Monoclonal Antibodies in Multiple Myeloma

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Objectives

- Identify monoclonal antibodies approved for treatment of multiple myeloma
- Evaluate combination chemotherapy / monoclonal antibody treatment regimens approved for treatment of multiple myeloma

Audience Response Question

How often are you involved in care involving patients with multiple myeloma?

1) Never
2) A few per month
3) Every week
4) I should be giving this presentation I do it so much

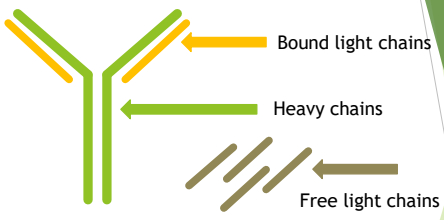
Multiple myeloma (MM)

- Plasma cell neoplasm
  - Monoclonal protein (M protein)
- 2018 US estimated statistics
  - 30,770 new cases
  - 12,770 deaths

Monoclonal gammopathy of undetermined significance (MGUS) → Asymptomatic multiple myeloma (smoldering) → Multiple myeloma

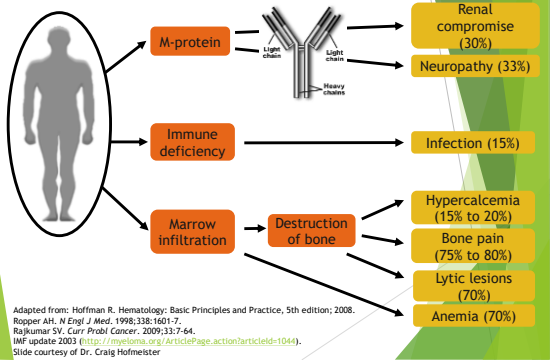
Plasma cell neoplasms. March 16, 2018. Available at: www.cancer.gov/types/myeloma/hp/myeloma-treatment-pdq

Plasma Cell → Immunoglobulins



- Serum / urine protein electrophoresis (SPEP)
- Immunofixation (IFIX)
- Serum free light chains
- Quantitative immunoglobulins (IgG, IgM, IgA)

Clinical Manifestations



Adapted from: Hoffman R. Hematology: Basic Principles and Practice, 5th edition; 2008.
Ropper AH. *N Engl J Med*. 1998;338:1601-7.
Rajkumar SV. *Curr Probl Cancer*. 2009;33:7-64.
IMF update 2003 (http://myeloma.org/ArticlePage.action?articleId=1044).
Slide courtesy of Dr. Craig Hofmeister

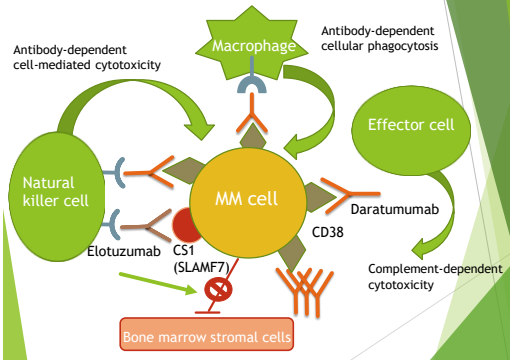
Monoclonal antibodies in MM

Graph blocked

ADCC – Antibody-dependent cell-mediated cytotoxicity
NK – Natural killer
ADCP – Antibody-dependent cellular phagocytosis
CDC – Complement-dependent cytotoxicity

van de Donk, NW. *Blood* 2016;127(6):681-95.

Mechanism of action



Adapted from Afifi S. *Ann Pharmacother* 2016;50(7):555-68.

Audience Response Question

Elotuzumab is approved for patients with multiple myeloma who have received 1 to 3 prior lines of therapy in combination with:

1) Bortezomib
2) Lenalidomide
3) Pomalidomide
4) Ixazomib

Elotuzumab ELOQUENT-2

- In combination with lenalidomide and dexamethasone in patients with 1 to 3 prior therapies
- Phase 3, open-label, multicenter trial, N = 646
  - Relapsed, refractory MM defined as 1 to 3 prior therapies
- Elotuzumab + lenalidomide + dexamethasone vs lenalidomide + dexamethasone
  - CrCl ≥ 30 ml/min
  - 6% of total population previous exposure to lenalidomide

	Cycles 1 and 2 28 day cycle				Cycles 3+ 28 day cycle			
Day of cycle	1	8	15	22	1	8	15	22
Elotuzumab 10 mg/kg IV	X	X	X	X	X	X	X	X
Lenalidomide 25 mg PO	Days 1-21				Days 1-21			
Dexamethasone PO	28	28	28	28	28	40	28	40
Dexamethasone IV	8	8	8	8	8	X	8	X

Lonial S *et al.* NEJM 2015;373(7):621-31.

Elotuzumab

- Median follow up 24.5 months
- Co-primary end points
  - Progression free survival (PFS) at 1 year: **19.4** months with elotuzumab vs **14.9** months without (P < 0.001)
  - Overall response rate 79% with elotuzumab vs 66% without (P < 0.001)
- 3 year follow up data PFS

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Lonial S *et al.* NEJM 2015;373(7):621-31.
Dimopoulos MA *et al.* BJH 2017;178:896-905.

Elotuzumab

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Lonial S *et al.* NEJM 2015;373(7):621-31.

Daratumumab single agent – SIRIUS

- As monotherapy in previously treated MM with at least 3 prior lines of therapy including proteasome inhibitor (PI) and immunomodulatory agent (IMID) or who are double refractory to PI and IMID
- Phase I/II, open label, multicenter trial
- Phase II dosing = **16 mg/kg IV** (N = 106)
  - 82% >3 prior lines of therapy (median – 5)
  - 80% previous stem cell transplant
- Primary endpoint

  Overall response rate (ORR)
- Median time to 1st

  response = 1 month

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Lonial S *et al.* Lancet 2016;387:1551-60.

Daratumumab Bortezomib Dexamethasone - CASTOR

- Daratumumab in combination with bortezomib in patients with MM after 1 prior line of therapy
- Phase 3, randomized, open label, multicenter, N = 498
  - Bortezomib and dexamethasone with and without daratumumab
  - Excluded for disease refractory to bortezomib or refractory to another PI
- Primary endpoint – PFS
- Median prior lines of therapy – 2
  - 67% prior PI
  - 61% prior stem cell transplant
  - ~22% high risk cytogenetics in each arm

Palumbo A *et al.* NEJM 2016;375:754-66.

Daratumumab Bortezomib Dexamethasone

- 12 month PFS **60.7%** with daratumumab vs **26.9%** without
- Median time to 1st response – 0.9 months

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Overall Response	With daratumumab (N = 240)	No daratumumab (N = 234)
# patients	199	148
Rate %	82.9%	63.2%

Palumbo A *et al.* NEJM 2016;375:754-66.

Daratumumab Bortezomib Dexamethasone

- Infusion reactions 45.3%
  - 98% with first dose
  - Dyspnea, bronchospasms, cough

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Palumbo A *et al.* NEJM 2016;375:754-66.

Daratumumab Lenalidomide Dexamethasone - POLLUX

- Daratumumab in combination with lenalidomide in patients with MM after 1 prior line of therapy
- Phase 3, randomized, multicenter, open-label, N = 569
- Lenalidomide and dexamethasone with or without daratumumab
  - Excluded if refractory to lenalidomide, CrCl < 30 ml/min
- Median previous line of therapy – 1
  - 86% previous PI
  - 55% previous IMID / 18% with prior lenalidomide
  - ~15-16% with high risk cytogenetics each arm
  - 63% with prior stem cell transplant

Dimopoulos MA *et al.* NEJM 2016;375:1319-31.

Daratumumab Lenalidomide Dexamethasone

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Dimopoulos MA *et al.* NEJM 2016;375:1319-31.

Daratumumab Lenalidomide Dexamethasone

- Adverse events >10% difference in daratumumab group
  - Neutropenia
  - Diarrhea
  - Upper respiratory tract infection
  - Cough
- Slightly higher rates of infection with daratumumab (28.3% vs 22.8%)
  - Pneumonia most common grade 3/4 infection similar rates both arms
- 47.7% infusion reaction – 92% with first dose
  - 5.3% of infusion reactions grade 3
  - No grade 4

Dimopoulos MA *et al.* NEJM 2016;375:1319-31.

Daratumumab Pomalidomide Dexamethasone - EQUULEUS

- Daratumumab in combination with pomalidomide in patients with MM after 2 prior lines of therapy including a PI and lenalidomide
- Phase 1b, non-randomized, open label, multicenter (N = 103)
- Primary safety endpoint – maximum dose daratumumab in combination with pomalidomide
  - Secondary endpoints – ORR and complete response (CR)
- 76% 3 or more prior lines of therapy (median = 4)
- 74% prior autologous stem cell transplant
- 25% high risk cytogenetics

Chari A *et al.* Blood 2017;130(8):974-81.

Daratumumab Pomalidomide Dexamethasone

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- Higher rate of neutropenia than expected with just pomalidomide/dexamethasone alone
- Similar rates of febrile neutropenia (8%) and grade 3/4 infection (32%)

PR - partial response
VGPR - very good partial response
CR - complete response
sCR - stringent complete response

Chari A *et al.* Blood 2017;130(8):974-81.

Audience Response Question

Daratumumab is approved for newly diagnosed, transplant ineligible patients with multiple myeloma in combination with:

1) Bortezomib
2) Lenalidomide
3) Pomalidomide
4) Bortezomib, melphalan, and prednisone

Daratumumab Bortezomib Melphalan Prednisone - ALCYONE

- Combination approved for newly diagnosed patients with MM, ineligible for stem cell transport
- Phase 3, randomized, multicenter, open-label (N = 706)
- Bortezomib, melphalan, prednisone with or without daratumumab
- Excluded if CrCl > 40 mL/min, peripheral neuropathy
- Primary endpoint – PFS
- 17% in daratumumab arm high risk cytogenetics

Mateos MV *et al.* NEJM 2018;378:518-28.

Daratumumab Bortezomib Melphalan Prednisone

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Mateos MV *et al.* NEJM 2018;378:518-28.

Daratumumab Bortezomib Melphalan Prednisone

Graph blocked

Mateos MV *et al.* NEJM 2018;378:518-28.

Daratumumab Dosing

- As a single agent or in combination with IMiD

Weeks / Cycles Q4 weeks	Schedule
1 - 8 / Cycles 1 and 2	Weekly (8 doses)
9 - 24 / Cycles 3 - 6	Every other week (8 doses)
25+ / Cycle 7+	Once every 4 weeks until progression

- In combination with bortezomib

Weeks / Cycle Q3 weeks	Schedule
1 - 9 / Cycles 1 - 3	Weekly (9 doses)
10 - 24 / Cycles 4 - 8	Once every 3 weeks (5 doses)
25+ / Cycle 9+	Once every 4 weeks until progression

- In combination with bortezomib, melphalan, prednisone

Weeks / Cycle Q6 weeks	Schedule
1 - 6 / Cycle 1	Weekly (6 doses)
7 - 54 / Cycles 2 - 9	Once every 3 weeks (16 doses)
25+ / Cycle 10+	Once every 4 weeks until progression

Daratumumab [package insert]: Horsham, PA: Janssen Biotech; 2018

Audience Response Question

Patients on daratumumab or elotuzmab need herpes zoster (shingles) prophylaxis?

1) Yes
2) No
3) The only thing I care about is infusion reactions

Pearls

- Shingles prophylaxis
  - Acyclovir or valacyclovir
  - Daratumumab specifies within 1 week of initiation and **3 months after**
- Pre-medications
  - Include montelukast for initial daratumumab infusions
  - Give 1 hour prior to start of infusions
- Infusion rate escalation

Daratumumab

	Dilution volume	Initial rate (first hour)	Rate increment*	Maximum rate
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion†	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions‡	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

~3.5 hour infusion

Elotuzumab

Cycle 1, Dose 1		Cycle 1, Dose 2		Cycle 1, Dose 3 and 4 and All Subsequent Cycles
Time Interval	Rate	Time Interval	Rate	Rate
0-30 min	0.5 mL/min	0-30 min	3 mL/min	
30-60 min	1 mL/min	30 min or more	4 mL/min	5 mL/min
60 min or more	2 mL/min	-	-	

~1 hour infusion

Daratumumab [package insert]: Horsham, PA: Janssen Biotech; 2018
Elotuzumab [package insert]: Princeton, NJ: Bristol-Myers Squibb; 2017

Future of Monoclonal Antibodies in MM

- New combinations and first line approvals
- New formulations
  - SQ daratumumab
- New monoclonal antibodies
  - Isatuximab – CD38
  - Siltuximab – IL6 inhibitor
  - There are many more!!!

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