Relapsed/Refractory Mantle Cell Lymphoma

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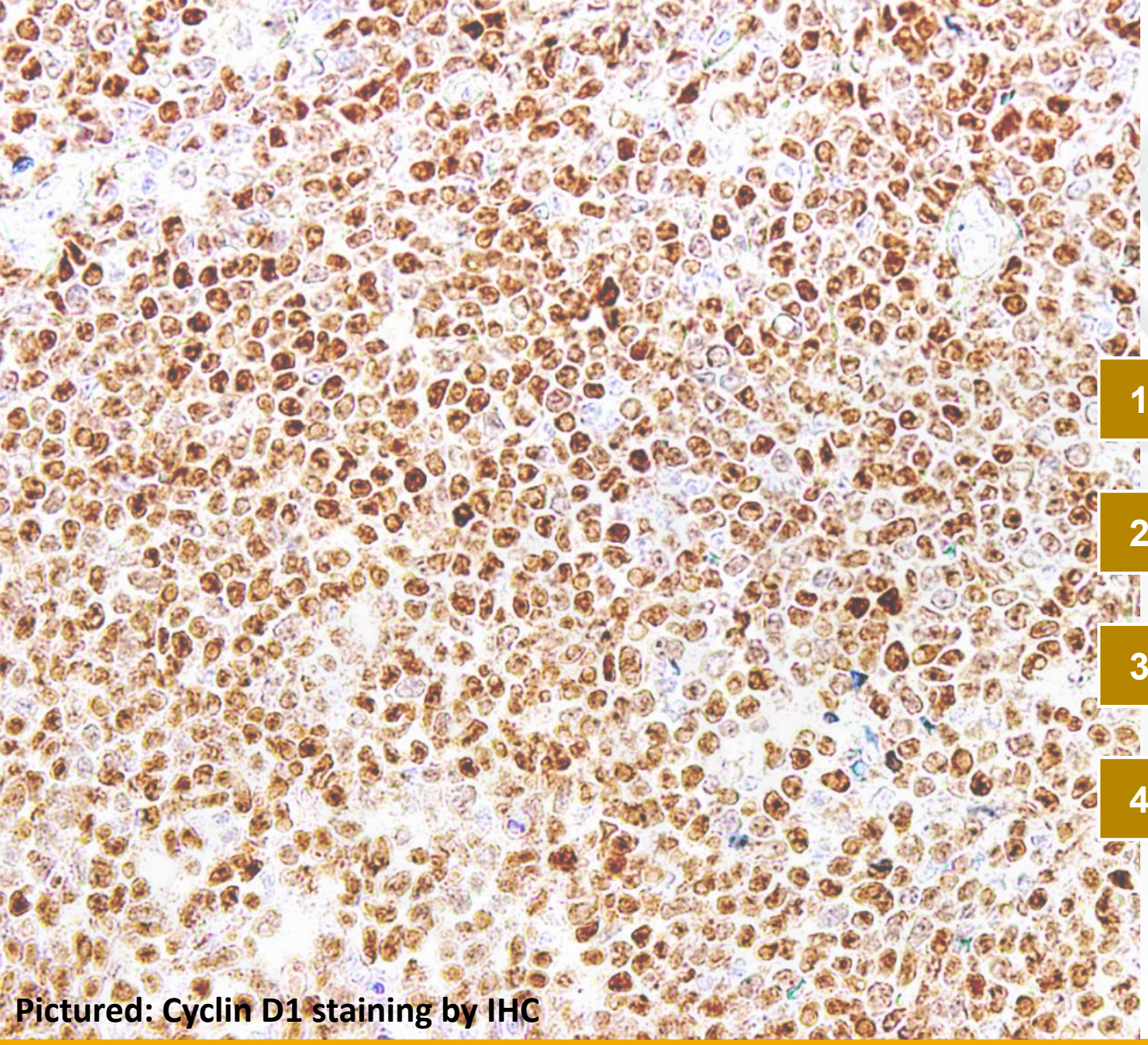


Pictured: Cyclin D1 staining by IHC

OUTLINE

1. Brief review of 1L MCL therapies
2. BTK inhibition
3. CD19 CAR-T therapy
4. Subsequent lines and emerging therapies in MCL

WHAT IS MANTLE CELL LYMPHOMA?

B-cell NHL, usually CD10(-) / CD5(+), with multiple described variants of differing clinical aggressiveness

- **nodal** (most common)
- **leukemic non-nodal** (often indolent, may mimic early-stage CLL)
- **blastoid / pleomorphic** (highly aggressive)

Defined by **t(11;14)**, leading to overexpression of **Cyclin D1**

Reminder:
Check for **t(11;14)** in any patient with suspected CLL, regardless of IHC profile

HIGH incidence of **extranodal involvement**, particularly GI tract

Central nervous system involvement is rare, and CNS prophylaxis is generally not used or recommended.

PRIMER ON FRONTLINE MCL THERAPIES

ALL patients with MCL should ideally be considered for clinical trial – please refer or reach out if you have questions!

Younger / fit patients – INTENSIVE therapy
- RHDA + platinum (cis, oxali, carbo)
- RDHAP / RCHOP
- NORDIC: RmaxiCHOP / R-AraC
- (HyperCVAD)

EA 4181

Older / less fit patients – less aggressive therapy
- R-Bendamustine → Ph III SHIELD: **BR + ibrutinib**
- VR-CAP
- RBAC500 (low-dose AraC)
- (Frail: R-lenalidomide)

BR/R-AraC+ acalabrutinib

BR + acalabrutinib

Consolidative autoSCT in CR1

EA 4151

+/- Maintenance rituximab x2-3 yrs

Maintenance rituximab x2-3 yrs

- Current 1L MCL therapies generally not considered curative
- Multiple ongoing studies evaluating the above paradigms

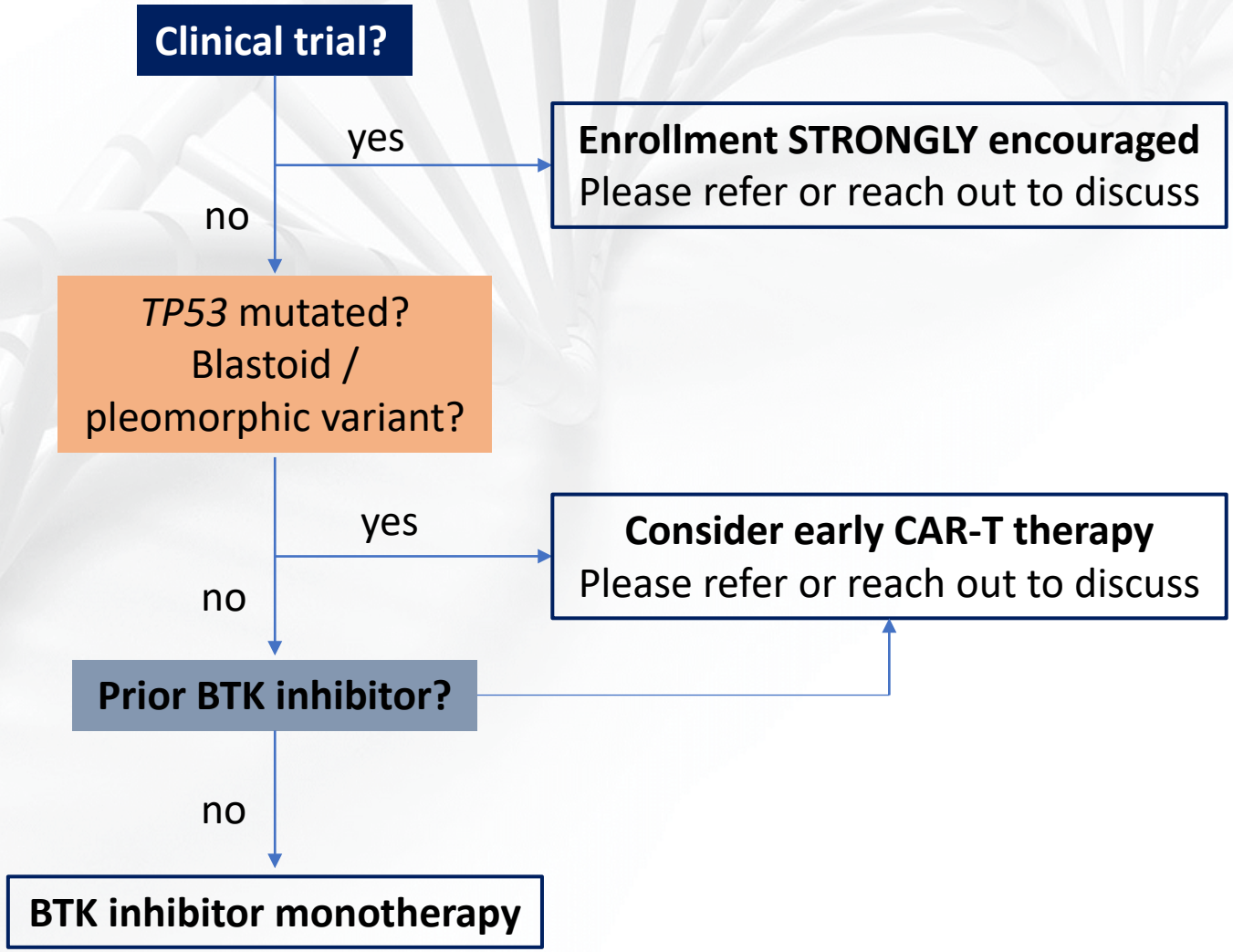
RELAPSED / REFRACTORY MANTLE CELL LYMPHOMA: SECOND LINE

Histologically confirmed R/R MCL

A few considerations:
Age, stage, performance status, medical comorbidities:
- Cardiac (esp. arrhythmias)
- Bleeding diathesis
- Headaches / arthralgias

Prior therapy in 1L setting
- BTKi exposure
- Any residual cytopenias?

Social support
Functional independence



Adapted from Eyre et al, Blood 2022; Romancik et al, Clin LML 2022

Next slide: **BTK inhibitor therapy**

BTK INHIBITOR THERAPY IN R/R MCL: IBRUTINIB

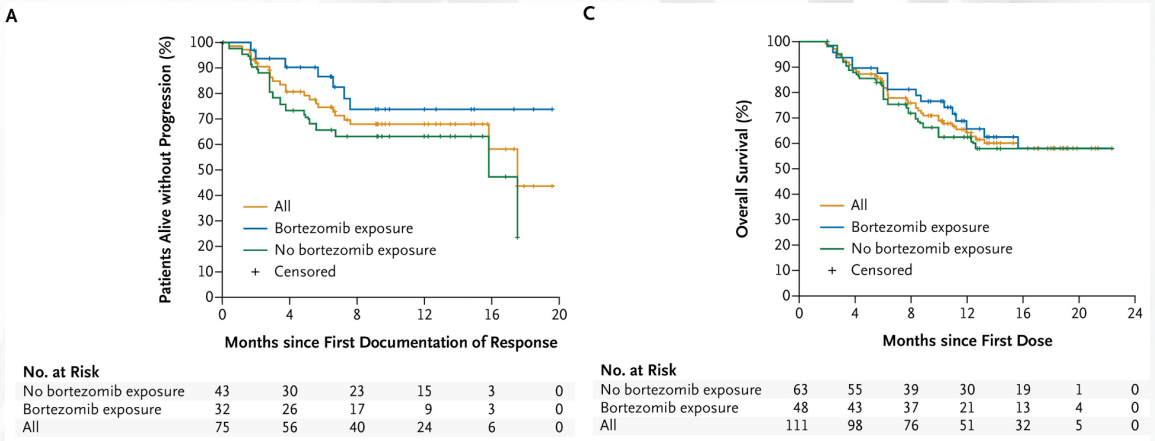
Phase II – ibrutinib 560mg daily

2 enrollment groups – 2+ vs <2 prior bortezomib cycles
Median 3 prior tx lines

ORR 68% **CR** 21% **mPFS** 17.5 months

Longer remission without prior bortezomib exposure

Identified **bleeding risk** as major toxicity of concern
– 4 pts with subdural hematoma while on warfarin



Subsequent Phase III – ibrutinib vs temsirolimus

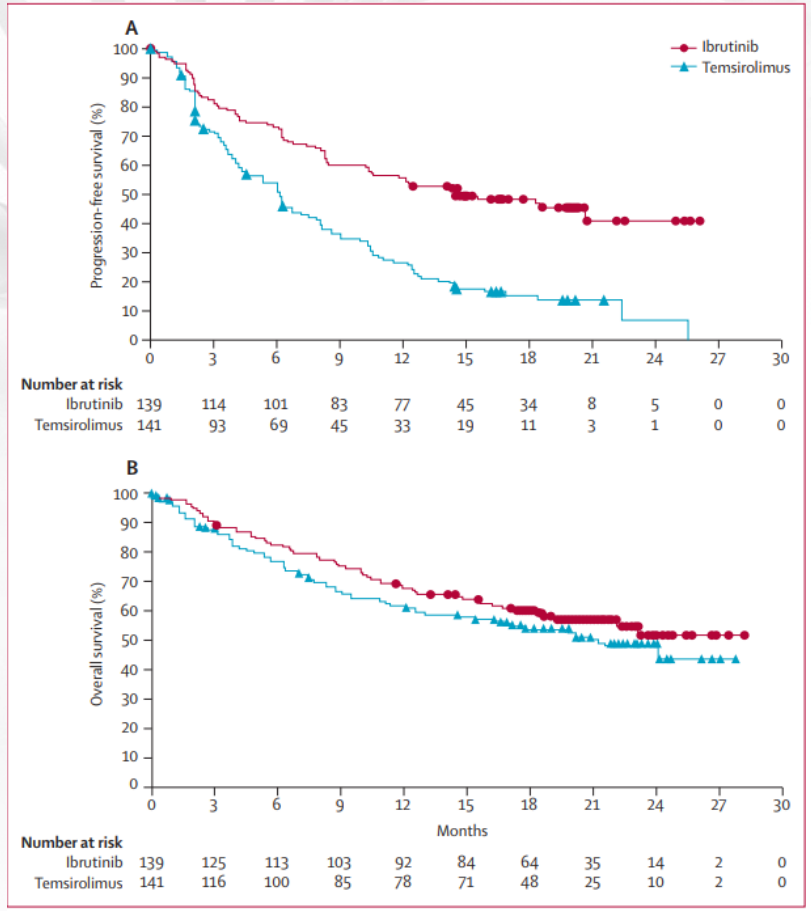
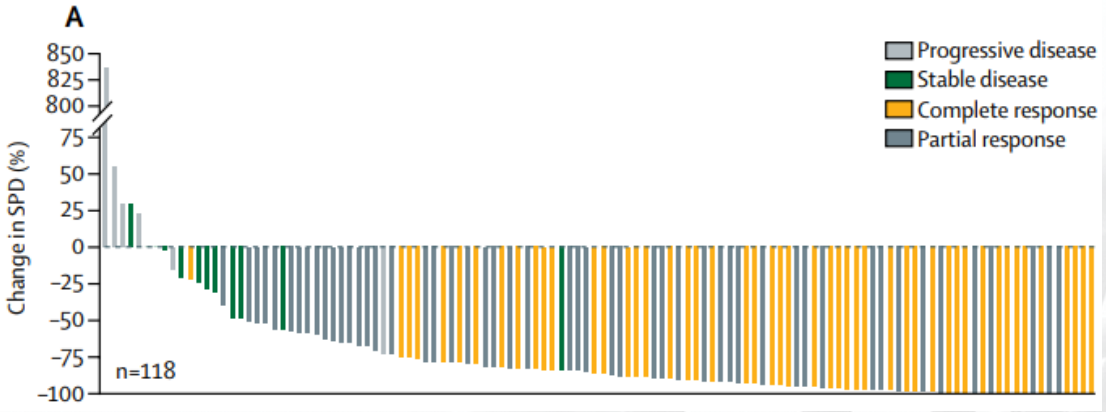


Figure 2: **Kaplan-Meier plots of progression-free survival and overall survival**
(A) Kaplan-Meier plot of progression-free survival by independent review committee assessment. (B) Kaplan-Meier plot of overall survival, intention-to-treat analysis set.

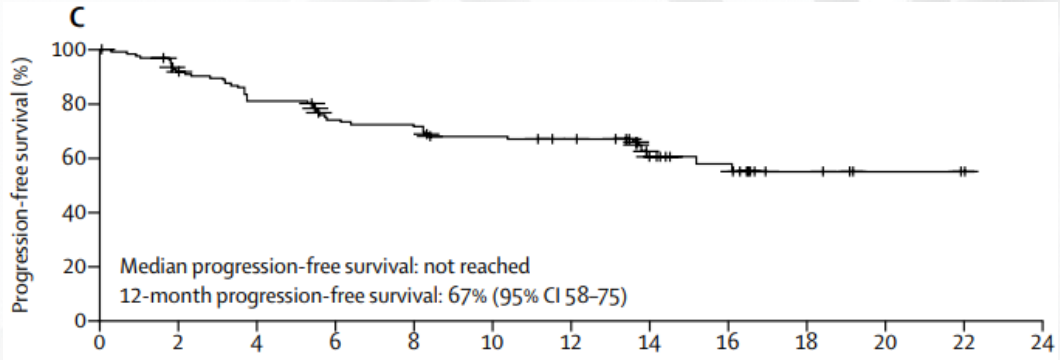
Wang M, …, Blum KA, NEJM 2013; Dreyling M et al, Lancet 2016

SECOND GENERATION BTK INHIBITOR THERAPY IN R/R MCL

Acalabrutinib – 100mg BID



ORR 81% **CR** 40% **mPFS** NR (at 15.2 mo FU)



Zanubrutinib – 320mg daily or 160mg BID

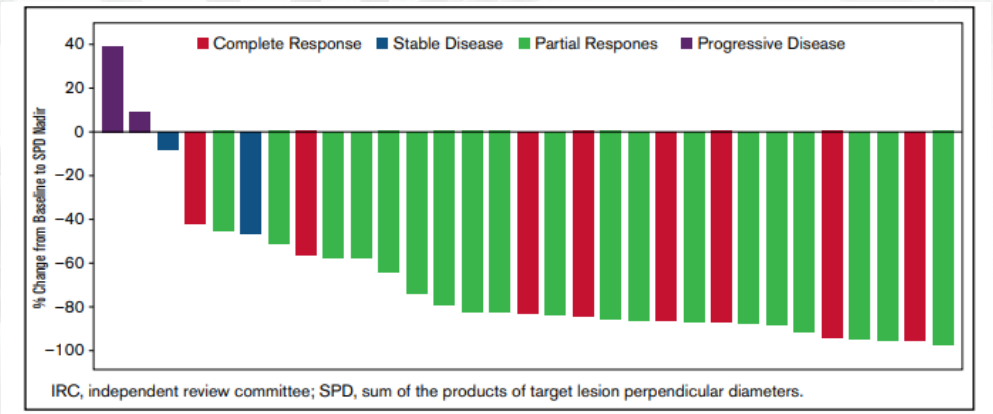
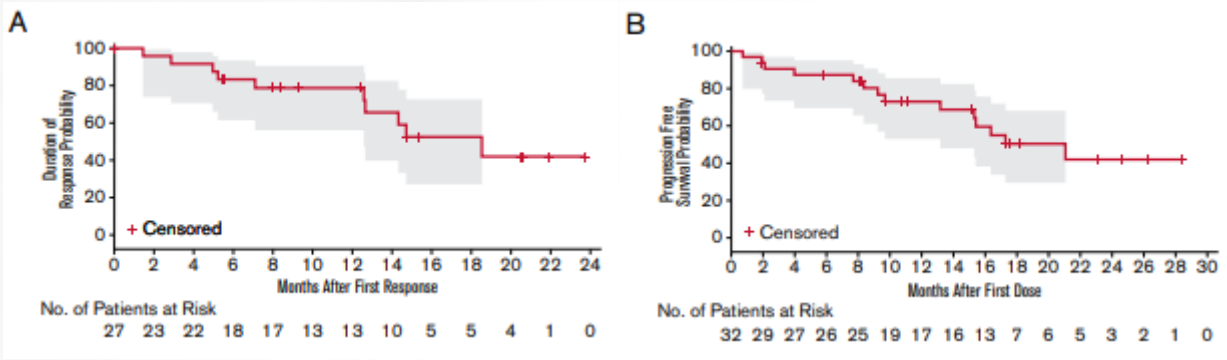


Figure 2. Best percentage change from baseline in target lesion sum of the products of target lesion perpendicular diameters (SPDs) by overall response assessed by IRC (N = 32).

ORR 84% **CR** 25% **mPFS** 21.1 months

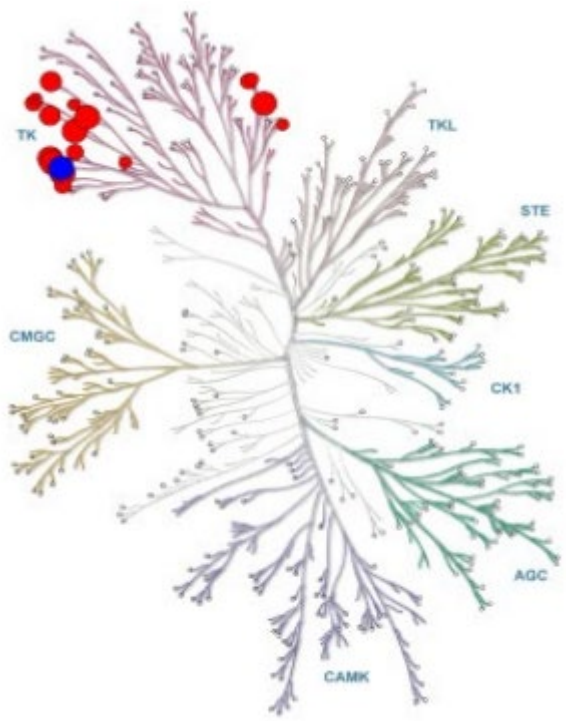


Wang M et al, Lancet 2018; Tam CS et al, Blood Adv 2021

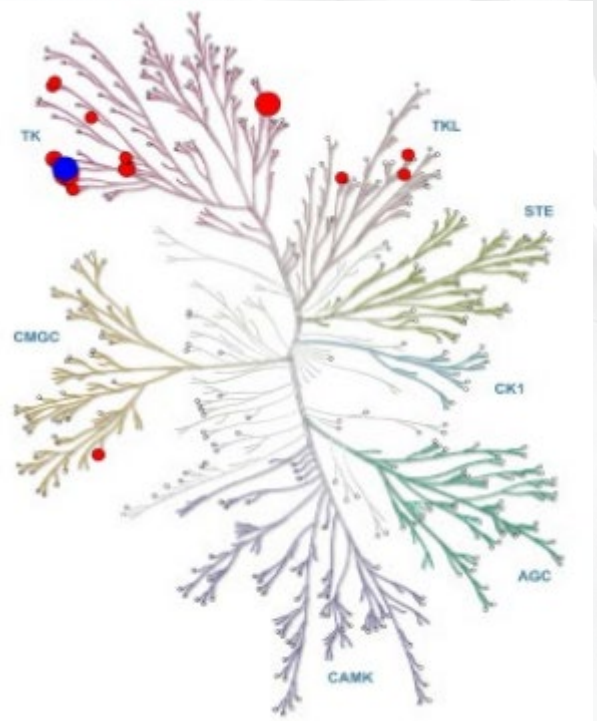
BTK INHIBITOR THERAPY IN RELAPSED/REFRACTORY MCL

FIRST generation

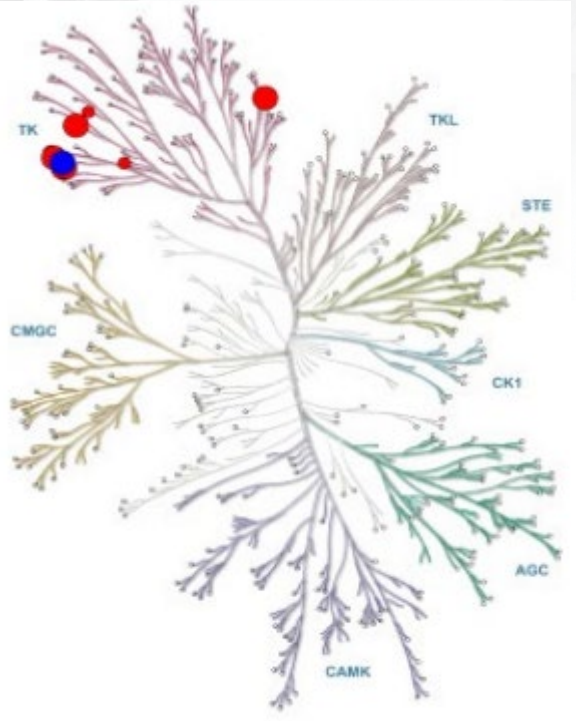
SECOND generation



Ibrutinib



Acalabrutinib



Zanubrutinib

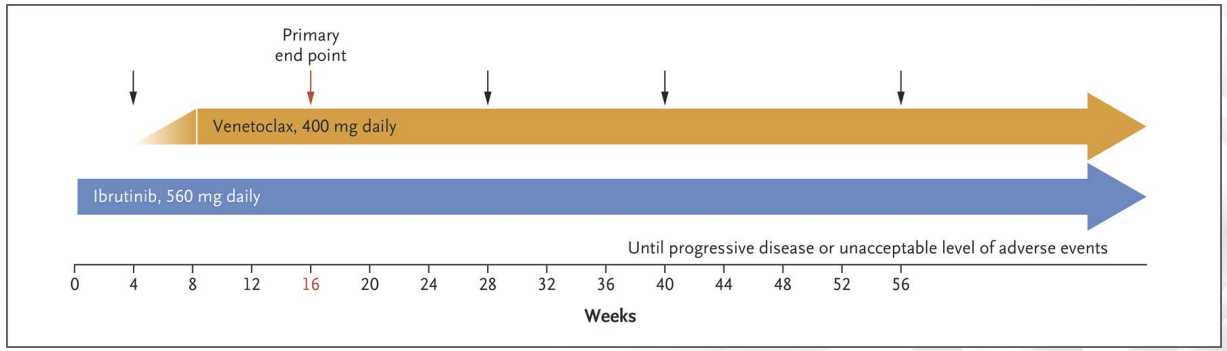
- BTK
- Off target kinases

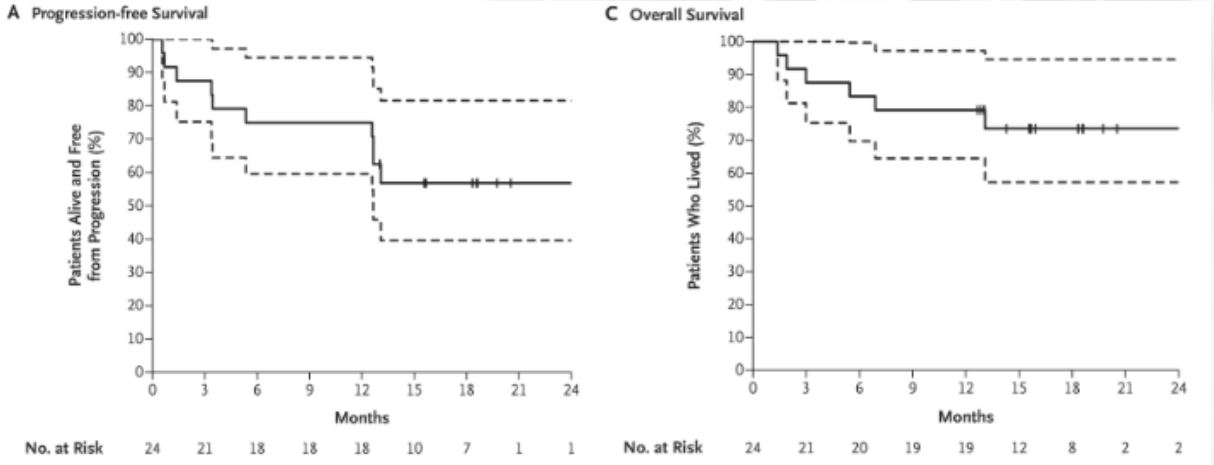
- 95-100% inhibition
- 90-95% inhibition
- 75-90% inhibition
- 50-75% inhibition

How should we decide which BTKi to use?

Shadman et al, ASH 2021

R/R MCL: IBRUTINIB PLUS VENETOCLAX





Single-arm, phase II study (Australia) N=24 enrolled
R/R MCL, or chemo-ineligible (July 2015 – Sept 2016)

TP53 mutated: 45.8% Blastoid/Pleo: 5%

First 4 weeks: Ibrutinib PO **560mg daily**
Week 5+: initiate venetoclax ramp-up, **50 → 400mg**
(amended to allow up to 800mg if no resp @ week 16)

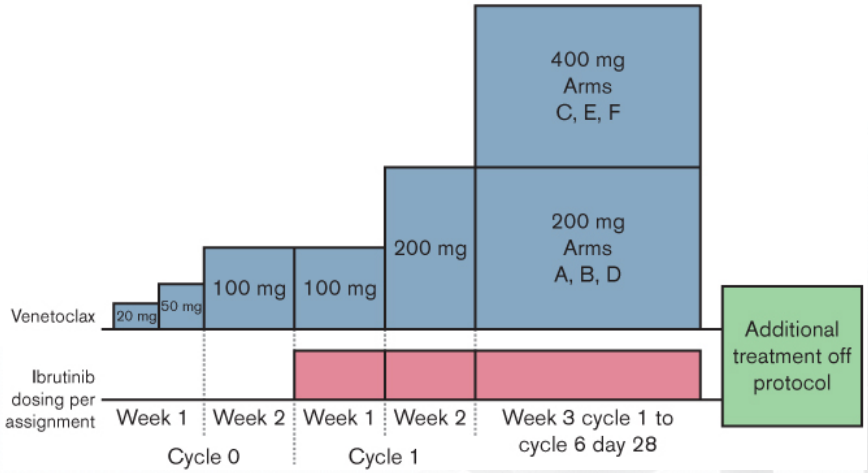
ORR 71%, CR 62% (at week 16) → **MRD clearance:**
Median PFS NR at 15.9 months
Flow cytometry – 67%
ASO-PCR – 38%

Ongoing Phase III study – SYMPATICO (NCT03112174)
R/R MCL, 1-5 prior lines of therapy

Ibrutinib *plus*: venetoclax vs placebo
N=352 – enrollment completed, results pending

Tam CS et al, NEJM 2018

R/R MCL: IBRUTINIB PLUS VENETOCLAX – ALTERNATIVE DOSING?



Dosing allocation and outcomes				
See dosing schedule for more information		Ibrutinib mg per day		
		280	420	560
Venetoclax max dose	400 mg	**Zone 2 / Arm C** N=8 ORR 6/8 PD on Rx 2/8 DLT 0/8	**Zone 3 / Arm E** N=5 (1 not evaluable) ORR 3/4 PD on Rx 2/4 DLT 2/5	**Zone 4 / Arm F** N=0
	200 mg	**Zone 1 / Arm A** N=2 ORR 2/2 PD on Rx 0/2 DLT 0/2	**Zone 2 / Arm B** N=16 ORR 15/16 PD on Rx 2/16 DLT 1/16	**Zone 3 / Arm D** N=4 ORR 2/4 PD on Rx 2/4 DLT 0/4

Multicenter phase IB study (US)
R/R MCL, BTKi naive

N=45 enrolled (Aug 2015-May 2019)
N=35 received study therapy

Designed as a **continual reassessment model (CRM)**
- "optimal" dose: N=10 assigned, DLT ≤25%, best ORR at 2 months
- "promising" for Ph2: ORR ≥60% at 2 months

First 2 weeks: venetoclax ramp-up begins
Week 3+: initiate ibrutinib – combination dosing per CRM

Overall efficacy: ORR 82.3%, CR 42.4% ---- no MRD testing performed
- Post C6 therapy at MD discretion; longer PFS w/ continued ibrutinib (not sig.)

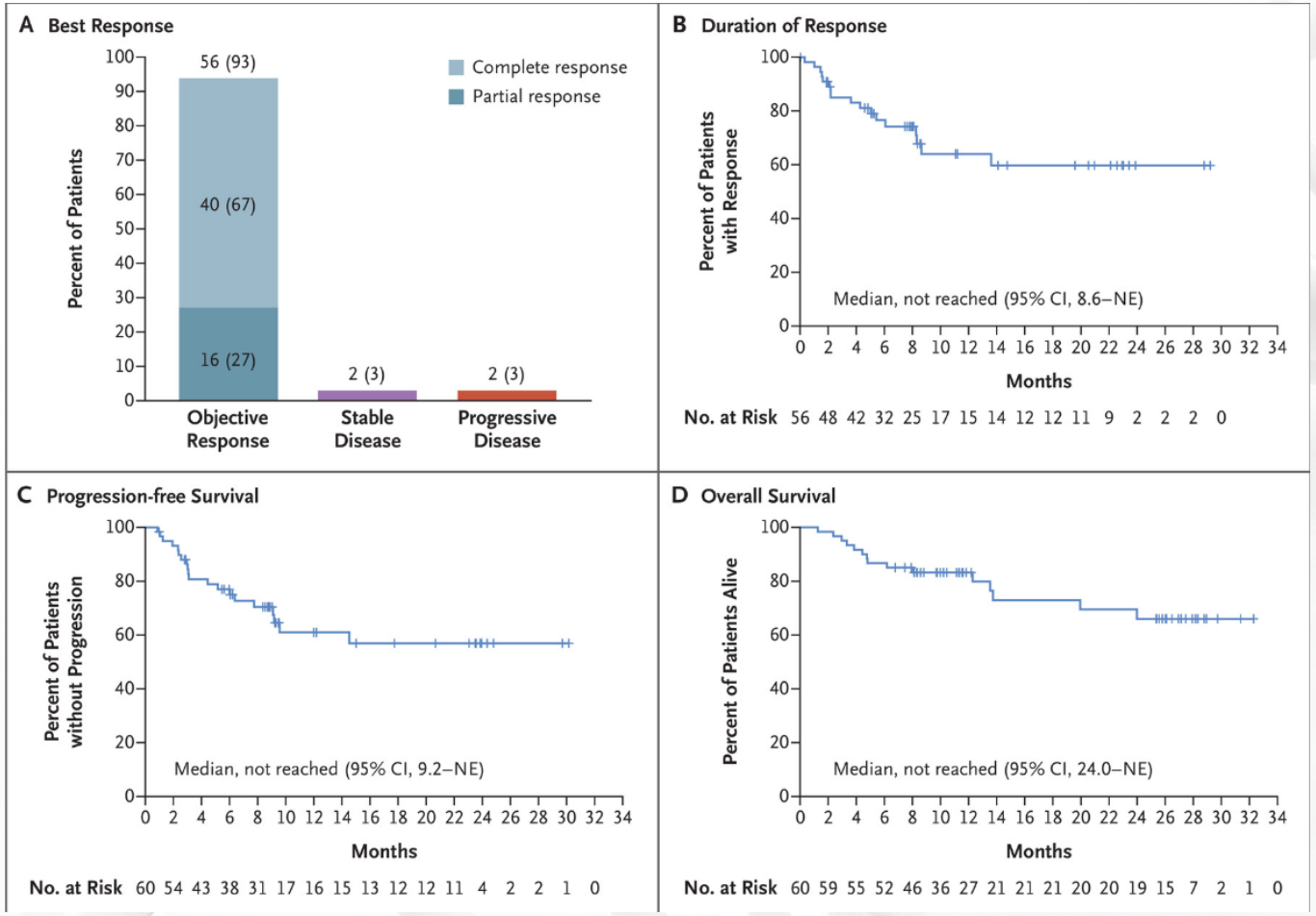
None assigned to dose strategy used in other studies (560mg / 400mg) due to high rates of dose-limiting neutropenia in earlier arms

Arm B identified as optimal dose: ORR 93.7%, CR 40%; DLT 1/16

This dosing strategy is not currently under further evaluation

Portell CA et al, Blood Advances 2022

CD19 CAR-T THERAPY IN RELAPSED/REFRACTORY MCL: ZUMA-2



Patients w/ prior bendamustine exposure may have decreased CAR-T cell functionality by in vitro analyses, esp. if received within 6m of apheresis

Brexucabtagene autoleucel (aka KTE-X19)

Autologous CD19.28z CAR-T product, with removal of host CD19-expressing cells

Multicenter phase II study – N=74, across 20 sites
- R/R MCL after 1-5 prior lines of therapy, including
  - Anthracycline and/or bendamustine, and
  - BTK inhibitor (ibrutinib or acalabrutinib)
- Dosing per axi-cel in DLBCL, brexu-cel in ALL

Bridging therapy PERMITTED: steroids or BTKi

TP53 mutated: 17% Blastoid/pleo: 31%

ORR 93%
CR 67% -- mDOR 28.2m

mPFS 25.8m
mOS 46.6m

Similar efficacy with vs without
TP53 mutation
blastoid/pleo morphology
high (>50%) Ki67 index

Wang M et al, NEJM 2020; Wang M et al, JCO 2022

NEW (BT)KID ON THE BLOCK: PIRTOBRUTINIB (LOXO-305)

Non-covalent BTK inhibitor

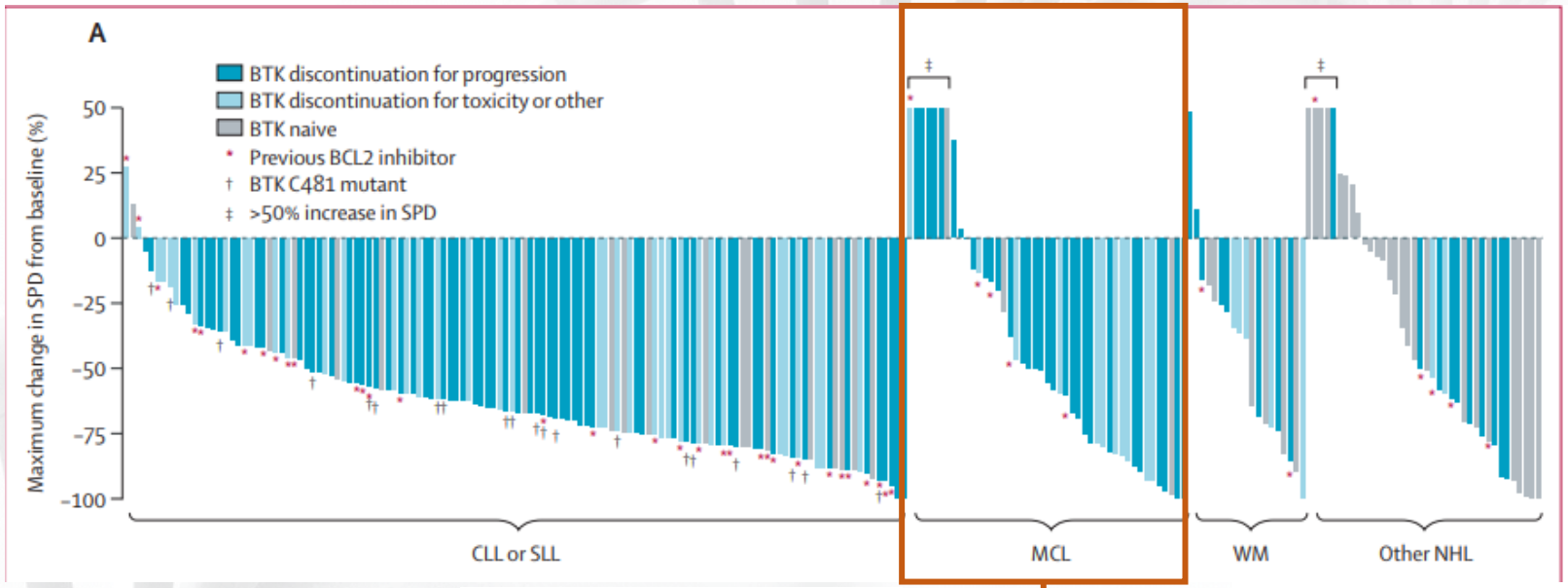
BRUIN: Phase I/II study in R/R B-cell malignancies

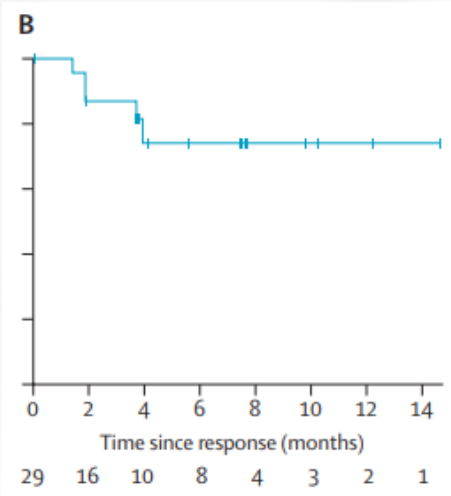
N=323 total → **N=61 with MCL**

Prior therapies: median 3 (range 2-4)
- BTKi: 93%
- Chemo: 92%
- AutoSCT: 25%

No DLTs observed; MTD not reached in Ph1
Recommended Ph2 dose: 200mg

Common AEs:
Fatigue (20%), diarrhea (17%), bruising (13%);
Gr 3 neutropenia 10%. **Afib:** Gr 1 = 1%; Gr 3 *not observed*.





ORR 52%
CR 25%
Median f/u 6m
(IQR 3-9m)

Mato AR et al, Lancet 2021

R/R MCL AFTER CAR-T THERAPY: THE NEW FRONTIER

Lenalidomide +/- rituximab*
Bortezomib (ixazomib)
Bendamustine (BR, RBAC)**

FDA approved
Modest single-agent activity
Studies pre-date BTKi

Also commonly used as bridge to CD19 CAR-T therapy

Venetoclax
- Phase I (n=28): **ORR** 75% **CR** 21% **mPFS** 14 months
- MCR (n=81): **ORR** 42% → *91% prior BTKi exposure*, vs none in Ph 1

Pirtobrutinib (aka LOXO-305; non-covalent BTKi)
- BRUIN Phase I/II: N=61 with MCL – **ORR** 52% **CR** 25% → *Reponses in 2 of 2 w/ prior CD19 CAR-T*

Zilovertamab vedotin (ROR1 antibody-drug conjugate)
- Phase I (n=15 with MCL): **ORR** 47% **CR** 13%

*R-Lenalidomide can also be considered as 1L MCL therapy in frail older patients who cannot receive chemotherapy
** if not used earlier in therapy

Romancik et al, Clin LML 2022

HOW I TREAT RELAPSED/REFRACTORY MCL IN 2022