Daratumumab: Uncovering a novel mechanism of action for an approved antibody therapy

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CD38 is ubiquitously expressed in Myeloma (on plasma cells and also other immune cells)

- Transmembrane receptor with enzymatic activity: produces cADPR and NAADP
- Regulates cellular calcium signaling
- Contributes to leukocyte “rolling” along endothelium: CD31 is the ligand for CD38
- Highly expressed in myeloma and other heme malignancies → good target antigen
Tumor specific Mechanisms of Action of Daratumumab in the Bone Marrow Microenvironment

- Human IgG1κ monoclonal antibody
  - Complement-dependent cytotoxicity (CDC)
  - Antibody-dependent cell-mediated cytotoxicity (ADCC)
  - Antibody-dependent cell-mediated phagocytosis (ADCP)
  - Induction of apoptosis
  - Modulation of cellular enzymatic activities associated with calcium mobilization and signaling

Combination of these activities leads to elimination of plasma cells from bone marrow in MM patients

Daratumumab was approved for treatment of relapsed/refractory myeloma, based on ph2 study.

Daratumumab + SOC significantly improves PFS above SOC alone in relapsed myeloma (ph3 studies CASTOR and POLLUX)

**POLLUX**
- Median (range) follow-up: 17.3 (0-24.5) months
- **Median PFS**
  - DRd: not reached; Rd: 17.5 months
  - HR: 0.37 (95% CI, 0.28-0.50; P <0.0001)

**CASTOR**
- Median (range) follow-up: 13.0 (0-21.3) months
- **Median PFS**
  - DVd: not reached; Vd: 7.1 months
  - HR: 0.33 (95% CI, 0.26-0.43; P <0.0001)
Daratumumab added to SOC results in > 4 fold increase in minimal residual disease negative (MRD-) rates (CASTOR and POLLUX ph3 trials)

A. POLLUX  
B. CASTOR

Evaluating the mechanism of action (MOA) in the clinic

**SIRIUS Clinical study**

**GEN501p2 Clinical study**

Daratumumab treatment increases CD8+ T cells in the periphery and the bone marrow

Dara reduces CD38+Tregs in periphery and marrow

Pre-treatment

CD38+ Treg

Post-1st Dara infusion

Tregs (CD3+CD4+CD25+CD127dim)

Dara also depletes CD38+ MDSC and regulatory B cells

Regulation of immune responses by different immunosuppressive cell populations

**Myeloid DerivedSuppressor Cells**

- CD8^+ cells
- CD4^+ cells
- Arginase 1, iNOS
- ROS, Cysteine
- TGF-β, Arginase 1
- MDSC
- MACROPHAGES
- NK cells
- NKG2D, IFN-γ
- IL-10

**Regulatory T Cells**

- Treg
- Metabolic disruption
- Cell-cell contact-mediated inhibition
- IL-10
- TGF-β, IL-35

**Regulatory B Cells**

- Breg
- Th1, IL-17
- Th1, IL-10
- Th1, IL-35
- Th1, IL-10
- Foxp3, Treg
- Cytotoxic T cells
- iNKT cells
- IL-10

References:

- Front. Oncol., 26 June 2013
- Front. Immunol., 19 June 2013
- Immunity, Volume 42, Issue 4, 2015, 607–612
Dara monotherapy treatment increased T-cell clonality (evaluated by TCR sequencing)

Responders (R) (≥PR) had increased clonality compared to Non-responders (NR)

T cell clonality significantly increased with DRd, but not with Rd

Significant increase in clonality in DRd treatment arm ($P = 3.00 \times 10^{-12}$)

No significant increase in clonality in Rd arm ($P = 0.665$)


Significant increases in clonality in patients treated with DRd compared to Rd alone ($P = 3.26 \times 10^{-10}$)

Median of TCR$\beta$ clonality score was 0.166 at baseline and increased to 0.263 at Cycle 3 in DRd arm.
Baseline T cell richness (diversity) correlates with PFS in DRd arm, but not Rd arm

Deep immune phenotype characterization: CyTOF (cytometry by time-of-flight)

Clinical trials samples have been collected for relapsed patients on monotherapy and combination treatments (SIRIUS, CASTOR, POLLUX). (peripheral)
CyTOF demonstrates changes in immune cell populations with Dara treatment

Daratumumab mediated T cell expansion is accompanied by increased Granzyme B production

Daratumumab reduced CD38+ immune suppressive cells, increased CD8+ T cell counts and T cell clonality

Could targeting CD38+ immune suppressive cells be a therapeutic approach in solid tumors?

**Daratumumab as an IO agent?**

**Hypothesis:** Malignancies (including solid tumors) with high levels of CD38\textsuperscript{high} immunosuppressive cells will be responsive to the combination of daratumumab with IO therapeutics and lead to improved clinical responses.
Emerging Data indicates CD38 could be a target in solid tumors

• Regulatory T cells, Regulatory B cells, MDSC are known to contribute to solid tumor progression and are therapeutic targets of interest for immunotherapy

• Recent data published or presented in meetings:
  • CD38 may be a target in NSCLC since it is expressed in ~20% of tumors and is increased in PD1 resistance.
  • In NSCLC mouse models, CD38 inhibition alone was able to reduce lung tumor growth, and combinations of CD38 and PDL1 inhibition were synergistic
  • In CLL, Daratumumab Decreases Treg-Mediated Immunosuppression and Potentiates CD8+ T-Cell-Induced Killing of Chronic Lymphocytic Leukemia (CLL) Cells Ex Vivo

• Current clinical trials testing whether Daratumumab could improve clinical response in solid tumors
  • Janssen NSCLC trial: Daratumumab in combination with Pembro in NSCLC
  • BMS mixed solid tumor trial: Daratumumab in combination with Nivolumab in solid tumors

Chen, Abstract #79, ASCO-SITC 2017
Translational Research spans drug development and can contribute novel scientific understanding of the therapy

The role of Translational Research.....

- Confirms proposed mechanism of action, evaluates novel mechanisms of action in clinical setting
- Identifies potential pharmacodynamic (PD) biomarkers to help select appropriate clinical dose
- Identifies potential predictive biomarkers
- Develops complementary and companion diagnostics
- Evaluates potential novel therapeutic combinations
- Determines resistance mechanisms
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