

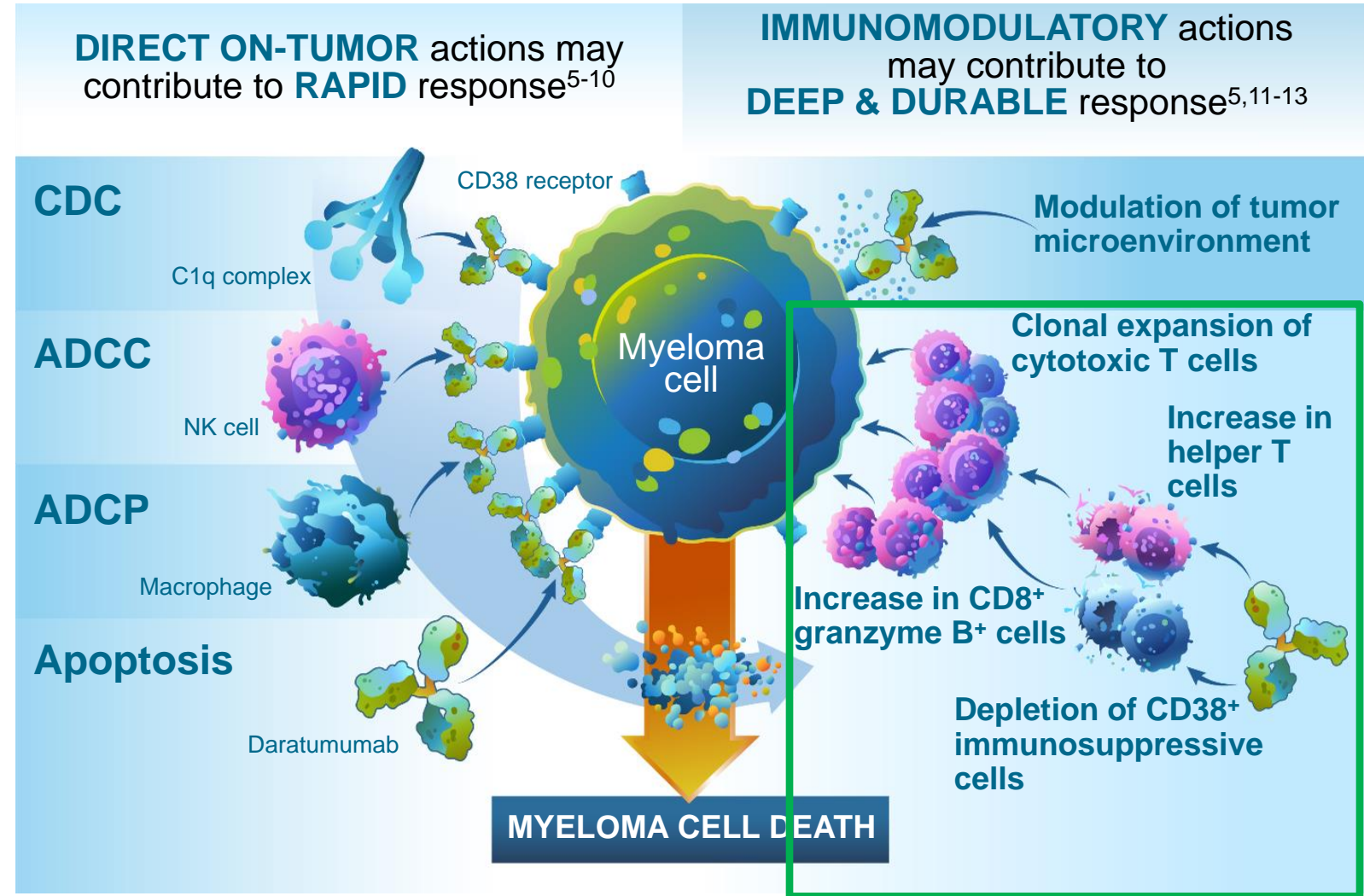
# Effects of Daratumumab on the Composition and Activation Status of Immune Cell Populations in CENTAURUS, a Phase 2 Randomized Study of Smoldering Multiple Myeloma (SMM) Patients

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# Daratumumab Acts Through Multiple Mechanisms

- **First-in-Class Antibody**
  - Human IgGk monoclonal antibody targeting CD38
- **Efficacy<sup>1-3</sup>**
  - Daratumumab-based combinations reduce the risk of progression or death and induce rapid, deep, and durable responses in RRMM and NDMM
- **Safety**
  - Safety profile is consistent across all indications
- **Approved<sup>4,5</sup>**
  - As **monotherapy** and in **combination** with standard of care regimens in RRMM in many countries
  - In **combination** with bortezomib, melphalan, and prednisone in non-transplant NDMM (United States, Brazil, etc.)

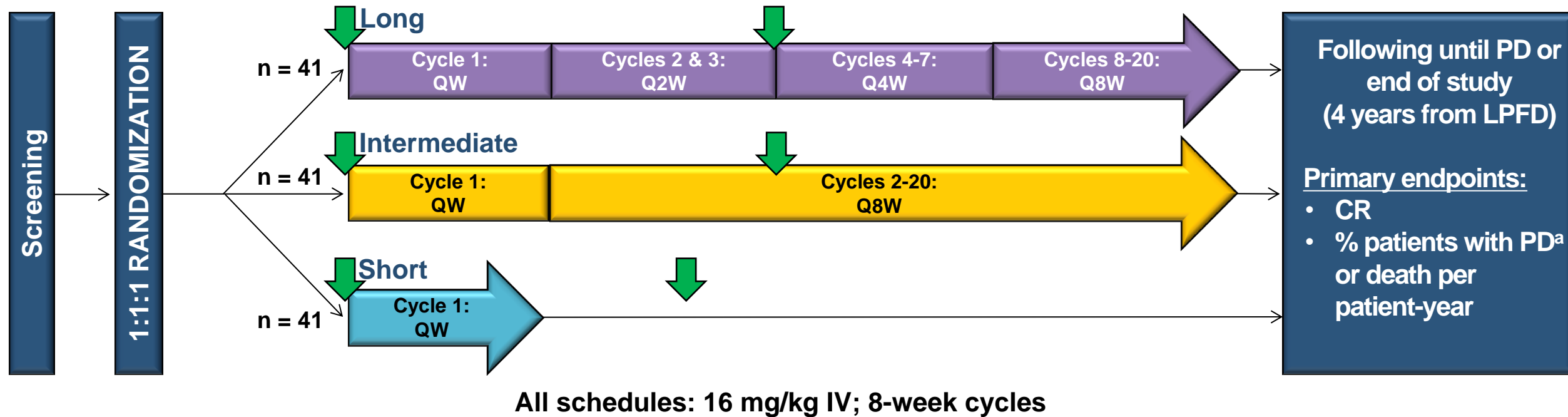


RRMM, relapsed/refractory multiple myeloma; NDMM, newly diagnosed multiple myeloma; CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cell-mediated cytotoxicity; NK, natural killer; ADCP, antibody-dependent cellular phagocytosis.

1. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766. 2. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331. 3. Mateos MV, et al. *N Engl J Med*. 2018;378:518-528. 4. Blair H. *Drugs*. 2017;77(18):2013-2024. 5. DARZALEX [US PI]. Horsham, PA: Janssen Biotech, Inc.; 2018. 6. Liszewski MK, et al. *Adv Immunol*. 1996;61:201-283. 7. Debets JM, et al. *J Immunol*. 1988;141(4):1197-1201. 8. Overdijk MB, et al. *mABs*. 2015;7(2):311-321. 9. Lokhorst HM, et al. *N Engl J Med*. 2015;373(13):1207-1219. 10. Plesner T, et al. Oral presentation at: ASH; December 8-11, 2012; Atlanta, GA. 11. Krejci J, et al. *Blood*. 2016;128(3):384-394. 12. Adams H, et al. Poster presented at: ASH; December 3-6, 2016; San Diego, CA. 13. Chiu C, et al. Poster presented at: ASH; December 3-6, 2016; San Diego, CA.

# CENTAURUS: Randomized Study of Daratumumab Monotherapy in Intermediate-risk and High-risk SMM

## CyTOF sample collection

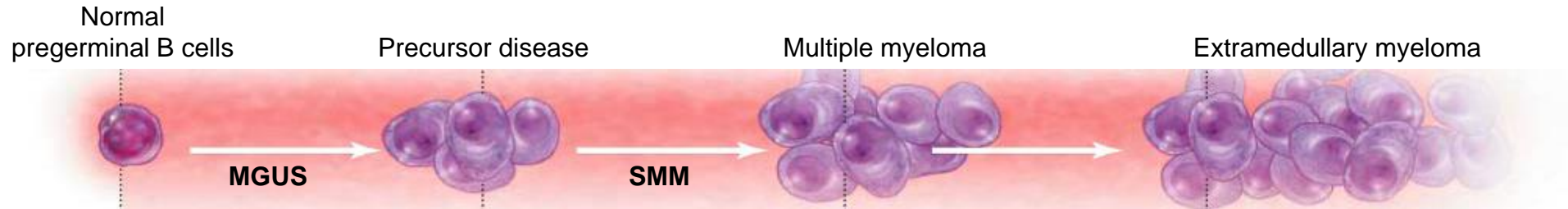


CyTOF, Cytometry by Time of Flight; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; IV, intravenous; PD, progressive disease; LPFD, last patient, first dose; CR, complete response; IMWG, International Myeloma Working Group.

<sup>a</sup>As defined by 2014 IMWG criteria for SMM.<sup>1</sup>

1. Rajkumar SV, et al. *Lancet Oncol.* 2014;15:e538-e548.

# CENTAURUS: Randomized Study of Daratumumab Monotherapy in Intermediate-risk and High-risk SMM



Korde N, et al. *Blood*. 2011;117(21):5573-5581.

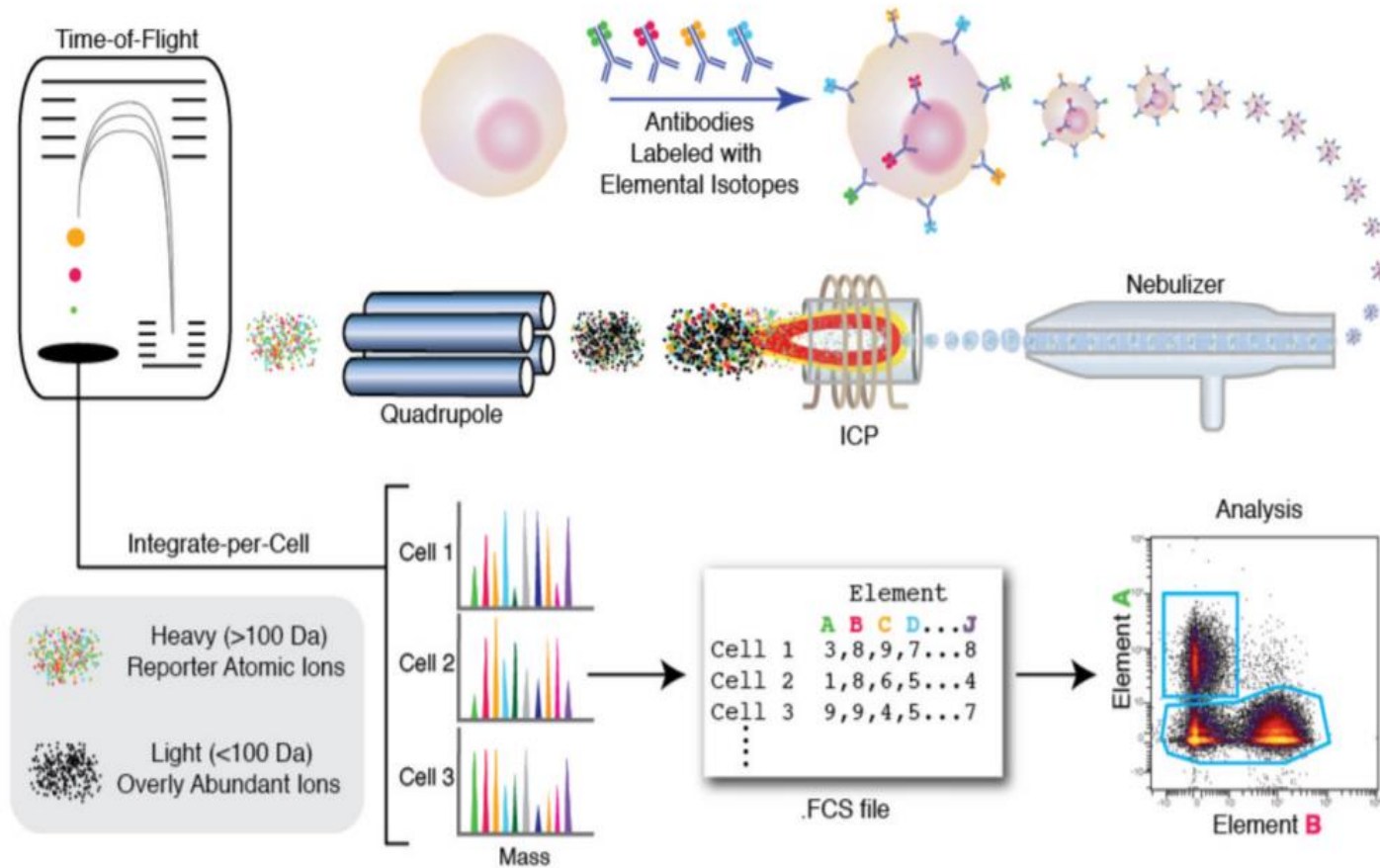
- Key inclusion criteria
  - Diagnosis of SMM <5 years
  - Bone marrow plasma cells  $\geq 10\%$  to  $< 60\%$  and  $\geq 1$  of the following:
    - Serum M-protein  $\geq 3$  g/dL (IgA  $\geq 2$  g/dL)
    - Urine M-protein  $> 500$  mg/24 hours
    - Abnormal sFLC ratio ( $< 0.126$  or  $> 8$ ) and serum M-protein  $< 3$  g/dL but  $\geq 1$  g/dL
    - Absolute involved sFLC  $\geq 100$  mg/L with an abnormal FLC ratio ( $< 0.126$  or  $> 8$ , but not  $\leq 0.01$  or  $\geq 100$ )
- Key exclusion criteria
  - Presence of  $\geq 1$  SLiM-CRAB myeloma-defining event<sup>a</sup> (as defined in the 2014 IMWG criteria<sup>1</sup>)
  - Clinically relevant organ dysfunction
  - Primary systemic AL amyloidosis

MGUS, monoclonal gammopathy of undetermined significance; sFLC, serum free light chain; AL, amyloid light chain.

<sup>a</sup>Defined as  $\geq 60\%$  bone marrow plasma cells, free Light chain involved/uninvolved ratio  $\geq 100$ ,  $> 1$  focal bone lesions on MRI, Calcium elevation, Renal insufficiency by creatinine clearance, Anemia, or Bone disease due to lytic bone lesions.

1. Rajkumar SV, et al. *Lancet Oncol*. 2014;15:e538-e548.

# Use of CyTOF in Complex Disease



Bendall SC, et al. *Trends Immunol.* 2012;33(7):323-332.

- CyTOF, **C**ytometry by **T**ime **O**f **F**light: discovery tool for next generation single cell analysis
  - High parameter analysis
    - 40+ analytes can be assessed simultaneously in a single 1-mL sample
    - Metal-conjugated antibodies allow higher resolution
- Surpasses traditional capabilities for biological investigation
  - Allows investigation of both tumor and microenvironment
  - Evaluate modulation of rare populations
  - Investigate new targets

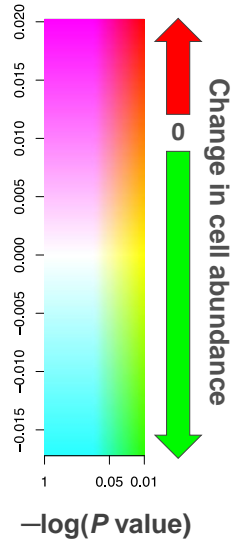
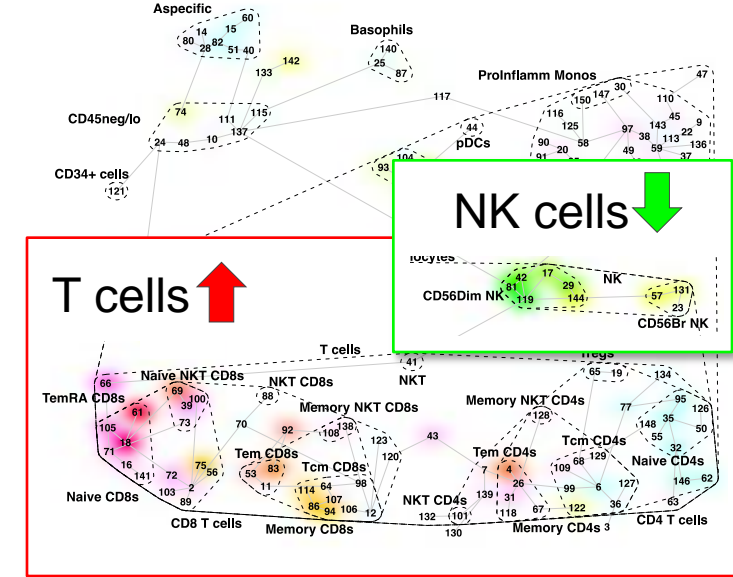
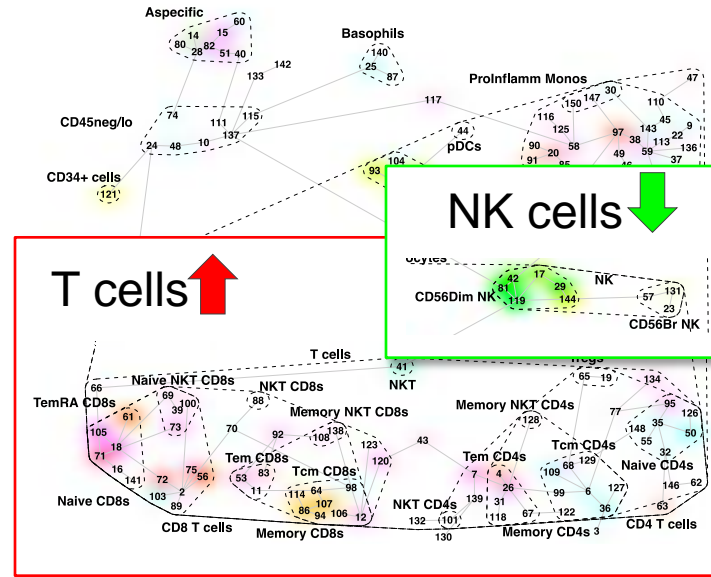
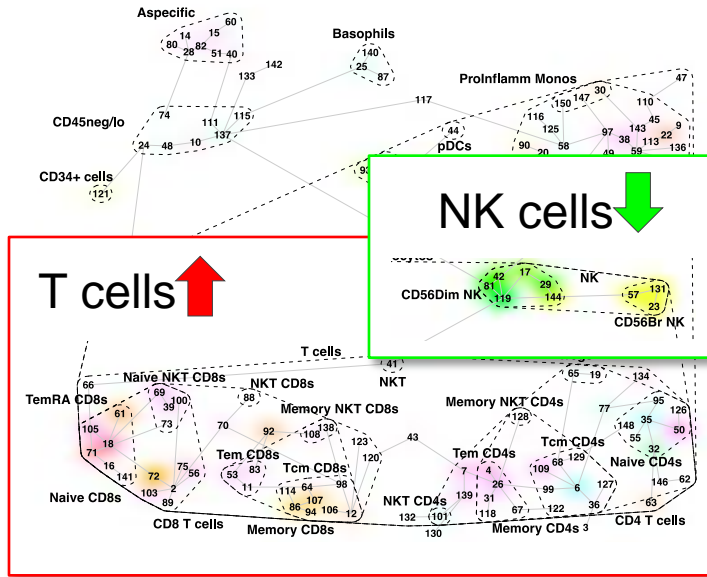


# Similar Impact of Dosing Schedules on Immune Cell Population Abundances

Long

Intermediate

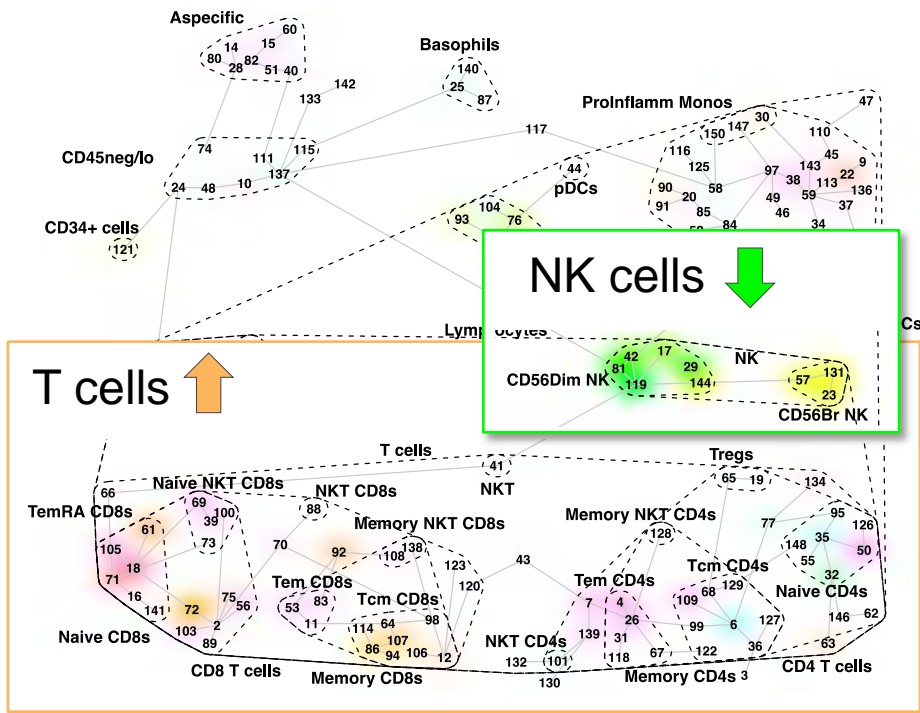
Short



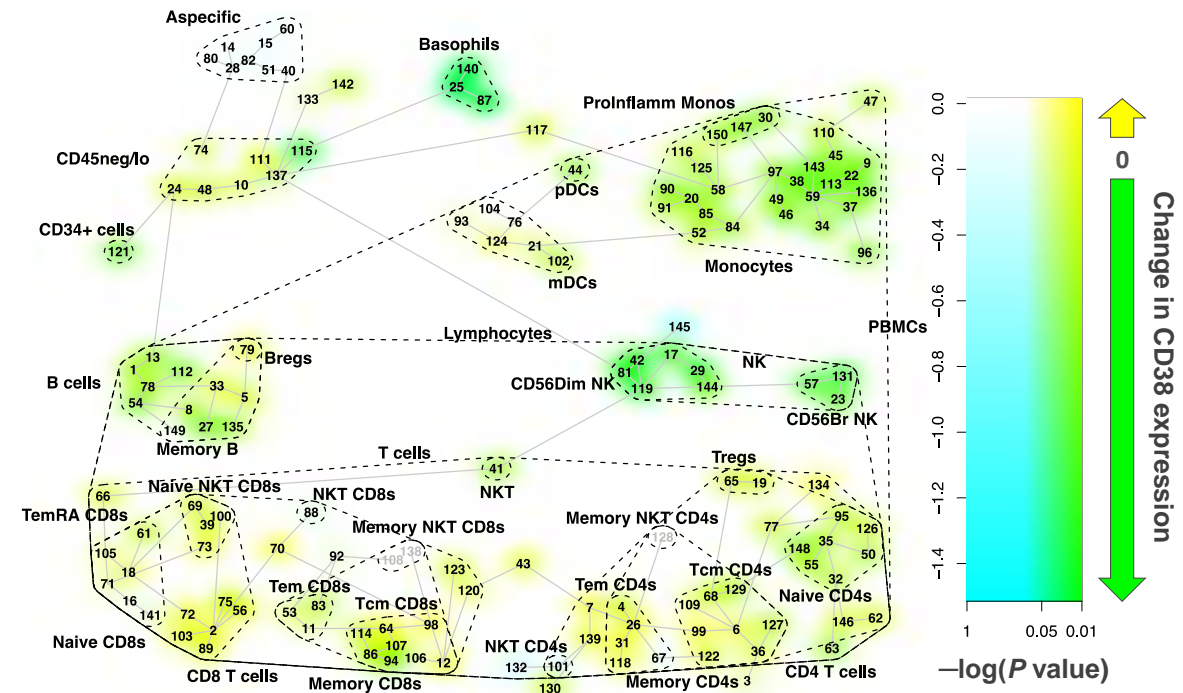
Pharmacodynamic changes were similar across treatment arms

# Daratumumab-induced Immune Modulation: Long Arm

## Cell abundance changes



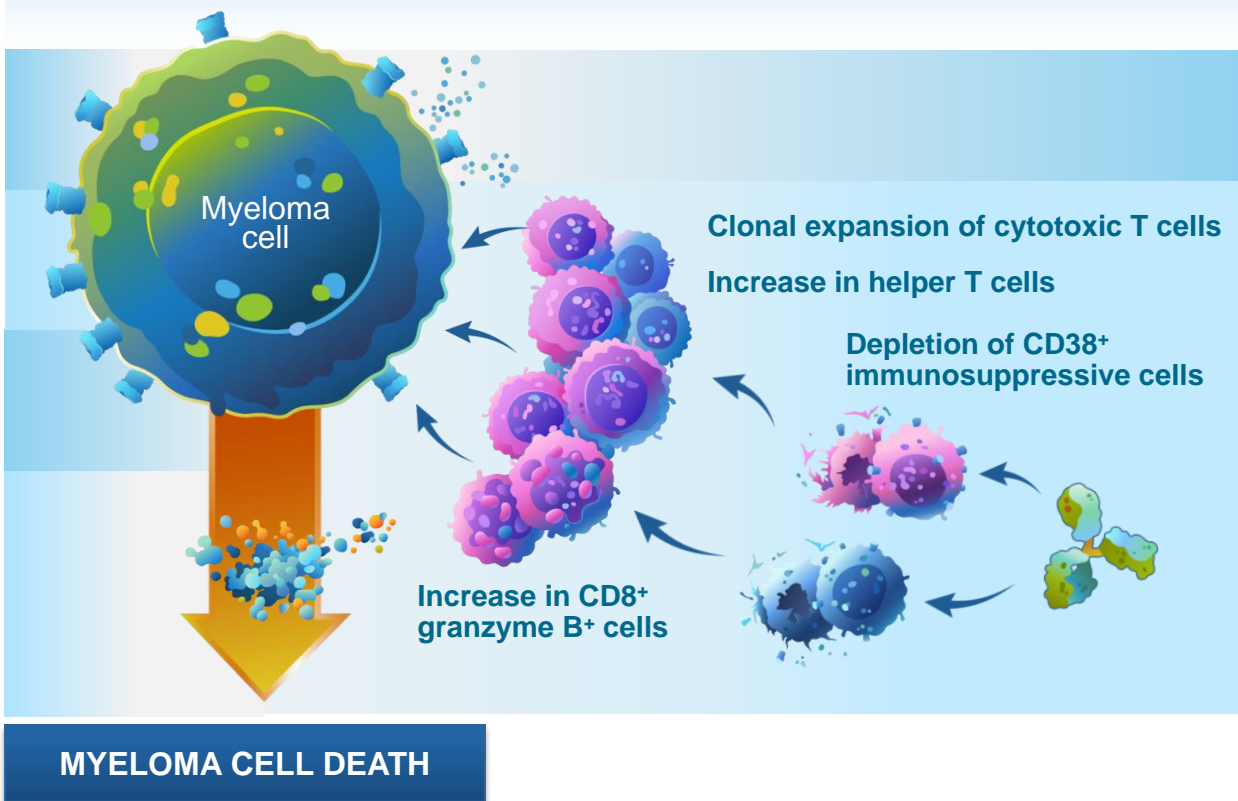
## CD38 expression changes



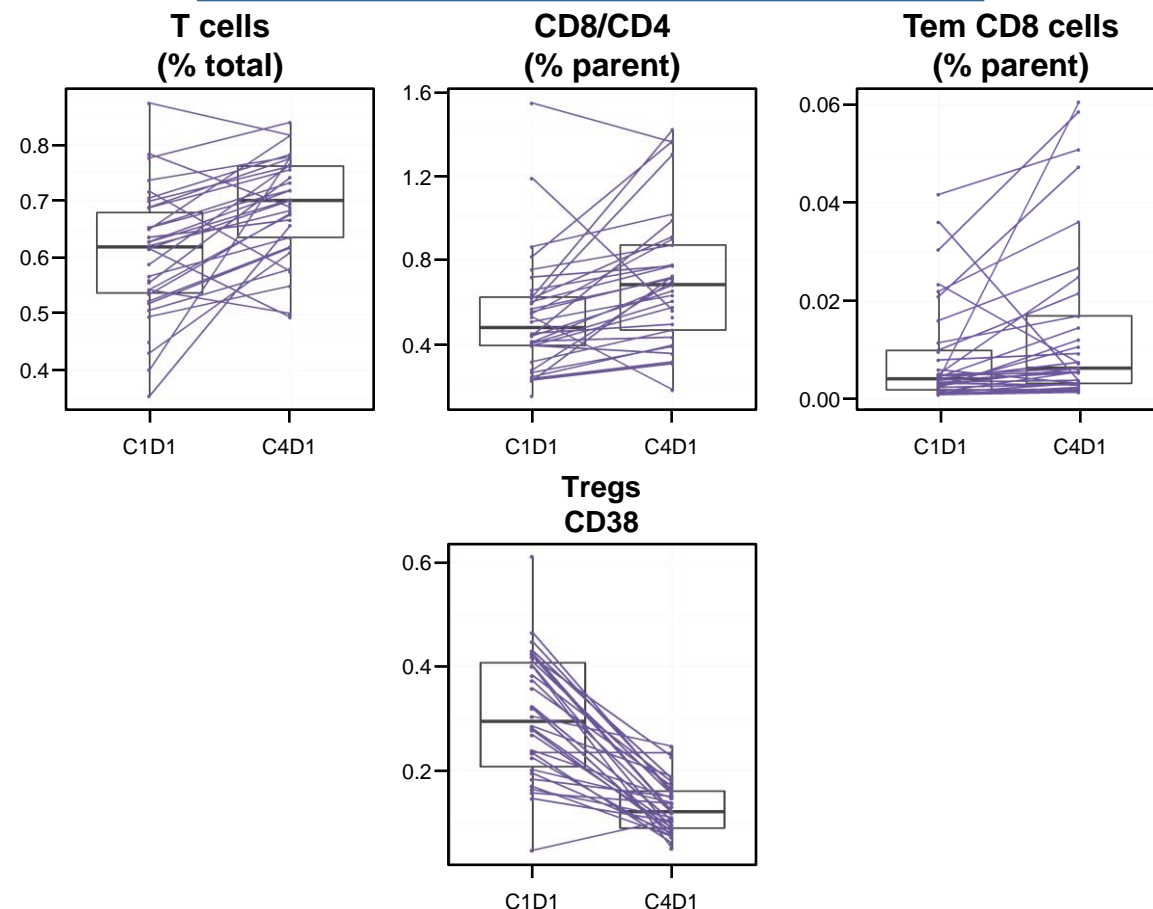
## Daratumumab in SMM results in increases in T-cell compartment, reduction of NK cells, and CD38 expression reduction across immune cell subsets

# Changes in T-cell Compartment

## IMMUNOMODULATORY Actions



## Long

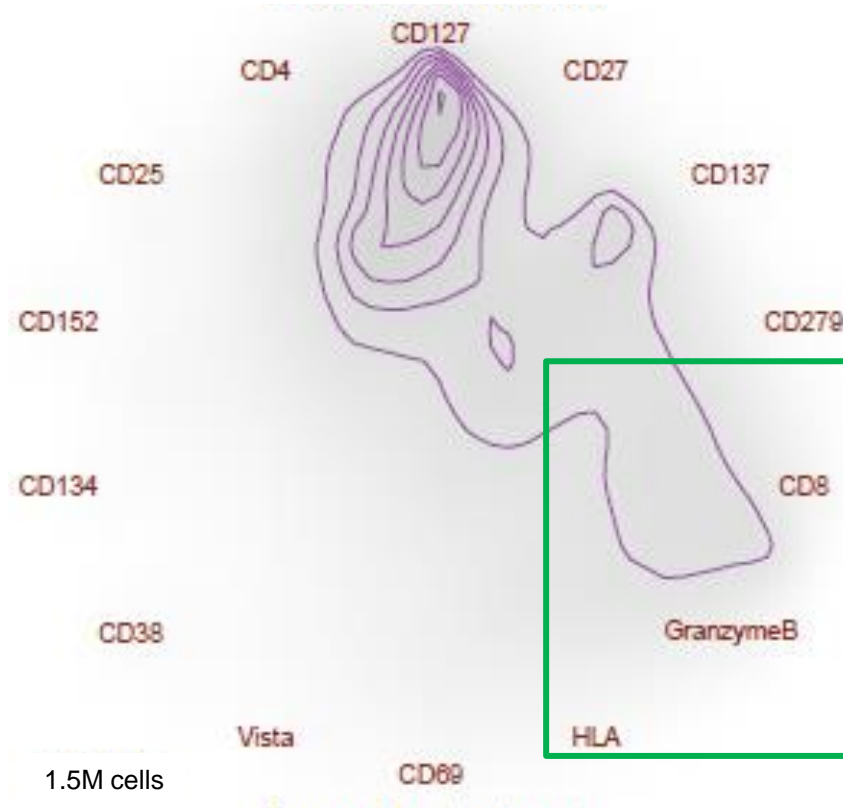


**Daratumumab in SMM results in total CD8 and CD8 effector memory T-cell expansion, and in CD38<sup>+</sup> suppressive Treg depletion**

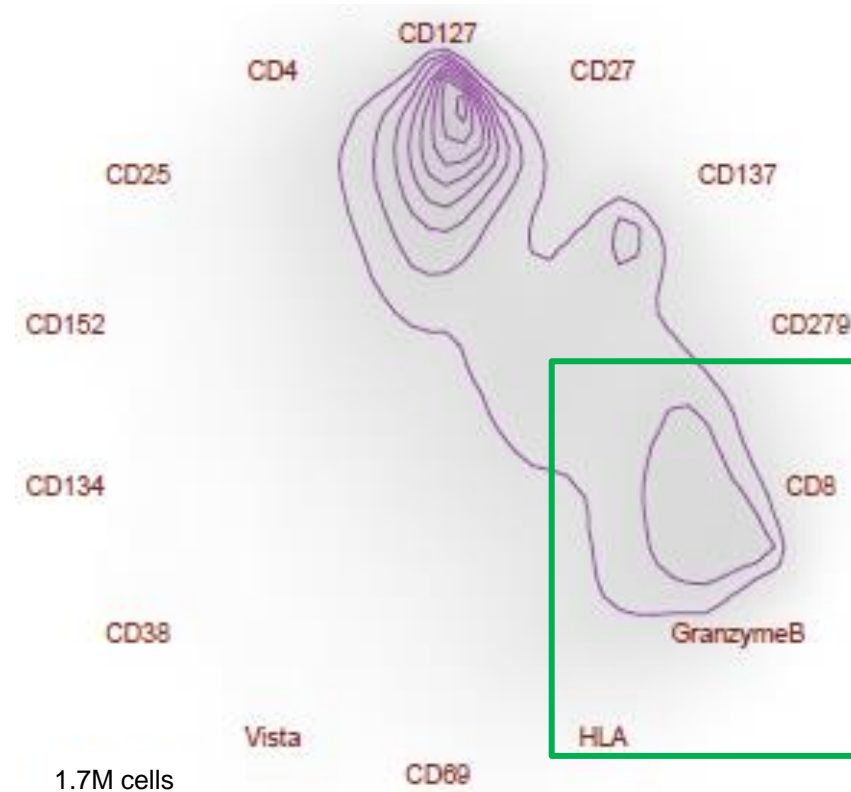


# T-cell Activation and Functionality: Increase in Granzyme B

Long: pretreatment



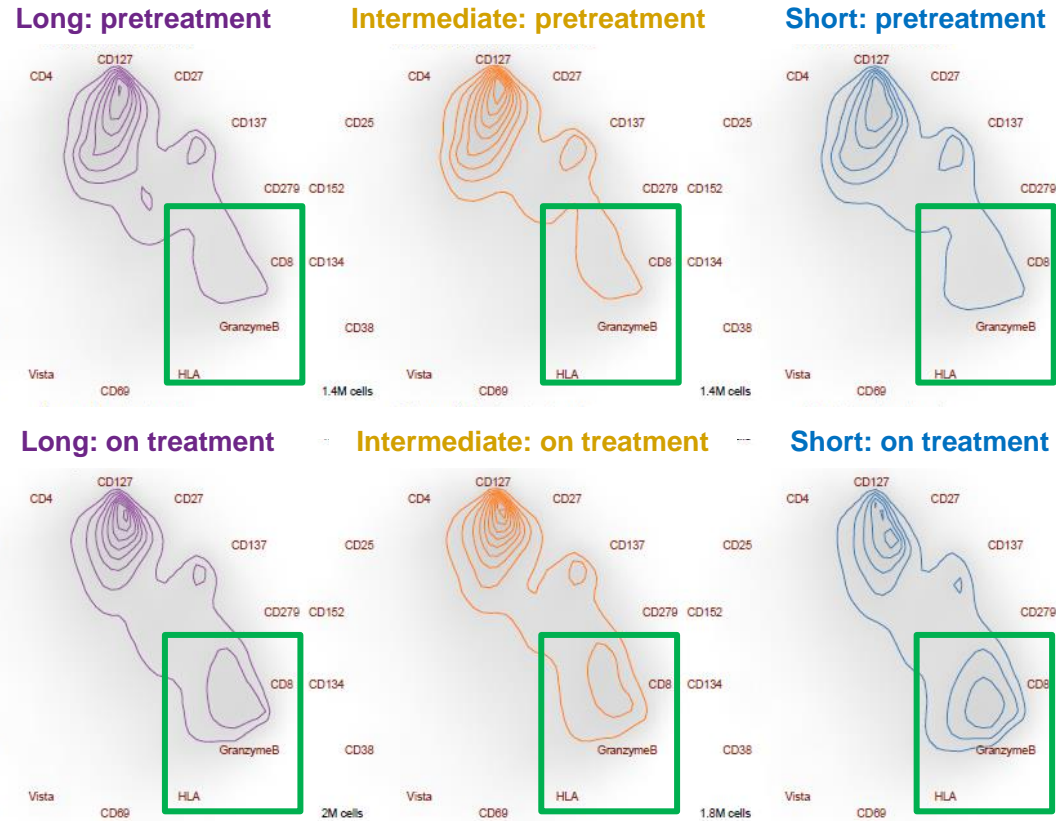
Long: on treatment



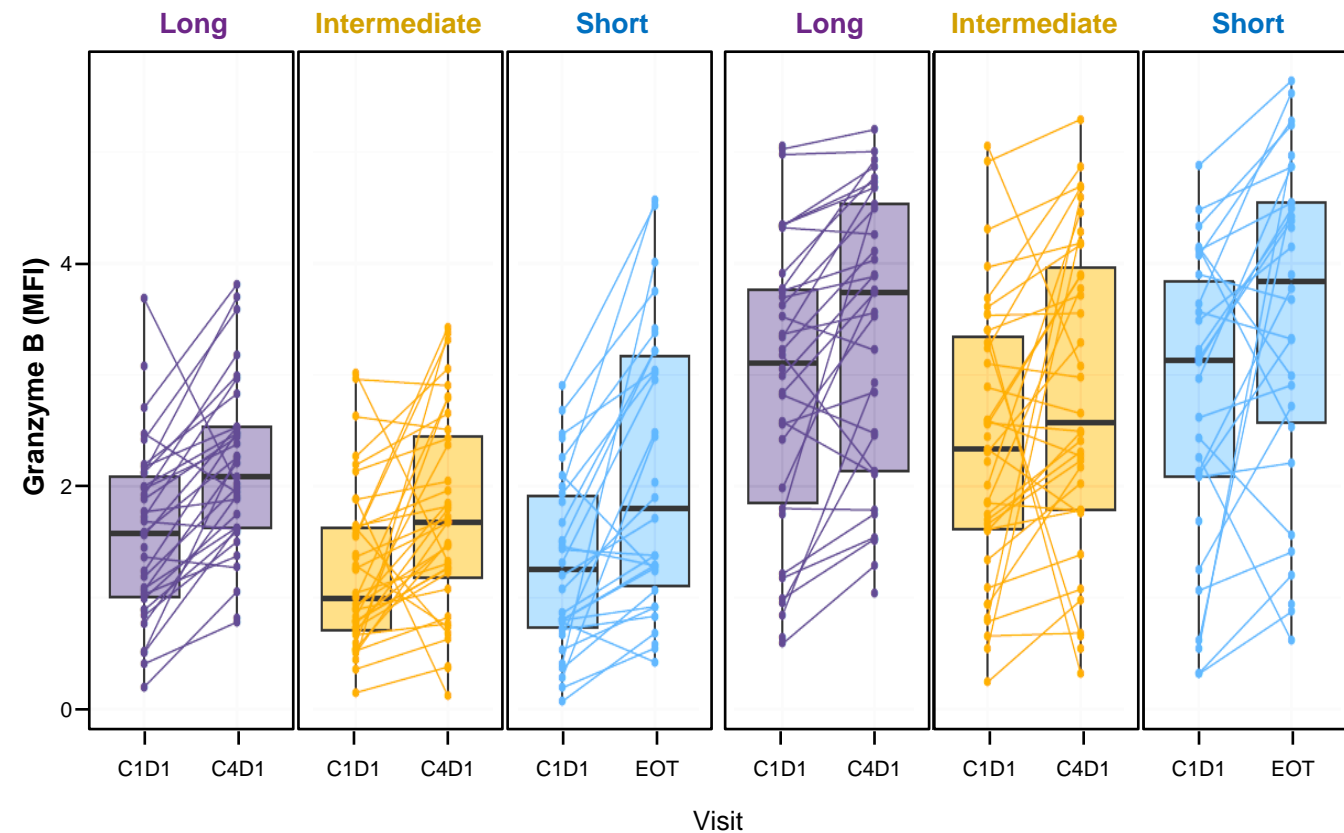
**Expanded T cells have an activated phenotype**

# T-cell Activation and Functionality: Increase in Granzyme B

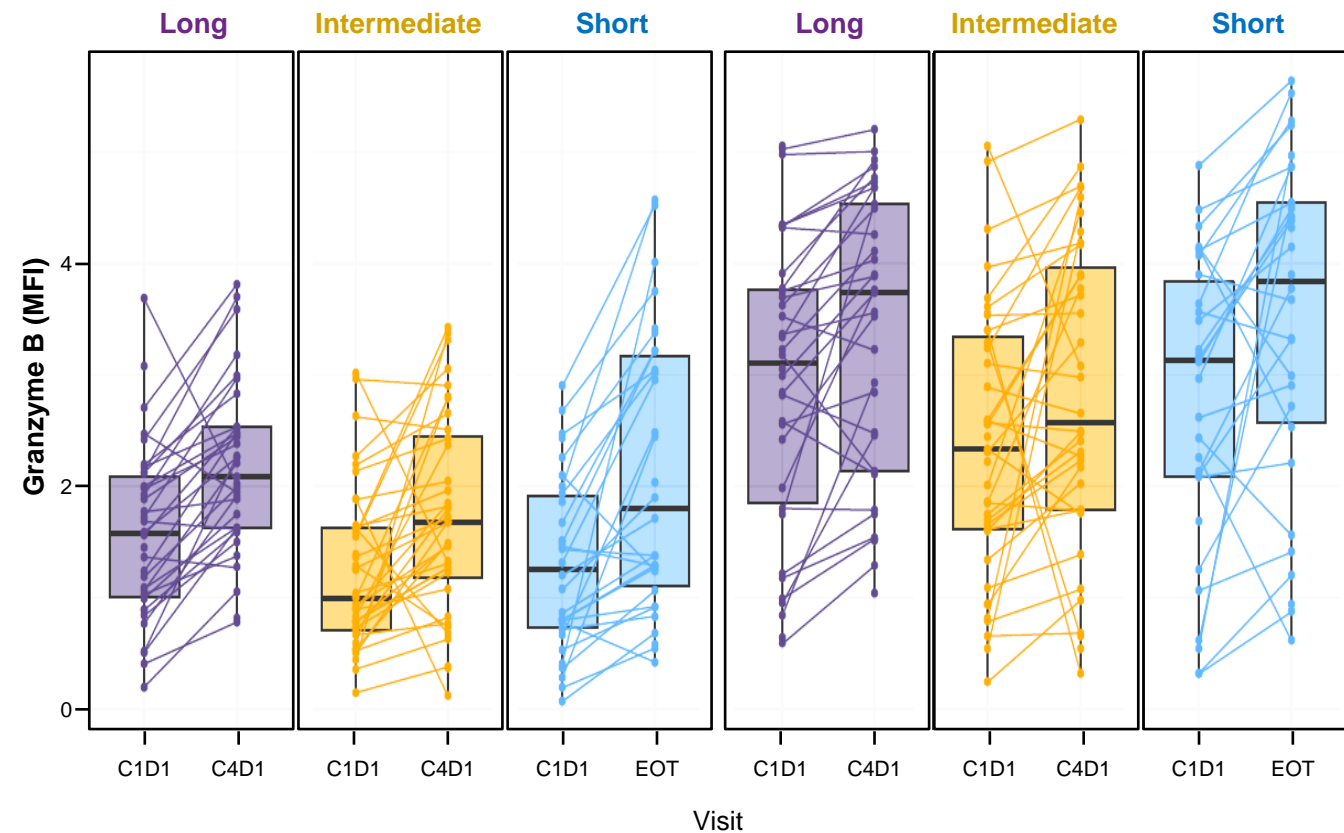
## Total T cells



## Central memory CD8 T cells



## Effector memory CD8 T cells



**Expanded T cells have an activated phenotype**

# Conclusions

- First application of CyTOF in a global SMM clinical trial
- Daratumumab administration across the 3 treatment arms induced:
  - T-cell profile changes
    - Expansion of total CD8 and effector memory CD8 T cells
    - Increased expression of activation markers in total T cells and in effector memory and central memory CD8 T cells
    - Depletion of suppressive immune cell populations
  - Immunomodulation that persists for  $\geq 6$  months on monotherapy

**This study builds upon the immunomodulatory activity of daratumumab in asymptomatic myeloma**

- ## CENTAURUS
- 11 countries