2nd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 13-14, 2021

Starhotels Majestic

Scientific board:
Marco Ladetto (Alessandria)
Umberto Vitolo (Candiolo-TO)

Mantle Cell Lymphoma

How I treat relapsed/refractory Mantle Cell Lymphoma

C. Visco

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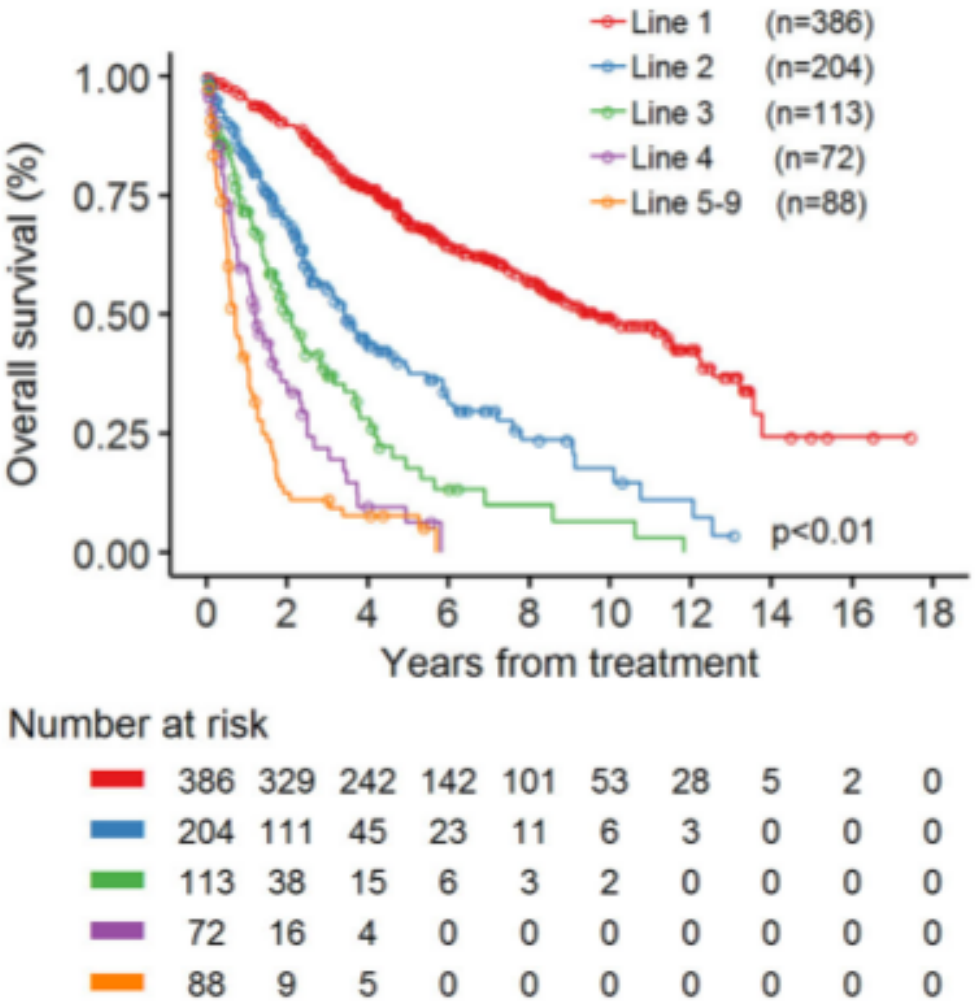
Disclosures of CARLO VISCO

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie	X		x		X	X	
Kite-Gilead						X	
Janssen	x		x		X	X	
Gentili					X	X	
Novartis						X	
Pfizer			x		x	x	
Roche						X	
Incyte						x	
Servier					x		

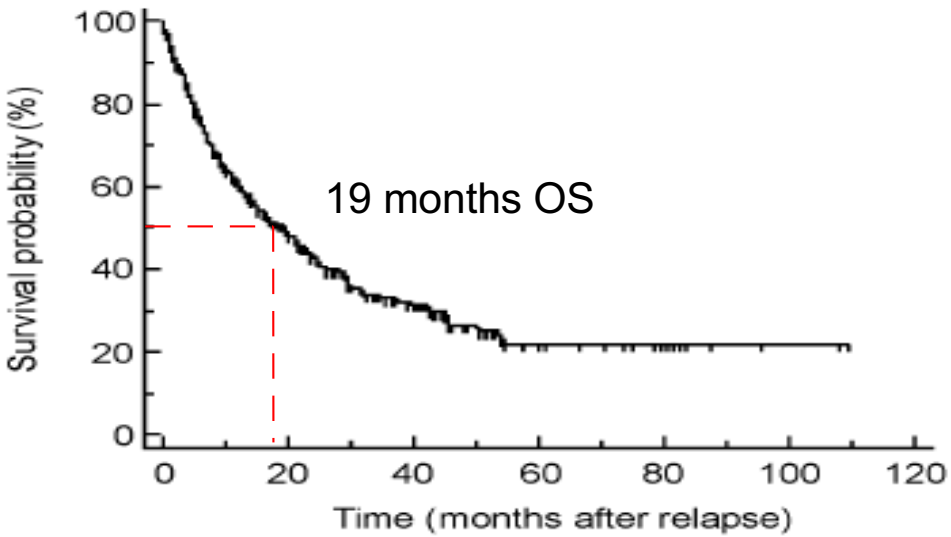
Life expectancy and number of previous lines



Kumar et al. Blood Cancer Journal 2019

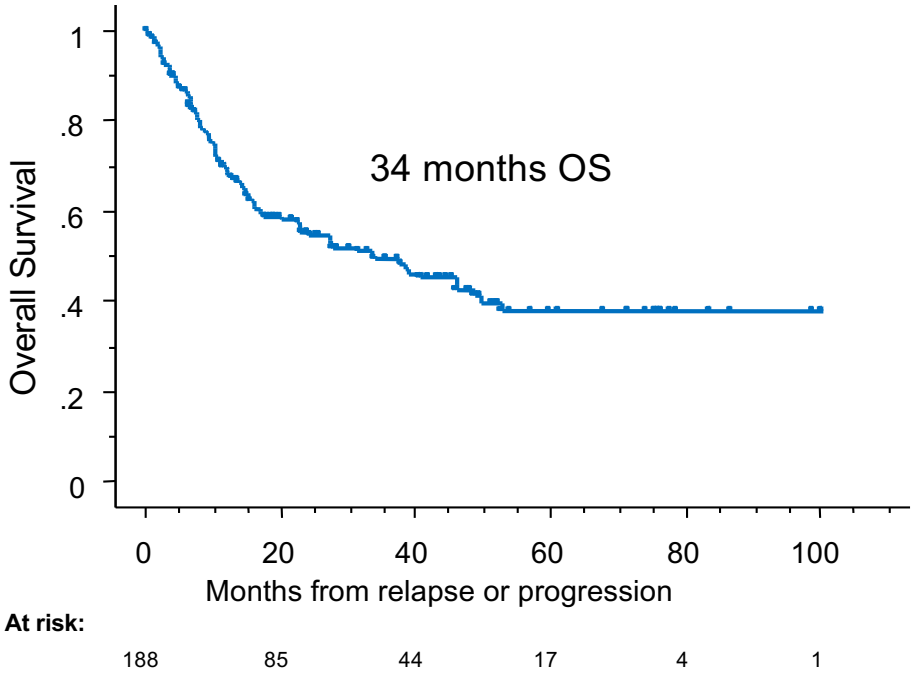
Patients relapsed after Auto transplant

Previous versus modern therapeutic era (HD-AraC, Benda, BTK-i etc)



EBMT registry 2000-2009 (n=360)

Dietrich S, Ann Oncol 2014



FIL study 2007-2017 (n=188)

Visco C, BJH 2019

Relapsed setting

How I treat patients at first relapse (Time to POD)

Difficult scenarios, tumor biology:

-TP53 mutations
-What to do when ibrutinib fails
-CAR T-cell therapy
-Still a role for allogeneic transplant?

Relapsed setting

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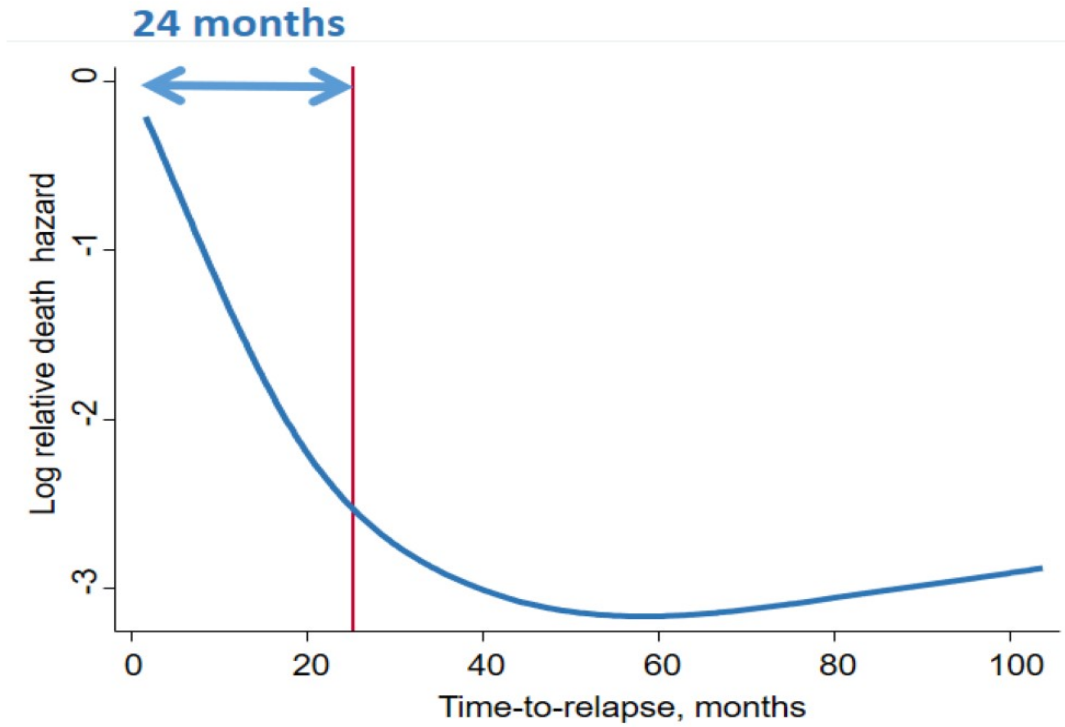
Definition of early POD

Trend in the risk of death*



First relapsed or refractory younger pts

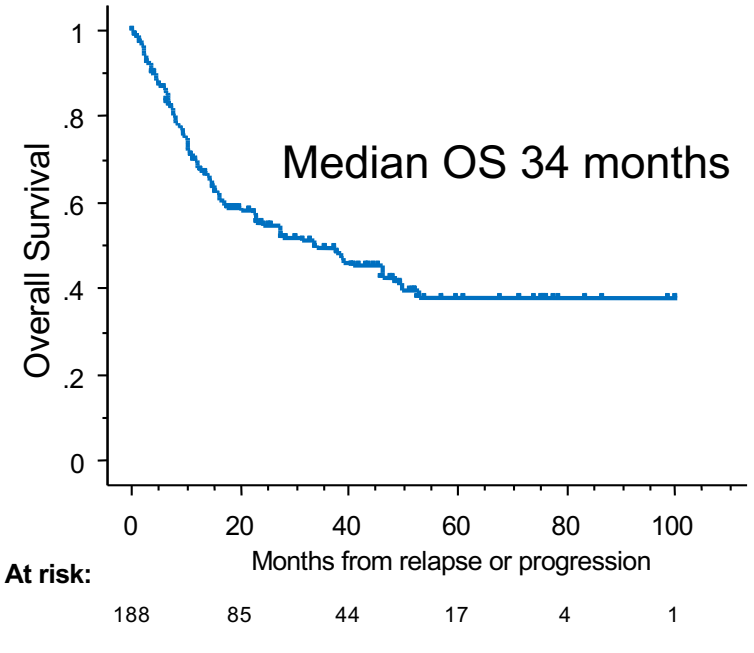
Visco et al, BJH 2018

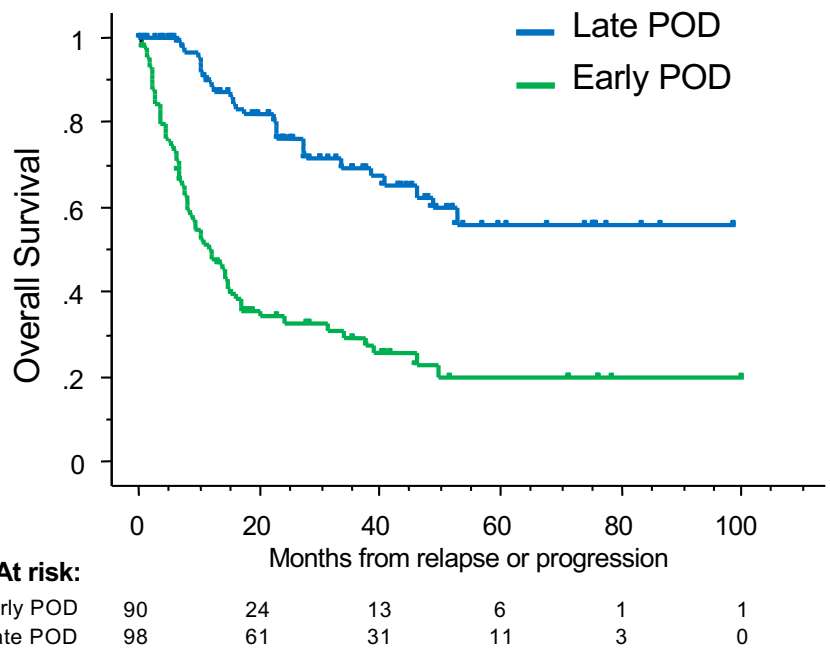
*linear regression model using restricted cubic splines to test the hypothesis that the relationship between time from MCL initial diagnosis to POD and survival was not linear but could be usefully summarized by a linear relationship

Survival from first relapse/progression

Rituximab + HD-AraC treated ± ASCT

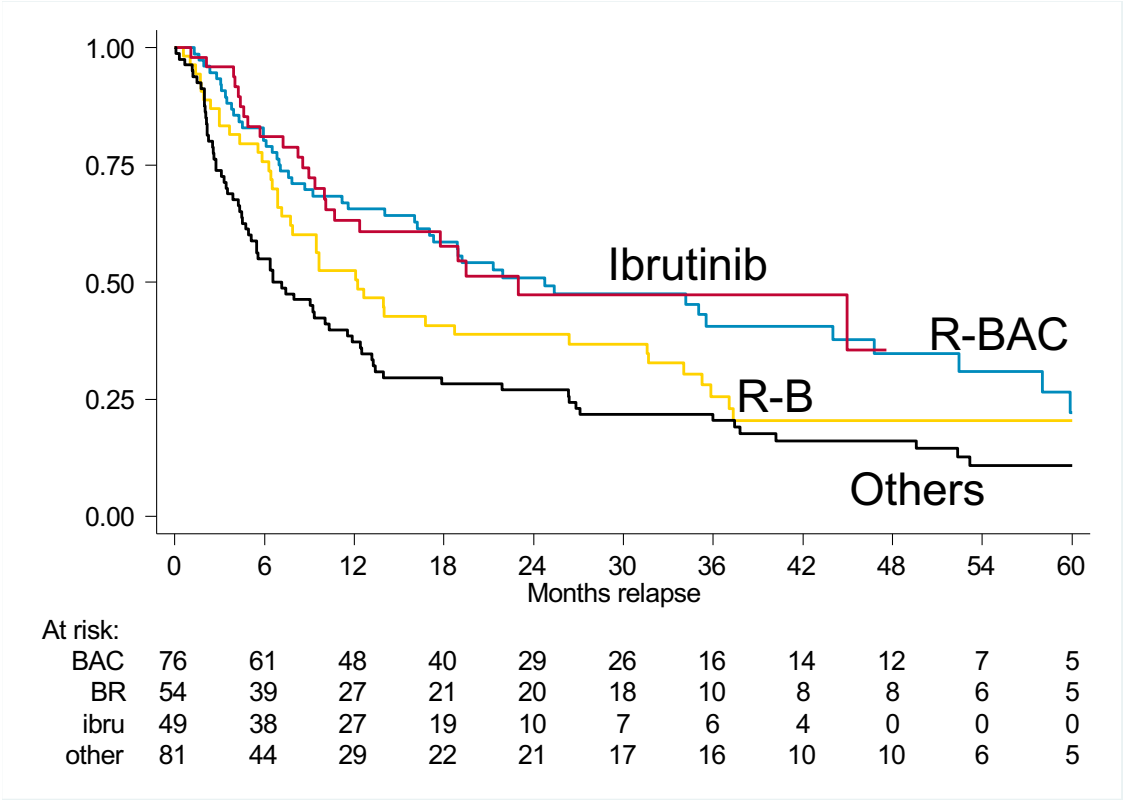
POD-24





Visco et al, Br J Haematol 2019

PFS according to second line therapy



Ibrutinib [PFS 24 (10-nr)]

R-BAC [PFS 25 (8-47)]

R-B [PFS 13 (3-26)]

Other regimens [PFS 7 (2-12)]

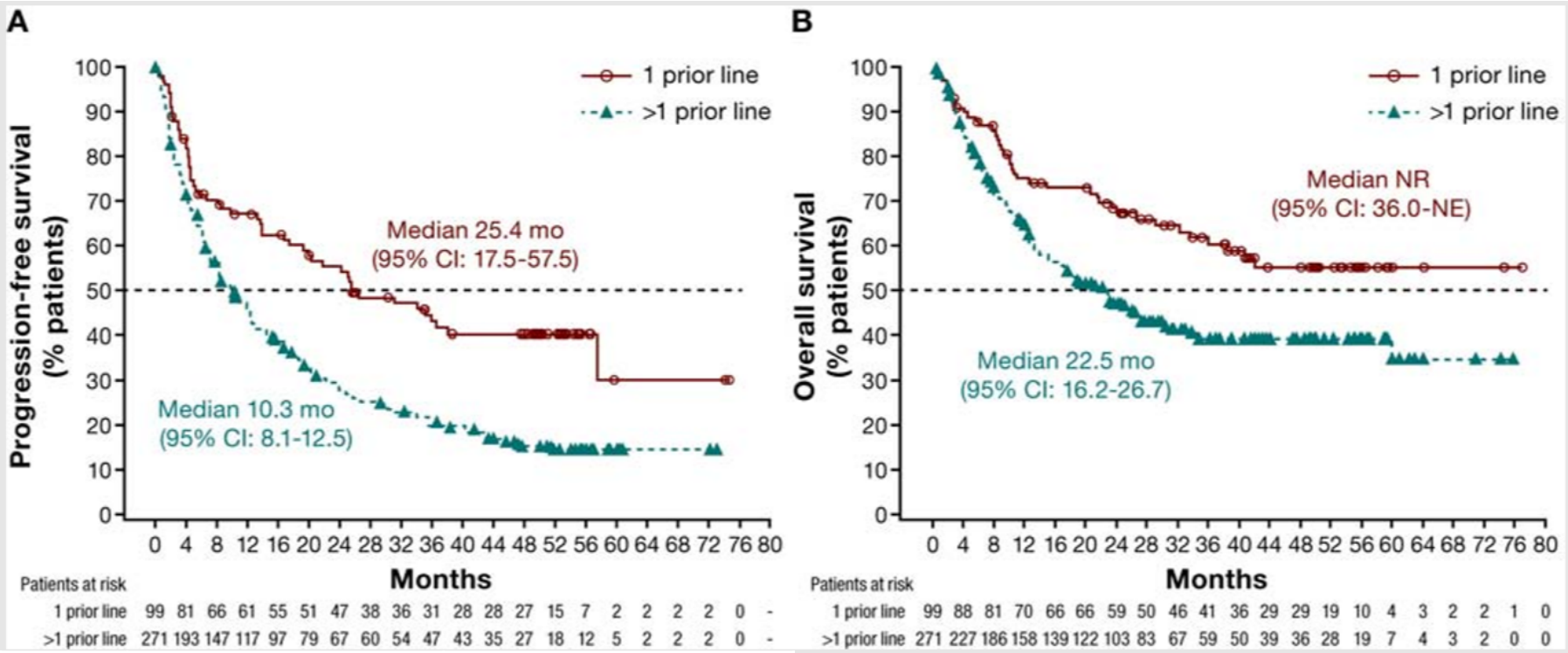
P=0.001
P=0.0002

First-relapsed younger patients

P=0.11 between R-BAC and R-B; p=0.07 between ibrutinib and R-B;
p=0.86 between ibrutinib and R-BAC; p=0.06 between R-B and other regimens

Visco et al, Leukemia 2020

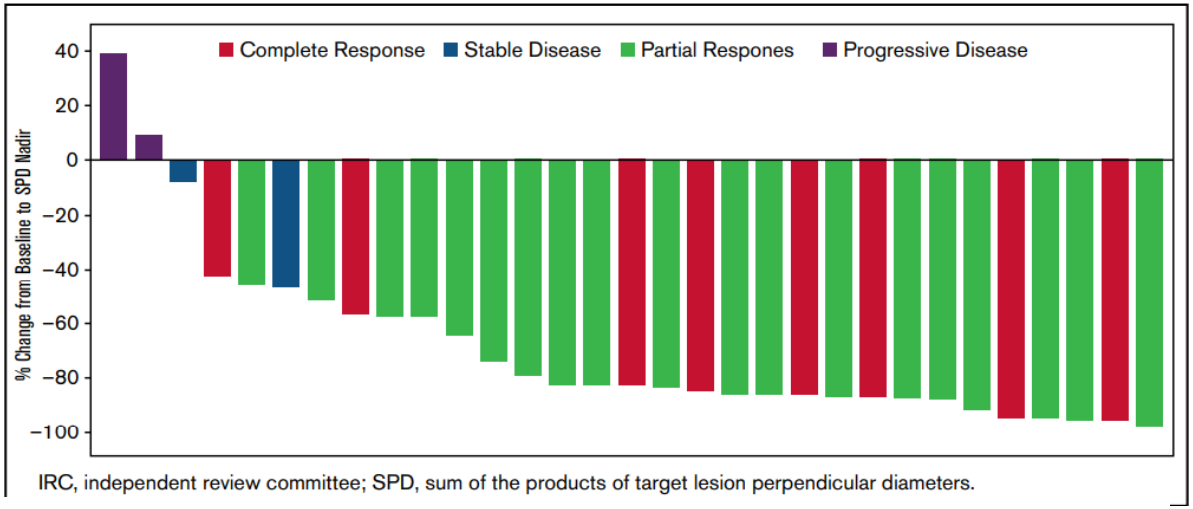
Ibrutinib: 1 Prior Line versus others (370 patients)



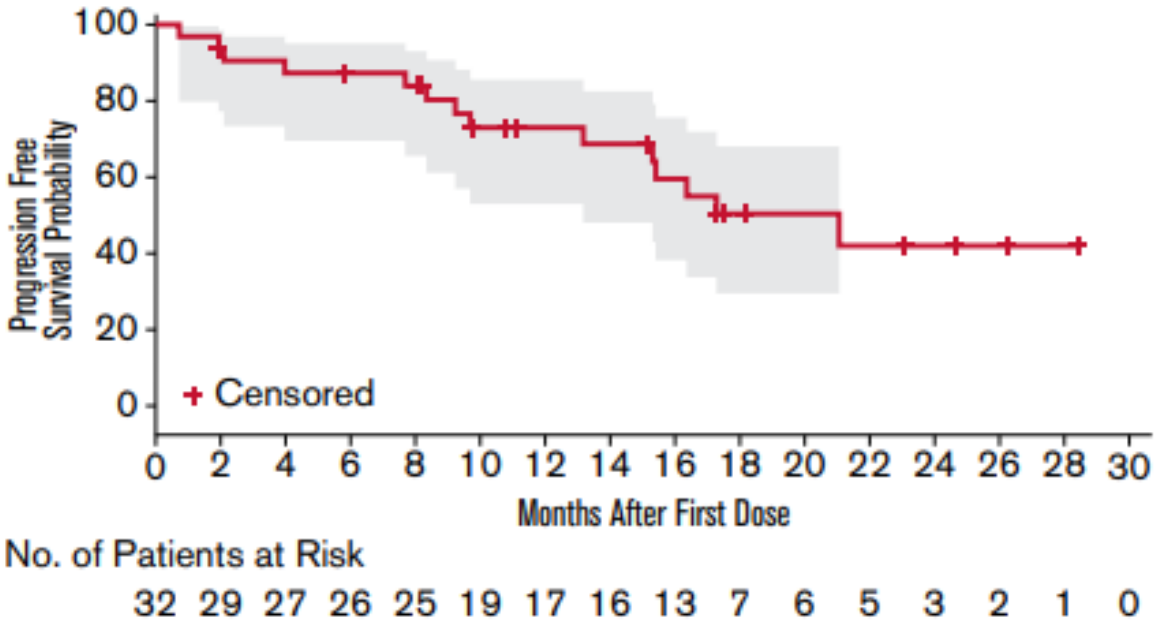
	1 prior line (n 99)	>1 prior line (n 271)
OR	77.8%	66.8%
CR	36.4%	22.9%

Rule et al, Haematologica 2019

Zanubrutinib for the treatment of relapsed or refractory mantle cell lymphoma



IRC, independent review committee; SPD, sum of the products of target lesion perpendicular diameters.



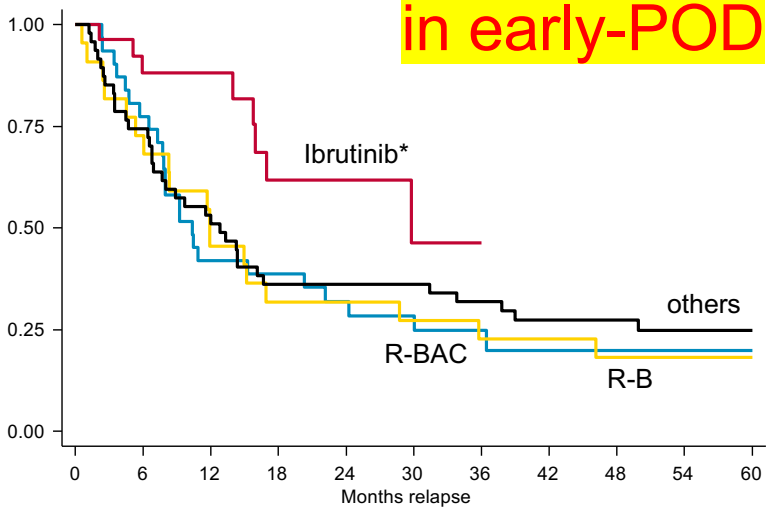
N=32; median age 70 (42-86)
N previous Tx = 1 (1-4)
HD-AraC ~ 40%

Tam C et al, Blood Advances 2021

OS, early versus late POD

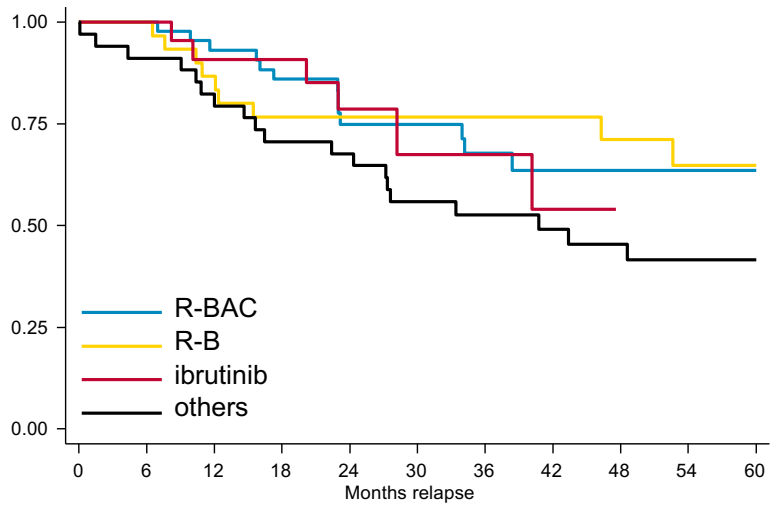
Early POD

Ibrutinib best choice in early-POD



At risk:											
BAC	31	24	13	12	9	8	5	4	3	3	3
BR	22	16	10	7	7	6	5	5	4	3	2
ibru	27	21	16	8	5	3	0	0	0	0	0
other	47	35	24	17	17	17	15	11	11	10	6

Late-POD



At risk:											
BAC	45	45	40	35	26	23	16	14	12	8	7
BR	32	30	26	23	22	20	16	15	13	10	9
ibru	23	22	20	18	10	6	6	4	0	0	0
other	34	31	27	24	23	19	16	13	12	8	7

*Ibru vs R-B and R-BAC (P=0.02); vs others (P=0.03)

Visco et al, Leukemia 2020

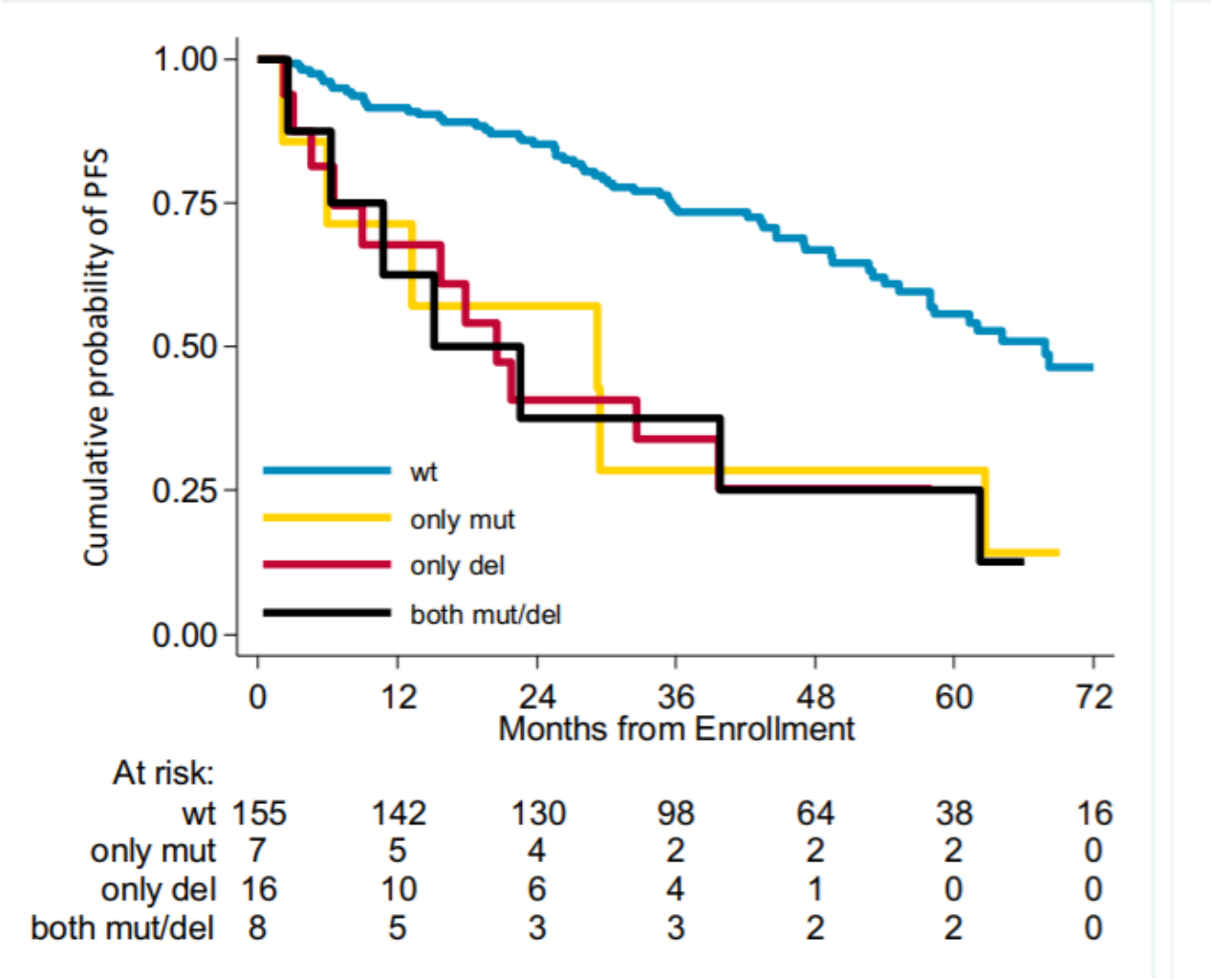
Relapsed setting

How I treat patients at first relapse (Time to POD)

Difficult scenarios, tumor biology:

-TP53 mutations
-What to do when ibrutinib fails
-CAR T-cell therapy
-Still a role for allogeneic transplant?

TP53 disruptions are poor prognostic biomarkers



At risk:

wt	155	142	130	98	64	38	16
only mut	7	5	4	2	2	2	0
only del	16	10	6	4	1	0	0
both mut/del	8	5	3	3	2	2	0

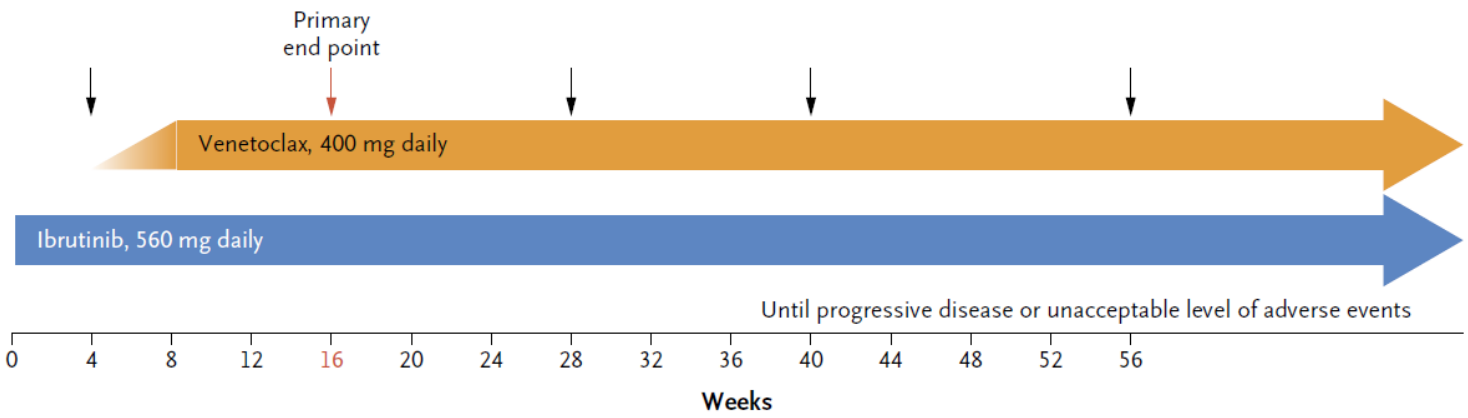
P53 mutations 8%
P53 deletions 13%
KMT2D mut/del 14%

Ferrero S et al, Haematologica 2019

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

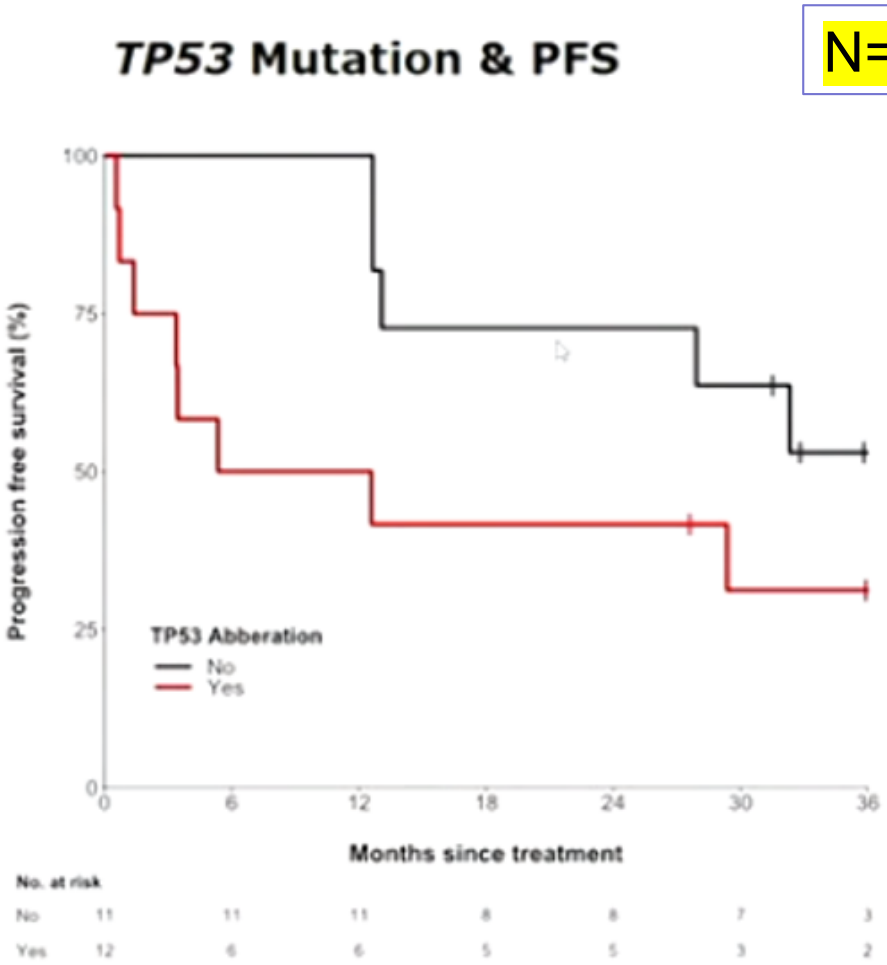
Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma

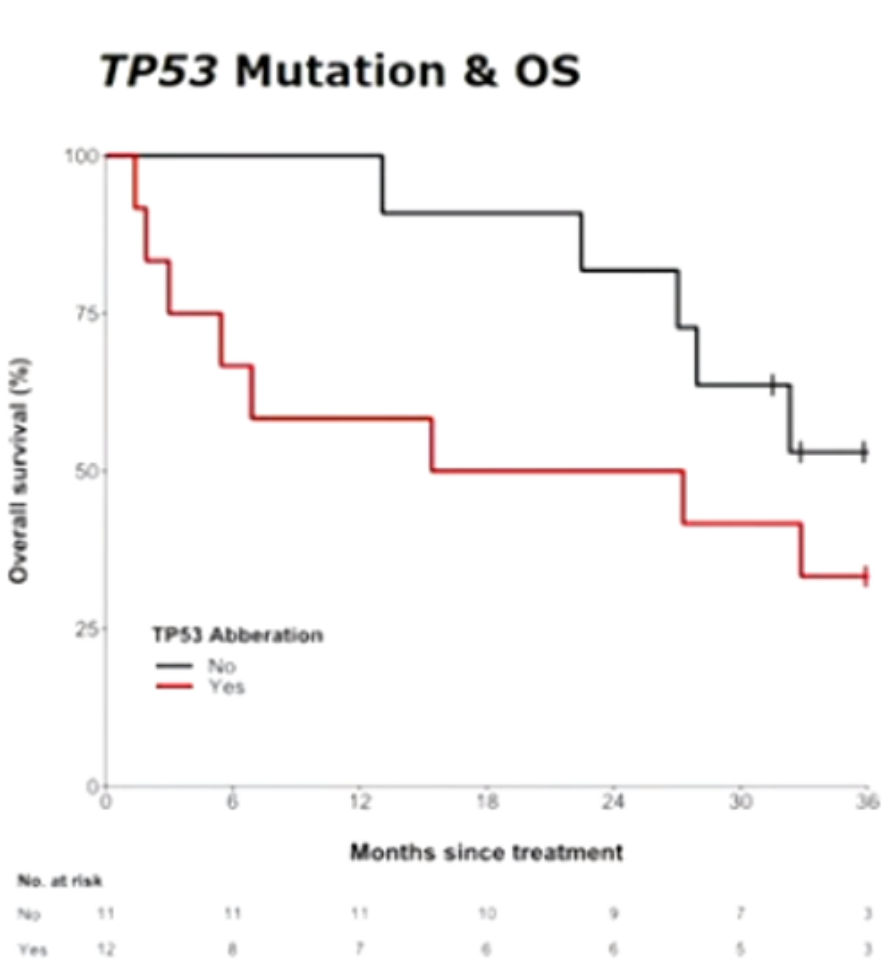


Tam CS et al, NEJM 2018

Three Year Update of the Phase II ABT-199 (Venetoclax) and Ibrutinib in Mantle Cell Lymphoma (AIM) Study

N=12





Sasanka M. Handunnetti, et al, ASH 2019

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

ZUMA-2 Patient Eligibility

Key Inclusion Criteria

- R/R MCL defined as
  - Disease progression after last regimen or
  - Failure to exhibit a CR or PR to the last regimen
- 1 – 5 Prior therapies that must have included
  - An anthracycline- or bendamustine-containing chemotherapy and
  - Anti-CD20 monoclonal antibody therapy and
  - Ibrutinib or acalabrutinib
- ≥ 1 Measurable lesion
- Age ≥ 18 years
- ECOG of 0 or 1
- Adequate bone marrow, renal, hepatic, pulmonary, and cardiac function
- ALC ≥ 100/μL

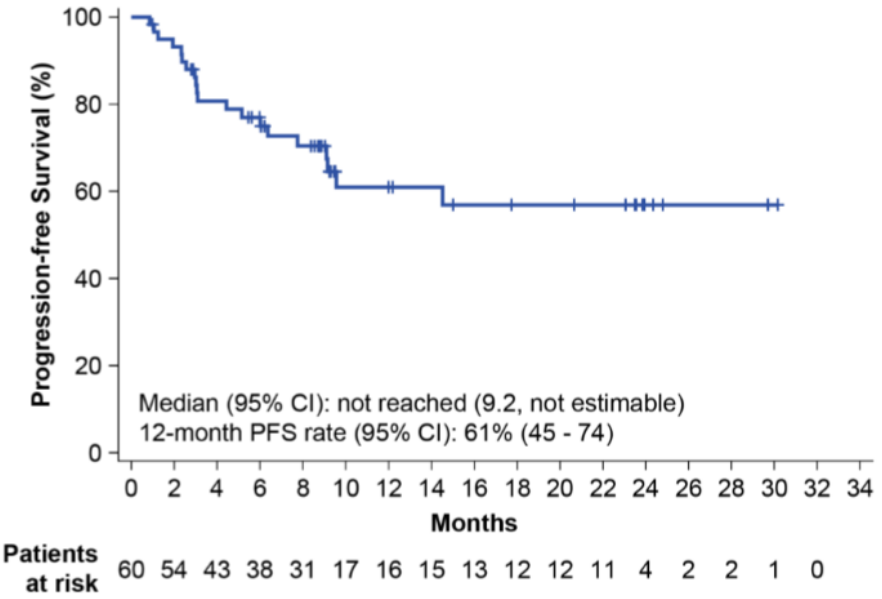
Key Exclusion Criteria

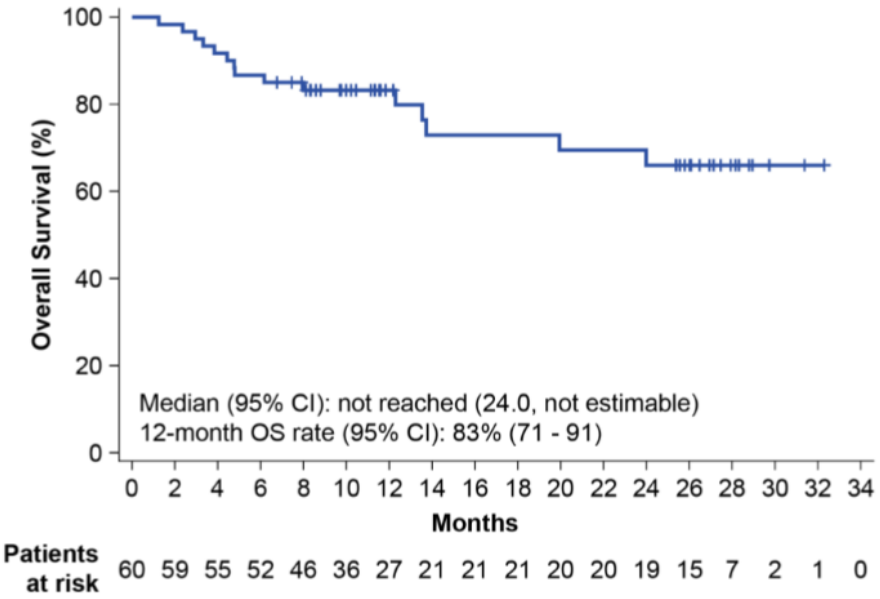
- Prior allogeneic SCT
- Prior CD19-targeted therapy
- Prior CAR T cell therapy
- Clinically significant infection
- History of or current CNS involvement by MCL or other CNS disorders

Wang M et al, NEJM 2020

Progression-Free Survival and Overall Survival ‡

- Median PFS and median OS were not reached after a median follow-up of 12.3 months

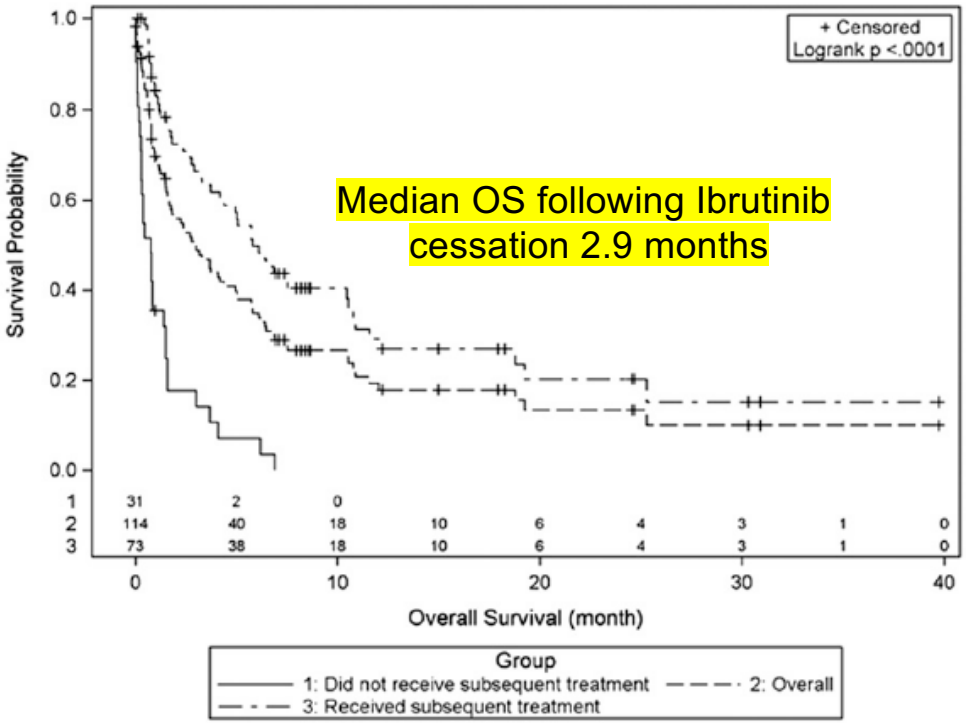




Morphologic characteristic of MCL			
Classical MCL	35	32	91 (77–98)
Pleomorphic MCL	4	4	100 (40–100)
Blastoid MCL	14	13	93 (66–100)
Ki-67 proliferation index			
<50%	14	14	100 (77–100)
≥50%	32	30	94 (79–99)
TP53 mutation detected			
Yes	6	6	100 (54–100)
No	30	30	100 (88–100)

Wang M et al, NEJM 2020

Post-BTKi Outcome



Median OS following Ibrutinib cessation 2.9 months

Characteristics	Number	Range, %, or 95% CI
All	114	
Median Age	68 y	46-85
Median prior systemic therapies	3	0-10

Response rates 29-32%

Few patients surviving beyond one year

Comment on Martin et al, page 1559

Ibrutinib: a force with a dark side?

Martin P et al, Blood 2016
Smith MR, Blood 2016
Wang M et al, ASH 2017

Options in BTK-i relapsed/refractoriness

R-BAC

ORR 83% (CR 60%), median PFS 9.3 months, 1/3 bridged to allo-SCT

Venetoclax

ORR 53% (CR 18%), median time to response 48 days, median PFS 3.2 months

Car-T

Relapsed or refractory status with BTK inhibitor			
Refractory to BTK inhibitor therapy	38	35	92 (79–98)
Relapse during or after BTK inhibitor therapy	19	19	100 (82–100)

Pirtobrutinib

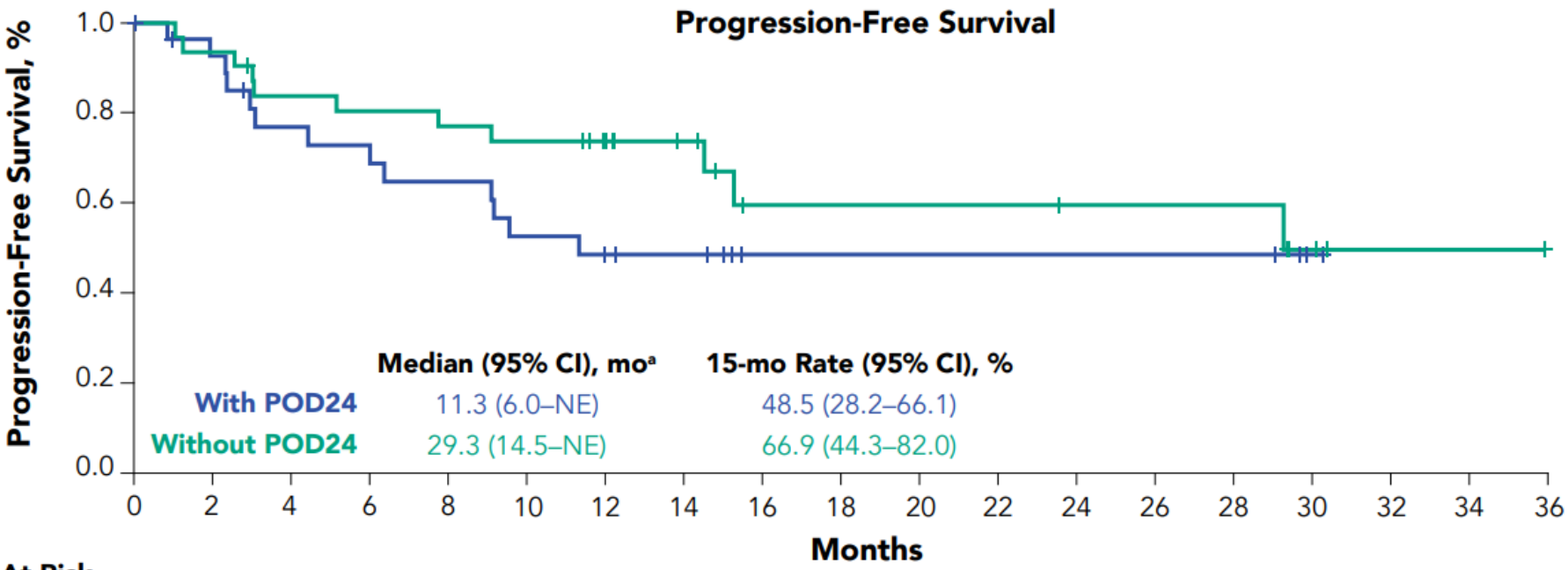
ORR 52% in 52 BTK-treated (of 30 BTK-refractory, ORR 50% with promising durability, but 6 months median f/u)

Bispecifics (CD20-CD3)

ORR in the range of 70%, update at ASH

McCullock et al, BJH 2019
Eyre et al, Haematologica 2019
Wang et al, NEJM 2020
Mato et al, Lancet 2021

POD24 and Car-T cell therapy



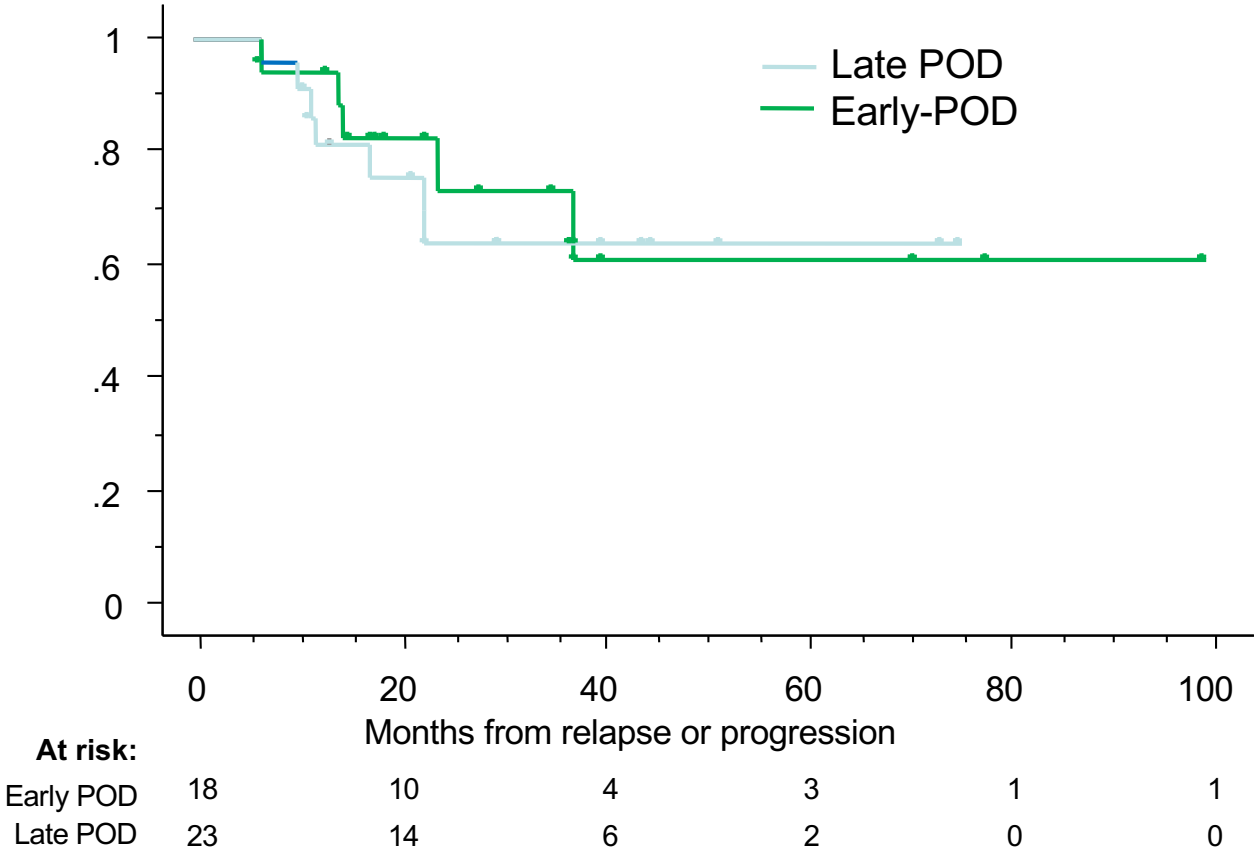
No. Patients At Risk

With POD24	28	24	19	18	16	13	11	10	6	6	6	6	6	6	6	1	0		
Without POD24	32	29	25	24	23	22	19	12	7	7	7	7	6	6	6	3	1	1	0

- After a median of 17.5 months of follow-up, KTE-X19 provided a high CR rate in patients with and without POD24, with median DOR and OS not reached in either group
  - Median PFS appeared to be shorter among patients with POD24, compared with those without POD24
- Patients with POD24 appeared to have lower CAR T-cell expansion than those without POD24
- Earlier intervention with CD19-directed CAR T-cell therapy may benefit patients with MCL with known high-risk factors[1]

Wang M et al, ASCO 2021

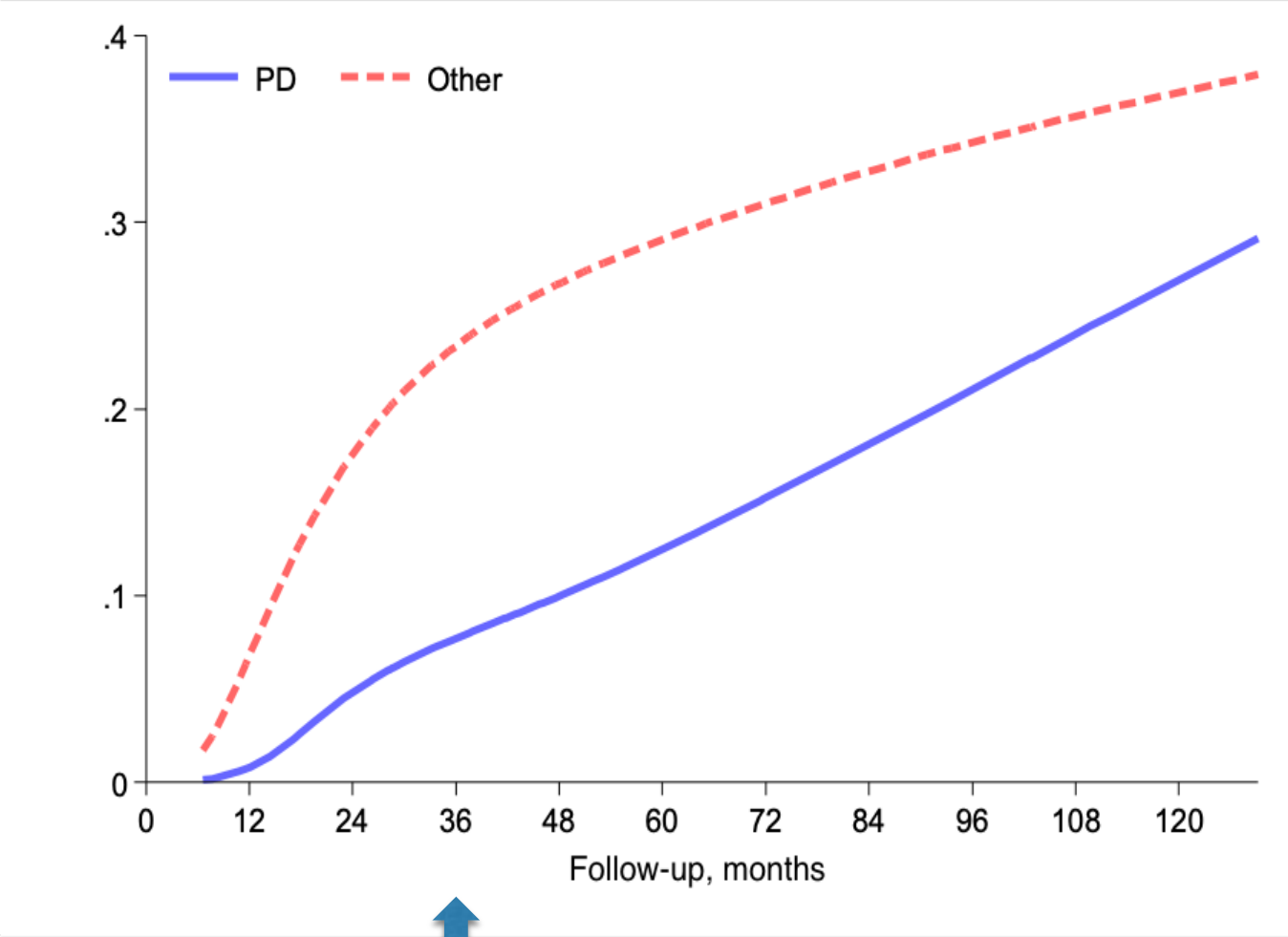
Survival from time of relapse/progression



Allo-transplanted patients

Visco, BJH 2018

Cumulative incidence of death for PD or other causes



8% vs 23%

Better outcome if not aGVHD, **≤2 prior lines, Age<60**

Arcari A et al, Leuk Lymph 2021

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Conclusions

- At first relapse use BTKi if early-POD or refractory
- Time to first relapse relevant all-life-long
- TP53 still an unmet need, as BTKi failure
- Expecting solid CarT-cells data on both aspects
- Possible residual role of Allo-SCT in younger patients

Grazie per l'attenzione