SPOTLIGHT ON MULTIPLE MYELOMA

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WELCOMING REMARKS

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Rye Brook, NY
WELCOMING REMARKS
SPOTLIGHT ON MULTIPLE MYELOMA

Gregory O. Proctor
Myeloma Patient
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The Bloodline with LLS, Podcast Guest
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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
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

Multiple Myeloma is a Cancer of the Bone Marrow Plasma Cells

BLOOD
- Myeloma is a cancer of the blood
- Myeloma crowds out normal blood forming cells, causing Anemia

Mutated Cancer Cell

BONES
- Surrounding Bone where Myeloma cells grow become damaged/weakened (lesions)
- Myeloma cells activate bone destruction ↑ blood Calcium levels

KIDNEYS
- Large amounts of M proteins can overwork or cause damage to the kidneys (Renal damage)

Calcium high
Renal (kidney) failure
Anemia
Bone destruction

↑ Monoclonal (M) proteins
**Multiple Myeloma Fast Facts**

- **Multiple Myeloma**
  - 2nd most common blood cancer
  - 35,730 estimated new cases of myeloma in 2023

- **Myeloma**
  - Most frequently diagnosed in people 65 to 74 years old
  - 138,451 U.S. patients living with myeloma in 2021

- **Incidence**
  - Black Incidence: 14.3/100,000
  - White Incidence: 6.2/100,000

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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

- **Immuuno 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
**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.
Staging Myeloma: The Importance of Genomic Testing

Conventional cytogenetic analysis (karyotyping)

Advances
- Genetic expression profiling (GEP)
- Whole-genome/whole-exome sequencing
- Plasma cell next generation sequencing

FISH (fluorescence in situ hybridization)

Staging Myeloma: FISH Testing helps to Assign Risk in Myeloma

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>High Risk</th>
<th>Standard Risk</th>
</tr>
</thead>
</table>
| 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) | **FISH:**
  - Hyperdiploid: *More than 1 pair of chromosomes (Trisomies)*
  - Translocation 11 and 14
  - Translocation 6 and 14
  - Others
  - Normal |

**Revised International Staging System for Multiple Myeloma**

*From International Myeloma Working Group*

- **Stage 1**
  - $\beta_2$-microglobulin under 3.6 mg/L
  - Normal Lactate Dehydrogenase (LDH)
  - NO High Risk Cytogenetics (FISH)

- **Stage 2**
  - Does not meet Criteria for Stage 1 or 3

- **Stage 3**
  - $\beta_2$-microglobulin over 5.5 mg/L
  - High Lactate Dehydrogenase (LDH)
  - AND High Risk Cytogenetics (FISH)
    - Deletion 17th chromosome
    - Translocation 4th and 14th
    - Translocation 14th and 16th
    - Translocation 14th and 20th


*Palumbo et al., JCO September 10, 2015 vol. 33 no. 26 2863-2869*

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**Immunomodulatory Drugs (IMiDs):**
- 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)

**AND OTHER NOVEL THERAPIES:**
- Selinexor (Xpovo)
- Idecabtagene vicleucel or Ide-cel (Abecma)
- Ciltacabtagene autoleucel or Cilta-cel (Carvykti)
- Tecfilastamab (Tecvayli)
- More to come...
**IMiDs for Multiple Myeloma**

**How does it work?** - **SCIENCE!**

- Direct inhibition of DNA synthesis of myeloma cells.

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**How does it work?** - **SCIENCE!**

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

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.
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.

**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.

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 2 yrs, and 3.8% at 3 years, with the highest incidence in
  elderly patients.

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

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

Rise of the Proteasome

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

Rise of the Proteasome

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 Ninlargo may cause a variety of gastrointestinal problems, such as constipation, diarrhea, and nausea/vomiting
• Using nausea medications and/or stool softeners before dosing
Targets on the Myeloma Cell Surface and Therapeutic Antibodies

- Bi-Specific Antibodies
  - Talquetamab
  - CAR-T
- Antibody Drug
  - Elotuzumab
  - Bi-Specific Antibodies
- Antibody Drug
  - Daratumumab and Darzalex Faspro
  - Isatuximab
  - TAK-079
  - MOR202
- Other Bi-Specific Antibodies
- Other CAR-Ts

Immune Therapies
- Ide-cel CAR-T
- Cilta-cel CAR-T
- Tecclistamab

Other Bi-Specific Antibodies

Antibody and Immune System Attack

- Increase production of cytotoxic macrophages
- Complement Protein Attack Myeloma Cells
- Attacking the Myeloma Cell Biology
- Inhibition of adhesion between the myeloma and bone marrow stromal cells
Side Effects of Steroids (dexamethasone)

Insomnia
- Healthy sleep habits
- Timing of dosing
- Medication to assist with sleeping as needed

Fluid retention
- Monitor for swelling of extremities and “puffy” face
- Monitor weight changes/gain
- Reduce dose

Mood changes
- Irritable, anxiety, difficulty concentrating
- Severe cases of depression
- Coordinate treatments with primary care provider

Dyspepsia—heartburn
- Dietary modifications (spicy, acidic foods)
- Avoid NSAIDs
- Acid-blocking medications
- Take with food

Elevation in glucose
- Monitor glucose and refer/treat as needed
- Coordinate with primary care provider

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.)
Treatment Sequence and Regimens for Active Myeloma

**Frontline treatment**
- **Induction**
  - Velcade/Revlimid/Dex (VRD)
  - Velcade/Thalomid/Dex (VTD)
  - Velcade/Cytoxan/Dex (CyBoRd)
  - Darzalex/Revlimid/Dex (DRD)
  - Darzalex/Velcade/Melphalan/Dex
  - Darzalex/Velcade/Thalidomide/Dex
  - Kyprolis/Revlimid/Dex (KRD)
  - Darzalex/Velcade/Revlimid/Dex (Dara-RVD)
  - Ninlaro/Revlimid/Dex (IRD)
- **Clinical trials**

**Consolidation**
- **SCT**
- Continue Induction
- Clinical trial
- **Maintenance**
- **Relapsed**
- **Rescue**
  - Dara/Pomalyst/Dex
  - Kyprolis/Pomalyst/Dex
  - Ninlaro/Pomalyst/Dex
  - Thalidomide
  - Revlimid/Dara
  - Clinical trial
  - Velcade
  - Ninlaro
  - Observation
  - Thalidomide
  - Revlimid/Dara
  - Clinical trial

**Newly Diagnosed MM**

- **Not Transplant Candidate**
  - High Risk
    - Revlimid/Velcade/Dex (RVD)
    - or Dara-Revlimid Dex (Dara-Rd)
    - 9 to 12 cycles
  - Standard Risk
    - RVD-light or Dara-RD
    - Others: D-VMP,D-VTD,RD 9 to 12 cycles
  - Velcade Based Maintenance of VRD or Continued Dara-Rd Maintenance

- **Transplant Candidate**
  - High Risk
    - Dara-RVD x 4 cycles
    - Other: KRD or Dara-KRD
  - Standard Risk
    - RVD or Dara-RVD
  - Early Auto SCT
    - Tandem SCT
  - Velcade (PI) Based Maintenance Continued Dara-Rd Maintenance

**Transplant Candidate**

- **Delayed Transplant Collect & store**
  - Continue Tx for 8m
- **Preferred**
  - Early Auto SCT
  - Revlimid Maintenance +/- Dara

**High Risk**
- Early Auto SCT
- Velcade (PI) Based Maintenance Continued Dara-Rd Maintenance

**Standard Risk**
- RVD or Dara-RVD

**CLINICAL TRIALS!**

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35/21/23

35

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

**Goals of Therapy: The Iceberg Model of Myeloma**

- **Symptomatic Myeloma**
  - Partial response: 50% reduction in M protein
  - Very good partial response: 90% reduction in M protein immunofixation positive only
  - Complete remission: No M-protein immunofixation negative
  - Minimal Residual Disease
    - Flow Cytometry
    - Next Generation Molecular testing

**Disease Burden (# of myeloma cells)**
- >1 Trillion
- >1 Billion
- >10 Million
- 1 myeloma cell in 100K to 1 million normal cells

**RVD + Stem Cell Transplant vs. RVD without Transplant**

- **Induction**
  - RVD cycles 2-3 (n = 357)
  - RVD cycles 2-3 (n = 365)
- **Consolidation**
  - No ASCT
  - ASCT: Melphalan IV + Stem Cell Support (n = 310)
  - RVD cycles 4-8
  - RVD cycles 4-5
- **Maintenance**
  - R (n = 291)
  - R (n = 289)

**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

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

- 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).

OVERALL SURVIVAL at 5 years (%): 79.2 vs. 80.7

Median duration of Partial Response or better, mo: 38.9 vs. 54.4

Negative MRD: 39.8 vs. 79


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

**Randomized 1:1**

- Transplant-eligible adults with Newly Diagnosed MM, with good performance status and kidney fxn (N = 207)

- **Primary endpoint: CR by end of consolidation**
GRIFFIN Randomized Phase II: Dara-RVD vs. RVD in Newly Diagnosed Multiple Myeloma

In the final analysis after >4 years of follow-up, the addition of DARA to RVd led to a Progression Free Survival benefit favoring the Dara-RVd arm with a **55% reduction in progression or death**

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
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

Relapsed Refractory Myeloma

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
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

**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.

**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

**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+Dex
- Ninlaro+Cytoxan+Dex
- Velcade+Cytoxan+Dex

1st Relapse on Velcade Maintenance
- Dara+Revlimid+Dex
- Elotuzumab+Revlimid+Dex
- Kyprolis+Revlimid+Dex
- Kyprolis+Pomalyst+Dex
- Dara+Pomalyst+Dex
- Dara+Kyprolis+Dex
- Ninlaro+Pomalyst+Dex
- Ninlaro+Cytoxan+Dex
- Velcade+Cytoxan+Dex
- Velcade+Pomalyst+Dex
- Isatuximab(Sarclisa)+Pomalyst+Dex
- Isatuximab(Sarclisa)+Kyprolis+Dex
- Isatuximab(Sarclisa)+Velcade+Dex

Followed by…1st or 2nd Stem Cell Transplant

1st Relapse off Tx or Maintenance
- Any of the above
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+Thalidomide+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)

>4 prior lines of therapy
- Aggressive Relapsed or Refractory
- Selinexor-Based therapy (Velcade, Dara, Kyprolis, etc.)
- Allogeneic Stem Cell transplant
- Ide-cel CAR-T (FDA approved 3/26/2021)
- Cilta-cel CAR-T (FDA approved 2/28/2022)
- Tecvision (FDA approved 10/25/2022)

Immunotherapeutic Options for Relapsed Myeloma

CAR T cells
- Ide-cel/Bz2121 (BCMA)
- Övre-cel/CD123 (BCMA)
- IN-4529 (BCMA)
- P-BCMA-101 (BCMA)
- Antibody-drug conjugates
- Belantumab-mofetil in (BCMA)
- Bispecific T cell engager
- AMG 420 (BCMA)

Monoclonal antibodies
- Daratumumab (CD38)
- Elotuzumab (SLAMF7)
- Isatuximab (CD38)
- TAK-079 (CD38)

Checkpoint inhibitors
- Nivolumab (PD-1)
- Pembrolizumab (PD-1)

Bispecific antibodies
- CC-93269 (BCMA)
- Tecvision (BCMA)
- REGN458 (BCMA)
- PF-06863135 (BCMA)

BMJ. 2020 Sep 21;370:m3176. doi: 10.1136/bmj.m3176.
The Horizon is Bright!

I attack invaders outside the cells!

I attack misbehaving and mutated cells!

CAR–T Immune Therapy

cancer cell
cytotoxic T cell
T cells are a type of white blood cell that attack and kill viruses and cancer cells. Chimeric antigen receptors (CARs) help T-cells recognize and destroy cancer cells. Program the patient’s T-cells with CAR to recognize and destroy the patient’s own cancer cells.

Generating super-soldiers: The production of CAR-T cells.

Retroviral vector

T-cell

Chimeric Antigen Receptor

CAR-T cell

facebook.com/pedromics
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

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
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:
  - T-cell apheresis to collect cells to construct bb2121 CAR-T
  - 3 days of Chemo with Fludarabine and Cyclophosphamide
  - 50 x 10^6 bb2121 CAR T-cells
  - 150 x 10^6 bb2121 CAR T-cells
  - 450 x 10^6 bb2121 CAR T-cells

- 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

Ida-cel CAR-T : Overall Response Rate

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

<table>
<thead>
<tr>
<th>Outcome by Prior Lines</th>
<th>3 Lines Tx (n = 15)</th>
<th>≥4 Lines Tx (n = 113)</th>
<th>All Ide-cel Patients (n = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>73</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>CR/sCR, n (%)</td>
<td>53</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>VGPR</td>
<td>0</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>PR</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

- 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


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

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

<table>
<thead>
<tr>
<th></th>
<th>Idecabtagene vicleucel KarMMa trial</th>
<th>Ciltacabtagene autoleucel CARTITUDE 1 trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase of Trial (pts infused)</td>
<td>2 (128)</td>
<td>1b/2 (97)</td>
</tr>
<tr>
<td>Follow-up, median (range)</td>
<td>13.3 mo (6.2-21.2)</td>
<td>21.7 mo (not reported)</td>
</tr>
<tr>
<td>Prior lines, median (range)</td>
<td>6 (3 to 16)</td>
<td>6 (3-18)</td>
</tr>
<tr>
<td>LD chemotherapy</td>
<td>Fludarabine 30mg/m²×3 d</td>
<td>Fludarabine 30mg/m²×3 d</td>
</tr>
<tr>
<td></td>
<td>Cyclo 300mg/m²×3 d</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>94 (73)</td>
<td>95 (97.9)</td>
</tr>
<tr>
<td>At dose: 450×10⁶ (n=54): 44 (81%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR or sCR, n (%)</td>
<td>42 (33)</td>
<td>82.5% (sCR)</td>
</tr>
<tr>
<td>At dose: 450×10⁶ (n=54): 21 (39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOR, median (95% CI)</td>
<td>10.7 mo (9.0-11.3)</td>
<td>Not reported</td>
</tr>
<tr>
<td>PFS, median (95% CI)</td>
<td>8.8 mo (5.6-11.6)</td>
<td>NR (16.8-NE)</td>
</tr>
<tr>
<td>At dose: 450×10⁶: 12.1 mo (8.8-12.3)</td>
<td></td>
<td>2-y PFS: 60.5% (48.5-70.4)</td>
</tr>
<tr>
<td>OS, median (95% CI)</td>
<td>24.8 mo (19.9-31.2)</td>
<td>NR (27.2-NE)</td>
</tr>
<tr>
<td>CRS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>107 (84)</td>
<td>92 (95)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>7 (5)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Neurotoxicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>23 (18)</td>
<td>20 (21)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>4 (3)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Infections, n (%)</td>
<td>88 (69)</td>
<td>56 (58)</td>
</tr>
<tr>
<td>Grade 3-4 Infections, n (%)</td>
<td>28 (22)</td>
<td>19 (20)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>44 (34)</td>
<td>14</td>
</tr>
</tbody>
</table>

Modified from Hematology Am Soc Hematol Educ Program 2022: 2022 (1)
Bi-specific T-cell engagers and antibodies (BiTEs) to bring the activated T cells to the cancer

BiTE antibody composed of two single-chain antibodies

Anti-CD3 (T-Cell) monoclonal antibody

Anti-tumor monoclonal antibody (such as BCMA or CD19)

T Cell

CD3

BCMA

Lytic granule

Teclistamab
(Tecvayli)

FDA APPROVED
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 (i.e., 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

MajesTEC-1: Efficacy Outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>All Patients (N = 165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD negativity, n (%), 95% CI</td>
<td>(n = 150)</td>
</tr>
<tr>
<td>At 10⁻³</td>
<td>37 (24.7; 18.0-32.4)</td>
</tr>
<tr>
<td>At 10⁻⁶</td>
<td>25 (16.7; 11.1-23.6)</td>
</tr>
<tr>
<td>Median DoR, mo</td>
<td>Not yet reached</td>
</tr>
<tr>
<td>Event-free survival rates, % (95% CI)</td>
<td></td>
</tr>
<tr>
<td>6-Mos</td>
<td>92.5 (80.6-97.2)</td>
</tr>
<tr>
<td>9-Mos</td>
<td>85.9 (70.0-93.7)</td>
</tr>
<tr>
<td>PFS rates, % (95% CI)</td>
<td></td>
</tr>
<tr>
<td>6-Mos</td>
<td>64.4 (56.0-71.7)</td>
</tr>
<tr>
<td>9-Mos</td>
<td>58.5 (48.8-67.0)</td>
</tr>
<tr>
<td>Median OS</td>
<td>Not yet reached</td>
</tr>
</tbody>
</table>

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


MajesTEC-1: Safety

- 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%)
  - Opportunistic infections: 9 (5.5%)
  
- Infections: any grade, 104 (63.0%); grade 3/4: 35.2%
- 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

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 \( \geq 4 \) 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.

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 bispecific T-cell engager for RRMM:
  - To determine whether a single dose of TCZ prior to the 1\textsuperscript{st} 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.

**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

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

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

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

- Table:
  - Median prior lines of therapy, n (range): 6 (3-15)
  - Exposure status, n (%):
    - CAR T-cell: 36 (70.6)*
    - Bispecific antibody: 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: 72.2 (54.8-85.8)
    - Bispecific antibody: 44.4 (21.5-69.2)

- Chart:
  - Overall Response Rate:
    - 62.7% (32/51)
    - ≥VGPR: 29.4% (9.8%, 5.9%, 17.6%)
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

Comparison of immunotherapy approaches in myeloma

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Bispecific T-cell engagers</th>
<th>CAR T-cell therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Off-the-shelf therapy (no delays)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Deep responses</td>
<td>One time treatment</td>
</tr>
<tr>
<td></td>
<td>Mostly grade 1-2 CRS/ICANS</td>
<td>Vacation from continuous therapy</td>
</tr>
<tr>
<td></td>
<td>Only initial dosing as inpatient</td>
<td>Deep responses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disadvantages</th>
<th>Bispecific T-cell engagers</th>
<th>CAR T-cell therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Continuous therapy until progression</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Weekly or biweekly dosing</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Significant immunosuppression</td>
<td>Significant immunosuppression</td>
</tr>
<tr>
<td></td>
<td>Specialized centers required</td>
<td>Potential for severe CRS/ICANS; prolonged cytopenias</td>
</tr>
<tr>
<td></td>
<td>Cost ($$)</td>
<td>Complex infrastructure required</td>
</tr>
<tr>
<td></td>
<td>Cost ($$$)</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Hematology Am Soc Hematol Educ Program 2022; 2022 (1): 163–172
Communicating With Your Health Care Team

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.
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

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
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

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!
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.
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.

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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
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