Hot Topic in Multiple Myeloma: The Evolving Role for Immunotherapy in Patients With Relapsed/Refractory Disease

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Patients With MM Are a Heterogeneous Group

Younger, fit

- Achieving longest possible remission/sustained disease control while preserving QoL?

Elderly, fit

- Achieving and maintaining responses while preserving QoL?

Frail/comorbidities

- Tolerability while preserving QoL?

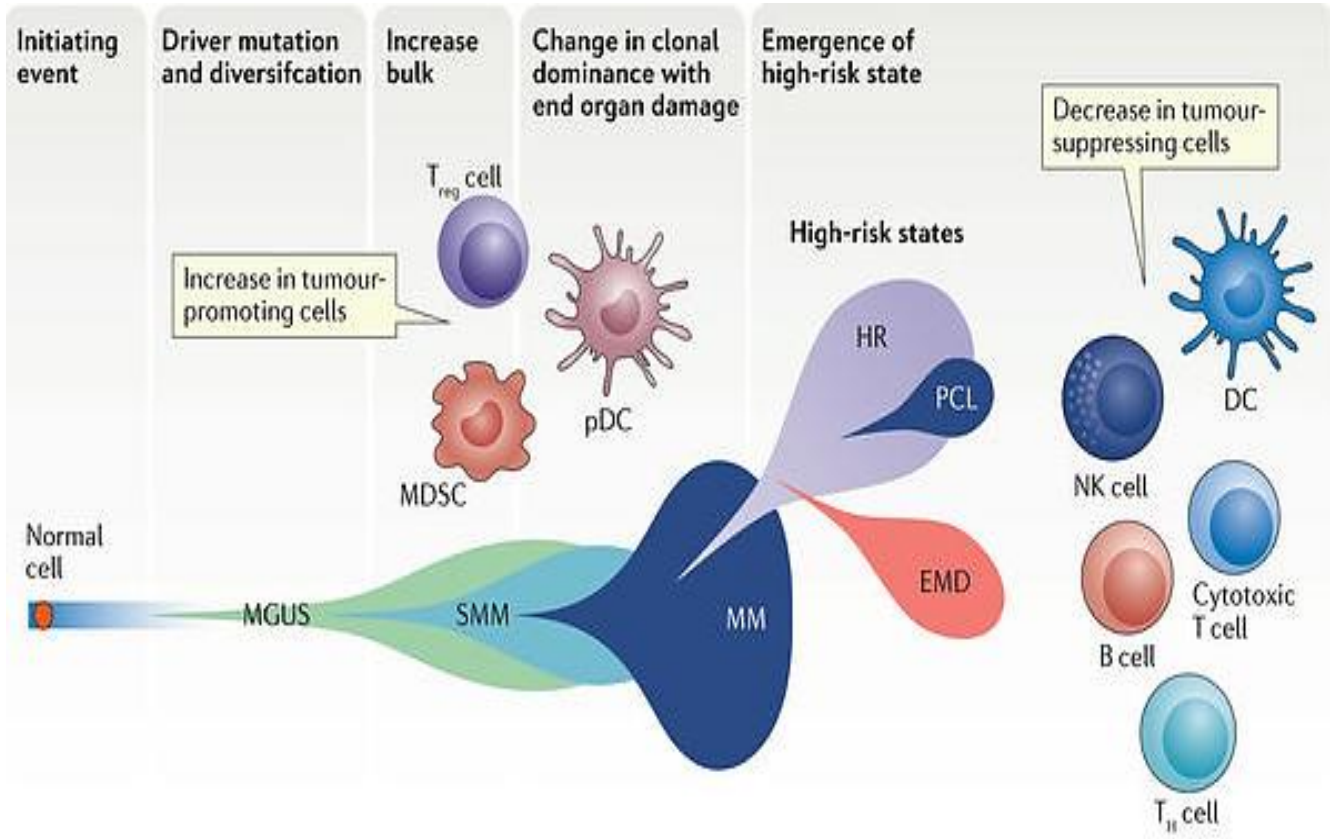
Very frail

- Palliative care while preserving QoL?

"The good physician treats the disease; the great physician treats the patient who has the disease"
Sir William Osler

MM, multiple myeloma; QoL, quality of life

Co-Evolution of Myeloma Clone With its Immune Microenvironment

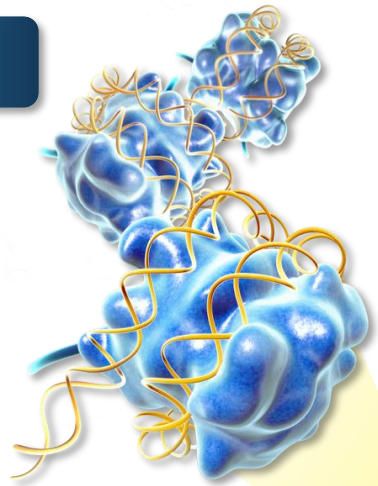


Pawlyn C, Morgan GJ. *Nat Rev Cancer.* 2017;17(9):543-556.

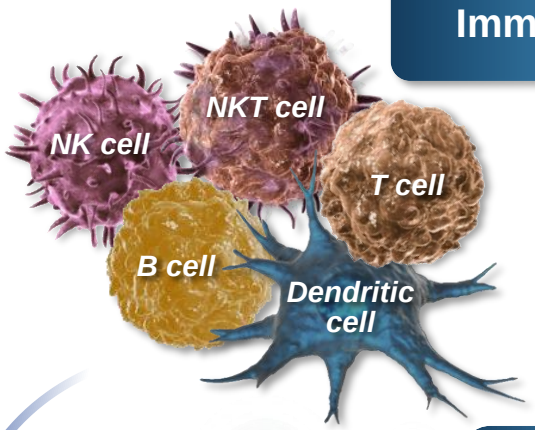
Multiple Myeloma Pathophysiology

Plasma Cells[1,2]

Focal lesions

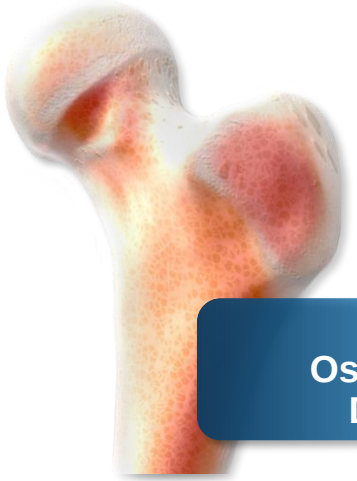


Immune Dysregulation[3-6,8,9,12]

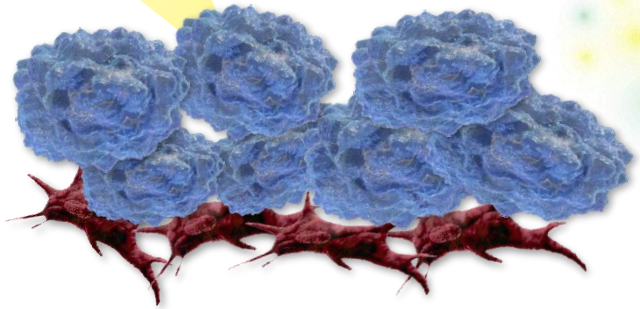


Infections

Lytic lesions



Clonal plasma cells



Disrupted Production of Cytokines and Growth Factors[5,8,10,1]

Macrophage, Osteoblast-Osteoclast Dysregulation[1,7,14]

Low blood counts

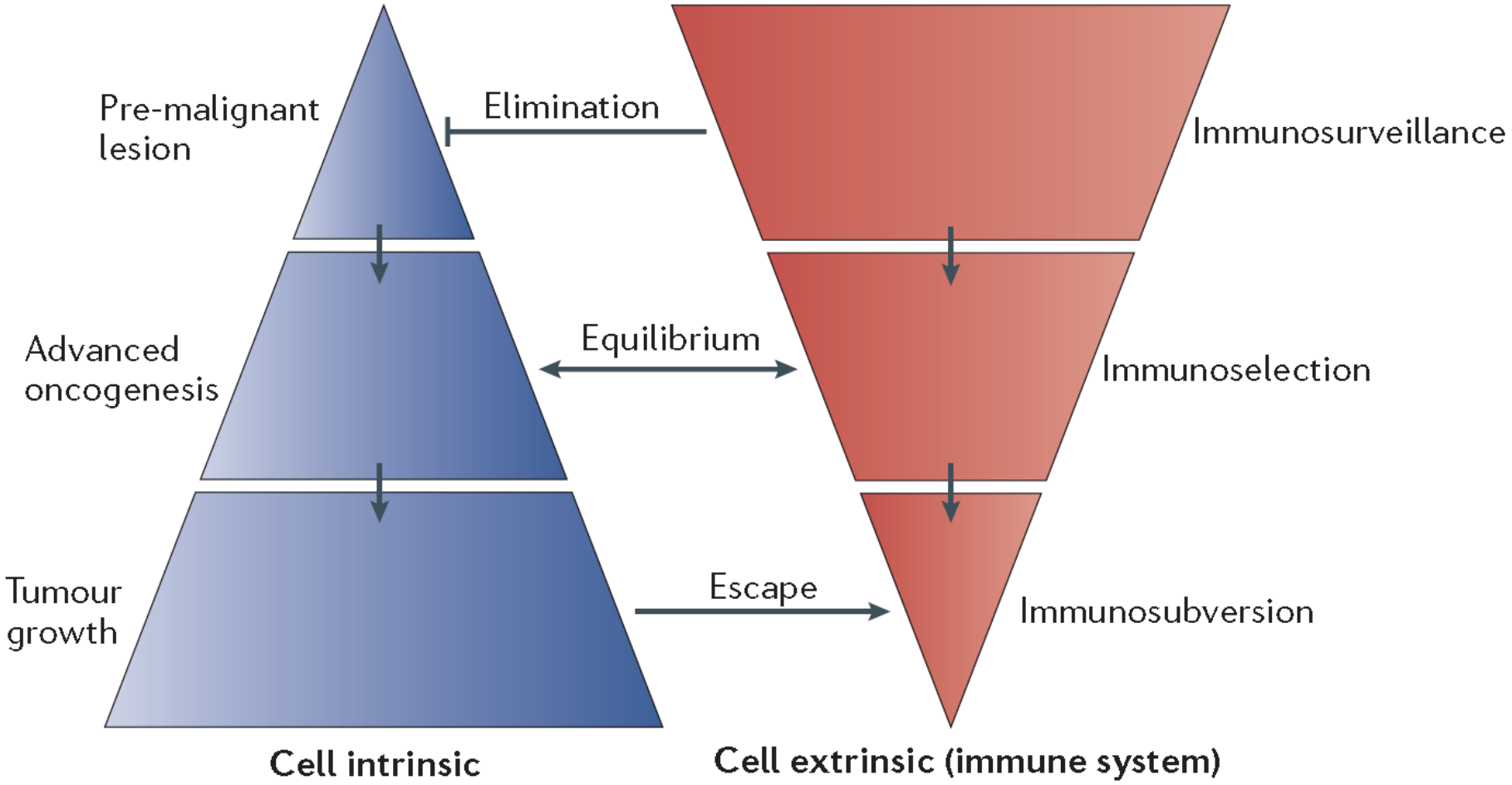
Aberrant Stromal Structure[1,5,13]

Tumor Microenvironment

ICAM1, intercellular adhesion molecule 1; NK, natural killer; NKT, natural killer T cell; TNF-α, tumor necrosis factor-α; VCAM1, vascular cell adhesion molecule 1

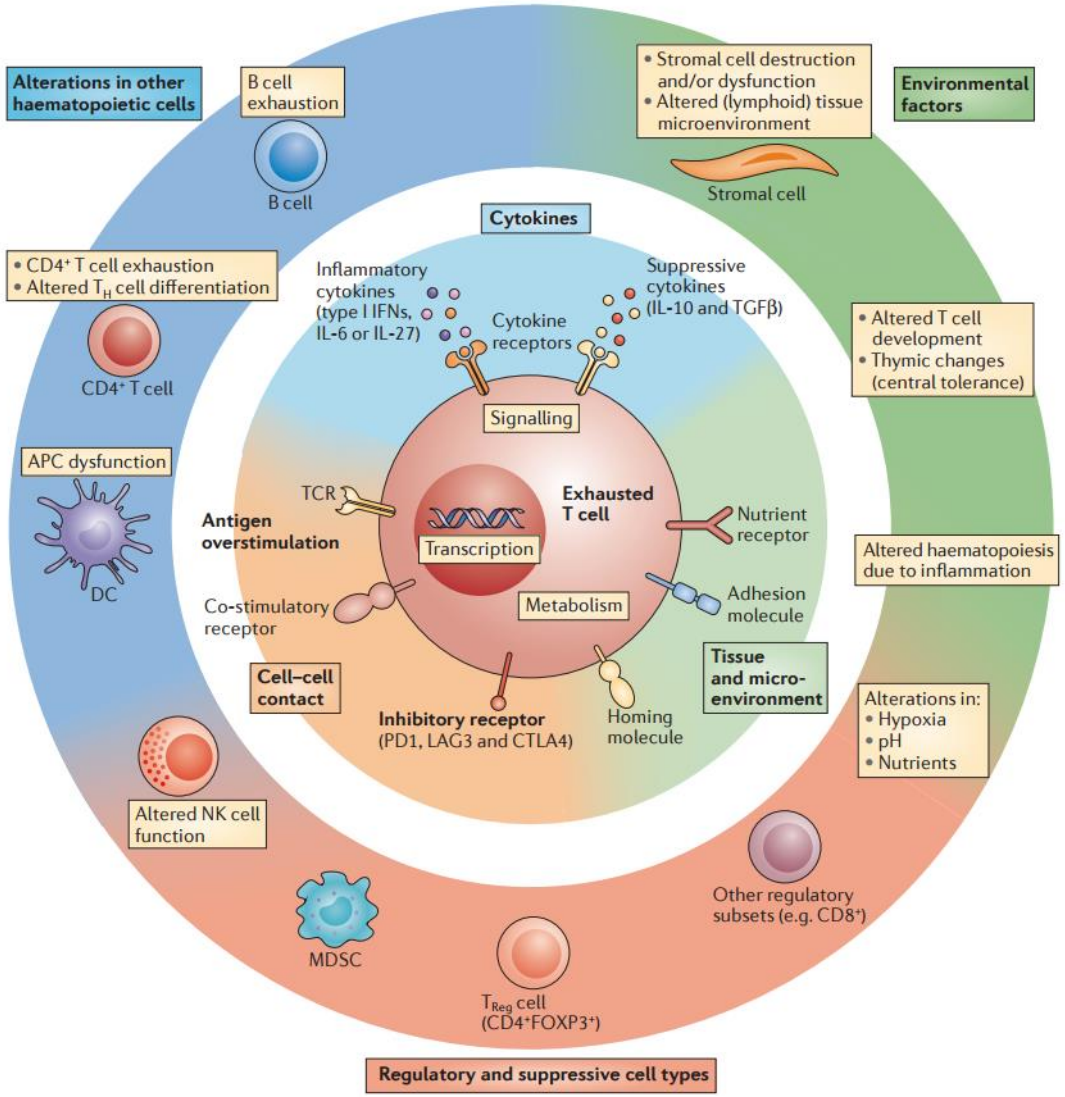
1. Raab MS, et al. *Lancet*. 2009;374(9686):324-339. 2. Morgan GJ, et al. *Nat Rev Cancer*. 2012;12(5):335-348. 3. Katodritou E, et al. *Am J Hematol*. 2011;86(12):967-973. 4. Braga WM, et al. *Clin Dev Immunol*. 2012;2012:293479. 5. Pratt G, et al. *Br J Haematol.* 2007;138(5):563-579. 6. Rosenblatt J, et al. *J Immunother.* 2011;34(5):409-418. 7. Kyle RA, et al. *N Engl J Med*. 2004;351(18):1860-1873. 8. Cook G, et al. *Blood Rev.1999;13(3):151-162*. 9. Bernal M, et al. *Hum Immunol.* 2009;70(10):854-857. 10. Gupta D, et al. *Leukemia*. 2001;15(12):1950-1961. 11. Jourdan M, et al. *Eur Cytokine Netw.* 1999;10(1):65-70. 12. Favaloro J, et al. *Leuk Lymphoma*. 2014;55(12):2893-2900. 13. Damiano JS, et al. *Blood*. 1999;93(5):1658-1667. 14. Oranger A. et al. *Clin Dev Immunol*. 2013; 2013:289458.

Oncogenesis As a Result of Interplay Between Cell Intrinsic and Immune Factors



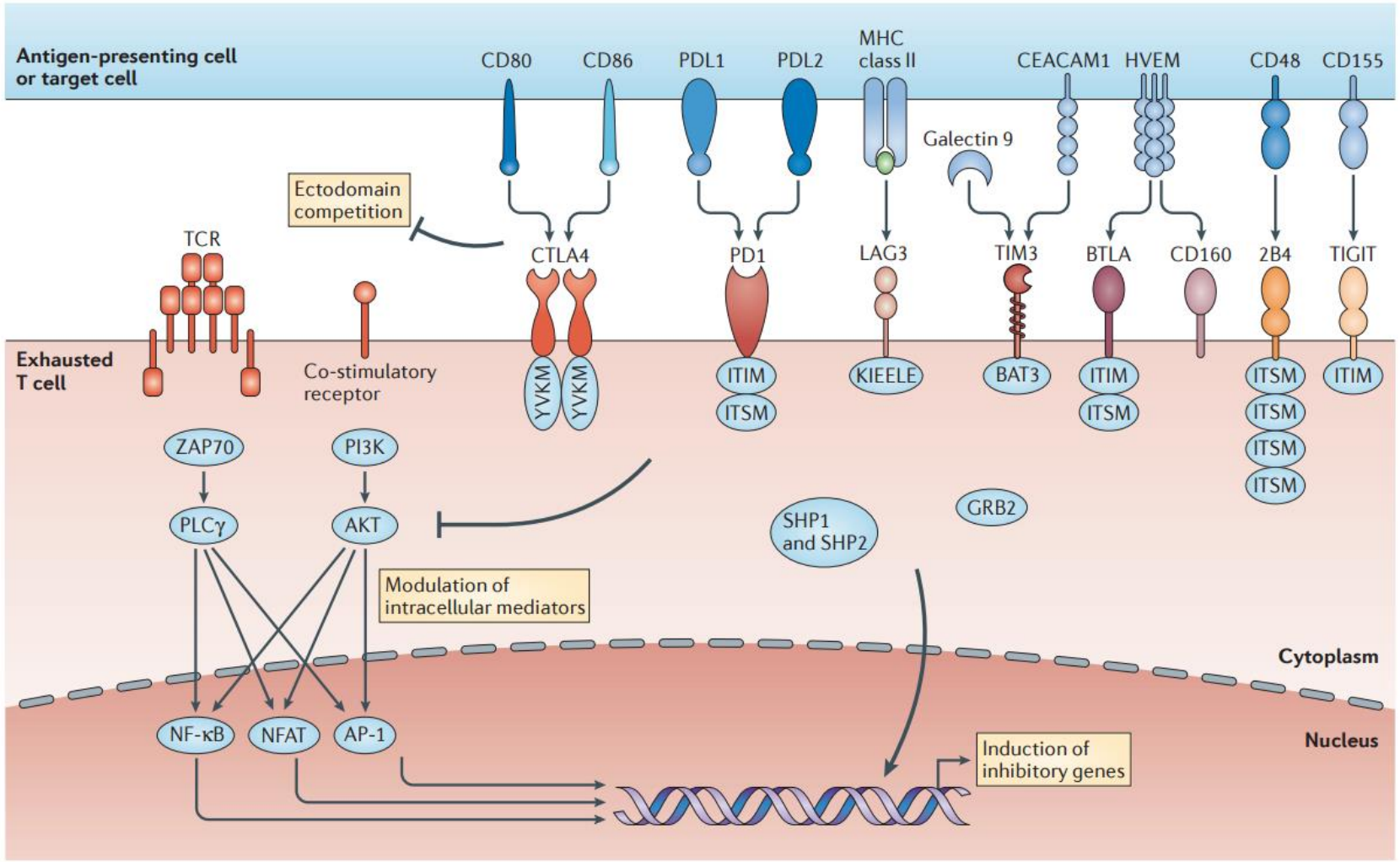
Zitvogel L, et al. *Nat Rev Immunol.* 2006;6(10):715-727.

Immunosuppressive Mechanisms



Wherry EJ, et al. *Nat Rev Immunol.* 2015;15(8):486-499.

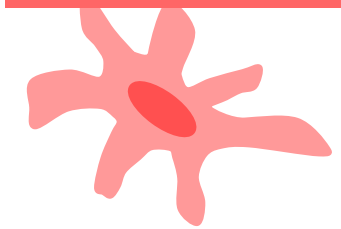
Immunosuppressive Interactions: Pathway Analysis



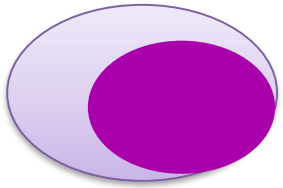
Wherry EJ, et al. *Nat Rev Immunol.* 2015;15(8):486-499.

Tumor promoting cells

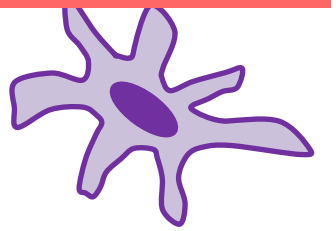
Reduction of immunosuppression



MDSCs



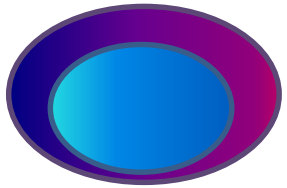
T-regs



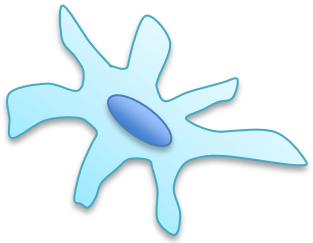
pDC

Anti-tumor cellular immunity

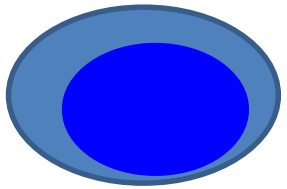
Induction of anti-MM activity



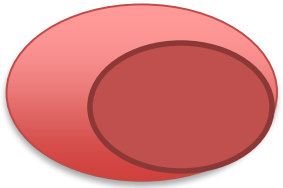
NK cells



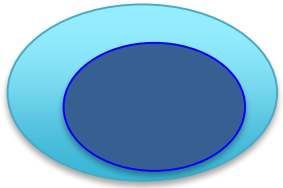
DC



Cytotoxic T cells



B cells

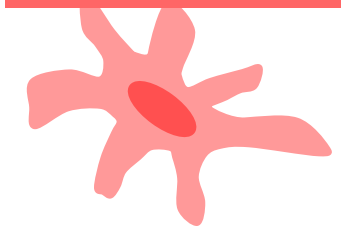


Th cells

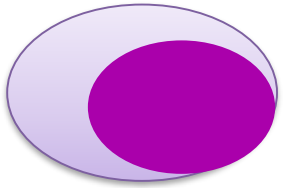
Adapted from: Cottini F, et al. *Clin Adv Hematol.* 2015;13(4):236-248.

Tumor promoting cells

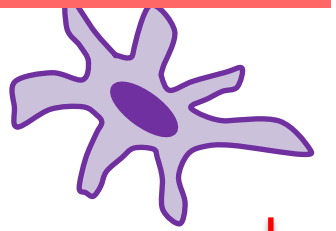
Reduction of immunosuppression



MDSCs



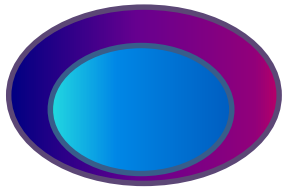
T regs



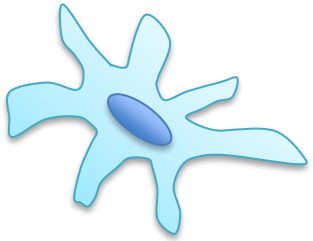
pDC

Induction of anti-MM activity

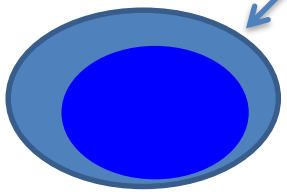
Anti-tumor cellular immunity



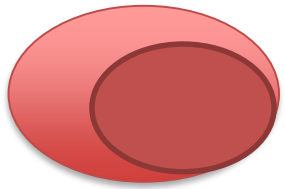
NK cells



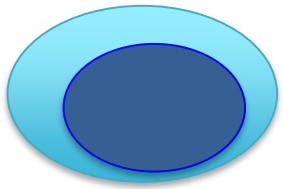
DC



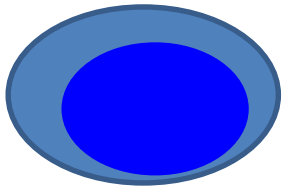
Cytotoxic T cells



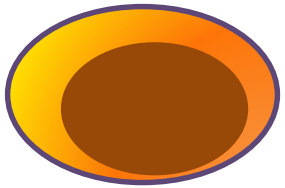
B cells



Th cells



Cytotoxic T cells



CAR T cells

IMIDs
Thalidomide, lenalidomide, pomalidomide

Checkpoint blockers
PD-L1/PD-1 inhibitors

Immune adjuvants
TLR-7/9 agonists

MoAbs
SLAMF7, CD38

Vaccines
Native idiotype protein, PVX-410, CD138, MM-DC

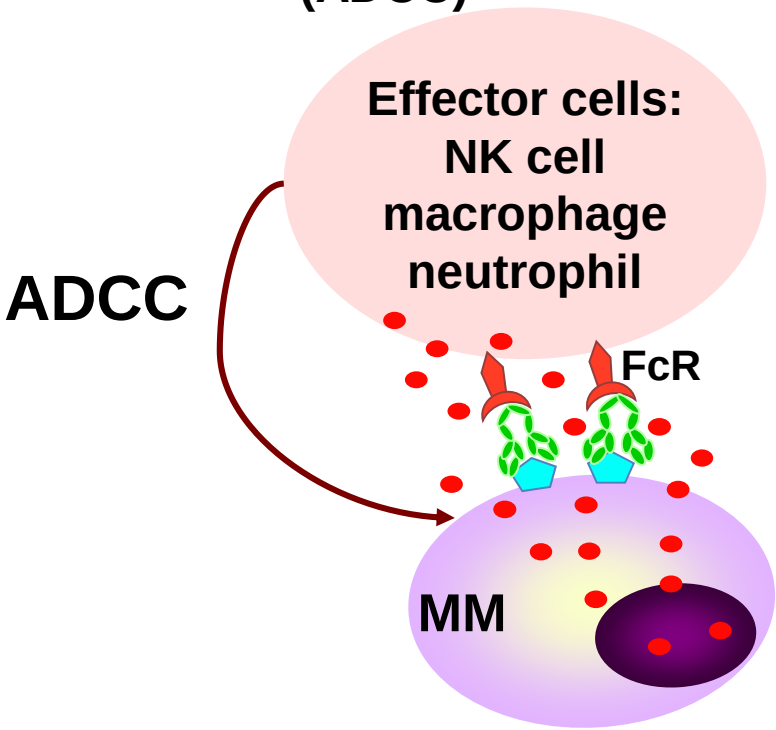
CAR T cells
anti-Kappa, CD138, BCMA, NKG2D

CAR, chimeric antigen receptor; MoAb, monoclonal antibody

Adapted from: Cottini F, et al. *Clin Adv Hematol.* 2015;13(4):236-248.

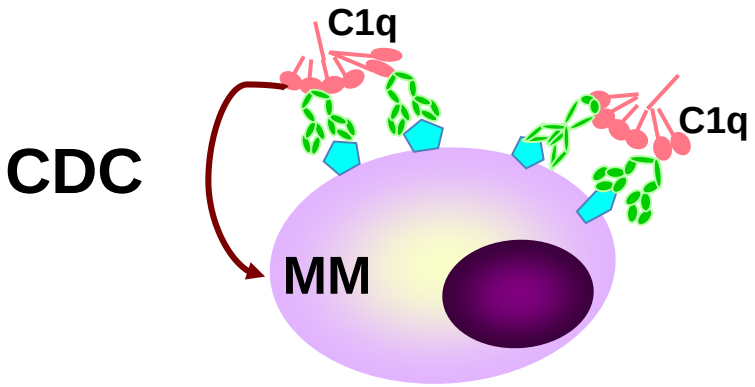
MoAb-Based Therapeutic Targeting of MM

Antibody-dependent Cellular Cytotoxicity (ADCC)



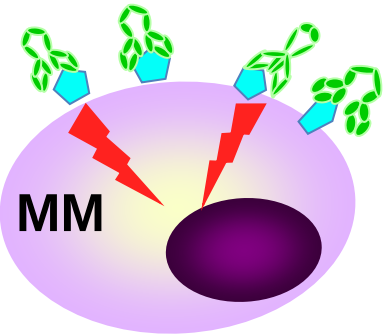
- Elotuzumab (SLAMF7)
- Daratumumab (CD38)
- SAR650984 (CD38)

Complement-dependent Cytotoxicity (CDC)



- Daratumumab (CD38)
- SAR650984 (CD38)

Apoptosis/growth arrest via intracellular signaling pathways



- huN901-DM1* (CD56)
- nBT062-maytansinoid/DM4* (CD138)
- Daratumumab (CD38)
- SAR650984 (CD38)
- GSK2857916* (BCMA)

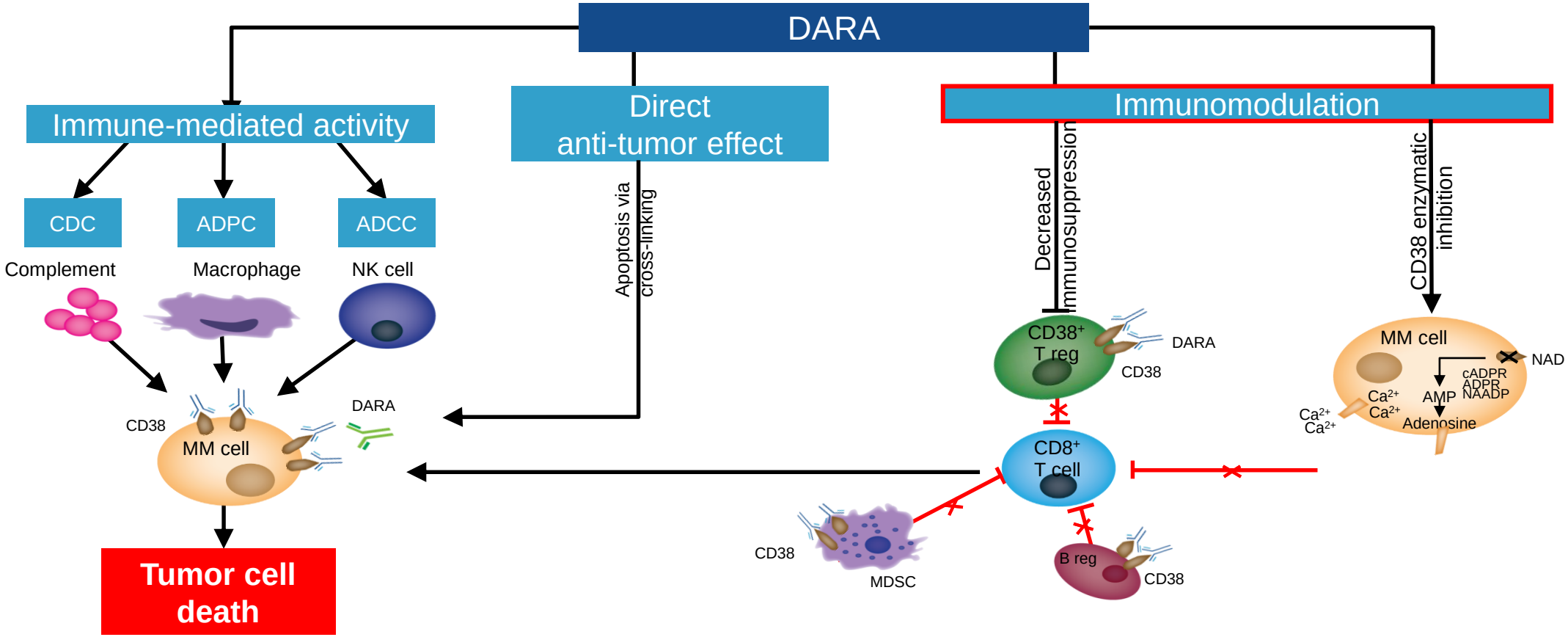
* Ab drug conjugate

Ab, antibody

Tai YT, et al. *Immunotherapy.* 2015;7(11):1187-1199.

Daratumumab Mechanism of Action

- **CD38 is highly and ubiquitously expressed on myeloma cells[1,2]**
- **DARA is a human IgG1 monoclonal antibody that binds CD38-expressing cells**
- **DARA binding to CD38 induces tumor cell death through direct and indirect mechanisms[3-5]**

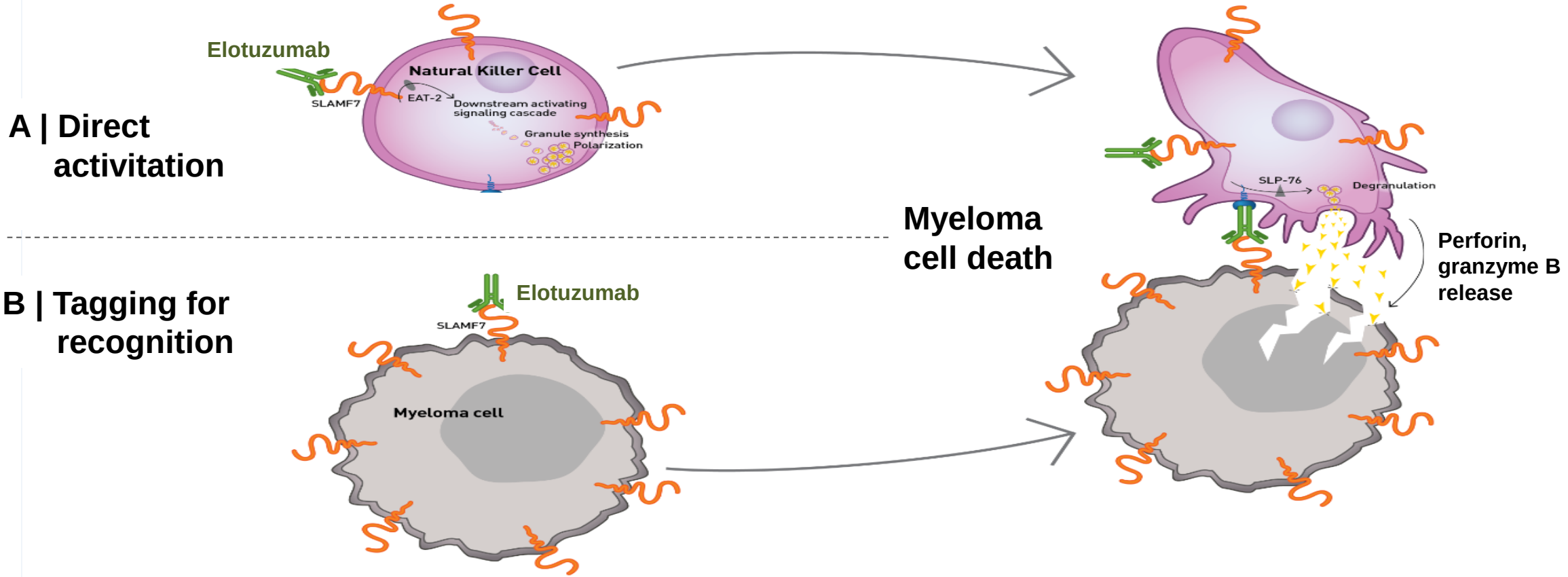


1. Lin P, et al. *Am J Clin Pathol*. 2004;121(4):482-488. 2. Santonocito AM, et al. *Leuk Res*. 2004;28(5):469-477. 3. de Weers M, et al. *J Immunol*. 2011;186(3):1840-1848. 4. Overdijk MB, et al. *MAbs*. 2015;7(2):311-321. 5. Krejcik J, et al. *Blood;*126: Abstract 3037.

Elotuzumab: An Immunostimulatory Antibody Directed to SLAMF7

Elotuzumab: Dual mechanism of action

- Directly activates NK cells
- Myeloma cells are tagged to facilitate NK cell recognition and targeted cell death via ADCC



Hsi ED, et al. *Clin Cancer Res*. 2008;14(9):2775-2784. Collins SM, et al. *Cancer Immunol Immunother*. 2013;62(12):1841-1849. Guo H, et al. *Mol Cell Biol*. 2015;35(1):41-51.

Approved MoAbs in RRMM

Lenalidomide + Dex versus Triplet Regimens

ELOQUENT-2[1]

Key inclusion criteria

- RRMM
- 1-3 prior lines of therapy
- Prior Len exposure permitted in 10% of study population (patients not refractory to Len)

Elo plus Len/Dex (E-Ld) schedule (n = 321)
Elo (10 mg/kg IV): Cycle 1 and 2: weekly;
Cycles 3+: every other week
Len (25 mg PO): days 1-21
Dex: weekly equivalent, 40 mg

Len/Dex (Ld) schedule (n = 325)
Len (25 mg PO): days 1-21;
Dex: 40 mg PO days 1, 8, 15, 22

Repeat every 28 days

Co-Primary endpoint: PFS and ORR

Secondary endpoints: OS, Duration of response, QoL, safety

POLLUX[2]

Key inclusion criteria

- RRMM
- ≥1 prior line of therapy
- Prior lenalidomide exposure, but not refractory
- Patients with creatinine clearance ≥30 mL/min

Dara plus Len/Dex (DRd) schedule (n = 286)
Daratumumab 16 mg/kg IV
- Qw in Cycles 1-2, q2w in Cycles 3-6, then q4w until PD

R 25 mg PO
- Days 1-21 of each cycle until PD

d 40 mg PO
- 40 mg weekly until PD

Len/Dex (Rd) schedule (n = 283)
Len (25 mg PO): days 1-21;
Dex: 40 mg PO days 1, 8, 15, 22

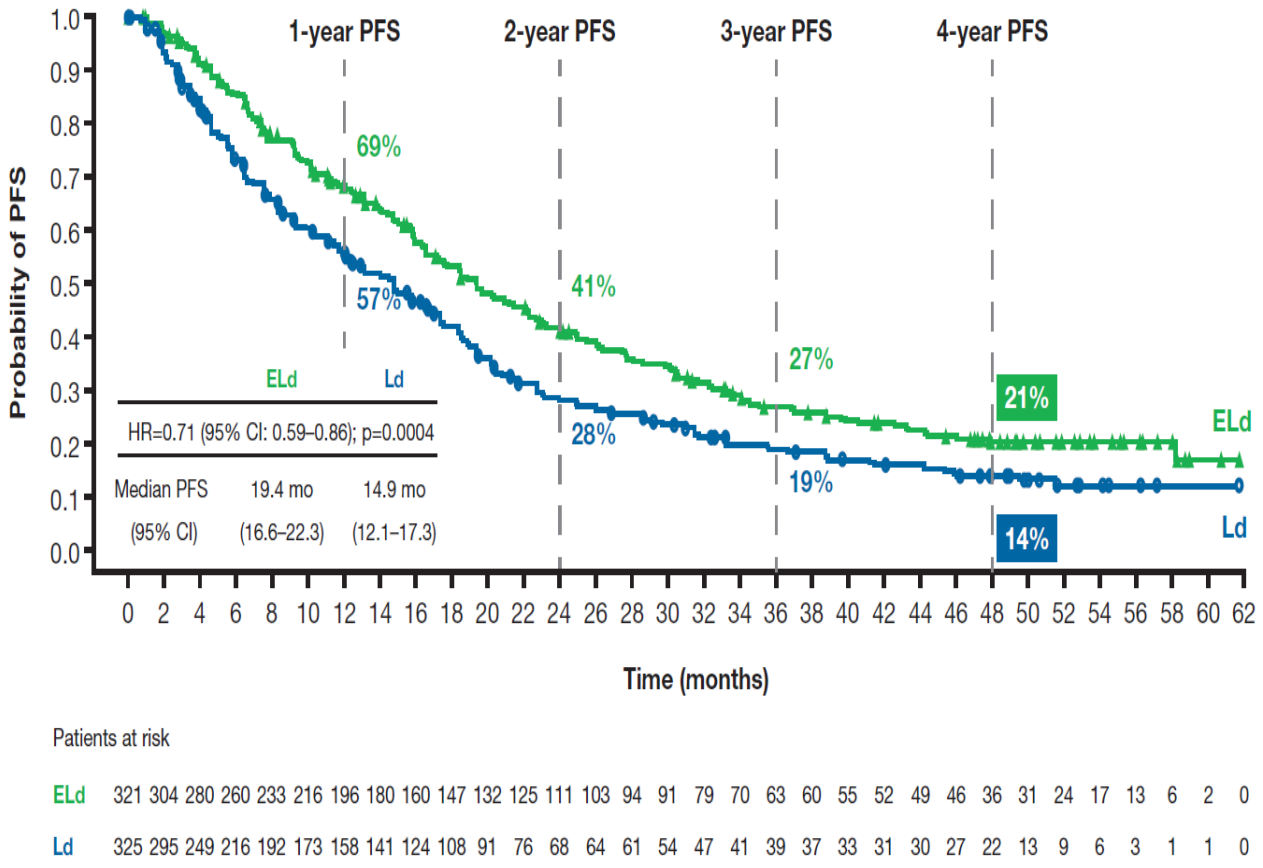
Repeat every 28 days

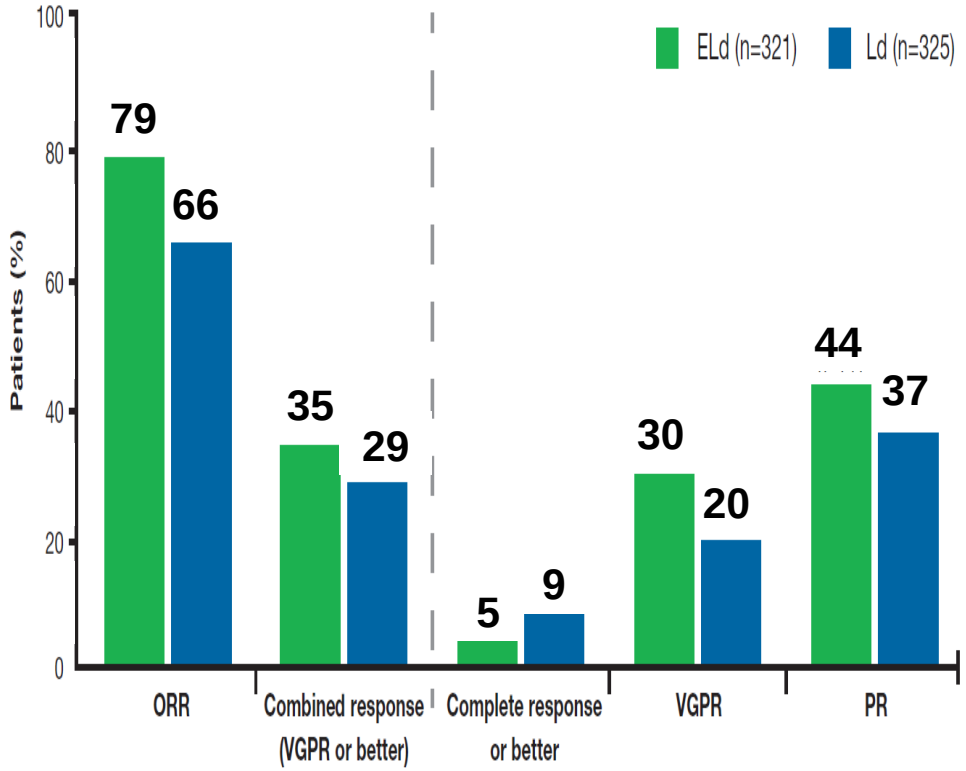
Primary endpoint: PFS

Secondary endpoints: TTP, OS, ORR, VGPR, CR, MRD, Time to response, Duration of response

1. Lonial S, et al. N *Engl J Med*. 2015;373(7):621-631. 2. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331.

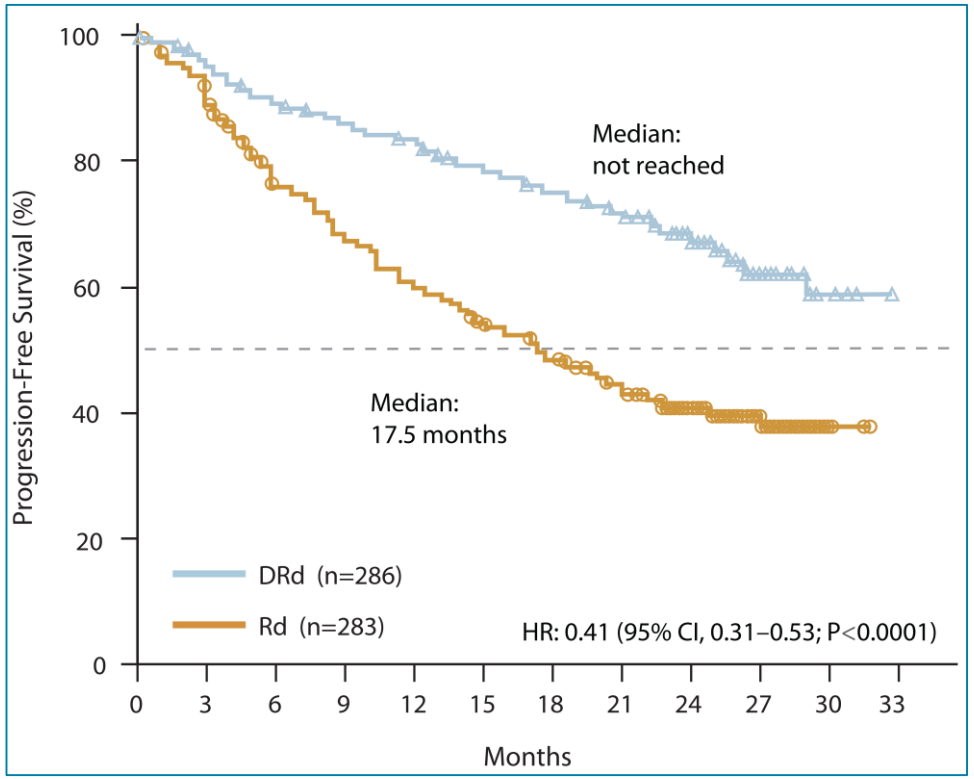
Updated Efficacy of ELOQUENT-2 Trial

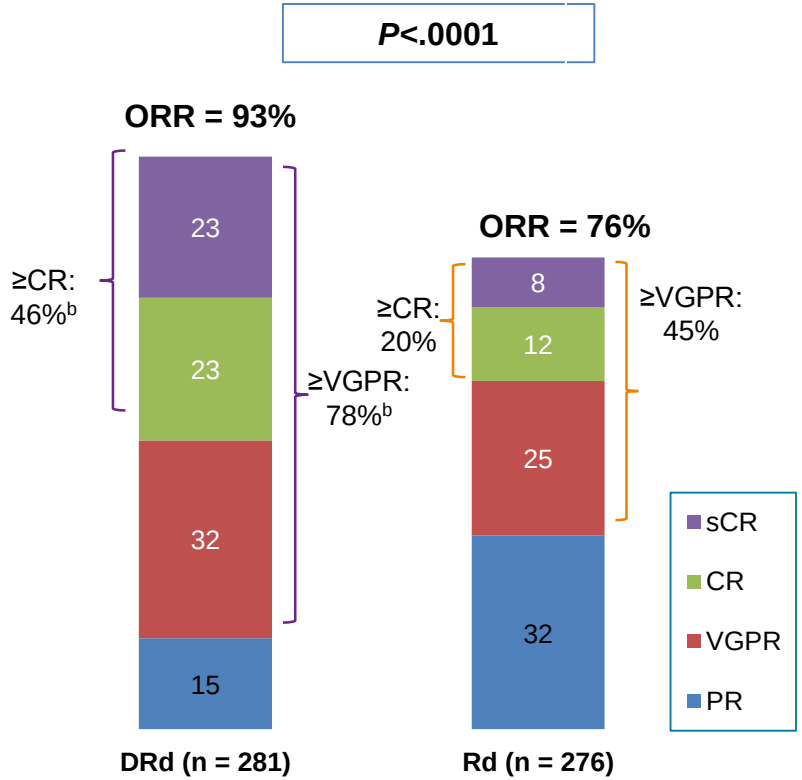




Dimopoulos MA, et al. *Haematologica*. 2017;102(s2): Abstract S456.

Updated Efficacy of POLLUX Trial





- **Median (range) follow-up: 17.3 (0-24.5) months**
- ***P*<.0001 for DRd vs Rd**

Response rates

San-Miguel J, et al. *Clin Lymphoma Myeloma Leuk*. 2017;17(Suppl 1):e17-e18.

Approved MoAbs in RRMM

Bortezomib + Dexamethasone vs Triplet Regimens

CASTOR

Key inclusion criteria

- RRMM
- ≥1 prior line of therapy
- Prior bortezomib exposure, but not refractory

Dara plus Len/Dex (DVd) schedule (n = 251)
Daratumumab (16 mg/kg IV)
Every week - cycle 1-3
Every 3 weeks - cycle 4-8
Every 4 weeks - cycles 9+

Vel: 1.3 mg/m^2 SC, days 1,4,8,11 - cycle 1-8
dex: 20 mg PO-IV, days 1,2,4,5,8,9,11,12 - cycle 1-8

Len/Dex (Vd) schedule (n = 247)
Vel: 1.3 mg/m^2 SC, days 1,4,8,11 - cycle 1-8
dex: 20 mg PO-IV, days 1,2,4,5,8,9,11,12 - cycle 1-8

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

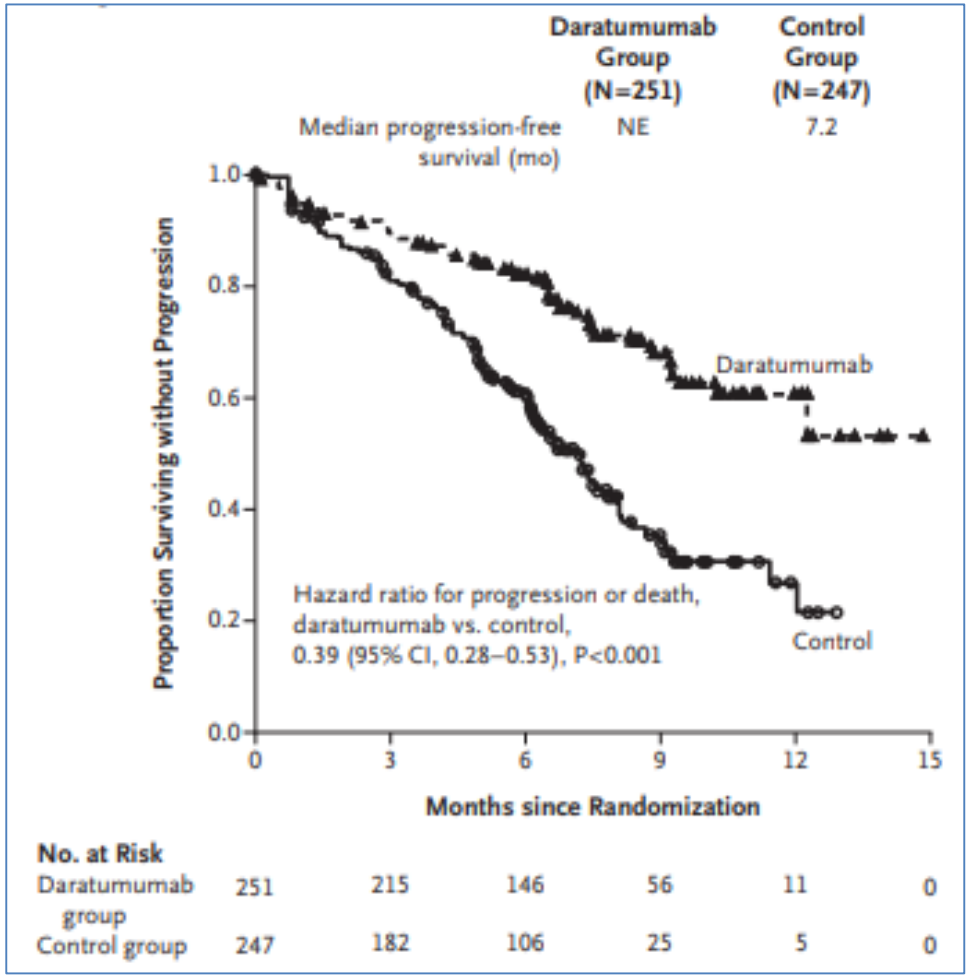
Primary endpoint: PFS

Secondary endpoints: TTP, OS, ORR, VGPR, CR, MRD, Time to response, Duration of response

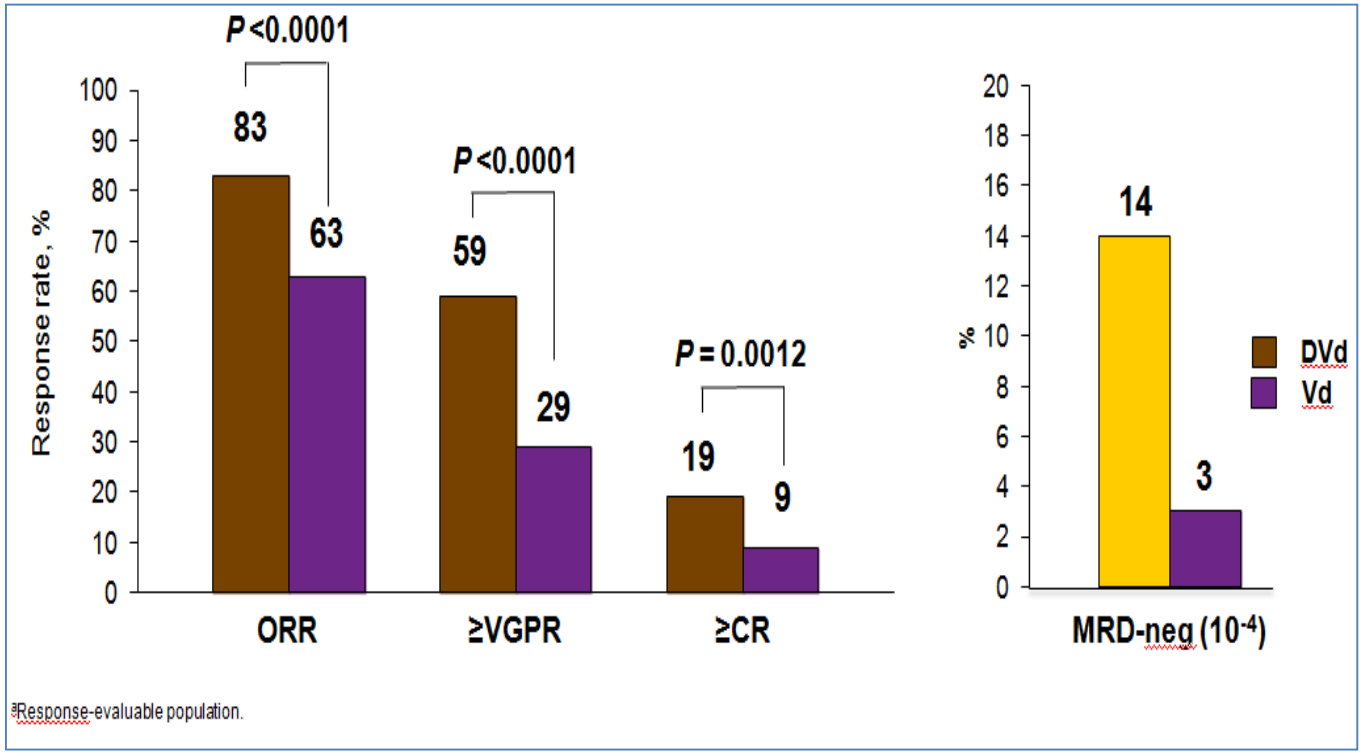
Palumbo A, et al. *N Engl J Med.* 2016;375(8):754-766.

Efficacy of CASTOR Trial

PFS

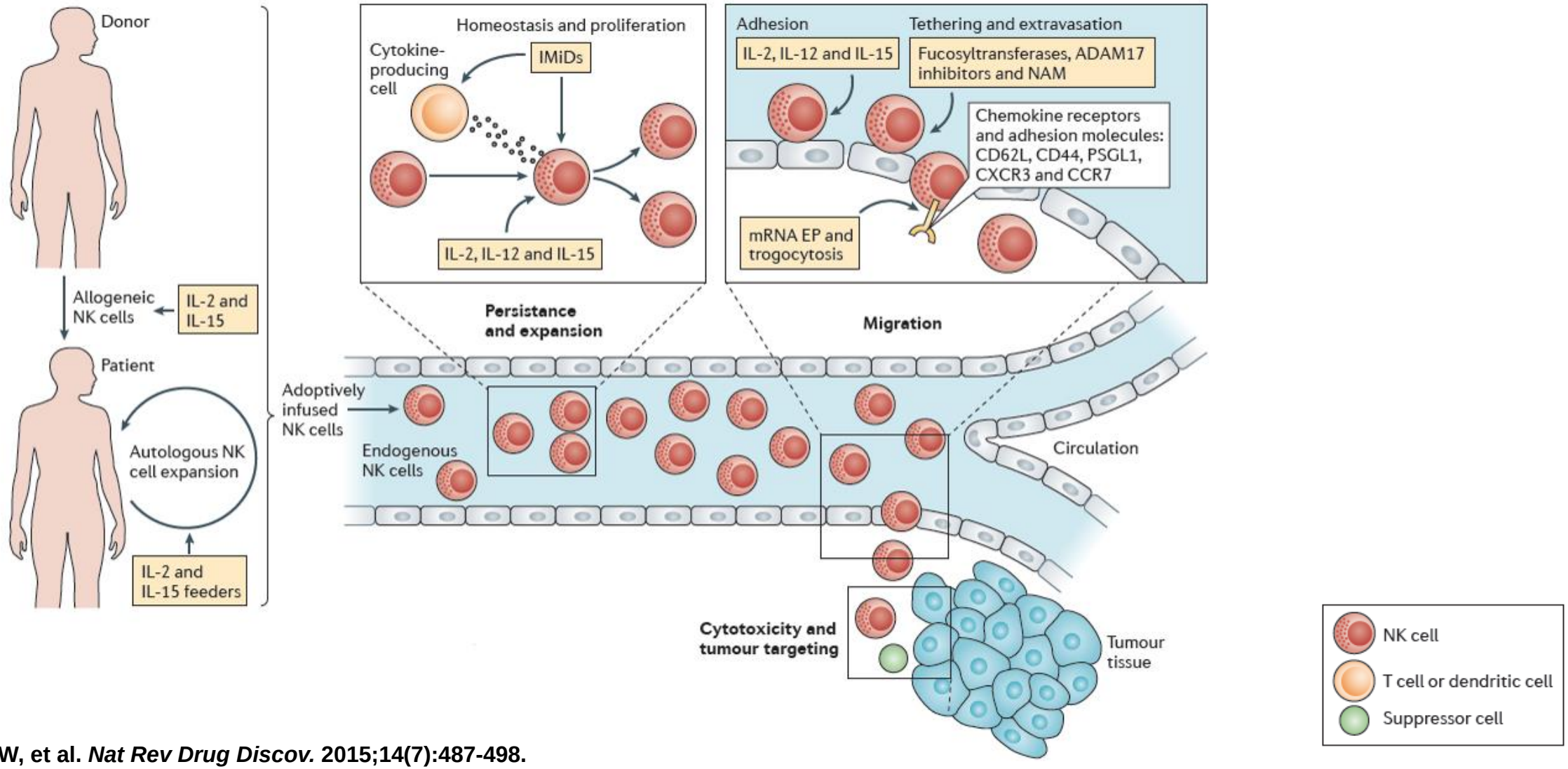


ORR



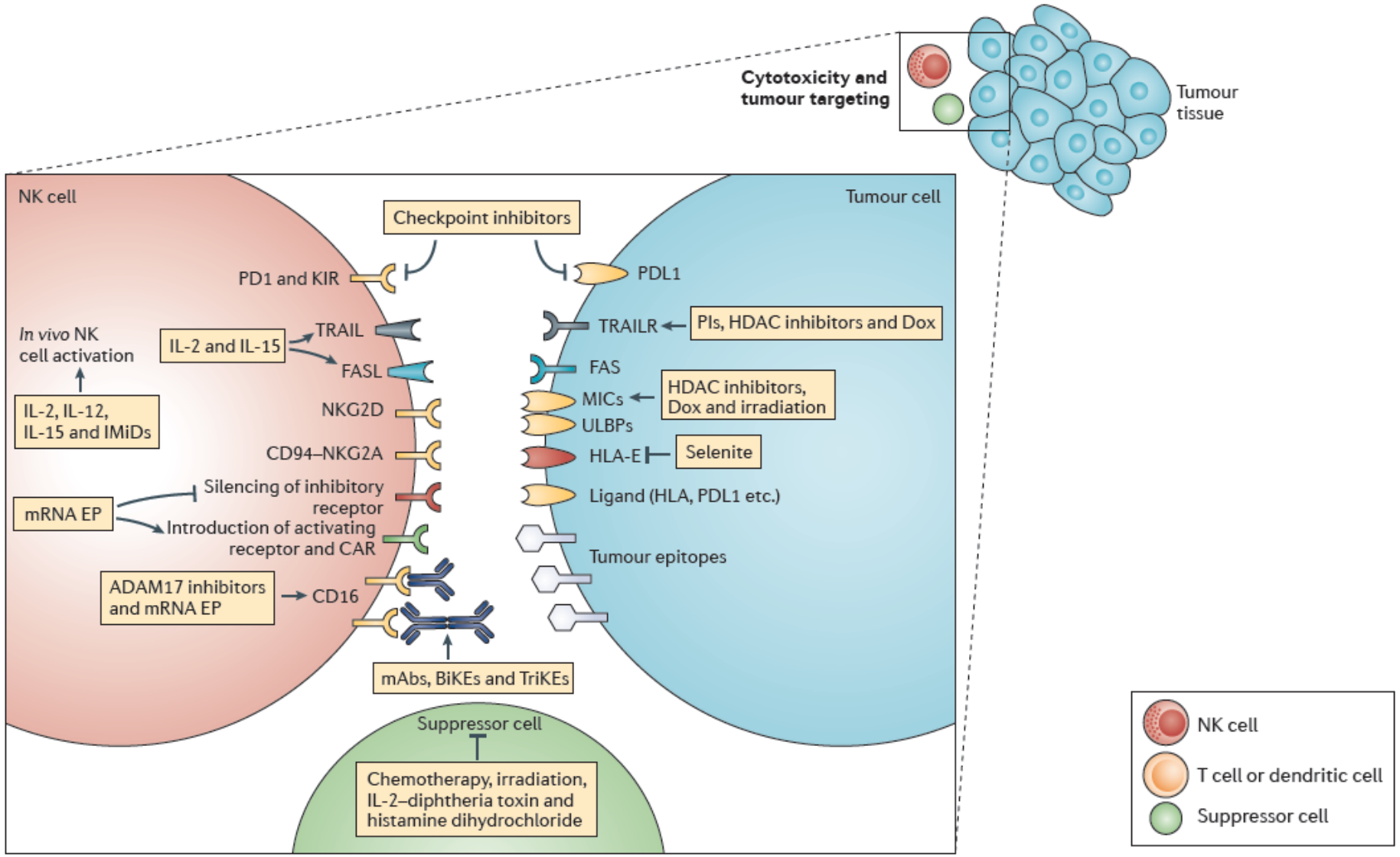
Palumbo A, et al. *N Engl J Med.* 2016;375(8):754-766.

Enhancing NK Cell Therapies



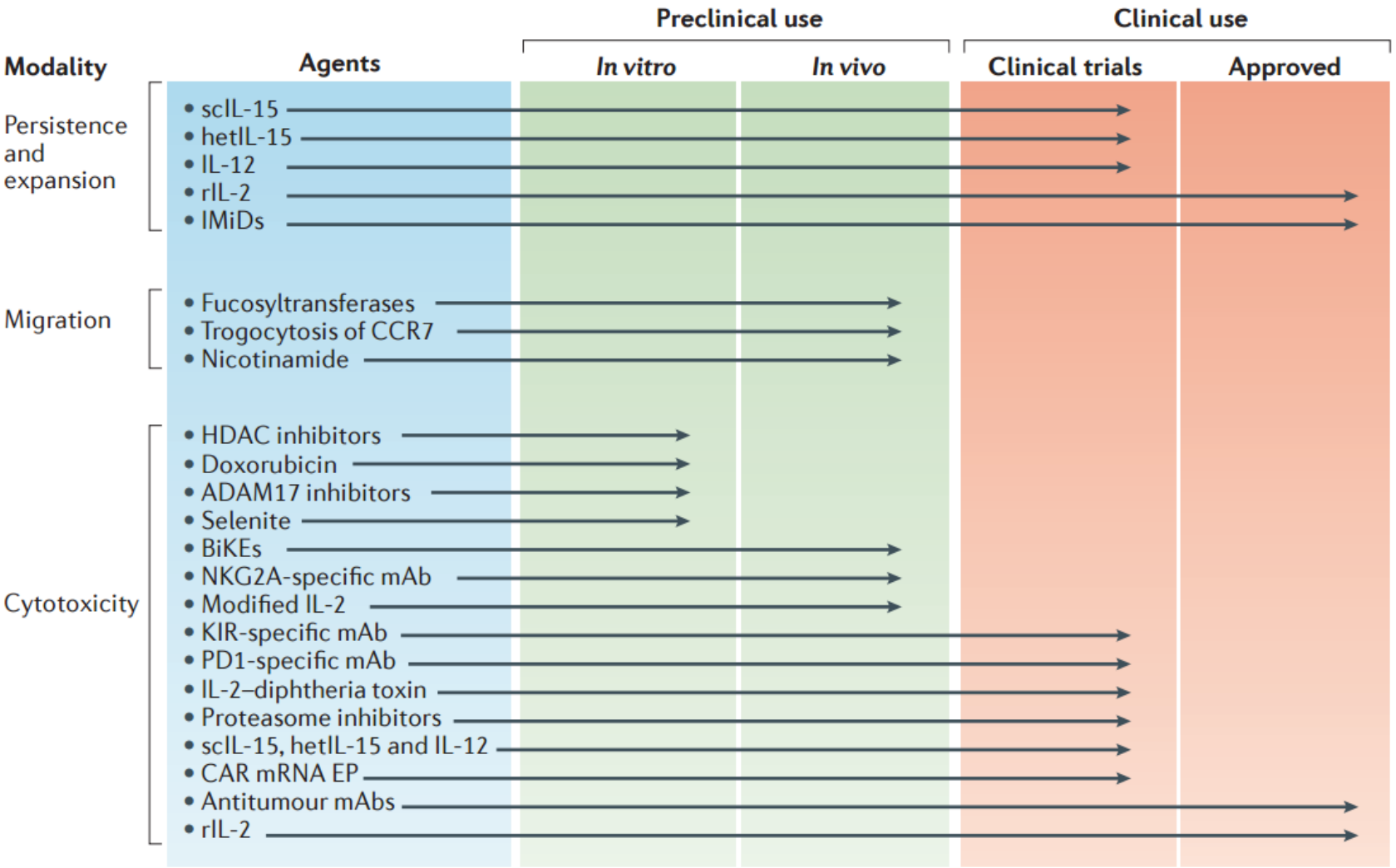
Childs RW, et al. *Nat Rev Drug Discov.* 2015;14(7):487-498.

Enhancing NK Cell Therapies



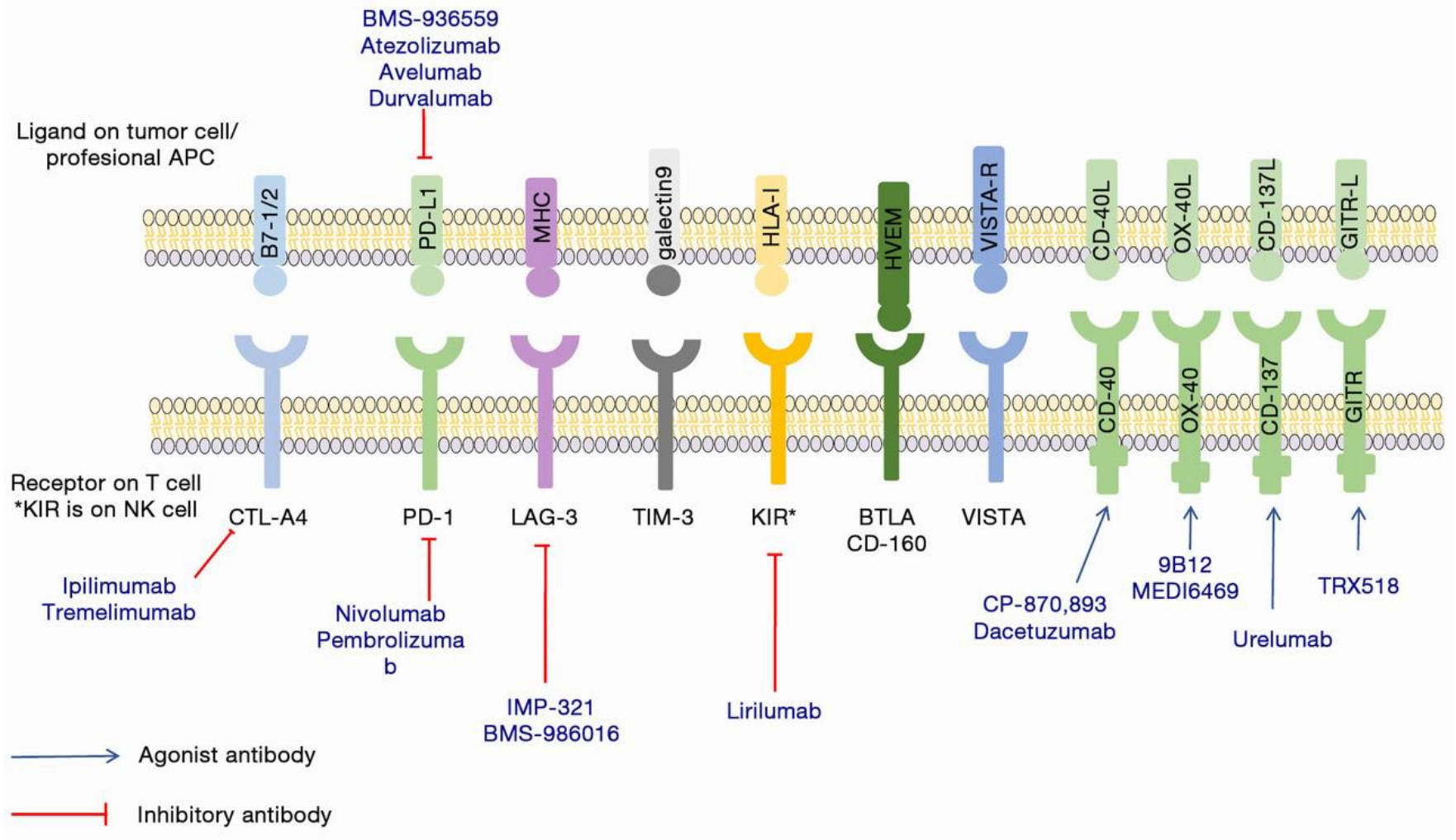
Childs RW, et al. *Nat Rev Drug Discov.* 2015;14(7):487-498.

NK Cell–Enhancing Drugs

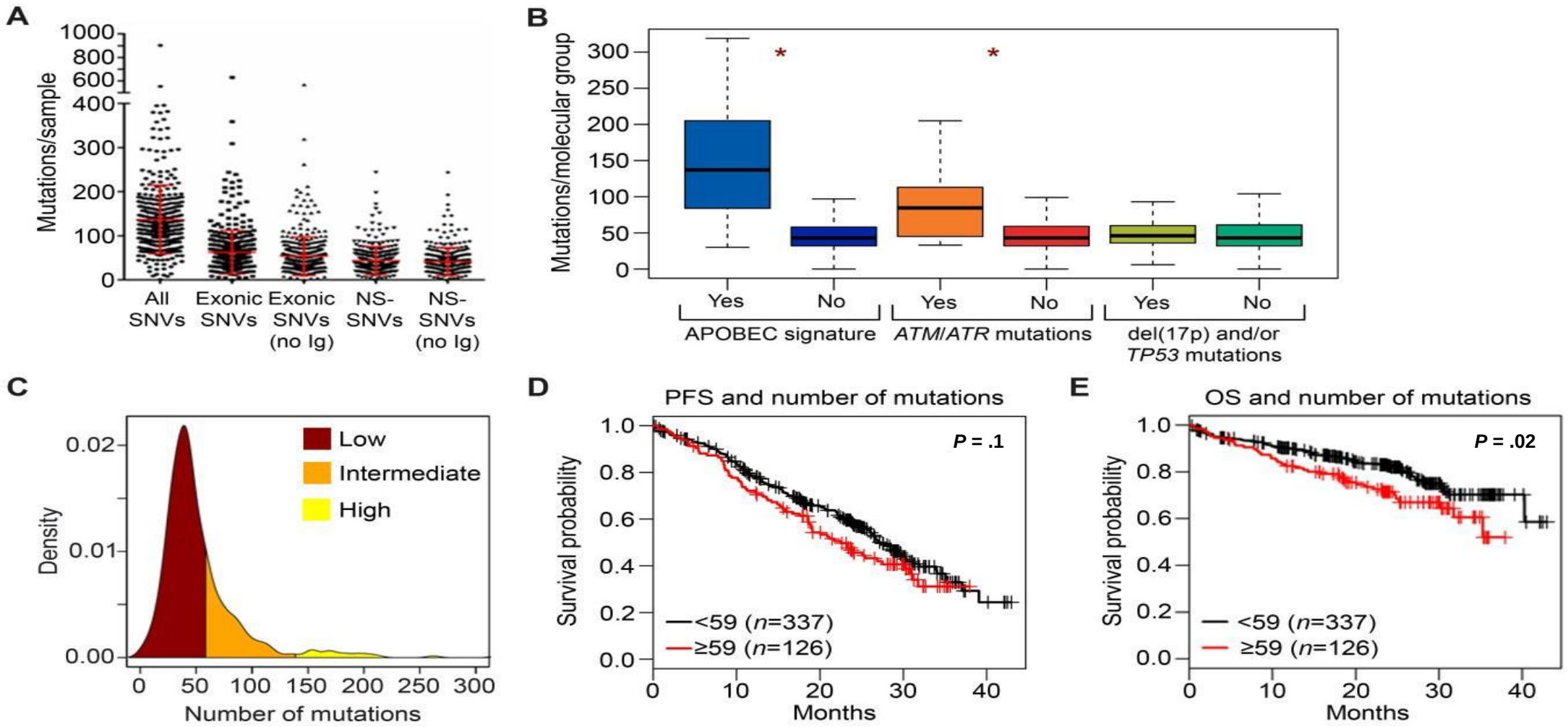


Childs RW, et al. *Nat Rev Drug Discov.* 2015;14(7):487-498.

Checkpoint Inhibition



Precision Immunotherapy and Mutational Load: Checkpoint Inhibition



OS, overall survival; PFS, progression-free survival

Checkpoint Inhibitors in RRMM

- **Pembrolizumab (August, 2017) – The FDA placed a clinical hold on two clinical trials**
  - **KEYNOTE-183 and KEYNOTE-185**

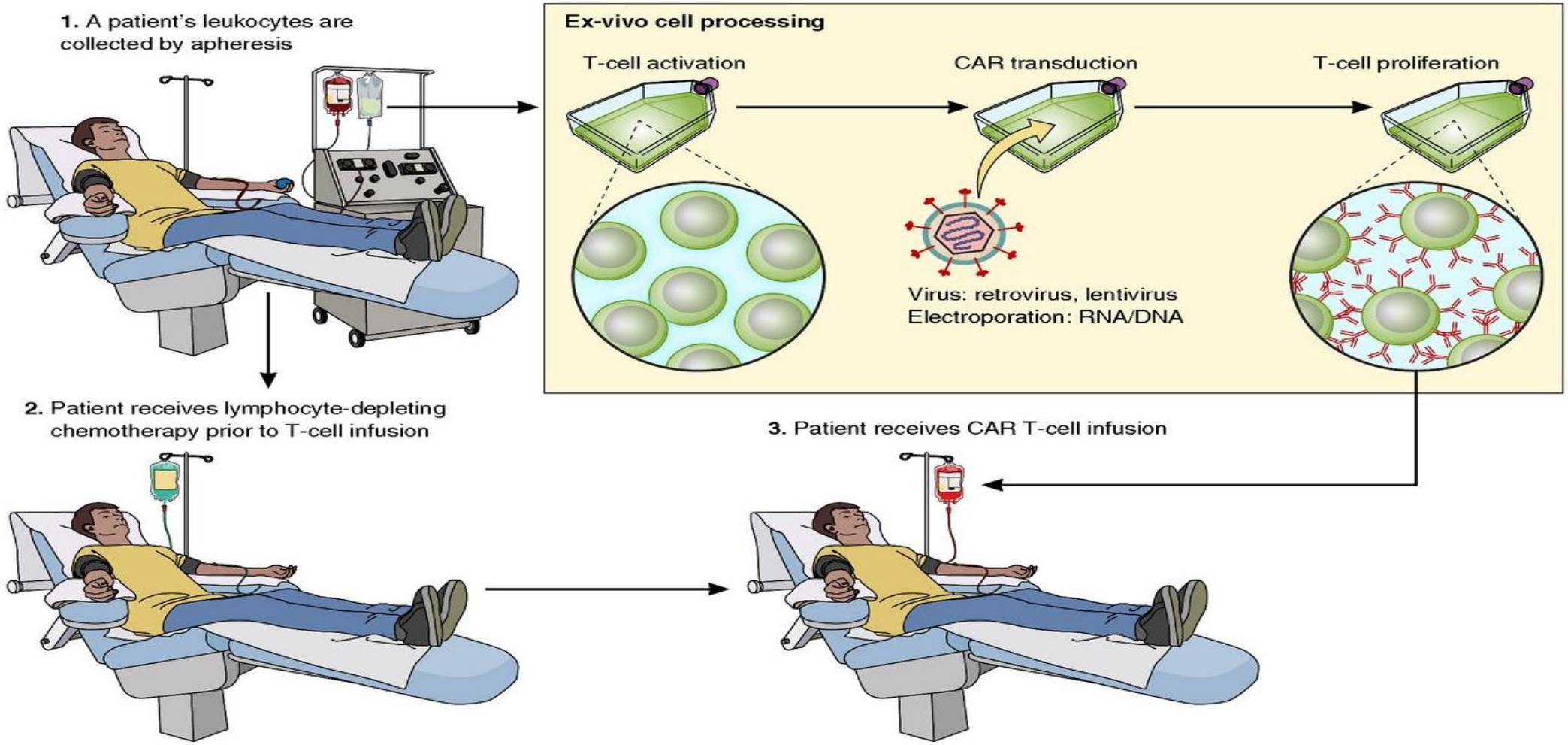
- **Nivolumab (December 2017)**
  - **The partial hold on CA204142 and CheckMate-039 were lifted in 12/17**
  - **The CheckMate-602 is no longer accruing patients but results are expected in 2018**

- **Durvalumab – the FDA placed a partial clinical hold on 3 trials in MM and a full clinical hold on one trial**
  - **The trials placed on partial clinical hold are: MEDI4736-MM-001, MEDI4736-MM-003, MEDI4736-MM-005**
  - **MEDI4736-MM-02 is on full clinical hold**

- **Atezolizumab – Phase Ib and Phase Ib/II studies have been lifted. The studies will continue in accordance with the protocol amendments agreed upon by the FDA.**

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574341.htm.https://news.bms.com/press-release/corporatefinancial-news/bristol-myers-squibb-provides-update-three-opdivo-based-combin. http://ir.celgene.com/releasedetail.cfm?ReleaseID=1039476. https://www.roche.com/dam/jcr:b92ed33a-95a6-43ae-822f-d7ce643d03a1/en/171205_TECENTRIQ_Heme_FDA_en.pdf.

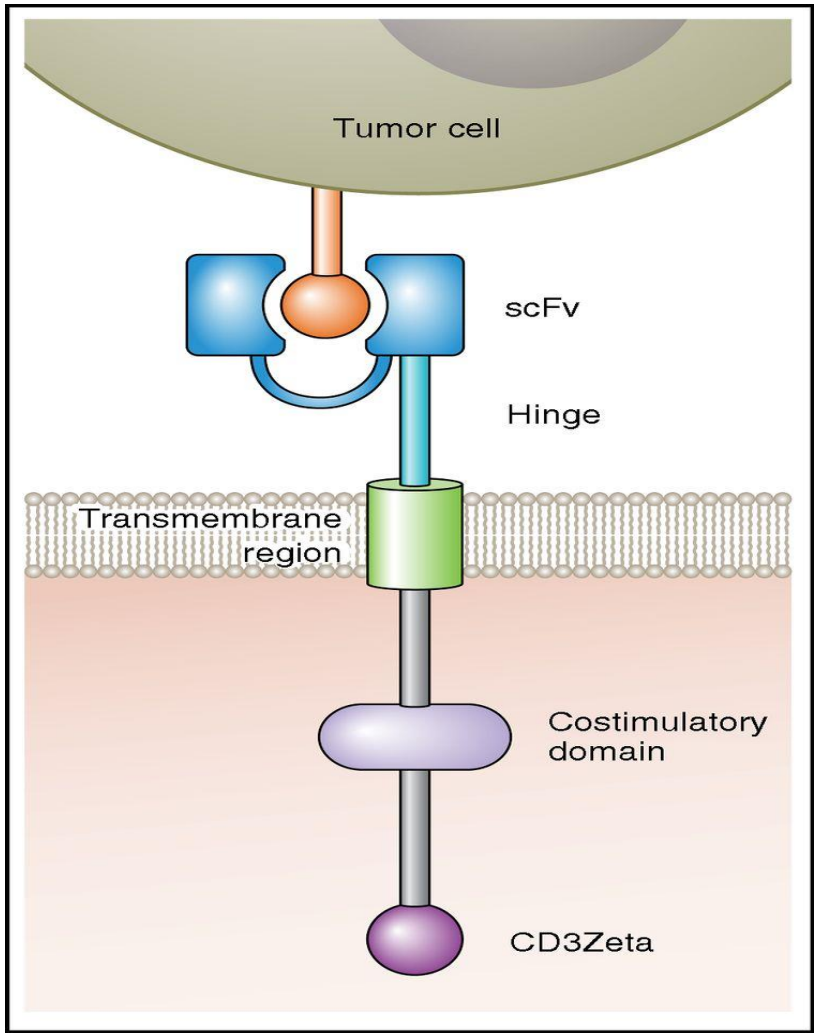
CAR T Cells



Mikkilineni L, et al. *Blood.* 2017;130(24):2594-2602.

CAR T-Cell Design

- CAR = Artificial fusion proteins that incorporate an antigen-recognition domain and T-cell signaling domain
- Specifically recognize a targeted antigen
- Not HLA-restricted
- Two signaling domains:
  - Costimulatory domain usually CD28 and 4-1BBB
  - T cell activation domain usually CD3z



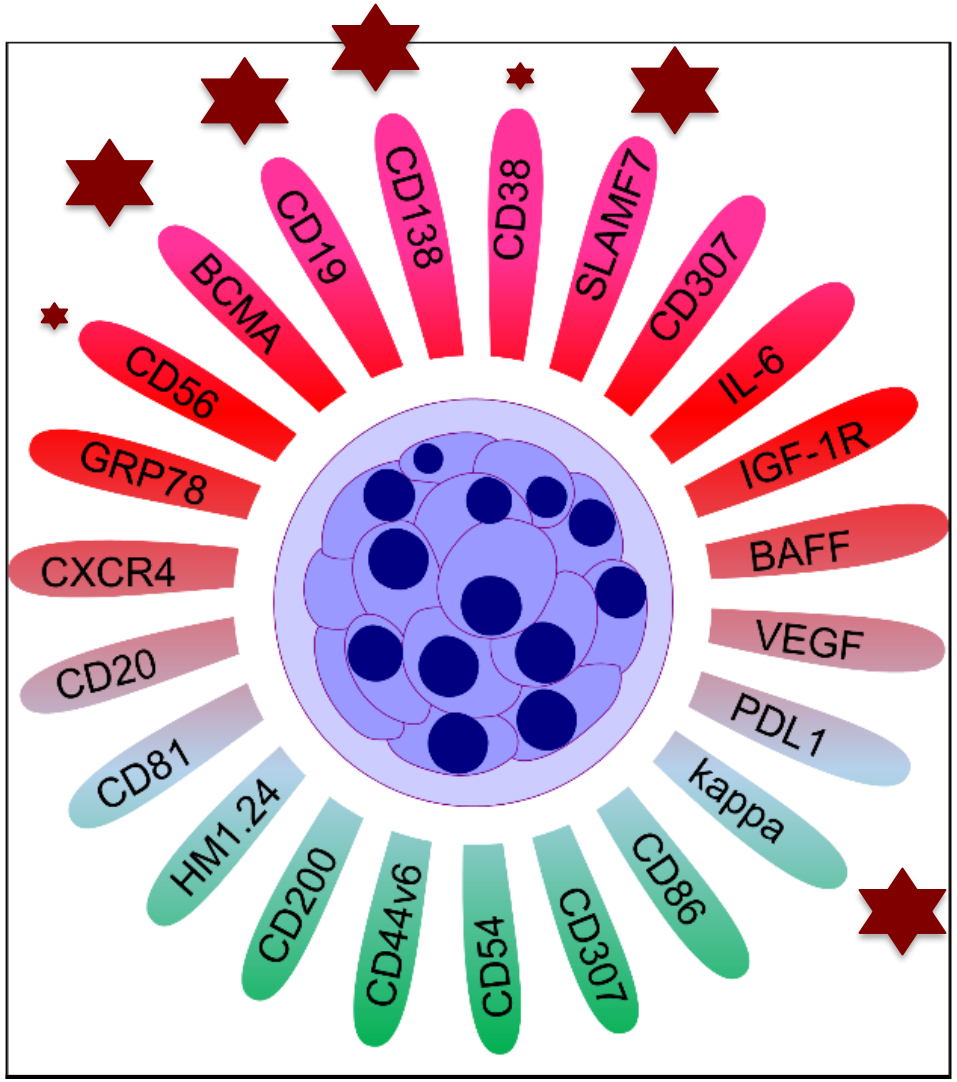
HLA, human leukocyte antigen

Mikkilineni L, et al. *Blood.* 2017;130(24):2594-2602.

Target Selection

Clinical trials underway

In vitro studies



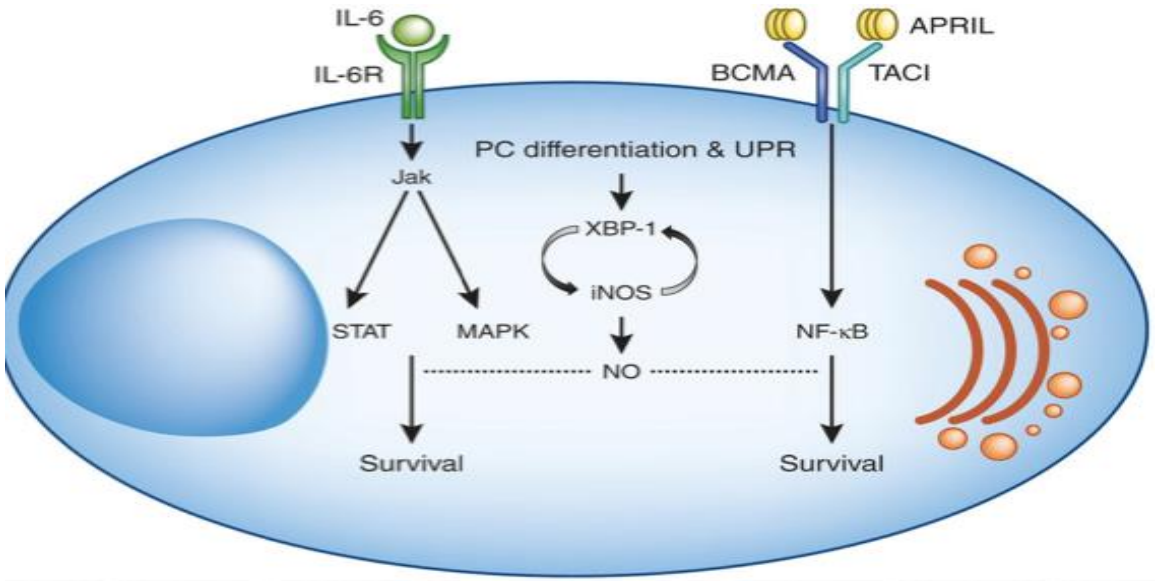
Chose target(s) based on tumor's immune-phenotype

Rasche L, et al. *Cancer Treat Rev.* 2017;55:190-199.

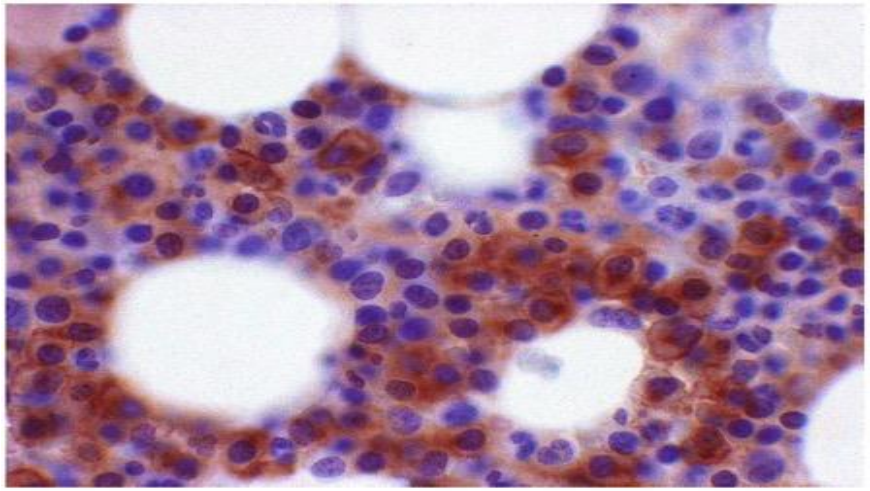
BCMA: A Promising Target in Multiple Myeloma

BCMA is member of the TNF receptor superfamily

- **Expressed nearly universally on multiple myeloma cells**
- **Expression largely restricted to plasma cells and some mature B cells**



Njau MN, et al. *Nat Immunol.* 2014;15(3):219-221.

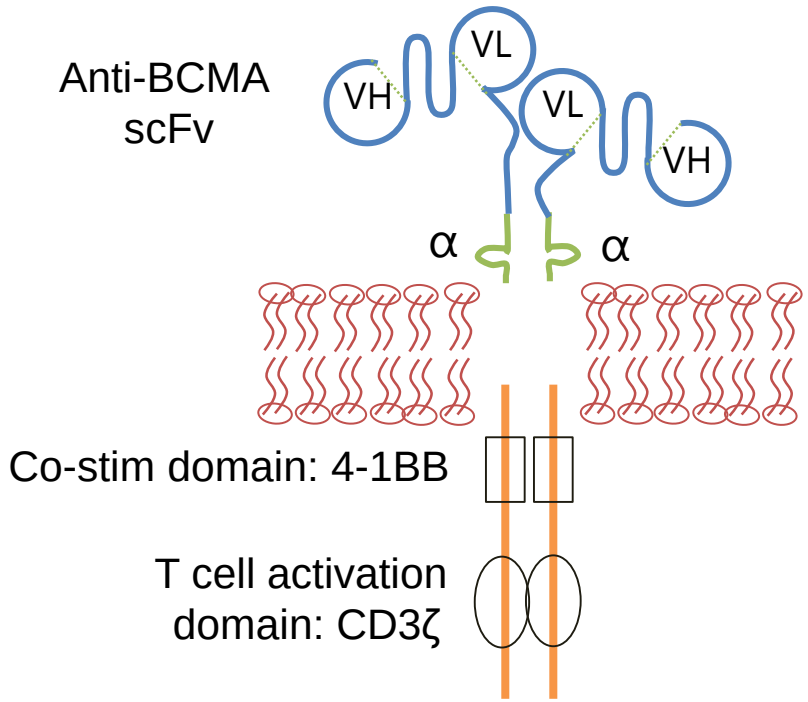


BCMA Expression on myeloma cells (brown color = BCMA protein)

Courtesy of: Yi Lin, MD, PhD – Mayo Clinic

bb2121

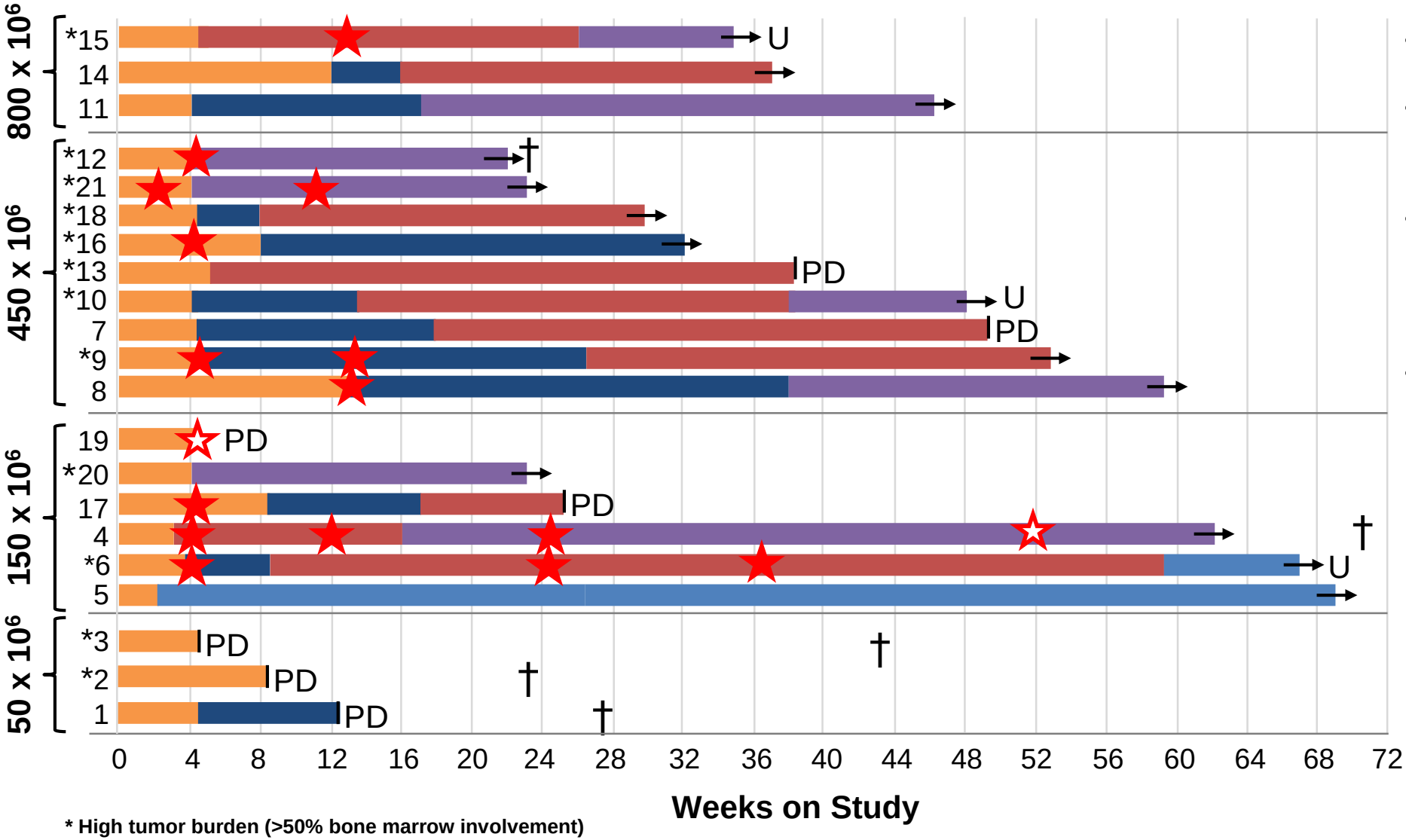
- **bb2121 is a second-generation CAR construct targeting BCMA, consisting of autologous T cells transduced with a lentiviral vector encoding a novel CAR incorporating:**
  - **A murine-derived anti-BCMA scFv**
  - **A 4-1BB costimulatory motif**
- **Multicenter, open-label, dose-escalation and dose-expansion trial in patients with R/R MM who received ≥3 prior lines of therapy or patients with double-refractory MM**
  - **Dose-escalation phase: ≥50% BCMA expression required**
  - **Dose-expansion phase: No BCMA expression required; prior daratumumab required**
- **Primary objectives: Safety, tolerability, and recommended phase II dose**



R/R, relapsed/refractory

Berdeja JG, et al. *Blood.* 2017;130(suppl): Abstract 740.

CRB-401: Tumor Response to bb2121



- **ORR: 94% (CR: 56%)**
- **MRD neg: 9 of 10 evaluable patients**
- **5 patients with ongoing responses >1 year**
- **Responses continue to improve as late as month 15 (VGPR to CR)**

CR/sCR · VGPR · PR · Stable Disease · MRD- · MRD+

† Deceased · U Unconfirmed response · PD Progressive disease

* High tumor burden (>50% bone marrow involvement)

MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good parital response

Berdeja JG, et al. *Blood.* 2017;130(suppl): Abstract 740.

Cocktail of CAR T Cells: CD19– and BCMA–Targeted CAR T Cells

- **Treatment approach**
  - **Day -30: T-cell apheresis to collect cells for individualized CAR T-cell therapy**
  - **Days -5, -4, -3: Lymphodepletion with cyclophosphamide 300 mg/m^2 + fludarabine 30 mg/m^2**
  - **Day 0: Infusion of 1 x 10^7/kg CD19-specific CAR T cells**
  - **Days 2, 3: Split-dose infusions of 4.5 (2.5-8.2) x 10^7/kg BCMA-specific CAR T cells**
- **Primary endpoints: Safety, tolerability. Secondary endpoints: ORR, DoR, CAR T-cell persistence**
- **Reported on 10 patients: All CD19 negative and 54.2% to 96.9% BCMA expression**
- **Mean follow-up: 23 weeks (range: 4-32). Response: 2CR, 1VGPR, and 6 PR**
- **CRS occurred in all patients; 2 patients (grade 3) received anticyctokine therapy**
- **Median time to CRS onset: 14.5 hrs (range: 6-29). Median CRS duration: 3.5 days (range: 1-9)**
- **Common nonhematologic AEs: Fever (n = 10), fatigue (n = 7), nausea/vomiting (n = 6), prolonged aPTT (n = 6), myalgia (n = 5)**

aPTT, activated partial thromboplastin time

Yan L, et al. *Blood.* 2017;130(suppl): Abstract 506.

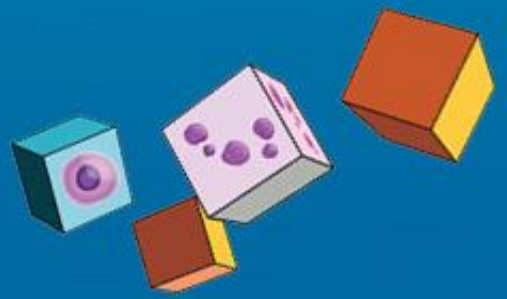
Conclusions

- **Immune dysregulation plays a key role in the pathogenesis and progression of multiple myeloma**
- **Two recently approved monoclonal antibodies (elotuzumab and daratumumab) are now a cornerstone therapies for RRMM**
- **The safety and efficacy of checkpoint inhibitors has yet to be confirmed, with excess toxicity identified when combined with IMiDs**
- **CAR T cells offer a promising approach with functional CAR T cells being generated from patients with MM and multiple promising targets including BCMA**

prIME ONCOLOGY

Aptitude Health Company

Treatment Decisions for Relapsed/Refractory Multiple Myeloma:



Fitting the Pieces Together