Development of Monoclonal Antibody Therapies in Multiple Myeloma

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Objectives

- Understand the mechanism of action of the monoclonal antibodies in myeloma
- Summarize the clinical trials that led to their approval
- Describe elotuzumab and daratumumab in clinical practice
- Define myeloma bone disease, with focus on denosumab

Myeloma: A Continuum of Disease

- MGUS
  - M-protein < 3 g/dL
  - Clonal plasma cells in the bone marrow < 10%
  - No myeloma defining events

- Smoldering MM
  - M-protein ≥ 3 g/dL
  - Clonal plasma cells in the bone marrow >10% but <60%
  - No myeloma defining events

- Multiple Myeloma
  - Underlying plasma cell proliferative disorder
  - AND 1 or more myeloma defining events
  - ≥ 1 CRAB feature
  - Clonal plasma cells in BM ≥ 60%
  - Serum free light chain ratio ≥ 100
  - ≥ 1 MRI focal lesion


Standard Approach to Myeloma Therapy

- Induction therapy, preferably with 3-drug regimen that includes immunomodulatory agent and proteasome inhibitor
- Transplant
- No Transplant
- Maintenance Therapy
- Salvage Treatment at Relapse

Faculty Disclosures

- Nothing to disclose
Targets for monoclonal antibody therapy in myeloma

Cell surface targets

- Signaling molecules
  - IL-6
  - RANKL
  - DKK1
  - VEGF
  - IGF-1
  - SDF-1
  - BAFF, APRIL

Monoclonal Antibodies in Multiple Myeloma

<table>
<thead>
<tr>
<th>Monoclonal Antibodies</th>
<th>Initial Approval Date</th>
<th>Target</th>
</tr>
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<tbody>
<tr>
<td>Daratumumab</td>
<td>November, 2015</td>
<td>CD38</td>
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<tr>
<td>Elotuzumab</td>
<td>November, 2015</td>
<td>SLAMF7</td>
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**Siltuximab**

- Chimeric human-mouse monoclonal IL-6 neutralizing antibody
- IL-6 known to activate cell survival and proliferation signaling pathways in myeloma cells, including JAK/STAT, MEK/ERK, and PI3-K pathways
- In preclinical models, siltuximab inhibited phosphorylation of ERK-1/2, STAT-1, STAT-3, and PI3-K/akt pathways in human MM cell lines in the presence of IL-6
- In preclinical models, siltuximab enhanced the cytotoxic and pro-apoptotic effects of dexamethasone, bortezomib, dexamethasone in human MM cells lines

**Monoclonal Antibodies in Multiple Myeloma**

- Daratumumab
  - Monotherapy
  - Daratumumab/bortezomib/dexamethasone
  - Daratumumab/lenalidomide/dexamethasone
  - Daratumumab/pomalidomide/dexamethasone
  - Daratumumab/bortezomib/melphalan/prednisone
- Elotuzumab
  - Elotuzumab/lenalidomide/dexamethasone
  - Elotuximab/pomalidomide/dexamethasone

**Clinical Trials and Observations**

**Phase 2 randomized study of bortezomib-melphalan-prednisone with or without siltuximab (anti-IL-6) in multiple myeloma**

- Bortezomib plus melphalan and prednisone (VMP) had been standard of care induction regimen in many parts of the world
- Randomized phase 2 trial enrolling newly diagnosed, transplant-ineligible pts with 1:1 randomization to VMP +/- siltuximab
- All patients received nine 42-day cycles of standard VMP.
- Patients in VMP + siltuximab arm received siltuximab 11 mg/kg every 3 weeks
The addition of Siltuximab to VMP led to minimal improvement in overall response and in particular very good partial response or better, but there was no difference in PFS (Median 17 months).

**Siltuximab Summary**
- Despite promising pre-clinical data suggesting synergistic effect with anti-myeloma agents dexamethasone, bortezomib, and melphalan, there was no clinical benefit associated with use of siltuximab in randomized trials in myeloma.
- The agent is the only FDA-approved therapy for patients with idiopathic Multicentric Castleman’s disease without HIV.

**Elotuzumab - Mechanism of Action**
- Phase 1, 3+3 design
- 3 dose levels of elotuzumab (5, 10, and 20 mg/kg) with standard len-dex
- 29 patients with median 3 prior lines of therapy
  - 70% with prior bortezomib
  - 60% with prior thalidomide
  - 76% with prior ASCT
  - 63% refractory to most recent line of therapy

- No dose limiting toxicities.
- High overall rate of response.
- Durable responses.
Elotuzumab: Efficacy in Clinical Trials
ELOQUENT-2 Study

- Elotuzumab 10 mg/kg
  - Cycles 1-2 d 1, 8, 15, 22
  - Cycle 3+ d 1, 15
- Lenalidomide 25 mg d 1-21
- Dexamethasone 40 mg wk/o Elo
- Dexamethasone 8 mg IV + 28 mg PO w/Elo
- Lenalidomide 25 mg d 1-21
- Dexamethasone 40 mg d 1, 8, 15, 22

Primary End-Points:
- PFS
- ORR

Secondary End-Points:
- Time to tumor response,
- Duration of response,
- Safety

Cycles repeated until disease progression, unacceptable toxicity, or withdrawal

Elo-Rd

<table>
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<tr>
<th>Median PFS (95% CI)</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>19.4 mos (16.6, 22.2)</td>
<td>0.73 (0.60, 0.89); P = .0014</td>
</tr>
</tbody>
</table>

1-year PFS 2-year PFS 3-year PFS
- 68%
- 41%
- 26%
- 57%
- 27%
- 18%

6 9 30 33 36 39 42 45 48
PFS (months)

Toxicities Associated with Elotuzumab

- Hematologic toxicity - increased rate of lymphocytopenia
- Non-hematologic toxicity - infusion reactions, increased rate of low-grade fatigue, cough, diarrhea, constipation
- No associated peripheral neuropathy
- No significant cardiovascular or vascular toxicity

Elotuzumab Summary

- Despite lack of significant single agent activity in relapsed MM, elotuzumab is synergistic with immunomodulatory agents lenalidomide and pomalidomide based on its stimulatory effect on NK cell activity, a cell population IMID agents also activate
- Elotuzumab has favorable side effect profile, and has relatively few overlapping side effects with the IMID agents
- Elotuzumab is one of few approved agents in MM that is not associated with peripheral neuropathy
- Elotuzumab plus lenalidomide-dexamethasone was approved by the FDA in 2015
- Elotuzumab plus pomalidomide-dexamethasone was approved by the FDA in 2018

Elotuzumab: Safety in Clinical Trials
ELOQUENT-2 Study

Infusion reactions of any grade were experienced by 10% of patients
- Most infusion reactions were Grade 1 or 2 and occurred during the first treatment cycle
- There were no Grade 4 or 5 infusion reactions

Elotuzumab Dosing and Administration

- Dosing Schedule

- Infusion start slow and then increase based on tolerance
- Dexamethasone and Premedications
  - Dexamethasone 28 mg PO → 3–24 hours before elotuzumab
  - Dexamethasone 8 mg IV
  - Diphenhydramine 25 mg–50 mg IV/PO or equivalent
  - Ranitidine 50 mg IV or 150 mg PO or equivalent
  - Acetaminophen 650 mg–100 mg PO

Daratumumab

- Fully human mAb that targets CD38 expressed on plasma cells and other lymphocyte subsets.
- CD38 is a transmembrane glycoprotein that mediates cell adhesion and signaling. High level of expression on malignant myeloma cells
- Daratumumab induces ADCC, CDC, and ADCP
- Decreases subpopulation of immunosuppressive regulatory T-cells (Tregs)
- Increases Helper and Cytotoxic T-cells

Monoclonal antibody - Daratumumab

- Human CD38 IgG monoclonal antibody
- Direct and indirect anti-myeloma activity
- Depletes CD38+ immunosuppressive regulatory cells
- Promotes T-cell expansion and activation

Phase I Study of Daratumumab in RR MM

- Part 1: Dose-escalation cohorts
  - Open label, weekly i.v. infusion, 8 weeks
  - Dose-escalation: 3+3 scheme
    - 0.005 → 0.05 → 0.1 → 0.5 → 1.0 → 2.0 → 4.0 → 8.0 → 16.0 → 24.0 mg/kg

- Part 2: Expansion cohort
  - Dose: 8 mg/kg and 16 mg/kg

- No DLTs in Part 1 dose escalation
- Response rate superior among patients treated at the 16 mg/kg dose, which was chosen as dose for subsequent trials with dara

- 569 patients
- 1 or more previous lines of therapy
- Prior lenalidomide permitted if len sensitive
- 1:1 randomization
  - lenalidomide and dexamethasone +/- daratumumab until disease progresses
**CASTOR: Bortezomib plus dex +/- daratumumab**

- **Response Rates (DVd vs RD)**
  - ORR 48.2% vs 39.2%
  - VGPR or better 28.1% vs 20.3%
  - CR or better 15.3% vs 12.0%
  - SDR 15.6% vs 20.3%

- **Key secondary endpoints**
  - OS: 17.5 (95% CI, 13.3-NE) months
  - ORR: 8.8 (95% CI, 6.6-15.4) months
  - MRD-negative rate (NGS; ≥ VGPR rate): 10–5)

- **Key eligibility criteria:**
  - ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; NA, North America; IV, intravenously; QW, once weekly; BMI, body mass index.

- **DMAP (Daratumumab/pomalidomide/ Dexamethasone)**

- **Key eligibility criteria:**
  - 498 patients
  - 1 or more previous lines of therapy
  - Prior bortezomib permitted if bortezomib sensitive
  - 1:1 randomization
    - Bortezomib and dexamethasone x 8 cycles versus
    - Dar plus bortez and dex x 8 cycles followed by dar maintenance

- **Key secondary endpoints:**
  - ORR, OS, PFS

- **Key endpoints:**
  - ORR: 8.8 (95% CI, 6.6-15.4) months
  - MRD-negative rate (NGS; ≥ VGPR rate): 10–5)
  - OS: 17.5 (95% CI, 13.3-NE) months
  - The estimated 12-month survival rate was 66% (95% CI, 55.6-74.8)

- **Nonrandomised Phase Ib**
  - Safety was the primary endpoint. Overall response rate (ORR) and minimal residual disease (MRD) by next-generation sequencing were secondary endpoints
  - 103 patients received a median (range) of 4 (1–13) prior therapies; 76% received ≥3 prior therapies
  - Safety was the primary endpoint. Overall response rate (ORR) and minimal residual disease (MRD) by next-generation sequencing were secondary endpoints
  - Nonrandomized Phase Ib
    - The estimated 12-month survival rate was 66% (95% CI, 55.6-74.8)
  - At a median follow-up of 13.1 months, the median progression-free survival was 8.8 (95% CI, 4.6-15.4) months and median overall survival was 17.5 (95% CI, 13.3-NE) months
  - The estimated 12-month survival rate was 66% (95% CI, 55.6-74.8)

- **EQUULEUS study**
  - Nonrandomised Phase Ib
  - Safety was the primary endpoint. Overall response rate (ORR) and minimal residual disease (MRD) by next-generation sequencing were secondary endpoints
  - 103 patients received a median (range) of 4 (1–13) prior therapies; 76% received ≥3 prior therapies
  - The safety profile of daratumumab plus pom-dex was similar to that of pom-dex alone, with the exception of daratumumab-specific infusion-related reactions (50%) and a higher incidence of neutropenia, although without an increase in infection rate
  - Common grade 3 adverse events were neutropenia (7%), anemia (16%), and leukopenia (24%)
  - ORR was 60% and was generally consistent across subgroups (58% in double-refractory patients). Among patients with a complete response or better, 29% were MRD negative at a threshold of 10–5

- **MAIA Study Design**

- **Phase 3 Randomized Study of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) in Patients With Newly Diagnosed Multiple Myeloma (NDMM) ineligible for Transplant (MAIA)**

- **Key eligibility criteria:**
  - Age (<75 vs ≥75 years)
  - Region (NA vs other)
  - ISS (I vs II vs III)
  - ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; NA, North America; IV, intravenously; QW, once weekly; BMI, body mass index.

- **Key endpoints:**
  - ORR: 8.8 (95% CI, 6.6-15.4) months
  - MRD-negative rate (NGS; ≥ VGPR rate): 10–5)
  - OS: 17.5 (95% CI, 13.3-NE) months
  - The estimated 12-month survival rate was 66% (95% CI, 55.6-74.8)
Efficacy: PFS

- 44% reduction in the risk of progression or death in patients receiving D-Rd

Conclusions

- D-Rd significantly reduced the risk of progression or death by 44% in patients with transplant-ineligible NDMM
- D-Rd induced significantly deeper responses, including 3.4-fold higher MRD-negative rate
- No new safety signals were observed using D-Rd in NDMM

These results support D-Rd as a new standard of care for patients with transplant-ineligible NDMM.
Toxicities Associated with Daratumumab

- Hematologic toxicity – increased rate of neutropenia, thrombocytopenia, and febrile neutropenia
- Non-hematologic toxicity – infusion reactions, as well as increased rate of diarrhea, dyspnea, cough, upper respiratory infection
- Minimal peripheral neuropathy
- No significant cardiovascular or vascular toxicity

Daratumumab Dosing and Administration

- 16 mg/kg IV infusion according to the following schedule for single agent and for combination with lenalidomide (28 day cycle):
  - Weeks 1–8: Weekly dosing
  - Weeks 9–24: Every 2 weeks
  - Week 25–disease progression: Every 4 weeks

- 16 mg/kg IV infusion according to the following schedule for combination with bortezomib (28 day cycle):
  - Weeks 1–9: Weekly dosing
  - Weeks 10–24: Every 3 weeks
  - Week 25–disease progression: Every 4 weeks

Infusion Rates

<table>
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<tr>
<th>Infusion</th>
<th>Total Volume</th>
<th>Initial Rate</th>
<th>Rate Increment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>1000 mL</td>
<td>50 mL/hour</td>
<td>50 mL/hour up to 200 mL/hour (for cardiac risk)</td>
</tr>
<tr>
<td>Subsequent</td>
<td>500 mL</td>
<td>50 mL/hour</td>
<td></td>
</tr>
<tr>
<td></td>
<td>500 mL</td>
<td>100 mL/hour</td>
<td></td>
</tr>
</tbody>
</table>

- Premedications
  - Methylprednisolone 100 mg IV or equivalent
  - Acetaminophen 650 mg – 1000 mg PO
  - Diphenhydramine 25 mg – 50 mg IV/PO or equivalent
  - Methylprednisolone 20 mg PO or equivalent → 1–2 days after

Daratumumab Summary

- Daratumumab possesses significant single agent activity and was initially FDA approved as monotherapy (with steroid pre-medication) for patients who had received 3 or more prior lines of therapy
- However, daratumumab is most active in combination with other anti-myeloma agents/classes
- has relatively few overlapping side effects with other commonly used agents
- there is minimal peripheral neuropathy
- The following daratumumab-containing combinations regimens are FDA approved:
  - Daratumumab plus lenalidomide in RR MM with 1 prior line
  - Daratumumab plus bortezomib in RR MM with 1 prior line
  - Daratumumab plus pomalidomide in RR MM with 2 prior lines
  - Daratumumab plus VMP in newly diagnosed MM
  - Dara plus len-dex in NDMM likely to be approved in 2019

Treatment Options in Relapsed Disease

Preferred Regimens for which there is Category 1 Evidence

- Daratumumab plus lenalidomide and dex
- Daratumumab plus bortezomib and dex
- Daratumumab plus pomalidomide and dex
- Elotuzumab plus lenalidomide and dex
- Carfilzomib plus lenalidomide and dex
- Ixazomib plus lenalidomide and dex
- Panobinostat plus bortezomib and dex
- Carfilzomib and dexamethasone
- Bortezomib and dexamethasone
- Lenalidomide and dexamethasone

Other options

- Cyclophosphamide, bortezomib, and dex
- Carfilzomib, cyclophosphamide, and dex
- Lenalidomide, bortezomib, and dexamethasone

Determinants of Treatment Choice in RR MM

Disease Characteristics

- Biochemical progression only versus biochemical progression with significant symptoms and/or organ involvement
- Rapid versus slow, gradual increase in paraprotein
- High versus standard risk cytogenetics
- Presence or absence of extramedullary disease

Characteristics of prior or ongoing therapy

- Brief versus prolonged response
- Depth of response
- Progression on current therapy
- Toxicities associated with prior therapy, including neuropathy, decreased cell counts, GI, or cardiac toxicity
Antibody Therapy in Myeloma Bone Disease

- Up to 90% of myeloma patients have bone lesions at time of diagnosis
- Myeloma and stromal cells secrete factors including RANKL, IL-3, and IL-6 that increase osteoclast function, and other factors such as DKK-1 that inhibit osteoblast activity
- RANKL mediates osteoclast formation, activation, and survival
- Zoledronic acid and pamidronate have been standard of care
- Denosumab – fully human monoclonal antibody that targets RANKL

Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomized, controlled, phase 3 study

- Denosumab is a fully human monoclonal antibody targeting RANKL, which is known to activate osteoclasts
- Zoledronic acid is current standard of care, and in previous phase 3 MRCIX trial comparing ZA to clodronate was associated with not only decrease in skeletal events but also improved PFS and OS
- 1718 patients randomized 1:1 to zoledronic acid or denosumab
- Primary endpoint: non-inferiority with respect to time to first skeletal event

Future Directions

- Use of elotuzumab and daratumumab in patients with high-risk smoldering myeloma
- Second generation anti-CD38 monoclonal antibodies – Isatuximab and MOR202
- Antibodies directed at novel targets such as BCMA
- Bi-specific antibodies

Griffin study

- Ongoing multicenter, randomized, open-label, active-controlled US study
- Sixteen pts received 4 induction cycles of dara-Vd every 21 days followed by stem cell (SC) mobilization, HDT, ASCT; 2 consolidation cycles of dara-Vd; and maintenance therapy with dara-R for 24 months
- By the end of consolidation (C6), all pts (100%) reached VGPR or better and 63% achieved CR or sCR per investigator assessments (using IMWG criteria)
- All 16 pts experienced 11 treatment-emergent adverse events (AE)
  - 10 (62.5%) pts having ≥1 serious AE (SAE), including 1 (6.25%) pt with ≥1 SAE related to dara
  - Fourteen (87.5%) pts had grade 3-4 AEs, with 11 (68.75%) related to dara
  - Most commonly reported grade 3-4 AEs included neutropenia, pneumonia, thrombocytopenia, lymphopenia, fatigue, neurotoxicity, leukopenia, and hypophosphatemia
  - Twelve (75%) pts experienced infections, including pneumonia (4), E Coli bacteremia, sinusitis, and gastroenteritis (1 each)
  - No deaths due to SAEs were reported, and no pt discontinued treatment due to an AE
  - Dara infusion reactions were reported in 5 (31.3%) pts. All 16 pts underwent successful mobilization with clodronate therapy, with a median follow-up time of 11.6 months, 15 of 16 (93.8%) pts remain progression-free on study treatment

Dara-RVD

Efficacy and Updated Safety Analysis of a Safety Run-in Cohort from Griffin, a Phase 2 Randomized Study of Daratumumab (Dara), Bortezomib (V), Lenalidomide (R), and Dexamethasone (D) in Patients (Pts) with Newly Diagnosed Indolent Multiple Myeloma (MM) Eligible for High-Dose Therapy (HDT) and Autologous Stem Cell Transplantation (ASCT)

Denosumab was non-inferior to zoledronic acid in terms of skeletal events, and was better tolerated with respect to renal toxicity
Isatuximab

- Isatuximab is a novel immunoglobulin G1 kappa anti-CD38 mAb that binds selectively to a specific epitope on CD38
- Can also induce direct apoptosis without cross-linking
- Potent inhibitor of CD38 enzymatic activity, which can impact on Ca2+ signaling

Phase III trial

- Multicenter, open-label ICARIA-MM trial
  - 307 patients with relapsed/refractory multiple myeloma on triplet regimen of isatuximab, pomalidomide, and low-dose dexamethasone or pomalidomide and dexamethasone alone
  - Isatuximab administered intravenously (IV) at 10 mg/kg once weekly for 4 weeks followed by bi-weekly for 28-day cycles

Results

- At median follow-up of 11.6 months, median PFS was 11.5 mos IsaPd vs 6.5 mos Pd; HR 0.596 (95% CI 0.44-0.81), P=0.001
- ORR (≥PR) was 60.4% IsaPd vs 35.3% Pd, P<0.0001. VGPR rate or better was 31.8% IsaPd vs 8.5% Pd
- Grade ≥3 AEs were observed in 86.8% IsaPd vs 70.5% Pd
- Inf. reactions were reported in 38.2% (2.6% grade 3-4) IsaPd
- Grade ≥3 infections were seen in 42.8% IsaPd and 30.2% Pd, grade ≥3 neutropenia in 84.9% (febrile 11.8%) IsaPd and 70.1% (febrile 2.0%) Pd.
- IsaPd significantly improved PFS and ORR vs Pd, with a manageable safety profile. IsaPd is an important new treatment option for the management of RRMM

B-Cell Maturation Antigen (BCMA)-Directed Therapies

- BCMA is a member of the Tumor Necrosis Factor (TNF) receptor superfamily
- Expression of the BCMA is restricted to the B-cell lineage – plasma cells and other mature B cells
- Majority of malignant plasma cells express BCMA
  -> Good target for multiple myeloma therapy
  1. BCMA Antibody Drug Conjugate (ADC) monoclonal antibody
  2. BCMA Bi-specific T-Cell Engager (BiTE) antibody
  3. BCMA Chimeric Antigen Receptor (CAR) T-Cell therapy
GSK2857916–DREAMM‐1 trial

- Overall, 30 patients were evaluated in Part 1, no BCs were observed.
- Part 2: Expansion.
- Patient 1: second-line refractory MM (Ki-67, 40%; treatment canceled).
- Patient 2: third-line chronic L-DAC, or follicular lymphoma (Ki-67 ongoing).
- Schedules: H/L, every 3 weeks.
- Treatment duration: up to 16 cycles (6-12 weeks).

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<tr>
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<th>N (%)</th>
<th>Grade 3/4</th>
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<tbody>
<tr>
<td>Any grade ≥3</td>
<td>28 (80)</td>
<td>N/A</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12 (34)</td>
<td>N/A</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Dry eye</td>
<td>1 (3)</td>
<td>N/A</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (14)</td>
<td>N/A</td>
</tr>
<tr>
<td>AST increased</td>
<td>2 (6)</td>
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<tr>
<td>Cough</td>
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<td>IRR</td>
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Trudel et al. ASH 2017

DREAMM‐1

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<td>Fatigue</td>
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BCMA Bi-specific T-Cell Engager(BiTE) Antibody

- BI 836909 – BCMA BiTE antibody that binds BCMA on plasma cells and CD3 on T-Cells, demonstrates effective anti-myeloma activity.
- Phase I, open-label, non-randomized.
- Dose Escalation of BI 836909 Monotherapy in Relapsed/Refractory Multiple Myeloma Patients.
- To characterize the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous BI 836909; to determine the maximum tolerated dose (MTD).

BCMA Chimeric Antigen Receptor (CAR) T-Cell therapy

- Chimeric Antigen Receptor (CAR) T-Cells:
  - Engineered molecules to recognize an antigen on a target cancer cell (e.g. BCMA on multiple myeloma cells).
  - Reintroduced into the patient to kill cancer cells.
  - Stay in the body and guard against cancer recurrence.

<table>
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<tr>
<th>CAR-T Cells</th>
<th>Bb2121</th>
<th>LCAR-B38M</th>
<th>CART-BCMA</th>
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<td>Lentiviral</td>
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<tr>
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<td>7</td>
<td>47</td>
<td>11</td>
</tr>
<tr>
<td>Efficacy</td>
<td>1 sCR (relapsed), 2 VGPR, 1 PR, 8 SD</td>
<td>11 CR/sCR, 8 VGPR, 2 PRs (4 eventual PD), n = 22</td>
<td></td>
</tr>
<tr>
<td>Responses in highest cell dose</td>
<td>9/11 in top dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td>Toxicity substantial (Gr3/4 CRS) but reversible esp in highest doses (9 x 10^6/kg); protocol modified to pts with lower tumor burden.</td>
<td>CRS in 63%; Gr3 5%; 2 deaths. Early report of 1 ≥Gr 3 neurotoxicity</td>
<td>Transient CRS in 29/35, no neurotoxicity in 17/21 patients (6 with Gr 3/4), with neurotoxicity in 3 patients</td>
</tr>
</tbody>
</table>

CAR-T cells

- Bb2121
- LCAR-B38M
- CART-BCMA

Transplant CRD patient in relapsed MM, with neurotoxicity at 1 year | No treatment related death
Advanced Pharmacy Services in Multiple Myeloma Clinic

- Manage drug therapy for cancer and supportive medications
- Anticoagulant therapy
- Bisphosphonate/Calcium/Vitamin D
- Other treatment-related prophylaxis
- Engage in patient care – efficient and optimized medication dosages with calendar
- Manage adverse drug events
- Opportunity to create collaborative practice agreement

Summary

- Novel treatment options for multiple myeloma are emerging rapidly in both newly diagnosed and relapsed settings
- Monoclonal antibodies were approved as single agent but now additional combinations are being used
- Pharmacists can play an integral role bridging a gap in patient care and improve care provided to oncology patients
- Future advances in myeloma treatment including immunotherapy continue to be explored