DARATUMUMAB

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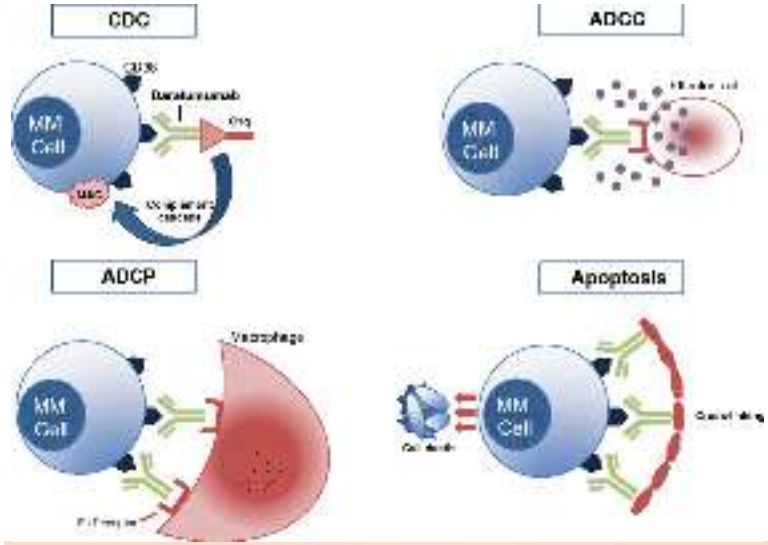
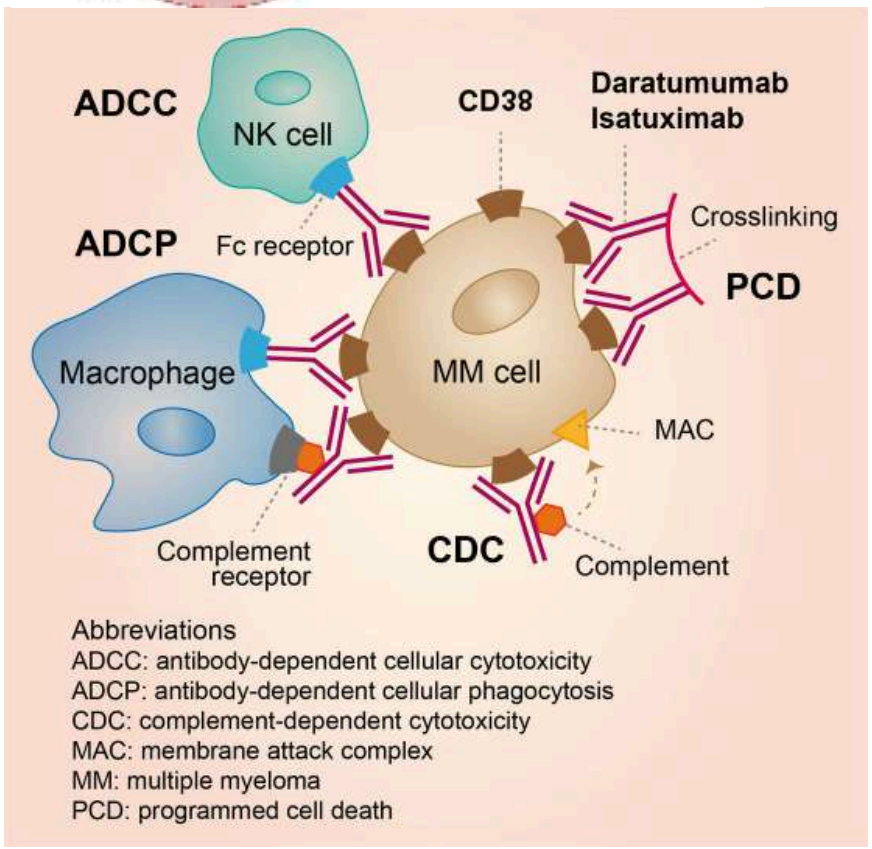
INTRODUCTION

- CD38 is a transmembrane glycoprotein expressed at high levels on plasma cells and NK cells.
- Daratumumab, a humanized Ig G1-kappa, targets CD38 on plasma and NK cells, is an approved treatment for multiple myeloma and for autoimmune diseases.
- New role in desensitization and chronic active ABMR.[needs more RCTs].
- Daratumumab reduced total and activated NK cells, which play a role in ABMR.





MECHANISM OF ACTION

The therapeutic effects of daratumumab in multiple myeloma are mainly based on the mechanism that daratumumab binds to CD38 expressed on the surface of multiple myeloma cells to induce rapid cell death of multiple myeloma cells through complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), apoptosis upon secondary crosslinking, and immunomodulatory effects via a decrease in immune suppressive cells.

Daratumumab Reduces Risk of Progression in High-Risk Smoldering Multiple Myeloma

SMOLDERING MULTIPLE MYELOMA: does daratumumab slow progression to active disease?

Randomized Controlled Trial

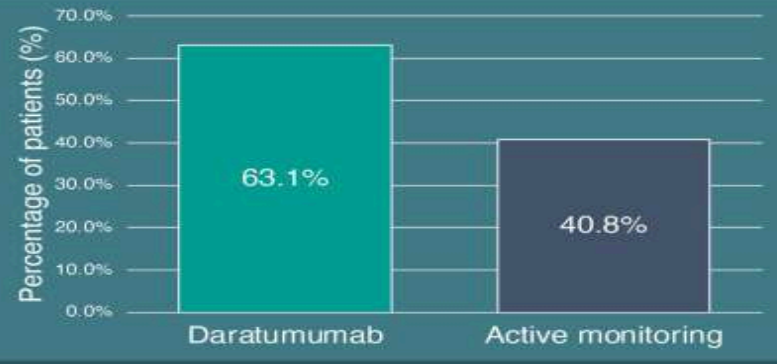
Active monitoring
Continued for 36 months or until confirmation of disease progression

390 patients with high-risk smoldering multiple myeloma randomized in a 1:1 ratio

Daratumumab
1800 mg subcutaneous monotherapy for 39 cycles

PRIMARY OUTCOMES

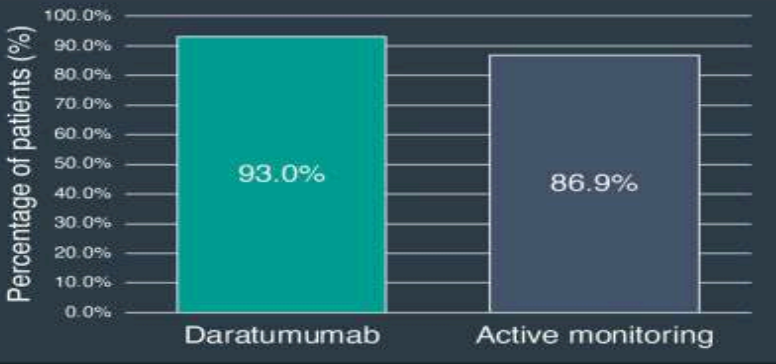
Progression-free survival at 5 years



Hazard ratio 0.49 95% CI, 0.36-0.67 $p < 0.001$

SECONDARY OUTCOMES

Overall survival at 5 years



Hazard ratio 0.52 95% CI, 0.27-0.98

Subcutaneous daratumumab monotherapy led to significantly lower risk of progression to active multiple myeloma or death among patients with smoldering multiple myeloma.

Dimopoulos, *et al. NEJM*. December 9, 2024.

Anti-CD38 Daratumumab Treatment of Chronic Active Antibody-mediated Kidney Allograft Rejection

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Study Design & Cohort

Retrospective Review

Adult KTR
Feb 2022 – Aug 2023

KTR with cABMR diagnosed > 6 months post-transplant

Monitored Outcomes:
eGFR, uACR, dd-cfDNA, DSA, renal biopsy, adverse events

Intervention

Subcutaneous Daratumumab

Flat dose 1,800 mg

Weekly for 4 weeks, followed by 3 quarterly doses

Findings

N=16
Adults with KTR diagnosed with cABMR
Median time transplant to treatment = 9 years

Biopsy Histology, 10 months After Treatment

13/16 showed improved microvascular inflammation scores

8/16 showed ABMR score decline (median ↓74%)

eGFR levels remained stable

11/16 showed uACR improvement

dd-cfDNA significantly decreased (median ↓85%)

eGFR, estimated glomerular filtration rate; uACR, urine albumin/creatinine ratio; DSA, donor-specific antibody

KI REPORTS
Kidney International Reports

Lye WC et al, 2025

Visual abstract by:
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Conclusion Subcutaneous daratumumab may be an effective treatment for chronic active antibody-mediated rejection (cABMR); larger randomized trials are warranted to study its role in the treatment for cABMR in kidney transplant recipients (KTR). Donor-derived cell-free (dd-cfDNA) may be a useful monitoring tool to predict and detect relapses.

Table 1 Daratumumab Premedication Protocol Used at Cedars-Sinai Medical Center Before This Study

Administer the following medications 1-3 hours before every infusion of daratumumab:

Acetaminophen 650 mg, orally

Diphenhydramine 50 mg, via intravenous push

Dexamethasone 20 mg, given intravenously before first infusion, then orally for subsequent infusions, if tolerated

Montelukast 10 mg, orally, before the first infusion only

Famotidine 20 mg, intravenously, before the first infusion only

Patients newly diagnosed with MM

Patients eligible for SCT

Induction therapy

- Proteasome inhibitors
  - Bortezomib
- Corticosteroids
  - Dexamethasone
- Alkylating agents
  - Melphalan, cyclophosphamide, bendamustine
- Anthracyclines
  - Doxorubicin

Patients not eligible for SCT

High-dose therapy

- Immunomodulators
  - Lenalidomide, thalidomide
- Proteasome inhibitors
  - Bortezomib
- Corticosteroids
  - Prednisone
- Alkylating agents
  - Melphalan, bendamustine
- Anthracyclines
  - Doxorubicin

Patients with relapsed and/or refractory MM

- Immunomodulators
  - Lenalidomide, pomalidomide
- Proteasome inhibitors
  - Bortezomib, carfilzomib, ixazomib
- Corticosteroids
  - Dexamethasone
- Monoclonal antibodies
  - Daratumumab, elotuzumab
- Histone deacetylase inhibitors
  - Panobinostat

Emerging therapies in ABMR