Sequencing of therapy for a patient with *TP53*-mutated MCL

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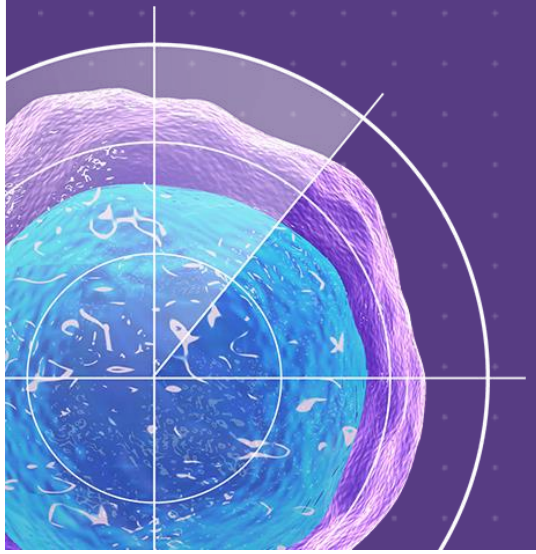


Disclosures

	Research funding	Consultancy
Celgene		√
Gilead–Kite		√
AstraZeneca		√
AbbVie	√	√
Roche		√
Janssen	√	√
Novartis		√
Loxo		√
BeiGene		√

Patients with *TP53*-mutated MCL at diagnosis

- 62-year-old male
- Bone marrow involvement: Yes (Stage IV)
- MIPI: Intermediate
- KI-67 expression: 30%
- Cyclin D1 positive
- *NOTCH1* mut: Yes
- *TP53* mut: Yes

First-line therapy:

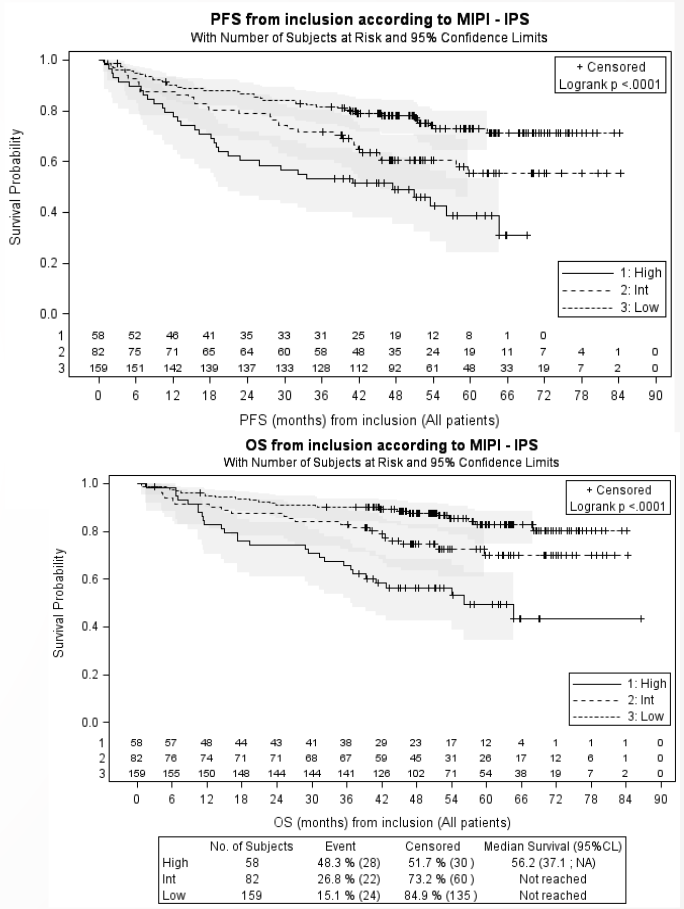
- R-DHAP
- ASCT
- Rituximab maintenance

Unfortunately, the patient relapsed.

High-risk factors (MD Anderson)

- Blastoid/pleomorphic histology
- *TP53* mutation or del17p
- Complex karyotype
- *MYC* positive by FISH
- Bulky tumor >7 cm and spleen >20 cm
- Ki-67 ≥30% in tissue biopsy

MIPI intermediate



Le Gouill S, et al. *NEJM.* 2017;377:1250-1260 (Supplementary Appendix).

ASCT, autologous stem cell transplantation; del17p, 17p deletion; FISH, fluorescent *in situ* hybridization; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; mut, mutated; OS, overall survival; PFS, progression-free survival; R-DHAP, rituximab + dexamethasone + high-dose cytarabine + cisplatin.

1 | What patient characteristics might influence treatment choice?

- Duration of response after transplantation
- p53 status
- Expected duration of response after iterative relapses

Outcomes in first R/R younger patients with MCL: MANTLE-FIRST

Figure 1. Early POD after ASCT (<2 years after initial diagnosis)†

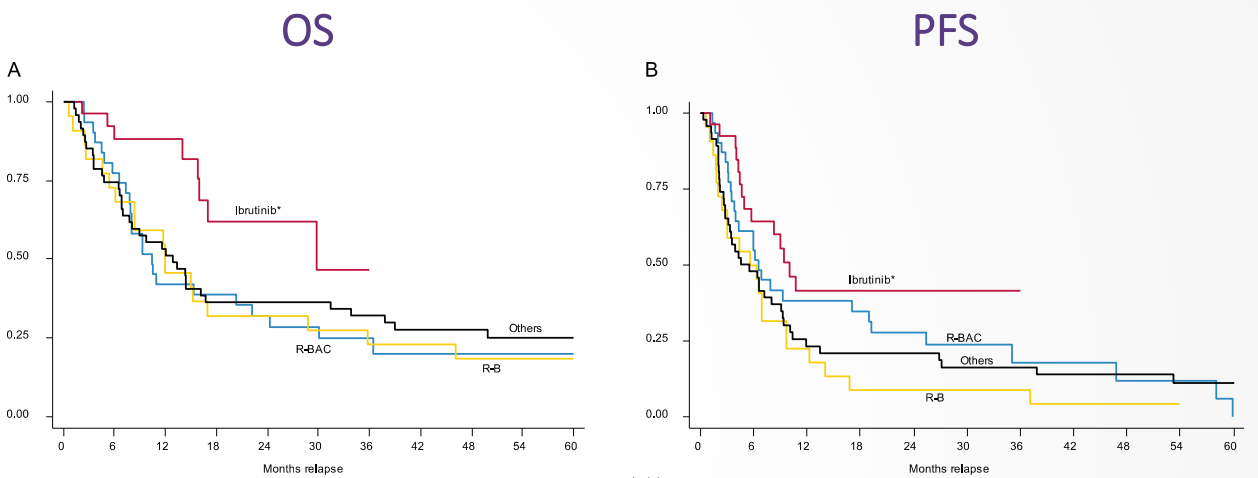
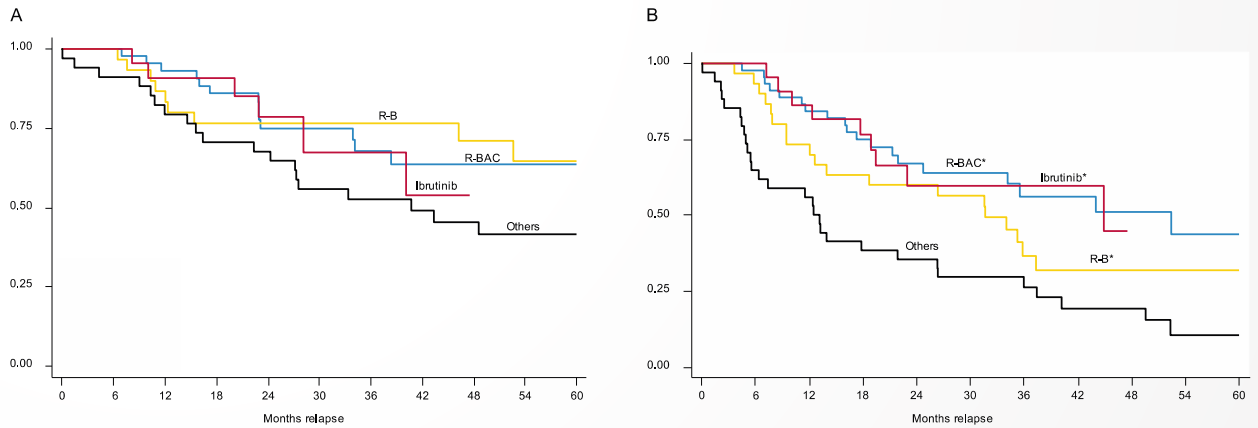


Figure 2. Late POD after ASCT (>2 years after initial diagnosis)‡



ASCT, autologous stem cell transplantation; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression-free survival; POD, progression of disease; R-B, rituximab + bendamustine; R-BAC, rituximab + bendamustine + cytarabine; R/R, relapsed or refractory.

*Statistically significant.

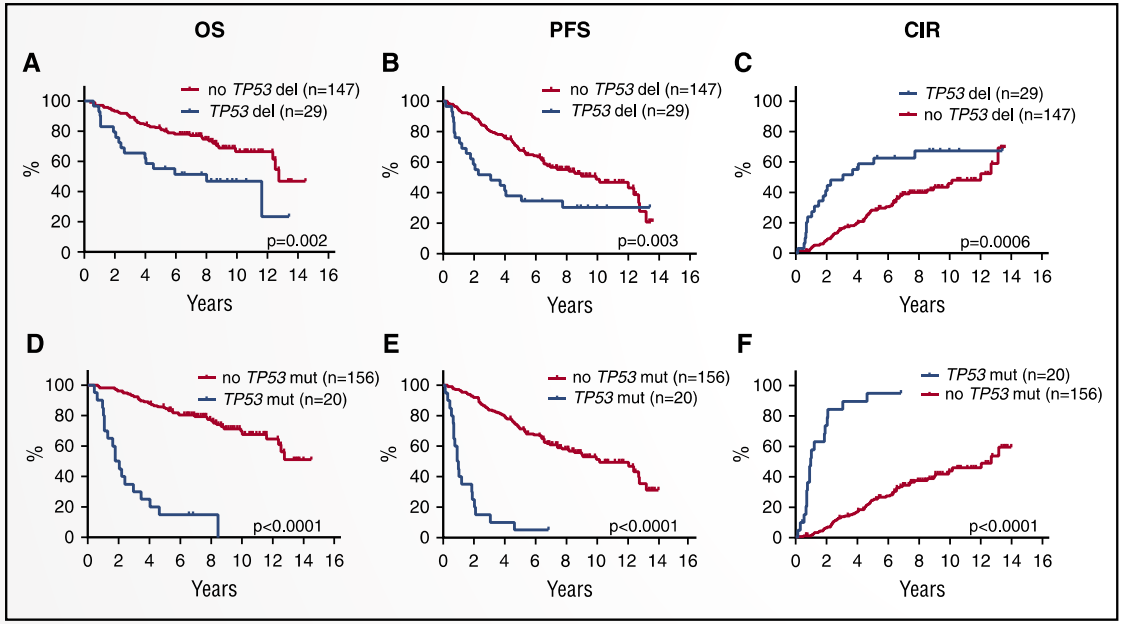
†**A** Ibrutinib *versus* R-B and R-BAC (P = 0.02); ibrutinib *versus* others (P = 0.03). **B** Ibrutinib *versus* R-B (P = 0.01); ibrutinib *versus* others (P = 0.02); ibrutinib *versus* R-BAC (P = 0.23).

‡**A** None of the differences between groups was statistically significant. **B** Ibrutinib *versus* others (P = 0.008); R-BAC *versus* others (P < 0.0001); R-B *versus* others (P = 0.02).

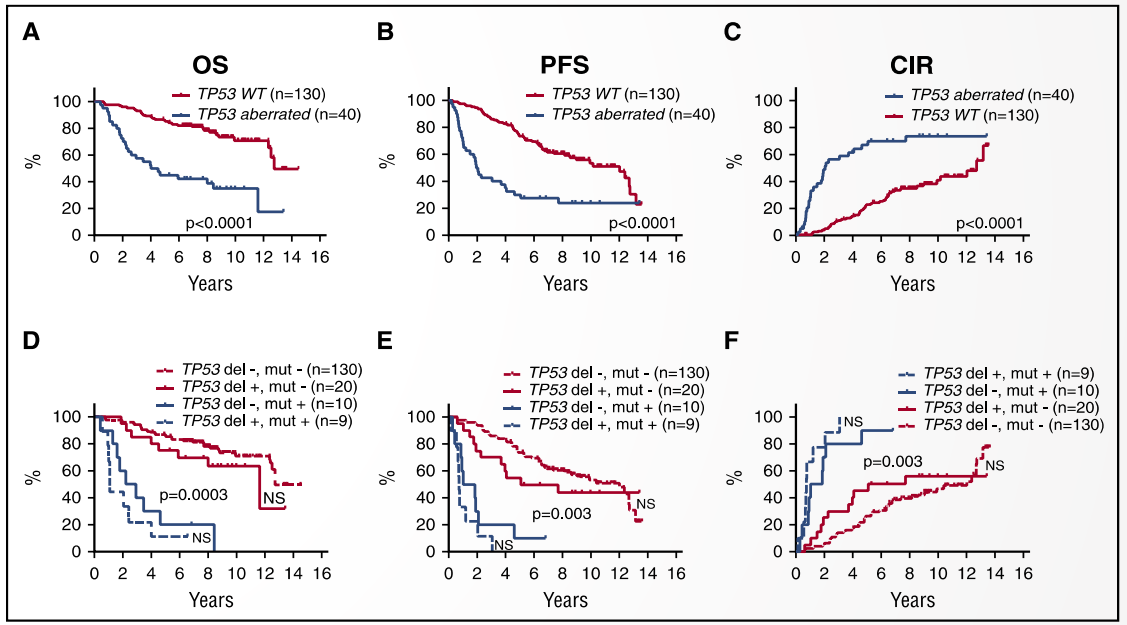
Visco C, et al. *Leukemia.* 2021;35:787-795.

TP53 mutations identify younger patients with MCL who do not benefit from intensive chemoimmunotherapy

TP53 del or mutation



TP53 abnormalities



CIR, cumulative incidence of relapse; del, deletion; MCL, mantle cell lymphoma; mut, mutated; OS, overall survival; NS, not significant; PFS, progression-free survival; WT, wildtype.

Eskelund CW, et al. *Blood.* 2017;130(17):1903-1910.

TP53 mutations identify younger patients with MCL who do not benefit from intensive chemoimmunotherapy

Multivariate Cox regression analyses (n = 147)

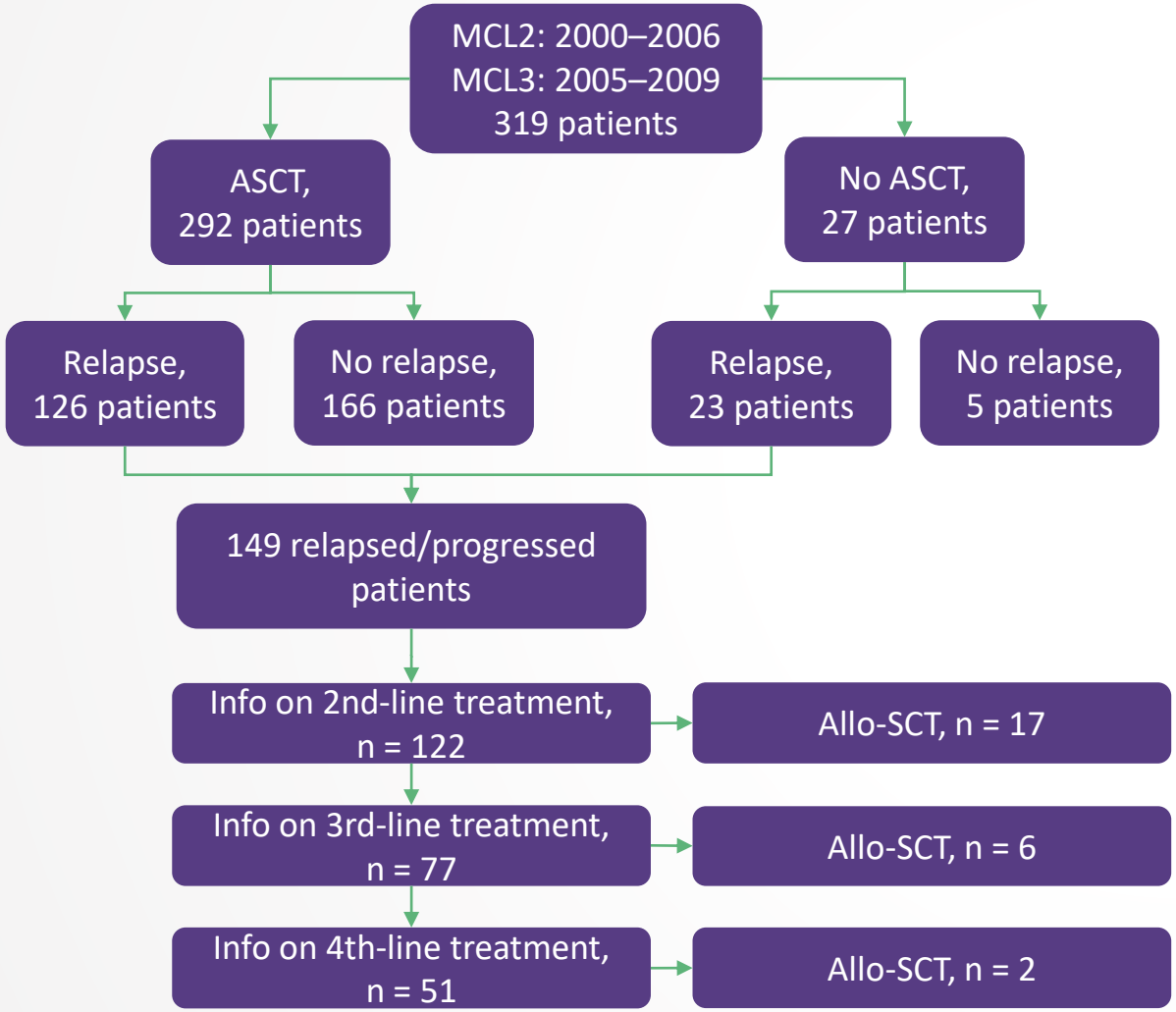
	OS			PFS			CIR		
Variables	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
mut *TP53*	6.2	2.6–14.9	<0.0001	6.8	3.4–13.8	<0.0001	6.9	3.3–14.5	<0.0001
mut *NOTCH1*	2.7	0.9–8.6	0.9	2.3	0.9–6.3	0.10	2.2	0.7–6.5	0.17
del *TP53*	1.4	0.7–2.8	0.37	1.5	0.9–2.7	0.15	1.7	0.9–3.0	0.10
del *CDKN2A*	1.3	0.6–2.7	0.55	1.3	0.7–2.4	0.40	1.3	0.7–2.5	0.43
Blastoid	1.3	0.6–2.5	0.53	0.8	0.4–1.6	0.62	0.9	0.4–1.7	0.65
MIPI-c high-risk*	1.8	0.9–3.9	0.11	2.2	1.2–4.0	0.01	2.6	1.4–4.9	0.003
mut *WHSC1*[†]	0.8	0.3–1.9	0.58	—	—	—	—	—	—

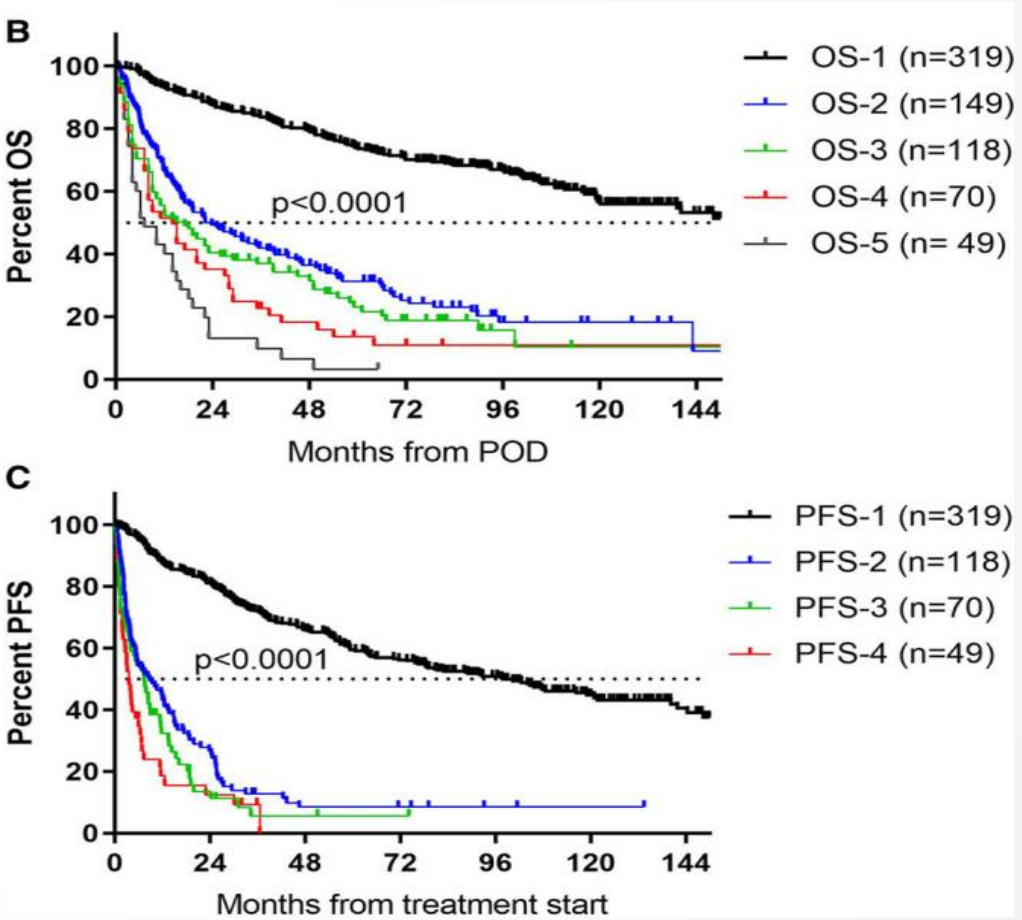
*MIPI-c index included as a bimodal variable of MIPI-c high-risk or not.
[†]*WHSC1* mutations only included for OS, as they did not show significant prognostic effect for PFS and CIR in univariate analyses.

CI, confidence interval; CIR, cumulative incidence of relapse; del, deletion; HR, hazard ratio; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; mut, mutated; OS, overall survival; PFS, progression-free survival.

Eskelund CW, et al. *Blood.* 2017;130 (17):1903-1910.

Long-term follow-up of patients who relapsed after MCL2 and MCL3 trials





Allo-SCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression-free survival.

Eskelund CW, et al. *Hemasphere.* 2020;5(1):e510.

2 | Currently available treatment options

- Standard chemotherapy
- BTKi alone
- Allo-SCT consolidation

Allo-SCT, allogeneic stem cell transplant; BTKi, Bruton’s tyrosine kinase inhibitor.

Outcomes in first R/R younger patients with MCL: MANTLE-FIRST

- For early POD-transplanted patients with MCL, ibrutinib prolongs OS.
- For late POD-transplanted patients with MCL, R-B = R-BAC = ibrutinib.

Figure 1. Early POD after ASCT (<2 years after initial diagnosis)†

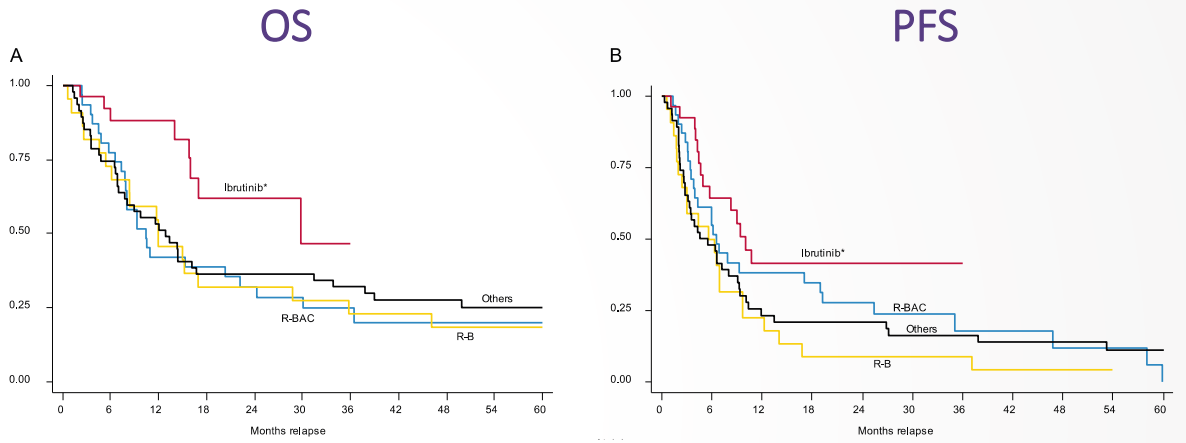
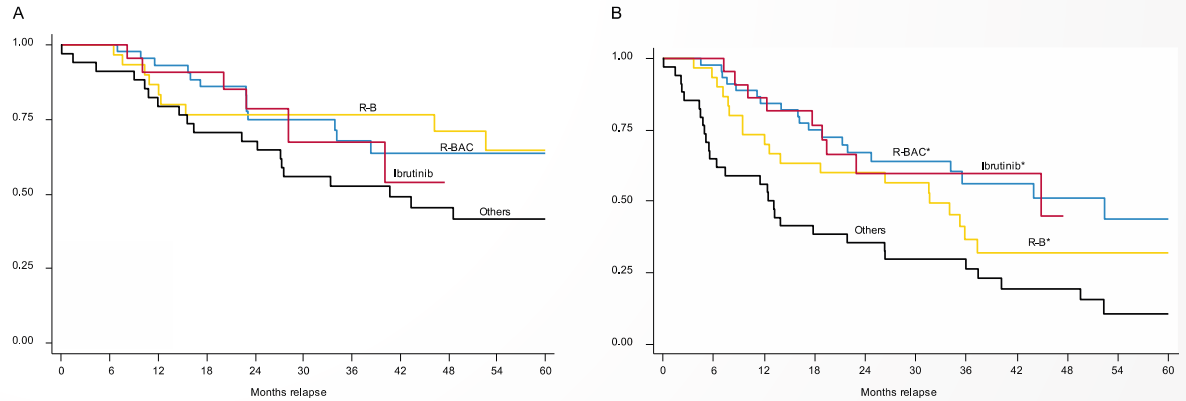


Figure 2. Late POD after ASCT (>2 years after initial diagnosis)‡



ASCT, autologous stem cell transplantation; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression-free survival; POD, progression of disease; R-B, rituximab plus bendamustine; R-BAC, R-B plus cytarabine.

*Statistically significant.

†**A** Ibrutinib *versus* R-B and R-BAC (P = 0.02); ibrutinib *versus* others (P = 0.03). **B** Ibrutinib *versus* R-B (P = 0.01); ibrutinib *versus* others (P = 0.02); ibrutinib *versus* R-BAC (P = 0.23).

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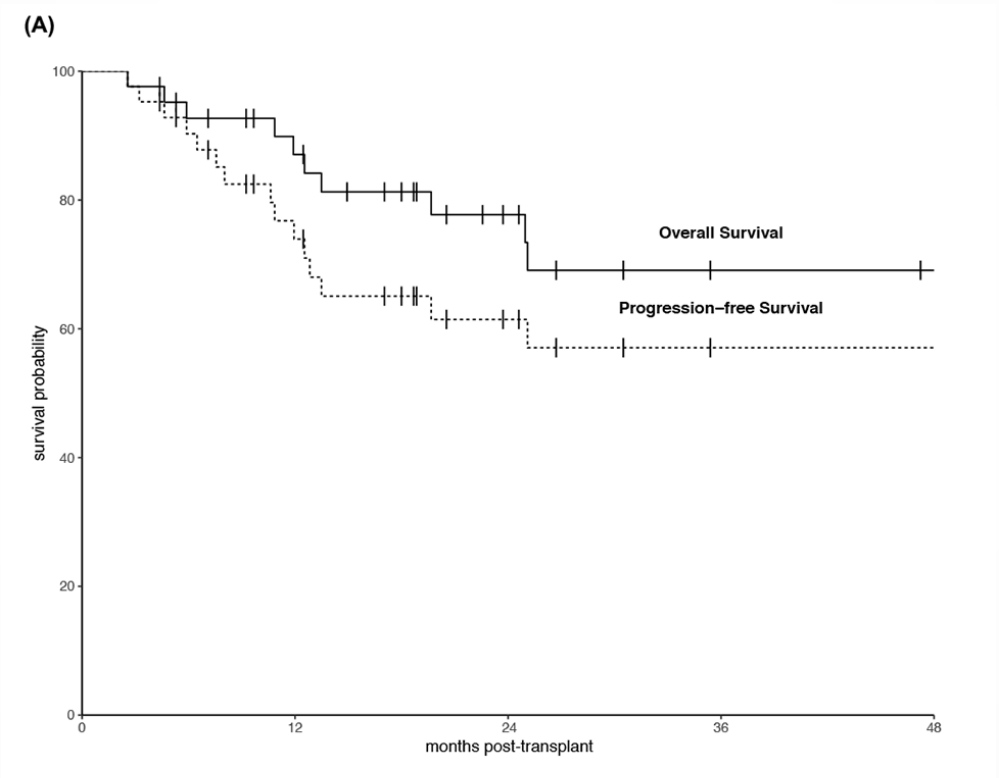
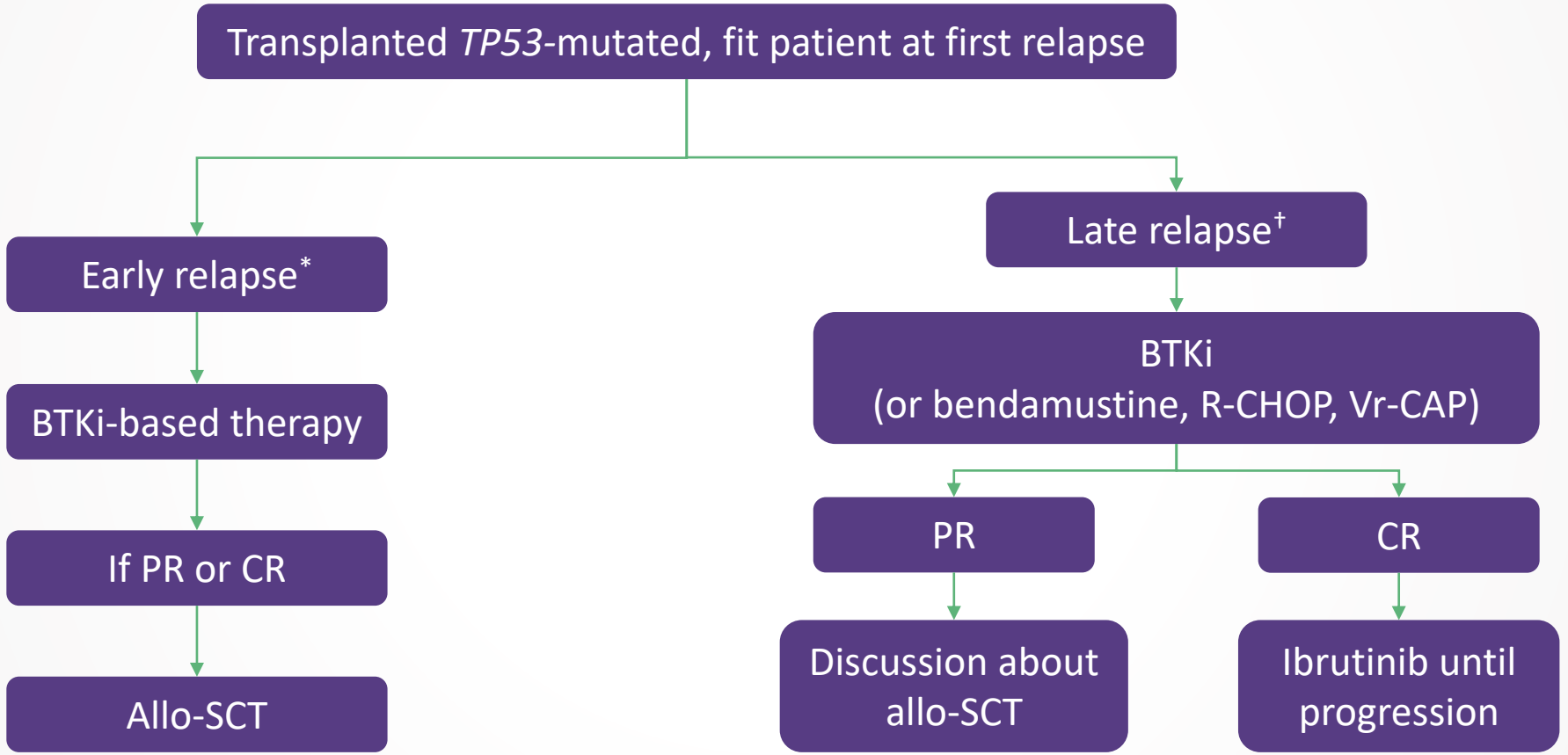
Visco C, et al. *Leukemia.* 2021;35(3):787-795.

Allo-HCT impacts on outcomes of MCL with *TP53* alterations



Allo-HCT, allogeneic hematopoietic cell transplantation; MCL, mantle cell lymphoma.
Lin R, et al. *Br J Haematol.* 2019;184(6):1006-1010.

How I would treat this patient in 2021



Allo-SCT, allogeneic stem cell transplant; BTKi, Bruton's tyrosine kinase inhibitor; CR, complete response; PR, partial response; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; Vr-CAP, bortezomib + rituximab + cyclophosphamide + epirubicin + prednisone.

*Primary refractory (progression of disease during induction, or within 6 months of induction) or disease progression between 6- and 24-months post-treatment.

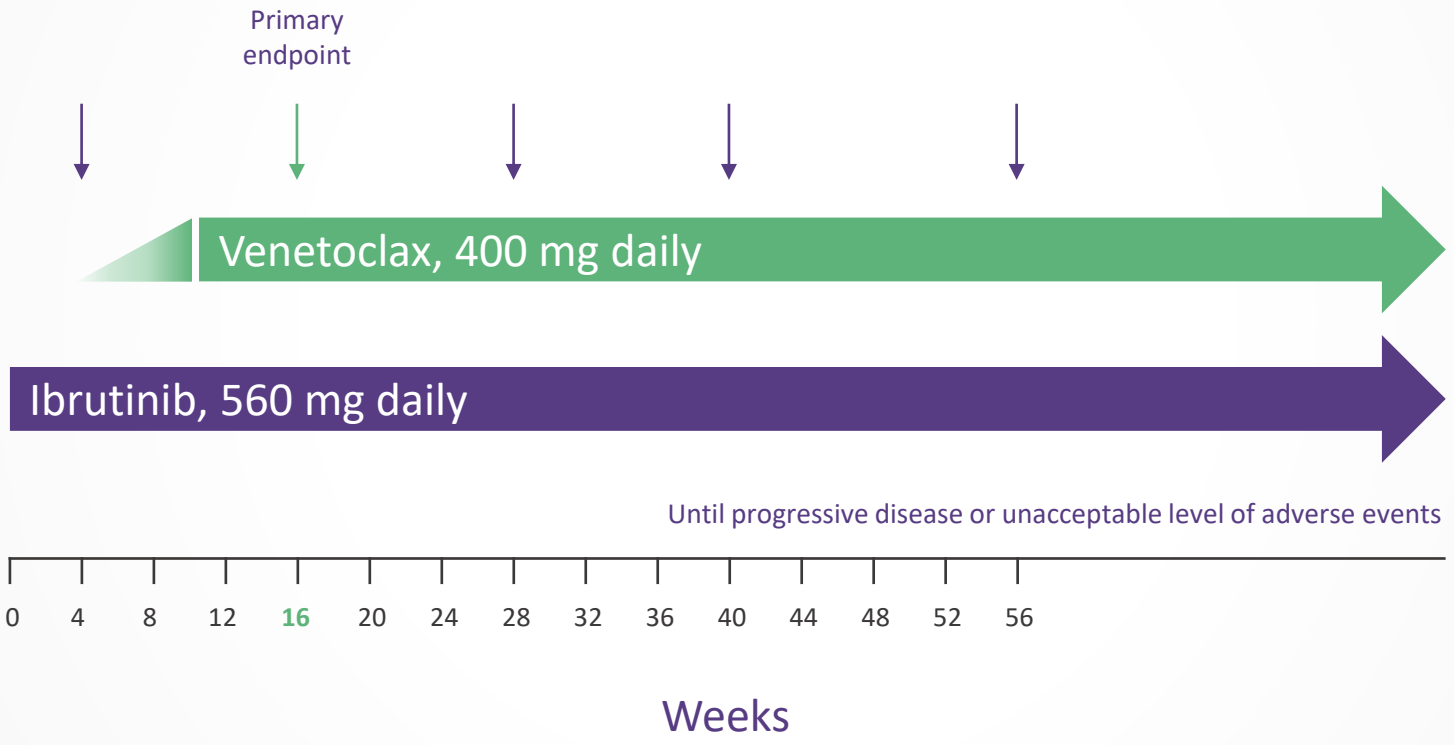
†Disease progression > 24 months following treatment.

3 | New agents that have the potential to be effective in MCL

- BTKi combination (AIM trial, OAsIs trial)
- CAR-T
- Other: MALT-1 inhibitor, PI3K inhibitor, Bcl-2 inhibitor, bispecific antibodies

Bcl-2, B-cell lymphoma 2; BTKi, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T cells; MCL, mantle cell lymphoma; PI3K, phosphoinositide 3-kinase.

Ibrutinib plus venetoclax (AIM trial)



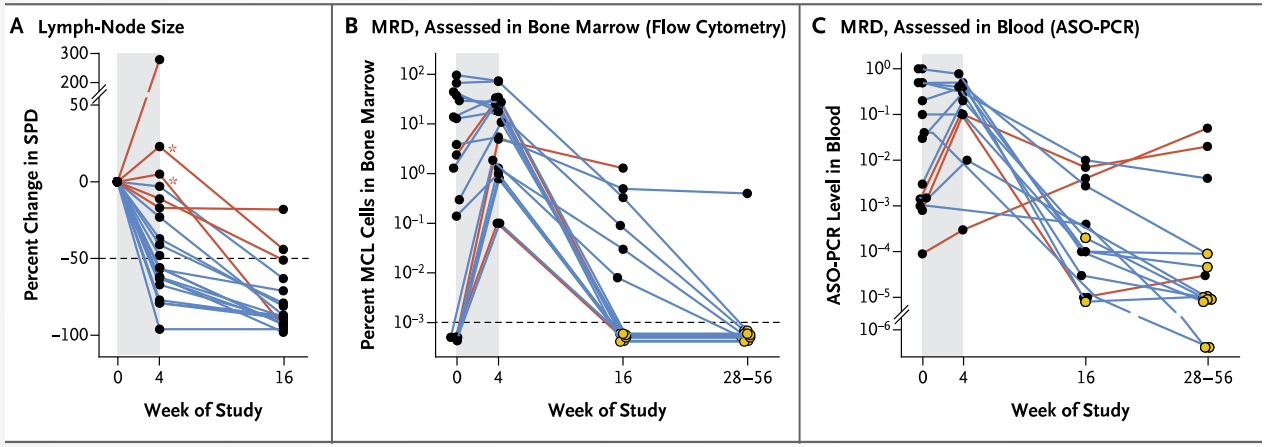
Tam C, *et al. N Engl J Med.* 2018;378:1211-1223.

Ibrutinib plus venetoclax (AIM trial)

TP53 status, number (%)	
Mutated with deletion	4 (17)
Mutated without deletion	7 (29)
Deleted without mutation	1 (4)

"Of the 12 patients who had a *TP53* mutation or deletion, 6 (50%) had a CR, with 5 remaining progression-free for 13–20 months at the time of the analysis."

Kinetics of response and clearance of MRD



Next step for R/R MCL:

Sympatico trial MCL

Ibrutinib *vs* ibrutinib + venetoclax

ASO-PCR, allele-specific oligonucleotide–polymerase chain reaction; CR, complete response; MCL, mantle cell lymphoma; MRD, measurable residual disease; R/R relapsed or refractory; SPD, sum of perpendicular diameters.

*Two patients who developed tumor lysis syndrome after the addition of venetoclax at a dose of 50 mg per day in Week 5.

Tam C, *et al. N Engl J Med.* 2018;378:1211-1223.

Ibrutinib, venetoclax plus obinutuzumab (OAsIs trial)

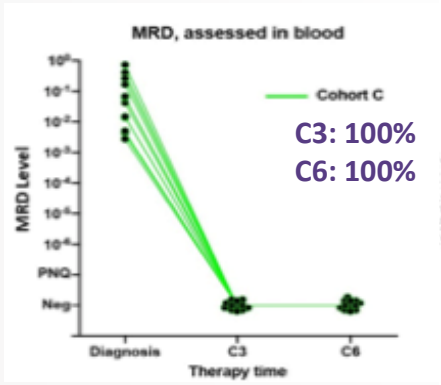
	Cycle 1				Cycle 1 bis				Cycle 2				Cycles	Maintenance	Until progression
Baseline	**W1**	**W2**	**W3**	**W4**	**W1**	**W2**	**W3**	**W4**	**W1**	**W2**	**W3**	**W4**	**C3–C6**	**C7–C23**	
Ibrutinib (560 mg/d)	D2														
Obinutuzumab (1 g)	D1	D8	D15		D1				D1				D1 each cycle	D1 every 2 cycles from C8	
Venetoclax (mg/d)					20	50	100	200	400	400	400	400			

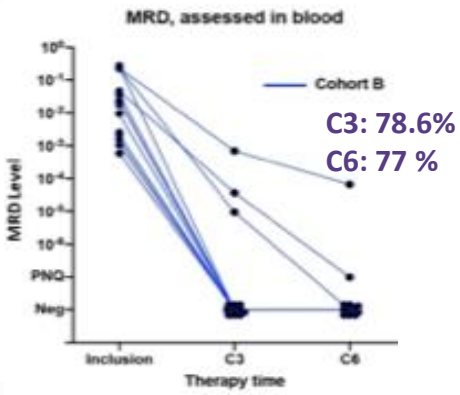
Bis, cycle 1b; C, cycle; D, day; W, week.

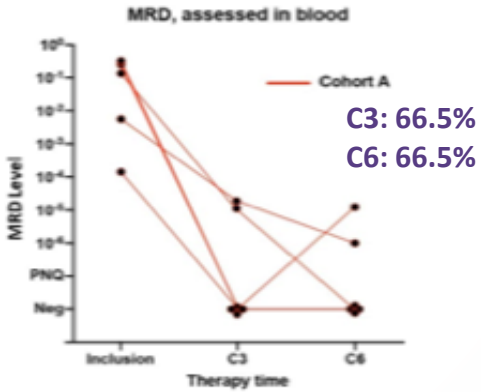
Le Gouill S, et al. *Blood.* 2019;134(Supplement_1):1530.

MRD by ASO-PCR in each cohort

Patients	Newly diagnosed	Relapsed	Relapsed
	Ibrutinib **Obinutuzumab** **Venetoclax**	**Ibrutinib** **Obinutuzumab** **Venetoclax**	**Ibrutinib** **Obinutuzumab**







Next step for <u>untreated</u> MCL:

OAsIs 2 trial

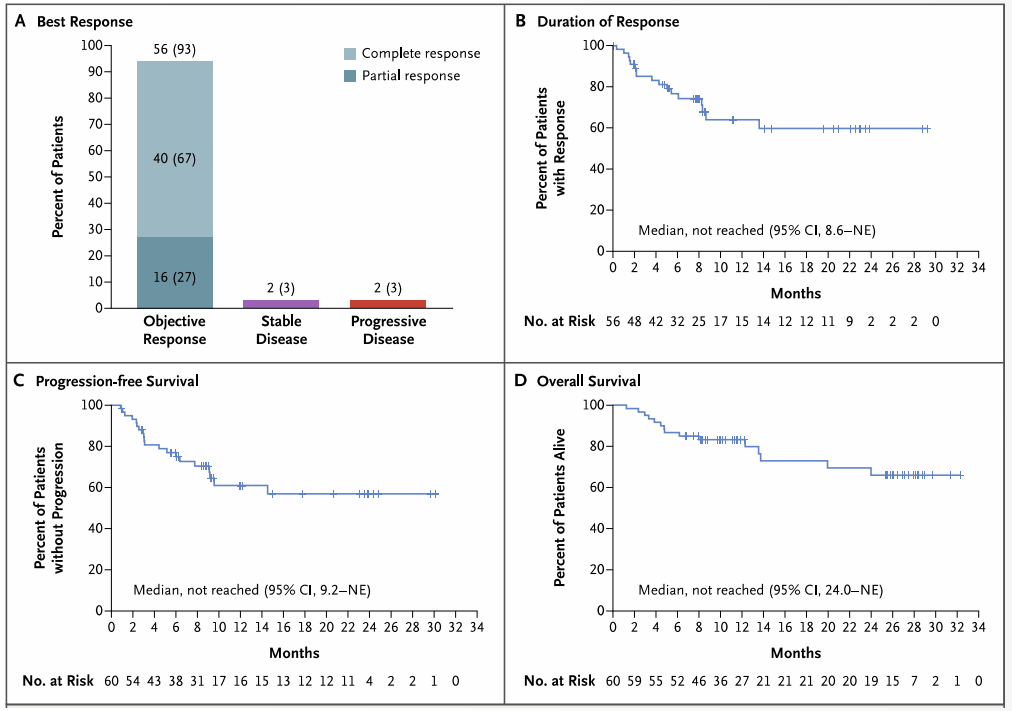
Ibrutinib/CD20 Ab *vs*
ibrutinib/venetoclax/CD20
(randomized, phase 2, >18years)

Ab, antibody; ASO-PCR, allele-specific oligonucleotide–polymerase chain reaction; C, cycle; MCL, mantle cell lymphoma; MRD, measurable residual disease.
Le Gouill S, et al. Blood. 2021;137(7):877-887.

CAR T-cell therapy for R/R MCL

Characteristic	Patients
Median age (range), years	65 (38–79)
Intermediate or high risk according to Simplified MIPI, number (%)*	38 (56)
Blastoid or pleomorphic morphologic characteristics of MCL, number (%)	21 (31)
Ki-67 proliferation index ≥30%, number/total number (%)*	40/49 (82)
TP53 mutation, number (%)	6/36 (17)

*Assessed at time of diagnosis.



Subgroup	No. of Patients	No. of Patients with Response	Percent of Patients with Objective Response (95% CI)
TP53 mutation detected			
Yes	6	6	100 (54–100)
No	30	30	100 (88–100)

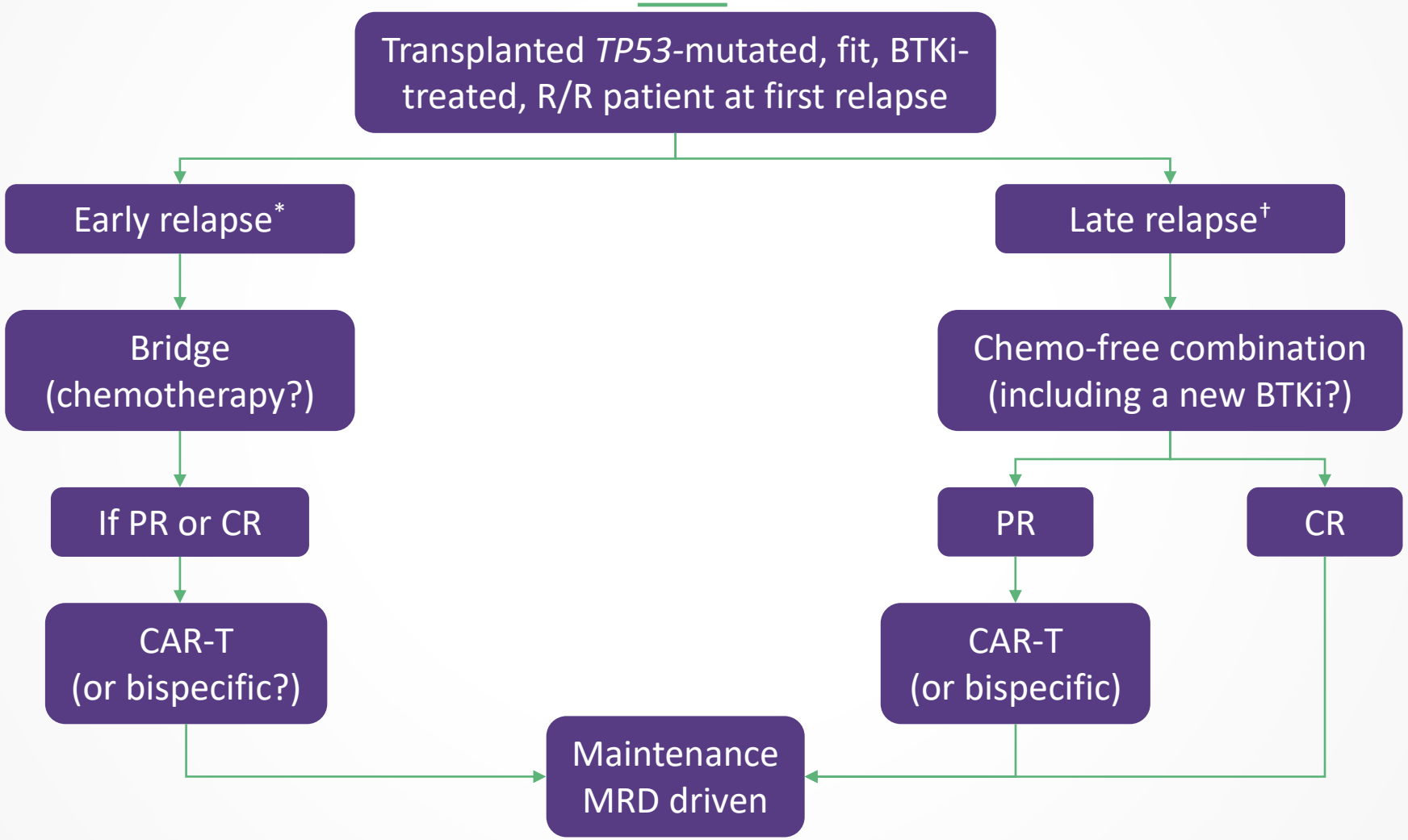
CAR, chimeric antigen receptor; CI, confidence interval; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; NE, non estimable; R/R relapsed or refractory.
Wang M, et al. *N Engl J Med.* 2020;382:1331-1342.

3 | New agents that have the potential to be effective MCL

- BTKi combination (AIM trial, OAsIs trial)
- CAR-T
- **Other: MALT-1 inhibitor, PI3K inhibitor, Bcl-2 inhibitor, bispecific antibodies**

Bcl-2, B-cell lymphoma 2; BTKi, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T cells; MCL, mantle cell lymphoma; PI3K, phosphoinositide 3-kinase.

How I will treat this patient in 202X



BTKi, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T cells; CR, complete response; MRD, measurable residual disease; PR, partial response; R/R, relapsed or refractory.
*Primary refractory (progression of disease during induction, or within 6 months of induction) or disease progression between 6- and 24-months post-treatment.
†Disease progression > 24 months following treatment.

Conclusion

- *TP53* abnormalities are a bad prognostic marker
- Short POD is a strong prognostic marker
- There is no consensus about *TP53*-driven therapy
- Short POD *TP53*-mut patients should be considered for allo-SCT and innovative strategies
- Long POD *TP53*-mut patients should be treated with BTKi at first relapse
- BTKi-based therapy will be used frontline in coming years, thus new strategies based on tumor MCL cell biology will have to emerge in the near future
- Future directions:
  - BTKi-based combos will be used frontline for all patients, including *TP53*-mut patients
  - Early use of cell therapy such as CAR-T
  - Use MRD-driven maintenance
  - Use pre-emptive of relapse treatment

allo-SCT, allogeneic stem cell transplant; BTKi, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T cells; MCL, mantle cell lymphoma; MRD, measurable residual disease; mut, mutated; POD, progression of disease.

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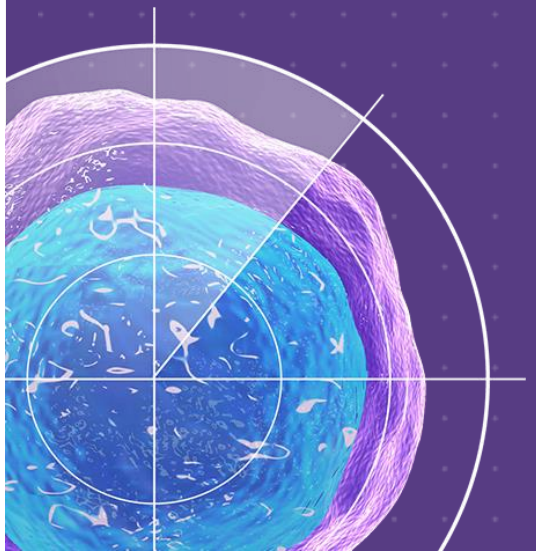
Thank you



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