Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

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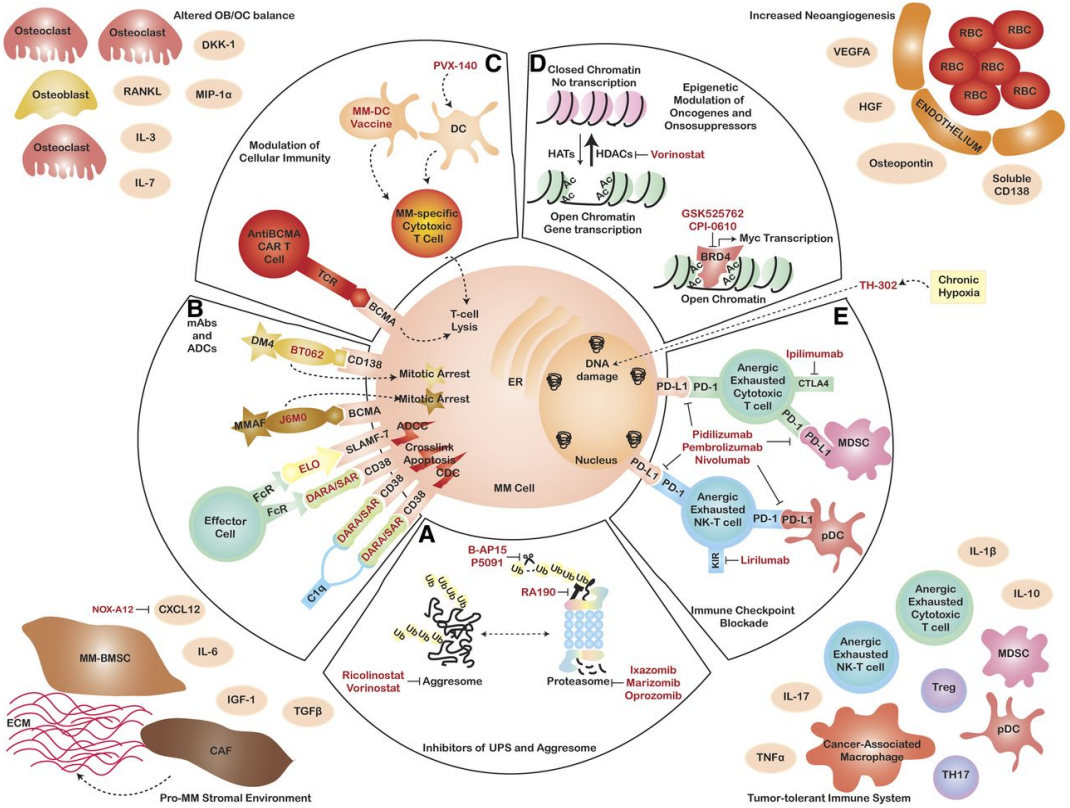
SC di Ematologia e CTMO
Ospedale Oncologico di Riferimento Regionale
«A. Businco»
Cagliari

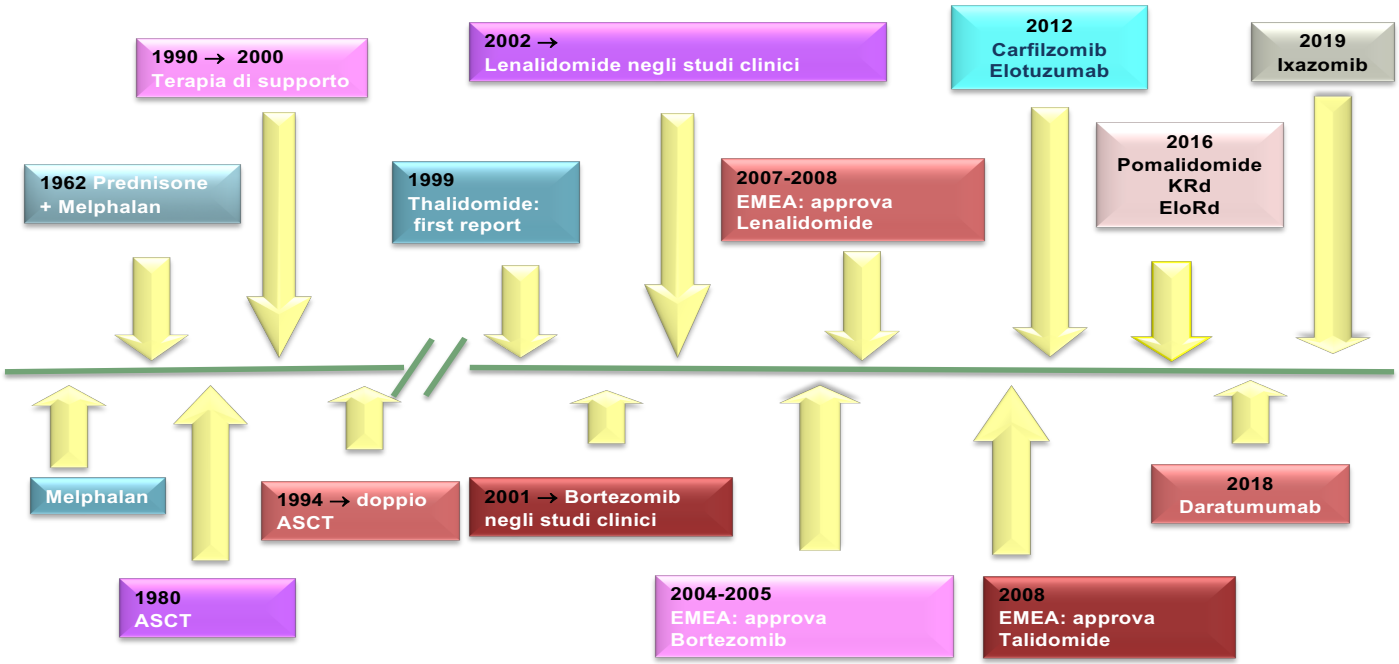
Nuovi farmaci
e nuovi meccanismi di azione

Multimodality targeting of MM in the context of the BM microenvironment

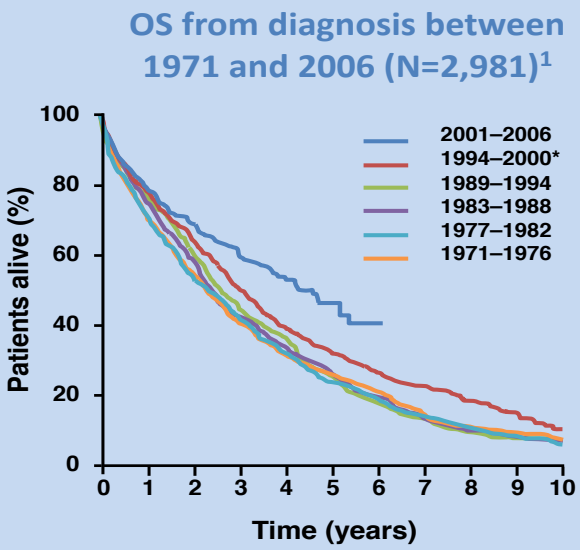


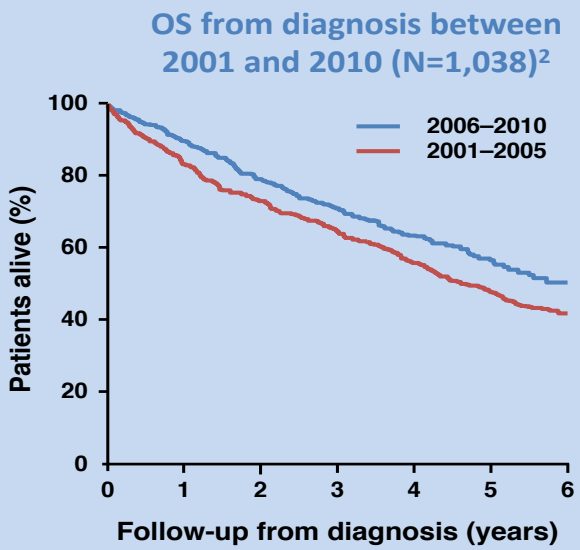
Giada Bianchi et al. Blood 2015;126:300-310

Storia della terapia del MM



Mortality remains high although novel agents have resulted in improved survival

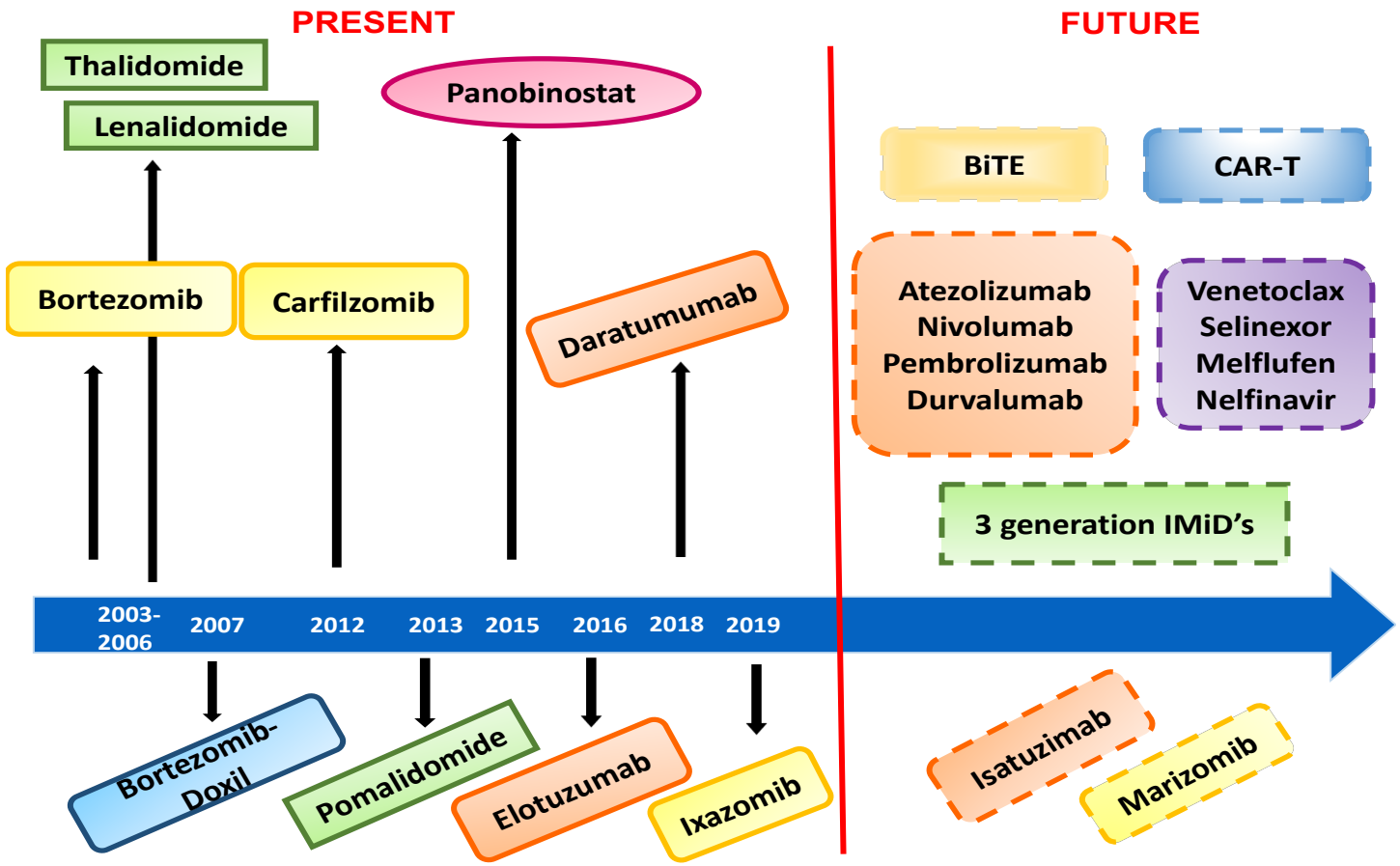


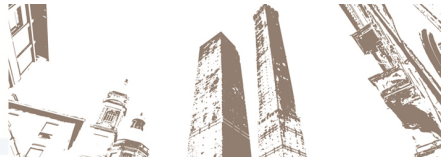


*Trend for improvement during this time period thought to be due to high-dose therapy and supportive care.

There is still a need for more efficient treatments offering higher response and better outcomes

OS, overall survival.
[1] Adapted from Kumar SK, et al. Blood 2008;111:2516–20; [2] Kumar SK, et al. Leukemia 2014;28:1122–8.


PRESENT
FUTURE
Thalidomide
Lenalidomide
Panobinostat
Bortezomib
Carfilzomib
Daratumumab
BiTE
CAR-T
Atezolizumab
Nivolumab
Pembrolizumab
Durvalumab
Venetoclax
Selinexor
Melflufen
Nelfinavir
3 generation IMiD's
2003-2006
2007
2012
2013
2015
2016
2018
2019
Bortezomib-Doxil
Pomalidomide
Elotuzumab
Ixazomib
Isatuzimab
Marizomib



Unmet Need

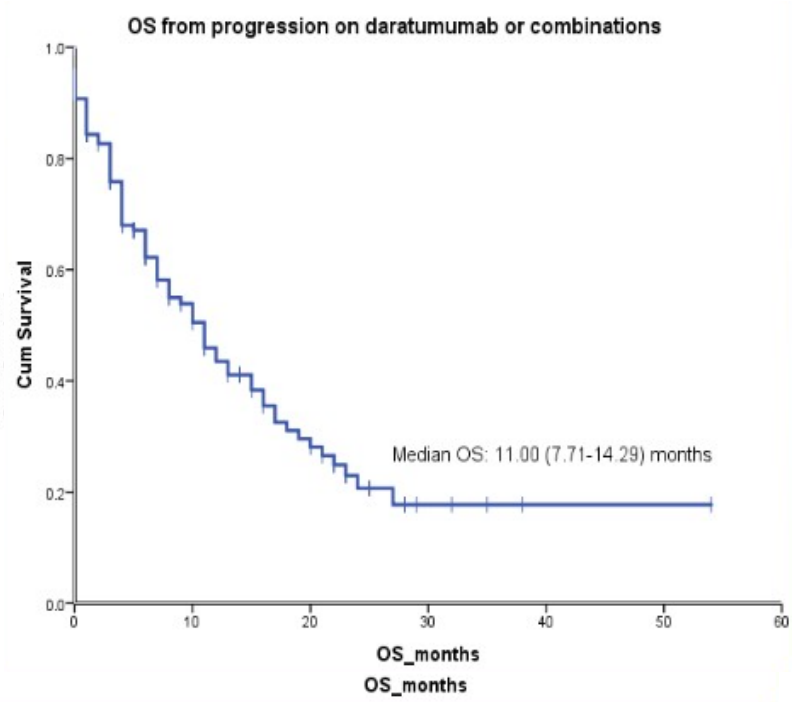
Frontline Treatment	Relapsed	Refractory or Intolerant
Expected survival (m)	20-50	14-16	6-10
Sensitivity to therapy	Sensitive	Less Sensitive/Resistant	Resistant
Treatment limitations/ comorbidities	Peripheral neuropathy (~15% at diagnosis)	>80% incidence of peripheral neuropathy Compromised marrow reserve Cytopenia	Intolerant to or ineligible for available therapy

Elderly population (↑ risk for heart, lung, renal, liver dysfunction, diabetes)

Adapted from: Durie BGM. Multiple Myeloma. International Myeloma Foundation. 2011/2012 edition.
Jagannath S. *Clin Lymphoma Myeloma*. 2008;8 Suppl 4:S149-S156.

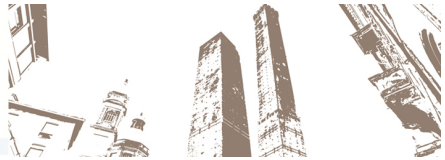
OS for refractory Myeloma patients in the Daratumumab era

- ✓ Median age is 64 years (range 32-82) and 54% were female
- ✓ Patients received a median of 6 lines of therapy and median time to start Datarumumab treatment from their diagnosis was 63 months (6-255 months)
- ✓ Majority were quad- and penta-refractory (86,9% and 70,8%, respectively)
- ✓ 32,3% of patients received Daratumumab as a single agent and most patients received a combination if IMiD (DPd: 50,8% and DRd: 6,2%) or a IP(DVd: 6,9%)



Nooka et al, ASH 2018

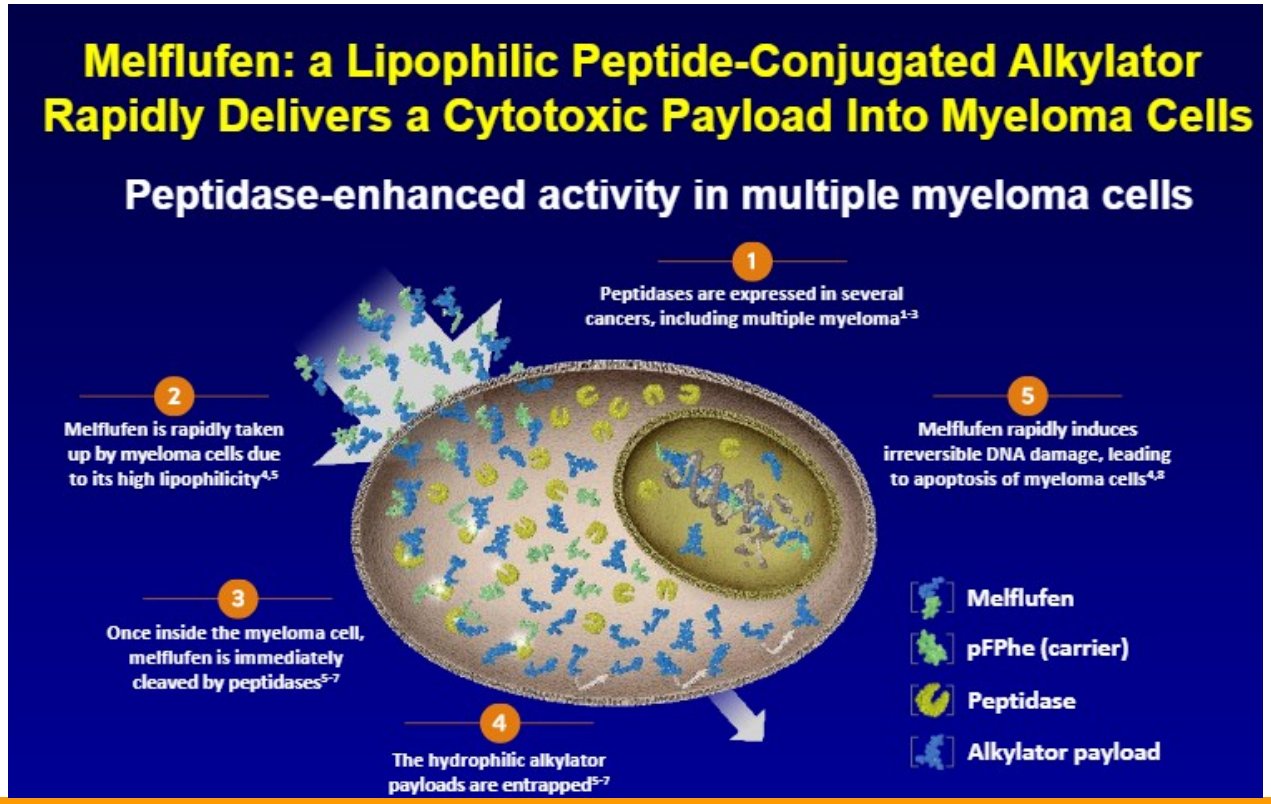
New Approaches in Late Relapse



- ✓ Most patients have cycled through common agents
- ✓ Chemotherapy based approaches while short term response, don't result in long term control
- ✓ Need new MOA or targets:

a. New chemotherapy
b. XPO1
c. New IMIDs
d. Bcl-2/MCL-1
e. Immune targeted agents

MELFLUFEN



Melflufen is 50-fold more potent than melphalan in myeloma cells *in vitro* due to increased intracellular alkylator activity[4,5]

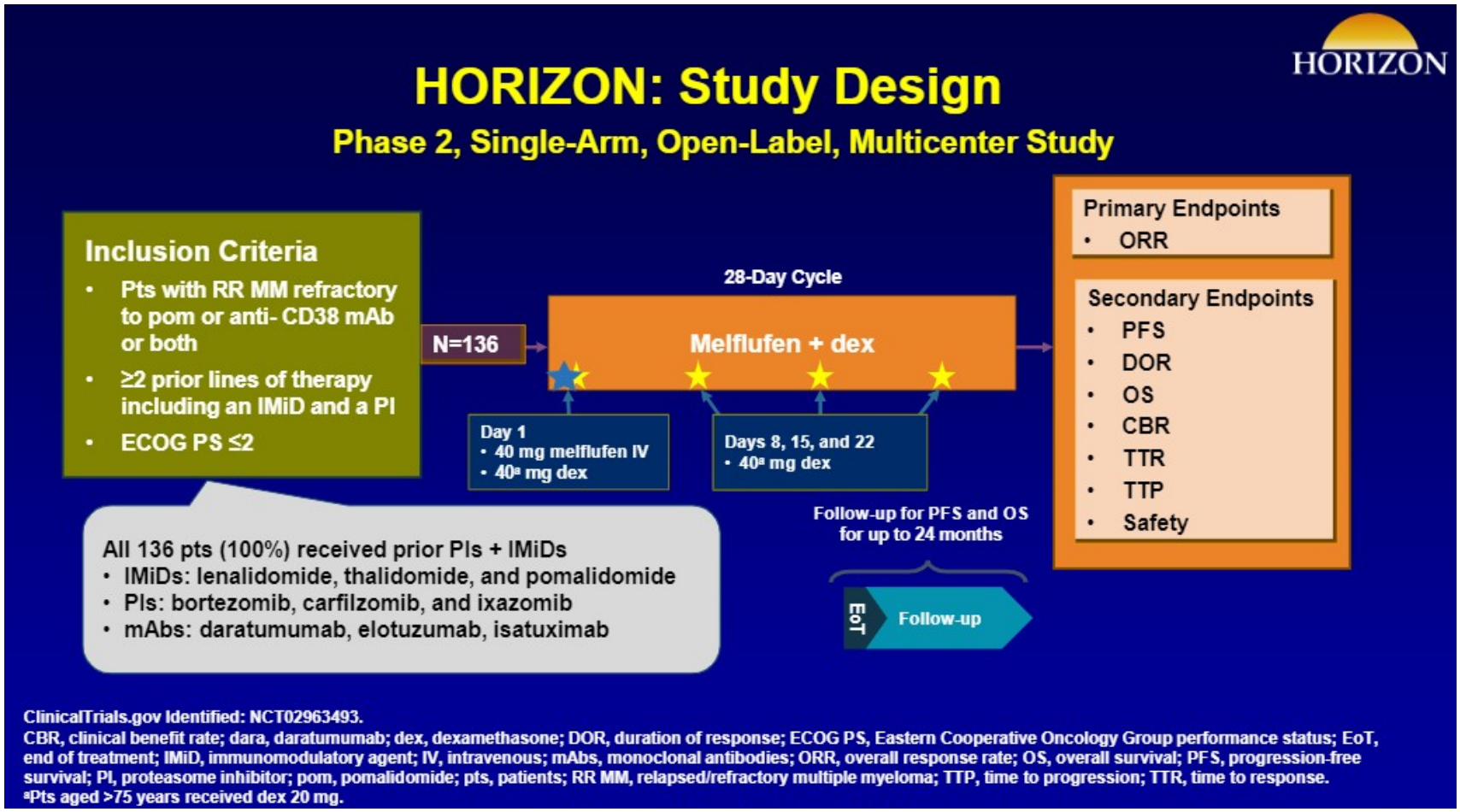
1. Hitzerd SM, et al. *Amino Acids*. 2014;46:793-808. 2. Moore HE, et al. *Mol Cancer Ther*. 2009;8:762-770. 3. Wickström M, et al. *Cancer Sci*. 2011;102:501-508. 4. Chauhan D, et al. *Clin Cancer Res*. 2013;19:3019-3031. 5. Wickström M, et al. *Oncotarget*. 2017;8:66641-66655. 6. Wickström M, et al. *Biochem Pharmacol*. 2010;79:1281-1290. 7. Gullbo J, et al. *J Drug Target*. 2003;11:355-363. 8. Ray A, et al. *Br J Haematol*. 2016;174:397-409.

HORIZON

Activity of Melflufen in RR MM Patients With Extramedullary Disease in the Phase 2 HORIZON Study (OP-106): Promising Results in a High-Risk Population

Paul G. Richardson, MD[1]; Maria-Victoria Mateos, MD, PhD[2]; Paula Rodríguez-Otero, MD[3]; Maxim Norkin, MD[4]; Alessandra Larocca, MD[5]; Hani Hassoun, MD[6]; Adrián Alegre, MD[7]; Agne Paner, MD[8]; Xavier Leleu, MD, PhD[9]; Christopher Maisel, MD[10]; Amitabha Mazumder, MD[11]; Johan Harmenberg, MD[12]; Catriona Byrne, RN[12]; Hanan Zubair, MSc[12]; Sara Thuresson, MSc[12]; and Joan Bladé, MD[13]

[1]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [2]Hospital Clínico Universitario de Salamanca, Salamanca, Spain; [3]Clínica Universidad de Navarra, Pamplona, Spain; [4]Baptist MD Anderson Cancer Center, Jacksonville, FL, USA; [5]University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy; [6]Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [7]Hospital Universitario de la Princesa, Madrid, Spain; [8]Rush University Medical Center, Chicago, IL, USA; [9]CHU de Poitiers, Poitiers, France; [10]Baylor Scott & White Charles A. Sammons Cancer Center, Dallas, TX, USA; [11]The Oncology Institute of Hope and Innovation, Glendale, CA, USA; [12]Oncopeptides AB, Stockholm, Sweden; and [13]Hospital Clínica de Barcelona - Servicio de Onco-Hematología, Barcelona, Spain


HORIZON
HORIZON: Study Design
Phase 2, Single-Arm, Open-Label, Multicenter Study
Inclusion Criteria
• Pts with RR MM refractory to pom or anti- CD38 mAb or both
• ≥2 prior lines of therapy including an IMiD and a PI
• ECOG PS ≤2
N=136
28-Day Cycle
Melflufen + dex
Day 1
• 40 mg melflufen IV
• 40[a] mg dex
Days 8, 15, and 22
• 40[a] mg dex
Primary Endpoints
• ORR
Secondary Endpoints
• PFS
• DOR
• OS
• CBR
• TTR
• TTP
• Safety
All 136 pts (100%) received prior PIs + IMiDs
• IMiDs: lenalidomide, thalidomide, and pomalidomide
• PIs: bortezomib, carfilzomib, and ixazomib
• mAbs: daratumumab, elotuzumab, isatuximab
Follow-up for PFS and OS for up to 24 months
EoT
Follow-up
ClinicalTrials.gov Identified: NCT02963493.
CBR, clinical benefit rate; dara, daratumumab; dex, dexamethasone; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EoT, end of treatment; IMiD, immunomodulatory agent; IV, intravenous; mAbs, monoclonal antibodies; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; pom, pomalidomide; pts, patients; RR MM, relapsed/refractory multiple myeloma; TTP, time to progression; TTR, time to response.
[a]Pts aged >75 years received dex 20 mg.

Baseline Characteristics and Prior Therapy

Patient Characteristics (n=130)	Non-EMD (n=86)	EMD (n=44)
Age, median (range), years	64 (35-86)	64 (43-82)
Time since diagnosis, median, years	6.6 (1.6-24.2)	5.5 (0.6-12.7)
No. of prior lines of therapy, median (range)	5 (2-10)	5 (3-12)
	%	%
Gender (male / female)	53 / 47	59 / 41
ISS stage I / II / III / unknown	42 / 29 / 23 / 6	43 / 23 / 27 / 7
ECOG PS 0 / 1 / 2 / unknown	27 / 58 / 13 / 2	18 / 64 / 16 / 2
High-risk cytogenetics[a] ≥2 high-risk abnormalities Del(17p)	57 25 19	52 10 13
Double-class (IMiD+PI) exposed / refractory	100 / 90	100 / 93
Triple-class (IMiD+PI+anti-CD38) exposed / refractory	71 / 63	93 / 91[b]
Anti-CD38 mAb exposed / refractory	72 / 72	93 / 93
Alkylator exposed / refractory	91 / 58	82 / 59
≥1 Prior ASCT ≥2 Prior ASCTs Relapsed/progressed within 1 year of ASCT	69 13 17	73 14 23
Refractory in last line of therapy	95	100

[a]High-risk cytogenetics [t(4;14), del(17/17p), t(14;16), t(14;20), nonhyperdiploidy, gain(1q) or karyotype del(13)] at study entry; data pending for 33 pts in the non-EMD group and 13 pts in the EMD group.
[b]Includes 2 PI-intolerant pts.

EMD and Prior Therapy

HORIZON

- 91% of EMD pts triple-class refractory and 73% penta-refractory
- No other significant differences seen between EMD and non-EMD pts, except anti-CD38 exposure
- EMD incidence higher with prior anti-CD38 exposure (*P*=0.01)
  - 41 of 103 (40%) anti-CD38 mAb exposed pts had EMD
  - 3 of 27 (11%) not anti-CD38 mAb exposed pts had EMD

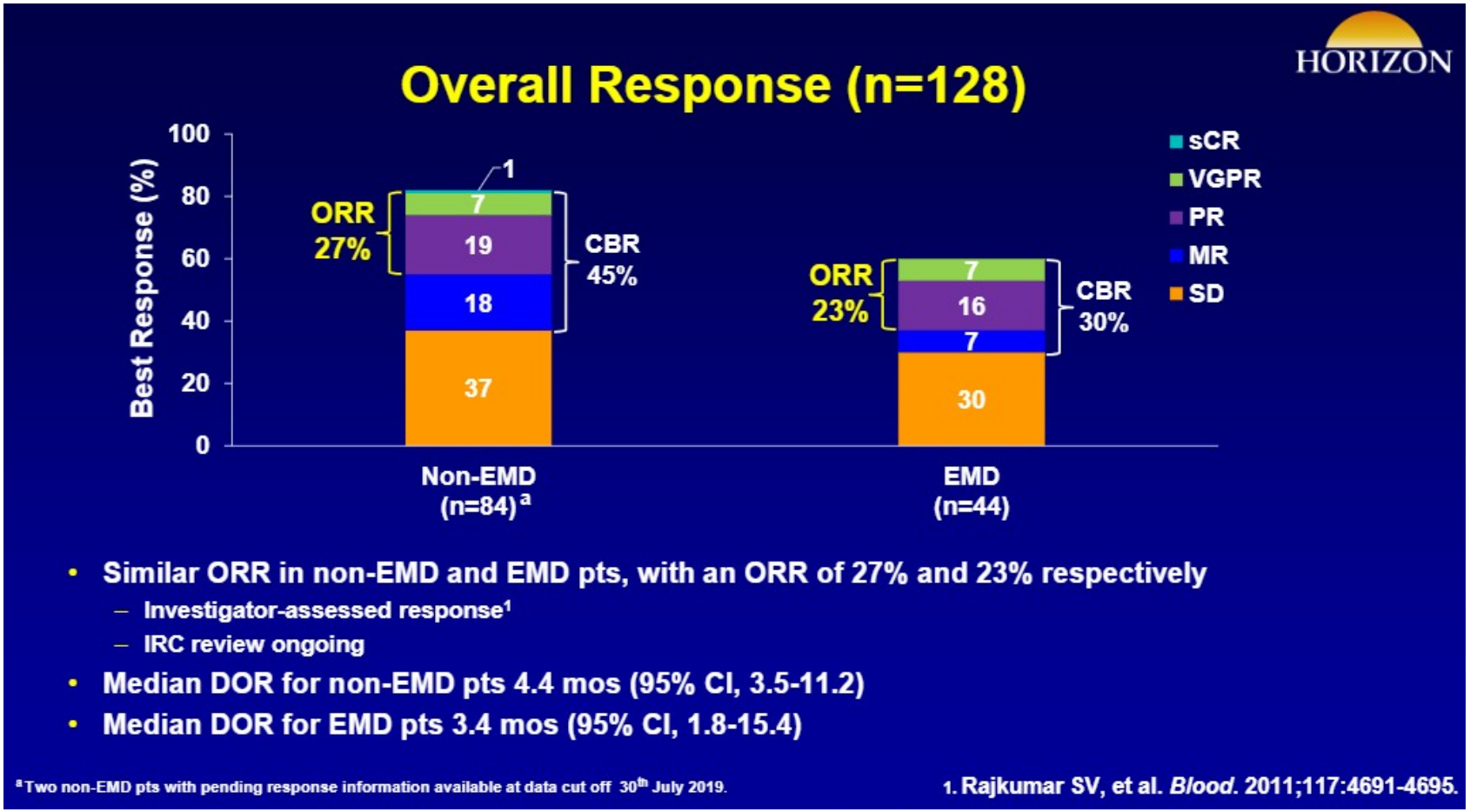
EMD Characteristics

HORIZON

Bone-related or Soft Tissue EMD, n (%)	EMD Pts	CNS Involvement
Pts with EMD[a]	44 (100)	5 (11)
Soft tissue[b]	26 (59)	2 (5)
Bone-related[c]	18 (41)	3 (7)

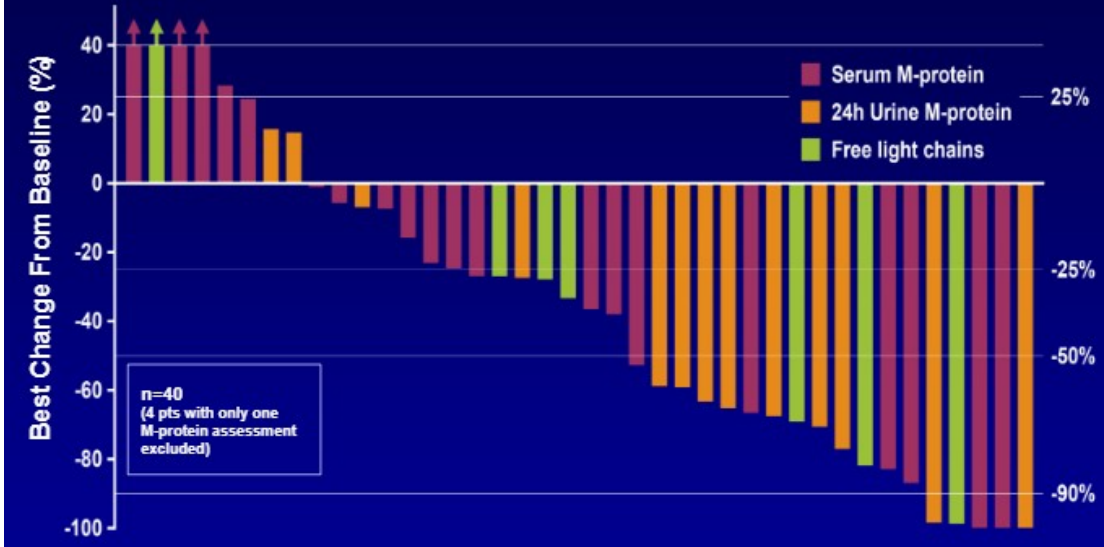
CNS, central nervous system; EMD, extramedullary disease; Pt, patient.
[a]Majority of pts had multiple lesions at baseline.
[b]Includes pts with both bone-related and soft tissue EMD.
[c]Three pts had bone-related EMD with extension into CNS.

- Method of baseline assessment for known or suspected EMD was by investigator choice including PET/CT, MRI and physical examination
- 59% of pts had soft-tissue EMD (with or without additional bone-related EMD) and 41% had bone-related EMD alone
- 5 pts (11%) had CNS involvement, of which 3 pts had bone-related EMD with extension into CNS
- Majority of pts (29 of 44) had multiple sites of EMD


HORIZON
Overall Response (n=128)
Best Response (%)
100
80
60
40
20
0
ORR 27%
CBR 45%
1
7
19
18
37
ORR 23%
CBR 30%
7
16
7
30
Non-EMD (n=84)[a]
EMD (n=44)
sCR
VGPR
PR
MR
SD
• Similar ORR in non-EMD and EMD pts, with an ORR of 27% and 23% respectively
– Investigator-assessed response[1]
– IRC review ongoing
• Median DOR for non-EMD pts 4.4 mos (95% CI, 3.5-11.2)
• Median DOR for EMD pts 3.4 mos (95% CI, 1.8-15.4)
[a]Two non-EMD pts with pending response information available at data cut off 30th July 2019.
1. Rajkumar SV, et al. Blood. 2011;117:4691-4695.

Response in EMD Pts (n=44)

HORIZON



n=44	ORR
Soft tissue n=26	19%
Bone-related n=18	28%
CNS n=5	0%

- PET/CT (including TIMC), MRI, physical exam for EMD assessment
- "Flaring" observed in EMD PET/CT imaging (reported by 2 lead sites)

Data cutoff 30 July 2019.

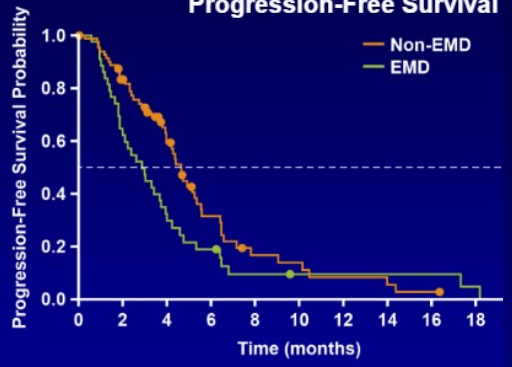
Disease Characteristics in Responding EMD Pts

HORIZON

No. Prior Lines of Therapy	Refractory Status	EMD	Response
5	Penta	Lymph nodes and paramediastinal masses	VGPR
6	Penta	Skull based mass with soft tissue extension	VGPR
6	Triple	Pulmonary masses	VGPR
8	Quad	Mandibular mass with soft tissue extension	PR
5	Quad	Multiple soft tissue plasmacytoma arising from iliac bone	PR
3	Quad	Pleural masses, hepatobiliary tract, right orbital plasmacytoma, L5 mass with spinal canal extension	PR
7	Penta	Multiple masses arising from the skull and ribs with soft tissue extension	PR
5	Penta	Multiple subcutaneous plasmacytoma affecting the trunk and extremities	PR
4	Penta	Multiple pleural and spinal masses with soft tissue extension	PR
4	Penta	Masses in mandible and sternum with soft tissue extension	PR

Progression-Free and Overall Survival EMD vs Non-EMD Pts

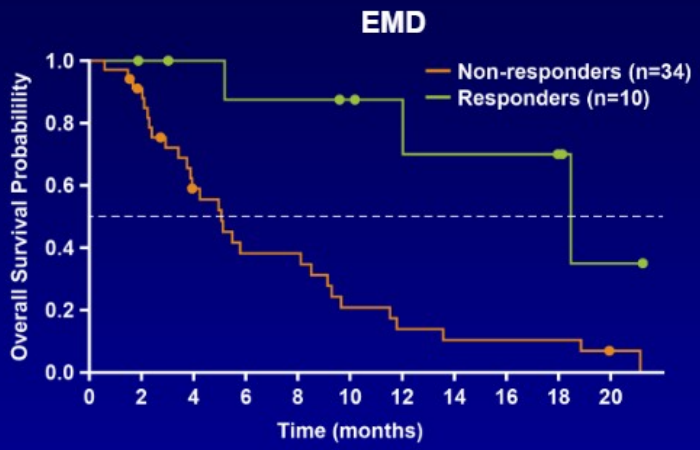
HORIZON

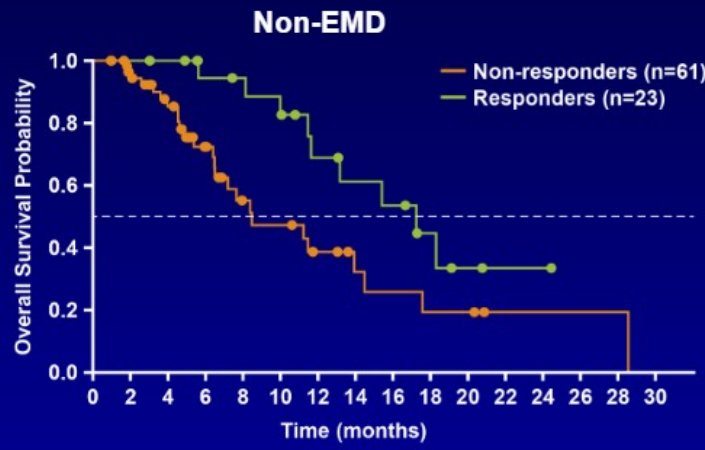


- Median PFS 2.9 mos (95% CI, 2.0-4.
  with EMD vs. 4.6 mos (95% CI, 4.0-
  without EMD

OS in EMD and Non-EMD Pts Stratified by Response

HORIZON





- Median OS in EMD responders vs. non-responders: 18.5 vs. 5.1 mos
- Median OS in Non-EMD responders vs. non-responders: 17.2 vs. 8.5 mos
  - Similar trend for PFS in responders vs. non-responders: 4.8 vs. 2.2 mos in EMD pts; 6.4 vs. 3.8 mos in non-EMD pts
- 54% of ITT pts received subsequent therapy with no significant difference in outcome between EMD vs. non-EMD pts[1]

Data cutoff 30 July 2019.

1. Gandhi UH, et al. *Blood*. 2018;132(suppl 1):Abstract 3233.

Grade 3 and 4 TEAEs (≥5%) in ITT Population

TEAEs,[a] n (%)	ITT (n=136)	
	Grade 3	Grade 4
Any AE	38 (28)	77 (57)
Hematologic AEs		
Thrombocytopenia	30 (22)	63 (46)
Neutropenia	44 (32)	48 (35)
Anemia	48 (35)	1 (1)
White blood cell count decreased	14 (10)	10 (7)
Leukopenia	4 (3)	5 (4)
Febrile neutropenia	6 (4)	2 (1)
Lymphopenia	5 (4)	2 (1)
Non-hematologic AEs		
Pneumonia	9 (7)	2 (1)

AE, adverse event; ITT, intention-to-treat; TEAE, treatment-emergent adverse event.
[a]Grade 3 and 4 AEs occurring in ≥5% of pts.

- Safety profiles for EMD and non-EMD pts similar
- Generally well tolerated, with manageable toxicity: no alopecia, 1 grade 2 mucositis only, no peripheral neuropathy
- Low overall incidence of other non-hematologic AEs including infections; no treatment-related deaths

Conclusions and Future Directions

HORIZON

- HORIZON has one of the largest cohorts of RR MM pts with EMD in a prospective clinical trial: enrollment near complete (N=156), final analysis pending
- Melflufen/dex has encouraging activity in advanced RR MM with EMD (ORR 23%, CBR 30%) or without EMD (ORR 27%, CBR 45%)
- Response to melflufen/dex in EMD higher than reported for other agents[1-5]
- Current median OS in responding EMD pts 18.5 mos vs. 5.1 mos in non-responders
- Incidence of EMD is higher than expected, and appears increased after prior anti-CD38 mAb therapy
- Results support continued evaluation of melflufen-based combination therapies for this population with unmet medical need
- Melflufen is being studied in 4 ongoing phase 2 and 3 trials with further trials planned

1. Usmani SZ, et al. *Blood*. 2016;128:37-44. 2. Celotto K, et al. *Am J Hematol Oncol*. 2017;13:21-23. 3. Jiménez-Segura R, et al. *Blood*. 2016;128:Abstract 5709. 4. Jiménez-Segura R, et al. *Eur J Haematol*. 2019;102:389-394. 5. Ichinohe T, et al. *Exp Hematol Oncol*. 2016;5:11.

First Clinical (Phase 1b/2a) Study of the CELMoD Iberdomide (CC-220) in Combination With Dexamethasone (DEX) in Patients With Relapsed/Refractory Multiple Myeloma (RRMM)

Sagar Lonial[1], Niels W.C.J. van de Donk[2], Rakesh Popat[3], Jeffrey A. Zonder[4], Monique C. Minnema[5], Jeremy Larsen[6], Tuong Vi Nguyen[7], Min S. Chen[7], Amine Bensmaine[7], Mariana Cota[7], Pieter Sonneveld[8]

[1]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [2]VU University Medical Center, Amsterdam, Netherlands; [3]NIHR UCLH Clinical Research Facility, University College London Hospitals NHS Foundation Trust, London, UK; [4]Karmanos Cancer Institute, Detroit, MI, USA; [5]University Medical Center Utrecht, Utrecht, Netherlands; [6]Mayo Clinic, Scottsdale, AZ, USA; [7]Celgene Corporation, Summit, NJ, USA; [8]Erasmus Medical Center, Rotterdam, Netherlands

RATIONALE

- IMiD immunomodulatory drug-based combination regimens are a current standard of care for patients with MM[1–3]
- Despite recent progress, MM remains incurable and new therapeutic options are needed, particularly for patients with relapsed / refractory disease[4,5]
- Iberdomide (CC-220; IBER) is a novel CELMoD cereblon E3 ligase modulator that
  - Co-opts cereblon to enable enhanced degradation of target proteins, including Ikaros and Aiolos, with 20 times higher affinity versus LEN and POM[6]
  - Enhanced direct antimyeloma and immune stimulatory activity in preclinical models[7]
  - Active in myeloma cell lines resistant to LEN and POM[8]
  - Synergizes with BORT and DARA, demonstrating enhanced apoptosis and antibody-dependent cellular cytotoxicity[9]
  - Induces NK cell proliferation and may help rescue NK cell depletion by DARA[9]

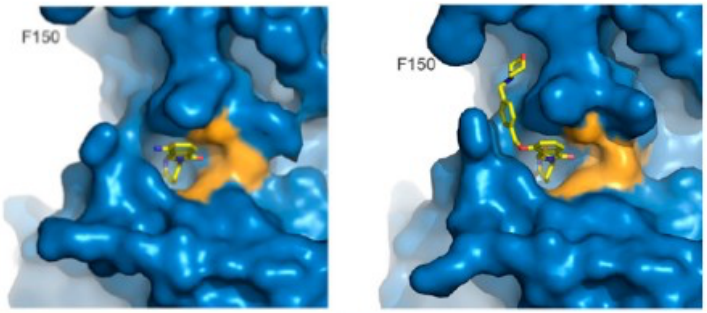
CELMoD, cereblon E3 ligase modulation drug; IMiD, immunomodulatory drug; LEN, lenalidomide; MM, multiple myeloma; POM, pomalidomide.

1. Richardson PG, et al. Blood. 2010;116:679-686. 2. Plesner T, et al. Blood. 2016;128:1821-1828.
3. Chari A, et al. Blood. 2017;130:974-981. 4. Sonneveld P, Broijl A. Haematologica. 2016;101:396-406.
5. Chim CS, et al. Leukemia. 2018;32:252-262. 6. Matyskiela ME, et al. J Med Chem. 2018;61:535-542.
7. Bjorklund CC, et al. Blood 2016;128:abstract 1591. 8. Bjorklund CC, et al. Unpublished data.
9. Amatangelo M, et al. Blood. 2018;132:abstract 1935.

IBERDOMIDE MECHANISM OF ACTION

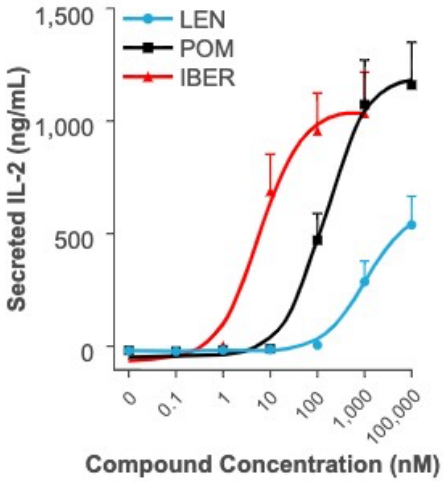
- IBER enhances in vitro immune stimulatory activity versus LEN and POM[1]

LEN[2] **IBER[2]**

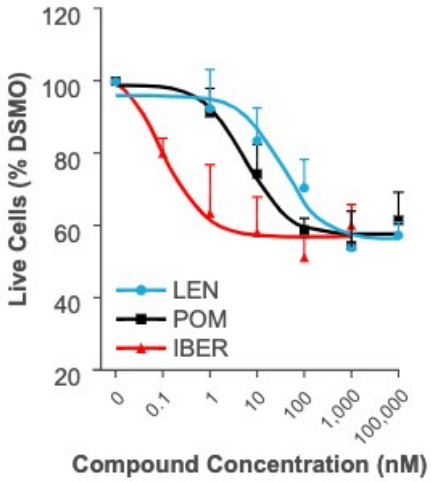


EC_{50}, nM[2]	Ikaros	Aiolos
LEN	67	87
POM	24	22
IBER	1	0.5

IL-2 Secretion by Treated PBMCs[1]



MM Cell Survival in Co-Culture With Treated PBMCs[1]



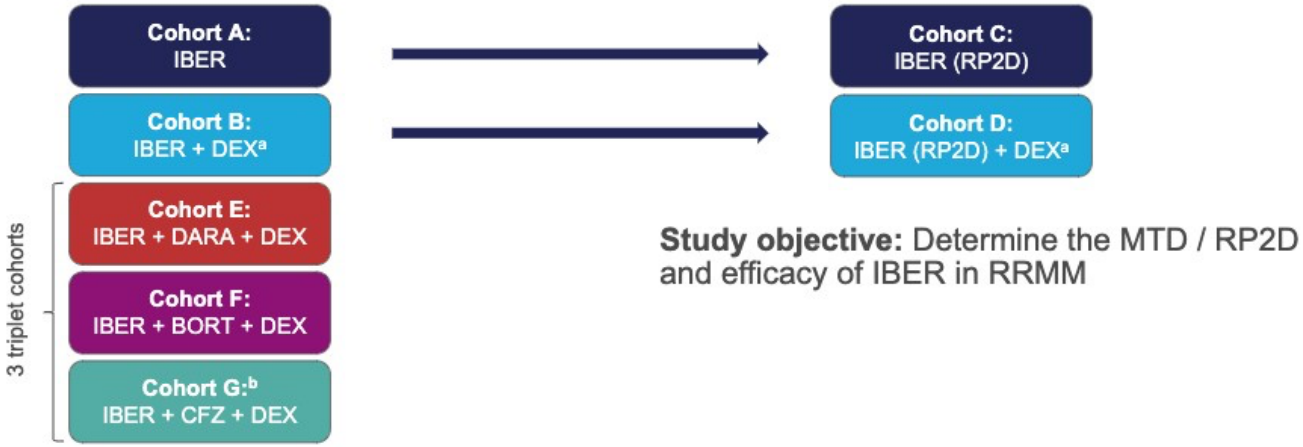
BORT, bortezomib; DARA, daratumumab; DSMO, dimethylsulfoxide; EC_{50}, half maximal effective concentration; IL, interleukin; NK, natural killer; PBMC, peripheral blood mononuclear cell.

1. Bjorklund CC, et al. Unpublished data. 2. Adapted with permission from Matyskiela ME, et al. J Med Chem. 2018;61:535-542 © 2018 American Chemical Society.

IBERDOMIDE MM-001 PHASE 1b/2a TRIAL: STUDY DESIGN

Phase 1

- RRMM
- Prior LEN or POM
- Prior proteasome inhibitor
- Documented PD during or within 60 days of last antimyeloma therapy

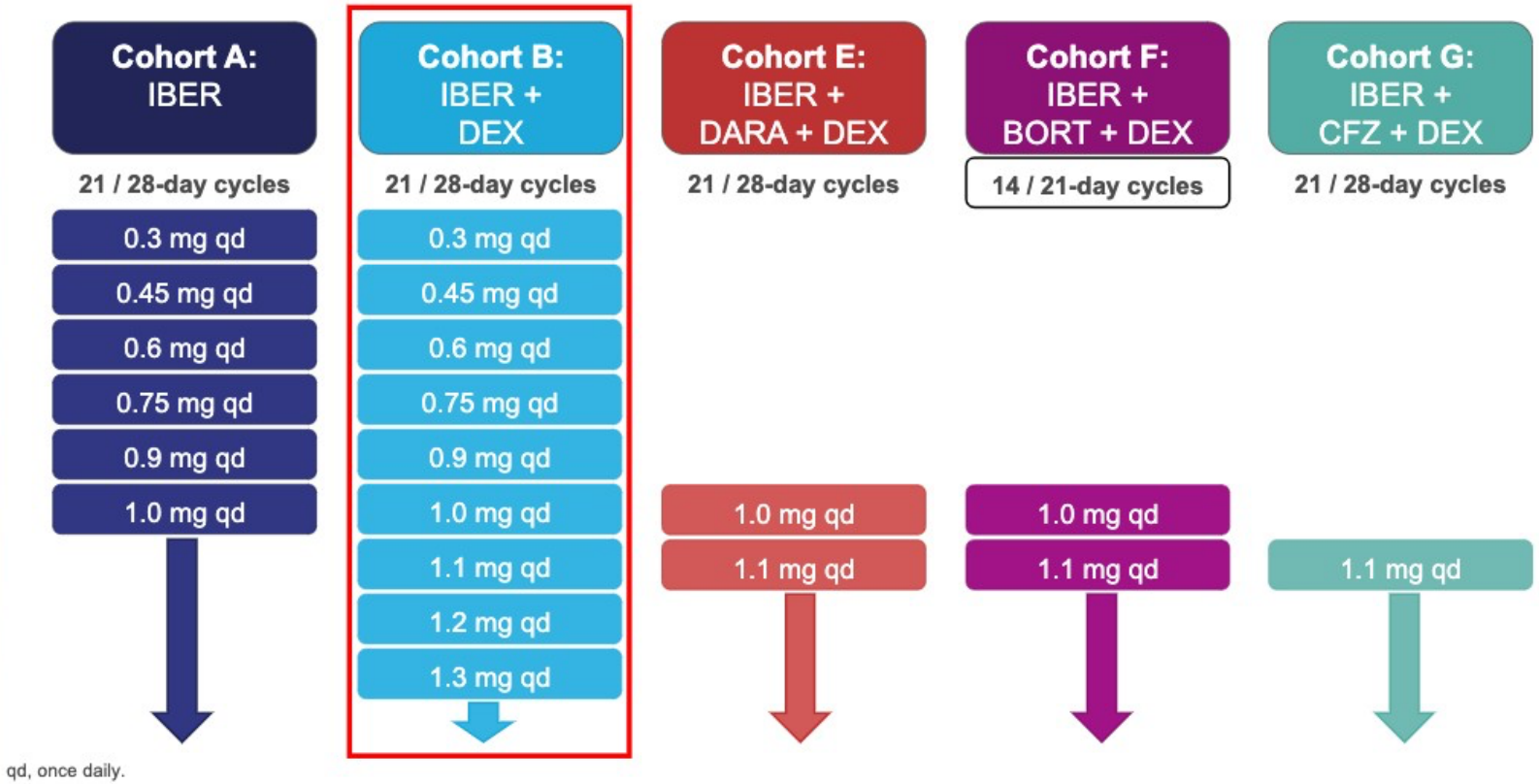


Phase 2

Study objective: Determine the MTD / RP2D and efficacy of IBER in RRMM

[a] DEX given at a dose of 40 mg (20 mg in patients aged > 75 years) on Days 1, 8, 15, and 22 of each 28-day cycle. [b] CFZ dosed once weekly (Cohort G1) or twice weekly (Cohort G2).
CFZ, carfilzomib; DEX, dexamethasone; MTD, maximum tolerated dose; PD, progressive disease; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma.

DOSE AND SCHEDULE



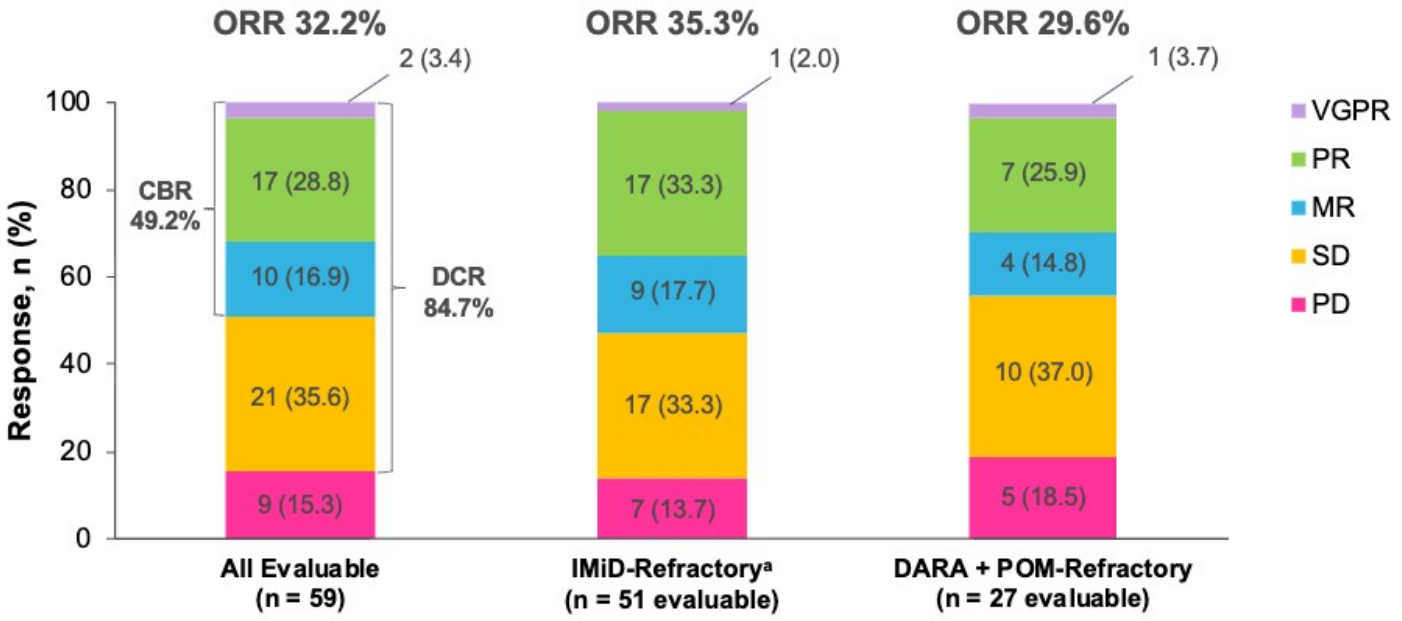
qd, once daily.

PRIOR THERAPIES

Characteristics	Cohort B (IBER + DEX) (N = 66)
Prior therapies, median (range), n	5 (2–12)
ASCT, n (%)	52 (78.8)
LEN, n (%)	66 (100)
POM, n (%)	45 (68.2)
Proteasome inhibitor, n (%)	66 (100)
CD38 monoclonal antibody, n (%)	49 (74.2)
LEN-refractory, n (%)	50 (75.8)
POM-refractory, n (%)	37 (56.1)
IMiD agent-refractory, n (%)[a]	57 (86.4)
Proteasome inhibitor-refractory, n (%)	44 (66.7)
CD38 monoclonal antibody-refractory, n (%)	47 (71.2)

[a] Includes LEN and / or POM.
ASCT, autologous stem cell transplantation.

RESPONSE



Evaluable patients include patients who have received ≥ 1 dose of IBER, had measurable disease at baseline, and ≥ 1 post-baseline response assessment.

[a] Includes LEN and POM.

CBR, clinical benefit rate; DCR, disease control rate; MR, minimal response; ORR, overall response rate; PR, partial response; SD, stable disease; VGPR, very good partial response.

COHORT B (IBER + DEX): DLTs BY DOSE LEVEL

Dose Level, mg	Patients, n	DLTs
0.3	10	–
0.45	3	–
0.6	3	–
0.75	3	–
0.9	13	–
1.0	13	–
1.1	10	–
1.2	8	1 patient: grade 4 sepsis
1.3	3	1 patient: grade 3 pneumonia

DLT, dose-limiting toxicity.

GRADE 3–4 TEAEs IN CYCLE 1

TEAEs and Events of Interest Occurring in Cycle 1, n (%)	Cohort B (IBER + DEX) (N = 66)	
	Grade 3	Grade 4
Anemia	10 (15.2)	0
Neutropenia	6 (9.1)	6 (9.1)
Febrile neutropenia	0	0
Thrombocytopenia	2 (3.0)	3 (4.5)
Fatigue	0	0
Peripheral sensory neuropathy	0	0
Diarrhea	0	0
Constipation	0	0
Deep vein thrombosis	0	0
Pulmonary embolism	0	0
Infection	7 (10.6)	1 (1.5)
Pneumonia[a]	2 (3.0)	0

[a] Includes Medical Dictionary for Regulatory Activities Terminology version 21.0 or higher Preferred Terms pneumonia, influenzal pneumonia, parainfluenzae viral pneumonia, and streptococcal pneumonia.

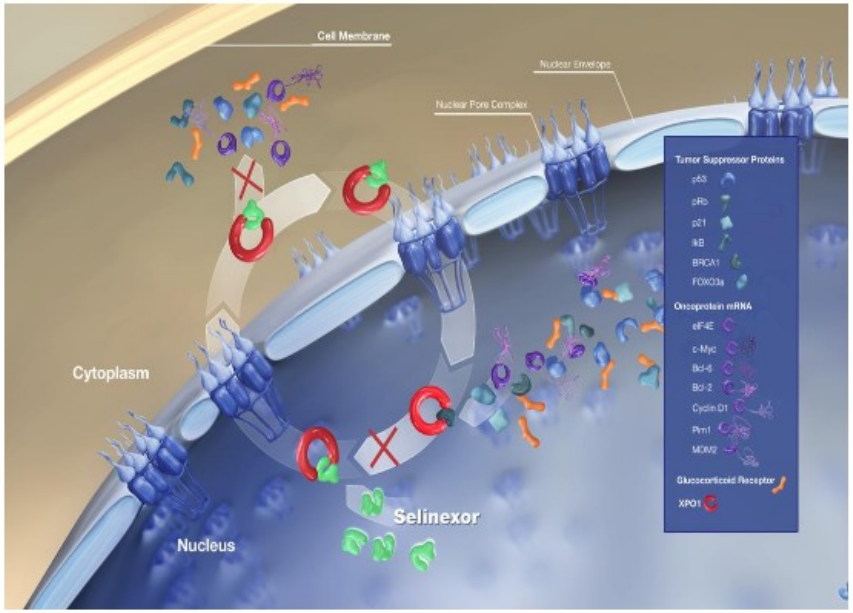
CONCLUSIONS

- IBER is a novel CELMoD compound with enhanced tumoricidal and immune stimulatory effects in preclinical studies[1]
  - Overcomes LEN and POM resistance[2]
- IBER + DEX showed a favorable safety and activity profile in patients with heavily pretreated RRMM
  - MTD / RP2D has not yet been reached
- ORR in patients refractory to LEN, POM, and / or CD38 antibody therapy was similar to that observed for whole cohort
- Enrollment continues in cohorts evaluating the combination of IBER + DEX with BORT, DARA, and CFZ as part of a broad development program for iberdomide

1. Bjorklund CC, et al. Blood. 2016;128:abstract 1591. 2. Bjorklund CC, et al. Unpublished data.

Selinexor:

First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE)[1-4]



Exportin 1 (XPO1) is the major nuclear export protein for:

- Tumor suppressor proteins (TSPs, e.g., p53, IκB, and FOXO)
- eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, cyclins)
- Glucocorticoid receptor (GR)

XPO1 is overexpressed in MM:

- High **XPO1** levels enable cancer cells to escape TSP-mediated cell cycle arrest and apoptosis
- **XPO1** levels correlate with poor prognosis and drug resistance

Selinexor is an oral selective **XPO1 inhibitor**; preclinical data supports that selinexor:

- Reactivates multiple TSPs by preventing nuclear export
- Inhibits oncoprotein translation
- Reactivates GR signaling in presence of dexamethasone

[1]Schmidt et al., Leukemia, 2013, [2]Tai et al., Leukemia, 2013, [3]Argueta et al., Oncotarget, 2018 [4]Turner et al, 2017 unpublished

Safety and Efficacy of the Combination of Selinexor, Lenalidomide and Dexamethasone (SRd) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

Darrell White, Richard LeBlanc, Christopher Venner, Nizar J. Bahlis, Suzanne Lentzsch, Cristina Gasparetto, Christine Chen, Brea Lipe, Heather Sutherland, Sascha Tuchman, Muhamed Baljevic, Rami Kotb, Michael Sebag, Natalie Callander, William Bensinger, Kazuharu Kai, Jianjun Liu, Heidi Sheehan, Daniel Nova Estepan, Jatin Shah, Gary Schiller

Background / Rationale: Selinexor and Lenalidomide Activity in Heavily Treated MM

STORM*: Selinexor + Dexamethasone[1]

Refractory to **Dara, PI**, and **IMiD**

ORR: 26.2%

ORR: 25.3% (Penta-Ref)

PFS: 3.7 months (Overall)

MM-009: Lenalidomide + Dexamethasone[2]

Patients ≥ 1 prior MM therapy

ORR: 61%

PFS: 11.1 months

Selinexor demonstrates synergistic activity in combination with lenalidomide *in vivo*[3]

*Selinexor (+ dex) received accelerated approval from the FDA for patients with RRMM, with ≥4 prior therapy regimens, and whose disease is refractory to at least 2 PIs, 2 IMiDs, and an anti-CD38 MoAb

[1]Chari et al., New England Journal of Medicine, 2019
[2]Weber et al., New England Journal of Medicine, 2007
[3]Carlson et al., ESH 2014

STOMP Study Design

Primary Objective: Determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D)

Patient Populations:

- **Arm SRd: selinexor + lenalidomide + dexamethasone – Patients who received ≥1 prior lines of therapy for MM**
- Arm SRd-NDMM: selinexor + lenalidomide + dexamethasone in newly diagnosed MM patients
- Arm SPd: selinexor + pomalidomide + dexamethasone
- Arm SVd: selinexor + bortezomib + dexamethasone
- Arm SKd: selinexor + carfilzomib + dexamethasone
- Arm SDd: selinexor + daratumumab + dexamethasone

SRd Dosing Scheme: 3 + 3 design was used for dose escalation phase

Oral Selinexor
60 mg BIW or QW
80 mg QW
28 day cycle

+

Oral Lenalidomide
25 mg QD
Daily, 21 day cycle

+

Oral Dexamethasone
20 mg BIW or **40 mg** QW

PO=per oral, BIW=twice-weekly, QW=once-weekly, QD=once daily

Patient Characteristics

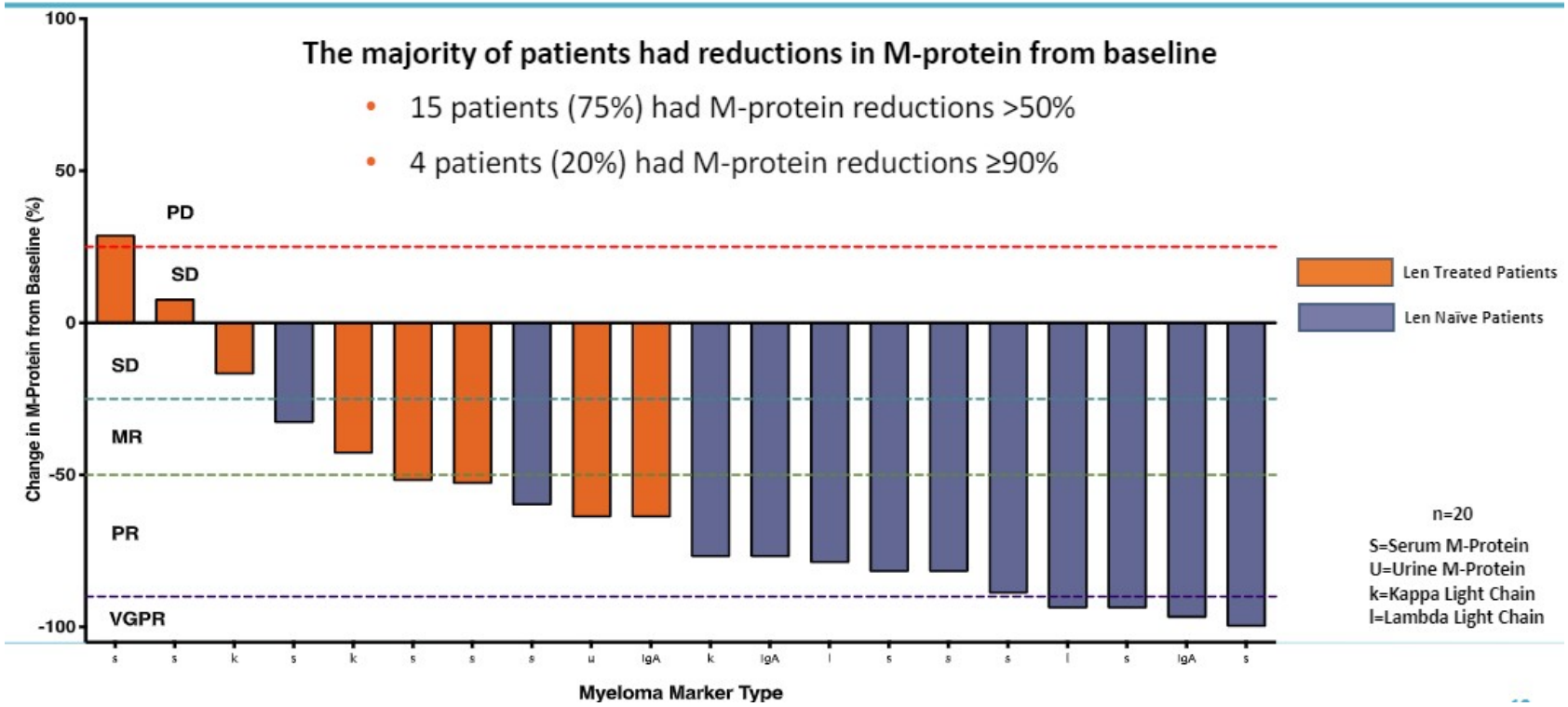
Patient Characteristics	N
Enrolled as of August 1, 2019 (Enrollment is complete)	**24**
60 mg selinexor BIW + 25 mg lenalidomide QD	5
80 mg selinexor QW + 25 mg lenalidomide QD	7
60 mg selinexor QW + 25 mg lenalidomide QD (RP2D)	**12**
Median Age, Years (range)	**67** (49 – 84)
Males : Females	**13** (54%) : **11** (46%)
Median Time from Diagnosis to SRd Treatment, Years (range)	4.5 (<1 – 22)
Median Prior Regimens All Patients (range)	**1 (1–8)**
Proteasome Inhibitor (Treated : Refractory)	24 (100%) : 13 (65%)
Lenalidomide (Treated : Refractory : Naïve)	9 (38%) : 5 (21%) : 15 (63%)
Autologous Stem Cell Transplant	12 (50%)
Median Prior Regimens RP2D Patients (range)	**4 (1–8)**
Lenalidomide (Treated : Refractory : Naïve)	5 (42%) : 3 (25%) : 7 (58%)

Dose Limiting Toxicities

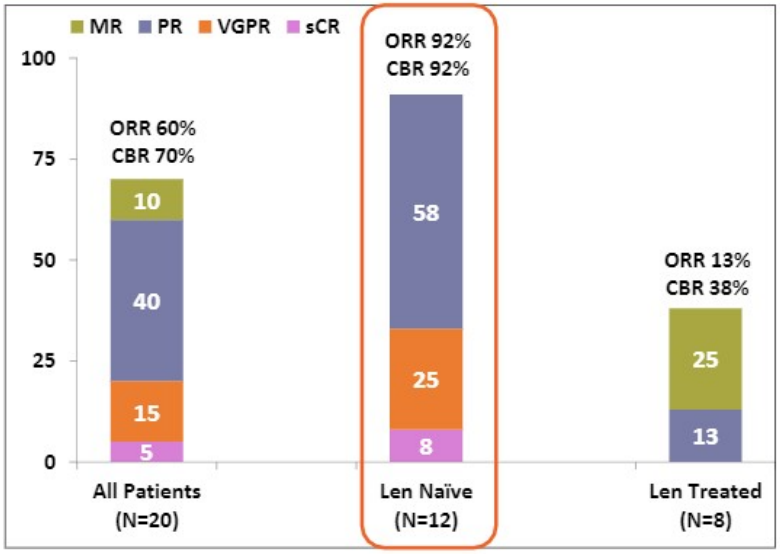
Selinexor Dose	Median Weeks on Treatment (range)	Dose Escalation DLT Evaluable Patients Enrolled (Number of Patients with DLT)	Dose-Limiting Toxicity (DLT)
60 mg BIW	6 (2-25)	**5 (4)**	G3 anorexia and weight loss, G4 thrombocytopenia, G4 thrombocytopenia and G3 fatigue, 4 missed doses
80 mg QW	13 (3-155)	**6 (2)**	G4 thrombocytopenia (2 cases)
60 mg QW	23 (2-122)	**6 (-)**	No DLTs were reported in the 60 mg QW cohort

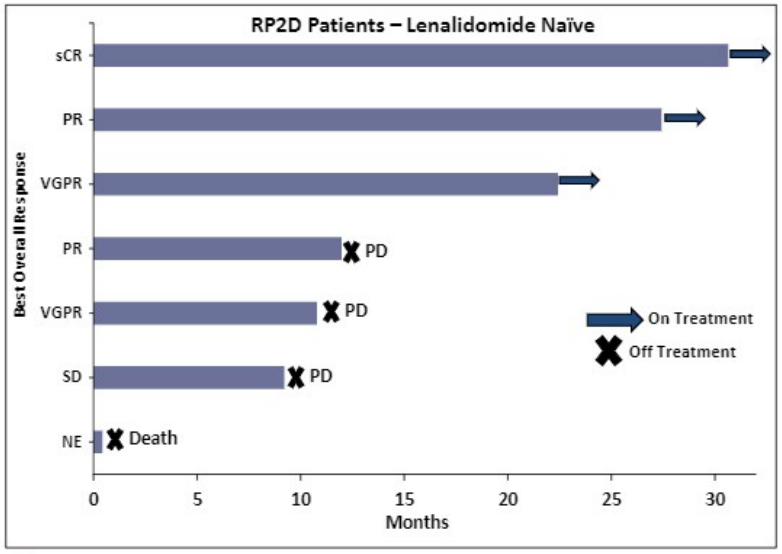
Based on tolerability, the RP2D of SRd is selinexor 60 mg QW, lenalidomide 25 mg QD, and dexamethasone 40 mg QW

SRd Efficacy – M-Protein Effect



Selinexor-Lenalidomide-Dexamethasone: Efficacy





- The median time to response (≥PR) was 1 month
- Among lenalidomide naïve RP2D patients, the median time on treatment was 12 months

Responses were adjudicated according to the *International Myeloma Working Group* criteria,*four patients not evaluable for response withdrew consent prior to disease follow-up. Two unconfirmed PRs, ORR=Overall Response Rate (sCR+VGPR+PR), CBR=Clinical Benefit Rate (ORR+MR), sCR=Stringent Complete Response, VGPR=Very Good Partial Response, PR=Partial Response, MR=Minimal Response. Responses as of August 1, 2019 based on interim unaudited data.

Treatment-Related Adverse Events in ≥10% Patients

AE Term	60 mg BIW, 80 mg QW Sel + 25 mg Len QD (N=12)			60 mg QW Sel + 25 mg Len QD – RP2D (N=12)			Total (N=24)
Hematologic	**Grade 1/2**	**Grade 3**	**Grade 4**	**Grade 1/2**	**Grade 3**	**Grade 4**	
Thrombocytopenia	**1 (8.3)**	**2 (16.7)**	**6 (50.0)**	**--**	**3 (25.0)**	**4 (33.3)**	**16 (66.7)**
Neutropenia	**--**	**5 (41.7)**	**2 (16.7)**	**--**	**4 (33.3)**	**4 (33.3)**	**15 (62.5)**
Anemia	3 (25.0)	1 (8.3)	--	1 (8.3)	1 (8.3)	--	**6 (25.0)**
Gastrointestinal							
Nausea	**8 (66.7)**	**--**	**--**	**6 (50.0)**	**1 (8.3)**	**--**	**15 (62.5)**
Anorexia	**5 (41.7)**	**2 (16.7)**	**--**	**5 (41.7)**	**--**	**--**	**12 (50.0)**
Vomiting	**4 (33.3)**	**--**	**--**	**4 (33.3)**	**--**	**--**	**8 (33.3)**
Constipation	5 (41.7)	--	--	1 (8.3)	--	--	**6 (25.0)**
Diarrhea	2 (16.7)	--	--	4 (33.3)	--	--	**6 (25.0)**
Asthenia	1 (8.3)	--	--	2 (16.7)	1 (8.3)	--	**4 (16.7)**
Altered Taste	3 (25.0)	--	--	--	--	--	**3 (12.5)**
Constitutional							
Fatigue	**5 (41.7)**	**2 (16.7)**	**--**	**4 (33.3)**	**2 (16.7)**	**--**	**13 (54.2)**
Weight Loss	**4 (33.3)**	**1 (8.3)**	**--**	**5 (41.7)**	**--**	**--**	**10 (41.7)**
Other							
Dehydration	1 (8.3)	--	--	2 (16.7)	1 (8.3)	--	**4 (16.7)**
Dizziness	2 (16.7)	--	--	2 (16.7)	--	--	**4 (16.7)**
Muscle Spasms	1 (8.3)	--	--	3 (25.0)	--	--	**4 (16.7)**
Vision Blurred	--	1 (8.3)	--	3 (25.0)	--	--	**4 (16.7)**

Safety data cutoff of August 1, 2019

- No treatment-related Grade 5 events were reported

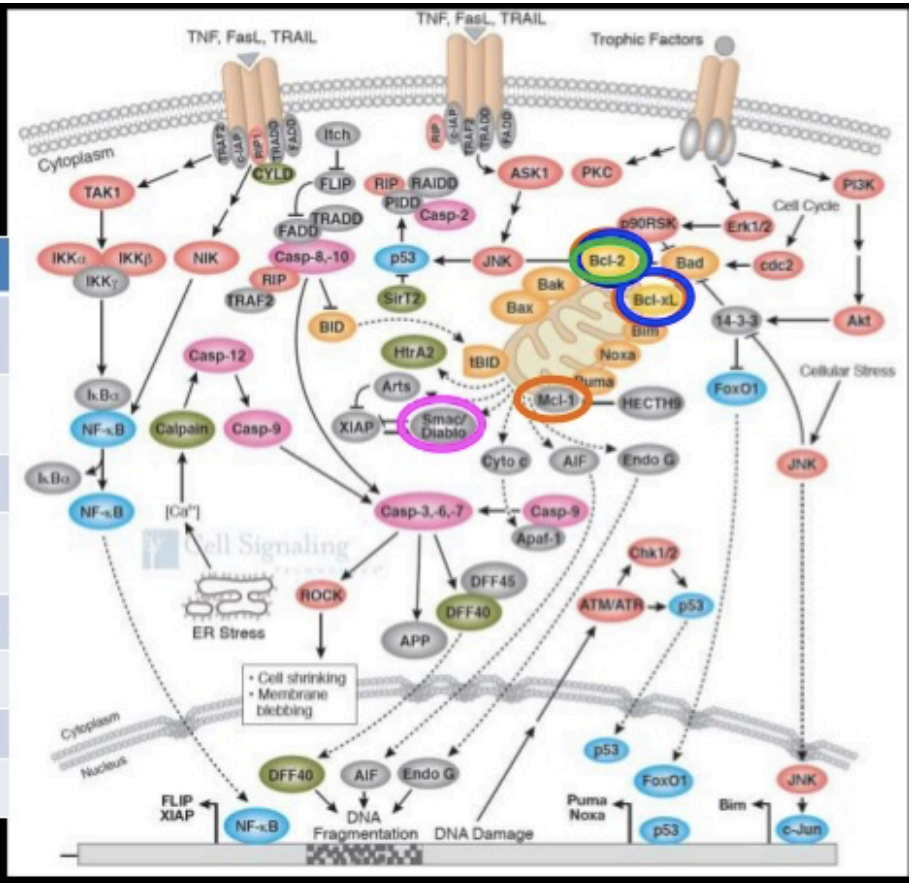
Conclusions – Safety & Efficacy

- **Selinexor is first in class XPO1 inhibitor now approved for RRMM**
- **Weekly Selinexor** 60 mg QW can be safely combined with full dose lenalidomide 25 mg QD, and dexamethasone 40 mg QW
- **Side Effect profile is consistent with no new signal**
  - **Most Common G3/4 AEs –** thrombocytopenia and neutropenia
  - **Low-grade Gastrointestinal Side Effects –** common and expected, and can be managed with appropriate supportive care and/or dose modifications
- **Combination is highly active with ORR – 92%** in lenalidomide-naïve patients
- **Combination is being evaluated in NDMM**

All oral combination of selinexor / lenalidomide / dexamethasone appears to be highly active, well tolerated and warrants further investigation

Apoptosis Regulation

Agent/Co	Mechanism	Ph
Oblimerson Genasense Genta	BCL2 AS	III
AT-101 Gossypol Ascenta	BH3 mimetic	II
Obatoclax Teva	BH3 mimetic	II
Navitoclax ABT-263 Abbvie	BH3 mimetic	II
ABT-199 Abbvie	BH3 mimetic	I/II
LY2181308 ISIS	Survivin AS	II
LCL-161	Smac mimetic	I
Birinapent	Smac mimetic	



Pathway map from Cell Signaling

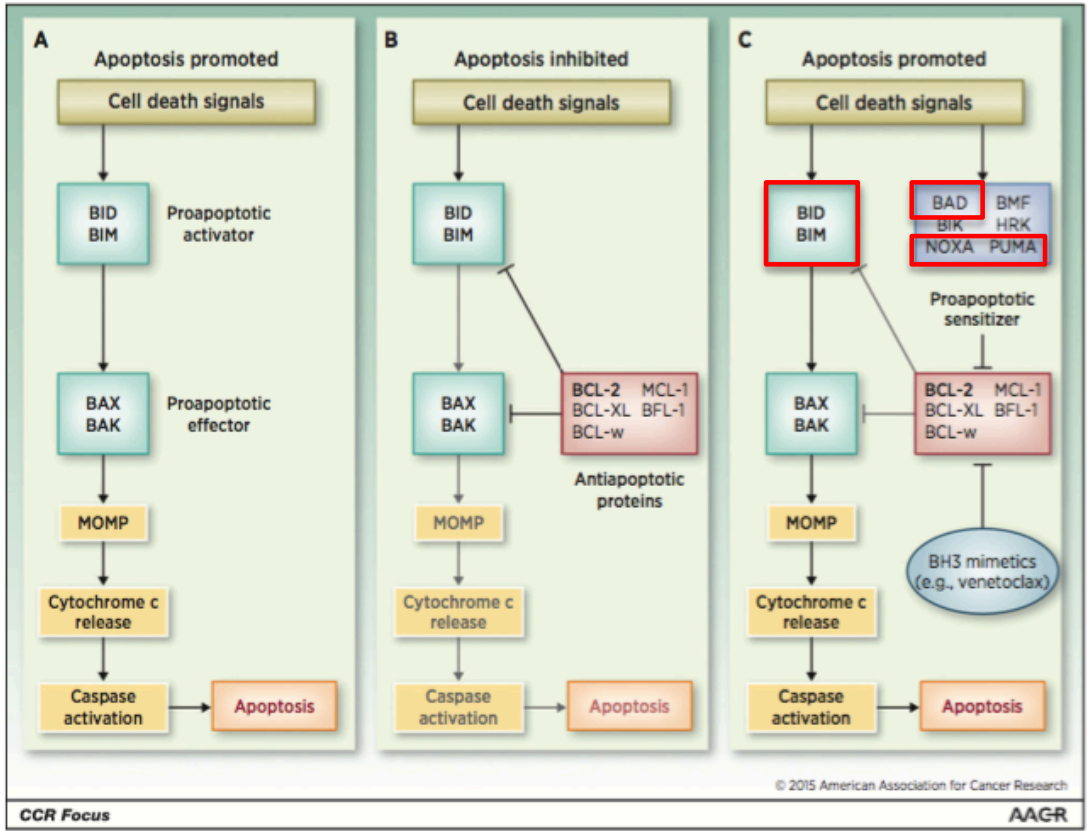
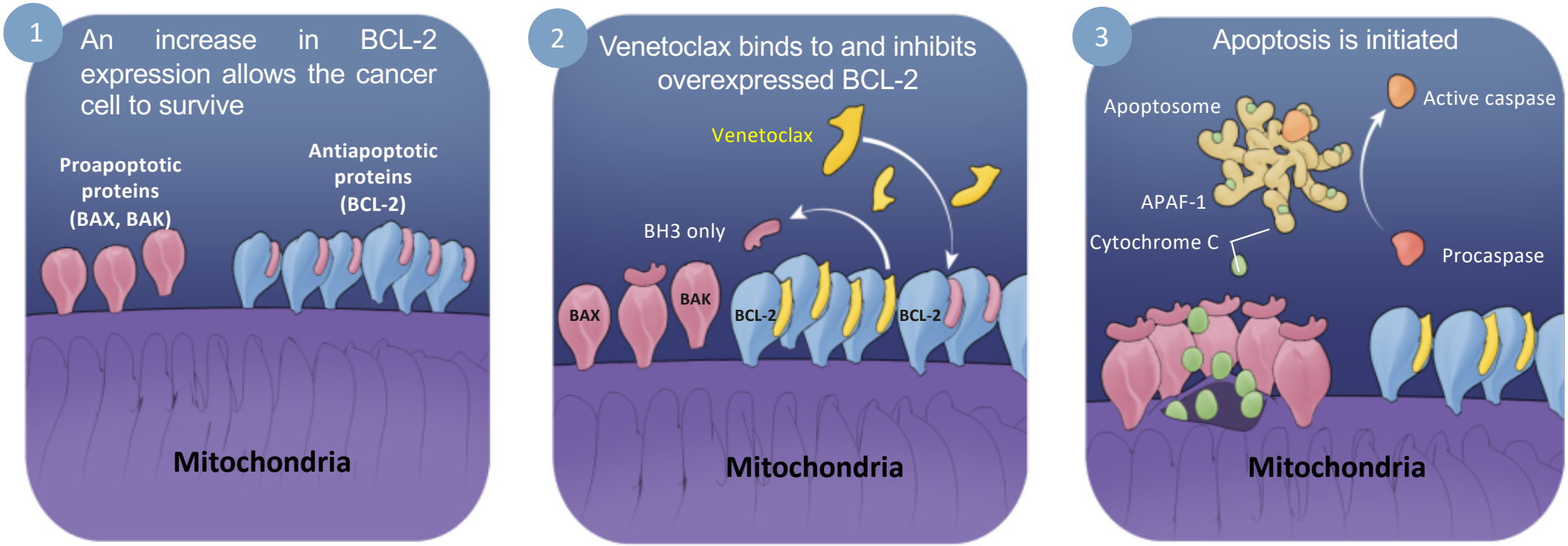


Figure 1.
Overview of pro- and antiapoptotic molecules. A, cell death signals trigger BID and BIM to activate BAX and BAK, which in turn initiate MOMP and lead to apoptosis. B, antiapoptotic molecules, including BCL-2, antagonize both activator and effector molecules and block the apoptotic cascade. C, cell death signals also activate sensitizer molecules, which antagonize antiapoptotic molecules and release the block on apoptosis. This physiologic role is pharmacologically recapitulated by BH3-mimetic drugs such as venetoclax.

Venetoclax: Mechanism of Action



Kumar S, et al. ASCO 2015. Abstract 8576.

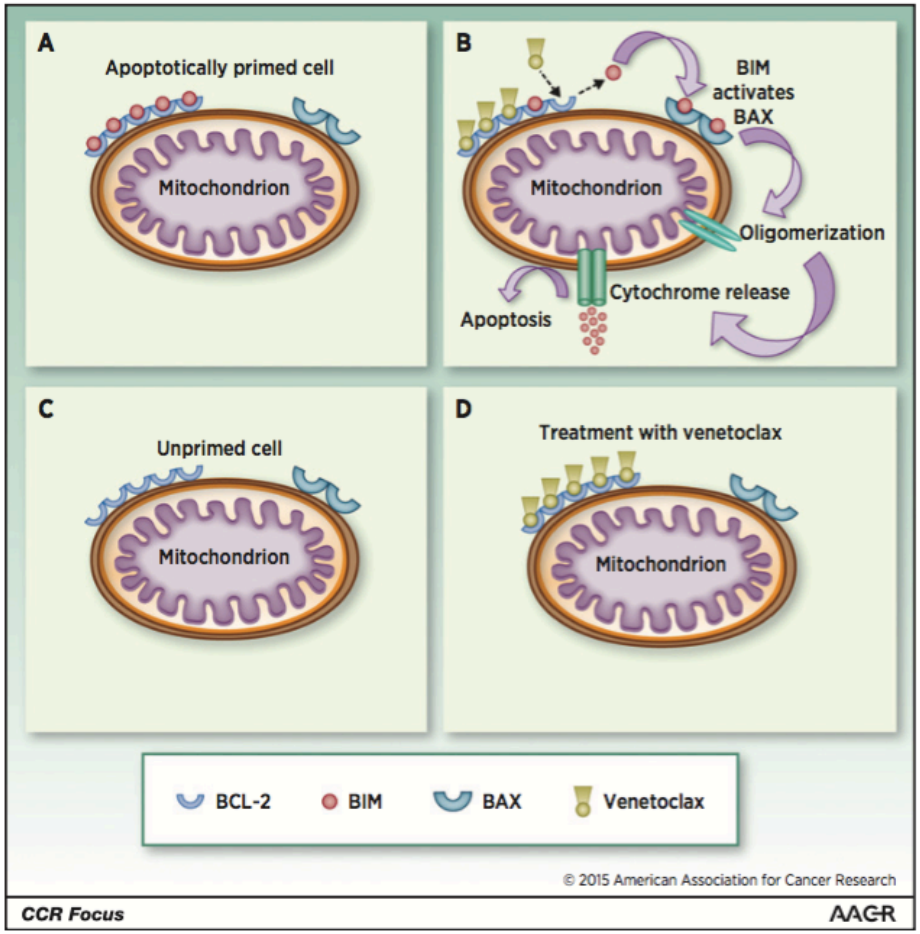
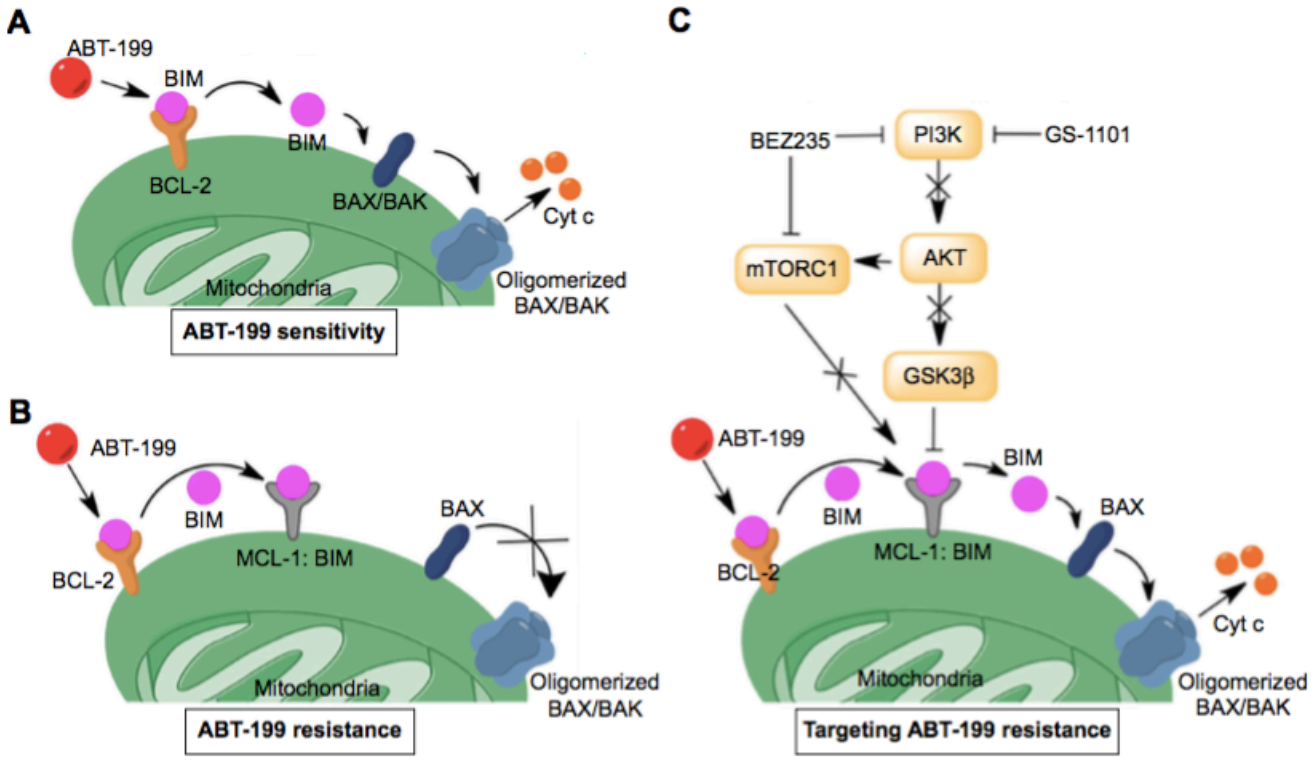


Figure 2.
Apoptotic priming and venetoclax (VCX) method of action. A, in an apoptotically primed cell, BCL-2 or other antiapoptotic molecules sequester BIM (or BID) and prevent interaction with effector molecules such as BAK or BAX. B, binding of VCX to BCL-2 displaces BIM, allowing it to interact with BAX (or BAK), which then oligomerizes and allows efflux of cytochrome C from the mitochondrion. C, a cell with a low degree of apoptotic priming has relatively little BIM or BID. In this case, treatment with VCX (D) has little effect in and of itself, though this might not preclude synergy with additional chemotherapy.

A model for Venetoclax resistance



Drug Design, Development and Therapy

Dovepress

REVIEW

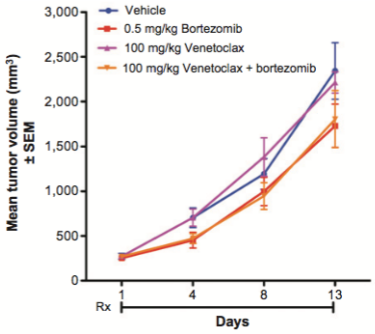
Development of venetoclax for therapy of lymphoid malignancies

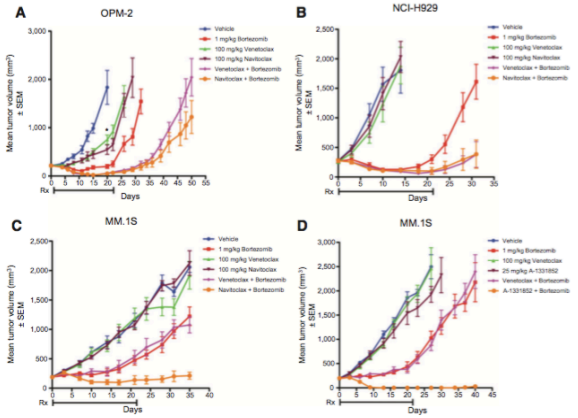
Background of combination therapy with Venetoclax in MM

✓The modest or marginal efficacy of Venetoclax as a single agent observed in three xenograft models in which **BCL-2**, **BCL-X_L**, and **MCL-1** were variably expressed is likely due to the coexpression of either **BCL-X_L** and/or **MCL-1** and therefore they focused on combination regimens with therapeutic agents that may inhibit their activity;

✓**Bortezomib** induces caspase-dependent degradation of **MCL-1** via upregulation of **NOXA**, a BH3-only protein that selectively neutralizes **MCL-1** prosurvival activity in HMCLs: the inhibition of **BCL-2** by venetoclax and downmodulation of **MCL-1** by bortezomib is sufficient to induce synthetic lethality in vivo;

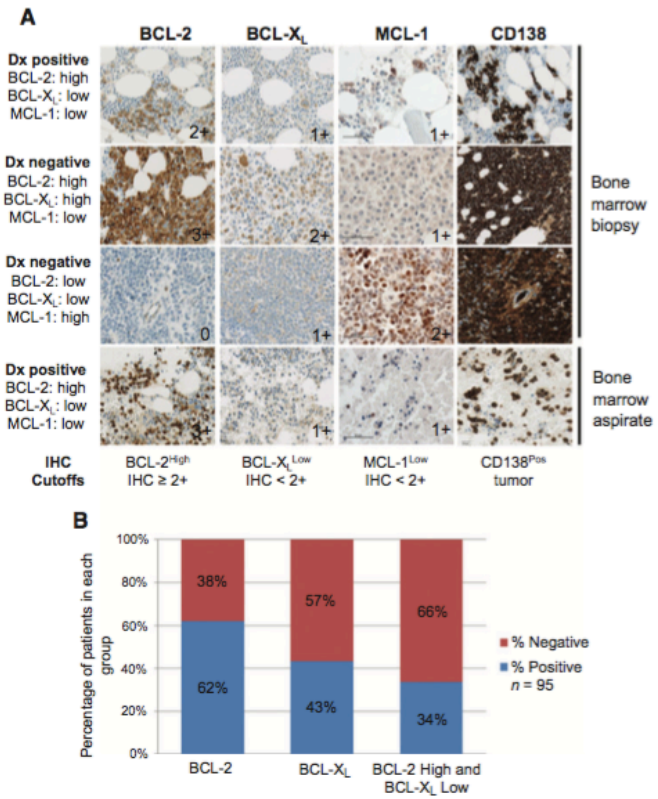
✓The data suggest that the combination of Venetoclax with bortezomib is most likely to be efficacious in multiple myeloma patients that coexpress **BCL-2** and **MCL-1** but not **BCL-X_L**.





Punnoose E.A.; Mol Cancer Ther; 15(5) May 2016

Background of combination therapy with Venetoclax in MM



Companion Diagnostics and Cancer Biomarkers

Molecular Cancer Therapeutics

Expression Profile of BCL-2, BCL-X$_L$, and MCL-1 Predicts Pharmacological Response to the BCL-2 Selective Antagonist Venetoclax in Multiple Myeloma Models

Elizabeth A. Punnoose[1], Joel D. Leverson[2], Franklin Peale[3], Erwin R. Boghaert[4], Lisa D. Belmont[5], Nguyen Tan[5], Amy Young[6], Michael Mitten[4], Ellen Ingalla[6], Walter C. Darbonne[1], Anatol Oleksijew[4], Paul Tapang[4], Peng Yue[5], Jason Oeh[6], Leslie Lee[6], Sophie Maiga[7], Wayne J. Fairbrother[8], Martine Amiot[7], Andrew J. Souers[4], and Deepak Sampath[6]

✓The data indicate that, in addition to **MCL-1**, **BCL-X$_L$** is heterogeneously expressed in HMCLs and patient samples. The expression profile of **BCL-X$_L$** relative to **BCL-2** and **MCL-1** may be an important predictor of response to venetoclax sensitivity as a monotherapy and in combination with bortezomib.

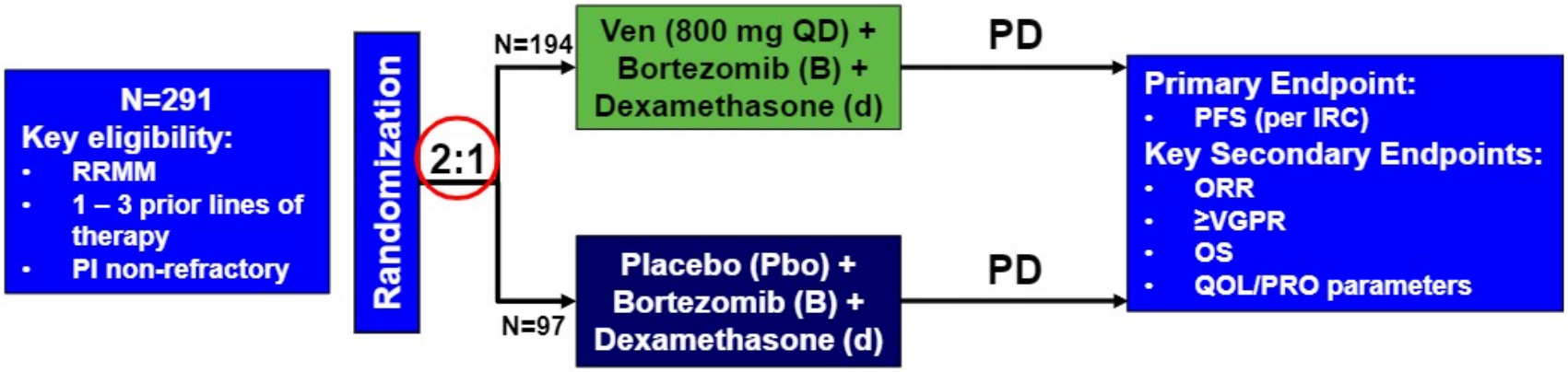
✓To determine the latter, the authors developed robust IHC assays for evaluating **BCL-2**, **BCL-X$_L$**, and **MCL-1** expression, and cutoffs for evaluating these potential predictive biomarkers in multiple myeloma patient samples.

A Phase 3 Study of Venetoclax or Placebo in Combination with Bortezomib and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma

Shaji K. Kumar[1], Simon J. Harrison[2], Michele Cavo[3], Javier de la Rubia[4], Rakesh Popat[5], Cristina Gasparetto[6], Vania Hungria[7], Hans Salwender[8], Kenshi Suzuki[9], Inho Kim[10], Elizabeth Punnoose[11], Wan-Jen Hong[11], Kevin J. Freise[12], Anjla Sood[12], Muhammad Jalaluddin[12], Jeremy A. Ross[12], James E. Ward[12], Paulo C. Maciag[12], Philippe Moreau[13]

[1]Mayo Clinic, Rochester, MN, USA; [2]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Victoria, Australia; [3]Seragnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy; [4]Hematology Service Hospital Dr Peset and School of Medicine and Dentistry, Catholic University of Valencia, Valencia, Spain; [5]Department of Hematology, University College London Hospitals, London, United Kingdom; [6]Duke University School of Medicine, Durham, NC, USA; [7]Clinica Sao Germano, Sao Paulo, Brazil; [8]Asklepios Tumorzentrum Hamburg, AK Altona and AK St. Georg, Hamburg, Germany; [9]Japanese Red Cross Medical Center, Tokyo, Japan; [10]Seoul National University, Seoul, South Korea; [11]Genentech, Inc., South San Francisco, CA, USA; [12]AbbVie, Inc., North Chicago, IL, USA; [13]Department of Hematology, University Hospital, Nantes, France

BELLINI Study Design



Cycles 1 – 8: 21-day, Bortezomib 1.3 mg/m^2 Days 1, 4, 8, 11 and dexamethasone 20 mg Days 1, 2, 4, 5, 8, 9, 11, 12

Cycles 9+: 35-day, Bortezomib 1.3 mg/m^2 Days 1, 8, 15, 22 and dexamethasone 20 mg Days 1, 2, 8, 9, 15, 16, 22, 23

Stratification factors	• Bortezomib sensitive vs naïve • Prior lines of therapy: 1 vs 2–3
Non-ranked secondary endpoints	PFS in BCL-2^{high} (IHC), DOR, TTP, MRD negativity rate, other PROs (GHS, fatigue)
Key subgroup analyses	t(11;14), high/standard-risk cytogenetics, and *BCL2* expression (gene expression)

DOR, duration of response; GHS, global health status; IHC, immunohistochemistry; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PRO, patient reported outcome; QD, daily; QOL, quality of life; RRMM, relapsed/refractory multiple myeloma; TTP, time to progression; VGPR, very good partial response.

Demographics and Baseline Characteristics

	Ven+Bd (N=194)	Pbo+Bd (N=97)
Median age, years (range)	66 (36, 87)	65 (44, 83)
≥ 65 years, n (%)	108 (56)	52 (54)
Multiple myeloma ISS, n (%)		
Stage 1	81 (42)	48 (50)
Stage 2	69 (36)	32 (33)
Stage 3	39 (20)	13 (14)
ECOG performance score, n (%)		
0	101 (52)	47 (49)
1 or 2	92 (48)	49 (51)
No. of prior lines of therapy, n (%)		
1	91 (47)	44 (45)
2 or 3	103 (53)	53 (55)
Prior stem cell transplant, n (%)	116 (59)	57 (59)
Prior exposure to PI, n (%)	135 (70)	68 (70)
Prior exposure to IMiD, n (%)	131 (68)	65 (67)
Prior exposure to PI + IMiD, n (%)	78 (40)	42 (44)

ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory drug; ISS, International Staging System; PI, proteasome inhibitor.

	Ven+Bd (N=194)	Pbo+Bd (N=97)
Type of measurable disease, n (%)		
IgG	115 (59)	47 (49)
IgA	40 (21)	25 (26)
FLC / Other	39 (20)	25 (26)
Cytogenetics, n (%)*		
High-risk†	31 (17)	18 (19)
Standard-risk‡	141 (78)	72 (77)
Unknown§	9 (5)	4 (4)
t(11;14) status, n (%)*		
Positive	20 (11)	15 (16)
Negative	152 (84)	74 (79)
Unknown§	9 (5)	5 (5)
BCL-2 expression (IHC), n (%)*		
High	93 (78)	47 (81)
Low	26 (22)	11 (19)

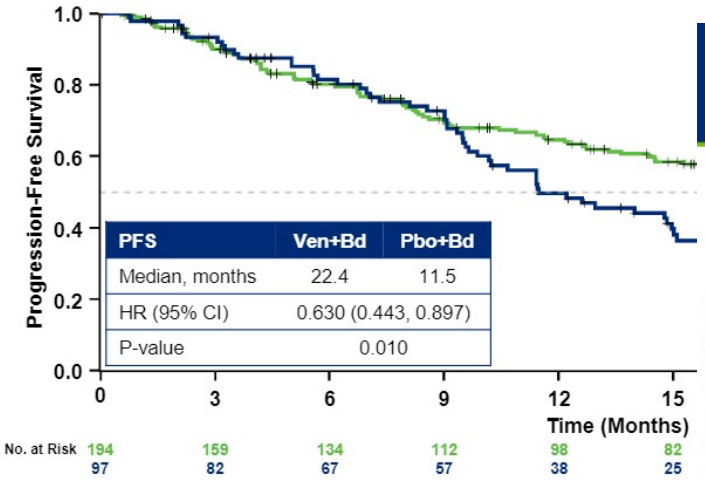
FLC, serum free light chain; IHC, immunohistochemistry.
* Percentage calculated by excluding patients with missing data
† t(4;14) or t(14;16) or del(17p)
‡ No high-risk cytogenetics
§ Sample was tested but results were inconclusive

Patient Disposition

Clinical Data Cut-off: 26 Nov 2018

	Ven+Bd (N=194)	Pbo+Bd (N=97)
Randomized, n (%)	**194 (100)**	**97 (100)**
Treated	193 (99.5)	96 (99)
Analysis population, n (%)		
Intent-to-treat (ITT) analysis set	194 (100)	97 (100)
Safety analysis set	193 (99.5)	96 (99)
Discontinued Ven/Pbo, n (%)	121 (62)	75 (77)
Primary reason for Ven/Pbo discontinuation, n (%)		
Progressive disease	55 (28)	56 (58)
Adverse event	31 (16)	8 (8)
Withdrew consent	15 (8)	4 (4)
Physician decision	10 (5)	5 (5)
Death	6 (3)	0
Median exposure, months (range)	9.9 (0.1, 24.7)	10.5 (0.1, 25.4)
Median follow-up time for overall survival, months (range)	19.0 (0.2, 24.8)	18.3 (0.0, 26.5)

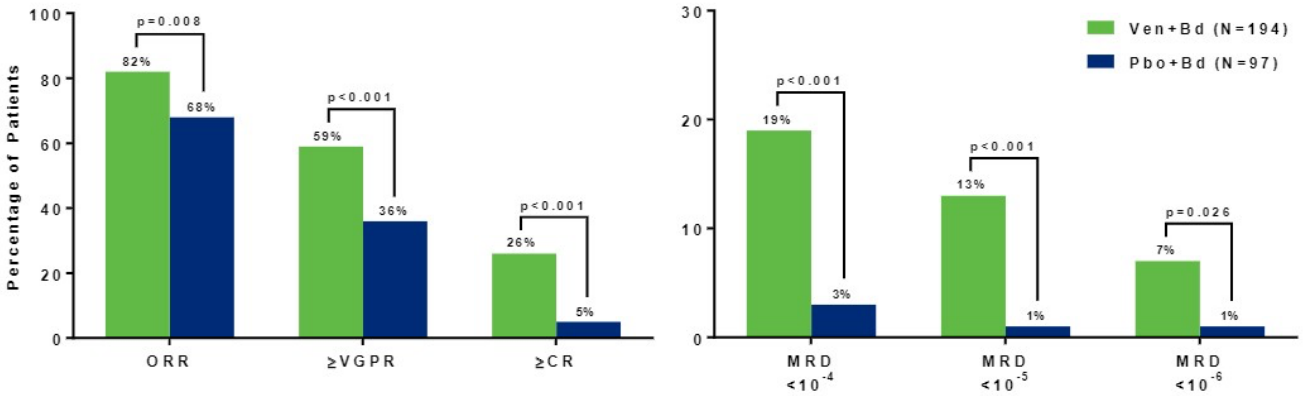
Primary Endpoint Analysis: Progression-Free Survival
All Patients (ITT), 26 Nov 2018



PFS	Ven+Bd	Pbo+Bd
Median, months	22.4	11.5
HR (95% CI)	0.630 (0.443, 0.897)	
P-value	0.010	

The BELLINI study met its primary endpoint with superior me

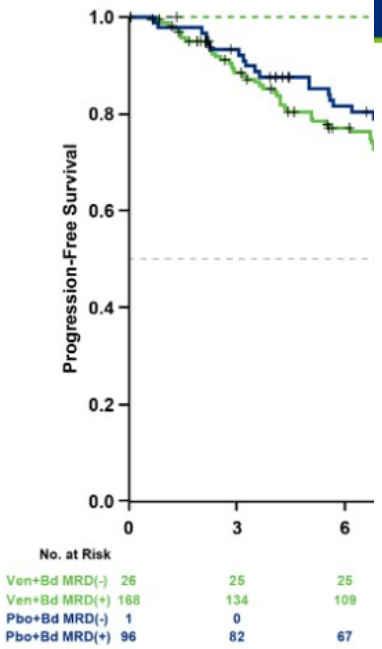
Clinical Response Rates in All Patients
26 Nov 2018



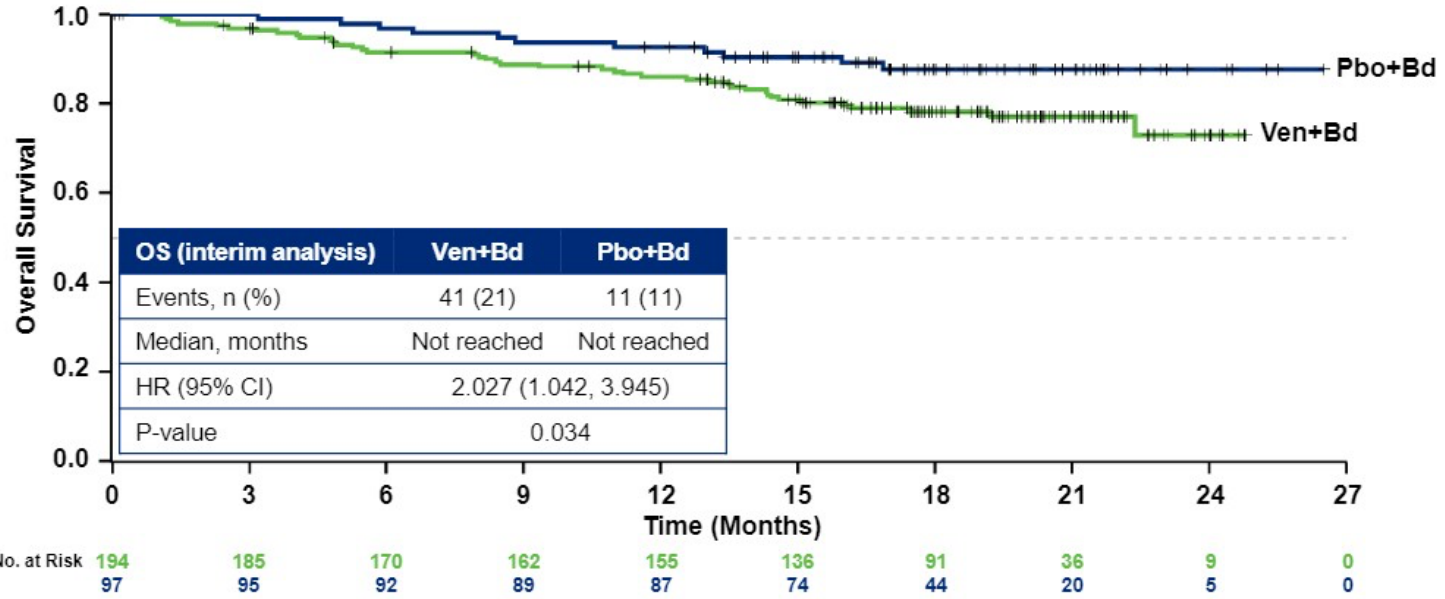
Overall response, ≥VGPR, ≥CR and MRD negativity rates were significantly higher with Ven+Bd

MRD assessment was performed by next-generation sequencing on bone marrow aspirate at time of CR/sCR

Progression-Free Survival by MRD (10^{-5}) Status
26 Nov 2018



Overall Survival
All Patients (ITT), 26 Nov 2018



OS (interim analysis)	Ven+Bd	Pbo+Bd
Events, n (%)	41 (21)	11 (11)
Median, months	Not reached	Not reached
HR (95% CI)	2.027 (1.042, 3.945)	
P-value	0.034	

A higher risk of death was observed in the Ven+Bd arm compared to Pbo+Bd at interim OS analysis

Summary of Cause of Death

Safety Population
(Only patients who received treatment

All deaths
- Infection
- Progressive disease
- Other*

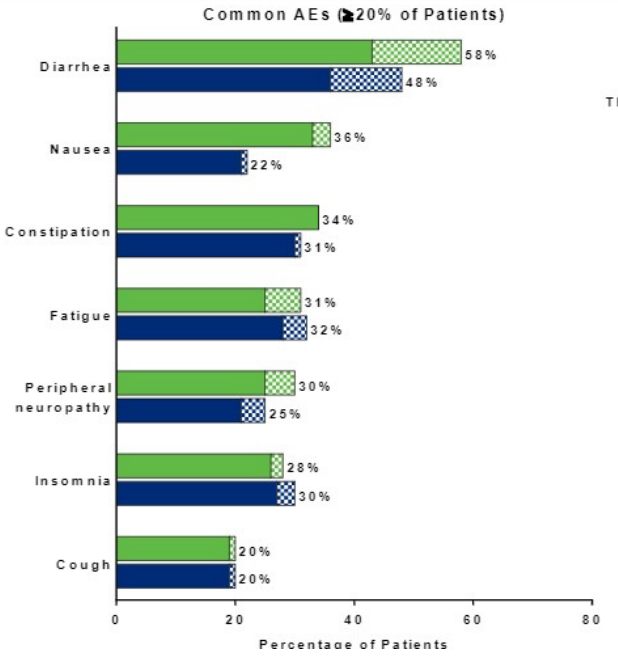
Deaths occurring within 30 days of las
- Infection
- Progressive disease
- Other

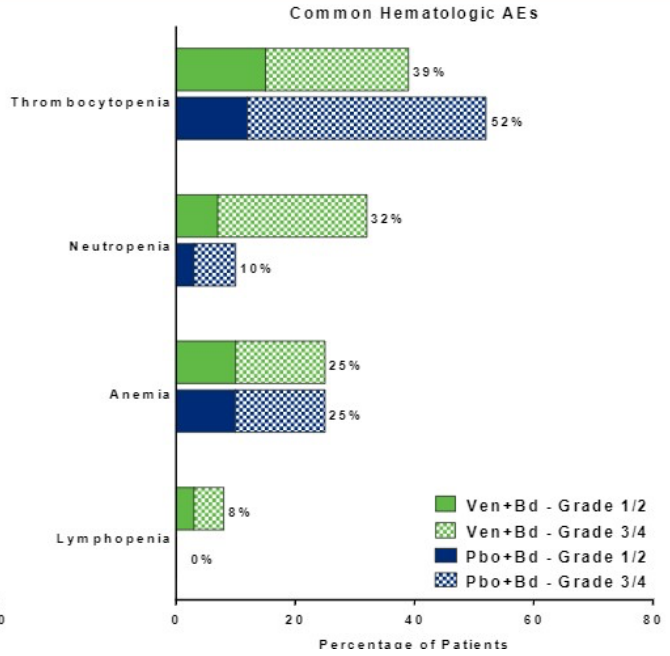
Deaths occurring after 30 days of last
- Infection
- Progressive disease
- Other

*Includes: cardiac/cardiopulmonary arrest (n = 4), congestiv

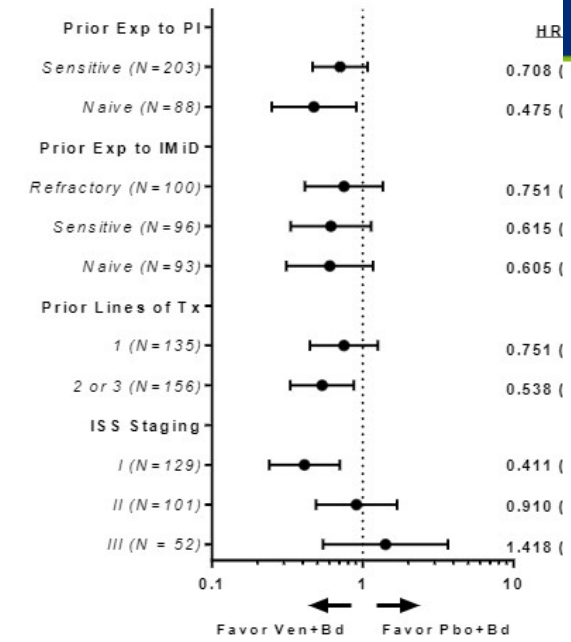
More deaths were observed in the Ven
treatment-emergent dea

Most Common Adverse Events



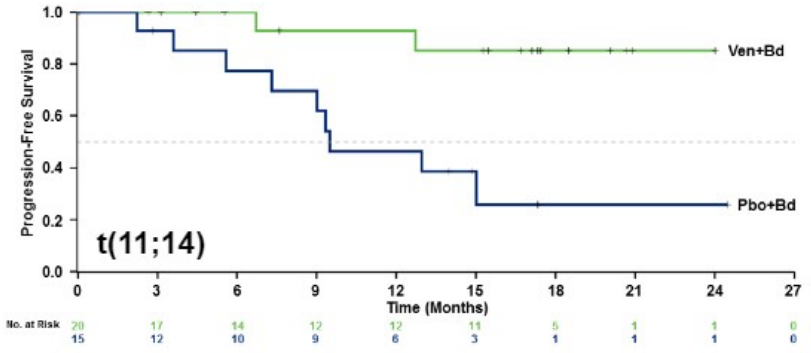


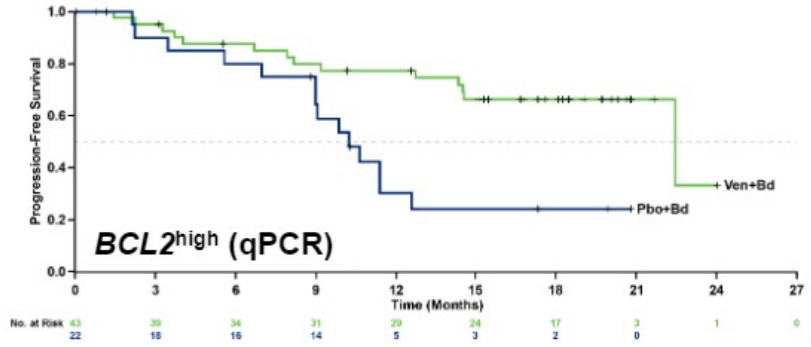
PFS Analysis in Key Subgroups
26 Nov 2018



Exp, exposure; Expr, expression; IHC, immunohistochemistry; IMiD, immunomodulat
ISS, International Staging System; PI, proteasome inhibitor; QT, quartile; Tx, therapy

Progression-Free Survival in Patients with t(11;14) or *BCL2*^{high} Expression



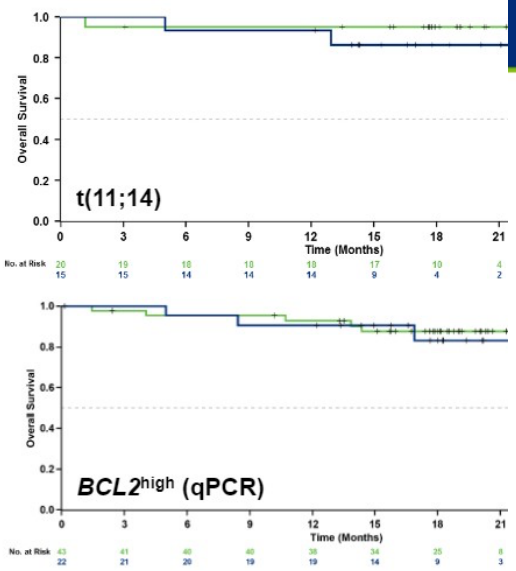


PFS: t(11;14)	Ven+Bd	Pbo+Bd
Median, months	Not reached	9.5
HR (95% CI)	0.110 (0.022, 0.560)	
P-value	0.002	

PFS: *BCL2*^{high} (Upper quartile)	Ven+Bd	Pbo+Bd
Median, months	22.4	10.2
HR (95% CI)	0.341 (0.146, 0.560)	
P-value	0.011	

26 Nov 2018

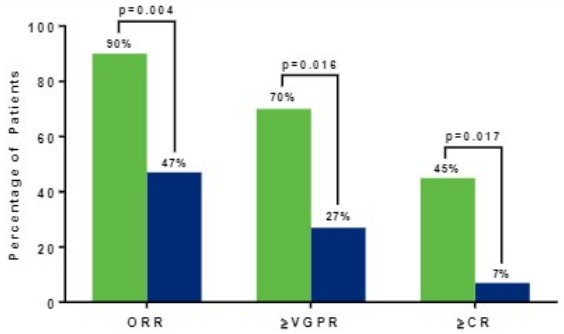
Overall Survival in Patients with t(11;14) or *BCL2*^{high} Expression

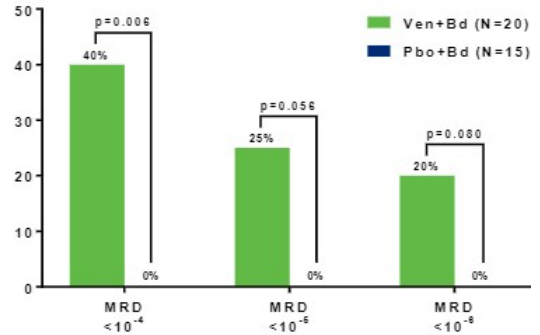


Clinical Response Rates in Patients with t(11;14) or *BCL2*^{high} Expression

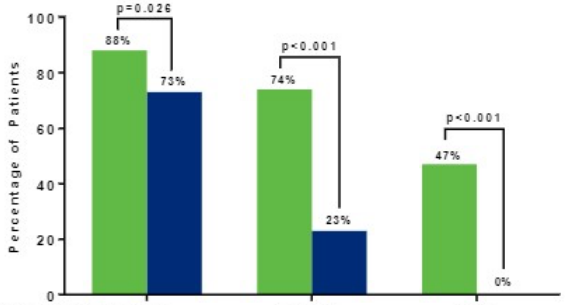
26 Nov 2018

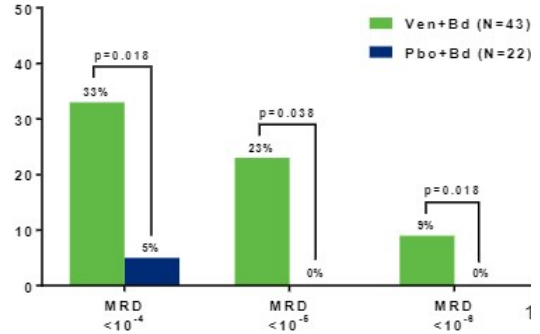
t(11;14)





***BCL2*^{high} (Upper quartile)**





MRD assessment was performed by next-generation sequencing on bone marrow aspirate at time of CR/sCR

Summary

- The addition of Ven to Bd significantly improved PFS, ORR, ≥VGPR, and MRD negativity rates in patients with RRMM
- An increase in deaths was observed with Ven+Bd
  - Treatment-emergent deaths mainly occurred early on during treatment, commonly due to infection and in the context of PD
- Patients with t(11;14) or *BCL2*^{high} had consistent clinical benefit when treated with Ven+Bd, and the benefit-risk profile appears to be favorable in these MM subsets
- Patients who achieved MRD negativity (10^{-5}) status had better outcome (PFS and OS)
- Future directions will be to focus on the t(11;14) and *BCL2*^{high} subgroups for development in MM studies with venetoclax, as well as additional risk mitigation measures

Mitochondrial Priming in MM

Nearly all MM is Mcl-1 primed.

Some are co-dependent on Bcl-2 or Bcl-x_L.

"Free" Mcl-1 is a sink for released Bim.

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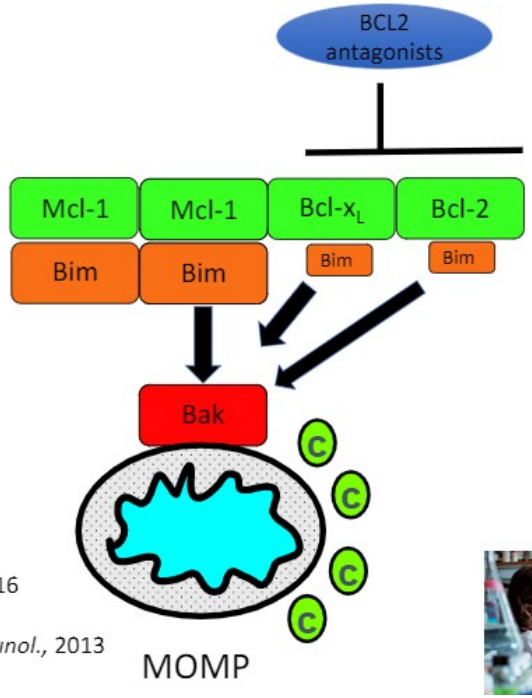
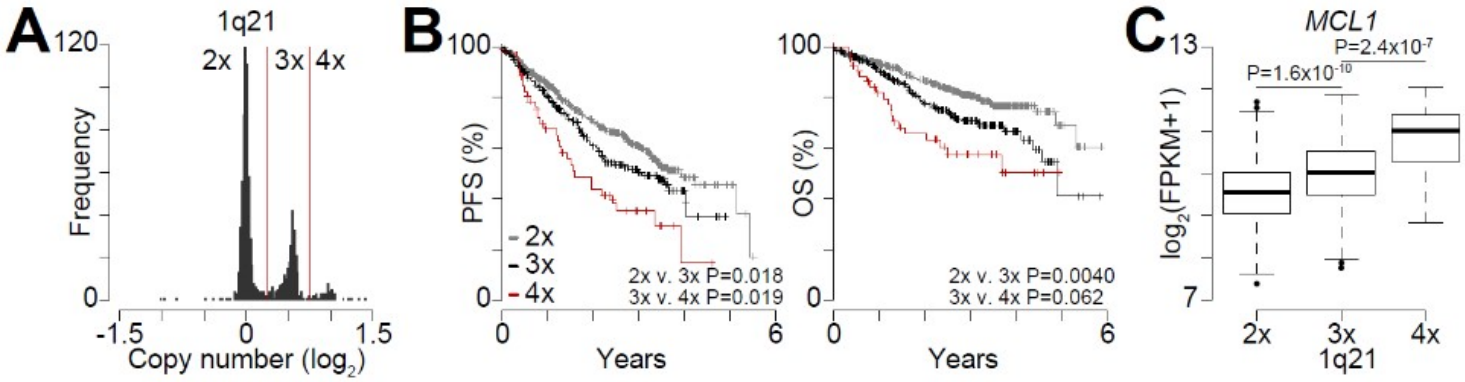
Zhang *et al.*, *Blood* 2002
Derene *et al.*, *Blood* 2002
Touzeau *et al.*, Leukemia, 2016
Gong *et al.*, *Blood*, 2016
Peperzak *et al.*, *Nature Immunol.*, 2013



Morales et al., Blood, 2008
Morales et al., Blood, 2011
Mannava et al., Blood, 2012
Matulis et al., Leukemia, 2016
Gupta et al., Blood, 2017

Alejo Morales
Shannon Matulis
Vikas Gupta
Metin Kurtoglu
Misha Nikiforov

MCL1 is important for survival and frequently amplified in multiple myeloma patients



CoMMpass (IA13)

Ben Barwick

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National Cancer Institute-Designated Comprehensive Cancer Center

Zhang *et al., Blood* 2002
Derene *et al., Blood* 2002
Morales et al., Blood, 2011
Gong *et al., Blood,* 2016
Kotschy A, *et al. Nature*, 2016
Lee T, *et al. FEBS Lett*, 2017
Caenepeel S, *et al. Cancer Discovery*, 2018
Hird, A. *et al. AACR, 2017*

Myeloid cell factor–1 is a critical survival factor for multiple myeloma

Bin Zhang, Ivana Gojo, and Robert G. Fenton

BLOOD, 15 MARCH 2002 • VOLUME 99, NUMBER 6

Antisense strategy shows that Mcl-1 rather than Bcl-2 or Bcl-x_L is an essential survival protein of human myeloma cells

Sophie Derenne, Brett Monia, Nicholas M. Dean, Jennifer K. Taylor, Marie-Josée Rapp, Jean-Luc Harousseau, Régis Bataille, and Martine Amiot

BLOOD, 1 JULY 2002 • VOLUME 100, NUMBER 1

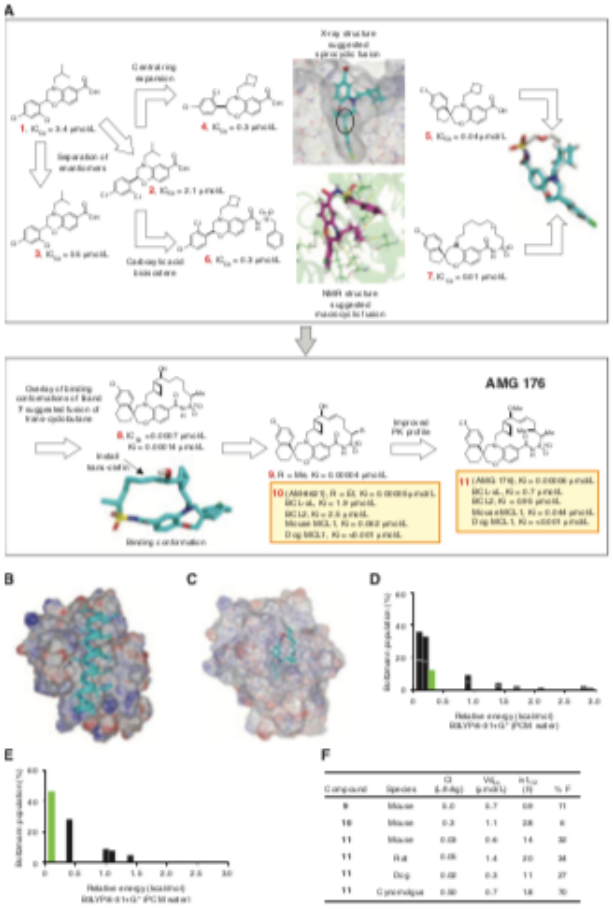
Leukemia (2005) 19, 1248–1252

www.nature.com/leu

Mcl-1 is overexpressed in multiple myeloma and associated with relapse and shorter survival

S Wuillème-Toumi[1], N Robillard[1], P Gomez[2], P Moreau[3], S Le Gouill[3], H Avet-Loiseau[1], J-L Harousseau[3], M Amiot[2] and R Bataille[2]

[1]Central Laboratory of Hematology, University Hospital of Nantes, France; [2]INSERM UMR 601, Nantes, France; and [3]Department of Clinical Hematology, University Hospital of Nantes, France



AMG 176, a Selective MCL1 Inhibitor, Is Effective in Hematologic Cancer Models Alone and in Combination with Established Therapies

Sean Caenepeel[1,2], Sean P. Brown[2,3], Brian Belmontes[1,2], Gordon Moody[1,2], Kathleen S. Keegan[4,5], Danny Chui[2,6], Douglas A. Whittington[7,8], Xin Huang[7,8], Leszek Poppe[2,9], Alan C. Cheng[10,11], Mario Cardozo[10,11], Jonathan Houze[8,12], Yunxiao Li[11,13], Brian Lucas[11,13], Nick A. Paras[11,13], Xianghong Wang[11,13], Joshua P. Taygerly[11,13], Marc Vimolratana[11,13], Manuel Zancanella[11,13], Liusheng Zhu[11,13], Elaina Cajulis[1,2], Tao Osgood[1,2], Jan Sun[1,2], Leah Damon[14], Regina K. Egan[14], Patricia Greninger[14], Joseph D. McClanaghan[14], Jianan Gong[15,16], Donia Moujalled[17], Giovanna Pomilio[17], Pedro Beltran[1,2], Cyril H. Benes[14], Andrew W. Roberts[15,16,18,19], David C. Huang[15,16], Andrew Wei[17], Jude Canon[1,2], Angela Coxon[1,2], and Paul E. Hughes[1,2]

Figure 1. Optimization of chemical matter to AMG 176. **A,** X-ray structure–based optimization of high-throughput screening hit to clinical candidate AMG 176. X-ray structure suggested spirocyclic fusion (circled). **B,** X-ray crystal structure of MCL1 bound to BIM (20). **C,** X-ray structure of MCL1 bound to AM-8621 reveals cryptic binding pocket (PDB code 6OQB). **D,** Quantum mechanical–derived conformational ensemble of 8 within 3 kcal/mol depicted as Boltzmann distribution. Binding conformation shown in green. Broken bars represent multiple conformations. PCM, polarizable continuum model. **E,** Quantum mechanical–derived conformational ensemble of 9 within 3 kcal/mol depicted as Boltzmann distribution. Binding conformation shown in green. Broken bars represent multiple conformations. **F,** Pharmacokinetic properties of 9, 10, and 11. Species refers to the species of animal in which the pharmacokinetic data were acquired.

OAB-080

A Phase 1, First-in-Human Study of AMG 176, a Selective MCL-1 Inhibitor, in Patients With Relapsed or Refractory Multiple Myeloma

Authors:
Andrew Spencer[1], Aaron Seth Rosenberg[2], Andrzej Jakubowiak[3], Noopur Raje[4], Manik Chatterjee[5], Suzanne Trudel[6], Nizar J. Bahlis[7], David S. Siegel[8], Stefan Wilop[9], Simon J. Harrison[10], Murthy NagaKrishna[11], Shyeilla Dhuria[12], Antreas Hindoyan[13], Zach McIver[13], Haby Henary[13], Phuong Khanh Morrow[13], Andrew Roberts[14]

Primary endpoints: safety, tolerability, and PK of AMG 176
Secondary endpoints: pharmacodynamic evaluation of MCL-1 inactivation and multiple myeloma response assessment.

Results: At the data cutoff date (March 15, 2019), **26** RRMM patients had received AMG 176 (median age **63.5** years). Patients had a median of 5 prior lines of therapy, and 20 patients (**77%**) received ≥ 5 prior therapy lines. Patients received a median (range) of **2** (1–8) cycles of study treatment. Most patients discontinued treatment due to progressive disease (n = 22 [85%])

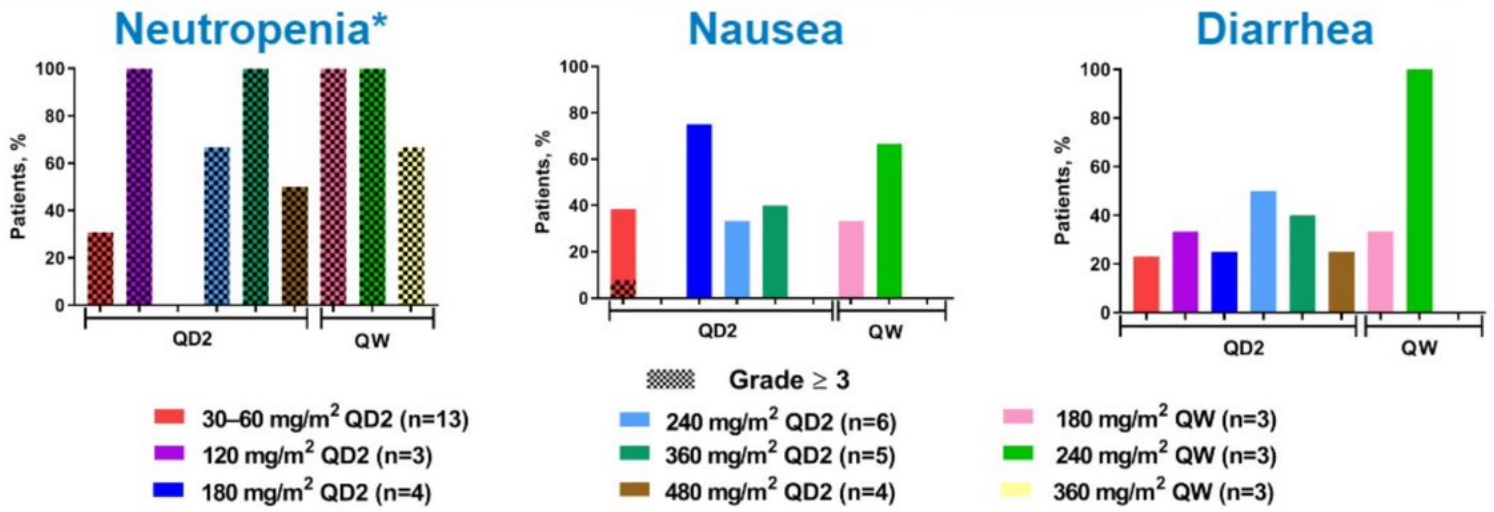
Best Tumor Response

- Best tumor response detected to date: partial response in 3 patients; stable disease in 8 patients

Cohort	n (%)	Treatment Duration, wk
Partial response		
50 mg/m^2 QD2	1 (25)	4.3
360 mg/m^2 QD2	1 (20)	7.7 (ongoing on-study)
240 mg/m^2 QW	1 (33)	18.3 (ongoing on-study)
Stable disease		
50 mg/m^2 QD2	1 (25)	14.1
60 mg/m^2 QD2	1 (33)	7.4
120 mg/m^2 QD2	2 (67)	10.1–10.4
360 mg/m^2 QD2	2 (40)	8.1–9.3
240 mg/m^2 QW	1 (33)	18.1 (ongoing on-study)
360 mg/m^2 QW	1 (33)	7.1

Responses were assessed according to International Myeloma Working Group criteria
Response data were captured in database through 8/9/2019

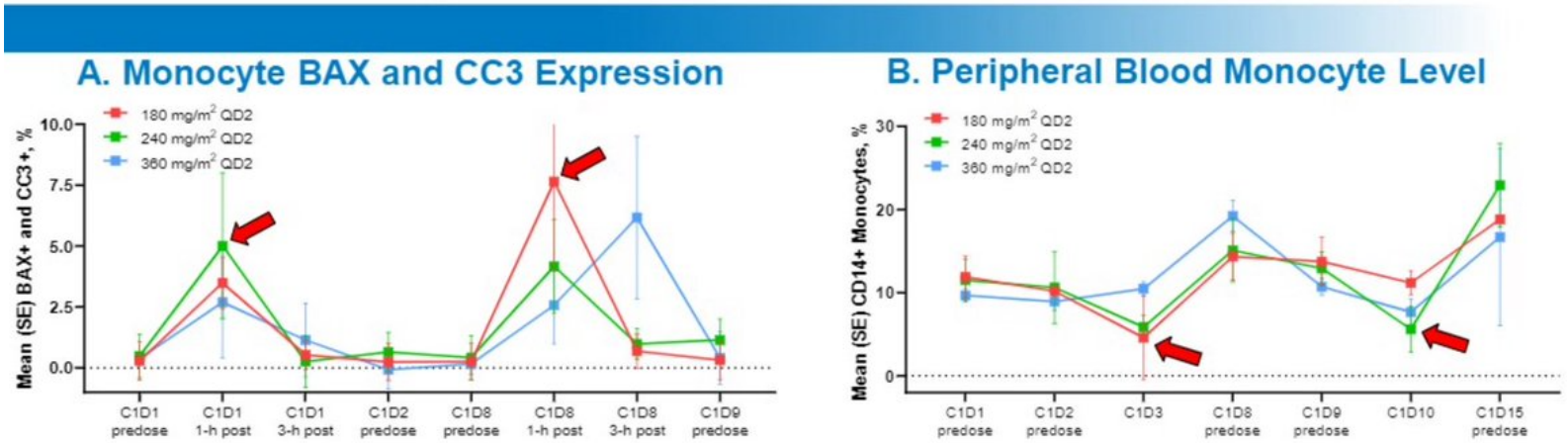
Summary of Adverse Events



- Two fatal AEs were observed (both in QD2 dose cohorts): tumor lysis syndrome (treatment related, 240 mg/m^2) and hepatic failure (due to disease progression)
- Two DLTs were observed (both in QD2 dose cohorts): tumor lysis syndrome (240 mg/m^2) and febrile neutropenia (360 mg/m^2); MTD has not yet been determined
- The majority of patients discontinued study drug because of disease progression (31/44 patients)

* Includes patients with neutropenia, decreased white blood cell count, decreased neutrophil count, or febrile neutropenia

Pharmacodynamics of AMG 176



- BAX activation and CC3 were detected in MCL1-dependent circulating monocytes 1 hour after the end of infusion at both step and target dose levels
- Reduction of peripheral blood monocyte levels was observed 1–2 days postdose, with recovery of counts before the next weekly administration

Results shown for patients who received QD2 dosing; lead-in dose of 120 mg/m² implemented in week 1 (Days 1 and 2), followed by target dose in subsequent weeks.
CC3 = cleaved caspase 3

Conclusions

- Initial results from this first-in-human study suggest that AMG 176 has acceptable tolerability in patients with RRMM at the doses evaluated, with early evidence of response in a highly refractory patient population
- Toxicities observed to date were predominantly hematologic or gastrointestinal; based on available data, safety profiles were comparable between once- and twice-weekly regimens
- Biomarker analyses provided evidence of pharmacodynamic activity for AMG 176
- MTD has not been determined, and investigation of the safety and efficacy of AMG 176 is ongoing

Conclusions

- ✓ New targets and agents are important options for refractory MM
- ✓ Understanding how to dose and how to schedule new agents is a critical question
- ✓ New targets may help to overcome resistence to previous agents
- ✓ Short and long term outcomes are linked to access

Grazie per l’attenzione