Highlights from
IMS 20th meeting 2023

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Terapie del MM refrattario con nuovi agenti: con inibitore di BCL-2 (senza/con PI o IMiD o anti-CD38)

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

EMATOLOGIA

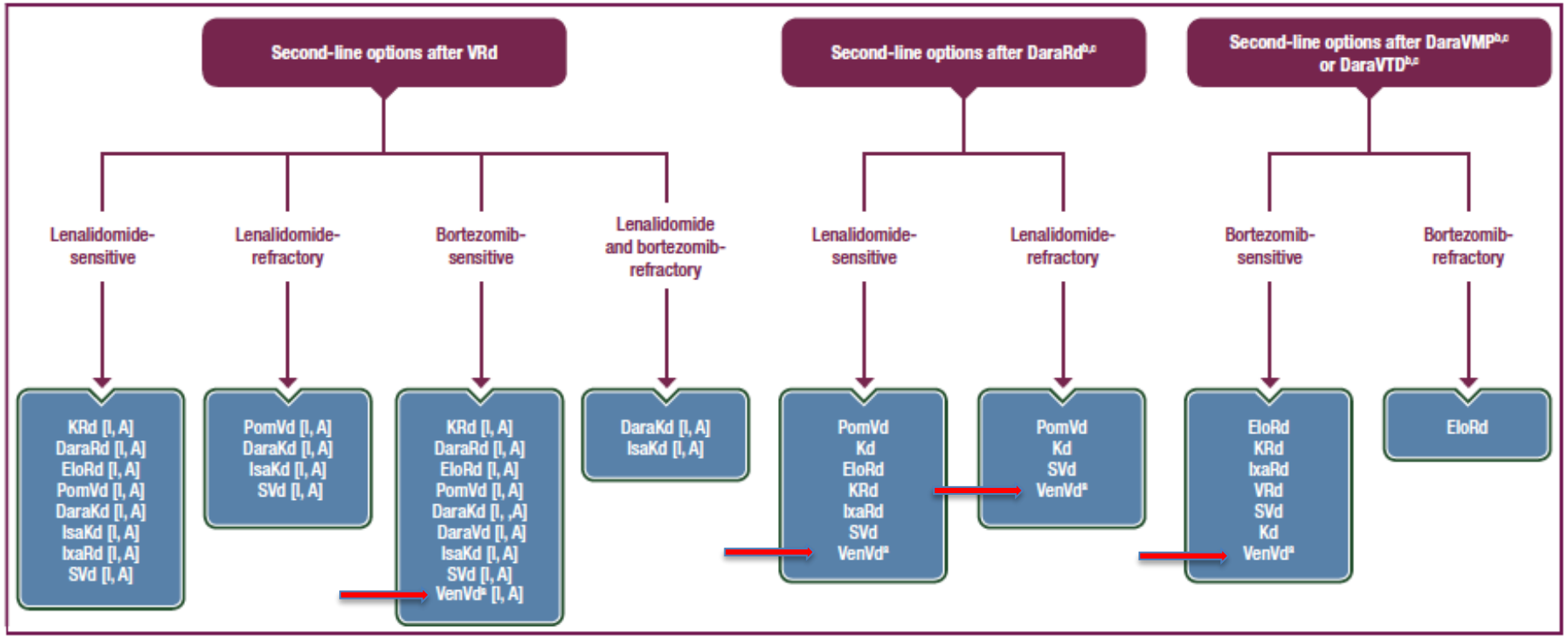
Conflitti di interesse

Research grant: Janssen

Honoraria: Jansenn, Abbvie, Amgen, Takeda, Sanofi

Advisory Board: Janssen, Pfizer, Amgen, Takeda

ESMO 2021



Annals of Oncology 2021

Outline

- **Venetoclax, t(11;14) e meccanismo d'azione**
- **Venetoclax single agent**
- **Bellini : Venetoclax+Bortezomib-dex vs Bortezomib-dex**
- **Canova: Venetoclax-dex vs Poma-dex**
- **Venetoclax+ Carfilzomib**
- **Daratumumab+Venetoclax; Dara+Bor+Venetoclax**
- **Venetoclax+Pomalidomide**

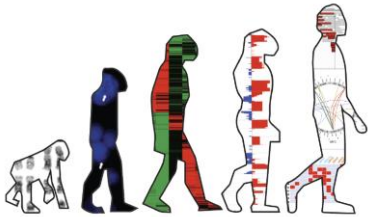
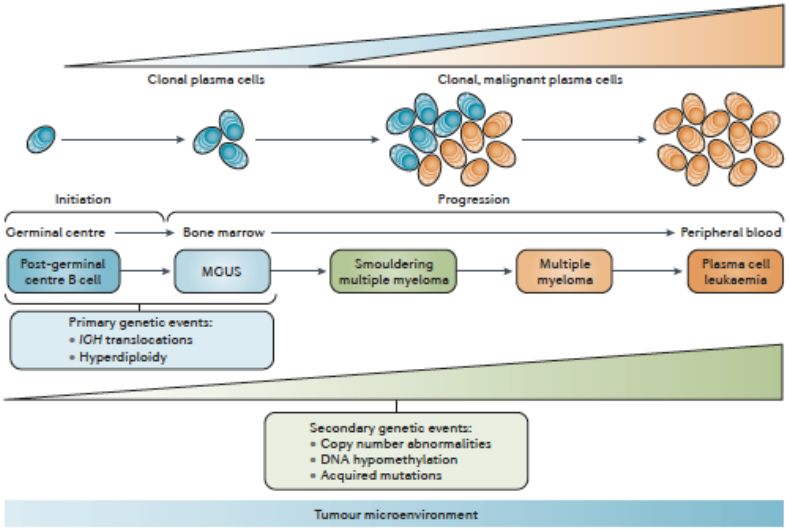
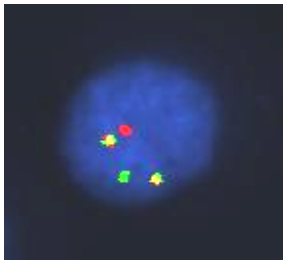


Table 1 | **Proportion of patients with the major clinical features of MM at presentation across molecular subtypes**

Molecular feature defining MM subtype	Bone-disease variant (%)	Renal-failure variant (%)	Anaemia variant (%)	Mixed variant (%)
Trisomies	36	4	14	45
t(11;14)	35	7	14	44
t(4;14)	26	6	23	45
t(14;16)	13	25	4	46
t(14;20)	0	0	0	1
t(6;14)	33	0	33	33
Unknown partner or deletion of IgH gene region	37	14	9	41

…noglobulin heavy chain; MM, multiple myeloma.





The multiple myelomas — current concepts in cytogenetic classification and therapy

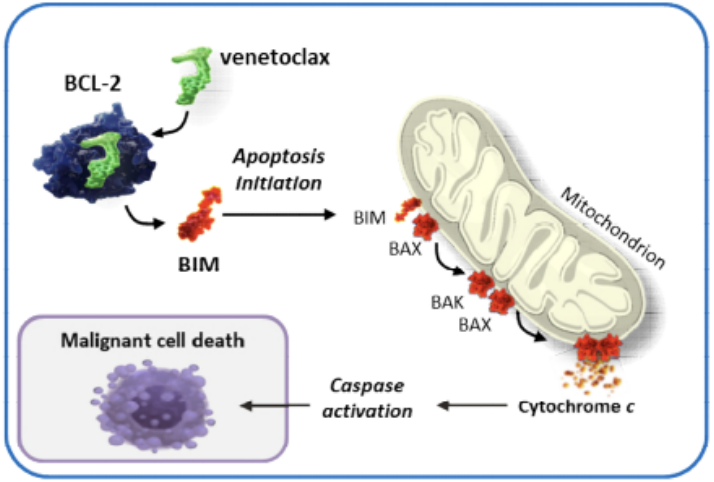
Shaji K. Kumar and S. Vincent Rajkumar*

2018

NATURE REVIEWS | CLINICAL ONCOLOGY

Introduction

- MM is a genetically complex disease, and underlying genetic aberrations may influence treatment outcomes as well as inform therapeutic decisions; however, biomarker-directed therapies are lacking
- t(11;14) is the most common translocation in MM, present in approximately 16%–24% of patients[1]
- BCL-2 is an anti-apoptotic protein that promotes cell survival in MM harboring t(11;14)[2]
- Venetoclax is a highly selective, potent, oral BCL-2 inhibitor that has shown encouraging efficacy and safety in patients with t(11;14)-positive RRMM[3-5]
  - In a Phase 1/2 study, 51 patients with t(11;14)-positive RRMM were treated with VenDex, resulting in ORRs of 48%–60%[5]

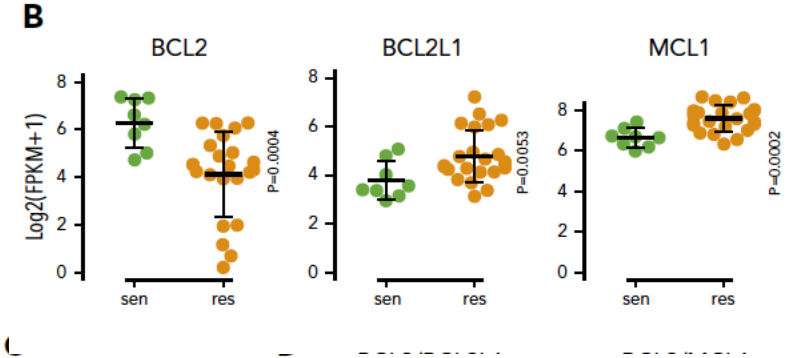


1. Bal S, et al. *Am J Cancer Res*. 2022;12(7):2950-2965. 2. Touzeau C, et al. *Leukemia*. 2014;28(1):210-212. 3. Kumar S, et al. *Blood*. 2017;130(22):2401-2409.
4. Kumar SK, et al. *Lancet Oncol*. 2020;21(12):1630-1642. 5. Kaufman JL, et al. *Am J Hematol*. 2021;96(4):418-427.
MM, multiple myeloma; ORR, overall response rate; PomDex, pomalidomide and dexamethasone; RRMM, relapsed/refractory MM; VenDex, venetoclax and dexamethasone.

LYMPHOID NEOPLASIA

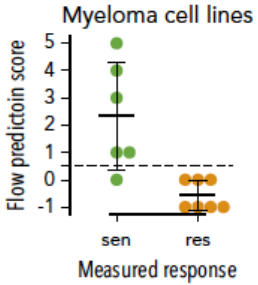
Venetoclax sensitivity in multiple myeloma is associated with B-cell gene expression

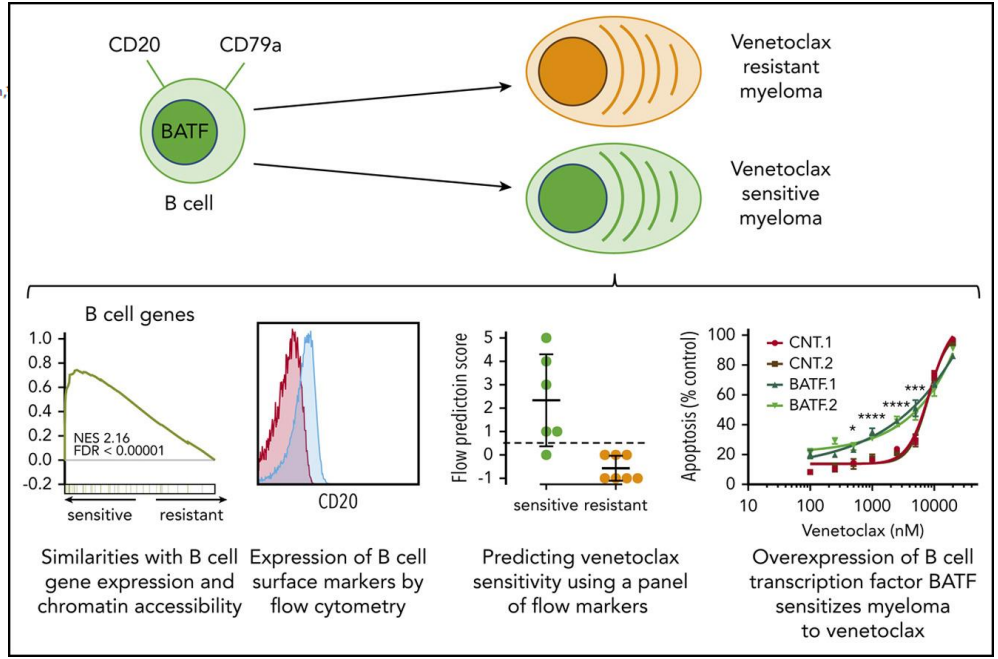
Vikas A. Gupta,[1] Benjamin G. Barwick,[1] Shannon M. Matulis,[1] Ryosuke Shirasaki,[2] David L. Jaye,[3] Jonathan J. Keats,[4] Benjamin Oberlton,[1] Nisha S. Joseph,[1] Craig C. Hofmeister,[1] Leonard T. Heffner,[1] Madhav V. Dhodapkar,[1] Ajay K. Nooka,[1] Sagar Lonial,[1] Constantine S. Mitsiades,[2] Jonathan L. Kaufman,[1] and Lawrence H. Boise[1]



Marker	Score
CD79a	+2
CD20	+2
CD45	+1
CD86	+1
CD28	-1

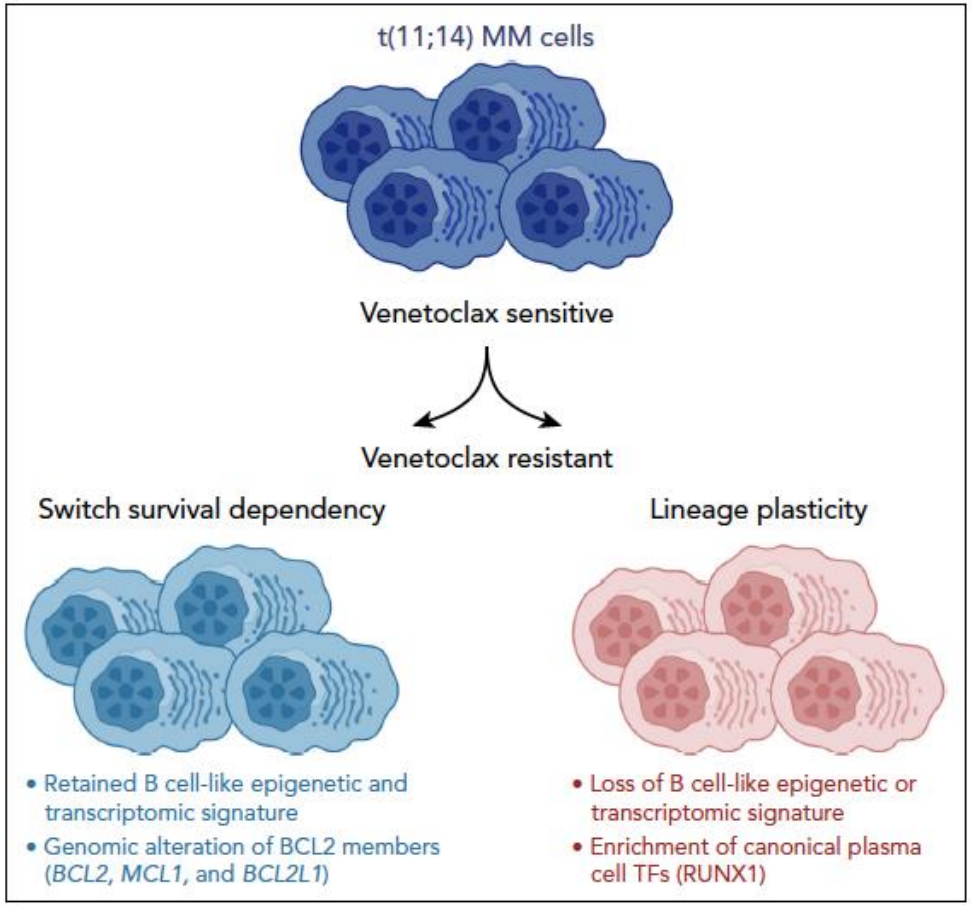
Sensitive	Resistant
≥1	≤0





Sensibilità associata a Bcl2 overespresso, markers flow B

Blood 2021



Leblay et al. Blood 2024

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- **Venetoclax, t(11;14) e meccanismo d'azione**
- **Venetoclax single agent+dex**
- **Bellini : Venetoclax+Bortezomib-dex vs Bortezomib-dex**
- **Canova: Venetoclax-dex vs Poma-dex**
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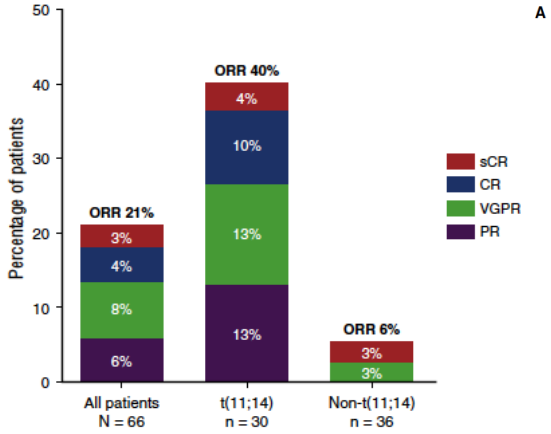
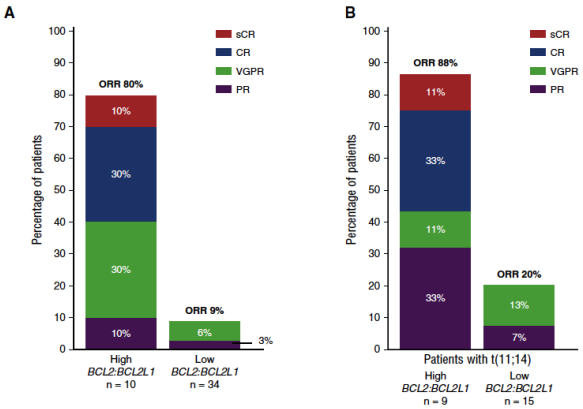
- **Daratumumab+Venetoclax; Dara+Bor+Venetoclax**
- **Venetoclax+Pomalidomide**

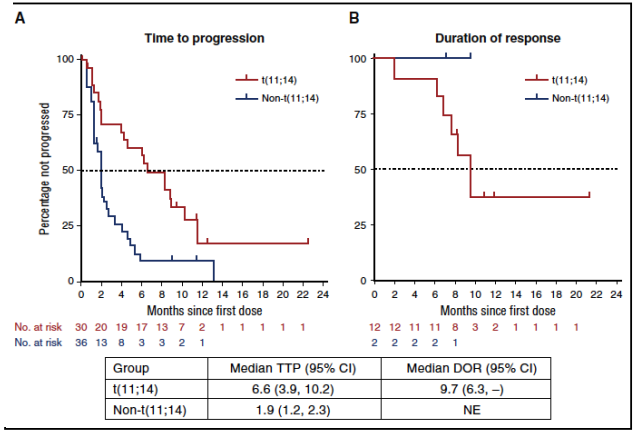
CLINICAL TRIALS AND OBSERVATIONS

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

Shaji Kumar,[1] Jonathan L. Kaufman,[2] Cristina Gasparetto,[3] Joseph Mikhael,[4] Ravi Vij,[5] Brigitte Pegourie,[6] Lofti Benboubker,[7] Thierry Facon,[8] Martine Amiot,[9] Philippe Moreau,[9] Elizabeth A. Punnoose,[10] Stefanie Alzate,[11] Martin Dunbar,[11] Tu Xu,[11] Suresh K. Agarwal,[11] Sari Heitner Enschede,[11] Joel D. Leverson,[11] Jeremy A. Ross,[11] Paulo C. Maciag,[11] Maria Verdugo,[11] and Cyrille Touzeau[9]







Group	Median TTP (95% CI)	Median DOR (95% CI)
t(11;14)	6.6 (3.9, 10.2)	9.7 (6.3, –)
Non-t(11;14)	1.9 (1.2, 2.3)	NE

Regimen (trial ID)	Phase/ number of patients	Dosing	Median number of prior lines (range)	Efficacy	Adverse events (grades 3 to 4)	Reference
Venetoclax Monotherapy (**NCT01794520**)	I/66	**Venetoclax:** dose escalation cohort (30 pts): 300 to 1,200 mg daily until progression **Venetoclax:** safety expansion cohort (36 pts): 1,200 mg daily until progression	5 (1–15)	**Pts (30): with t(11;14)** ORR: 40%, > VGPR: 27% mTTP: 6.6 months (3.9–10.2) mDOR: 9.7 months **Pts (33) without t(11;14):** ORR: 6%, > VGPR: 6% mTTP: 1.9 months (1.2–2.3)	Thrombocytopenia (26%), neutropenia (21%), anemia (14%), and leukopenia (14%)	Kumar S et al. (33)
Venetoclax plus Dexamethasone (**NCT01794520**)	I/20 II/31	**Venetoclax:** 800 mg daily; **Dexamethasone** 40 mg oral (20 mg for pts ≥75 years of age) on days 1, 8, and 15 of each 21-day cycle	3 (1–7)/ 5 (2–12)	ORR: 60%/48% mTTP: 12.4 months/ estimated mTTP: 10.8 months/ mDOR: 12.4 months/ estimated DOR at 12 months: 61%	Lymphopenia (20%), thrombocytopenia (10%), neutropenia (10%), anemia (12%), and hypophosphatemia (10%)	Kaufman JL et al. (34)

Blood 2017

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Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial

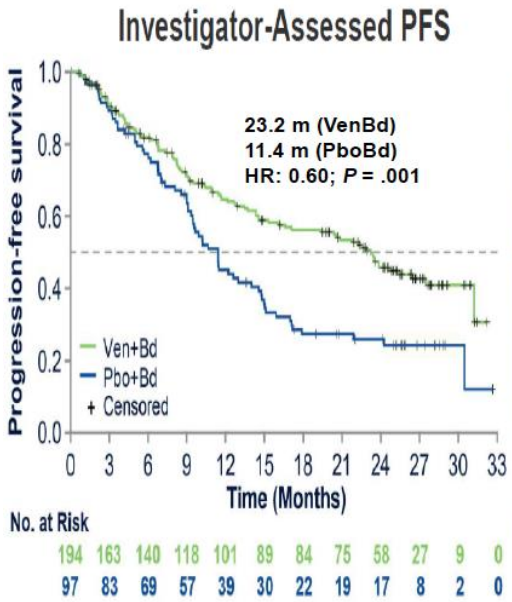
Regimen (trial ID)	Phase/ number of patients	Dosing	Median number of prior lines (range)
Venetoclax or Placebo plus Bortezomib and Dexamethasone (BELLINI, **NCT02755597**)	III/291	**Venetoclax** (800 mg daily) (194 pts) or **Placebo** (97 pts); **Bortezomib** (1.3 mg/m²) on days 1, 4, 8, and 11 during cycles 1 to 8 and days 1, 8, 15, and 22 during cycles 9 and beyond; **Dexamethasone** (20 mg) on days 1, 2, 4, 5, 8, 9, 11, and 12 during cycles 1 to 8 and on days 1,2, 8, 9, 15, 16, 22, and 23 during cycles 9 and beyond. Treatment was given in 21-day cycles for the first eight cycles and 35-day cycles from	2 (1–3)

	All patients in intention-to-treat population			Patients with t(11;14) translocation			Patients with high *BCL2* expression		
	Venetoclax group (n=194)	Placebo group (n=97)	p value	Venetoclax group (n=20)	Placebo group (n=15)	p value*	Venetoclax group (n=66)	Placebo group (n=32)	p value*
Stringent complete response	15 (8%)	2 (2%)	0·054	4 (20%)	0	0·102	5 (8%)	0	0·268
Complete response	36 (19%)	3 (3%)	0·00028	5 (25%)	1 (7%)	0·129	19 (29%)	0	0·0019
Very good partial response	63 (32%)	30 (31%)	0·800	5 (25%)	3 (20%)	0·842	23 (35%)	9 (28%)	0·663
Partial response	45 (23%)	31 (32%)	0·112	4 (20%)	3 (20%)	0·560	9 (14%)	15 (47%)	0·00085
Minimal response	3 (2%)	10 (10%)	0·00061	0	4 (27%)	0·0064	0	4 (13%)	0·017
Stable disease	14 (7%)	10 (10%)	0·381	0	3 (20%)	0·035	3 (5%)	2 (6%)	1·00
Progressive disease	10 (5%)	5 (5%)	0·990	0	0	..	2 (3%)	0	0·816
Overall response rate (partial response or better)	159 (82%)	66 (68%)	0·0081	18 (90%)	7 (47%)	0·0038	56 (85%)	24 (75%)	0·367
Very good partial response or better	114 (59%)	35 (36%)	0·00029	14 (70%)	4 (27%)	0·016	47 (71%)	9 (28%)	0·00013
Complete response or better (post-hoc)	51 (26%)	5 (5%)	..	9 (45%)	1 (7%)	..	24 (36%)	0	0·00024
Minimal residual disease									
10^{-4}	37 (19%)	3 (3%)	0·00021	8 (40%)	0	0·0062	18 (27%)	1 (3%)	0·0104
10^{-5}	26 (13%)	1 (1%)	0·00066	5 (25%)	0	0·056	12 (18%)	0	0·025
10^{-6}	14 (7%)	1 (1%)	0·026	4 (20%)	0	0·080	6 (9%)	0	0·190
Median duration of response, months (95% CI)	Not reached (21·0–not reached)	12·8 (9·2–15·5)	..	Not reached	12·2 (7·9–not reached)	..	Not reached (21·0–not reached)	8·8 (7·6–not reached)	..

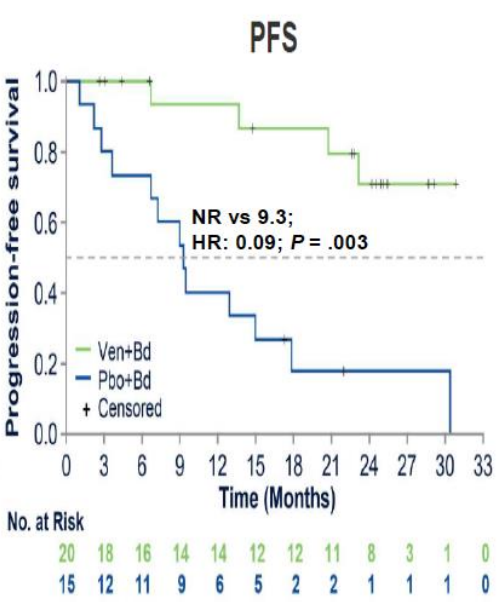
	Venetoclax group (n=194)	Placebo group (n=97)
Median age, years (IQR)	66 (59–73)	65 (61–71)
Age ≥65 years	108 (56%)	52 (54%)
Sex		
Males	97 (50%)	55 (57%)
Females	97 (50%)	42 (43%)
Multiple myeloma International Staging System		
Stage 1	81 (42%)	48 (49%)
Stage 2	69 (36%)	32 (33%)
Stage 3	39 (20%)	13 (13%)
Not evaluable or missing data	5 (3%)	4 (4%)
Eastern Cooperative Oncology Group performance status		
0	101 (52%)	47 (48%)
1 or 2	92 (47%)	49 (51%)
Missing	1 (1%)	1 (1%)
Median time since diagnosis, years (IQR)	3·5 (2·1–5·8)	4·0 (2·1–5·7)
Number of previous lines of therapy		
1	91 (47%)	44 (45%)
2 or 3	103 (53%)	53 (55%)
Cytogenetic risk		
High risk*	31 (16%)	18 (19%)
Standard risk†	141 (73%)	72 (74%)
Unknown or missing data	22 (11%)	7 (7%)
t(11;14) status		
Positive	20 (10%)	15 (15%)
Negative	152 (78%)	74 (76%)
Unknown or missing	22 (11%)	8 (8%)
BCL-2 expression (immunohistochemistry)‡		
High	93/119 (78%)	47/58 (81%)
Low	26/119 (22%)	11/58 (19%)

Lancet 2020

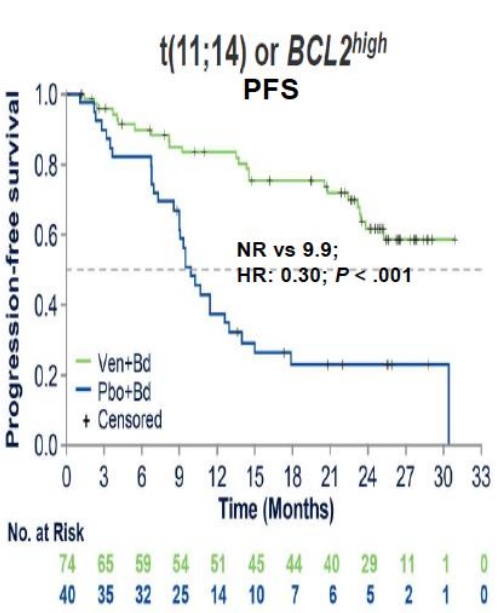
PFS in all patients



PFS in patients with t(11;14)



PFS by t(11;14) and *BCL2* status



	Venetoclax group (n=193)				Placebo group (n=96)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any	25 (13%)	102 (53%)	54 (28%)	11 (6%)	11 (11%)	57 (59%)	26 (27%)	1 (1%)
Diarrhoea	83 (43%)	28 (15%)	0	0	35 (36%)	11 (11%)	0	0
Nausea	64 (33%)	6 (3%)	0	0	20 (21%)	1 (1%)	0	0
Constipation	65 (34%)	0	0	0	29 (30%)	1 (1%)	0	0
Fatigue	49 (25%)	10 (5%)	0	0	27 (28%)	4 (4%)	0	0
Neuropathy peripheral	48 (25%)	8 (4%)	1 (1%)	0	20 (21%)	4 (4%)	0	0
Upper respiratory tract infection	53 (27%)	3 (2%)	0	0	22 (23%)	2 (2%)	0	0
Insomnia	50 (26%)	4 (2%)	0	0	26 (27%)	3 (3%)	0	0
Thrombocytopenia	22 (11%)	13 (7%)	15 (8%)	0	6 (6%)	10 (10%)	19 (20%)	0
Anaemia	21 (11%)	27 (14%)	1 (1%)	0	10 (10%)	13 (14%)	1 (1%)	0
Neutropenia	10 (5%)	16 (8%)	19 (10%)	0	2 (2%)	5 (5%)	2 (2%)	0
Pneumonia	10 (5%)	22 (11%)	5 (3%)	3 (2%)	6 (6%)	7 (7%)	2 (2%)	0

- Alto rate mortalità x infezioni in Ven arm 14 vs 1
- FDA ha sospeso trial a marzo 2019

In conclusion, the results of BELLINI suggest that venetoclax plus bortezomib and dexamethasone compared with placebo plus bortezomib and dexamethasone significantly improves progression-free survival, overall response rate, and the rate of very good partial responses or better, although the increased risk of death indicates an unfavourable risk–benefit profile for biologically unselected patients with relapsed or refractory multiple myeloma. The finding that patients with t(11;14) and those with high *BCL2* expression appear to have a more favourable risk–benefit profile than patients without t(11;14) and with low *BCL2* expression suggests that a biomarker-driven approach might be appropriate for the use of venetoclax in multiple myeloma. This concept is

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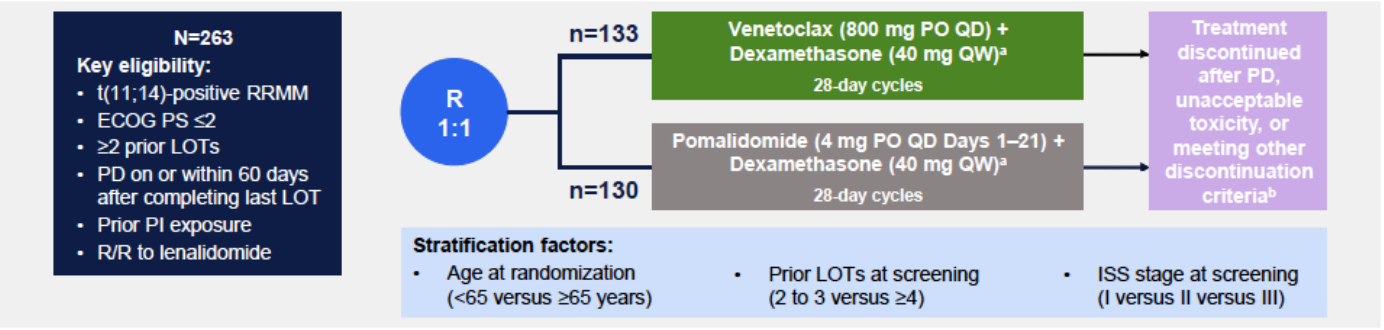
CANOVA is an ongoing, randomized, global, multicenter, open-label Phase 3 study of VenDex versus PomDex in t(11;14)-positive RRMM



- **Primary Endpoint**
  - PFS per IRC in the ITT population
- **Analysis Populations**
  - ITT population: all randomized patients
  - Safety analysis set: all patients who received ≥1 dose of study drug
- **Key Secondary Endpoints**
  - ORR and ≥VGPR per IRC (based on IMWG 2016)
  - OS
  - MRD negativity rate ($<10^{-5}$)
  - PRO parameters (**Supplemental Materials**; scan Conclusions slide QR code)
    - Time to deterioration of disease symptoms[c]
    - Time to deterioration of physical functioning[d]

[a]Patients aged ≥75 years received dexamethasone 20 mg QW. Dexamethasone could be administered IV when PO was not possible. [b]Patients who discontinued treatment due to PD were followed for survival and posttreatment information; those who discontinued treatment due to a reason other than PD remained on study and continued disease assessments until confirmed PD, death, or withdrawal of consent. [c]As measured by the EORTC QLQ Multiple Myeloma Module 20 disease symptom domain. [d]As measured by the EORTC QLQ Core 30 physical functioning domain.
ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; IMWG, International Myeloma Working Group; IRC, independent review committee; ISS, International Staging System; ITT, intent to treat; LOT, line of therapy; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; PO, oral; PomDex, pomalidomide and dexamethasone; PRO, patient-reported outcome; QD, once daily; QW, once weekly; R, randomized; R/R, relapsed/refractory; RRMM, R/R multiple myeloma; VenDex, venetoclax and dexamethasone; VGPR, very good partial response.

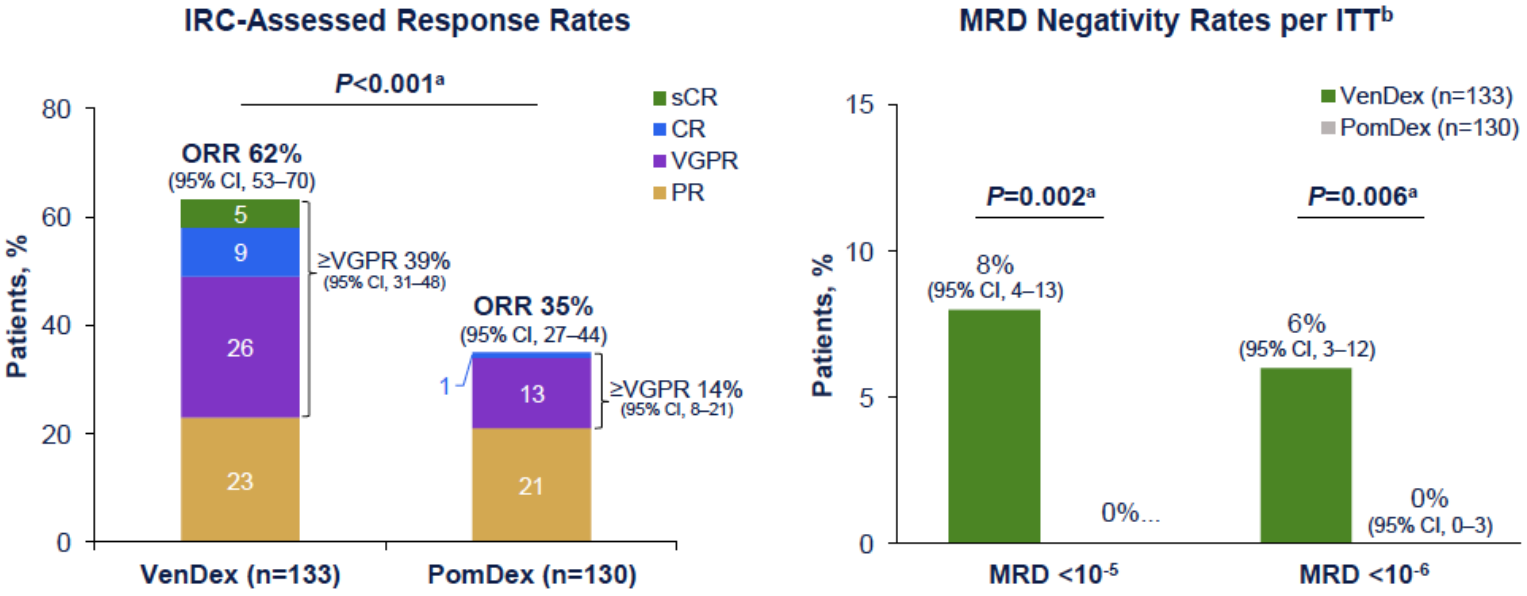
Patient baseline demographics and clinical characteristics

Baseline characteristic	VenDex (n=133)	PomDex (n=130)
Median age (range), years	67 (39–85)	66 (37–89)
<65 years, n (%)	56 (42)	58 (45)
≥65 years, n (%)	77 (58)	72 (55)
≥75 years, n (%)	29 (22)	23 (18)
Male, n (%)	81 (61)	69 (53)
Race, n (%)[a]		
Asian	40 (31)	40 (31)
Black or African American	1 (1)	2 (2)
White	88 (68)	85 (66)
Hispanic or Latino ethnicity, n (%)[a]	6 (5)	4 (3)
ECOG PS, n (%)		
0 to 1	118 (89)	124 (95)
2	15 (11)	6 (5)
IMWG consensus risk[a,b]		
Standard risk, n (%)	91 (93)	88 (92)
High risk, n (%)	7 (7)	8 (8)
Missing, n	35	34
Cytogenetic risk factors, n/N (%)		
del(17p)	14/66 (21)	15/66 (23)
gain(1q) (≥3 copies)	13/51 (25)	17/47 (36)

Baseline characteristic	VenDex (n=133)	PomDex (n=130)
ISS stage at screening, n (%)		
I	67 (50)	60 (46)
II	40 (30)	46 (35)
III	26 (20)	24 (18)
Median number of prior LOTs (range)	3 (2–8)	2 (2–8)
Prior LOTs at screening, n (%)		
2 to 3	98 (74)	97 (75)
2	58 (44)	72 (55)
3	40 (30)	25 (19)
≥4	35 (26)	33 (25)
Prior ASCT, n (%)[a]	69 (97)	74 (99)
Refractory to PI, n (%)	109 (82)	95 (73)
Refractory to IMiD, n (%)	128 (96)	127 (98)
Refractory to lenalidomide	128 (96)	125 (96)
Refractory to anti-CD38 mAb, n (%)	47 (35)	50 (38)
Refractory to PI + IMiD, n (%)	105 (79)	94 (72)
Refractory to PI + IMiD + anti-CD38 mAb, n (%)	40 (30)	42 (32)

[a]Percentages were based on the number of patients with available data. Race information was missing for 6 patients (VenDex, n=4; PomDex, n=2), ethnicity for 2 patients in the VenDex arm, and prior stem cell transplant information was missing for 117 patients (VenDex, n=62; PomDex, n=55). [b]High risk was defined as ISS stage II/III and del(17p) per IMWG consensus on risk stratification (Chng WJ, et al. *Leukemia*. 2014;28(2):269-277).
ASCT, autologous stem cell transplant; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; ISS, International Staging System; LOT, line of therapy; mAb, monoclonal antibody; PI, proteasome inhibitor; PomDex, pomalidomide and dexamethasone; VenDex, venetoclax and dexamethasone.

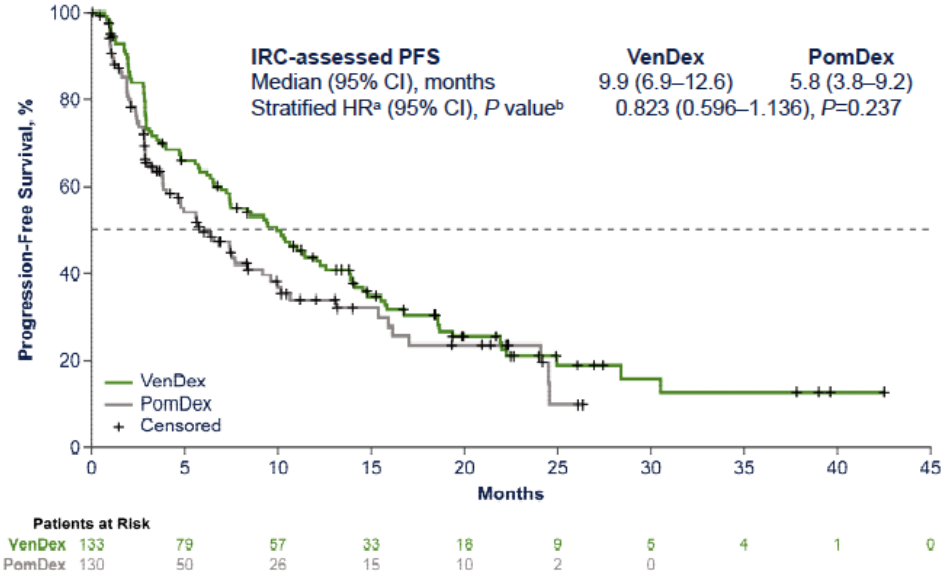
VenDex resulted in higher and deeper responses compared with PomDex



- The median DOR per IRC was 13.8 months (95% CI, 10.1–18.4) with VenDex versus 13.0 months (95% CI, 8.3–23.6) with PomDex

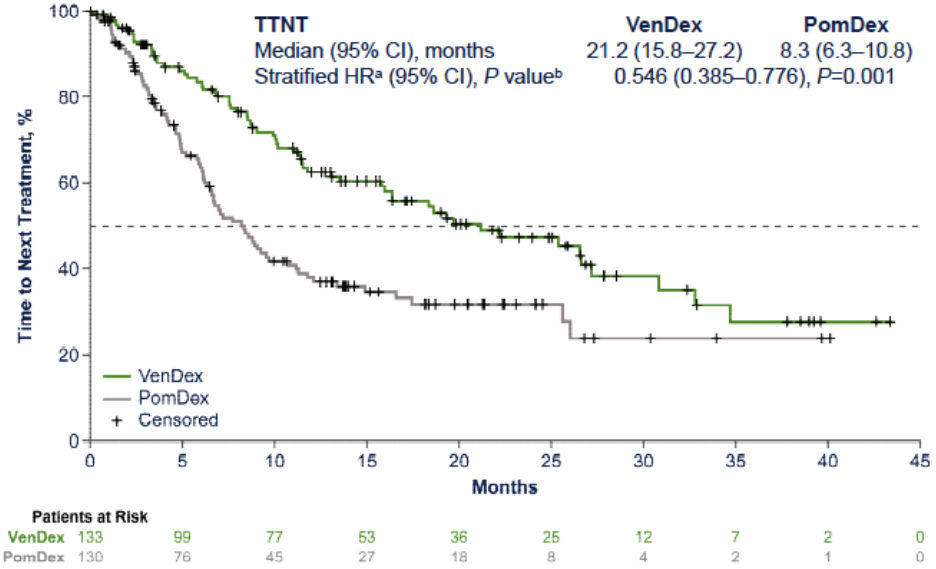
The primary endpoint of IRC-assessed PFS was longer with VenDex versus PomDex but did not meet statistical significance

- The median follow-up time was 24.9 months for VenDex and 25.6 months for PomDex
- The concordance[c] between IRC- and investigator-assessed PFS was 94%



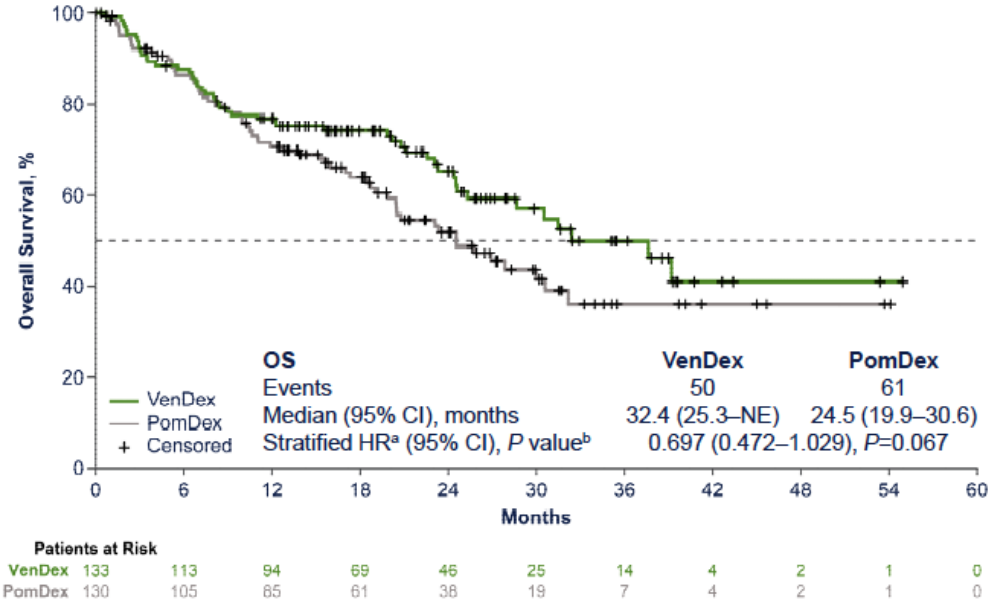
[a]HR for PFS was determined by a stratified Cox proportional hazard model. [b]*P* value was determined by stratified log-rank test. [c]The overall concordance rate was defined as the percentage of patients who had PD by both IRC and investigator and patients who were non-PD by both IRC and investigator among all patients.
HR, hazard ratio; IRC, independent review committee; PD, progressive disease; PFS, progression-free survival; PomDex, pomalidomide and dexamethasone; VenDex, venetoclax and dexamethasone.

The time to next treatment was longer with VenDex versus PomDex

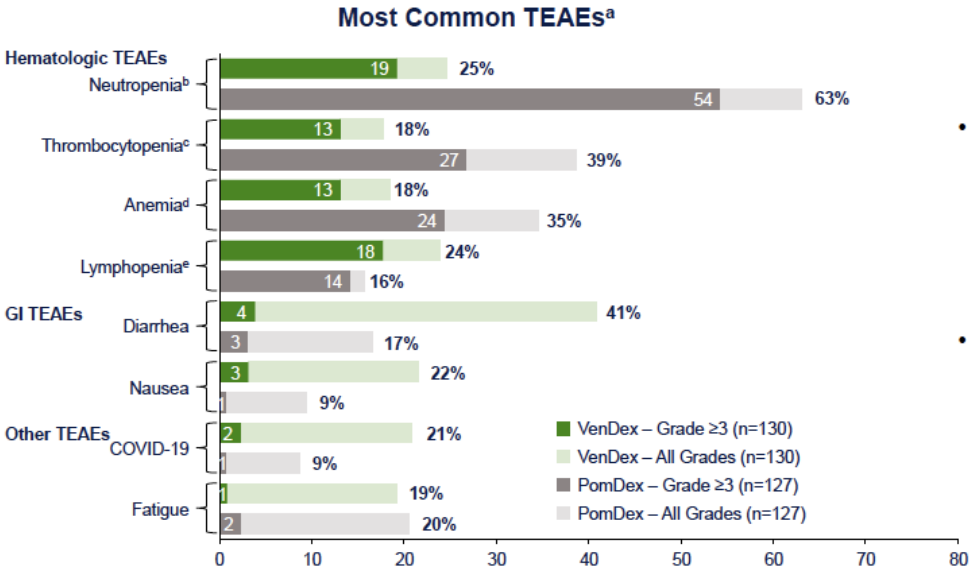


VenDex resulted in numerically longer OS versus PomDex after a median 24.9 months of follow-up

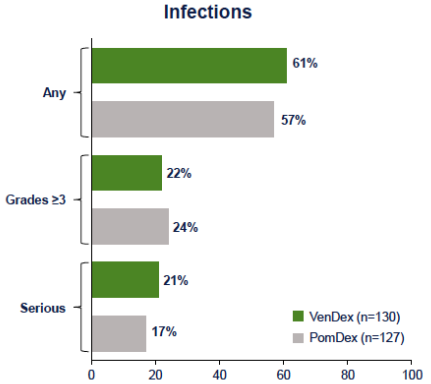
- 62 patients (47%) in the VenDex arm and 78 (60%) in the PomDex arm went on to receive subsequent anti-MM therapy
- The types of posttreatment anti-MM therapies received were generally balanced between VenDex and PomDex (**Supplemental Materials**; scan Conclusions slide QR code)



The safety profiles were consistent with the known safety profile of each individual study drug, with no new safety signals observed for venetoclax



- Laboratory TLS occurred in 4 patients in the VenDex arm and 2 patients in the PomDex arm; there were no cases of clinical TLS
- Treatment-related TEAEs are presented in the **Supplemental Materials** (scan Conclusions slide QR code)



[a]Includes any-grade TEAEs occurring in ≥20% of patients in either treatment arm. [b]Includes preferred terms of neutropenia and neutrophil count decreased. [c]Includes preferred terms of thrombocytopenia and platelet count decreased. [d]Includes preferred terms anemia and hemoglobin decreased. [e]Includes preferred terms of lymphopenia and white blood cell count decreased.
GI, gastrointestinal; PomDex, pomalidomide and dexamethasone; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome; VenDex, venetoclax and dexamethasone.

Outline

- **Venetoclax, t(11;14) e meccanismo d'azione**
- **Venetoclax single agent**
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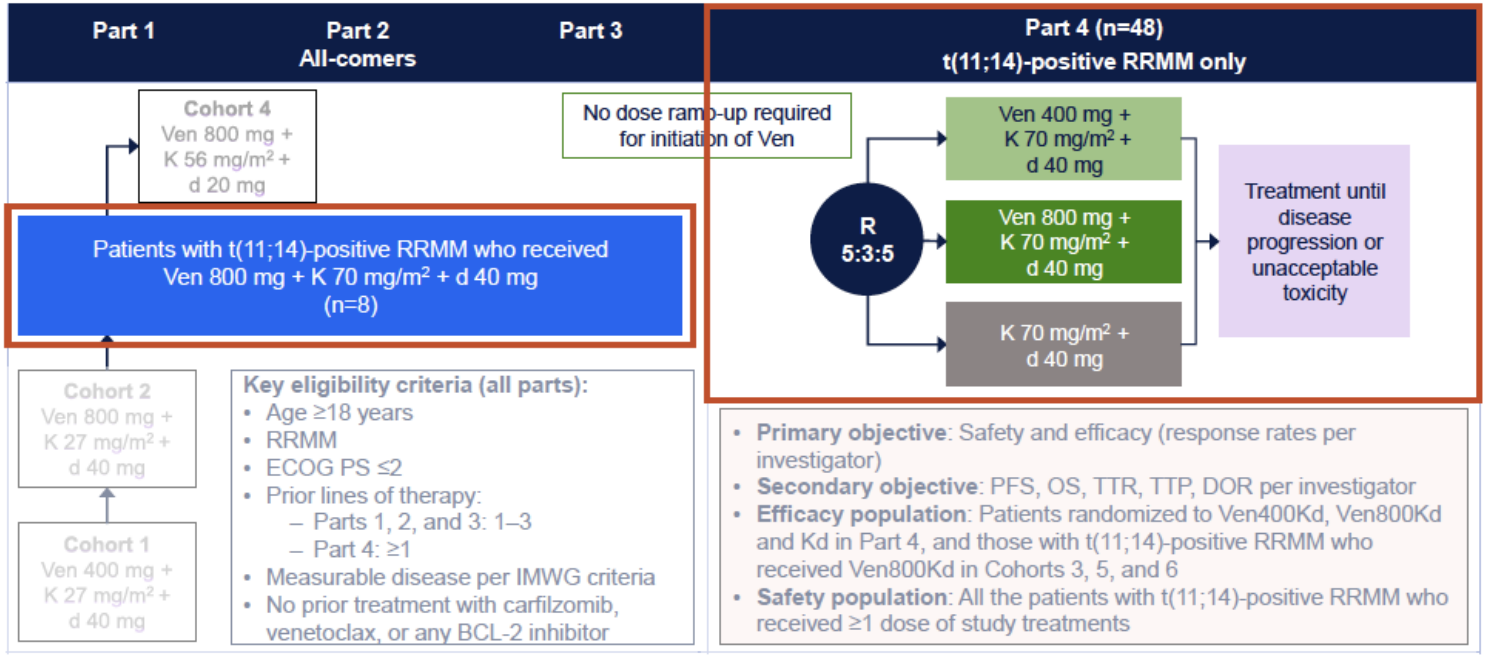
- **Canova: Venetoclax-dex vs Poma-dex**
- **Venetoclax+ Carfilzomib**
- **Daratumumab+Venetoclax; Dara+Bor+Venetoclax**
- **Venetoclax+Pomalidomide**

Ongoing, open-label, multicenter Phase 2 study of venetoclax in combination with Kd in patients with RRMM (NCT02899052)



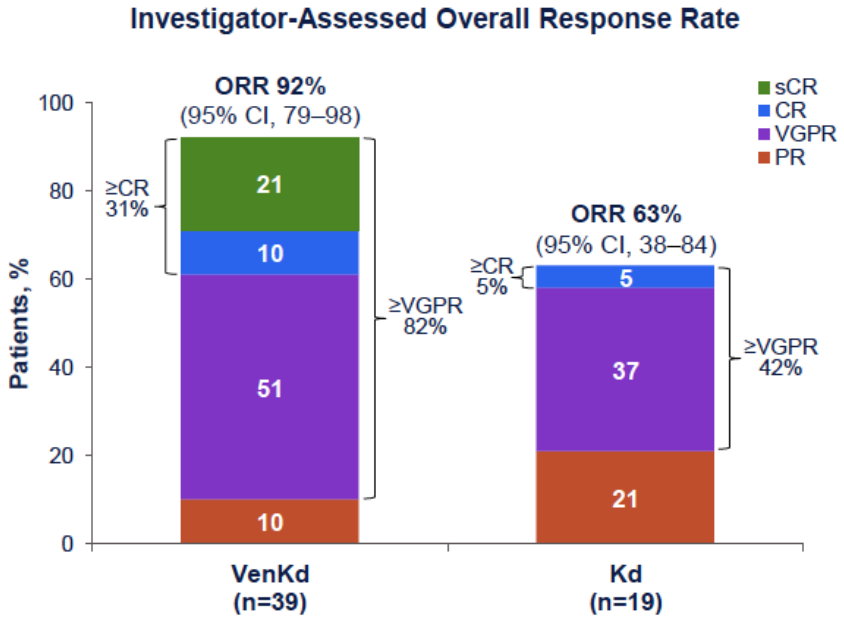
Ven was administered orally once daily on Days 1–28, with no dose ramp-up. K was administered once weekly on Days 1, 8, and 15 as a 30-minute infusion or per institutional guidelines. Dexamethasone was administered once weekly on Days 1, 8, 15, and 22 (patients aged ≥75 years could receive 20 mg). Antimicrobial prophylaxis included acyclovir for prevention of herpes zoster infection and trimethoprim/sulfamethoxazole while receiving treatment and levofloxacin for the first 90 days of the study and after development of Grade 4 neutropenia.
DOR, duration of response; ECOG PS Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; IV, intravenous; Kd, carfilzomib + dexamethasone; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; R, randomization; RRMM, relapsed/refractory multiple myeloma; TTP, time to progression; TTR, time to response; Ven400Kd, venetoclax 400 mg + carfilzomib + dexamethasone; Ven800Kd, venetoclax 800 mg + carfilzomib + dexamethasone.

Patient baseline characteristics were well balanced between treatment groups

Characteristic (N=58)	Ven400Kd (n=19)	Ven800Kd (n=20)[a]	Kd (n=19)
Median age (range), years	71 (45–84)	71 (47–78)	73 (57–83)
≥65, n (%)	12 (63)	13 (65)	14 (74)
Male, n (%)	10 (53)	11 (55)	10 (53)
Race, n (%)			
White	17 (89)	18 (90)	15 (79)
Black or African American	2 (11)	2 (10)	4 (21)
Other	0	0	0
Geography, n (%)			
North America	6 (32)	12 (60)	12 (63)
Europe	11 (58)	6 (30)	6 (32)
ECOG PS, n (%)			
0	9 (47)	10 (50)	7 (37)
1-2	10 (53)	10 (50)	12 (63)
Median time from initial diagnosis (range), years[b]	4.1 (0.2–17.9)	4.1 (0.4–12.9)	3.4 (0.6–14.1)
ISS stage, n (%)			
I	5 (26)	9 (45)	6 (33)
II	5 (26)	6 (30)	8 (44)
III	8 (42)	5 (25)	2 (11)

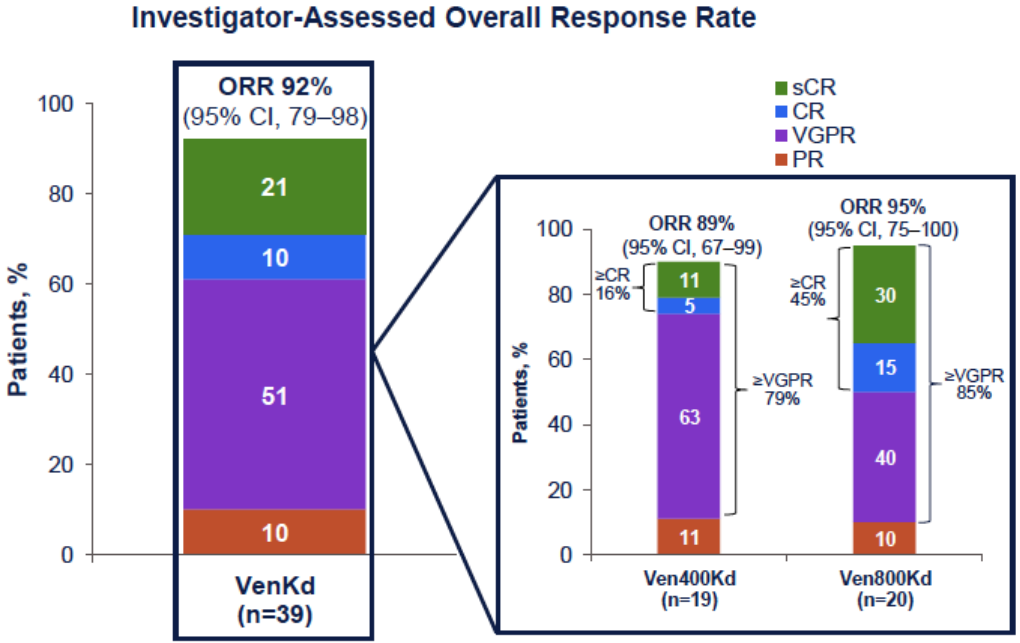
Characteristic (N=58)	Ven400Kd (n=19)	Ven800Kd (n=20)[a]	Kd (n=19)
IMWG cytogenetic risk, n (%)			
High risk	3 (16)	3 (15)	3 (16)
Standard risk	11 (58)	15 (75)	7 (37)
Unknown	5 (26)	2 (10)	9 (47)
High-risk cytogenetics, n (%)			
del(17p)	4 (21)	4 (20)	6 (32)
gain(1q) (≥3 copies)	3 (16)	9 (45)	2 (11)
gain(1q) and/or del(17p)	7 (37)	11 (55)	7 (39)
Median number of prior lines of therapy (range)	2 (1–4)	2 (1–5)	2 (1–5)
Prior exposure to PI, n (%)	18 (95)	18 (90)	16 (89)
Refractory to PI	10 (53)	14 (70)	10 (56)
Prior exposure to IMiD, n (%)	17 (89)	17 (85)	16 (89)
Refractory to IMiD	16 (84)	14 (70)	14 (78)
Refractory to lenalidomide	12 (63)	13 (65)	13 (72)
Prior exposure to anti-CD38 mAb, n (%)	4 (21)	6 (30)	9 (50)
Refractory to daratumumab	4 (21)	6 (30)	8 (44)
Refractory to PI + IMiD, n (%)	8 (42)	9 (45)	6 (33)
Refractory to PI + IMiD + anti-CD38 mAb, n (%)	3 (16)	2 (10)	4 (22)

Addition of venetoclax to Kd produced an overall response rate of 92% in patients with t(11;14)-positive RRMM



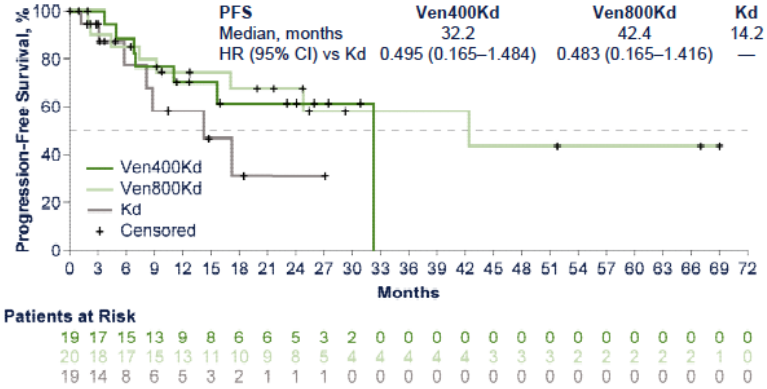
CR, complete response; Kd, carfilzomib + dexamethasone; ORR, overall response rate; PR, partial response; RRMM, relapsed/refractory multiple myeloma; sCR, stringent CR; Ven400Kd, venetoclax 400 mg + carfilzomib + dexamethasone; Ven800Kd, venetoclax 800 mg + carfilzomib + dexamethasone; VenKd, venetoclax + carfilzomib + dexamethasone; VGPR, very good PR.

Addition of venetoclax to Kd produced an overall response rate of 89%–95% in patients with t(11;14)-positive RRMM

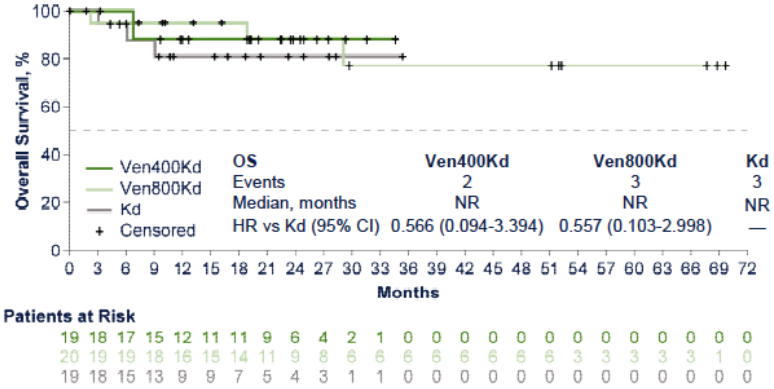


Addition of venetoclax to Kd resulted in longer median PFS vs Kd alone, and median OS has not yet been reached in any group

Investigator-Assessed PFS in All Patients

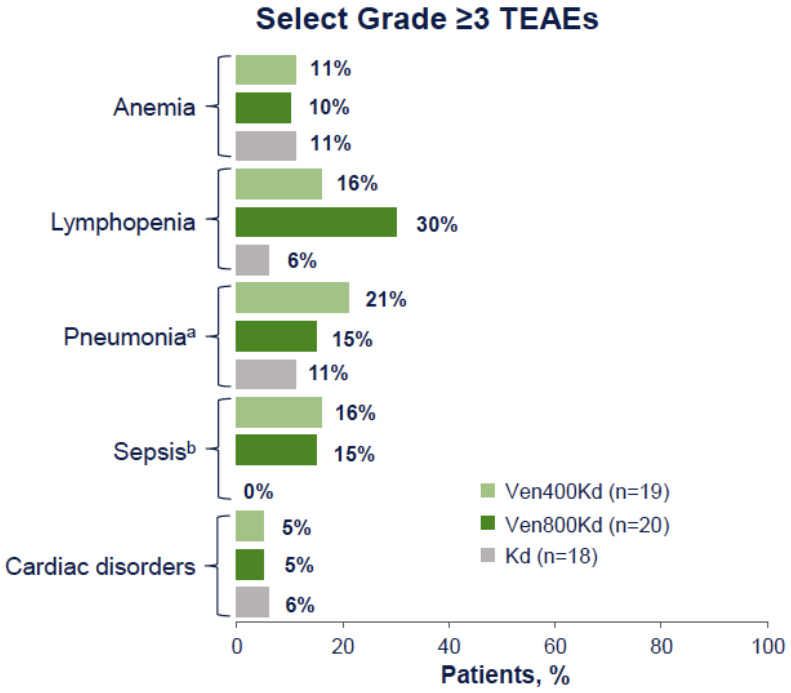


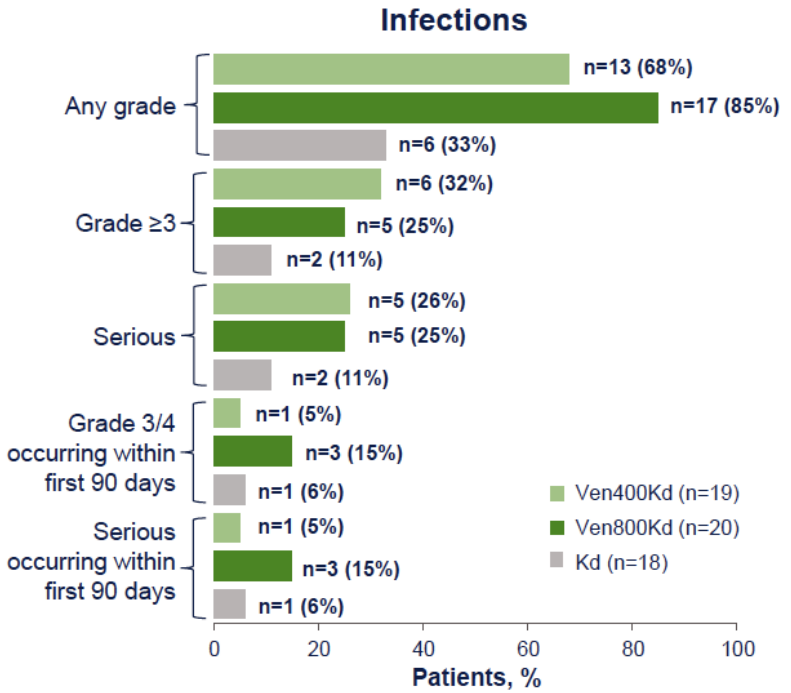
OS in All Patients



	Ven400Kd (n=19)	Ven800Kd (n=20)	Kd (n=19)
Median follow-up, months (range)	22.4 (1.8–34.7)	24.9 (2.2–69.7)	16.8 (0.0–35.4)
Median DOR, months (95% CI)	31.3 (14.8–NR)	41.5 (16.1–NR)	16.3 (6.5–NR)
Median TTR, months (95% CI)	1.0 (1.0–1.1)	1.0 (1.0–1.2)	1.3 (1.0–4.2)
Median TTP, months (95% CI)	32.2 (11.1–NR)	42.4 (17.1–NR)	17.2 (5.8–NR)

Infection rates were higher in the venetoclax treatment groups vs Kd alone





Outline

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VenDd vs DVd in t(11;14) R/R MM:

Multicenter dose-escalation/dose-expansion phase I/II study

Adult (≥18 yr of age) patients with t(11;14)-positive* R/R MM with PD after ≥1 previous line of therapy including a PI or IMiD; ECOG PS ≤2
(N = 81)

Part 1 (nonrandomized dose escalation/dose expansion)†

Part 3 (randomized, open label)§

(28-day cycles)

Venetoclax 400 mg or 800 mg QD +
Daratumumab 16 mg/kg IV or 1800 mg SC‡ +
Dexamethasone 40 mg QW PO or IV
(n = 55)

Bortezomib + **Daratumumab** + **Dexamethasone**
dosed per current label
(n = 26)

Primary endpoint: PFS, response rates (ORR, ≥ VGPR, ≥ CR)

Secondary endpoints: MRD negativity¶

Other endpoints: safety

*As determined by central laboratory plasma cell–enriched FISH. †Patients from part 1 who received 400 mg or 800 mg of venetoclax were included in analysis of part 3. ‡Cycles 1-2: D1, 8, 15, 22; cycles 3-6: D1, 15; cycle 7+: D1. §Patients stratified 4:2:5 to receive Ven400Dd, Ven800Dd, or DVd. ¶At time of suspected sCR/CR, MRD negativity ($<10^{-5}$ and $<10^{-6}$) determined in BM aspirates by NGS and assessed again at 6 and 12 mo post confirmation.

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VenDd vs DVd in t(11;14) R/R MM: PFS (Primary Endpoint)

Outcome	VenDd (n = 55)	DVd (n = 26)
Median PFS, mo (95% CI)	46.1 (40.6-NE)	15.5 (7.5-NE)
12-mo PFS rate, % (95% CI)	94.2 (83.1-98.1)	59.9 (35.5-77.6)
18-mo PFS rate, % (95% CI)	87.9 (74.4-94.4)	47.6 (24.1-68.0)
24-mo PFS rate, % (95% CI)	77.7 (62.1-87.4)	39.7 (17.0-61.8)
33-mo PFS rate, % (95% CI)	74.3 (57.8-85.1)	39.7 (17.0-61.8)
Events, n	16	11

Median PFS was longer in VenDd arm (46.1 mo) compared with DVd arm (15.5 mo)

33-mo PFS rate was higher in VenDd arm (74.3%) compared with DVd arm (39.7%)

Bahlis. ASH 2023. Abstr 338.

VenDd vs DVd in t(11;14) R/R MM: Safety Summary

Safety Summary	VenDd (n = 55)	DVd (n = 24)*
Treatment exposure ▪ Mean tx duration, mo (SD) ▪ Median tx duration, mo (range)	 26.3 (14.4) 24.8 (1.2-57.8)	 11.9 (10.3) 9.6 (0.5-35.8)
Any-grade AE, n (%)	54 (98.2)	23 (95.8)
Grade ≥3 AE, n (%)	43 (78.2)	18 (75.0)
Any-grade neutropenia, n (%) ▪ Grade 3/4 neutropenia	9 (16.4) 7 (12.7)	1 (4.2) 0
Any-grade thrombocytopenia, n (%) ▪ Grade 3/4 thrombocytopenia	4 (7.3) 2 (3.6)	8 (33.3) 6 (25.0)
SAEs, n (%)	28 (50.9)	7 (29.2)
All deaths, n (%) ▪ SAEs resulting in death†	8 (14.5) 1 (1.8)	5 (20.8) 0

Safety Events (Events/100 PY)	VenDd (n = 55) (PY = 122.8)	DVd (n = 24)* (PY = 25.3)
AEs	1244 (1012.8)	351 (1384.8)
SAEs	65 (52.9)	17 (67.1)
Grade 3/4 AEs‡	165 (134.3)	61 (240.7)
All deaths ▪ AEs resulting in death†	8 (6.5) 2 (1.6)	5 (19.7) 0

*n = 2 patients randomized but never received drug dose. †n = 1 patient treated for 49 cycles experienced 2 SAEs (septic shock, multiorgan failure) that resulted in death. ‡National Cancer Institute Common Terminology Criteria for Adverse Events.

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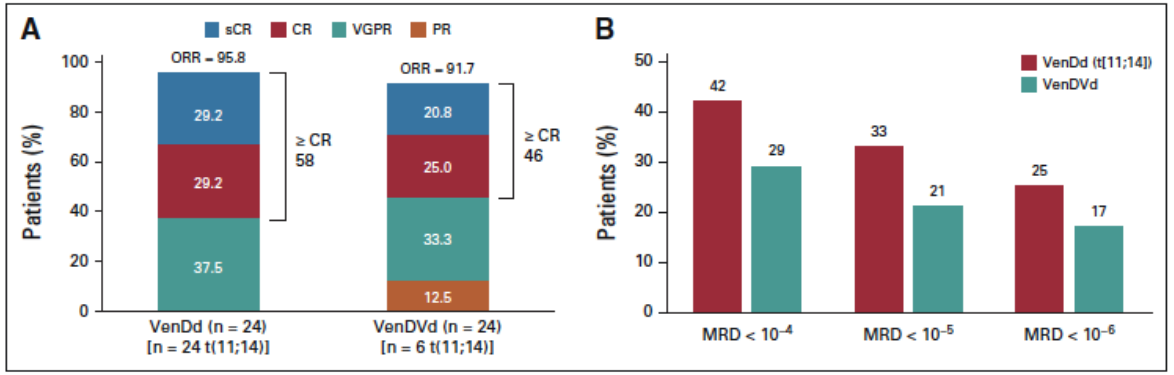
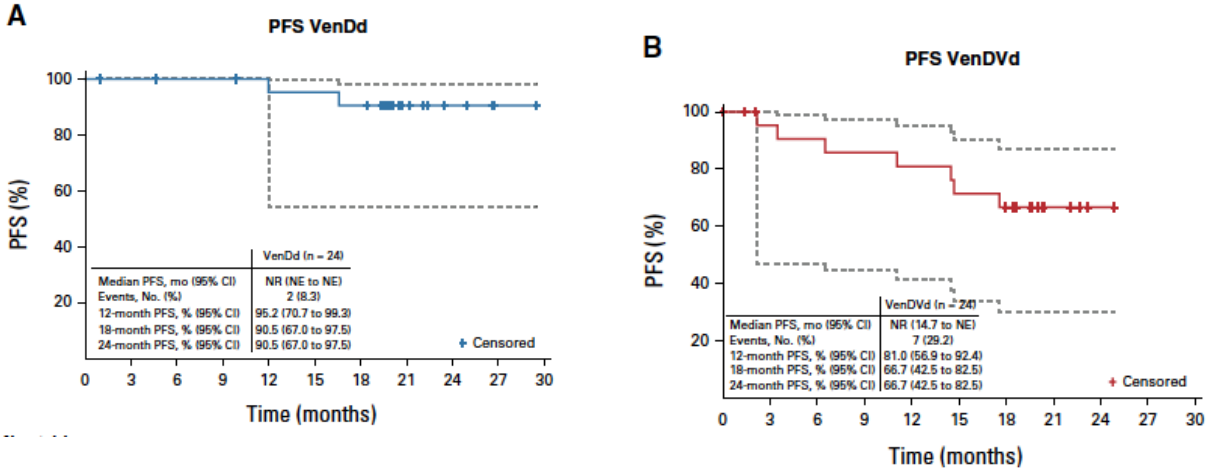
TABLE 1. Patient Demographics and Baseline Characteristics

Characteristic	Part 1 t(11;14) VenDd (n = 24)	Part 2 VenDVd (n = 24)
Median age, years (range)	63 (51-76)	64 (41-80)
ECOG performance status, No. (%)		
0	13 (54)	16 (67)
1	11 (46)	7 (29)
2	0	1 (4)
ISS stage, No. (%)		
I	7 (29)	9 (38)
II and III	14 (58)	14 (58)
Not evaluable or unknown	3 (13)	1 (4)
Cytogenetic abnormalities,[a] No. (%)		
t(11;14)	24 (100)	6 (25)
t(4;14)	0 (0)	0 (0)
t(14;16)	0 (0)	1 (4)
del(17p)	1 (4)	3 (13)
gain(1q) (≥ 3 copies)	9 (38)	1 (4)
Hyperdiploid[b]	3 (13)	2 (8)
High risk[c]	1 (4)	4 (17)
No. of prior lines of therapy, median (range)	2.5 (1-8)	1 (1-3)





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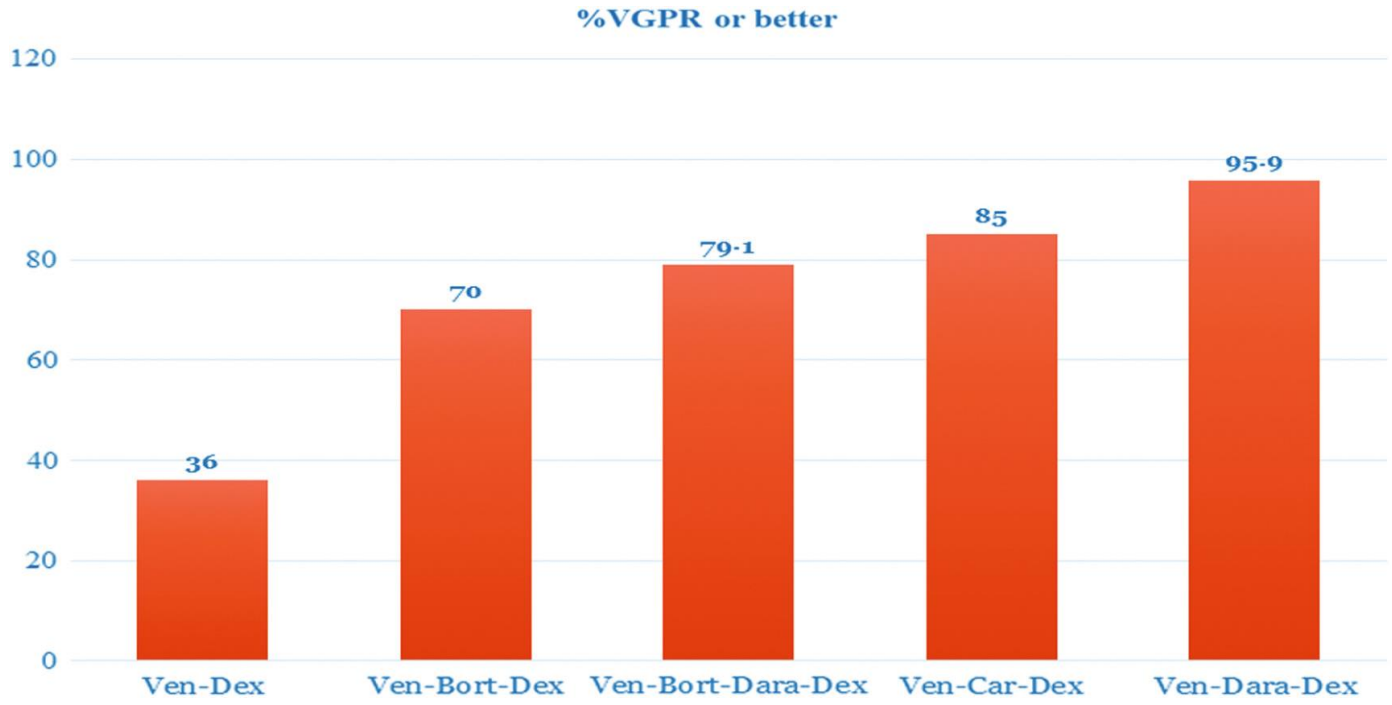
%VGPR or better
120
100
80
60
40
20
0
36
70
79-1
85
95-9
Ven-Dex
Ven-Bort-Dex
Ven-Bort-Dara-Dex
Ven-Car-Dex
Ven-Dara-Dex

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- **Venetoclax+Pomalidomide**

Venetoclax 400 mg die x 28 gg
Pomalidomide 4 mg die x 21 gg
Dex 40 mg settimanale

Fase II inMM RR >1L; lena refrattari

Venetoclax, pomalidomide, and dexamethasone in RRMM

Table 1 Patient Demographics and Baseline Characteristics

Characteristic	t(11;14) n = 3	Non-t(11;14) n = 5	All Patients N = 8
Median age, y (range)	68 (67-74)	66 (60-77)	67.5 (60-77)
ECOG performance status, n (%)			
0	0 (0)	0 (0)	0 (0)
1	3 (100)	5 (100)	8 (100)
ISS stage, n (%)			
I	0 (0)	1 (20)	1 (13)
II/III	2 (67)	2 (40)	4 (50)
Not evaluable/unknown	1 (33)	2 (40)	3 (38)
Cytogenetic abnormalities, n (%)			
t(4;14)	0 (0)	0 (0)	0 (0)
t(14;16)	0 (0)	1 (20)	1 (13)
del(17p)	1 (33)	0 (0)	1 (13)
gain(1q) (≥ 3 copies)	1 (33)	2 (40)	3 (38)
No. prior lines of therapy, median (range)	3.0 (1-4)	1.0 (1-5)	1.5 (1-5)
1, n (%)	1 (33)	3 (60)	4 (50)
≥ 2, n (%)	2 (67)	2 (40)	4 (50)
Prior exposure to PI, n (%)	—	—	8 (100)
Refractory to PI	—	—	2 (25)
Prior exposure to lenalidomide, n (%)	—	—	8 (100)
Refractory to lenalidomide	—	—	6 (75)[a]

Table 2 Summary of Treatment-Emergent Adverse Events

TEAEs by Preferred Term, n (%)[a]	All Patients N = 8	
	Any Grade	Grade ≥ 3
Any TEAE	8 (100)	8 (100)
Neutropenia	6 (75)	6 (75)
Anemia	4 (50)	1 (13)
Fatigue	4 (50)	0 (0)
Hypokalemia	4 (50)	0 (0)
Dyspnea	3 (38)	0 (0)
Hyperglycemia	3 (38)	0 (0)
Hypophosphatemia	3 (38)	1 (13)
Leukopenia	3 (38)	3 (38)
Thrombocytopenia	3 (38)	1 (13)

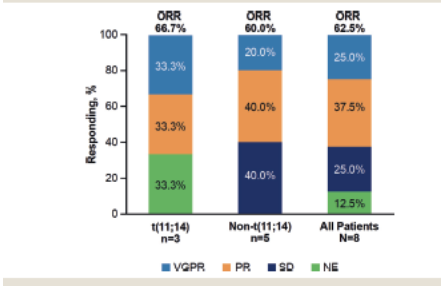
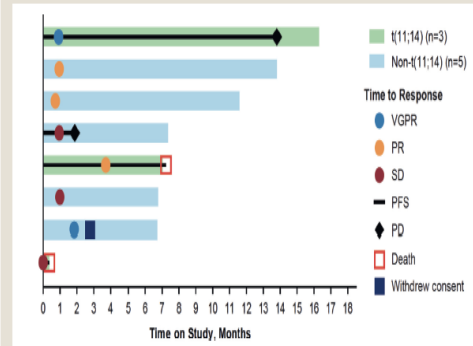


Figure 3 Patient responses over time.
Abbreviations: PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease; VGPR = very good partial response.



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Conclusioni

- Venetoclax è efficace nel MM R/R
- Efficacia maggiore in MM e t(11;14) e overespressione BCL2
- Warning su dosaggi / combinazioni e rischio infettivo