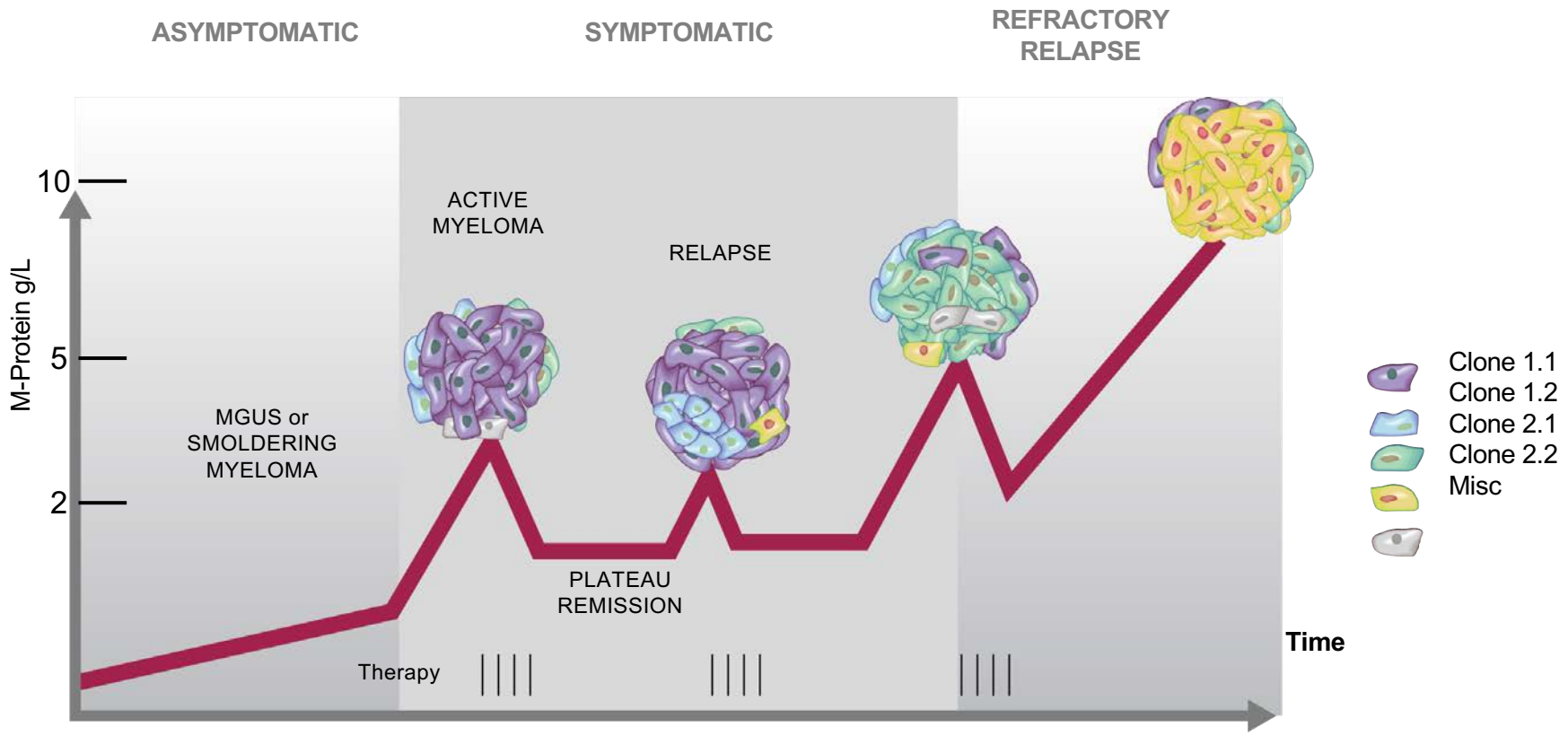
# Selection and Sequencing of Therapies for Patients with Relapsed/Refractory Myeloma

**Joseph Mikhael, MD, MEd, FRCPC**
Chief Medical Officer, International Myeloma Foundation
Professor, Translational Genomics Research Institute (TGen)
City of Hope Cancer Center

# Relapsing Nature of Multiple Myeloma: Clones Change over Time



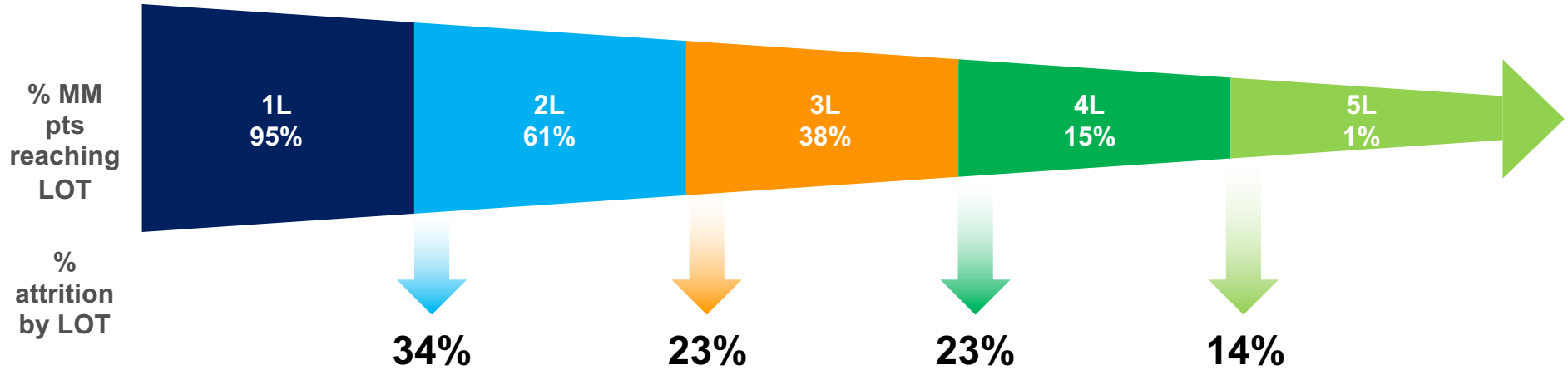

MGUS = monoclonal gammopathy of undetermined significance

Adapted from Dr. Brian Durie and Keats JJ, et al. *Blood*. 2012;120:1067-1076.

tgen AN AFFILIATE OF City of Hope

INTERNATIONAL MYELOMA FOUNDATION

# Only few MM patients reach later lines of therapy




**In every new LOT, ~15-35% of patients are lost**

*Figure adapted from: Yong, K et al. Br J Haematol 2016;175(2):252-264.*

tgen AN AFFILIATE OF City of Hope

INTERNATIONAL MYELOMA FOUNDATION

# An Approach to Relapsed MM

- It is not a simple algorithm of treatment #1 then 2 then 3…
- Important to leverage the benefit of multiple mechanisms of action in combination therapy

Categories:

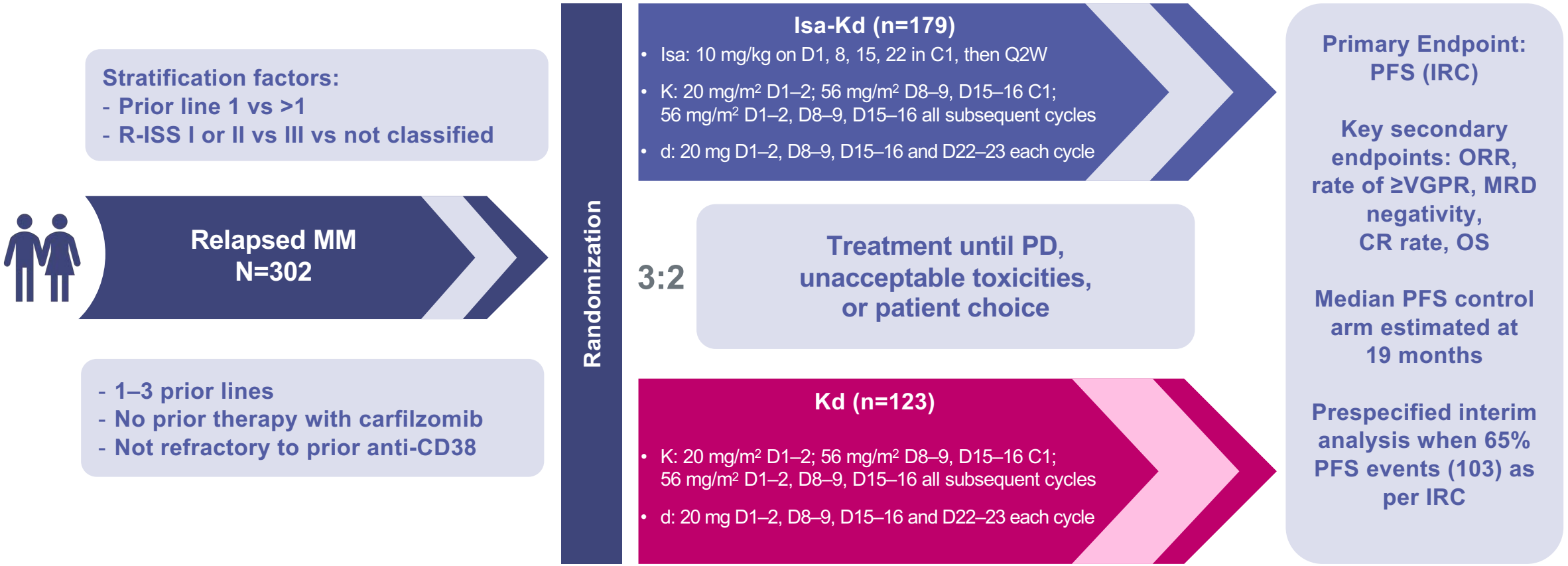
- 1-3 prior lines
- Later Relapse
- Refractory to PI, IMiD and MoAb = Triple-Class Refractory

Principles

- Depth of Response matters… *likely incorporate MRD soon*
- High risk vs standard risk… *more aggressive Rx in high risk*
- Balance efficacy and toxicity… *initially and constantly assess*

# IKEMA

## Study design: Isa-Kd vs Kd in relapsed multiple myeloma




Sample size calculation: ~300 patients and 159 PFS events to detect 41% risk reduction in hazard rate for PFS with 90% power and one-sided 0.025 significance level

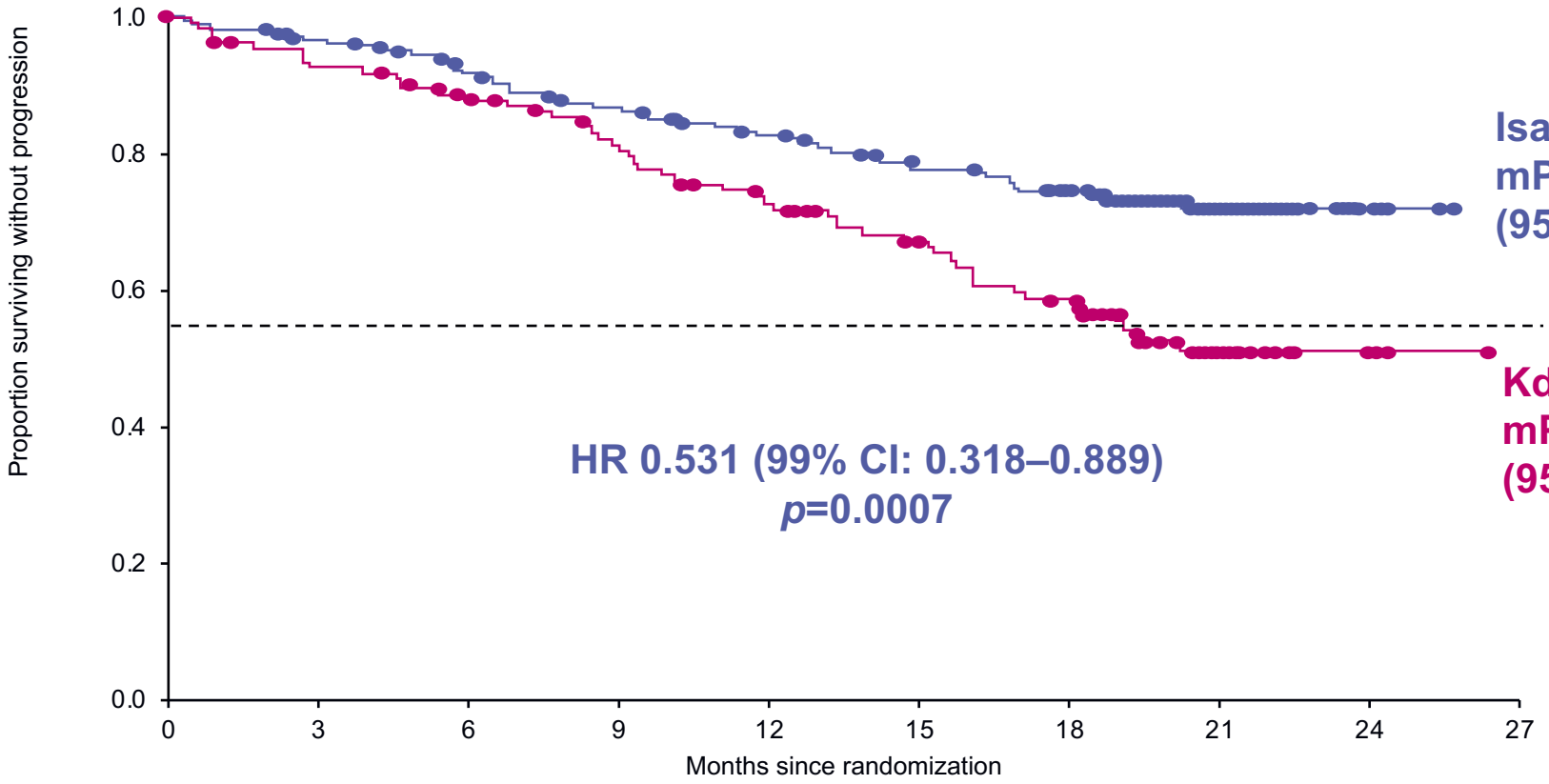
Moreau P, et al. Future Oncol. 2020;16:4347–4358.

IKEMA study: NCT03275285

C, cycle; CD, cluster of differentiation; CR, complete response; D, day; d, dexamethasone; IRC, Independent Response Committee; Isa, isatuximab; K, carfilzomib; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q2W, once every 2 weeks; R-ISS, Revised International Staging System; VGPR, very good partial response.

# IKEMA

## Interim PFS analysis – IRC assessment in ITT population (primary endpoint)



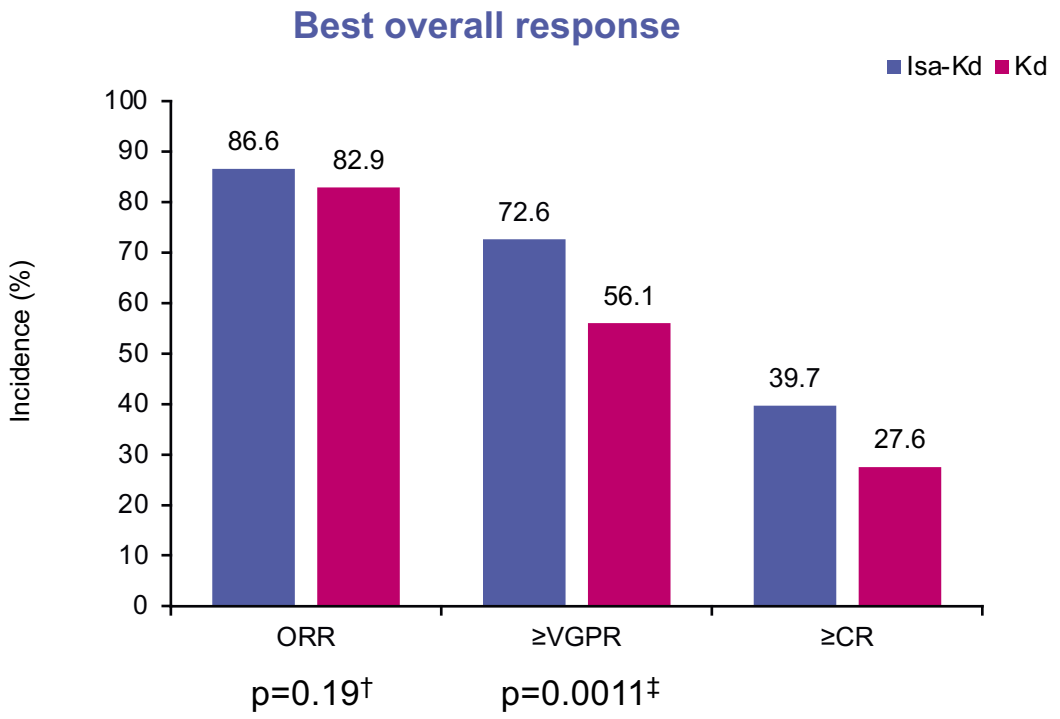

| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Isa-Kd | 179 | 164 | 151 | 136 | 124 | 110 | 100 | 36 | 5 | 0 |
| Kd | 123 | 108 | 99 | 85 | 72 | 61 | 50 | 19 | 6 | 0 |

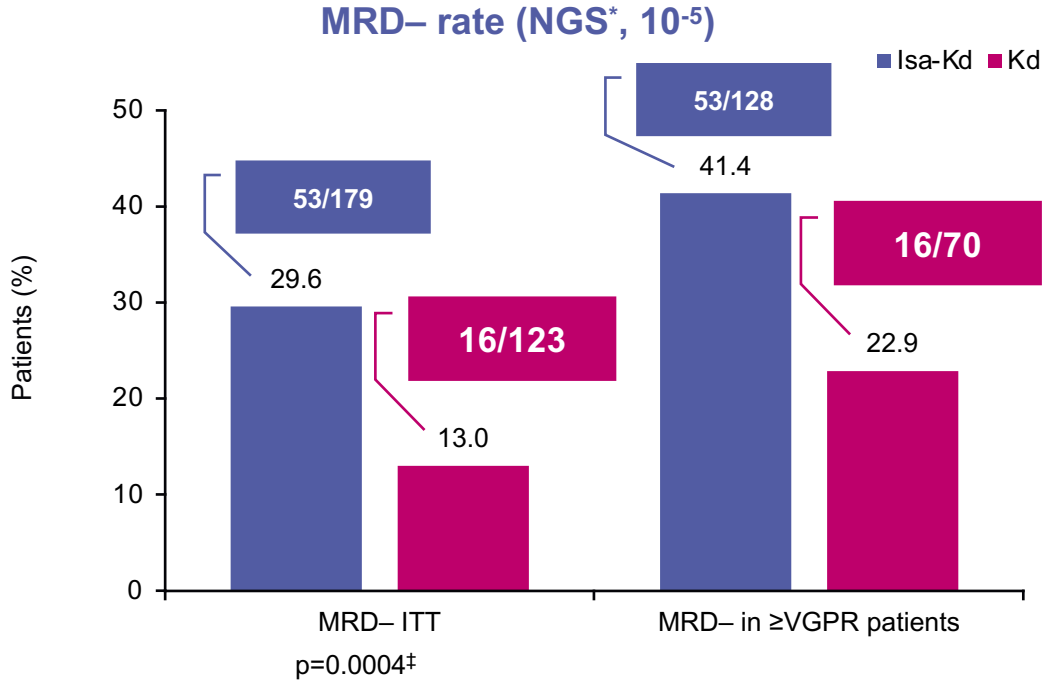
One-sided *p* value, level of significance <0.005

**Isa-Kd showed improvement in PFS with 47% reduction of risk of progression or death vs Kd**

CI, confidence interval; d, dexamethasone; HR, hazard ratio; IRC, Independent Review Committee; Isa, isatuximab; ITT, intent to treat; K, carfilzomib; m, median; NE, not estimable; NR, not reached; PFS, progression-free survival

# IKEMA
# Depth of response

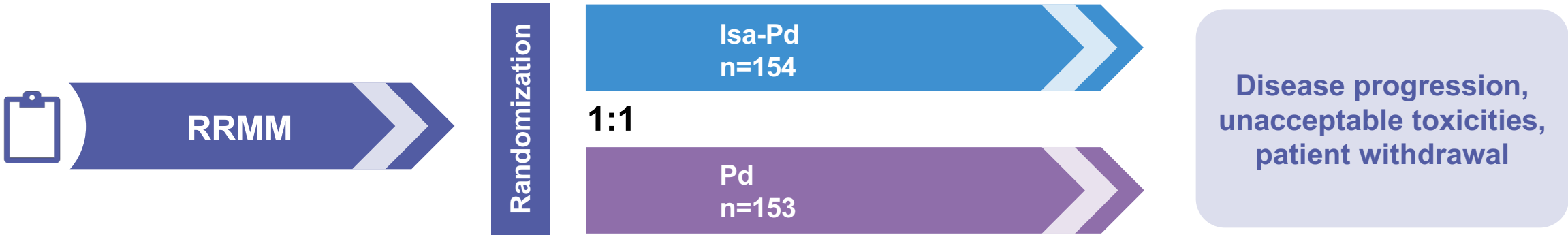


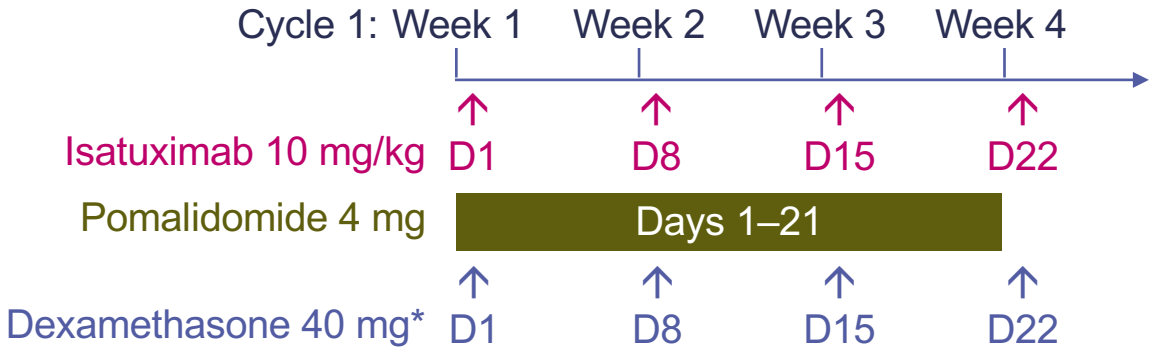

**The MRD– rate more than doubled in patients receiving Isa-Kd and was approximately 30% in the ITT population**

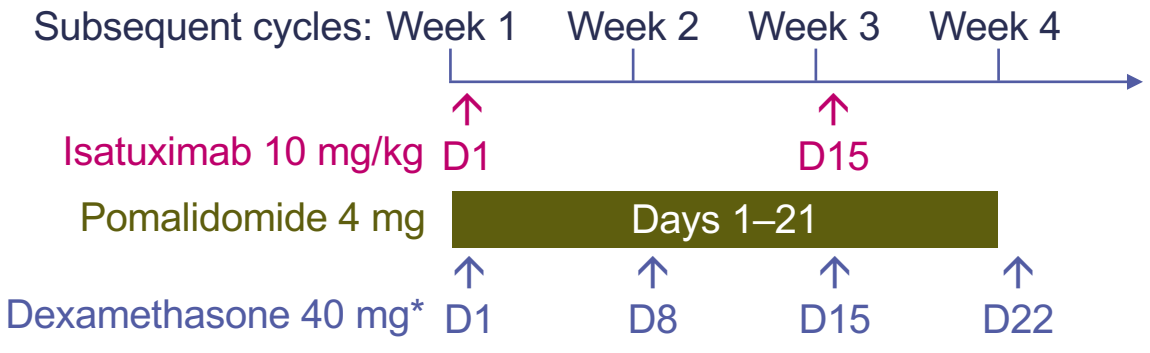
*Adaptive Biotechnologies NGS, MRD testing performed at time of VGPR or CR. †Stratified Cochran-Mantel-Haenszel test. One-sided significance level is 0.025. ‡Provided for descriptive purposes only.
CR, complete response; d, dexamethasone; ITT, intent-to-treat; Isa, isatuximab; K, carfilzomib; MRD, minimal residual disease; neg, negative; NGS, next generation sequencing; ORR, overall response rate; PFS, progression-free survival; VGPR, very good partial response.

# ICARIA: Isa-Pd vs Pd
## Study design




**Sample size calculation: ~300 patients required to detect an HR of 0.6 with 90% power and 1-sided type 1 error of 2.5%**




*Dexamethasone dose was 20 mg in patients aged ≥75 years
d, dexamethasone; HR, hazard ratio; Isa, isatuximab; P, pomalidomide; RRMM, relapsed/refractory multiple myeloma

Richardson PG, et al. Future Oncol 2018;14:1035–47;
Attal M, et al. Lancet. 2019, Manuscript in Press

SANOFI GENZYME

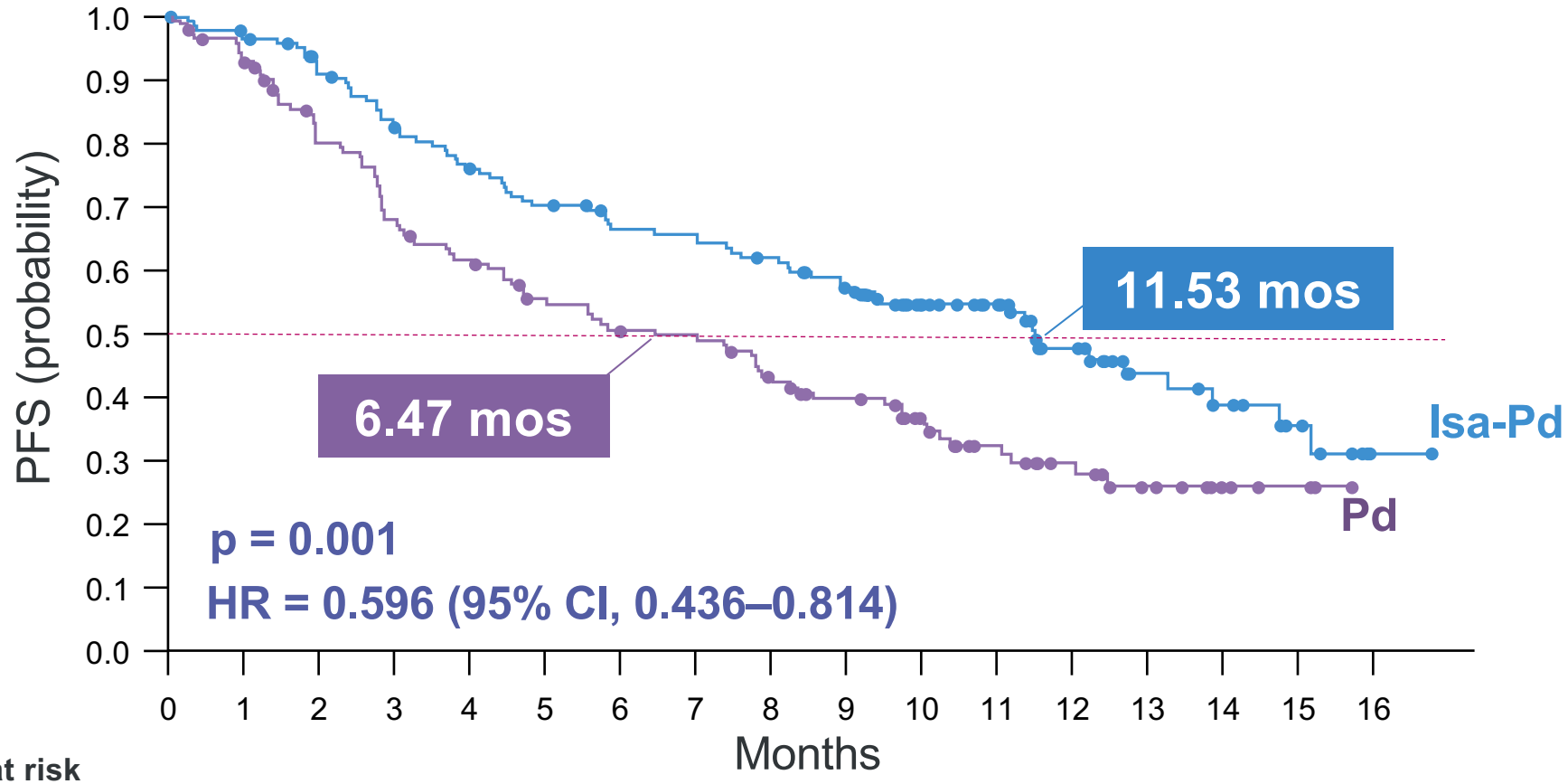
# ICARIA: Isa-Pd vs Pd
## Key patient demographics

| | Isa-Pd (n=154) | Pd (n=153) |
|---|---|---|
| Median age, years (range) | 68 (36–83) | 66 (41–86) |
| Age category, n (%) | | |
| <65 years | 54 (35.1) | 70 (45.8) |
| 65–75 years | 68 (44.2) | 54 (35.3) |
| ≥75 years | 32 (20.8) | 29 (19.0) |
| Prior history of asthma / COPD, n (%) | 16 (10.4) | 17 (11.1) |
| CrCl [eGFR*] <60 mL/min/1.73m², n (%) | 55/142 (38.7) | 49/145 (33.8) |

*By MDRD
COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; d, dexamethasone;
eGFR, estimated glomerular filtration rate; Isa, isatuximab; MDRD, Modification of Diet in Renal Disease Study; P, pomalidomide

Attal M, et al. Lancet. 2019, Manuscript in Press

# ICARIA: Isa-Pd vs Pd
## PFS (IRC assessment – primary endpoint)




| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Isa-Pd | 154 | 129 | 106 | 89 | 81 | 52 | 30 | 14 | 1 |
| Pd | 153 | 105 | 80 | 63 | 51 | 33 | 17 | 5 | 0 |

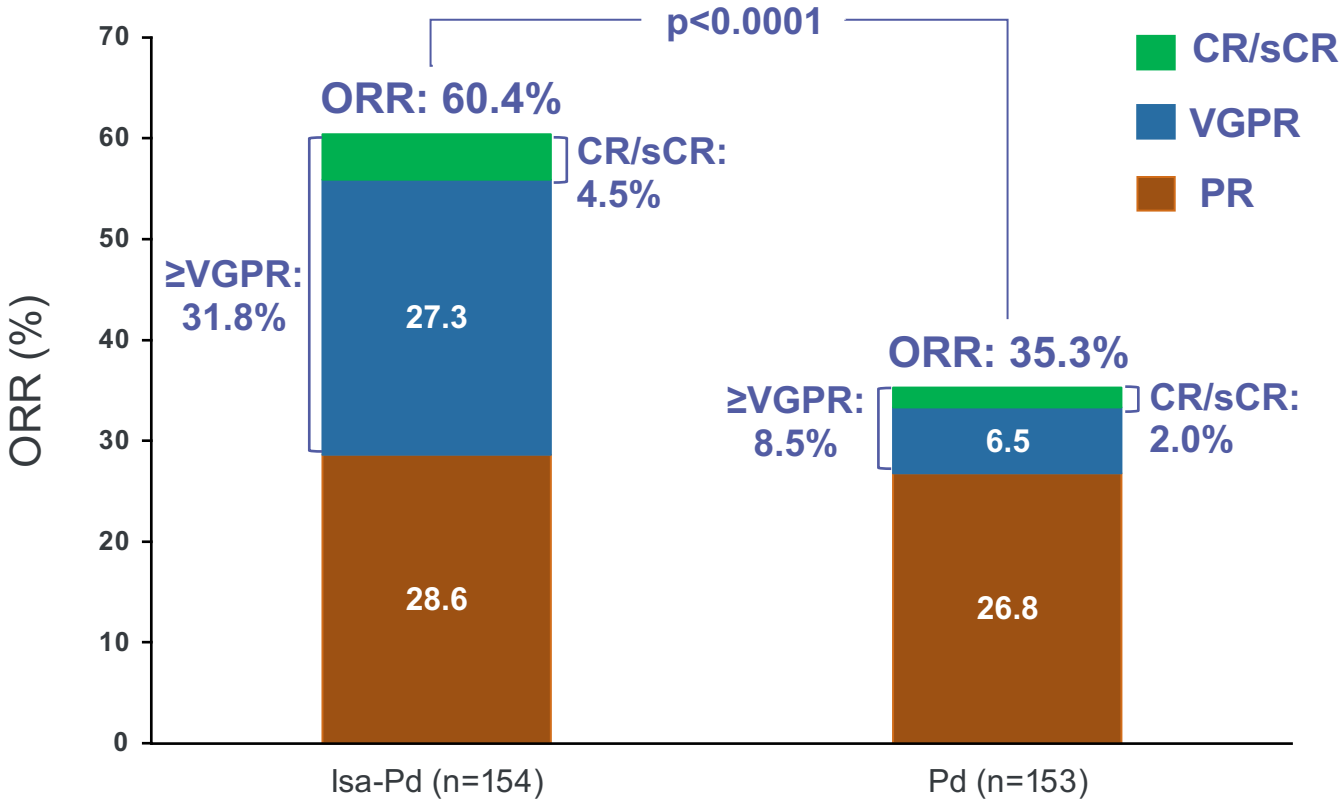
**Statistically significant improvement in PFS**

Data cut-off 11 Oct, 2018

CI, confidence interval; d, dexamethasone; HR, hazard ratio; IRC, Independent Review Committee; Isa, isatuximab;, mos, months; PFS, progression-free survival; P, pomalidomide

Attal M, et al. Lancet. 2019, Manuscript in Press

# ICARIA: Isa-Pd vs Pd
## Response summary (IRC assessment)




**Median time to 1st response: Isa-Pd 35 days vs Pd 58 days**

**Addition of Isa to Pd resulted in significant improvement in overall and depth of response**

Data cut-off 11 Oct, 2018
CR, complete response; d, dexamethasone; IRC, Independent Review Committee; Isa, isatuximab; ORR, overall response rate; P, pomalidomide; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Attal M, et al. Lancet. 2019, Manuscript in Press

SANOFI GENZYME

# Daratumumab vs Isatuximab: Both agents are VERY similar

Some biological differences but not apparently clinically significant

Practical differences

*Dosing*

Dara weekly x4, q2 weekly x8 then q4 weeks

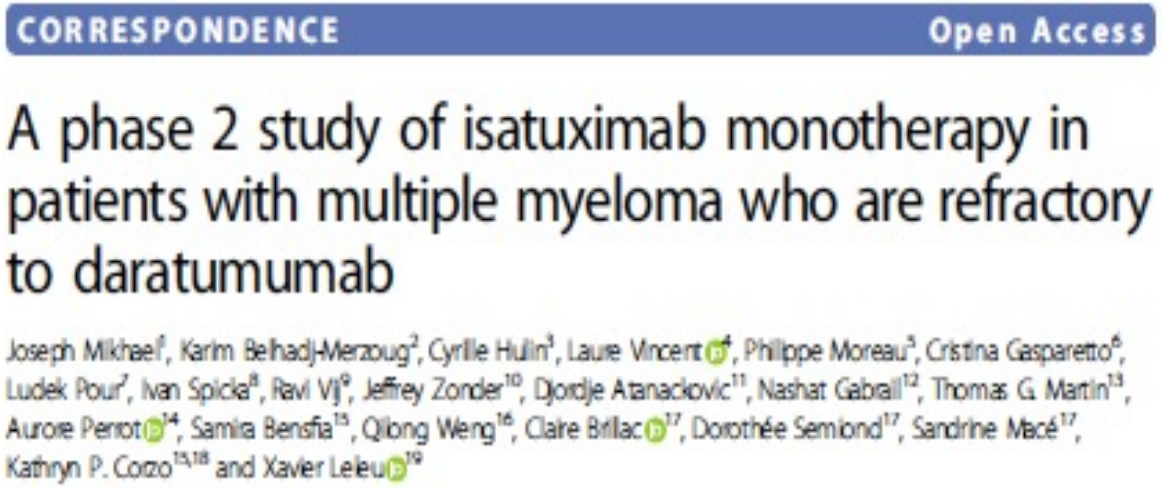
Isa weekly x4 then q2 week

*Administration*

Dara IV over 6-8 hours first 2 then 2-4 hours

Dara SQ over 5 minutes!

Isa IV 3.5 hours then 2 hours, then 75 mins



CORRESPONDENCE Open Access

A phase 2 study of isatuximab monotherapy in patients with multiple myeloma who are refractory to daratumumab

Joseph Mikhael[1], Karim Belhadj-Merzoug[2], Cyrille Hulin[3], Laure Vincent[4], Philippe Moreau[5], Cristina Gasparetto[6], Ludek Pour[7], Ivan Spicka[8], Ravi Vij[9], Jeffrey Zonder[10], Djordje Atanackovic[11], Nashat Gabrail[12], Thomas G. Martin[13], Aurore Perrot[14], Samira Bensfia[15], Qilong Weng[16], Claire Brillac[17], Dorothée Semiond[17], Sandrine Macé[17], Kathryn P. Cozzo[15,18] and Xavier Leleu[19]

*IMPORTANT – one agent does NOT seem to overcome resistance to the other*

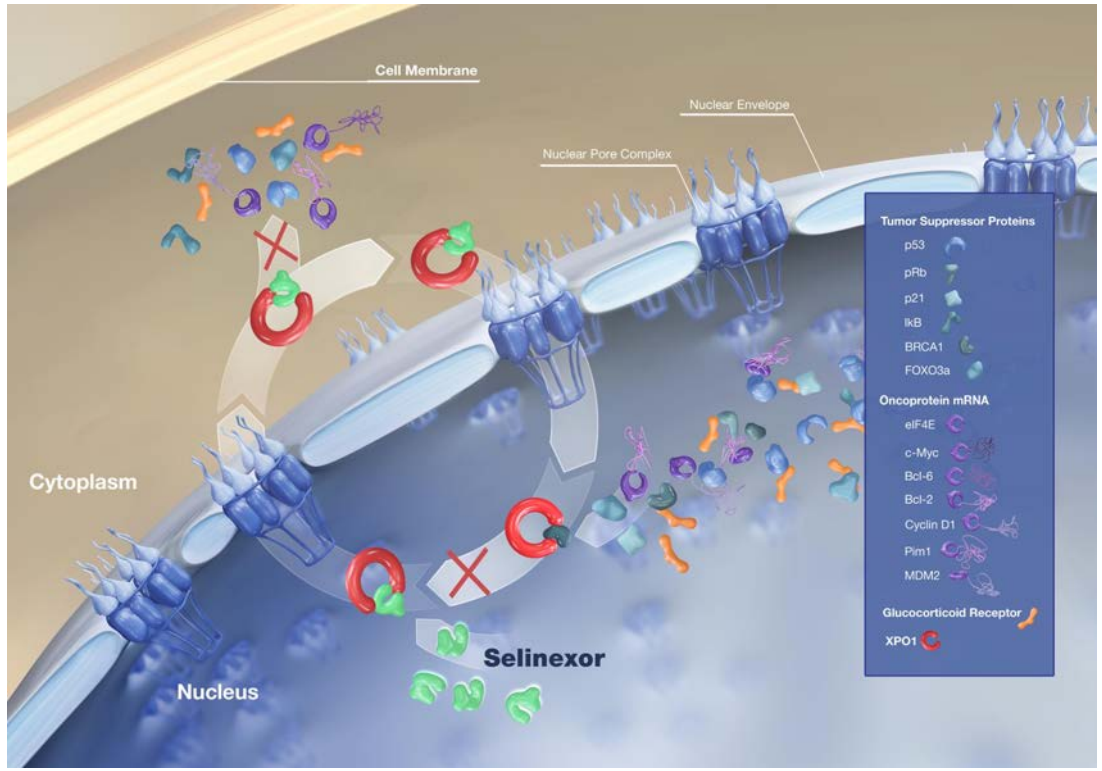
*We have much more to learn about CD38 resistance…*

tgen AN AFFILIATE OF City of Hope

INTERNATIONAL MYELOMA FOUNDATION

# Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE)

## The novel MOA of selinexor targets some hallmarks of cancer biology by targeting XPO1, the nuclear export protein central to the hallmark processes




For illustrative purposes only

**Hallmarks of cancer include[1]:**

- Self-sufficiency in growth signals
- Insensitivity to anti-growth signals
- Evasion of apoptosis
- Sustained angiogenesis
- Limitless replicative potential

**XPO1 overexpression:**

- Inactivates tumor suppressor proteins (eg, p53) by mislocalization[2]
- Enhances proto-oncoprotein translation (eg, c-myc, Bcl-2)[2,3]
- Correlates with poor clinical outcomes and poor response to treatment[4-6]

**XPO1 inhibition by selinexor targets these hallmarks by:**

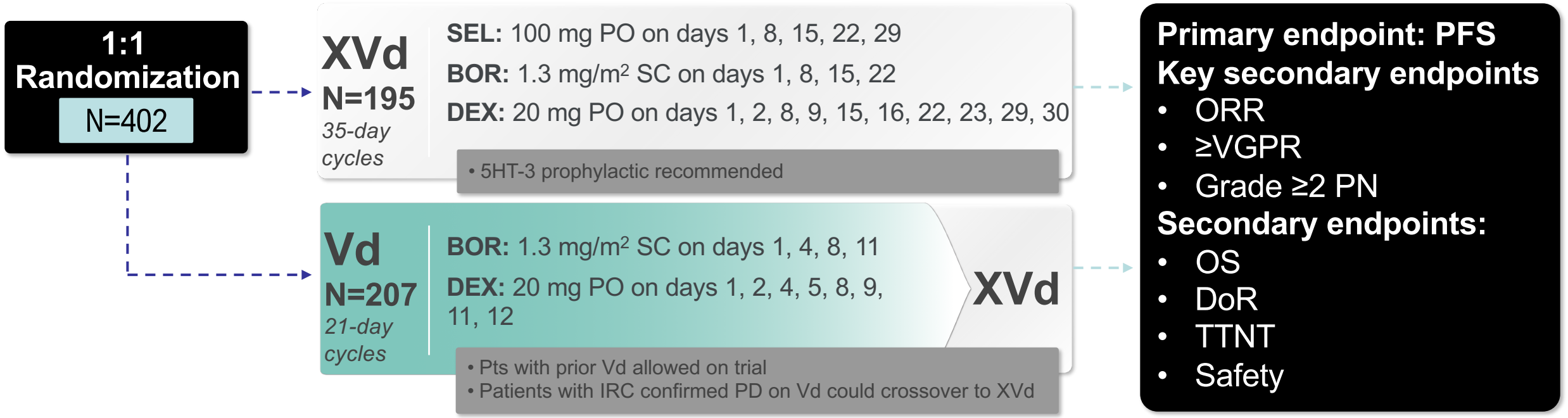
- Reactivating multiple tumor suppressor proteins by preventing nuclear export[2,7]
- Inhibiting oncoprotein translation by sequestering mRNA in the nucleus[2,7]
- Blocks DNA damage repair [2,7]
- Reactivating glucocorticoid receptor signaling in presence of dexamethasone[8-10]

XPO1, Exportin 1.

**1.** Hanahan D, et al. Cell. 2000;100(1):57-70. **2.** Sun Q, et al. Signal Transduct Target Ther. 2016;1:16010. **3.** Gandhi UH, et al. Clin Lymphoma Myeloma Leuk. 2018;18(5):335-345. **4.** Noske A, et al. Cancer. 2008;112(8):1733-1743. **5.** Shen A, et al. Neurosurgery. 2009;65(1):153-159. **6.** Huang W, et al. Clin Invest Med. 2009;32(6):E315. **7.** Wang AY, Liu H. Stem Cell Investig. 2019;6:6. **8.** Chen CI, et al. Blood. 2014;124(21):4773. **9.** Kashyap T, et al. Blood. 2015;126(23):3683. **10.** Argueta C, et al. Oncotarget. 2018;9(39):25529-25544.

tgen® AN AFFILIATE OF City of Hope.

# BOSTON: phase 3, global, randomized, open label, controlled study in patients with multiple myeloma who had received 1-3 prior therapies




The XVd regimen requires approximately **40% less bortezomib** than Vd which entails **37% fewer clinic visits** over the first 6 months of treatment

DoR, duration of response; IRC, independent review committee; PN, peripheral neuropathy; TTNT, time to next treatment; X, Selinexor.

tgen AN AFFILIATE OF City of Hope

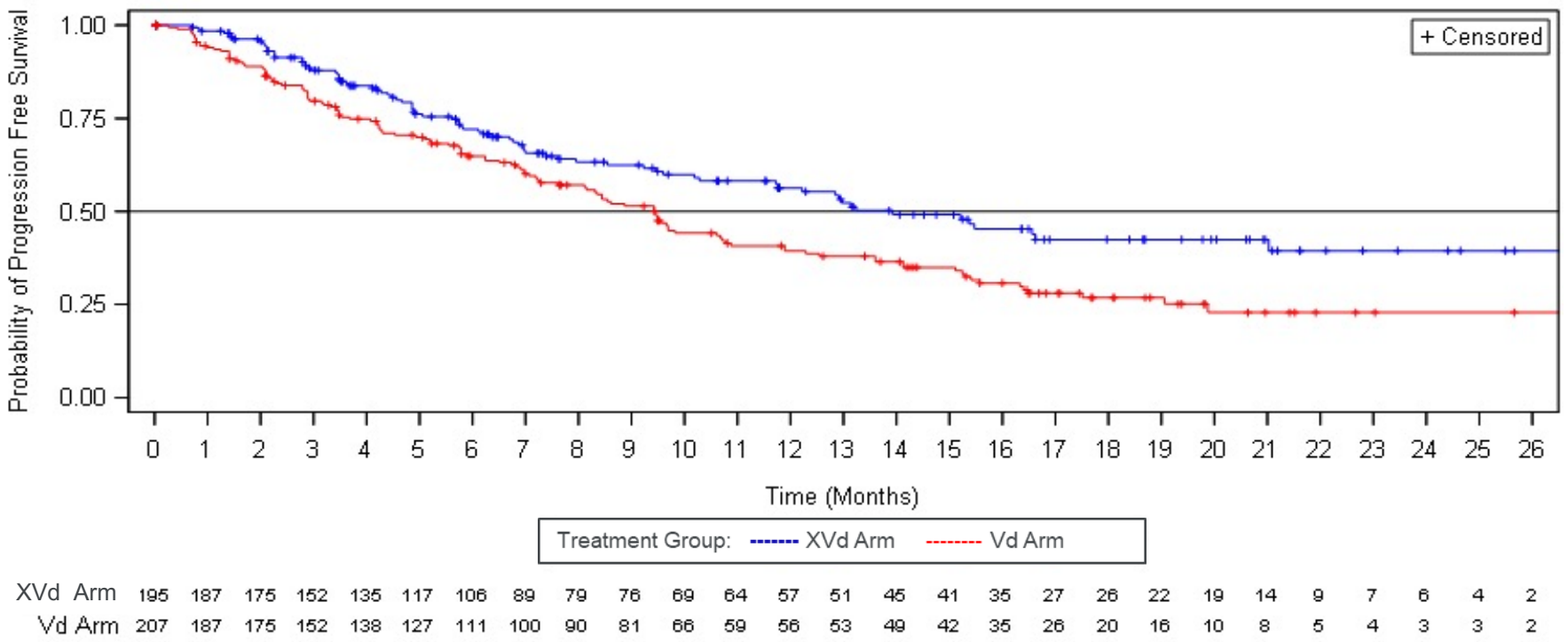
Grosicki S, et al. *Lancet*. 2020;396:1563-1573

INTERNATIONAL MYELOMA FOUNDATION

# BOSTON
# Primary endpoint – PFS with XVd vs Vd

| | XVd (n=195) | Vd (n=207) |
|---|---|---|
| **Median PFS, mos (95% CI)** | **13.93 (11.73, NE)** | **9.46 (8.11, 10.78)** |

HR=0.7020 (95% CI: 0.5279, 0.9335); one-sided *P*=0.0075




**This data represents:**

1. **An increase of 4.47 months in median PFS**
2. **A 30% reduction in the risk of disease progression or death**

Note – 50% of patients in the intervention had HIGH RISK cytogenetics

Grosicki S, et al. *Lancet*. 2020;396:1563-1573; Karyopharm Therapeutics Inc. Data on file.

tgen AN AFFILIATE OF City of Hope

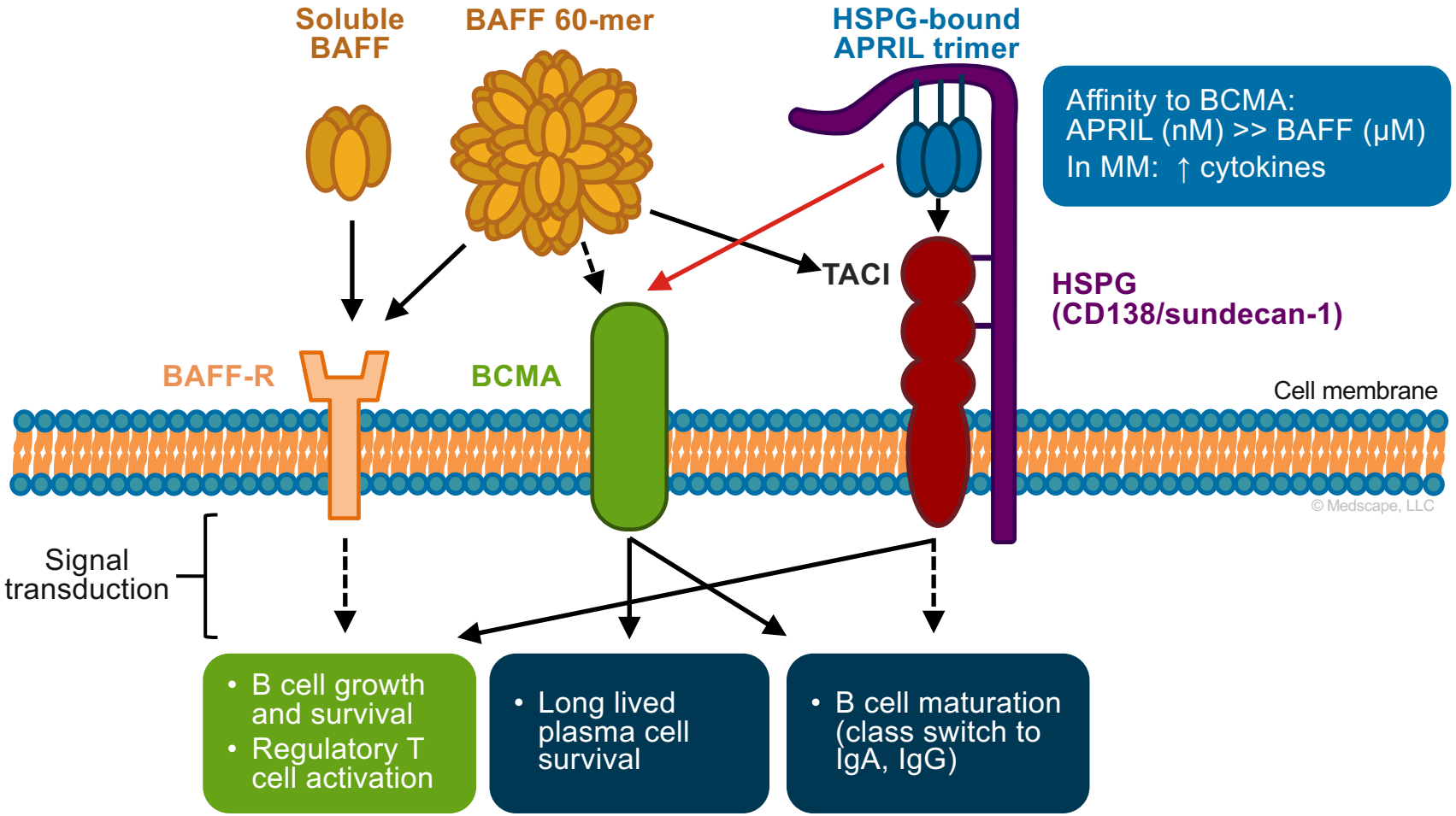
INTERNATIONAL MYELOMA FOUNDATION

# My Take on BOSTON

- PLUS
  - First phase 3 trial to properly use weekly bortezomib
  - Provides another option for lenalidomide refractory disease
  - Selinexor is much better tolerated in weekly dosing
  - 50% of patients had HIGH RISK disease
  - Now combining Selinexor with Carfilzomib and Daratumumab!
- MINUS
  - Bortezomib, even weekly, is not an ideal relapse partner
    - Limited by neurotoxicity, usually seen prior and not most potent PI

PS. Don't dismiss selinexor due to toxicity – it can work well but has to be administered carefully, with 2 anti-nauseants, especially in the first month

# BCMA-targeted therapy
## *MOA*

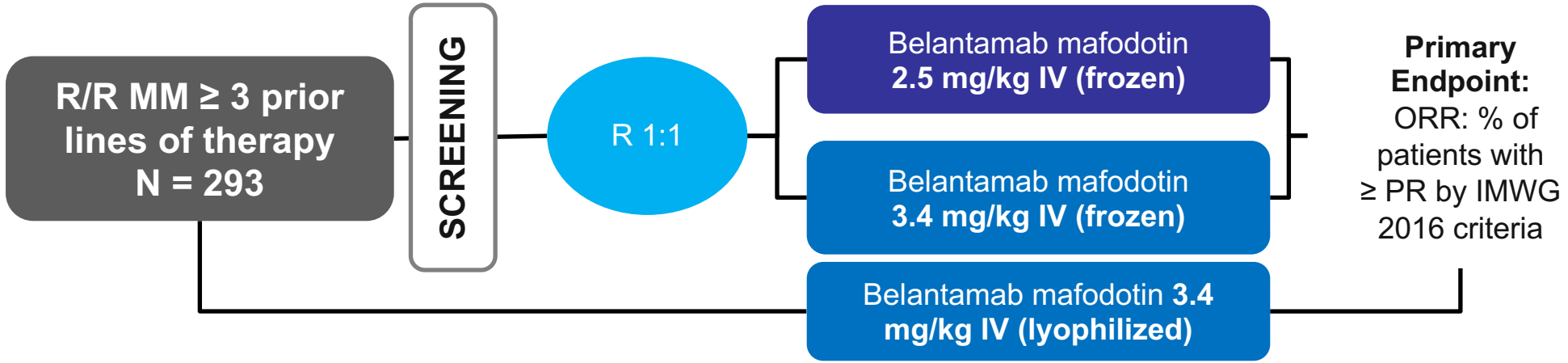



BAFF, B-cell activation factor; BCMA, B-cell maturation antigen; HSPG, heparin sulfate proteoglycan; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor.

Tai Y-T, et al. *Immunotherapy.* 2015;7:1187–1199.

# Belantamab mafodotin
## *DREAMM-2 trial study design*

- Belantamab mafodotin
  - ADC: Anti-BCMA mAb conjugated to auristatin F through a non-cleavable linker




Belantamab mafodotin administered once every 3 weeks until disease progression or unacceptable toxicity

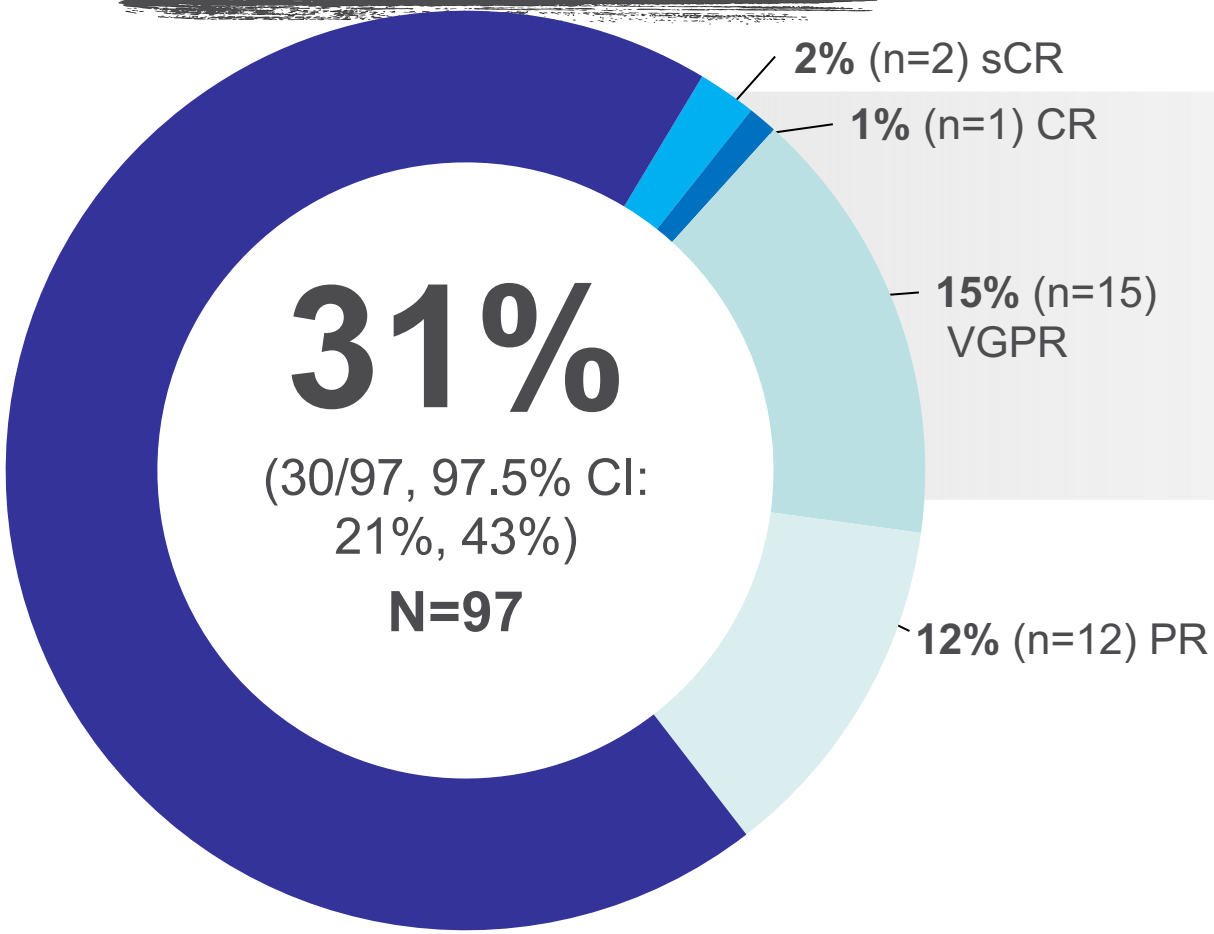
Belantamab mafodotin-blmf (2.5 mg/kg): FDA accelerated approval on August 5, 2020 for R/R MM after ≥ 4 prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an immunomodulatory agent

ADC, antibody-drug conjugate

Lonial S, et al. *Lancet Oncol.* 2020;21:207-221;
https://www.fda.gov/drugs/drug-approvals-and-databases/fda-granted-accelerated-approval-belantamab-mafodotin-blmf-multiple-myeloma FDA.gov

# DREAMM-2 efficacy results

## Overall Response Rate[1]




**60% of responding patients (n=18/30) had a very good partial response or better[1]**

Lonial S, et al. *Lancet Oncol.* 2020;21:207-221

# DREAMM-2
## *Safety overview*

| Number of Patients With Event (Safety Population), n (%) | Belantamab Mafodotin 2.5 mg/kg (n = 95) | | | Belantamab Mafodotin 3.4 mg/kg (n = 99) | | |
|---|---|---|---|---|---|---|
| | Grade 1/2 | Grade 3 | Grade 4 | Grade 1/2 | Grade 3 | Grade 4 |
| **Keratopathy or corneal epithelium changes** | 41 (43) | 26 (27) | 0 | 53 (54) | 20 (20) | 1 (1) |
| Thrombocytopenia | 14 (15) | 8 (8) | 11 (12) | 24 (24) | 11 (11) | 22 (22) |
| Anemia | 4 (4) | 19 (20) | 0 | 12 (12) | 22 (22) | 3 (3) |
| Nausea | 23 (24) | 0 | 0 | 31 (31) | 1 (1) | 0 |
| Pyrexia | 18 (19) | 2 (2) | 1 (1) | 21 (21) | 4 (4) | 0 |
| **Blurred vision** | 17 (18) | 4 (4) | 0 | 28 (28) | 2 (2) | 0 |
| Infusion-related reactions | 17 (18) | 3 (3) | 0 | 15 (15) | 1 (1) | 0 |
| Increased aspartate aminotransferase | 17 (18) | 2 (2) | 0 | 18 (18) | 6 (6) | 0 |
| Fatigue | 13 (14) | 2 (2) | 0 | 21 (21) | 5 (5) | 0 |
| **Dry eye** | 12 (13) | 1 (1) | 0 | 23 (23) | 0 | 0 |
| Neutropenia | 4 (4) | 5 (5) | 4 (4) | 12 (12) | 12 (12) | 3 (3) |



Lonial S, et al. *Lancet Oncol.* 2020;21:207-221

# Belantamab mafodotin-blmf
## *Ocular toxicity warning*

- Changes in the corneal epithelium resulting in changes in vision including severe vision loss and corneal ulcer, and symptoms, such as blurred vision and dry eyes
- Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms
  - Withhold until improvement and resume, or permanently discontinue, based on severity
- Available only through REMS program
  - Prescribers must be certified with the program by enrolling and completing training
  - Prescribers must counsel patients about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose
  - Patients must be enrolled in the REMS program and comply with monitoring
  - Healthcare facilities must be certified with the program and verify that patients are authorized
  - Wholesalers and distributers must only distribute to certified healthcare facilities

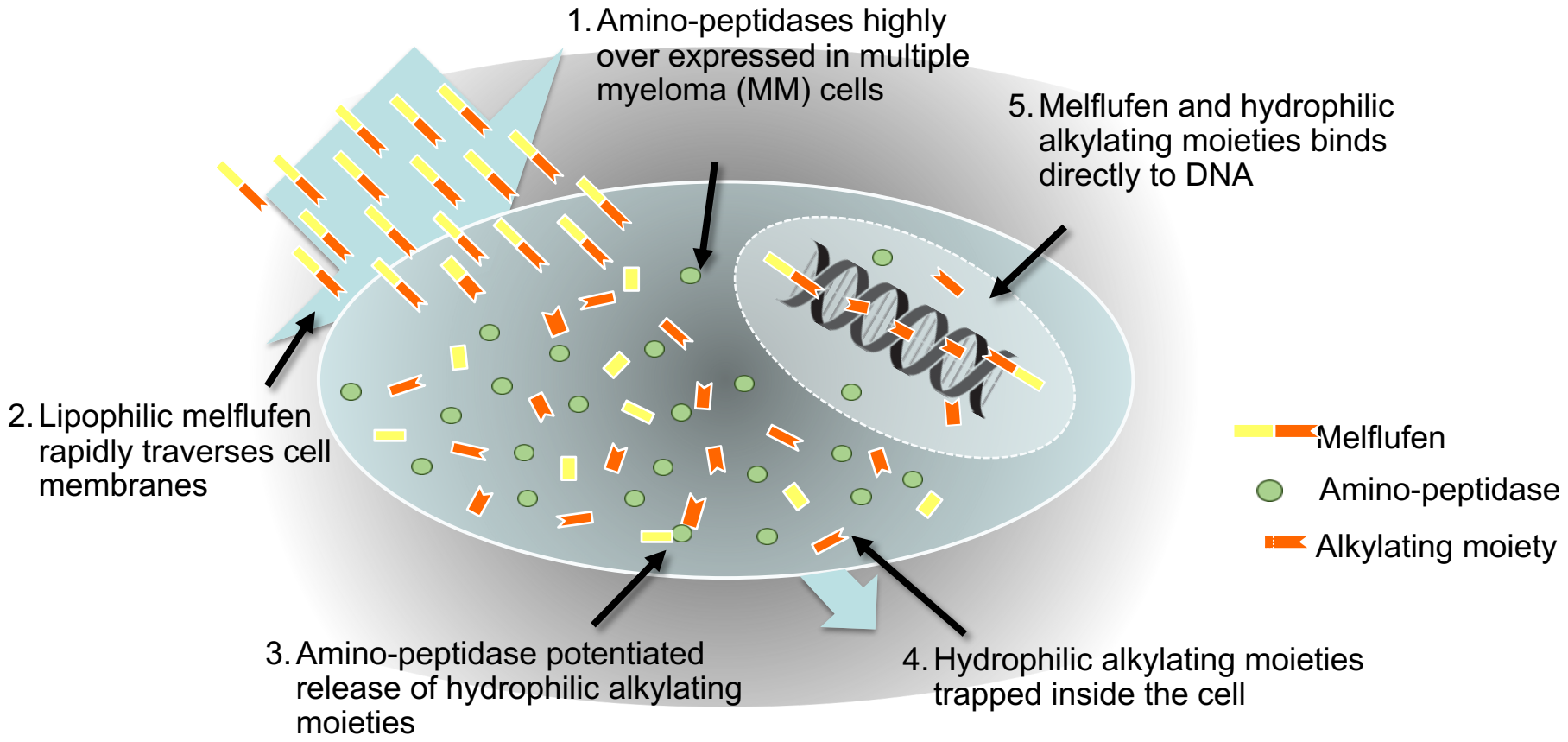


BLENREP (belantamab mafodotin-blmf) PI 2020.

# My take – belantamab mafodotin

- The first BCMA directed therapy in MM
- Impressive response rates
- Corneal toxicity remains a significant issue, however
  - REMS program in the US/risk management plan in Europe – must see eye specialist before EACH dose!
  - Possible dose adjustment in the future
- Will be important to see it combined with other agents
- Very accessible to community centers (no risk of CRS)
- Now being combined with MULTIPLE other MM agents

# Melphalan flufenamide (Melflufen) is a peptidase enhanced therapy with an alkylating payload




1. Chauhan D, et al. *Clin Cancer Res*. 2013;19:3019; 2. Wickström M, et al. *Invest New Drugs*. 2008;26:195; 3. Ray A, et al. *Br J Haematol*. 2016;174:397; 4. Strese S, et al. *Biochem Pharmacol*. 2013;86:888; 5. Wickström M, et al. *Oncotarget*. 2017;8:66641.

tgen AN AFFILIATE OF City of Hope

INTERNATIONAL MYELOMA FOUNDATION

# Key findings of the HORIZON study of melflufen/Dex – subset of 97 patients with 4 prior lines AND refractory to at least one PI, IMID and CD38 mAb

- Baseline – median 6 prior lines, 70% prior ASCT and 75% refractory to alkylation
- Response rate 23.7% with median DOR 4.2 months
- PFS 3.8 months, OS 9.1 months
- In EMD the ORR was 15%

- Key points
  - Very heavily pretreated with median 6 prior lines (Indication mandates 4 prior LINES)
  - Hematologic toxicities are main adverse events
  - Must be given with a central line
  - Very attractive in light of less use of alkylation but also can overcome resistance

EMD, extramedullary disease

# OCEAN: Melflufen/dexamethasone vs pomalidomide/dexamethasone in RRMM

## Updated results of the phase 3 OCEAN study (NCT03151811)

Trial met its primary end point of superior progression-free survival (PFS) with melflufen vs the pomalidomide combination as assessed by independent review committee (IRC; HR, 0.792; 95% CI, 0.640-0.979; P = .0311)

Key secondary end point of the trial, overall survival (OS), favored the control arm (HR, 1.104; 95% CI, 0.846-1.441)

## FDA alerts patients and health care professionals about clinical trial results showing an increased risk of death associated with melphalan flufenamide - CDER Alert (July 28, 2021)

**ISSUE:** FDA is alerting patients and health care professionals that a clinical trial (OCEAN, Study OP-103) evaluating melphalan flufenamide with dexamethasone to treat patients with multiple myeloma showed an increased risk of death.

The trial compared melphalan flufenamide with low-dose dexamethasone to pomalidomide with low-dose dexamethasone in patients with relapsed or refractory (resistant) multiple myeloma following 2-4 lines of prior therapy and in patients who were resistant to lenalidomide in the last line of therapy.

**RECOMMENDATIONS:**

- FDA encourages health care professionals to review patients' progress on melphalan flufenamide and discuss the risks of continued administration with each patient in the context of other treatments.
- Patients currently receiving melphalan flufenamide should also discuss with their health care professional the risks and benefits of receiving melphalan flufenamide.

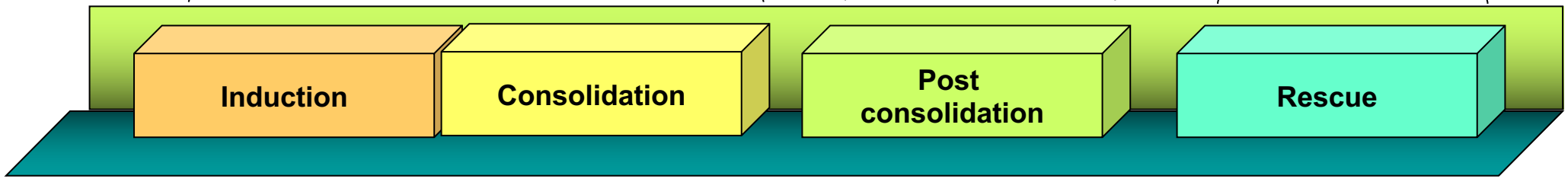
tgen® AN AFFILIATE OF City of Hope.

INTERNATIONAL MYELOMA FOUNDATION

# The Evolution of Myeloma Therapy

**Now**

| Induction | Consolidation | Post consolidation | Rescue |
|---|---|---|---|
| VD | SCT | Nothing | Bortezomib |
| Len/Dex | Tandem ASCT (?) | Thalidomide? | Lenalidomide |
| CyBorD | | Bortezomib | Carfilzomib |
| VTD | | Ixazomib | Pomalidomide |
| VRD | | Lenalidomide | Selinexor |
| KRD | | Combinations | Panobinostat |
| D-VMP | | | Daratumumab |
| DRD | | | Ixazomib |
| | | | Elotuzumab |
| | | | Isatuximab |
| | | | Belantamab mafodotin |
| | | | Melphalan flufenamide |
| | | | Idecabtagene autoleucel |
| Front line treatment | | Maintenance | Relapsed |




**New**

| Induction | Consolidation | Post consolidation | Rescue |
|---|---|---|---|
| D-VRD | "more" induction? | Daratumumab? | CAR T-Cell Therapy |
| Isa-VRD | | Carfilzomib? | Bispecific/Trispecific Antibodies |
| D-KRD | | Lenalidomide + PI | Cell Modifying Agents |
| Isa-VRD | | | Venetoclax? |
| | | | PD-1/PDL-1 Inhibition? |
| | | | Multiple small molecules |
| | | | ++++++++ |

ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; Cy, cyclophosphamide; d- daratumumab; D/dex, dexamethasone; isa, isatuximab; K, carfilzomib; M, melphalan; PD-L1, programmed death ligand-1; PI, proteasome inhibitor; Rev, lenalidomide; V, bortezomib

tgen AN AFFILIATE OF City of Hope

INTERNATIONAL MYELOMA FOUNDATION

# Case

- 68-year-old woman with p53 deletion kappa light chain myeloma
- Has 10-year history of myeloma including
  - CyBorD then ASCT, maintenance lenalidomide
  - KPD at relapse
  - Aggressive relapse with EMD and p53 deletion treated with DPACE then second ASCT
  - Next relapse treated with DPD
  - Selinexor monotherapy for 10 months with VGPR
  - Belantamab mafodotin for 6 months with PR, treatment delays due to keratopathy
  - Progressive disease with extensive marrow and EMD involvement
  - Starting cycle 2 melphalan flufenamide (MR after cycle 1)