Venetoclax in multiple myeloma

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Disclosures: P Moreau

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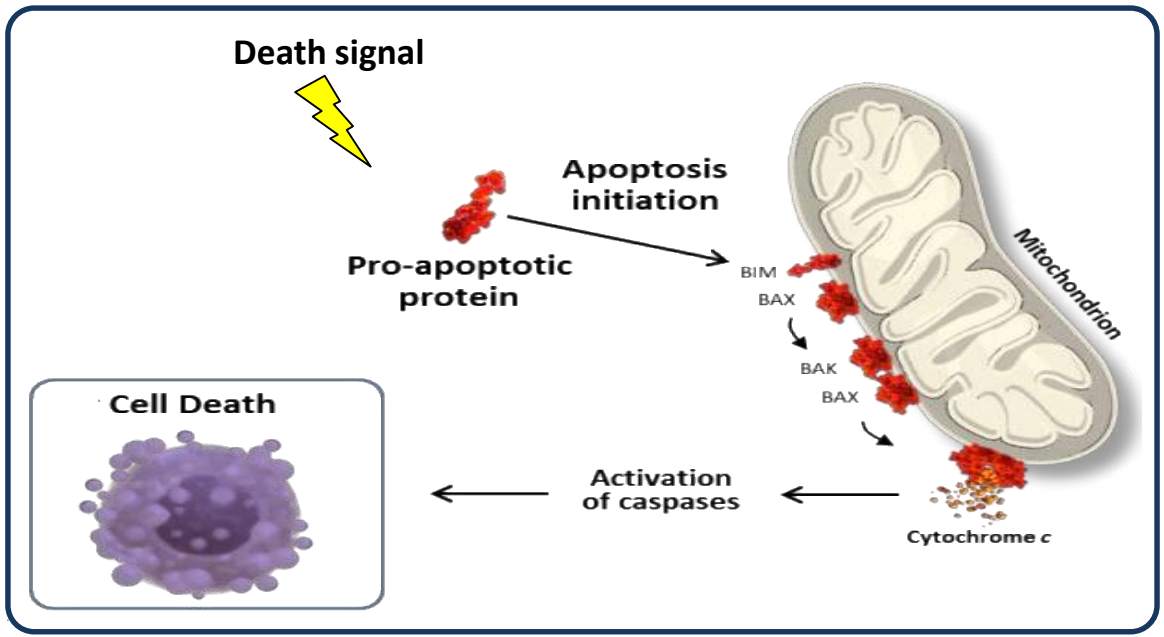
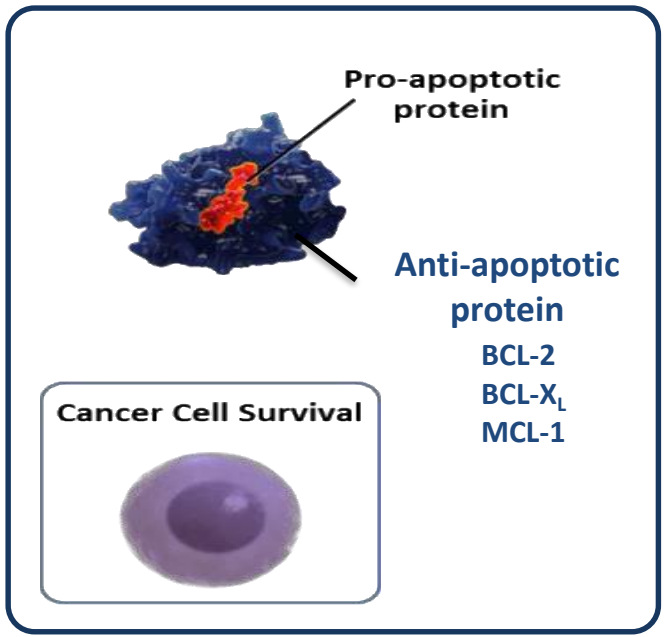
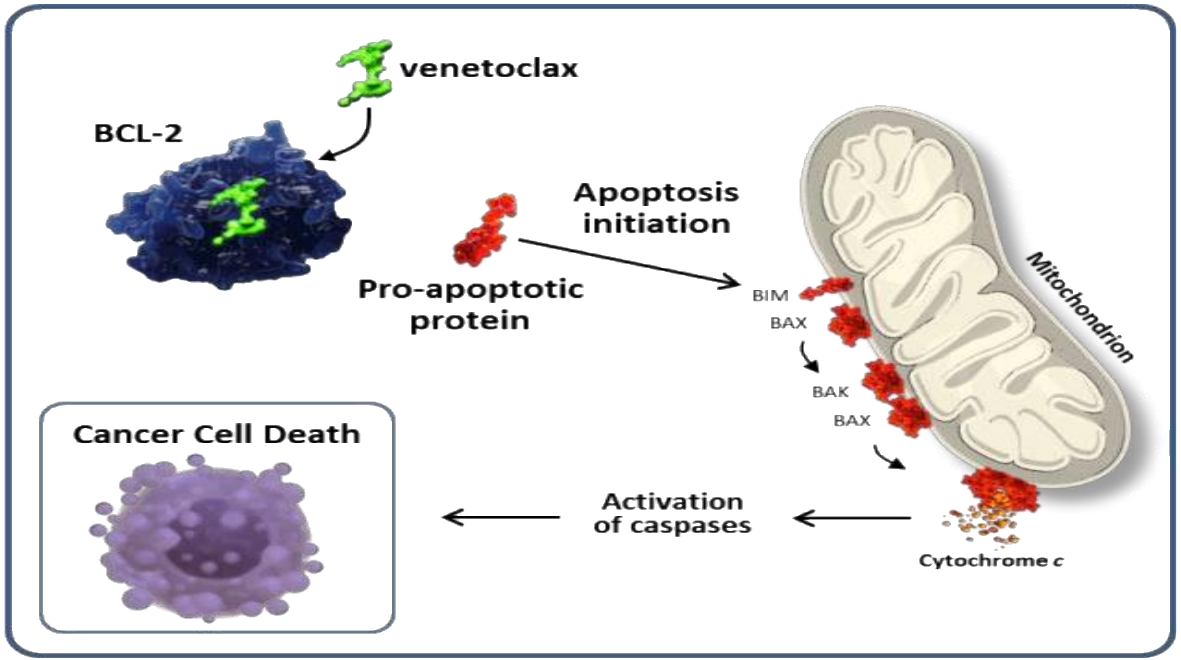
Venetoclax : the first Bcl-2 specific BH3 mimetic





Adapted from Letai et al. Nat Rev Cancer. 2008 ;8(2):121-32.

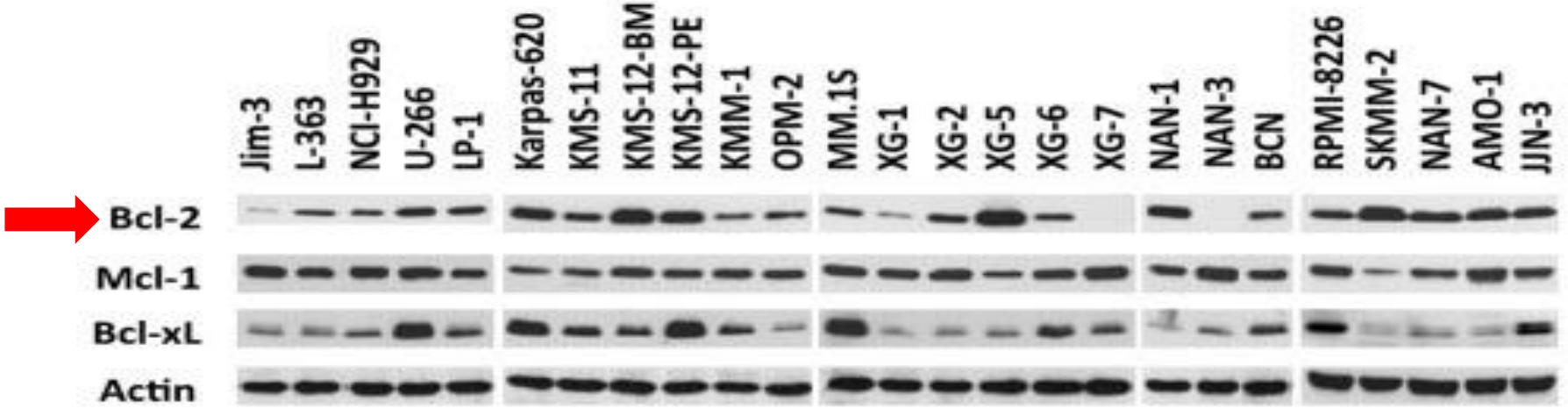
Venetoclax : the first Bcl-2 specific BH3 mimetic



Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis)

Souers et al. Nat Med. 2013;19(2):202-8

Bcl-2 is overexpressed in a subset of human myeloma cell lines



Bodet et al. Blood 2011 6;118(14):3901-10

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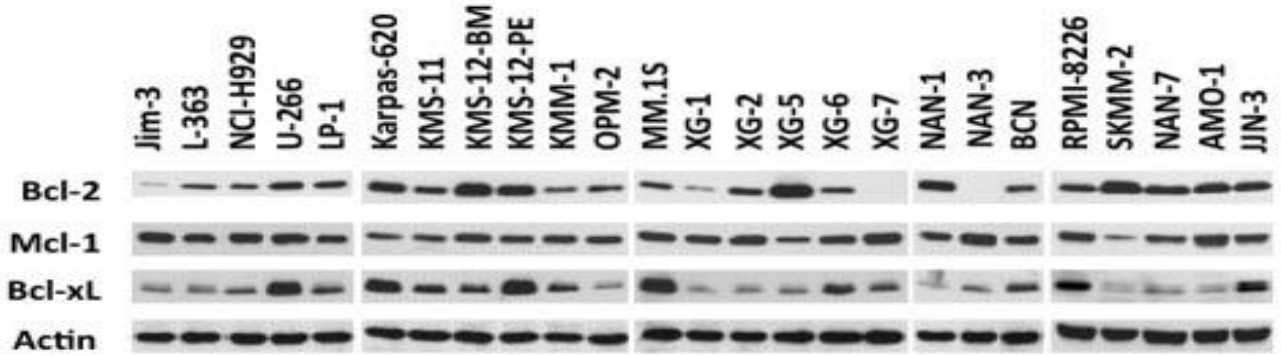
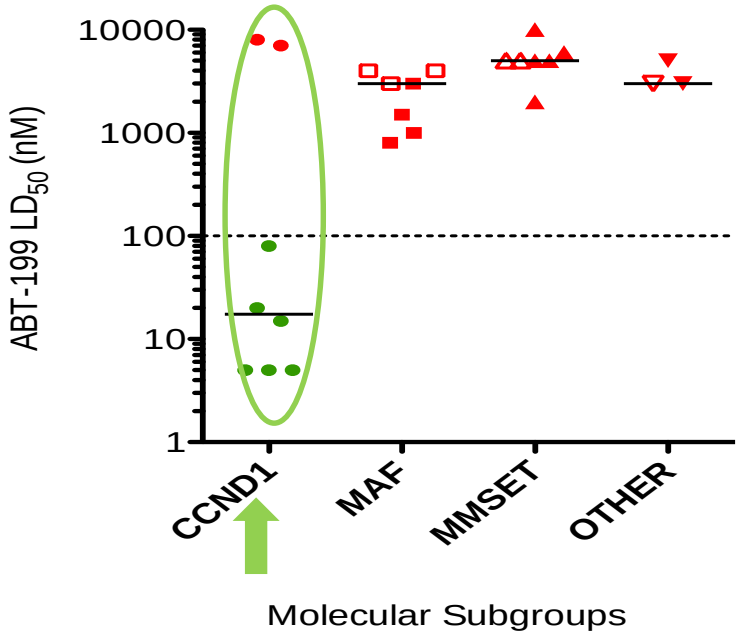


Can we identify a subgroup of patients with Bcl-2 dependant myeloma and therefore able to respond to venetoclax ?

Bodet et al. Blood 2011 6;118(14):3901-10

Preclinical data



Sensitivity to Venetoclax is restricted to myeloma cells harboring the t(11;14) translocation

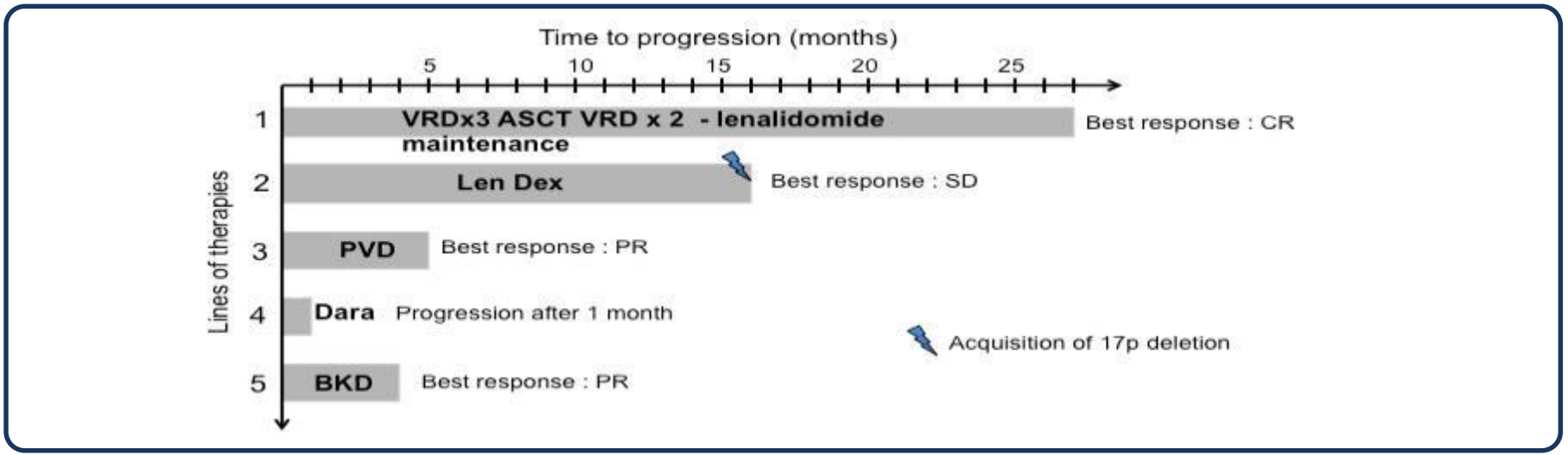
Touzeau et al. Leukemia 2014 ; 28(1):210-2

Efficacy of venetoclax in a very advanced patient – case report

- **30 year old patient**

- **Relapsed MM refractory to alkylating agents, bortezomib, lenalidomide, pomalidomide, carfilzomib, bendamustine et daratumumab**

- **FISH: t(11,14), del17P**



Touzeau, Moreau. Haematologica. 2017 ;102(3):e112-e114

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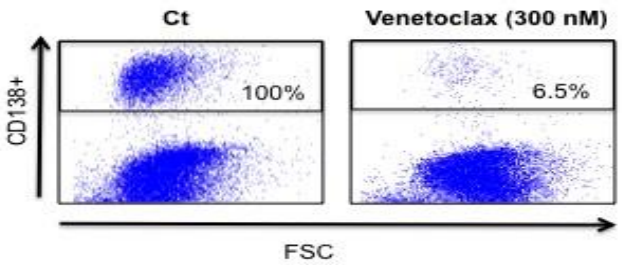
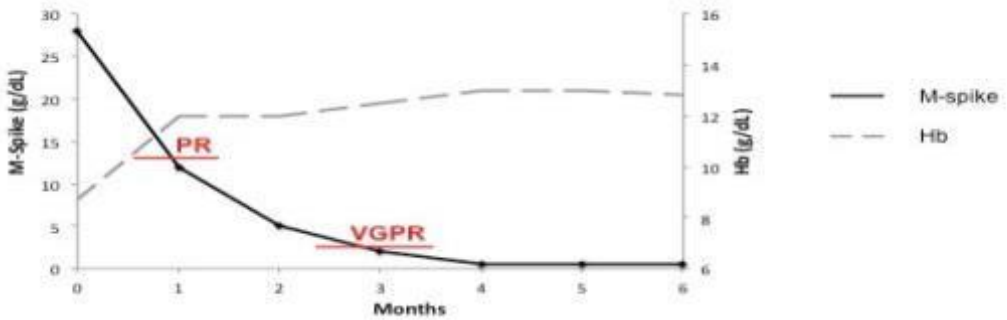


In-vitro sensitivity to venetoclax



Clinical response : Venetoclax (1200 mg/day) + Dex (40 mg/week)
(patient progressed after 10 months of therapy)

Touzeau, Moreau. Haematologica. 2017 ;102(3):e112-e114

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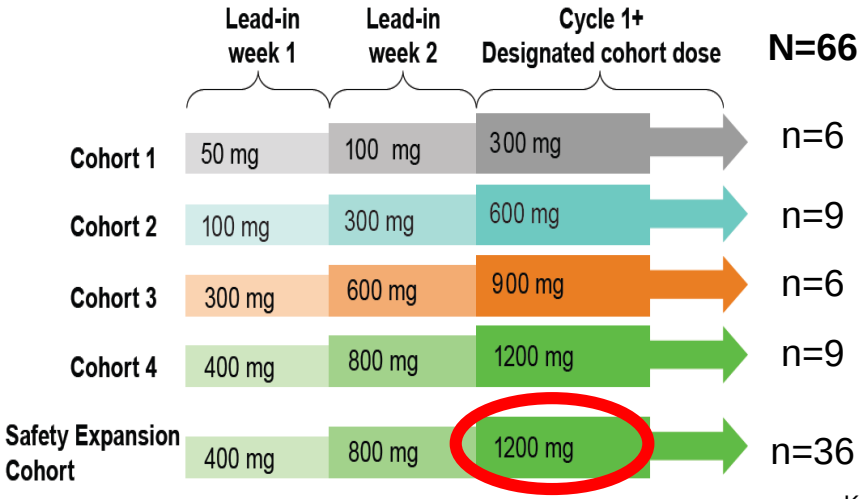
2017 130: 2401-2409
doi:10.1182/blood-2017-06-788786 originally published online October 10, 2017

Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma

Shaji Kumar, Jonathan L. Kaufman, Cristina Gasparetto, Joseph Mikhael, Ravi Vij, Brigitte Pegourie, Lofti Benboubker, Thierry Facon, Martine Amiot, Philippe Moreau, Elizabeth A. Punnoose, Stefanie Alzate, Martin Dunbar, Tu Xu, Suresh K. Agarwal, Sari Heitner Enschede, Joel D. Leverson, Jeremy A. Ross, Paulo C. Maciag, Maria Verdugo and Cyrille Touzeau

Dosing and Enrollment

- Following a 2-week lead-in period, patients were treated on a 21-day cycle with daily venetoclax (300 to 1200 mg)
- Patients who progressed while receiving monotherapy could have dexamethasone added to venetoclax and continue on study



Kumar s, et al. Blood 2017;130:2401–2409 + suppl

	N=66
Age, median (range), years	63 (31–79)
ISS stage, n (%)	
Stage I	24 (38)
Stage II/III	39 (62)
Unknown	3
Cytogenetic abnormalities, n (%)	
t(11;14)	30 (46)
t(4;14)	6 (9)
del(17p)	12 (18)
del(13q)	32 (48)
Hyperdiploid	27 (41)
No. of prior lines of therapy,[a] median (range)	5 (1–15)
Autologous stem cell transplant, n (%)	50 (76)
Bortezomib/refractory, n (%)	62 (94)/46 (70)
Lenalidomide/refractory, n (%)	62 (94)/51 (77)
Bortezomib and lenalidomide refractory, n (%)	40 (61)
Refractory to last prior therapy, n (%)	52 (79)

Kumar S, et al. Blood 2017;130:2401–2409

Summary of Adverse Events (AEs)

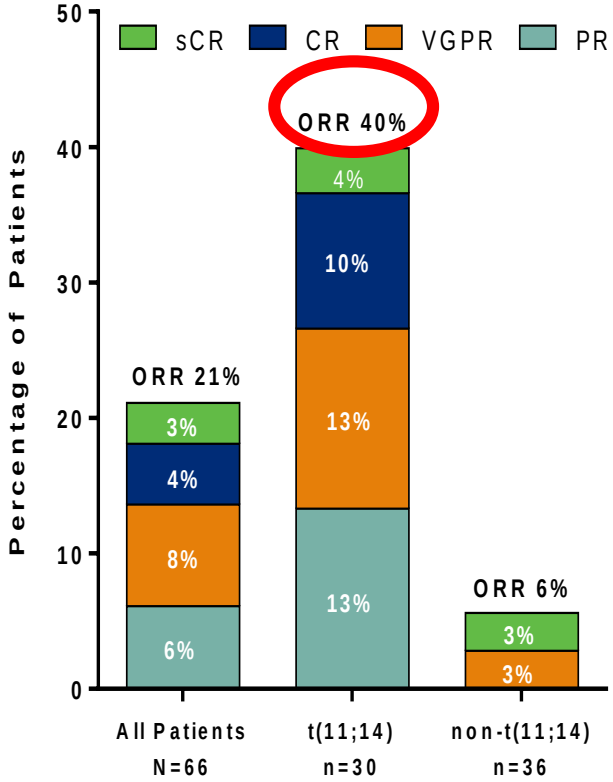
n (%)	Any Grade	Grade 3/4
Total	**66 (100)**	**45 (68)**
Hematologic		
Thrombocytopenia	21 (32)	17 (26)
Neutropenia	18 (27)	14 (21)
Anemia	15 (23)	9 (14)
Leukopenia	15 (23)	9 (14)
Lymphopenia	12 (18)	10 (15)
Non-hematologic		
Nausea	31 (47)	2 (3)
Diarrhea	24 (36)	2 (3)
Fatigue	18 (27)	3 (5)
Back pain	14 (21)	5 (8)
Vomiting	13 (20)	2 (3)

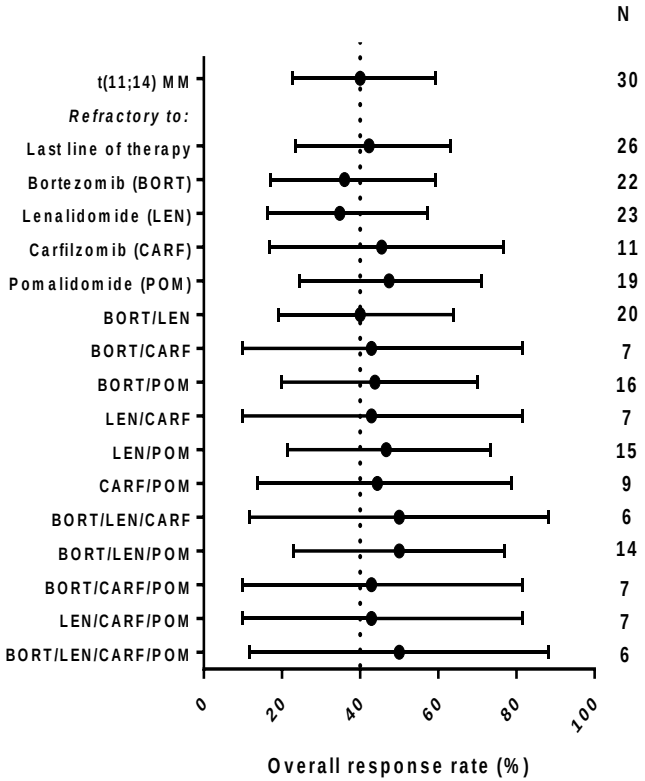
AEs for ≥20% of patients for any grade AE or for ≥10% with grade 3 or 4 AEs.

- Two patients had dose-limiting toxicities at 600 mg of abdominal pain and nausea
- Serious AEs (≥2% of patients): pneumonia (8%), sepsis (5%), pain, pyrexia, cough, and hypotension (3% each)
- No events of TLS were reported
- MTD was not reached

Kumar S, et al. Blood 2017;130:2401–2409

Objective Response Rates in All Patients and by t(11;14) Status

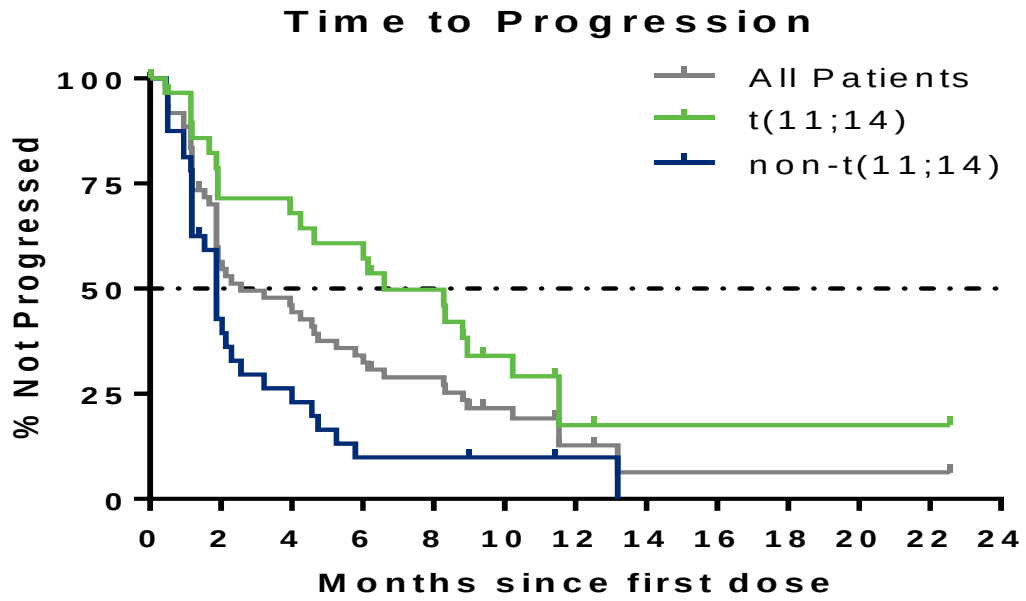




Data cutoff of 19Aug2016

Kumar S, et al. Blood 2017;130:2401–2409

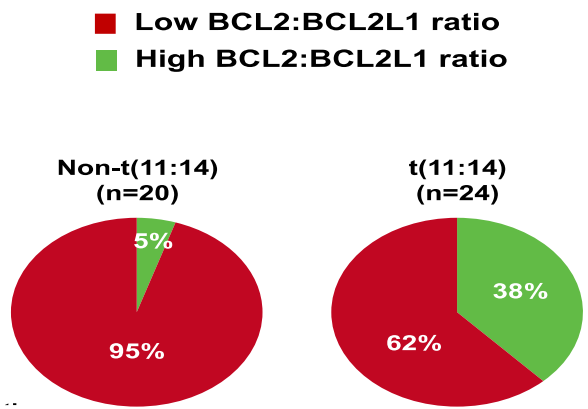
Time to porgression



Median duration of response = 10 months

Kumar et al. Blood 2018

Ratio Bcl-2/ Bcl-X_L as biomarker of response



Kumar et al. Blood 2018

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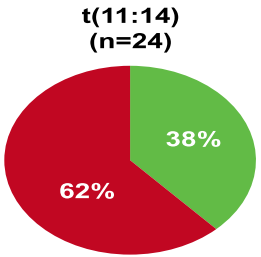

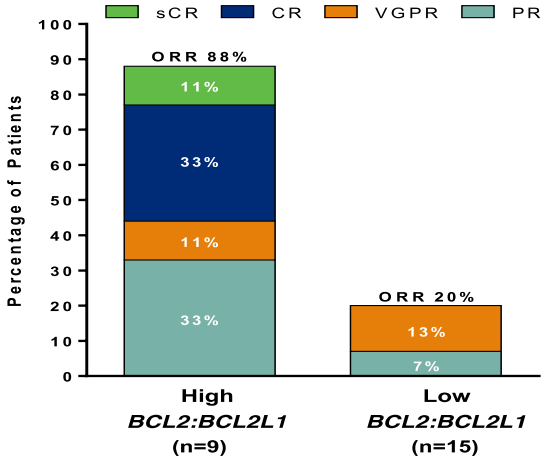

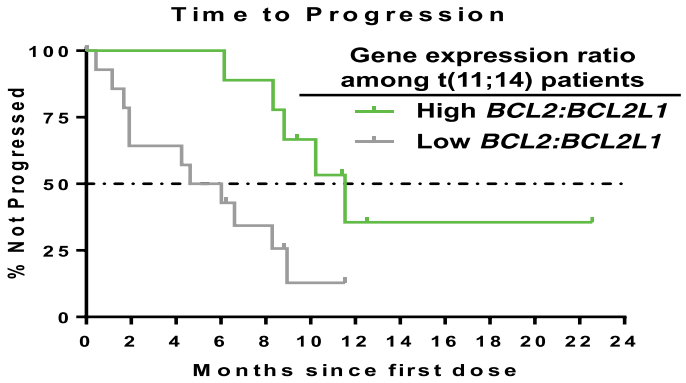

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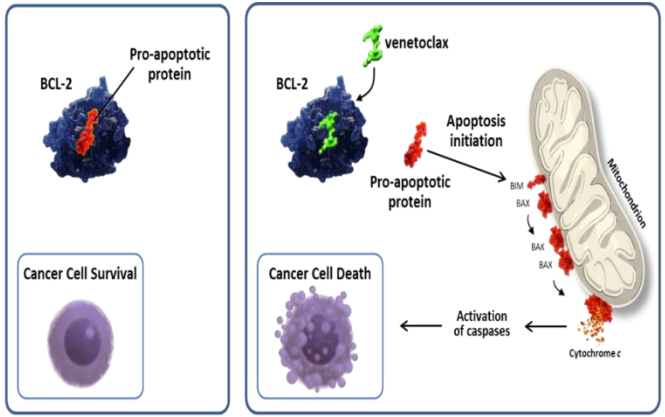
2017 130: 2392-2400
doi:10.1182/blood-2017-06-788323 originally published online August 28, 2017

Promising efficacy and acceptable safety of venetoclax plus bortezomib and dexamethasone in relapsed/refractory MM

Philippe Moreau, Asher Chanan-Khan, Andrew W. Roberts, Amit B. Agarwal, Thierry Facon, Shaji Kumar, Cyrille Touzeau, Elizabeth A. Punnoose, Jaclyn Cordero, Wijith Munasinghe, Jia Jia, Ahmed Hamed Salem, Kevin J. Freise, Joel D. Leverson, Sari Heitner Enschede, Jeremy A. Ross, Paulo C. Maciag, Maria Verdugo and Simon J. Harrison

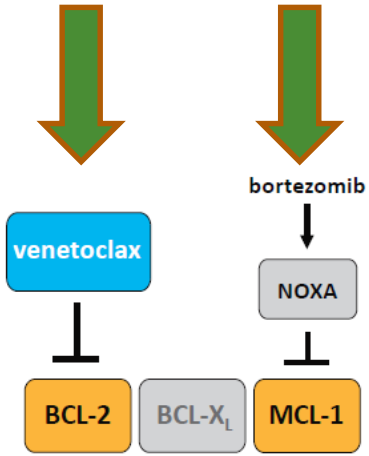
Background

- Anti-apoptotic proteins BCL-2 and MCL-1 promote multiple myeloma (MM) cell survival
- Venetoclax is a selective, orally available small molecule BCL-2 inhibitor[1] and bortezomib can indirectly inhibit MCL-1[2]
- When combined, venetoclax can enhance the activity of bortezomib in MM cell lines and xenograft models[2]



BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.[1-3]

Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).[4-6]



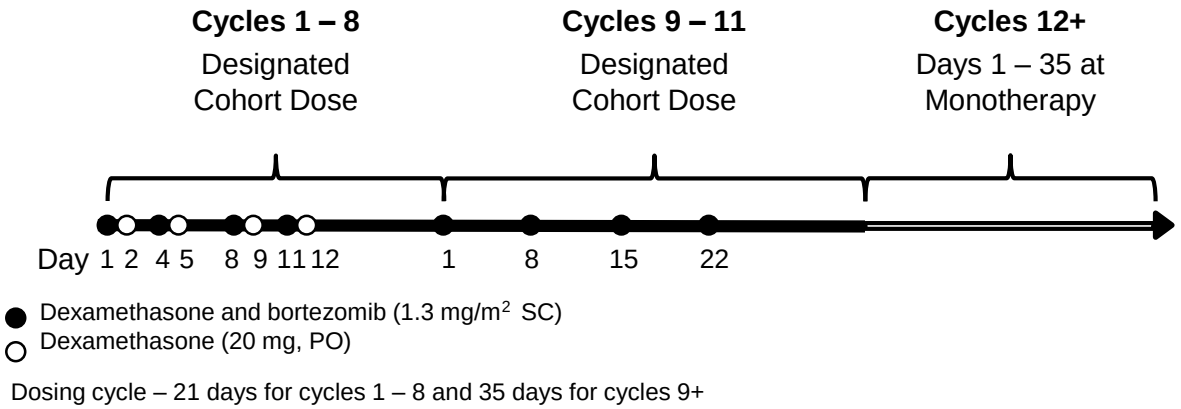
$BCL\text{-}2^{high}$ $MCL\text{-}1^{high}$

1. Leverson JD, et al. *Sci Transl Med* 2015; 7:279ra40. 2. Czabotar, et al. *Nature Reviews* 2014;15:49-63. 3. Plati J, Bucur O, Khosravi-Far R. *Integr Biol (Camb)* 2011;3:279-296.
4. Certo M, et al. *Cancer Cell*. 2006;9(5):351-65. 5. Souers AJ, et al. *Nat Med*. 2013;19(2):202-8. 6. Del Gaizo Moore V et al. *J Clin Invest*. 2007;117(1):112-21.

1. Roberts AW et al. N Engl J Med 2016;374:311-322;
2. Punnoose E et al. Mol Cancer Ther 2016;15(5):1132-44

Dosing and Enrollment

- Patients received 50–1200 mg venetoclax per designated dose escalation cohorts



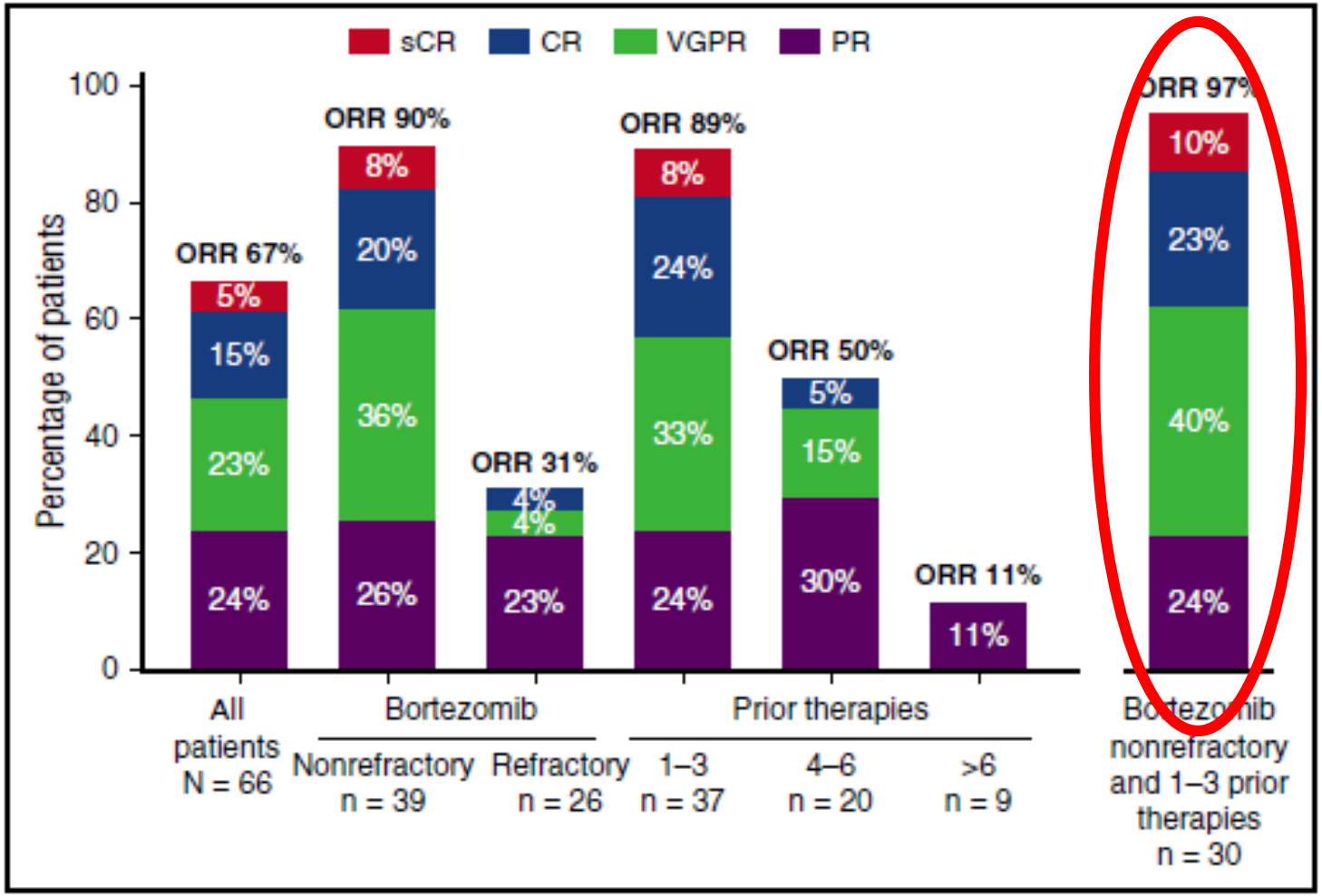
Enrollment by Dose Cohort													
Dose (mg)	50	100	200	300	400	500	600	800	1000	1200	Total DE	SE	Total DE + SE
n	3	6	5	7	6	7	5	3	3	9	**54**	12	**66**

Moreau P, et al. Blood 2017;130:2392–2400 and Suppl

Patient Characteristics

	N = 66
Age, median (range), years	64 (38–79)
ISS stage, n (%)	
Stage I	21 (35)
Stage II/III	39 (65)
Unknown	6
Cytogenetic abnormalities, n (%)	
t(11;14)	9 (14)
t(4;14)	5 (8)
del(17p)	15 (23)
del(13q)	30 (45)
Hyperdiploid	30 (45)
No. of prior lines of therapy, median (range)	3 (1–13)
Stem cell transplant, n (%)	39 (59)
Prior bortezomib/refractory, n (%)	53 (80)/26 (39)
Prior lenalidomide/refractory, n (%)	48 (73)/35 (53)
Refractory to last prior therapy	40 (61)

Moreau P, et al. Blood 2017;130:2392–2400



Moreau P, et al. Blood 2017;130:2392–2400

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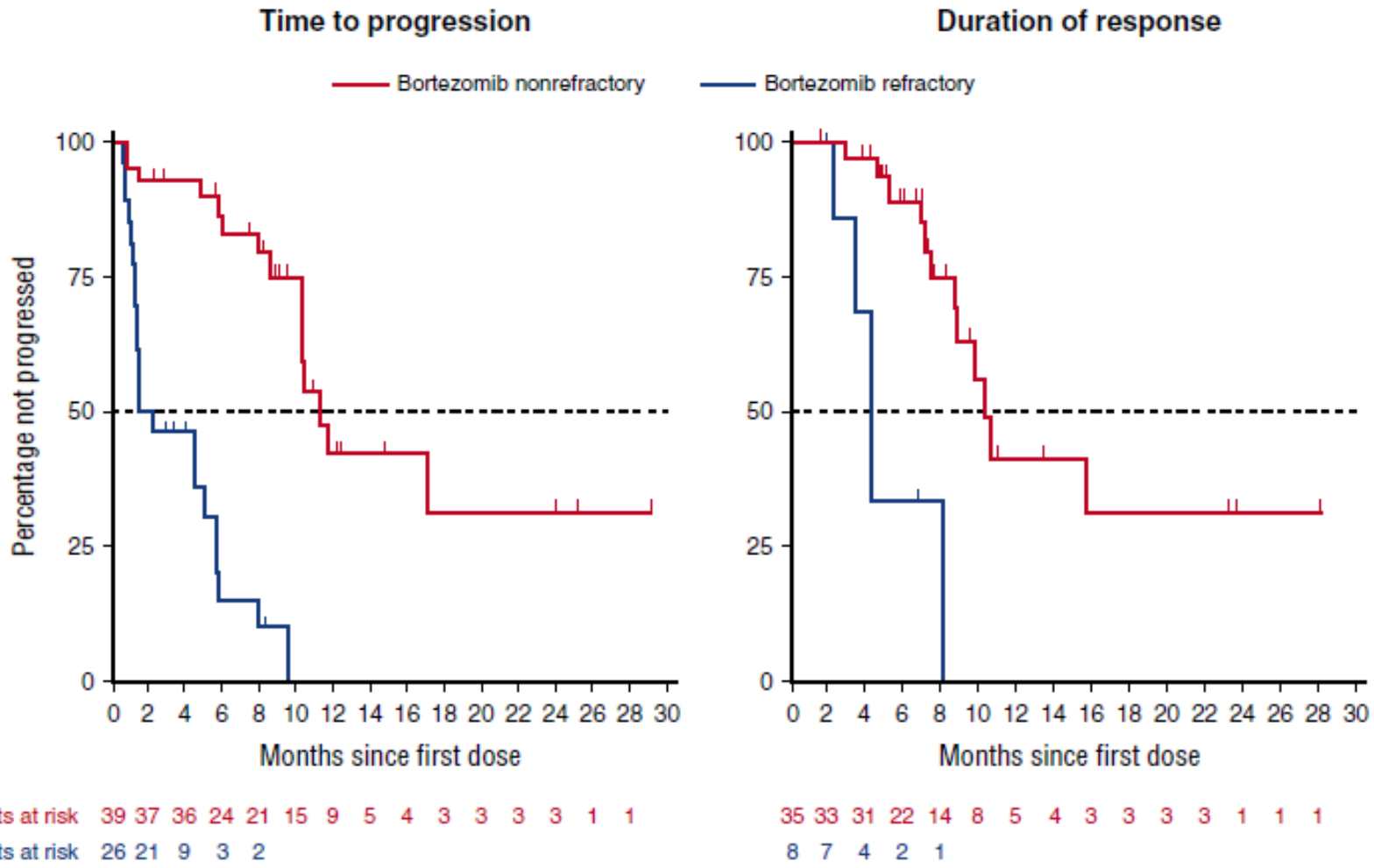
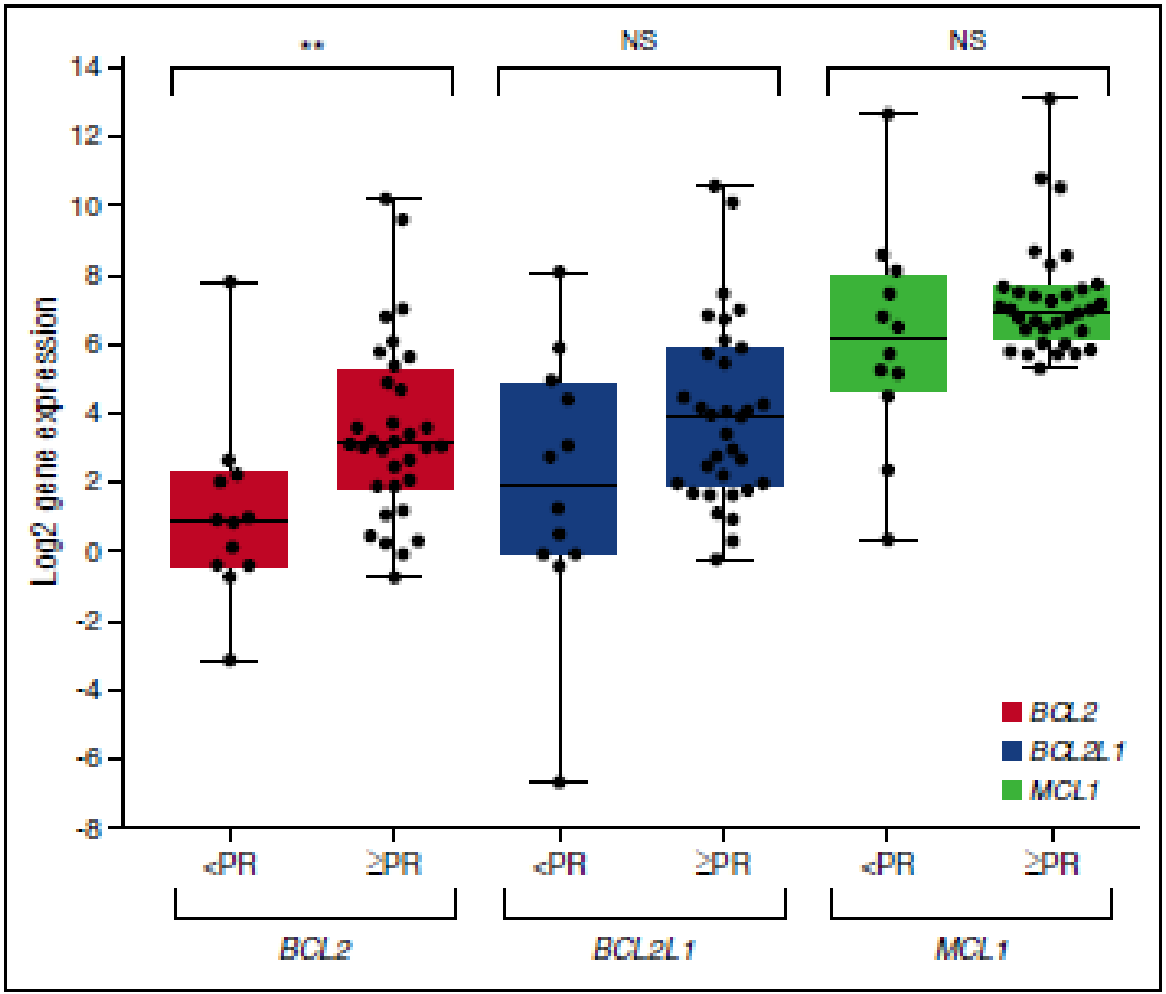


Moreau P, et al. Blood 2017;130:2392–2400



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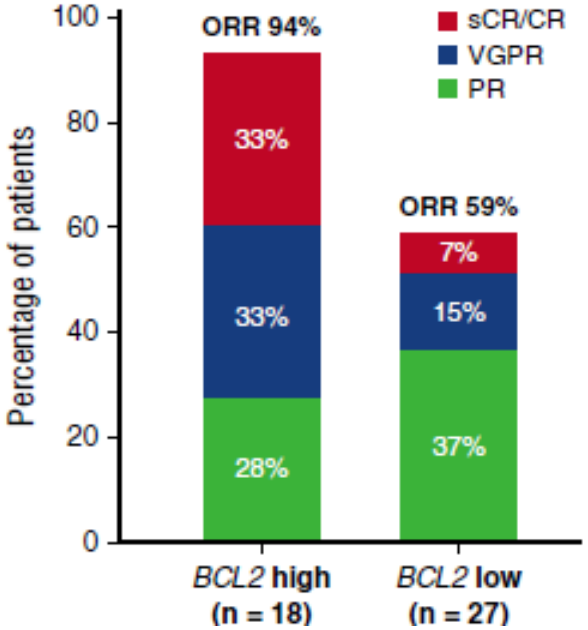

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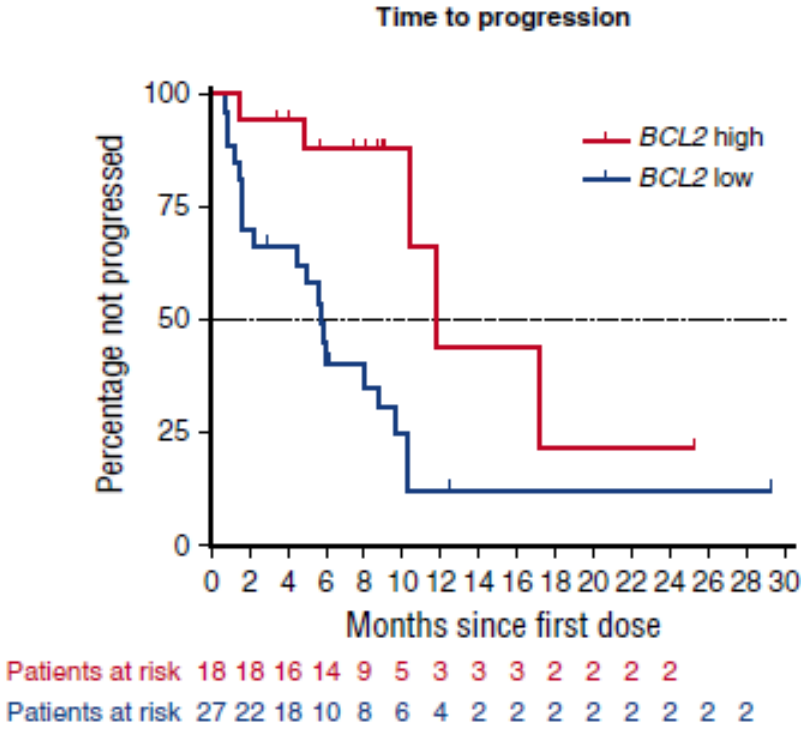
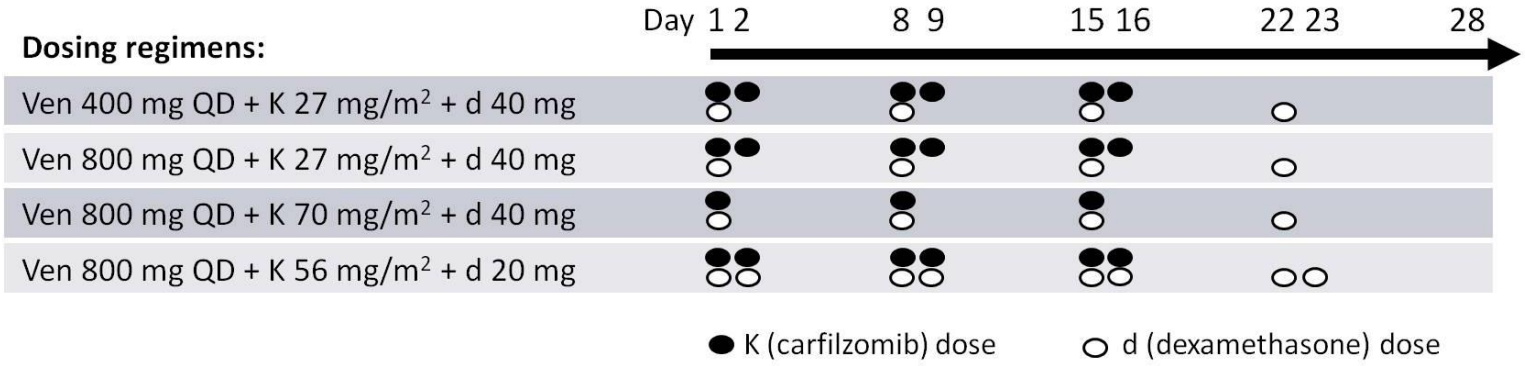


Moreau P, et al. Blood 2017;130:2392–2400

Phase 2 Study of Venetoclax Plus Carfilzomib and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma--Dosing

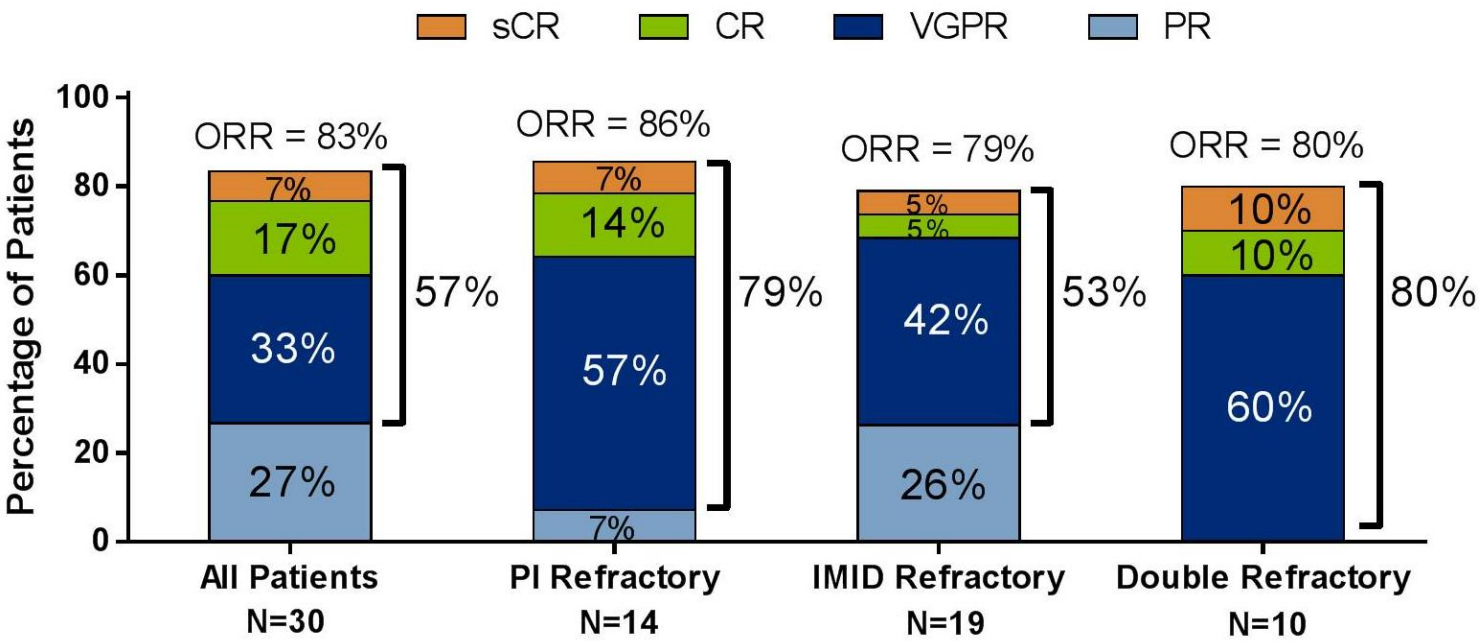
- Patients received treatment in 28-day cycles:



- Carfilzomib was administered at 20mg/m^2 on cycle 1 days 1 and 2
- The 27mg/m^2 and 56mg/m^2 carfilzomib twice weekly dosing were based on the USPI
- Patients stay on combination therapy for up to 18 cycles with the option to continue on venetoclax monotherapy

Costa L, at. 2018 ASCO Annual Meeting

Phase 2 Study of Venetoclax Plus Carfilzomib and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma—ORRs



Costa L, at. 2018 ASCO Annual Meeting

Venetoclax : a hope for plasma cell leukemia patients?

The prognosis of PCL remains
very poor despite the use of novel agents

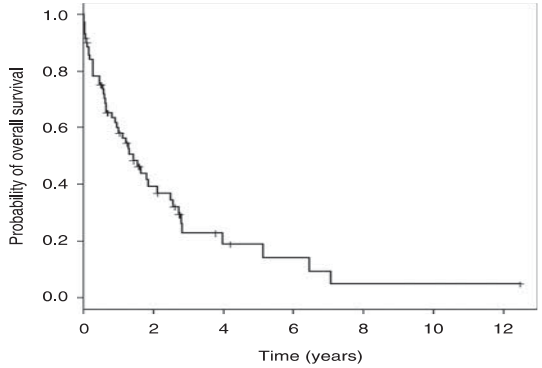


Table 3. Genetic Aberrations in 32 Patients and Association With Overall Survival

	No (%)	HR (95% CI)	*P**	Adjusted *P*†
Copy number analysis				
Hyperdiploidy (≥ 49 Chr)	3 (9)	1.48 (0.44 to 4.93)	.5250	1.00
CNAs ≥ 20	16 (50)	1.54 (0.47 to 5.00)	.4741	1.00
CNAs < 6	5 (16)	1.50 (0.49 to 4.59)	.4791	1.00
Whole/partial loss del 13	19 (59)	4.00 (1.32 to 12.09)	.0141	.0846
1q gain	17 (53)			
MYC locus rearrangement	9 (28)			
Loss/del TP53	9 (28)			
CDKN2C locus homozygous deletion	5 (16)			
FISH				
t(11;14)	16 (50)	0.95 (0.31 to 2.96)	.9303	1.00
t(4;14)	2 (6)	1.53 (0.47 to 5.01)	.4840	1.00
t(14;16)	5 (16)			
del 17p	9 (28)			

Abbreviations: Chr, chromosomes; CNAs, copy number abnormalities; del, deletion; FISH, fluorescence in situ hybridization; HR, hazard ratio.
*Univariable Cox proportional hazard analysis.
†Univariable analyses with Bonferroni adjustment.

t(11;14) is found in up to 50%
of PCL patients

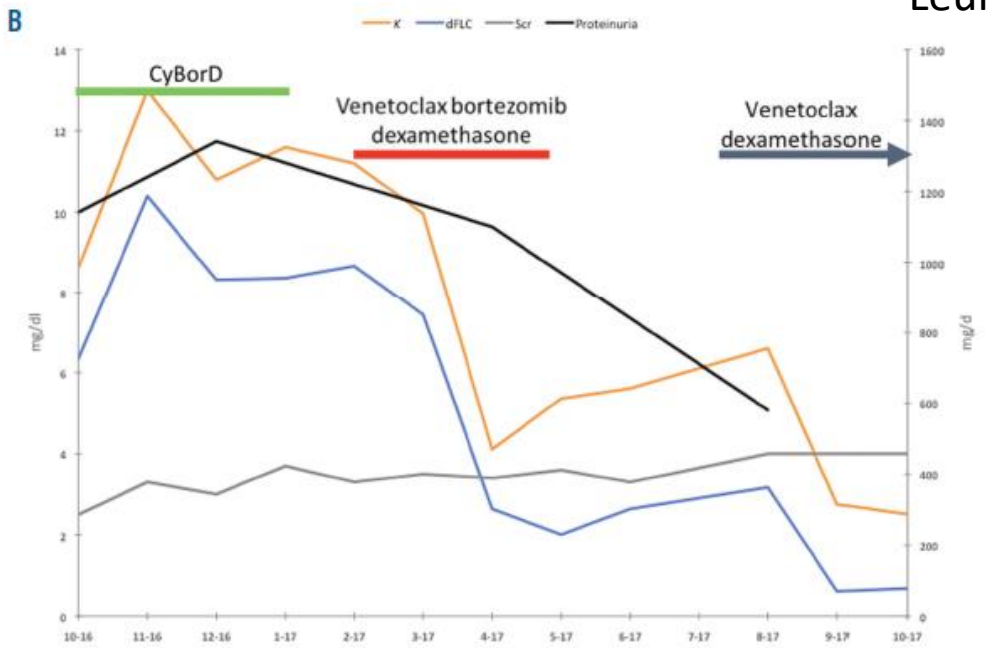
De Larrea, Leukemia 2013
Royer, J Clin Oncol 2016

Venetoclax : a hope for AL-amyloidosis patients?

Venetoclax induced a complete response in a patient with immunoglobulin light chain amyloidosis plateaued on cyclophosphamide, bortezomib and dexamethasone

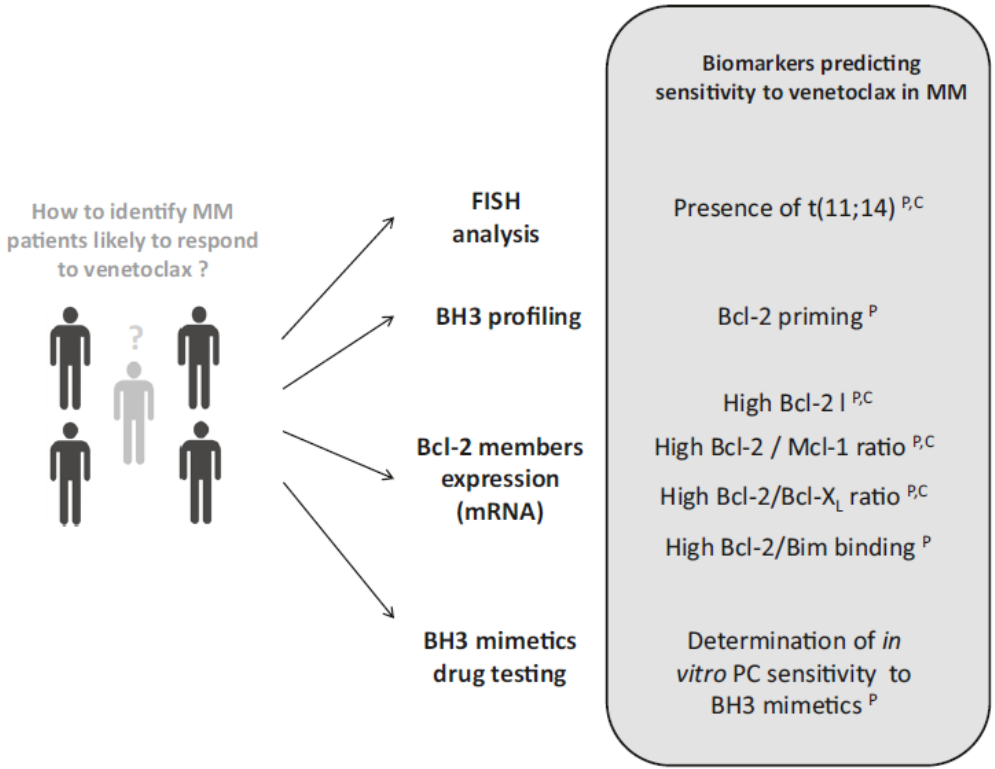
haematologica 2018; 103:e135

Leung et al



t(11;14) is found in up to 50% of patients with AL-amyloidosis

Venetoclax: clinical development in myeloma



Touzeau, Moreau. Leukemia 2018 (review)

Venetoclax: clinical development in myeloma

Table 2 Venetoclax for the treatment of multiple myeloma: selected ongoing clinical trials

Study	Identifier	Phase	Regimen	Population	Status
M13-367	NCT01794520	Phase 1/2	Venetoclax + dexamethasone	R/R MM with t(11 ;14)	Recruiting
M13-494	NCT03539744	Phase 3 RCT	Venetoclax, dexamethasone versus pomalidomide dexamethasone	R/R MM with t(11 ;14)	Recruiting
M12-901	NCT01794507	Phase 1	Venetoclax + bortezomib, dexamethasone	R/R MM	Active, not recruiting
M14-031	NCT02755597	Phase 3 RCT	Bortezomib, dexamethasone ± venetoclax	R/R MM	Active, not recruiting
M15-538	NCT02899052	Phase 1/2	Venetoclax + carfilzomib, dexamethasone	R/R MM	Recruiting
M16-085	NCT03567616	Phase 1/2	Venetoclax + pomalidomide, dexamethasone	R/R MM	Active, not recruiting
M15-654	NCT03314181	Phase 1/2	Venetoclax + daratumumab, dexamethasone + daratumumab, bortezomib, dexamethasone	R/R MM	Recruiting
MC168C	NCT03399539	Phase 1/2	Venetoclax + ixazomib, dexamethasone	R/R MM	Not yet recruiting
BO39813	NCT03312530	Phase 1/2	Venetoclax + cobimetinib + atezolizumab	R/R MM	Recruiting

MM multiple myeloma, *R/R* relapsed/refractory, *RCT* randomized controlled trial

Touzeau , Moreau. Leukemia 2018 (review)

Conclusions

- **Venetoclax: first (?) targeted-therapy in MM**
- **Combination with Pis**
- **AL-amyloidosis, plasma cell leukemia**