22nd

INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

APRIL 4 - 5, 2025

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22nd INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

Challenges in Treating Patients with TP53-Mutated Mantle Cell Lymphoma

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Disclosures

Consulting, honoraria, and or speaker bureau: Kite/Gilead, SeaGen, ADC Therapeutics, Celgene/BMS, Janssen, Beigene, Abbvie, AstraZeneca, Epizyme, Merck, Eli Lily, Genmab, Abbvie

p53 in Mantle Cell Lymphoma

- MCL accounts for ~6% of all NHL
  - Incidence of p53 abnormality in untreated pts 15-25%
  - Aggressive variants have much higher incidence (40+ %) than “typical” MCL

- Testing for p53 aberration = standard part of workup
  - TP53 sequencing is preferred
  - Per NCCN IHC can be used as surrogate in 1L (confirmed by sequencing)
  - P53 overexpression (IHC) in 75%+ of those with mutation, rare in WT
    - Missense 50-75%
    - Deletion ~10%

- Improving survival trends with time – small molecular inhibitors, immunotherapy
  - P53 abnormal MCL remains area unmet need
  - Remains associated with shorter PFS and OS in chemo, CIT, and targeted therapy eras
  - Clinical trial is strongly recommended for these patients.

NCCN Guideline B-cell Lymphomas, version 2.2025. Yang P et al, Cancer Gene Therapy. 2018;25(5-6):129-140.Eskelund C et al, Blood. 2017 Oct 26;130(17):1903-1910. Jain P, Wang M. Am J Hematol. 2019 Jun;94(6):710-725. Nordstrom L, eta l. Br J Haematol. 2014;166(1):98-108. Nolan J et al. Leuk Lymphoma. 2022;63(14):3504-3507.

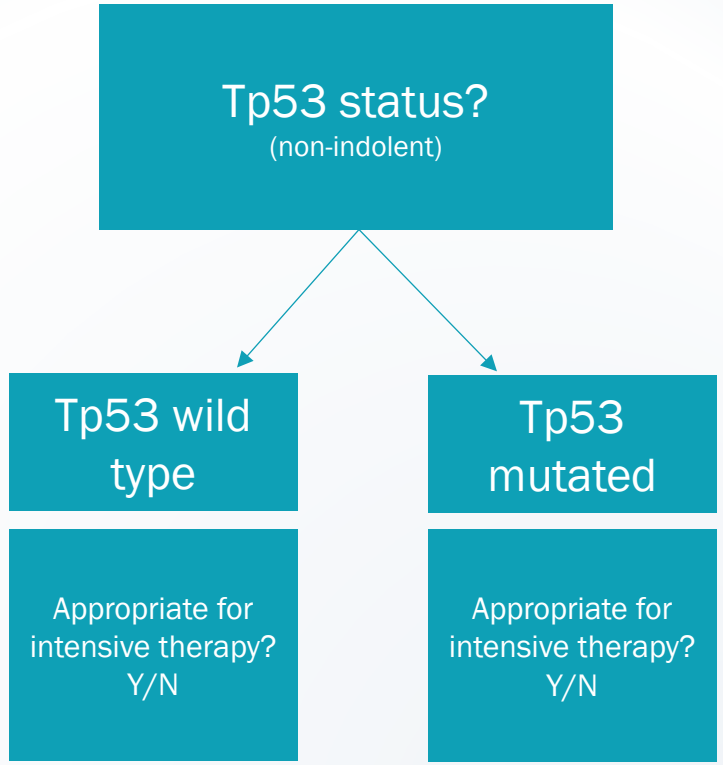
Current MCL treatment landscape

1L decision points

- P53 mutation aberration? (IHC, FISH, sequencing)
  - yes - clinical trial or novel therapy-based 1L
- High dose chemo +/- auto transplant candidate?
- Maintenance?
  - Covalent btki + rituximab
    - Off label other than acalabrutinib/rituximab post BR in 1L
  - Less intensive induction: Rituximab alone

2L+

- If prior CIT only, BTKi most common 2nd line
- CART if prior CIT+BTKi
- Clinical trial participation
- severall other options available



NCCN version 2.2025

TRIANGLE

Phase 3, treatment naïve MCL

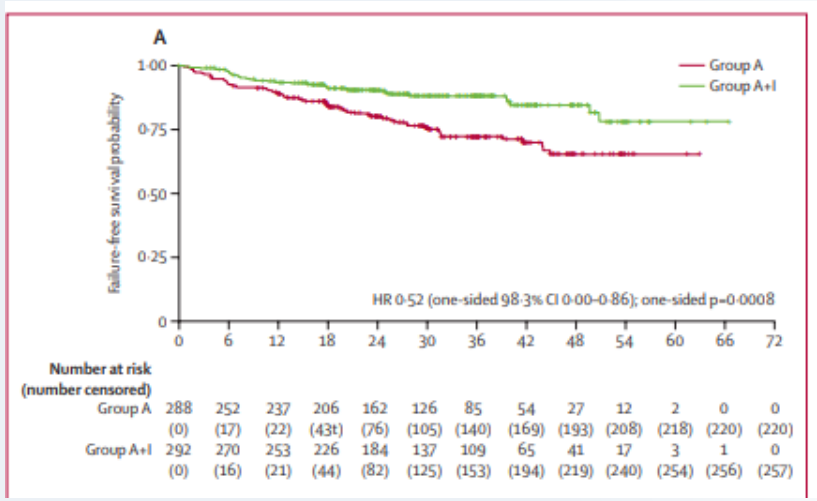
A = CIT + auto
I = CIT + ibrutinib (no auto)
A+I = CIT + ibrutinib + auto

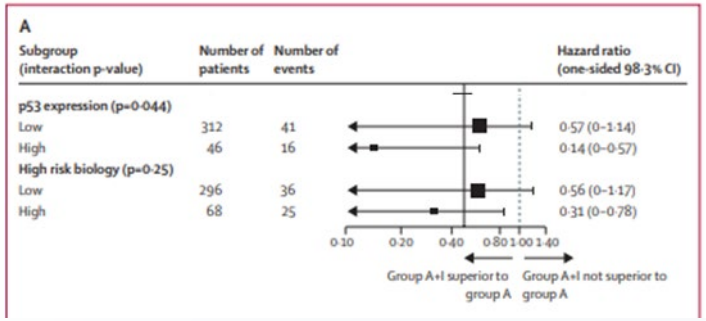
N=870, 1:1:1, superiority study

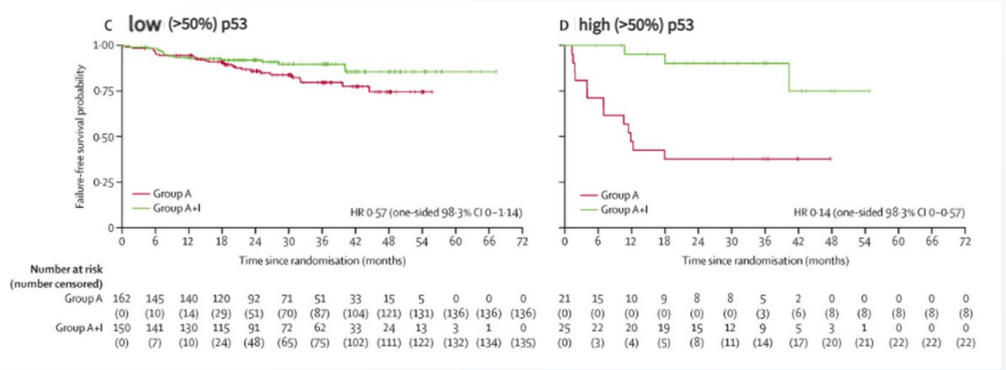
Rituximab maintenance allowed – given in 56% of pts

Primary endpt: failure free survival

	A (CIT+auto)	A+I	I (CIT+ibrutinib)
Blastoid P53 expression >50% High risk biology	11% 11% 17%	13% 14% 21%	12% 16% 23%
3 year FFS	71% 72%	**88% (HR 0.52, CI 0-0.86)** ongoing	86% (HR 1.77, CI 0-3.76) ongoing





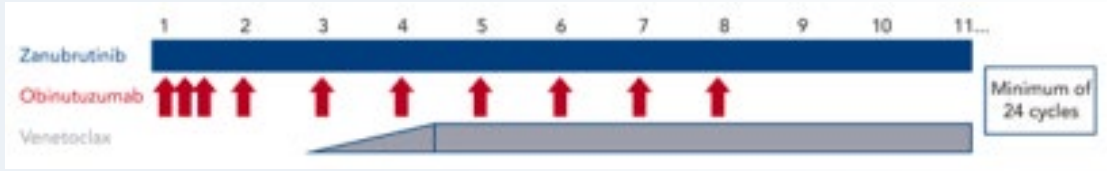


Who may benefit from transplant?
Can chemotherapy be minimized?
Apply to alternate btki?
Is maintenance rituximab needed?

Dreyling M et al, Lancet. 2024; 403(10441):2293-2306.

BOVen: TN MCL with p53 mutation

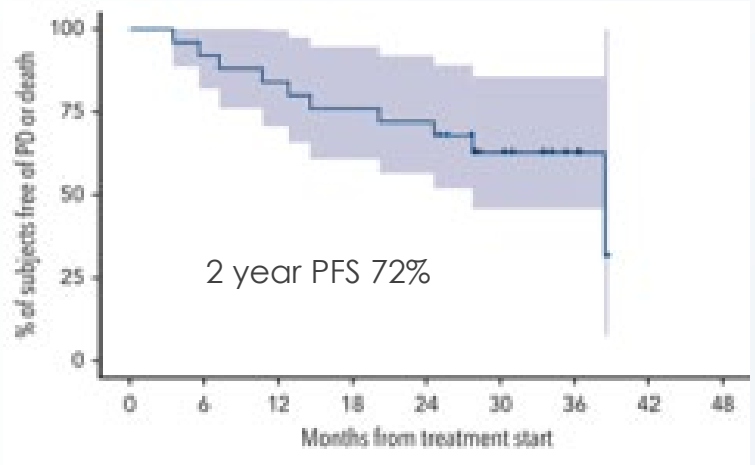
- Phase 2: zanubrutinib+obinutuzumab+ venetoclax
- N=25



  - If CR + uMRD after 24 cycles, treatment discontinued
  - If <CR or +MRD = continue ven/zanu

- ORR 96%, CRR 88%
  - uMRD 10^{-5} 95% and 10^{-6} 84% @ C13

- Ongoing study, NCCN endorsed



Kumar A, et al. Blood (2025) 145 (5): 497-507.

Less aggressive induction

ECHO

- Phase 3, TN MCL, age 65+, BR +/- continuous acalabrutinib
- P53 mutation known in 7.4% A+BR, 9.7% placebo+BR

Lenalidomide +rituximab induction x12 then maintenance to pod

- Low/intermediate MIPI, or high with contraindication for chemotherapy
- P53 status NR

Acalabrutinib continuous + rituximab 24 mo

- Ph2, single institution, N=50
- Tp53 status available in 43/50 pts, 12 = p53 aberrant (PFS and OS not significant different)

Wang M et al. EHA2024, Hemaspohere 2024;8 abstractLB3439. Dreyling M et al Blood(2024) 144 supplement 1); 1626. Ruan J, Martin P et al. Blood 2018; 132:2016-2025. Juan J et al. NEJM 2015;272:1835-1844. Jain P et al. Hematol Oncol 2023; 41:150-151.

ZUMA-2

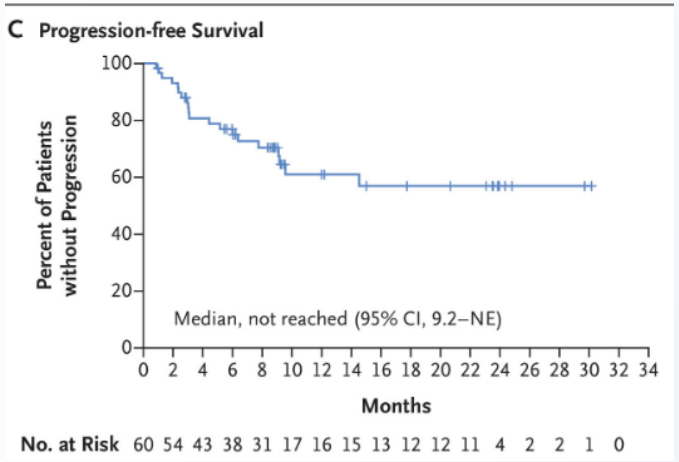
Multicenter, Ph2

- N=74 enrolled 10/2016 - 4/2019
  - Manufactured for 71 (96%)
  - Administered to 68 (92%)
  - 6/36 with p53 mutation
- Up to 5 prior lines of treatment
- progressed during or after BTKi
- Primary endpt ORR

Table 1. Baseline Characteristics of All 68 Treated Patients.*

Characteristic	Patients
Median age (range) — yr	65 (38–79)
Intermediate or high risk according to Simplified MIPI — no. (%)†‡	38 (56)
Blastoid or pleomorphic morphologic characteristics of MCL — no. (%)	21 (31)
Ki-67 proliferation index ≥30% — no./total no. (%)‡	40/49 (82)
TP53 mutation — no. (%)	6/36 (17)

	ORR	CRR
ALL	93% (56/60)	67% (40/60)
TP53 wild type	100% (30/30)	
TP53 mutation	100% (6/6)	



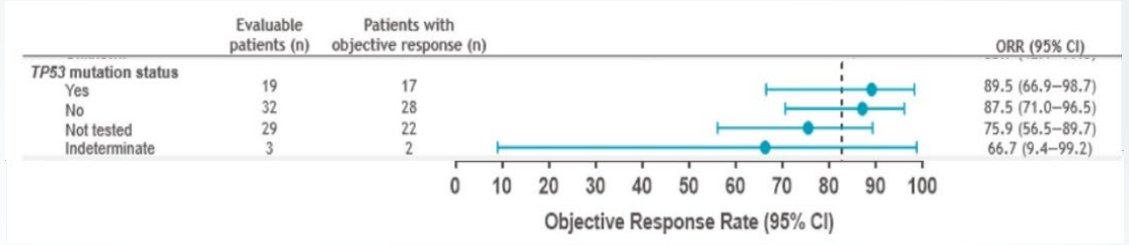
Wang M, et al. NEJM 2020 Apr 2;382(14):1331-1342.

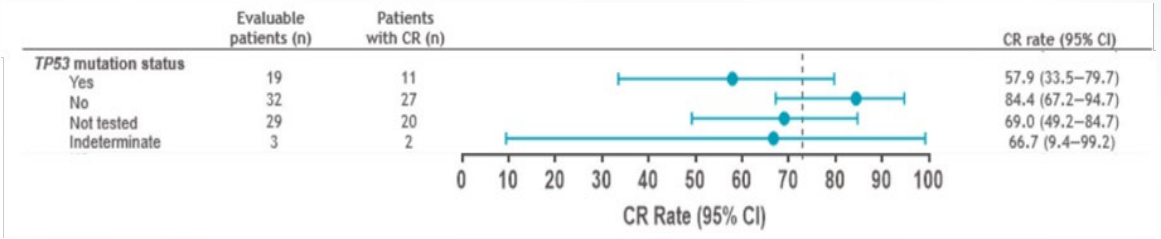
Lisocabtagene maraleucel (liso-cel): TRANSCEND NHL 001MCL cohort

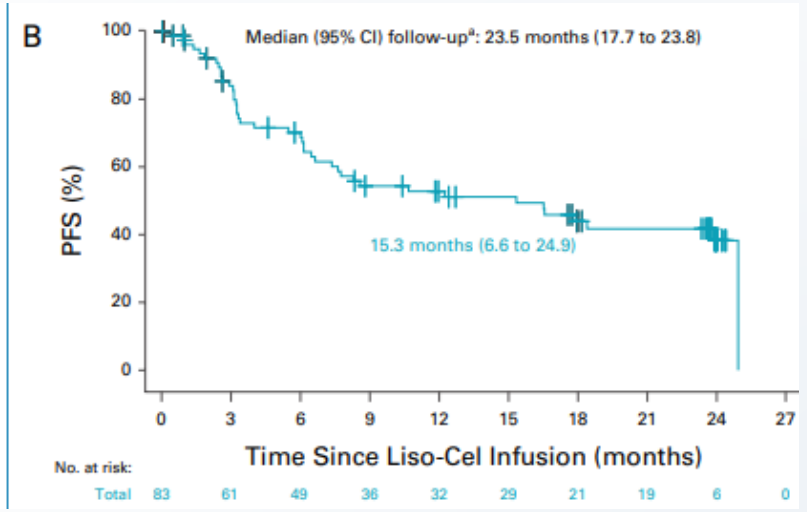
- MCL, 2+ prior lines (including cd20, alk inhibitor, & btki)
- Primary endpt AEs, DLTs, and ORR

- N=104 leukapheresed, N=88 infused
  - 53% btki refractory (med prior tx 3, range 3-11)
  - **23% p53 mutation (5% indeterminate, 34% not done)**

- ORR 83%, CRR 72%
- mDOR 15.7 mo, mOS 15.3 mo







Wang M et al. J clin Oncol, 2024 Apr 1; 42(10):1146-1157.

Pirtobrutinib in R/R MCL

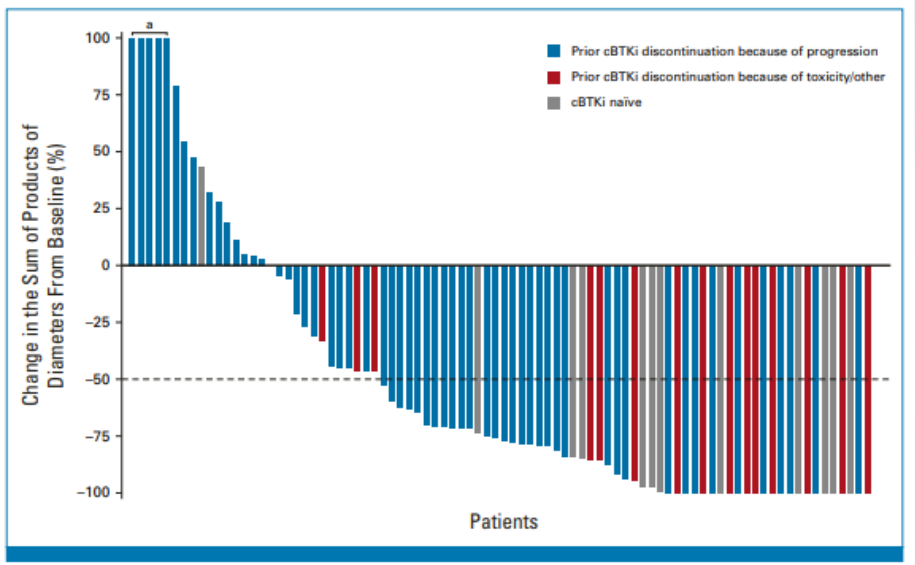
BRUIN ph ½

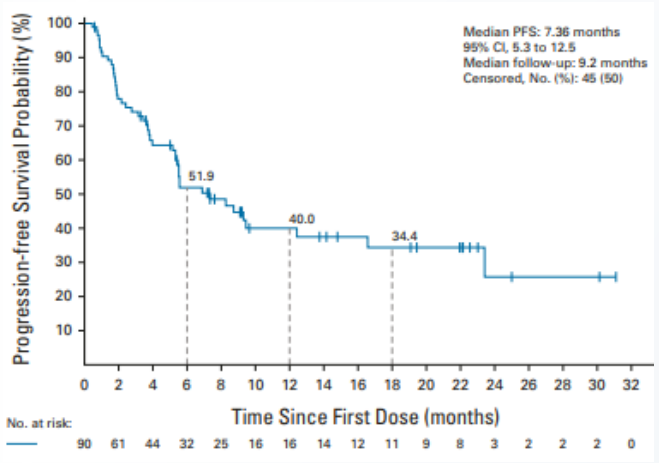
R/R MCL, median prior tx=3

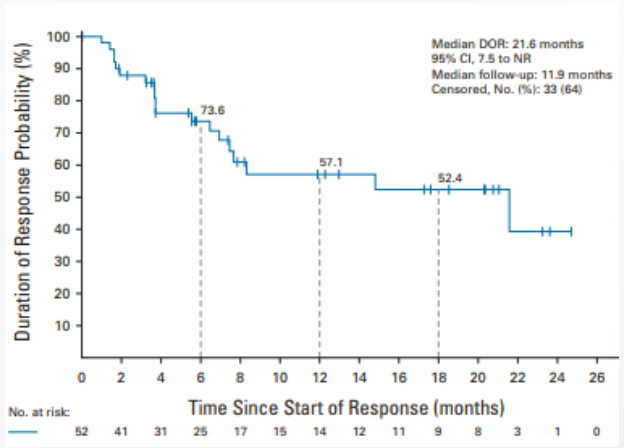
N=90 btki pretreated, 14 btki naive

Primary endpt ORR= 57% (CRR 20%)

Blastoid = 9 pts (p53 status NR)





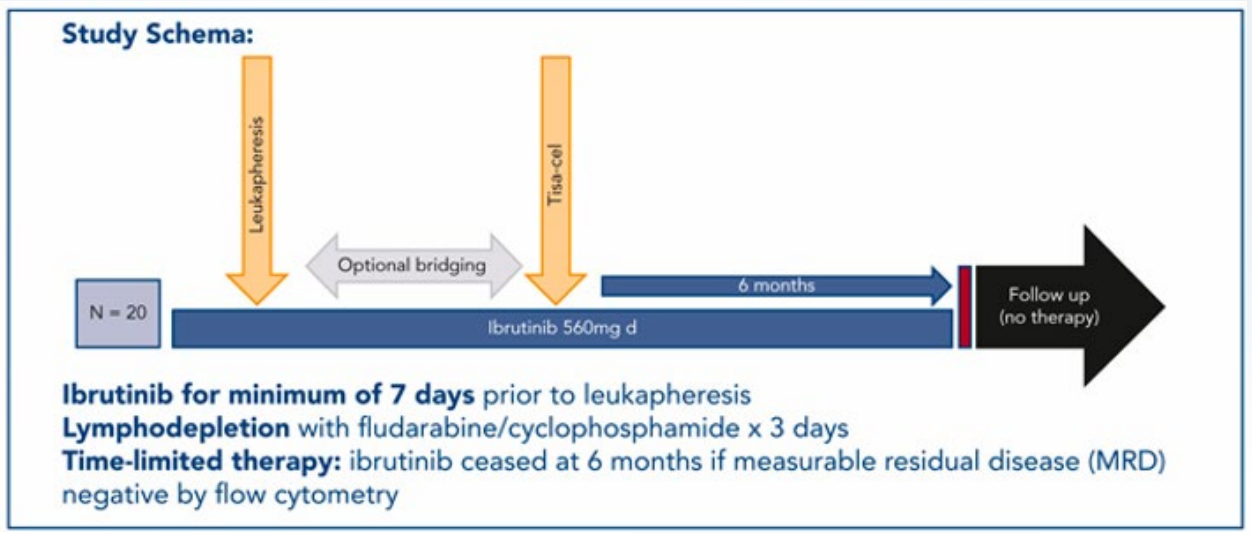


Wang ML, Jurczak W, Zinzani PL, et al. Pirtobrutinib in covalent bruton tyrosine kinase inhibitor pretreated mantle-cell lymphoma. *J Clin Oncol*. 2023;41(24):3988-3997

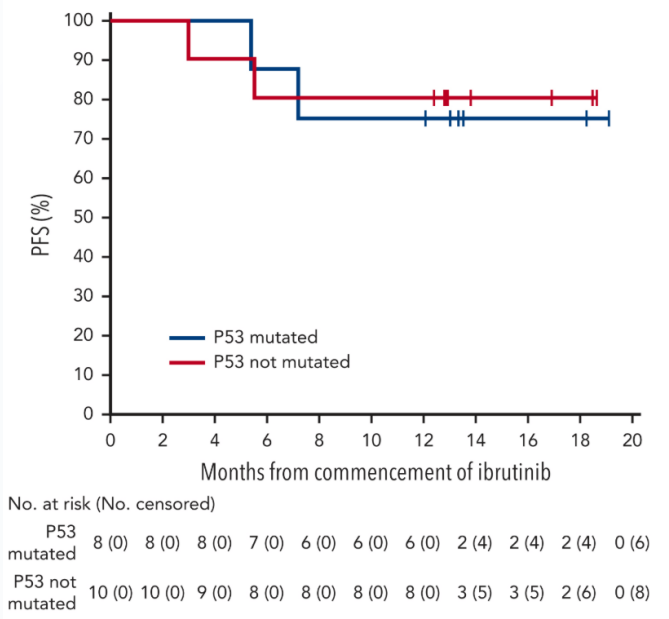
TARMAC (ibrutinib + tisa-cel)

R/R MCL

- 9 pts tp53 aberrant (7 deletion + mutation)
- 2 pts tp53 status unknown



- Median prior tx = 2, 50% BTKi exposed
- Primary endpt CR @ 4 mo post infusion = 80% (uMRD flow 70%, BGS 40%)
- 2ndary end pt = response in p53 aberrant subgroup (similar)
  - CR @4 mo 88%, 67% uMRD
- 12 mo PFS 75%, 12 mo OS 100% (@13 mo med fu)
- CRS 75%, 20% gr 3.
- NE 10% (all gr 1-2)



Minson A, et al. Blood (2024) 143 (8): 673-684.

Glofitamab

Ph 1/2 , R/R MCL cohort

- 1+ prior lines (median 2, range 1-5)
- N=60, ORR 85% (CRR 78%)
  - P53 mutation 8%, wild type 2%, missing/unknown 90%
  - ORR p53 abnormal 60% (3/5), unknown/missing 87% (47/54)

Venetoclax

Ph 1 venetoclax monotherapy

- N=28, median prior tx = 3 (range 1-7)
- ORR= 75% (CRR 21%). Median PFS 14mo
  - P53 data - NR

SYMPATICO

- Ph3, ven 2 years+ibrutinib continuous
  - 3 cohorts: 1L, and ven+ibr vs placebo+ibr in R/R MCL
-

Outcomes (95% CI)	1L	R/R	Total
TP53 wild type	n=44	n=75	N=119
Median PFS (mo)	NR	46.9	NR
+*TP53* mutation	n=29	n=45	N=74
Median PFS (mo)	22.0	20.9	20.9

Phillips T et al. J Clin Oncol, 2025 Jan 20; 43(3):318-328. Davids MS et al. J. Clin. Oncol. 2017;35:826–833. Wang M, J Clin Oncol. June 2024;42(16)suppl.

Future directions in p53 abnormal MCL

- Enitociclib: CDK9 inhibtiors
- Entosplentinib : syk inhibitor
- Parsaclisib: pi3k delta inhibitor
- Abemaciclib: CDK4/6 inhibitor

- Consolidation bispecific/CART post SMI-based induction +/- CIT

- Sequencing remains a main question

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Thank you

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