LEUKEMIA & LYMPHOMA SOCIETY®

SPOTLIGHT ON MULTIPLE MYELOMA

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Karmanos Cancer Institute at McLaren Greater Lansing
Lansing, MI

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WELCOMING REMARKS

SPOTLIGHT ON MULTIPLE MYELOMA

Lizette Figueroa-Rivera, MA
Senior Director, Education & Support
The Leukemia & Lymphoma Society
Rye Brook, NY

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WELCOMING REMARKS
SPOTLIGHT ON MULTIPLE MYELOMA



Gregory O. Proctor
Myeloma Patient
Honored Hero, Visionaries of The Year San Antonio
Executive Leadership Team, Light The Night San Antonio
The Bloodline with LLS, Podcast Guest
*Making Good Food Choices, Recipes for Health S*eries, LLS Video Series

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WELCOMING REMARKS
SPOTLIGHT ON MULTIPLE MYELOMA

This program is supported by

Bristol Myers Squibb™ GSK Karyopharm® Therapeutics

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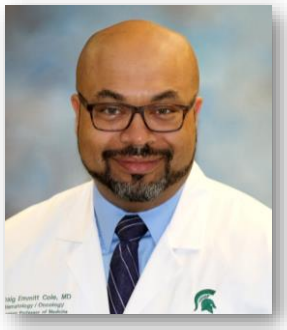
PRESENTATION

SPOTLIGHT ON MULTIPLE MYELOMA



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DISCLOSURES

SPOTLIGHT ON MULTIPLE MYELOMA

Craig Emmitt Cole, MD

- Consultation and Speaking: Sanofi
- Consultation and Speaking: Abbvie
- Consultation and Speaking: Pfizer
- Consultation: Genentech
- Research Support: GlaxoSmithKline

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Today's Discussion

- Multiple Myeloma -101
- How to treat myeloma using new therapies
  - Newly diagnosed myeloma
    - Tools of the trade
    - Side effect management
  - Relapsed Refractory MM
    - CAR T-cell therapy for myeloma
    - Bi-specific antibodies
- Patient empowerment: how to communicate with your doctor
- Questions

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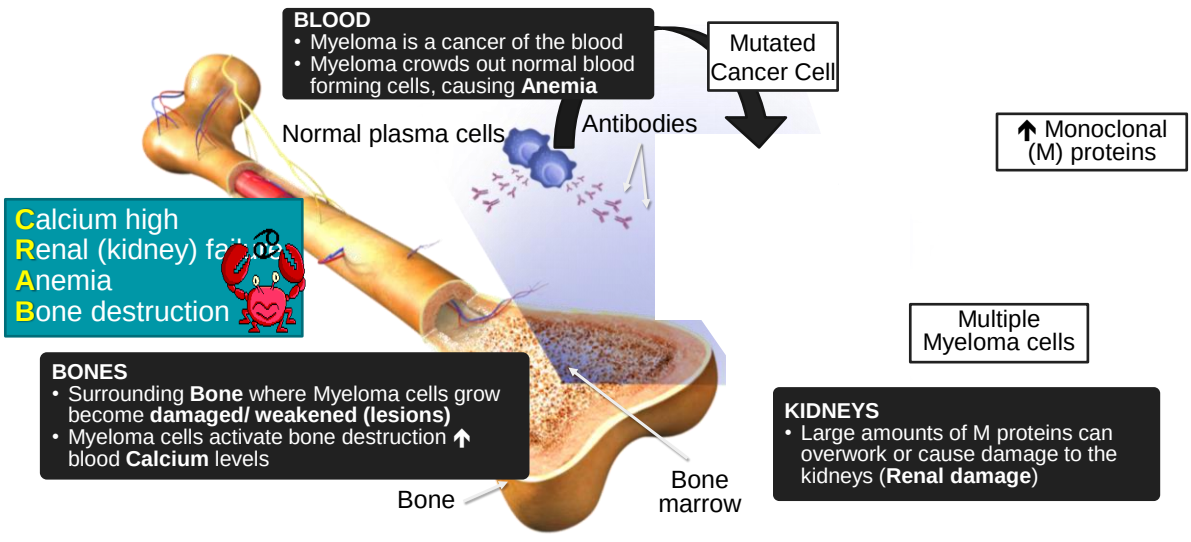
Multiple Myeloma is a Cancer of the Bone Marrow Plasma Cells



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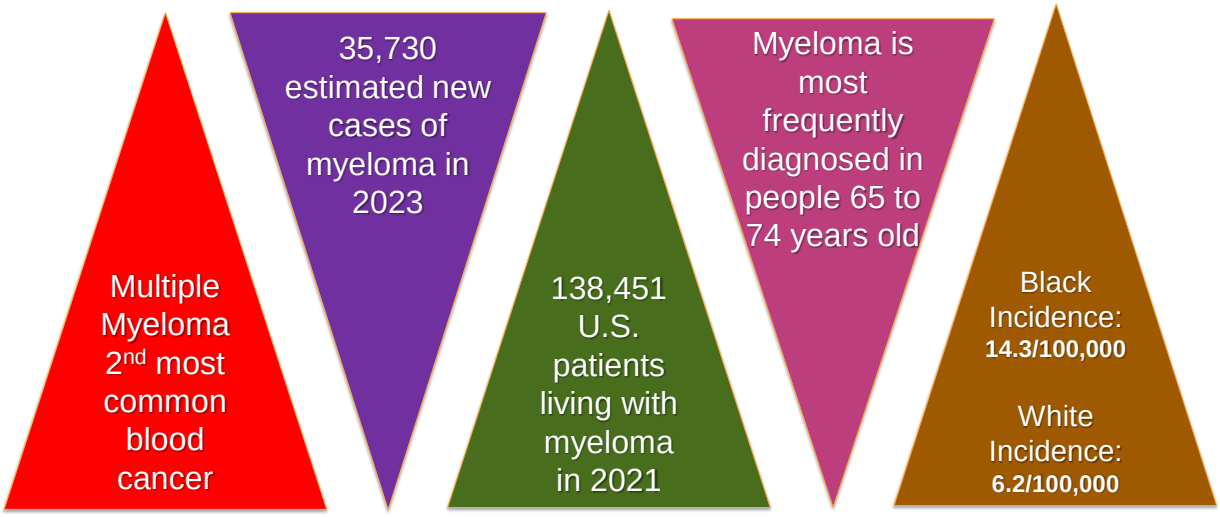
Multiple Myeloma Fast Facts



Leukemia & Lymphoma Society. Facts and Statistics. http://www.lls.org/facts-and-statistics/facts-and-statistics-overview#Myeloma.
SEER Cancer Stat Facts: Myeloma. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/mulmy.html
North American Association of Central Cancer Registries (NAACCR), 2021 http://www.naaccr.org/DataandPublications/CINAPubs.aspx

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Diagnosing Myeloma: Learn Your Labs!

- **CBC** – Number of **red blood cells**, white blood cells, and platelets
- **CoMP** – Measure levels of albumin, **calcium**, and **creatinine**. Assess function of kidney, liver, and **bone status** (alkaline phosphatase) and the extent of disease.
- **Beta2 MicroG** – Determine the level of a protein that indicates the **presence/extent of MM and kidney function**: **USED FOR STAGE**
- **LDH** Lactate Dehydrogenase – Determine the level of myeloma cell **production and extent** of MM : **USED FOR STAGE**
- **Serum Protein EP** – **Detect the presence and level of M protein = *how much myeloma***
- **Immuno Fixation** – **Identify the *type* of abnormal antibody proteins: IgG, IgA, κ,or λ**
- **Serum FreeLight Chain** – **Freelite test measures free light chains (kappa or lambda) in blood = *how much myeloma***
- **Urine Protein EP** – **Detect Bence-Jones proteins (otherwise known as myeloma light chains) in urine (*present or not present*)**
- **24-hr Urine Analysis** – **Determine the presence and levels of M protein and Bence Jones protein in the urine = *how much myeloma***

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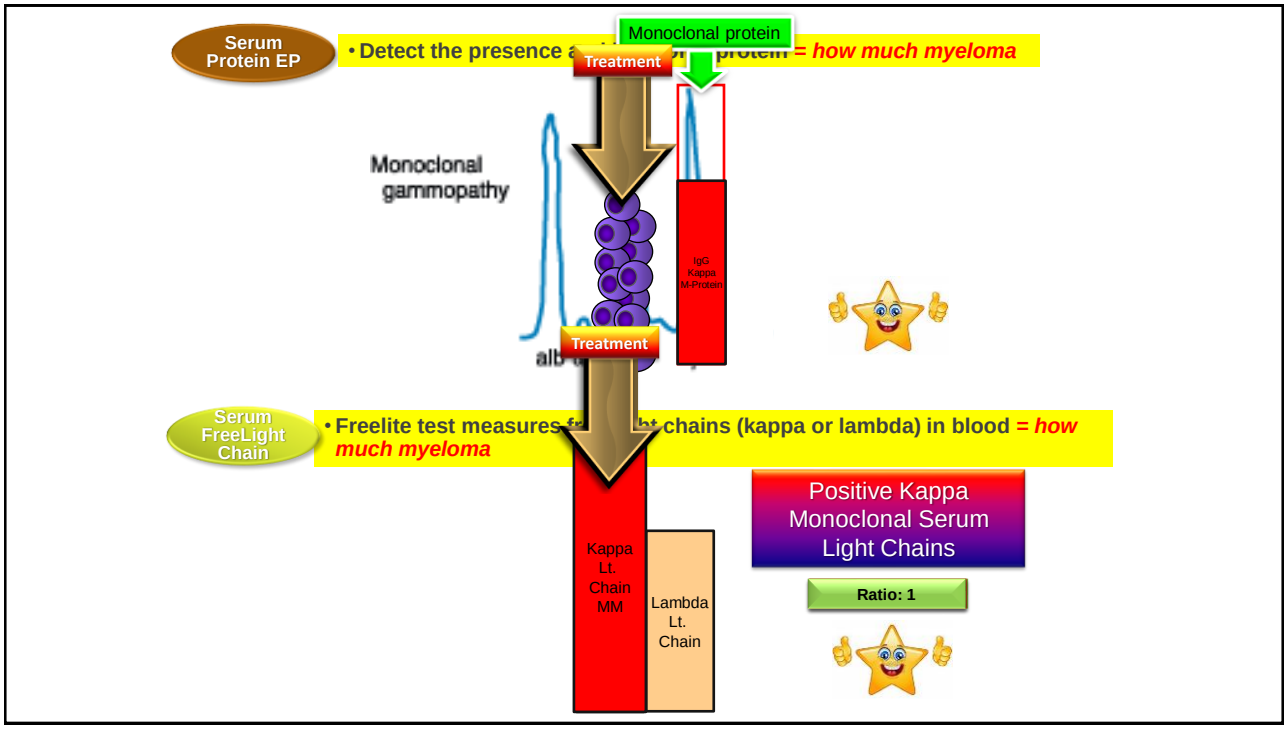

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Diagnosis of Multiple Myeloma

- Conventional X-rays reveal punched-out lytic lesions, osteoporosis, or fractures in 75% of patients.
- FDG PET/CT appears to be more sensitive (85%) than skeletal survey for the detection of small lytic bone lesions.
- Diagnosis is confirmed with bone marrow demonstrating greater than **10% involvement by malignant plasma cells with either CRAB or SLiM**

Malignant Plasma cells seen on biopsy
AND ≥1 "CRAB" feature

C: Calcium elevation (>11 mg/dL)
R: Renal- low kidney function; (serum creatinine >2 mg/dL)
A: Anemia –low red blood count (Hb <10 g/dL)
B: Bone disease (≥1 lytic lesions on skeletal radiography, CT, or PET-CT)

OR have ≥1 SLiM 'high risk" features:

S: >60% Plasma Cells on Bone Marrow biopsy
Li: Serum light chain ratio >100
M: >1 lytic lesions on MRI (or PET/ CT scan)

About 10% to 20% of patients with newly diagnosed myeloma will not have any symptoms.

Kyle RA et al. Mayo Clin Proc Jan;78(1): 2003. Nanni C et al. European Journal of Nuclear Medicine and Molecular Imaging Vol. 33:2006 Dimopoulos MA, et al. Leukemia. *2009*

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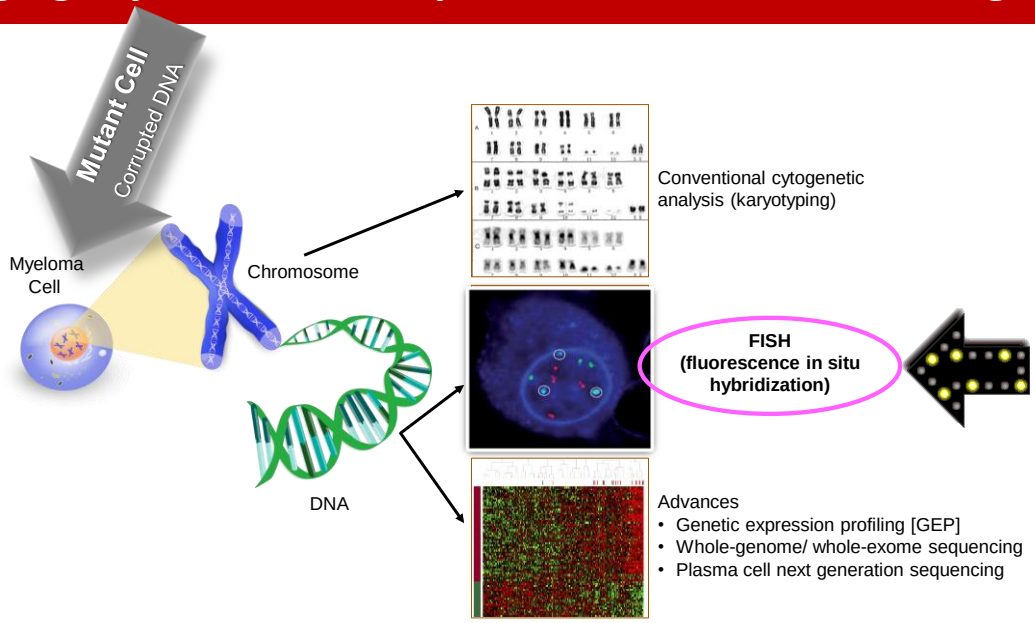
Staging Myeloma: The Importance of Genomic Testing



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Staging Myeloma: FISH Testing helps to Assign Risk in Myeloma

Risk Category	High Risk	Standard Risk
Findings on Chromosome (FISH) Analysis Results in the Bone marrow	**FISH:** • **Deletion 17th chromosome** • **Gain of chromosome 1q** • **Translocation 4 and 14** • **Translocation 14 and 16** • **Translocation 14 and 20** **NGS: p53 mutation** (on chrom 17) • **Double Hit Myeloma: 2 high risk genetic abnormalities** • **Triple Hit Myeloma: 3 or more high risk genetic abnormalities**	**FISH:** • **Hyperdiploid: *More than 1 pair of chromosomes (Trisomies)*** • **Translocation 11 and 14** • **Translocation 6 and 14** • **Others** • **Normal**

*Based on the Updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines 2013 Mikhael JR et al. *Mayo Clin Proc.* 2013;88:360.

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Revised International Staging System for Multiple Myeloma
From International Myeloma Working Group

Stage 1	Stage 2	Stage 3
β2-microglobulin under 3.6 mg/L	Does not meet Criteria for Stage 1 or 3	β2-microglobulin over 5.5 mg/L
Normal Lactate Dehydrogenase (LDH)		**HIGH** Lactate Dehydrogenase (LDH)
AND		AND
NO High Risk Cytogenetics (FISH)		**High Risk Cytogenetics (FISH)** Deletion 17th chromosome Translocation 4th and 14th Translocation 14th and 16th Translocation 14th and 20th

*Based on the Updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines 2013 Mikhael JR et al. *Mayo Clin Proc*. 2013;88:360.
Palumbo et al. *JCO*. September 10, 2015 vol. 33 no. 26 2863-2869

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AND OTHER NOVEL THERAPIES:
Selinexor (Xpovio)
Idecabtagene vicleucel or Ide-cel (Abecma)
Ciltacabtagene autoleucel or Cilta-cel (Carvykti)
Teclistamab (Tecvayli)
More to come…

Immunomodulatory [illegible]:
Thalomid(*Thalidomide*), Revlimid(*Lenalidomide*), Pomalyst(*Pomalidomide*)

Proteasome Inhibitors (Pis):
Velcade(*Bortezomib*), Ninlaro(*Ixazomib*), Kyprolis(*Carfilzomib*)

Antibodies Against Myeloma (Immunotherapy):
Darzelex (*Daratumumab*), Sarclisa(*Isatuximab*), Empliciti(*Elotuzumab*)

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IMiDs for Multiple Myeloma

How does it work?-SCIENCE!

- Direct inhibition of DNA synthesis of myeloma cells.

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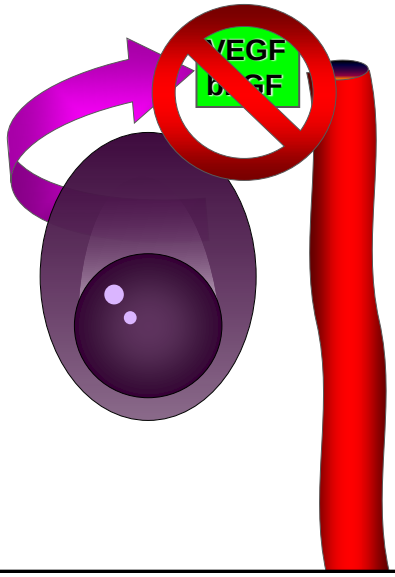
IMiDs for Multiple Myeloma



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- Inhibition of blood vessel synthesis in the bone marrow.

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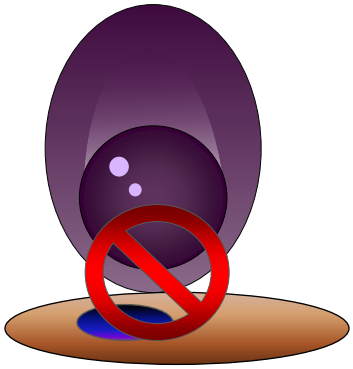
IMiDs for Multiple Myeloma



How does it work?-SCIENCE!

- Direct inhibition of DNA synthesis of myeloma cells.
- Inhibition of blood vessel synthesis in the bone marrow.
- Inhibition of adhesion between the myeloma and bone marrow stromal cells.

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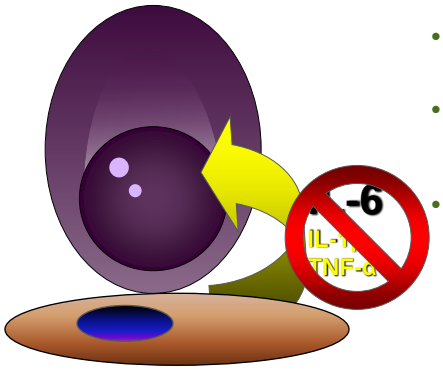
IMiDs for Multiple Myeloma



How does it work?-SCIENCE!

- Direct inhibition of DNA synthesis of myeloma cells.
- Inhibition of blood vessel synthesis in the bone marrow.
- Inhibition of adhesion between the myeloma and bone marrow stromal cells.
- Inhibition of the release of the cytokines IL-6, TNF-α, and IL-1β.

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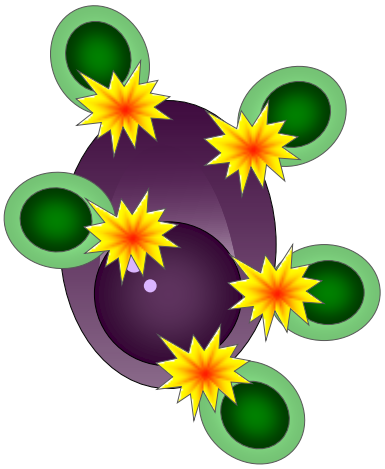
IMiDs for Multiple Myeloma



How does it work?-SCIENCE!

- Direct inhibition of DNA synthesis of myeloma cells.
- Inhibition of blood vessel synthesis in the bone marrow
- Inhibition of adhesion between the myeloma and bone marrow stromal cells.
- Inhibition of the release of the cytokines IL-6, TNF-α, and IL-1β
- Activation of the body's natural killer cells (T-cells) which attack the myeloma cells.

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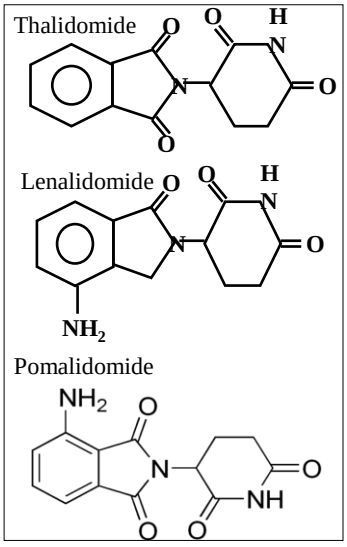
Evolution of the IMiD Biologic Therapies

- 1990s, several thalidomide analogs were synthesized to increase efficacy and minimize toxicity.
- 2006 FDA approves Lenalidomide (Revlimid).
  - Revlimid is felt to be 50 to 2000 more potent than thalidomide.
  - Phase 2 trial 91% new myeloma achieved responses with Lenalidomide plus dexamethasone.
- 2013 FDA approves Pomalidomide.
  - Pomalyst and dexamethasone given to multi-refractory myeloma with response rates of 35 to 65%.
  - Combination of pomalidomide, bortezomib, and dexamethasone in relapsed MM response rates of 72%.
- CELMODs are the next class of IMiD with Iberdomide (CC-220) is now in clinical trials
  - Second generation CELMOD is Mezigdomide (CC-92480) felt to be more potent than iberdomide



Blood. 2005;106:4050-4053. Blood. 2013 Jan 14. [Epub ahead of print]. Exp Hematol Oncol. 2012; 1: 27; J Clin Oncol. 2009;27(30):5008-5014. Blood 2022; 140 (Supplement 1): 1366–1368.

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IMiD (Revlimid) Side Effects

Hematologic Side Effects:

- Neutropenia (ANC <1000) was reported in 26% of patients treated with lenalidomide–dexamethasone (Rd) for 18 cycles and in 28% of those on continuous Rd in the FIRST trial (RD vs MPT)
- Thrombocytopenia (platelets <50,000) occurred in 8% of patients
- Higher risk of blood clots requires use of prophylaxis
  - Daily aspirin vs. other oral anticoagulants (Eliquis, Xarelto, etc..)

Non-Hematologic side effects:

- Infections (22%), fatigue (9%), cardiac disorders (7%), venous thromboembolism (6%), and asthenia (6%)
- Low risk of secondary cancers
  - Cumulative incidence of 0.7% at 1 yr., 2.3% at 2yrs, and 3.8% at 3 years, with the highest incidence in elderly patients.

Leukemia 32, 1542–1560 (2018). N Engl J Med. 2014 Sep 4;371(10):906-17.

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IMiD (Revlimid) Side Effects: Diarrhea

- Long-term therapy with lenalidomide may result in a specific form of diarrhea, the so-called **bile salt malabsorption syndrome**
  - Which seems to result from damage of the lining of the intestine causing accumulation of bile acids in the small bowel

- Treatment of Revlimid bile salt malabsorption syndrome
  - Hold Revlimid
  - Imodium
  - Dietary fat intake should be reduced (to 20% of total calories)
  - Treatment with bile acid binders: colestipol or cholestyramine

Leukemia 32, 1542–1560 (2018). N Engl J Med. 2014 Sep 4;371(10):906-17.

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Revlimid Side Effects: Others

- Fatigue:
  - Sleep hygiene, good fluid intake, regular exercise, dose reduction
- Cramps:
  - L-glutamine, fluid hydration, normalizing magnesium and potassium levels, use of muscle relaxants, and moving and stretching the affected areas
- Rash:
  - Hold Revlimid, antihistamines or topical steroids are recommended, occasional low-dose oral prednisone
  - Consider restart after rash has resolved

Leukemia 32, 1542–1560 (2018). N Engl J Med. 2014 Sep 4;371(10):906-17.

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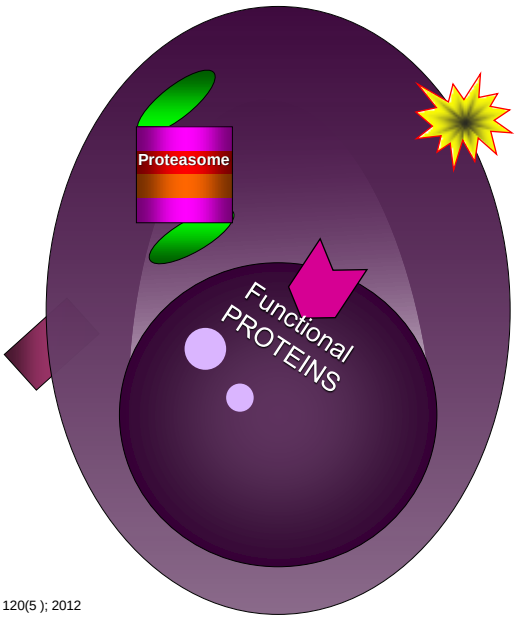
Rise of the Proteasome



R Vij et al. Br J Haem, June 2012. ; MOREAU et al. BLOOD, AUG VOL 120(5); 2012

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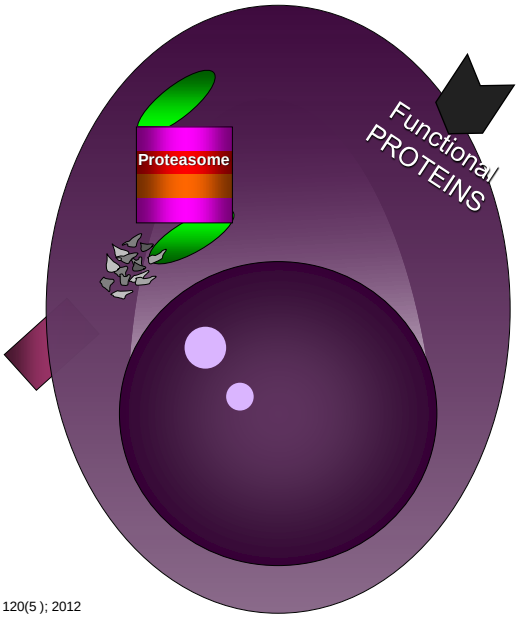
Rise of the Proteasome



R Vij et al. Br J Haem, June 2012. ; MOREAU et al. BLOOD, AUG VOL 120(5); 2012

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Rise

R Vij et al. Br J Haem, June 2012. ; MOREAU et al. BLOOD, AUG VOL 120(5); 2012

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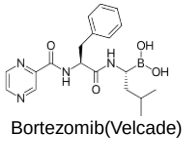
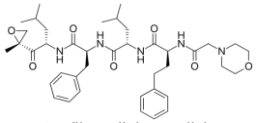
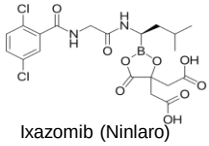
Rise of the Proteasome

- Bortezomib(velcade) approved by the FDA in 2003 in patients with relapsed refractory myeloma.
  - Several phase 2 trials in newly diagnosed myeloma with bortezomib-dexamethasone induction.
    - Responses 66% to 90%, including 15% to 21% Complete Responses!
- 2012 FDA approves Carfilzomib(Kyprolis); second-generation **irreversible** Proteasome inhibitor
  - In refractory myeloma with 48% response rates. Higher in combination
- Ixazomib (Ninlaro) is an oral boronated reversible proteasome inhibitor currently approved by the FDA in 11/2015
  - Clinical trials showing use in relapsed and newly diagnosed MM


Bortezomib(Velcade)


Carfilzomib(Kyprolis)


Ixazomib (Ninlaro)

R Vij et al. Br J Haem, June 2012. ; MOREAU et al. BLOOD, AUG VOL 120(5); 2012; Blood. 2014;124(7):1047–1055; Cancers 2020, 12, 265; doi:10.3390/cancers12020265

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Side Effects of Proteasome Inhibitors

Neurologic

- Peripheral neuropathy side effect that affects the nerves, resulting in pain, tingling, burning sensations, and numbness in the hands and feet
- Peripheral neuropathy may be caused by Velcade
- Risk is lower with subq dosing vs. IV and weekly vs. 2x weekly dosing
- Treated with medications and ↑ activity

Cardio-vascular

- Cardiovascular side effects including high blood pressure or congestive heart failure can occur with Kyprolis
- Risk is lowered with good BP control

Gastro-intestinal

- Velcade and Ninlaro may cause a variety of gastrointestinal problems, such as constipation, diarrhea, and nausea/vomiting
- Using nausea medications and/or stool softeners before dosing

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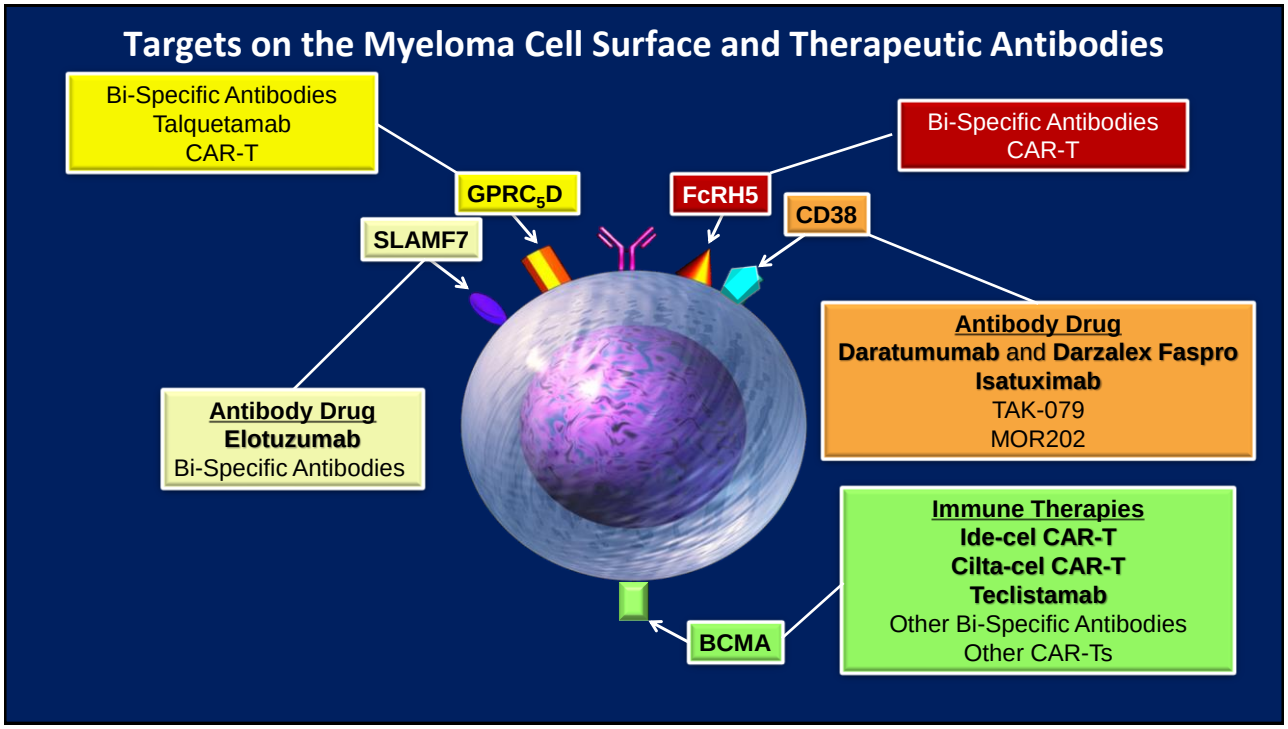
Targets on the Myeloma Cell Surface and Therapeutic Antibodies
Bi-Specific Antibodies
Talquetamab
CAR-T
GPRC5D
SLAMF7
FcRH5
Bi-Specific Antibodies
CAR-T
CD38
Antibody Drug
Daratumumab and Darzalex Faspro
Isatuximab
TAK-079
MOR202
Antibody Drug
Elotuzumab
Bi-Specific Antibodies
Immune Therapies
Ide-cel CAR-T
Cilta-cel CAR-T
Teclistamab
Other Bi-Specific Antibodies
Other CAR-Ts
BCMA

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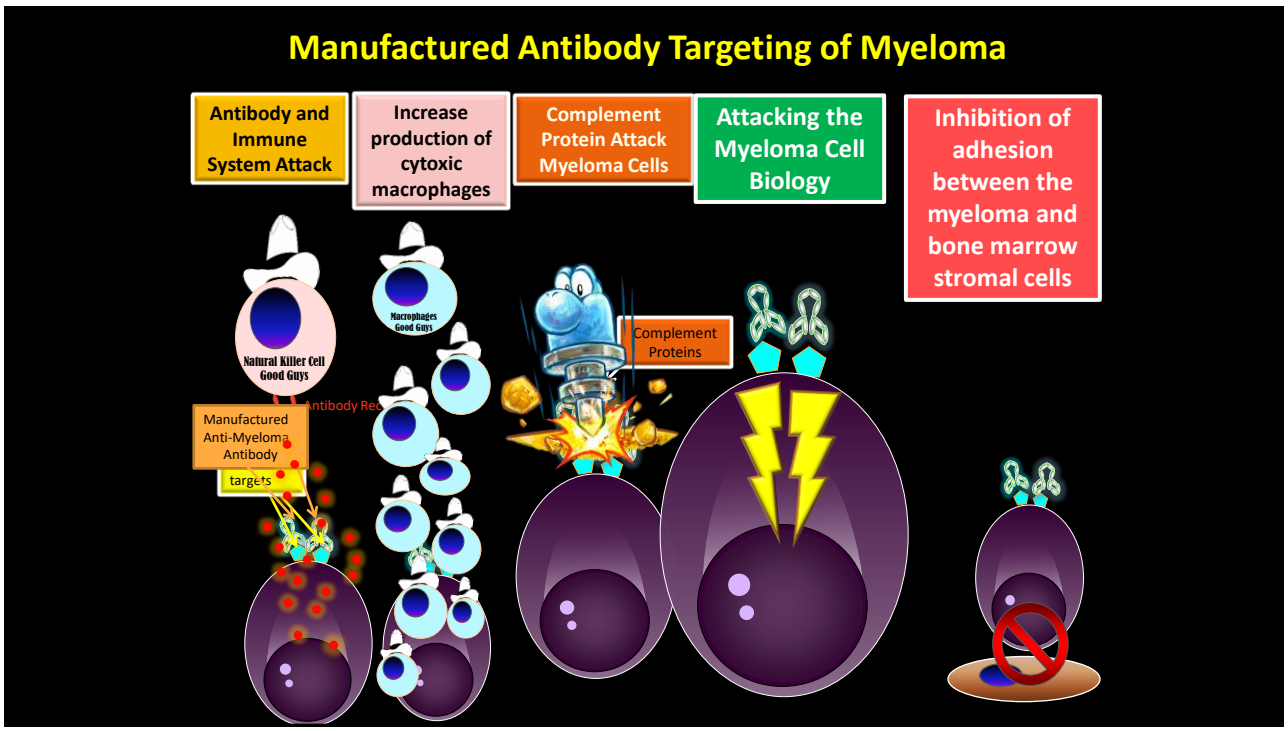
Manufactured Antibody Targeting of Myeloma
Antibody and Immune System Attack
Increase production of cytoxic macrophages
Complement Protein Attack Myeloma Cells
Attacking the Myeloma Cell Biology
Inhibition of adhesion between the myeloma and bone marrow stromal cells
Natural Killer Cell Good Guys
Macrophages Good Guys
Complement Proteins
Manufactured Anti-Myeloma Antibody
targets

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Side Effects of Steroids (dexamethasone)

Insomnia	Fluid retention	Mood changes	Dyspepsia–heartburn	Elevation in glucose
• Healthy sleep habits • Timing of dosing • Medication to assist with sleeping as needed	• Monitor for swelling of extremities and "puffy" face • Monitor weight changes/gain • Reduce dose	• Irritable, anxiety, difficulty concentrating • Severe cases of depression • Coordinate treatments with primary care provider	• Dietary modifications (spicy, acidic foods) • Avoid NSAIDs • Acid-blocking medications • Take with food	• Monitor glucose and refer/treat as needed • Coordinate with primary care provider

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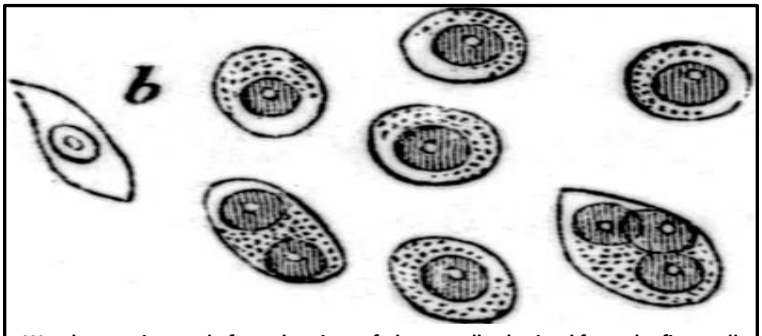
Newly Diagnosed Myeloma



Wood engraving made from drawings of plasma cells obtained from the first well described myeloma patient Thomas Alexander McBean, January 1846
Dublin Quarterly Journal of Medical Sciences. 1846;2:85–95.)

34

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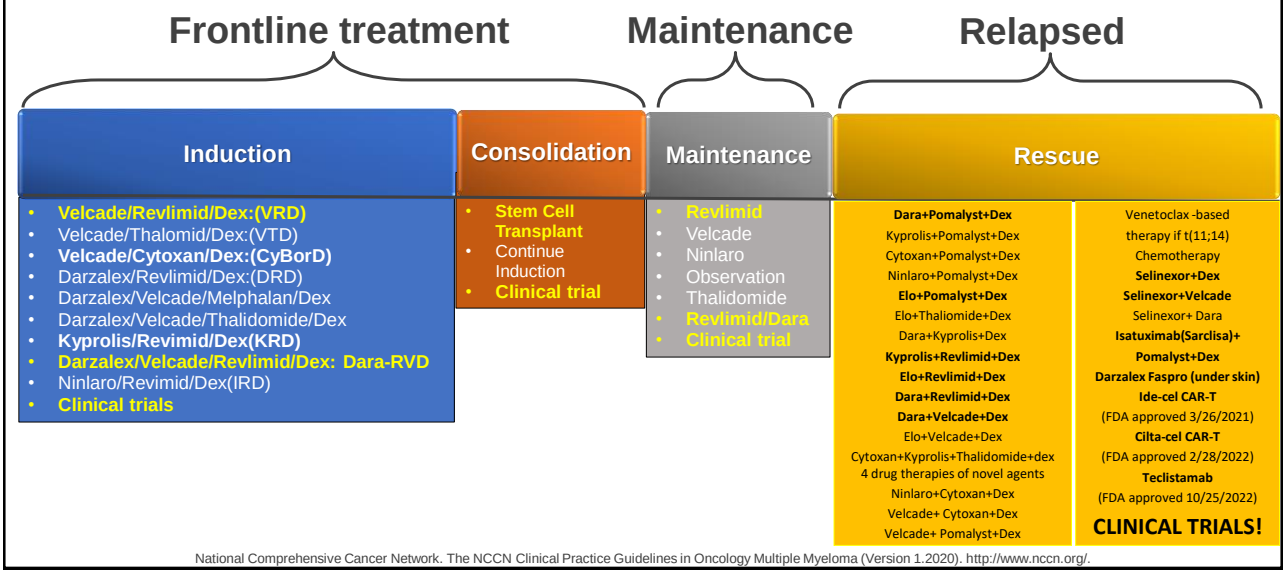
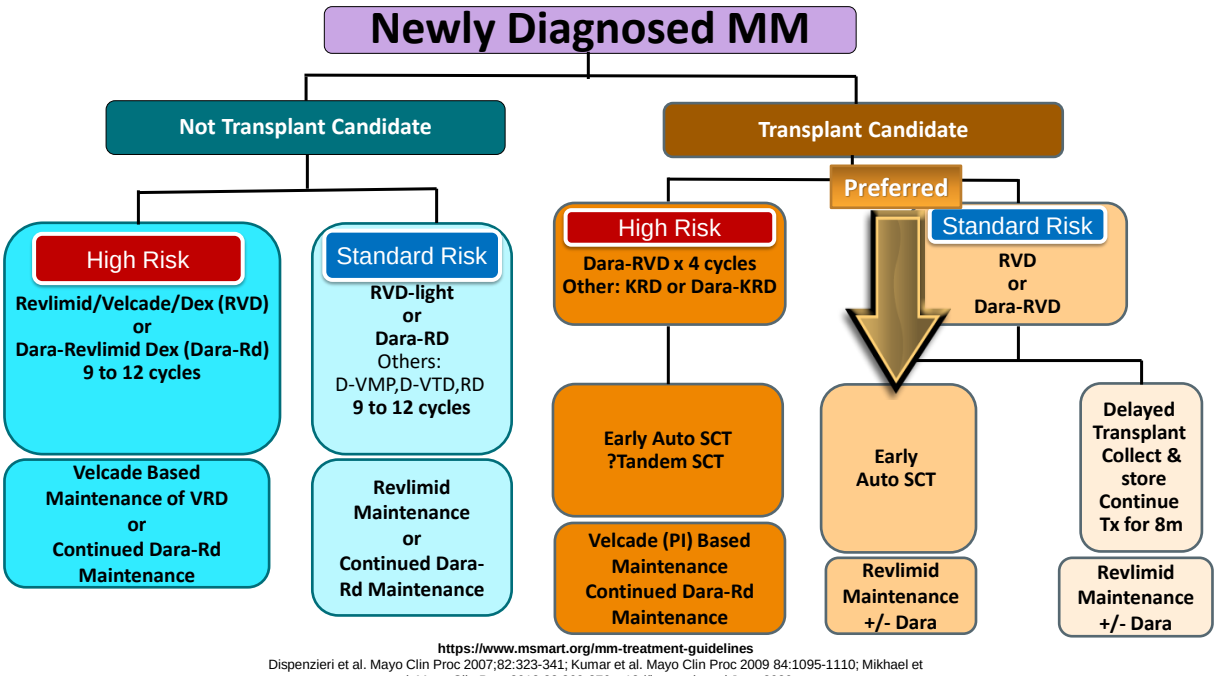
Treatment Sequence and Regimens for Active Myeloma



National Comprehensive Cancer Network. The NCCN Clinical Practice Guidelines in Oncology Multiple Myeloma (Version 1.2020). http://www.nccn.org/.

35



https://www.msmart.org/mm-treatment-guidelines

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v18 //last reviewed June 2020

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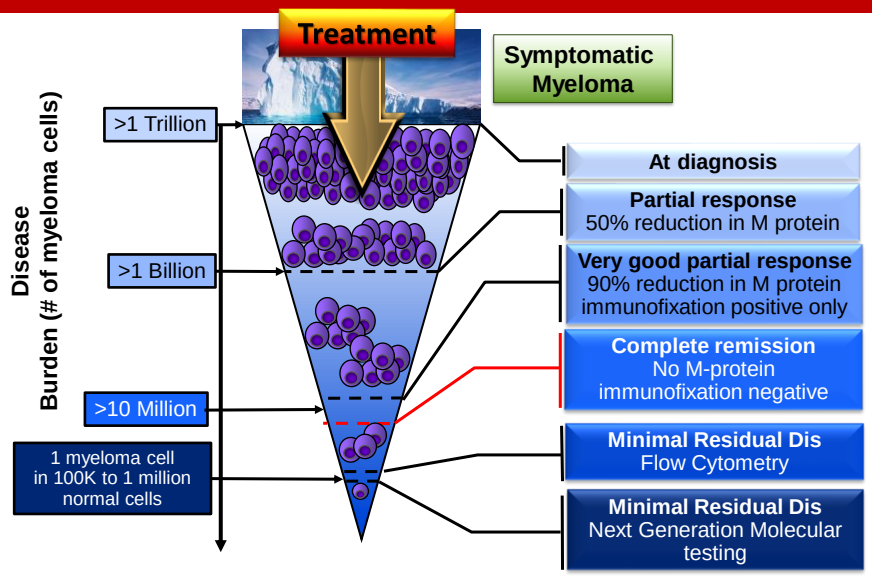
Goals of Therapy: The Iceberg Model of Myeloma



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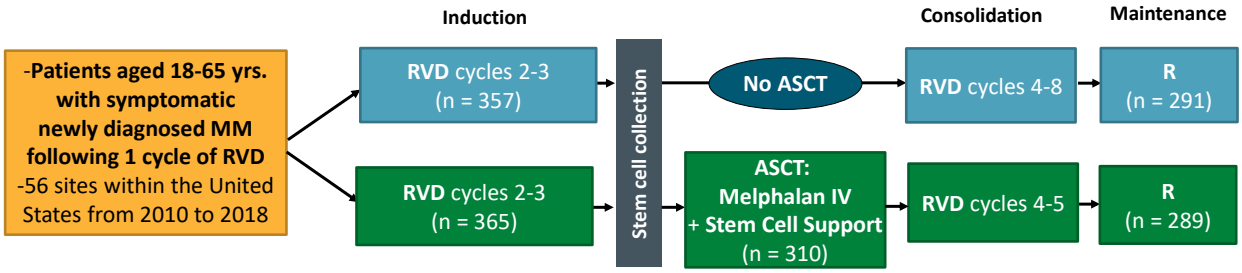
RVD +Stem Cell Transplant vs. RVD without Transplant

DETERMINATION Trial of Newly Diagnosed MM



End Points of Study and Follow-up

- Primary end point: progression-free survival (time to next relapse)
- Secondary end points included:
  - Response rates, overall survival, quality of life, and adverse events
- Follow-up on participant status : median of 6 years

N Engl J Med. 2022 Jul 14;387(2):132-147. doi: 10.1056/NEJMoa2204925

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RVD +Stem Cell Transplant vs. RVD without Transplant
DETERMINATION Trial of Newly Diagnosed MM
RESULTS

Parameter	RVd- No Transplant (n = 357)	RVD with Up Front Transplantation (n = 365)	P Value Is it Significant?
Grade 3 or 4 toxicities	78	94	YES! P<0.001
OVERALL SURVIVAL at 5 years (%)	9.2	80.7	NO
Median duration of Partial Response or better, mo	38.9	54.4	YES! .003
Negative MRD	39.8	79	

- At a median follow-up of 76.0 months, the risk of disease progression or death was 53% higher in the RVD-alone group than in the transplantation group (P<0.001)

N Engl J Med. 2022 Jul 14;387(2):132-147. doi: 10.1056/NEJMoa2204925

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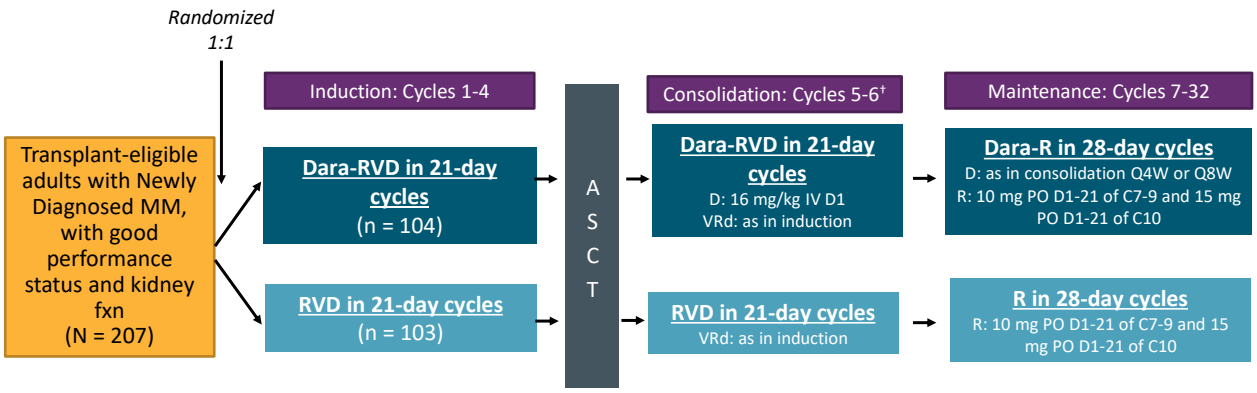
GRIFFIN Randomized Phase II: Dara-RVD vs. RVD in Newly Diagnosed Multiple Myeloma

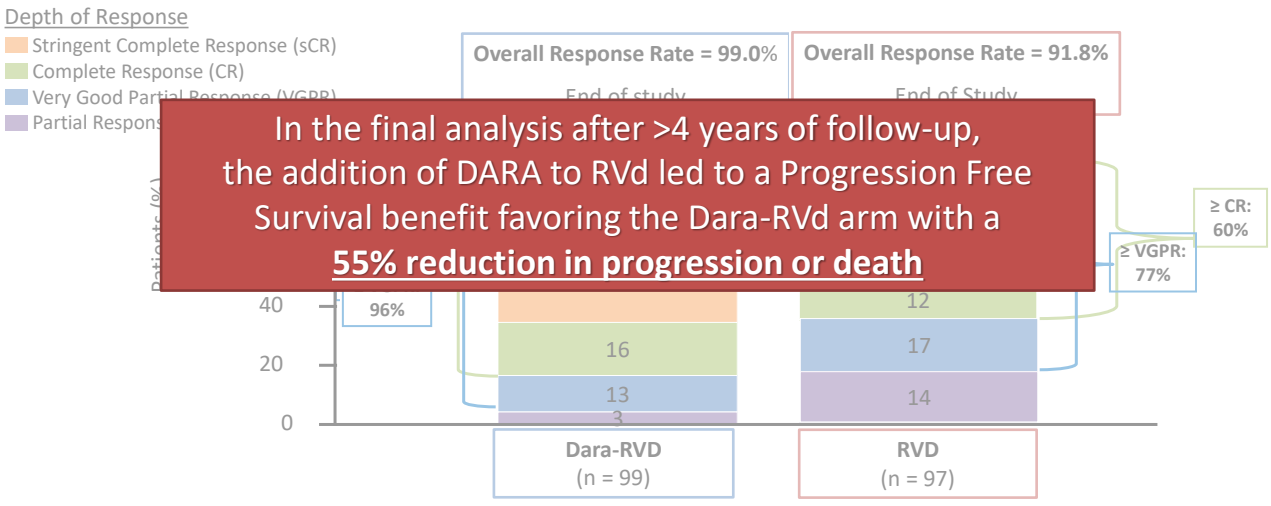


- Primary endpoint: CR by end of consolidation

Kaufman. ASH 2020. Abst.594; Voorhees PM etal. Blood. 2020 Aug 20;136(8):936-945.

40

GRIFFIN Randomized Phase II: Dara-RVD vs. RVD in Newly Diagnosed Multiple Myeloma

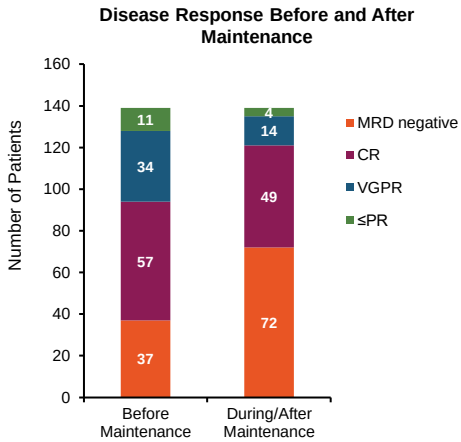


Voorhees PM et al. Blood. 2020 Aug 20;136(8):936-945. Sborov et al. IMS Annual Meeting. 2022 Aug 26; Abst# OAB-057

41

Maintenance Therapy

- Maintenance is to prevent disease progression for as long as possible while maintaining favorable quality of life
- Data from 4 randomized trials of Revlimid (lenalidomide) maintenance vs. no maintenance
  - The results of the analysis showed that Revlimid maintenance therapy is associated:
    - Significant **improvement in progression-free survival**
    - **Modest improvement in overall survival**
- **Duration of maintenance is unknown**



Alonso R et al. Blood Adv. 2020;4:2163.

42

Bone Support & Control of Bone Pain

Multiple myeloma can cause weakened areas in the bone called osteolytic lesions which can compress the spinal cord or cause bone destruction.

- Bone strengthening drugs: bisphosphonates (**pamidronate** & **Zometa**) or monoclonal antibodies (**Xgeva**) are given at diagnosis and continued for at least 2 years
- **Vitamin-D and Calcium supplements to help bone healing**
- Orthopedic support
  - Physical therapy, physical medicine consults, orthopedic/neuro surgery, radiation therapy, etc.
- Minimally invasive procedures: kyphoplasty or vertebroplasty
- Use of medication to control pain
- Anticonvulsants and antidepressants for treat relieve pain from nerve damage or numbness

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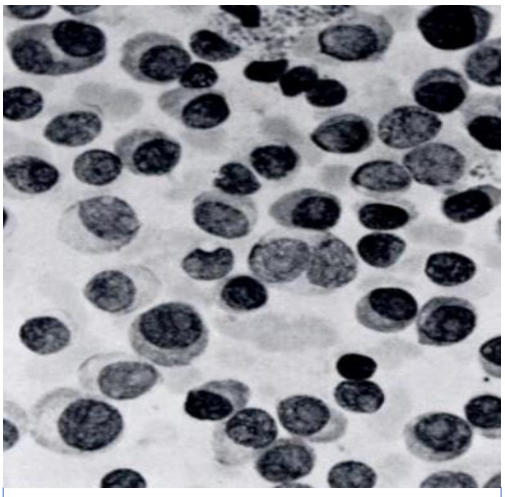
Relapsed Refractory Myeloma



Blood (1949) 4 (3): 201–216.

44

What is Relapsed Multiple Myeloma ?

- Relapsed multiple myeloma is when the cancer returns after treatment
  - Usually after a period of remission or response.

Relapsed = Recurrent =Progressive

- Since multiple myeloma does not have a cure, it is likely that at some point patients will have a relapse
- With therapy, relapsed myeloma patients can achieve a second response
- Refractory myeloma is when myeloma is not responsive to therapy.

"RRMM" = Relapsed Refractory Multiple Myeloma

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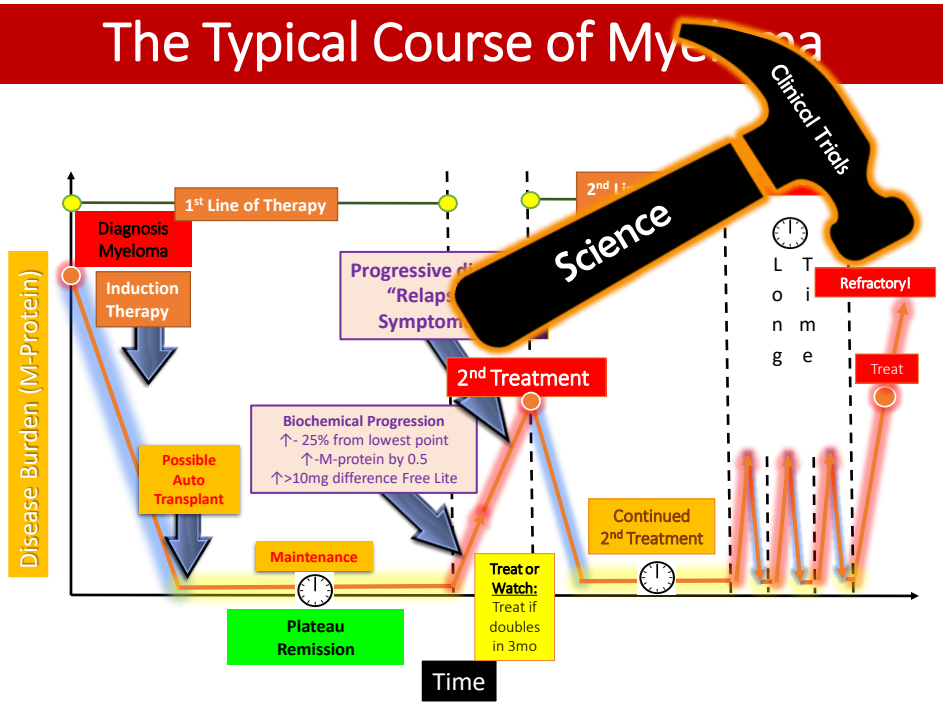
The Typical Course of Myeloma



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Conditions influencing the selection of treatment for patients with relapsed/refractory myeloma

Disease-related
- Duration of response to last therapy.
- C.R.A.B. symptoms
- Kinetics of relapsed disease
  - Rapid progression vs. slow progression

High Risk Relapse
- High LDH
- Disease outside bone/ bone marrow
- Translocations t(4:14), del(17p), and del(13q14) mutations
- Secondary mutations
  - RAS, FGFR3, MYC, or loss or mutation in TP53

Patient-related
- Age
- Level of activity
- Neuropathy
- Blood counts
- Kidney impairment
- Recent blood clots, heart attack, stroke events

Regimen-related
- Number of previous lines of therapy.
- Relapsing while **on or off** maintenance.
- Previous drug exposure (new vs. classic agents)
- Previous transplant with short <3yrs vs. prolonged response >3yrs.

Mayo Clin Proc. 2017;92(4):578-598

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Treatment Options For Relapsed Myeloma

1st Relapse on Revlimid Maintenance

Dara+Velcade+Dex
Dara+Pomalyst+Dex
Dara+Kyprolis+Dex
Elotuzumab+Pomalyst+Dex
Kyprolis+Pomalyst+Dex
Elotuzumab+Velcade+Dex
Ninlaro+Pomalyst+
Ninlaro+Cytoxan+D
Velcade+ Cytoxan+
Velcade+ Pomalyst+
Isatuximab(Sarclisa)+Pom
Isatuximab(Sarclisa)+Kypr
Followed by…1st or 2nd Stem Cell Transplant

1st Relapse on Velcade Maintenance

Dara+Revlimid+Dex
Elotuzumab+Revlimid+Dex
Kyprolis+Revlimd+Dex
Kyprolis+Pomalyst+Dex
Dara+Pomalyst+Dex
Dara+Kyprolis+Dex
uzumab+Pomalyst+Dex
ab(Sarclisa)+Pomalyst+Dex
ab(Sarclisa)+Kyprolis+Dex
y…1st or 2nd Stem Cell Transplant

CLINICAL TRIALS

1st Relapse off Tx or Maintenance

Any of the above

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Treatment Options For Relapsed Myeloma

2nd or Later Relapsed

Dara+Pomalyst+Dex
Kyprolis+Pomalyst+Dex
Cytoxan+Pomalyst+Dex
Ninlaro+Pomalyst+Dex
Elo+Pomalyst+Dex
Elo+Thaliomide+Dex
Dara+ Thalidomide+Dex
Dara+Kyprolis+Dex
Kyprolis+Revlimid+Dex
Elo+Revlimid+Dex
Dara+Revlimid+Dex
Dara+Velcade+Dex
Elo+Velcade+Dex
Cytoxan+Kyprolis+Thalidomide+dex
Selinexor+Based therapy (Velcade, Dara, Kyprolis, etc..)
Isatuximab(Sarclisa)+Pomalyst+Dex
Isatuximab(Sarclisa)+Kyprolis+Dex
Darzalex FASPRO (given under skin) with above therapies
Venetoclax -based therapy if t(11;14)

CLINICAL TRIALS

>4 prior lines of therapy Aggressive Relapsed or Refractory

Selinexor+Based therapy (Velcade, Dara, Kyprolis, etc..)
ic Stem Cell transplant
Ide-cel CAR-T
pproved 3/26/2021)
Cilta-cel CAR-T
(FDA approved 2/28/2022)
Teclistamab
(FDA approved 10/25/2022)

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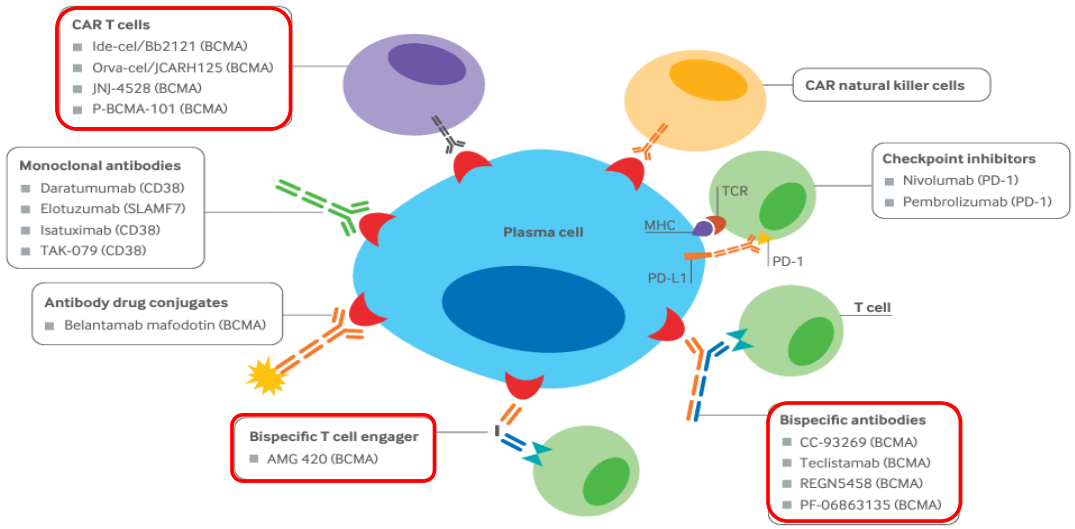
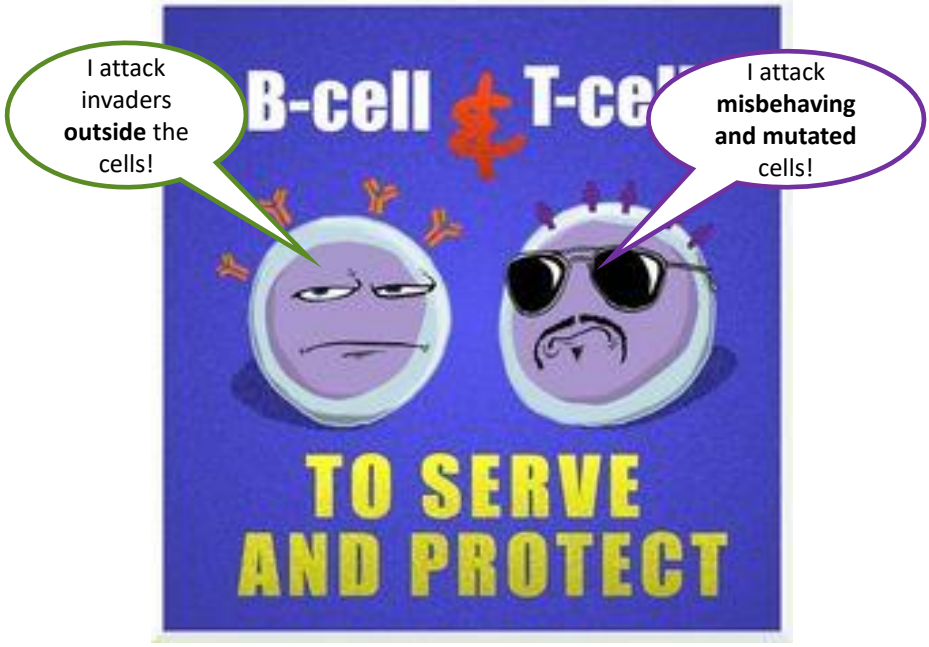
Immunotherapeutic Options for Relapsed Myeloma



BMJ. 2020 Sep 21;370:m3176. doi: 10.1136/bmj.m3176.

50



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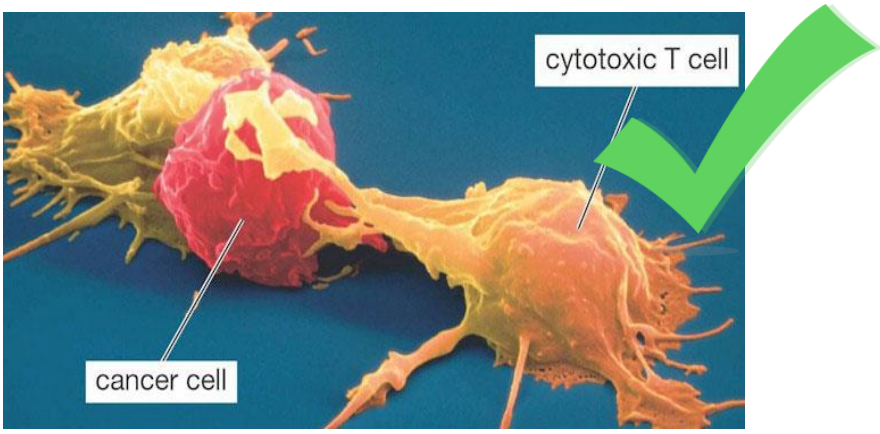
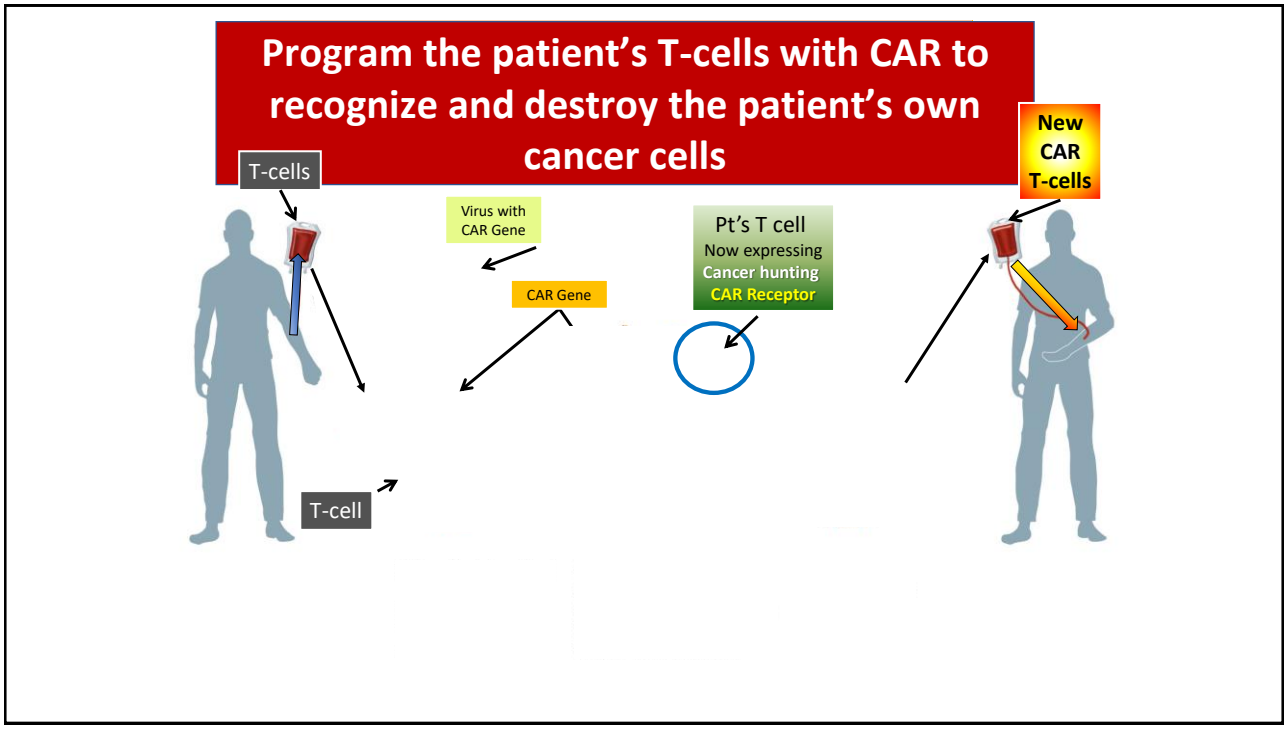
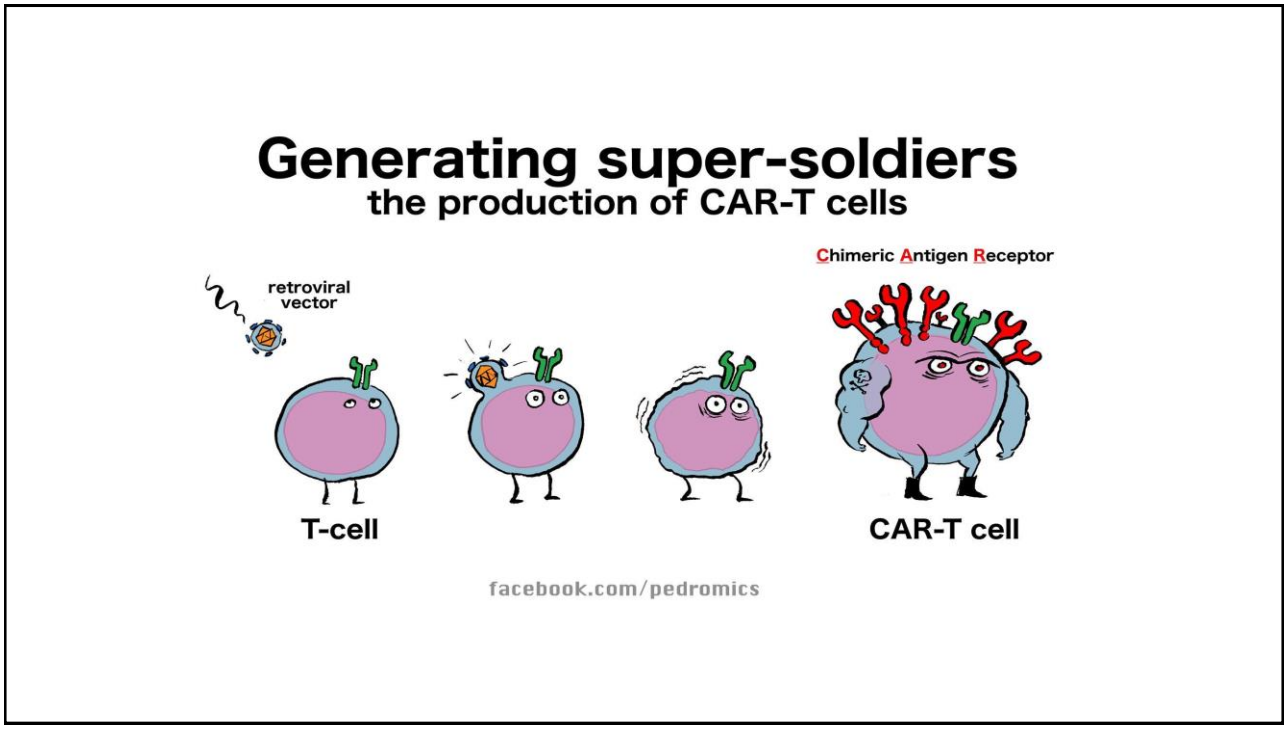
CAR –T Immune Therapy



52


Program the patient's T-cells with CAR to recognize and destroy the patient's own cancer cells
T-cells
Virus with CAR Gene
CAR Gene
Pt's T cell
Now expressing
Cancer hunting
CAR Receptor
New CAR T-cells
T-cell

53


Generating super-soldiers
the production of CAR-T cells
retroviral vector
Chimeric Antigen Receptor
T-cell
CAR-T cell
facebook.com/pedromics

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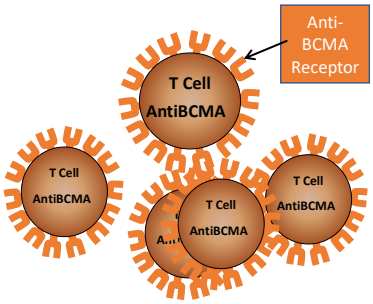
CAR-BCMA T-Cells in Myeloma: Background

- B-cell maturation antigen (BCMA) is expressed myeloma cells and is a potential target for CAR T-cell therapy for MM.
- T cells can be genetically modified to express chimeric antigen receptors (CARs) specific for BCMA or other proteins associated with cancer.
- The patient's own T-cells are stimulated, transduced with BCMA retroviruses, and cultured for 9-14 days before re-infusion.
- The CAR-T cells engage myeloma cells thru BCMA.
  - T-cells are activated and then kill the myeloma cells
  - The CAR-T cells also have another built-in switch which causes the CAR-Ts to expand in number and potency

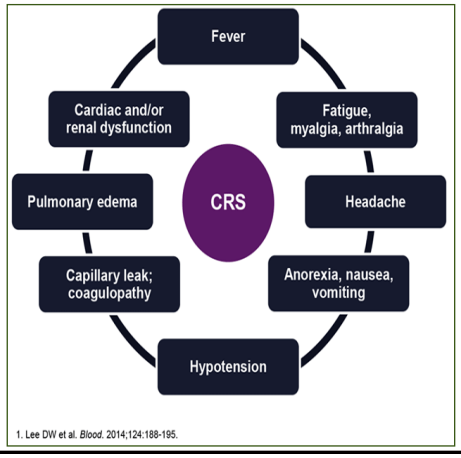


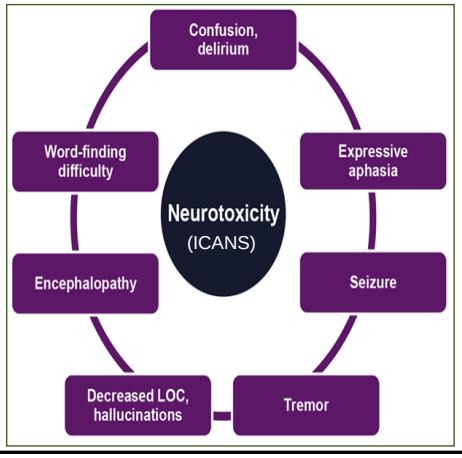
J Clin Oncol 35, 2017 (suppl; abstr LBA3001); 22nd EHA Congress; June, 2017;Abstract S142; Cohen AD, et al. ASH 2017. Abstract 505

55

Toxicities of CAR-T:
Cytokine Release Syndrome and Neurotoxicity

- **Cytokine Release Syndrome (CRS)** is a severe inflammation reaction related to T-cell engagement to the target
- CRS can be mild (grade 1) to severe (grade 4) causing multisystem organ failure
- **Immune effector cell-associated neurotoxicity syndrome ICANS** is the neurologic toxicity of CAR-T
- The cause of the neurotoxicity is unknown





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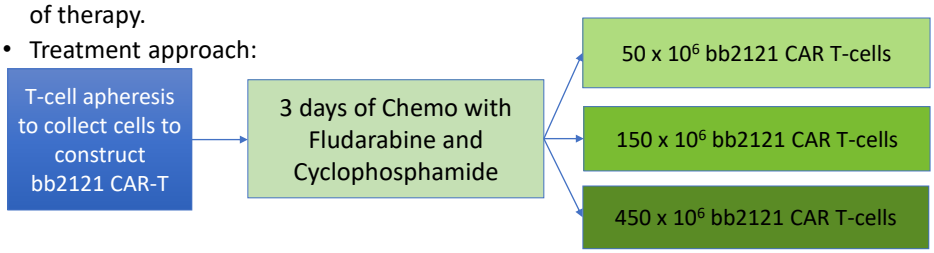
Idecabtagene vicleucel (Ida-cel) BCMA-directed CAR T-cell therapy

- Multicenter KarMMa Phase II trial in pts with R/R MM who received ≥ 3 prior lines of therapy.
- Treatment approach:



- 128 consecutive patients who received Ida-cel (bb2121) infusion were reported
  - The median age was 61 years (range, 33 to 78)
  - 35% had a high-risk cytogenetic profile
  - Median number of previous regimens was 6
- The manufacturing of Ida-cel was successful for 99% of the patients
- Anti-BCMA CAR was expanded over a period of 10 days

Raje N et al. N Engl J Med 2019;380:1726-1737

57

Ida-cel CAR-T : Overall Response Rate

Outcome	Ide-cel 150 x 10^6 (n = 4)	Ide-cel 300 x 10^6 (n = 70)	Ide-cel 450 x 10^6 (n = 54)	All Ide-cel Patients (n = 128)
ORR, n (%)	2 (50)	48 (69)	44 (81)	**94 (73)**
CR/sCR, n (%)	1 (25)	20 (29)	21 (39)	**42 (33)**

Outcome by Prior Lines	3 Lines Tx (n = 15)	≥4 LinesTx (n = 113)	All Ide-cel Patients (n = 128)
ORR, n (%)	73	73	73
CR/sCR, n (%)	53	30	33
VGPR	0	23	20
PR	20	20	20

- **Median follow-up: 24.8 mo (range: 1.7-33.6 mo)**
- **Median Duration of response 10.9 mo (9.0-11.4)**
- **Median PFS at 300 x 106 CAR T-cells was 5.8 mo vs 12.2 mo with 450 x 106 CAR T-cells**

Anderson. ASCO 2021. Abstr 8016.

58

Idecabtagene vicleucel (Ida-cel) BCMA-directed CAR T-cell therapy

- Idecabtagene vicleucel BCMA-directed CAR T-cell therapy FDA approved for R/R MM **after ≥4 previous lines of therapy**, including an IMiD, a PI, and an anti-CD38 mAb
- In patients with R/R MM, use of idecabtagene vicleucel CAR T-cell therapy in KarMMA trial continued to result in durable responses, regardless of number of prior therapy lines
  - Median follow-up of 24.8 mo: ORR in all patients, 73%; CR/sCR, 33%
  - Median DoR: 10.9 mo; median PFS: 8.6 mo
  - Median OS: 24.8 mo, and >20 mo in most subgroups at high risk of progression

Chari. NEJM. 2019;381:727. Lonial. Lancet Oncol. 2020;21:207. Raje. NEJM. 2019;380:1726. Anderson. ASCO 2021. Abstr 8016

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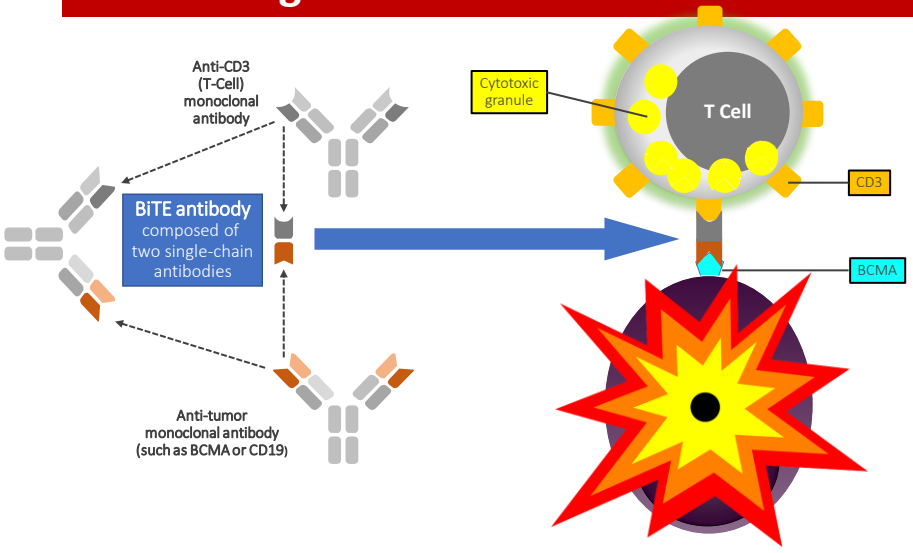
Safety and Efficacy Data of the 2 FDA approved CAR-Ts

	Idecabtagene vicleucel KarMMa trial	Ciltacabtagene autoleucel CARTITUDE 1 trial
Phase of Trial (pts infused)	2 (128)	1b/2 (97)
Follow-up, median (range)	13.3 mo (0.2-21.2)	21.7 mo (not reported)
Prior lines, median (range)	6 (3 to 16)	6 (3-18)
LD chemotherapy	Fludarabine 30 mg/m^2×3 d Cyclo 300 mg/m^2×3 d	Fludarabine 30 mg/m^2×3 d Cyclo 300 mg/m^2×3 d
Efficacy		
ORR, n (%)	**94 (73)** **At dose: 450×10^6 (n=54): 44 (81%)**	**95 (97.9)**
CR or sCR, n (%)	42 (33) At dose: 450×10^6 (n=54): 21 (39)	82.5% (sCR)
DOR, median (95% CI)	**10.7 mo (9.0-11.3)**	**Not reported**
PFS, median (95% CI)	8.8 mo (5.6-11.6) At dose: 450×10^6 : 12.1 mo (8.8-12.3)	NR (16.8-NE) 2-y PFS: 60.5% (48.5-70.4)
OS, median (95% CI)	**24.8 mo (19.9-31.2)**	**NR (27.2-NE)**
CRS, n (%)		
Overall	107 (84)	92 (95)
Grade 3-4	7 (5)	4 (4)
Neurotoxicity, n (%)		
Overall	23 (18)	20 (21)
Grade 3-4	4 (3)	9 (9)
Infections, n (%)	**88 (69)**	**56 (58)**
Grade 3-4 infections, n (%)	**28 (22)**	**19 (20)**
Death, n (%)	44 (34)	14

Modified from Hematology Am Soc Hematol Educ Program 2022; 2022 (1)

60

Bi-specific T-cell engagers and antibodies (BiTEs) to bring the activated T cells to the cancer



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Teclistamab (Tecvayli)

Cancer Research
MICHIGAN STATE UNIVERSITY

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MajesTEC-1: Study Design

- First-in-human, open-label, dose-escalation/dose-expansion phase I/II trial
  - Median follow-up: 7.8 mo (range: 0.5+ to 18); data cutoff: September 7, 2021

Patients with R/R MM who received ≥3 prior lines of therapy and were triple-class exposed (ie, received IMiD, PI, and anti-CD38 mAb); no prior BCMA therapy (N = 165)

→ Week 1: Teclistamab step-up doses of 0.06 and 0.3 mg/kg SC

→ Cycles 1+: Teclistamab 1.5 mg/kg SC once weekly

→ *Continue until PD, intolerance, withdrawal, physician decision, or death*

F/u 2 yr after LPI

- Primary endpoint: Overall Response Rate (ORR)
- Key secondary endpoints: DoR, ≥VGPR, ≥CR, sCR, TTR, MRD status, PFS, OS, safety, PK, immunogenicity, PROs

Moreau. ASH 2021. Abstr 896. NCT03145181. NCT04557098.

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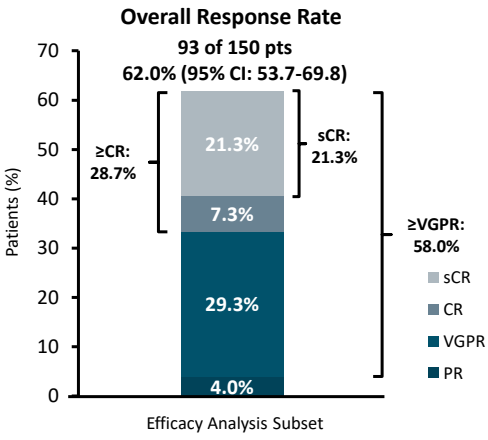
MajesTEC-1: Efficacy Outcomes



Event	All Patients (N = 165)
MRD negativity, n (%, 95% CI) ▪ At 10^{-5} ▪ At 10^{-6}	(n = 150) 37 (24.7; 18.0-32.4) 25 (16.7; 11.1-23.6)
Median DoR, mo	Not yet reached
Event-free survival rates, % (95% CI) ▪ 6-Mos ▪ 9-Mos	 92.5 (80.6-97.2) 85.9 (70.0-93.7)
PFS rates, % (95% CI) ▪ 6-Mos ▪ 9-Mos	 64.4 (56.0–71.7) 58.5 (48.8–67.0)
Median OS	Not yet reached

Moreau. ASH 2021. Abstr 896.

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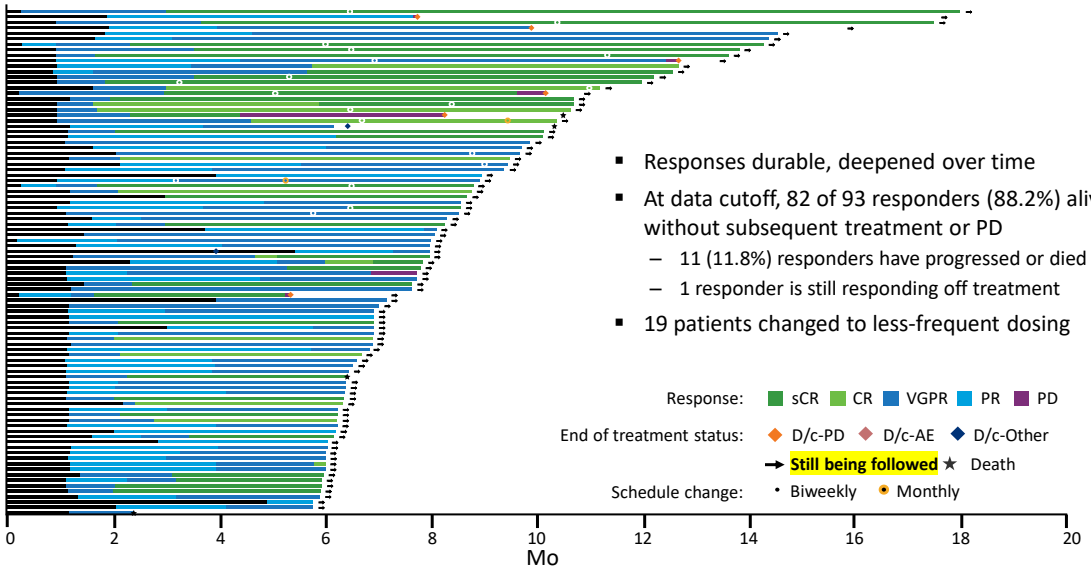
MajesTEC-1: Response Durability



- Responses durable, deepened over time
- At data cutoff, 82 of 93 responders (88.2%) alive, without subsequent treatment or PD
  - 11 (11.8%) responders have progressed or died
  - 1 responder is still responding off treatment
- 19 patients changed to less-frequent dosing

Moreau. ASH 2021. Abstr 896.

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MajesTEC-1: Safety

AEs in ≥20% of Patients, n (%)	All Patients (N =165)	
	Any Grade	Grade 3/4
Hematologic		
▪ **Neutropenia**	**108 (65.5)**	**94 (57.0)**
▪ Anemia	82 (49.7)	57 (34.5)
▪ Thrombocytopenia	63 (38.2)	35 (21.2)
▪ Lymphopenia	56 (33.9)	53 (32.1)
Nonhematologic		
▪ **CRS**	**118 (71.5)**	**1 (0.6)**
▪ Injection site erythema	42 (25.5)	0
▪ Fatigue	41 (24.8)	3 (1.8)
▪ Nausea	40 (24.2)	1 (0.6)
▪ Headache	36 (21.8)	1 (0.6)
▪ Diarrhea	34 (20.6)	4 (2.4)

- No patients required teclistamab dose reduction; only 1 patient discontinued due to AE (adenoviral pneumonia)
- Serious Adverse Events: 88 (53.3%)
  - Teclistamab-related per investigator: 33 (20.0%)
- Injection-site reactions (all grade 1/2): 58 (35.2%)
- **Infections: any grade, 104 (63.0%); grade 3/4: 35.2%**
  - **Opportunistic infections: 9 (5.5%)**
- **Hypogammaglobulinemia-Low normal antibody levels: 119 (72.1%)**
  - **41 patients received IVIG at any time during the study (at physician discretion)**
- 9 deaths due to AEs; none related to teclistamab
  - 7 COVID-19, 1 pneumonia, 1 hemoperitoneum

Moreau. ASH 2021. Abstr 896.

66

Teclistamab Approval

- On October 25, 2022, the Food and Drug Administration granted accelerated approval to teclistamab-cqyv (Tecvayli), the first bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager
- Approved for relapsed or refractory multiple myeloma who have received **≥4 prior lines of therapy**, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.
- Because of the risks of CRS and neurologic toxicity, including ICANS, teclistamab-cqyv is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), called the Tecvayli REMS
- REMS program requires an inpatient hospital stay for the first 3 step up doses

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-teclistamab-cqyv-relapsed-or-refractory-multiple-myeloma

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Pretreatment with Tocilizumab Prior to Bispecific Cevostamab Showed a Marked Reduction in CRS

- Tocilizumab (TCZ) is a monoclonal antibody which blocks the IL-6 receptor
- TCZ pretreatment arm was added GO39775 Phase I study of cevostamab, an FcRH5xCD3 bi-specific T-cell engager for RRMM
  - To determine whether a single dose of TCZ prior to the 1st dose of cevostamab can reduce CRS
- 35.7% of pts in the TCZ arm experienced CRS as compared to 90.9% in the non-TCZ group
- No negative impact on anti-tumor activity was observed
  - ORR in the TCZ arm was 50% compared to 37.2% in pts receiving 90mg without TCZ pretreatment

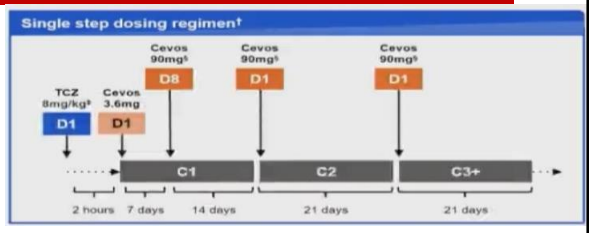
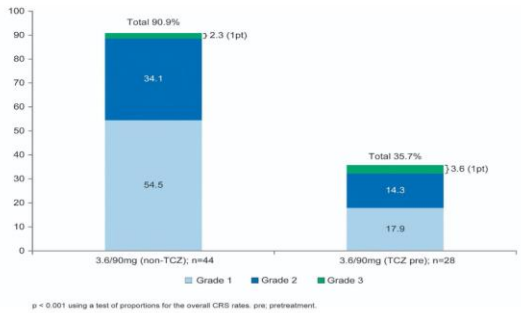


Figure: Patients (%) with CRS by grade assessed using ASTCT criteria

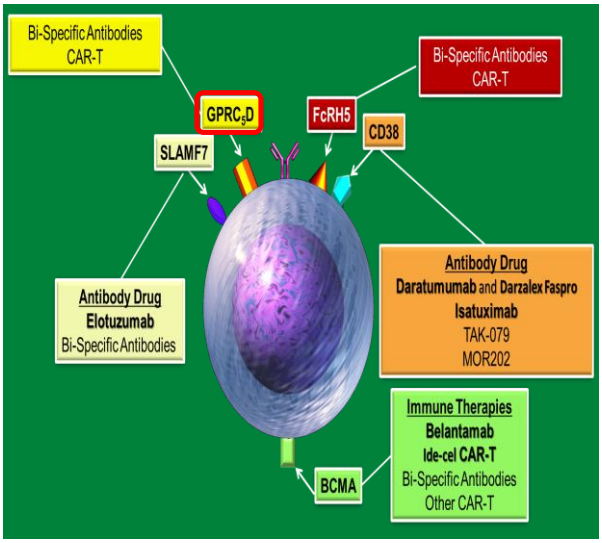


Trudel. ASH 2022. Abstr 567.

68

Talquetamab in MM: Background

- GPCR5D: orphan receptor highly expressed on MM cells relative to normal cells
- Talquetamab: first-in-class bispecific IgG4 antibody binding **GPCR5D and CD3 receptors**
- Phase I ORR of 64% to 70% with talquetamab shown with QW and Q2W dosing
- Current analysis reports updated data from pivotal phase II MonumenTAL-1 study including



Verkleij. Blood Adv. 2021;5:2196. Pillarisetti. Blood. 2020;135:1232. Chari. ASH 2020. Abstr 290. Minnema. ASCO 2022. Asbtr 8015. Chari. NEJM. 2022;387:2232

69

MonumenTAL-1: Study Design

- Multicenter, open-label phase I/II trial

Adults with measurable RRMM

Phase I: progression on or intolerance to all established therapies
Phase II: ≥3 prior lines of therapy that included a PI, an IMiD, and an anti-CD38 antibody

- Talquetamab 0.4 mg/kg SC QW* (n = 143)
- Talquetamab 0.8 mg/kg SC Q2W* (n = 145)
- Prior T-Cell Therapy Group: Talquetamab 0.4 mg/kg SC QW or 0.8 mg/kg SC Q2W (n = 51)

*Previous anti-BCMA therapy allowed; T-cell redirection therapy naive.

- Primary endpoint (phase II): ORR
- Secondary endpoints (phase II): DoR, ≥ VGPR rate, ≥ CR, sCR rate, TTR, PFS, OS, MRD, safety

Chari. ASH 2022. Abstr 157. NCT03399799. NCT04634552.

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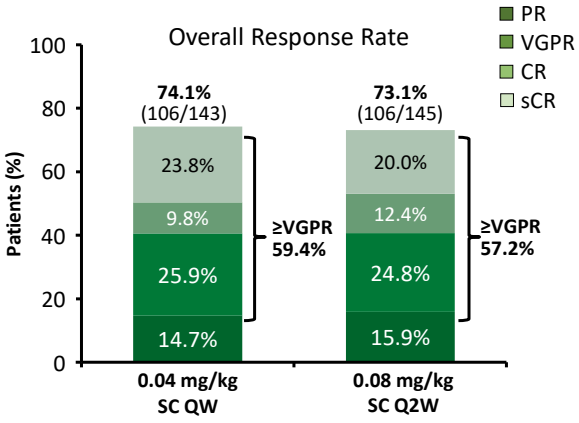
MonumenTAL-1: Overall Response Rate



- Overall Response Rate was similar for both dosing schedules
  - Triple-class refractory: 72.6% (63.1-80.9) QW and 71.0% (61.1–79.6) Q2W
  - Penta-drug refractory: 71.4% (55.4–84.3) QW and 70.6% (52.5–84.9) Q2W

Chari. ASH 2022. Abstr 157.

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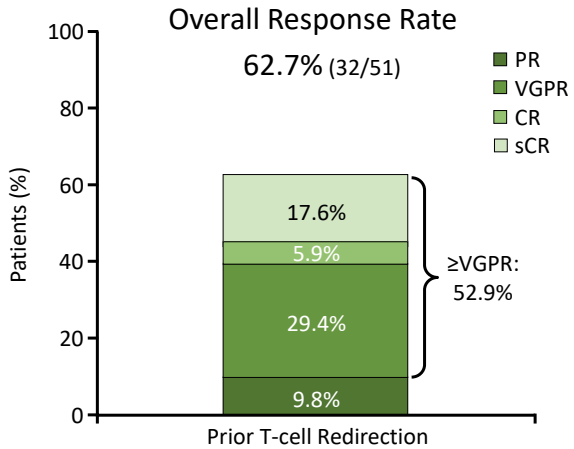
MonumenTAL-1: ORR in Patients With Prior T-Cell Therapy

Characteristic	Patients (n = 51)
Median prior lines of therapy, n (range)	6 (3-15)
Exposure status, n (%) ▪ CAR T-cell ▪ Bispecific antibody	 36 (70.6)* 18 (35.3)*
Refractory status, n (%) ▪ Belantamab	4 (7.8)
Median DoR, mo (range)	12.7 (3.7-NE)
ORR by prior therapy, % (95% CI) ▪ **CAR T-cell** ▪ **Bispecific antibody**	 **72.2 (54.8-85.8)** **44.4 (21.5-69.2)**



Median follow-up (range): 11.8 mo (1.0-25.4).

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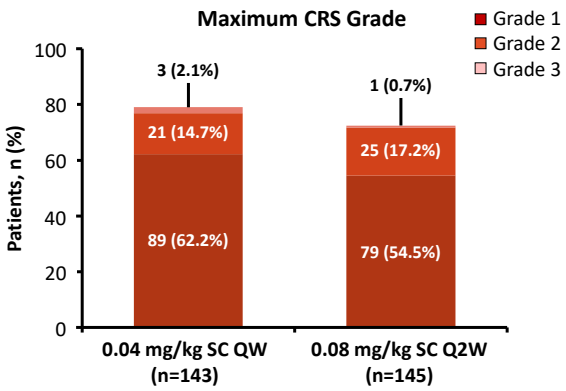
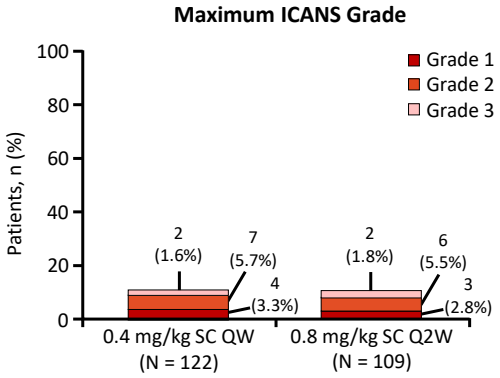
MonumenTAL-1: Cytokine-Release Syndrome and ICANS



- Most cases of CRS occurred during step-up doses or first full dose and were grade 1 or 2



- Majority of ICANS events were grade 1 or 2, with an occurrence of 10% to 11% of patients at RP2D

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Comparison of immunotherapy approaches in myeloma

	Bispecific T-cell engagers	CAR T-cell therapy
Advantages	Off-the-shelf therapy (no delays)	-
	-	One time treatment Vacation from continuous therapy
	Deep responses	**Deep responses**
	Mostly grade 1-2 CRS/ICANS	-
	Only initial dosing as inpatient	Only initial dosing as inpatient
Disadvantages	-	Administration delays due to manufacturing time
	Continuous therapy until progression	-
	Weekly or biweekly dosing	-
	Significant immunosuppression	Significant immunosuppression
	-	Potential for severe CRS/ICANS; prolonged cytopenias
	Specialized centers required	Complex infrastructure required
	Cost ($$)	Cost ($$$)

Adapted from Hematology Am Soc Hematol Educ Program 2022; 2022 (1): 163–172

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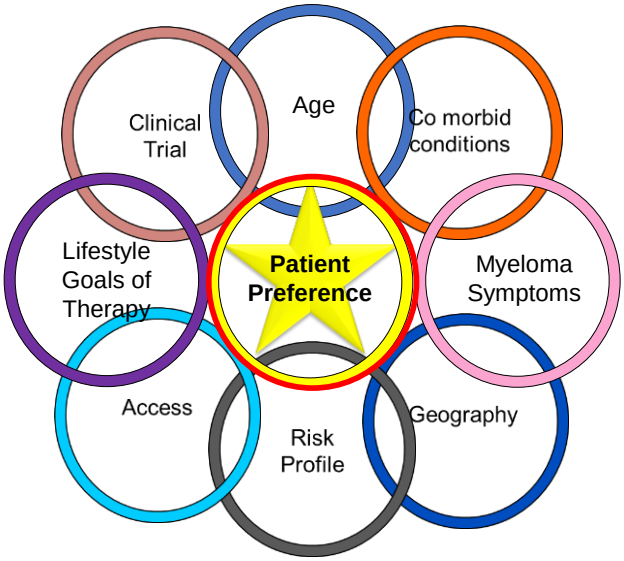
Communicating With Your Health Care Team



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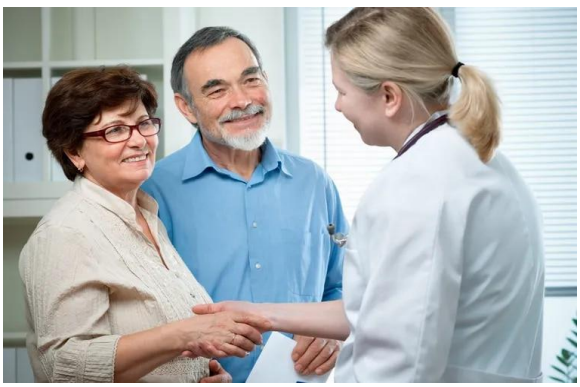
Choosing Your Health Care Team

- You should feel **respected and listened to** by your doctor, nurse, care extenders, social worker and others on your team
- Ideally you can work with a doctor who's **experienced in treating multiple myeloma**
- You should be able to **talk openly** with your health care team and **trust their advice**



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Second Opinion

- **You have the right** to get a second opinion.
- A second opinion can help you:
  - Confirm your diagnosis
  - Give you more information about treatment options
  - Additional chance to hear about your disease
  - Talk to other experts
  - Introduce you to clinical trials
  - Help you learn which health care team you'd like to work with, and which facility

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Open Communication Is Key

- Tell your health care team about:
  - Your **symptoms**, and how they impact your life
  - Any **treatment side effects** you feel, and how they impact your life
  - Financial toxicity of therapy
  - Your **goals for treatment** (they may change over time)
  - **Your questions and concerns**
- It's important to **work together** with your doctor for the best outcome
  - When a doctor recommends a treatment, share your concerns about side effects and ask questions about other options

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Preparing For Your Doctor Visit

- Write questions down before you go to the doctor; bring them to your appointment and use them to talk to your health care team
  - Write down/ record the answers to these questions.
  - Keep copies of your lab work, x-rays, and biopsies
- **Bring a friend or family member with you**
- Tell your doctor and nurse about all medications you are using, including over the counter medications, vitamins, or supplements

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It's important to know…

What are YOUR goals of therapy

How to read your myeloma protein level

What is your MM risk/ stage

What are your therapy options

What is your response to tx

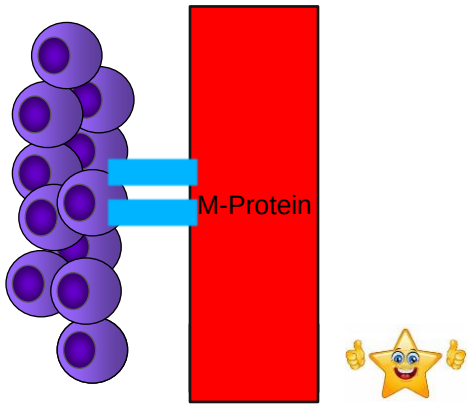
Know what side effects to expect so you can report them

Who is on your care team

Obtain a second opinion

Ask about clinical trials

Be informed and empowered in 2023!



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ASK A QUESTION

SPOTLIGHT ON MULTIPLE MYELOMA

Ask a question by phone:

Press star (*) 1 on your keypad to ask a question
To remove your question press star (*) 2 on your keypad

Ask a question by web:

Type your question in the “Ask a Question” box under the speaker video window

Due to time constraints, we can only take one question per person.
Once you’ve asked your question, the operator will transfer you back into the audience line.

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LLS EDUCATION & SUPPORT RESOURCES

HOW TO CONTACT US:

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials: **www.LLS.org/InformationSpecialists**

Call: (800) 955-4572
Monday to Friday, 9 a.m. to 9 p.m. ET

Chat live online: www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET

Email: www.LLS.org/ContactUs
All email messages are answered within one business day.

CLINICAL TRIAL SUPPORT CENTER
Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.
www.LLS.org/Navigation

NUTRITION CONSULTATIONS
Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.
www.LLS.org/Consult

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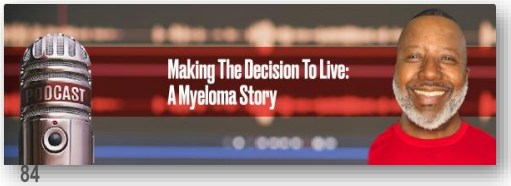
LLS EDUCATION & SUPPORT RESOURCES

Online Chats

Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit **www.LLS.org/Chat**

Education Videos

View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit **www.LLS.org/EducationVideos**



Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.TheBloodline.org**

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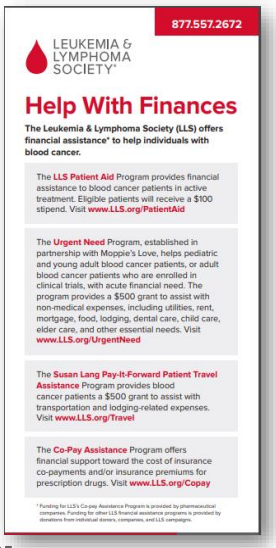
LLS EDUCATION & SUPPORT RESOURCES



The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: **www.LLS.org/Finances**

To order free materials: **www.LLS.org/Booklets**

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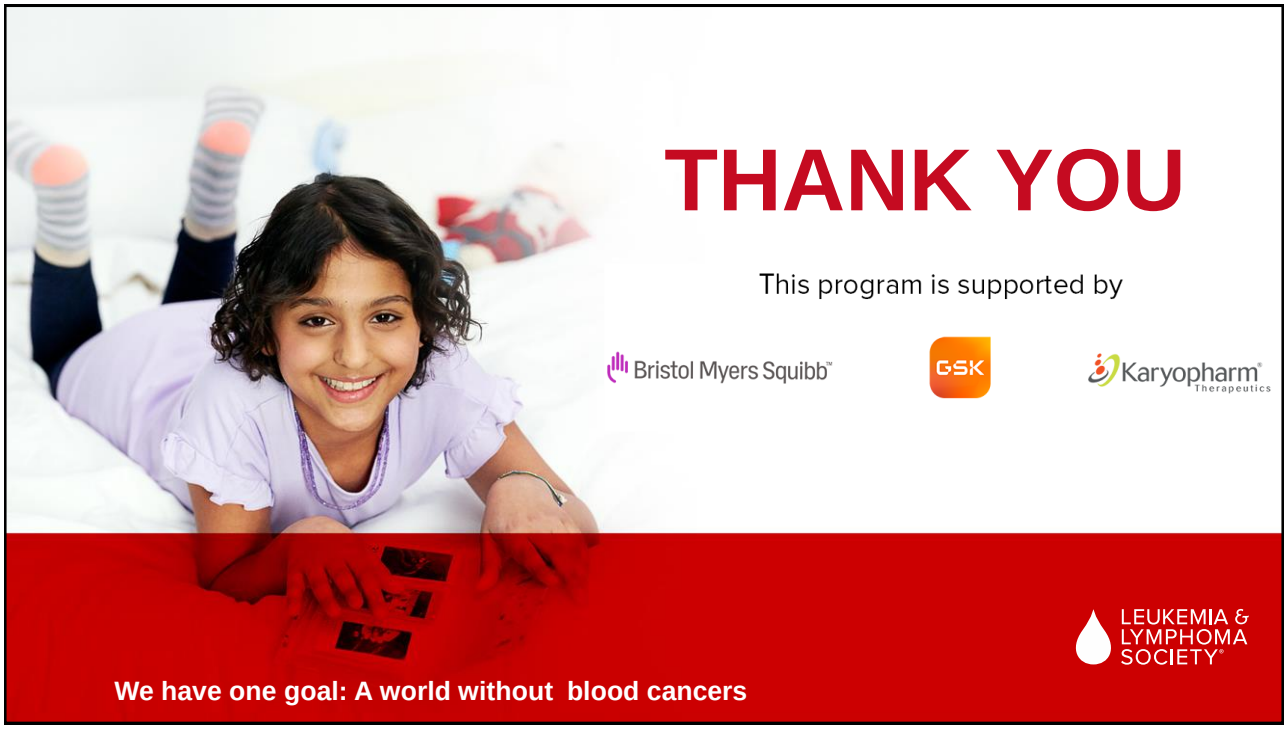

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