Optimal Frontline Treatment for MCL

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Winship DDHO 2025

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EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

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Disclosures

- Consultant/Advisor/Speaker: ADC Therapeutics, AstraZeneca, BeiGene, Janssen
- Researcher: AstraZeneca, BeiGene, BMS, Genentech, Lilly, Novartis, Nurix, Takeda

MCL Presentation is Heterogeneous

- Indolent Presentation
  - Typically leukemic non-nodal
  - No disadvantage with observation
- Typical “Classic” Presentation
- Aggressive/High-Risk
  - Pathologic Features
  - Molecular Features
  - Clinical Features

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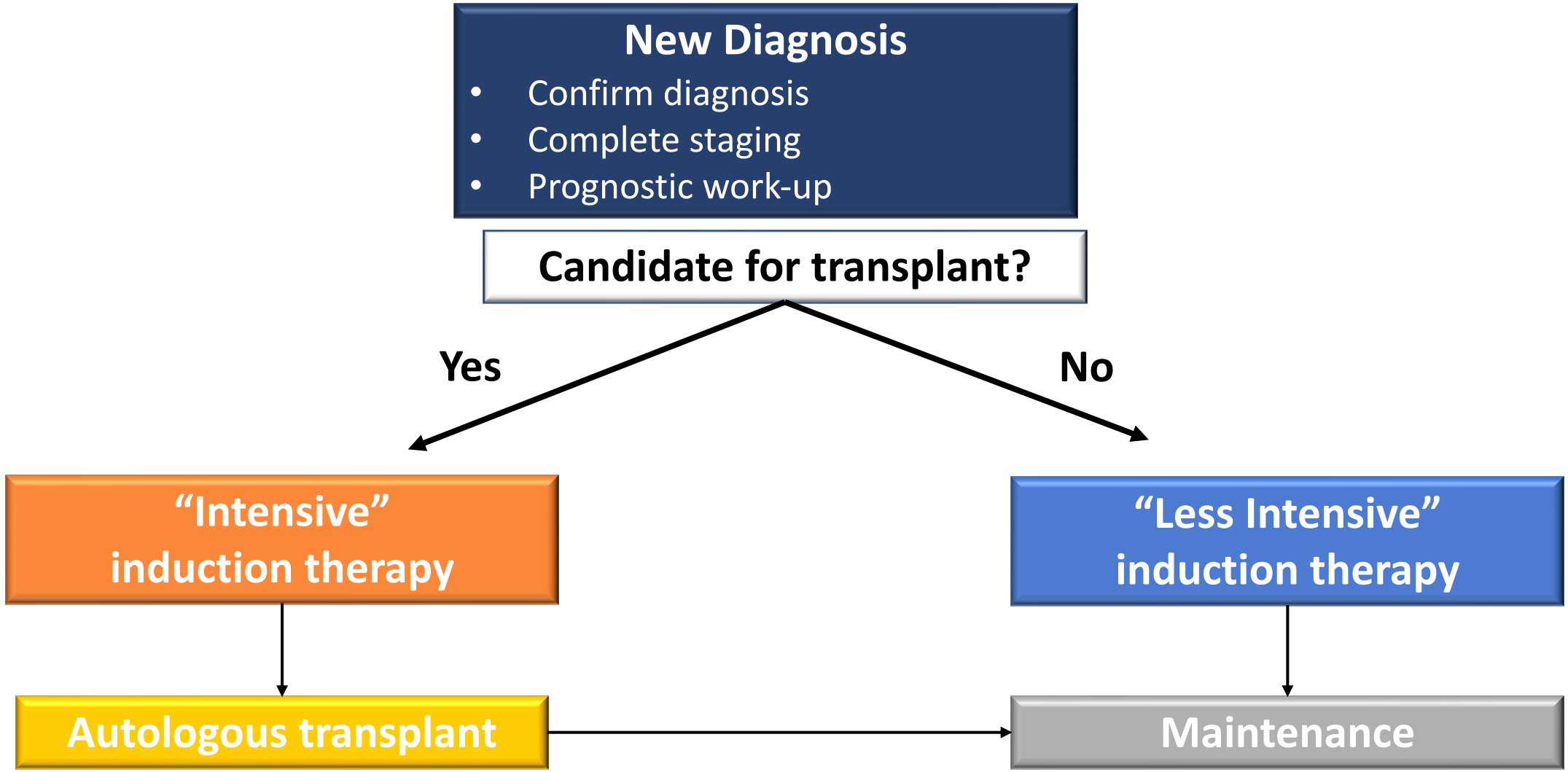
  - Molecular Features
  - Clinical Features

There is no substitute for how a patient looks in clinic

Historic Approaches to MCL



Historic Approaches to MCL

Key Questions

1) Does everyone need treatment?
2) Is there any role for stem cell transplant?
3) Is there still a role for chemotherapy?
4) What about higher risk disease?

Observation – Cautionary Tale

Leukemic non-nodal mantle cell lymphoma (nnMCL) is not necessarily equivalent to indolent MCL: A report from the LEO Cohort Study.

Tony Z. Zhuang[1,2], Yuan Chen[3], Jeffrey M. Switchenko[3], Suheil Albert Atallah-Yunes[5], Georgios Pongas[6], Marcus P. Watkins[7], Nanmeng Yu[8], Patrick M. Reagan[9], David L. Jaye[4], Kiran R. Vij[7], Andrew L. Feldman[10], Melissa C. Larson[11], Shaun Riska[11], Umar Farooq[8], Izidore S. Lossos[6], Brad S. Kahl[7], Yucai Wang[5], Christopher R. Flowers[1], James R. Cerhan[11], Peter Martin[12*], **Jonathon B. Cohen[2*].**

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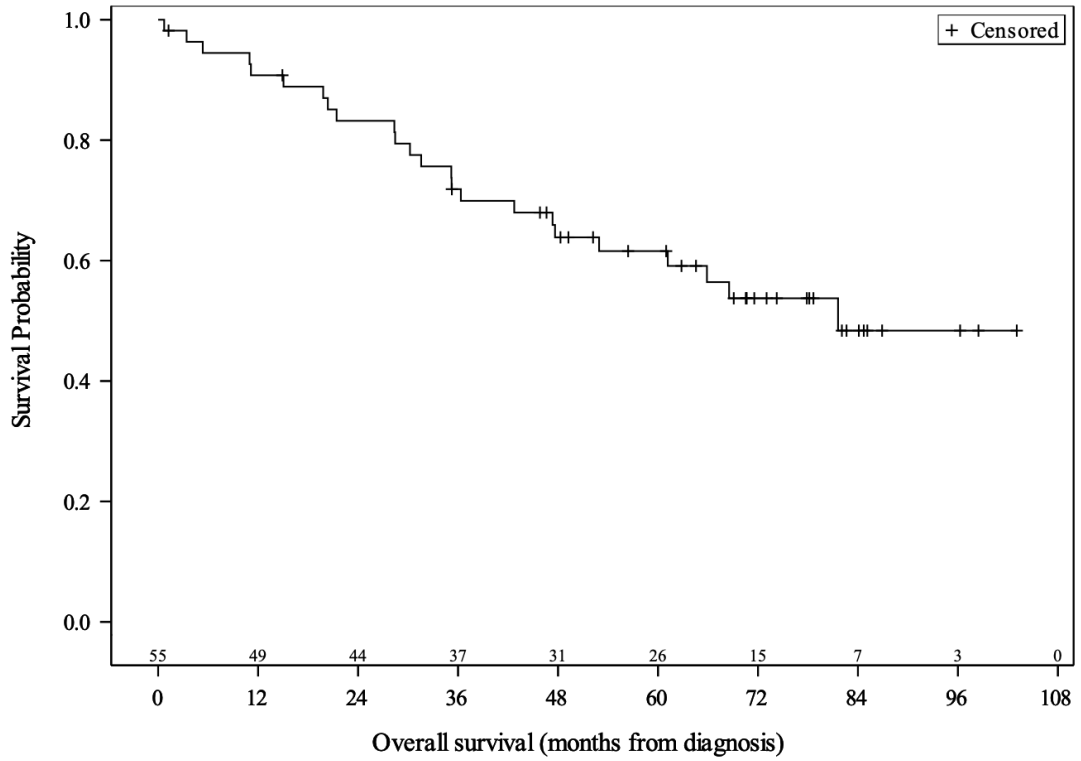
Lymphoma Epidemiology of Outcomes

Analysis of MCL Cases from LEO Study:

- 55 Leukemic non-nodal cases
- 11/55 patients died from lymphoma during observation
- Traditional high-risk features associated with early death
- 5 year Lymphoma-specific survival ~ 80%



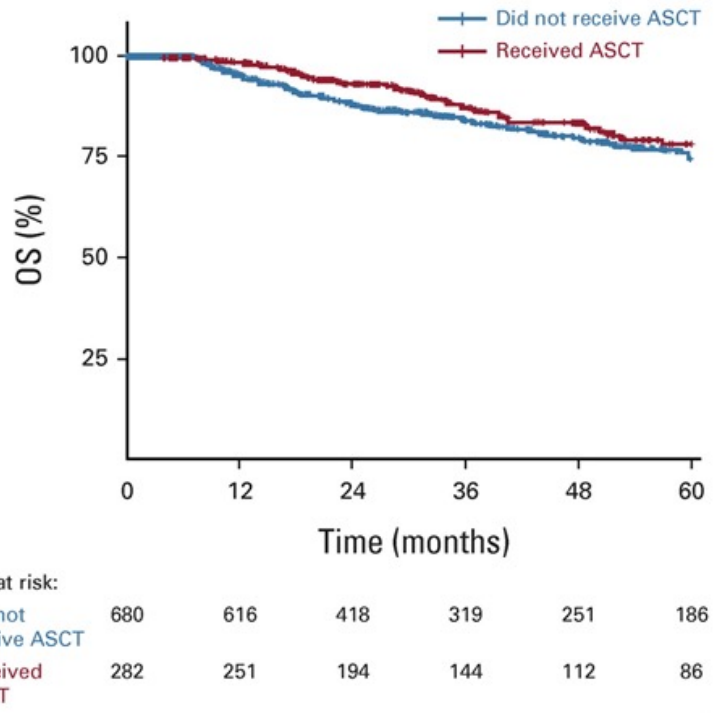
Zhuang et al, ICML 2025

Role of ASCT questioned by real-world data

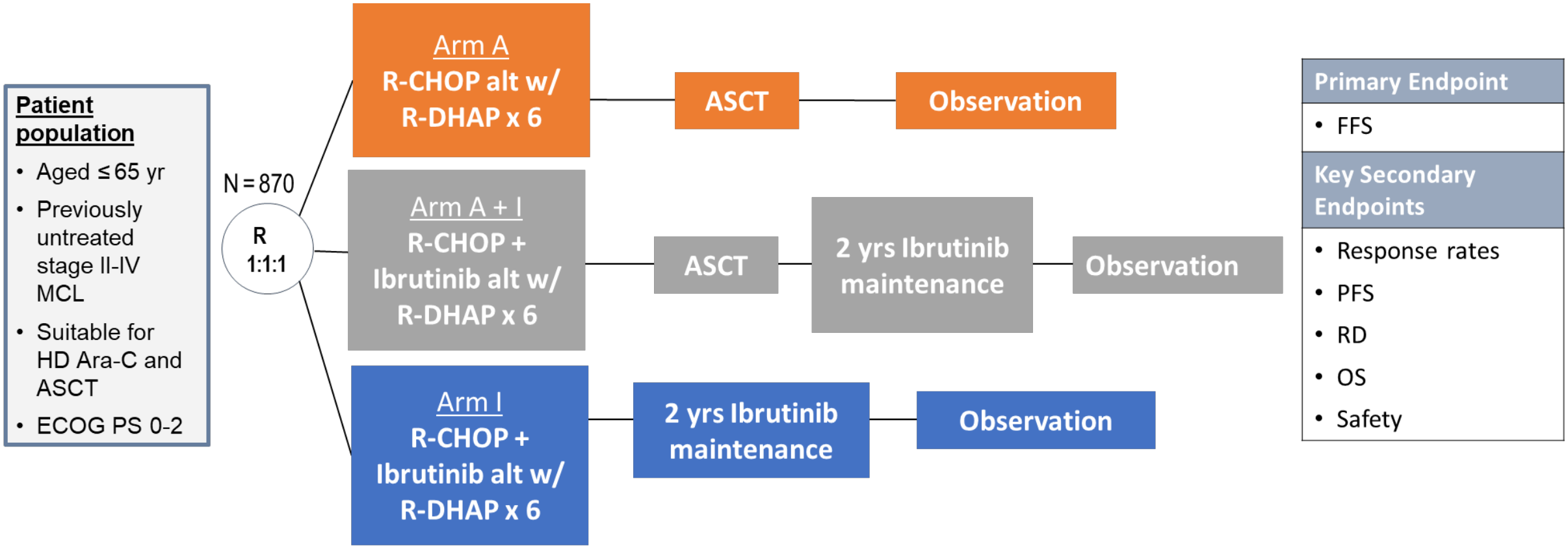
original reports

Treatment Outcomes and Roles of Transplantation and Maintenance Rituximab in Patients With Previously Untreated Mantle Cell Lymphoma: Results From Large Real-World Cohorts

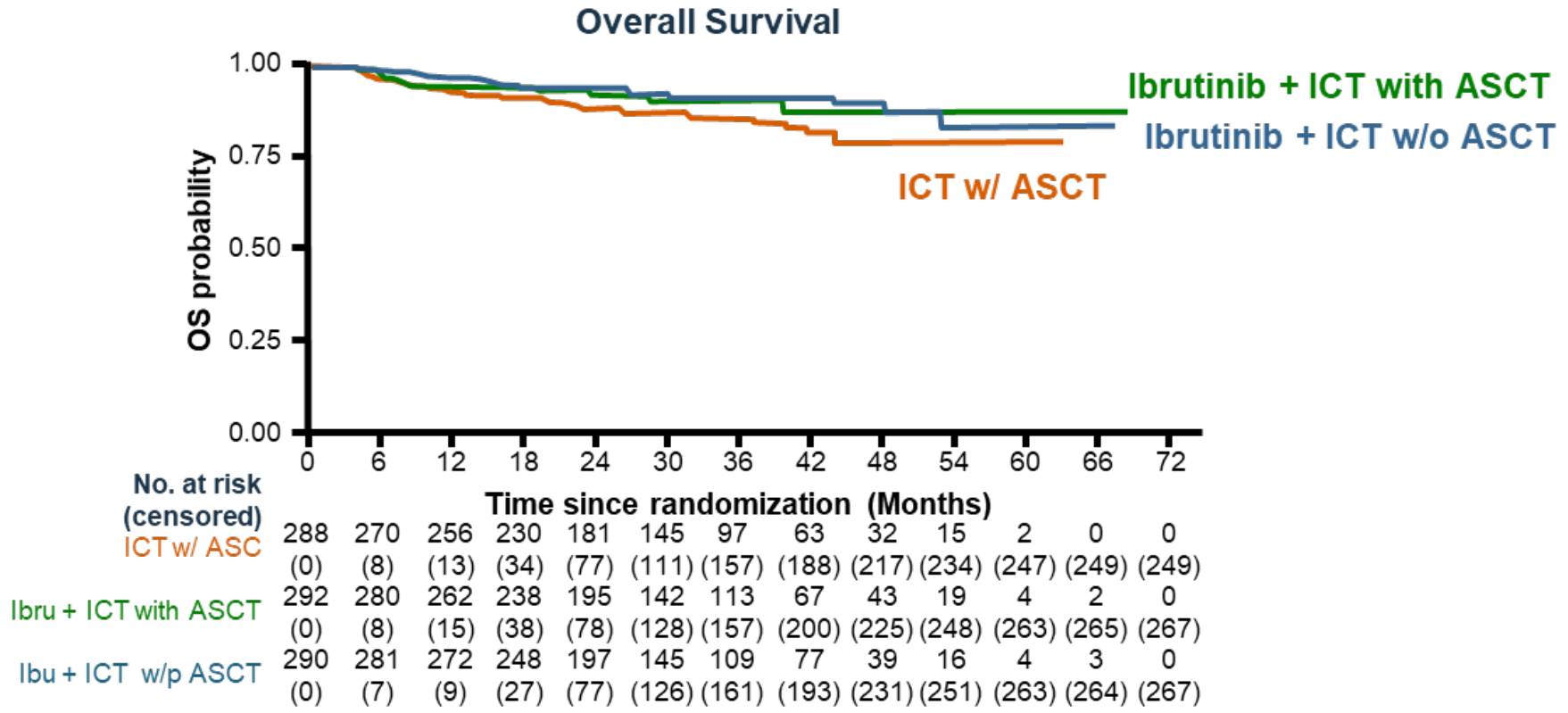
Peter Martin, MD[1]; Jonathon B. Cohen, MD, MS[2]; Michael Wang, MD[3]; Anita Kumar, MD[4]; Brian Hill, MD, PhD[5]; Diego Villa, MD[6]; Jeffrey M. Switchenko, PhD, MS[7]; Brad Kahl, MD[8]; Kami Maddocks, MD[9]; Natalie S. Grover, MD[10]; Keqin Qi, PhD[11]; Lori Parisi, MPH[12]; Katherine Daly, PharmD, MS[12]; Angeline Zhu, PhD[12]; and Gilles Salles, MD, PhD[4]



TRIANGLE Study



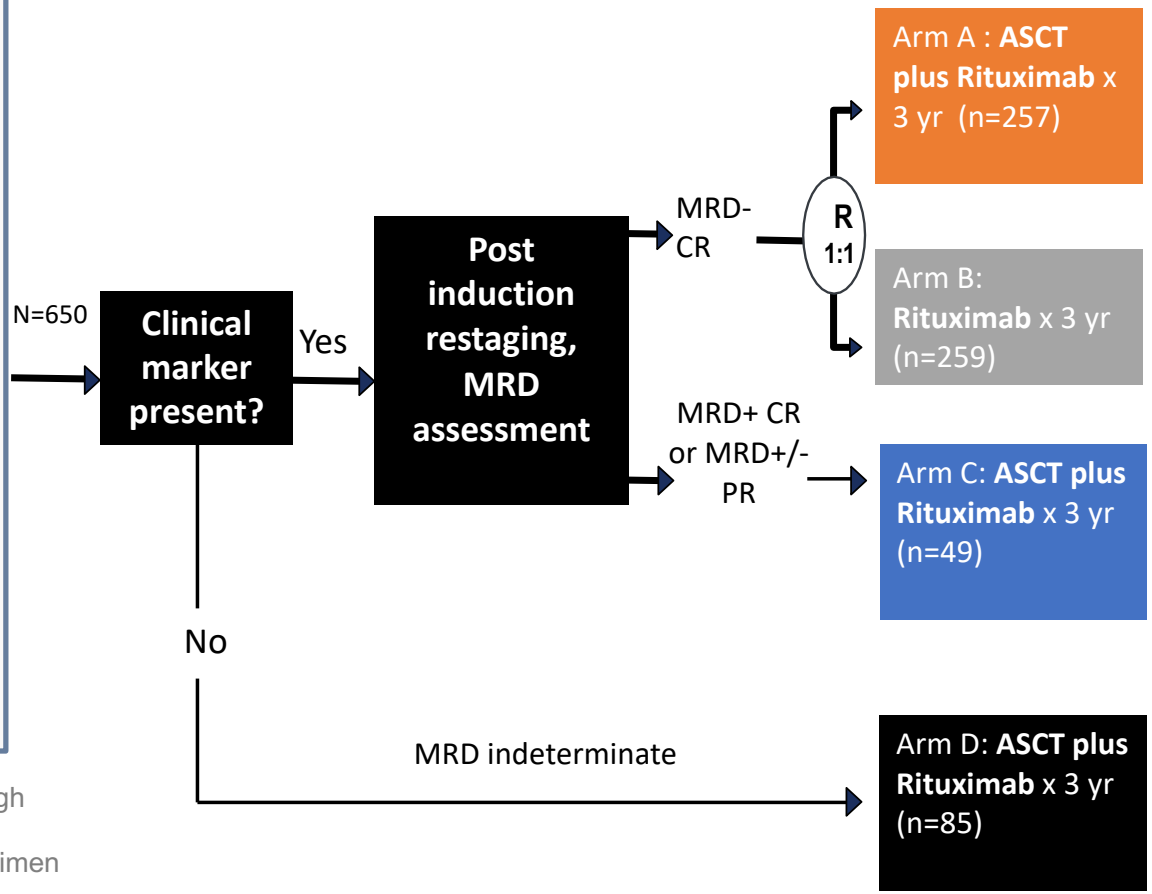
Use of ibrutinib maintenance eliminates need for ASCT



EA4151 Evaluated role of ASCT in Patients achieving MRD(-) CR

Patient population

- Patient aged ≥18 and ≤70 years
- MCL in first remission
- Candidate for ASCT
- Any rituximab-containing induction regimen allowed, including BTKi
- Induction therapy must be delivered within 120 days prior to preregistration and up to 300 days between first day of treatment and preregistration



Stratification by MIPI-c (high/high intermediate) and low/low-intermediate) and induction regimen (intensive vs non-intensive).

Primary Endpoint

- OS (Arm A vs Arm B)

Key Secondary Endpoints

- PFS (Arm A vs Arm B)
- 2- and 5- y OS and PFS for :patients classified as:
  - MRD+ CR
  - MRD- PR
  - MRD+ PR
- 2- and 5-y OS for patients classified as MRD indeterminate
- Safety

ASCT, autologous stem cell transplantation; MIPI-c, combined Mantle Cell Lymphoma International Prognostic Index.

Fenske TS, et al. *Blood*. 2024;144 (Suppl_2):LBA-

ASH 2024: No evidence of benefit of ASCT in patients with MRD(-) CR

The 66th ASH Annual Meeting Late-Breaking Abstracts

LATE BREAKING ABSTRACTS

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Lack of Benefit of Autologous Hematopoietic Cell Transplantation (auto-HCT) in Mantle Cell Lymphoma (MCL) Patients (pts) in First Complete Remission (CR) with Undetectable Minimal Residual Disease (uMRD): Initial Report from the ECOG-ACRIN EA4151 Phase 3 Randomized Trial

Timothy S. Fenske, MD[1], Xin Victoria Wang, PhD[2], Brian G. Till, MD[3], Kristie A. Blum, MD[4], Matthew Lunning, DO[5], Hillard M. Lazarus, MD[6], Paul A.S. Fishkin, MD[7], Lale Kostakoglu Shields, MDMPH[8], David W. Scott, MBChB, PhD[9], Ann S. LaCasce, MD MMSc[10], Patrick B. Johnston, MD PhD[11], Amanda F. Cashen, MD[12], Leslie L. Popplewell, MD MPH[13], Robert M. Dean, MD[14], Nausheen Ahmed, MD[15], Nirav N. Shah, MD[16], Nina D. Wagner-Johnston, MD[17], Boyu Hu, MD[18], Bhagirathbhai R. Dholaria, MBBS[19], Richard F. Little, MD MPH[20], Jonathan W. Friedberg, MD[21], John P. Leonard, MD[22], Brad S. Kahl, MD[12]

	Arm A: MRD- CR **ASCT + Rituximab**	Arm B: MRD- CR **Rituximab w/o ASCT**	Arm C: MRD+ CR or MRD+/- PR **Rituximab + ASCT**	Arm D: MRD Indeterminant **ASCT + Rituximab**
3-y OS, %	82.1	82.7	81.9	85.1
3-y PFS, %	76.6	77.4	76.9	73.4

ASH 2024: No evidence of benefit of ASCT in patients with MRD(-) CR

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Several patients moved from PR to CR

	Arm A: MRD- CR **ASCT + Rituximab**	Arm B: MRD- CR **Rituximab w/o ASCT**	Arm C: MRD+ CR or MRD+/- PR **Rituximab + ASCT**	Arm D: MRD Indeterminant **ASCT + Rituximab**
3-y OS, %	82.1	82.7	81.9	85.1
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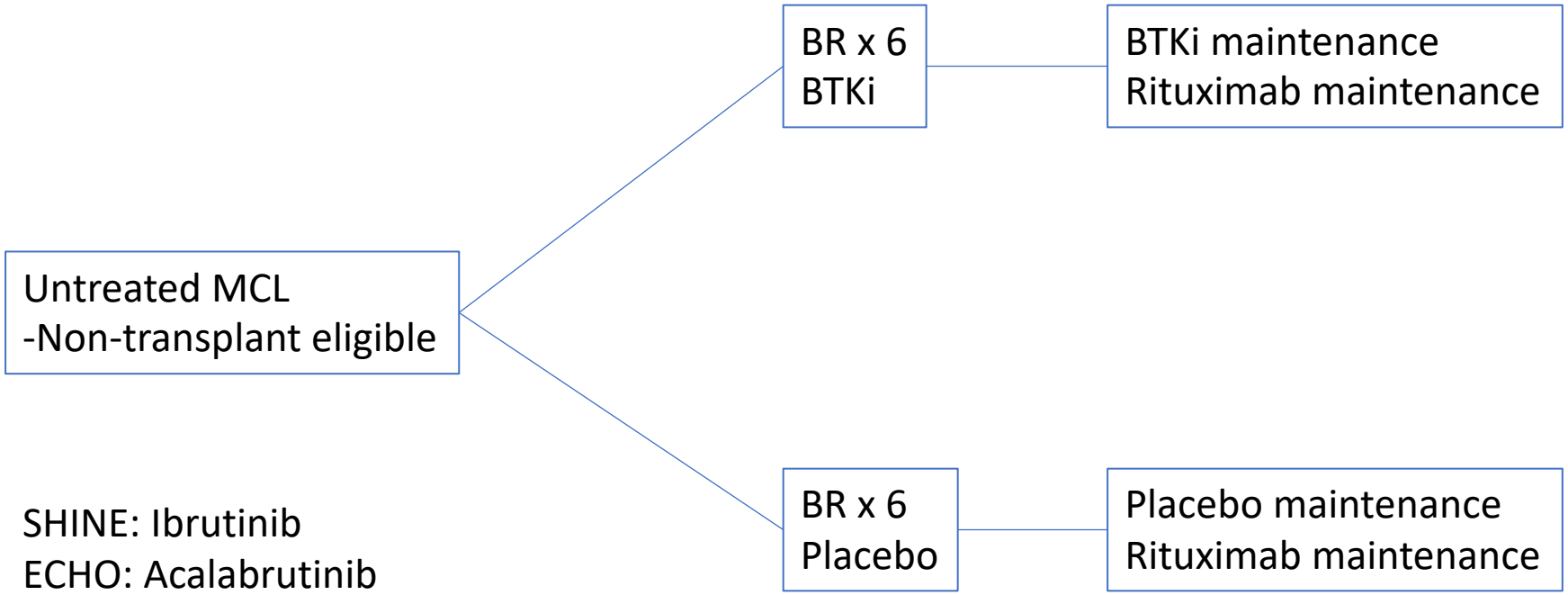
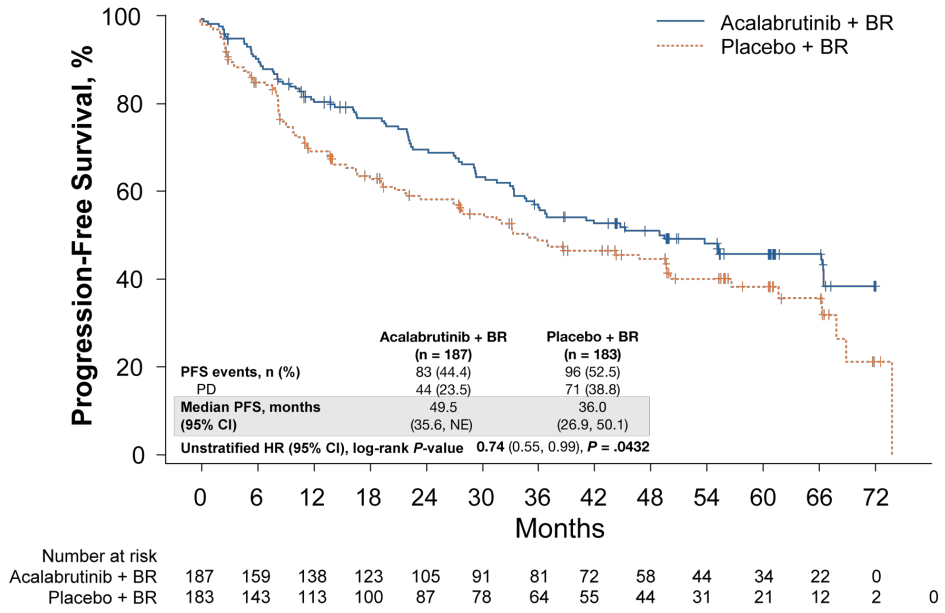
BR +/- BTK Inhibitors: SHINE and ECHO



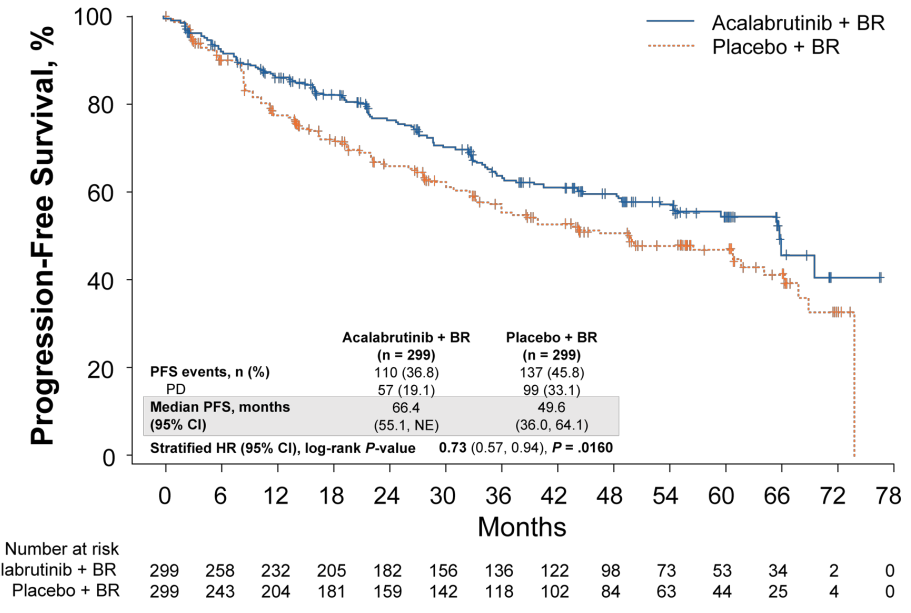
SHINE: Ibrutinib
ECHO: Acalabrutinib

Two Studies Suggest PFS Benefit for BTKi with B-R

PFS in High-risk Population



PFS in Full Analysis Population[1]



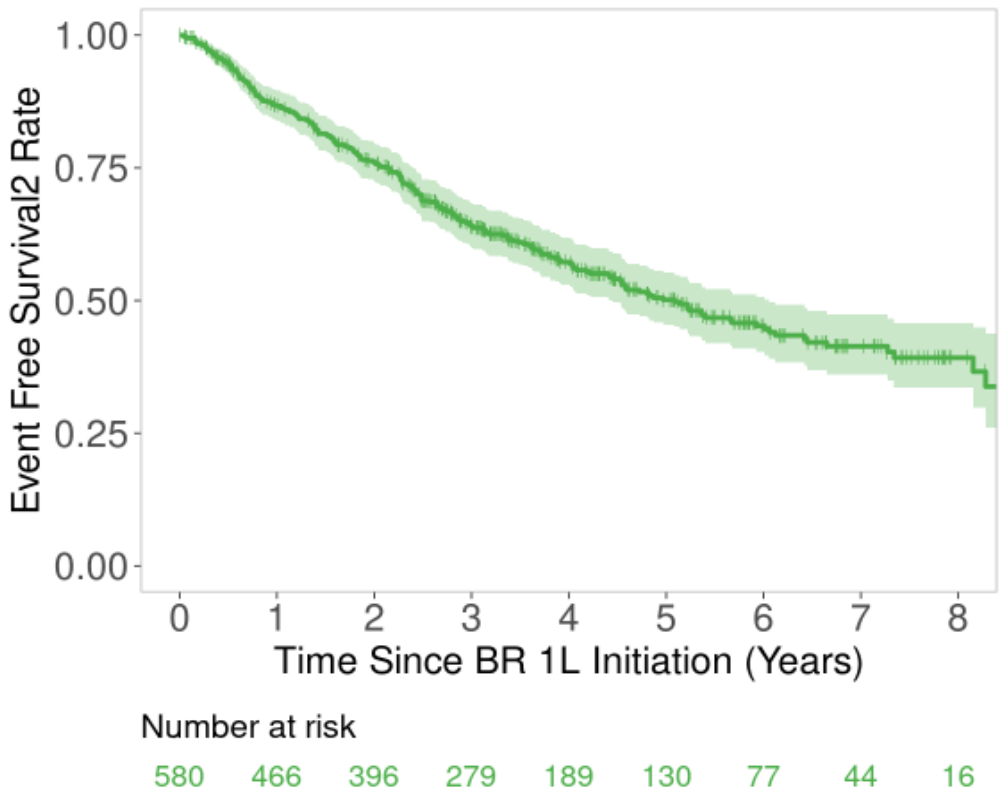
Note: Very few patients in ECHO study had TP53 mutation status assessed

Dreyling et al, ICML 2025

Is combination better than sequencing?

	This study, Age ≥65	Ibrutinib Arm in SHINE	Acalabrutinib Arm in ECHO
Patient number	580	261	299
Age, median (range)	73 (65-91)	71 (65-86)	71 (65-85)
Age ≥65	581 (100%)	261 (100%)	299 (100%)
ORR to 1L BR	88.0%	89.7%	91.0%
CR rate to 1L BR	72.1%	65.5%	66.6%
Rituximab maintenance	266 (45.9%)	206 (78.9%)	Not reported (required by design)
BTKi use	At 2L: 210 (78.7%) of 267 who had 2L (36.2% of all 581)	1L: 100% by design	1L: 100% by design
Median EFS/PFS (months)	EFS: 33.5 (95% CI 29.3-36.3) ITT EFS2: 61.0 (95% CI 53.0-72.7)	PFS: 80.6 (95% CI 61.9-NE)	PFS: 66.4 (95% CI 55.1-NE)
OS	55.4% at 5 years, 47.5% at 7 years	55.0% at 7 years	~65% at 5 years

EFS 2: BR followed by BTKi



Median EFS2: 61.0 (95% CI 53.0-72.7) months
5-year EFS2: 50.1% (95% CI 45.5%-55.2%)

Identification of High Risk MCL

Clinical

- Age
- LDH
- Tumor bulk
- Comorbidities
- MCL International Prognostic Index (MIPI)

Biologic

- Nodal vs Non-nodal
- Histology (blastoid, pleomorphic)
- Rate of proliferation by ki-67
  - MIPI-C
- Gene Expression Profiling
- MCL-35 gene signature

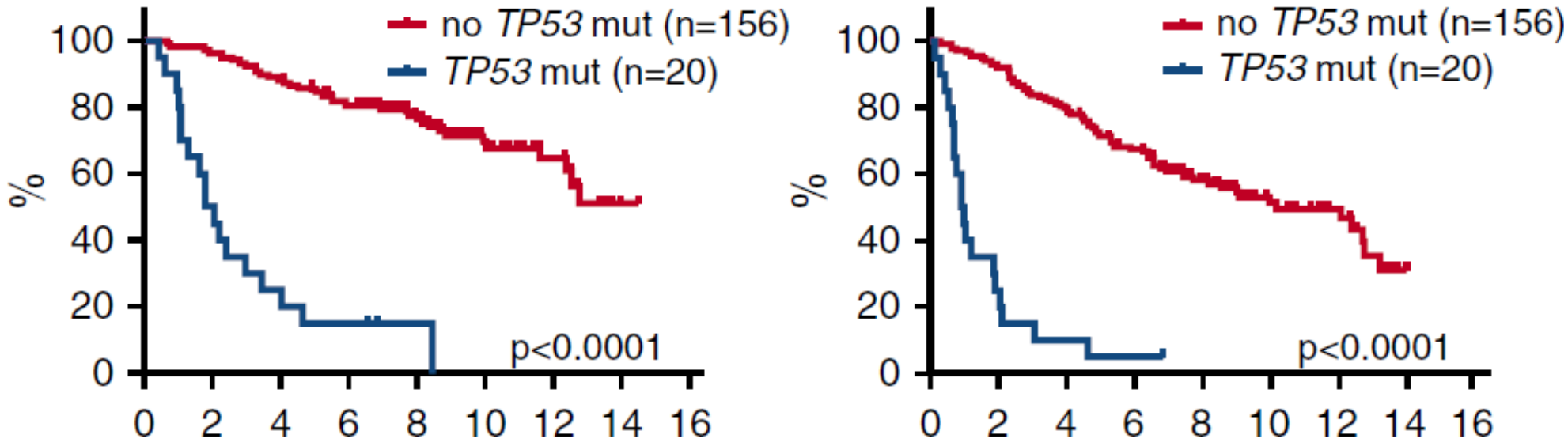
Genetic Aberrations

- Genomic Complexity
  - Karyotype (≥3) alterations
- Individual Genes and Mutational Profile
  - ***TP53 Aberrations: mutations, deletion, p53 IHC overexpression***
  - Others include: *CCND1 mutations, NOTCH1 and 2, SMARCA4, KMT2D, CDKN2A/B* deletions, ATM
  - MYC alterations: gains and rearrangements

TP53 aberrations main driver of treatment decisions

Chemo + ASCT Less Effective with TP53 Aberrations

MCL Younger Study

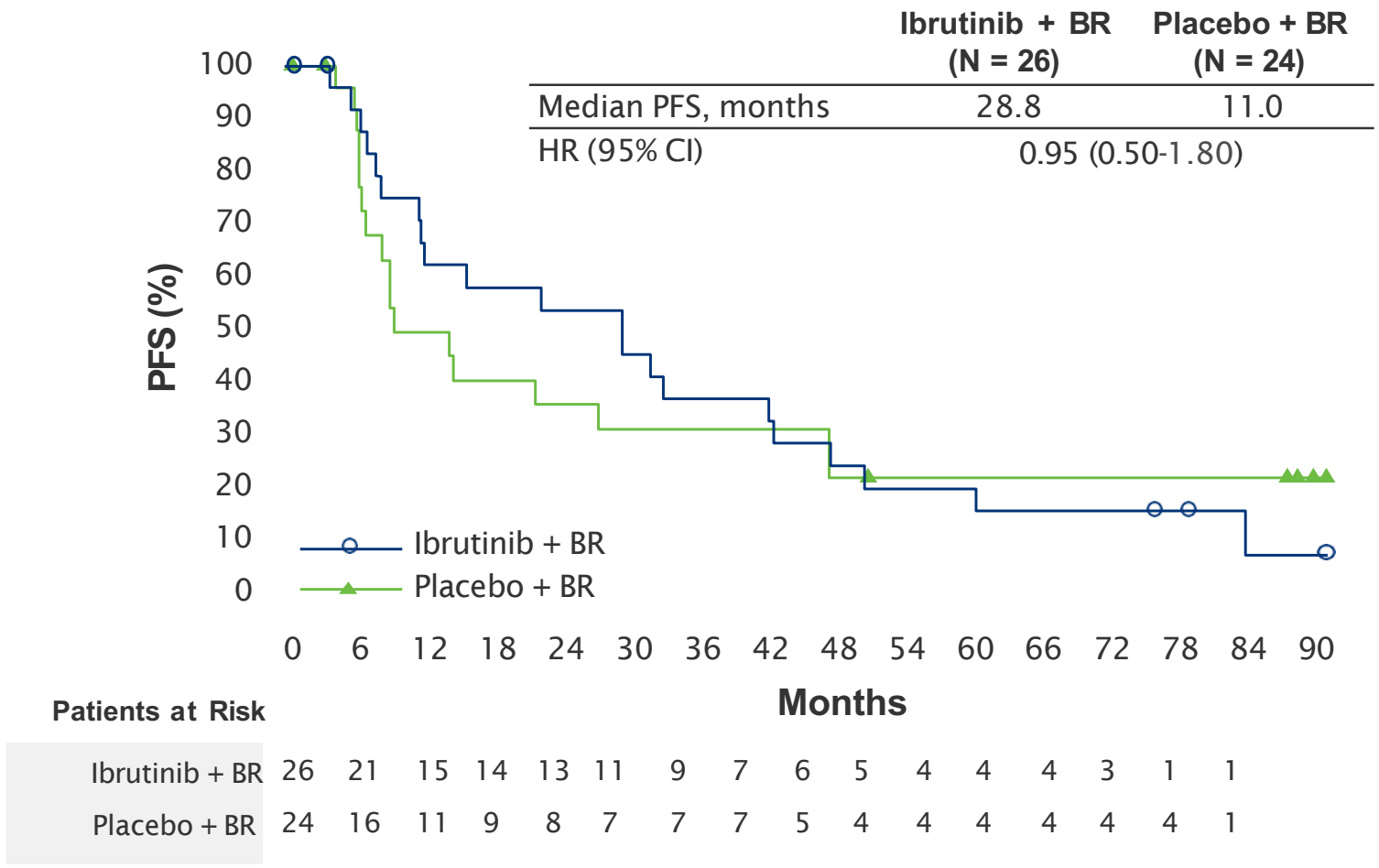


Eskelund et al, Blood 2017

BR + Ibrutinib for TP53 mutated

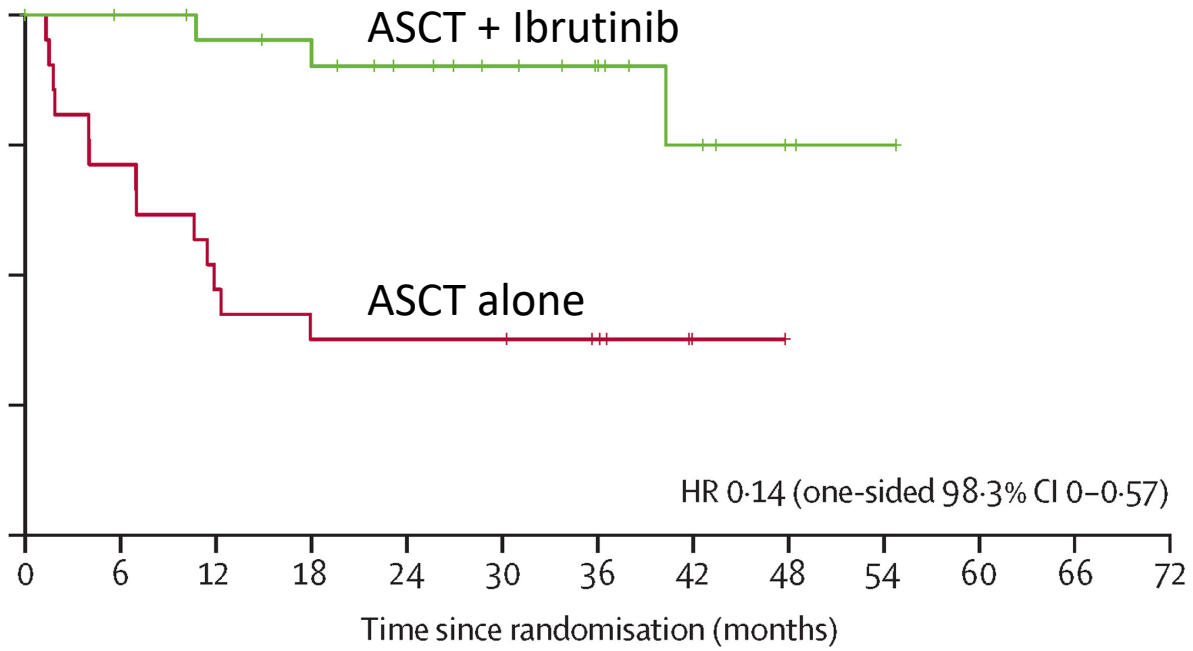
SHINE Study:

BR +/- Ibrutinib



Wang et al *NEJM* 2023, Dreyling et al ASH 2024

BTKi-containing chemo-immunothearpy for TP53-mutated MCL



21	15	10	9	8	8	5	2	0	0	0	0	0
(0)	(0)	(0)	(0)	(0)	(0)	(3)	(6)	(8)	(8)	(8)	(8)	(8)
25	22	20	19	15	12	9	5	3	1	0	0	0
(0)	(3)	(4)	(5)	(8)	(11)	(14)	(17)	(20)	(21)	(22)	(22)	(22)

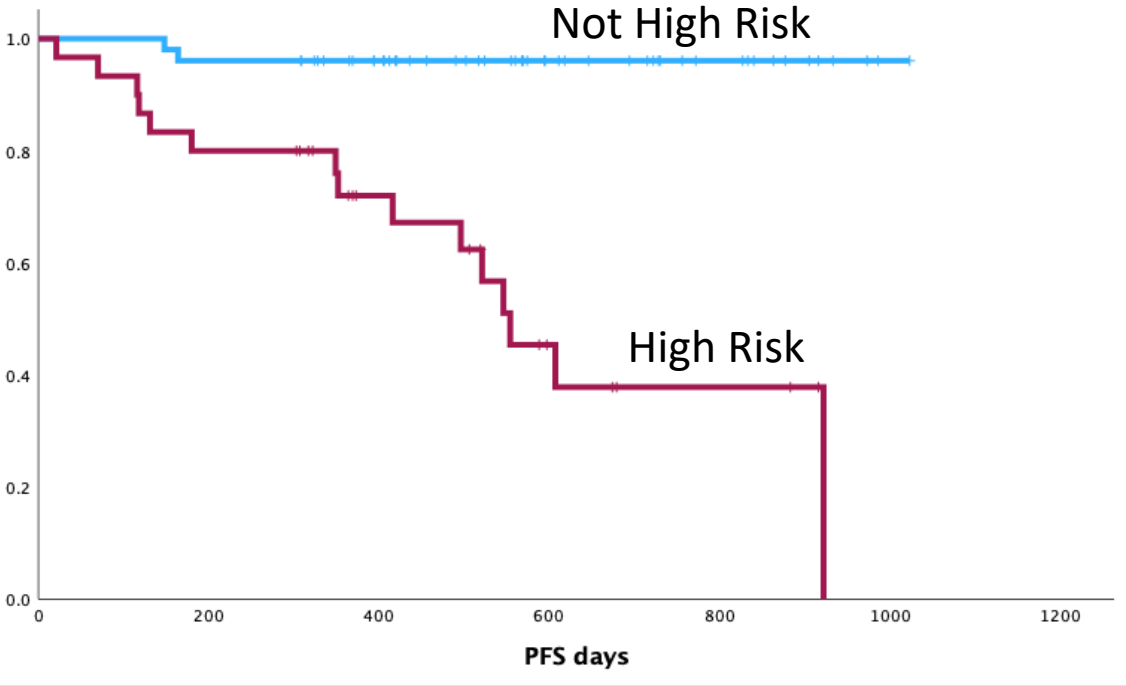
Increased expression of TP53 by IHC

Dreyling et al, Lancet 2024

R-BTKi for High Risk MCL

ENRICH Trial: R-Chemo vs R-Ibrutinib

- High Risk (Ki67 > 30%, TP53 mutation, Blastoid)



Jerkeman et al ASH 2024

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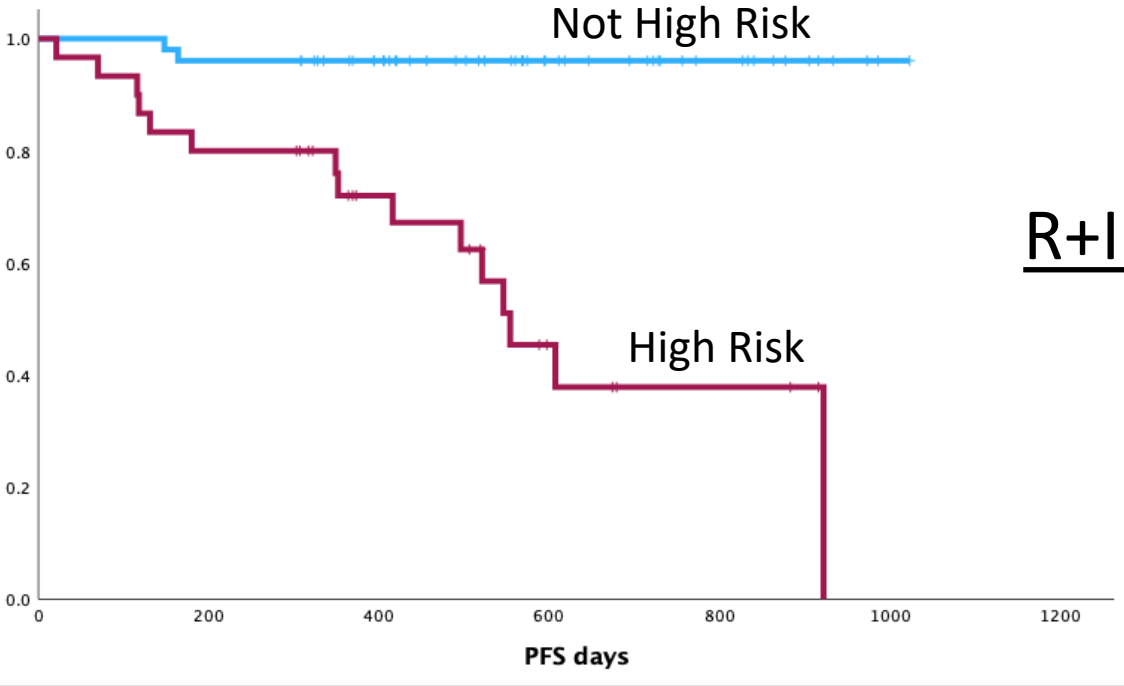
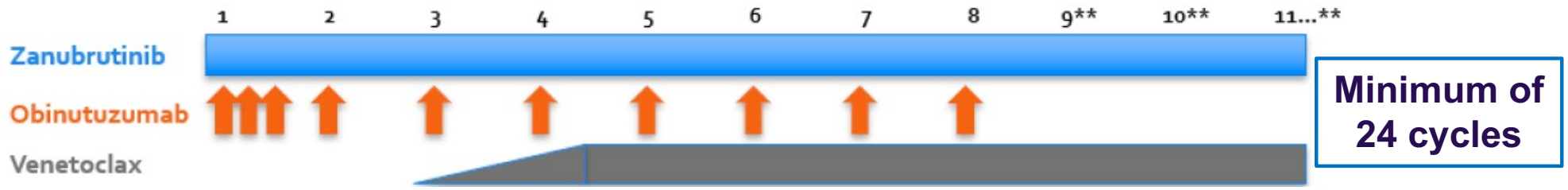


R+Ibrutinib not sufficient

Jerkeman et al ASH 2024

Combination of BTKi with Venetoclax may be Successful

BOVen Study: Zanubrutinib, Obinutuzumab + Venetoclax



Dosing:

Zanubrutinib 160 mg oral twice daily
Until EOT or intolerance**

Obinutuzumab 1000 mg IVPB
Cycle 1: day 1, 8, 15
Cycle 2-8: day 1

Venetoclax 400mg oral daily
5-week ramp-up: 1 week each of 20mg; 50mg; 100mg; 200mg; 400 mg oral daily

After 24 cycles, MRD-driven approach to limit treatment duration in selected patients:

CR and uMRD	Stop treatment
<CR and/or dMRD	Continue ZANU and VEN

Kumar et al, Blood 2025

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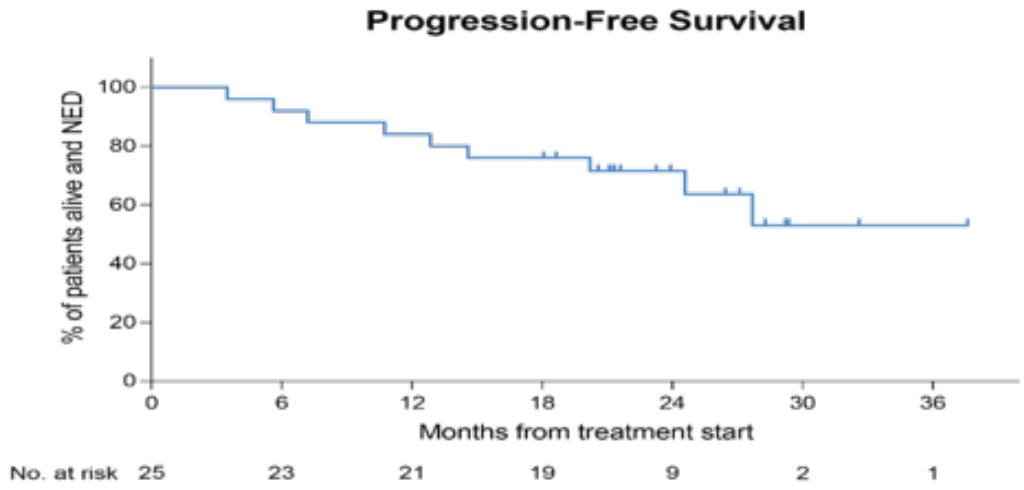
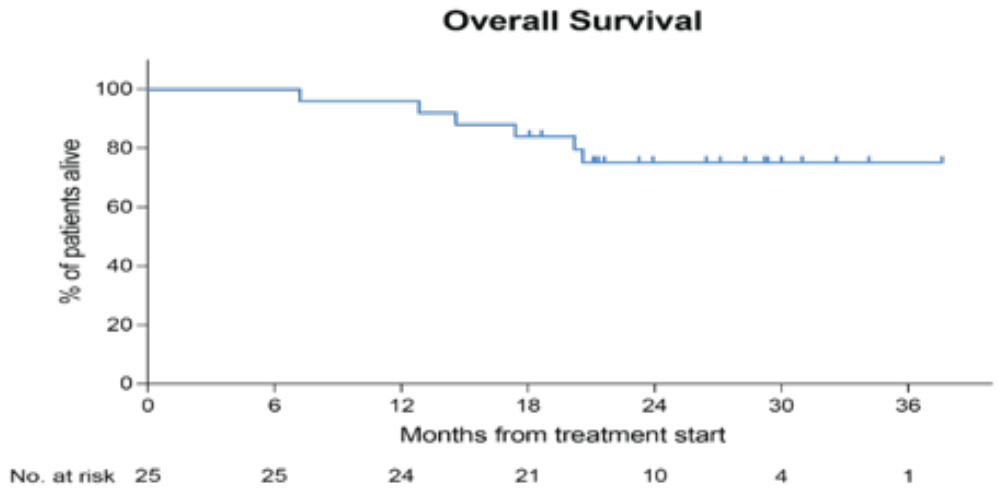




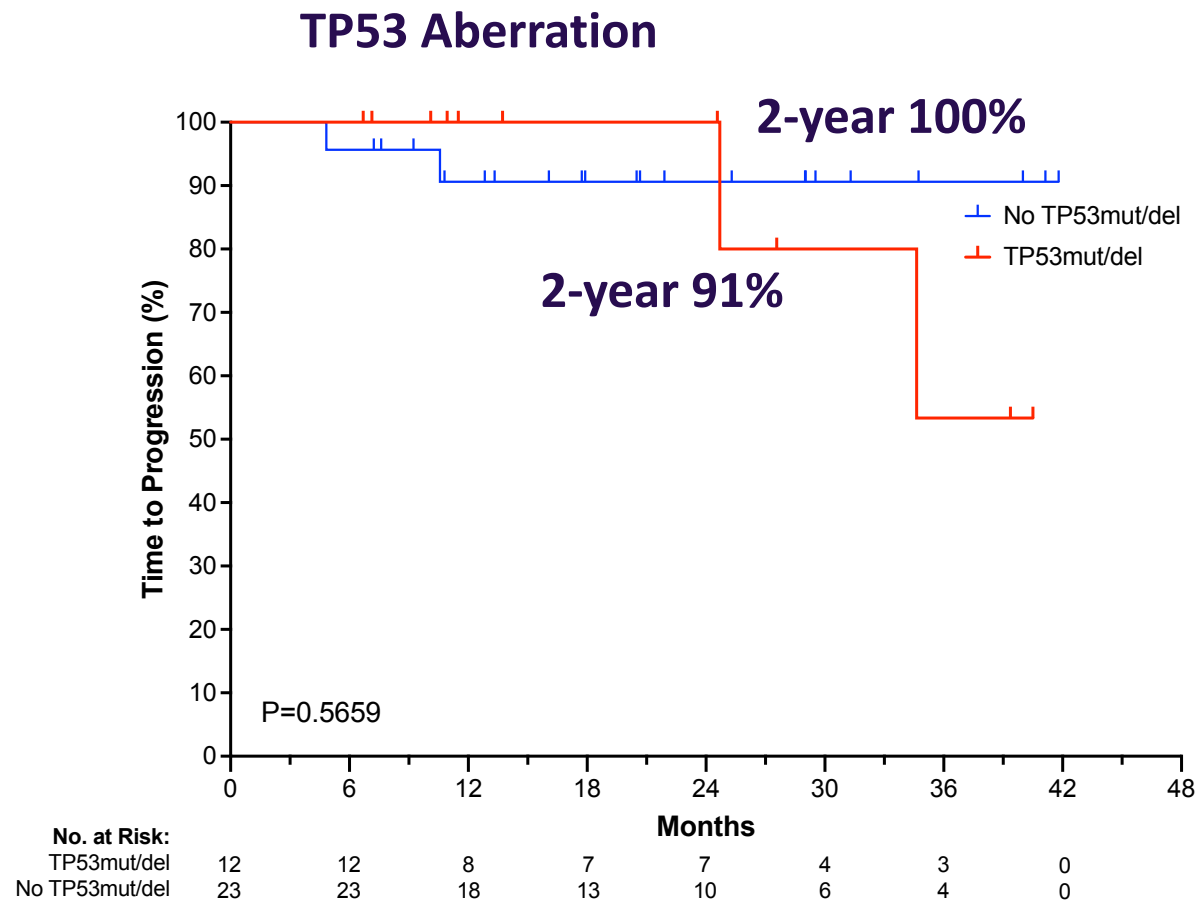
2-year PFS: 72% [95% CI: 56, 92]
Median PFS: not reached

2-year OS: 75% [95% CI: 58, 93]
Median OS: not reached

Kumar et al, Blood 2025

Combination of BTKi with Venetoclax may be Successful

- ViPOR Regimen
  - Venetoclax
  - Ibrutinib
  - Prednisone
  - Obinutuzumab
  - Lenalidomide



Median (range) follow-up = 27.6 (3.1-57.5) mo.

Melani et al, ASH 2024

Chemo-Free Combinations

- Promising results in high-risk (TP53-mutated) patients
  - R-BTKi alone unlikely to result in long-term remission
- No randomized data (BOVen and ViPOR)
- High cost and not toxicity-free
- Clinical trials remain important

- I am not transitioning away from chemo in my own practice…yet

Conclusions & Other Thoughts

- Outcomes with MCL continue to improve
- Likely very limited role for ASCT
  - Consider in a patient who cannot receive BTKi
- BTKi now standard in frontline treatment, at least using TRIANGLE approach.
- BR vs BR + BTKi still somewhat unclear.
- High risk patients still unmet need.

THANK YOU!