Making Sense of Relapsed and Refractory Multiple Myeloma

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We all know that VRd is the SOC* for Newly Diagnosed Multiple Myeloma

But what do we do about Relapse/Refractory Multiple Myeloma (RRMM)?

NCCN Preferred Suggestions:

Preferred Regimens for 1-3 prior lines	Almost all of these are “category 1”
Bortez/Len/Dex	If progressing on PI/Imid comb
Carfilzomib/Len/Dex	Ix/Pom/dex
Dara/Bortez/Dex	Pom/Bortez/Dex
Dara/Carfilzomib/Dex	After 2 prior lines incl lenalidomide and PI
Dara/Len/Dex	Isa/Pom/Dex
Isatuximab/carfilzomib/dex	Dara/Pom/Dex

*Certain Caveats May Apply

Goals of This Talk

Discuss recent trials in Relapsed MM

- Initially focus on “hard-to-use,” therapies

Discuss my personal approach to RRMM

I’m going to try and stay out of the weeds, but we need to understand the strengths and weaknesses of each of these trials to better apply them to our patients

The Elephant in the Room

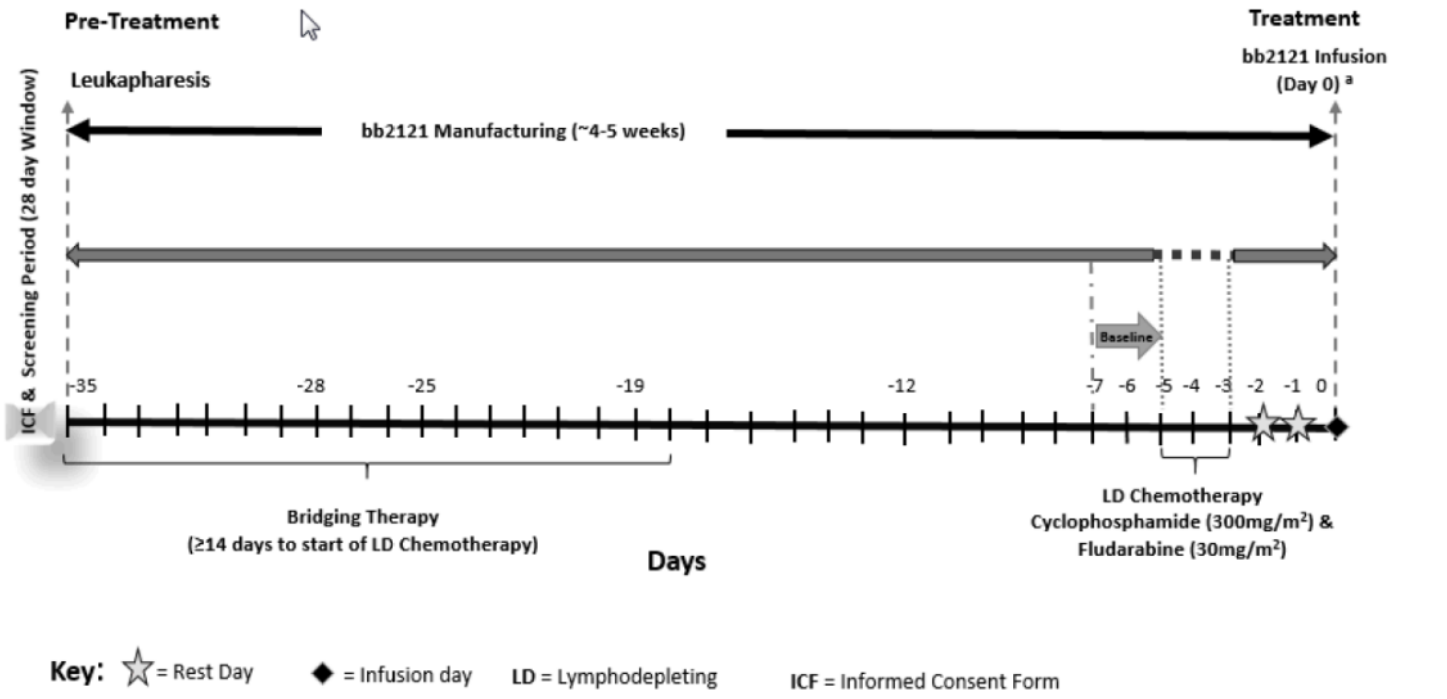
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

Nikhil C. Munshi, M.D., Larry D. Anderson, Jr., M.D., Ph.D., Nina Shah, M.D., Deepu Madduri, M.D., Jesús Berdeja, M.D., Sagar Lonial, M.D., Noopur Raje, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Albert Oriol, M.D., Philippe Moreau, M.D., Ibrahim Yakoub-Agha, M.D., Ph.D., Michel Delforge, M.D., Michele Cavo, M.D., Hermann Einsele, M.D., Hartmut Goldschmidt, M.D., Katja Weisel, M.D., Alessandro Rambaldi, M.D., Donna Reece, M.D., Fabio Petrocca, M.D., Monica Massaro, M.P.H., Jamie N. Connarn, Ph.D., Shari Kaiser, Ph.D., Payal Patel, Ph.D., Liping Huang, Ph.D., Timothy B. Campbell, M.D., Ph.D., Kristen Hege, M.D., and Jesús San-Miguel, M.D., Ph.D.

Treatment Schema



NOTES:

a. Subjects must remain within a 30-minute transportation ride to the treating hospital and must have a dedicated caregiver(s) stay at all times from day of bb2121 infusion through Month 1 post bb2121 infusion.

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Idecel: Demographics

Variable	Total Cohort (n=128)
Median Age (range)	61 (33-78)
Male sex	76 (59%)
Extramedullary Dz	50 (39%)
ECOG 0	57 (45%)
ECOG 1	68 (53%)
ECOG 2	3 (2%)
R-ISS 1	14 (11%)
R-ISS 2	90 (70%)
R-ISS 3	31 (16%)

Variable	Total Cohort (n=128)
High Risk Cytogenetics	45 (35%)
Bridging Therapy	112 (88%)
Median Prior Therapy	6 (3-16)

Key Exclusions:
eGFR <45
ANC <1.25
Plt < 75
EF <45%

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Toxicity: Grade 3-4

AE	Number (%) / Comment
Heme Tox	Common (lymphodepletion + CAR-T)
Febrile Neutropenia	20 (16%)
Hypophosphatemia	20 (16%)
Hypocalcemia	10 (8%)
Hyponatremia	7 (5%)
Cytokine Release Syndrome	7 (5%) (including 1 grade 5)
Neurotox	4 (3%)

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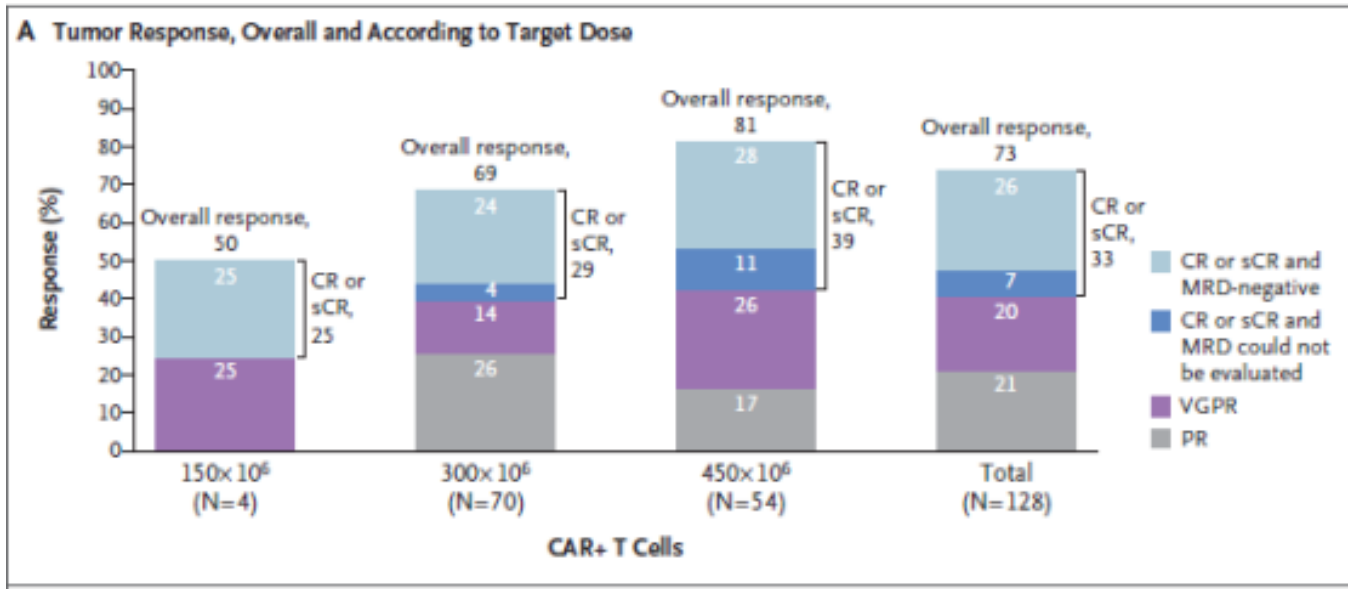
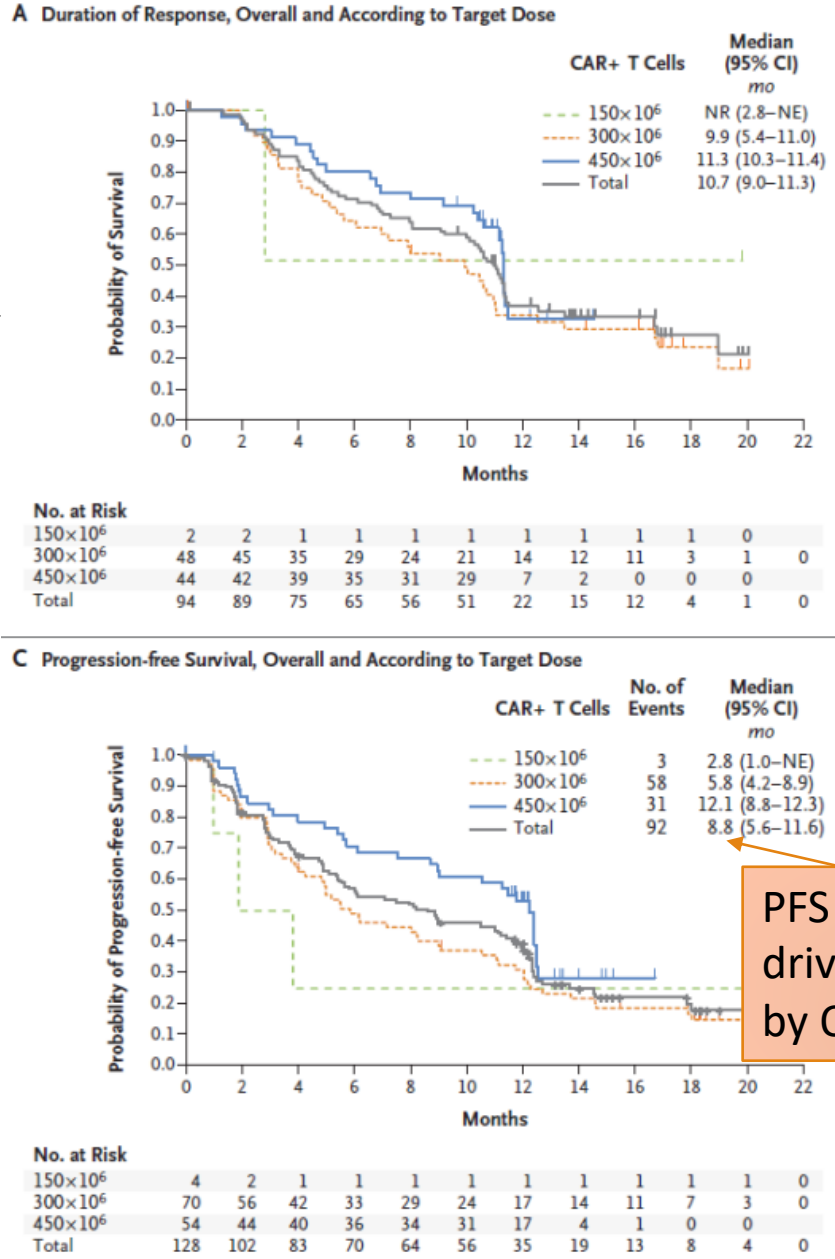
Results





PFS driven by ORR

What are the hurdles?

- Availability:
  - Unfortunately, not available at UCDCC
  - Even at sites that have Idecel, manufacturing slots are quite limited
- Caregiver support
  - At least a month or two post-Idecel
  - Even though not as toxic as autologous SCT, it is as time and labor intensive
- Cost
- Approved for patients with 4 prior lines of therapy

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DREAMM-2: Belantamab Mafodotin

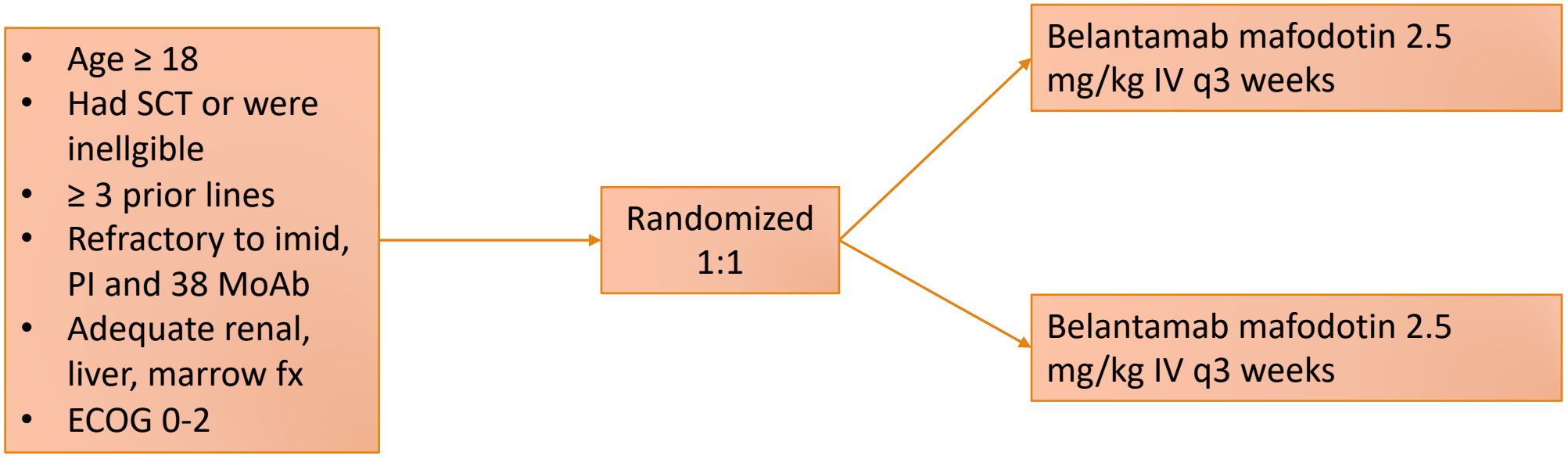
Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study

Sagar Lonial, Hans C Lee, Ashraf Badros, Suzanne Trudel, Ajay K Nooka, Ajai Chari, Al-Ola Abdallah, Natalie Callander, Nikoletta Lendvai, Douglas Sborov, Attaya Suvannasankha, Katja Weisel, Lionel Karlin, Edward Libby, Bertrand Arnulf, Thierry Facon, Cyrille Hulin, K Martin Kortüm, Paula Rodríguez-Otero, Saad Z Usmani, Parameswaran Hari, Rachid Baz, Hang Quach, Philippe Moreau, Peter M Voorhees, Ira Gupta, Axel Hoos, Eric Zhi, January Baron, Trisha Piontek, Eric Lewis, Roxanne C Jewell, Elisha J Dettman, Rakesh Popat, Simona Degli Esposti, Joanna Opalinska, Paul Richardson, Adam D Cohen

Longer Term Outcomes With Single-Agent Belantamab Mafodotin in Patients With Relapsed or Refractory Multiple Myeloma: 13-Month Follow-Up From the Pivotal DREAMM-2 Study

Sagar Lonial, MD [1]; Hans C. Lee, MD[2]; Ashraf Badros, MD [3]; Suzanne Trudel, MD[4]; Ajay K. Nooka, MD [1]; Ajai Chari, MD [5]; Al-Ola Abdallah, MD[6]; Natalie Callander, MD[7]; Douglas Sborov, MD[8]; Attaya Suvannasankha, MD[9]; Katja Weisel, MD[10]; Peter M. Voorhees, MD[11]; Lynsey Womersley, MSc[12]; January Baron, MS[13]; Trisha Piontek, BSN[13]; Eric Lewis, MD[14]; Joanna Opalinska, MD[13]; Ira Gupta, MD[13]; and Adam D. Cohen, MD[15]

Lonial et al Lancet Onc 2020;
Lonial et al Cancer 2021



Lonial et al Lancet Onc 2020;
Lonial et al Cancer 2021

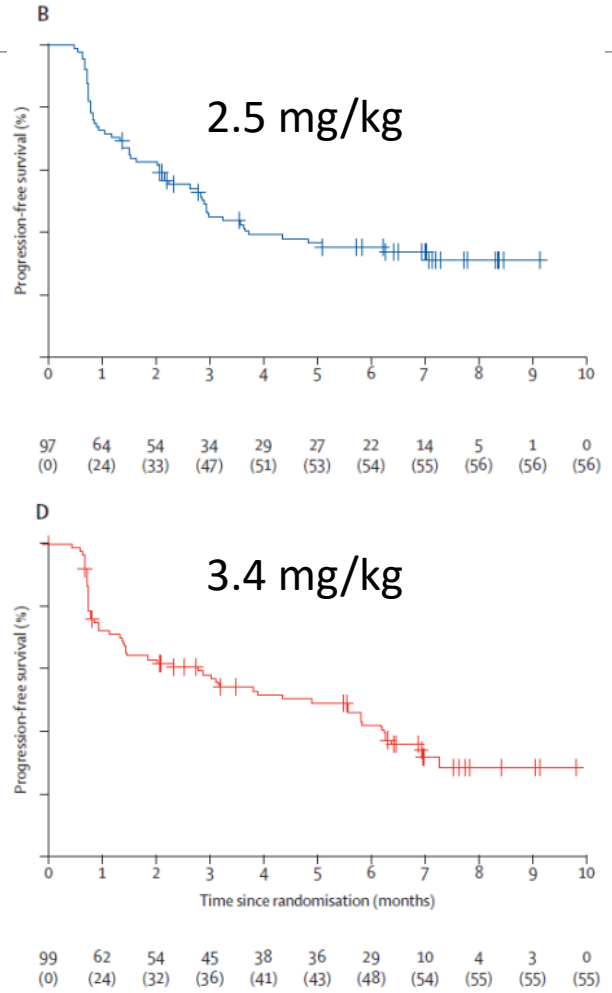
Demographics

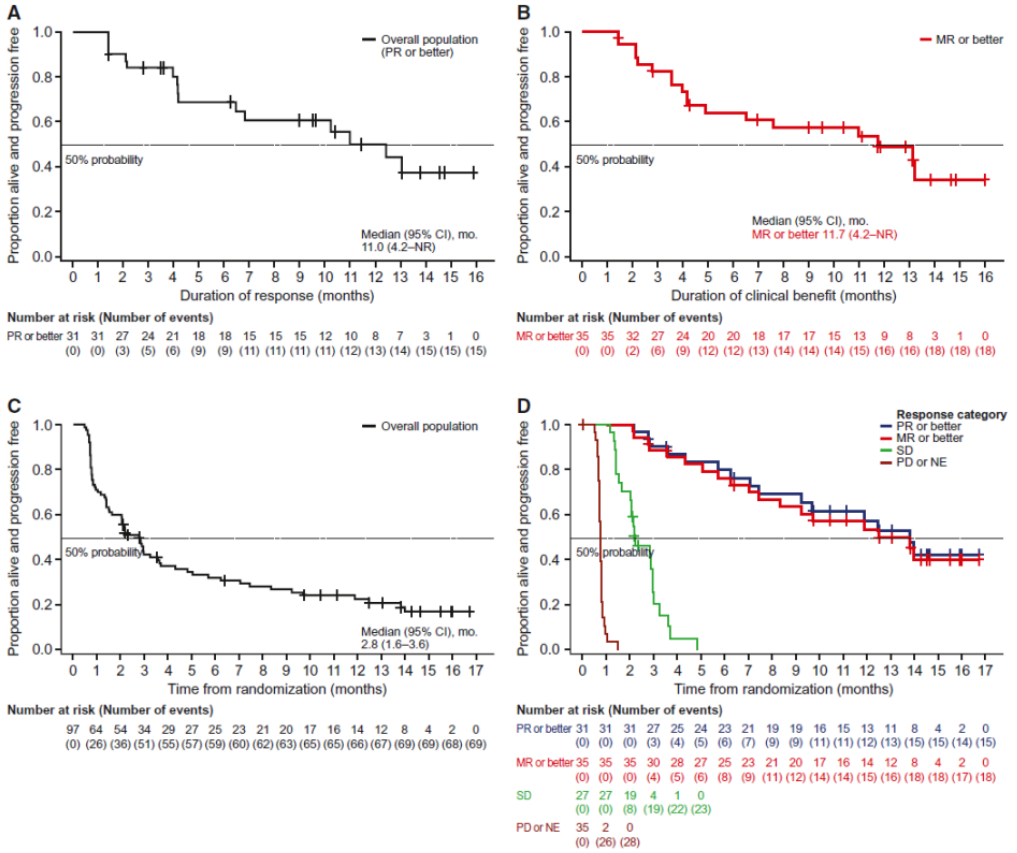
	2.5 mg/kg (N=97)	3.4 mg/kg (N=99)
Age	65 (60-70)	67 (61-72)
eGFR > 90	20%	17%
eGFR 60-90	49%	52%
eGFR 30-60	25%	22%
eGFR 15-30	2%	5%
ISS 1	22%	18%
ISS 2	34%	52%
ISS 3	43%	30%
High Risk Cyto	42%	47%

	2.5 mg/kg (N=97)	3.4 mg/kg (N=99)
Prev Therapy	7 (3-21)	6 (3-21)

Lonial et al Lancet Onc 2020;
Lonial et al Cancer 2021

DREAMM-2 Results



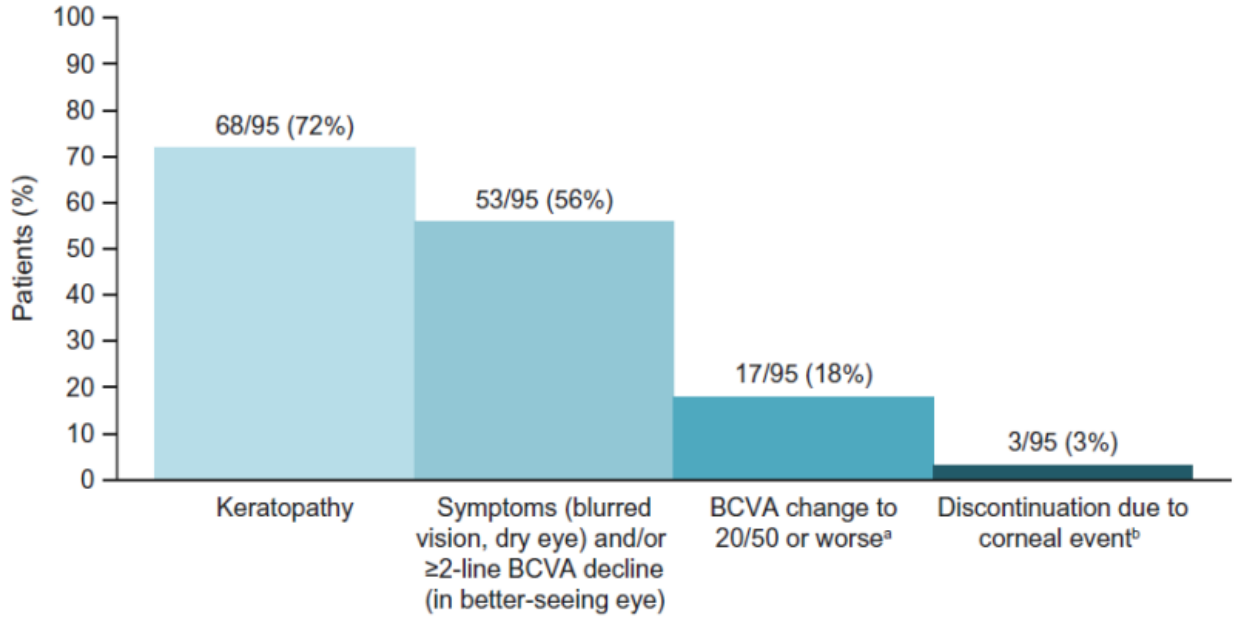


Lonial et al Lancet Onc 2020;
Lonial et al Cancer 2021

Belantamab Toxicity (2.5 mg/kg cohort)

TABLE 4. Most Common Adverse Events (Occurring in ≥15%) and Grade ≥3 Adverse Events (Occurring in ≥5%) in the Overall Population[a]

	Belamaf 2.5 mg/kg, N = 95: No. of Patients (%)	
Event	Any Grade	Grade ≥3
Any event	93 (98)	80 (84)
Eye examination finding		
Keratopathy[b]	68 (72)	44 (46)
Change in BCVA	51 (54)	29 (31)
Thrombocytopenia[c]	36 (38)	21 (22)
Anemia	26 (27)	20 (21)
Blurred vision[d]	24 (25)	4 (4)
Nausea	24 (25)	0 (0)
Pyrexia[e]	22 (23)	4 (4)
Aspartate aminotransferase increased	20 (21)	2 (2)
Infusion-related reaction[f]	20 (21)	3 (3)
Fatigue	15 (16)	2 (2)
Neutropenia[g]	14 (15)	10 (11)
Dry eye[h]	14 (15)	1 (1)
Hypercalcemia	14 (15)	7 (7)
Lymphocyte count decreased	13 (14)	12 (13)
Pneumonia	9 (9)	6 (6)



Lonial et al Lancet Onc 2020;
Lonial et al Cancer 2021

What do we do with Belantamab?!

Patients are scared of ocular toxicity

WE'RE scared of ocular toxicity

Important to note that in DREAMM-2 patients with ocular toxicity, most recovered

- This is hampered by incomplete follow up in patient who came off trial
- However, we can reassure patients in this regard

The REMS program is challenging

However, 30% single agent response combined with duration of response of 11 months in encouraging

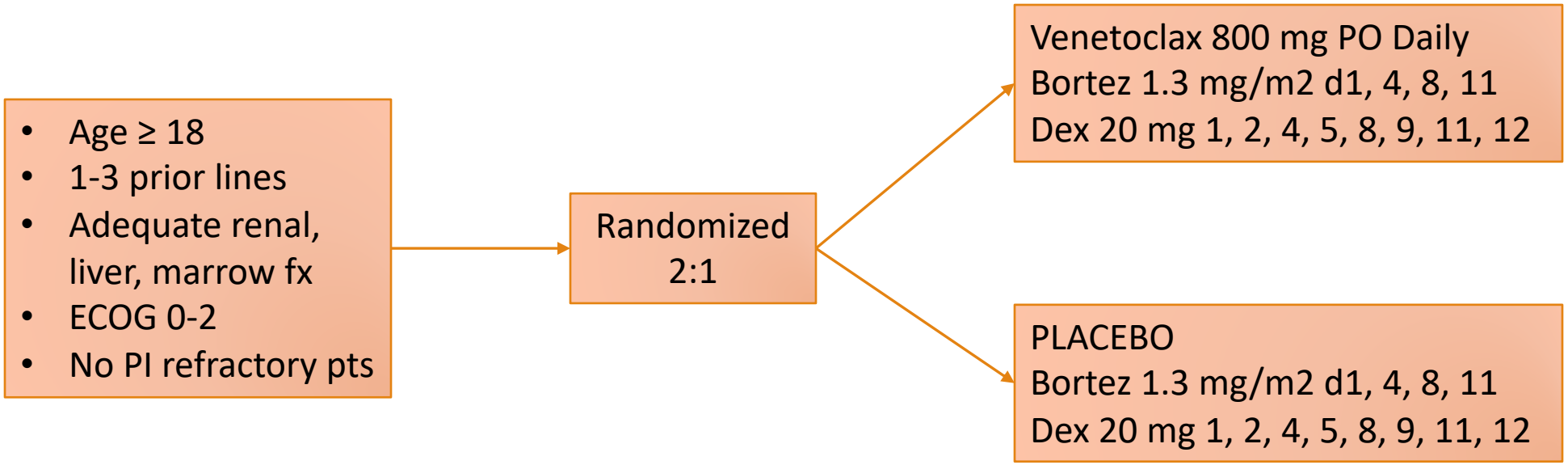
Making Sense of BELLINI: Venetoclax for multiple myeloma

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

Shaji K Kumar, Simon J Harrison, Michele Cavo, Javier de la Rubia, Rakesh Popat, Cristina Gasparetto, Vania Hungria, Hans Salwender, Kenshi Suzuki, Inho Kim, Elizabeth A Punnoose, Wan-Jen Hong, Kevin J Freise, Xiaoqing Yang, Anjla Sood, Muhammad Jalaluddin, Jeremy A Ross, James E Ward, Paulo C Maciag, Philippe Moreau

Kumar et al Lancet 2020

BELLINI: Design



Kumar et al Lancet 2020

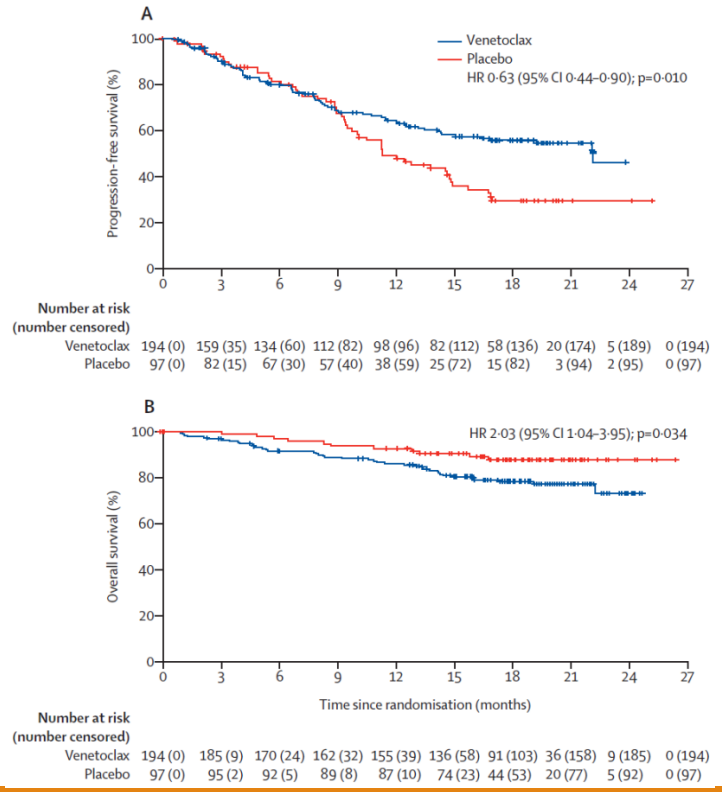
Demographics

	Ven (N=194)	Placebo (N=97
Age	66 (59-73)	65 (61-71)
ISS 1	42%	49%
ISS 2	36%	33%
ISS 3	20%	13%
High Risk Cyto	16%	19%
T(11;14)	10%	15%

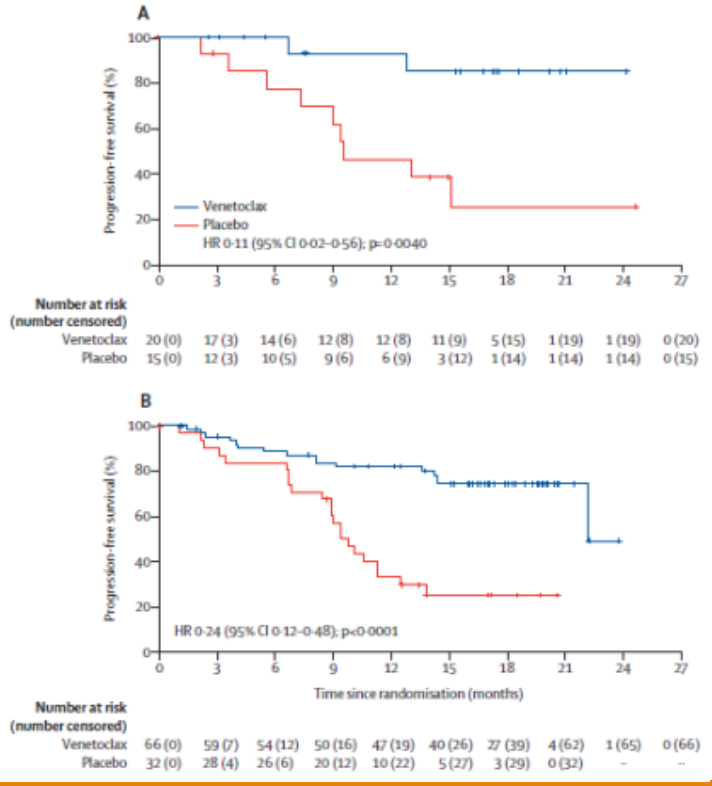
	Ven (N=194)	Placebo (N=97
1 prior line	47%	45%
2-3 prior line	53%	55%
PI Exposed	70%	70%
Imid Exposed	68%	67%
SCT	60%	59%

BELLINI: Paradoxical Results

TOTAL COHORT: PFS AND OS



T(11;14) AND HIGH BCL2 GROUPS, PFS



Kumar et al Lancet 2020

So what happened?

At data cut off, 41 deaths in the Ven arm, and 11 in the placebo

- Didn't cross the stopping threshold and a second interim analysis is pending

11 grade 5 (deaths) on the Ven arm, only 1 on the placebo

- 9 ven deaths were clearly infectious, several others suspicious,
- Many deaths occurred after cessation of therapy (and were frequently infectious)

So – how do we use this drug effectively?

- Select the right patient
  - t(11;14)
  - Can consider "high" BCL2 levels, though these aren't well defined
- Antimicrobial prophylaxis is a must – consider PJP, VZV and routine bacterial coverage

Other Trials

Trial	# Prior Therapy	Intervention Arm	Control Arm	PFS intervention	PFS Control
IKEMA	1-3	Isatuximab / Carfilzomib / dex	Carfilzomib / dex	Not reached	19.2 months
CANDOR	1-3	Daratumumab / Carfilzomib / dex	Carfilzomib / dex	Not reached	15.8 months
APOLLO	1-3	Daratumumab / Pomalidomide/ dex	Pomalidomide/ dex	12.4 months	6.9 months

So how do we synthesize all this

First – you can find a phase 2 or 3 trial to support almost any treatment regimen you like

Early on (1-3 prior lines) you have lots of options

- I present options to the patient that rely on changing AT LEAST one class of drug
- Since we have no real head to head data comparing triplets, there's no "right answer" – offer patients options based on potential toxicity profiles and administration schedules
- Shoot for triplets if you think the patient can tolerate it

Later in therapy we frequently need to recycle meds

- Don't forget about cytotoxic therapies like oral cyclophosphamide which get left by the wayside in the "modern era"

Belantamab, Selinexor, venetoclax and idecaptegene-vicleucel have novel and challenging side effect profiles, but can be effective

- We as clinicians need to learn how to modify doses and provide appropriate supportive care

Finally….

We need better trials.

While demonstrating efficacy of triplets over doublets remains relevant, we as a physicians need to demand comparisons of triplets – we and our patients need this data