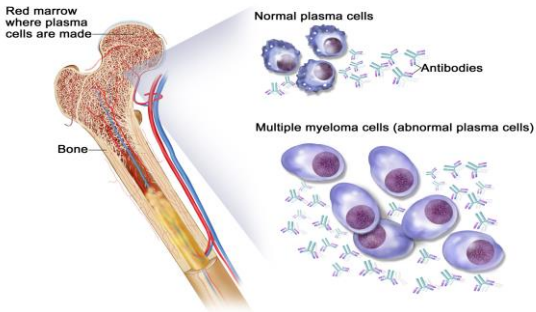




Daratumumab: An Overview, and Methods to Mitigate Interference With Patient Testing

William Crews M.D.
Medical Director, Laboratory Services

Multiple Myeloma



<http://www.cancer.gov/types/myeloma>



Statistics—Multiple Myeloma

- **Highly treatable but rarely curable**
 - Median age at diagnosis – 69 years
 - 1.6% of new cancer cases in U.S.
 - 5-year survival rate - 47% (current)
 - 5-year survival rate - 31% (1999)
- **2016 (Estimated)**
 - New diagnoses-30,000
 - Deaths-12,600

cancer.gov



Treatment Options—Multiple Myeloma

• **Immunomodulatory agents**

- Thalidomide (Immunoprin)
- Lenalidomide (Revlimid)

• **Proteasome Inhibitors**

- Bortezomib (Velcade)
- Carfilzomib (Kyprolis)

• **Stem Cell Transplantation**

- Autologous
- Allogeneic



Treatment Options—Multiple Myeloma

• **Monoclonal Ab**

- Daratumumab (Darzalex) Nov 2015
- Elotuzumab (Empliciti) Nov 2015



Future Monoclonal Antibodies

• **Clinical Testing/Research Phase**

- Isatuximab (anti-CD38)
- MOR202 (anti-CD38)

• **Preclinical/Development**

- Ab79
- Ab19



Daratumumab

The Journal of Immunology

Daratumumab, a Novel Therapeutic Human CD38 Monoclonal Antibody, Induces Killing of Multiple Myeloma and Other Hematological Tumors

Michel de Weers,^{1*} Yu-Tzu Tai,^{1,2} Michael S. van der Veer,³ Joost M. Bakker,⁴ Tom Vink,⁵ Danielle C. H. Jacobs,⁶ Lukas A. Oomen,⁷ Matthias Prepp,⁸ Thomas Valerius,¹ Jerry W. Shottstra,¹ Tuna Mutis,³ Wim K. Bleeker,⁹ Kenneth C. Anderson,^{1,2} Henk M. Lokhorst,¹ Jan G. J. van de Winkel,^{1,10*} and Paul W. H. I. Parren⁶

The Journal of Immunology, 2011, 186:1840-1848



Daratumumab

• **Aliases**

- Darazalex
- DARA

• **Indication**

- Single use agent
- Received ≥3 prior therapies
- Failed at least one IM therapy and one PI therapy



DARA Mechanism of action

• **Binds to CD38**

• **Induces cell death in MM cells by:**

- Complement dependent cytotoxicity (CDC)
- Ab-Dependent Cellular Cytotoxicity (ADCC)
- Apoptosis

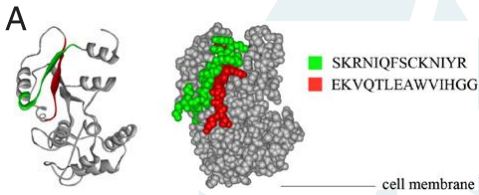


CD38

- **Type II transmembrane glycoprotein**
 - 20aa cytoplasmic tail
 - 256aa extracellular domain
- **Function**
 - Receptor-mediated adhesion and signaling events
 - Enzymatic activities (intracellular calcium mobilization)
- **Overexpressed in MM cells**



CD38



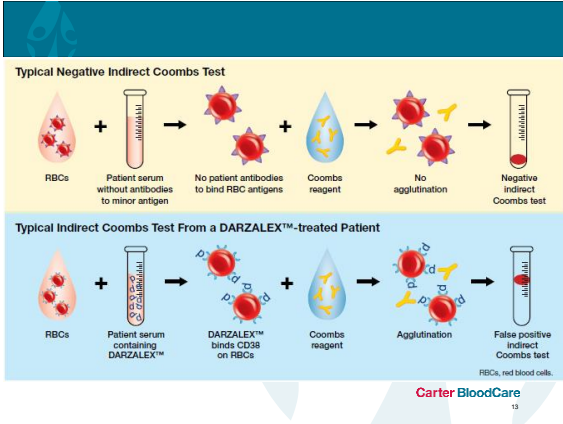
NEW METHODS AND APPROACHES

Resolving the daratumumab interference with blood compatibility testing

Claudia I. Chapuy,¹ Rachel T. Nicholson,¹ Maria D. Aguad,¹ Bjoern Chapuy,² Jacob P. Laubach,² Paul G. Richardson,² Parul Doshi,³ and Richard M. Kaufman¹

Volume 55, June 2015 TRANSFUSION 1545





DARA Clinical Interference

- SPEP
- IFE
- FC
- Blood compatibility testing

Carter BloodCare 14

Advancing Transfusion and Cellular Therapies Worldwide

Association Bulletin #16-02

DARZALEX
(daratumumab)
injection for intravenous infusion
100 mg/50 mL, 400 mg/200 mL

Understanding DARZALEX™ Interference with Blood Compatibility Testing

Carter BloodCare
We save lives by making transfusion possible.

To: Transfusion Services Managers

From: Hospital Relations
William Crews, MD
Medical Director of Laboratory Services, Carter BloodCare

Date: January 11, 2016
Re: Update Daratumumab (DARZALEX)

Carter BloodCare 15

Mitigation Techniques

- **Communication**
 - Discuss with Oncology Department
 - Notify if patient is/will receive DARA
- **Denaturation**
 - Dithiothreitol (DTT)
- **Neutralization**
 - CD38
- **Other**
 - cord cells



Mitigation via Denaturation

- **Dithiothreitol (DTT)**
- **Reducing agent**
 - Dissolves disulfide bonds
- **What about trypsin?**



Complication of DTT

- **Denatures Antigen groups**
 - Kell
 - Cartwright
 - Lutheran
 - JMH
 - Raph
 - Dombrock
 - Knops
 - Scianna
 - Indian



Mitigation by Neutralization

- Soluble CD38
- Mouse anti-DARA idiotype antibody



CBC Protocol

- 32 Patients to date
- Prior to receiving DARA
 - T/S
 - Phenotype/Genotype
 - Crossmatched RBCs
- After receiving DARA
 - Blood Type
 - DTT-treated Ab screen
 - K neg or Phenotypically matched RBCs



Phenotype vs Genotype

Phenotype

- Not started DARA
- Sure of transfusion Hx

Genotype

- DARA started
- Hx of recent transfusion
- Adverse reaction/not responding



Summary

- **Daratumumab**
 - Human IgG1 CD38 mAb
 - Binds CD38
 - Effective in killing tumor cells via multiple MOA
- **Mitigation allows for safe transfusion of patients**
- **Will likely see additional CD38 mAbs in future**

