (11.6%)
CRS SAE	23 (38.3)
Tocilizumab Administered	22 (36.7%)

Higher dose of obinutuzumab may limit risk

10% of Patients stopped treatment due to CRS

Phillips et al, J Clin Oncol 2025

My Current Approach



- Chemotherapy used infrequently in the relapsed setting (possibly as bridge to more definitive treatment)
- Early relapsing disease and progression on a BTKi are still high risk situations
- Anyone with relapsed disease should be evaluated for cellular therapy options

- Combination therapies *may* improve outcomes but this is not clear at present
  - Several studies not particularly encouraging:
    - PrE0404 – Ibrutinib + Ixazomib
    - Uva Study – Ibrutinib + Venetoclax

Cohen JB, Clin Lymphoma Myeloma Leukemia 2026; Portell CA, Blood Adv 2022

Current MCL Trials at Emory

A052101 (PI: Cohen) – Rituximab + Zanubrutinib in Older Patients with MCL

IM-1021-101 (PI: Schneider) – Phase 1 Study of IM-1021 in Patients with Advanced Malignancies

- ROR1 targeted ADC – Topoisomerase 1 Payload

NOVA-BCL6-1 (PI: Cohen) – Multicenter Phase 1 Study of LY4584180 in Hematologic Malignancies

- BCL6 targeted oral agent

Q&A