Multiple Myeloma Therapies
What lies in the future?

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Medical College of Wisconsin
Conflict of Interest

Am a consultant or advisor and grant recipient from virtually every company that works in the Myeloma field.

"Yes, I am employee of the month again. And yes, I'm the one who chooses the employee of the month. And no, I don't see a conflict of interest."
Funny Medical Terminology

Adenoma - What you say to your mother when you don't know the answer

Aerobe - A garment worn around the house

Alimentary - What Holmes said to Watson

Anally - Occurring yearly

Antepartum - When your father's sister goes home

Anti-Body - Against everyone

Artery - The study of paintings

Atonic - Goes with your gin
Framework for Newly Diagnosed MM—Patient Treatment Plan

Eligibility for Transplant:
Co-morbidities
- PS
- Age

Transplant Candidate
- Induction Therapy
- Stem Cell Harvest
- ASCT (early vs delayed)
- Consolidation and/or Maintenance

Not Transplant Candidate
- Induction therapy
- Maintenance or extended therapy phase
MAINTENANCE AFTER TRANSPLANT: A MUST!

<table>
<thead>
<tr>
<th>Study</th>
<th>REVLIMID</th>
<th>Placebo</th>
<th>Median Overall Survival (Years)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1 (US)</td>
<td>n=231</td>
<td></td>
<td>9.3 years (95% CI 8.5, NE)</td>
<td>0.59 (0.44, 0.78)</td>
</tr>
<tr>
<td>Study 2 (EU)</td>
<td>n=307</td>
<td></td>
<td>7.3 years (95% CI 6.7, 9.0)</td>
<td>0.90 (0.72, 1.13)</td>
</tr>
<tr>
<td>Study 1 (US)</td>
<td>n=229</td>
<td></td>
<td>7.0 years (95% CI 5.9, 8.6)</td>
<td>0.63 (0.46, 0.86)</td>
</tr>
</tbody>
</table>

Reference: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm542791.htm
<table>
<thead>
<tr>
<th>Study</th>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>ISS III</th>
<th>High risk cytogenetics</th>
<th>Follow-up (months)</th>
<th>Induction</th>
<th>Conditioning</th>
<th>SDT regimen</th>
<th>Maintenance (HDT +SDT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIMEMA RV-MM –PI-209</td>
<td>Palumbo</td>
<td>2014</td>
<td>273</td>
<td>23.6%</td>
<td>28.8%</td>
<td>51.2</td>
<td>Rd</td>
<td>Mel 200 x 2</td>
<td>MPR</td>
<td>LEN (till progression) vs. None</td>
</tr>
<tr>
<td>RV-MM-EMN-441</td>
<td>Gay F</td>
<td>2015</td>
<td>256</td>
<td>29%</td>
<td>21.8%</td>
<td>52</td>
<td>Rd</td>
<td>MEL 200 x 2</td>
<td>CRD</td>
<td>LEN + P vs. LEN (till progression)</td>
</tr>
<tr>
<td>IFM/DFCI 2009</td>
<td>Attal M</td>
<td>2015</td>
<td>700</td>
<td>18%</td>
<td>12.8%</td>
<td>44</td>
<td>RVD</td>
<td>MEL 200</td>
<td>RVD x 8</td>
<td>LEN x 1 year</td>
</tr>
<tr>
<td>EMN02/HO95</td>
<td>Cavo M</td>
<td>2016</td>
<td>1192</td>
<td>21%</td>
<td>25%</td>
<td>26</td>
<td>CyBorD</td>
<td>MEL 200 x 1 or 2</td>
<td>VMP x 4</td>
<td>LEN till progression</td>
</tr>
</tbody>
</table>
## Minimal Residual Disease and Transplant

<table>
<thead>
<tr>
<th>ARMS</th>
<th>MRD negativity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDT (EARLY)</td>
<td>79%</td>
</tr>
<tr>
<td>SDT (DELAYED)</td>
<td>65%</td>
</tr>
</tbody>
</table>

Attal et al. NEJM 2017
Minimal Residual Disease: New Definitions for CR

- S.S. Patient
- Newly diagnosed $1 \times 10^{12}$
- Disease burden
- CR
- Stringent CR
- Molecular/flow CR
- Sequencing CR
- True Cure? $0.0$

Disease burden levels:
- Newly diagnosed: $1 \times 10^{12}$
- CR: $1 \times 10^{8}$
- Stringent CR: $1 \times 10^{4}$
- Molecular/flow CR
- Sequencing CR
- True Cure?: $0.0$
VACCINE POST TRANSPLANT (CTN 1401)

- **Enrollment 1**: MM Initial Therapy (M) → Mel200 AutoHCT → Response Assessment → Randomization → d50
- **Enrollment 2**: Dendritic Cell Precursor Collection → Vaccinations + Len + GM-CSF
- **Assessment of CR**: Len Alone → Len + GM-CSF → HCT → d90
TREATMENT MILESTONES IN MULTIPLE MYELOMA

Preclinical and clinical studies leading to FDA approvals in MM

- 2006 Thalidomide
- 2012, 2015 Carfilzomib
- 2015 Panobinostat

Improvement in overall survival from median of 3 to 8-10 years

- 2003, 2005, 2008 Bortezomib (BTZ)
- 2007 Doxil + BTZ
- 2013, 2015 Pomalidomide
- 2015 Ixazomib
- 2006, 2014 Lenalidomide
- 2015 Daratumumab
- 2015 Elotuzumab

Immunomodulatory agent
Monoclonal antibody
Proteasome inhibitor
HDAC inhibitor

Follow-up from diagnosis (years)
Proportion surviving

© 2016 American Association for Cancer Research

Prehistory Myeloma

- Multiple myeloma has probably been present as a human disease for centuries.
- There is evidence that multiple myeloma might date back to the time of the ancient Egyptians.

- Four cases of possible multiple myeloma were found in Native American skeletons from 200 to 900AD.
Clinical Trials

MAKING MYELOMA History
New Drugs – Are they Chemotherapy?

“We’ve found a mass. The good news is we have weapons of mass destruction.”
CD38 ANTIBODIES
TRANSPLANT INELGIBILBE - WHAT IS NEW?
SWOG S0777: Study Design

- Randomized phase III trial of VRd vs Rd
  
  Stratified by ISS stage I/II/III and intent to transplant at progression

  Previously untreated active MM (CRAB criteria) with measurable disease (including FLC) and CrCl > 30 cc/min (N = 525)

  - Primary endpoint: PFS
  - Secondary endpoints: ORR, OS, safety

  Lenalidomide 25 mg/day PO D1-21 + Dexamethasone 40 mg/day PO D1,8,15,22 for six 28-day cycles (eligible n = 230)

  Bortezomib 1.3 mg/m² IV D1,4,8,11 + Lenalidomide 25 mg/day PO D1-14 + Dexamethasone 20 mg/day D1,2,4,5,8,9,11,12 for eight 21-day cycles (eligible n = 243)

  Rd maintenance until PD, unacceptable toxicity, or withdrawal of consent

Median follow-up: 55 mos
Median time on maintenance: 385 days
All pts received aspirin 325 mg/day; bortezomib pts received HSV prophylaxis

### SWOG S0777: Survival Outcomes

<table>
<thead>
<tr>
<th>Survival, Mos</th>
<th>VRd (n = 242)</th>
<th>Rd (n = 229)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>43</td>
<td>30</td>
<td>0.712</td>
<td>.0018*</td>
</tr>
<tr>
<td></td>
<td>(0.560 - 0.906)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>75</td>
<td>64</td>
<td>0.709</td>
<td>.025†</td>
</tr>
<tr>
<td></td>
<td>(0.516 - 0.973)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*1-sided P value.
†2-sided P value.

- PFS, OS increase remain significant when age-adjusted in multivariate analysis
- Other significant factors: ISS stage III, 65 yrs of age or older

CAN WE MOVE DARATUMUMAB UPFRONT?

RANDOMIZE

- Dara-VRD x4
- VRD x4

INDUCTION
- Dara-VRD x4
- VRD x4

TRANSPLANT
- STEM CELL TRANSPLANT
- Dara-VRD X 2
- Dara + LEN

CONSOLIDATION

MAINTENANCE
- STEM CELL TRANSPLANT
- VRD X2
- LEN

MMY2004 RANDOMIZED PHASE II TRIAL
ALCYONE STUDY DESIGN

Key eligibility criteria:
- Transplant-ineligible NDMM
- ECOG 0-2
- Creatinine clearance ≥40 mL/min
- No peripheral neuropathy grade ≥2

Stratification factors
- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

1:1 Randomization (N = 706)

VMP × 9 cycles (n = 356)
- Bortezomib: 1.3 mg/m² SC
  - Cycle 1: twice weekly
  - Cycles 2-9: once weekly
- Melphalan: 9 mg/m² PO on Days 1-4
- Prednisone: 60 mg/m² PO on Days 1-4

D-VMP × 9 cycles (n = 350)
- Daratumumab: 16 mg/kg IV
  - Cycle 1: once weekly
  - Cycles 2-9: every 3 weeks
- Same VMP schedule

D
- Cycles 10+
  - 16 mg/kg IV
  - Every 4 weeks: until PD

Follow-up for PD and survival

Primary endpoint:
- PFS

Secondary endpoints:
- ORR
- ≥VGPR rate
- ≥CR rate
- MRD (NGS; 10⁻⁵)
- OS
- Safety

Statistical analyses
- 360 PFS events: 85% power for 8-month PFS improvement
- Interim analysis: ~216 PFS events

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; EU, European Union; SC, subcutaneously; PO, orally; D, daratumumab; IV, intravenously; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; NGS, next-generation sequencing; OS, overall survival.

*8-month PFS improvement over 21-month median PFS of VMP.
EFFICACY: PFS

• Median (range) follow-up: 16.5 (0.1-28.1) months

12-month PFS

18-month PFS

% surviving without progression

0 100

20 80

40 60

60 76%

87%

72%

50%

No. at risk

VMP 356 303 276 261 231 127 61 18 2 0

D-VMP 350 322 312 298 285 179 93 35 10 0

Months

HR, 0.50
(95% CI, 0.38-0.65; P <0.0001)

50% reduction in the risk of progression or death in patients receiving D-VMP

HR, hazard ratio; CI, confidence interval.

*Kaplan-Meier estimate.
QUIZ

Walgreens Enema Syringe
FIGURE 1-16 An attempt at resuscitating an apparently drowned person using the modified Dutch method. One resuscitator is assisting respiration by massaging the chest. The fumigator is instilling tobacco smoke through the rectum. *(From Morch, 1985, with permission.)*
Relapsed, Refractory Disease:
New Agents
CURRENT TREATMENTS OPTIONS-- for relapse

- DARATUMAB-REVLIMID-DEXAMETHASONE
- DARATUMUMAB-VELCADE-DEXAMETHASONE
- DARATUMUMAB-POMALIDOMIDE-DEXAMETHASONE
- CARFILZOMOB-REVLIMID-DEXAMETHASONE
- ELOTUZUMAB-REVLIMID-DEXAMETHASONE
- IXAZOMIB-REVLIMID-DEXAMETHASONE
Phases of Clinical Trials

- Phase I studies primarily concerned with assessing the drug's safety. How much can be safely given?
- Phase II test for efficacy. How well does the drug work in this disease?
- Phase III – How well does the new drug compare against standard treatment?

"We'll just mill around till he's asleep, and then send him back up. This operation is actually for a placebo effect."
Don’t wait for other people – Jump in

I just heard there’s a drug in trials that might stop my cancer!!

Great! Are you going to volunteer to participate for the trial?

Of course not... why would I do that?

I wouldn’t either. Sure hope they get some results soon...
Taming Measles Virus to Create an Effective Cancer Therapeutic

Measles virus (MV) has been a longtime bane of the human race. Once described by Pasteur (18th century) as "the worst切尔病", MV is now being targeted to attack myeloma cells exactly where they hide. CD46, a cell surface antigen, is the receptor for MV and is highly expressed on the surface of myeloma cells. The MV virus, after some modifications, can be used to specifically target and destroy these cancer cells.
Exportin 1 (XPO1) is the nuclear exporter for the majority of tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR), and eIF4E-bound oncoprotein mRNAs.

Selinexor is a first-in-class XPO1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids and suppresses oncoprotein expression.
## SELINEXOR: EFFICACY

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>ORR (%)</th>
<th>CBR (%)</th>
<th>VGPR (%)</th>
<th>PR (%)</th>
<th>MR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>78</td>
<td>16 (21%)</td>
<td>26 (33%)</td>
<td>4 (5%)</td>
<td>12 (15%)</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>Quad Refractory</td>
<td>48</td>
<td>10 (21%)</td>
<td>14 (29%)</td>
<td>2 (4%)</td>
<td>8 (17%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Penta Refractory</td>
<td>30</td>
<td>6 (20%)</td>
<td>12 (40%)</td>
<td>2 (7%)</td>
<td>4 (13%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>6 Doses / Month</td>
<td>51</td>
<td>10 (20%)</td>
<td>15 (29%)</td>
<td>3 (6%)</td>
<td>7 (14%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>8 Doses / Month</td>
<td>27</td>
<td>6 (22%)</td>
<td>11 (41%)</td>
<td>1 (4%)</td>
<td>5 (19%)</td>
<td>5 (19%)</td>
</tr>
</tbody>
</table>

Venetoclax induces cell death in multiple myeloma (MM) cell lines and primary samples, particularly those positive for the translocation t(11;14), which correlates with higher ratios of \( BCL2 \) to \( MCL1 \) and \( BCL2 \) to \( BCL2L1 \) (\( BCL-X_L \)) mRNA\(^1\,\^2\).

VENETOCLAX: EFFICACY

BCMA – THE NEW TARGET

✶ BCMA expressed on normal and malignant plasma cells
  ● Promotes MM cell survival

✶ BCMA-targeted therapies, including CAR T cells, show pre-clinical and early clinical activity in myeloma

✶ Penn/Novartis CART-BCMA cells
  ● Autologous T cell product
  ● Human anti-BCMA scFv
  ● CD3ζ/41BB stimulatory domains
  ● Lentiviral vector
  ● CD3/CD28 bead-stimulated manufacturing

1. T cells are collected from the patient’s blood.

2. In the laboratory, the chimeric antigen receptor (CAR) is added to the patient’s T cells.

3. The CAR T cells are infused into the patient.

IN THE BODY

CAR T cells recognize the patient's cancer cells.

CAR T cells kill the patient’s cancer cells.

CAR T cells multiply.
TUMOR RESPONSE

- 17/18 (94%) ORR, 10/18 (56%) CR at active doses
- 9/10 evaluable patients MRD negative
- Durable ongoing responses over 1 year
- Responses continue to improve as late as month 15 (VGPR to CR)
- Median PFS not reached in active dose cohorts
  - 4 patients progressed
  - Median follow up 40 weeks

Patient 12 died of cardiopulmonary arrest
Patient 4 died of MDS following discontinuation

*High Tumor Burden (>50% Bone Marrow Involvement)

CR/sCR  VGPR  PR  Stable Disease  PD  MRD-
Deceased  U  Unconfirmed response  MRD+

Weeks on Study

50 x 10^6  150 x 10^6  450 x 10^6  800 x 10^6
SELECT TREATMENT EMERGENT TOXICITIES

- No dose-limiting toxicities (DLTs) observed in dose escalation
- Cytopenias mostly related to Cy/Flu lymphodepletion
  - Recovery to Grade < 3 cytopenias by Month 2 following infusion:
    - ANC ≥ 1000/mm$^3$ – 70% of patients
    - PLT ≥ 75/mm$^3$ – 75% of patients
- 5 deaths
  - 3 due to disease progression at 50 × 10$^6$ dose
  - 2 in patients treated at active doses in CR at the time of death (cardiac arrest, MDS following discontinuation)
- 14 patients experienced 1 or more SAEs
  - CRS* Grade 1-2 that required hospitalization per protocol (N=4)
  - Pyrexia (N=2)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Overall n (%)</th>
<th>Grade 3 or higher n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome</td>
<td>15 (71)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Neurotoxicity$^2$</td>
<td>5 (24)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18 (86)</td>
<td>18 (86)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (52)</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Anemia</td>
<td>14 (67)</td>
<td>12 (57)</td>
</tr>
</tbody>
</table>

$^1$Data cut-off of October 2, 2017
$^2$Neurotoxicity includes the preferred terms: depressed level of consciousness, confusional state, bradyphrenia, somnolence

*CRS uniformly graded according to Lee et al., Blood 2014;124:188-195
## COMPARISON OF BCMA TARGETED CAR-T CELLS

<table>
<thead>
<tr>
<th></th>
<th>Anti-BCMA CAR (1)</th>
<th>Bb2121 (2)</th>
<th>LCAR-B38M (3)</th>
<th>CART-BCMA (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group/Company</strong></td>
<td>NCI</td>
<td>Bluebird/Celgene/NCI</td>
<td>Nanjing Legend Biotech</td>
<td>Novartis/UPenn</td>
</tr>
<tr>
<td><strong>Binder/co-stimulatory signaling</strong></td>
<td>Murine/CD3 &amp; CD28</td>
<td>Murine/CD3 &amp; 41-BB</td>
<td>Murine/CD3 &amp; 41-BB</td>
<td>Fully human/CD3 &amp; 41-BB</td>
</tr>
<tr>
<td><strong>Transfection</strong></td>
<td>Gamma-retroviral</td>
<td>Lentiviral</td>
<td>Lentiviral</td>
<td>Lentiviral</td>
</tr>
<tr>
<td><strong>Trial ID</strong></td>
<td>NCT02215967</td>
<td>NCT02658929</td>
<td>NCT03090659</td>
<td>NCT02546167</td>
</tr>
<tr>
<td><strong>BCMA expression required?</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Median prior lines of therapy</strong></td>
<td>7</td>
<td>7</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td><strong>Reported Efficacy</strong></td>
<td>1 CR (relapsed), 7 PRs in 16 patients</td>
<td>10 CRs, 6 VGPRs, 1 PR in 18 patients</td>
<td>15 CRs and 13 PRs in 35 patients</td>
<td>2 CRs, 3 VGPRs, 6 PRs in 24 patients</td>
</tr>
<tr>
<td><strong>Safety Data</strong></td>
<td>Substantial but reversible</td>
<td>1 death, cardiopulmonary arrest (unrelated)</td>
<td>Transient CRS</td>
<td>1 death – progressive disease/candidemia</td>
</tr>
</tbody>
</table>

2. Berdeja J et al, ASH 2017  
3. Wanghong Zao et al, ASCO 2017  
TARGETING BCMA: GSK2857916

GSK2857916
- is a humanized
- afucosylated IgG1 anti-BCMA
antibody conjugated to a microtubule
disrupting agent MMAF via a stable,
protease resistant maleimidocaproyl
linker

DREAMM-1 RESPONSE

ORR = 60% (21/35; 95% CI: 42.1%, 76.1%)

- 1 sCR, 2 CR, 15 VGPR, 3 PR

Trudel et al. ASH 2017
### RESPONSE contd..

<table>
<thead>
<tr>
<th></th>
<th>sCR %</th>
<th>CR %</th>
<th>VGPR %</th>
<th>PR %</th>
<th>NE %</th>
<th>ORR* %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Part 2</strong>&lt;br&gt; (N=35)</td>
<td>3</td>
<td>6</td>
<td>43</td>
<td>9</td>
<td>9</td>
<td>60</td>
</tr>
<tr>
<td><strong>Prior daratumumab</strong>&lt;br&gt; (N=14)</td>
<td>7</td>
<td>0</td>
<td>21</td>
<td>14</td>
<td>14</td>
<td>43</td>
</tr>
<tr>
<td><strong>Refractory to both IMiD and PI</strong>&lt;br&gt; (N=31)</td>
<td>3</td>
<td>6</td>
<td>42</td>
<td>6</td>
<td>10</td>
<td>58</td>
</tr>
<tr>
<td><strong>Refractory to IMiD, PI and prior daratumumab</strong>&lt;br&gt; (N=12)</td>
<td>8</td>
<td>0</td>
<td>25</td>
<td>8</td>
<td>17</td>
<td>42</td>
</tr>
</tbody>
</table>

*Note: ORR* = Overall Response Rate*
### Progression-free Survival and duration of response

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Progressed or died</th>
<th>Censored, f/u ended</th>
<th>Censored, f/u ongoing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>35</td>
<td>15 (43%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17 (49%)</td>
<td></td>
</tr>
</tbody>
</table>

**Progression-free survival (months)**

- **Q1 (95% CI)**: 2.3 (0.7, 6.8)
- **Median (95% CI)**: 7.9 (3.1, -)
- **Q3 (95% CI)**: N/A

**Duration of response (months)**

- **Q1 (95% CI)**: 6.7 (1.6, -)
- **Median (95% CI)**: N/A (6.7, -)
- **Q3 (95% CI)**: N/A

---

*Trudel et al. ASH 2017*
mAb-Based Therapeutic Targeting of Tumor

**Antibody-dependent cellular cytotoxicity (ADCC)**
- Elotuzumab (SLAMF7)
- Daratumumab, Isatuximab, MOR202, TAK079 (CD38)
- Lucatumumab or dacetuzumab (CD40)

**Complement-dependent cytotoxicity (CDC)**
- Daratumumab, Isatuximab, MOR202, TAK079 (CD38)

**Apoptosis/growth arrest via targeting signaling pathways**
- Siltuximab (IL-6)
- BHQ880 (DKK1)
- RAP-011 (activin A)
- Daratumumab/Isatuximab (CD38)

**Antibody-delivery of toxic payload (ADC)**
- Brentuximab (CD30)
- huN901-DM1 (CD56)
- nBT062-maytansinoid (CD138)
- GSK (BCMA)
- SGN (CD48A)

**Bispecific Monoclonal Antibodies**
- BCMA
- SLAMF7
- CD123
- CD38

Adapted from Tai YT, Anderson KC. Bone Marrow Res. 2011;2011:924058.
Bispecific Monoclonal Antibodies (BiTE, Duobodies, etc.)

- BCMA
- CD38
- SLAMF7

Frankel SR et al. 2013 Current Opinion in Chemical Biology
Anti CD 74 Ab Drug Conjugate

FIGURE 1

A. Score 0

Score 1

Score 2

Score 3

B. $p = 0.25$ (Mann-Whitney)

Average INT intensity

Newly diagnosed

Relapsed/refractory

C.

Number of samples

Cytokeratin staining score

FIGURE 2

A. Vehicle

1 mg/kg STRO-001

Similar response with 3 and 10 mg/kg STRO-001

B. %CD43+ cells

Days post inoculation

Cytokeratin expression

STRD-001 (mg/kg)
Antibody-coupled T cell receptor (ACTR) in Myeloma

BCMA – APRIL – TACI AXIS
April Antibody in MM

Tai et al, Blood 2016
IMMUNE APPROACHES SUMMARY

1. Agents that reverse tumor-mediated immune paralysis
   - Immunomodulatory drugs
   - Immune checkpoint inhibitors

2. Agents that selectively target the malignant clone
   - Monoclonal antibodies
   - Chimeric Antigen Receptor (CAR) T cells
   - Dendritic cell or peptide vaccine

3. Agents that activate immune cells to target the tumor

Adjuvant therapy
Immune booster
- "Connecting flights"

Passive immunity
Targeting a receptor
- Truly “targeted” therapy

Active therapy
Delivering cells
- Risk "off-target" effects

CCR New Strategies
AAGR

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Neri P et al. CCR 2016
Beyond Single Hypothesis Testing: Master Protocols

Functional high-risk patients

Profiling for alterations (NCT02884102)

- No detectable actionable alterations
  - Backbone regimen + immune checkpoint inhibitor
- RAF/RAS mutations
  - MAPKi
  - MAPKi + backbone regimen
- IDH mutations
  - IDHi
  - IDHi + backbone regimen
- CCND1 activating mutation
  - CDKi
  - CDKi + backbone regimen
- PI3K/AKT activating mutations
  - AKTi
  - AKTi + backbone regimen
- FGFR3 activating mutations
  - FGFRi
  - FGFRi + backbone regimen
- t(11;14)
  - BCLI
  - BCLI + backbone regimen
## Multiple Myeloma Precision Medicine Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Population</th>
<th>Gene Mutations Targeted</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNJ-42756493 + dexamethasone</td>
<td>RRMM</td>
<td>FGFR3</td>
</tr>
<tr>
<td>Dabrafenib(^t) + Trametinib</td>
<td>RRMM</td>
<td>BRAF, NRAS, or KRAF</td>
</tr>
<tr>
<td>Idasanutlin + ixazomib + dexamethasone</td>
<td>RRMM</td>
<td>17p deletion</td>
</tr>
<tr>
<td>NCI-MATCH</td>
<td>Advanced MM</td>
<td>Various</td>
</tr>
<tr>
<td>GSK-2816126</td>
<td>Advanced MM</td>
<td>Enhancer of Zeste 2 (EZH2)</td>
</tr>
<tr>
<td>Targeted Agent and Profiling Utilization Registry Study (TAPUR)</td>
<td>MM</td>
<td>NRAS, KRAS, VEGFR, Bcr-Abl, SRC, MET, mTOR, ERBB2, BRAFV600E, etc.</td>
</tr>
</tbody>
</table>
Single-cell RNA-Seq (scRNA-Seq)

Tissue (e.g. tumor) → Isolate and sequence individual cells → Gene 1

Cell 1

Compare gene expression profiles of single cells

| Read Counts | Cell 1 | Cell 2 | Gene 1 | Gene 2 | Gene 3 | Gene 4 | ...
|-------------|--------|--------|--------|--------|--------|--------|--------
| Gene 1      | 18     | 0      |        |        |        |        | ...
| Gene 2      | 1010   | 506    |        |        |        |        | ...
| Gene 3      | 0      | 49     |        |        |        |        | ...
| Gene 4      | 22     | 0      |        |        |        |        | ...

Principal Component 1 → Principal Component 2
Sources of Information and what to do with them?

https://www.myeloma.org/understanding/online-information-resources
CONCLUSIONS

• Significant progress made in myeloma treatment armamentarium

• Disease relapse inevitable --- BUT...

• Great potential with newer therapies (immune and non-immune approaches)

• Goal—deep and lasting remissions; potential cure
NEW AGENT TRIALS AT MEDICAL COLLEGE OF WISCONSIN

- Vaccine (MM-DC fusion)
- PROMISS
- Oprozomib
- Anti cd 74
- Anti-April Aduro
- BCMA BITE – short acting / long acting
- Tak 079 anti CD38
- GSK 2857916
- Car-T: 4 trials (UNM, JUNO, bb21, and Jansen)
OVERCOME
THROUGH
COURAGE
& STRENGTH

AND CLINICAL TRIALS
QUESTIONS?
RUN, WALK OR BIKE TO
HELP SCIENCE CRUSH CANCER
JOIN CRUSH A SUMMER-LONG CHALLENGE TO BENEFIT CANCER RESEARCH
SIGN UP AT MCWCANCERCRAUSH.COM