Disclosures

Craig Cole, MD has no relevant financial interests to disclose.
What We Will Discuss Today

• Definitions
  – What is a response with myeloma treatment?

• Novel Agents
  – BCL-2 and BCL-2 inhibitors
  – Check-point inhibitors

• Clinical Trials
  – Facts and Myths
What are we talking about?
Definitions in Myeloma Treatment….

**Did it work?:**
International Myeloma Working Group Response Criteria

- **Complete response (CR)**
  - Treatment where there are $\leq 5\%$ plasma cells in the bone marrow and/or no evidence of laboratory myeloma proteins in the serum or urine.

- **Very good partial response (VGPR)**
  - Treatment outcome where there is a greater than $90\%$ decrease in M protein

- **Partial response (PR)**
  - Treatment outcome where there is a greater than $50\%$ decrease in M protein

- **Stable disease (SD)**
  - Treatment outcome where the disease has not responded to therapy (no change in M-protein) but has not progressed.
What are we talking about? Definitions in Myeloma Treatment....

**Did it work?**
- **Overall response rate (ORR)**
  Percentage of patients who respond in a clinical trial with a partial response (>50% reduction) or better.
- **Clinical Benefit Rate (CBR)**
  Percentage of patients who respond in a clinical trial with STABLE DISEASE or better (anything other than progressive disease).

**How long did it work/ what are the side effects?**

**OS**: Overall Survival

**PFS**: Progression-Free Survival (from start of new treatment until it’s failure)

**AE**: Adverse Events- Bad side effects
Old Therapies for Myeloma

Bone marrow stromal cell

Myeloma Cell

Non specific Targeting MM cell: Chemo, Steroids

Currently Available Therapies Targeting Myeloma Cells in the Bone Marrow Microenvironment

**Antibodies to target cell surface:**
- Daratumumab
- Elotuzumab
- Isatuximab

**Cytokines, growth factors:**
- IL-6, VEGF
- IGF-1, SDF-1α
- BAFF, APRIL, BSF-3

**Checkpoint Inhibitors:**
- Anti-PD-1
- Anti-CTLA-4

**Bone marrow stromal cell:**
- ICAM-1
- LFA-1
- VCAM-1, fibronectin
- VLA-4

**Discovery of the biology of MM and Bone Marrow microenvironment**

Currently Available Therapies Targeting Myeloma Cells in the Bone Marrow Microenvironment

Antibodies to target cell surface:
- Daratumumab
- Elotuzumab
- Isatuximab

Cytokines, growth factors:
- IL-6, VEGF
- IGF-1, SDF-1α
- BAFF, APRIL, BSF-3

Adhesion molecules:
- VCAM-1, fibronectin
- VLA-4

Myeloma Cell

Non specific Targeting MM cell: Chemo, Steroids

Discovery of the biology of MM and Bone Marrow microenvironment

Therapies TARGETING MM Biology

Proteasome inhibitors:
- Velcade, Kyprolis, Ixazomib

IMiDs:
- Thalomid, Revlimid, Pomalyst

HDAC inhibitor:
- Farydak, Ricolostat

BCL-2 Inhibitors
- Venetoclax

Inhibitors of Nuclear Export
- Selinexor

Currently Available Therapies Targeting Myeloma Cells in the Bone Marrow Microenvironment

**Antibodies to target cell surface:**
- Daratumumab
- Elotuzumab
- Isatuximab

**Cytokines, growth factors**
- IL-6, VEGF
- IGF-1, SDF-1α
- BAFF, APRIL, BSF-3

**Checkpoints Inhibitors**

**Bone marrow stromal cell**

**More Biology on the way!**

**Non specific Targeting MM cell:**
- Chemo, Steroids

**Discovery of the biology of MM and Bone Marrow micro-environment**

**Therapies TARGETING MM Biology**
- Proteasome inhibitors:
  - Velcade, Kyprolis, Ixazomib
- IMiDs:
  - Thalomid, Revlimid, Pomalyst
- HDAC inhibitors:
  - Farydak, Ricolostat
- BCL-2 Inhibitors
  - Venetoclax
- Inhibitors of Nuclear Export
  - Selinexor

**Myeloma Cell**

- GSK-3β
- FKHR
- Caspase-9
- NF-κB
- mTOR
- Bad

**Adhesion molecules**
- ICAM-1
- LFA-1
- MUC-1
- VCAM-1, fibronectin
- VLA-4

**More Biology on the way!**

Applying the Science: Novel Agents in Myeloma

WHOA...

SLOW DOWN THERE
Application of Science: BCL-2 and Chromosome 11 and 14
Application of Science: BCL-2 and Chromosome 11 and 14

Cytokines
Signal for MM growth

Cytokine receptor

JAK2

STAT3

RAF

MER/ERK

BCL-2

PI3-K

Akt

Anti- Cell Death/Pro-Survival
Cytokines
Signal for MM growth

Cytokine Receptor
JAK2 → STAT3
MER/ERK
RAF
PI3-K → Akt

BCL-2!
Anti- Cell Death
Pro-Survival

Translocation of chromosome #11 and #14

Application of Science: BCL-2 and Chromosome 11 and 14
Cytokines
Signal for MM growth

STOP BCL-2
..an inhibitor

Translocation of chromosome #11 and #14

Anti-Cell Death
Pro-Survival

Cytokine
Receptor

JAK2
STAT3

MER/ERK
RAF
PI3-K
Akt

BCL-2

1 1
1 4

Anti-Cell Death
Pro-Survival
YEAH BOSS...
CLEAR AS MUD
Venetoclax for Relapsed/Refractory MM: Background

- Survival of cancer cells is promoted by proteins BCL-2 and which allow cells to survive and proliferate.
  - Overexpression of Bcl-2 in some cancers has sometimes shown to be linked with increased resistance to chemotherapy.
- **Venetoclax (Venclexta) is a oral (pill) Bcl-2 inhibitor.**
  - It blocks (Bcl-2) protein leading to programmed cell death of cancer cells.
- FDA approval for high risk types of chronic lymphocytic leukemia (CLL) in 2015.
- In CLL the common side effects were low white blood cell count, nausea, anemia, diarrhea, upper respiratory tract infection, fatigue.
  - Major side effect in CLL was *Tumor Lysis Syndrome* (sudden cancer cell death with unstable electrolytes).

Venetoclax Monotherapy for Relapsed/Refractory MM: Background

• Laboratory studies show venetoclax induces Myeloma cell death in cell line samples.
  – Cells positive for translocation 11 and 14 (t11;14) are particularly susceptible.
  – t11;14 correlated with higher ratios of $BCL2/MCL1$ genes and $BCL2/BCL2L1$ (BCL-X$_L$) mRNA.

• This exploratory (Phase-1) study evaluated safety and tolerability of venetoclax solo-therapy in pts with previously treated MM.

Venetoclax Monotherapy for Relapsed/Refractory MM: Phase I Study Design

66 Pts with previously treated MM

More than 70% no longer responsive to Velcade or Revlimid; 61% refractory to both

(k = 6) Venetoclax 50 mg* | Venetoclax 100 mg* | Venetoclax 300 mg*

(k = 9) Venetoclax 100 mg* | Venetoclax 300 mg* | Venetoclax 600 mg*

(k = 6) Venetoclax 300 mg* | Venetoclax 600 mg* | Venetoclax 900 mg*

(k = 9) Venetoclax 400 mg* | Venetoclax 800 mg* | Venetoclax 1200 mg*

(Safety cohort; k = 36) Venetoclax 400 mg* | Venetoclax 800 mg* | Venetoclax 1200 mg*

Pts who progressed on venetoclax could add dexamethasone and continue on study.

## Venetoclax Monotherapy for Relapsed/Refractory MM: Overall Response Rate

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>Overall Population (N = 66)</th>
<th>Pts With t(11;14) (n = 30)</th>
<th>Pts Without t(11;14) (n = 36)</th>
<th>Pts With High BCL2/BCL2L (n = 9)</th>
<th>Pts With Low BCL2/BCL2L (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall RR</td>
<td>21</td>
<td>40</td>
<td>6</td>
<td>88</td>
<td>20</td>
</tr>
<tr>
<td>sCR</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>CR</td>
<td>4</td>
<td>10</td>
<td>0</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>VGPR</td>
<td>8</td>
<td>13</td>
<td>3</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Partial R</td>
<td>6</td>
<td>13</td>
<td>0</td>
<td>33</td>
<td>7</td>
</tr>
</tbody>
</table>

Venetoclax Monotherapy for Relapsed/Refractory MM: Conclusions

- In pts with previously treated MM, BCL-2 inhibitor venetoclax solo-therapy was safe and tolerable.
  - Dose-limiting toxicity at 600 mg was abdominal pain, nausea (n = 2).
  - Tumor lysis syndrome (sudden cancer cell death with unstable electrolytes) was NOT documented.

- Overall Response Rate: 21% for total population

- **Overall Response Rate in t(11;14) patients**: 40%
  - Higher Overall Response Rates, deeper responses, and greater time to progression in patients with t(11;14)
  - Venetoclax activity independent of previous treatment history in pts with t(11;14)
  - Higher ORR also seen in pts with high vs low BCL2/BCL2L1 ratio

- This is Precision Therapy in Myeloma!

What is Precision Medicine?

Without Precision Medicine:
- Patient
- Same therapy
- Benefit, no benefit, adverse effects

With Precision Medicine:
- DNA tests
- t(11;14) or BCL-2
- Each patient benefits
- Tailored therapy

Venetoclax
The Horizon is Bright!

B-cell & T-cell

To Serve and Protect
Immune checkpoint inhibitors to treat cancer

• The Immune system has the ability to tell between **normal cells** from **abnormal cells**.
  – This lets the immune system attack the bad cells while leaving the normal cells alone.

• **The immune system uses “checkpoints”** – molecules on certain immune cells to attack abnormal cells or leave normal cells alone.

• **Cancer cells sometimes find ways to use these checkpoints to avoid being attacked** by the immune system.
Good Guy cell
PD-1 and PD-L1 fit perfectly
Good Guy cell

PD-1 and PD-L1 fit perfectly

NO IMMUNE SYSTEM ATTACK!
PD-1 T-Cell ATTACK!

BAD Guy cell

NO PD-L1 BAD!!

IMMUNE SYSTEM ATTACK!

BAD Guy cell
Bad Guy cell disguised As a Good Guy

PD-1 and PD-L1 fit perfectly

T-Cell NO ATTACK!

MULTIPLE MYELOMA
Bad Guy cell disguised As a Good Guy

Myeloma (wolf)
PDL-1/ PD-1 (Sheep Clothing)

PD-1 and PD-L1 fit perfectly

MULTIPLE MYELOMA
Immune System Attack!

PD-L1 Antibody
Atezolizumab (Tecentriq)
Removes PD-L1

PD-1 Antibody
Without PD-L1

T-Cell ATTACK!

Anti PD-1 Antibody
Pembrolizumab (Keytruda)
Nivolumab (Opdivo)
Removes PD-1

Bad Guy cell is seen as a BAD CELL!
Check-point inhibitor studies

- Anti PD-L1 antibodies FDA approved:
  - Atezolizumab approved for bladder cancer treatment.

- Anti PD-1 antibodies FDA approved:
  - Nivolumab is approved to treat melanoma, lung cancer, kidney cancer and Hodgkin’s lymphoma.
  - Pembrolizumab is approved to treat melanoma and lung cancer.

- At the ASCO 2016 the first Check-point inhibitor study was presented.
  - KEYNOTE-023: phase I study evaluating pembrolizumab 200mg + Revlimid 25mg + Dexamethasone 40mg in pts with Relapsed/Refractory MM with more than 3 prior therapies.
    - Overall Response rate: 50%
    - Revlimid failure (refractory) response rate: 38%
    - 88% of pts showed some decrease in M protein or free light chains from baseline

Pembrolizumab, Pomalidomide, Dexamethasone for Relapsed Refractory MM

Pts with R/R MM and 2 lines of previous tx including IMid and PI; (N = 48)

Pembrolizumab 200 mg IV Days 1, 14 + Pomalidomide 4 mg PO Days 1-21 + Dexamethasone 40 mg PO Days 1, 7, 14, 21 Q28D

Mo 24

Responders

Pembrolizumab 200 mg IV/mo + Pomalidomide 4 mg PO + Dexamethasone 40 mg PO

---

**Characteristic** | **Pts (N = 48)**
--- | ---
Median lines of earlier therapy (range) | 3 (2-5)
Refractory, %
- Proteasome inhibitors (Velcade/Kyprolis) | 79
- Revlimid | 90
- IMiDs + proteasome inhibitors | 73

## Pembrolizumab, Pomalidomide, Dexamethasone for R/R MM: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>All Severities</th>
<th>High Severity Grade &gt; 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>In &gt; 30% of pts</td>
<td>Fatigue, Neutropenia, Hyperglycemia, Thrombocytopenia, Anemia</td>
<td>Dizziness, Constipation, infection, Short of breath, Edema</td>
</tr>
<tr>
<td>In &gt; 20% to 30% of pts</td>
<td>Lymphopenia, Muscle spasms, Rash, Diarrhea</td>
<td>Infection, Pneumonia, Nausea</td>
</tr>
<tr>
<td>In ≥ 10% to 20% of pts</td>
<td>Hypotension, Peripheral neuropathy, Arrhythmia</td>
<td></td>
</tr>
<tr>
<td>Immune Reaction AEs in any pt</td>
<td>Pneumonitis (12%), Hypothyroidism (10%), Adrenal Hepatitis Vitiligo</td>
<td>Hypothyroidism, Pneumonitis</td>
</tr>
</tbody>
</table>

Pembrolizumab, Pomalidomide, Dexamethasone for R/R MM:
How well does it work?

<table>
<thead>
<tr>
<th>Response, %</th>
<th>Full Population (N = 45)</th>
<th>Refractory to 2 Classes (n = 32)</th>
<th>High-Risk Cytogenetics (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>65</td>
<td>68</td>
<td>56</td>
</tr>
<tr>
<td>Clinical benefit</td>
<td>72</td>
<td>69</td>
<td>60</td>
</tr>
<tr>
<td>Best response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sCR</td>
<td>7</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>CR</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>VGPR</td>
<td>20</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>PR</td>
<td>36</td>
<td>44</td>
<td>41</td>
</tr>
<tr>
<td>MR</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>SD</td>
<td>23</td>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>PD</td>
<td>5</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>sCR + CR+ VGPR, %</td>
<td>29</td>
<td>24</td>
<td>15</td>
</tr>
</tbody>
</table>

### Pembrolizumab, Pomalidomide, Dexamethasone for R/R MM: Duration of Response and Survival

<table>
<thead>
<tr>
<th>Outcome in months</th>
<th>Full Efficacy Population (N = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of response</td>
<td>16.3 (9.9-19.1)</td>
</tr>
<tr>
<td>Median Progression Free Surv</td>
<td>17.4 (11.7-18.8)</td>
</tr>
<tr>
<td>Median Overall Survival</td>
<td>Not reached (18.8-not reached)</td>
</tr>
</tbody>
</table>

- PFS significantly longer in low-risk vs high-risk subgroups.
- Side effects occurred in ~ 50% of the study population
  - Discontinuation in only 10%; most side effects were manageable.
  - Most dose reductions were due to Pomalyst

Clinical Trials

CLINICAL TRIALS ON PEOPLE?

GOOD
The Original Standard for Multiple Myeloma: Urethane Therapy

- Urethane was first prepared in the nineteenth century.
  - Was known to inhibit plant root growth and a chemical weapon.
- 1947-report that urethane produced a significant response in two patients with myeloma.
- For almost 20 years, urethane was the standard treatment for multiple myeloma.
- 1966 - Randomized clinical trial between urethane and cola in myeloma.

No difference in survival!

How Medical Care Advances:

- Toxicity of Therapy: Bad
- Effectiveness of Therapy: Poor, Little to None, GREAT
Where does the standard of care come from?

Clinical Trials!
What are Clinical Trials?

• Cancer clinical trials are:
  – Carefully controlled research studies
  – Conducted by doctors to improve the care and treatment of cancer patients

• The aim of a clinical trial is to:
  – Study a new therapy or a new use for an already approved therapy

• Compare a new treatment with a standard treatment to find out which one works better and/or has fewer side effects

• Each cancer clinical trial has a written detailed study design called a written protocol.
  – What drug or drug(s) are being tested.
  – Safety measures throughout the clinical trial program.
  – Who is eligible for the clinical trial.
Initial development of new drug in lab ➔ Drug studied in lab and animals ➔ Food and Drug Administration (FDA) approves the new drug for human clinical trials ➔ The drug can now be studied in people in carefully controlled clinical trials

Clinical trials: A key step in drug development
**Types of Clinical Trials**

**Phase 1:** investigates for *safety and side effects*, as well as dosage and best way to give treatment.
- Includes 20 or more people

**Phase 2:** determines *how well does it work* and safety.
- Includes 50 to 300 people

**Phase 3:** looks at effectiveness, side effects and safety *in comparison with other standard treatments*
- Includes 100s to 1000s of people

Drug receives FDA approval, it’s available to everyone, and it might become standard practice!

**Phase 4:** gathers more information after FDA approval
Many cancer clinical trials are “randomized” to enable doctors to compare new treatments with standard treatments.

Patients are divided into different groups at random:

- “Control group” receives the best standard treatment available
- “Treatment group” receives the treatment under study
If I enter a clinical trial, there’s a good chance that I could receive a placebo

Fact or Myth

Fact: Placebos are rarely used in cancer clinical trials
A clinical trial is a treatment of last resort

Fact or Myth

Fact: There are clinical trials for people at every stage of disease
Clinical trials are riskier than FDA-approved drugs

Fact: Treatment on a clinical trial has as good a chance for success as standard treatment
If my doctor doesn’t mention clinical trials, it must not be right for me.

Fact or Myth

Fact: Your doctor may not be aware or remember that there is a clinical trial for you.
What do you think?

The trial is more important than the patient.

Fact or Myth

Fact: Never! You can stop your participation on a clinical trial at ANY TIME and for ANY reason.
What do you think?

If I enter a clinical trial, I’ll be a “guinea pig”

Fact or Myth

Fact: Clinical trials provide patients either the best treatment currently available, or a new and possibly more effective therapy
Clinical trial protocols ensure that patients are closely monitored.

- Patients get a lot of attention and support!
- Patients are watched closely by their doctor, as well as other members of their medical team and research team to ensure their safety.
Safety in clinical trials

• Sponsor asks outside experts to review merit of study.

• Many centers have a protocol review committee and a safety board to review the trial before its approved.

• Institutional Review Board (committee of experts):
  – Looks at trial’s scientific, legal and ethical merit.
  – Are risks minimized and reasonable vs. anticipated benefits?
  – Is informed consent process in place and documented? (no coercion or “undue” influence to participate).
  – Does data monitoring include patient safety data?
  – Is there a process to protect privacy of patients?
Process of informed consent

• Your doctor must give you an **informed consent document** before you enroll in a clinical trial.
  – Must be in a language you understand.
  – Ask for a language interpreter if needed.

• **Bring an advocate!**

• Ask your doctor to explain anything you don’t understand.

Take your time in reading and signing the informed consent form. You may take back your consent to participate at any time.
# Selected Novel Drugs Being Explored in Clinical Trials

## Third/Fourth-generation agents

<table>
<thead>
<tr>
<th>Novel classes of Therapy</th>
<th>Proteasome inhibitors</th>
<th>IMIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>marizomib, oprozomib, ixazomib</td>
<td>CC-220</td>
</tr>
</tbody>
</table>

## Novel classes of Therapy

<table>
<thead>
<tr>
<th>Monoclonal antibodies</th>
<th>anti-CD38, anti–CD-138 conjugate, anti-BCMA conjugate, antiSLAM7-conjugate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check Point Inhibitors</td>
<td>Durvalumab, Atezolizumab, Pembrolizumab Nivolumab</td>
</tr>
<tr>
<td>BTKi</td>
<td>Ibrutinib, AVL-292</td>
</tr>
<tr>
<td>HDAC inhibitors</td>
<td>panobinostat,* romidepsin, ricolinostat</td>
</tr>
<tr>
<td>Pleiotropic Pathway Modifier</td>
<td>CC:122</td>
</tr>
<tr>
<td>Kinesin Spindle Inh</td>
<td>ARRY</td>
</tr>
<tr>
<td>CDK</td>
<td>PD0332991, SCH727965, AT7519</td>
</tr>
<tr>
<td>BCL antagonist</td>
<td>ABT263</td>
</tr>
<tr>
<td>HSP90</td>
<td>Ganetespib (STA-9090)</td>
</tr>
<tr>
<td>SINE XPO antagonist</td>
<td>KPT-330 (Selinexor)</td>
</tr>
<tr>
<td>FGFR3</td>
<td>TKI258, MFGR1877S</td>
</tr>
<tr>
<td>17p mutated</td>
<td>Idasanutlin</td>
</tr>
</tbody>
</table>
Clinical Trials are an important option for everyone!
Clinical Trials can be for newly diagnosed, with limited disease, or advanced disease.
Clinical Trials are appropriate and safe for people of different ages, genders, and races.
Clinical Trials that include people of ethnicity are critical to knowing if a treatment really works!
Clinical Trials take into account all the above factors as well as stage of disease, other treatments used, and presence of any other medical conditions to assure safety.

Remember…communication with your healthcare team is important in making treatment decisions about standard treatment or clinical trial treatment!
Thank You!
For Your Time and Attention