CD38: from the lab to the clinic and back again

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Immuno-therapy in multiple myeloma

**Immunotherapy**

- **Active**
  - Designed to act on the immune system itself
    - I-O therapies
      - Immune effector cell modulators
        - Checkpoint Inhibitors
        - Co-stimulatory agonists
    - Therapeutic cancer vaccines
      - Cell-based
        - DC-based cancer vaccines
      - Single antigen/peptide-based
    - Unspecific
      - Cytokines
        - Interleukins
        - Interferons
      - IMiDs
  - Therapeutic cancer vaccines
    - Single antigen/peptide-based
      - Tumor-directed mAbs
        - Anti-CD38
      - Tumor-directed mAbs
    - Adoptive cell therapies
      - Adoptive T-cell therapy

**Passive**
- Designed to act on the tumor
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      - Anti-CD38
  - Cell therapies
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DC, dendritic cell; IMiD, immunomodulatory agent; I-O, immuno-oncology; mAb, monoclonal antibody.

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CD38 as a Therapeutic Target

- High expression on myeloma cells combined with its role in cell signaling suggested CD38 as a potential therapeutic antibody target for treatment of multiple myeloma (MM)

Generation of the first CD38 mAb for MM

- Human Ig transgenic mice were immunized with recombinant CD38 protein and CD38-transfected NIH 3T3 cells
- Generation of hybridomas (fusion of mice spleen/lymph node cells with SP2/0 MM cells)
- Testing of 42 anti-CD38 mAbs in CDC assays
  → only one mAb was capable to induce CDC
  → this antibody was selected for further testing=daratumumab

Laboratory evaluations → Clinical evaluation
- Phase 1
- Phase 2
- Phase 3

Clinical management
- Activity
- MoA
- Mechanisms of resistance
- MoSynergy
- IRR
- Interference in blood transfusion tests
- Interference in SPEP/IFE

IMWG Criteria (for measurable disease at baseline)

Cohort A 8mg/kg
Cohort B 8mg/kg
Cohort C 8mg/kg
Cohort D 16mg/kg

S - Serum, U - Urine, F - FLC
Mechanisms of action
mAbs targeting cell surface Ags

ADC P

Macrophage

ADCC

NK Cell

Fc Receptor

Lysis

ADC

Myeloma Cell

Direct Effects

Alterations in intracellular signaling
Inhibition of function of growth factor receptors
Inhibition of function of adhesion molecules

Antigen

Signaling Cascades

MAC

C1q

CDC

Cell Death
but, CD38 is rapidly reduced on MM cells, also in patients with deep and durable responses

Bone marrow MM cells

![Bar graph showing MFI CD38 levels over time](Image)

- **Start**
- Inf 10
- PD
- PD +6M

Counts

- Patient 1:
- Patient 2:
- Patient 3:
- Patient 4:

Before start of treatment

During daratumumab treatment before the 10th infusion

At the time of progressive disease
CD38 is rapidly reduced on MM cells also in patients with deep and durable responses.
Does DARA also have other effects?
CD38, also expressed on other cells....
Tregs

Similar observations with Bregs and MDSCs
Decrease in CD38+ Tregs
Functional relevance

Multifactorial mechanism of action

Suppression of CD38+ immune regulatory cells

Enhancement of T-cell responses

Induction of clonal T-cell expansion
Daratumumab: waterfall plot

Best Change in Response Paraprotein from monotherapy study

16 mg/kg: ORR 36%²

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How to improve CD38 mAb monotherapy results → rationale of combinations

Daratumumab-combinations based on preclinical evaluations

- IMID-based
- PI-based
- IMID/PI-based
- +alkylator
- ATRA
- .....
LENALIDOMIDE

DARA and Len: synergistic killing of MM cells from a LEN/Bort-double refractory MM patient

**SCREEN**

**RANDOMIZE**

**DRd (n = 286)**

DARA 16 mg/kg IV: weekly for 8 weeks, then q2w for 16 weeks, then q4w thereafter;
Lenalidomide 25 mg PO: d 1–21 per cycle;
Dexamethasone 40 mg PO: weekly

**Rd (n = 283)**

Lenalidomide 25 mg PO: d 1–21 per cycle;
Dexamethasone 40 mg PO: weekly

**Cycles:** 28 days

**Key eligibility criteria**

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

**Stratification factors**

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

**Primary endpoint**

- PFS

**Secondary endpoints**

- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

**Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg<sup>a</sup>, paracetamol, and an antihistamine**

<sup>a</sup>On daratumumab dosing days, dexamethasone was administered 20 mg premed on Day 1 and 20 mg on Day 2; DRd, daratumumab, lenalidomide, and dexamethasone; SC, subcutaneous; q2w, every 2 weeks; q4w, every 4 weeks; Rd, lenalidomide and dexamethasone. Dimopoulos et al. Presented at EHA 2016 (Abstract LB2238), oral presentation. Dimopoulos MA, et al. N Engl J Med 2016;375:1319-1331.
POLLUX: Efficacy in the 1 to 3 prior lines subgroup

**18-month PFS**
- DRd: 77%
- Rd: 50%

Median: 18.4 months

HR: 0.36 (95% CI, 0.26-0.49; \(P < 0.0001\))

Responses continue to deepen in the DRd group with longer follow-up
Determinants of response
Determinants of efficacy:
Patients treated in GEN501 or Sirius

\[ P = 0.005 \]

\( MFI \text{ CD38} \)

Complement inhibitors

**PR**

- CD46
- CD55
- CD59

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<tr>
<th>MFI</th>
<th>Start</th>
<th>Inf 10</th>
<th>PD</th>
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<tr>
<td>CD46</td>
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**NS**

- Start Inf 10 PD
ATRA upregulates CD38 expression on MM cells

DARA PLUS ATRA

DARA PLUS ATRA

DARA + ATRA at the time of Progressive Disease

![Bar chart showing MFI CD38, CD55, and CD59 levels at different time points.](chart.png)
DARA PLUS ATRA

- Phase 1/2 study of ATRA + DARA in patients who do not respond to daratumumab as single agent or who progress during daratumumab therapy

1. SCHEME OF STUDY

Registration

Part A
Daratumumab (16 mg/kg):
Weekly for 8 wks, then Q2W for 16 wks, then Q4W thereafter

Progressive disease after cycle 1, less than MR after cycle 2, less than PR after cycle 3, or progression during daratumumab therapy after previous response, then proceed to Part B

Part B
Daratumumab (16 mg/kg):
Weekly for 8 wks, then Q2W for 16 wks, then Q4W thereafter

ATRA: 15-45 mg/m² in two doses per day, starting the morning two days before the daratumumab infusion (days -2, -1, and 0; day 0 is the day of daratumumab infusion; 6 gifts)

https://clinicaltrials.gov/ct2/show/NCT02751255?term=ATRA+daratumumab&rank=1
DARA-NIVO study: RRMM
starting Q2 2017

- Anti-CD38: Daratumumab
- Anti-PD1: Nivolumab
- IMID: Lenalidomide
- Steroid: Dexamethasone
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- Phase 3 ➞ Clinical management

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S: Serum, U: Urine, F: FLC
Infusion reactions with DARA

Percentiles of patients with worst IRR grade per infusion
GEN501p2 - MMY2002, 16 mg/kg

1st Infusion 2nd Infusion Subsequent Infusions
DIRA

![Image of a graph showing the effects of Daratumumab and Anti-Daratumumab on a complex experiment result. The graph indicates the concentrations of Daratumumab and Anti-Daratumumab in milligrams per milliliter (mg/mL) and the outcomes labeled as + or - for different conditions. The graph suggests the presence of a complex interaction between the two substances.](image-url)
Laboratory evaluations → Clinical evaluation
- Phase 1
- Phase 2
- Phase 3

Clinical management

- Activity
- MoA
- Mechanisms of resistance
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- IRR
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