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## Speaker Introduction

Luke received his Bachelor of Science in Biochemistry from Saint Cloud State University in Saint Cloud, Minnesota and his Doctor of Pharmacy degree from the University of Minnesota College of Pharmacy in Minneapolis, Minnesota. Luke completed his PGY1 training at Nebraska Medicine in Omaha, Nebraska. Luke is currently a PGY2 oncology pharmacy resident at University of Utah Health/Huntsman Cancer Institute in Salt Lake City, Utah. His career interests are hematology, oncology, and bone marrow transplant.

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Luke Brinkman, PharmD
11/06/2021



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## I've Got Pills, They're Multiplying: New Drug Updates in Multiple Myeloma

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## Disclosure

- Relevant Financial Conflicts of Interest
  - **CE Presenter, {Luke Brinkman}:**
    - None
  - **CE mentor, {Alyson Clough }:**
    - None
  - **CE mentor, {Kelley Julian}:**
    - Oncopeptides, advisory board (2020)
    - Karyopharm, advisory board (2020)
- Off-Label Uses of Medications
  - None



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## Learning Objectives

### Pharmacist

- Describe the pathophysiology of multiple myeloma
- Differentiate between drug targets in multiple myeloma, while evaluating new agents and their place in phase of treatment
- Formulate a treatment approach for patients with relapsed/refractory multiple myeloma using the new therapies and information discussed

### Technician

- Discuss multiple myeloma and the symptoms a patient may present with
- Review recently approved treatment options for multiple myeloma
- Differentiate between these new agents and their side effect profiles



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## Incidence of Multiple Myeloma (MM)

- New cases in 2021 (estimated): 34,920
- Percent of all new cancer cases: 1.8%
- Deaths in 2021 (estimated): 12,410
- Percent of all cancer deaths: 2.0%
- Median age at diagnosis: 69 years

SEER Cancer Stat Facts: Multiple Myeloma. Retrieved from: https://seer.cancer.gov/statfacts/html/mulmy.html



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## 5-Year Survival

- Not curable
- Relative 5-year survival: 55.6%
- Median age at time of death: 75 years

SEER Cancer Stat Facts: Multiple Myeloma. Retrieved from: https://seer.cancer.gov/statfacts/html/mulmy.html



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## Plasma Cell Disorders

- Multiple myeloma
- Non-IgM MGUS
- Smoldering MM
- IgM MGUS
- Light chain MGUS
- Solitary plasmacytoma
- Solitary plasmacytoma with minimal marrow involvement

MGUS: Monoclonal gammopathy of undetermined significance

Rajkumar SV. *American journal of hematology*; 2020: *95*(5), 548-567.

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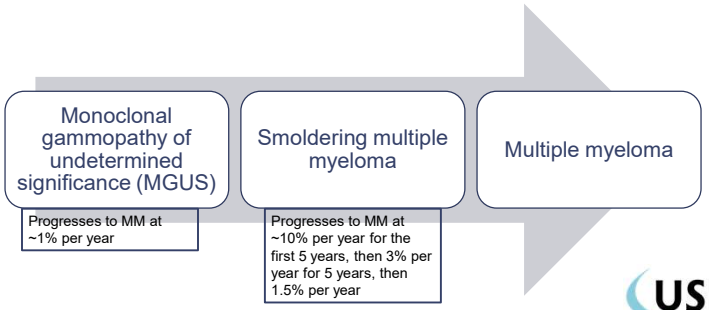
## Classification of Multiple Myeloma




Rajkumar SV. *American journal of hematology*; 2020: *95*(5), 548-567.

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## Signs/Symptoms

- Hypercalcemia (>11.5mg/dL)
- Renal failure (<40mL/min)
- Anemia (Hgb <10g/dL)
- Bone disease

C: hypercalcemia
R: renal failure
A: anemia
B: lytic bone lesions

NCCN Guidelines: Multiple Myeloma. Version 1.2022. 8/16/2021
Rajkumar SV. *American journal of hematology*; 2020: *95*(5), 548-567.

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## Risk Factors

- Male
- African-American
- Older age
- Radiation exposure
- Chemical exposure

Rajkumar SV. *American journal of hematology*; 2020: *95*(5), 548-567.

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## Risk Stratification

- **Low risk**
  - >10-year overall survival
- **Standard risk**
  - 7-year overall survival
- **High risk**
  - 2-year overall survival

Chng WJ, Dispenzieri A, et al. *Leukemia*; 2014: 28(2), 269-277.

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## Diagnosis

**International Myeloma Working Group criteria**

- One or more myeloma defining events
  - CRAB: hyper**c**alcemia, **r**enal failure, **a**nemia, lytic **b**one lesions
  - Clonal bone marrow plasma cells ≥60%
  - Serum free light chain ratio ≥100
  - MRI with >1 focal lesion

**AND**

- Evidence of ≥10% clonal plasma cells or biopsy-proven plasmacytoma ≥10%

Rajkumar SV. *American journal of hematology*; 2020: 95(5), 548-567.

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## SLiM-CRAB Diagnosis

- **S: sixty**
  - ≥ 60% clonal plasma cells
- **Li: light chain**
  - Involved/uninvolved free light chain ratio of ≥100
- **M: MRI**
  - More than one focal marrow lesion (non-osteolytic)

NCCN Guidelines: Multiple Myeloma. Version 1.2022. 8/16/2021

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## Diagnosis

- Physical exam
- CBC/CMP
- Serum and urine analysis
- Bone marrow biopsy
- Cytogenetic studies
- CT +/- PET/CT
- MRI

NCCN Guidelines: Multiple Myeloma. Version 1.2022. 8/16/2021
Rajkumar SV. *American journal of hematology*; 2020: 95(5), 548-567.

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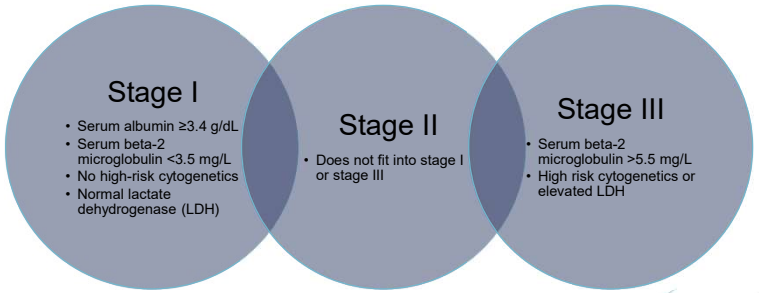
## Staging




Rajkumar SV. *American journal of hematology*; 2020: 95(5), 548-567.

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## Traditional Treatment Options

**Immunomodulatory agents (IMiDs)**
- Thalidomide
- Lenalidomide
- Pomalidomide

**Proteasome inhibitors**
- Bortezomib
- Carfilzomib
- Ixazomib

**Anti-CD38 monoclonal antibodies**
- Daratumumab
- Isatuximab

Cytotoxic Therapies

Corticosteroids

Rajkumar SV. *American journal of hematology*; 2020: 95(5), 548-567.

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## Treatment Strategies- First Line

VRd x 3-4 cycles
- Autologous stem cell transplant → Maintenance
- Continue VRd for 5-8 cycles → Maintenance

D-RVD

KRD +/- daratumumab

CyBorD +/- daratumumab

VRd: bortezomib, lenalidomide, dexamethasone
- Overall response rates 82-97%
- Progression free survival 36-43 months

Rajkumar SV. *American journal of hematology*; 2020: 95(5), 548-567.

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## Treatment Strategies- Relapsed/Refractory

**Lenalidomide Non-refractory**
- DRd: daratumumab, lenalidomide, dexamethasone
- KRd: carfilzomib, lenalidomide, dexamethasone
- ERd: elotuzumab, lenalidomide, dexamethasone
- IRd: ixazomib, lenalidomide, dexamethasone

Rajkumar SV. *American journal of hematology*; 2020: 95(5), 548-567.

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## Treatment Strategies- Relapsed/Refractory

Lenalidomide refractory

- DVd: daratumumab, bortezomib, dexamethasone
- DPd: daratumumab, pomalidomide, dexamethasone
- IsaPd: isatuximab, pomalidomide, dexamethasone
- KPd: carfilzomib, pomalidomide, dexamethasone
- EPd: elotuzumab, pomalidomide, dexamethasone

Rajkumar SV. *American journal of hematology*; 2020: *95*(5), 548-567.





## Subcutaneous Daratumumab

| IV daratumumab | Sub-Q daratumumab hyaluronidase |
|---|---|
| • First infusion: ~7 hours<br>• Subsequent infusions: ~3-4 hours<br>• Infusion related reactions | • 1800mg daratumumab/15mL<br>• Administration time: 3-5 minutes<br>• Fewer reactions |

Mateos MV, Nahi H, et al. *The Lancet Haematology*; 2020: 7(5), e370-e380.





## New Agents for Multiple Myeloma Treatment

| | |
|---|---|
| Belantamab mafodotin | Idecabtagene vicleucel |
| Melflufen | Selinexor |





## Belantamab mafodotin-blmf (Blenrep™)

- Approved August 2020
- B-cell maturation antigen (BCMA)
  - Cell surface receptor on MM cells
  - Not typically present on naïve and memory B-cells
- Belantamab mafodotin is an anti-BCMA antibody-drug conjugate
  - Microtuble disrupting agent monomethyl auristatin F (MMAF)
- Delivers MMAF to BCMA expressing cells

Lonial S, Lee HC, et al. *The lancet oncology*; 2020: *21*(2), 207-221.

## DREAMM-2 Study Design

- Open-label, two-arm, phase II study
- Belantamab mafodotin 2.5 mg/kg (n=97) or 3.4 mg/kg (n=99)
  - 1:1 randomization
- Dosed once every 3 weeks
- Continued until disease progression or unacceptable toxicity
- June 2018-January 2019

Lonial S, Lee HC, et al. *The lancet oncology*; 2020: 21(2), 207-221.

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## DREAMM-2

**Inclusion criteria**

- Age ≥18 years
- R/R multiple myeloma with ≥3 lines of therapy
  - Immunomodulators
  - Proteasome inhibitors
  - Anti-CD38 monoclonal antibody
- ECOG 0-2

**Exclusion criteria**

- Previous BCMA therapy
- Systemic high dose corticosteroids
- Investigational drugs (≤14 days or 5 half lives)
- Allogeneic stem cell transplant
- Corneal epithelial disease
- Serious or unstable pre-existing medical condition

Lonial S, Lee HC, et al. *The lancet oncology*; 2020: 21(2), 207-221.

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## DREAMM-2 Outcomes

| Outcome | Belantamab 2.5 mg/kg (n=97) | Belantamab 3.4 mg/kg (99) |
|---|---|---|
| Proportion of patients receiving an overall response* | 31 (37%) | 34 (34%) |
| Duration of response (median) | Not reached at median 6.3 month follow up | Not reached at median 6.9 month follow up |
| Progression free survival (PFS) (median) | 2.9 months | 4.9 months |
| Overall survival (OS) (median) | Not reached | Not reached |
| Proportion of patients achieving minimal response or better | 33 (34%) | 39 (39%) |
| Death | 32 (33%) | 31 (31%) |

*Primary outcome

Lonial S, Lee HC, et al. *The lancet oncology*; 2020: 21(2), 207-221.

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## DREAMM-2 Adverse Events

| Adverse Event | Belantamab 2.5 mg/kg (n=95) | Belantamab 3.4 mg/kg (99) |
|---|---|---|
| Adverse event leading to permanent discontinuation | 8 (8%) | 10 (10%) |
| Keratopathy (grade 3-4) | 26 (27%) | 21 (21%) |
| Thrombocytopenia | 19 (20%) | 33 (33%) |
| Anemia | 19 (20%) | 25 (25%) |
| Neutropenia | 13 (14%) | 27 (27%) |
| Pneumonia (grade ≥3) | 4 (4%) | 11 (11%) |
| Serious event causing death | 3 (3%) | 7 (7%) |

Lonial S, Lee HC, et al. *The lancet oncology*; 2020: 21(2), 207-221.

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## DREAMM-2 Applications

| Limitations | Strengths |
|---|---|
| • Short duration of follow up<br>• Not compared against a standard of care arm | • Positive outcome in patients refractory to proteasome inhibitors, immunomodulators, and received an anti-CD38 monoclonal antibody |

Lonial S, Lee HC, et al. *The lancet oncology*; 2020: 21(2), 207-221.

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## Idecabtagene vicleucel (Abecma™)

Anti-BCMA chimeric antigen receptor (CAR) T-cell therapy

- Modified T-cells targeted towards the BCMA receptor

Approved March 26th, 2021

Munshi NC, Anderson Jr LD, et al. *New England Journal of Medicine*; 2021: *384*(8), 705-716.

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## KarMMa Study

- Single-group, phase II study
- Lymphodepletion with fludarabine and cyclophosphamide
- Target dose of cells: 150 x $10^6$, 300 x $10^6$, or 450 x $10^6$ CAR-T positive cells
- 140 patients received ide-cel

Munshi NC, Anderson Jr LD, et al. *New England Journal of Medicine*; 2021: *384*(8), 705-716.

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## KarMMa Patient Demographics

| Characteristic | Patients (n=128) |
|---|---|
| Median age | 61 years (range 33-78) |
| Median time since diagnosis | 6 years (range 1-18) |
| High tumor burden | 65 (51%) |
| Extramedullary disease | 50 (39%) |
| Stage III disease | 21 (16%) |
| High risk cytogenetics | 45 (35%) |
| Median previous regimens | 6 (range 3-16) |
| Previous autologous transplant | 120 (94%) |

Munshi NC, Anderson Jr LD, et al. *New England Journal of Medicine*; 2021: *384*(8), 705-716.

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## KarMMa

| Inclusion criteria | Exclusion criteria |
|---|---|
| • 18 years or older<br>• Received at least 3 prior therapies (including immunomodulator, proteasome inhibitor, and anti-CD38 antibody)<br>• Refractory disease to last treatment<br>• Measurable disease<br>• Adequate organ function | • CNS involvement<br>• Plasma cell leukemia<br>• Inadequate bone marrow function<br>• Allogeneic stem cell transplant<br>• Gene therapy treatment including anti-BCMA therapy. |

Munshi NC, Anderson Jr LD, et al. *New England Journal of Medicine*; 2021: *384*(8), 705-716.

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## KarMMa Outcomes

| Outcome | Ide-cel (n=128) |
|---|---|
| Overall response* | 94 (73%) |
| Complete response or better | 42 (33%) |
| Time to response (median) | 1 month |
| Duration of response (median) | 10.7 months |
| Progression free survival (median) | 8.8 months |
| Overall survival (median) | 19.4 months |

*Primary outcome

Munshi NC, Anderson Jr LD, et al. *New England Journal of Medicine*; 2021: *384*(8), 705-716.

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## KarMMa Adverse Events

| Adverse Event | Ide-cel (128) |
|---|---|
| Cytokine release syndrome (CRS) | 107 (84%) |
| CRS grade 3-5 | 6 (5.5%) |
| Neurotoxicity | 23 (18%) |
| Grade 3-4 adverse event | 99% |
| Neutropenia | 114 (89%) |
| Anemia | 77 (60%) |
| Thrombocytopenia | 67 (52%) |
| Infection | 88 (69%) |
| Death | 44 (34%) |

Supportive care considerations:
- CRS/neurotoxicity
- Infection prophylaxis

Munshi NC, Anderson Jr LD, et al. *New England Journal of Medicine*; 2021: *384*(8), 705-716.

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## KarMMa

| Limitations | Strengths |
|---|---|
| • Single arm study<br>• Limited number of patients<br>• CAR-T therapy is complex | • Positive outcome in patients refractory to proteasome inhibitors, immunomodulators, and received an anti-CD38 monoclonal antibody |

Munshi NC, Anderson Jr LD, et al. *New England Journal of Medicine*; 2021: *384*(8), 705-716.

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## Melflufen (Pepaxto™)

- Peptide drug conjugate of melphalan and flufenamide
- Melfulfen is highly lipophilic and taken up into myeloma cells
- Action within 2 hours compared to melphalan 6 hours
- Approved February 26th, 2021





## OCEAN

- Open-label, multicenter, phase 1-2 study
- Phase 1
  - Dose escalation
- Phase 2
  - Melflufen 40mg IV on day 1 of 28-day cycles
  - Dexamethasone 40mg once weekly

Richardson PG, Bringhen S, et al. *The Lancet Haematology*; 2020: 7(5), e395-e407.





## OCEAN Phase II

| Inclusion criteria | Exclusion |
|---|---|
| • Adults ≥18 years of age<br>• Relapsed/refractory MM with measurable disease<br>• ≥2 prior lines of therapy (including lenalidomide and bortezomib)<br>• Refractory to last line of treatment<br>• Adequate organ function | • Mucosal or internal bleeding<br>• Platelet transfusion refractory<br>• Known infection<br>• Intolerance to steroids |

Richardson PG, Bringhen S, et al. *The Lancet Haematology*; 2020: 7(5), e395-e407.





## OCEAN Phase II Outcomes

| Outcome | Melflufen (n=45) |
|---|---|
| Overall response* | 14 (31%) |
| Duration of response | 8.4 months |
| Clinical benefit | 22 (49%) |
| Median progression free survival | 5.7 months |
| Median overall survival | 20.7 months |

*Primary outcome

Richardson PG, Bringhen S, et al. *The Lancet Haematology*; 2020: 7(5), e395-e407.

## OCEAN Phase II Adverse Events

| Adverse Event | Patients (n=45) |
|---|---|
| Thrombocytopenia | 73% |
| Neutropenia | 69% |
| Anemia | 64% |
| Pyrexia | 40% |
| Asthenia | 31% |
| Fatigue | 29% |
| Nausea | 27% |

Supportive care considerations:
- Platelet transfusions
- GCSF/TPO agonists
- Infection prophylaxis

Richardson PG, Bringhen S, et al. *The Lancet Haematology*; 2020: 7(5), e395-e407.

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## OCEAN Phase II Analysis

**Limitations**
- Small cohort size
- Single arm design

**Strengths**
- Clinical and long-term benefits in heavily pretreated patients

Richardson PG, Bringhen S, et al. *The Lancet Haematology*; 2020: 7(5), e395-e407.

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## OCEAN Phase III Study

Randomized, head-to-head, superiority, open-label, phase III study

Melflufen + dexamethasone
- Melflufen 40mg IV on day 1
- Dexamethasone 40mg on days 1,8,15, and 22 of 28-day cycles

Pomalidomide + dexamethasone
- Pomalidomide 4mg PO daily on days 1-21
- Dexamethasone 40mg on days 1,8,15,22 of 28-day cycles

Schjesvold F, Robak P, et al. *Future Oncology*; 2020: *16*(11), 631-641.

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## Selinexor (Xpovio™)

Exportin 1 (XPO1)
- Nuclear exporter of tumor suppressor proteins

Selinexor inhibits XPO1
- Binds to cargo binding pocket and causes activation of tumor suppressor proteins that would have otherwise been exported
- Leads to apoptosis of MM cells

Approved December 2020

Chari A, Vogl DT et al. *New England Journal of Medicine*; 2019: *381*(8), 727-738.

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## STORM Study

Phase II study

Part 1 – evaluated 2 dosing schedules

- 21% of patients with partial response or better

Part 2 – phase IIB

- Multicenter, open label study
- Selinexor 80mg + dexamethasone 20mg on days 1 and 3 each week of a 4-week cycle

Chari A, Vogl DT et al. *New England Journal of Medicine*; 2019: *381*(8), 727-738.

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## STORM Demographics

| Characteristic | Patients (n=122) |
|---|---|
| Median age | 65.2 years |
| Median duration of myeloma | 6.6 years |
| High risk cytogenetics | 53% |
| Median previous therapies | 7 (range 3-18) |
| Previous stem cell transplant | 102 (84%) |
| Previous CAR-T therapy | 2 (2%) |

Chari A, Vogl DT et al. *New England Journal of Medicine*; 2019: *381*(8), 727-738.

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## STORM

**Inclusion criteria**

- Measurable myeloma
- Previous treatment with bortezomib, carfilzomib, lenalidomide, pomalidomide, and an alkylating agent
- Disease refractory to at least: one immunomodulator, one proteasome inhibitor, daratumumab, glucocorticoids, and the most recent regimen
- ECOG 0-2
- Adequate organ function

**Exclusion criteria**

- Systemic light chain amyloidosis
- Active CNS involvement
- Grade 3 peripheral neuropathy or higher
- Grade 2 painful neuropathy or higher

Chari A, Vogl DT et al. *New England Journal of Medicine*; 2019: *381*(8), 727-738.

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## STORM Outcomes

| Outcome | Selinexor (n=122) |
|---|---|
| Overall response* | 32 (26%) |
| Median time to response | 4.1 weeks (range 1-14) |
| Duration of response | 4.4 months |
| Clinical benefit | 48 (39%) |
| Median progression free survival | 3.7 months |
| Median overall survival | 8.6 months |

*Primary outcome

Chari A, Vogl DT et al. *New England Journal of Medicine*; 2019: *381*(8), 727-738.

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## STORM Adverse Events

| Adverse Event | Patients (n=122) |
|---|---|
| Thrombocytopenia | 73% |
| Nausea | 72% |
| Anemia | 67% |
| Death | 23% |

Supportive care considerations:
- Platelet transfusions
- Antiemetics

Chari A, Vogl DT et al. *New England Journal of Medicine*; 2019: *381*(8), 727-738.





## STORM Analysis

| Limitations | Strengths |
|---|---|
| • Small patient population<br>• Frequent dose modifications<br>• No comparator group | • Included patients with reduced renal function, thrombocytopenia, and neutropenia<br>• Heavily pretreated patient population with progressive disease |

Chari A, Vogl DT et al. *New England Journal of Medicine*; 2019: *381*(8), 727-738.





## Comparing the New Agents

| | Belantamab | Ide-Cel | Melflufen | Selinexor |
|---|---|---|---|---|
| Approval date | 8/2020 | 3/2021 | 2/2021 | 12/2020 |
| Mechanism of Action | Anti-BCMA antibody-drug conjugate | Anti-BCMA CAR-T cell therapy | Peptide drug conjugate of melphalan and flufenamide | XPO1 inhibition |
| Overall response | 34-37% | 73% | 31% | 26% |
| PFS | 2.9-4.9 months | 8.8 months | 5.7 months | 3.7 months |
| Overall survival | Not reached | 19.4 months | 20.7 months | 8.6 months |
| Main adverse effects | Keratopathy, thrombocytopenia, anemia, neutropenia | CRS, neurotoxicity, neutropenia | Thrombocytopenia, neutropenia, anemia, pyrexia | Thrombocytopenia, nausea, anemia |
| Other considerations | REMS for ocular toxicity | | | Included patients with renal impairment, thrombocytopenia, and neutropenia |





## In the Pipeline

**Iberdomide**
- New immunomodulator
- Greater activity compared to pomalidomide and lenalidomide

**CAR-T**
- CD-38
- SLAMF7
- Light chain targeted CAR-T

**BCL2 inhibitors**

Bjorklund CC, Kang J, et al. *Leukemia*; 2020: *34*(4), 1197-1201.
Yang Y, Li Y, et al. *Journal of Hematology & Oncology; 2020: 13*(1), 1-25.

## Conclusion

Multiple myeloma is an uncurable hematologic malignancy

Many new agents have recently been approved to treat relapsed or refractory multiple myeloma

Most data available for these new agents come from phase II studies

Future studies and more information is needed to properly evaluate these agents in combination with other therapies