

2020



Progetto Ematologia Romagna

***La terapia con anti-BCL2
nel linfoma mantellare***

Carlo Visco

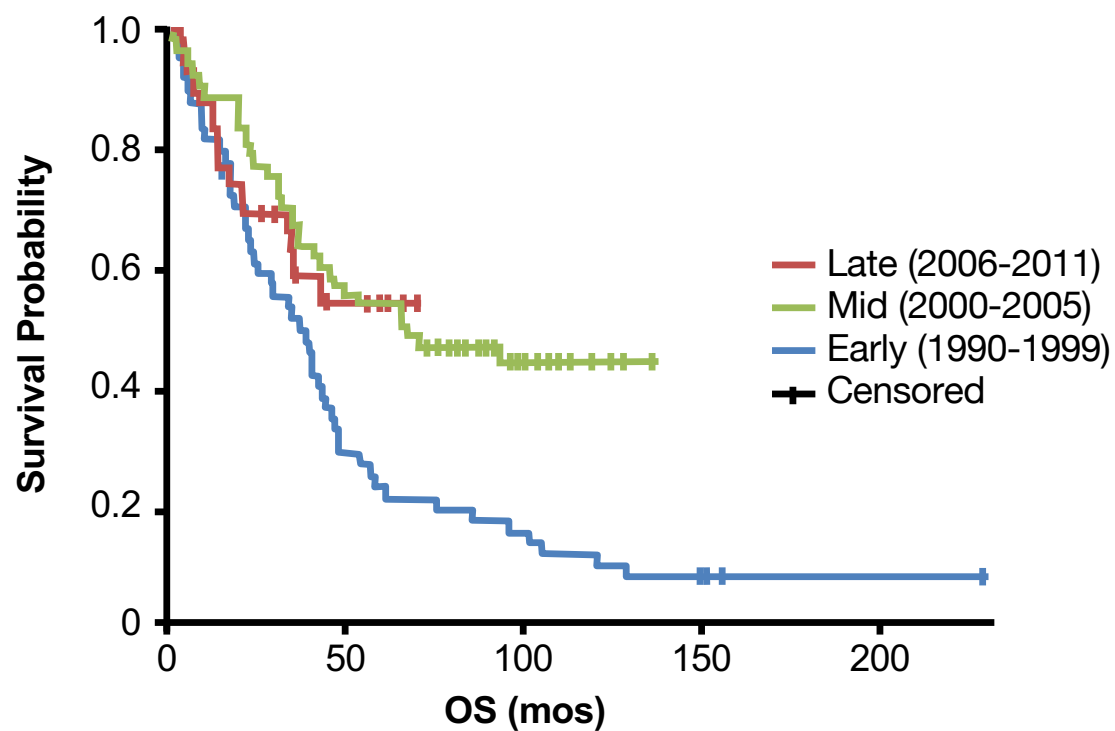
Conflitti di interesse da dichiarare

- Partecipazione ad Advisory Board ditta AbbVie



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Survival for Patients With MCL



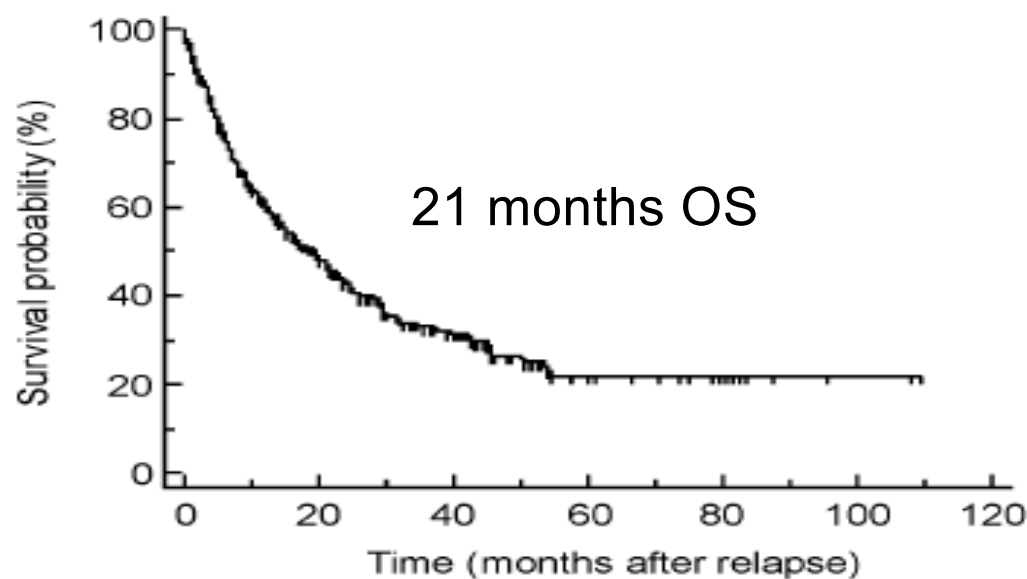
University of Nebraska. Unpublished data.



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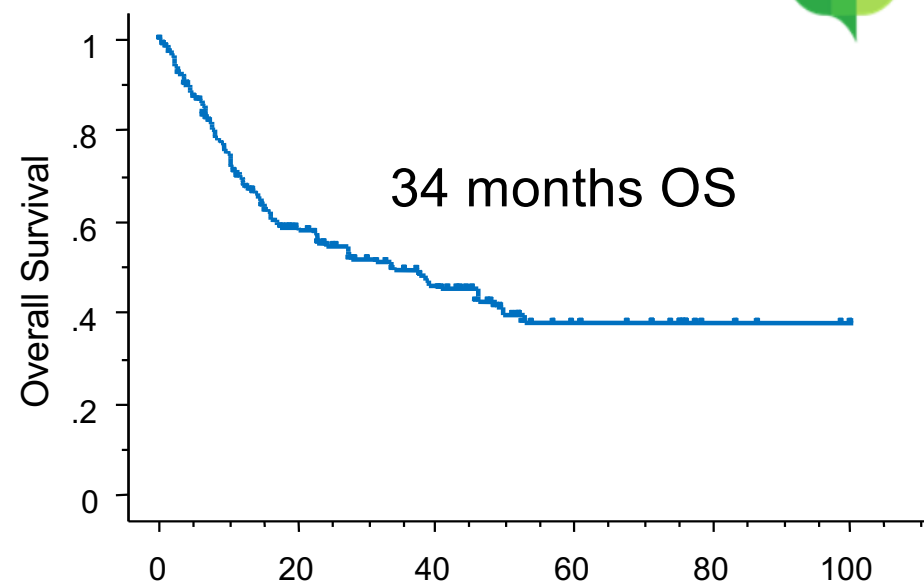
Survival of r/r MCL after upfront autologous transplant: previous versus modern era (HDAC)

EBMT registry 2000-2009 (n=360)



Dietrich S, Ann Oncol 2014

FIL study 2007-2017 (n=188)

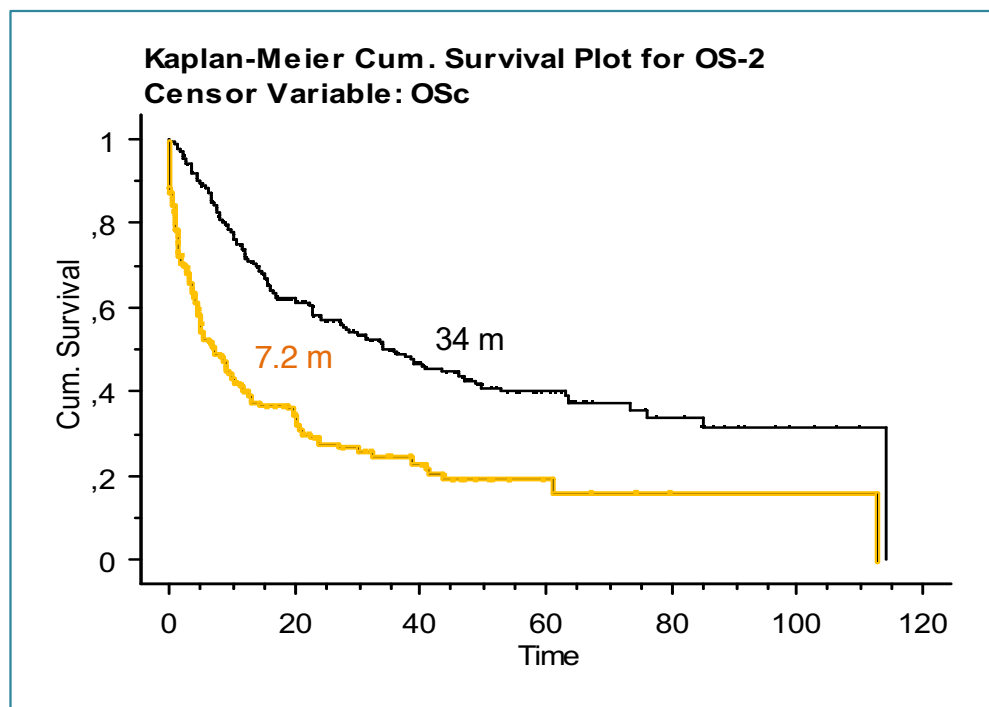


Visco C, BJH 2019



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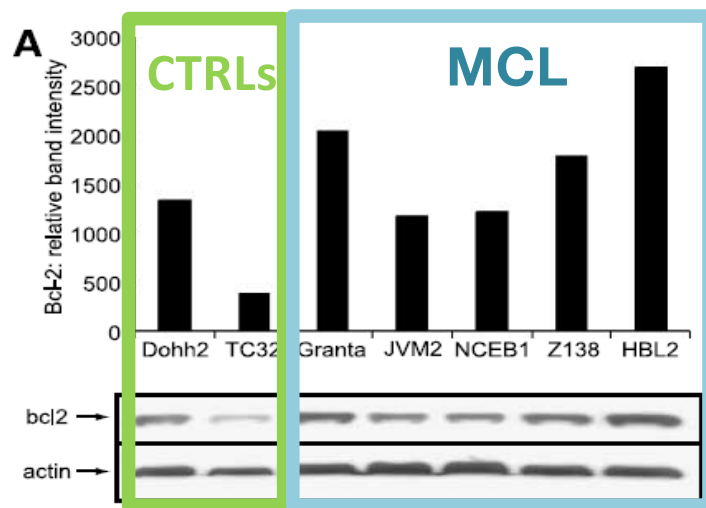
MANTLE-FIRST: OS after *first vs second* relapse



Strong need for
new drugs in the
r/r setting

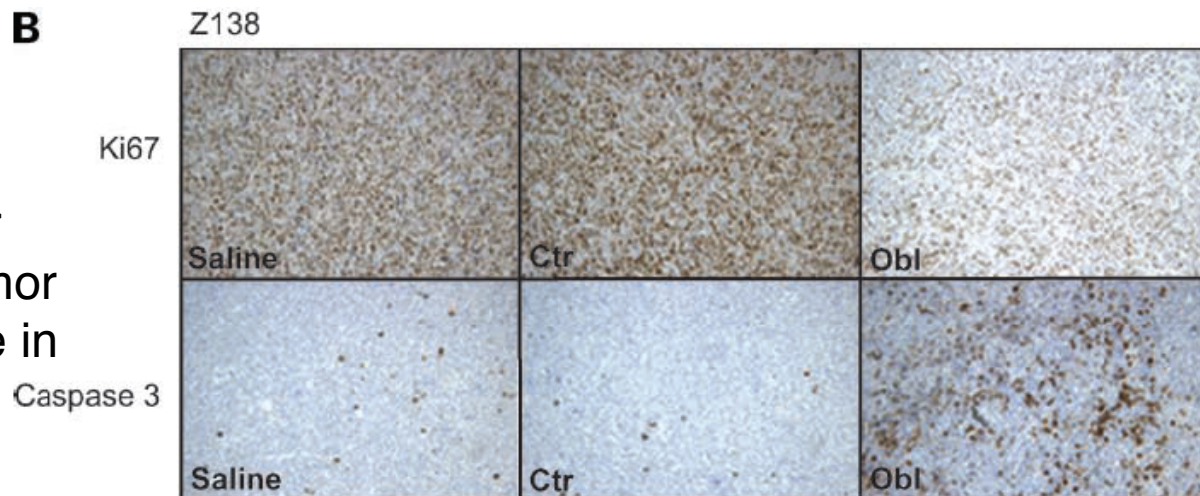
Visco C et al, unpublished data

BCL2 expression and pre-clinical evidence



BCL2 expression in MCL at least 2-fold higher than t(14;18) FL

Z-138 xenografts exhibit a significant tumor growth delay following BCL2 inhibition. Tumor growth delay was associated with decrease in proliferation and increase in apoptosis





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ORIGINAL ARTICLE

Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia

Andrew W. Roberts, M.B., B.S., Ph.D., Matthew S. Davids, M.D.,
John M. Pagel, M.D., Ph.D., Brad S. Kahl, M.D., Soham D. Puvvada, M.D.,
John F. Gerecitano, M.D., Ph.D., Thomas J. Kipps, M.D., Ph.D.,
Mary Ann Anderson, M.B., B.S., Jennifer R. Brown, M.D., Ph.D.,
Lori Gressick, B.S., Shekman Wong, Ph.D., Martin Dunbar, Dr.P.H.,
Ming Zhu, Ph.D., Monali B. Desai, M.D., M.P.H., Elisa Cerri, M.D.,
Sari Heitner Enschede, M.D., Rod A. Humerickhouse, M.D., Ph.D.,
William G. Wierda, M.D., Ph.D., and John F. Seymour, M.B., B.S., Ph.D.

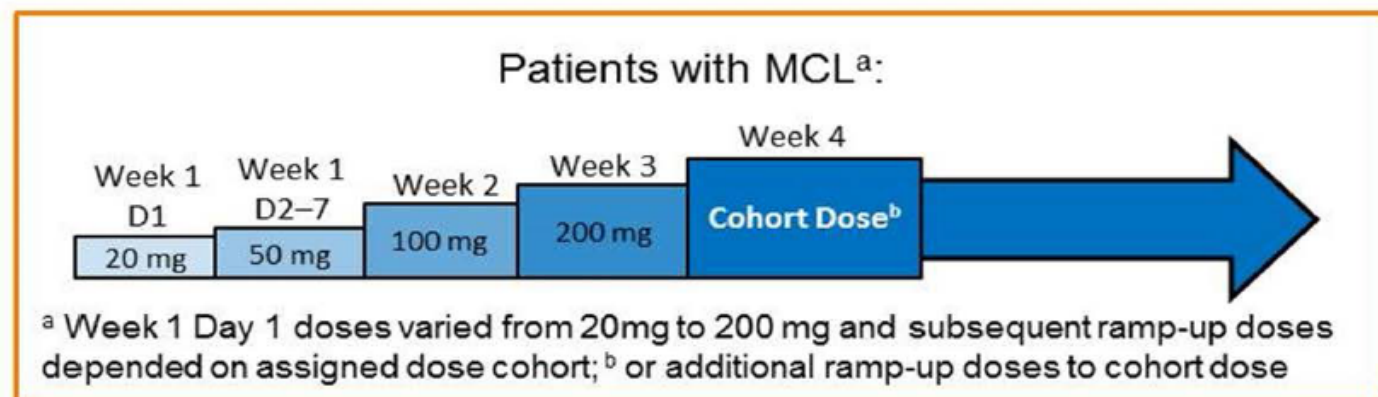
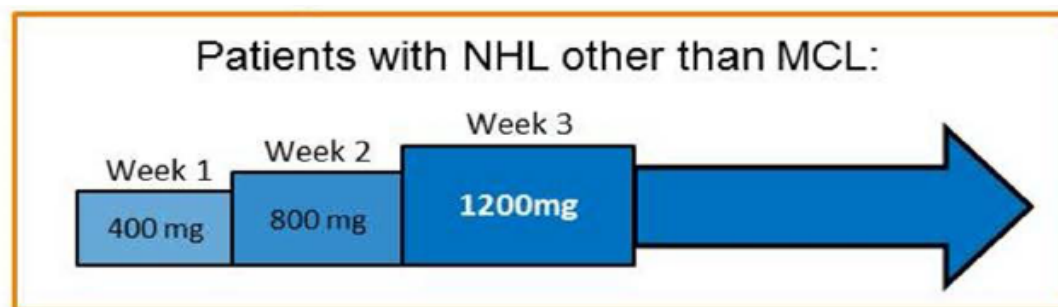
[January 28, 2016](#)

N Engl J Med 2016; 374:311-322



A Phase 1 Study of Venetoclax (ABT-199) in Patients with R/R NHL

Patients received venetoclax once daily until progressive disease or unacceptable toxicity at target doses from 200 to 1,200 mg in dose-escalation and safety expansion cohorts





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Patients characteristics

Characteristic, n (%)		All N=106	MCL n=28	FL n=29	DLBCL n=41 ^a	Other ^b n=8
Age, years	Median (range)	66 (25–86)	72 (35–85)	64 (46–75)	67 (25–86)	63 (56–73)
Prior therapies	Median (range)	3 (1–10)	3 (1–7)	3 (1–10)	3 (1–8)	4 (2–6)
	Rituximab-refractory	33 (31)	8 (29)	8 (28)	16 (39)	1 (33)
Bulky nodes	>5 cm	49 (48)	16 (59)	8 (29)	22 (54)	3 (38)
	>10 cm	14 (14)	3 (11)	2 (7)	8 (20)	1 (13)
LDH	> Upper Limit of Normal	45 (44)	7 (27)	10 (35)	27 (68)	1 (13)

^a Includes 7 patients DLBCL-Richter's transformation

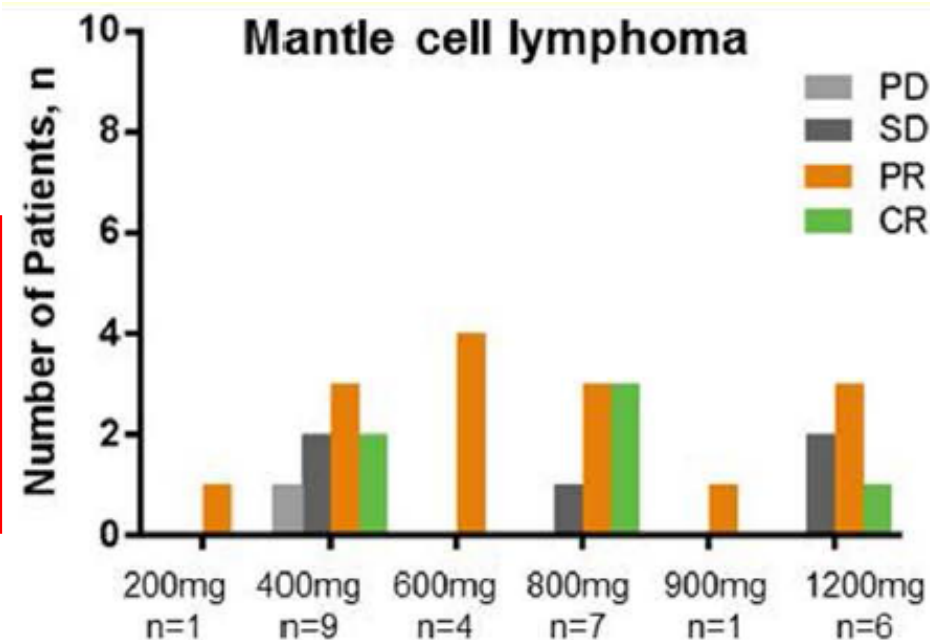
^b Includes n=4 WM, n=3 MZL, n=1 MM



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Objective response

Best Objective Response, n (%)	All N=106	MCL n=28
Overall Response	47 (44)	21 (75)
CR	14 (13)	6 (21)
PR	33 (31)	15 (54)
SD	32 (30)	5 (18)
PD	23 (22)	1 (4)





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Treatment-Emergent Adverse Events

All Grade AEs (in $\geq 15\%$ patients), n (%)	N=106
Any AE	103 (97)
Nausea	51 (48)
Diarrhea	47 (44)
Fatigue	43 (41)
Decreased appetite	22 (21)
Vomiting	22 (21)
Anemia	19 (18)
Constipation	19 (18)
Headache	19 (18)
Neutropenia	19 (18)
Cough	18 (17)
Back pain	17 (16)
Upper respiratory tract infection	16 (15)

Grade 3/4 AEs (in $\geq 5\%$ patients), n (%)	N=106
Any Grade 3/4 AE	57 (54)
Anemia	17 (16)
Neutropenia	13 (12)
Thrombocytopenia	10 (9)
Fatigue	6 (6)

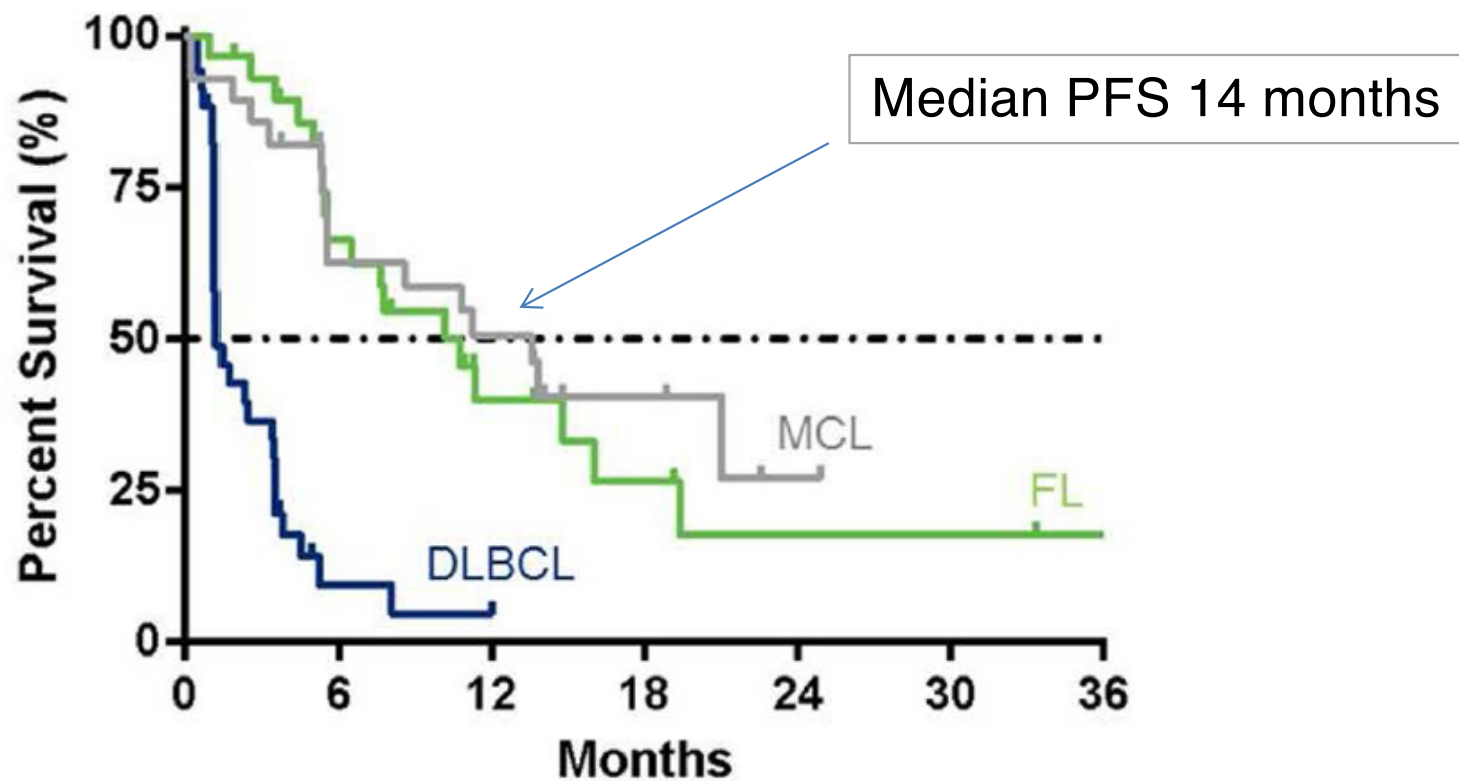
Serious Adverse Events (in ≥ 2 patients), n (%)	N=106
Any SAE	35 (33)
Diarrhea	3 (3)
Hyponatremia	3 (3)
Influenza	3 (3)

* Two TLS (1 MCL 200 mg), no clinical sequelae



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Progression-free survival by histology

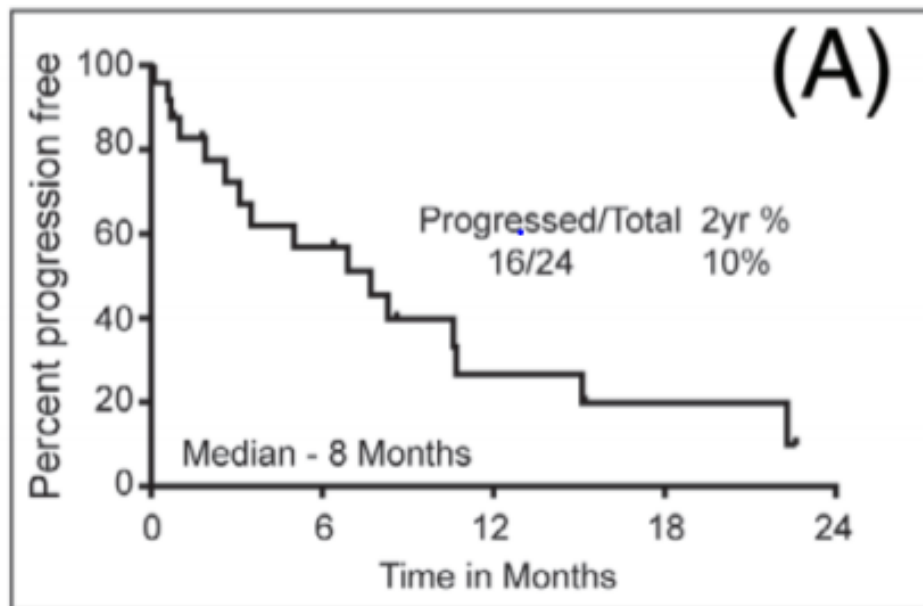


MCL: 28 16 12 4 1



Efficacy of venetoclax in high risk relapsed MCL

N=24 r/r patients (median 5 prior tx); 67% had progressed on BTKi and 54% had blastoid or pleomorphic histology.



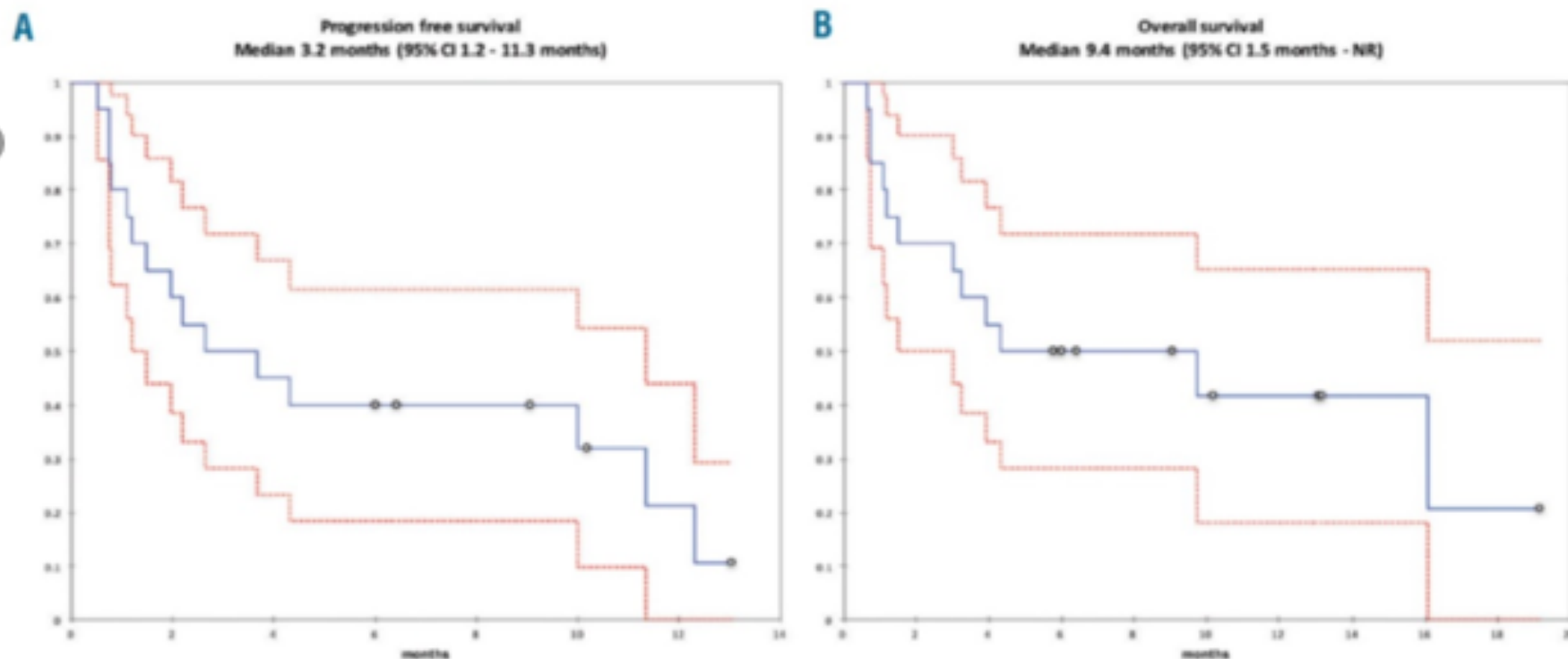
ORR 50%, CR 21%

Whole-exome sequencing (WES) from 7 pts: venetoclax resistance in MCL is predominantly associated with non-BCL2 gene mutations



BTK refractory patients

N=20 patients; **ORR 53% (CR 35%)**; median time to response 48 days;
Median PFS 3.2 months and median OS 9.4 months



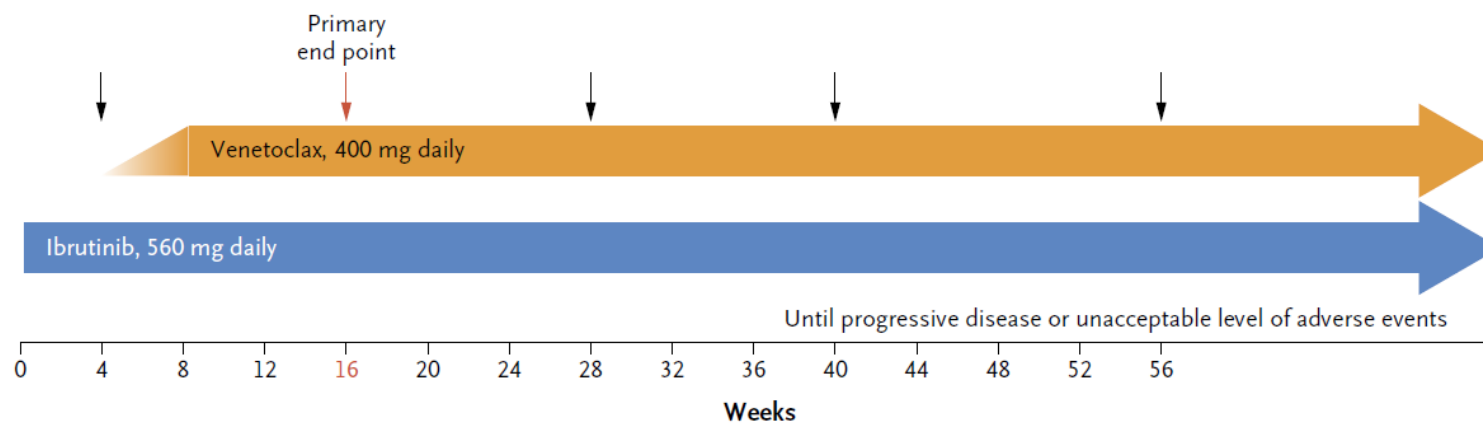


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ORIGINAL ARTICLE

Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma





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Anti-BTK+BCL2 treatment tolerability

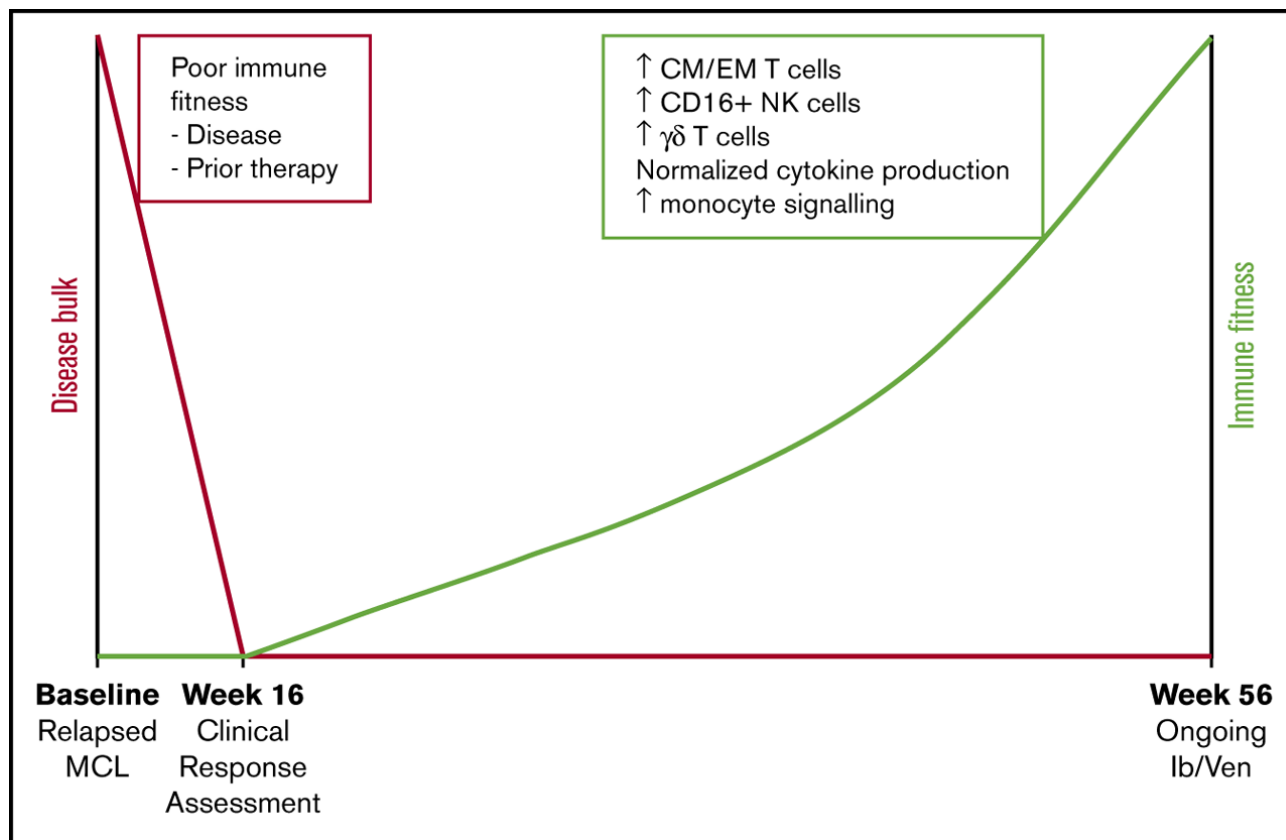
Event	Any Grade (N=24)	Grade 3 or Higher (N=24)
	<i>no. of patients with event (%)</i>	
Any adverse event	24 (100)	17 (71)
Diarrhea	20 (83)	3 (12) [†]
Fatigue	18 (75)	0
Nausea or vomiting	17 (71)	0
Bleeding, bruising, or postoperative hemorrhage	13 (54)	1 (4)
Musculoskeletal or connective-tissue pain	12 (50)	1 (4)
Cough or dyspnea	11 (46)	1 (4)
Soft-tissue infection	10 (42)	2 (8) [‡]
Upper respiratory tract infection	10 (42)	0
Gastroesophageal reflux	9 (38)	0
Neutropenia	8 (33)	8 (33)
Lower respiratory tract infection	8 (33)	2 (8)
Anemia	7 (29)	3 (12)
Rash	7 (29)	0
Oral mucositis	5 (21)	0
Cramps	5 (21)	0
Sensory peripheral neuropathy	5 (21)	0
Thrombocytopenia	5 (21)	4 (17)
Tumor lysis syndrome	2 (8)	2 (8)
Atrial fibrillation	2 (8)	2 (8)

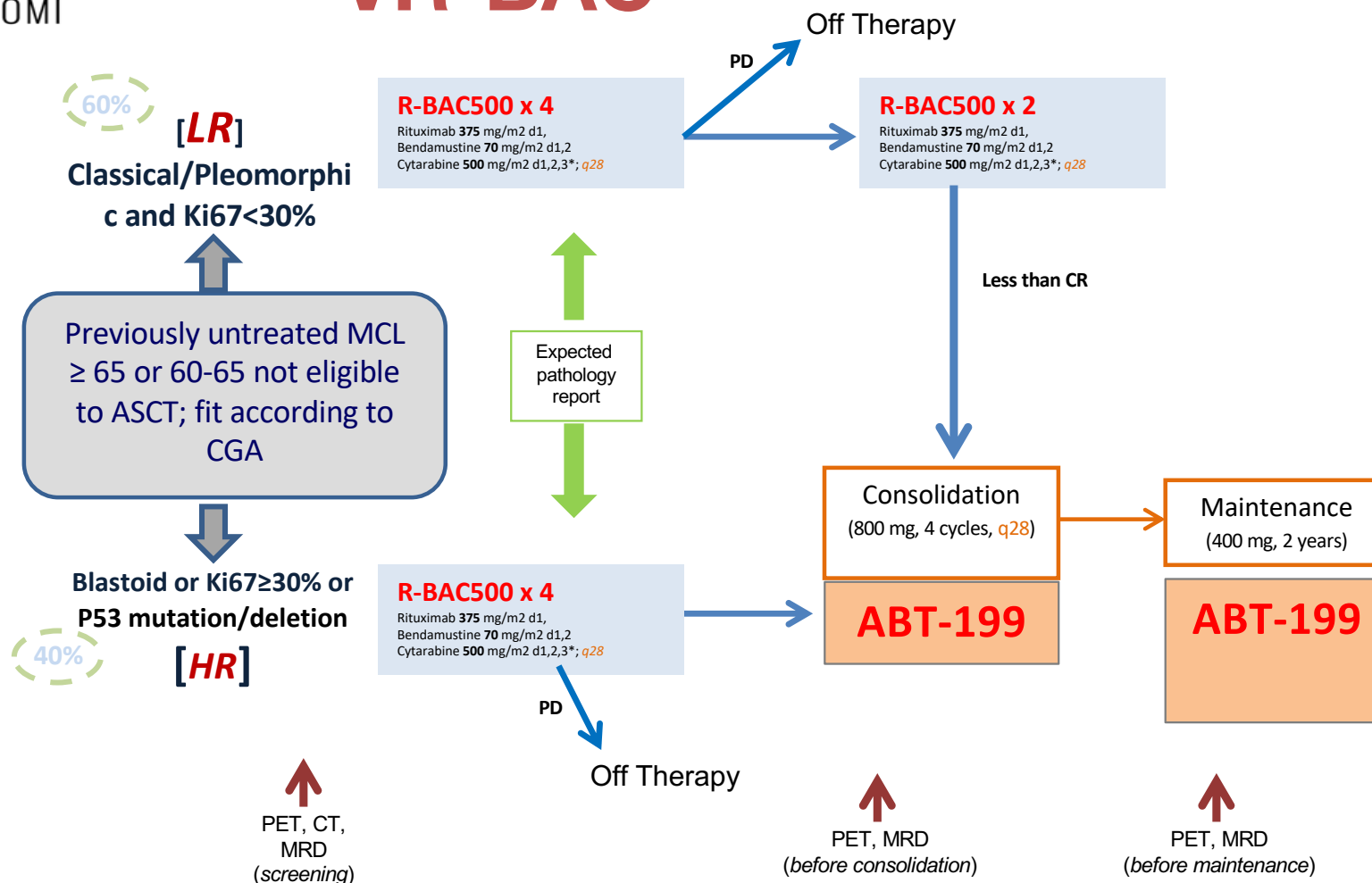


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Immune recovery in patients with MCL

Long-term ibrutinib and venetoclax combination therapy







FONDAZIONE
ITALIANA
LINFOMI

Grazie per l'attenzione

