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MCL: CASE BASED APPROACH TO MANAGEMENT

Reem Karmali, MD, MS
Associate Professor of Medicine
Northwestern University
Robert H. Lurie Comprehensive Cancer Center

DISCLOSURES

- **Consulting Fees:** Celgene Corporation, Gilead Sciences, Juno Therapeutics, Kite Pharma, Janssen, Karyopharm, Pharmacyclics, Morphosys, Epizyme, Genentech, EUSA
  Grants/Research Support: Celgene Corporation/Juno Therapeutics/BMS, Takeda, BeiGene, Gilead Sciences/Kite
- **Speakers Bureau:** AstraZeneca, BeiGene, Morphosys
- **Advisory Board:** Calithera

Objectives

- Therapeutic options for frontline MCL
  - Role of autologous stem cell transplantation
- Special considerations for high risk patients
  - *TP53* mutated
- Therapeutic options for relapsed/refractory
  - BTK inhibitor sub-optimal response vs failure
  - Role for CART
  - Pipeline therapeutics

Case 1: MCL Frontline

- 62 yo M with HTN presents with new enlarged L cervical LN
- Endorses weight loss and increased fatigue for 6 months
- Excisional biopsy of neck LN = MCL, with t(11; 18), SOX 11 (+), Ki-67 of 40%, TP53 negative by IHC
- PET/CT with extensive disease; BM biopsy with 60% involvement with MCL
- Intermediate risk MIPI
- Started on bendamustine-rituximab induction
- Referred to Transplant Center for consideration for autologous stem cell transplantation (autoSCT)

How Would You Treat?

A. Consolidation with autologous stem cell transplantation

B. Consolidation with autologous stem cell transplantation followed by maintenance rituximab

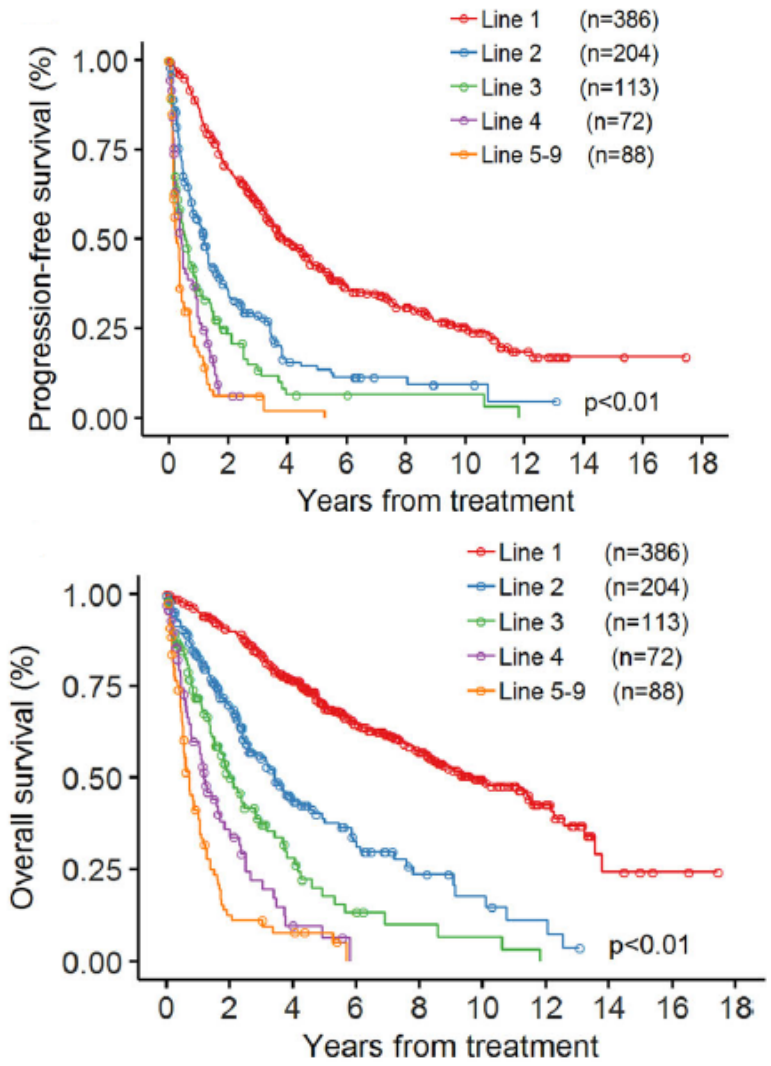
C. Maintenance rituximab

D. Maintenance ibrutinib

MCL: Disease Trajectory

- Mantle cell lymphoma (MCL) is a rare B-cell non-Hodgkin lymphoma (NHL) that remains incurable despite high response rates with intensive chemotherapy.
- Relapsing and remitting course is expected with diminishing returns for subsequent lines of therapy
- High-risk disease features:
  - high MIPI score, elevated Ki-67, TP53 aberrancies, complex karyotype, blastoid/pleomorphic variant.

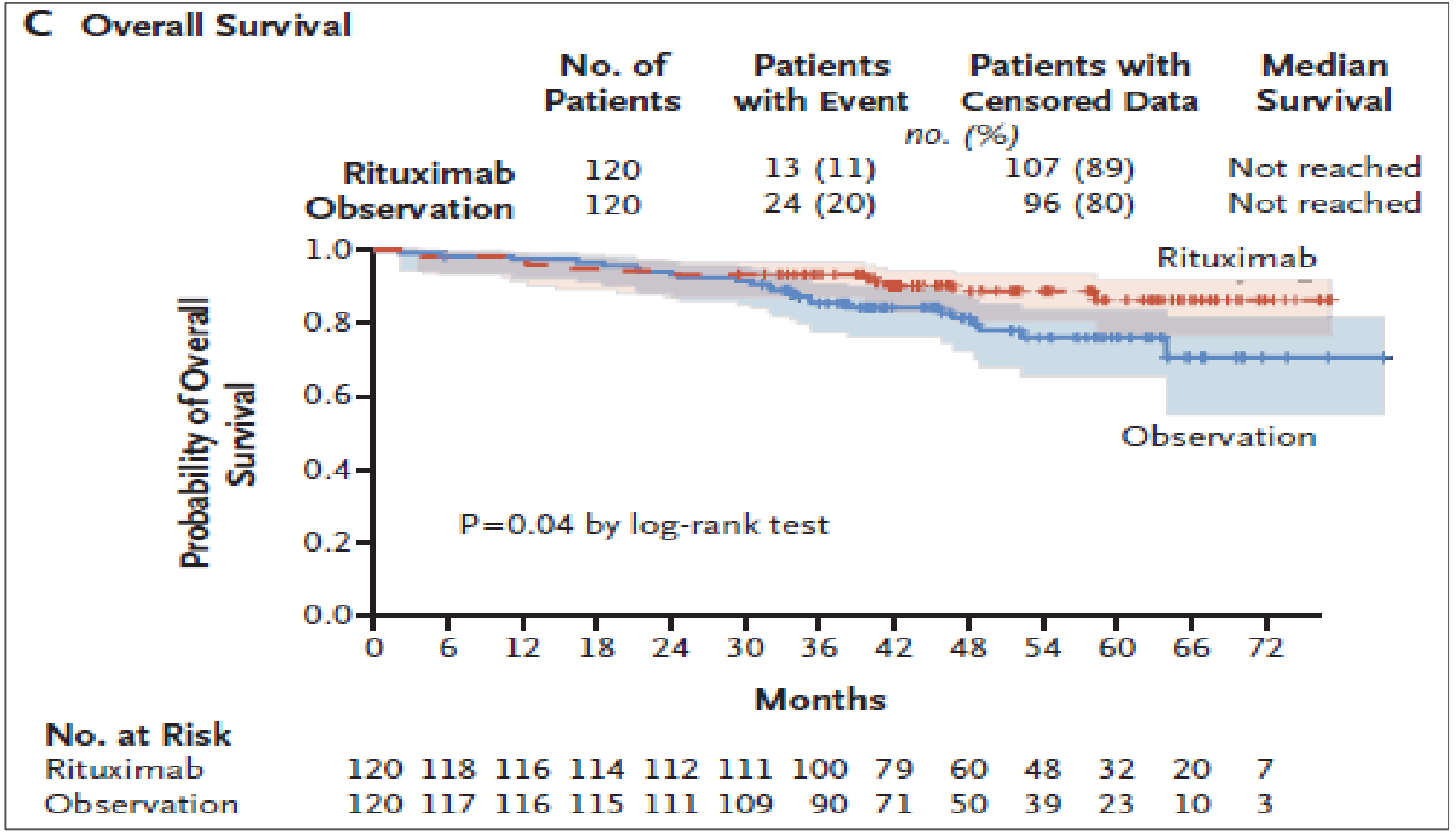
MSK retrospective analysis 2000 -2014 (N=404)



Robak, Lancet Oncol 2018; Visco, Lancet Hematol 2017; Le Gouill, NEJM 2017; Kumar, Blood Cancer Journal 2019

MCL Frontline: AutoSCT and/or Rituximab Maintenance

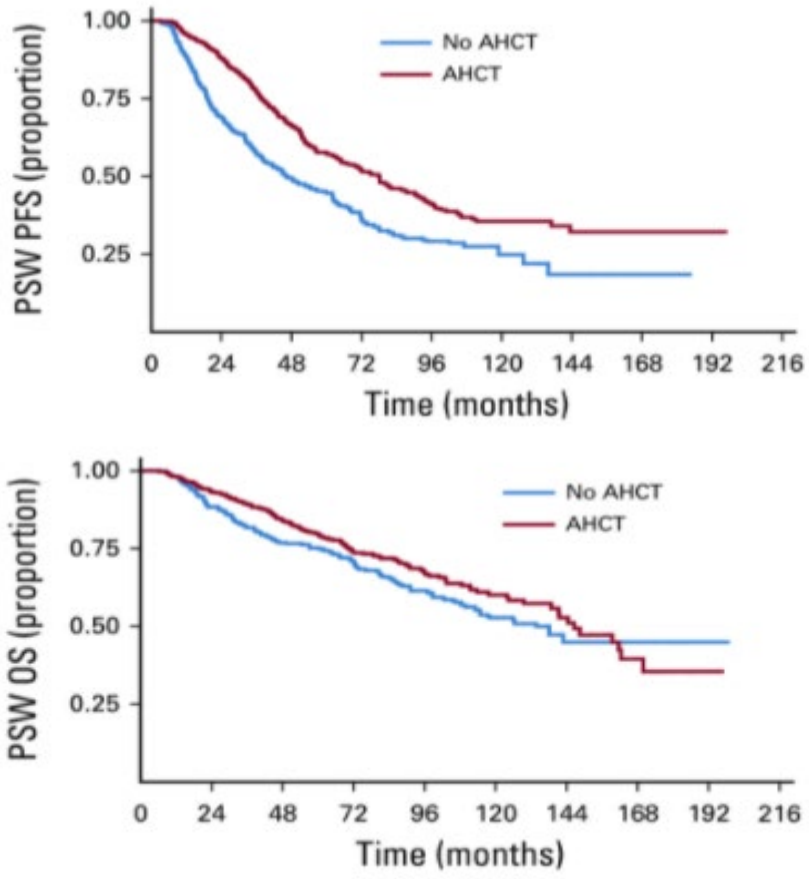
Phase III study Induction followed by autoSCT consolidation +/- maintenance rituximab



Le Gouill et al., NEJM 2017

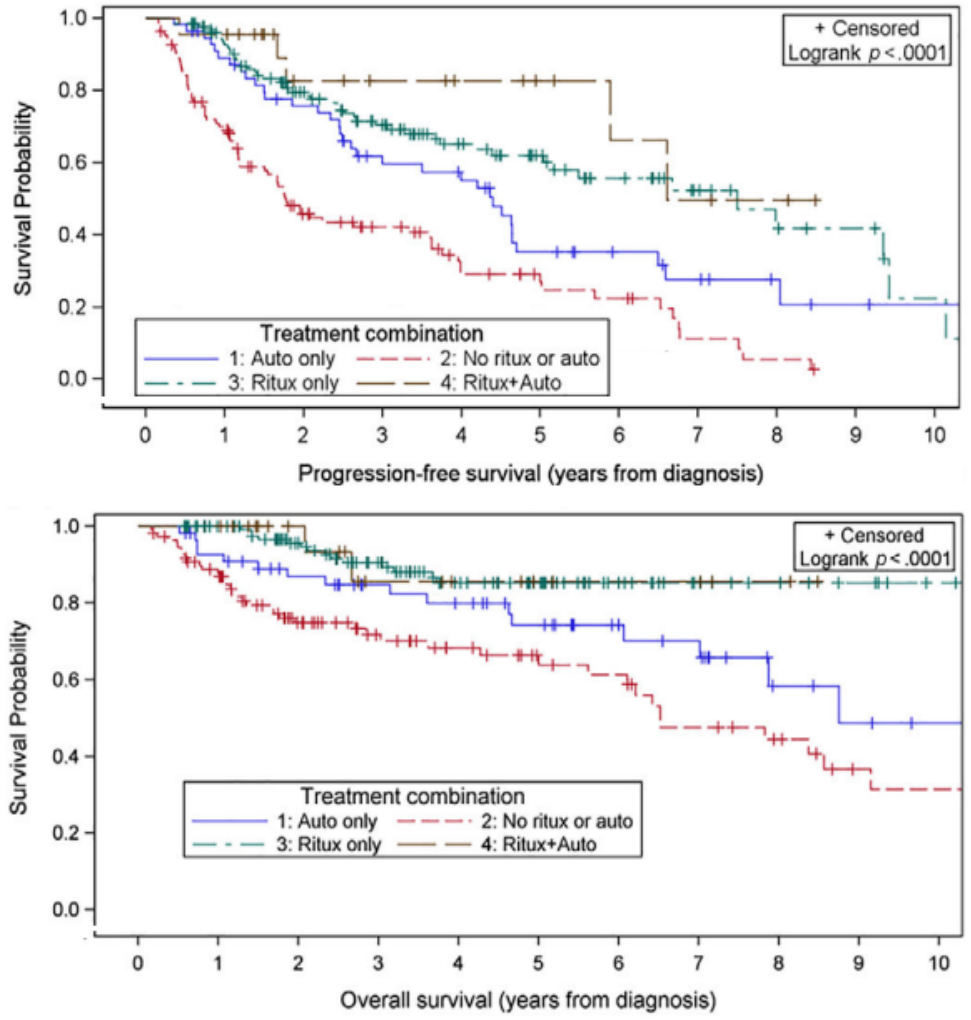
Do We Really Need the AutoSCT ???

Large retrospective data comparing autoSCT (n=370) vs no autoSCT (n=636) in patients ≤ 65



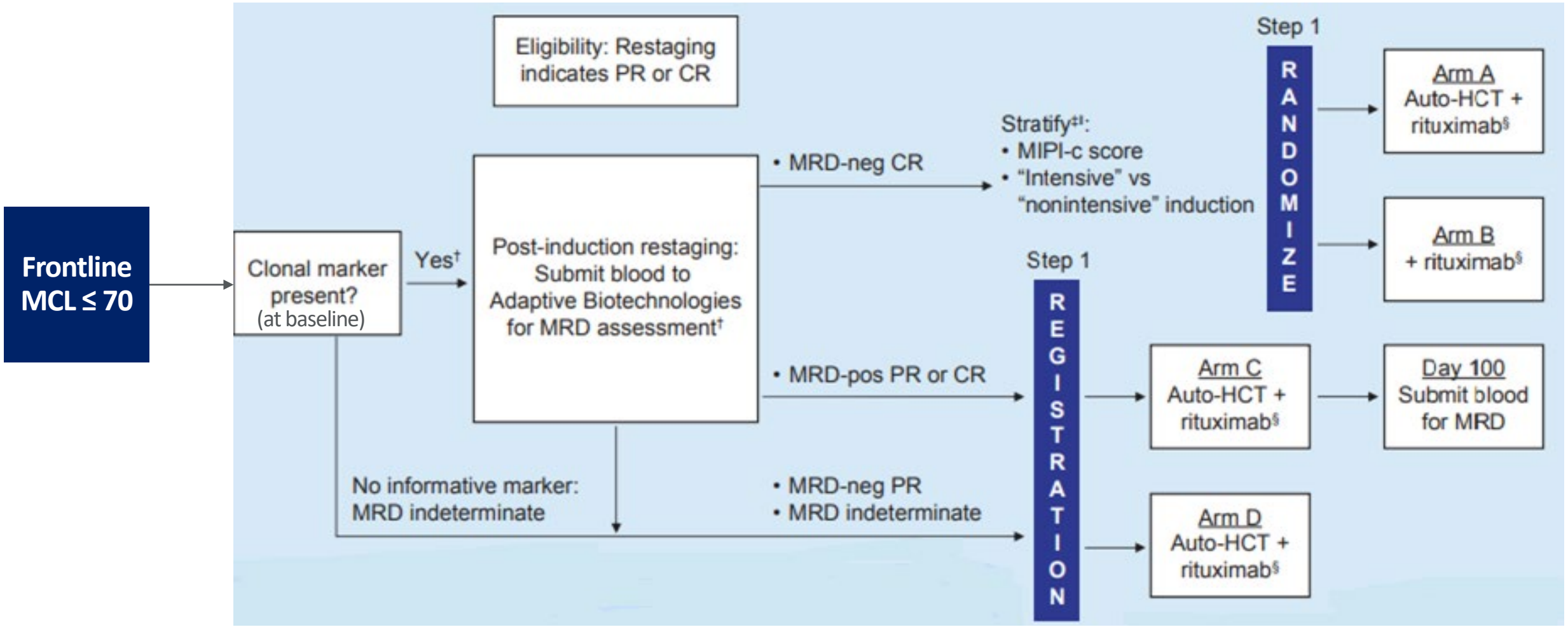
Gerson et al., JCO 2019

Large retrospective data comparing no treatment vs autoSCT +/- rituximab vs rituximab alone in ≥ 65



Karmali et al., Am J Hematol. 2021

ECOG 4151: AutoSCT + Maintenance vs Maintenance Alone



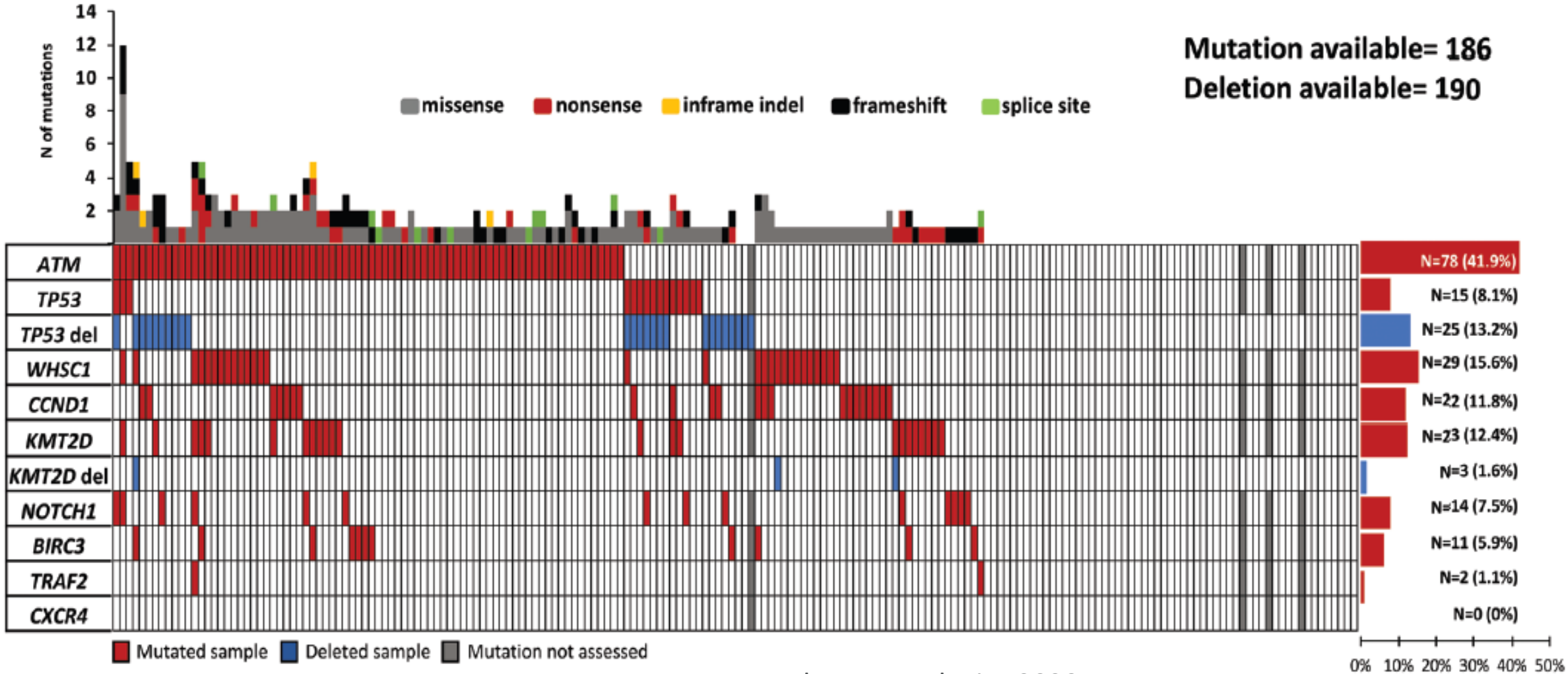
Primary Objective: Compare overall survival (OS) in MCL patients MRD-negative first CR for auto-HCT → MR versus MR alone (without auto-HCT)

Case 2: MCL Frontline – *TP53* Mutated

- 62 yo M with HTN presents with new enlarged L cervical LN, weight loss and increased fatigue for 6 months
- Excisional biopsy of neck LN = MCL, with t(11; 18), SOX 11 (+), Ki-67 of 60%, ***TP53* scattered staining by IHC of 40% of cells**
  - PET/CT with extensive disease; BM biopsy with 60% involvement with MCL
  - Intermediate risk MIPI
  - **NGS on tissue identified a *TP53* mutation**
- Started on bendamustine-rituximab induction
- Referred to Transplant Center for consideration for autoSCT

Prevalence of *TP53* Mutations and Deletions in MCL

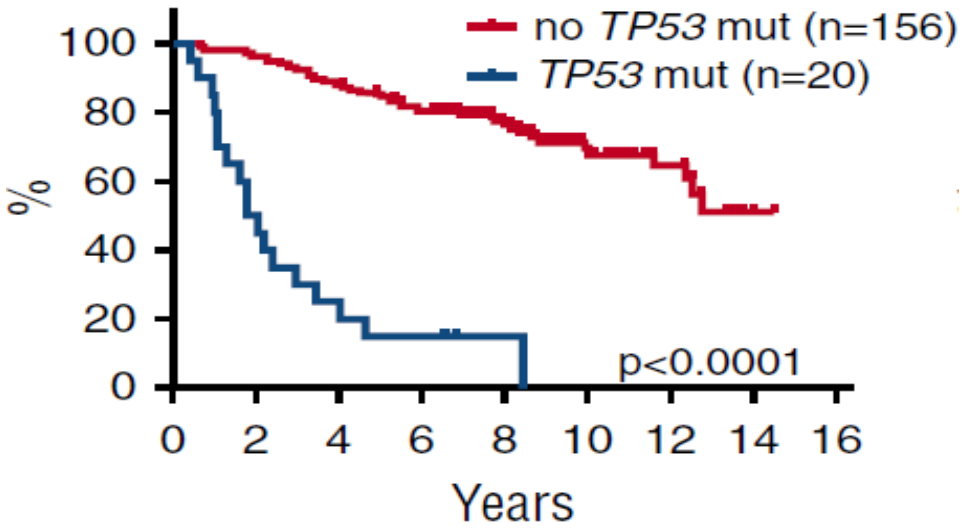
- Prevalence of *TP53* mutations and deletions



Ferrero et al, Haematologica 2020

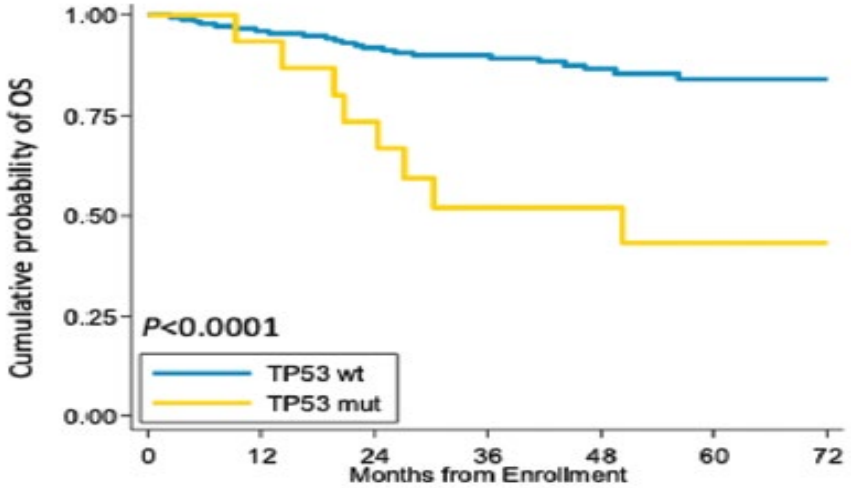
High Intensity Chemotherapy in *TP53* Mutated MCL

Patients with *TP53* mutations do not benefit from high-intensity chemotherapy



NB: *TP53* del did not impact OS in MVA

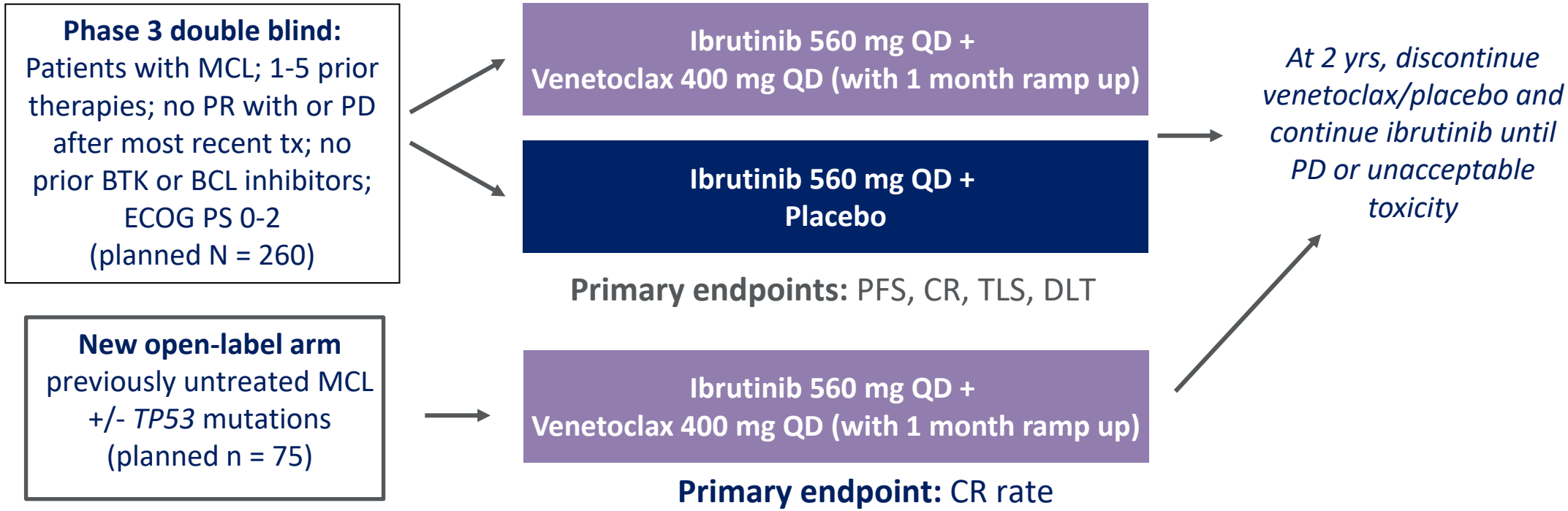
Esklund et al, Blood 2017



Ferrero et al, Haematologica 2020

Alternatives in *TP53* Mutated MCL?

- General trend to consider novel targeted agents in these high risk patients **UPFRONT**
  - **SYMPATICO**: Phase 3 ibrutinib + venetoclax vs ibrutinib alone for R/R MCL + treatment-naïve MCL including *TP53* mutated (new arm added Jan 2021) – ONGOING

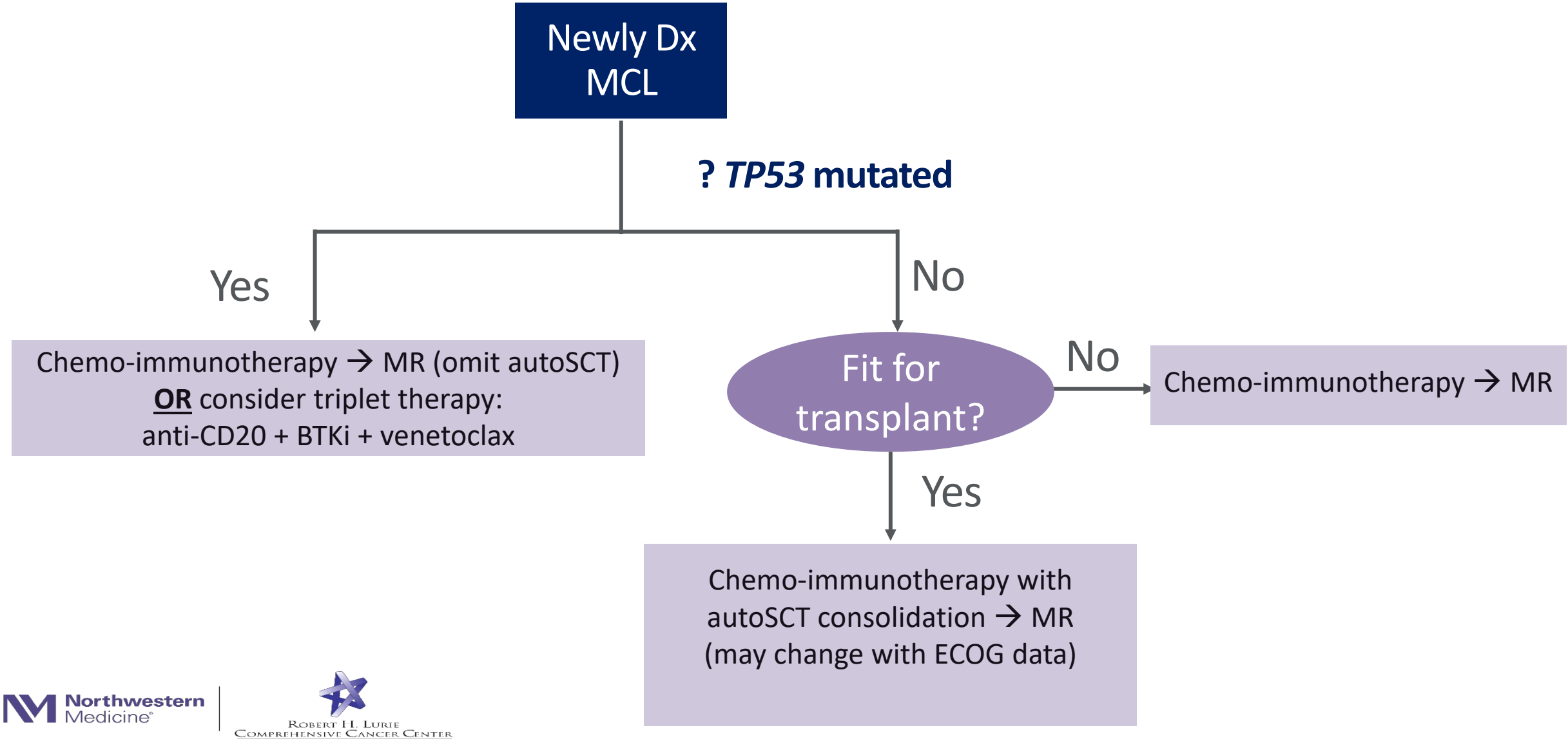


Alternatives in *TP53* Mutated MCL?

- General trend to consider novel targeted agents in these high risk patients **UPFRONT**
  - **OAsIs**: ibrutinib, obinutuzumab, and venetoclax in R/R and treatment-naïve MCL (Le Gouill et al., Blood 2021)
    - n=24 R/R MCL – 5 with *TP53* mutation; n=15 treatment naïve – 2 with *TP53* mutation
    - **MRD negative rate in all evaluable patients (PB): 81% including patients with *TP53* mutation**
    - **1 year PFS = 100% in *TP53* mutated treatment naïve patients**
  - **BOVeN** = zanubrutinib, obinutuzumab, and venetoclax in CLL (all subsets) and MCL with *TP53* mutation irrespective of variant allele frequency
    - **PET-CR rate after 3 cycles: 80%; follow-up too short for PFS determination**

NO SET PROTOCOL FOR THESE PATIENTS YET

Treatment Algorithm for Frontline MCL



Case: Relapsed/Refractory MCL

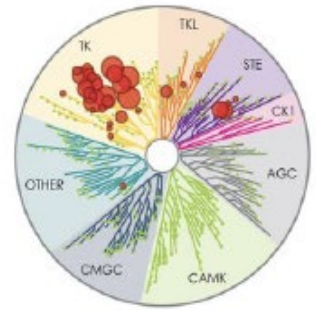
- 71 yo M with HTN, CAD with stents on ASA, presents with bilateral axillary LAD, drenching night sweats and intermittent diarrhea
- Excisional biopsy of R axillary LN: MCL, with t(11; 18), SOX 11 (+), Ki-67 of 30%, TP53 negative by IHC
- PET/CT with extensive disease including GIT involvement, BM biopsy with 30% involvement with MCL
- High risk MIPI
- Treated with R-BAC x 6 cycles with complete response
- Received maintenance rituximab every 2 months thereafter
- Relapsed 15 months later

Options for R/R MCL – BTK Naive

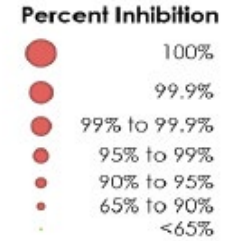
BTKi	# R/R MCL	ORR (%)	CR (%)	mPFS (mo)
Ibrutinib*				
Wang, 2015	111	67	23	13.6
Dreyling, 2016	280	72	19	14.6
Acalabrutinib* (Wang, 2019)	124	81	43	20
Zanubrutinib*				
Song, 2020	68	84	59	22.1
Tam, 2019	37 w/ MCL	84	22	18.5
Bortezomib* (Goy, 2009)	155	33	8	9.2
Lenalidomide* (Goy 2013)	54	78	19	8.7
Ibrutinib + Venetoclax (Tam 2018)				
Parsaclisib (Mehta 2021)	108	69	18	12.0

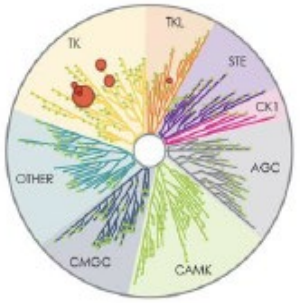
1st gen:

2nd gen:

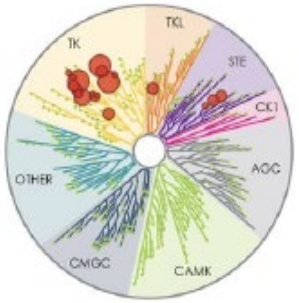


Ibrutinib





Acalabrutinib



Zanubrutinib

*FDA approved

Case Continued: R/R MCL and BTK Sub-Optimal Response

- The patient was started on ibrutinib 560 mg daily
- After 6 months of treatment, PET/CT with Deauville 4; CT correlate with 30% decrease in tumor burden consistent with stable disease
- Patient was continued on ibrutinib therapy
- CTs with clear progression of disease 3 months later

How Would You Treat?

A. Switch to venetoclax

B. Switch to bortezomib

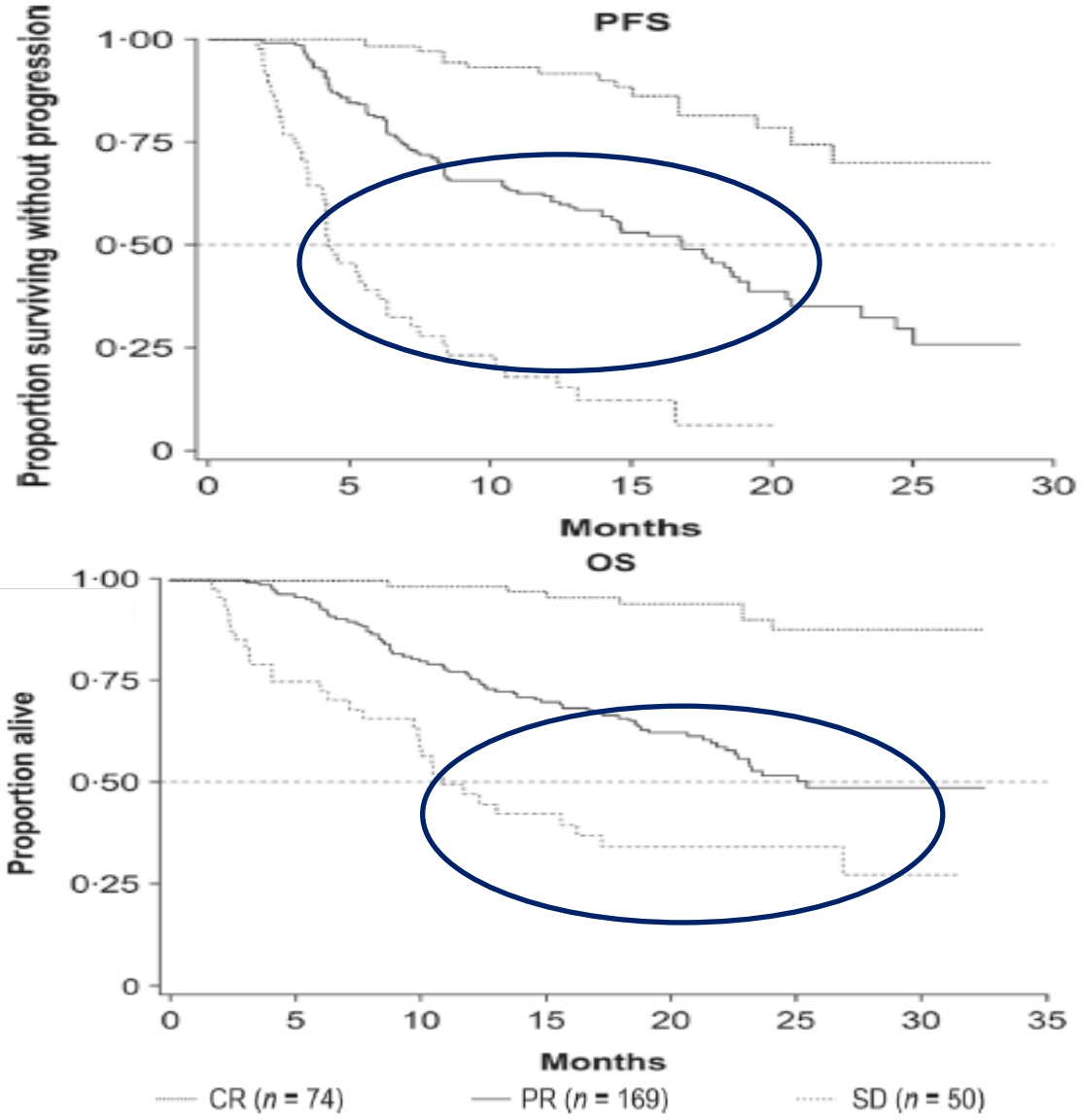
C. CAR T-cell therapy

D. Switch to lenalidomide

R/R MCL - Knowledge Gaps in the BTKi Era

- Predictors of poor response to BTKi limited
- Data for switching therapy after no response/ progression on BTKi
  - Options limited and outcomes typically poor
- Unclear how to define sub-optimal response to BTKi
  - SD and even perhaps persistent PR?
- NO DATA for switching for sub-optimal response
  - Clear that response will not last
  - Start thinking about next treatment!

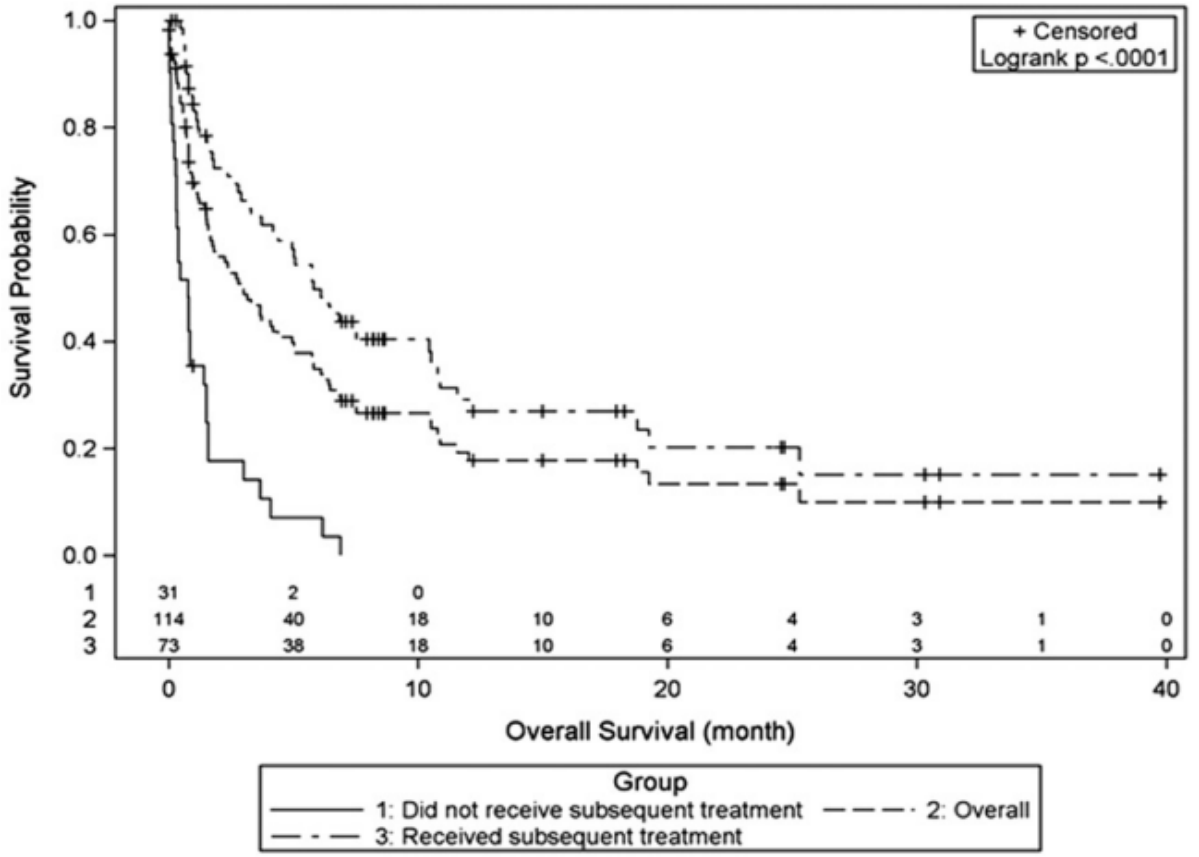
PFS and OS with Ibrutinib according to response



Rule et al., Hematol Onc 2017

BTKi failure: Mechanisms of Resistance and Outcomes in MCL

Gene or chromosome region affected	Mechanism of BTKi resistance
BTK	Turns covalent bond into noncovalent
PLCγ2	Constitutive activation of BCR signaling pathway
CARD11	BTK-independent activation of BCR signaling pathway
ARID2, SMARCA2, SMARCA4	Increased BCL-XL, an anti-apoptotic protein, limiting cell death
TRAF2, TRAF3, BIRC3, MAP3K14	Constitutive activation of alternative NF-kB pathway leading to cell survival independent of BCR signaling



- Median OS after ibrutinib failure:
  - < 2-3 months
  - < 0.5 months without therapy

Stephens et al., Blood 2021, Martin et al., Blood 2016, McCulloch et al., BJH 2021

Options for BTKi Failure?

	Data in all R/R MCL patients				Data in patients with prior BTKis			
	N	ORR (%)	CR (%)	Median PFS	N	ORR (%)	CR (%)	Median PFS
Lenalidomide - Imid* (Trneny 2016; Wang 2016)	54	78	19	8.7 months	13	15	0	Not reported (mDOR 20 wks)
Venetoclax - BCL-2 inhibitor (Davids 2021; Eyre 2018)	28	75	21	11.3 months	20	53	18	3.2 months
Parsaclisib - CDK4/CDK6 inh (Zinzani 2020, Mehta 2020)	108	70	15	11.1 months	53	25	2	3.7 months
R-BAC – Chemotherapy (McCulloch 2020)	20	80	75	NR*	36	83	N/A	10.1 months
Brexucabtagene - CD19 CART* (Wang 2020)	--	--	--	--	68	93	67	Not reached (f/u 12.3 months)
Lisocabtagene -CD19 CART (Palomba 2020)	--	--	--	--	32 (28 with prior BTKi)	84	59	Not reported
Pirtobrutinib - Non-covalent BTKi (Mato 2021)	56	52	25	Not reported	52	52	25	Not reported
Glofitamab - Bispecific Ab (Phillips 2021)	4	75	75	Not reported	17	82	65	Not reported

* FDA approved for R/R MCL

ZUMA-2: Brexucabtagene Autoleucel in R/R MCL

- International, open-label phase II trial

Patients with relapsed/refractory MCL; 1-5 prior therapies; ≥1 measurable lesion; ECOG PS 0/1 (N = 74)

Optional Bridging Therapy

Ibrutinib 560 mg/d *or*
Acalabrutinib 100 mg BID *or*
Dexamethasone 20-40 mg/d x 1-4 d *or*
Methylprednisolone
(n = 25)

Conditioning Chemotherapy

Fludarabine 30 mg/m^2 +
Cyclophosphamide
500 mg/m^2 on Days -5, -4, -3
(n = 69)

CAR T-Cells

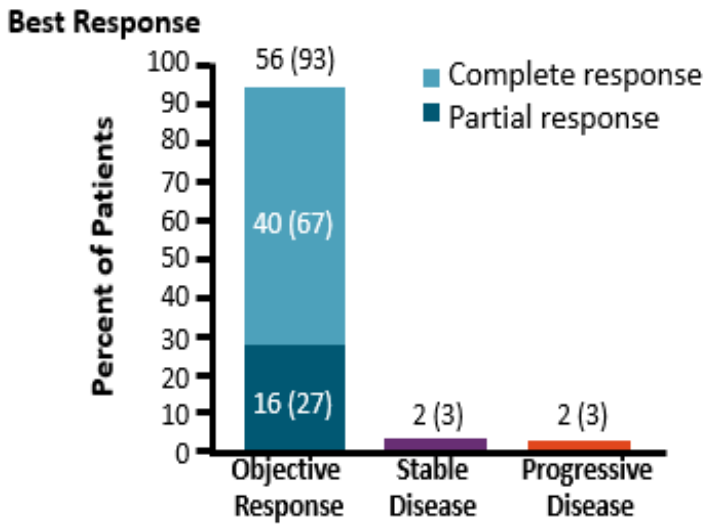
Brexu-cel
2 x 10^6 cells/kg on Day 0
(n = 68)

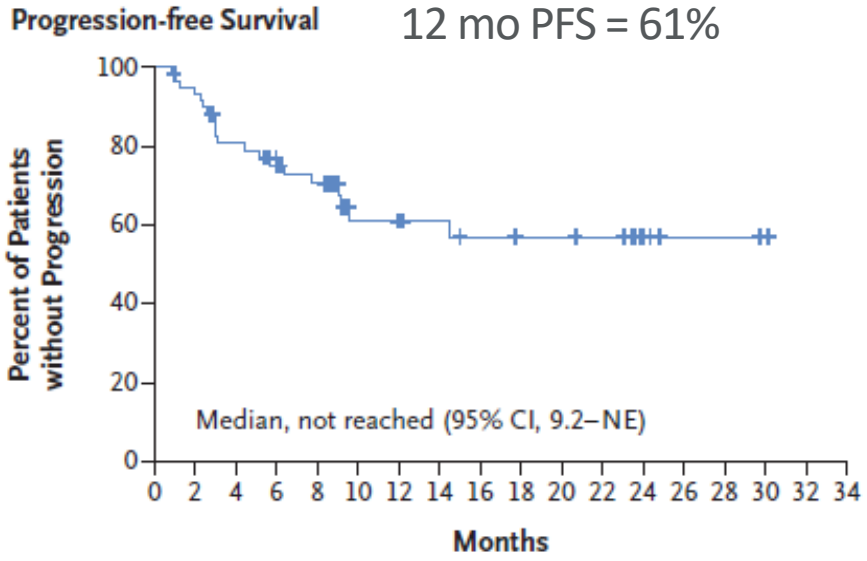
Primary endpoint: ORR

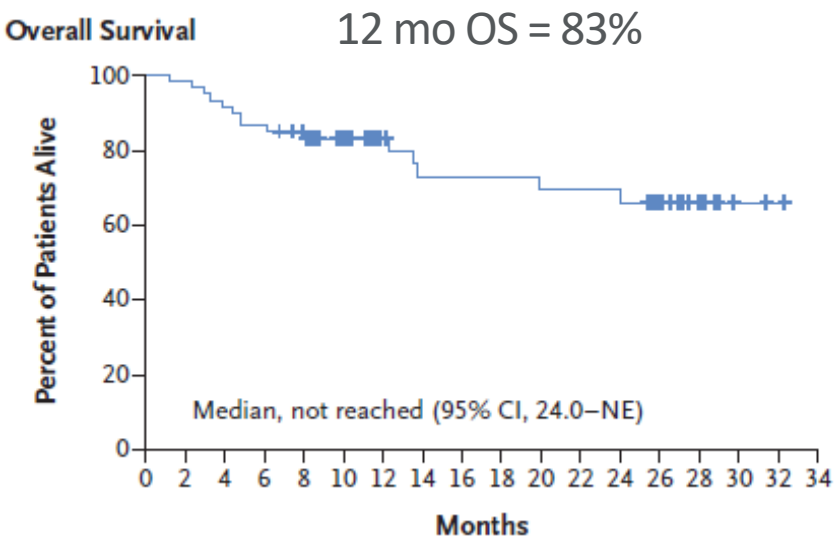
- 88% refractory to BTKi
- 17% patients with known *TP53* mutation
- 31% with blastoid /pleomorphic histology

Wang et al. NEJM. 2020

ZUMA-2: Efficacy Brexucabtagene Autoleucel in R/R MCL







- Similar outcomes in BTKi refractory and *TP53* mutated
- Most common grade ≥3 AEs = cytopenias (94%) and infections (32%)
- CRS in 91% (15% grade 3/4); ICANS in 63% (31% with grade 3/4)

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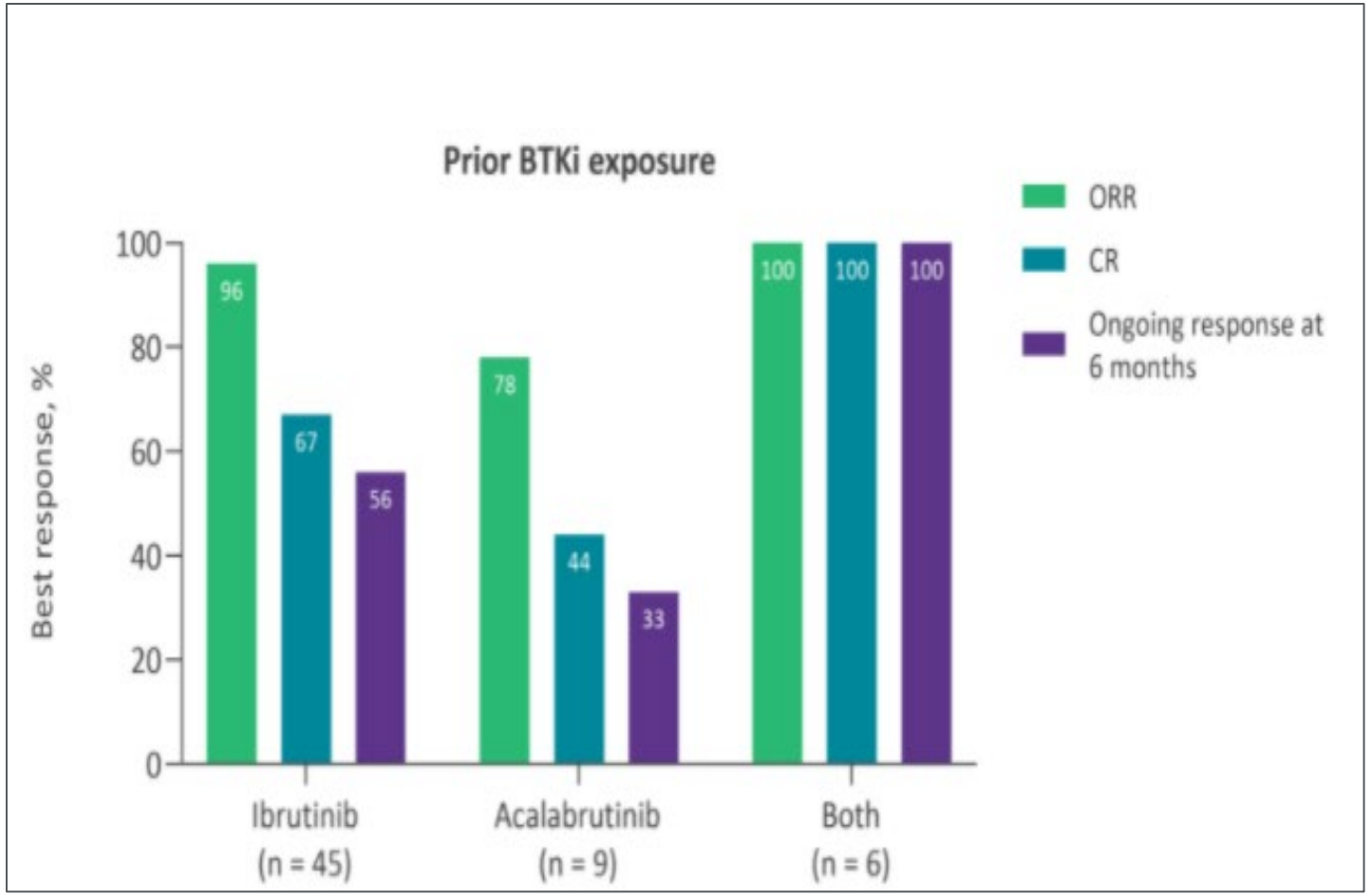
Wang et al., NEJM. 2020

ZUMA-2: Response and Toxicity According to Prior BTKi Exposure

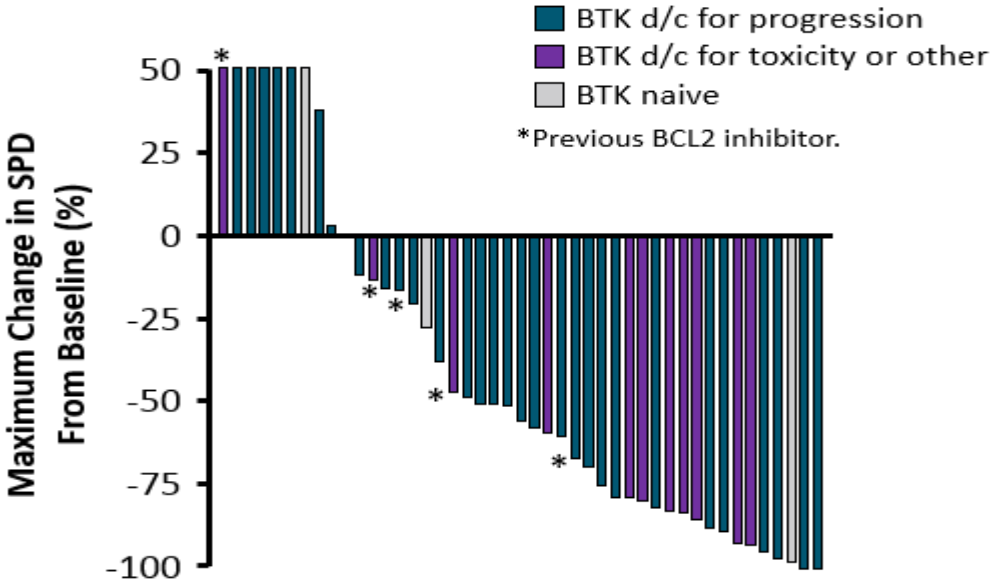


Grade ≥3 events, %	BTKi exposure		
	Ibrutinib (n = 52)	Acalabrutinib (n = 10)	Both (n = 6)
CRS	17	10	0
Neurologic events	31	10	67

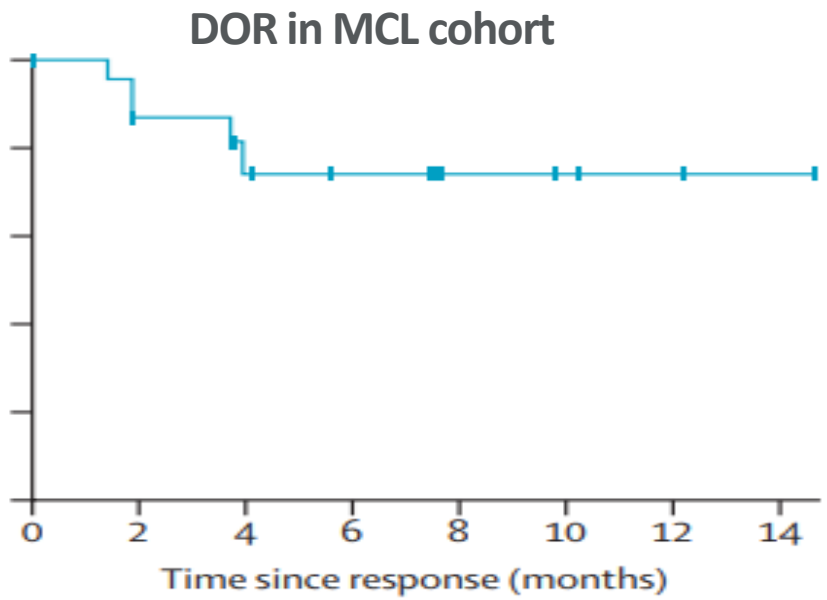
Wang et al., ESBMT 2021

BRUIN: Pirtobrutinib (LOXO-305, non-covalent BTKi) in R/R MCL

- First-in-human, multicenter, open-label phase I/II trial for R/R B-NHL (N = 323) including 61 patients with MCL



84% (76/90) of patients with >50% reduction

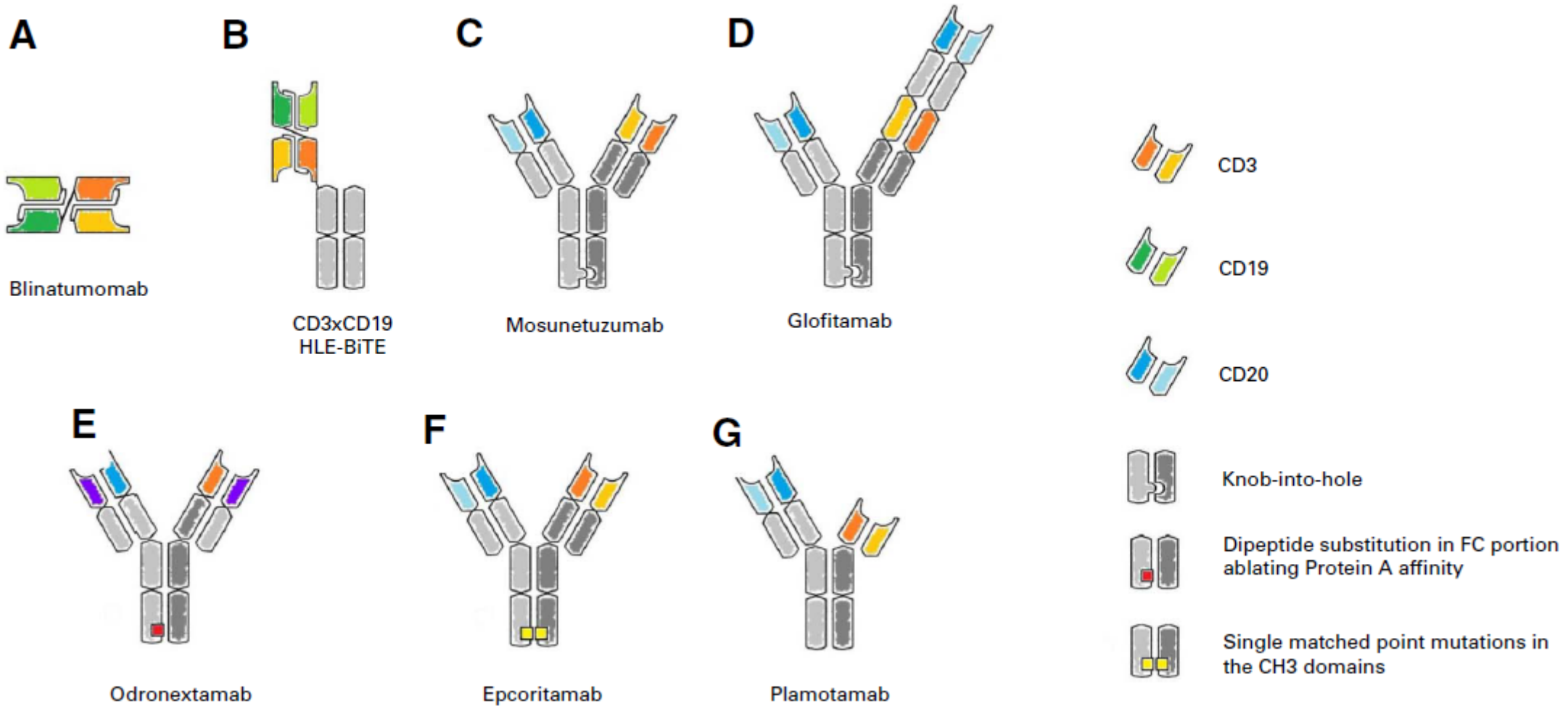


	Efficacy evaluable, n	Responders, n	ORR (%)	CR (%)
All MCL patients	56	29	52	25
MCL patients with prior BTKi exposure	52	27	52	25

**NEXT STEP: Phase III BRUIN-MCL-321: Pirtobrutinib vs Investigator's Choice of BTKi in R/R MCL

Mato et al., Lancet. 2021.

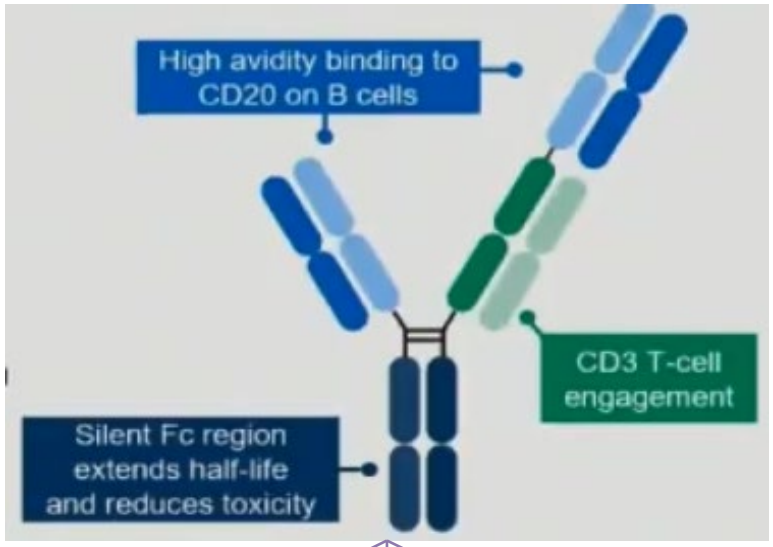
Bispecific Antibodies (BsAb) in B-cell Malignancies



Lussano et al., JCO 2021

Glofitamab (BsAb): R/R MCL - Efficacy

Basic Study Design

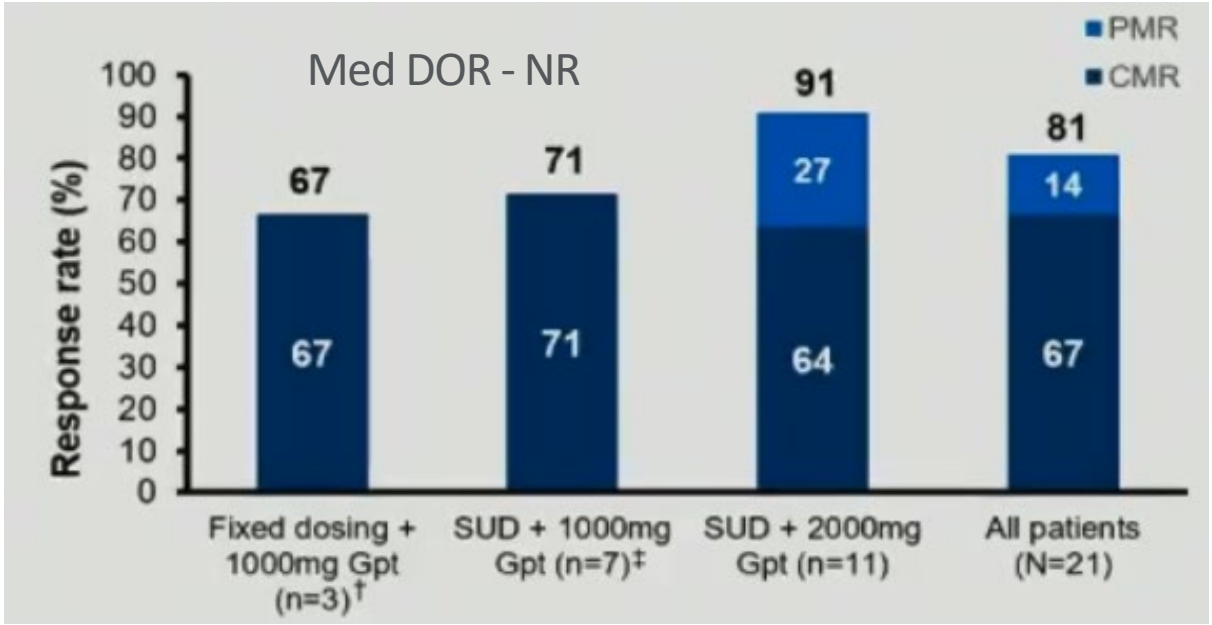


Glofitamab Fixed Dosing + 1000 mg GPT

Glofitamab SUD + 1000 mg GPT

Glofitamab SUD + 2000 mg GPT

Median F/U fixed dosing - ~ 26 mo; for all pts = 1.4 mo



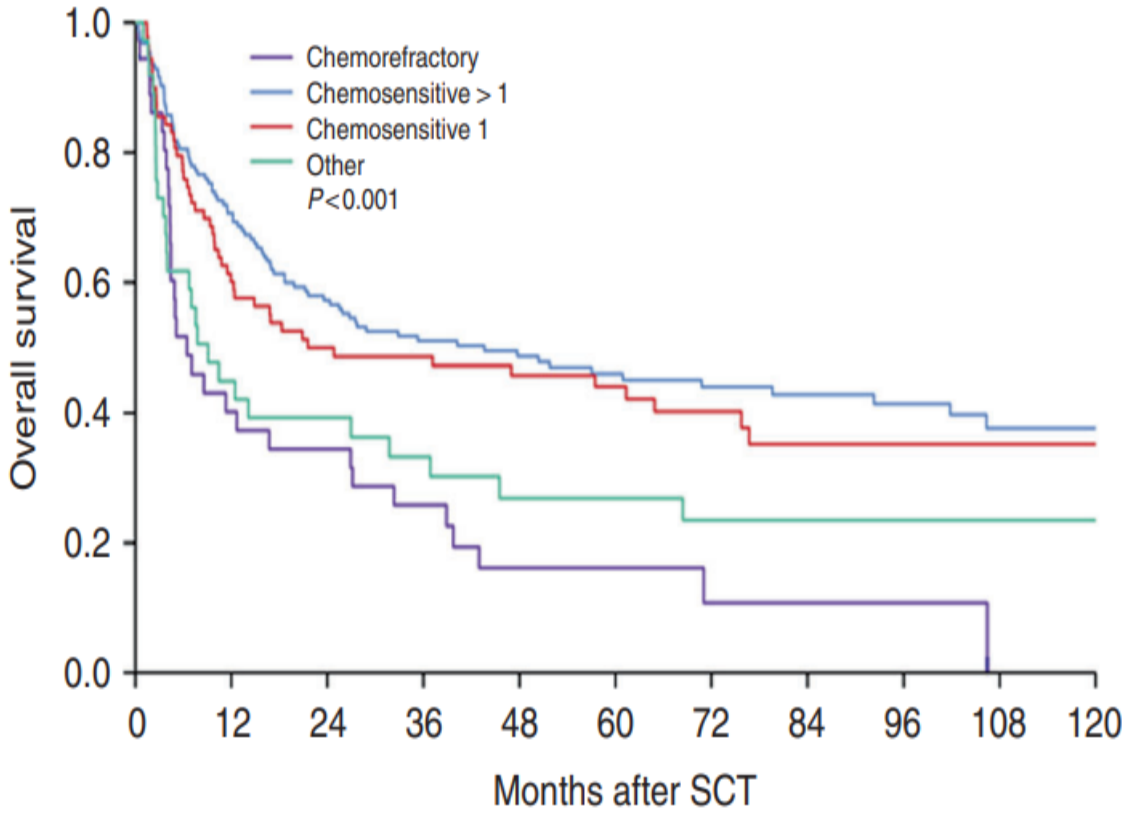
Response rates by prior BTKi therapy in pts with MCL receiving glofitamab*

	Prior BTKi therapy	
%	Yes (n=17)	No (n=4)
ORR	82.4	75.0
CMR	64.7	75.0
PMR	17.6	0

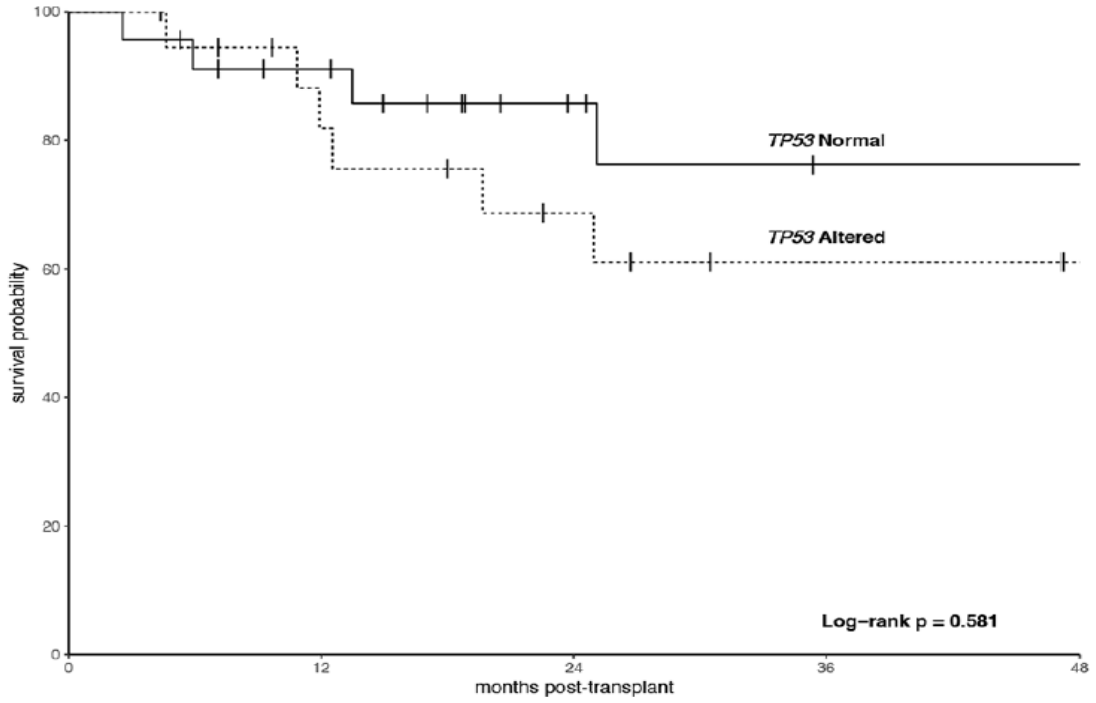
Phillips et al., ASH 2021 Abtr 130

Reduced Intensity Allo-SCT in R/R MCL

RIC allo-SCT in MCL by line of therapy

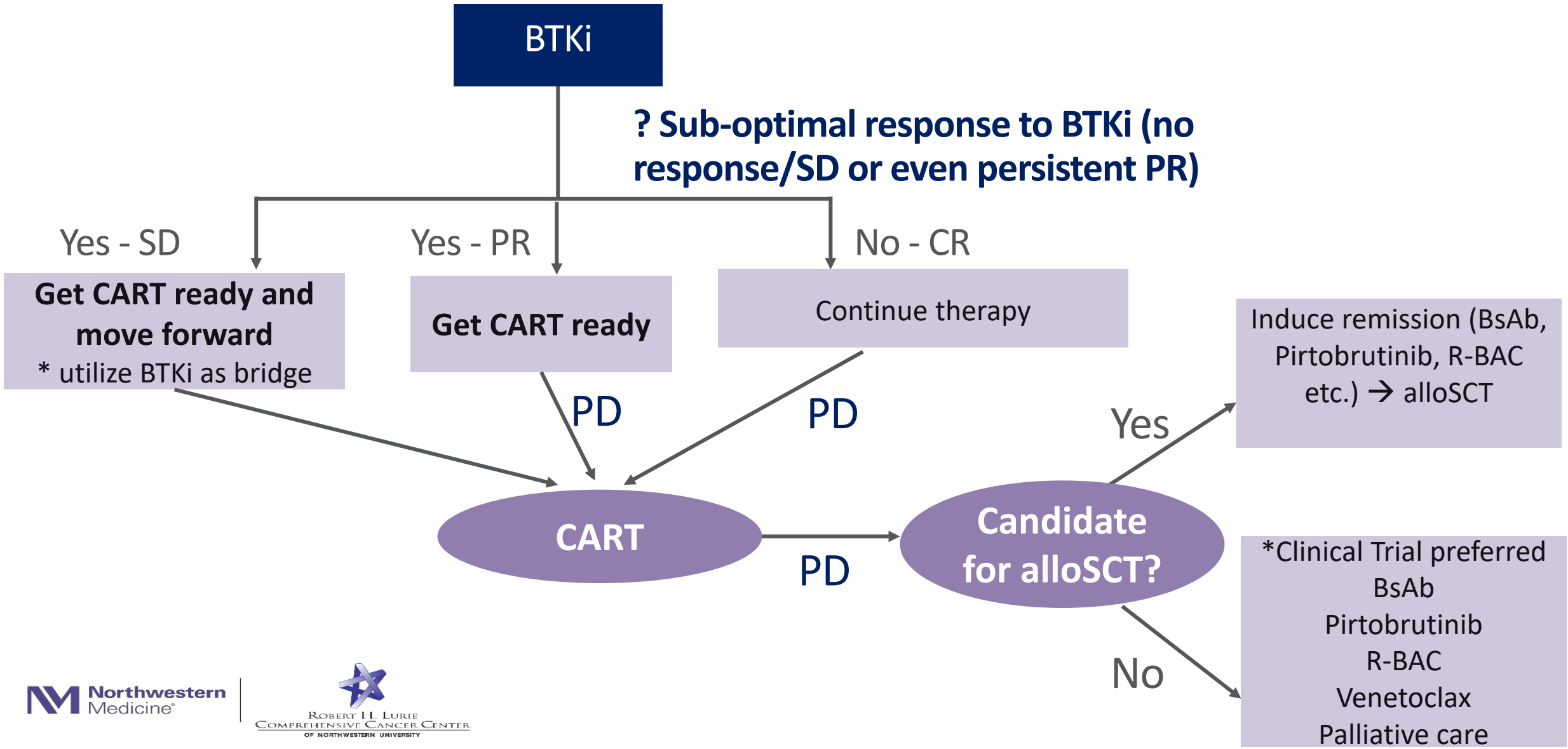


Relapsed MCL by *TP53* status



Robinson et al., BMT 2018; Lin et al., BJH 2019

Treatment Algorithm for R/R MCL



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THANKS!