
*Pellegrino Musto*

*Direzione Scientifica*
*IRCCS, Centro di Riferimento Oncologico di Basilicata,*
*Rionero in Vulture (Pz)*

# Immunoterapia nel Mieloma Multiplo oggi: gli Anticorpi Monoclonali

# IL MIELOMA MULTIPLO

**RESPONSABILI SCIENTIFICI**
Marco Gobbi
Mario Petrini

**VIAREGGIO**
**29 marzo 2017**
GRAND HOTEL ROYAL

# My Agenda

- The complex network of anti-myeloma immunity vs myeloma escape
- MoAbs in multiple myeloma: general overview
- Daratumumab: mechanism(s) of action, updated results (ASCO/ASH 2016) and new studies
- Elotuzumab: mechanism(s) of action, updated results (ASCO/ASH 2016) and new studies
- Other MoAbs: immune check-point modulators
- How immunotherapy with MoAbs could modify end-points of multiple myeloma treatment

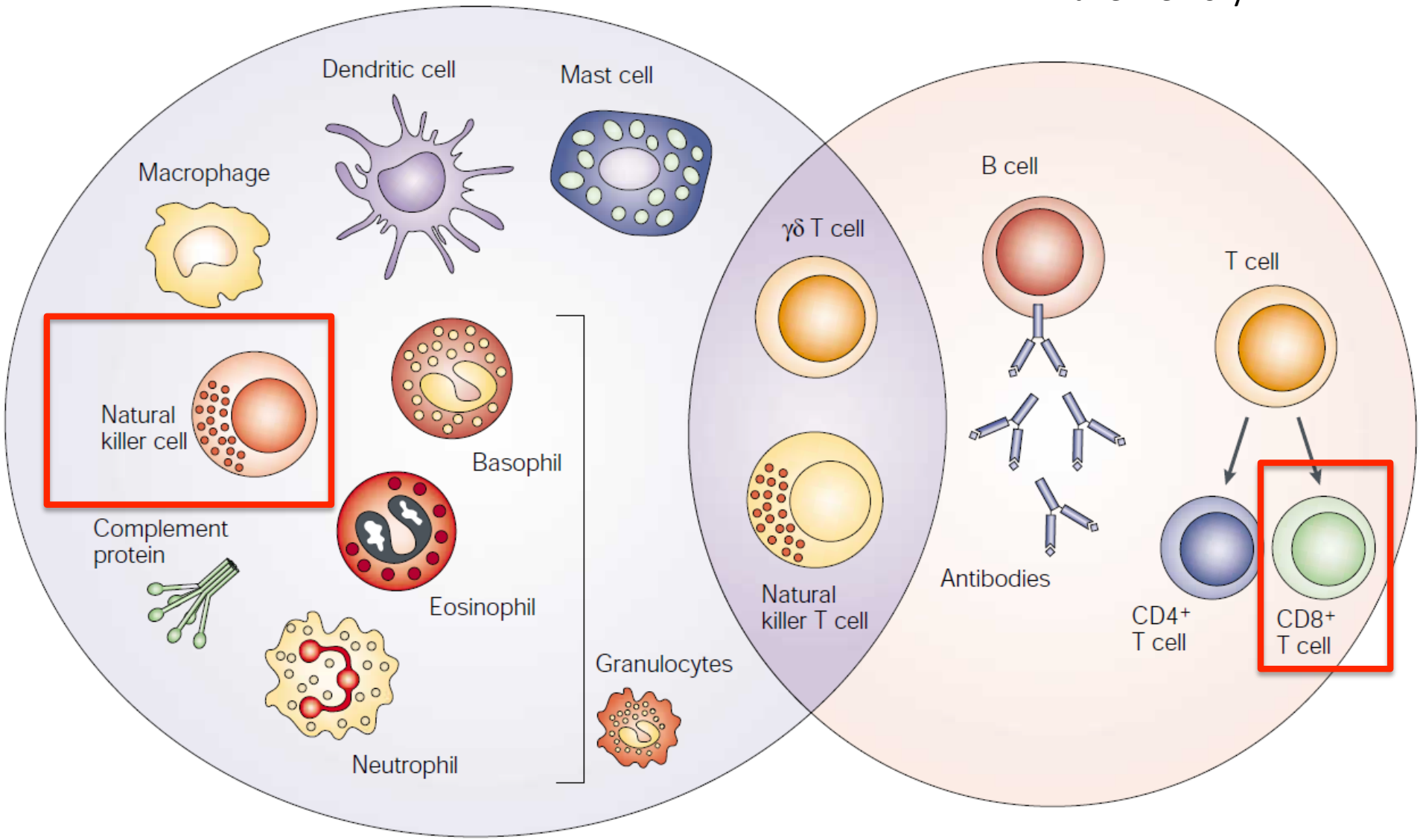
# My Agenda

- **The complex network of anti-myeloma immunity vs myeloma escape**
- MoAbs in multiple myeloma: general overview
- Daratumumab: mechanism(s) of action, updated results (ASCO/ASH 2016) and new studies
- Elotuzumab: mechanism(s) of action, updated results (ASCO/ASH 2016) and new studies
- Other MoAbs: immune check-point modulators
- How immunotherapy with MoAbs could modify end-points of multiple myeloma treatment

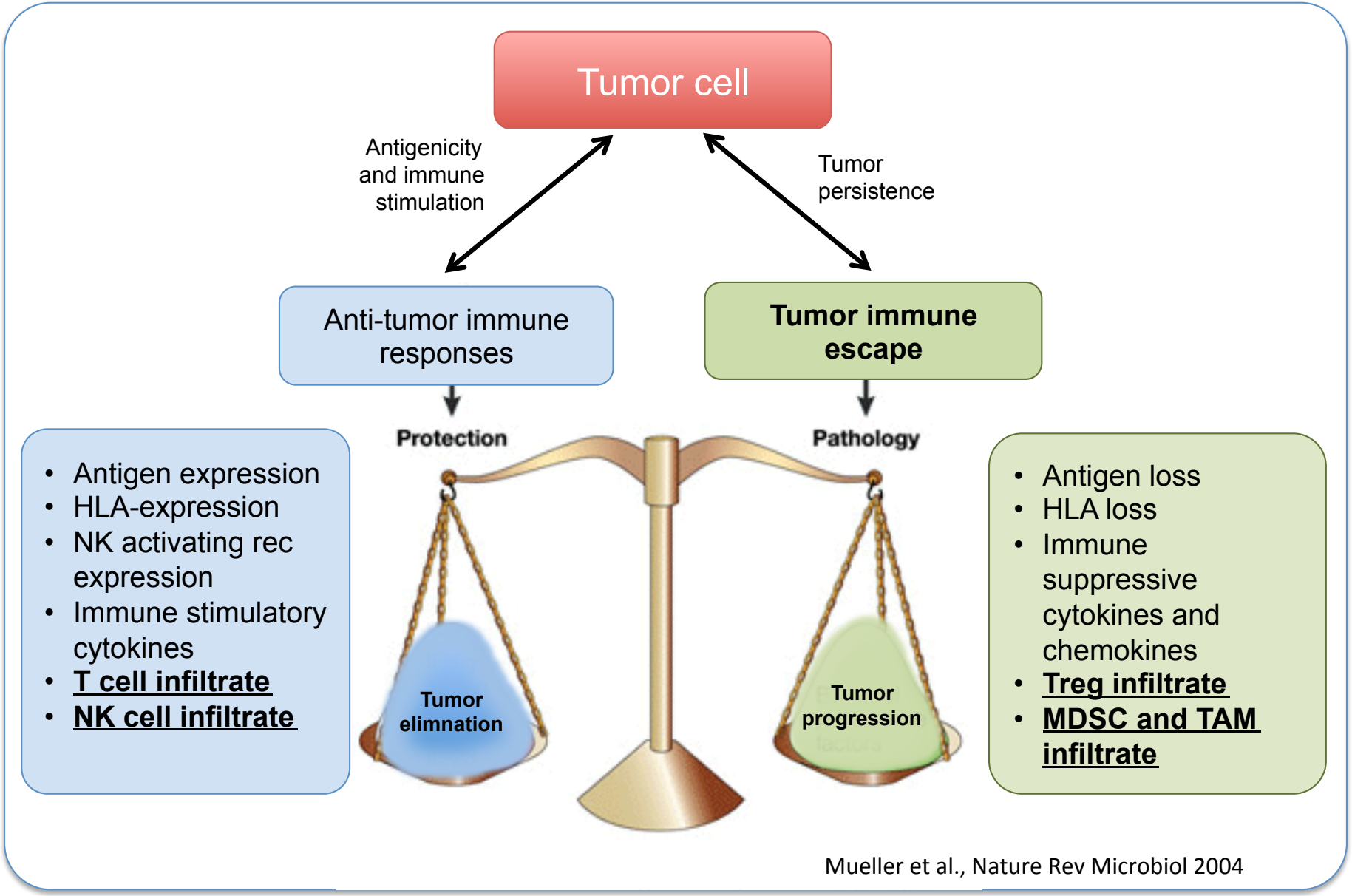
# The complex network of anti-tumor immunity

**INNATE IMMUNITY**
Ready and rapid response

**ADAPTIVE IMMUNITY**
Slow response
Priming required
Immune memory

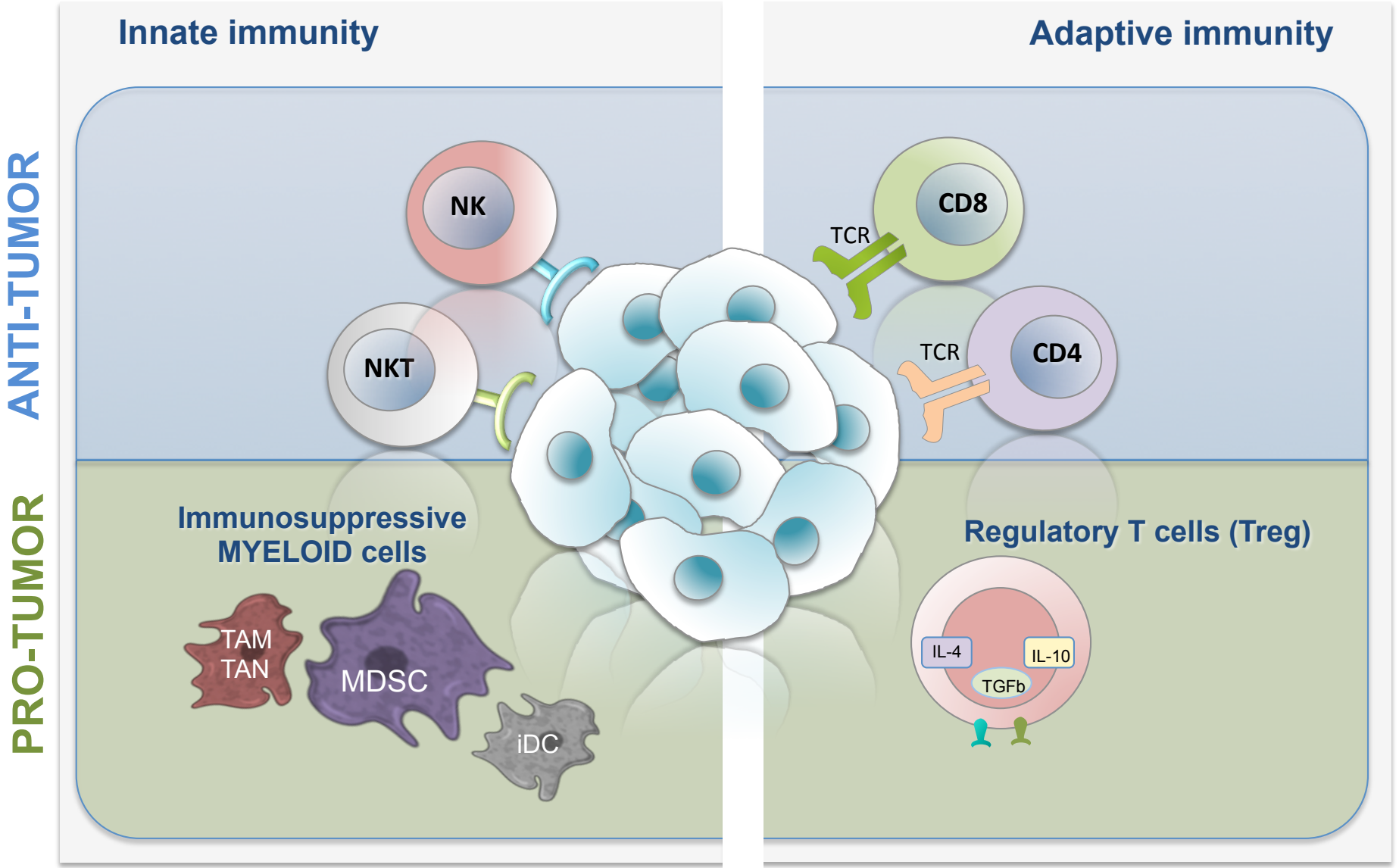


# Immune escape leads to tumor persistence




Treg: T-regulatory lymphocytes; MDSC: myeloid derived suppressive cells; TAM: tumor infiltrating macrophages

# Tumor immunity: the key players

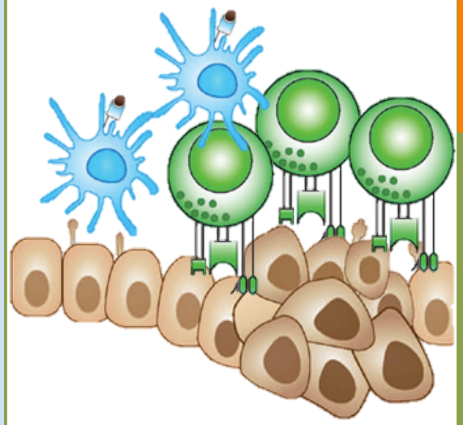


# Diverse *immune signatures* of tumor microenvironment

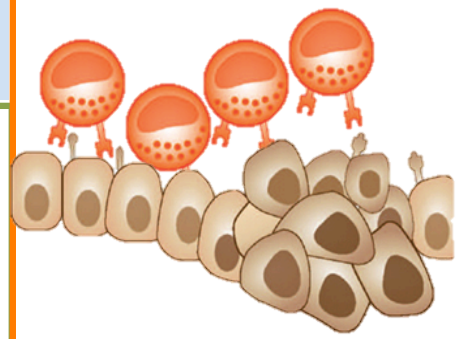
## Immune response
(anti-tumor effectors)

- **Antigen strenght**
- **HLA-expression**
- **CXCR9, 10 chemokines**

### Prevalent T cells



### Prevalent NK cells

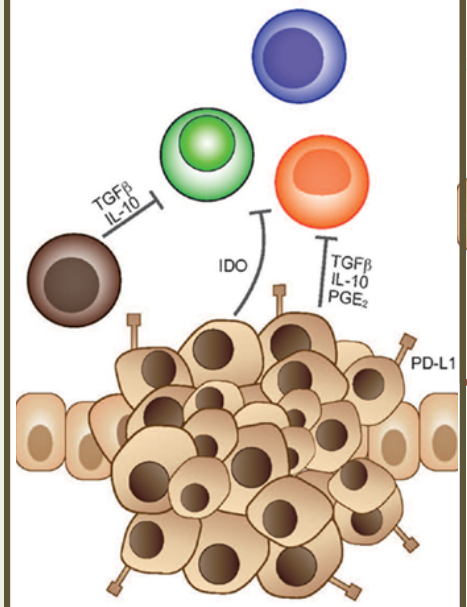


- **HLA loss**
- **IL-12, IL-15**
- **CCL3, CCL4**

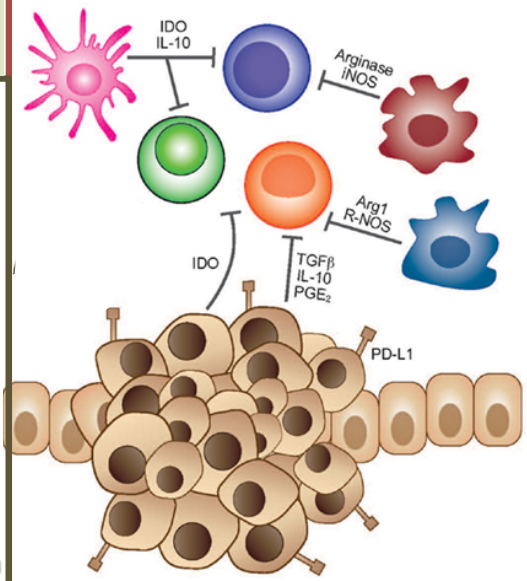
## Immune escape
(pro-tumor immune suppressive cells)

- **T cell response**
- **High TCR affinity**
- **Acute inflammatory factors**

### Prevalent Treg cells




### Prevalent myeloid cells



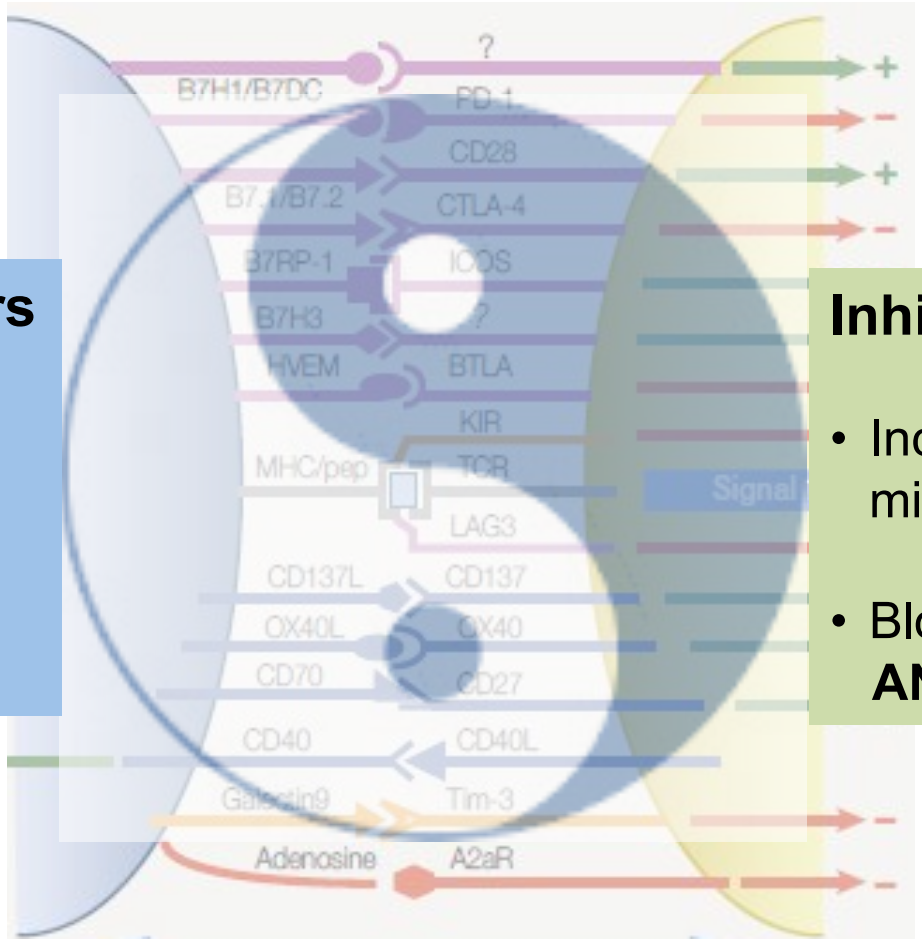

- **Wound-healing factors**
- **G-CSF, GM-CSF, M-CSF**

Chen et al., Cancer Discovery 2016

# Immune cells are regulated by a balance between activatory and inhibitory signals

**Activatory receptors**

- Decreased in tumor microenvironment
- Inducible by **AGONIST drugs**




**Inhibitory receptors**

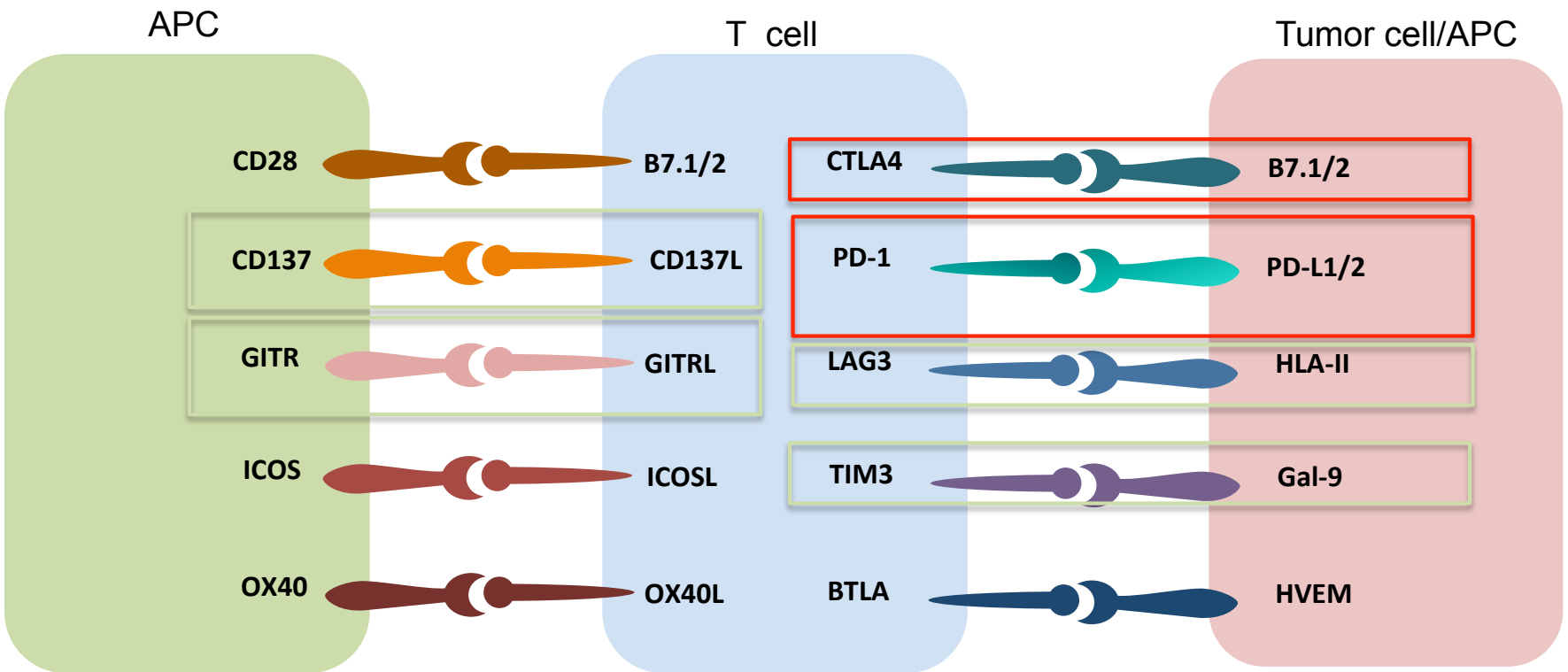
- Increased in tumor microenvironment
- Blockable by **ANTAGONIST drugs**

# T cell function is finely tuned by modulating receptors

**Activatory**

- CD70
- GITR
- ICOS
- CD137
- OX40

- **Inhibitory**
  - **PD-1**
  - **CTLA4**
  - Tim3
  - LAG3
  - BTLA



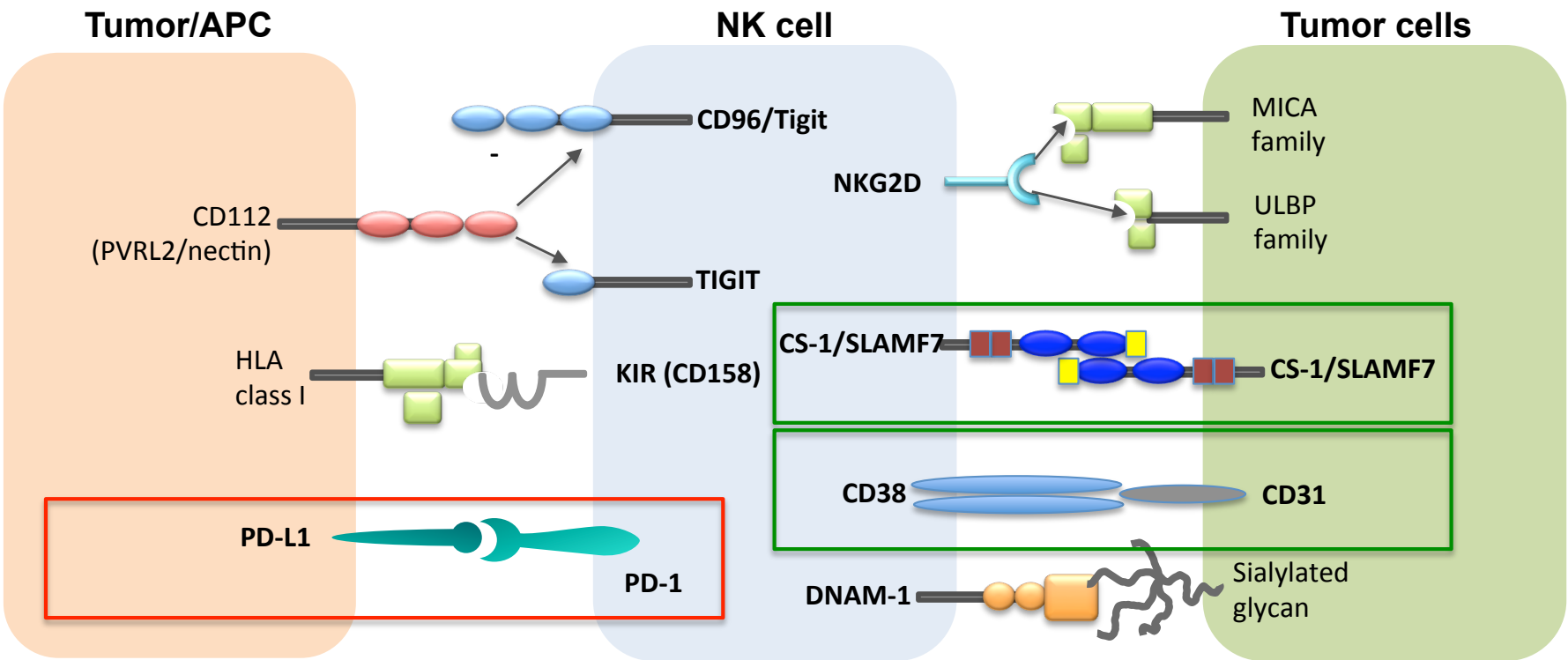
# NK cell receptors that can be targeted by modulating mAbs

**Inhibitory**

- KIRs
- CD96/TIGIT
- **PD1/PDL1**

**Activatory**

- NKG2D
- **SLAMF7, CD38**
- DNAM-1
- CD137



REVIEW ARTICLE

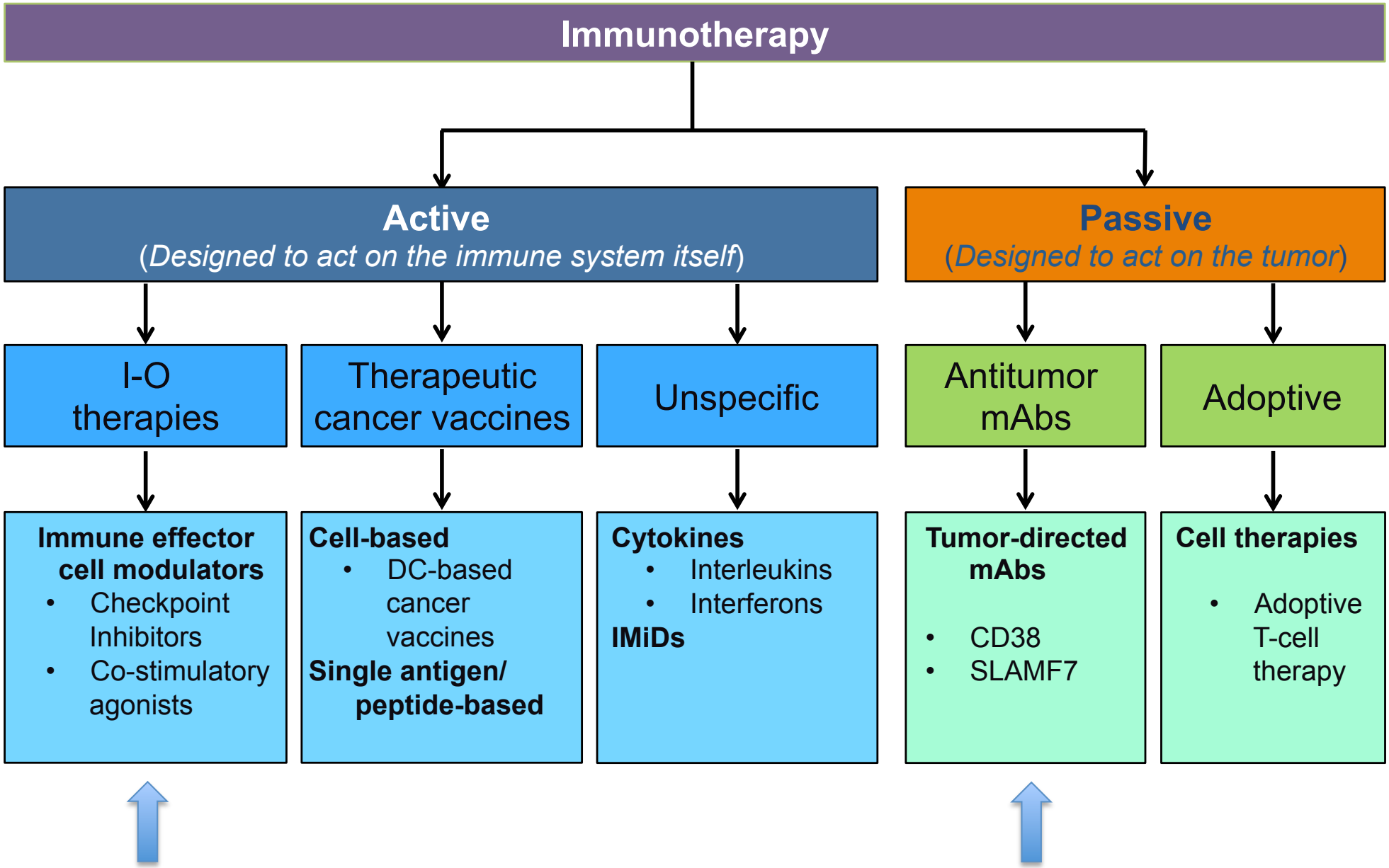
# Is immunotherapy here to stay in multiple myeloma?

Paula Rodríguez-Otero,[1] Bruno Paiva,[1] Monika Engelhardt,[2] Felipe Prósper[1] and Jesús F. San Miguel[1]

EUROPEAN HEMATOLOGY ASSOCIATION
Ferrata Storti Foundation
**Haematologica** 2017
Volume 102(3):423-432


**Figure 3. There are four major targets for cancer immunotherapy.** 1. Direct target of surface tumor antigens with monoclonal antibodies; 2. Boost immune effector using adoptive cell therapy; 3. Improve immunity against tumors with vaccines; 4. Overcome immune suppression with checkpoint blockade. IMiDs: immunomodulatory drugs; inh: inhibitor.

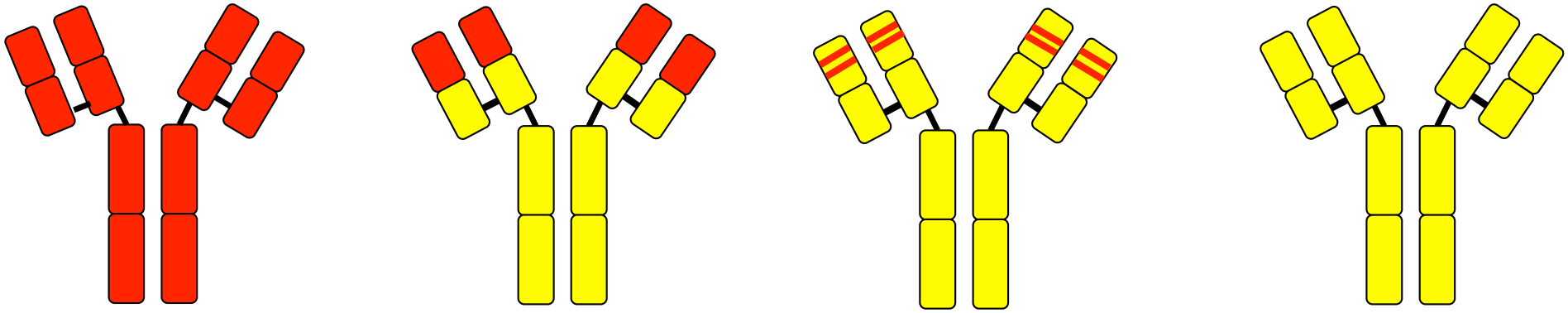
# Immunotherapies under investigation for Multiple Myeloma



# My Agenda

- The complex network of anti-myeloma immunity vs myeloma escape
- **MoAbs in multiple myeloma: general overview**
- Daratumumab: mechanism(s) of action, updated results (ASCO/ASH 2016) and new studies
- Elotuzumab: mechanism(s) of action, updated results (ASCO/ASH 2016) and new studies
- Other MoAbs: immune check-point modulators
- How immunotherapy with MoAbs could modify end-points of multiple myeloma treatment

# Structures of antibodies and their Humanization to overcome immunogenicity

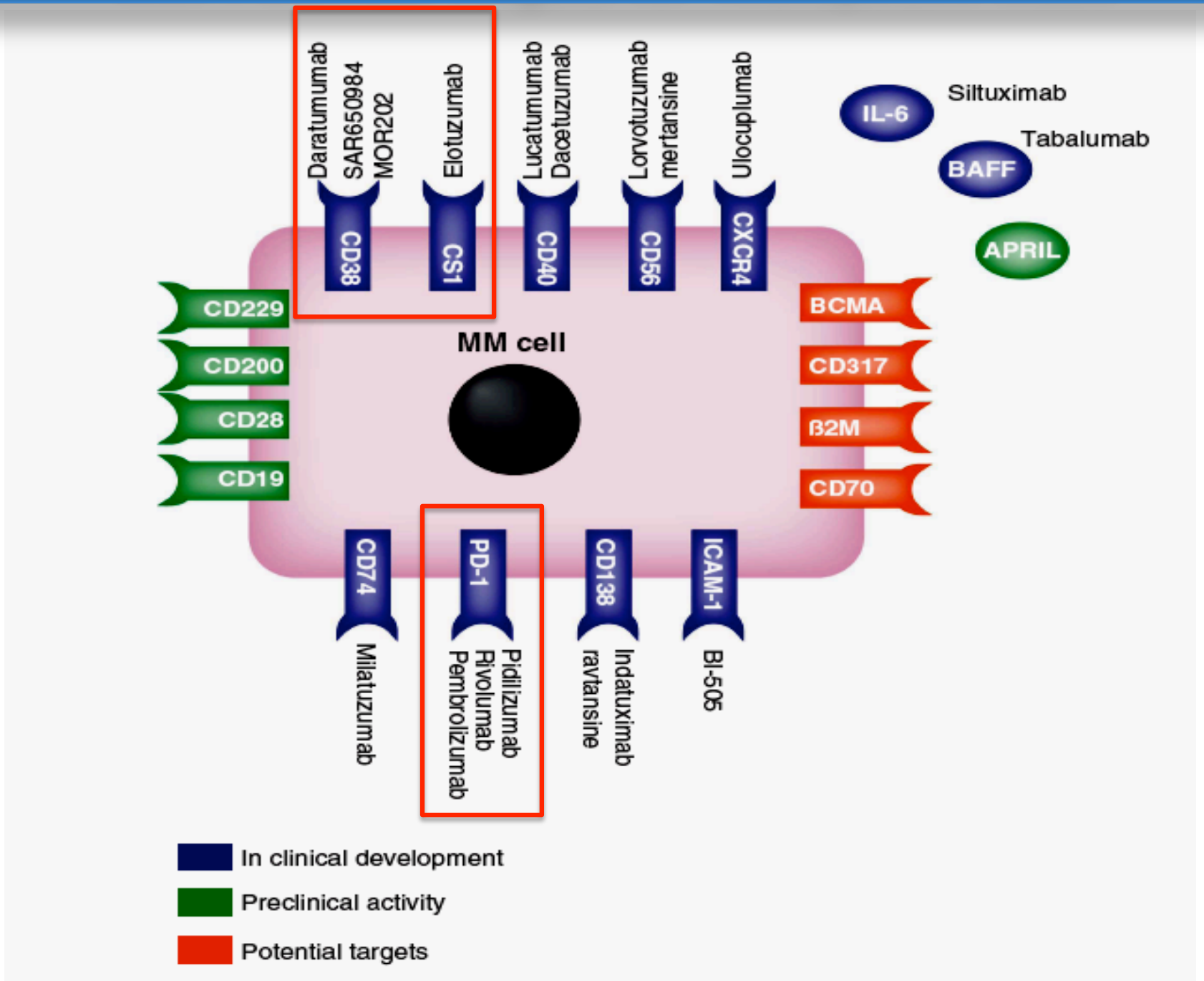


| Mouse | Chimeric | Humanized | Human |
|---|---|---|---|
| **'momab'** = fully murine<br><br>(Tositumomab) | **'ximab'** = chimeric mouse or rat Ig variable regions; human constant regions<br><br>(Rituximab Isatuximab) | **'zumab'** = humanized chimeric mAb with only complementarity determining regions being mouse origin<br><br>(Bevacizumab Elotuzumab) | **'umab'** = fully human<br><br>(Daratumumab MOR 202) |

\+ Immunogenicity -

Adapted from Imai & Takaoka. Nature Reviews Cancer 2006; 6: 714-727

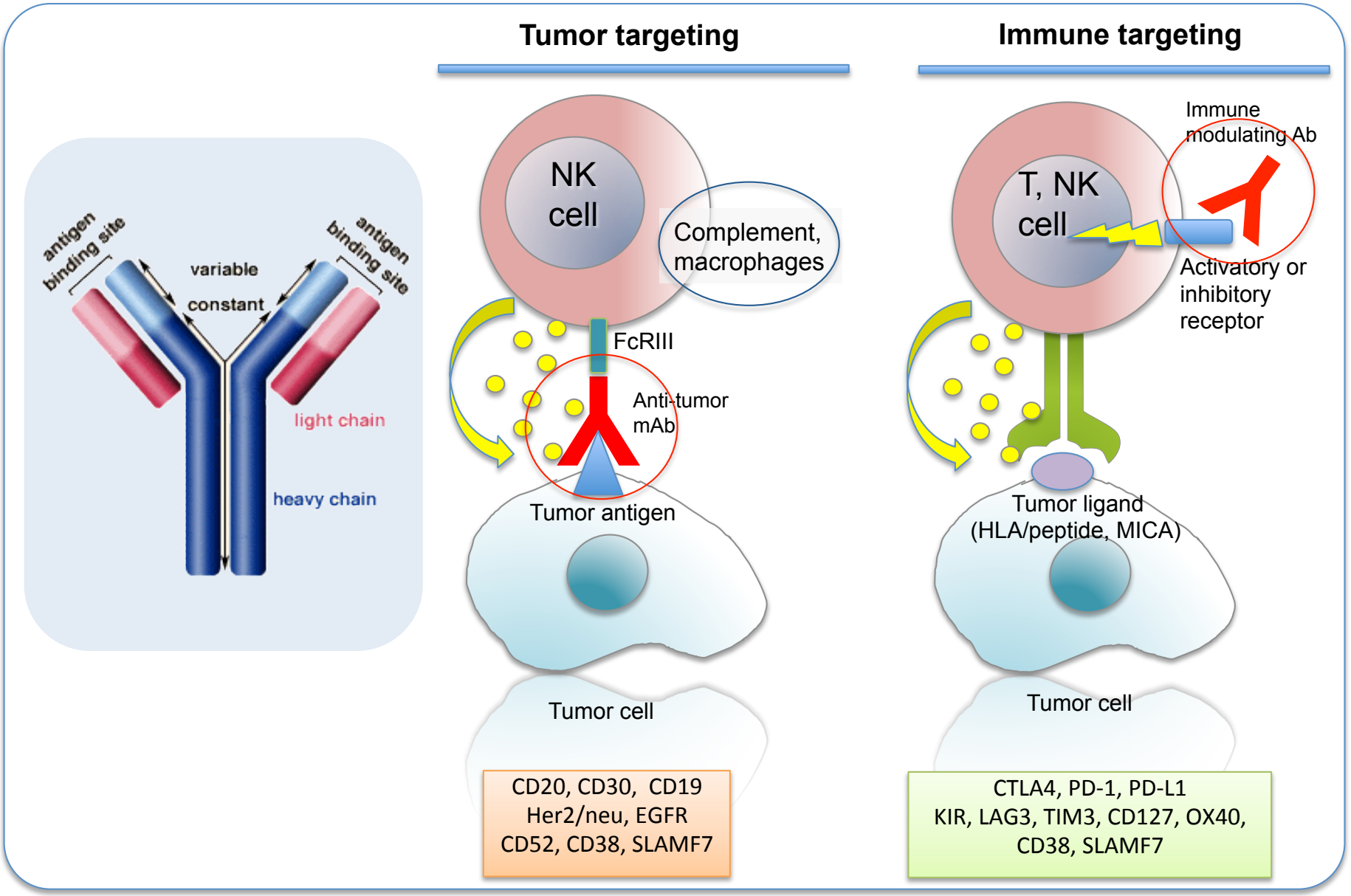
# MM: Potential Targets for Therapeutic Mabs



# Anticorpi monoclonali nel Mieloma Multiplo

| Bersaglio | mAb | | | Stadio dello sviluppo |
|---|---|---|---|---|
| **Molecole di superficie** | | | | |
| SLAMF7 (CS1) [(Signaling Lymphocytic Activation Molecule Family 7 (Cell Surface 1)] | Elotuzumab | approvato da FDA & EMA | Umanizzato | Fase 1/2/3 |
| CD38 (Cluster of Differentiation 38) | Daratumumab<br>Isatuximab (SAR650984)<br>MOR202 | approvato da FDA & EMA | Totalmente umano<br>Chimerico<br>Totalmente umano | Fase 1/2/3/4<br>Fase 1/2<br>Fase 1/2 |
| CD138 (Cluster of Differentiation 138) | Indatuximab ravtansine (BT062) | | | Fase 1/2 |
| BCMA (B-Cell Maturation Antigen ) | J6M0-mcMMAF (GSK2857916) | | | Fase 1 |
| **Molecole segnale** | | | | |
| IL-6 (Interleukin-6) | Siltuximab | | | Fase 2 |
| RANKL (RANK Ligand) | Denosumab | | | Fase 3 |
| VEGF (Vascular Endothelial Growth Factor) | Bevacizumab | | | Fase 2 |
| DKK1 (Dickkopf 1) | BHQ880 | | | Fase 2 |
| **Inibitori del checkpoint immunitario** | | | | |
| PD-1 (Programmed Cell Death-1) | Pembrolizumab<br>Nivolumab<br>Pidilizumab | | | Fase 1/2/3<br>Fase 1/2<br>Fase 1/2 |
| PD-L1 (Programmed Cell Death-Ligand 1) | Durvalumab | | | Fase 1 |
| CTLA4 (Cytotoxic T-Lymphocyte Antigen 4) | Ipilimumab | | | Fase 1/2 |
| KIR (Killer Inhibiting Receptor) | Lirilumab | | | Fase 1 |

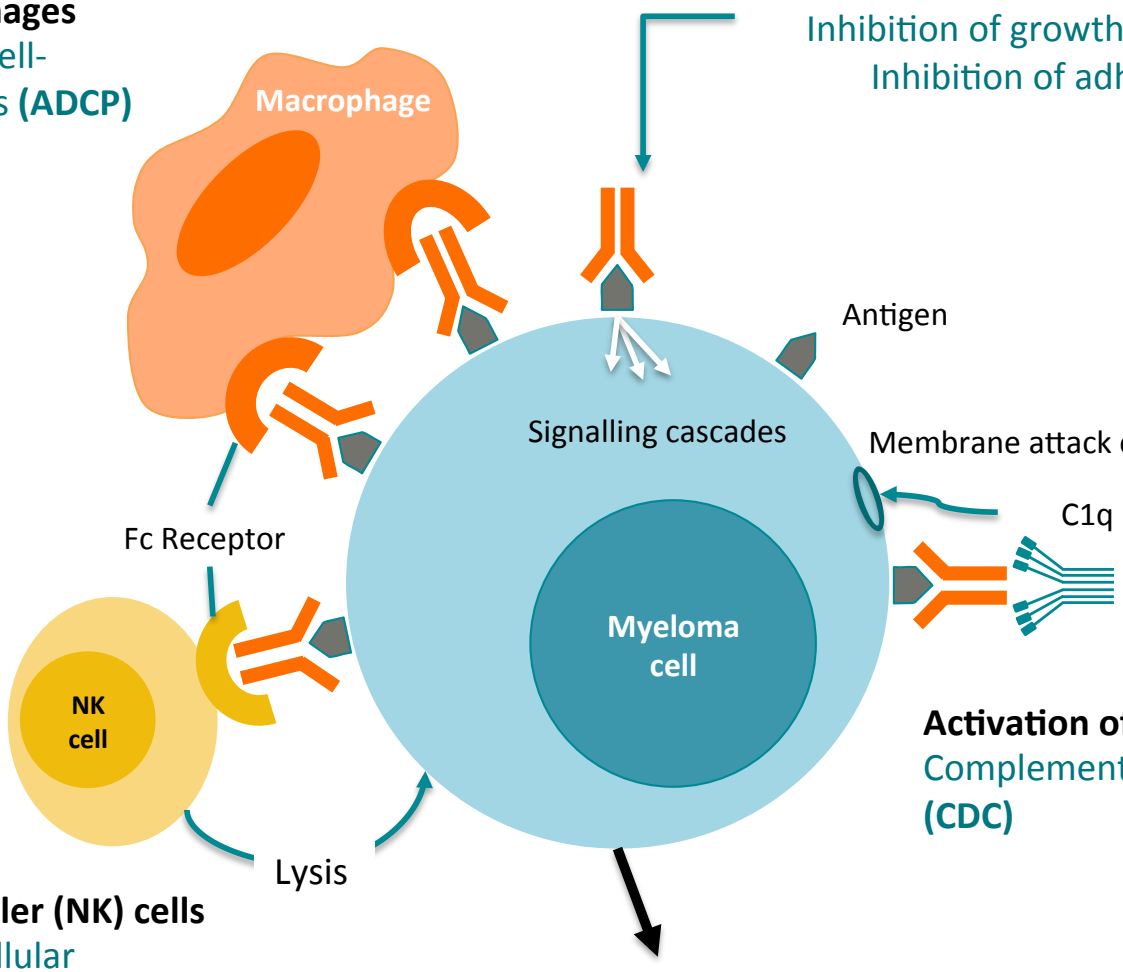
# ImmunOncology: mAbs as immune modulators



# Monoclonal antibodies act through different modes of action in MM

**Direct effects**
Alterations in intracellular signalling
Inhibition of growth factor receptor function
Inhibition of adhesion molecule function

**Activation of macrophages**
Antibody-dependent cell-mediated phagocytosis **(ADCP)**




**Activation of the complement system**
Complement-dependent cytotoxicity **(CDC)**

**Activation of natural killer (NK) cells**
Antibody-dependent cellular cytotoxicity **(ADCC)**

van de Donk NW et al. Blood 2016;127:681-95

**Table 2.** Anti SLAMF7 monoclonal antibody: clinical trials in MM

| *Study* | *Phase* | n | *Design* | *Population* | *Key message* |
|---|---|---|---|---|---|
| Zonder *et al.*[73] | 1 | 34 | Elotuzumab monotherapy<br>Dose escalation | Relapsed/refractory<br>Prior therapies (median) = 4 | First in human<br>No MTD identified<br>No objective responses |
| Lonial *et al.*[74] | 1 | 28 | Len – Dex plus elotuzumab<br>Dose escalation for elotuzumab | Relapsed/refractory<br>Prior therapies (median) = 3 | No MTD identified<br>ORR = 82% |
| Jakubowiak *et al.*[77] | 1 | 28 | Bort – Dex plus elotuzumab<br>Dose escalation for elotuzumab | Relapsed/refractory<br>Prior therapies (median) = 2 | No MTD identified<br>ORR = 48% |
| Richardson *et al.*[75] | 2 random | 73 | Len – Dex plus elotuzumab<br>10 mg/kg vs 20 mg/kg | Relapsed/refractory<br>Prior therapies (median) = 2 | ORR = 84% |
| Jakubowiak *et al.*[78] | 2 random | 152 | Bort – Dex ± elotuzumab | Relapsed/refractory<br>Prior therapies (median) = 1 | Similar response rate in the 2 arms<br>Elotuxumab/bortezomib/dexamethasone resulted in better mPFS : 9.7 vs 6.9 months |
| Lonial *et al.*[76]<br>*Eloquent 2* | 3 | 646 | Len – Dex ± elotuzumab | Relapsed/refractory<br>Prior therapies (median) = 2 | Elotuxumab/lenalidomide/dexamethasone resulted in:<br>better ORR : 79 vs 66%<br>better PFS : 19,4 vs 14,9 months<br>similar toxicity (except grade 1/2 IRR in 10% of patients) |

Abbreviations: Bort, bortezomib; Len, lenalidomide; IRR, infusion related reactions; MTD, maximal tolerated dose; ORR, overall response rate; PFS, progression-free survival.

**Table 4.** Anti CD38 monoclonal antibody: clinical trials in MM

| *Study* | *Phase* | n | *Design* | *Population* | *Key message* |
|---|---|---|---|---|---|
| Lokhorst *et al.*[84]<br>*GEN501* | 1–2 | 104 | Daratumumab monotherapy<br>Dose escalation | Relapsed/refractory<br>Prior therapies (median) = 4<br>Dual refractory = 64% | No MTD identified<br>For the 16 mg/kg cohort : ORR = 36% and mPFS = 5.6 months |
| Lonial *et al.*[85]<br>*SIRIUS* | 2 | 106 | Daratumumab monotherapy<br>16 mg/kg IV, weekly for 8 weeks, every 2 weeks for 16 weeks and then monthly | Relapsed/refractory<br>Prior therapies (median) = 5<br>Dual refractory = 82% | At the dose of 16 mg/kg:<br>ORR = 29.2%<br>median duration of response = 7.4 months<br>mPFS = 3.7 months |
| Palumbo *et al.*[86]<br>*CASTOR* | 3 | 498 | Bortezomib–Dexamethasone ± Daratumumab | Relapsed/refractory<br>Prior therapies (median) = 2 | Addition of daratumumab significantly improved ORR (83 vs 63%), CR rate (19 vs 9%) and mPFS (61% reduction in risk of progression) |
| Dimopoulos *et al.*[87]<br>*POLLUX* | 3 | 569 | Lenalidomide–Dexamethasone ± Daratumumab | Relapsed/refractory<br>Prior therapies (median) = 1 | Addition of daratumumab significantly improved ORR (93 vs 76%), CR rate (43 vs 19%) and mPFS (63% reduction in risk of progression) |

Abbreviations: CR, complete response; MTD, maximal tolerated dose; mPFS, median progression-free survival; ORR, overall response rate.

**Touzeau et al, Leukemia 2017**

**Table 1.** Ongoing clinical trials with anti-PD-1 mAbs in multiple myeloma.

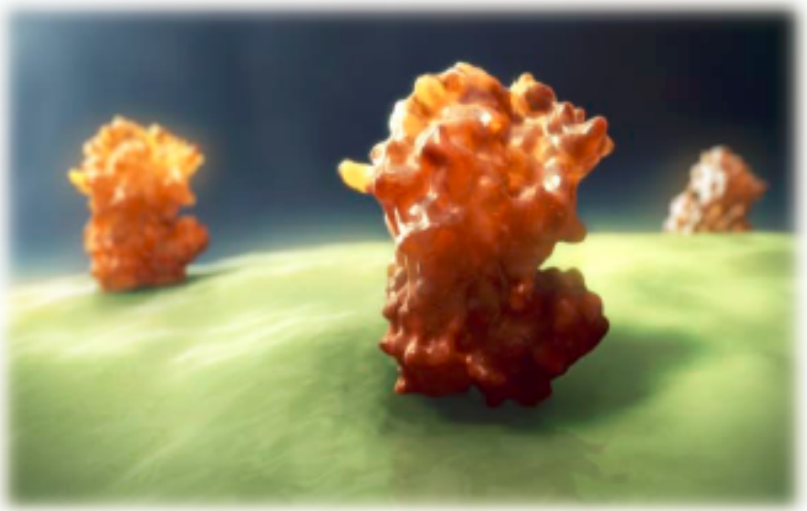
| Title | Experimental arm | Active comparator | Condition | Estimated enrollment | Identifier |
|---|---|---|---|---|---|
| Pembrolizumab | | | | | |
| Study of pembrolizumab (MK-3475) in combination with dinaciclib* (MK-7965) in hematologic malignancies (MK-3475–155)(KEYNOTE-155) | Pembrolizumab and Dinaciclib | x | relapsed or refractory multiple myeloma (among others) | Active recruitment 138 pat. | NCT02684617 Phase 1 |
| A trial of pembrolizumab (MK-3475)in participants with blood cancers (MK-3475–013)(KEYNOTE-013) | Pembrolizumab | x | relapsed or refractory multiple myeloma | Active recruitment 222 pat. | NCT01953692 Phase 1 |
| A study of pembrolizumab (MK-3475) in combination with standard of care treatments in participants with multiple myeloma (MK-3475–023/KEYNOTE-023) | Pembrolizumab+Lenalidomide+Dexamethasone Pembrolizumab+Carfilzomib+Dexamethasone | x | relapsed or refractory multiple myeloma | Active recruitment 85 pat. | NCT02036502 Phase 1 |
| ACP-196¶ in combination with pembrolizumab, for treatment of hematologic malignancies (KEYNOTE145) | ACP-196 +Pembrolizumab | x | Multiple Myeloma (among others) | Active recruitment 324 pat. | NCT02362035 Phase 1/2 |
| Anti-PD-1 (MK-3475) and IMiD (Pomalidomide) combination i mmunotherapy in relapsed/refractory multiple myeloma | Pembrolizumab+Pomalidomide +Dexamethasone | x | Relapsed or refractory multiple myeloma | Active recruitment 48 pat. | NCT02289222 Phase 1/2 |
| Pembrolizumab (MK-3475) in MM patients with residual disease | Pembrolizumab | x | Residual disease of MM | Active recruitment 20 pat. | NCT02636010 Phase 2 |
| Phase 2 multi-center study of anti-PD-1 during lymphopenic state after HDT/ASCT for multiple myeloma | HDM → ASCT → Pembrolizumab+Lenalidomide | x | Multiple myeloma of any stage | Active recruitment 50 pat. | NCT02331368 Phase 2 |
| Phase 2 multi-center study of anti-PD-1 during lymphopenic state after HDT/ASCT for multiple myeloma | HDM → ASCT → Lenalidomid+Pembrolizumab | x | Multiple myeloma of any stage | Active recruitment 50 pat. | NCT02331368 Phase 2 |
| Study of pomalidomide and low dose dexamethasone with or without pembrolizumab (MK-3475) in refractory or relapsed and refractory multiple myeloma (rrMM) (MK-3475–183/KEYNOTE-183) | Pembrolizumab+ Pomalidomide+ Dexamethasone | Pomalidomide+ Dexamethasone | ≥ 2 lines of treatment (including IMID and PI) | Active recruitmen t 300 pat. | NCT02576977 Phase 3 |
| Study of lenalidomide and dexamethasone with or without pembrolizumab (MK-3475) in participants with newly diagnosed treatment naive multiple myeloma (MK-3475–185/KEYNOTE-185) | Pembrolizumab+ Lenalidomide+ Dexamethasone | Lenalidomide+ Dexamethasone | Newly diagnosed multiple myeloma, patients ineligible for ASCT | Active recruitment 640 pat. | NCT02579863 Phase 3 |
| Pembrolizumab for smoldering multiple myeloma (SMM) | Pembrolizumab | x | Smolderi ng multiple myeloma | Not yet recruiting 16 pat. | NCT02603887 Phase NA |
| Pidilizumab | | | | | |
| Lenalidomide and pidilizumab in treating patients with relapsed or refractory multiple myeloma | Pidilizumab+Lenalidomide | x | Relapsed or refractory multiple myeloma | Active recruitment 53 pat. | NCT02077959Phase 1/2 |
| Nivolumab | | | | | |
| Ipilimumab‖ or nivolumab in treating patients with relapsed hematologic malignancies after donor stem cell transplant | Nivolumab Ipilimumab | x | Relapsed or refractory multiple myeloma (among others) | Active recruitment 113 pat. | NCT01822509 Phase 1 |
| Safety study of nivolumab by itself or in combination with ipilimumab or in combination with lirilumab† in patients with lymphoma and multiple myeloma | Nivolumab Nivolumab+Ipilimumab Nivolumab+Lirilumab | x | Relapsed or refractory multiple myeloma (among others) | Active recruitmen t 315 pat. | NCT01592370 Phase 1 |
| Study of combined check point inhibition after autologous haematopoietic stem cell transplantation in patients at high risk for post-transplant recurrence (CPIT001) | HDM → ASCT → Nivolumab+Ipilimumab | x | Newly diagnosed multiple myeloma, MM with stable disease (among others) | Not yet recruiting 42 pat. | NCT02681302 Phase 1/2 |
| Study of combinations of nivolumab, elotuzumab‡, pomalidomide and dexamethasone in multiple myeloma (CheckMate 602) | Nivolumab+Pomalidomide+Dexamethasone Nivolumab+Pomalidomide+ Elotuzumab+Dexamethasone | Pomalidomide+ Dexamethasone asone | Relapsed or refractory multiple myeloma | Active recruitment 406 pat. | NCT02726581 Phase 3 |

*Dinaciclib—inhibitor of cyclin-dependent kinases (CDKs)
¶APC-196—novel Bruton's tyrosine kinase inhibitor
‖Ipilimumab—anti-CTLA-4 mAb
†Lirilumab—the second-generation anti-KIR mAb
‡Elotuzumab—anti-CS1 mAb

# My Agenda

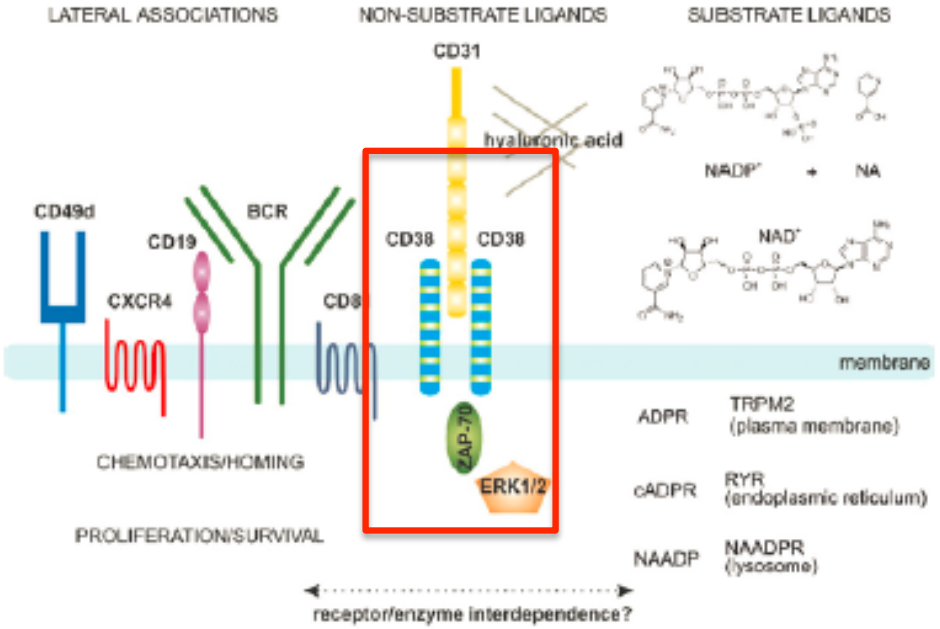
- The complex network of anti-myeloma immunity vs myeloma escape
- MoAbs in multiple myeloma: general overview
- **Daratumumab: mechanism(s) of action, updated results (ASCO/ASH 2016) and new studies**
- Elotuzumab: mechanism(s) of action, updated results (ASCO/ASH 2016) and new studies
- Other MoAbs: immune check-point modulators
- How immunotherapy with MoAbs could modify end-points of multiple myeloma treatment

# CD38, cell surface receptor and an ectoenzyme, is a rational therapeutic target for treatment of myeloma



- Type II transmembrane protein (m.w. ≈45 kDa)
- Highly and uniformly expressed on myeloma cells
  - CD38 present on CD4, CD8, NK cells and B lymphocytes at a relatively low level
  - Also some CD38 expression on tissues of non-hematopoietic origin

- CD38 has several intracellular functions
  1. Regulates signaling, homing and adhesion in close contact with BCR complex and CXCR4
  2. Regulates activation and proliferation of human T lymphocytes
  3. As an ectoenzyme, CD38 interacts with NAD+ and NADP+, which are converted to cADPR, ADPR, and NAADP in intracellular Ca2+-mobilization




Malavasi et al Blood 2011, 118:3470-3478

# CD38 Expression in Myeloma Cells and Other Lymphoid and non Lymphoid Tissues

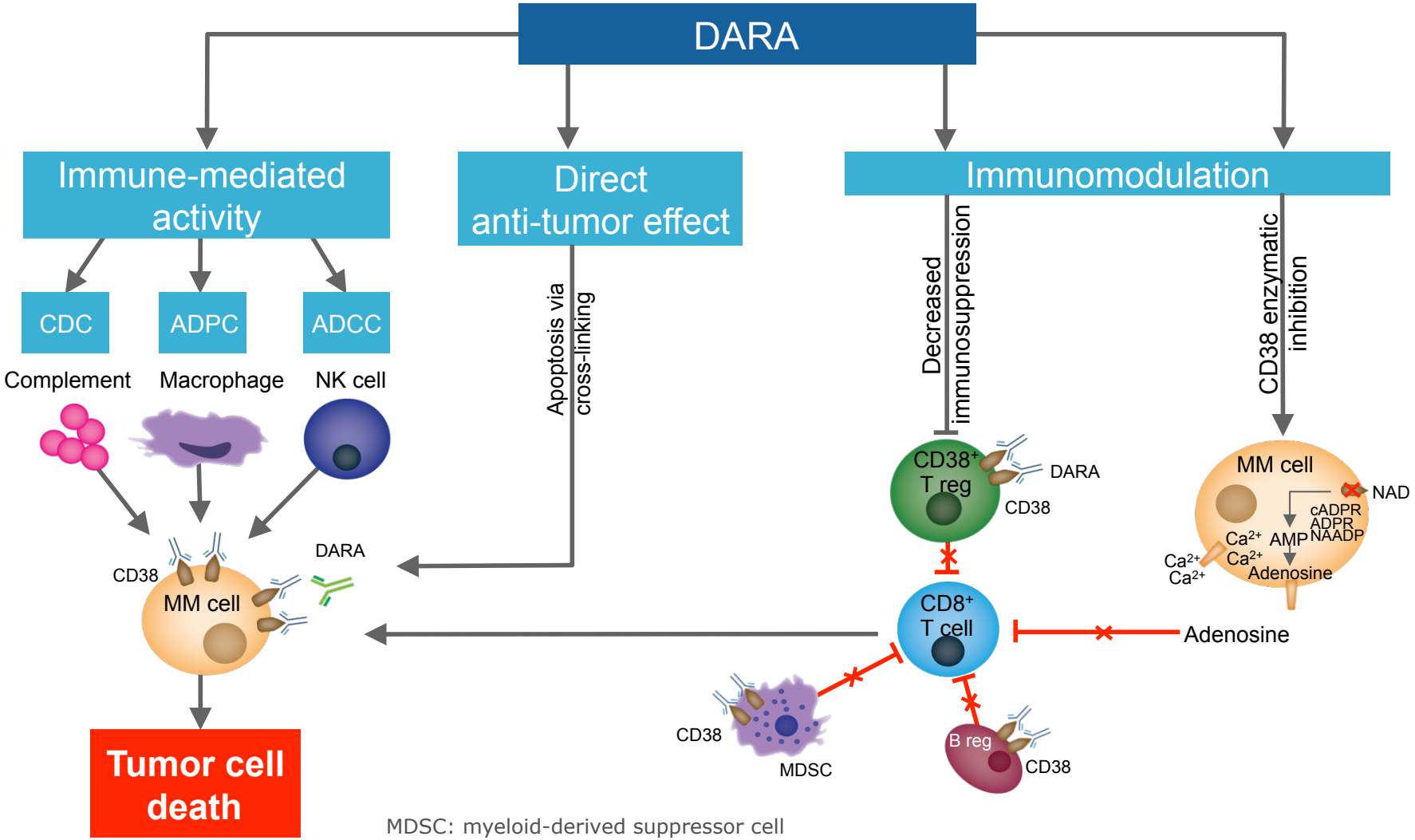
| Lymphoid tissue | Cell population |
|---|---|
| Blood | T cells (precursors, activated)<br>B cells (precursors, activated)<br>Myeloid cells (monocytes, macrophages, dendritic cells)<br>NK cells<br>Erythrocytes<br>Platelets |
| Cord blood | T and B lymphocytes, monocytes |
| Bone marrow | Precursors<br>Plasma cells |
| Thymus | Cortical thymocytes |
| Lymph nodes | Germinal center B cells |

| Non lymphoid tissues | Cell population |
|---|---|
| Bone | Osteoclasts |
| Brain | Purkinje and other cells |
| Eye | Cornea<br>Ganglion cells of the retina |
| Bowel | Intraepithelial and lamina propria lymphocytes |
| Pancreas | β cells |
| Muscles | Miocytes |
| Prostate | Epithelial cells |
| Kidney | Glomeruli |

- Marked quantitative differences in expression levels between normal cells and neoplastic cells (highly and uniformly expressed on myeloma cells) make CD38 an attractive target for immunotherapy treatment
- Relatively low expression on normal lymphoid and myeloid cells and in some tissues of non-hematopoietic origin
- CD38 is not expressed by pluripotent hemopoietic stem cells


1. Malavasi F, et al. *Physiol Rev*. 2008;88(3):841-886.
2. Lin P, et al. *Am J Clin Pathol*. 2004;121(4):482-488.
3. Santonocito AM, et al. *Leuk Res*. 2004;28(5):469-477.
4. Deaglio S, et al. *Leuk Res*. 2001;25(1):1-12.
5. Theilgaard-Monck, et al. *Bone Marrow Transplant 2003;32:1125-133;*
6. Terstappen, et al. *Blood 1991;77:1218-227.*

# Daratumumab: mechanism of action




MDSC: myeloid-derived suppressor cell

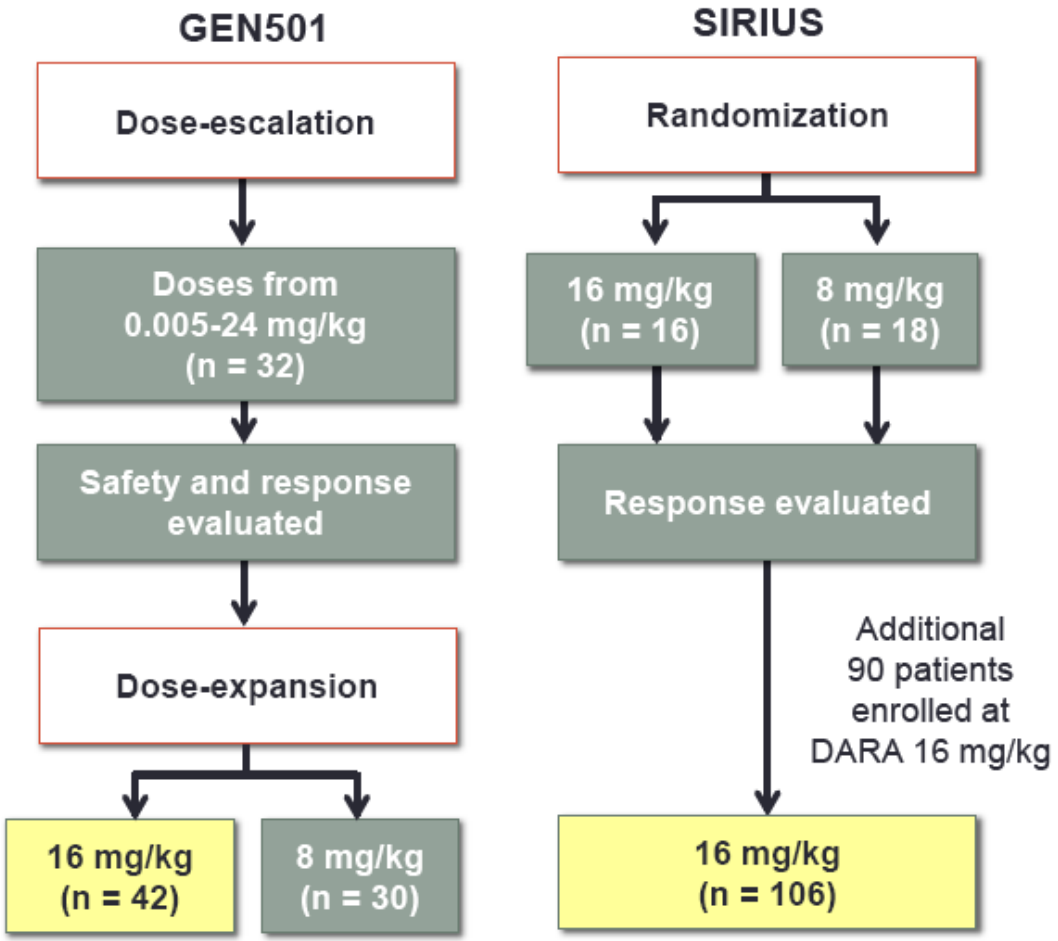
Usmani, SZ et al. Presented at ASH 2015 (Abstract 29), oral presentation

# Clinical Efficacy of Daratumumab Monotherapy in Patients with Heavily Pretreated Relapsed or Refractory Multiple Myeloma

Pooled analysis Studies GEN501 and MMY2002 (Sirius)

Median number of previous lines of therapy: 5 (2-14), including pomalidomide (55%) and carfilzomib (39%)

- ≥18 years of age, ECOG status ≤2[1,2]
- GEN501[1]
  - Open-label, multicenter, phase 1/2, dose-escalation and dose-expansion study
  - Relapsed from or refractory to ≥2 prior lines of therapy including PIs and IMiDs
- SIRIUS[2]
  - Open-label, multicenter, phase 2 study
  - Patients had received ≥3 prior lines of therapy, including a PI and an IMiD, or were double refractory to a PI and an IMID
- DARA was approved by the FDA on November 16, 2015, based on these studies




**16 mg/kg**
**N = 148**

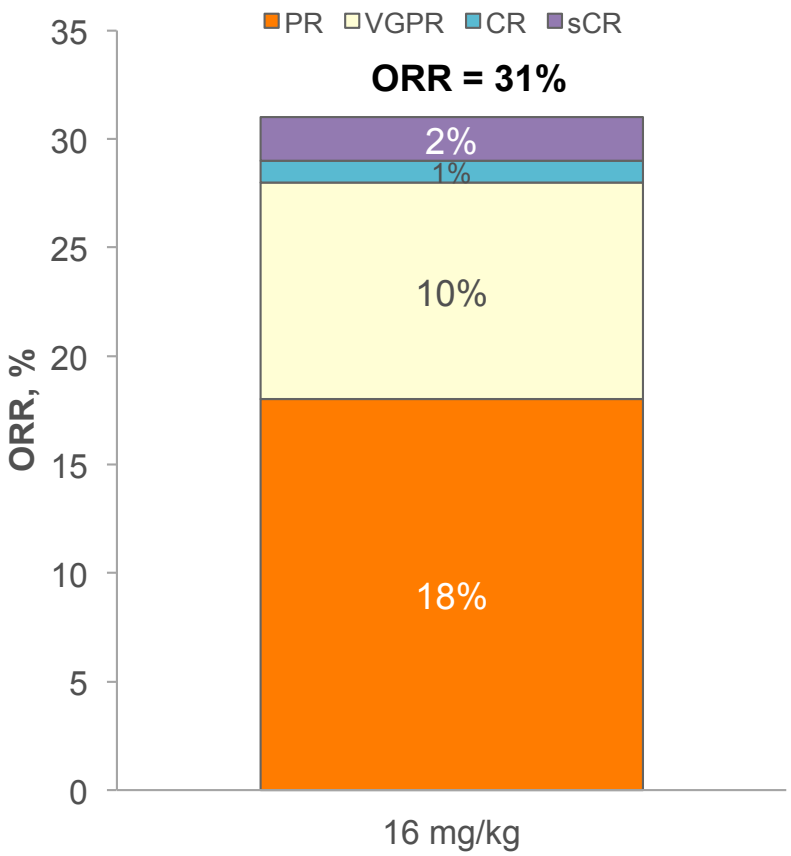
**Median follow-up of 20.7 months**


1. Lokhorst HM, *N Engl J Med*. 2015;373(13):1207-1219
2. Lonial S. *Lancet*. 2016;387(10027):1551-1560.


Usmani, SZ. Blood. 2016. http://dx.doi.org/10.1182/blood-2016-03-705210.

# Efficacy in Combined Analysis

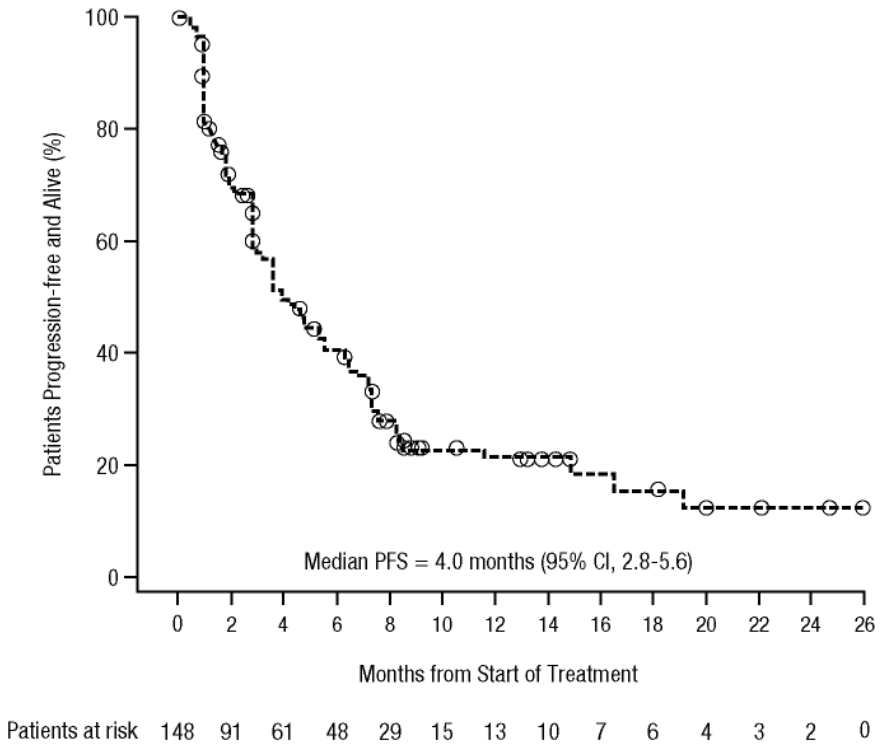
| | 16 mg/kg (N = 148) | |
|---|---|---|
| | **n (%)** | **95% CI** |
| **ORR (sCR+CR+VGPR+PR)** | **46 (31)** | **23.7-39.2** |
| Best response | | |
| sCR | 3 (2) | 0.4-5.8 |
| CR | 2 (1) | 0.2-4.8 |
| VGPR | 14 (10) | 5.3-15.4 |
| PR | 27 (18) | 12.4-25.4 |
| MR | 9 (6) | 2.8-11.2 |
| SD | 68 (46) | 37.7-54.3 |
| PD | 18 (12) | 7.4-18.5 |
| NE | 7 (5) | 1.9-9.5 |
| VGPR or better (sCR+CR +VGPR) | 19 (13) | 7.9-19.3 |
| CR or better (sCR+CR) | 5 (3) | 1.1-7.7 |

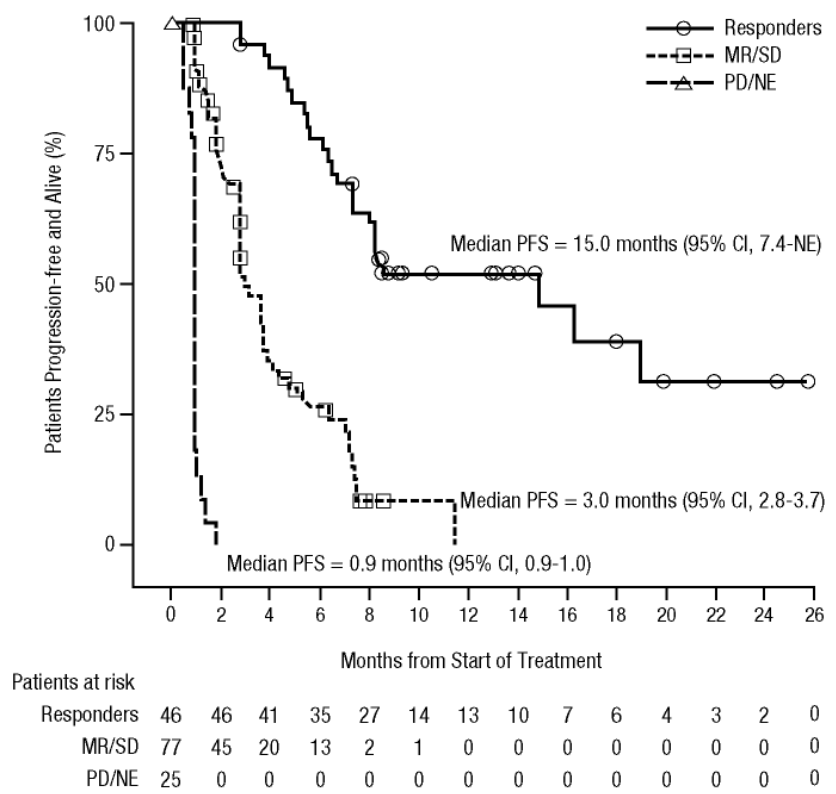



- **ORR = 31%**
- **CBR = 83% → OS benefit observed also in SD/MR pts**
- Median (range) **TTR: 0.95** (0.5-5.6) months
- Median **DOR = 7.6** (95% CI, 5.6-NE) months; responses deepened with continued treatment (7/10 PR → VGPR; 3 PR → CR - 1 patient - sCR - 2 patients)

Usmani, SZ. Blood. 2016. http://dx.doi.org/10.1182/blood-2016-03-705210.

# Daratumumab Monotherapy – PFS



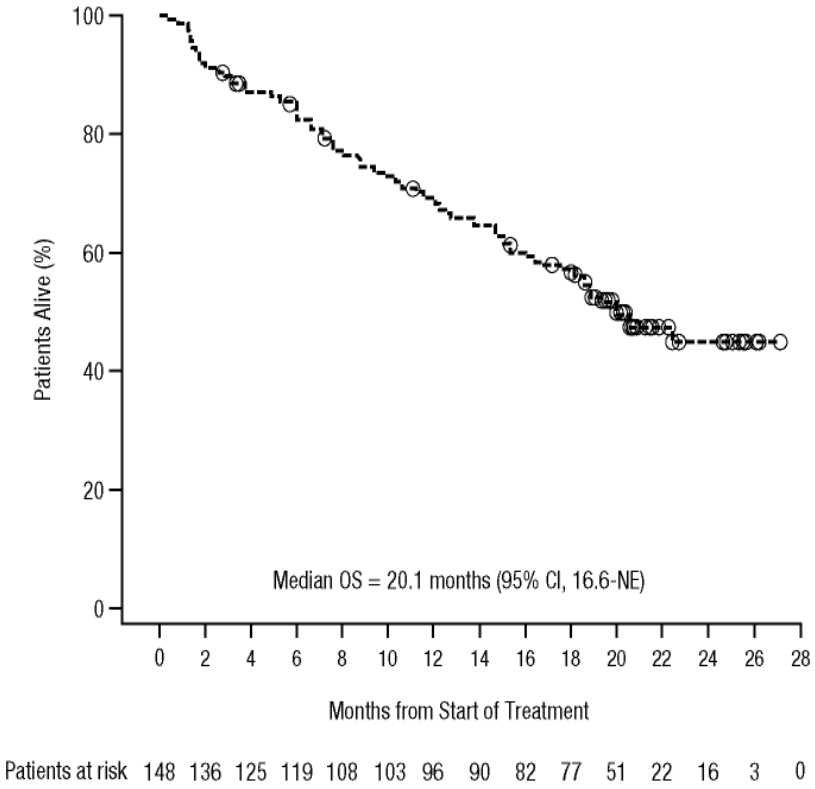




- After a **median follow-up of 20.7 months** (0.5-27.1 months), the **median PFS** was **4.0 months** (95% CI, 2.8-5.6 months)
- Overall, 12-month PFS rate was 21.6% (95% CI, 14.4%-29.8%)

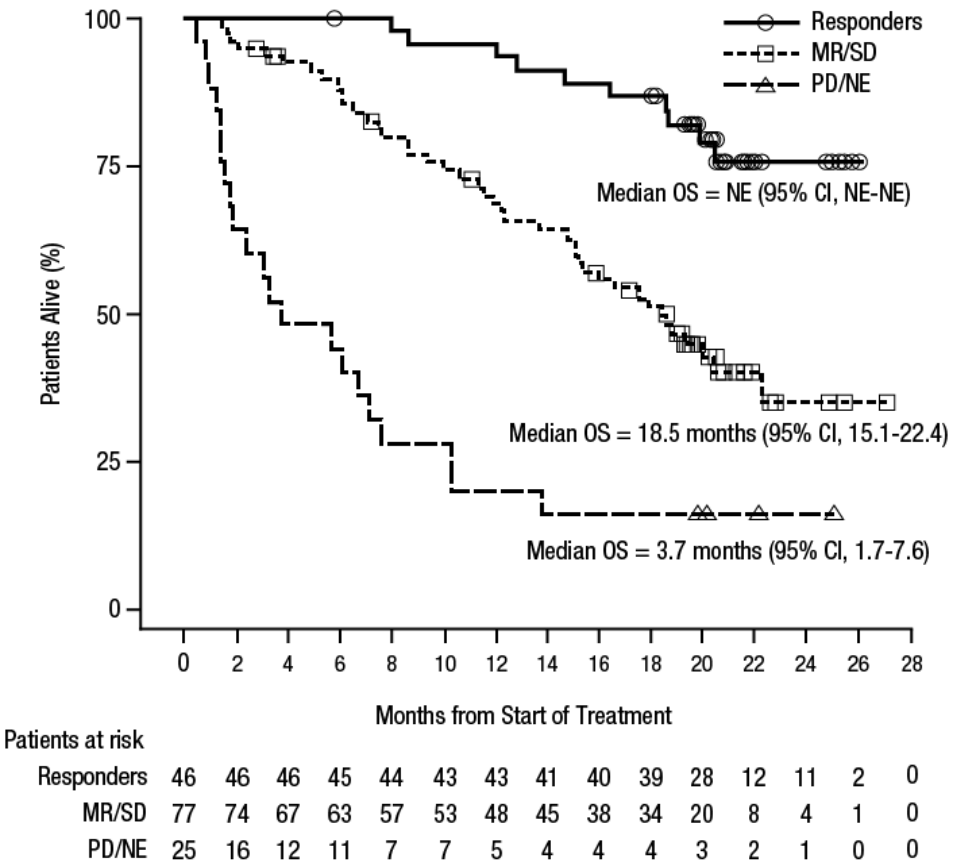
- **Median PFS** for **≥ PR** vs MR/SD vs PD/NE (**15.0 months** [95% CI, 7.4-NE months] vs 3.0 months [95% CI, 2.8-3.7 months] vs 0.9 months [95% CI, 0.9-1.0 months])15

Usmani, SZ. Blood. 2016. http://dx.doi.org/10.1182/blood-2016-03-705210.

# Daratumumab Monotherapy – OS




- The **median OS** (combined study) **20.1 months** (95% CI, 16.6-NE months)
- The **18-month** and **24-month OS** rates **56.5%** (95% CI, 47.9%-64.2%) and **45.0%** (95% CI, 35.5%-54.1%)




- Median OS for **≥PR** vs MR/SD vs PD/NE (**NE months** [95% CI,NE -NE] vs **18.5** [95% CI,15.1-22.4] vs 3.7 [95% CI, 1.7-7.6 months])

Usmani, SZ. Blood. 2016. http://dx.doi.org/10.1182/blood-2016-03-705210.

# Patient Disposition

| | 16 mg/kg Combined N = 148 |
|---|---|
| **Discontinued from treatment, n (%)** | 136 (91.9) |
| Progressive Disease | 123 (83.1) |
| **Adverse event** | **6 (4.1)** |
| Physician decision | 4 (2.7) |
| Withdrawal of consent | 3 (2.0) |

- In the combined dataset
  - Median (range) duration of follow-up = **20.7 (1-27) months**
  - Median (range) duration of treatment = **3.4 (0-26) months**
  - Median (range) number of infusions = **12 (1-40)**

- There were **3 deaths** that were recorded as being **due to AEs**
  - **Not related to study treatment**
  - Consisted of viral H1N1 infection, pneumonia, and aspiration pneumonia

Usmani, SZ. Blood. 2016. http://dx.doi.org/10.1182/blood-2016-03-705210.

# Incidence and Severity of Most Common (≥20%) Treatment-emergent Adverse Events (TEAEs)

| | 16 mg/kg N = 148 | | |
|---|---|---|---|
| **Event, n (%)** | **All grades** | **Grade ≥3** | **Grade 4** |
| Fatigue | 62 (41.9) | 3 (2.0) | 0 |
| Nausea | 44 (29.7) | 0 | 0 |
| Anemia | 42 (28.4) | **26 (17.6)** | 0 |
| Back pain | 40 (27.0) | 4 (2.7) | 0 |
| Cough | 38 (25.7) | 0 | 0 |
| Thrombocytopenia | 32 (21.6) | **13 (8.8)** | **8 (5.4)** |
| Upper respiratory tract infection | 32 (21.6) | 1 (0.7) | 0 |
| Neutropenia | 31 (20.9) | **11 (7.4)** | **4 (2.7)** |

TEAE, treatment-emergent adverse event.

AEs were consistent with the individual GEN501 and SIRIUS studies; no new safety signals were identified

Usmani, SZ. Blood. 2016. http://dx.doi.org/10.1182/blood-2016-03-705210.

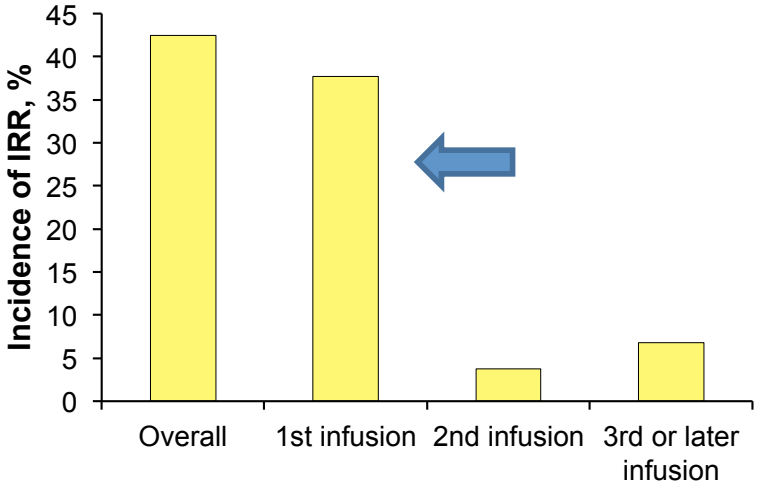
# Infusion related reactions (IRRs) ≥ 5%

| | 16 mg/kg N = 148 | |
|---|---|---|
| **Event, n (%)** | **All grades** | **Grade ≥3** |
| Nasal congestion | 17 (11.5) | 0 |
| Cough | 12 (8.1) | 0 |
| Rhinitis allergic | 10 (6.8) | 0 |
| Chills | 10 (6.8) | 0 |
| Throat irritation | 9 (6.1) | 0 |
| Dyspnea | 8 (5.4) | 1 (0.7) |
| Nausea | 8 (5.4) | 0 |

IRR, infusion-related reaction.

**IRRs were observed in 48% of patients and those observed in ≥ 5% of patients were mainly respiratory conditions**

- **4 (2.7%) patients had grade ≥3 IRRs** (bronchospasm [n = 2]; dyspnea, hypoxia, and hypertension [n = 1 each])
- **95.8% of IRRs were observed during the first infusion** and the incidence of IRRs decreased during the second (7.0%) and subsequent (7.0%) infusions
- **IRRs were managed** with pre- and post-infusion medications, (antihistamines, corticosteroids, and paracetamol/acetaminophen)
- Supportive care treatment with **G-CSF** was required by 12 patients **(8.1%)**
- **46 (31.1%) patients received transfusions** during the study: red blood cell and platelet transfusions received by 44 (29.7%) and 14 (9.5%) of patients, respectively, **without any AE related to hemolysis**.
- **No patients discontinued** treatment due to IRRs (in MMY2002 SIRIUS study)




Usmani, SZ. Blood. 2016. http://dx.doi.org/10.1182/blood-2016-03-705210.

*Daratumumab in specific populations*

*Liver dysfunction.* No dose modifications are necessary for patients with mild hepatic impairment based on population pharmacokinetic analysis. No data are available for moderate or severe hepatic impairment (accessed 19 July 2016).

*Renal dysfunction.* DARA is not metabolized by the kidney; such that renal failure is not a contraindication for treatment. The GEN501 and SIRIUS trials each included patients with mild-to-moderate renal failure, creatinine clearance 30–60 ml/min and the ORR in these patients was 26.2%. [Lonial *et al.* 2016b]. No data are available to provide guidance on patients with severe renal impairment.

*Advanced age.* The GEN501 was administered to 16 patients aged 65–74 years, 56% of whom responded [Lokhorst *et al.* 2015], while none of the 4 patients over age 75 responded. In the SIRIUS trial, 36 patients were aged 65–74 years, and 12 patients were 75 years or older. The ORR in these subgroups of patients was 25% and 33.3%, respectively, suggesting that the efficacy of DARA is equivalent in all age groups.

**Costello C, Ther Adv Hematol 2017**

# Current Dara dosing: no apparent relationship with AEs

**Table 2. Comparison of AE Rates Between Predicted DARA Exposure Quartiles From the Combined Analysis**

| | Exposure quartiles,[a] % (95% CI) | | | |
|---|---|---|---|---|
| AE | 1st | 2nd | 3rd | 4th |
| IRRs | 63 (50-75) | 56 (43-69) | 51 (38-64) | 47 (35-60) |
| Grade ≥3 | 9 (3-18) | 4 (1-10) | 2 (<1-8) | 4 (1-11) |
| Thrombocytopenia | 18 (11-31) | 23 (13-35) | 18 (9-29) | 14 (7-25) |
| Grade ≥3 | 16 (8-27) | 14 (7-25) | 12 (6-22) | 11 (4-20) |
| Neutropenia | 7 (2-16) | 16 (8-27) | 19 (11-31) | 12 (6-22) |
| Grade ≥3 | 7 (2-16) | 9 (3-18) | 11 (4-20) | 4 (1-10) |
| Anaemia | 25 (15-37) | 37 (25-50) | 16 (8-27) | 16 (8-27) |
| Grade ≥3 | 16 (8-27) | 25 (15-37) | 7 (2-16) | 9 (3-18) |
| Lymphopenia | 9 (3-18) | – | 4 (1-10) | 4 (1-10) |
| Grade ≥3 | 5 (1-13) | – | 4 (1-10) | 4 (1-11) |
| Infections | 40 (28-53) | 54 (42-67) | 56 (43-69) | 61 (49-73) |
| Grade ≥3 | 5 (1-13) | 12 (6-22) | 12 (6-22) | 5 (1-13) |

AE, adverse event; DARA, daratumumab; CI, confidence interval; IRR, infusion-related reaction; $C_{max,1st}$, maximal concentration after the first infusion; $C_{post\text{-}infusion,max}$, maximal end-of-infusion concentration.

[a]End-of-infusion concentration after $C_{max,1st}$ was used as the exposure measure for analyses on IRRs, while $C_{post\text{-}infusion,max}$ was used as the exposure measure for analyses on other AEs.

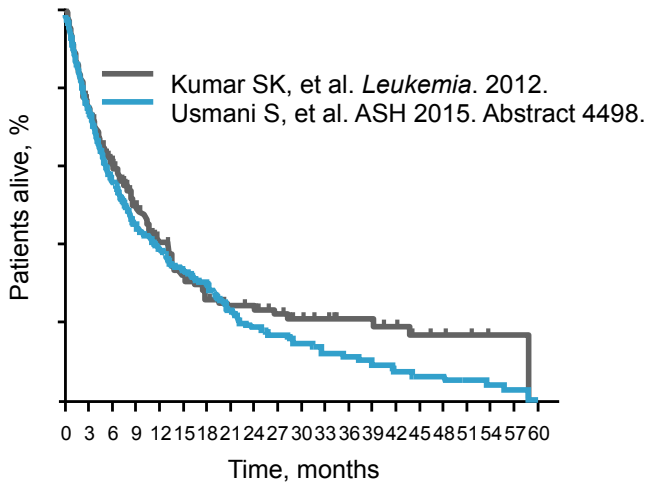
The quartiles for $C_{max,1st}$ are: Quartile 1 (≤134 µg/mL), Quartile 2 (>134-245 µg/mL), Quartile 3 (>245-310 µg/mL), and Quartile 4 (>310-470 µg/mL).

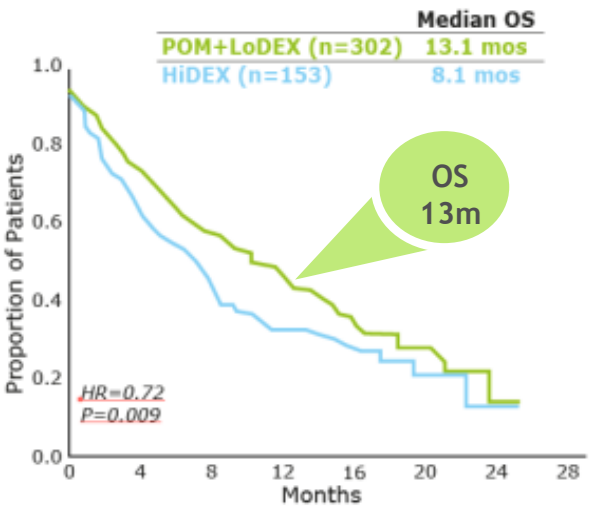
The quartiles for $C_{post\text{-}infusion,max}$ are: Quartile 1 (≤270 µg/mL), Quartile 2 (>270-511 µg/mL), Quartile 3 (>511-907 µg/mL), and Quartile 4 (>907-1,840 µg/mL).

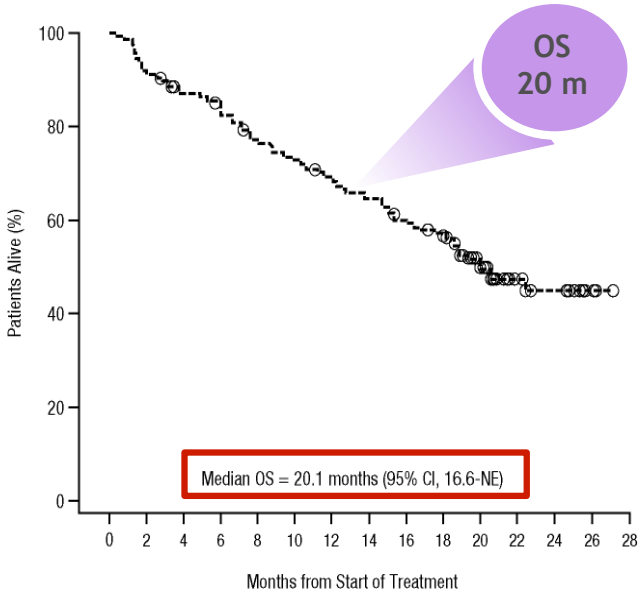
- **No apparent relationship was identified between drug exposure and adverse events** of interest: infusion-related reaction (IRR), thrombocytopenia, anemia, neutropenia, lymphopenia
- Overall event rate of **infection appeared to numerically increase with drug exposure**, however this **trend was not observed for infections Grade 3 or higher.**

Xu et al Poster BP057 IMW 2015 Rome

# The Breakthrough (BT) population outcome




**RRMM:**

**Median OS 5-9 months** in patients relapsed or refractory MM after ≥3 prior lines of therapy, including IMID and PI

1. Kumar SK, et al. Leukemia. 2012;26(1):149-157.
2. Usmani S, et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 4498.

**Pomalidomide:**

**Median OS 13,1months** in patients relapsed or refractory MM after ≥2 prior lines of therapy, including IMID and PI

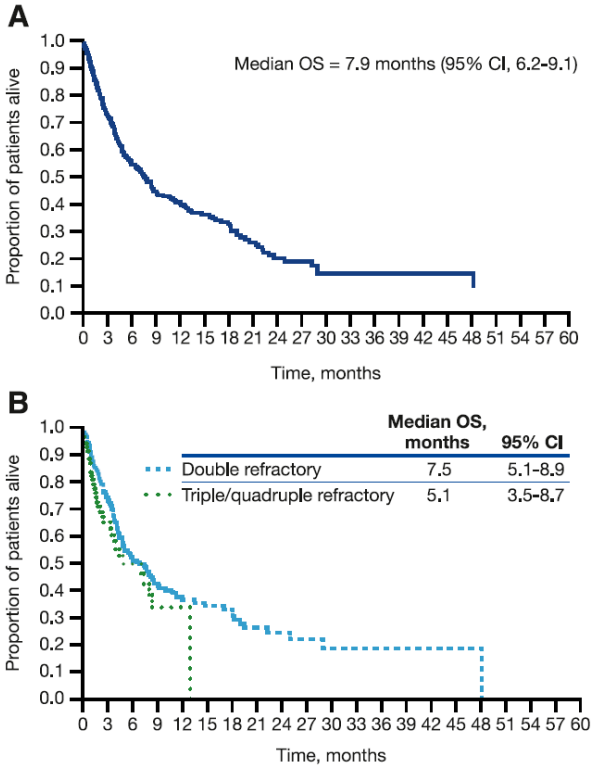
San Miguel J et al. Lancet Oncol 2013; 14: 1055–66

**Daratumumab – Single Agent:**

**Median OS of 20 months** in patients with relapsed or refractory, double refractory or relapsed after ≥3 lines of therapy, including pomalidomide and carfilzomib

Usmani S et al. Blood. 2016;128(1):37-44

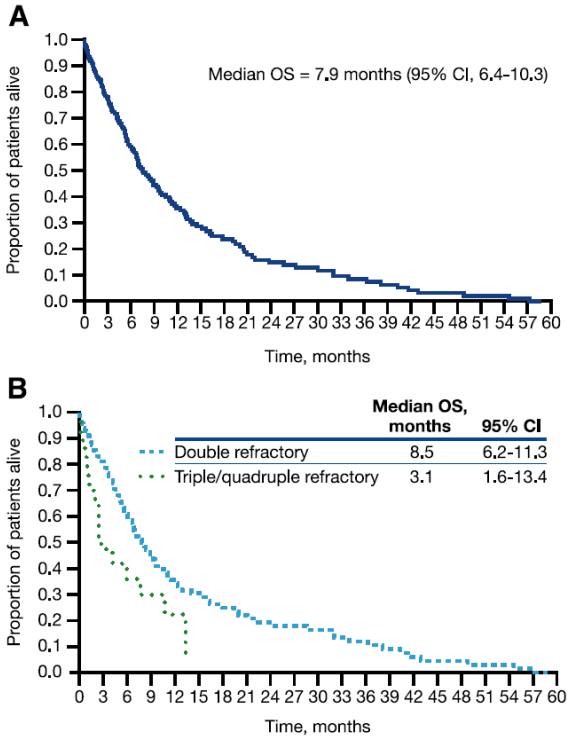
# The Breakthrough (BT) population outcome




**Real World Data - IMS Database**

**Median OS 5-7.5 months** in patients relapsed or refractory MM after ≥3 prior lines of therapy, including IMID and PI

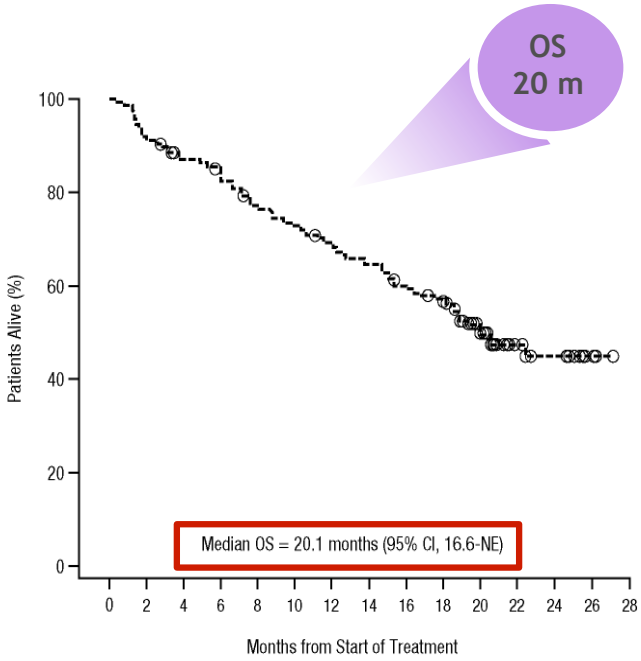
Usmani S et al. TheOncologist 2016;21:1–7




**Real World Data - OPTUM Database**

**Median OS 3-8.5 months** in patients relapsed or refractory MM after ≥3 prior lines of therapy, including IMID and PI

Usmani S et al. TheOncologist 2016;21:1–7



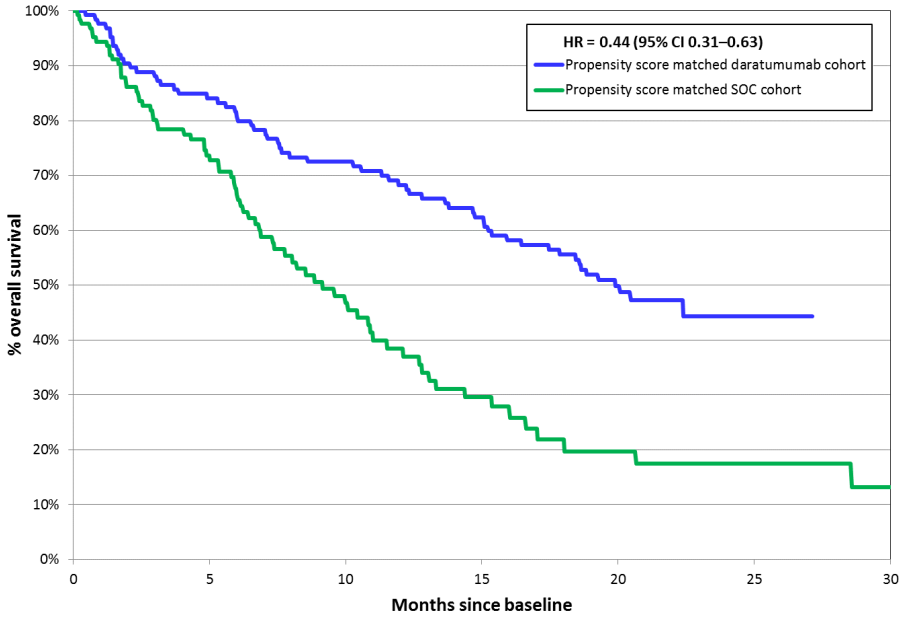

**Daratumumab – Single Agent:**

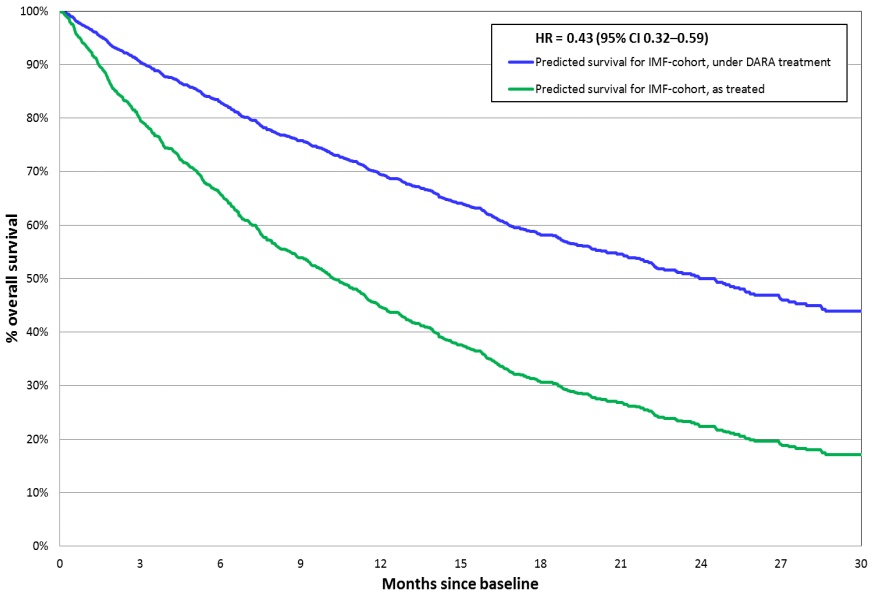
**Median OS of 20 months** in patients with relapsed or refractory, double refractory or relapsed after ≥3 lines of therapy, including pomalidomide and carfilzomib

Usmani S et al. Blood. 2016;128(1):37-44

# Adjusted Comparisons Suggest Daratumumab Is Associated With Prolonged Survival Compared With Standard of Care (SOC) Therapies in Patients With Heavily Pretreated and Highly Refractory Multiple Myeloma

- The unadjusted HR for OS was 0.51 (95% CI, 0.39-0.67);
- After PSM, comparisons found significant improvement in favor of DARA relative to SOC for OS (HR = 0.44 [95% CI, 0.31-0.63])
- Median OS was 19.9 months in the DARA group and 9.2 months in the SOC group
- Median predicted OS was 24.5 months in the DARA group and 10.3 months in the SOC group




## OS in DARA and SOC Cohorts Formed Using PSM (propensity score matching)

Kumar et al, Abstract n. 4517 ASH 2016

# Daratumumab
# Regulatory Update

**November 2015: FDA**

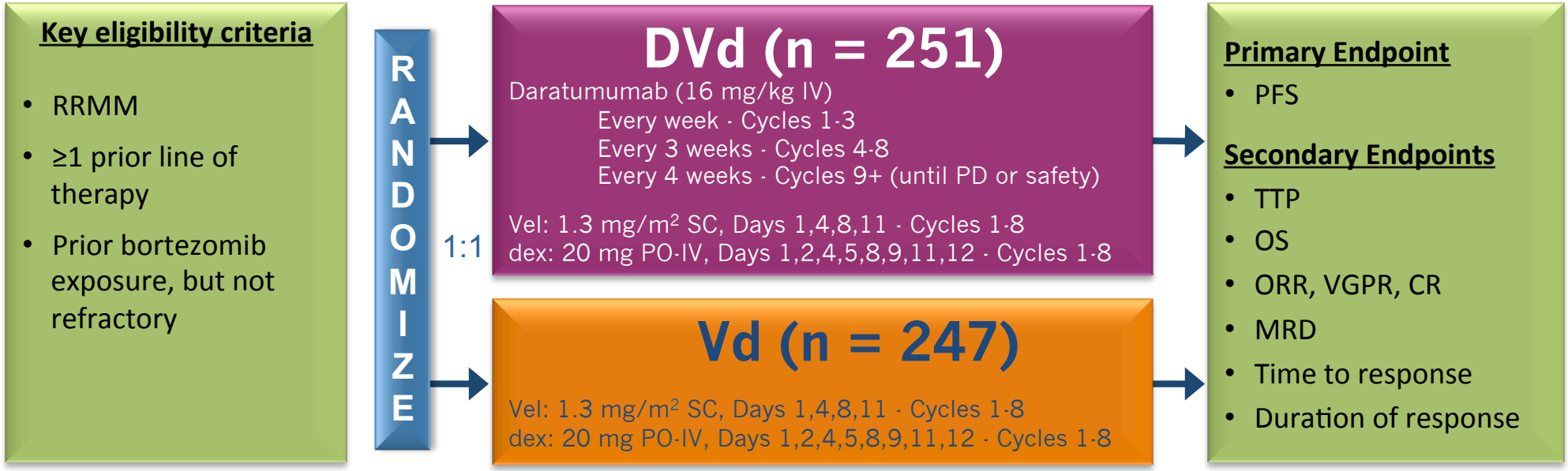
*"Daratumumab is indicated for the treatment of patients with multiple myeloma who have received **at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory** to a PI and an immunomodulatory agent."*

**April 2016: EMA**

*"Daratumumab as **monotherapy** is indicated for the treatment of adult patients with **relapsed and refractory** multiple myeloma, whose **prior therapy included a proteasome inhibitor and an immunomodulator**y agent and who have demonstrated **disease progression on the last therapy**."*

# CASTOR MMY3004 DaraVd vs Vd

## Multicenter, randomized, open-label, active-controlled, phase 3 study




- Cycles 1-8: repeat every 21 days
- Cycles 9+: repeat every 28 days

**Statistical analyses**

- 295 PFS events: 85% power for 4.3-month PFS improvement
- Interim analysis: ~177 PFS events

**Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/hour permitted**

RRMM, relapsed or refractory multiple myeloma; DVd, daratumumab/bortezomib/dexamethasone; IV, intravenous; Vel, bortezomib; SC, subcutaneous; dex, dexamethasone; PO, oral; Vd, bortezomib/dexamethasone; PFS, progression-free survival; TTP, time to progression; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.

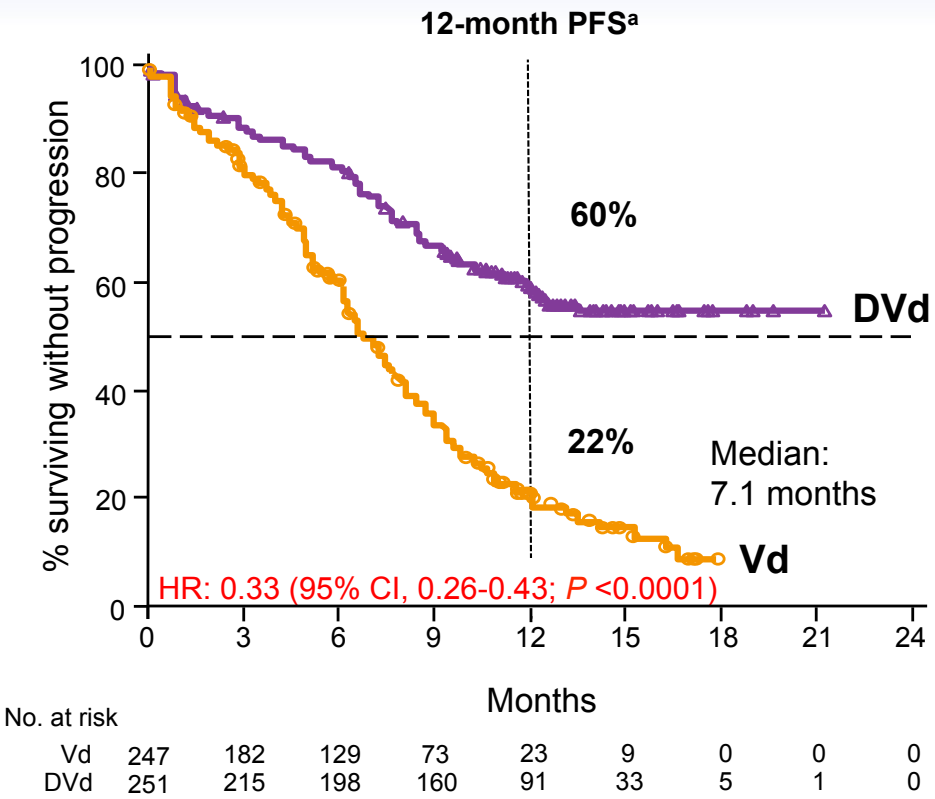
Palumbo et al. N Engl J Med 2016;375:754-66

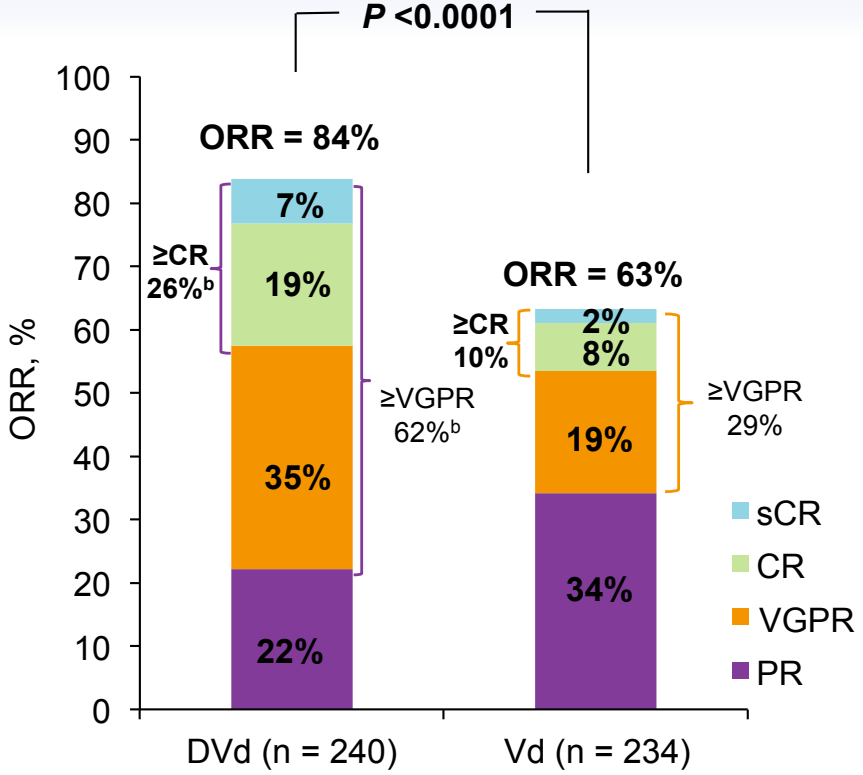
## ASH 2016, Abstract n. 1150

- Efficacy of Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone in Relapsed or Refractory Multiple Myeloma Based on Prior Lines of Therapy: Updated Analysis of CASTOR


- Maria-Victoria Mateos,[1] Jane Estell,[2] Wolney Barreto,[3] Paolo Corradini,[4] Chang-Ki Min,[5] Eva Medvedova,[6] Ming Qi,[7] Jordan Schecter,[8] Himal Amin,[8] Xiang Qin,[7] William Deraedt,[9] Tineke Casneuf,[9] Christopher Chiu,[7] A. Kate Sasser,[7] Ajay Nooka[10]
- [1]University Hospital of Salamanca/IBSAL, Salamanca, Spain; [2]Haematology Department, Concord Cancer Centre, Concord Hospital, Concord, NSW, Australia; [3]Hospital Santa Marcelina, Sao Paulo, Brazil; [4]Fondazione IRCCS Instituto Nazionale dei Tumori, Milan, Italy; [5]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; [6]Oregon Health & Science University, Portland, Oregon, USA; [7]Janssen Research & Development, LLC, Spring House, PA, USA; [8]Janssen Research & Development, LLC, Raritan, NJ, USA; [9]Janssen Research & Development, Beerse, Belgium; [10]Winship Cancer Institute, Emory University, Atlanta, GA, USA.

# Updated Efficacy



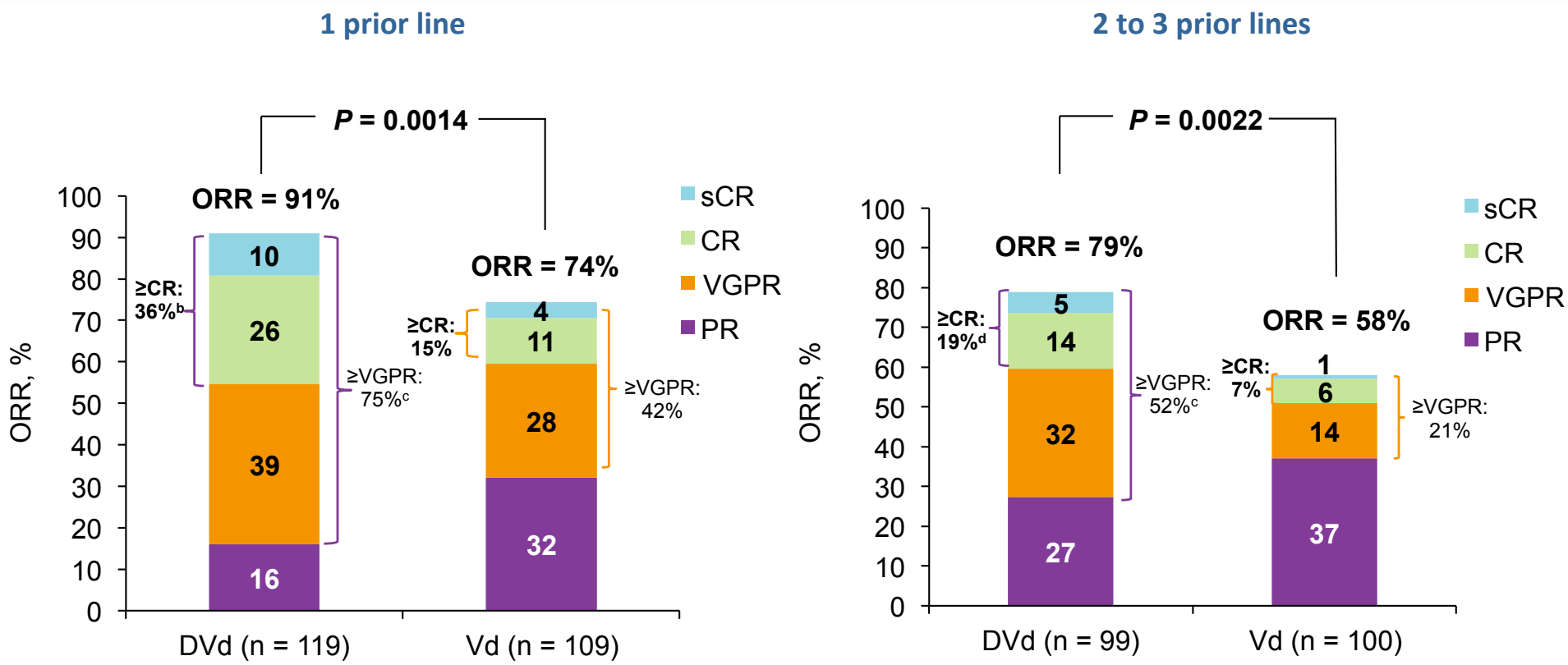




- Median (range) follow-up: 13.0 (0-21.3) months
- An additional 7% of patients receiving DVd achieved ≥CR with longer follow-up

**Responses continue to deepen in the DVd group with longer follow-up**

ITT, intent-to-treat.
Note: PFS = ITT population; ORR = response-evaluable population.
[a]Kaplan-Meier estimate.
[b]*P* <0.0001 for DVd versus Vd.

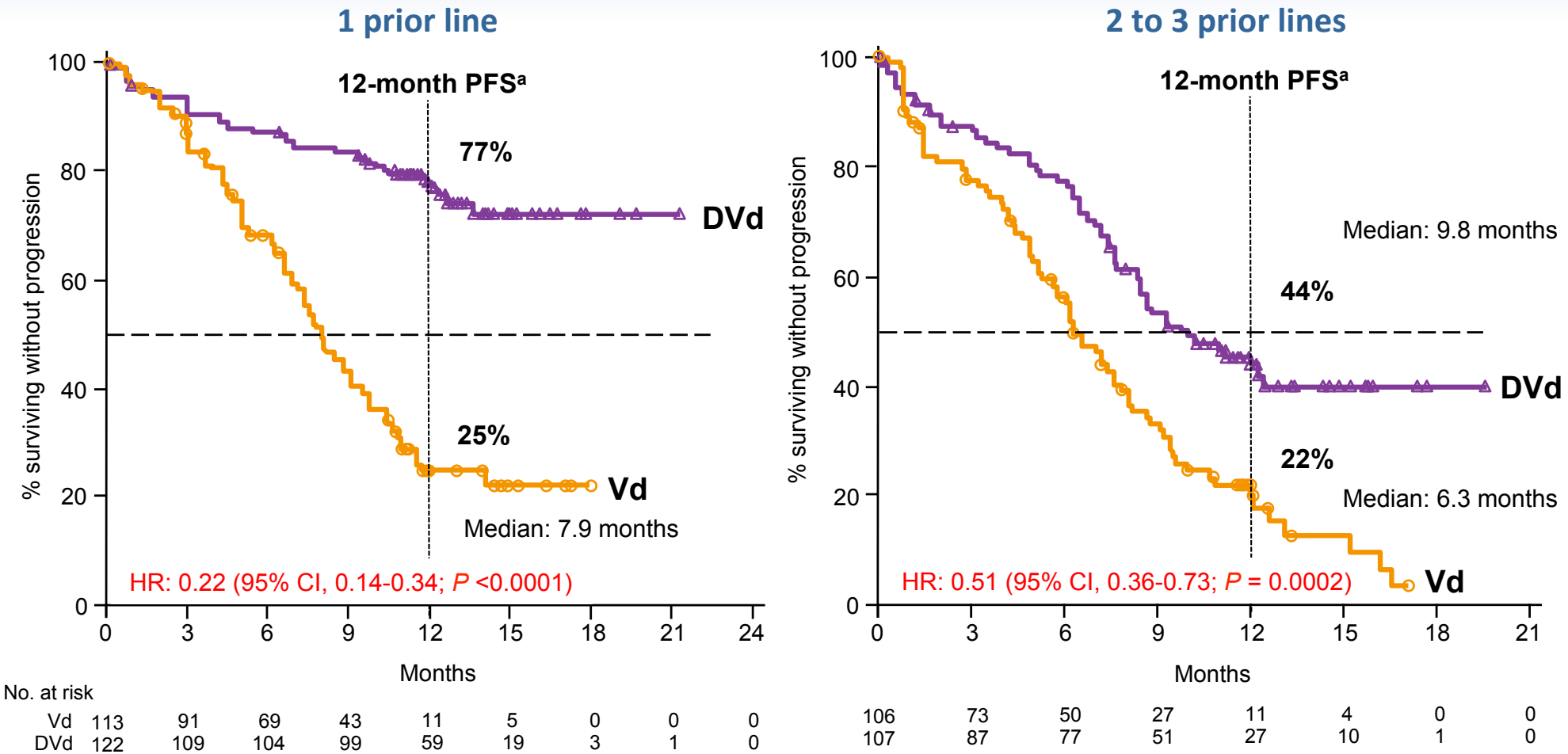
# ORR by Prior Lines[a]




**More patients achieve a deeper response with DVd after 1 prior line of treatment**

[a]Response-evaluable population.
[b]*P* = 0.0006 for DVd vs Vd.
[c]*P* <0.0001 for DVd vs Vd.
[d]*P* = 0.0133 for DVd vs Vd.

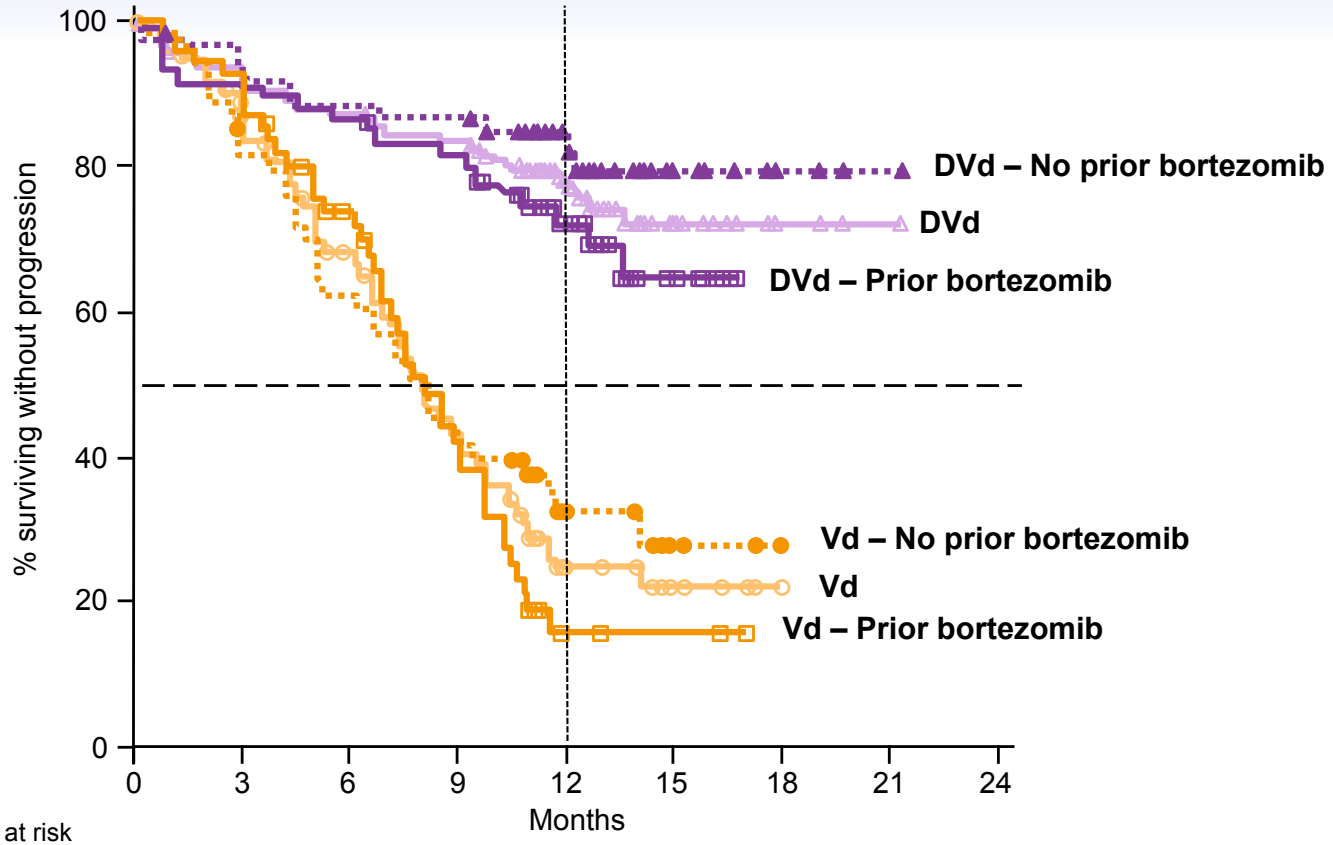
# PFS: Prior Lines of Treatment




**DVd is superior to Vd regardless of prior lines of therapy, with greatest benefit observed in 1 prior line**

[a]Kaplan-Meier estimate.

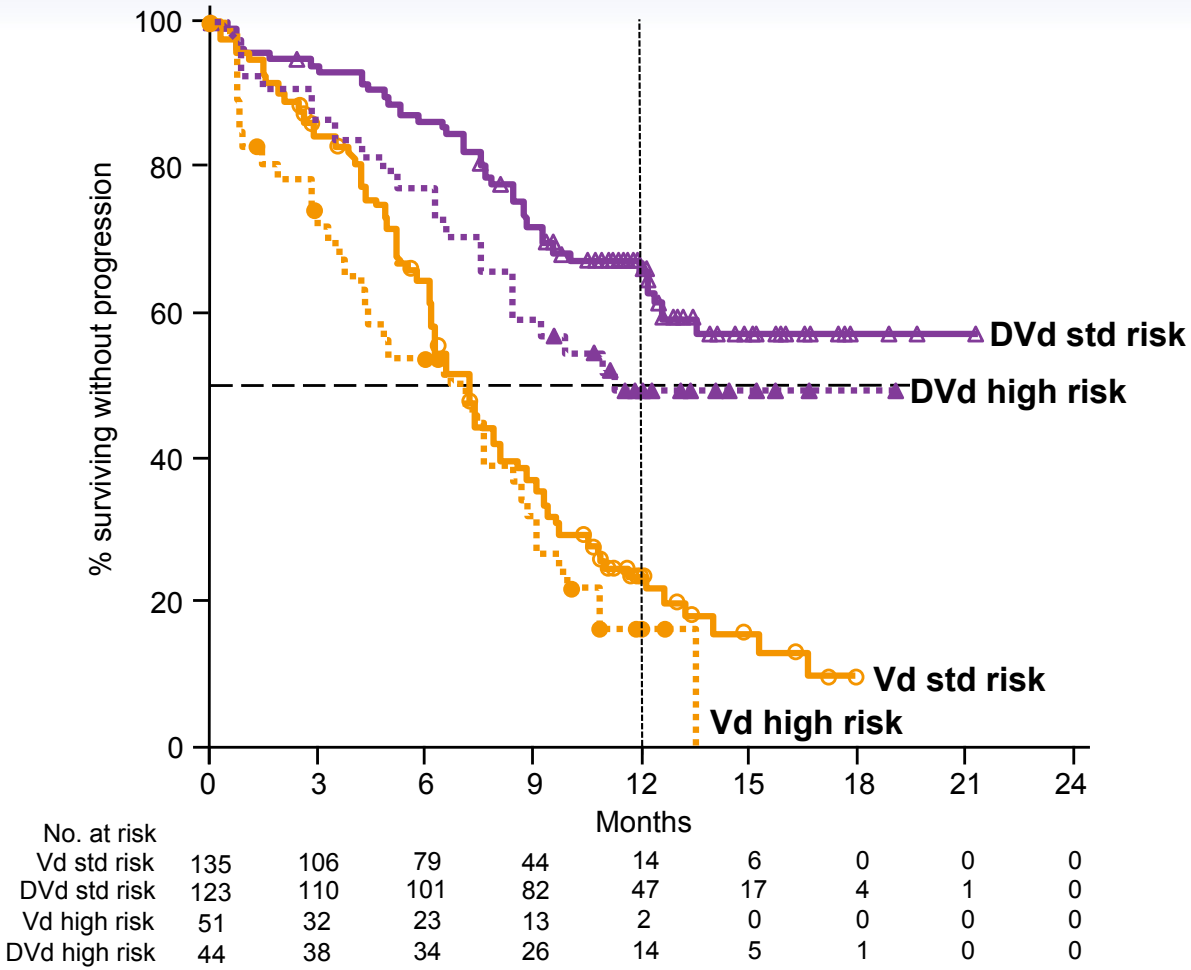
# PFS by Prior Bortezomib Exposure: 1 Prior Line Population




| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Vd | 113 | 91 | 69 | 43 | 11 | 5 | 0 | 0 | 0 |
| DVd | 122 | 109 | 104 | 99 | 59 | 19 | 3 | 1 | 0 |
| Vd – No prior bortezomib | 56 | 43 | 33 | 23 | 8 | 3 | 0 | 0 | 0 |
| DVd – No prior bortezomib | 60 | 54 | 52 | 51 | 30 | 10 | 3 | 1 | 0 |
| Vd – Prior bortezomib | 57 | 48 | 36 | 20 | 3 | 2 | 0 | 0 | 0 |
| DVd – Prior bortezomib | 62 | 55 | 52 | 48 | 29 | 9 | 0 | 0 | 0 |

**DVd provides treatment benefit regardless of prior bortezomib exposure**

# PFS: Cytogenetic Risk in All Evaluable Patients[a]



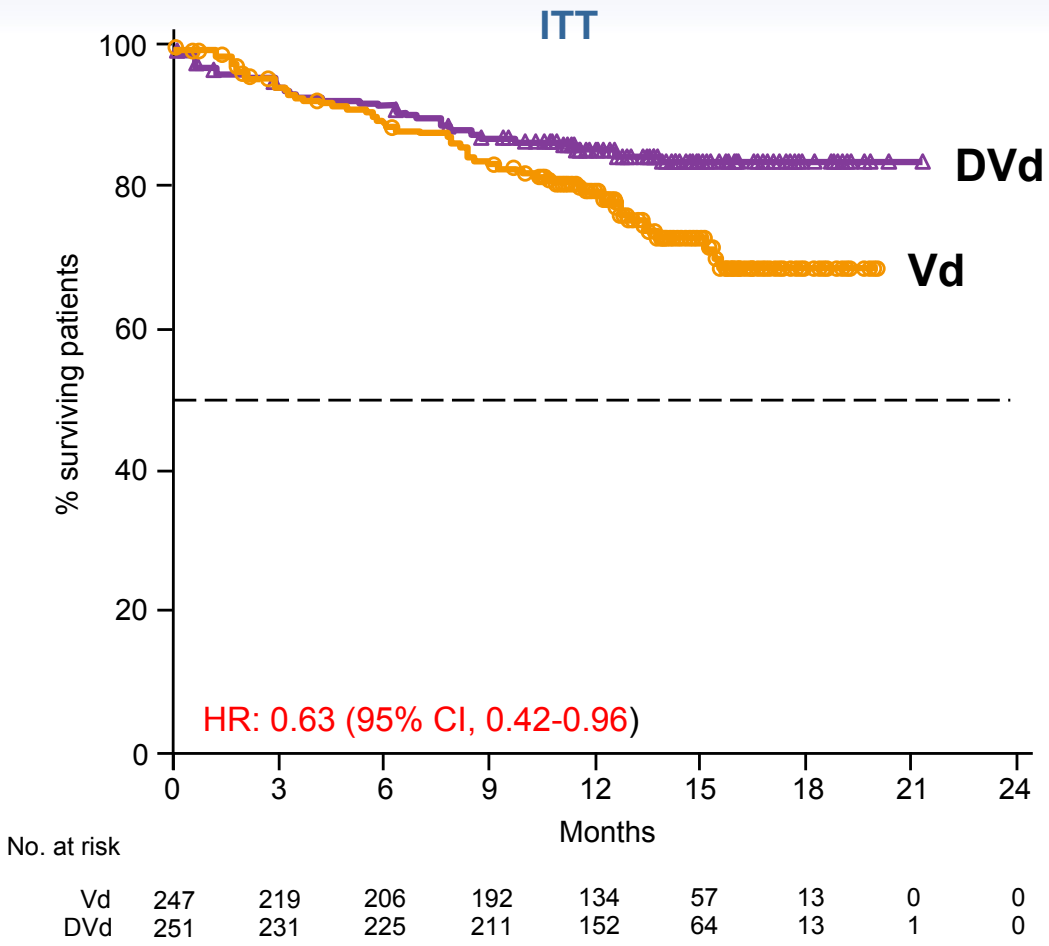

| High risk[b] | DVd n = 44 | Vd n = 51 |
|---|---|---|
| Median PFS, mo | **11.2** | **7.2** |
| HR (95% CI) | 0.49 (0.27-0.89) | |
| *P* value | 0.0167 | |
| | n = 44 | n = 47 |
| ORR, % | **82** | **62** |
| *P* value | 0.039 | |

| Standard risk | DVd n = 123 | Vd n = 135 |
|---|---|---|
| Median PFS, mo | **NR** | **7.0** |
| HR (95% CI) | 0.29 (0.20-0.43) | |
| *P* value | <0.0001 | |
| | n = 118 | n = 131 |
| ORR, % | **85** | **64** |
| *P* value | 0.0003 | |

**DVd improves outcomes regardless of cytogenetic risk**

NR, not reached.
[a]ITT/Biomarker risk–evaluable analysis set.
[b]Central NGS. High-risk patients had any of t(4;14), t(14;16), or del17p. Standard-risk patients had an absence of high-risk abnormalities.

# OS




- **OS events**
  - 37 (15%) in DVd
  - 58 (24%) in Vd
- **OS HR for DVd versus Vd by prior lines:**
  - 1 prior line = HR: 0.42 (95% CI, 0.19-0.93)
  - 1 to 3 prior lines = HR: 0.54 (95% CI, 0.34-0.84)

**Curves are beginning to separate, but OS data are immature**

Median OS was NR; results did not cross the prespecified stopping boundary.

# Most Common (≥20%) Treatment-emergent Adverse Events (TEAEs): CASTOR

| Patients | DVd | Vd |
|---|---|---|
| Number treated | 243 | 237 |
| Patients with TEAE, % | | |
| Thrombocytopenia | 59 | 44 |
| Sensory peripheral neuropathy (PN) | 47 | 38 |
| Diarrhea | 32 | 22 |
| Anemia | 26 | 31 |
| Upper respiratory tract infection | 25 | 18 |
| Cough | 24 | 13 |
| Fatigue | 21 | 25 |
| Constipation | 20 | 16 |

Palumbo et al. N Engl J Med 2016;375:754-66

# Infusion-related Reactions (IRRs): CASTOR

| | Safety Analysis Set DVd (n = 243) | |
|---|---|---|
| | All grades | Grade 3 |
| Patients with IRRs, % | **45** | **9** |
| Most common (>5%) IRRs | | |
| Dyspnea | 11 | 2 |
| Bronchospasm | 9 | 3 |
| Cough | 7 | 0 |

- **No grade 4 or 5** IRRs observed
- **98%** of patients with IRRs experienced the event on the **first infusion**
- **2 patients discontinued due to IRRs**
  - Bronchospasm in the first patient
  - Bronchospasm, laryngeal edema, and skin rash in the second patient

Palumbo et al. N Engl J Med 2016;375:754-66

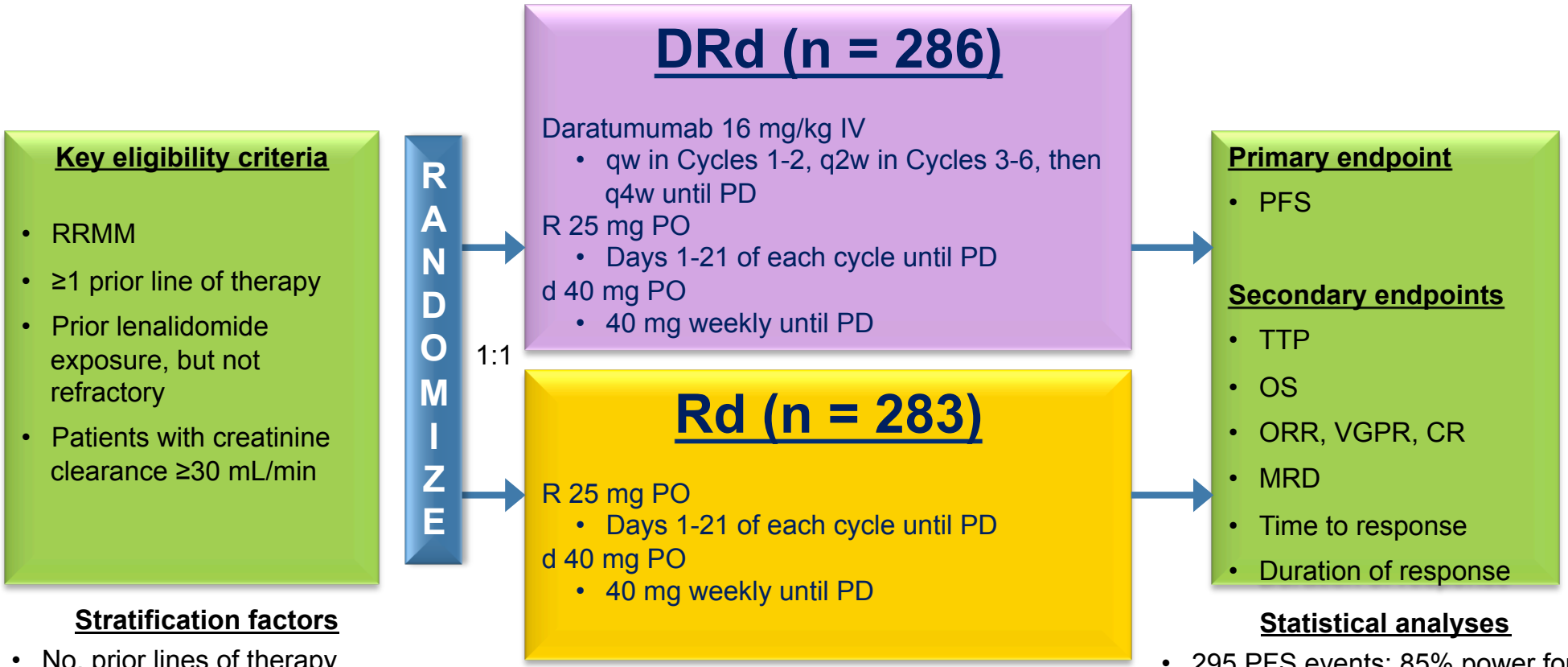
# PI-based Studies

| | Daratumumab DVd vs Vd | Carfilzomib Kd vs Vd[1] | Panobinostat PVd vs Vd[2,3] | Elotuzumab EVd vs Vd[4] |
|---|---|---|---|---|
| PFS HR (95% CI) | **0.39 (0.28-0.53)** | 0.53 (0.44-0.65) | 0.63 (0.52-0.76) | 0.72 (0.59-0.88) |
| PFS, median mo | **NE** | 18.7 | 12.0 | 9.7 |
| ≥VGPR | **59%** | 54% | 28% | 36% |
| ≥CR | **19%** | 13% | 11% | 4% |
| Duration of response, mo | **NE** | 21.3 | 13.1 | 11.4 |
| OS HR (95% CI) | **0.77 (0.47-1.26)** | 0.79 (0.58-1.08) | 0.94 (0.78-1.14) | 0.61 (0.32-1.15) |


1. Dimopoulos MA, et al. *Lancet Oncol*. 2016;17(1):27-38.
2. San-Miguel JF, et al. *Lancet Oncol*. 2014;15(11):1195-1206.
3. San-Miguel JF, et al. *Blood*. 2015;126(23):Abstract 3026.
4. Jakubowiak A, et al. *Blood*. 2016. Epub ahead of print.

# POLLUX MMY3003 Dara-Rd vs Rd

Multicenter, randomized (1:1), open-label, active-controlled, phase 3 study




**Stratification factors**

- No. prior lines of therapy
- ISS stage at study entry
- Prior lenalidomide

Cycles: 28 days

**Statistical analyses**

- 295 PFS events: 85% power for 7.7-month PFS improvement
- Interim analysis: ~177 PFS events

Premedication for the DRd treatment group consisted of dexamethasone 20 mg,[a] paracetamol, and an antihistamine

[a]On daratumumab dosing days, dexamethasone was administered 20 mg premedication on Day 1 and 20 mg on Day 2.
ISS, International Staging System; R, lenalidomide; IV, intravenous; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; PO, oral; d, dexamethasone; TTP, time to progression; MRD, minimal residual disease.

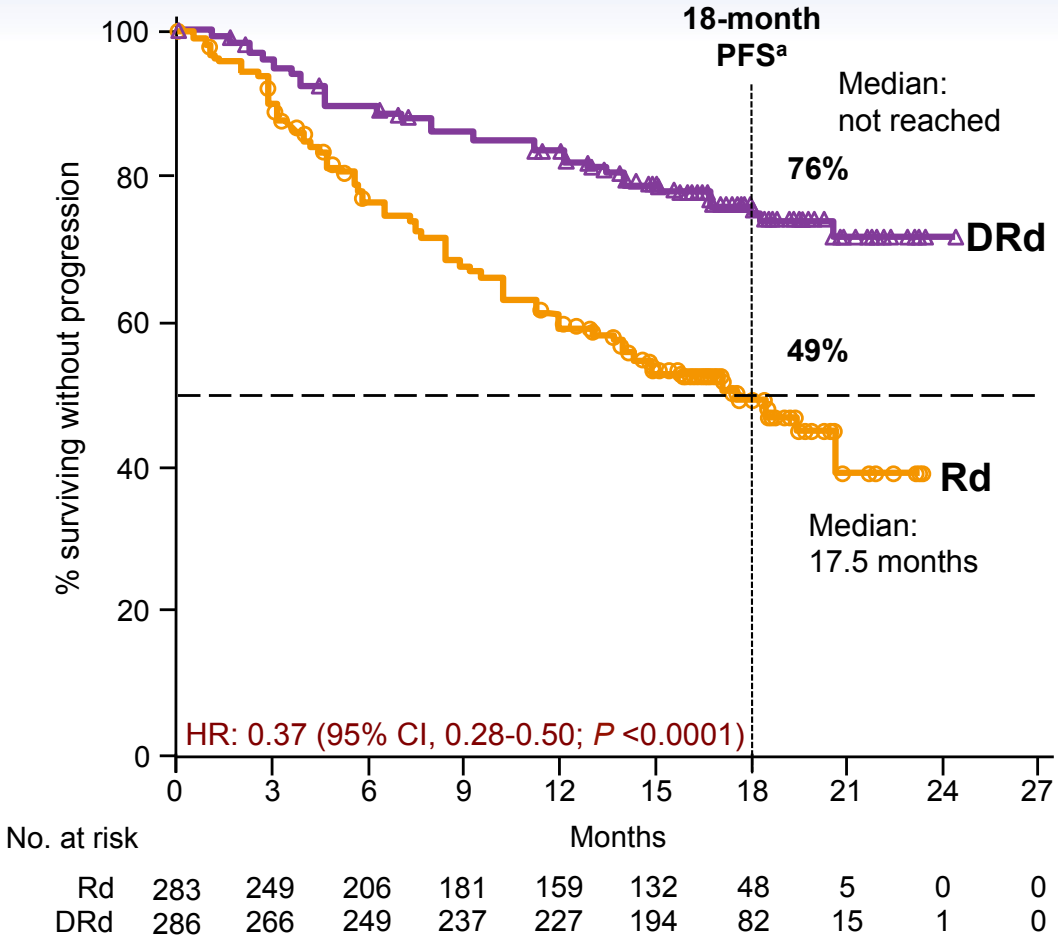
Dimopoulos er al. N Engl J Med 2016;375:1319-31

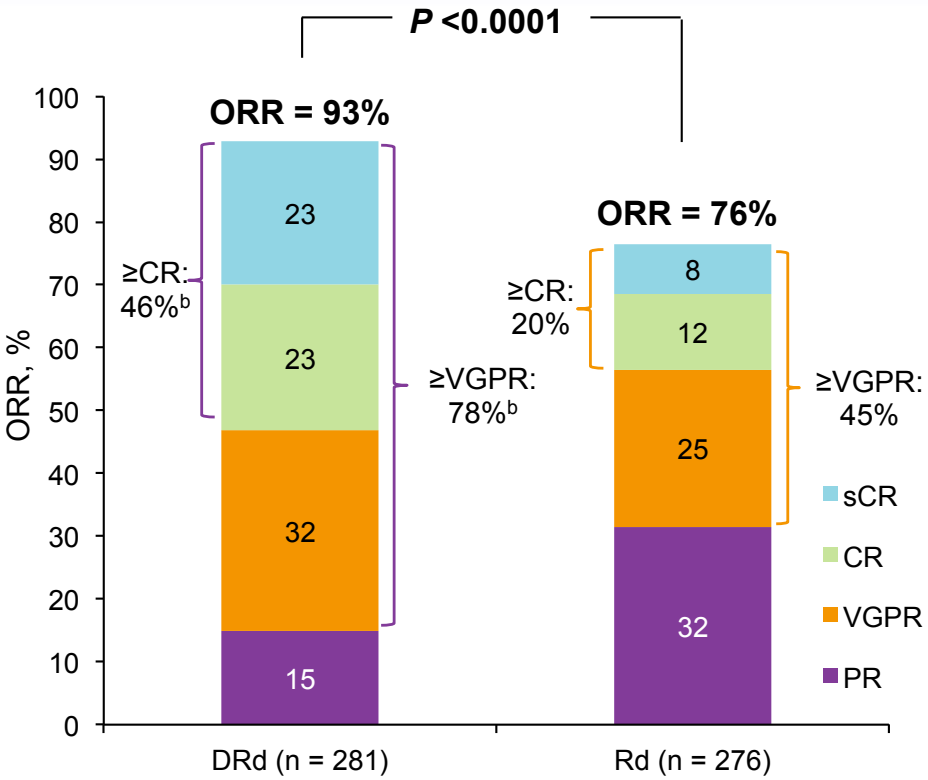
# ASH 2016, Abstract n. 489

- Efficacy of Daratumumab, Lenalidomide, and Dexamethasone Versus Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma Patients With 1 to 3 Prior Lines of Therapy: Updated Analysis of POLLUX


- Saad Z. Usmani,[1] Meletios A. Dimopoulos,[2] Andrew Belch,[3] Darrell White,[4] Lotfi Benboubker,[5] Gordon Cook,[6] Merav Leiba,[7] James Morton,[8] P. Joy Ho,[9] Kihyun Kim,[10] Naoki Takezako,[11] Nushmia Z. Khokhar,[12] Mary Guckert,[12] Kaida Wu,[12] Xiang Qin,[12] Tineke Casneuf,[13] Christopher Chiu,[12] A. Kate Sasser,[12] Jesus San-Miguel[14]
- [1]Levine Cancer Institute/Carolinas HealthCare System, Charlotte, NC, USA; [2]National and Kapodistrian University of Athens, Athens, Greece; [3]Department of Oncology, University of Alberta Cross Cancer Institute, Edmonton, Alberta, Canada; [4]QEII Health Sciences Center, Dalhousie University, Halifax, Nova Scotia, Canada; [5]Service d'Hématologie et Thérapie Cellulaire, Hôpital Bretonneau, Centre Hospitalier Régional Universitaire (CHRU), Tours, France; [6]St James's Institute of Oncology, Leeds Teaching Hospitals NHS Trust and University of Leeds, Leeds, UK; [7]Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel; [8]Icon Cancer Care, South Brisbane, QLD, Australia; [9]Institute of Haematology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia; [10]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [11]Department of Hematology, National Hospital Organization Disaster Medical Center of Japan, Tachikawa, Japan; [12]Janssen Research & Development, LLC, Spring House, PA, USA; [13]Janssen Research & Development, Beerse, Belgium; [14]Clínica Universidad de Navarra-CIMA, IDISNA, Pamplona, Spain.

# Updated Efficacy



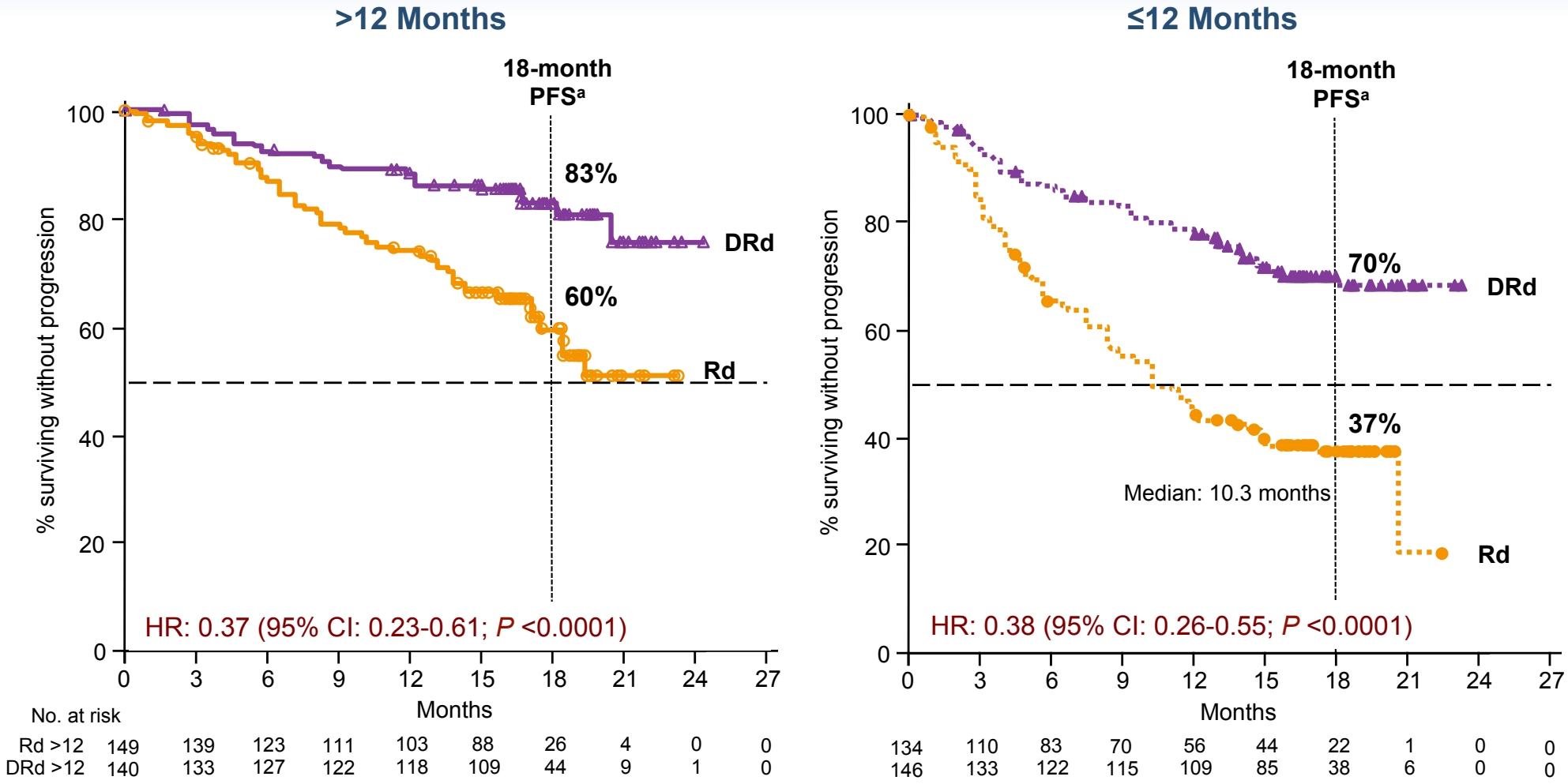




- Median (range) follow-up: 17.3 (0-24.5) months

**Responses continue to deepen in the DRd group with longer follow-up**

HR, hazard ratio; CI, confidence interval; sCR, stringent complete response; PR, partial response; ITT, intent-to-treat.
Note: PFS = ITT population; ORR = response-evaluable population.
[a]Kaplan-Meier estimate.
[b]*P* <0.0001 for DRd vs Rd.

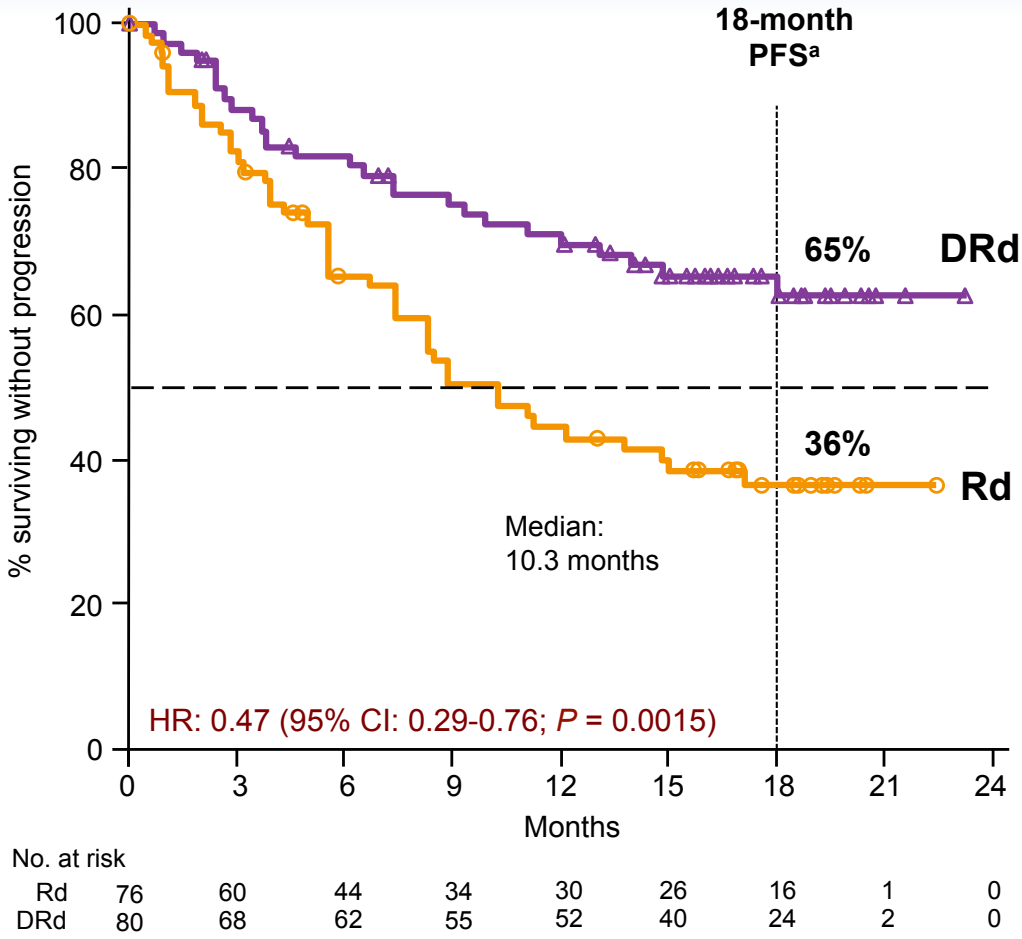
# Time From Last Line of Therapy to Study Treatment of > or ≤12 Months

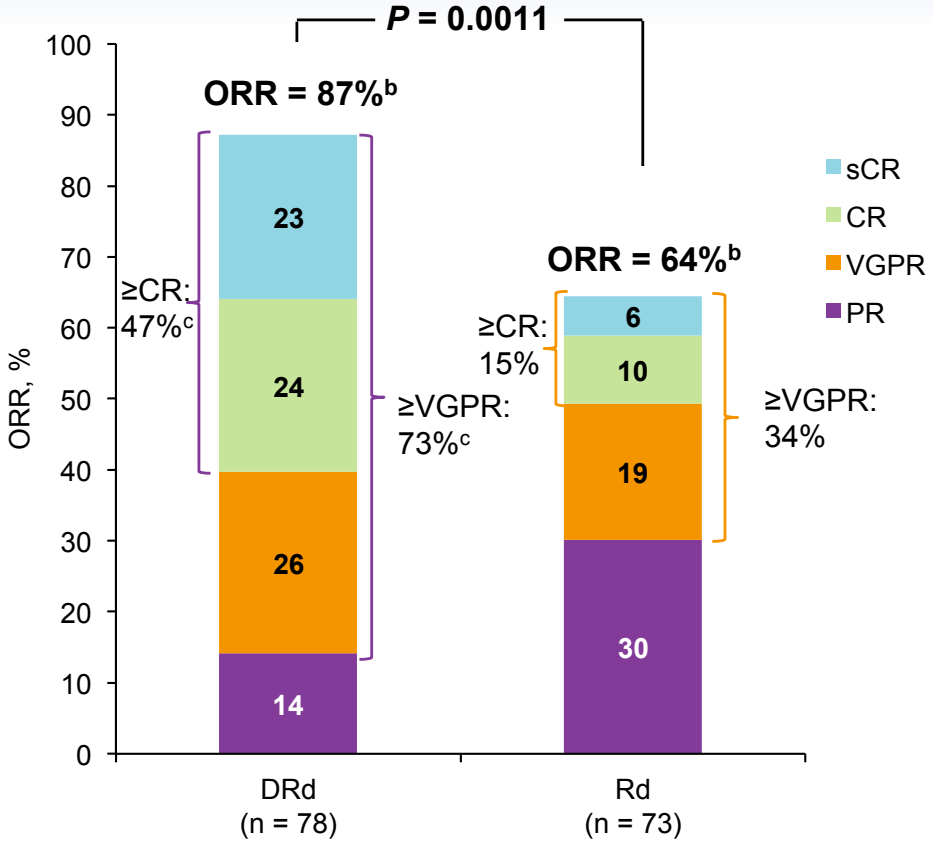



**DRd is superior to Rd regardless of time since last therapy**

[a]Kaplan-Meier estimate.

# Refractory to Last Line of Therapy



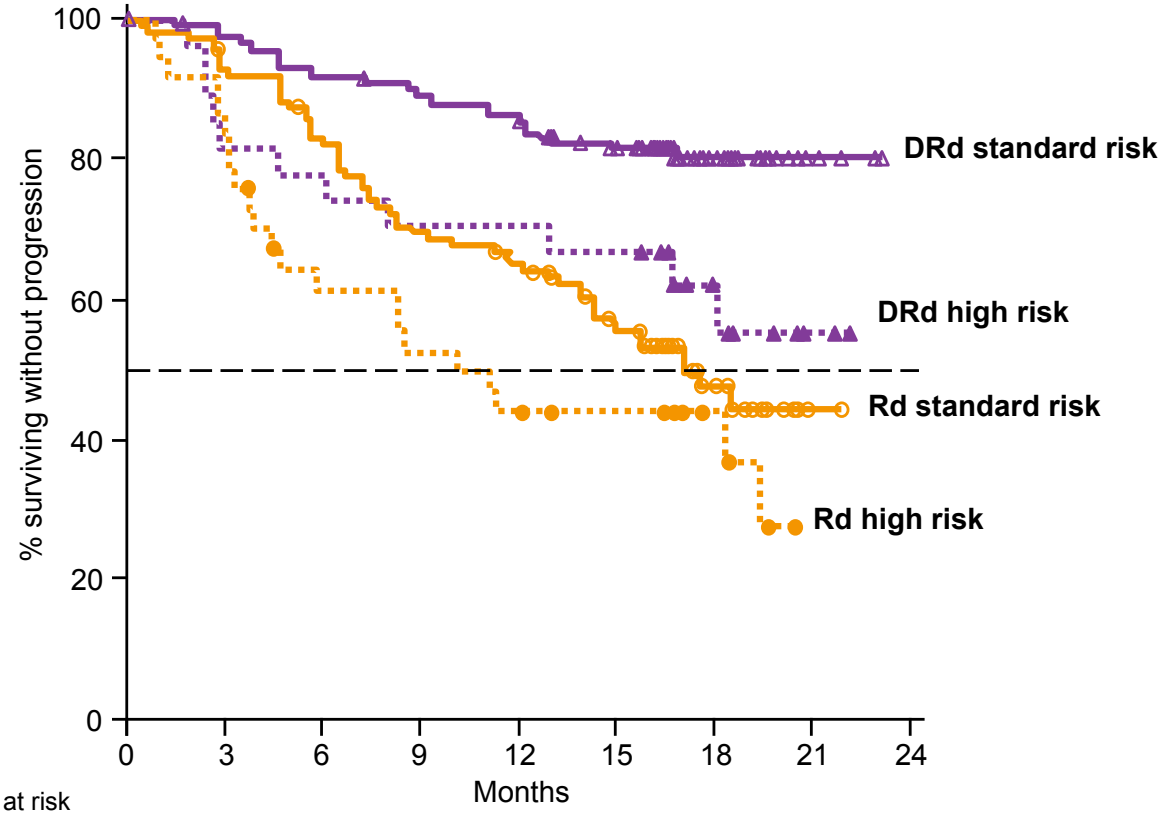




**DRd benefits patients refractory to last line of therapy**

[a]Kaplan-Meier estimate.
[b]Response-evaluable population.
[c]*P* <0.0001 for DRd vs Rd.

# PFS: Cytogenetic Risk in All Evaluable Patients[a]

- Comparable results in 1 to 3 prior lines population




| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Rd std risk | 113 | 104 | 92 | 77 | 71 | 57 | 20 | 1 | 0 |
| DRd std risk | 133 | 128 | 120 | 116 | 111 | 98 | 41 | 4 | 0 |
| Rd high risk | 37 | 32 | 21 | 18 | 15 | 13 | 6 | 0 | 0 |
| DRd high risk | 28 | 22 | 21 | 19 | 19 | 18 | 9 | 2 | 0 |

| **High risk** | **DRd** n = 28 | **Rd** n = 37 |
|---|---|---|
| Median PFS, mo | **NR** | **10.2** |
| HR (95% CI) | 0.44 (0.19-1.03) | |
| *P* value | 0.0475 | |
| | n = 27 | n = 36 |
| ORR, % | **85** | **67** |
| *P* value | NS | |

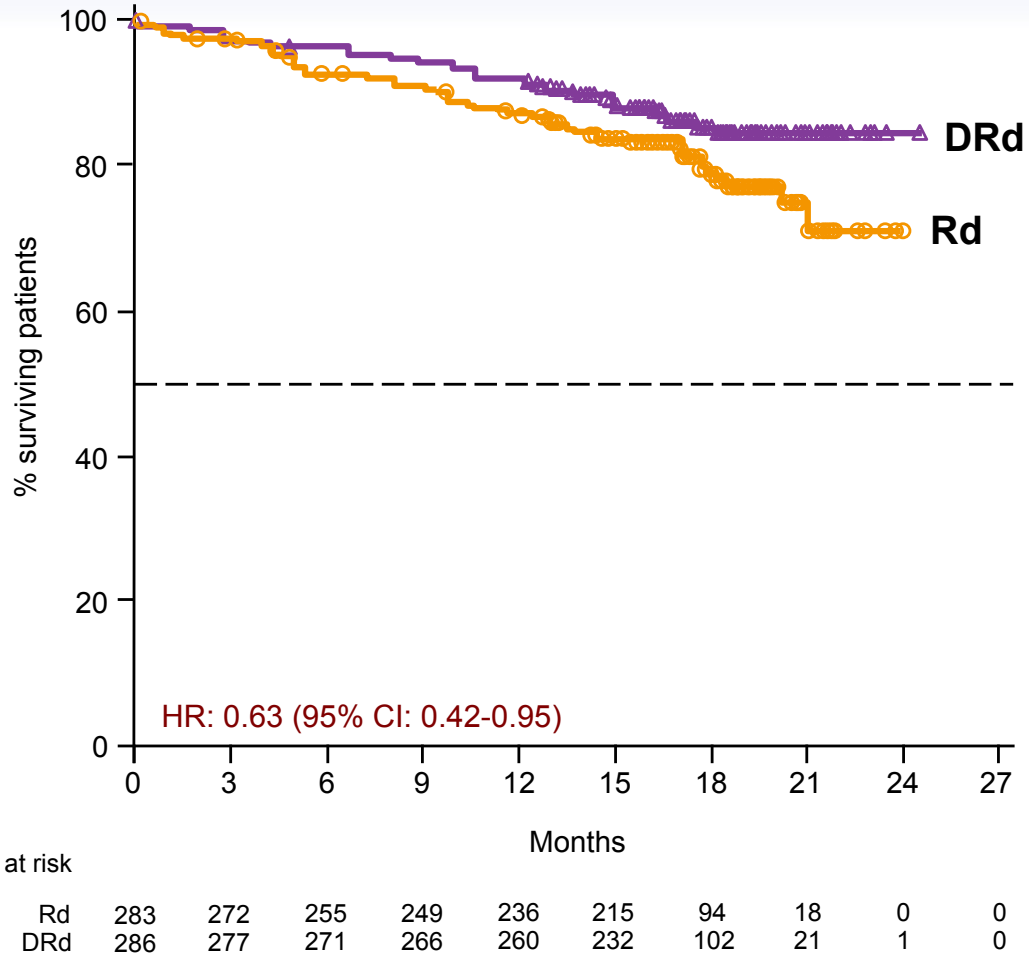
| **Standard risk** | **DRd** n = 133 | **Rd** n = 113 |
|---|---|---|
| Median PFS, mo | **NR** | **17.1** |
| HR (95% CI) | 0.30 (0.18-0.49) | |
| *P* value | <0.0001 | |
| | n = 132 | n = 111 |
| ORR, % | **95** | **82** |
| *P* value | 0.0020 | |

**DRd improves outcomes regardless of cytogenetic risk**

NR, not reached; NS, not significant.

[a]ITT/Biomarker risk–evaluable analysis set. High-risk patients had any of t(4;14), t(14;16), or del17p. Standard-risk patients had an absence of high-risk abnormalities.

# OS




No. at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Rd | 283 | 272 | 255 | 249 | 236 | 215 | 94 | 18 | 0 | 0 |
| DRd | 286 | 277 | 271 | 266 | 260 | 232 | 102 | 21 | 1 | 0 |

- **OS events**
  - 40 (14%) in DRd
  - 56 (20%) in Rd

**Curves are beginning to separate, but OS data are immature**

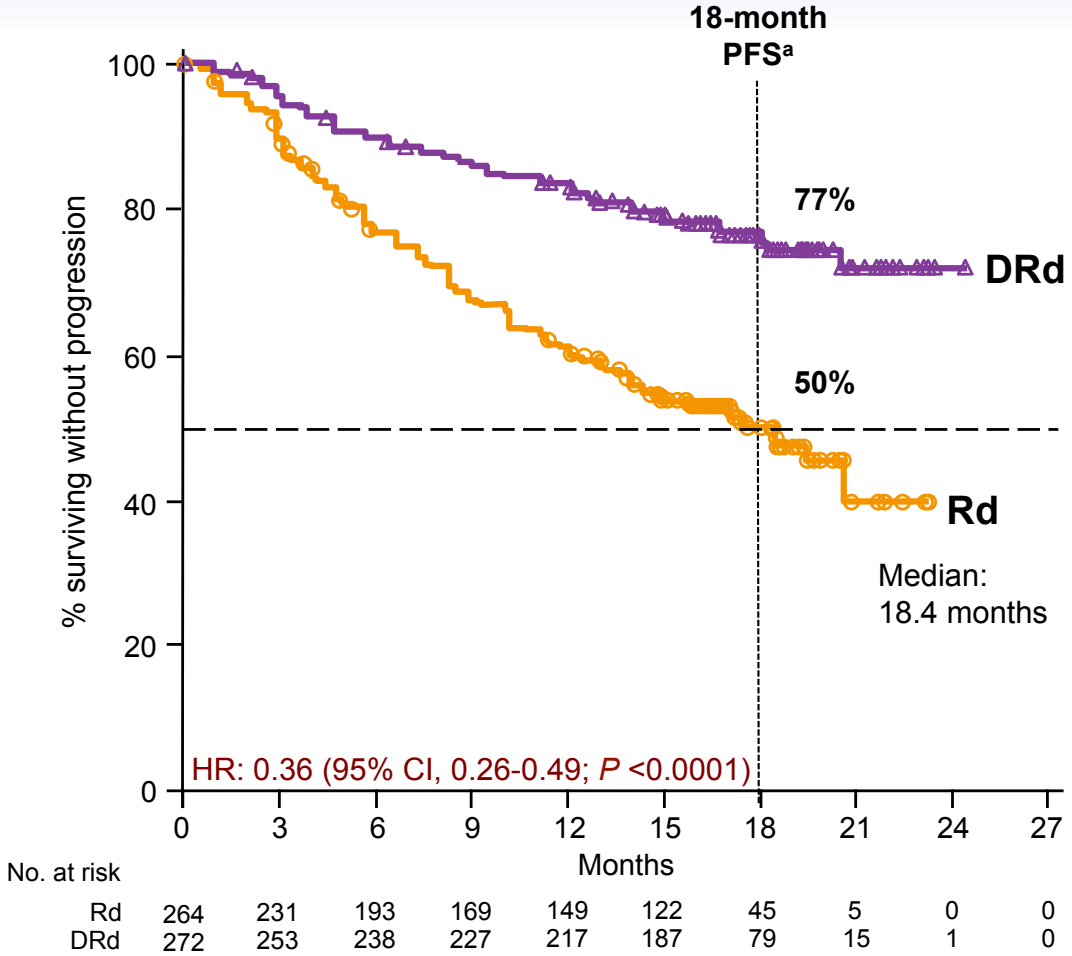
ITT population.
Median OS was not reached; results did not cross the prespecified stopping boundary.

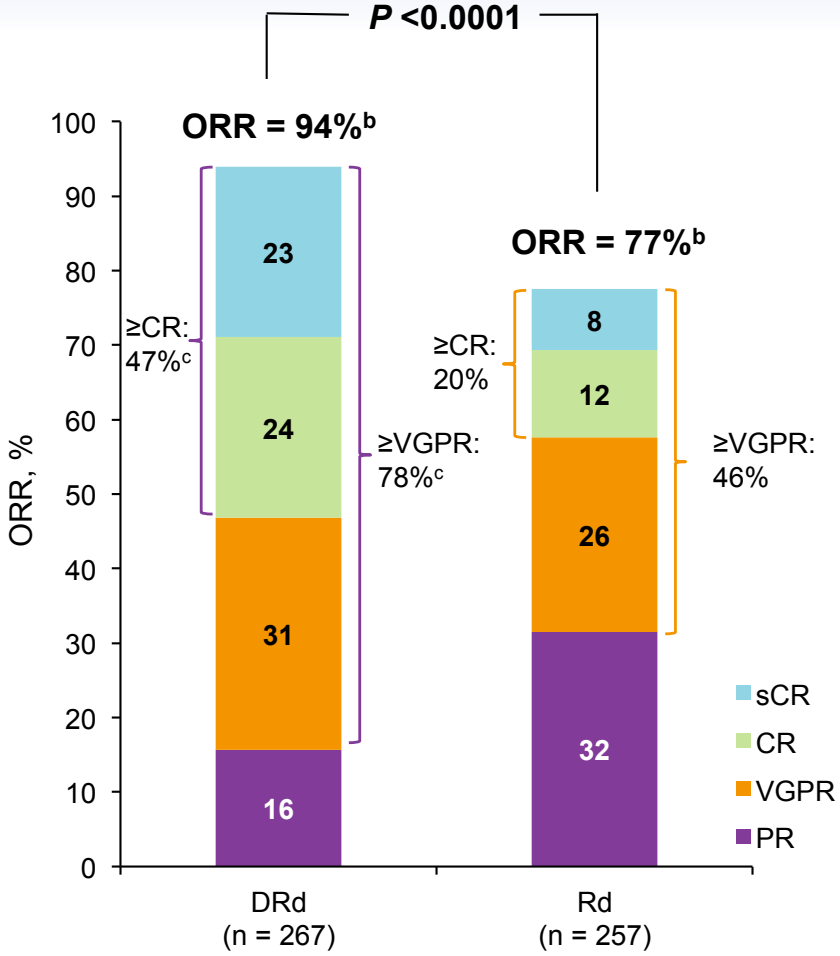
## ASH 2016, Abstract n. 1151

- Efficacy of Daratumumab, Lenalidomide, and Dexamethasone Versus Lenalidomide and Dexamethasone Alone for Relapsed or Refractory Multiple Myeloma Among Patients With 1 to 3 Prior Lines of Therapy Based on Previous Treatment Exposure: Updated Analysis of POLLUX


- Philippe Moreau,[1] Jonathan L. Kaufman,[2] Heather Sutherland,[3] Marc Lalancette,[4] Hila Magen,[5] Shinsuke Iida,[6] Jin Seok Kim,[7] Miles Prince,[8] Tara Cochrane,[9] Nushmia Z. Khokhar,[10] Mary Guckert,[10] Xiang Qin,[10] Albert Oriol[11]
- [1]Hematology, University Hospital Hôtel-Dieu, Nantes, France; [2]Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA; [3]Cell Separator Unit and Leukemia/Bone Marrow Transplant Program, University of British Columbia, Vancouver, BC, Canada; [4]Hotel-Dieu de Québec, Québec City, Québec, Canada; [5]Institute of Hematology, Davidoff Cancer Center, Beilinson Hospital, Rabin Medical Center, Petah-Tikva and Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel, Petah Tikva, Israel; [6]Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [7]Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, Seoul, South Korea; [8]University of Melbourne, Peter MacCallum Cancer Centre, Melbourne, Australia; [9]Gold Coast University Hospital, Southport, QLD, Australia; [10]Janssen Research & Development, LLC, Spring House, PA, USA; [11]Institut Català d'Oncologia, Institut Josep Carreras, Hospital Germans Trias I Pujol, Barcelona, Spain.

# Efficacy in the 1 to 3 Prior Lines Subgroup

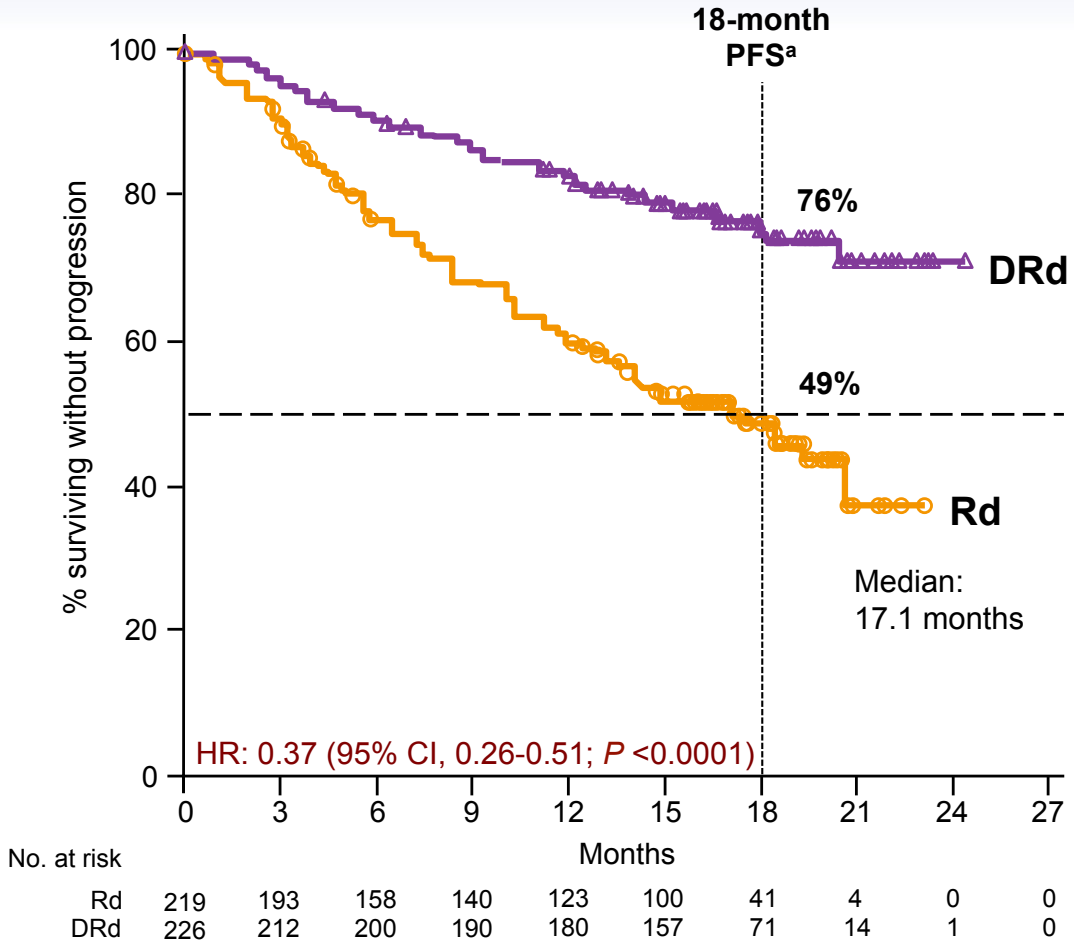


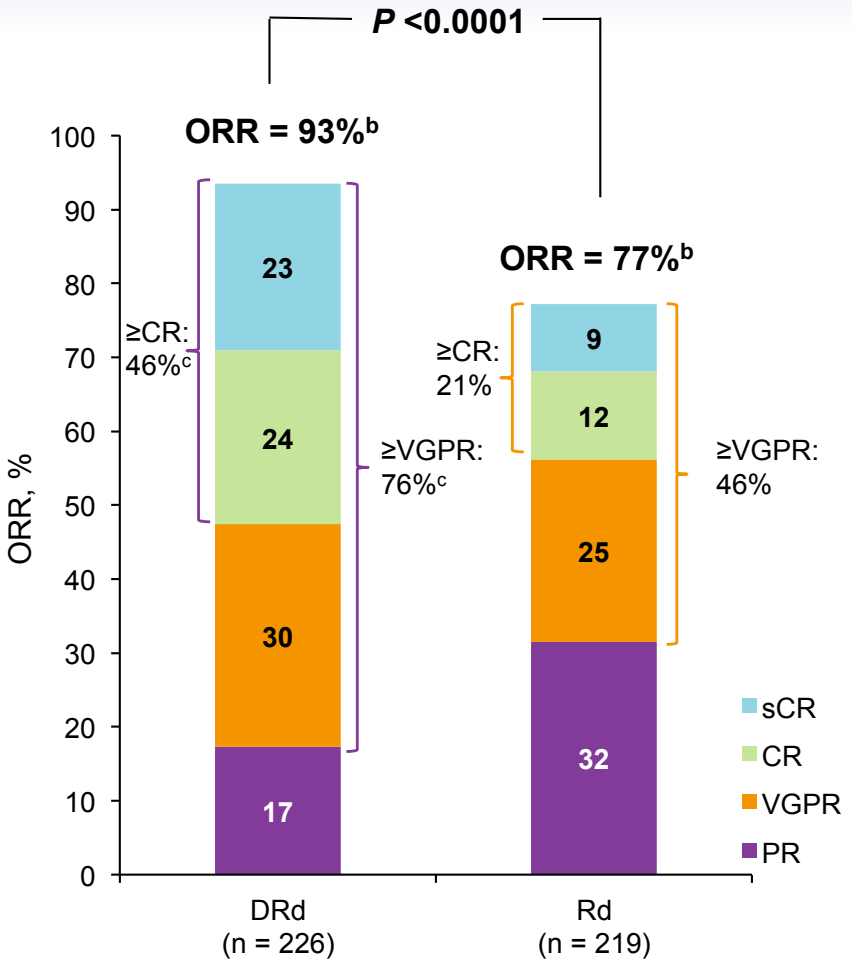




**Responses continue to deepen in the DRd group with longer follow-up**

HR, hazard ratio.
[a]Kaplan-Meier estimate.
[b]Response-evaluable population.
[c]*P* <0.0001 for DRd vs Rd.

# Lenalidomide-naïve in 1 to 3 Prior Lines

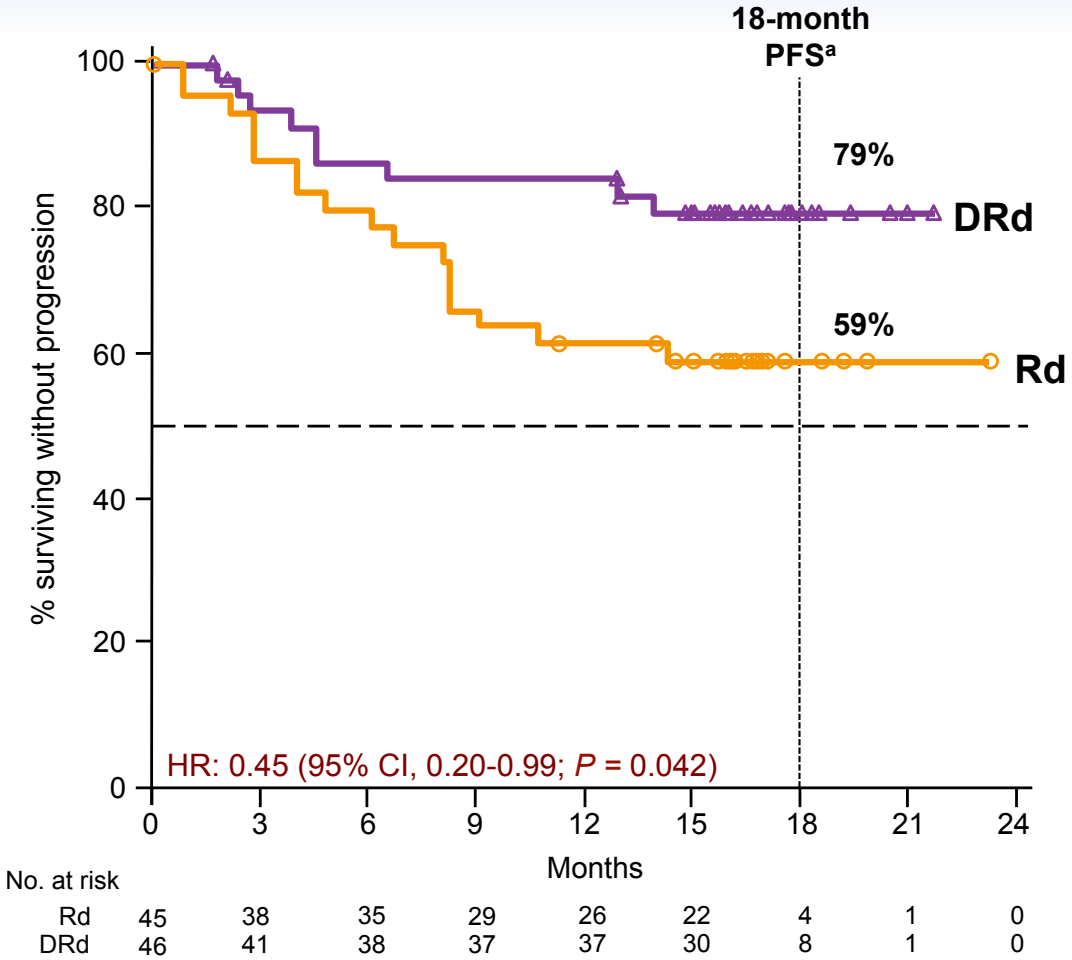


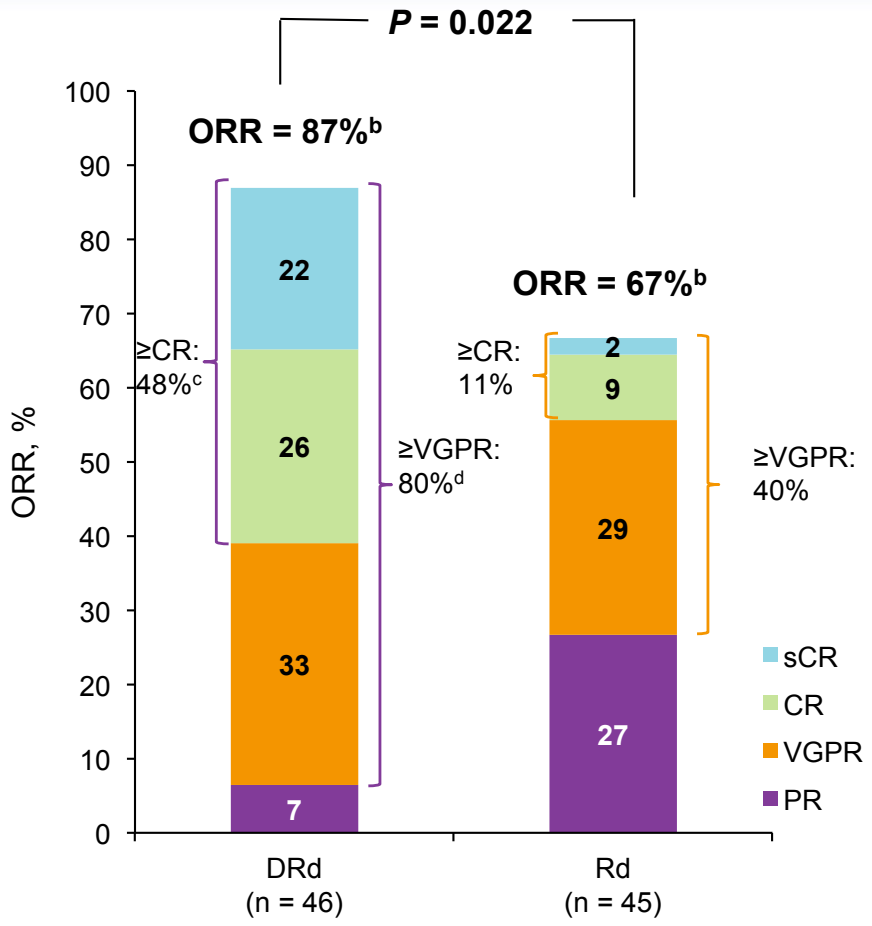




**DRd maintains treatment benefit in lenalidomide-naïve patients**

[a]Kaplan-Meier estimate.
[b]Response-evaluable population.
[c]*P* <0.0001 for DRd vs Rd.

# Lenalidomide-exposed in 1 to 3 Prior Lines

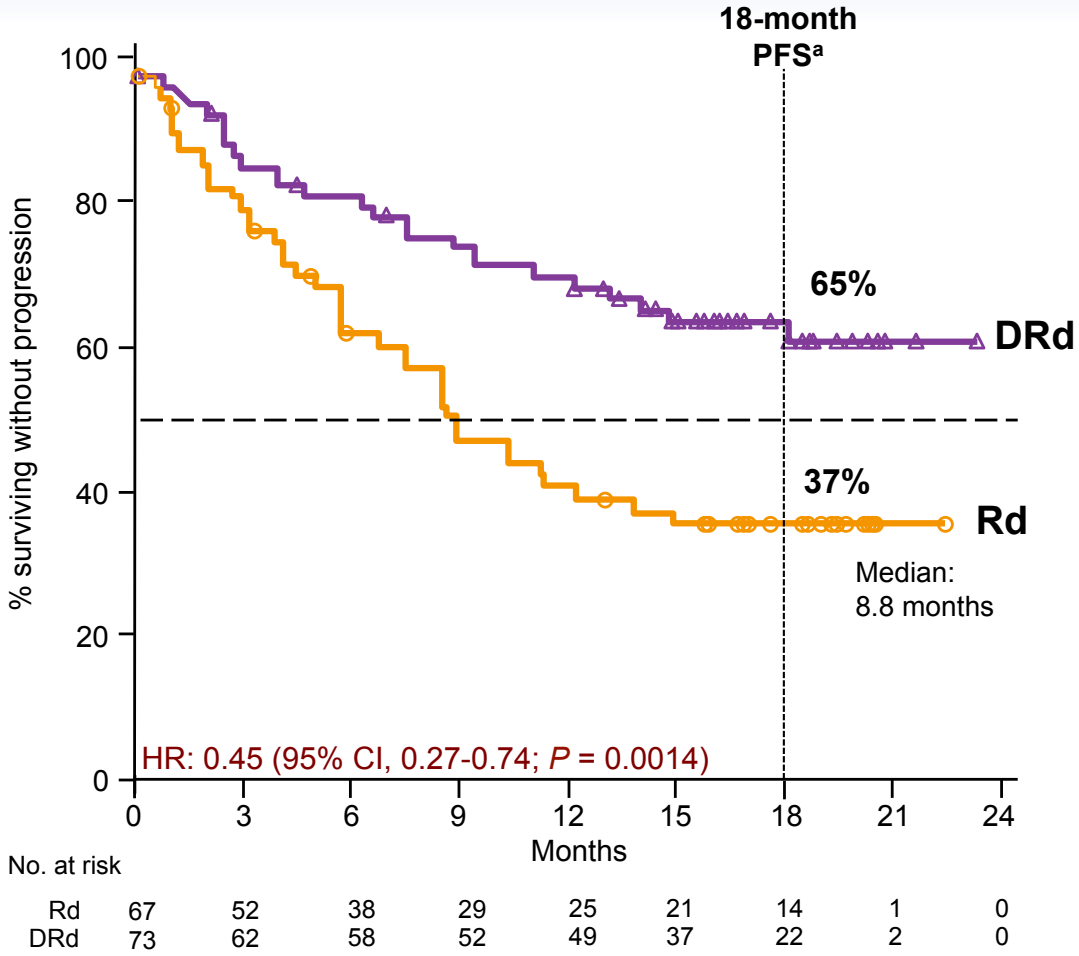


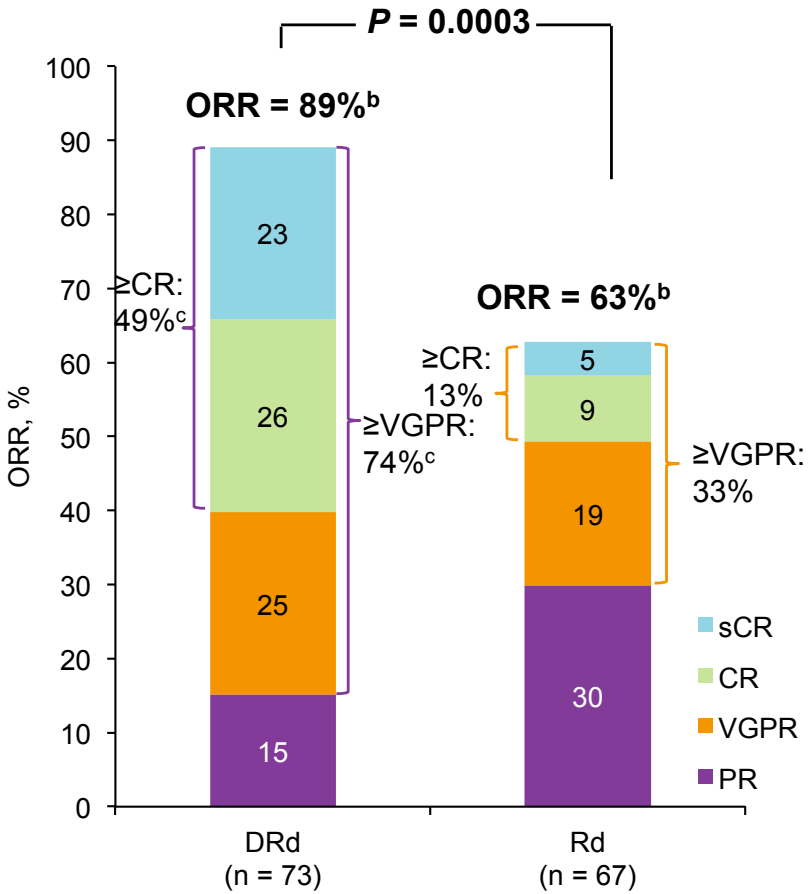




**DRd improves outcomes regardless of prior treatment with lenalidomide**

[a]Kaplan-Meier estimate.
[b]Response-evaluable population.
[c]*P* = 0.0001 for DRd vs Rd.
[d]*P* <0.0001 for DRd vs Rd.

# Refractory to Last Line of Therapy: 1 to 3 Prior Lines

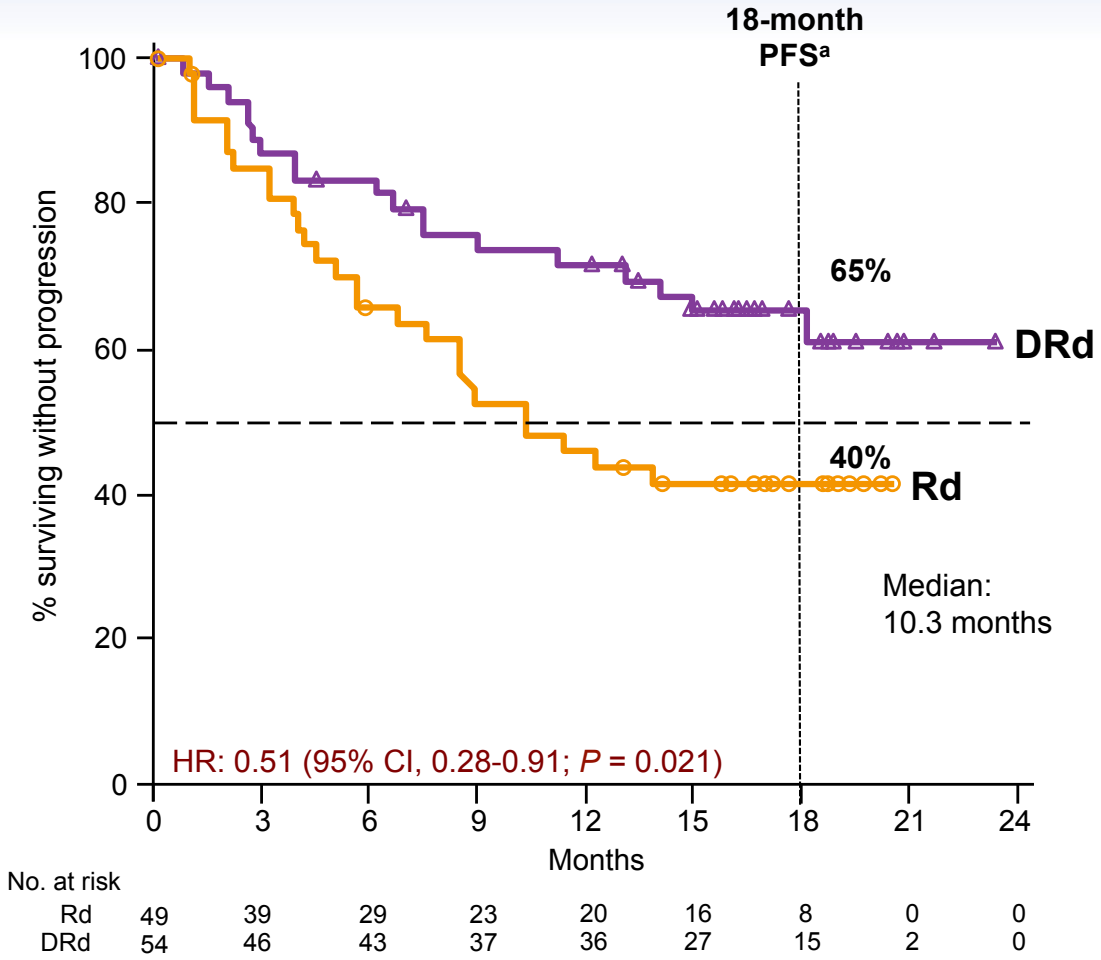


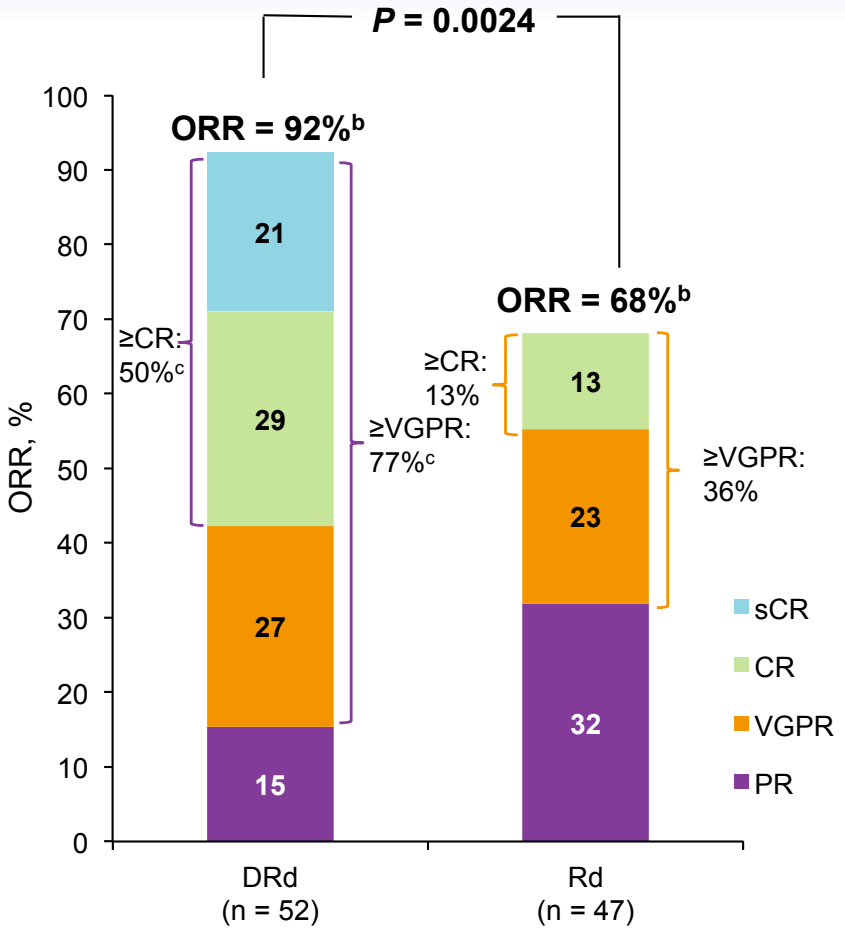




**DRd treatment benefit observed in patients refractory to last line of therapy**

[a]Kaplan-Meier estimate.
[b]Response-evaluable population.
[c]*P* <0.0001 for DRd vs Rd.

# Bortezomib-refractory in 1 to 3 Prior Lines




**DRd significantly improves outcomes irrespective of bortezomib refractoriness**

[a]Kaplan-Meier estimate.
[b]Response-evaluable population.
[c]*P* <0.0001 for DRd vs Rd.

# Dara-Rd vs Lenalidomide-based Studies

| | POLLUX DRd vs Rd | ASPIRE KRd vs Rd[1] | ELOQUENT-2 ERd vs Rd[2,3] | TOURMALINE-MM1 IRd vs Rd[4] |
|---|---|---|---|---|
| PFS HR (95% CI) | **0.37 (0.27-0.52)** | 0.69 (0.57-0.83) | 0.73 (0.60-0.89) | 0.74 (0.59-0.94) |
| ORR | **93%** | 87% | 79% | 78% |
| ≥VGPR | **76%** | 70% | 33% | 48% |
| ≥CR | **43%** | 32% | 4% | 14% |
| Duration of response, mo | **NE** | 28.6 | 20.7 | 20.5 |
| OS HR (95% CI) | **0.64 (0.40-1.01)** | 0.79 (0.63-0.99) | 0.77 (0.61-0.97) | NE |


1. Stewart AK, et al. *N Engl J Med*. 2015;372(2):142-152.
2. Lonial S, et al. *N Engl J Med*. 2015;373(7):621-631.
3. Dimopoulos MA, et al. *Blood*. 2015;126(23):Abstract 28.
4. Moreau P, et al. *N Engl J Med*. 2016;374(17):1621-1634.

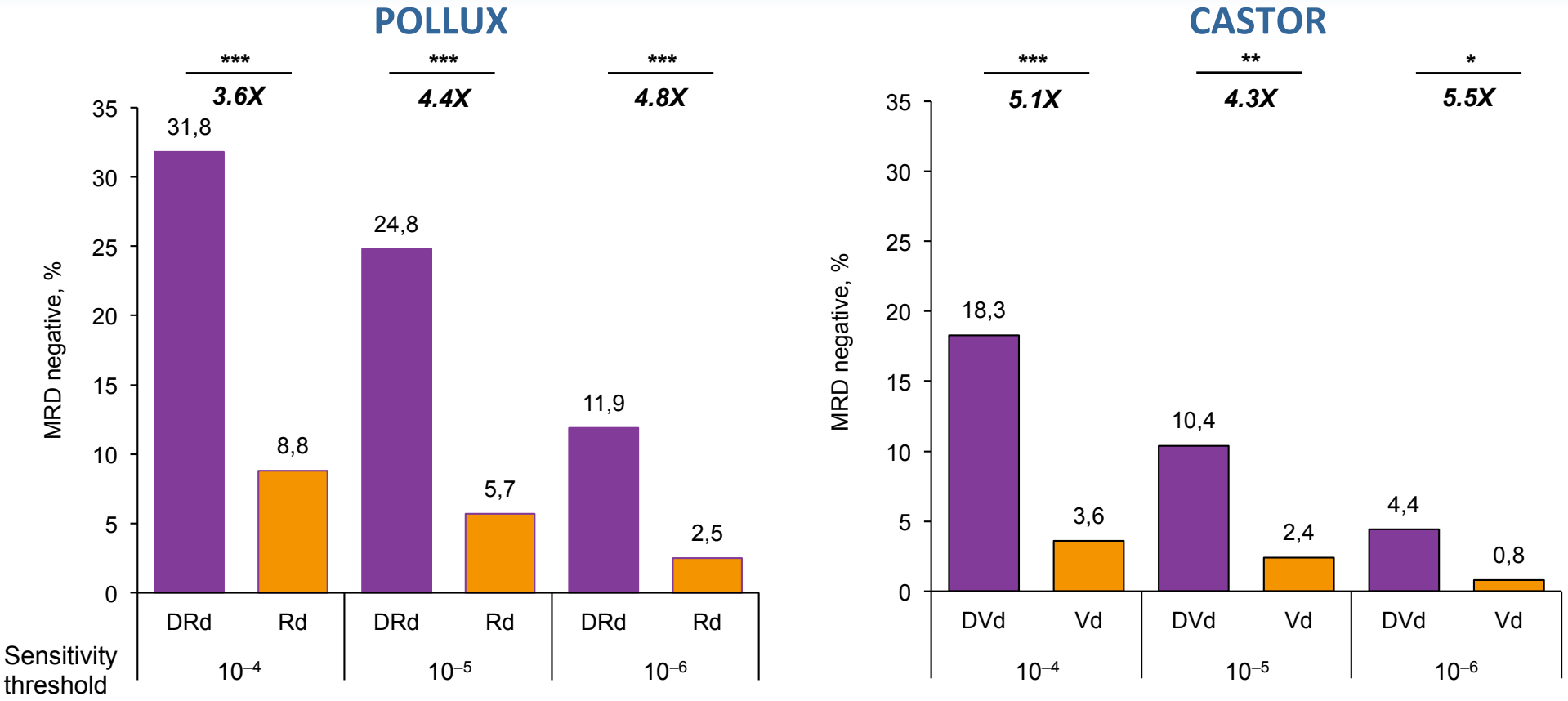

Dimopoulos er al. N Engl J Med 2016;375:1319-31

K, carfilzomib; E, elotuzumab; N, ixazomib.

# ASH 2016, Abstract: 246

- Evaluation of Minimal Residual Disease (MRD) in Relapsed/Refractory Multiple Myeloma (RRMM) Patients Treated With Daratumumab in Combination With Lenalidomide Plus Dexamethasone or Bortezomib Plus Dexamethasone (Castor vs Pollux)
- Hervé Avet-Loiseau,[1] Tineke Casneuf,[2] Christopher Chiu,[3] Jacob Laubach,[4] Je-Jung Lee,[5] Philippe Moreau,[6] Torben Plesner,[7] Hareth Nahi,[8] Nushmia Z. Khokhar,[3] Ming Qi,[3] Jordan Schecter,[9] Victoria Carlton,[10] Xiang Qin,[3] Kevin Liu,[9] Kaida Wu,[3] Sen Hong Zhuang,[9] Tahamtan Ahmadi,[3] A. Kate Sasser,[3] Jesus San-Miguel[11]
- MRD was evaluated at 3 sensitivity thresholds: $10^{-4}$, $10^{-5}$, and $10^{-6}$
- MRD-negativity rate = proportion of patients with negative MRD test results at any time during treatment
- A stringent, unbiased MRD evaluation was applied
  - MRD-negativity counts were evaluated against the intent-to-treat (ITT) population
  - Any patient in the ITT population not determined to be MRD negative was scored as MRD positive
  - A minimum cell input equivalent to the given sensitivity threshold was required to determine MRD negativity
    - ie, MRD at $10^{-6}$ required that ≥1 million cells were evaluated

# Proportion of MRD-negative Patients at $10^{-4}$, $10^{-5}$, and $10^{-6}$ Thresholds



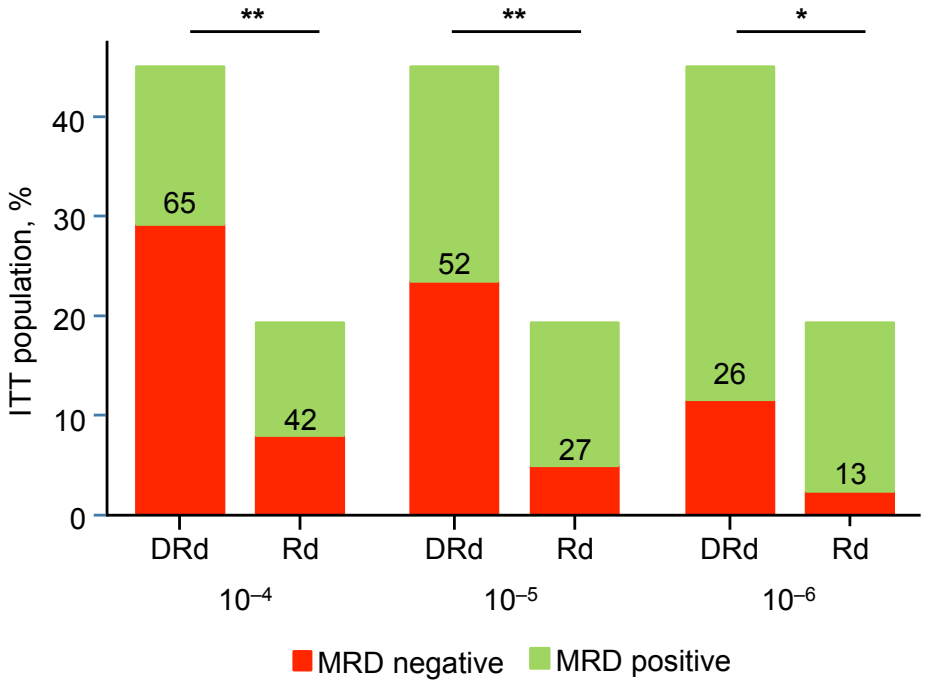

- Daratumumab in combination with standard of care significantly improved MRD-negative rates at all thresholds

*** ***P*** **<0.0001.**
** ***P*** **<0.005.**
* ***P*** **<0.05.**

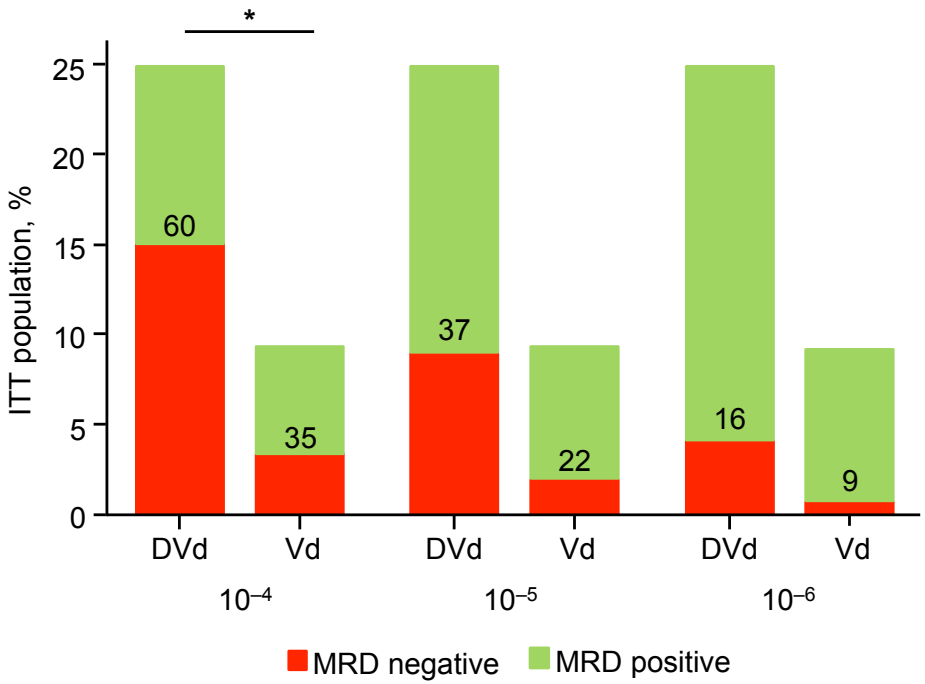
*P* values calculated using likelihood-ratio chi-square test.

# MRD Negativity Among Patients With ≥CR

## POLLUX




## CASTOR




- Values refer to the percentage of MRD-negative patients among those who achieved ≥CR in a given treatment arm

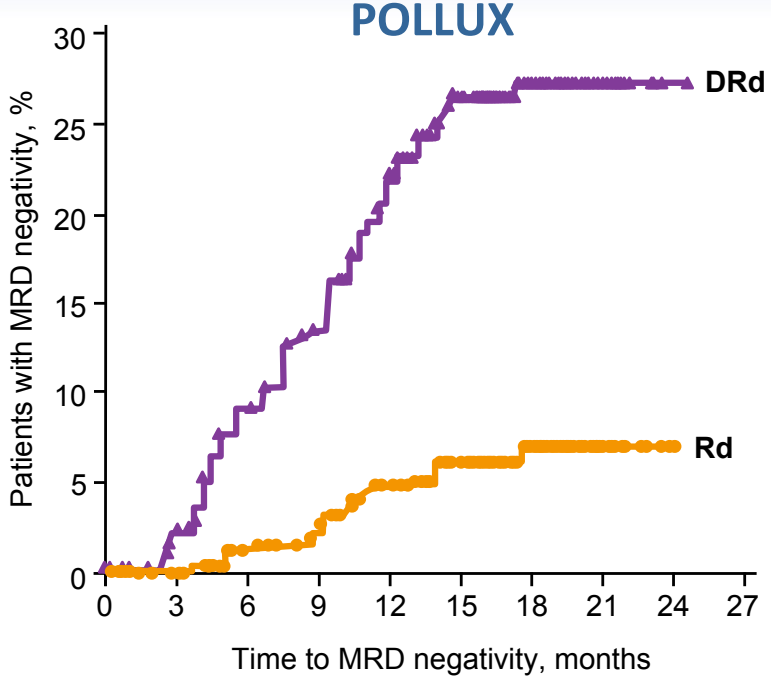
** ***P*** **<0.005.**
* ***P*** **<0.05.**

**Consistently higher MRD-negative rates in patients with ≥CR treated with a daratumumab-containing regimen**

*P* values calculated using likelihood-ratio chi-square test.

# Time to MRD ($10^{-5}$)

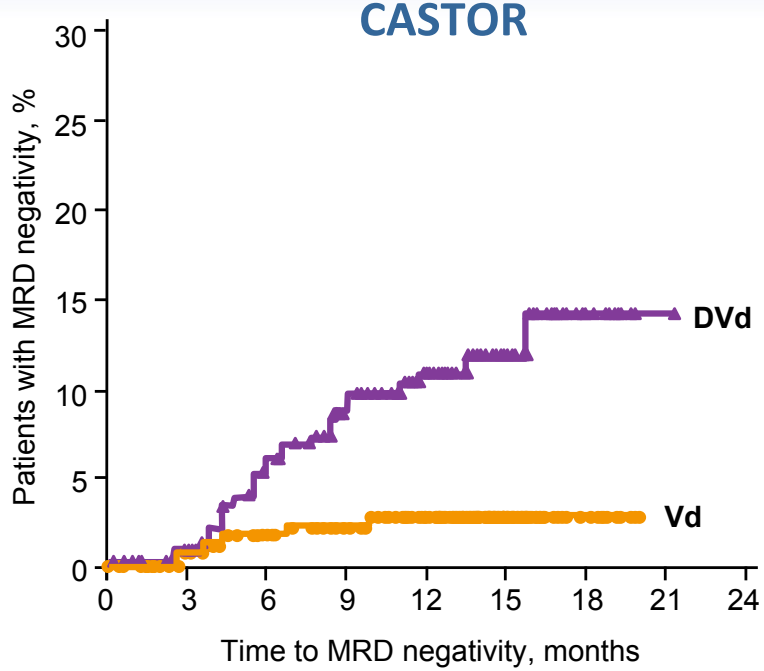
## POLLUX




**Patients at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Rd | 283 | 272 | 252 | 243 | 225 | 202 | 83 | 18 | 0 | 0 |
| DRd | 286 | 271 | 247 | 229 | 202 | 169 | 71 | 15 | 1 | 0 |

## CASTOR




**Patients at risk**

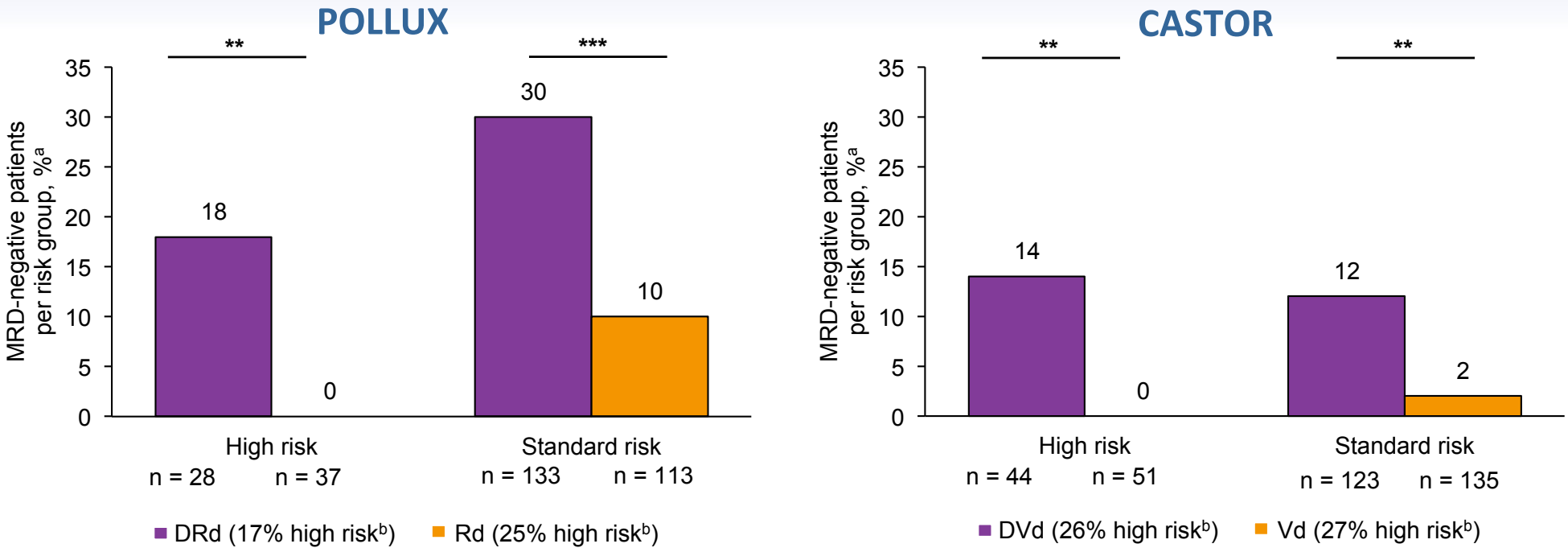
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Vd | 247 | 217 | 202 | 187 | 130 | 55 | 13 | 0 | 0 |
| DVd | 251 | 229 | 212 | 190 | 137 | 58 | 12 | 1 | 0 |

- Rapid accumulation of MRD-negative events in patients treated with daratumumab-containing regimens versus standard of care
- MRD-negative patients continued to accumulate over time in both studies

**Majority of patients maintain MRD negativity; patients will continue to be followed annually**

Only 1 MRD-negative sample counted per patient.

# MRD at $10^{-5}$ by Cytogenetic Risk by NGS




- No high-risk MRD-negative patients have progressed or converted to MRD positive
  - High risk = any of t(4;14), t(14;16), del17p
  - Standard risk = conclusive absence of all 3 markers

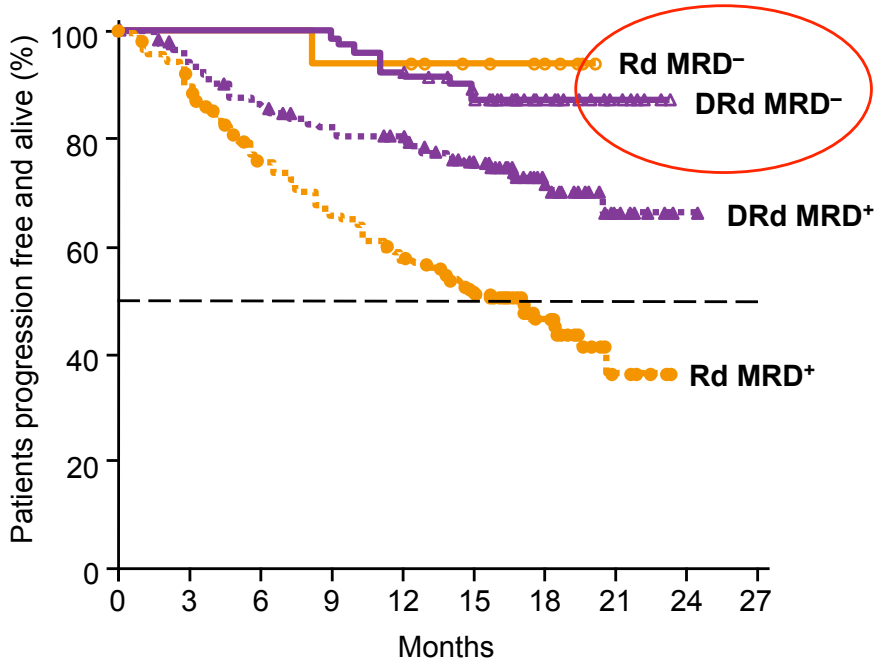
**In high-risk patients, MRD-negative status was achieved only in those treated with daratumumab-containing regimens**

*P* values calculated using likelihood-ratio chi-square test.
[a]Percentage of patients within a given risk group and treatment arm.
[b]Percentage of patients within a given treatment arm, within the biomarker-evaluable population.

*** ***P*** **<0.0001.**
** ***P*** **<0.005.**

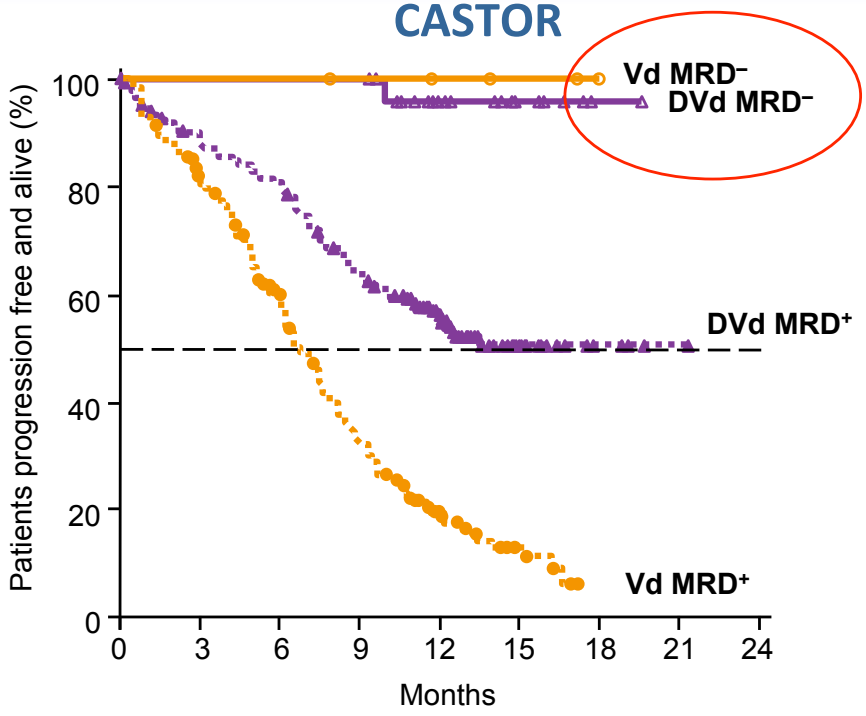
# PFS According to MRD Status at $10^{-5}$

## POLLUX




| Patients at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Rd MRD negative | 16 | 16 | 16 | 15 | 15 | 12 | 10 | 0 | 0 | 0 |
| DRd MRD negative | 71 | 71 | 71 | 70 | 66 | 57 | 28 | 6 | 0 | 0 |
| Rd MRD positive | 267 | 233 | 190 | 166 | 144 | 120 | 38 | 5 | 0 | 0 |
| DRd MRD positive | 215 | 195 | 178 | 167 | 161 | 137 | 54 | 9 | 1 | 0 |

## CASTOR




| Patients at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Vd MRD negative | 6 | 6 | 6 | 5 | 3 | 2 | 0 | 0 |
| DVd MRD negative | 26 | 26 | 26 | 26 | 15 | 7 | 1 | 0 |
| Vd MRD positive | 241 | 176 | 123 | 68 | 20 | 7 | 0 | 0 |
| DVd MRD positive | 225 | 189 | 172 | 134 | 76 | 26 | 4 | 1 |

Lower risk of progression in MRD-negative patients

PFS benefit in MRD-positive patients who received daratumumab-containing regimens versus standard of care

# ASH 2016, Abstract n. 492

- Clinical Efficacy of Daratumumab, Pomalidomide, and Dexamethasone in Relapsed, Refractory Myeloma Patients: Utility of Retreatment With Daratumumab Among Refractory Patients
- Ajay K. Nooka, Nisha Joseph, Lawrence H. Boise, Charise Gleason, Jonathan L. Kaufman, Sagar Lonial
- Winship Cancer Institute of Emory University, Atlanta, GA, USA.
- We have evaluated our institutional experience of DARA in combination with POM and dexamethasone, and the utility of this combination among patients refractory to DARA and POM
- In this analysis, we have evaluated all patients who have received DARA–POM-D for relapsed or relapsed and refractory myeloma and were treated at Emory University from January 2015 through July 2016
  - Naïve to DARA and POM (Cohort 1) n = 19
  - Refractory to DARA and/or POM (Cohort 2) n = 22
  - Refractory to DARA and POM (Cohort 3) n = 12
- Responses were evaluated using International Myeloma Working Group criteria

# Refractory Status

| Refractory to, n (%) | Cohort 1 (n = 19) (DARA and POM naïve) | Cohort 2 (n = 22) (DARA or POM ref) | Cohort 3 (n = 12) (DARA and POM ref) |
|---|---|---|---|
| Median (range) number of prior lines | 3 (1-7) | 5 (3-13) | 6.5 (3-13) |
| Last lines of therapy | 19 (100) | 22 (100) | 12 (100) |
| Bortezomib | 14 (74) | 22 (100) | 12 (100) |
| Carfilzomib | 2 (11) | 16 (73) | 8 (67) |
| Lenalidomide | 19 (100) | 22 (100) | 12 (100) |
| Melphalan | 17 (90) | 20 (91) | 11 (92) |
| POM | 0 (0) | 21 (95) | 12 (100) |
| DARA | 0 (0) | 13 (59) | 12 (100) |
| Bortezomib+lenalidomide | 14 (74) | 22 (100) | 12 (100) |
| Quad-refractory* | 0 (0) | 15 (69) | 8 (67) |
| Penta-refractory† | 0 (0) | 8 (37) | 8 (67) |

*Quad-refractory: refractory to lenalidomide, POM, bortezomib, and carfilzomib.
†Penta-refractory: refractory to lenalidomide, POM, bortezomib, carfilzomib, and DARA.

# Best Responses With DARA–POM-D Regimen

| | Cohort 1 (n = 19) (DARA and POM naïve) | Cohort 2 (n = 22) (DARA or POM ref) | Cohort 3 (n = 12) (DARA and POM ref) |
|---|---|---|---|
| ORR | 17 (89%) | 9 (40.9%) | 4 (33.3%) |
| sCR | 7 (36.8%) | | |
| CR | 1 (5.3%) | | |
| VGPR | 3 (15.8%) | 1 (4.5%) | 1 (8.3%) |
| PR | 8 (42.1%) | 8 (36.4%) | 3 (25%) |
| MR/SD | 1 (5.3%) | 9 (40.9%) | 6 (50%) |
| PD | 1 (5.3%) | 4 (18.2%) | 2 (16.7%) |
| Median cycles | 15 (1-23) | 3 (1-8) | 3 (1-8) |

CR, complete response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease.

- Median PFS for all cohorts: 7 months (median follow-up of 16 months)
- Median PFS for Cohort 1: not reached (median follow-up of 17 months)
- Median PFS for Cohort 3: 3 months (median follow-up of 8 months)

# Open-label, Multicenter, Dose-escalation Phase 1b Study to Assess the Subcutaneous Delivery of Daratumumab in Patients (Pts) With Relapsed or Refractory Multiple Myeloma (PAVO)

## Phase 1b, open-label, multicenter, dose-finding, proof of concept study

**Key eligibility criteria**

- RRMM with measurable disease
- ≥2 prior lines of treatment
- Not received anti-CD38 therapy

**Group 1 (n = 8)**
DARA: 1,200 mg
rHuPH20: 30,000 U

→

**Group 2[a] (n = 45)**
DARA: 1,800 mg
rHuPH20: 45,000 U

**Primary endpoints**

- $C_{trough}$ of DARA at Cycle 3/Day 1
- Safety

**Secondary endpoints**

- ORR
- CR
- Duration of response
- Time to response

**Dosing schedule**

- Approved schedule for IV
  - 1 Cycle = 28 days

**Infusion time**

- 1,200 mg: 20-min infusion (60 mL)
- 1,800 mg: 30-min infusion (90 mL)

**Pre-[b]/post-infusion medication**

Acetaminophen, diphenhydramine, montelukast, and methylprednisolone

RRMM, relapsed or refractory multiple myeloma; $C_{trough}$, trough concentration; ORR, overall response rate; CR, complete response; PK, pharmacokinetic.
[a]Group 2 comprises 4 distinct cohorts, each treated with DARA 1,800 mg and rHuPH20 45,000 U. $C_{trough}$ on Cycle 3/Day 1 in Group 1 supported dose selection for Group 2. The study evaluation team reviewed safety after Cycle 1 and PK after Cycle 3/Day 1 for each group.
[b]Administered 1 hour prior to infusion.

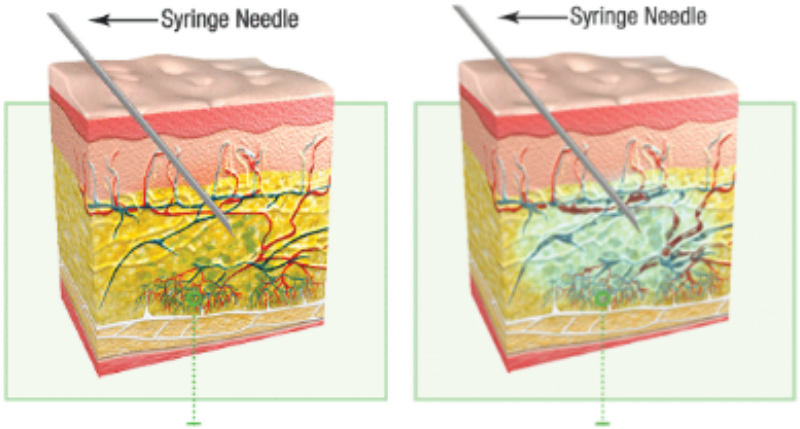
Usmani,et al. ASH Meeting 2016, abs. 1149

# Recombinant Human Hyaluronidase

- The ENHANZE™ platform of recombinant human hyaluronidase (rHuPH20) temporarily breaks down the hyaluronan barrier, allowing rapid absorption of injected drugs[1]

- Herceptin SC® and MabThera SC® are approved in Europe as co-formulate products with rHuPH20[2,3]
  - Dosing time is 5 to 8 minutes with subcutaneous (SC) administration versus 0.5 to 6 hours with IV[4-6]

**Schematic of rHuPH20[1]**

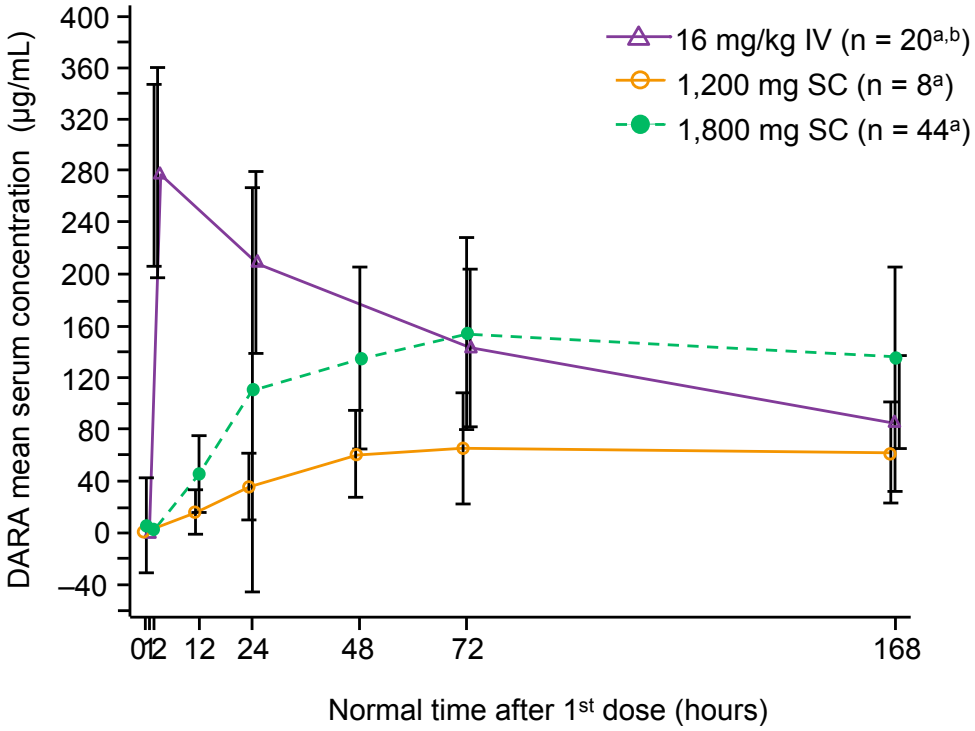



**Aim: To determine the safety, pharmacokinetics, and efficacy of DARA as SC administration**

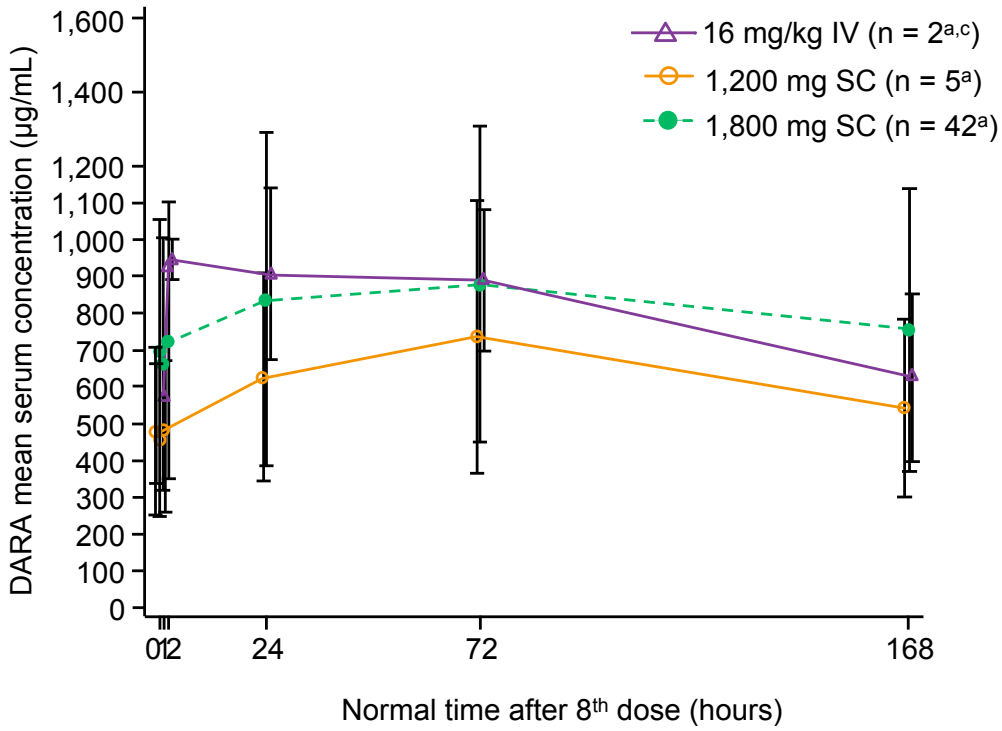

1. Halozyme Therapeutics. Mechanism of action for Hylenex recombinant (hyaluronidase human injection). www.hylenex.com/mechanism-of-action. Accessed November 8, 2016.
2. European Medicines Agency. Herceptin: EPAR – product information. 2016.
3. European Medicines Agency. MabThera: EPAR – product information. 2016.
4. Ismael G, et al. *Lancet Oncology*. 2012;13(9):869-878.
5. Shpilberg O, et al. *Br J Cancer*. 2013;109(6):1556-1561.
6. De Cock E, et al. *PLoS One*. 2016;11(6):e0157957.

# Dose Mean (SD) Profiles

## 1st dose mean



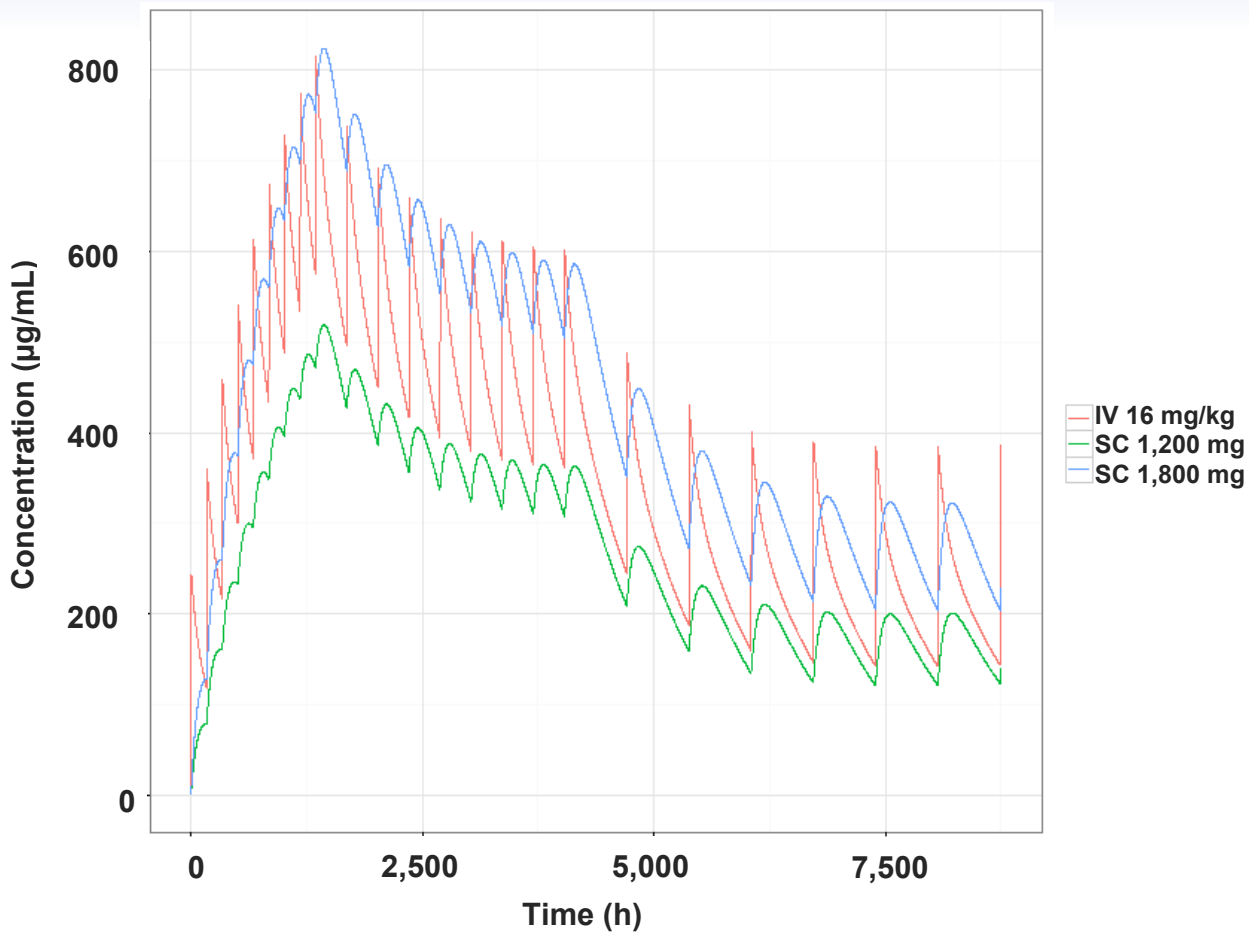

## 8th dose mean




**PK for the 1,800-mg SC dose is consistent with the 16-mg/kg IV dose, with comparable $C_{trough}$ and variability**

SD, standard deviation.
[a]Number of patients with full PK profile at pre-dose.
[b]From study GEN501 Part 2.
[c]From study GEN501 Part 1.

# Simulation of Mean Concentration-Time Profiles of DARA Following SC and IV Dosing[a]




- Similar $C_{max}$ for SC 1,800 mg versus IV 16 mg/kg overall
- Lower $C_{max}$ for SC 1,800 mg during the initial weekly administration
- Higher $C_{trough}$ for SC 1,800 mg versus SC 1,200 mg

$C_{max}$, peak plasma concentration.
[a]Dosing schedule is once weekly in Cycles 1 to 2, every 2 weeks in Cycles 3 to 6, and every 4 weeks thereafter.

# Grade 3/4 TEAEs: PAVO (Dara s.c.)

| Grade 3/4 TEAEs (>1 patient), % (n) | 1,200 mg n = 8 | 1,800 mg n = 45 |
|---|---|---|
| **Hematologic** | | |
| Anemia | **13** (1) | **13** (6) |
| Thrombocytopenia | **13** (1) | **7** (3) |
| Neutropenia | **13** (1) | **7** (3) |
| Lymphopenia | **0** (0) | **7** (3) |
| **Nonhematologic** | | |
| Hypertension | **25** (2) | **4** (2) |
| Fatigue | **25** (2) | **2** (1) |
| Device-related infection | **0** (0) | **4** (2) |
| Hyponatremia | **0** (0) | **4** (2) |

**AE profile of DARA-PH20 was consistent with IV DARA**

# IRRs: PAVO (Dara s.c.)

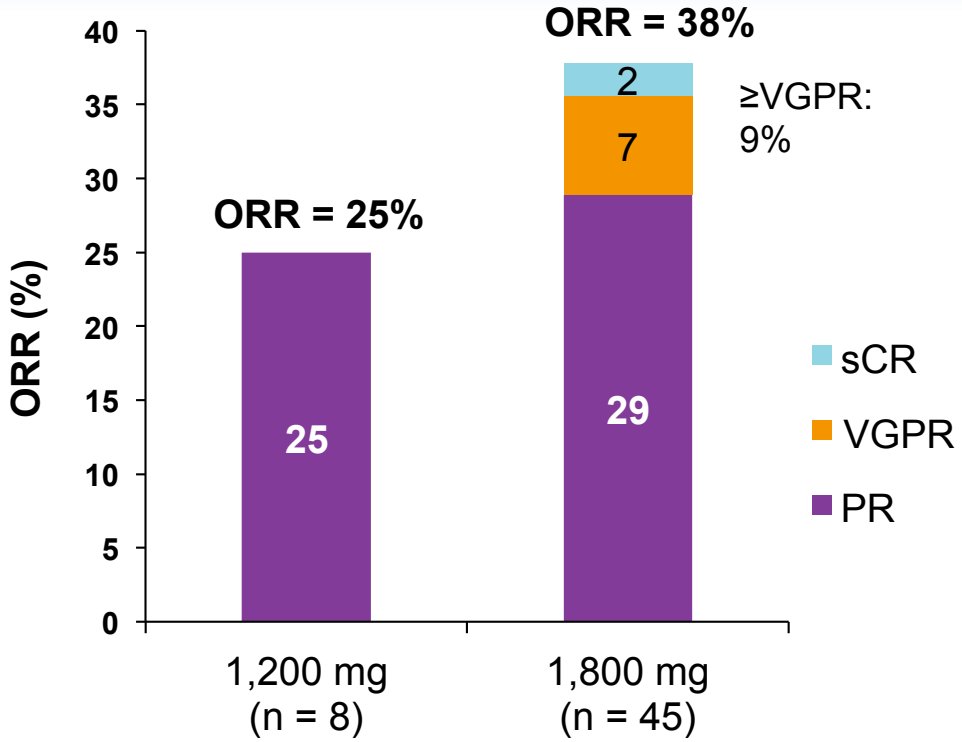
| | 1,200 mg n = 8 | 1,800 mg n = 45 |
|---|---|---|
| IRR, % (n) | **13** (1) | **24 (11)** |
| Chills | **13** (1) | **9** (4) |
| Pyrexia | **0** (0) | **9** (4) |
| Pruritus | **0** (0) | **4** (2) |
| Dyspnea | **13** (1) | **0** (0) |
| Flushing | **0** (0) | **2** (1) |
| Hypertension | **0** (0) | **2** (1) |
| Hypotension | **0** (0) | **2** (1) |
| Nausea | **0** (0) | **2** (1) |
| Non-cardiac chest pain | **13** (1) | **0** (0) |
| Oropharyngeal pain | **0** (0) | **2** (1) |
| Paresthesia | **0** (0) | **2** (1) |
| Rash | **0** (0) | **2** (1) |
| Sinus headache | **0** (0) | **2** (1) |
| Tongue edema | **0** (0) | **2** (1) |
| Vomiting | **0** (0) | **2** (1) |
| Wheezing | **0** (0) | **2** (1) |

- All IRRs in the 1,800-mg group were grade 1 or 2
- One grade 3 IRR of dyspnea in the 1,200-mg group
- No grade 4 IRRs were observed
- All IRRs occurred during or within 4 hours of the first infusion
- No IRRs occurred during subsequent infusions in either group
- Abdominal wall SC injections were well tolerated

**Low IRR incidence and severity with DARA SC**

# ORR

| Response | 1,200 mg n = 8 | 1,800 mg n = 45 |
|---|---|---|
| **ORR, % (n)** | **25** (2) | **38** (17) |
| sCR | **0** (0) | **2** (1) |
| CR | **0** (0) | **0** (0) |
| VGPR | **0** (0) | **7** (3) |
| PR | **25** (2) | **29** (13) |
| MR | **13** (1) | **11** (5) |
| SD | **50** (4) | **38** (17) |
| PD | **13** (1) | **13** (6) |




- Responses to DARA-PH20 were observed across both groups

**Deeper responses were observed in the 1,800-mg group**

sCR, stringent complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease.
Response-evaluable set.

# Daratumumab Development in all MM Settings

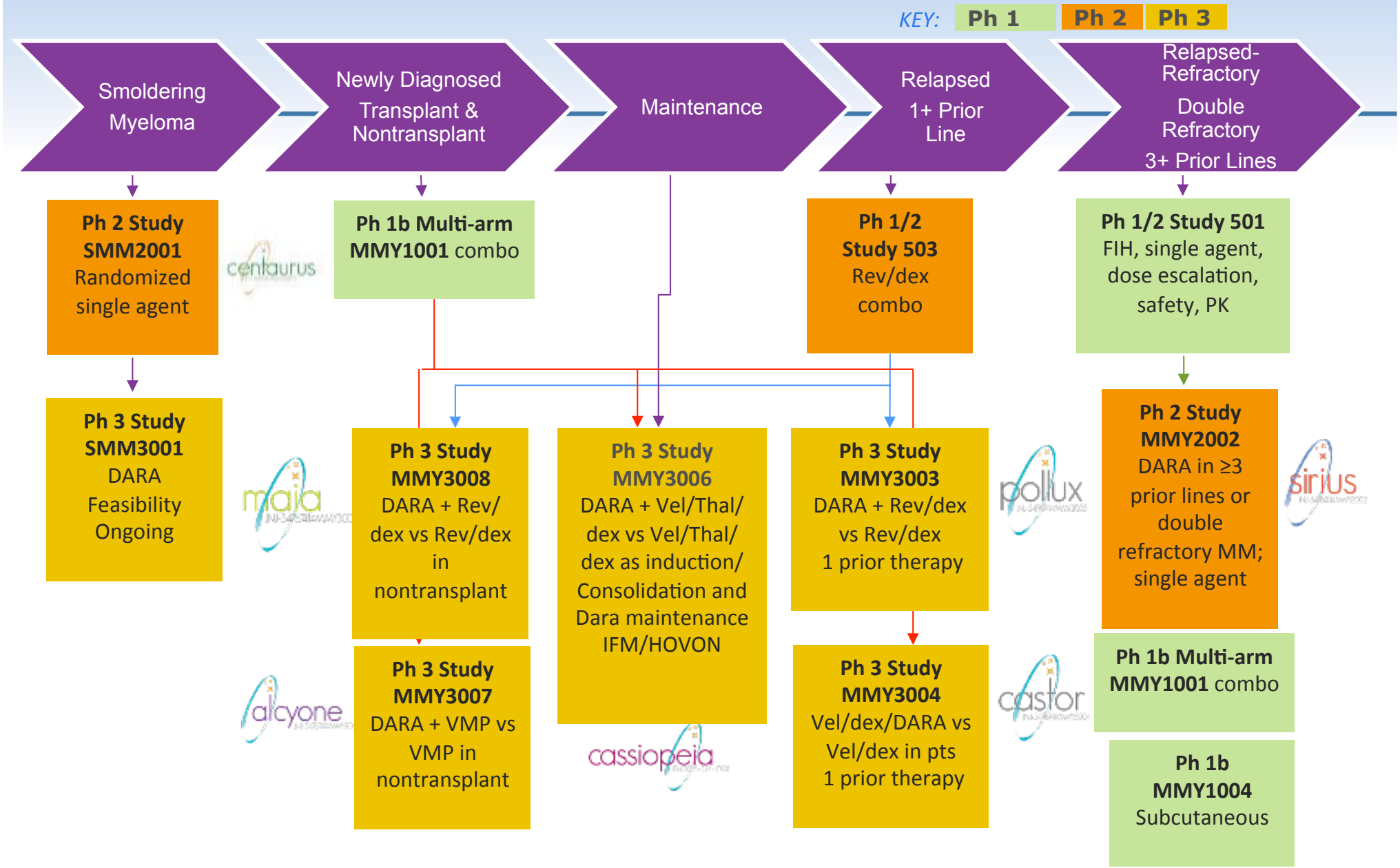


**Table 3.** Characteristics of anti CD38 antibodies

| | *Daratumumab* | *Isatuximab* | *MOR202* |
|---|---|---|---|
| Origin | Human | Humanized | Human |
| Development phase | Approved | Phase 1/2 | Phase 1/2 |
| Binding | +++ | +++ | ++ |
| CDC | +++ | + | ++ |
| ADCC | ++ | ++ | ++ |
| PCD | – | ++ | – |
| ADCP | +++ | NA | ++ |
| Ectoenzyme modulation | + | +++ | – |

Abbreviations: ADCC, antibody-dependent cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; PCD, programmed cell death.

Touzeau et al, Leukemia 2017

Isatuximab (SAR650984) is a humanized anti-CD38 antibody with potent activity against myeloma *in vitro* with enhanced activity in combination with pomalidomide.[95,96] In the dose escalation part of the Phase 1 portion of the trial (NCT01749969), isatuximab ⩾10 mg/kg IV given every other week (q2w) or 10 mg/kg weekly (qw) induced responses in 6/19 recipients (ORR 32%). The most common treatment-emergent adverse events were fatigue and nausea with few grade 3/4 events (pneumonia 6%). A dose finding study performed in 96 heavily pretreated patients (median number of prior therapies = 5).[97] Combination trials with lenalidomide and dexamethasone and proteasome inhibitors (NCT02232850 and NCT02513186) have been performed or are ongoing. In an ongoing phase 1b trial combining isatuximab with pomalidomide and dexamethasone in 14 patients with relapsed/refractory disease the overall response rate was 62% with frequent fatigue and upper respiratory tract symptoms.[98] In a phase 1b combination study with carfilzomib including 11 patients the most frequent serious adverse event was pneumonia and the overall response rate was 80% (NCT02332850).[99]


95 Deckert J, Wetzel MC, Bartle LM, Skaletskaya A, Goldmacher VS, Vallee F *et al.* SAR650984, a novel humanized CD38-targeting antibody, demonstrates potent antitumor activity in models of multiple myeloma and other CD38+ hematologic malignancies. *Clin Cancer Res* 2014; **20**: 4574–4583.

96 Jiang H, Acharya C, An G, Zhong M, Feng X, Wang L *et al.* SAR650984 directly induces multiple myeloma cell death via lysosomal-associated and apoptotic pathways, which is further enhanced by pomalidomide. *Leukemia* 2015; **30**: 399–408.

97 Martin T, Richter J, Vij R, Cole C, Atanackovic D, Zonder J *et al.* A dose finding phase II trial of isatuximab (SAR650984, Anti-CD38 mAb) as a single agent in relapsed/refractory multiple myeloma. *Blood* 2015, 126 (Abstract 509).

98 Richardson PG, Mikhael J, Usmani SZ, Raje N, Bensinger W, Campana F *et al.* Preliminary results from a phase Ib Study of isatuximab in combination with pomalidomide and dexamethasone in relapsed and refractory multiple myeloma. *Am Soc Hematol* 2016; (Abstract 2123).

99 Martin TG, Mannis GN, Chari A, Munster P, Campana F, Hui AM *et al.* phase Ib study of isatuximab and carfilzomib in relapse and refractory multiple myeloma. *Am Soc Hematol* 2016; (Abstract 2111).


A phase 1/2 trial is investigating the MOR202 anti-CD38 antibody in relapsing/refractory patients as a single agent or in combination with an IMiD is currently ongoing (NCT01421186). Interim results on, the first 66 patients showed that the infusion of 16 mg/kg alone or in combination with lenalidomide or pomalidomide was well tolerated with 5/16 responses in the single agent cohort and 8/12 in the combination arms.[100]

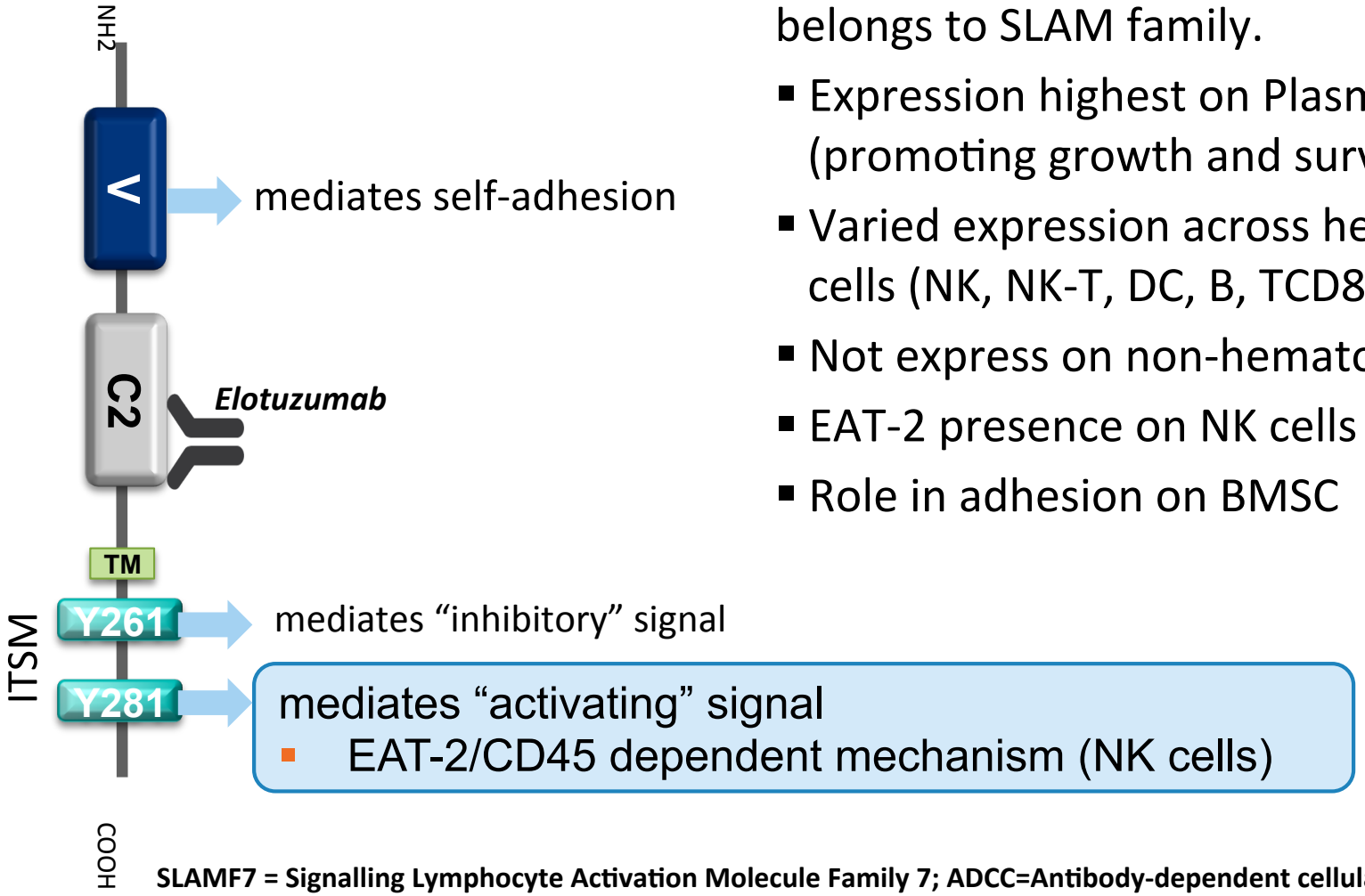

100 Raab MS, Chatterjee M, Goldschmidt H, Agis H, Blau I, Einsele H *et al.* A phase I/IIa study of the CD38 antibody MOR202 alone and in combination with pomalidomide or lenalidomide in patients with relapsed or refractory multiple myeloma. *Am Soc Hematol* 2106; (Abstract 1152).


**Touzeau et al, Leukemia 2017**

# My Agenda

- The complex network of anti-myeloma immunity vs myeloma escape
- MoAbs in multiple myeloma: general overview
- Daratumumab: mechanism(s) of action, updated results (ASCO/ASH 2016) and new studies
- **Elotuzumab: mechanism(s) of action, updated results (ASCO/ASH 2016) and new studies**
- Other MoAbs: immune check-point modulators
- How immunotherapy with MoAbs could modify end-points of multiple myeloma treatment

# SLAMF7/CS1 as a Target

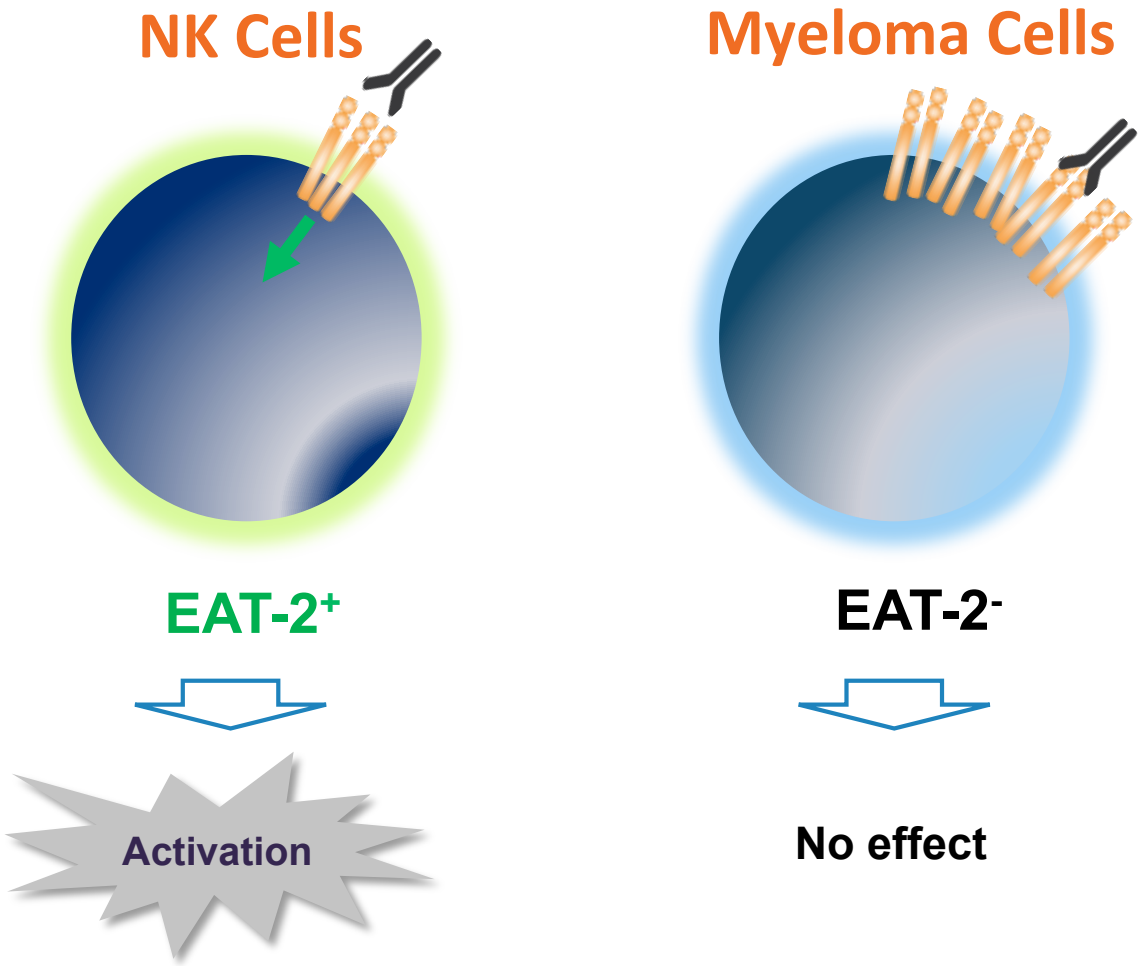



CS1 is a cell surface glycoprotein that belongs to SLAM family.

- Expression highest on Plasma Cells (promoting growth and survival)
- Varied expression across hematopoietic cells (NK, NK-T, DC, B, TCD8+, PC)
- Not express on non-hematopoietic cells
- EAT-2 presence on NK cells activates cells
- Role in adhesion on BMSC

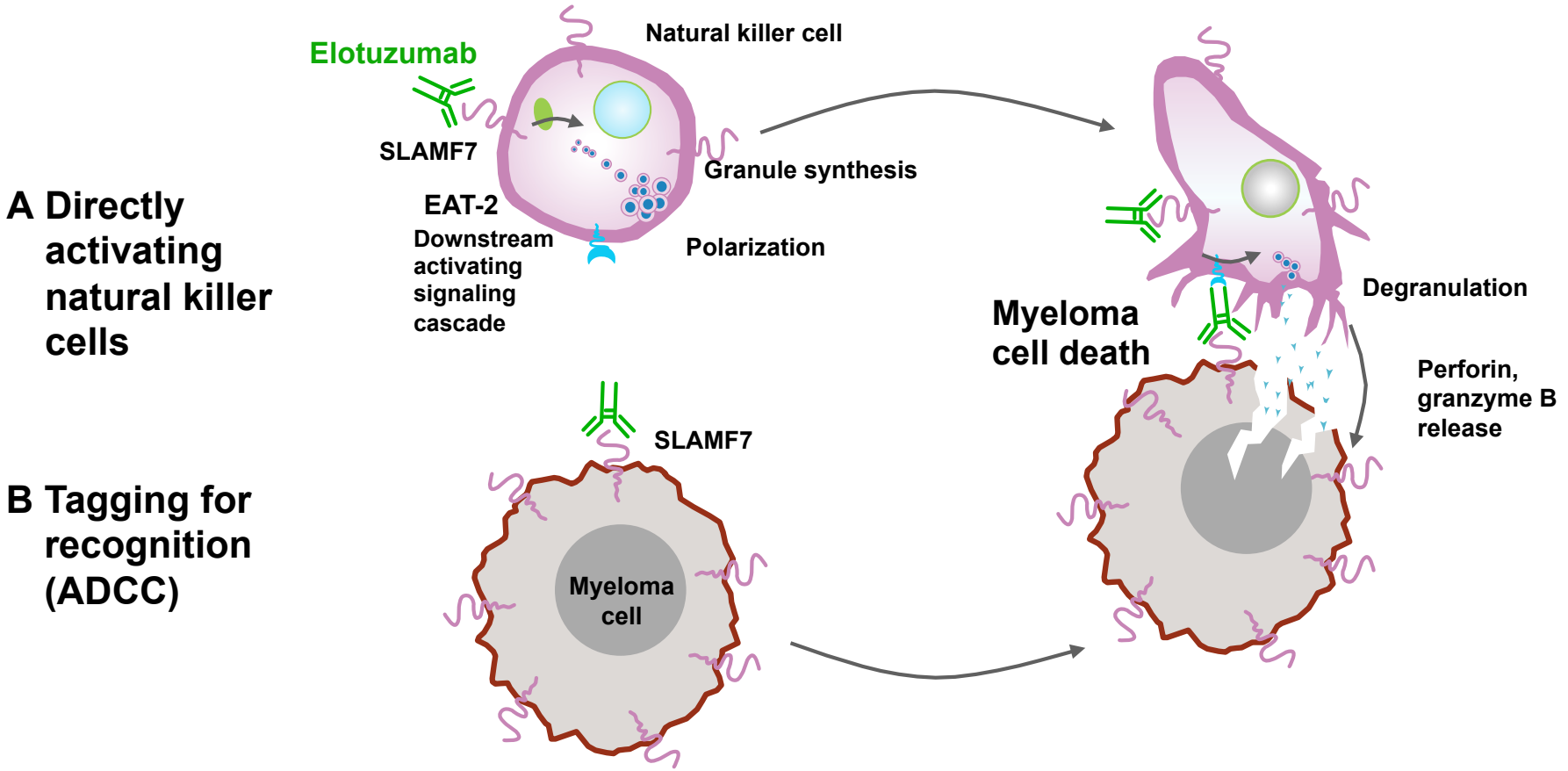
**SLAMF7 = Signalling Lymphocyte Activation Molecule Family 7; ADCC=Antibody-dependent cellular cytotoxicity**
ITSM = Intracellular Tyrosine Switch Motif
EAT-2 = Ewing's Sarcoma associated transcript 2

# Differential SLAMF7 Signalling: Elotuzumab Activates NK Cells but not Myeloma Cells



# Elotuzumab: Immunostimulatory Mechanism of Action

- Elotuzumab is an immunostimulatory monoclonal antibody that recognizes SLAMF7, a protein highly expressed by myeloma and natural killer cells[1]
- Elotuzumab causes myeloma cell death via a dual mechanism of action[2]



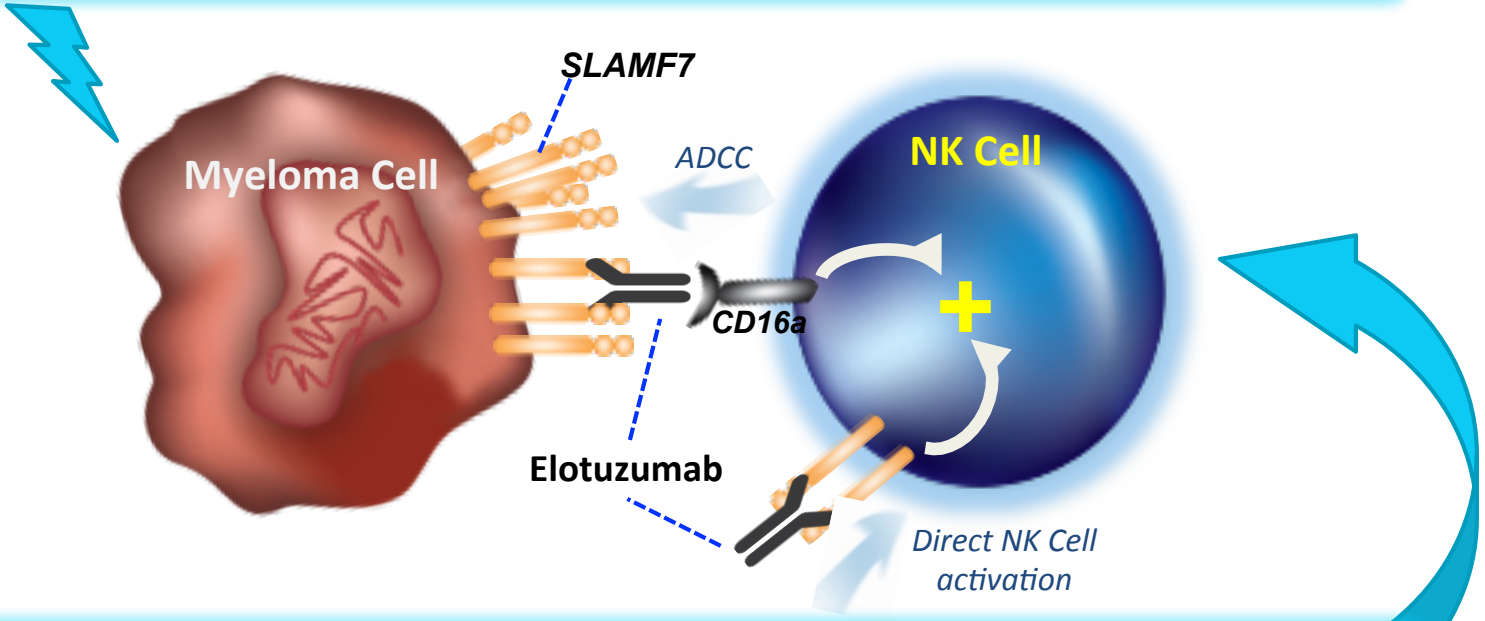

1. Hsi ED et al. *Clin Cancer Res* 2008;14:2775–84; 2. Collins SM et al. *Cancer Immunol Immunother* 2013;62:1841–9
ADCC=antibody-dependent cell-mediated cytotoxicity; SLAMF7=signaling lymphocytic activation molecule F7

# MM: Overall Results forTherapeutic Mabs (i)

| Target | Drug | Combination | n (no. evaluable for response) | Median number of prior therapies | Response rates (%) (evaluable patients) | | |
|---|---|---|---|---|---|---|---|
| | | | | | ⩾ PR | VGPR | CR |
| CD38 | DARA 16 mg/kg | — | 20 (20) | 4 (2–12)[a] | 35 | 5 | 10 |
| | DARA 16 mg/kg | — | 106 (106) | 5 (2–14) | 29 | 9 | 3 |
| | DARA 2–16 mg/kg | LEN–DEX | 45 (43) | 2 (1–4)[a] | 91 | 44 | 14 |
| | DARA 16 mg/kg | BORT–DEX | 6 (6) | 0 (newly diagnosed) | 100 | 50 | 0 |
| | DARA 16 mg/kg | BORT–MEL–PRED | 8 (8) | 0 (newly diagnosed) | 100 | 50 | 0 |
| | DARA 16 mg/kg | BORT–THAL–DEX | 11 (10) | 0 (newly diagnosed) | 100 | 20 | 10 |
| | DARA 16 mg/kg | POM–DEX | 24 (11) | ⩾2 prior lines[b] | 55 | 9 | 18 |
| | SAR650984 ⩾10 mg/kg | — | 19 (19) | 6.5 (2–16)[c] | 32 | 0 | 16 |
| | SAR650984 10 mg/kg | LEN–DEX | 24 (24) | 7 (2–14)/4 (1–9)[a] | 63 | 29 | 8 |
| | MOR202 | ± DEX | 42 (23) | 4 (2–11)[a] | 4 | 4 | 0 |
| CS1 | ELO | — | 35 (34) | 4.5 (2–10) | 0 | 0 | 0 |
| | ELO | THAL–DEX | 40 (40) | 3 (1–8) | 40 | 10 | 8 |
| | ELO | BORT | 28 (27) | 2 (1–3) | 48 | NR | 7 |
| | ELO | BORT–DEX | 77 (77) | 29% ⩾2 | 65 | 30 | 4 |
| | ELO | LEN–DEX | 29 (28) | 3 (1–10) | 82 | 29 | 4 |
| | ELO 10 mg/kg | LEN–DEX | 36 (36) | 55% ⩾2[c] | 92 | 50 | 14 |
| | ELO | LEN–DEX | 321 (321) | 2 (1–4) | 79 | 28 | 4 |

# Elotuzumab Synergizes with Lenalidomide to Enhance Myeloma Cell Death

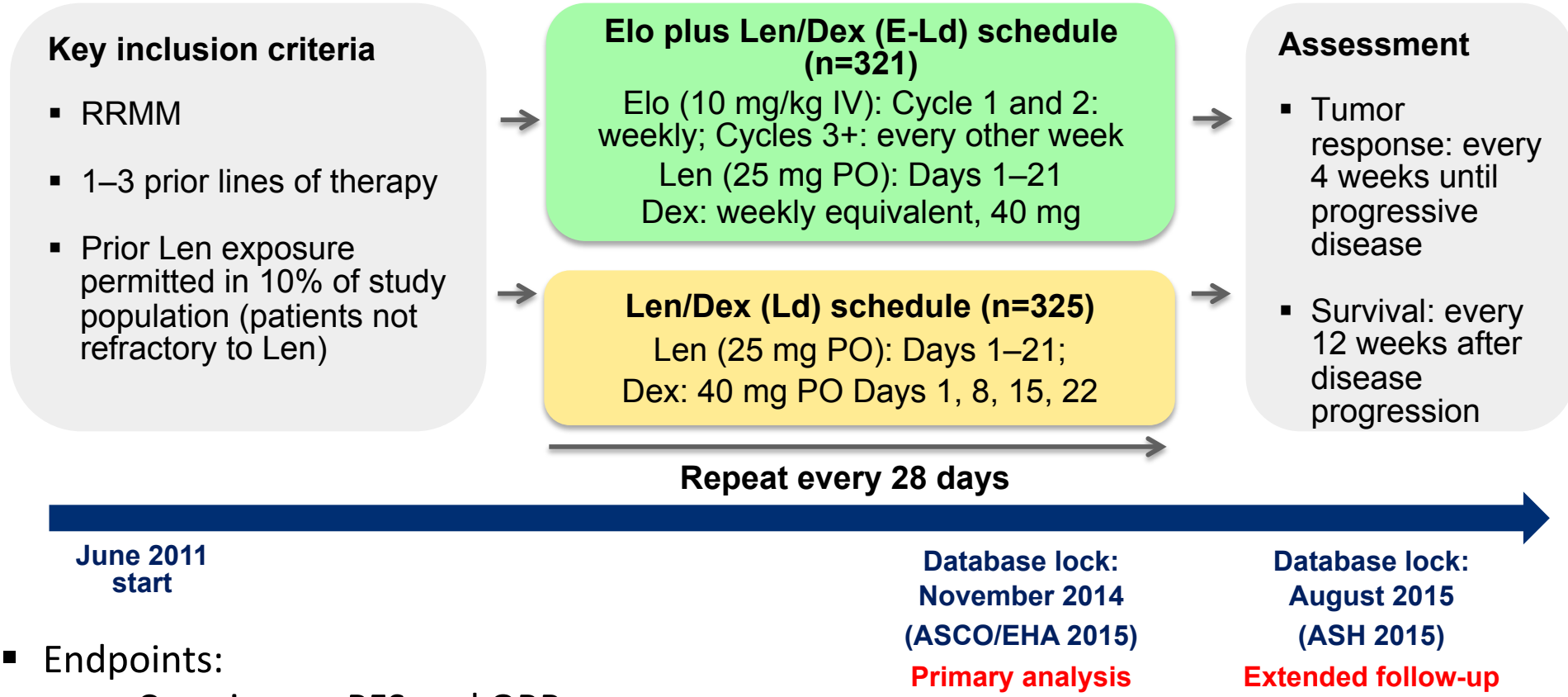
**Lenalidomide**
Induces myeloma cell injury and lowers threshold for NK cell-mediated killing of myeloma cells by elotuzumab




**Lenalidomide**[1]
Enhances adaptive and innate immune system including production of IL2 to increase NK cell activity

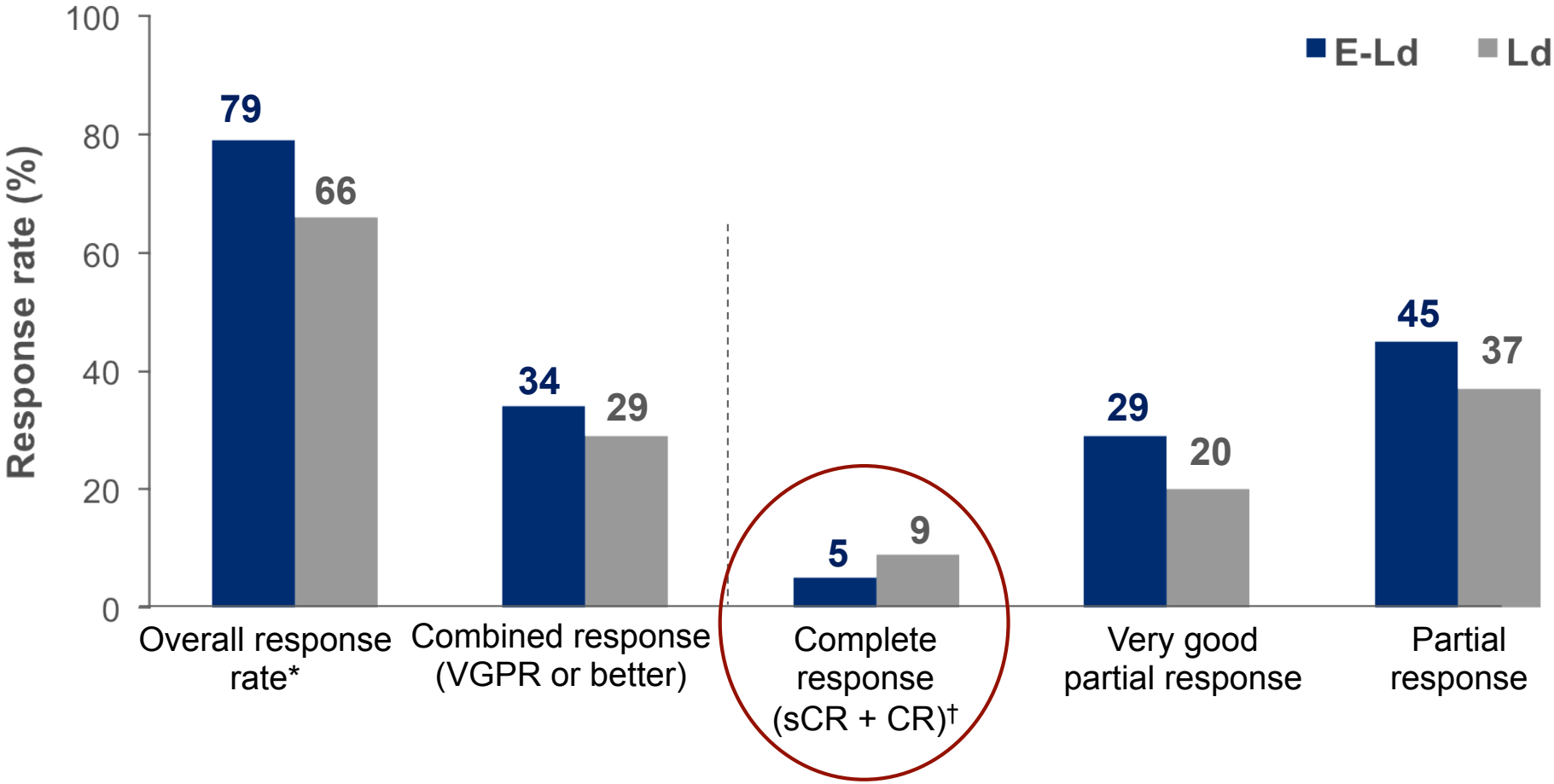
# ELOQUENT-2 Study Design

- Open-label, international, randomized, multicenter, phase 3 trial (168 global sites)




- Endpoints:
  - Co-primary: PFS and ORR
  - Other: OS, DOR, quality of life, safety
- All patients received premedication to mitigate infusion reactions prior to elotuzumab administration; Elotuzumab IV infusion administered ~ 2–3 hours

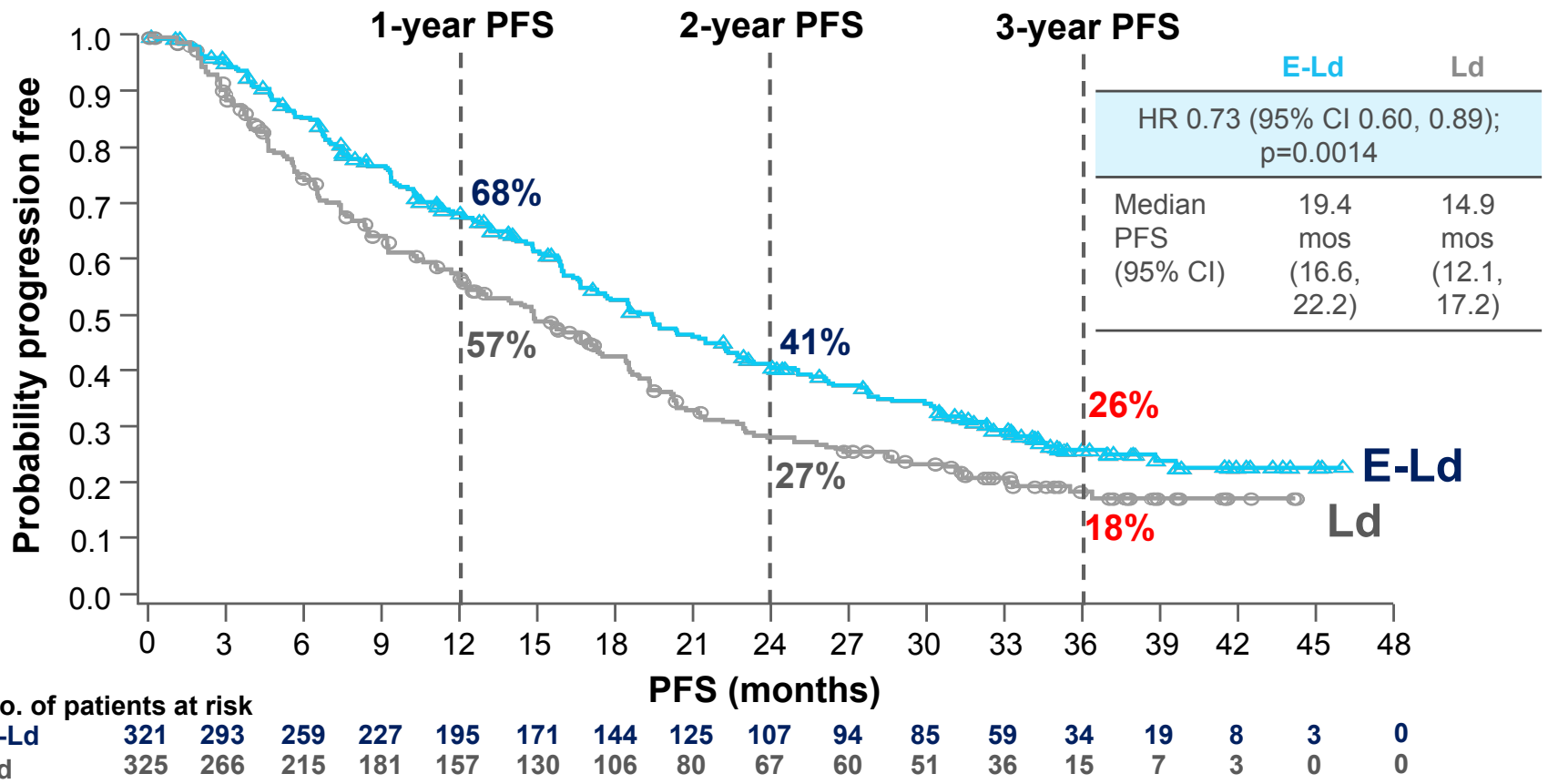
# Co-Primary Endpoint: Overall Response Rate




*Defined as partial response or better

†Complete response rates in the E-Ld group may be underestimated due to interference from therapeutic antibody in immunofixation and serum protein electrophoresis assay

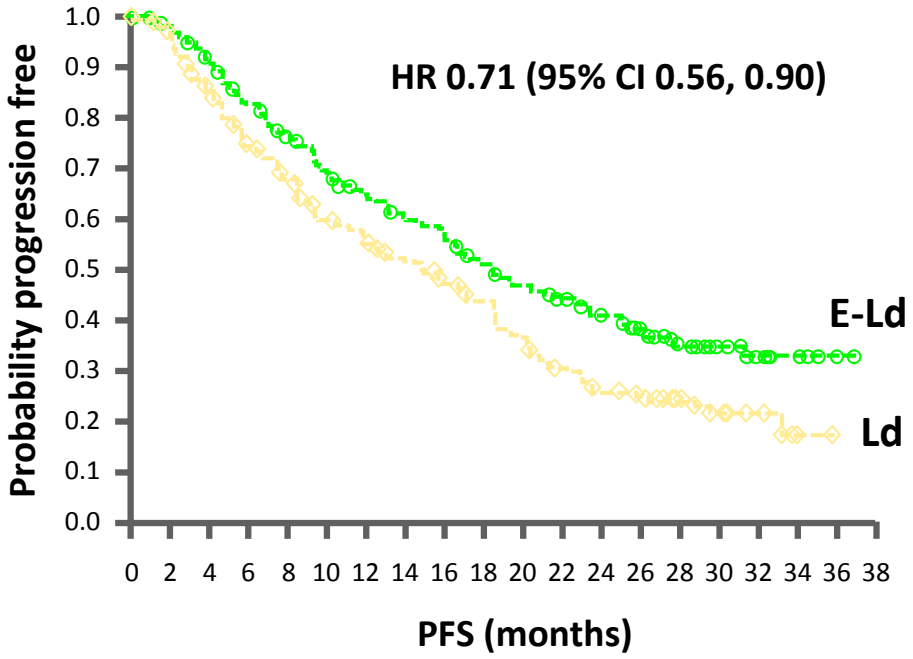
# Co-Primary Endpoint: Extended Progression-Free Survival




**PFS benefit with E-Ld was maintained over time (vs Ld):**
- **Overall 27% reduction in the risk of disease progression or death**
- **Relative improvement in PFS of 44% at 3 years**

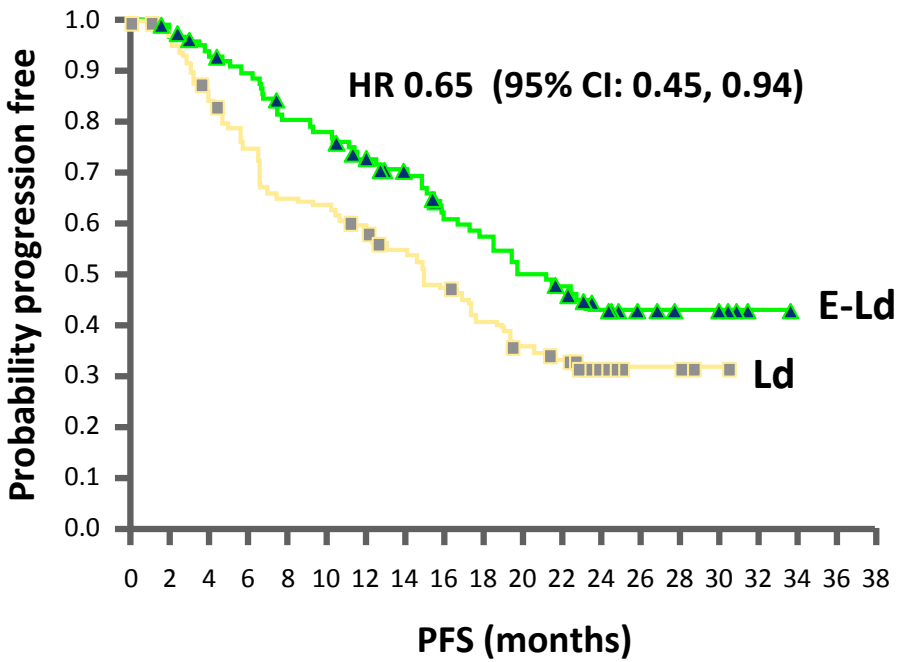
# Progression-Free Survival With or Without del(17p)

**del(17p)-**




**E-Ld: median (95% CI): 18.46 (15.84, 22.77)**
**Ld: median (95% CI): 14.85 (11.86, 18.43)**

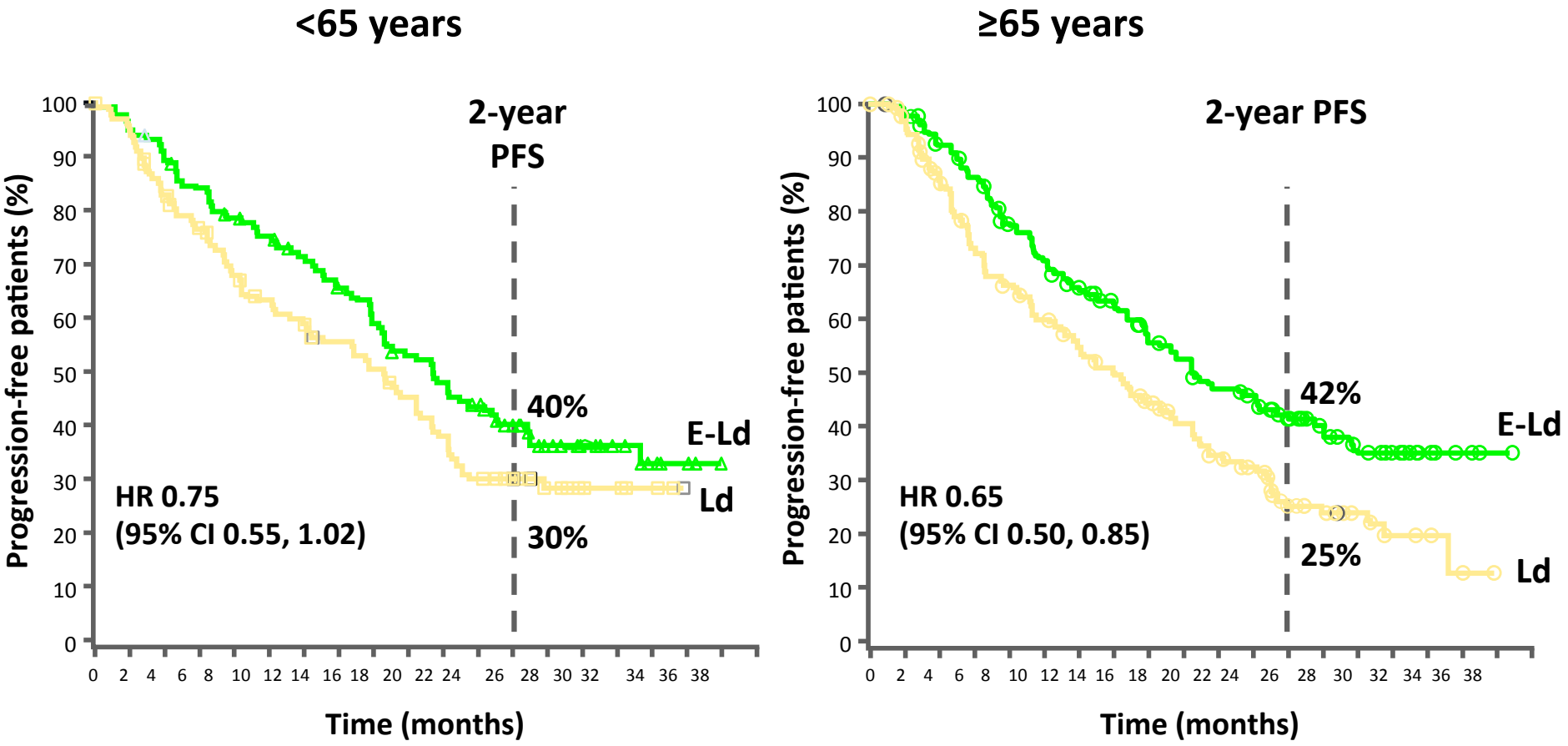
**del(17p)+**




**E-Ld: median (95% CI): 21.19 (16.62, NE)**
**Ld: median (95% CI): 14.92 (10.61, 18.50)**

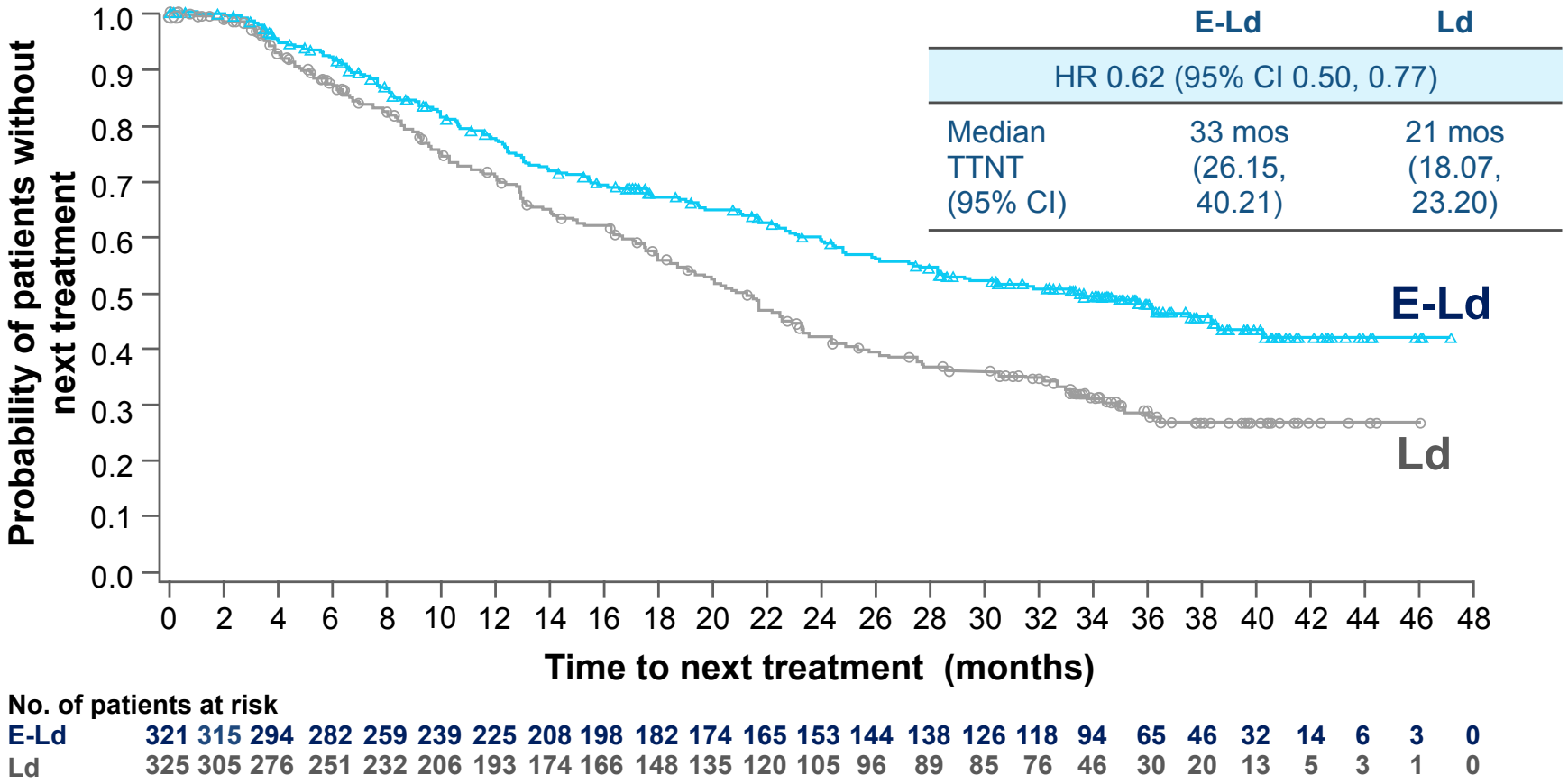
Lonial S et al ASCO 2016 (Abstract 8037) *Poster presentation*

# Progression-Free Survival According to Age



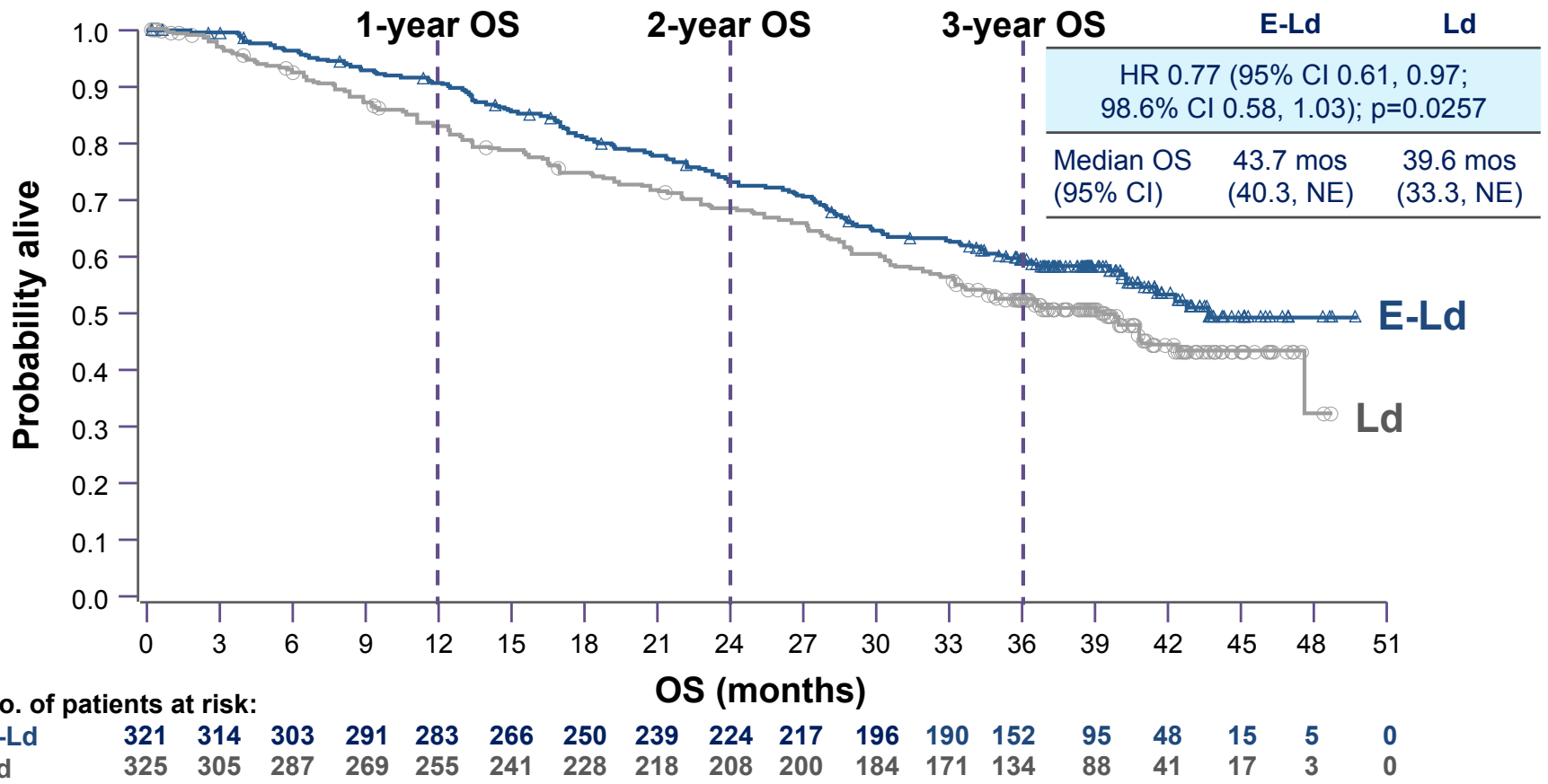

Lonial S et al ASCO 2016 (Abstract 8037) *Poster presentation*

# Time to Next Treatment




**E-Ld-treated patients had a median delay of 1 year in the time to next treatment vs Ld-treated patients**

# Interim Overall Survival




**Prespecified interim analysis for overall survival indicates a strong trend (p=0.0257) with early separation sustained over time for E-Ld vs Ld**

# ELOQUENT-2: Infusion Reactions[1,2]

| Event, n (%)[1] | ERd (n=318) | | |
|---|---|---|---|
| | Grade 1/2 | Grade 3 | Grade 4/5 |
| **Infusion reaction** | **29 (9)** | **4 (1)** | **0** |
| Pyrexia | 10 (3) | 0 | 0 |
| Chills | 4 (1) | 0 | 0 |
| Hypertension | 3 (1) | 1 (<1) | 0 |

- **Infusion reactions occurred in 10% of patients (1% grade 3) [1,2]**
- **70% of infusion reactions occurred with the first dose[1,2]**
- **Elotuzumab infusion was interrupted in 15 (5%) patients due to an infusion reaction (median interruption duration 25 minutes)[1,2]**
- **2 (1%) patients discontinued the study due to an infusion reaction[1,2]**

ERd, elotuzumab, lenalidomide/dexamethasone.

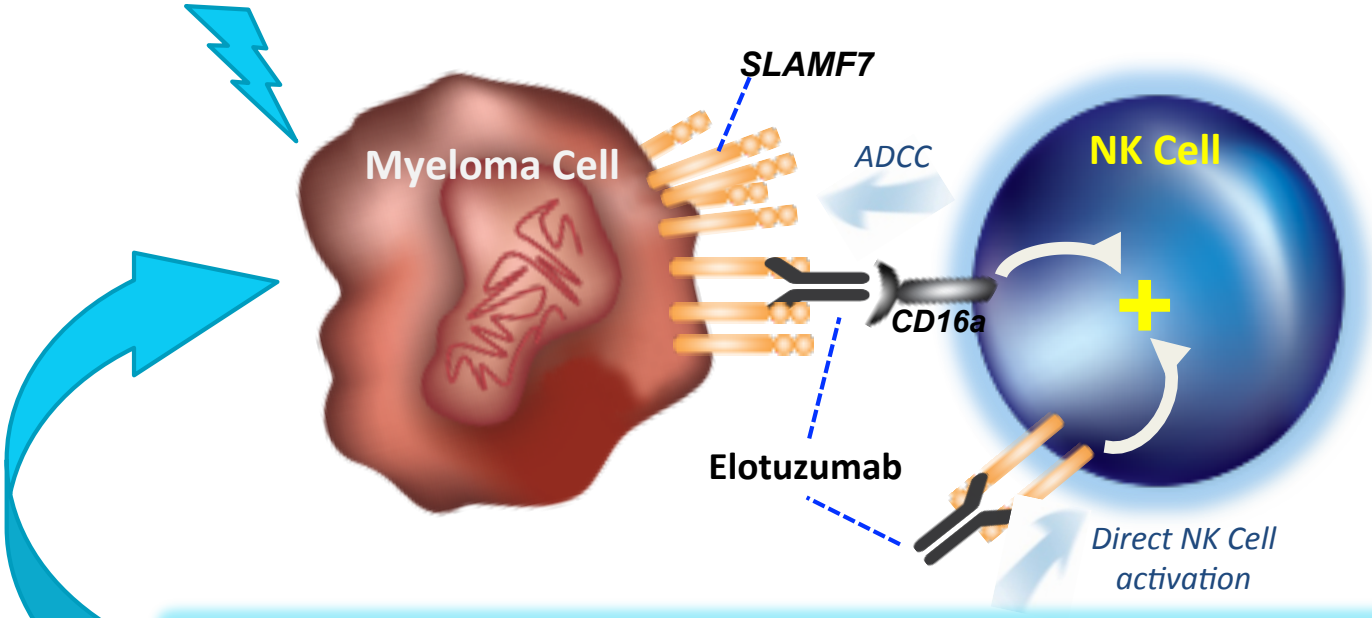
1. Lonial S et al. Oral presentation at ASCO 2015. Abstract 8508. 2. Lonial S et al. *N Engl J Med*. 2015;373:621-631.

- **November 2015:** U.S. Food and Drug Administration (FDA) granted approval for Elotuzumab, a SLAMF7-directed immunostimulatory antibody, indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies

- **May 2016 (FDA):** Elotuzumab is indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy

# Elotuzumab Synergizes With Bortezomib To Enhance Myeloma Cell Death

**Bortezomib**
Induces myeloma cell injury and lowers threshold for NK cell-mediated killing of myeloma cells by elotuzumab




**Bortezomib**[1]
Sensitizes MM cells to killing by NK cells by enhancing activating ligands and reducing inhibitory ligands on MM cells

# Randomized phase 2 study: elotuzumab plus bortezomib/dexamethasone vs bortezomib/dexamethasone for relapsed/refractory MM

Andrzej Jakubowiak,[1] Massimo Offidani,[2] Brigitte Pégourie,[3] Javier De La Rubia,[4] Laurent Garderet,[5] Kamel Laribi,[6] Alberto Bosi,[7] Roberto Marasca,[8] Jacob Laubach,[9] Ann Mohrbacher,[10] Angelo Michele Carella,[11] Anil K. Singhal,[12] L. Claire Tsao,[12] Mark Lynch,[13] Eric Bleickardt,[13] Ying-Ming Jou,[14] Michael Robbins,[15] and Antonio Palumbo[16]

[1]Myeloma Program, Section of Hematology/Oncology, University of Chicago Medical Center, Chicago, IL; [2]Clinica di Ematologia, Azienda Ospedaliero Universitaria Ospedali Riuniti di Ancona, Ancona, Italy; [3]Centre Hospitalier Universitaire de Grenoble–Hôpital Albert Michallon, Grenoble, France; [4]Hospital Universitario Doctor Peset and Universidad Católica "San Vicente Mártir," Valencia, Spain; [5]Service d'hématologie, Hôpital Saint Antoine, Paris, France; [6]Department of Hematology, Centre Hospitalier, Le Mans, France; [7]Department of Hematology, Azienda Ospedaliero Universitaria Careggi, Florence, Italy; [8]Department of Hematology, Azienda Ospedaliera Universitaria–Policlinico di Modena, Modena, Italy; [9]Department of Hematology/Oncology, Dana-Farber Cancer Institute, Boston, MA; [10]Division of Hematology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; [11]Hematology Unit, Istituto di Ricovero e Cura a Carattere Scientifico San Martino–Istituto Scientifico Tumori, Genoa, Italy; [12]Statistics, AbbVie Biotherapeutics Inc, Redwood City, CA; [13]Oncology Clinical Development, Bristol-Myers Squibb, Wallingford, CT; [14]Global Biometric Sciences, Bristol-Myers Squibb, Hopewell, NJ; [15]Exploratory Clinical and Translational Research–Oncology, Bristol-Myers Squibb, Princeton, NJ; and [16]Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy

## Key Points

- Elotuzumab, an immunostimulatory antibody, prolongs PFS with no added clinical toxicity when combined with Bd vs Bd alone in RRMM.
- Based on results from this phase 2 study, further investigation of elotuzumab with a proteasome inhibitor in RRMM is warranted.

**In this proof-of-concept, open-label, phase 2 study, patients with relapsed/refractory multiple myeloma (RRMM) received elotuzumab with bortezomib and dexamethasone (EBd) or bortezomib and dexamethasone (Bd) until disease progression/unacceptable toxicity. Primary endpoint was progression-free survival (PFS); secondary/exploratory endpoints included overall response rate (ORR) and overall survival (OS). Two-sided 0.30 significance level was specified (80% power, 103 events) to detect hazard ratio (HR) of 0.69. Efficacy and safety analyses were performed on all randomized patients and all treated patients, respectively. Of 152 randomized patients (77 EBd, 75 Bd), 150 were treated (75 EBd, 75 Bd). PFS was greater with EBd vs Bd (HR, 0.72; 70% confidence interval [CI], 0.59-0.88; stratified log-rank $P = .09$); median PFS was longer with EBd (9.7 months) vs Bd (6.9 months). In an updated analysis, EBd-treated patients homozygous for the high-affinity FcγRIIIa allele had median PFS of 22.3 months vs 9.8 months in EBd-treated patients homozygous for the low-affinity allele. ORR was 66% (EBd) vs 63% (Bd). Very good partial response or better occurred in 36% of patients (EBd) vs 27% (Bd). Early OS results, based on 40 deaths, revealed an HR of 0.61 (70% CI, 0.43-0.85). To date, 60 deaths have occurred (28 EBd, 32 Bd). No additional clinically significant adverse events occurred with EBd vs Bd. Grade 1/2 infusion reaction rate was low (5% EBd) and mitigated with premedication. In patients with RRMM, elotuzumab, an immunostimulatory antibody, appears to provide clinical benefit without added clinically significant toxicity when combined with Bd vs Bd alone. Registered to ClinicalTrials.gov as NCT01478048.**
**(*Blood*. 2016;127(23):2833-2840)**

**Table 2. Overall response rate and best overall response**

| Treatment response | EBd (n = 77) | Bd (n = 75) |
|---|---|---|
| **Overall response rate, n (%)*** | 51 (66) | 47 (63) |
| 95% CI | 55-77 | 51-74 |
| **Best overall response, n (%)** | | |
| Stringent CR | 0 | 1 (1) |
| CR | 3 (4) | 2 (3) |
| Very good partial response | 25 (33) | 17 (23) |
| Partial response | 23 (30) | 27 (36) |
| Minimal response | 4 (5) | 5 (7) |
| Stable disease | 13 (17) | 14 (19) |
| Progressive disease | 4 (5) | 4 (5) |
| Not evaluable | 5 (7) | 5 (7) |

Data cutoff: August 10, 2015.

*Overall response rate was defined as partial response or better, according to the modified IMWG criteria.

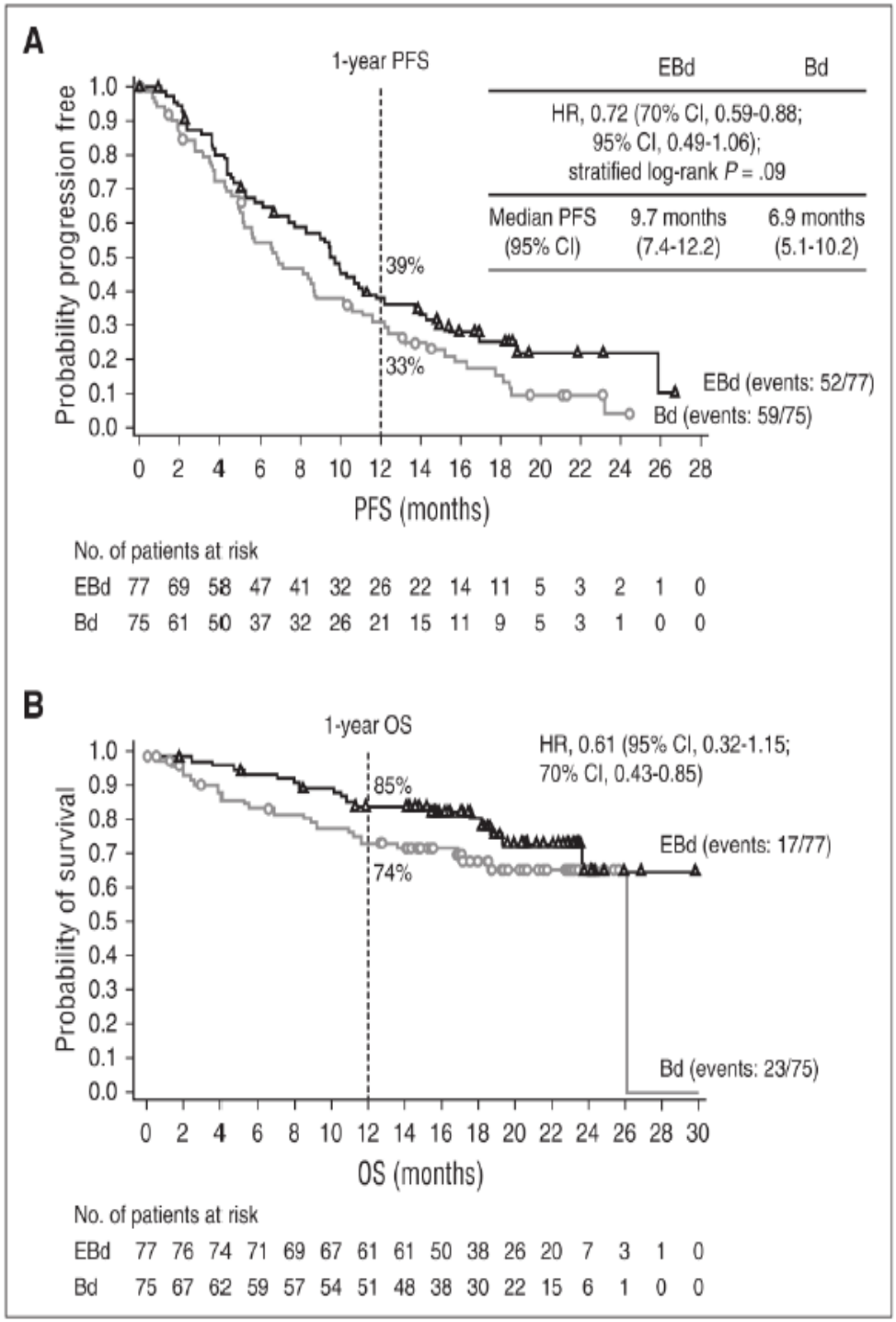
**Table 3. Adverse events in at least 25% of patients**

| | EBd (n = 75) | | Bd (n = 75) | |
|---|---|---|---|---|
| Events* | Any grade† | Grade 3-4 | Any grade† | Grade 3-4 |
| All AEs | 75 (100) | 53 (71) | 72 (96) | 45 (60) |
| Infections | 50 (67) | 16 (21) | 40 (53) | 10 (13) |
| Diarrhea | 33 (44) | 6 (8) | 25 (33) | 3 (4) |
| Constipation | 30 (40) | 1 (1) | 22 (29) | 0 |
| Cough | 33 (44) | 1 (1) | 18 (24) | 0 |
| Anemia | 28 (37) | 5 (7) | 22 (29) | 5 (7) |
| Peripheral neuropathy | 27 (36) | 7 (9) | 27 (36) | 9 (12) |
| Pyrexia | 28 (37) | 0 | 21 (28) | 3 (4) |
| Peripheral edema | 22 (29) | 3 (4) | 18 (24) | 0 |
| Insomnia | 22 (29) | 1 (1) | 14 (19) | 1 (1) |
| Asthenia | 21 (28) | 3 (4) | 22 (29) | 2 (3) |
| Fatigue | 22 (29) | 3 (4) | 19 (25) | 1 (1) |
| Paresthesia | 20 (27) | 0 | 14 (19) | 4 (5) |
| Nausea | 20 (27) | 1 (1) | 16 (21) | 1 (1) |
| Thrombocytopenia | 12 (16) | 7 (9) | 20 (27) | 13 (17) |

Data are n (%) of patients. Data cutoff: August 10, 2015.

*AEs were categorized using the Medical Dictionary for Regulatory Activities and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3).[12]

†Grade 5 AEs occurred in 4 patients in the EBd group and 6 patients in the Bd group.



# Study CA204-007: ERd in MM Patients with Normal and Impaired Renal Function[1,2]

**A Phase Ib Study of Elotuzumab in Combination With Lenalidomide and Dexamethasone in Subjects With Multiple Myeloma and Normal Renal Function, Severe Renal Impairment, or End-Stage Renal Disease Requiring Dialysis**

N=26

Key Eligibility Criteria

- Symptomatic MM, either newly diagnosed or relapsed/refractory
- Previous lenalidomide treatment permitted if not discontinued due to grade ≥3 AE
- Subjects with active plasma cell leukemia, acute renal failure, or significant cardiac disease not permitted
- Previous treatment with elotuzumab or any IMiD (except previous thalidomide or lenalidomide) not permitted

**Elotuzumab**
10 mg/kg IV
Cycle 1: day 1
Cycles 2–3: days 1, 8, 15, 22
Cycle ≥4: days 1, 15

**Lenalidomide**
Dosing according to renal function, all cycles days 1–21
Normal renal function: 25 mg PO daily
Severe renal impairment: 15 mg PO every 48 hours
End-stage renal disease: 5 mg PO daily

**Dexamethasone**
40 mg PO on weeks without elotuzumab
8 mg IV + 28 mg PO on weeks with elotuzumab

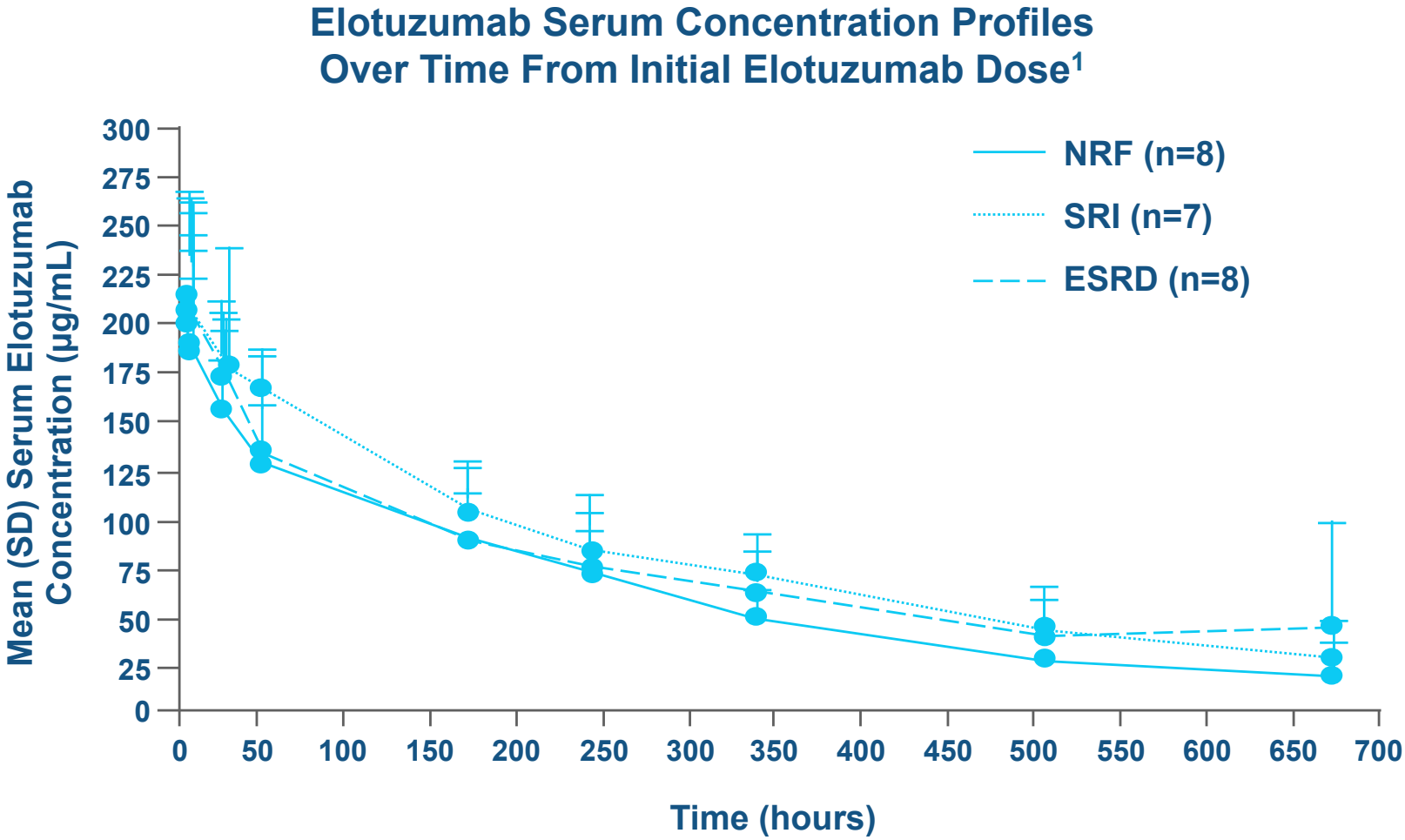
*Treatment administered in 28-day cycles until progression, unacceptable toxicity, or withdrawal of consent*

- Primary Endpoints: PK
- Secondary Endpoint: Safety

AE, adverse event; ERd, elotuzumab, lenalidomide/dexamethasone; IMiD, immunomodulatory agent; IV, intravenous; MM, multiple myeloma; PK, pharmacokinetics; PO, orally.

1. Clinicaltrials.gov. NCT01393964. 2. Berdeja J et al. *Clin Lymphoma Myeloma Leuk*. 2015 Dec 21. [Epub ahead of print].

# Study CA204-007: Pharmacokinetics (1)




Adapted from Berdeja J et al. 2015.[1]

ESRD, end-stage renal disease; NRF, normal renal function; SD, standard deviation; SRI, severe renal impairment.

1. Berdeja J et al. *Clin Lymphoma Myeloma Leuk*. 2015 Dec 21. [Epub ahead of print].

# Phase 2 Study of ERd in Smoldering Multiple Myeloma (SMM): Study Design and Patient Characteristics[1]

- Patients with high-risk SMM received 8 cycles of ERd induction therapy
  - Cycles 1-2: elotuzumab 10 mg/kg IV (days 1, 8, 15, and 22) + lenalidomide 25 mg PO (days 1-21) + dexamethasone 40 mg PO (days 1, 8, 15, and 22)*
  - Cycles 3-8: elotuzumab 10 mg/kg IV (days 1, 8, and 15) + lenalidomide 25 mg PO (days 1-21) + dexamethasone 40 mg PO (days 1, 8, and 15)*
- After 8 cycles or best response, patients were given the option to harvest stem cells for future ASCT
- Patients then received 16 cycles of maintenance therapy
  - Elotuzumab 20 mg/kg IV (day 1) + lenalidomide 25 mg PO (days 1-21)
- Study endpoints included:
  - Primary: 2-year PFS rate
  - Secondary: response rate, TTP, DOR, OS, safety, MRD, molecular evolution of tumor cells, role of immune cells in SMM progression

| Characteristic | n=47 |
|---|---|
| Median age, years | 63 |
| Heavy chain, %<br>IgG<br>IgA | <br>63.8<br>31.9 |
| Light chain, %<br>Kappa<br>Lambda | <br>57.5<br>42.6 |
| Median bone marrow plasma cells, % | 20.0 |
| Median β2-microglobulin, mg/dL | 2.2 |
| High-risk cytogenetics, %<br>del(17p)<br>t(4;14) | 38.1<br>9.5<br>11.9 |

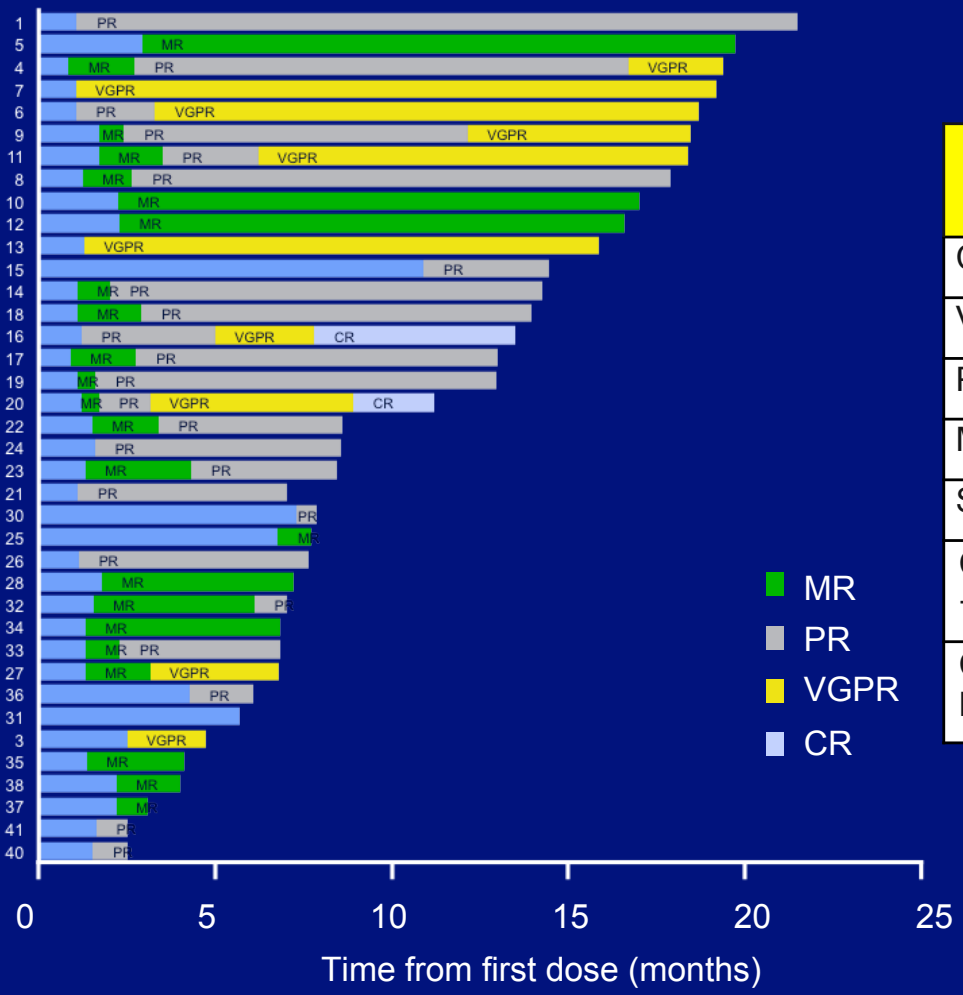
*An initial cohort of 11 patients were randomized to receive low-dose dexamethasone; this treatment arm was closed due to similar activity and toxicity to the high-dose dexamethasone arm. ASCT, autologous stem cell transplant; DOR, duration of response ERd, elotuzumab + lenalidomide/ dexamethasone; Ig, immunoglobulin; IV, intravenous; MRD, minimal residual disease; PFS, progression-free survival; PO, oral; OS, overall survival; SMM, smoldering multiple myeloma; TTP, time to progression.



1. Ghobrial IM et al. Oral presentation at ASH 2016. Abstract 976.

# Phase 2 Study of ERd in SMM: Response to Therapy[1]

**Response to Therapy (n=38)**

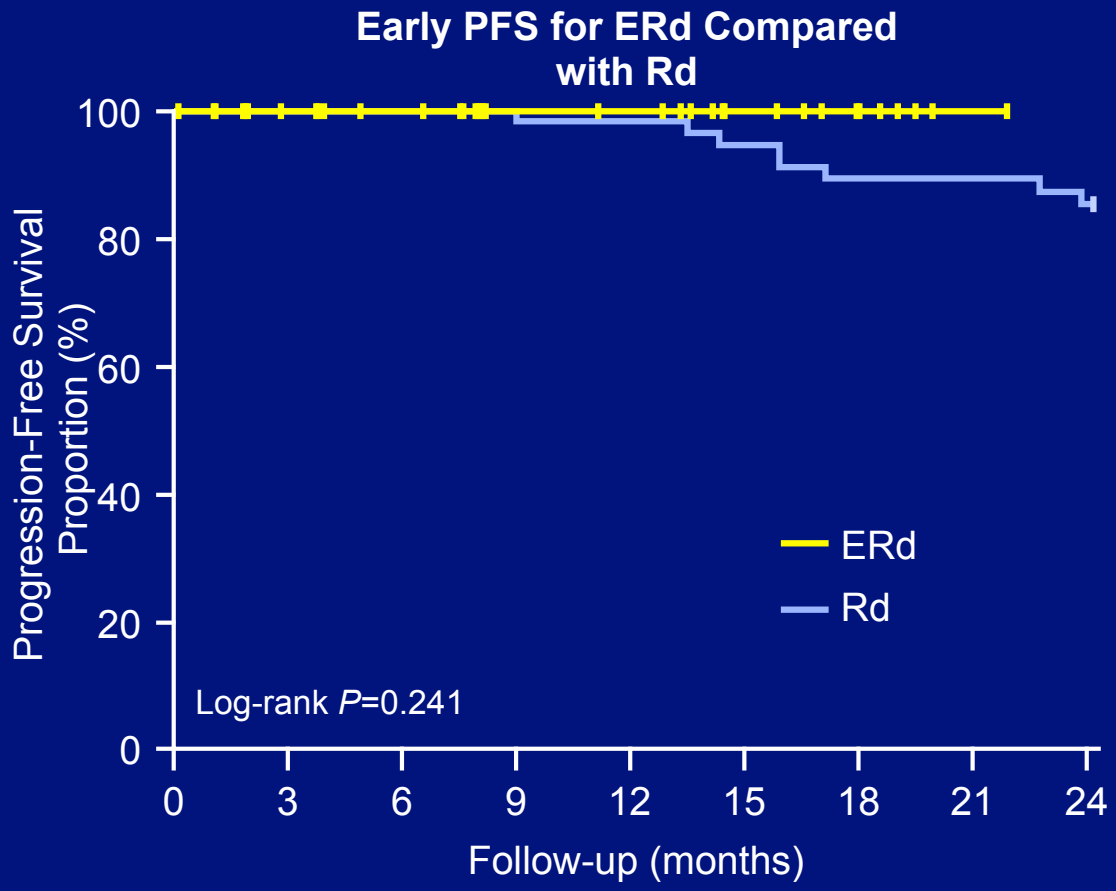



**Response to Therapy for Patients Receiving ≥9 Cycles (n=23)**

| Best Response | n (%) |
|---|---|
| CR | 2 (8.7) |
| VGPR | 6 (26.1) |
| PR | 11 (47.8) |
| MR | 4 (17.4) |
| SD | 0 |
| CR + VGPR + PR + MR | **23 (100)** |
| CR + VGPR + PR | **19 (82.6)** |

CR, complete response; ERd, elotuzumab + lenalidomide/dexamethasone; MR, minimal response; PR, partial response; SD, stable disease; SMM, smoldering multiple myeloma; VGPR, very good partial response. 1. Ghobrial IM et al. Oral presentation at ASH 2016. Abstract 976.

# Phase 2 Study of ERd in SMM: Early Progression-Free Survival[1]



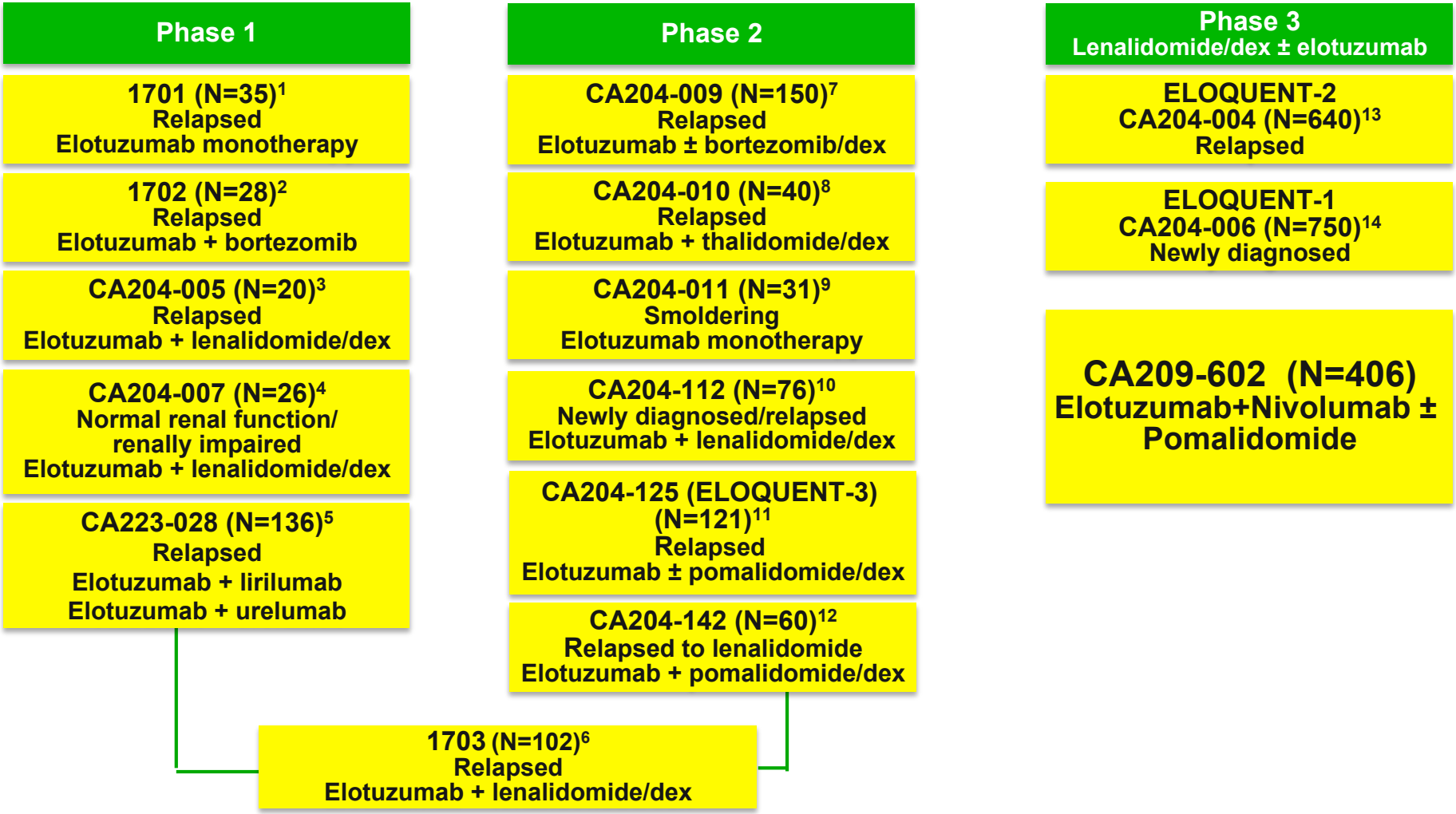

| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Rd | 57 | 56 | 56 | 55 | 55 | 52 |
| | 49 | 49 | 47 | | | |
| ERd | 47 | 35 | 30 | 18 | 17 | 11 |
| | 6 | 1 | 0 | | | |

ERd, elotuzumab + lenalidomide/dexamethasone; PFS, progression-free survival; Rd, lenalidomide/dexamethasone; SMM, smoldering multiple myeloma.



1. Ghobrial IM et al. Oral presentation at ASH 2016. Abstract 976.

# Elotuzumab Clinical Development Program




Dex, dexamethasone.

1. Clinicaltrials.gov. NCT00425347. 2. Clinicaltrials.gov. NCT00726869. 3. Clinicaltrials.gov. NCT01241292. 4. Clinicaltrials.gov. NCT01393964. 5. Clinicaltrials.gov. NCT02252263. 6. Clinicaltrials.gov. NCT00742560. 7. Clinicaltrials.gov. NCT01478048.
8. Clinicaltrials.gov. NCT01632150. 9. Clinicaltrials.gov. NCT01441973. 10. Clinicaltrials.gov. NCT02159365. 11. Clinicaltrials.gov. NCT02654132. 12. Clinicaltrials.gov. NCT02612779. 13. Clinicaltrials.gov. NCT01239797. 14. Clinicaltrials.gov. NCT01335399.

# Study CA204-006 (ELOQUENT-1): ERd vs Rd in NDMM[1]

## A Phase 3, Randomized, Open-Label Trial of Lenalidomide/Dexamethasone With or Without Elotuzumab in Subjects with Previously Untreated Multiple Myeloma

**N=750**

**Key Eligibility Criteria**

- Newly diagnosed MM with no prior systemic anti-myeloma therapy
- Measurable disease
- Subjects who are not candidates for high-dose therapy plus stem-cell transplant because of age or coexisting conditions
- Subjects with active plasma cell leukemia, HIV, or active hepatitis A, B, or C not permitted
- Smoldering MM, defined as asymptomatic MM with absence of lytic bone lesions
- Monoclonal Gammopathy of Undetermined Significance (MGUS)

R

**Elotuzumab**
10 mg/kg IV
Cycles 1 & 2: days 1, 8, 15, 22
Cycles 3–18: days 1, 15
Cycles ≥19: 20 mg/kg monthly

**Lenalidomide**
25 mg PO days 1–21

**Dexamethasone**
Weeks without Elo: 40 mg PO
Weeks with Elo: 8 mg IV + 28 mg PO

**Lenalidomide**
25 mg PO days 1–21

**Dexamethasone**
40 mg PO weekly

***Follow-up every 4 weeks for tumor assessment until progression and every 16 weeks for survival***

**Start Date:** May 2011
**Estimated Study Completion Date:** July 2020
**Estimated Primary Completion Date:** April 2018
**Status:** Ongoing, not recruiting participants

- **Primary Endpoints:** PFS
- **Secondary Endpoints:** ORR, OS

Elo, elotuzumab; ERd, elotuzumab, lenalidomide/dexamethasone; HIV, human immunodeficiency virus; IV, intravenous; MGUS, monoclonal gammapathy of undetermined significance; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally; R, randomized; Rd, lenalidomide/dexamethasone.

1. Clinicaltrials.gov. NCT01335399.

# Study CA204-142: EPd in Patients with RRMM to Prior Treatment with Lenalidomide[1]

## Phase 2, Single Arm Study of Elotuzumab in Combination With Pomalidomide and Low Dose Dexamethasone (EPd) in Patients with Multiple Myeloma Relapsed or Refractory to Prior Treatment with Lenalidomide

**N=60**

**Key Eligibility Criteria**

- Relapsed or refractory MM to a prior lenalidomide regimen
  - Relapse: PD ≤6 months after achieving PR
  - Refractory: PD on treatment or within 60 days of last therapeutic dose*
- Must have received prior 1 or 2 lines of treatment that included ≥2 consecutive cycles of lenalidomide (full therapeutic dose)
- Measurable disease

**Elotuzumab**
10 mg/kg IV
Cycles 1 & 2: days 1, 8, 15, 22
Cycles 3–6: days 1, 15
Cycles ≥7: 20 mg/kg monthly (Day 1)

**Pomalidomide**
4 mg PO days 1–21

**Dexamethasone†**
Weeks without Elo: 40 mg PO
Weeks with Elo: 8 mg IV + 28 mg PO
Days 1, 8, 15, 22 of each cycle

**Start Date:** November 2015
**Estimated Study Completion Date:** November 2024
**Estimated Primary Completion Date:** November 2024
**Status:** Recruiting participants

- **Primary Endpoint:** PFS
- **Secondary Endpoints:** ORR, OS

*Note: the lenalidomide-based regimen to which the patient has relapsed or been refractory to, is not required to be the most recent regimen received.
† For patients who are ≤75 years old. For patients >75 years old, the dexamethasone doses are 8 mg PO + 8 mg IV on weeks with elo, and 20 mg PO on weeks without elo. Elo, elotuzumab; IV, intravenous; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PD, progressive diease; PFS, progression-free survival; PO, orally; PR, partial response; R, randomized; RRMM, relapsed/refractory multiple myeloma.

1. Clinicaltrials.gov. NCT02612779.

# Study CA204-125 (ELOQUENT-3): EPd vs Pd in RRMM[1,2]

## Open-label, Randomized Phase 2 Trial of Pomalidomide/Dexamethasone With or Without Elotuzumab in RRMM

**N=121**

**Key Eligibility Criteria**

- Refractory MM or RRMM
- ≥2 prior lines of therapy with at least 2 consecutive cycles of lenalidomide and PI alone or in combination
- Refractory to lenalidomide and PI, and to last treatment
- Measurable disease
- Prior treatment with pomalidomide not permitted
- Prior ASCT within 12 weeks not permitted

**Start Date:** March 2016
**Estimated Study Completion Date:** November 2018
**Estimated Primary Completion Date:** May 2017
**Status:** Recruiting participants

R

**Elotuzumab**
10 mg/kg IV
Cycles 1 & 2: days 1, 8, 15, 22
20 mg/kg IV
Cycles 3+: day 1

**Pomalidomide**
4 mg PO days 1–21 of each cycle

**Dexamethasone**
Cycles 1 and 2: 28 mg + 8 mg IV* or
8 mg PO + 8 mg IV†; days 1, 8, 15, 22
Cycles 3+: Same as prior cycles on weeks with elotuzumab; 40 mg PO* or 20 mg PO† on weeks without elotuzumab

**Pomalidomide**
4 mg PO days 1–21 of each cycle

**Dexamethasone**
40 mg* or 20 mg† PO days 1, 8, 15, 22

- **Primary Endpoint:** PFS
- **Secondary Endpoints:** ORR, OS

*For patients aged ≤75 years. †For patients aged >75 years. Cycles are 28 days.
ASCT, autologous stem cell transplant; EPd, elotuzumab + pomalidomide/dexamethasone; IV, intravenous; MM, multiple myeloma; PI, proteasome inhibitor; ORR, overall response rate; OS, overall survival; Pd, pomalidomide/dexamethasone; PFS, progression-free survival; PO, orally; R, randomized; RRMM, relapsed/refractory multiple myeloma.

1. Clinicaltrials.gov. NCT02654132. 2. San Miguel J et al. Poster presentation at ASCO 2016. Abstract TPS8066.

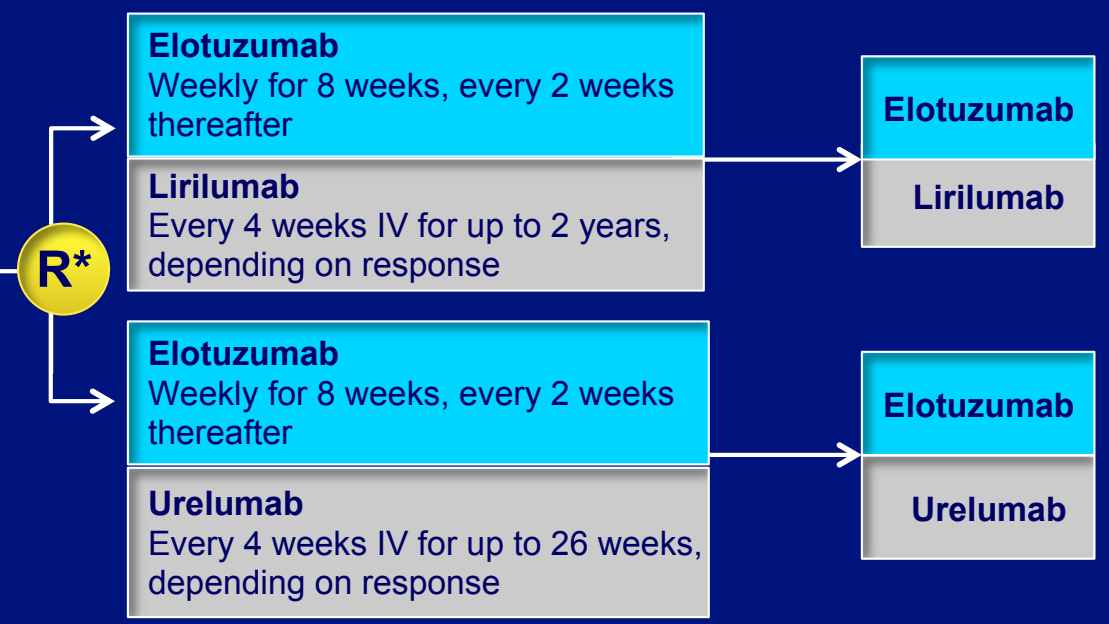
# Study CA223-028: Safety and Tolerability of Elotuzumab With Either Lirilumab or Urelumab in RRMM[1]

## A Phase 1 Open-Label Dose Escalation and Randomized Cohort Expansion Study of the Safety and Tolerability of Elotuzumab Administered in Combination With Either Lirilumab or Urelumab in Subjects With Multiple Myeloma

**N=136**

### Key Eligibility Criteria

- Histological confirmation of multiple myeloma with measurable disease (by IMWG criteria)
- Relapsed/refractory multiple myeloma; subjects who are post-autologous transplant and have achieved very good partial response or complete response with MRD




**Start Date:** December 2014
**Estimated Study Completion Date:** April 2017
**Estimated Primary Completion Date:** April 2017
**Status:** Ongoing, not recruiting participants

- **Primary Endpoints:** Safety
- **Secondary Endpoints:** BOR, ORR, mDOR, mTTR, PFSR, M-protein levels, MRD status for post-ASCT subjects, pharmacokinetics, biomarker status (NK and T-cell numbers, phenotypic and functional measures in cohort expansion subjects), occurrence of specific anti-drug antibodies (ADA)

ASCT, autologous stem cell transplant; BOR, best overall response; IMWG, International Myeloma Working Group; mDOR, median duration of response; MRD, minimal residual disease; mTTR, median time to response; NK, natural killer; ORR, overall response rate; PFSR, progression-free survival rate; R, randomization; RRMM, relapsed/refractory multiple myeloma.

*Part 1 is non-randomized; part 2 is randomized

1. Clinicaltrials.gov. NCT02252263.

Am J Hematol. 2017 Feb 18. doi: 10.1002/ajh.24687. [Epub ahead of print]

# A phase 2 safety study of accelerated elotuzumab infusion, over less than 1 hour, in combination with lenalidomide and dexamethasone, in patients with multiple myeloma.

Berenson J1, Manges R, Badarinath S, Cartmell A, McIntyre K, Lyons R, Harb W, Mohamed H, Nourbakhsh A, Rifkin R.

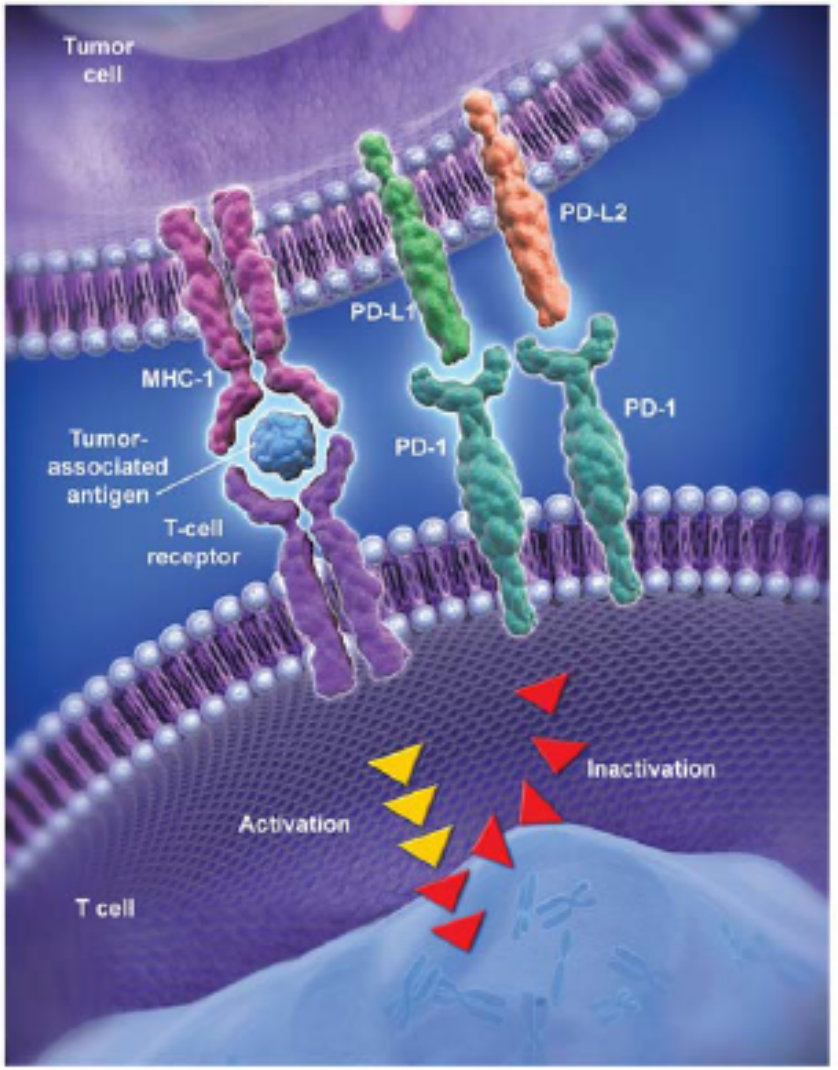
Elotuzumab, an immunostimulatory SLAMF7-targeting monoclonal antibody, induces myeloma cell death with minimal effects on normal tissue. **In a previous phase 3 study in patients with relapsed/refractory multiple myeloma (RRMM), elotuzumab (10 mg/kg, ~3-hour infusion),** combined with lenalidomide and dexamethasone, demonstrated durable efficacy and acceptable safety; 10% (33/321) of patients had infusion reactions (IRs; Grade 1/2: 29; Grade 3: 4). This phase 2 study NCT02159365) investigated an accelerated infusion schedule in 70 patients with newly diagnosed multiple myeloma or RRMM. The primary endpoint was cumulative incidence of Grade 3/4 IRs by completion of treatment Cycle 2. Dosing comprised elotuzumab 10 mg/kg intravenously (weekly, Cycles 1-2; biweekly, Cycles 3+), lenalidomide 25 mg (daily, Days 1-21) and dexamethasone (28 mg orally and 8 mg intravenously, weekly, Cycles 1-2; 40 mg orally, weekly, Cycles 3+), in 28-day cycles. Premedication with diphenhydramine, acetaminophen, and ranitidine (or their equivalents) was given as in previous studies**. If no IRs occurred, infusion rate was increased in Cycle 1 from 0.5 to 2 mL/min during dose 1 (~2 hours 50 min duration) to 5 mL/min for the entire infusion by dose 3 and also during all subsequent infusions (~1-hour duration).** Median number of treatment cycles was six. No Grade 3/4 IRs occurred; only one Grade 1 and one Grade 2 IR occurred, both during the first infusion. These data support the safety of a faster infusion of elotuzumab administered over ~1 hour by the third dose, providing a more convenient alternative dosing option for patients.

# My Agenda

- The complex network of anti-myeloma immunity vs myeloma escape
- MoAbs in multiple myeloma: general overview
- Daratumumab: mechanism(s) of action, updated results (ASCO/ASH 2016) and new studies
- Elotuzumab: mechanism(s) of action, updated results (ASCO/ASH 2016) and new studies
- **Other MoAbs: immune check-point modulators**
- How immunotherapy with MoAbs could modify end-points of multiple myeloma treatment

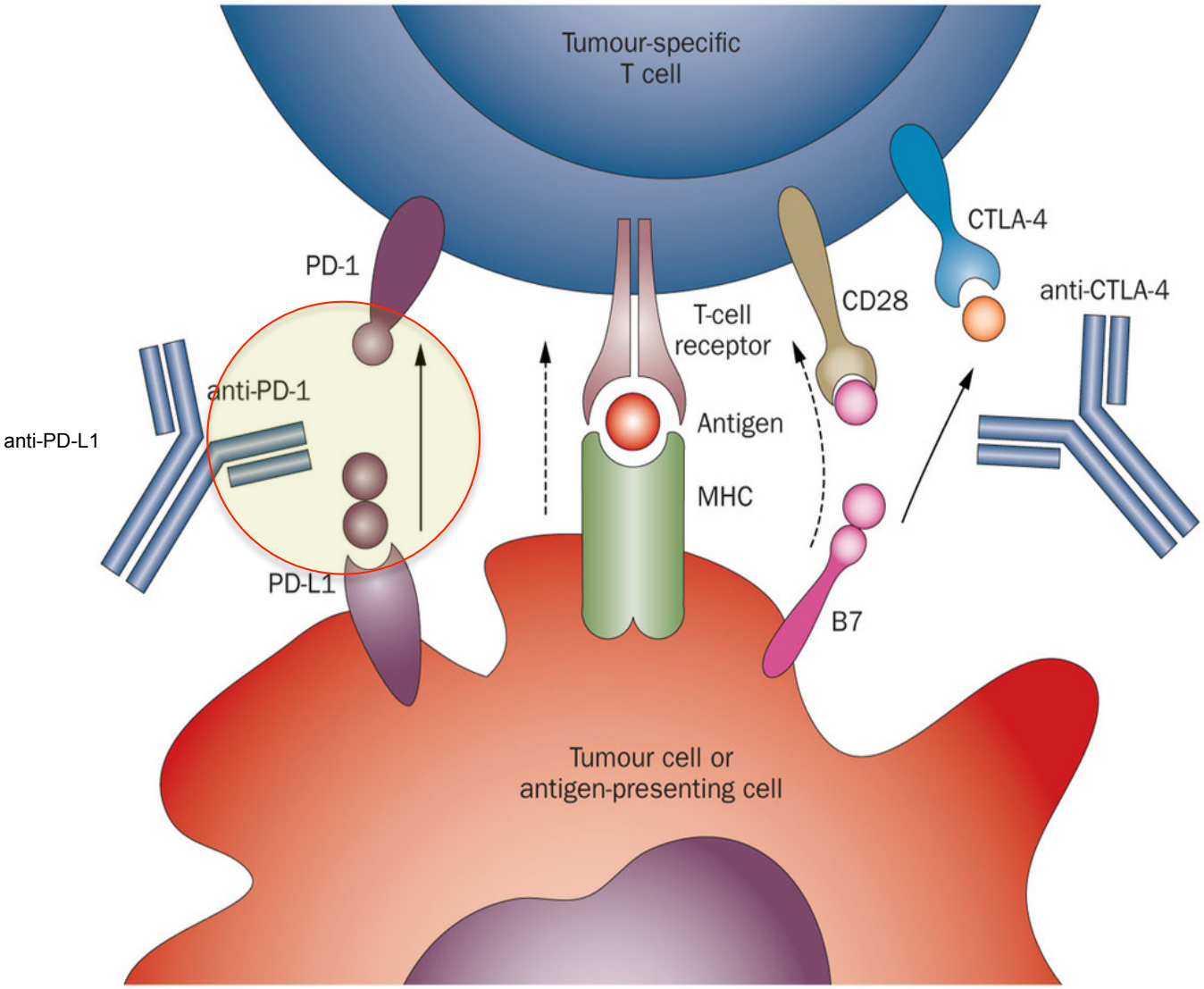
# PD-1: Programmed Death Receptor

- Upregulated on the surface of activated T-cells
- Ligands: PD-L1 & PD-L2, are expressed on the surface of APC & Tumor cells
- Binding of the PD-1 receptor to its ligands, PD-L1 and PD-L2, inhibits T-cell activation
- The PD-1 pathway is often exploited by tumors to evade immune surveillance[1,2,3]
- TILs have been shown to express significantly higher levels of PD-1[4]
- Up-regulation of PD-L1 expression levels have been described in: melanoma (40-100%), NSCLC (35-95%), and linked to poor clinical outcomes[5, 6]




1. Topalian SL et al. *Curr Opin Immunol.*2012;24:207-12; 2.Chen DS et al, *Clin Cancer Res.* 2012;18:6580-7; 3. Butte MJ et al, *Immunity.* 2007;27:111-22; 4. Mellman I et al. *Nature*, 2011;480:480-9; 5. Konishi J et al, *Clin Cancer Res* 2004;10:5094-100; 6. Liu J et al, *Blood.* 2007;110:296-304.

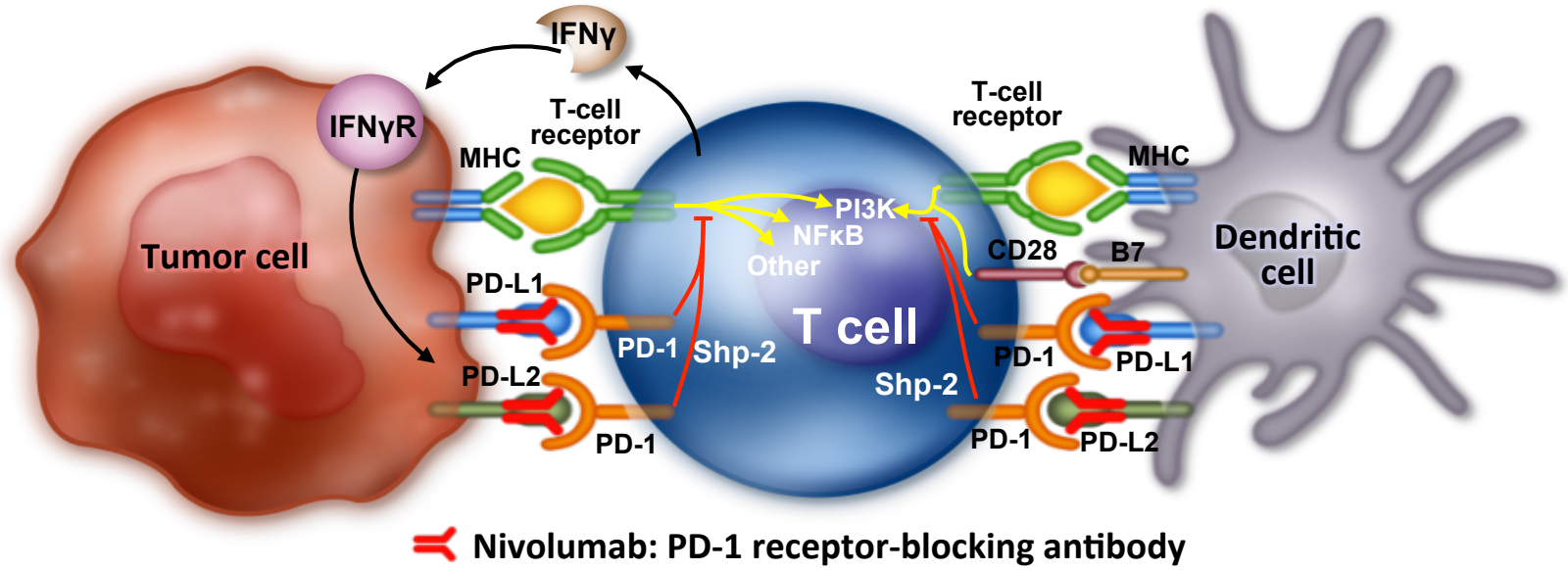
# PD-1/PD-L1 blockade in cancer therapy




Nguyen et al., Nature Rev Immunol 2015

# PD-1 pathway and Nivolumab

- Nivolumab is a fully human immunoglobulin G4 monoclonal antibody targeting the programmed death-1 (PD-1) immune checkpoint pathway
- Nivolumab binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-1 ligands, PD-L1/PD-L2, to restore T-cell antitumor function[1,2]



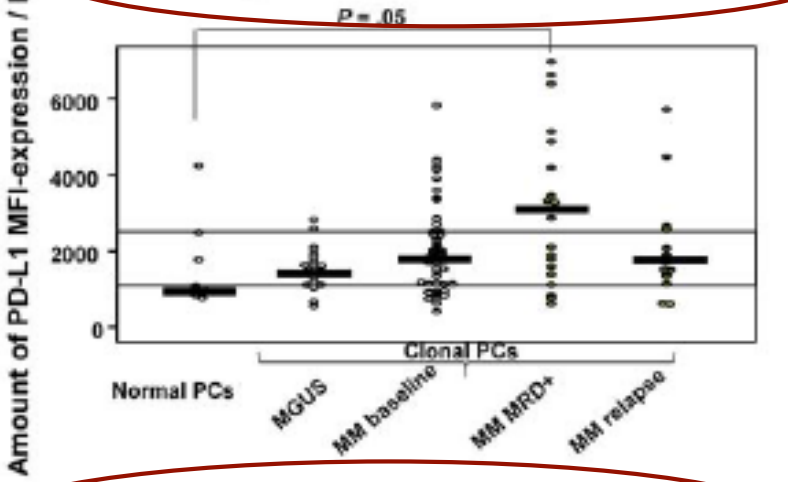

1. Brahmer JR et al. *J Clin Oncol* 2010;28:3167–75; 2. Wang C et al. *Cancer Immunol Res* 2014;2:846–56

# Is There a Role for PD-1 Inhibitors in Multiple Myeloma?

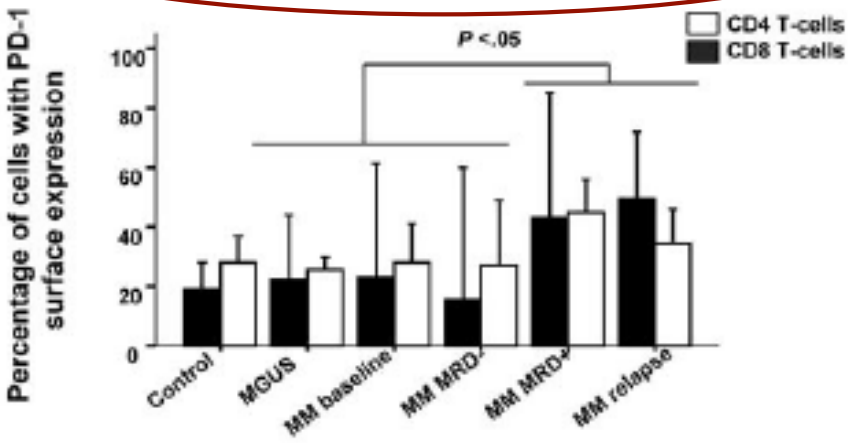
***PD-L1 expression is present in PCs[1,2]***

[1]Liu J et al, Blood. 2007;110(1):296-304; [2]Tamura H, et al. Leukemia. 2013;27:464-72.

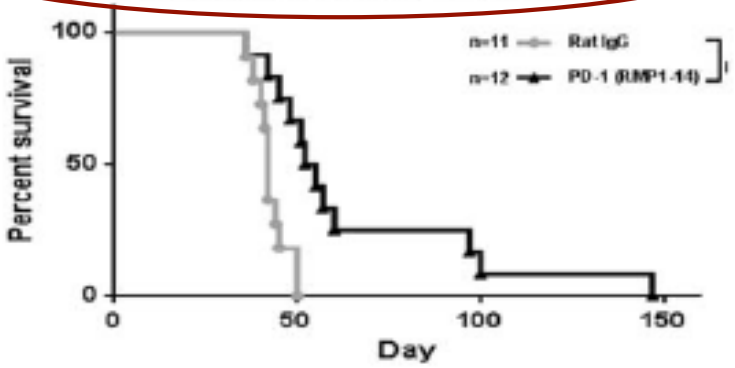
***PD-L1 expression across all disease stages***

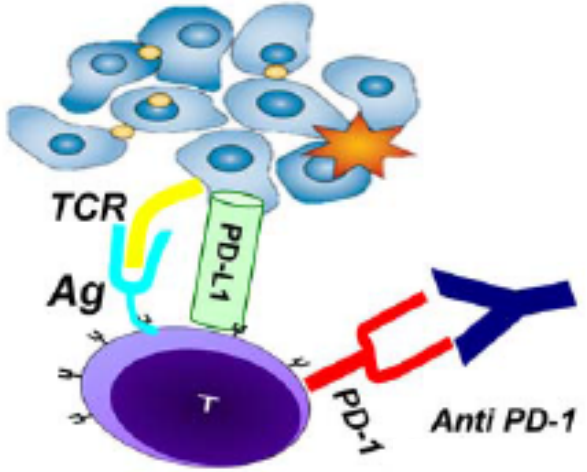



***Increase PD-1 among T-cells of MRD/RR pts.***




**Anti–PD-1 in C57BL/KaLwRijHsd syngeneic mice with 5TGM-1 PD-L1$^{+ve}$ MM cells**




Paiva B, et al. *Leukemia*. 2015. 2015;29:2110-3.

# Nivolumab in MM Phase 1 Program:
# CA209-039 Study Design[1,2]

**A Phase 1 Dose-Escalation Study to Investigate the Safety, Pharmacokinetics, Immunoregulatory Activity, and Preliminary Antitumor Activity of Anti-Programmed-Death 1 (PD-1) Antibody (Nivolumab, BMS936558) and the Combination of Nivolumab and Ipilimumab and Lirilumab in Subjects with Relapsed or Refractory Hematologic Malignancy[1]**

**N=315**

**Key Eligibility Criteria**
- Histological confirmation of relapsed or refractory hematologic malignancy
- Measurable disease

R

- **Nivolumab (dose escalation)**
  1 or 3 mg/kg IV on weeks 1 and 4, Q2W thereafter
- **Nivolumab**
  IV as specified
- **Ipilimumab**
  IV as specified
- **Nivolumab**
  IV as specified
- **Lirilumab**
  IV as specified

***Response measured every 4 weeks until progression***

**Start Date: June 2012**
**Estimated Study Completion Date: March 2018**
**Estimated Primary Completion Date: July 2017**
**Status: Currently recruiting participants; enrollment closed for nivolumab monotherapy arm**

- **Primary Endpoints: DLTs, safety**
- **Secondary Endpoints: ORR, PK, PFS, mSWAT, immunogenicity, PD-L1 expression levels**

IV, intravenous; DLT, dose-limiting toxicity; mSWAT, modified severity weighted assessment tool; ORR, overall response rate; PD-L1, programmed death ligand 1; PK, pharmacokinetics; PFS, progression-free survival; R, randomized.

1. Clinicaltrials.gov. NCT01592370. 2. Lesokhin AM et al. *J Clin Oncol.* June 2016 [Epub ahead of print].

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*

Listen to the podcast by Dr Westin at www.jco.org/podcasts

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on June 6, 2016.

Supported by Bristol-Myers Squibb, grants from the National Institutes of Health (U54CA163125 and P01AI056299 to G.J.F. and R01CA161026 to M.A.S.), and a grant from the Miller Fund (to M.A.S.).

Presented at the 56th Annual Meeting of the American Society of Hematology, San Francisco, CA, December 6-9, 2014; 20th Congress of the European Hematology Association, Vienna, Austria, June 11-14, 2015; and 13th International Conference on Malignant Lymphoma, Lugano, Switzerland, June 17-20, 2015.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT01592370.

Corresponding author: Alexander M. Lesokhin, MD, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065; e-mail: lesokhia@mskcc.org.



0732-183X/16/3423w-2698w/$20.00

DOI: 10.1200/JCO.2015.65.9789

## ABSTRACT

**Purpose**

Cancer cells can exploit the programmed death-1 (PD-1) immune checkpoint pathway to avoid immune surveillance by modulating T-lymphocyte activity. In part, this may occur through overexpression of PD-1 and PD-1 pathway ligands (PD-L1 and PD-L2) in the tumor microenvironment. PD-1 blockade has produced significant antitumor activity in solid tumors, and similar evidence has emerged in hematologic malignancies.

**Methods**

In this phase I, open-label, dose-escalation, cohort-expansion study, patients with relapsed or refractory B-cell lymphoma, T-cell lymphoma, and multiple myeloma received the anti–PD-1 monoclonal antibody nivolumab at doses of 1 or 3 mg/kg every 2 weeks. This study aimed to evaluate the safety and efficacy of nivolumab and to assess *PD-L1/PD-L2* locus integrity and protein expression.

**Results**

Eighty-one patients were treated (follicular lymphoma, n = 10; diffuse large B-cell lymphoma, n = 11; other B-cell lymphomas, n = 10; mycosis fungoides, n = 13; peripheral T-cell lymphoma, n = 5; other T-cell lymphomas, n = 5; multiple myeloma, n = 27). Patients had received a median of three (range, one to 12) prior systemic treatments. Drug-related adverse events occurred in 51 (63%) patients, and most were grade 1 or 2. Objective response rates were 40%, 36%, 15%, and 40% among patients with follicular lymphoma, diffuse large B-cell lymphoma, mycosis fungoides, and peripheral T-cell lymphoma, respectively. Median time of follow-up observation was 66.6 weeks (range, 1.6 to 132.0+ weeks). Durations of response in individual patients ranged from 6.0 to 81.6+ weeks.

**Conclusion**

Nivolumab was well tolerated and exhibited antitumor activity in extensively pretreated patients with relapsed or refractory B- and T-cell lymphomas. Additional studies of nivolumab in these diseases are ongoing.

*J Clin Oncol 34:2698-2704. © 2016 by American Society of Clinical Oncology*

**Table 1.** Baseline Characteristics

| Characteristic | B-Cell Lymphoma, No. (%) | T-Cell Lymphoma, No. (%) | Multiple Myeloma, No. (%) |
|---|---|---|---|
| No. of patients | 31 | 23 | 27 |
| Age, years | | | |
| Median | 65 | 61 | 63 |
| Range | 23-74 | 30-81 | 32-81 |
| Sex | | | |
| Female | 11 (35) | 8 (35) | 15 (56) |
| Male | 20 (65) | 15 (65) | 12 (44) |
| Race | | | |
| White | 29 (94) | 17 (74) | 22 (81) |
| Black | 1 (3) | 3 (13) | 5 (19) |
| Asian | 1 (3) | 1 (4) | 0 |
| Other | 0 | 2 (9) | 0 |
| ECOG performance status | | | |
| 0 | 16 (52) | 4 (17) | 13 (48) |
| 1 | 12 (39) | 18 (78) | 13 (48) |
| 2 | 0 | 0 | 1 (4) |
| Not reported | 3 (10) | 1 (4) | 0 |
| Extranodal involvement | 8 (26) | 4 (17) | NA |
| Prior systemic therapies | | | |
| 2-3 | 15 (48) | 6 (26) | 12 (44) |
| 4-5 | 7 (23) | 9 (39) | 8 (30) |
| ≥ 6 | 5 (16) | 5 (22) | 6 (22) |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NA, not applicable.

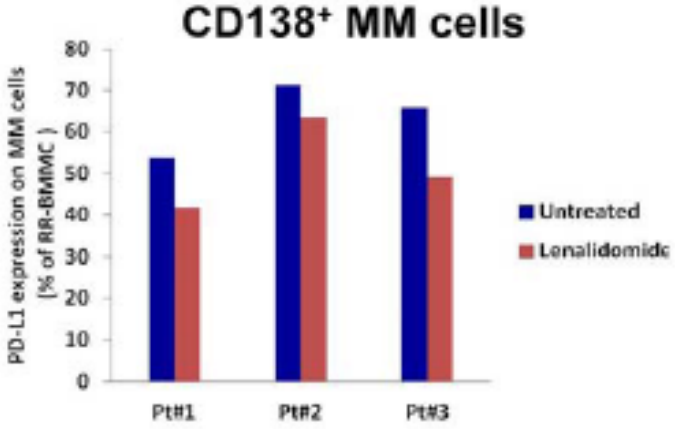
**Table 3.** Efficacy Results

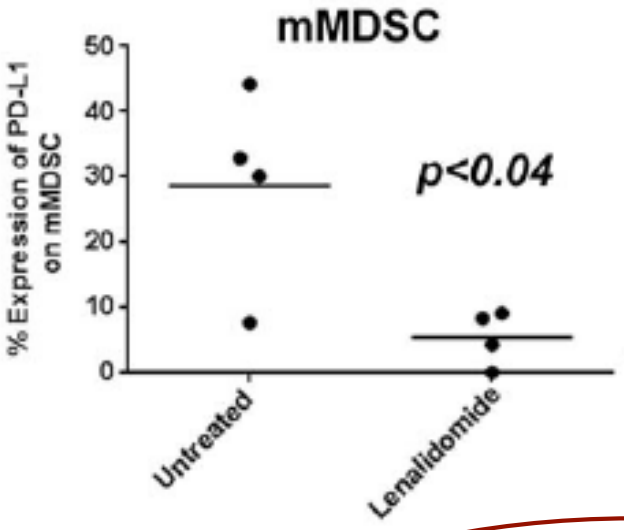
| Tumor | OR, No. (%) | CR, No. (%) | PR, No. (%) | SD, No. (%) | Median PFS, Weeks (95% CI) |
|---|---|---|---|---|---|
| B-cell lymphoma (n = 31) | 8 (26) | 3 (10) | 5 (16) | 16 (52) | 23 (7 to 44) |
| DLBCL (n = 11) | 4 (36) | 2 (18) | 2 (18) | 3 (27) | 7 (6 to 29) |
| FL (n = 10) | 4 (40) | 1 (10) | 3 (30) | 6 (60) | NR (7 to NR) |
| Other B-cell lymphoma (n = 10) | 0 | 0 | 0 | 7 (70) | 11 (3 to 39) |
| T-cell lymphoma (n = 23) | 4 (17) | 0 | 4 (17) | 10 (43) | 10 (7 to 33) |
| MF (n = 13) | 2 (15) | 0 | 2 (15) | 9 (69) | 10 (7 to 35) |
| PTCL (n = 5) | 2 (40) | 0 | 2 (40) | 0 | 14 (3 to NR) |
| Other CTCL (n = 3) | 0 | 0 | 0 | 0 | 7 (6 to NR) |
| Other non-CTCL (n = 2) | 0 | 0 | 0 | 1 (50) | 10 (2 to 18) |
| Multiple myeloma (n = 27) | 1 (4) | 1 (4)* | 0 | 17 (63) | 10 (5 to 15) |

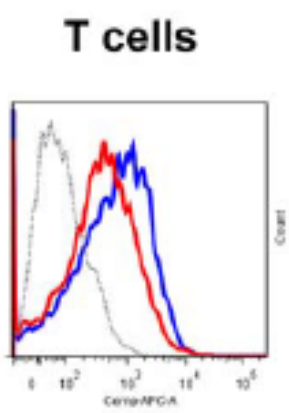
Abbreviations: CR, complete response; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MF, mycosis fungoides; NR, not reported; OR, objective response; PFS, progression-free survival; PR, partial response; PTCL, peripheral T-cell lymphoma; SD, stable disease.

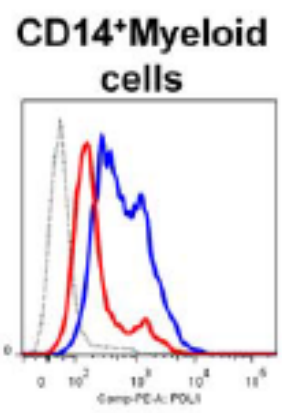
*CR was obtained after radiotherapy. SD was the best response to nivolumab.

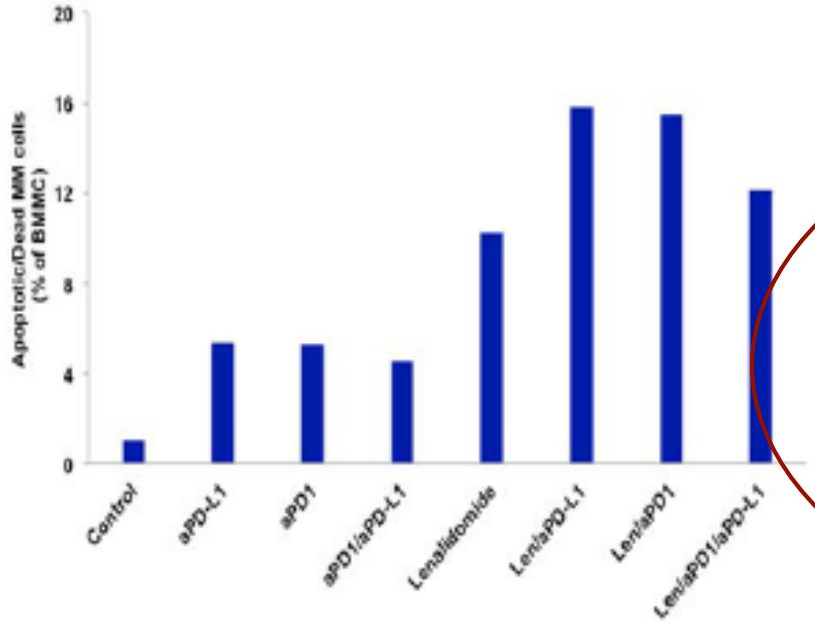
# Rationale For The Combination in MM: Synergistic Effect Between PD-1 Inhibitor and IMiDs



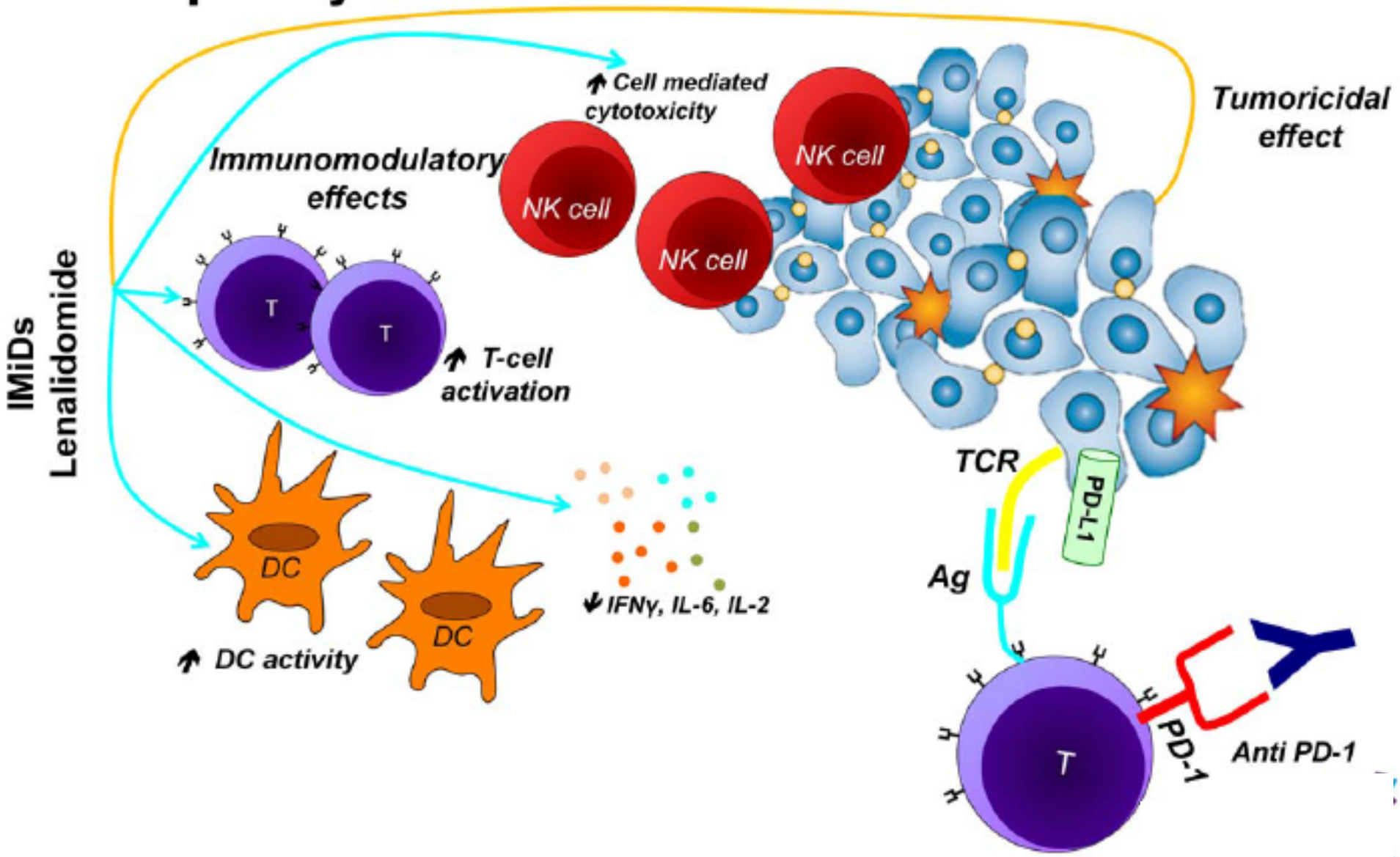




- Lenalidomide reduces PD-L1 and PD-1 expression on MM cells & T and Myeloid Derived Suppressor cells
- Lenalidomide enhances checkpoint blockade induced effector cytokine production in MM bone marrow & induced cytotoxicity against MM cells

Görgün G. et al. Clin Cancer Res. 2015;21:4607-18.

# Are IMiDs and PD-1 Inhibitors Synergistic in Multiple Myeloma?



# Nivolumab in MM Phase 3 Program:
# CheckMate 602 Study Design[1]

**An Open-label, Randomized Phase 3 Trial of Combinations of Nivolumab, Elotuzumab, Pomalidomide, and Dexamethasone in RRMM**

**N=406**

**Key Eligibility Criteria**
- Refractory or RRMM
- Received ≥2 lines of prior therapy, which must have included an IMiD and a PI alone or in combination

R

- **Nivolumab** IV as specified
- **Pom-d** PO as specified
- **Nivolumab** IV as specified
- **Elotuzumab** IV as specified
- **Pom-d** PO as specified
- **Pom-d** PO as specified

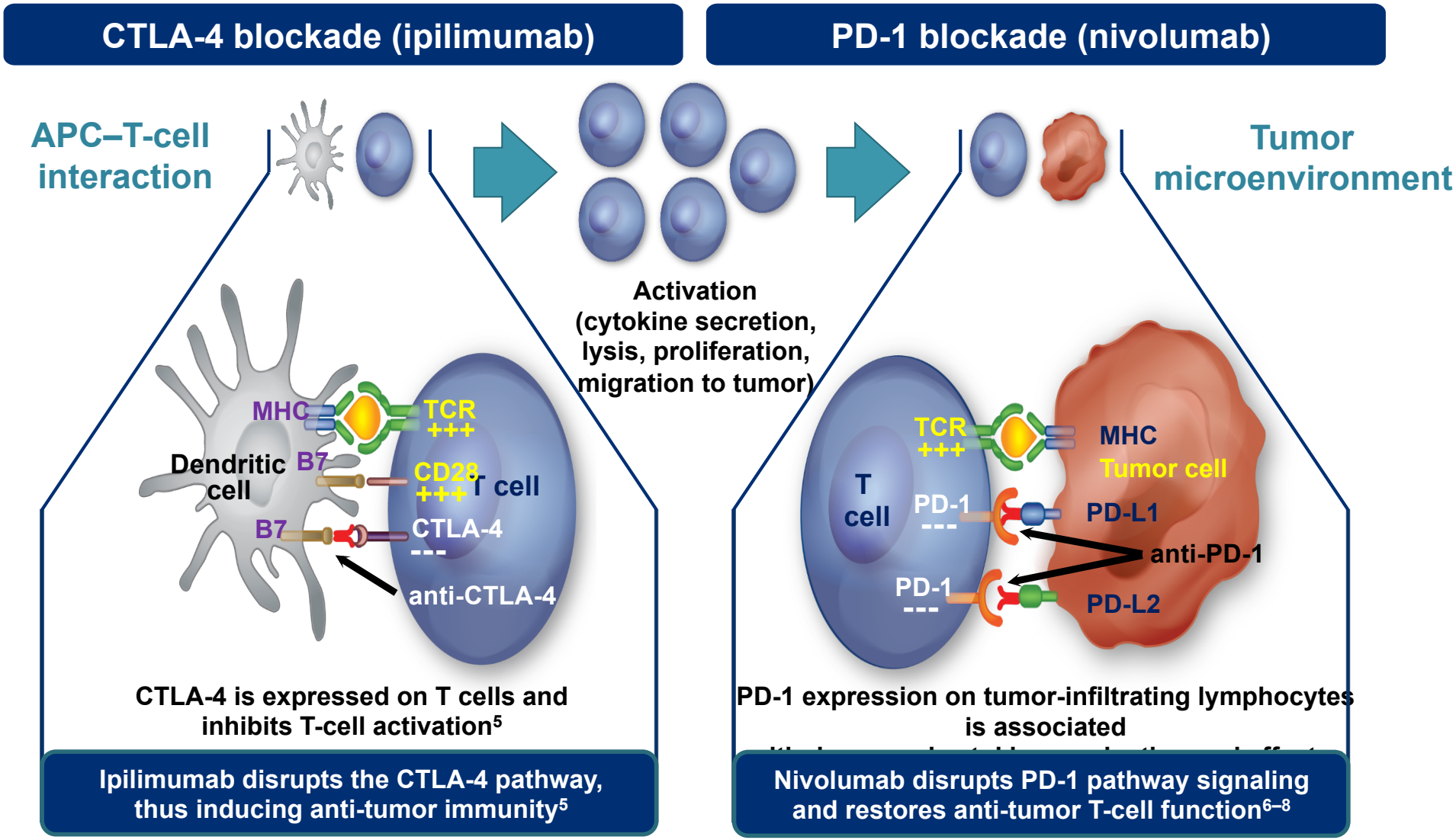
**Start Date: April 2016**
**Estimated Study Completion Date: July 2020**
**Estimated Primary Completion Date: June 2018**
**Status: Currently recruiting participants**

- **Primary Endpoints: ORR, PFS**
- **Secondary Endpoints: TTR, DOR, investigator-assessed PFS and ORR**

IV, intravenous; ORR, overall response rate; PFS, progression-free survival; Pom-d, pomalidomide/dexamethasone; R, randomized; RRMM, relapsed/refractory multiple myeloma; TTR, time to response.

1. Clinicaltrials.gov. NCT02726581.

# Nivolumab and Ipilimumab Mechanism of Action




APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen 4; MHC, major histocompatibility complex; PD-1, programmed death receptor-1; PD-L1/2, programmed death receptor ligand 1/2; TCR, T-cell receptor

# A Phase 1 Study of Nivolumab in Combination With Ipilimumab for Relapsed or Refractory Hematologic Malignancies (CheckMate 039, combination cohort)

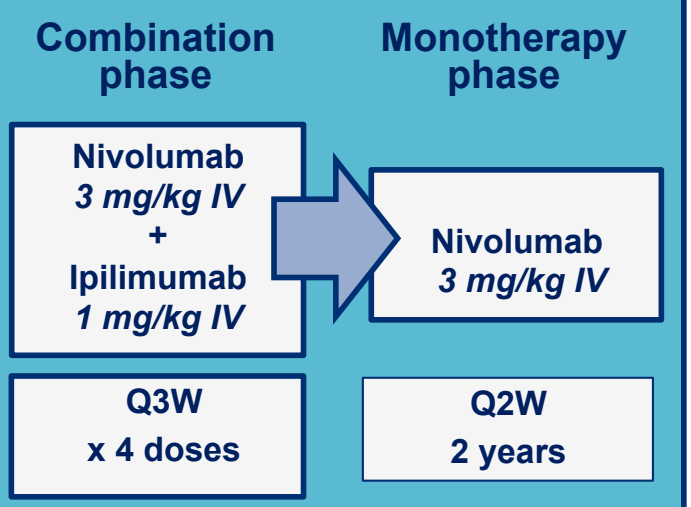
**Phase 1, non-randomized, non-comparative, sequential cohort pilot study**

## Inclusion Criteria

**Relapsed/refractory lymphoid malignancies:**

- **Hodgkin lymphoma**
- **B-cell lymphoma[a]**
- **T-cell lymphoma[b]**
- **Multiple myeloma** (7 patients)
- No prior organ or allogeneic bone marrow transplantation
- No prior immune checkpoint blockade therapy

## Treatment




**Treatment until disease progression, toxicity, or maximum duration of 2 years**

## Endpoints

***Primary***

- Safety and tolerability

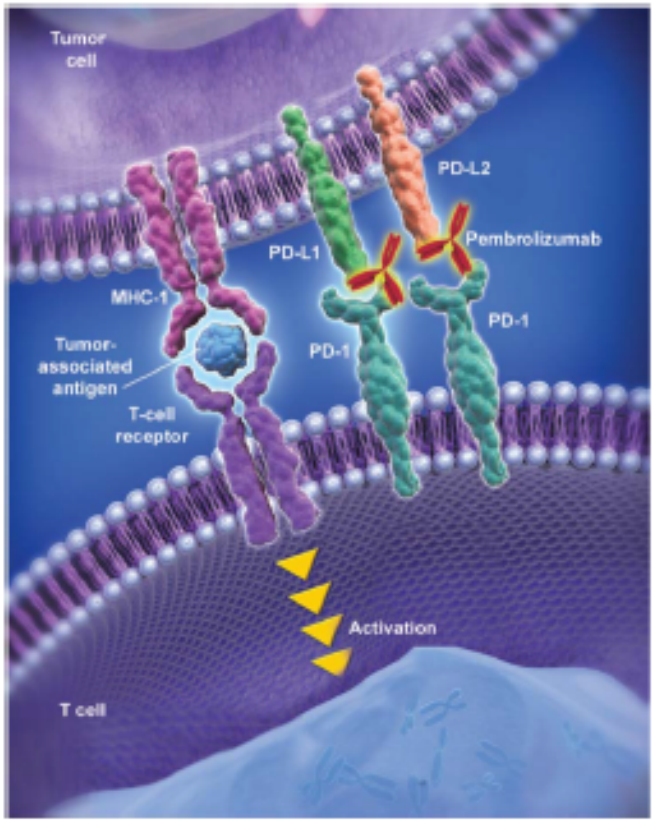
***Secondary***

- INV-assessed best overall response
- Duration of response
- Progression-free survival
- Biomarker analyses

[a]Includes follicular B-cell lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). [b]Includes cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL) INV, investigator; IV, intravenously; Q2W, every 2 weeks; Q3W, every 3 weeks

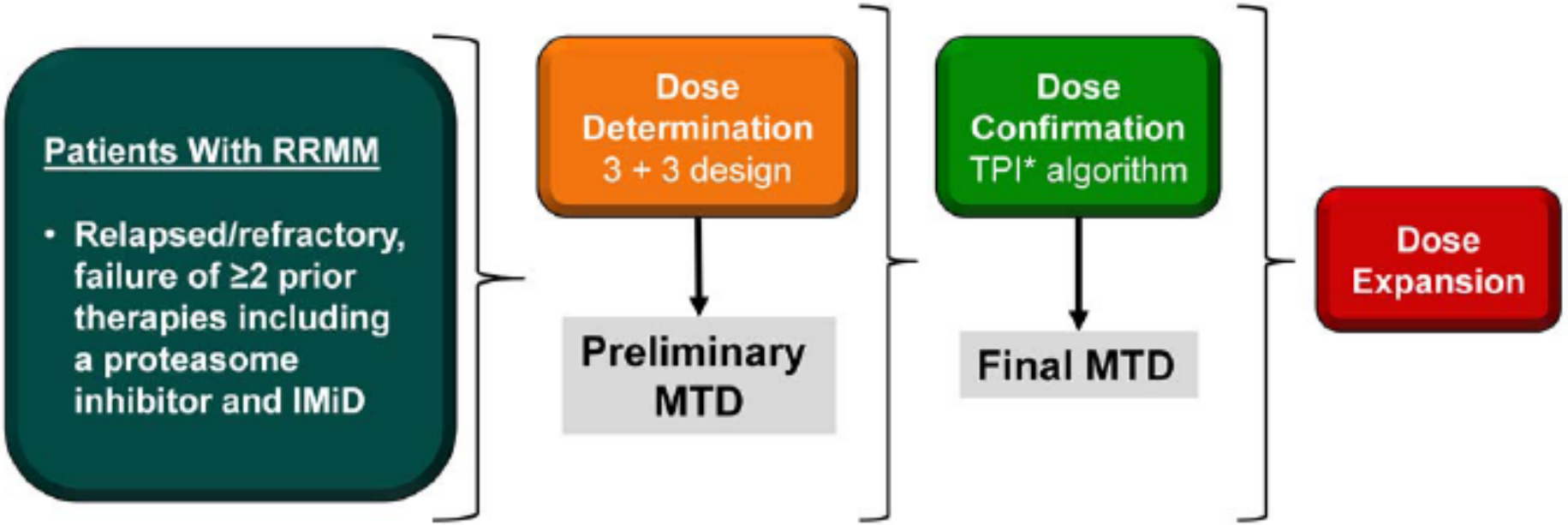
# Pembrolizumab and the PD-1 Pathway

- The programmed death 1 (PD-1) pathway is frequently altered in cancer, leading to inhibition of active T-cell–mediated immune surveillance of tumors[1]
- Pembrolizumab is a highly selective, humanized monoclonal anti–PD-1 antibody designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2
  - Pembrolizumab is approved globally for advanced melanoma, and in the United States for metastatic, PD-L1–positive non–small cell lung carcinoma[2,3]
- PD-1 inhibition may act synergistically with IMiDs to enhance tumor suppression
  - PD-L1 is expressed in most plasma cells from patients with MM[4]
  - PD-L1 expression is associated with higher MM cell proliferation and resistance to antimyeloma chemotherapy[5]
  - Lenalidomide reduces PD-L1 and PD-1 expression on MM cells, and enhances checkpoint blockade–induced effector cytokine production in MM bone marrow and induced cytotoxicity against MM cells[6]




1. Francisco LM et al. *Immunol Rev*. 2010;236:219-242. 2. Keytruda (pembrolizumab) for injection, for intravenous use [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2015. 3. Keytruda summary of product characteristics. Hoddesdon, UK: Merck Sharp & Dohme Limited; 2015. 4. Liu J et al. *Blood*. 2007;110:296-304. 5. Tamura H et al. *Leukemia*. 2013;27:464-472. 6. Gorgun G et al. *Clin Cancer Res*. 2015;21:4607-4618.

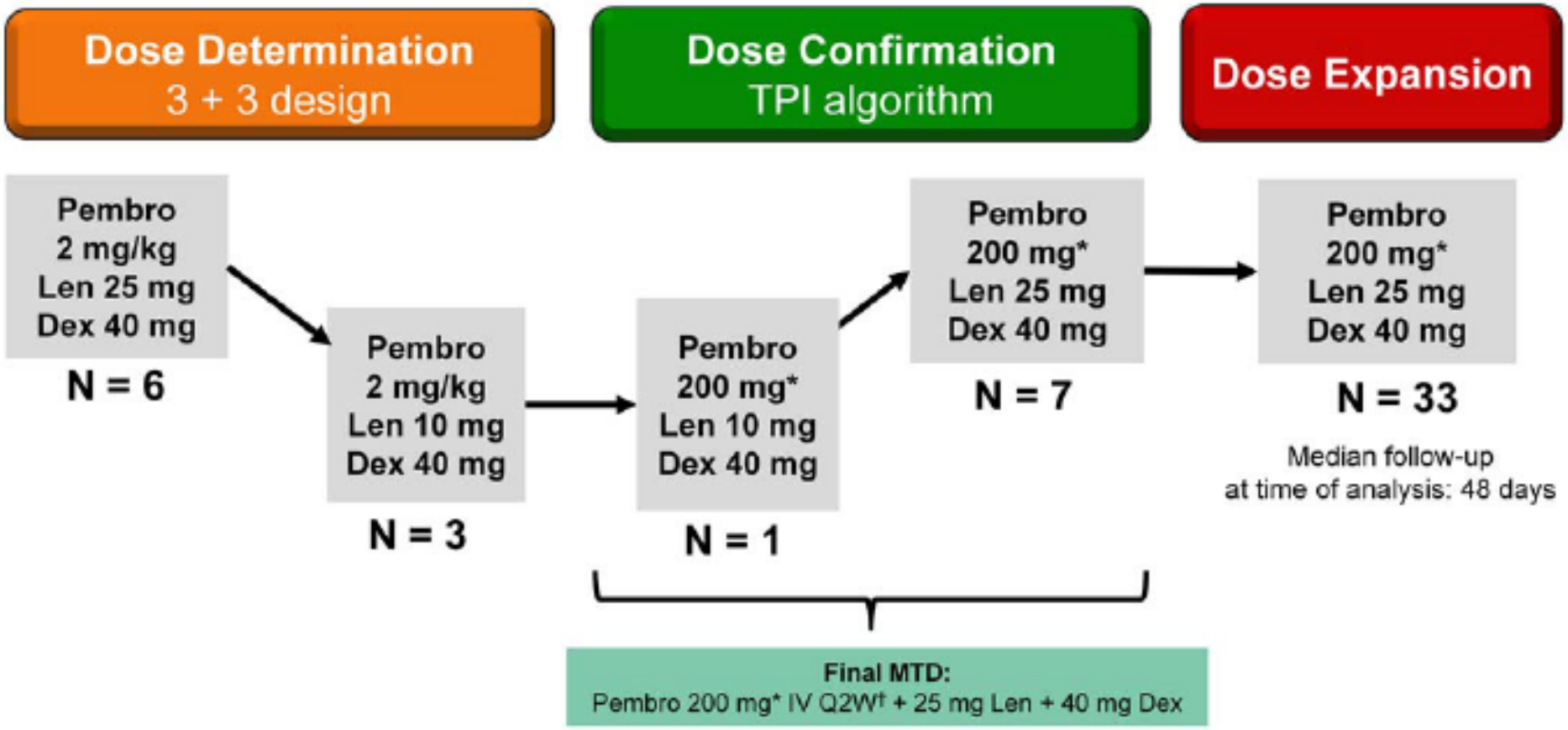
# KEYNOTE-023: Phase 1 Trial of Pembrolizumab + Lenalidomide and Low Dose Dexamethasone in RRMM




- **Primary end points**: Safety and tolerability
- **Secondary end points**: ORR, DOR, PFS, OS

*TPI = Toxicity Probability Interval (Ji Y et al. *Clin Trials*. 2007;4:235-244)

# KEYNOTE-023: Study Chronology




- **Safety analysis: all patients enrolled in the study (N = 50)**
- **Efficacy analysis: patients in the dose determination and confirmation stages (N = 17)**

*Pembrolizumab 2 mg/kg ≈ 200 mg fixed dose Q2W (based upon PK/PD studies)
†Pembrolizumab IV 30 minutes (no premedication) Q2W, lenalidomide 1-21 day, dexamethasone weekly

# KEYNOTE-023: Prior Lines of Therapies

| | Pembro + Len + Dex N = 50 |
|---|---|
| **Prior therapies, median (range)** | 4 (1-5) |
| **≥3 Lines of therapy, n (%)** | 36 (**72**) |
| **Prior therapies, n, (%)**<br>Lenalidomide<br>Bortezomib<br>Pomalidomide<br>Carfilzomib | <br>48 (**96**)<br>48 (**96**)<br>13 (**26**)<br>11 (**22**) |
| **Prior ASCT, n (%)** | 43 (**86**) |

| | Pembro + Len + Dex N = 50 | |
|---|---|---|
| **Refractory to lenalidomide, n (%)*** | 38 (**76**) | |
| Double refractory | 15 (30) | **50%** |
| Triple refractory | 6 (12) | |
| Quadruple refractory | 4 (8) | |
| **Refractory to bortezomib, n (%)** | 32 (64) | |
| **Refractory, last line, n (%)** | 40 (**80**) | |
| **Refractory to lenalidomide as last line, n (%)** | 10 (20) | |

*Double refractory = Len/Bort
Triple refractory = Len/Bort/Pom or Len/Bort/Carf
Quadruple refractory = Len/Bort/Pom/Carf
Data cutoff date: September 22, 2015

# KEYNOTE-023: Antitumor Activity
## Dose Determination and Dose Confirmation Stages

| N (%) | Total N = 17 | Len Refractory* N = 9 |
|---|---|---|
| Overall Response Rate | 13 (**76**) | 5 (**56**) |
| Very Good Partial Response | 4 (**24**) | 2 (**22**) |
| Partial Response | 9 (**53**) | 3 (**33**) |
| Disease Control Rate† | 15 (**88**) | 7 (**78**) |
| Stable Disease | 3 (**18**) | 3 (**33**) |
| Progressive Disease | 1 (**6**) | 1 (**11**) |

*3 patients double refractory and 1 triple refractory (Len/Bor +Pom)
†Disease Control Rate = CR +VGPR + PR + SD >12 weeks.
Data cutoff date: September 22, 2015

# Patient Case 2: Double Refractory with EMD Disease: sCR After Two Cycles

**PRIOR THERAPIES:**

**1st line**:

- Bort-Dex-Adrya + ASCT
- Response:
  - CR (DOR 3 y)

**2nd line:**

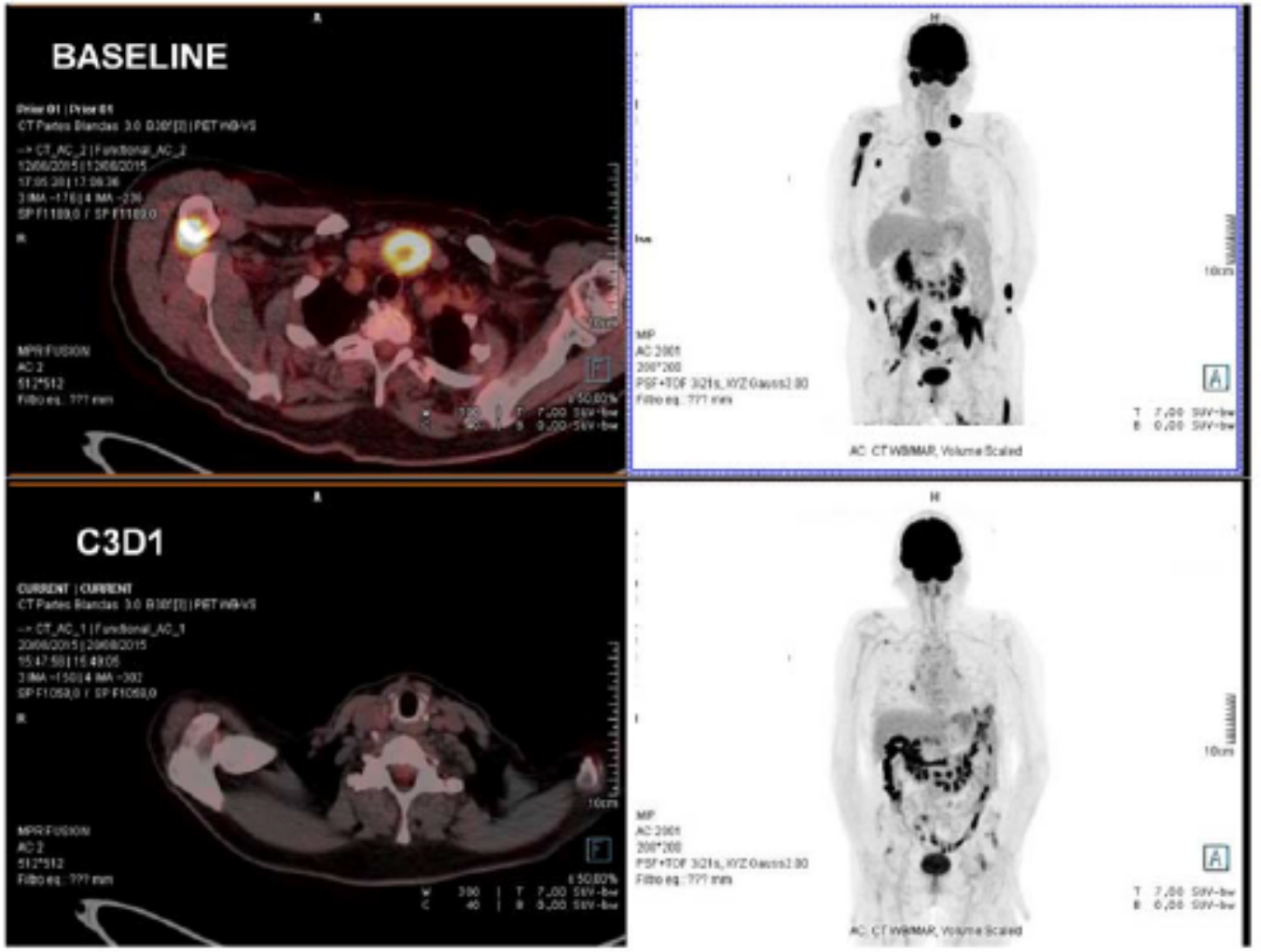
- Len-Dex
- Refractory

**3rd line:**

- VMP
- Refractory

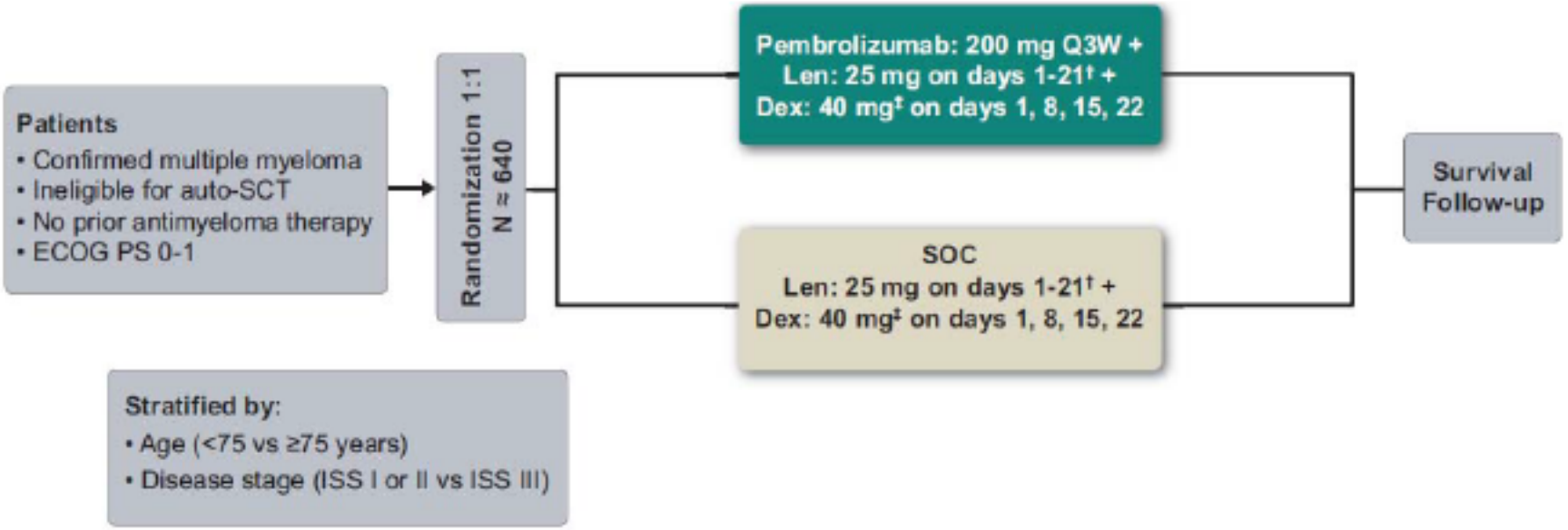
**4th line:**

- Pembro + Len-Dex
- Response:
  - sCR after 2 cycles



# Study Design

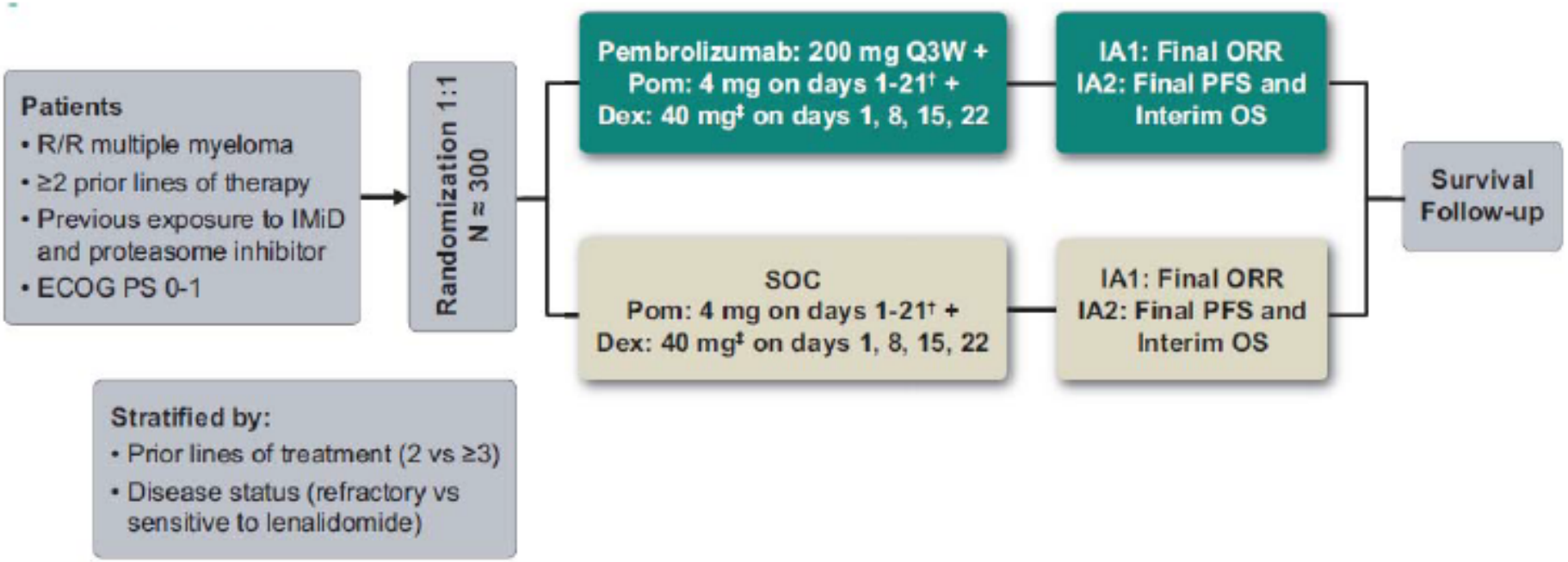
- KEYNOTE-185 is a randomized, active-controlled, multicenter, open-label trial of lenalidomide and low-dose dexamethasone with or without pembrolizumab in patients with newly diagnosed and treatment-naive MM who are ineligible for auto-SCT




auto-SCT = autologous stem cell transplantation; Dex = dexamethasone; ECOG PS = Eastern Cooperative Oncology Group performance status; ISS = International Staging System; OS = overall survival; PFS = progression-free survival; Len = lenalidomide; Q3W = once every 3 weeks; SOC = standard of care. †28-day cycle ‡20 mg dexamethasone is recommended for patients aged >75 years

# Study Design

- KEYNOTE-183 is a randomized, active-controlled, multicenter, open-label trial of pomalidomide and low-dose dexamethasone with or without pembrolizumab in patients with rrMM who have undergone at least 2 lines of prior treatment, are refractory to their last line of treatment, and have been previously exposed to an IMiD (such as lenalidomide or thalidomide) and a proteasome inhibitor (such as bortezomib, ixazomib, or carfilzomib)




Dex = dexamethasone; ECOG PS = Eastern Cooperative Oncology Group performance status; IA1 = interim analysis 1; IA2 = interim analysis 2; IMiD = immunomodulatory drug; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; Pom = pomalidomide; Q3W = every 3 weeks; R/R = relapsed/refractory; SOC = standard of care. †28-day cycle. ‡20 mg dexamethasone is recommended for patients aged >75 years.

# My Agenda

- The complex network of anti-myeloma immunity vs myeloma escape
- MoAbs in multiple myeloma: general overview
- Daratumumab: mechanism(s) of action, updated results (ASCO/ASH 2016) and new studies
- Elotuzumab: mechanism(s) of action, updated results (ASCO/ASH 2016) and new studies
- Other MoAbs: immune check-point modulators
- **How immunotherapy with MoAbs could modify end-points of multiple myeloma treatment**

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

# Systematic Literature Review and Network Meta-Analysis of Treatment Outcomes in Relapsed and/or Refractory Multiple Myeloma

*Chrissy H.Y. van Beurden-Tan, Margreet G. Franken, Hedwig M. Blommestein, Carin A. Uyl-de Groot, and Pieter Sonneveld*

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on February 27, 2017.

Corresponding author: Chrissy H.Y. van Beurden-Tan, 's Gravendijkwal 230, 3015 CE Rotterdam, the Netherlands; e-mail: h.tan@erasmusmc.nl.



0732-183X/17/3599-1/$20.00

A B S T R A C T

**Purpose**
Since 2000, many new treatment options have become available for relapsed and/or refractory multiple myeloma (R/R MM) after a long period in which dexamethasone and melphalan had been the standard treatment. Direct comparisons of these novel treatments, however, are lacking. This makes it extremely difficult to evaluate the relative added value of each new treatment. Our aim was to synthesize all efficacy evidence, enabling a comparison of all current treatments for R/R MM.

**Methods**
We performed a systematic literature review to identify all publicly available phase III randomized controlled trial evidence. We searched Embase, MEDLINE, MEDLINE In-Process, Cochrane Central Register of Controlled Clinical Trials, and the Web site www.ClinicalTrials.gov. In addition, two trials presented at two international hematology congresses (ie, ASCO 2016 and European Hematology Association 2016) were added to include the most recent evidence. In total, 17 randomized controlled trials were identified, including 18 treatment options. The evidence was synthesized using a conventional network meta-analysis. To include all treatments within one network, two treatment options were combined: (1) bortezomib monotherapy and bortezomib plus dexamethasone, and (2) thalidomide monotherapy and thalidomide plus dexamethasone.

**Results**
The combination of daratumumab, lenalidomide, and dexamethasone was identified as the best treatment. It was most favorable in terms of (1) hazard ratio for progression-free survival (0.13; 95% credible interval, 0.09 to 0.19), and (2) probability of being best (99% of the simulations). This treatment combination reduced the risk of progression or death by 87% versus dexamethasone, 81% versus bortezomib plus dexamethasone, and 63% versus lenalidomide plus dexamethasone.

**Conclusion**
Our network meta-analysis provides a complete overview of the relative efficacy of all available treatments for R/R MM. Until additional data from randomized studies are available, on the basis of this analysis, the combination of daratumumab, lenalidomide, and dexamethasone seems to be the best treatment option.

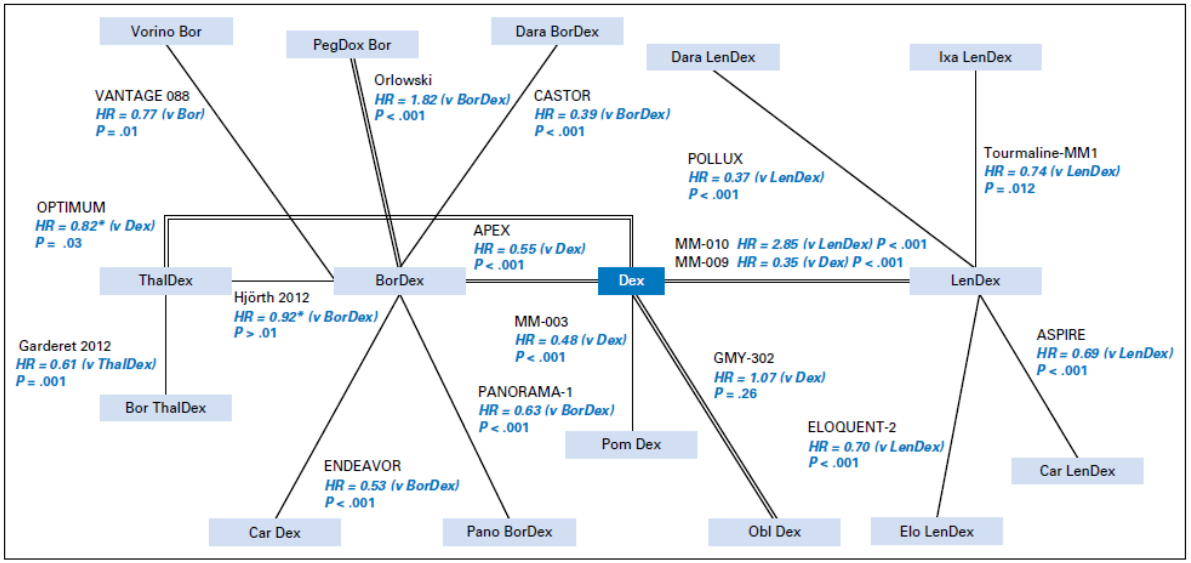



**Fig 3.** Network of relapsed/refractory multiple myeloma randomized controlled trials used for the network meta-analysis. (*) Estimated from other values; double lines indicate use of time to progression instead of PFS outcome; dark blue box indicates the reference treatment. Bor, bortezomib; Car, carfilzomib; Dara, daratumumab; Dex, dexamethasone; Elo, elotuzumab; HR, hazard ratio; Ixa, ixazomib; Len, lenalidomide; Obl, oblimersen; Pano, panobinostat; PegDox, pegylated liposomal doxorubicin; PFS, progression-free survival; Pom, pomalidomide; Thal, thalidomide; Vorino, vorinostat.

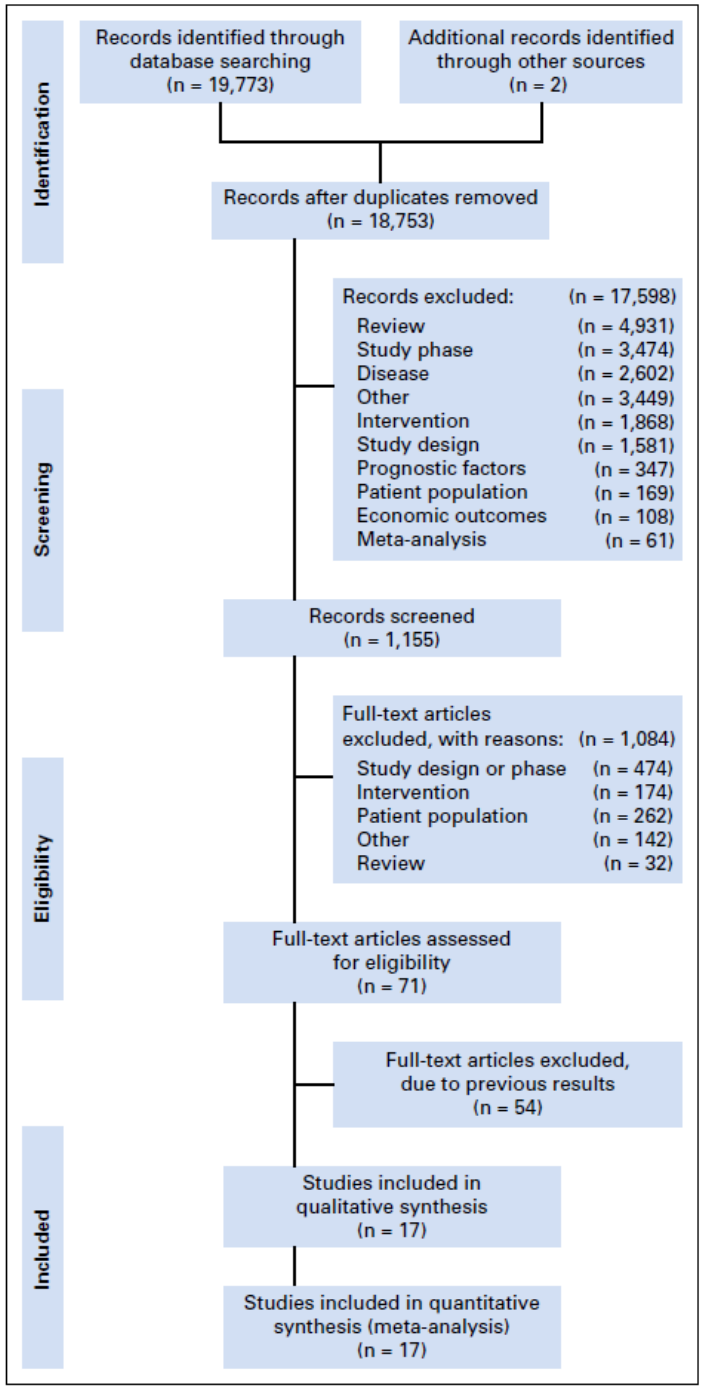



**Fig 1.** PRISMA flowchart of relapsed/refractory multiple myeloma randomized controlled trials.

**Table 1.** Trial Details and Patient Characteristics

| Trial Name/First Author | NCT No. | Research | Control | Duration | Median Age, years (range) | Median Prior Regimens (range) | Primary Objective |
|---|---|---|---|---|---|---|---|
| GMY302[1] | NCT00017602 | Oblimersen plus dexamethasone | Dexamethasone | Dec 2000-Apr 2009 | 59 or 65 | 41% 1 to 2; 59% > 3 | TTP |
| APEX[14] | NCT00048230 | Bortezomib | Dexamethasone | Jun 2002-Dec 2004 | 62 (48-74) | 2 | TTP |
| MM-009[17] | NCT00056160 | Lenalidomide plus dexamethasone | Dexamethasone | Jan 2003-Oct 2008 | 64 (36-86) | 62% > 2 | TTP |
| MM-010[3] | NCT00424047 | Lenalidomide plus dexamethasone | Dexamethasone | Sep 2003-Nov 2013 | 63 (33-84) | 68% > 2 | TTP |
| Orlowski[12] | NCT00103506 | Pegylated liposomal doxorubicin plus bortezomib | Bortezomib | Dec 2004-Jun 2014 | NR | NR | TTP |
| Garderet[6] | NCT00256776 | Thalidomide plus bortezomib plus dexamethasone | Bortezomib plus dexamethasone | Jul 2005-Jun 2013 | 61 (29-76) | NR | TTP |
| OPTIMUM[8] | NCT00452569 | Thalidomide | Dexamethasone | Feb 2006-Jan 2009 | 63 (33-85) | 57% 1; 30% 2; and 12% 3 | TTP |
| Hjorth[7] | NCT00602511 | Thalidomide plus dexamethasone | Bortezomib plus dexamethasone | Oct 2007-Dec 2010 | 71 (38-85) | NR | PFS |
| VANTAGE 088[2] | NCT00773747 | Vorinostat plus bortezomib | Bortezomib | Dec 2008-Jun 2015 | 61 (30-85) | 2 (1-3) | PFS |
| PANORAMA-1[15] | NCT01023308 | Panobinostat plus bortezomib plus dexamethasone | Bortezomib plus dexamethasone | Dec 2009-Jul 2015 | 63 (56-69) | 2 (1-3) | PFS |
| ASPIRE[16] | NCT01080391 | Carfilzomib plus lenalidomide plus dexamethasone | Lenalidomide plus dexamethasone | Jul 2010-Oct 2017 | 64 (31-91) | 2 (1-3) | PFS |
| MM-003[10] | NCT01311687 | Pomalidomide plus dexamethasone | Dexamethasone | Mar 2011-Sep 2017 | 64 (35-84) | 5 (2-14) | PFS |
| ELOQUENT-2[9] | NCT01239797 | Elotuzumab plus lenalidomide plus dexamethasone | Lenalidomide plus dexamethasone | Mar 2011-Mar 2018 | 66 (37-91) | 2 (1-4) | PFS |
| ENDEAVOR[4] | NCT01568866 | Carfilzomib plus dexamethasone | Bortezomib plus dexamethasone | Jun 2012-Dec 2018 | 65 (35-89) | 2 (1-2) | PFS |
| Tourmaline-MM1[11] | NCT01564537 | Ixazomib plus lenalidomide plus dexamethasone | Lenalidomide plus dexamethasone | Aug 2012-Dec 2020 | 66 (30-91) | 59% 1; 77% relapsed; 11% refractory; 11% RR | PFS |
| POLLUX[22] | NCT02076009 | Daratumumab plus lenalidomide plus dexamethasone | Lenalidomide plus dexamethasone | May 2014-Sep 2020 | NR | NR | PFS |
| CASTOR[23] | NCT02136134 | Daratumumab plus bortezomib plus dexamethasone | Bortezomib plus dexamethasone | Aug 2014-Mar 2017 | NR | 2 (1-10) | PFS |

Abbreviations: APEX, Assessment of Proteasome Inhibition for Extending Remissions; MM-003, Multiple Myeloma-003; MM-009, Multiple Myeloma-009; MM-010, Multiple Myeloma-010; NCT, National Clinical Trial; NR, not reported; PFS, progression-free survival; RR, relapsed and refractory; TTP, time to progression.

| Study and First Author | Study Reference | Experimental Arm | Control Arm | Experimental Total | Control Total | Median Follow-Up (months) | Hazard Ratio (95% CI), PFS |
|---|---|---|---|---|---|---|---|
| **Thalidomide** | | | | | | | |
| Kropff[9] | OPTIMUM | Thal | Dex | 122 | 126 | NR | 0.82 (0.68 to 0.99)* |
| Hjorth[7] | | ThalDex | BorDex | 67 | 64 | NR | 0.92 (0.68 to 1.25) |
| **Lenalidomide** | | | | | | | |
| Weber[17] | MM-009 | LenDex | Dex | 177 | 176 | 26.2 *v* 12.9 | 0.35 (0.27 to 0.47)* |
| Dimopoulos[3] | MM-010 | LenDex | Dex | 176 | 175 | 16.4 | 0.35 (0.27 to 0.46)* |
| **Pomalidomide** | | | | | | | |
| San Miguel[10] | MM-003/NIMBUS | PomDex | Dex | 302 | 153 | 10 | 0.48 (0.39 to 0.6) |
| **Bortezomib** | | | | | | | |
| Richardson[14] | APEX | Bor | Dex | 333 | 336 | 8.3 | 0.55 (0.41 to 0.74)* |
| Garderet[6] | | BorThalDex | ThalDex | 135 | 134 | 24 | 0.61 (0.45 to 0.82) |
| **Carfilzomib** | | | | | | | |
| Stewart[16] | ASPIRE | CarLenDex | LenDex | 396 | 396 | 32.2 *v* 31.5 | 0.69 (0.57 to 0.83) |
| Dimopoulos[4] | ENDEAVOR | CarDex | BorDex | 464 | 465 | 16.4 | 0.53 (0.44 to 0.64) |
| **Ixazomib** | | | | | | | |
| Moreau[11] | TOURMALINE-MM1 | IxaLenDex | LenDex | 360 | 362 | 14.8 *v* 14.6 | 0.74 (0.59 to 0.94) |
| **Vorinostat** | | | | | | | |
| Dimopoulos[2] | VANTAGE 088 | VorinoBor | Bor | 317 | 320 | 14.2 | 0.77 (0.64 to 0.93) |
| **Panobinostat** | | | | | | | |
| San-Miguel[15] | PANORAMA-1 | PanoBorDex | BorDex | 387 | 381 | 6.47 *v* 5.59 | 0.63 (0.52 to 0.76) |
| **Elotuzumab** | | | | | | | |
| Lonial[9] | ELOQUENT-2 | EloLenDex | LenDex | 321 | 325 | 24.5 | 0.7 (0.57 to 0.85) |
| **Daratumumab** | | | | | | | |
| Palumbo[23] | CASTOR | DaraBorDex | BorDex | 251 | 247 | 7.4 | 0.39 (0.28 to 0.54) |
| Dimopoulos[22] | POLLUX | DaraLenDex | LenDex | 286 | 283 | 13.5 | 0.37 (0.27 to 0.51) |
| **Other** | | | | | | | |
| Orlowski[12] | | PegDoxBor | Bor | 324 | 322 | 7.2 | 0.55 (0.43 to 0.71)* |
| Chanan-Khan[1] | GMY302 | OblDex | Dex | 110 | 114 | NR | 1.07 (0.79 to 1.45)* |

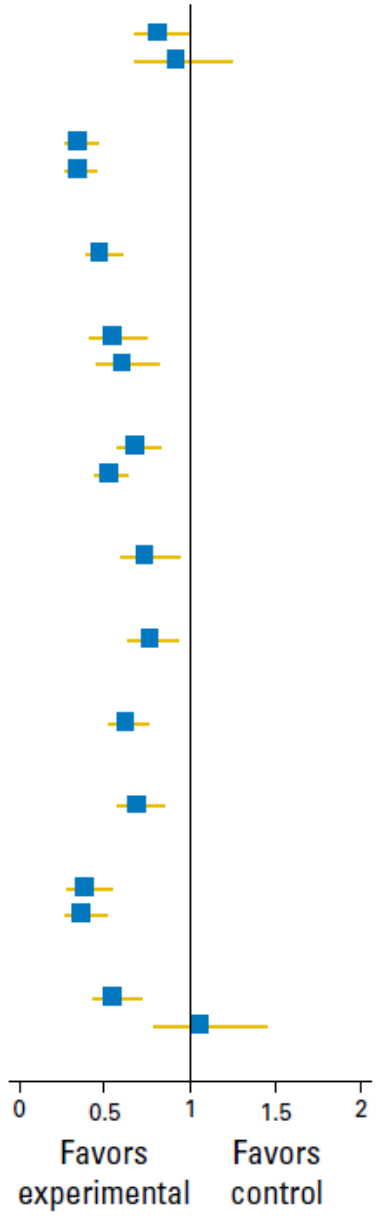



**Fig 2.** Extracted data. (*) Time-to-progression data used instead of PFS; when median follow-up was reported for the treatment arms separately, the numbers are presented as median follow-up for experimental treatment versus median follow-up for control arm. APEX, Assessment of Proteasome Inhibition for Extending Remissions; Bor, bortezomib; Car, carfilzomib; Dara, daratumumab; Dex, dexamethasone; Elo, elotuzumab; Ixa, ixazomib; Len, lenalidomide; MM-003, Multiple Myeloma-003; MM-009, Multiple Myeloma-009; MM-010, Multiple Myeloma-010; NR, not reported; Obl, oblimersen; Pano, panobinostat; PegDox, pegylated liposomal doxorubicin; PFS, progression-free survival; Pom, pomalidomide; Thal, thalidomide; Vorino, vorinostat.

| Treatment | % Being Best Treatment | Hazard Ratio *v* Dexamethasone (95% CrI), PFS |
|---|---|---|
| DaraLenDex | 99 | 0.13 (0.09 to 0.19) |
| CarLenDex | 0 | 0.24 (0.18 to 0.32) |
| EloLenDex | 0 | 0.25 (0.19 to 0.33) |
| DaraBorDex | 1 | 0.27 (0.18 to 0.38) |
| IxaLenDex | 0 | 0.26 (0.19 to 0.35) |
| CarDex | 0 | 0.36 (0.26 to 0.48) |
| LenDex | 0 | 0.35 (0.29 to 0.43) |
| PegDoxBor | 0 | 0.37 (0.26 to 0.52) |
| PanoBorDex | 0 | 0.43 (0.31 to 0.56) |
| BorThalDex | 0 | 0.47 (0.33 to 0.65) |
| PomDex | 0 | 0.48 (0.39 to 0.6) |
| VorinoBor | 0 | 0.52 (0.38 to 0.69) |
| BorDex | 0 | 0.67 (0.53 to 0.84) |
| ThalDex | 0 | 0.76 (0.64 to 0.9) |
| Dex | 0 | 1 |
| ObIDex | 0 | 1.08 (0.79 to 1.45) |

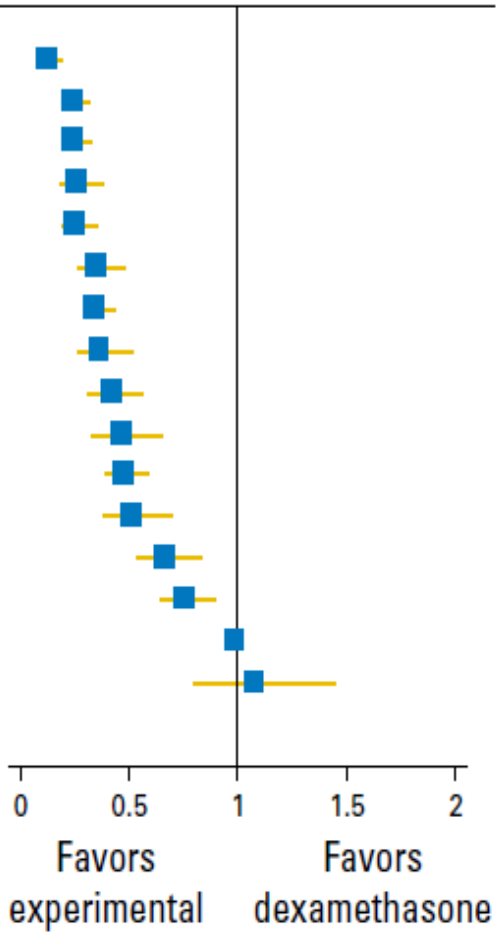
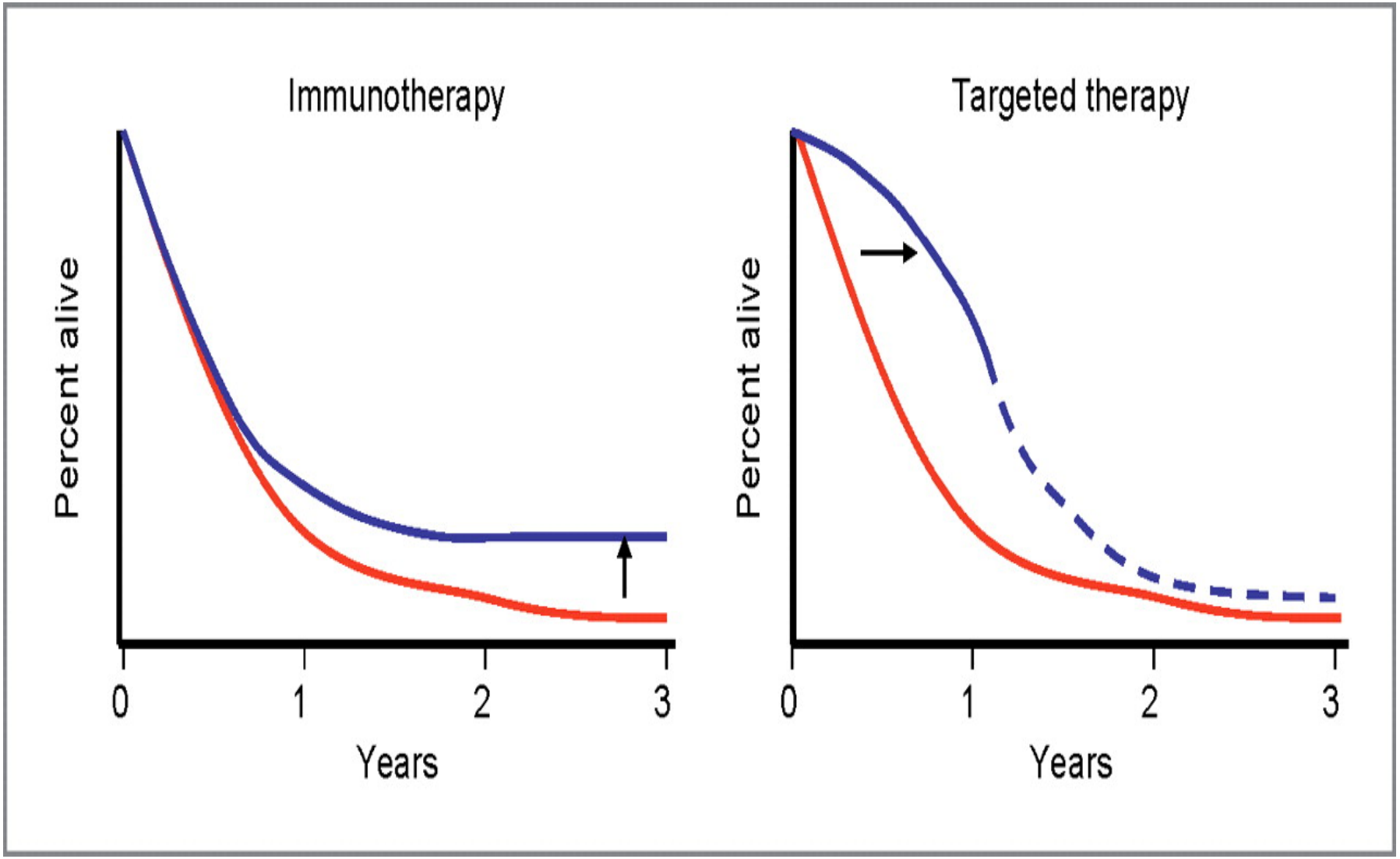
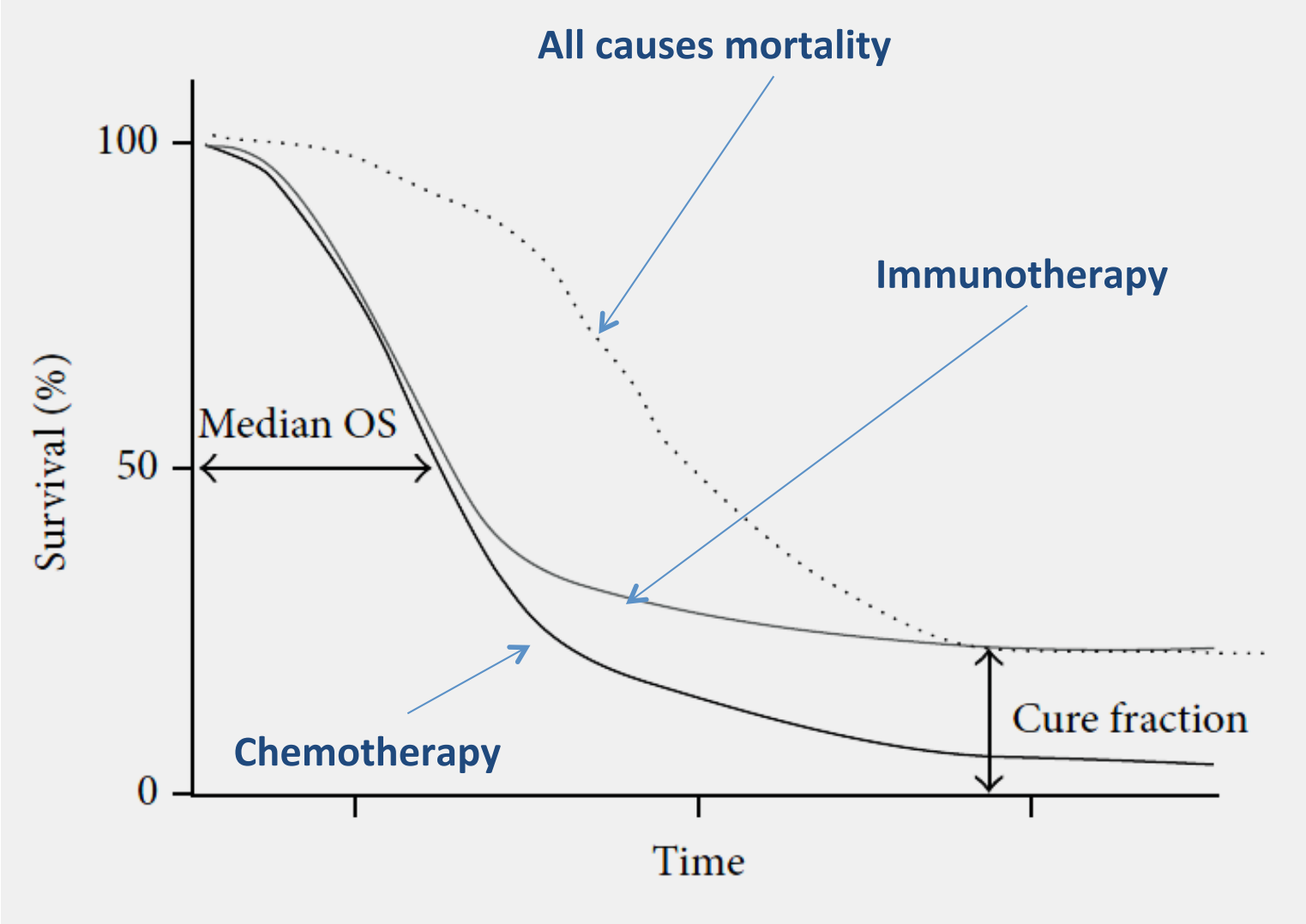



**Fig 4.** Forest plot of network meta-analysis results. Bor, bortezomib; Car, carfilzomib; CrI, credible interval; Dara, daratumumab; Dex, dexamethasone; Elo, elotuzumab; Ixa, ixazomib; Len, lenalidomide; Obl, oblimersen; Pano, panobinostat; PegDox, pegylated liposomal doxorubicin; PFS, progression-free survival; Pom, pomalidomide; Thal, thalidomide; Vorino, vorinostat.




Nguyen et al., Nature Rev Immunol 2015

Effects of immunotherapy and targeted therapy on melanoma survival curves. Immunotherapy strategies have the notorious ability to induce a low percentage but highly durable tumor responses, resulting in a plateau in the tail of the survival curve. Targeted therapy blocking driver oncogenes in melanoma induces rapid tumor responses, but most are not durable, resulting in an early improvement in the survival curve but unclear beneficial effects on the tail of the curve




- Median OS provides a measure of when 50% of patients will die, it does not provide a true reflection of the survival time that may be expected from the patients who are alive after the median OS is reached
- Median OS is considered less suitable for survival curves that are skewed to the right since it does not differentiate the proportion of patients alive or dead after 50% of the patients have died

# Thank you