ASSOCIATION OF COMMUNITY CANCER CENTERS

Multiple Myeloma Lecture Series

Clinical Updates in Multiple Myeloma

Dr. David Vesole, MD PhD

Tuesday, August 7, 2018
1 – 2PM Eastern

ACCC
Association of Community Cancer Centers

ACCC Overview

Hira Chowdhary, MPH MS
Project Manager, Provider Education

The Association of Community Cancer Centers (ACCC)

The Association of Community Cancer Centers (ACCC) promotes the entire continuum of quality cancer care for our patients and our communities. Since 1974, ACCC has been helping oncology professionals adapt to the complex changes of delivering quality cancer care.

ACCC members rely on the Association to bring them information on cancer program management, reimbursement issues, legislative and regulatory changes at the state and national levels, community cancer program standards, NCI-funded community clinical research, hospital alliances and physician relationships, and more.

More than 23,000 cancer care professionals from over 2,400 hospitals and practices nationwide are affiliated with ACCC

Clinical Updates in Multiple Myeloma

David Vesole, MD PhD

David H. Vesole, MD, PhD

Co-Chief, Myeloma Division
Director, Myeloma Research
John Theurer Cancer Center
Hackensack UMC
Professor of Medicine
Director, Myeloma Program
Georgetown University

BEST OF ASCO 2018: PLASMA CELL DYSRASIAS

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Lombardi Comprehensive
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Multiple Choice Question:
Which of the following statements is true?

A. Pembrolizumab in combination with either lenalidomide or pomalidomide improves PFS in myeloma.

B. Preliminary results demonstrate that CAR T cells are safe, effective and potentially curative in RRMM.

C. Carfilzomib at 70 mg/m2 weekly is more efficacious and comparable toxicity to carfilzomib 27 mg/m2 given twice weekly.

D. Venetoclax plus carfilzomib only is effective in MM expressing t(11;14).

IMMUNOTHERAPY

FDA analysis of pembrolizumab trials in multiple myeloma: Immune related adverse events and response Abstract 8008

Aviva C. Krauss, MD
OHOP/DHP

PD-1 Inhibitors: Differential Efficacy in Various Heme Malignancies

VOLUME 34 · NUMBER 23 · AUGUST 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study

Alexander M. Lesokhin, Stephen M. Ansell, Philippe Armand, Emma C. Scott, Ahmad Halwani, Martin Gutierrez, Michael M. Millenson, Adam D. Cohen, Stephen J. Schuster, Daniel Lebovic, Madhav Dhodapkar, David Avigan, Bjoern Chapuy, Azra H. Ligon, Gordon J. Freeman, Scott J. Rodig, Deepika Cattry, Lili Zhu, Joseph F. Grosso, M. Brigid Bradley Garelik, Margaret A. Shipp, Ivan Borrello, and John Timmerman

Tumor	OR, No. (%)
B-cell lymphoma (n = 31)	8 (26)
DLBCL (n = 11)	4 (36)
FL (n = 10)	4 (40)
Other B-cell lymphoma (n = 10)	0
T-cell lymphoma (n = 23)	4 (17)
MF (n = 13)	2 (15)
PTCL (n = 5)	2 (40)
Other CTCL (n = 3)	0
Other non-CTCL (n = 2)	0
Multiple myeloma (n = 27)	1 (4)

- Promising in various lymphomas
- No single agent efficacy in relapsed or refractory multiple myeloma
  - Consistent findings in pembrolizumab Phase 1b study (*Ribrag et al, EHA, 6/2017*)

2 Randomized Controlled Trials of Pembrolizumab Added to SOC in Multiple Myeloma

Keynote 183

Relapsed/refractory MM

Stratified by:

-# prior lines of tx (2 vs ≥ 3)

-Dz status (refractory vs sensitive to len)

1:1

- Pembrolizumab 200 mg Q3W
  Pomalidomide 4 mg days 1-21, 28 –day cycle
  Dexamethasone 40 mg on days 1, 8, 15, 22
- Pomalidomide 4 mg days 1-21, 28 –day cycle
  Dexamethasone 40 mg on days 1, 8, 15, 22

Primary Endpoints: PFS, OS

Keynote 185

Newly diagnosed MM

Stratified by:

-Age (< vs ≥ 75y)

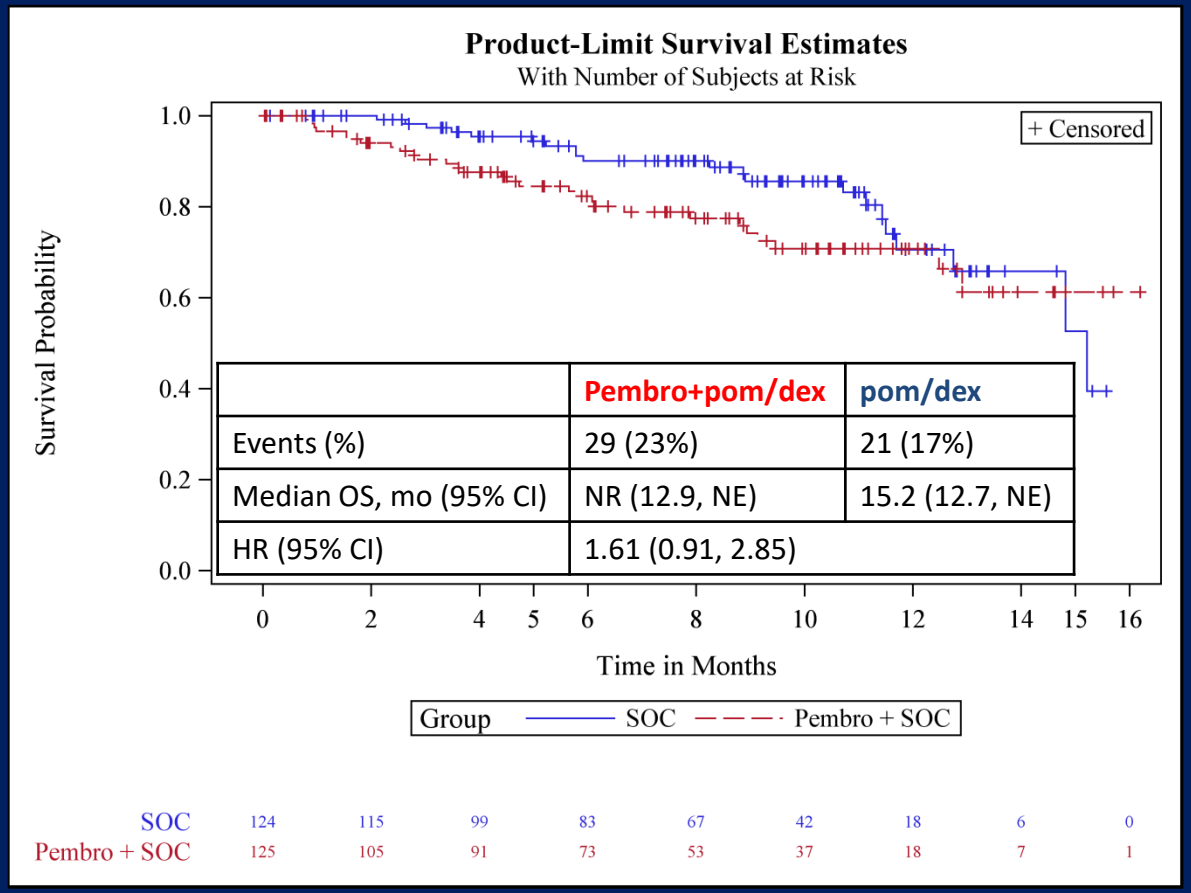
-ISS* (I vs II vs III)

1:1

- Pembrolizumab 200 mg Q3W
  Lenalidomide 25 mg days 1-21, 28 –day cycle
  Dexamethasone 40 mg on days 1, 8, 15, 22
- Lenalidomide 25 mg days 1-21, 28 –day cycle
  Dexamethasone 40 mg on days 1, 8, 15, 22

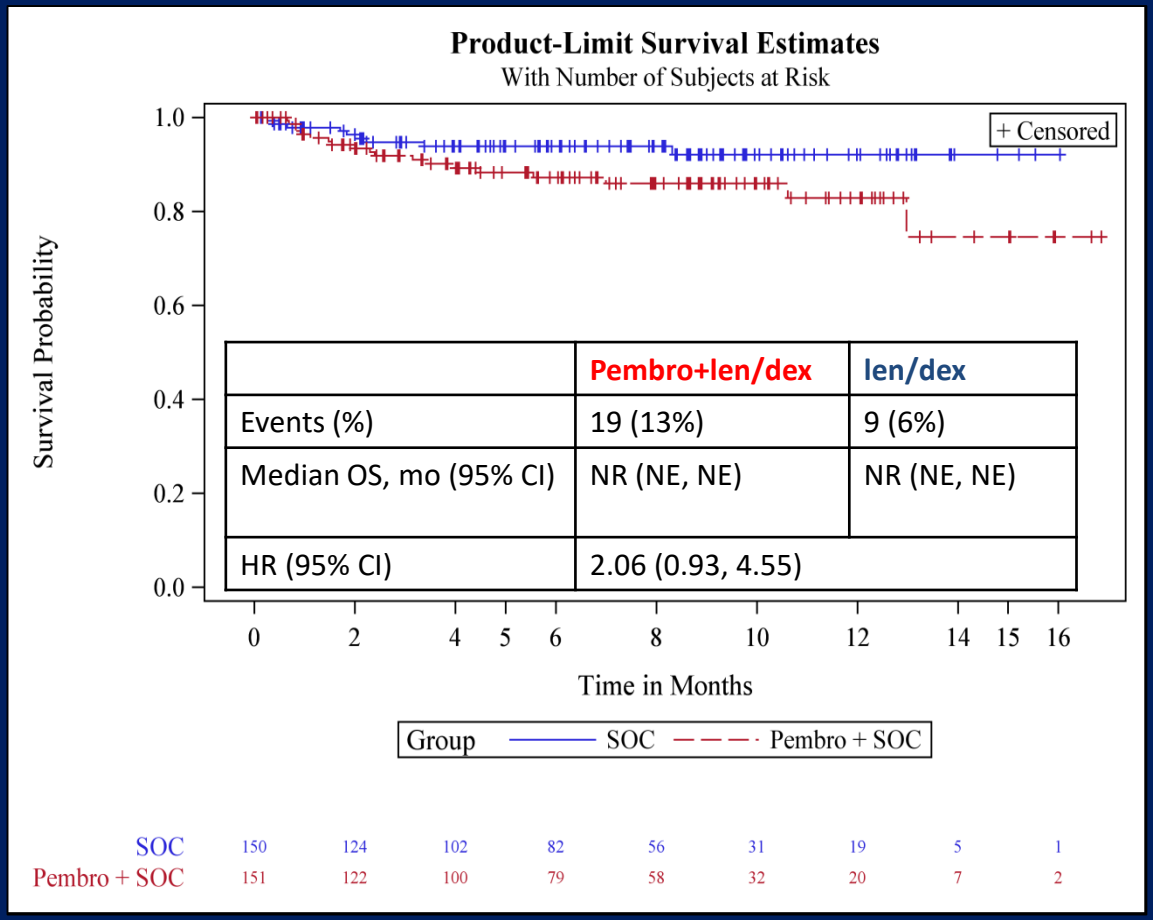
Primary Endpoint: PFS

KN183 Results



- N=125 (Pembro-pom-dex), N=124 (pom-dex)
- Median follow-up: 8.1 months
- Causes of death (Pembro-pom-dex): myocarditis, SJS, MI, pericardial hemorrhage, cardiac failure, respiratory tract infection, neutropenic sepsis, sepsis, MOD, respiratory failure, and unknown
- SAEs: 63% vs 46%
- Efficacy:
  - ORR: 34% Pembro-pom-dex arm vs. 40% Pom-dex arm
  - Time-to-progression HR: 1.14 (95% CI: 0.75, 1.74)

KN185 Results



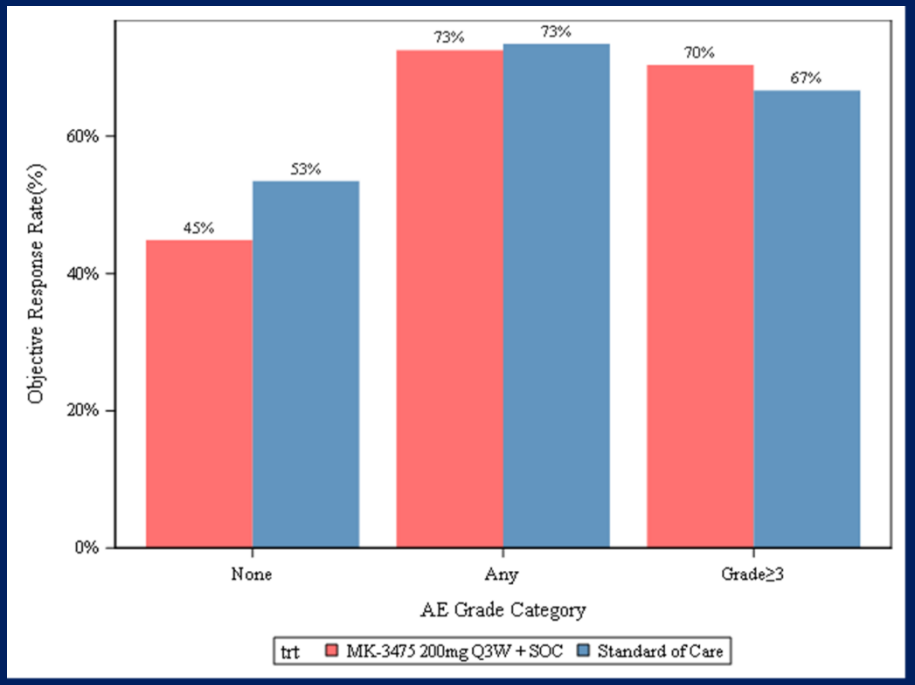
	Pembro+len/dex	len/dex
Events (%)	19 (13%)	9 (6%)
Median OS, mo (95% CI)	NR (NE, NE)	NR (NE, NE)
HR (95% CI)	2.06 (0.93, 4.55)	

- Median follow-up: 6.6 months
- Causes of death (pembro-len-dex): intestinal ischemia, cardiorespiratory arrest, suicide, PE, cardiac arrest, pneumonia, sudden death, myocarditis, large intestine perforation, and cardiac failure
- SAEs: 54% vs 39%
- Efficacy:
  - ORR: 64% Pembro-len-dex arm vs. 62% Len-dex arm
  - Time-to-progression HR: 0.55 (95% CI: 0.20, 1.50)

Immune Related AEs and Response

- Unique AEs not c/w IMID class effect
- Lenalidomide with or without Pembolizumab showed increased response rates in those with irAEs

	KN183 (Rel/Refr)		KN185 (Newly diagnosed)	
	Pembro+	**Pom/Dex**	**Pembro+**	**Len/Dex**
Any irAE	58%	45%	68%	44%
G≥3 irAE	**18%**	**13%**	**36%**	**8%**
SAE	63%	46%	54%	39%
ORR	34%	40%	64%	62%



Summary

- Decreased OS on 2 randomized trials using anti-PD-1 + SOC vs SOC in 2 populations
  - Relapsed/refractory multiple myeloma
    - ORR: no difference with or without irAE
  - Newly diagnosed multiple myeloma
    - Increased ORR in patients with irAE
    - Increased irAE rate

ABSTRACT 8007

bb2121 Anti-BCMA CAR T Cell Therapy in Patients With Relapsed/Refractory Multiple Myeloma: Updated Results From a Multicenter Phase I Study

Abstract 8007

Noopur Raje, MD,[1] Jesus Berdeja, MD,[2] Yi Lin, MD, PhD,[3] Nikhil Munshi, MD,[4] David Siegel, MD, PhD,[5] Michaela Liedtke, MD,[6] Sundar Jagannath, MD,[7] Deepu Madduri, MD,[7] Jacalyn Rosenblatt, MD,[8] Marcela Maus, MD, PhD,[1] Ashley Turka,[9] Lyh Ping Lam, PharmD,[9] Richard A. Morgan, PhD,[9] M. Travis Quigley,[9] Monica Massaro, MPH,[9] Kristen Hege, MD,[10] Fabio Petrocca, MD,[9] and James N. Kochenderfer, MD[11]

bb2121 CAR-T Update

- BCMA is the latest promising target in MM
- At least 3 broad highly promising approaches directed at BCMA:
  - CAR-T cells vs. BCMA
  - BiTE (CD3 – BCMA bispecific engager)
  - Antibody Drug Conjugate vs. BCMA

  - bb2121 data presented by Raje et al. largest and most mature with CAR-T approach in MM
  - At least 18 (+) trials of BCMA directed CAR-T cells going on world wide

bb2121 data

- bb2121 CAR-T - active and induces deep responses rapidly
- More CR/VGPR than PR; **Early MRD negativity (m PFS 17.7 mo)**
- **Soluble BCMA – not an issue (as was feared)**
- Safety comparable / better than most other CAR-T in MM and Lymphoma
- **Response correlates with CAR-T cell expansion**
- Cell dose matters (>150 e6 needed for bb2121)
- **BCMA expression did not matter for response – early data**
- **Patients still relapsed (median DOR for responders ~ 12 mo)**
- **MRD Negativity – what does it mean in this setting?**
- **NOT yet a CURE !**

COMPARISON OF BCMA TARGETED CAR-T CELLS

	Anti-BCMA CAR (16 pts at highest dose)	Bb2121 (22 pts at full dose)	LCAR-B38M (35 pts)	CART-BCMA (24 pts)
Group/Company	NCI	Bluebird/NCI	Nanjing Legend Biotech	Novartis/Upenn (No BCMA expression cut off)
Binder/co-stimulatory signaling	Murine/CD3 & CD28	Murine/CD3 & 4-1-BB	Murine/CD3 & 4-1-BB	Fully human/CD3 & 4-1BB
Transfection	Gamma-retroviral	Lentiviral	Lentiviral	Lentiviral
Lymphodepletion	Flu/CY d-5 to -3	Flu/CY d-5 to -3	CY	None / with CY
Median prior lines of therapy	9.5 (63% Refr)	8 (32% penta refr)	3	9
Reported Efficacy	ORR- 81% VGPR -63% EFS – median 31 wks	ORR – 95.5% mDOR – 10.8 mo 100% MRD neg	15 CRs/13 PRs in 35 19 with longer f/u 100% ORR; 74% CR No CR pt relapsed at 6 mo	2 CRs, 3 VGPRs, 6 PRs in 24 patients Only 4 responders progressed at 40 weeks
Safety Data	Substantial but reversible	Manageable CRS	Transient CRS	1 death – progressive disease/candidaemia

1. Brudno et al, JCO May 2018 2. Raje et al, ASCO 2018 3. Wanghong Zao et al, ASCO 2017 4. Cohen A, et al. ASH

The future for CAR-T … many more questions

- Efficacy in earlier phase of disease :
  - earlier in relapse / Post induction (in HR-MM)
- Dual targeting (CD 19 - BCMA)
- Other targets – CD 38; Kappa LC; CD138; Lewis Y Antigen, CS-1, NY1-ESO
- Mechanisms of loss of response
  - Loss BCMA expression / Shedding
- Universal CAR-T (third party; off the shelf)
- Elimination of viral transduction

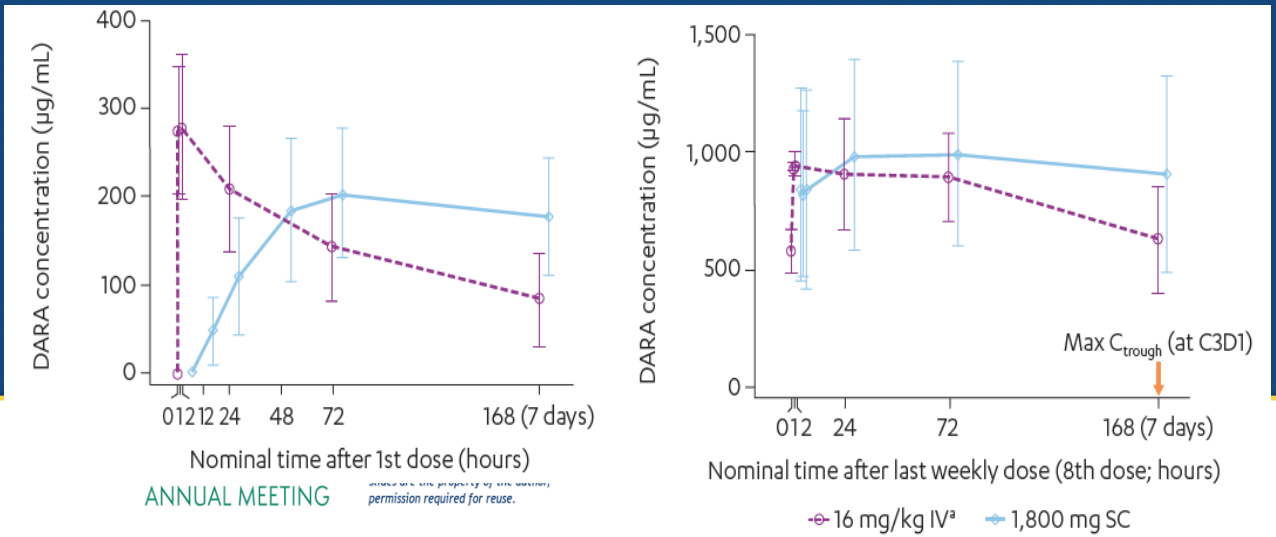
Subcutaneous daratumumab in patients with relapsed or refractory multiple myeloma (RRMM): Part 2 update of the open label, multicenter, dose escalation Phase Ib study (PAVO) (abstract 8013)

Ajai Chari, Saad Z. Usmani, Maria-Victoria Mateos, Niels WCJ van de Donk, Jonathan L. Kaufman, Philippe Moreau, Albert Oriol, Torben Plesner, Lotfi Benboubker, Kevin Liu, Peter Hellemans, Tara Masterson, Pamela L. Clemens, Andrew Farnsworth, Hareth Nahi, Jesus San-Miguel

- Daratumumab (Dara) is a monoclonal antibody targeting CD38
  - Single agent activity in advanced MM (ORR ~ 30%)
  - Compelling activity in combination with PI or IMIDs: Dara Rd > Rd, Dara Vd > Vd, Dara VMP > VMP
- IV Dara is safe but
  - IRR occur in about 40-50% of patients / mostly first infusions
  - First infusion duration of about 8 hours
- Dara SC : pre-mixed co-formulation of daratumumab and recombinant human hyaluronidase with a higher daratumumab concentration, lower injection volume, and shorter injection time with manual SC injection in the abdomen

Dara IV or SC?

	Dara IV [1]	Dara SC [2] N=25
Median number of prior therapies Refractoriness	5 (2-14) 86% double refractory	3 (2-9) 56% double refractory
ORR	31%	52%
Administration time	First infusion ~ 7h Second infusion ~ 4.3h Third infusion ~ 3.5h	3-5 min
IRR	40-50%	16%



1- Usmani SZ, et al. *Blood*. 2016;128(1):37-44
2- Chari A et al, ASCO 2018 abstract 8013

Daratumumab in Combination with Carfilzomib and Dexamethasone in Lenalidomide-refractory Patients with Relapsed Multiple Myeloma: Subgroup Analysis of MMY1001
Abstract 8002

Ajai Chari,[1] Joaquín Martinez-Lopez,[2] Maria-Victoria Mateos,[3] Joan Bladé,[4] Sagar Lonial,[5] Lotfi Benboubker,[6] Albert Oriol,[7] Bertrand Arnulf,[8] Jesus San-Miguel,[9] Luis Pineiro,[10] Andrzej Jakubowiak,[11] Carla de Boer,[12] Jianping Wang,[13] Jordan Schecter,[13] Philippe Moreau[14]

[1]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [2]Hospital 12 de Octubre/CNIO/Complutense University, Madrid, Spain; [3]University Hospital of Salamanca/IBSAL, Salamanca, Spain; [4]Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain; [5]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [6]Hôpital Bretonneau, Centre Hospitalier Régional Universitaire (CHRU), Tours, France; [7]Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Barcelona, Spain; [8]Hôpital Saint Louis, Paris, France; [9]Clínica Universidad de Navarra-CIMA, IDISNA, CIBERONC, Pamplona, Spain; [10]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [11]University of Chicago Medical Center, Chicago, IL, USA; [12]Janssen Biologics, Leiden, The Netherlands; [13]Janssen Research & Development, LLC, Raritan, NJ, USA; [14]University Hospital Hôtel-Dieu, Nantes, France

*ClinicalTrials.gov Identifier: NCT01998971.

Study Design: D-Kd Arm of MMY1001

- Open-label, nonrandomized, multicenter, phase 1b study in RRMM patients
- Per protocol, DARA was administered as a **single first dose (n = 10)** or as a **split first dose (n = 75)**

Eligibility/treatment

- Relapsed MM
  - 1-3 prior lines of therapy, including bortezomib and an IMiD
  - Len-refractory pts allowed
- Carfilzomib-naïve
- ECOG status ≤2
- LVEF ≥40%
- ANC ≥1 × 10^9/L
- Platelet count ≥75 × 10^9/L

Dosing schedule (28-day cycles)

DARA:

- **Split first dose[a]: 8 mg/kg Days 1-2 of Cycle 1**
- Single first dose: 16 mg/kg on C1D1
- 16 mg/kg IV QW on Cycles 1-2, Q2W on Cycles 3-6, and Q4W thereafter until PD

Carfilzomib[b]:

- 20 mg/m^2 IV Cycle 1 Day 1
- Escalated to 70 mg/m^2 Cycle 1 Day 8+; **weekly (Days 1, 8, 15)** until PD

Dexamethasone: 40 mg/week (Days 1, 8, 15, 22) IV or PO until PD

Endpoints

Primary

- Safety, tolerability

Secondary

- ORR and duration of response
- OS

Exploratory

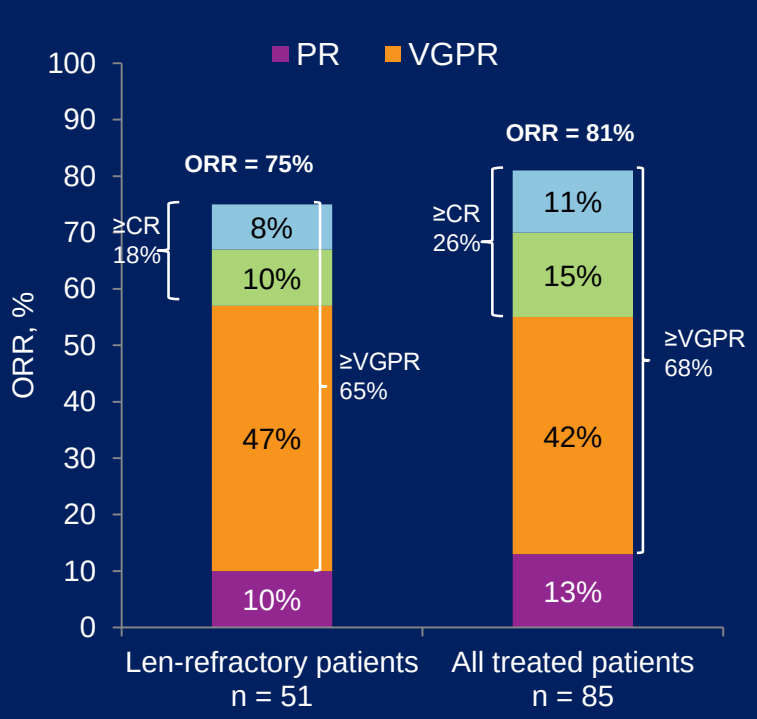
- PFS
- MRD (NGS)[c]
- PK

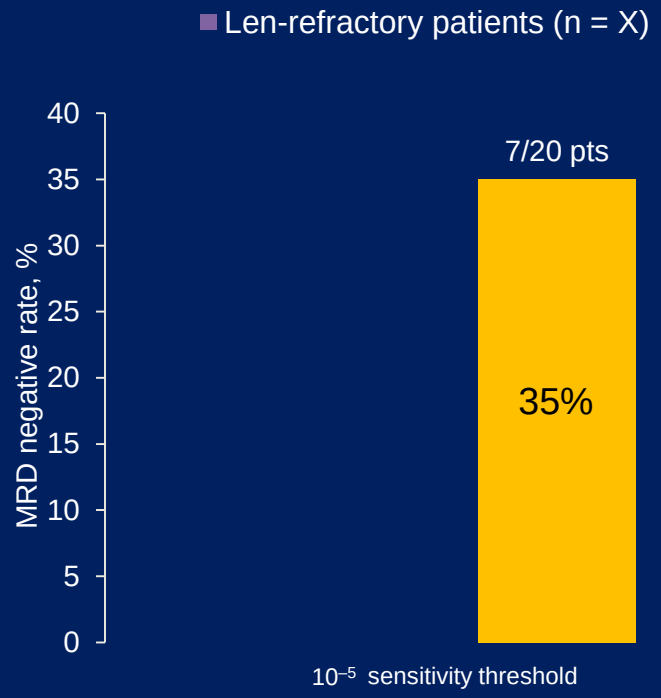
ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; ANC, absolute neutrophil count; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; IV, intravenous; PO, oral; OS, overall survival; MRD, minimal residual disease; NGS, next generation sequencing; PK, pharmacokinetic; IFE, immunofixation; IRR, infusion-related reaction.

[a]In 500-mL dilution volume.
[b]Both 20 mg/m^2 and 70 mg/m^2 were administered as 30-min IV infusions.
[c]Among patients evaluated for MRD, MRD was assessed using NGS at time of suspected CR and at 12 and 18 mo after initial dose. In cases where daratumumab is suspected of interfering with IFE and preventing clinical CR response calls, subjects with VGPR may also be evaluated for MRD.

Overall Response and Confirmed MRD-negative Rates[a]

- Median follow up: 12.0 months
- Among all-treated patients evaluated for MRD (n = 20), 7 patients achieved MRD negativity at 10^{-5}
  - Post-screening MRD testing was not conducted for the remaining patients (n = 65)





Responses are anticipated to deepen over longer follow up

PR, partial response; CR, complete response; sCR, stringent complete response.

Carfilzomib + mAbs

KD with Isa or Dara?

	Dara KD [1] N=85	Isa KD [2] N=33
KD dose and schedule	20 / 70 mg/m2 D1,8,15	20/27 mg/m2 D1,2,8,9,15,16
Median prior therapy (range)	2 (1-3)	3 (2-8)
Prior Carfilzomib	No	Yes, 30% refractory to CFZ
ORR	86%	61%
Thrombocytopenia Gr3+ Neutropenia Gr 3+ Hypertension Gr 3+ IRR	27% 18% 12% 42%	3% 3% 9% 48%

Isa 10 mg/kg QW x4 then Q2W dose was selected as the optimal dose for the expansion cohort based on ORR, safety and PK modeling.
Dara 16 mg/kg QWx 8 then Q2w x 8 then Q4W

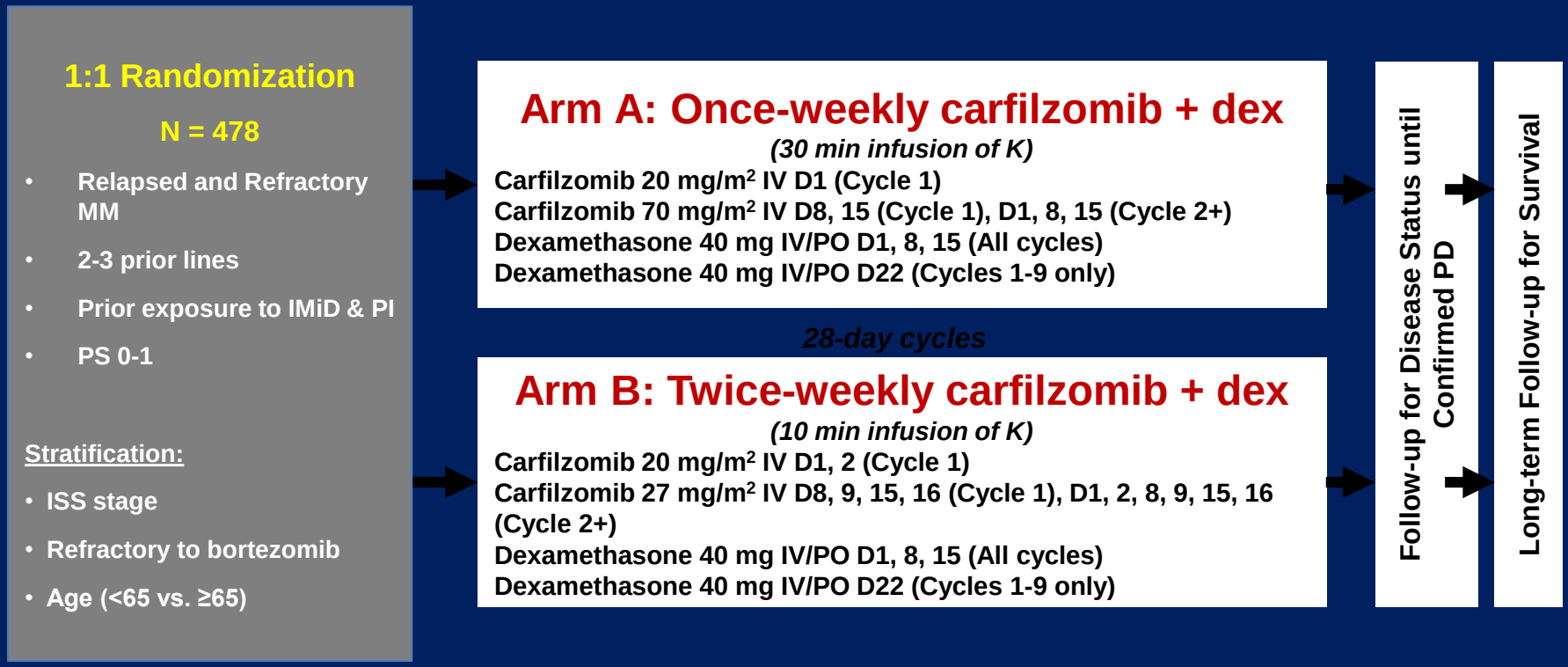
1- Lonial S et al, ASH 2017 130:1869, Chari ASCO 2018; 8002
2- Chari, A et al. ASCO 2018 abstract 8014

CARFILZOMIB-BASED THERAPIES

- A.R.R.O.W.-once weekly-abstract 8000
- Carfilzomib + venetoclax-abstract 8004
- Car/len/dex once weekly-abstracts 8017/8022

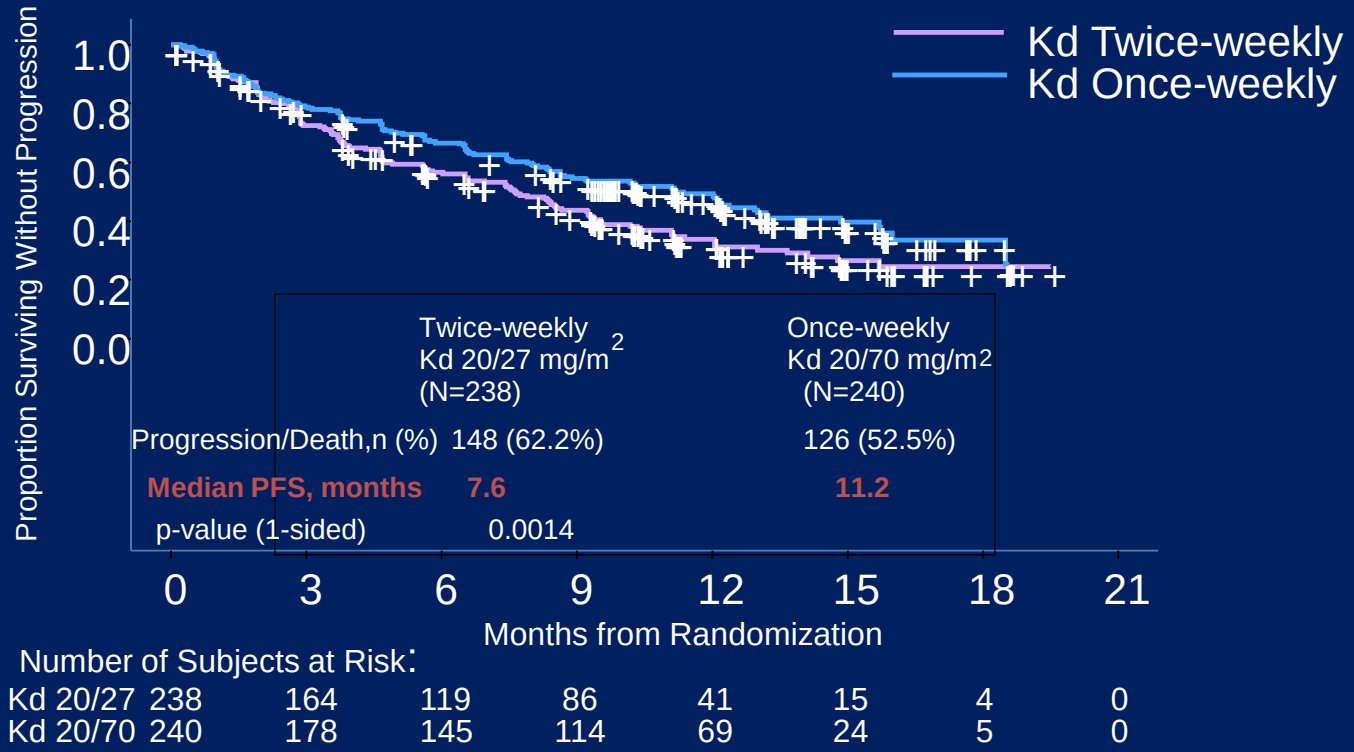
- Is there a more convenient way of giving Carfilzomib?
- Does Carfilzomib have a dose response?
- Is toxicity comparable to conventional dosing
- What about combinations?: Abstract 8017/8022

A.R.R.O.W. Study Design



Mateos et al abstract 8000

Primary Endpoint: Progression-Free Survival Assessed by Computational Algorithm Based on IMWG-URC



Adverse Events of Interest

AE, % (SMQN)	Once-weekly Kd (n=238)		Twice-weekly Kd (n=235)	
	All grades	Grade ≥3	All grades	Grade ≥3
Peripheral neuropathy	4	0	7	<1
Acute renal failure	7	4	7	6
Cardiac failure	4	3	5	4
Ischemic heart disease	2	1	1	1
Pulmonary hypertension	2	0	1	<1

- Safety findings were consistent with the known safety profile of carfilzomib, and no new risks were identified.

AE, adverse event; SMQN, standardized MedDRA Query, narrow scope

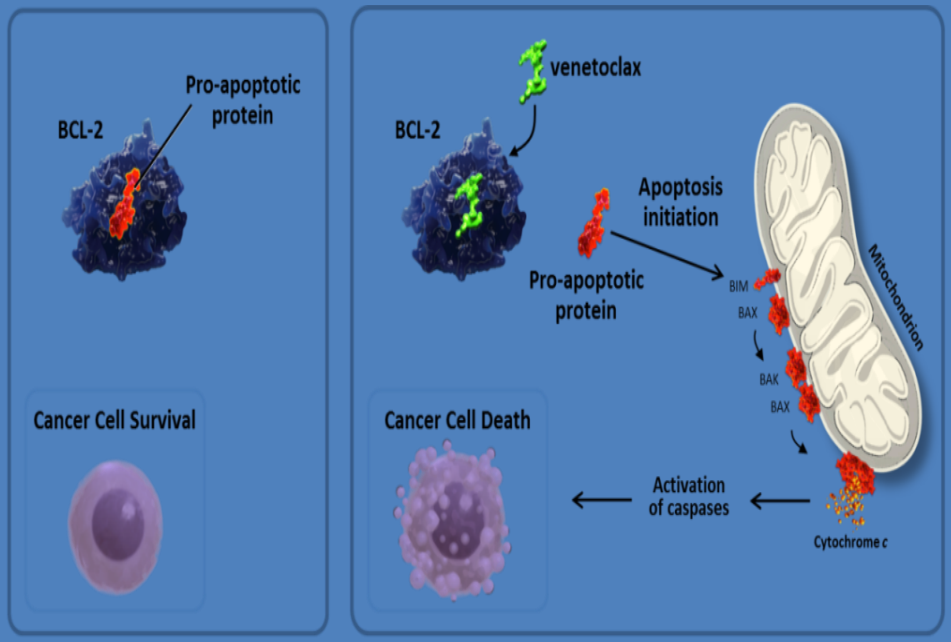
Phase 2 Study of Venetoclax Plus Carfilzomib and Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma
Abstract 8004

Luciano J. Costa,[1] Edward Stadtmauer,[2] Gareth Morgan,[3] Gregory Monohan,[4] Tibor Kovacsovics,[5] Nicholas Burwick,[6] Andrzej Jakubowiak,[7] Mehrdad Mobasher,[8] Kevin Freise,[9] Jeremy A. Ross,[9] John Pesko,[9] Wijith Munasinghe,[9] Jaclyn Cordero,[9] Lura Morris,[9] Paulo Maciag,[9] Orlando F. Bueno,[9] Shaji Kumar[10]

[1]University of Alabama at Birmingham, Birmingham, AL; [2]University of Pennsylvania, Philadelphia, PA; [3]University of Arkansas for Medical Sciences, Little Rock, AR; [4]University of Kentucky, Lexington, KY; [5]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [6]VA Puget Sound Health Care System, University of Washington, Seattle, WA; [7]The University of Chicago Medicine, Chicago, IL; [8]Genentech Inc., South San Francisco, CA; [9]AbbVie Inc., North Chicago, IL, [10]Mayo Clinic, Rochester, MN

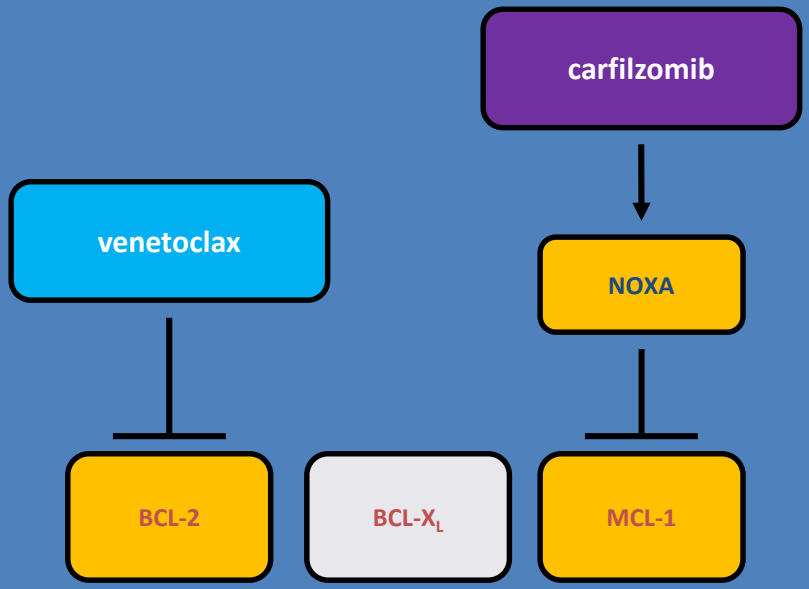
Background

- Anti-apoptotic proteins BCL-2 and MCL-1 promote multiple myeloma (MM) cell survival
- Venetoclax is a selective, orally available small molecule BCL-2 inhibitor[1-6]
- Carfilzomib (K) is a proteasome inhibitor and can indirectly inhibit MCL-1[7-9]



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

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

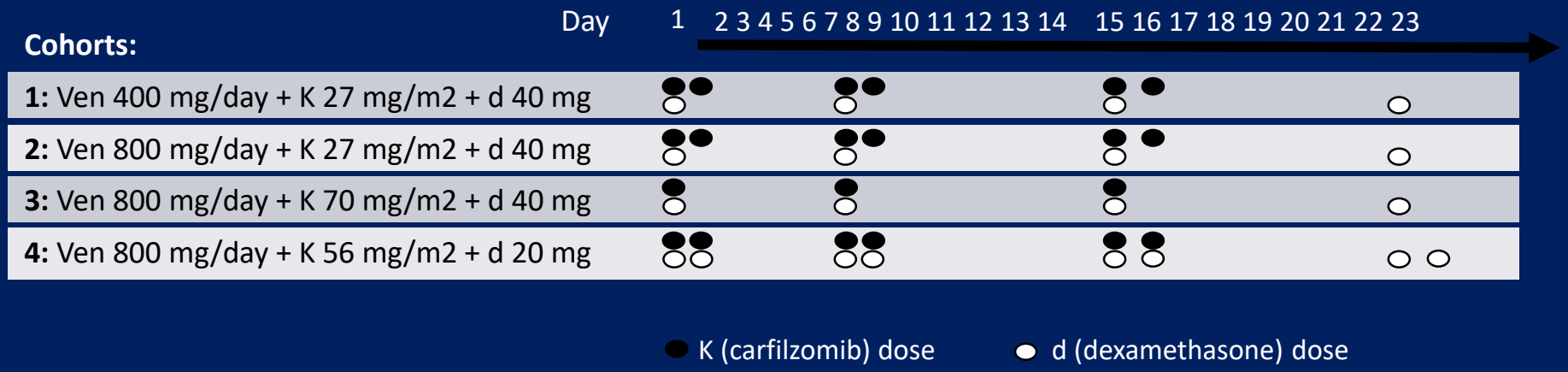


1. Leverson JD, et al. Sci Transl Med 2015; 7:279ra40. **2.** Czabotar, et al. Nature Reviews 2014; 15:49-63. **3.** Plati J, et al. Integr Biol (Camb). 2011;3:279-296. **4.** Certo M, et al. Cancer Cell. 2006;9:351-365. **5.** Souers AJ, et al. Nat Med 2013; 19(2): 202-8. **6.** Del Gaizo Moore V, et al. J Clin Invest 2007; 117(1): 112-21.

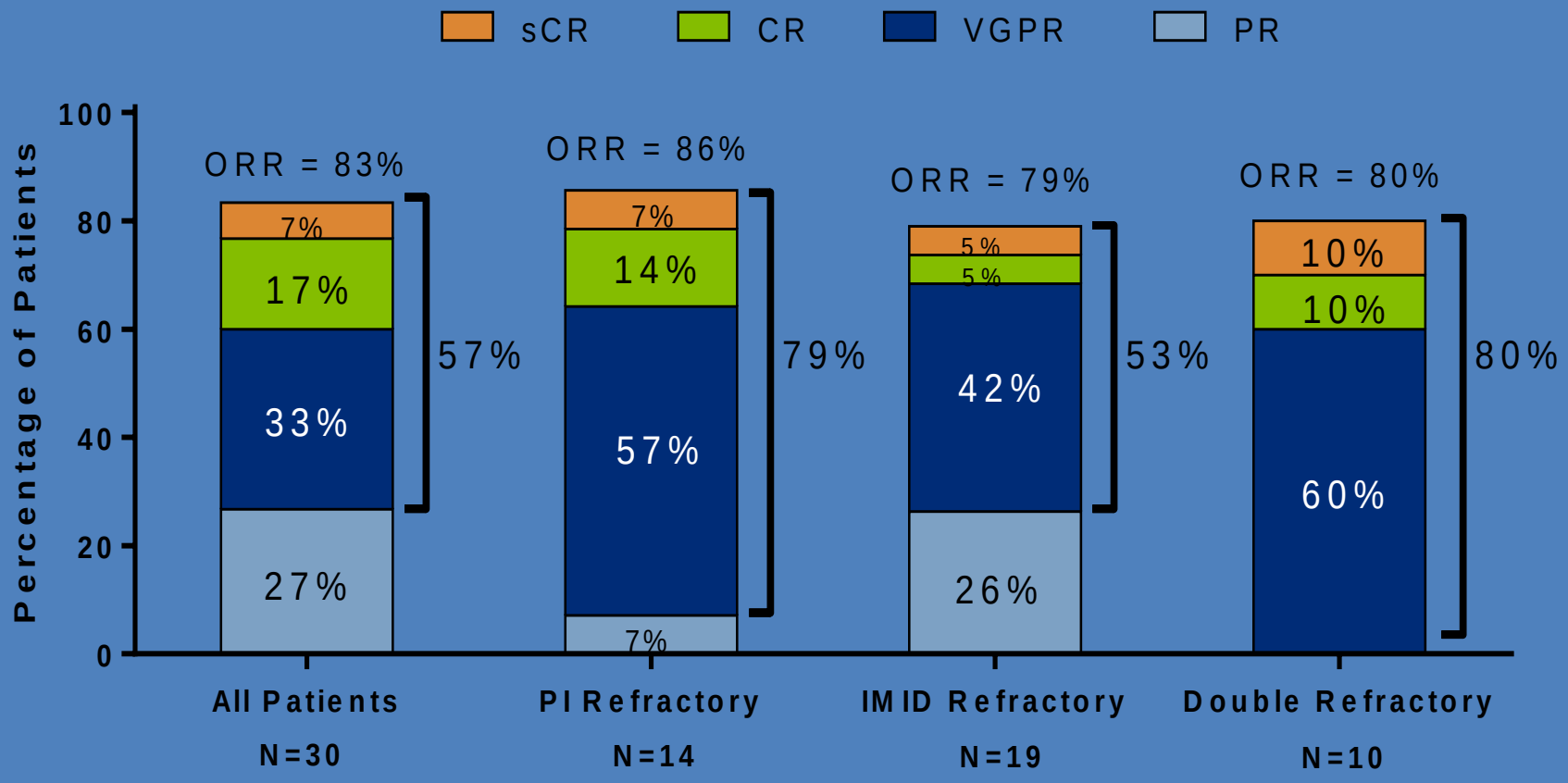
7. Roberts AW et al. N Eng J Med 2015; 374:311-22. **8.** Fan F et al. Cancer Lett 2014;343(2):286-94. **9.** Ponder K., et al. Cancer Bio & Ther 2016; 17(7):769-777

Dosing

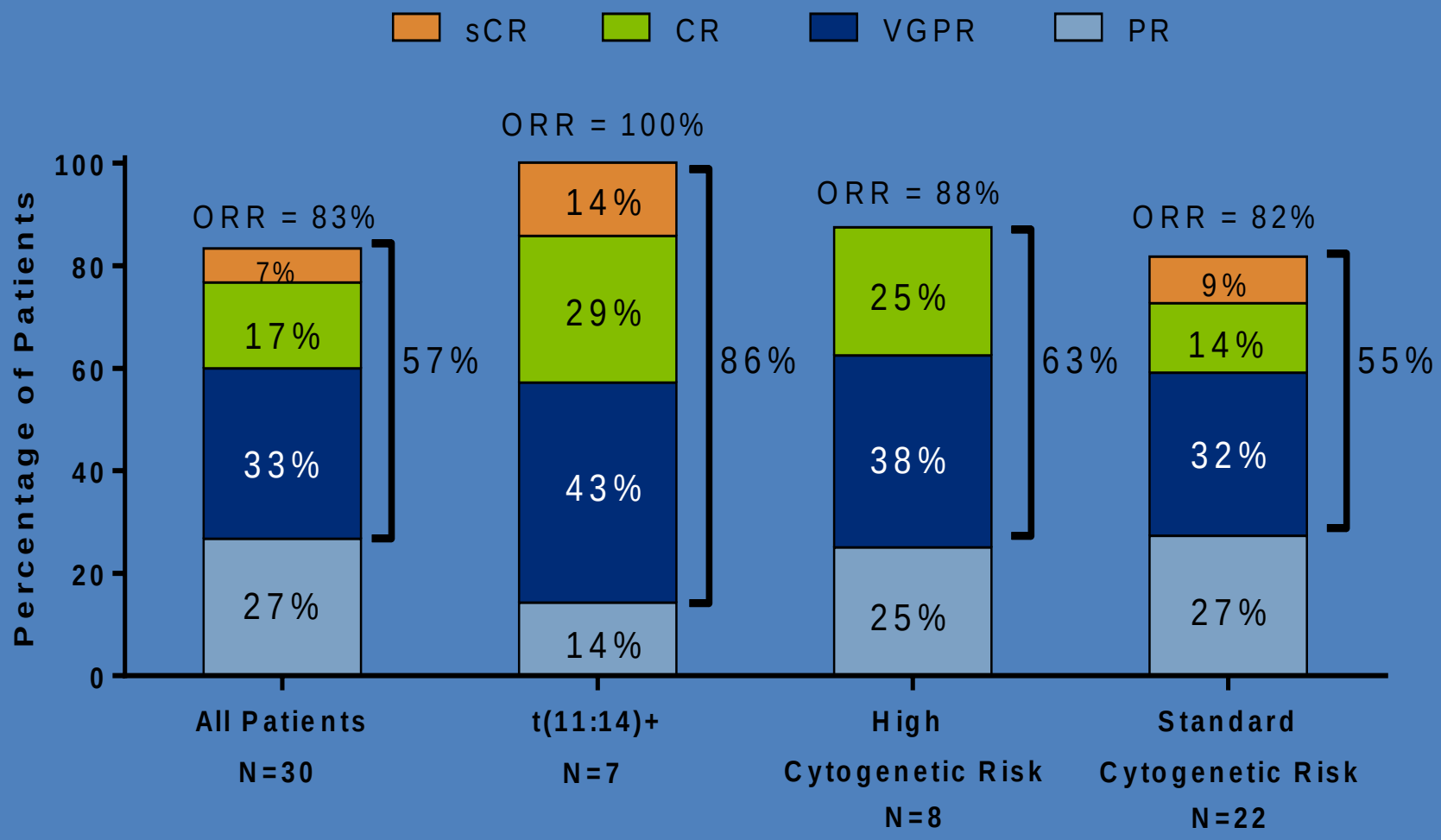
Patients received treatment in 28-day cycles



Objective Responses in All Patients and Those Refractory to PIs and IMiDs



Objective Responses in Patients Based on Cytogenetic Risk Status



Summary of Safety

Adverse event, n (%)	Any Grade	Grade 3/4
Total	**33 (79)**	**12 (29)**
Diarrhea	24 (57)	0
Fatigue	16 (38)	3 (7)
Platelet count decreased	13 (31)	3 (7)
Nausea	12 (29)	1 (2)
Lymphocyte count decreased	9 (21)	6 (14)

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

Serious adverse event, n (%)	Total
Any serious event	**5 (12)**
Acute kidney injury	2 (5)
Influenza	2 (5)
Pneumonia	2 (5)

Serious adverse events in ≥2 patients

- 1 case of laboratory TLS:
  - patient was t(11:14)+
  - hospitalized and received hydration and allopurinol
  - TLS labs resolved and treatment resumed

Carfilzomib/lenalidomide/dex in RRMM

Richez et al Abstract 8017

- N = 28
- ORR 93%, with 89% ≥VGPR and 61% ≥CR. The Median TTP and OS at 12 m were 89% and 95%, respectively.
- 29% of pts dc'd, 50% due to adverse events (AEs)

Biran et al Abstract 8022

- N = 22
- ORR 90% (56 mg/m^2) and 89% (70 mg/m^2); 20.0% (56 mg/m^2) and 30.4% (70 mg/m^2) a CR or sCR
- Incidence grade ≥3 Aes was 70.0% (56 mg/m^2) and 71.7% (70 mg/m^2). Discontinuation due to Aes was 20.0% (56 mg/m^2) and 17.4% (70 mg/m^2).

IMiDs

Pomalidomide, Bortezomib, and Low-Dose Dexamethasone (PVd) vs Bortezomib and Low-Dose Dexamethasone (Vd) in Lenalidomide-Exposed Patients With Relapsed or Refractory Multiple Myeloma: Phase 3 OPTIMISMM Trial

Abstract 8001

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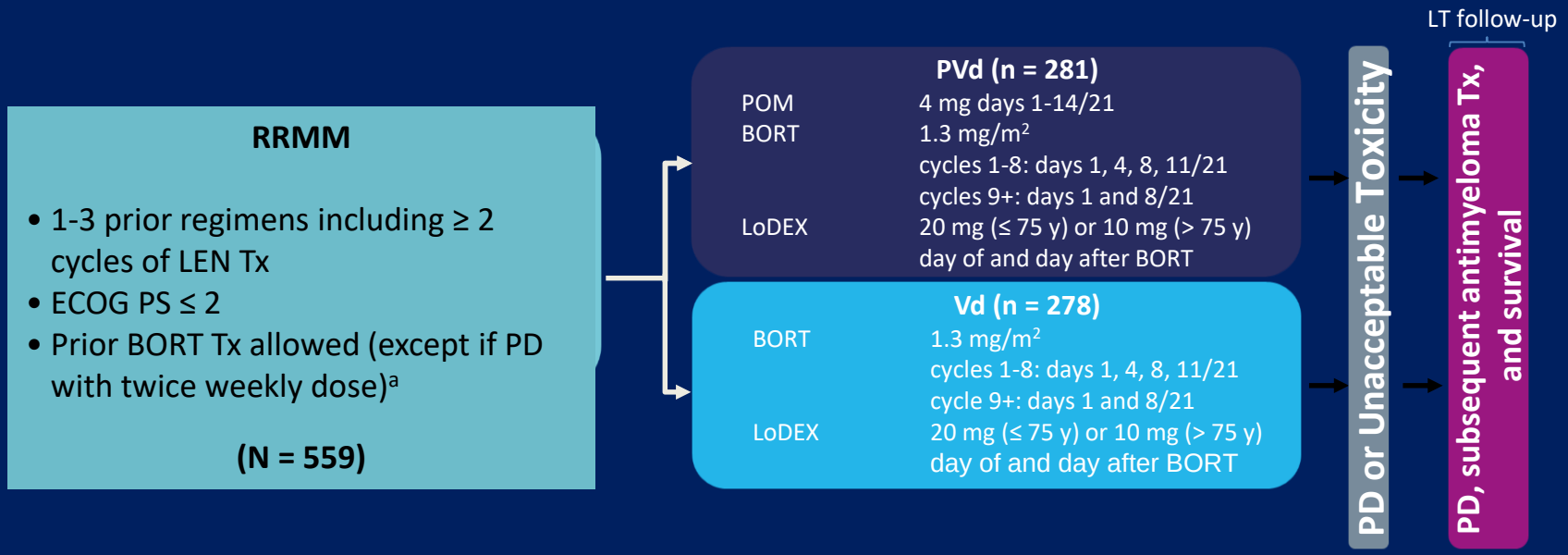
OPTIMISMM Study Design and Methods



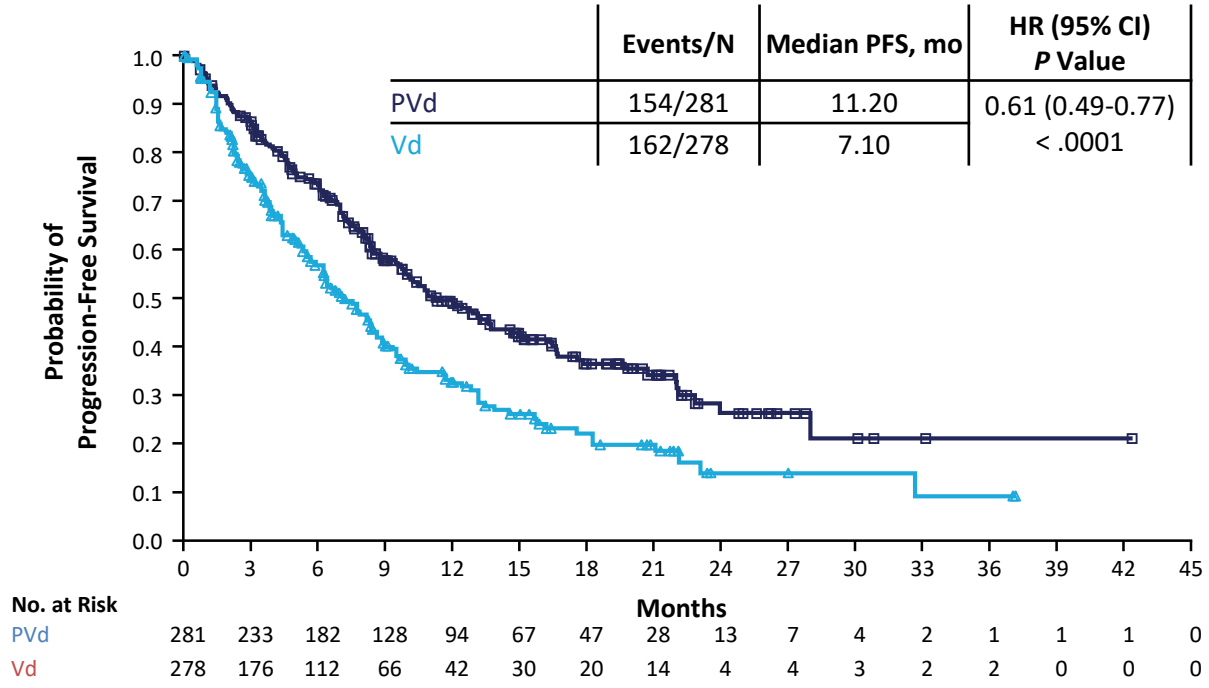
- **Stratification**
  - age (≤ 75 y vs > 75 y)
  - number of prior antimyeloma regimens (1 vs > 1)
  - β2-microglobulin levels at screening (< 3.5 mg/L vs ≥ 3.5 to ≤ 5.5 mg/L vs > 5.5 mg/L)
- **Study endpoints**
  - Primary: PFS
  - Secondary: OS, ORR by IMWG criteria, DOR, safety
  - Key exploratory: TTR, PFS2, efficacy analysis in subgroups
- **Data cutoff:** October 26, 2017

[a] Patients with PD during therapy or within 60 days of the last dose of a BORT-containing therapy under the approved dosing schedule of 1.3 mg/m^2 twice weekly were excluded.

BORT, bortezomib; DOR, duration of response; IMWG, International Myeloma Working Group; LT, long-term; PFS2, progression-free survival after next line of therapy; TTR, time to response.

Progression-Free Survival (ITT Population)

- OPTIMISMM met its primary endpoint, demonstrating a clinically meaningful and statistically significant improvement in PFS with PVd vs Vd



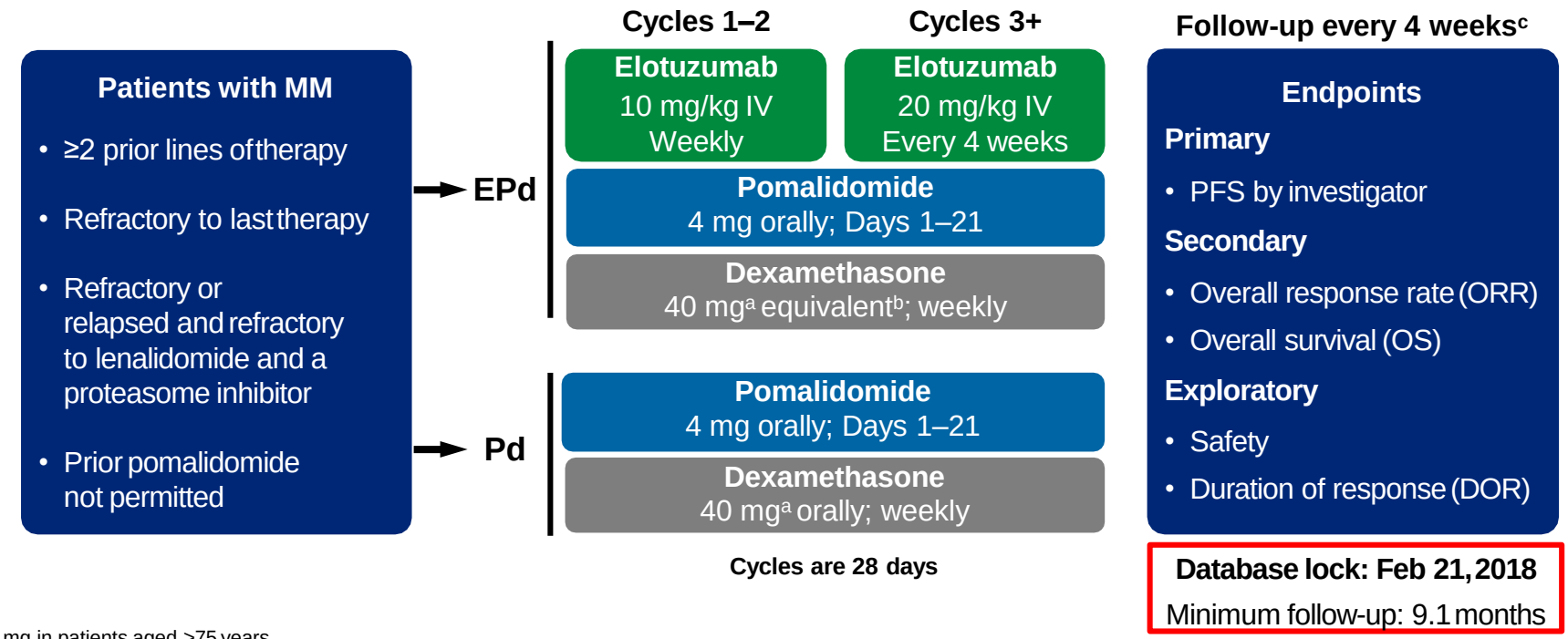
	PVD [1] (N=50)	PVD [2] (N=34)	Elo-PVD [3] N=33
Bortezomib schedule	1.3 mg/m2 D1,8,15,22/ 28	1.3 mg/m2 D1,4,8,11 / 21	1.3 mg/m2 D1,8,15/ 28
Pomalidomide schedule	4 mg Po D1-21 / 28	4 mg Po D1-14 / 21	4 mg Po D1-21 / 28
Lenalidomide refractory %	100%	100%	NR but 100% exposed and 33% prior Pom, 24% priorCD38 mab
Bortezomib exposed %	58%	97% but refractory pts excluded	PI exposed 100%
Median prior lines (range)	2 (1-5)	2 (1-4)	3 (1-9)
ORR	86%	65%	52%
Median PFS	13.7 months	NR (DOR 7.4 months)	9.7
Gr3+ Neutropenia Gr3+ Lung infections	70% 10%	44% 18%	34% 14%

1- Paludo et al. Blood (2017) 130 (10):1198
2- Richardson et al. Leukemia (2017) 31: 2695
3- Yee et al. ASCO 2018 abstract 8012

OF NOTE, at EHA Elo-Pom/Dex superior PFS to Pom/dex (10.3 mo vs 4.7 mo, p.0078 HR 0.54; ORR 53% vs 26%, p .0029).

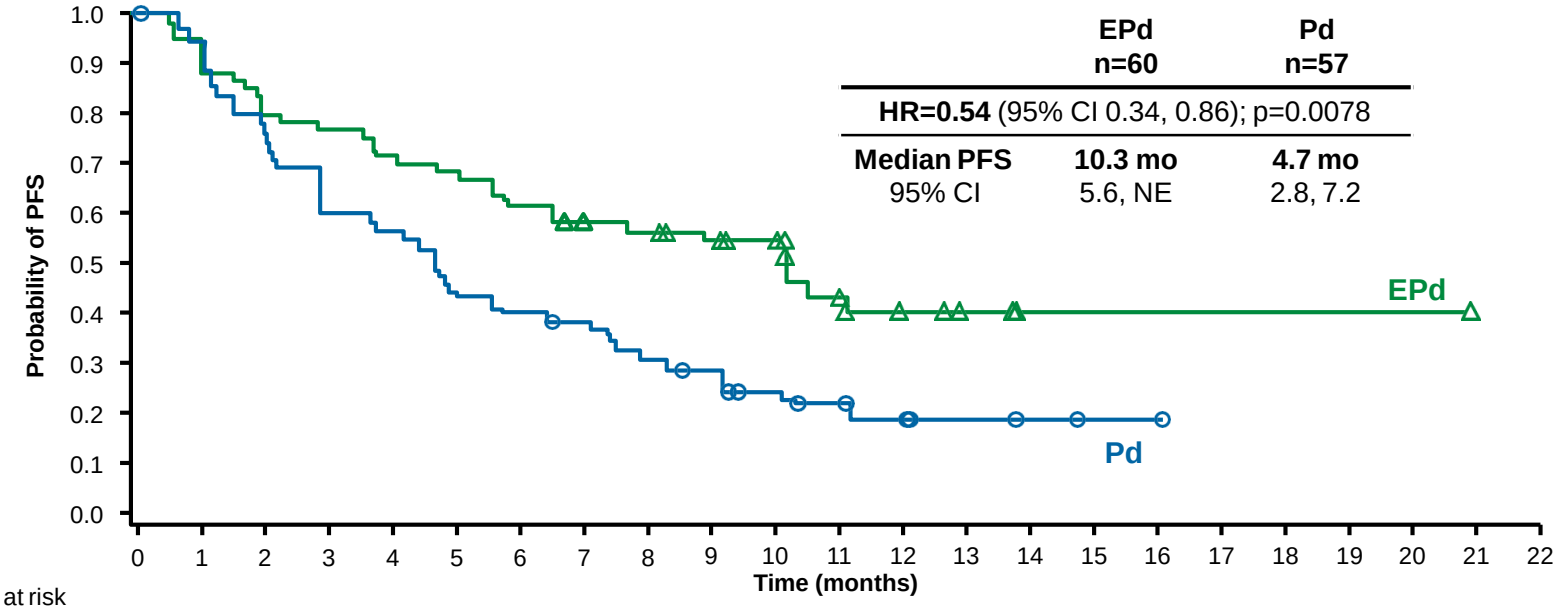
ELOQUENT-3 Study Design

An international, open-label, randomized, phase 2 trial (NCT02654132), with a 2-sided α=0.2 and 85% power to detect a true HR of 0.57



[a]20 mg in patients aged >75 years
[b]Dexamethasone was split between oral (28 or 8 mg in patients aged ≤75 or >75 years) and IV (8 mg) doses on days with elotuzumab
[c]Follow-up continued until disease progression; follow-up for survival occurred at least every 12 weeks
HR, hazard ratio

Progression-Free Survival (ITT Definition)



Patients at risk

EPd	60	54	48	46	43	41	37	33	32	27	25	15	7	4	1	1	1	1	1	1	1	0
Pd	57	51	42	33	31	24	22	20	16	14	10	8	6	3	2	1	1	0	0	0	0	0

- 46% reduction in the risk of progression or death with EPd
- Median PFS was more than twice as long with EPd vs Pd

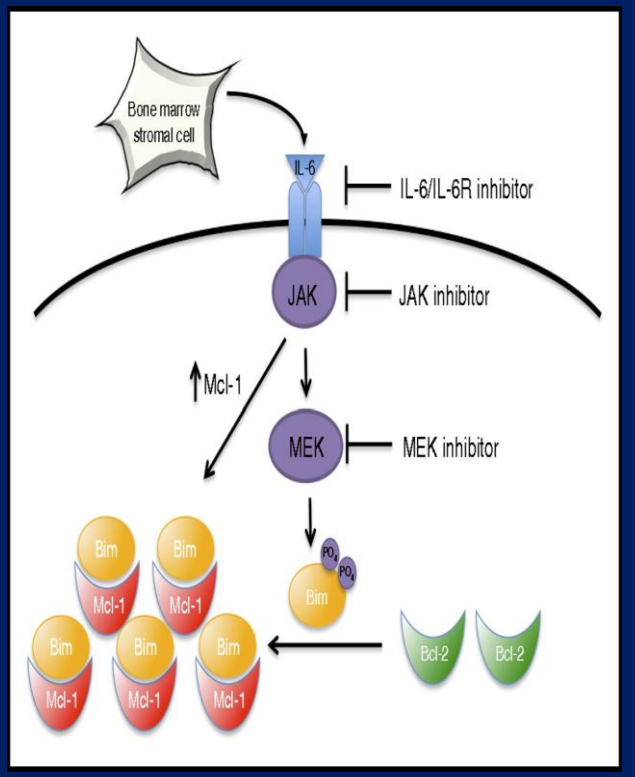
ITT, intent-to-treat; NE, not estimable

ODD MAN OUT…

- Ruxolitinib + Lenalidomide in MM: abstract 8005
- Ibrutinib + rituximab in WM: abstract 8003

Ruxolitinib+Lenalidomide+Methylpred

- IL-6 supports myeloma, activating JAK-STAT tyrosine kinases. Easier to treat myeloma depends on this microenvironment support (Oliveira MB et al)
- Constitutive NF-kB activation allows MM cells to be IL-6 independent (Yang et al).
- No JAK2 V617F mutation in myeloma (Fiorini A et al)
- High concentrations & doses of Ruxolitinib with Len/Dex *in vitro* and in a murine model improved killing (Chen H et al).
- Ruxolitinib 25 BID (13 pts) +/- high dose dex (7 pts combo) with no responses (NCT00639002).



Oliveira MB et al. Anti-myeloma effect sof ruxolitinib combined with bortezomib and lenalidomide. *Cancer Letters*. 2017.
Yang Y et al. Constitutive NF-kB activation confers IL-6 independence and resistance to ruxolitinib in murine plasmacytoma. *JBC*. 2011
Gupta VA et al. Bone marrow microenvironment derived signals induce Mcl-1 dependence in multiple myeloma. *Blood.* 2017
Fiorini A. Screening of JAK2 V617F mutation in multiple myeloma. *Leukemia.* 2006.
Chen H. Anti-myeloma activity by the combination of Ruxolitinib with Lenalidomide and steroids. ASH 2014.

Ruxolitinib + Lenalidomide + Methylprednisolone

What response rate would make this trial a clear win?

- ASPIRE: ORR 66%, ≥ VGPR 40%
  (20% Len exposed, ≈15% refractory to Thal, ≈7% refractory Len)
- TOURMALINE: ORR 72%, ≥ VGPR 39%
  (12% Len exposed, 47% Thal exposed, 25% Thal refractory)
- POLLUX: ORR 76%, ≥ VGPR 49%
  (17% Len exposed, 44% Thal exposed, 4-9% IMiD refractory)
- **This trial: ORR 40%, ≥ VGPR 8%**
  (100% IMiD exposed, 50% Len refractory)

Randomized Phase 3 Trial of Ibrutinib/Rituximab vs Placebo/Rituximab in Waldenström's Macroglobulinemia
Abstract 8003

Meletios A. Dimopoulos, MD[1]; Alessandra Tedeschi, MD[2]; Judith Trotman, FRACP[3]; Ramón García-Sanz, MD, PhD[4]; David MacDonald, MD[5]; Veronique Leblond, MD, PhD[6]; Beatrice Mahe, MD[7]; Charles Herbaux, MD[8]; Constantine Tam, MBBS[9]; M. Lia Palomba, MD[10]; Jeffrey V. Matous, MD[11]; Chaim Shustik, MD[12]; Efstathios Kastritis, MD[1]; Steven P. Treon, MD, PhD[13]; Jianling Li, MS[14]; Zeena Salman, BS[14]; Thorsten Graef, MD, PhD[14]; Christian Buske, MD[15] on behalf of the iNNOVATE Study Group and the European Consortium for Waldenström's Macroglobulinemia

[1]National and Kapodistrian University of Athens School of Medicine, Athens, Greece; [2]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [3]Concord Hospital, University of Sydney, Concord, Australia; [4]Hospital Universitario de Salamanca, Salamanca, Spain; [5]The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada; [6]Département d' Hématologie Hôpital Pitié-Salpêtrière APHP, UPMC Université Paris, Paris, France; [7]Centre Hospitalier Universitaire de Nantes, Nantes, France; [8]Centre Hospitalier Régional Universitaire de Lille, Institute of Hematolog-Tranfusion, Lille, France; [9]Peter MacCallum Cancer Centre & St. Vincent's Hospital and the University of Melbourne, Melbourne, Australia; [10]Memorial Sloan Kettering Cancer Center, New York City, NY, USA; [11]Colorado Blood Cancer Institute, Denver, CO, USA; [12]Royal Victoria Hospital at McGill University Health Centre, Montreal, Canada; [13]Dana-Farber Cancer Institute, Boston, MA, USA; [14]Pharmacyclics LLC, an AbbVie Company, Sunnyvale, CA, USA; [15]Comprehensive Cancer Center Ulm, Institute of Experimental Cancer Research, University Hospital of Ulm, Ulm, Germany.

Ibrutinib + Rituximab vs Rituximab alone [iNNOVATE]

Eligibility	• Hb<10g/dL, Plt < 100K, bulky adenopathy, organomegaly, B symptoms, hyperviscosity, symptomatic neuropathy, cryoglobulinemia • Rituximab sensitive
Treatment	Rituximab weeks 1-4 and 17-20 +/- Ibrutinib 420 mg daily
Priors	45% newly diagnosed
Responses	• ≥PR 72% Ibrutinib+R vs 32% R alone (p<0.0001) • 30-month PFS at 26.5 month f/u: 82% vs 28% (p<0.0001). • No OS benefit
Adverse events	8% couldn't tolerate I / 4% couldn't tolerate R alone No 'unexpected' toxicities

Ibrutinib + Rituximab vs Rituximab alone [iNNOVATE]

- Infusion-related reactions: 1% vs 16% R alone
- Grade ¾ atrial fibrillation – 12% vs 1% R alone
- Pneumonia/upper respiratory tract – 12% vs 3% R alone

Multiple Choice Question:
Which of the following statements is true?

A. Pembrolizumab in combination with either lenalidomide or pomalidomide improves PFS in myeloma.

B. Preliminary results demonstrate that CAR T cells are safe, effective and potentially curative in RRMM.

C. Carfilzomib at 70 mg/m2 weekly is more efficacious and comparable toxicity to carfilzomib 27 mg/m2 given twice weekly.

D. Venetoclax plus carfilzomib only is effective in MM expressing t(11;14).

SUMMARY

- PD-1 inhibitors in myeloma appear dead on arrival
- Once weekly carfilzomib 70 mg/m2 is superior to twice weekly carfilzomib at 27 mg/m2
- Once weekly carfilzomib/lenalidomide/dexamethasone is active but with moderate toxicities
- Carfilzomib + monoclonal antibodies or venetoclax looks very promising
- CAR T cell data is encouraging but the data sets are small with short follow up; CRS in MM is less than ALL and NHL
- Subcutaneous daratumumab in myeloma (and amyloidosis) should be FDA approved in the not too distant future
- Pomalidomide/bortezomib/dex is superior to pomalidomide/dex
- Ruxolitinib+Lenalidomide+Methylprednisolone is promising even in len-refractory MM
- Ibrutinib + rituximab is superior to rituximab alone in WM

DISCUSSION

Question & Answer

Joe Kim, MD, MPH, MBA

QUESTION ANSWER

Submit questions for the speaker using the chat box.

End

Thank you!