Multiple Myeloma
What is the Therapy of the Future?

Rafat Abonour, M.D.
Harry and Edith Galdstein Professor of Cancer Research
How to Overcome Multiple Myeloma

• Understand How myeloma cells survive.
• Understand the nature of the originating cell
• Understand that not all myeloma cells created equally.
• Understand the importance of the patients’ immune system
Growing Myeloma Is Complicated

Myeloma cells

Tumor-derived osteoclast activating factors
- Macrophage inflammatory protein 1α
- Interleukin-3

(+)

Stromal cells
- RANKL
- Interleukin-6

(−)

Tumor-derived osteoblast inhibitory factors
DKK1, IL3, sFRP2, IL-7, TNF
Sclerostin

Bone

Osteoclasts

Osteoblasts

Osteocytes

The Originating Cell is Stubborn

• myeloma “stem” cell
  – Do not cycle, dormant
  – Very drug resistant
  – Spin off new myeloma cells
Clonal Heterogeneity Impacts Outcome
One Nasty Disease: One Nasty Family

Keats et al. Blood 2012: 120: 1067
Treatment Combinations Now and Then

**NEW**
- VD
- Rev/Dex
- CyBorD
- VTD
- VRD
- VRD
- CDR
- SCT
- VD/VRD
- Lenalidomide
- Bortezomib
- Bortezomib
- Lenalidomide
- Thalidomide
- Carfilzomib
- Pomalidomide
- Dratumumab
- Elotuzumab
- HDAC
- Bendamustine

**OLD**
- Thal/Dex
- VAD
- DEX
- SCT
- Nothing
- Prednisone
- Thalidomide
- Few options
Induction Regimens

• Several new classes of drugs are being used in the management of multiple myeloma patients:
  • Proteasome inhibitors
  • Immune modulatory drugs.
  • Monoclonal Antibodies
• The choice of initial induction therapy can be influenced by the underlying medical conditions of the patients and their prognostic features.
IMPACT OF NOVEL THERAPY 2012/2013

Median 7.3 years

5 YEAR SURVIVAL BY AGE

<table>
<thead>
<tr>
<th>AGE</th>
<th>2006-2010</th>
<th>2001-2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 65 YRS</td>
<td>73%</td>
<td>63%</td>
</tr>
<tr>
<td>&gt; 65 YRS</td>
<td>56%</td>
<td>31%</td>
</tr>
</tbody>
</table>

2012 ASH Abstract #3972 Kumar et al
What are Clinical Trials

• A systemic investigation of new drugs not yet approved by regulatory agencies.
• Are voluntary and you can stop participating any time.
• In cancer trials there may be a placebo but it is added to an accepted treatment. No one will just get placebo.
What are the types of Clinical Trials

- Phase I testing the safety of new drug
- Phase II testing the safety of new drugs
- Phase III testing new drug against old drug to see which is better
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

**Bone marrow stromal cell**
- FGFR3
- CS1
- CD138
- BAFF-R
- IGF1R
- CD38
- TNFα
- TGFβ
- VEGF
- Smad
- NF-κB

**Myeloma Cell**
- Migration
- Akt
- GSK-3β
- FKHR
- Caspase-9
- NF-κB
- mTOR
- Bad
- PI3-K
- JAK/STAT3
- Bcl-xL
- Mcl-1
- MEK/ERK
- MEK/ERK
- p27Kip1
- NF-κB
- Bad
- PKC

**Survival**
- Anti-apoptosis
- Cell cycle

**Proliferation**
- Anti-apoptosis
- Cell cycle

**Therapies TARGETING Myeloma Biology**
- **Proteasome inhibitors:** Velcade, Kyprolis, Ixazomib
- **Immunomodulatory Drugs (IMiDs):** Thalomid, Revlimid, Pomalyst
- **HDAC inhibitor:** Farydak, Ricolostat
- **BCL-2 Inhibitors:** Venetoclax
- **Inhibitors of Nuclear Export:** Selinexor

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

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

**More Biology on the way!**

Achieving Great cytoreduction ($\geq$ VGPR/CR) = Superior Results

Depth of Response Influence Time to Progression

- Presentation
- PR
- VGPR
- CR
- stringent CR

**Total number of tumor cells**
- $10^9$
- $10^8$
- $10^7$
- $10^6$
- $10^5$
- $10^4$
- $10^3$
- $10^2$
- $10^1$
- $10$
- 0

**MRD**

**Undetectable MRD**

**(Operational cure)**

- Diagnosis
- End of therapy
- Time to progression

- a) MGUS-like patients
- b) Sustained vs. unsustained CR according to cytogenetics
- c) Quiescent or controlled levels of detectable MRD
- d) Late relapse on patients with undetectable MRD
- e) Long-term disease control in patients with undetectable MRD
Is three better than two?

SWOG S0777 Study Design (continued)

VRd

After induction

Rd Maintenance Until PD, Toxicity or Withdrawal

- Lenalidomide 25 mg PO days 1-21
- Dexamethasone 40 mg PO days 1, 8, 15, 22

Rd

- All patients received Aspirin 325 mg/day
- VRd patients received HSV prophylaxis

Durie et al, ASH 2015
VRd vs Rd: three drugs are better

<table>
<thead>
<tr>
<th></th>
<th>VRd</th>
<th>Rd</th>
<th>HR; P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>43</td>
<td>30</td>
<td>0.712; .0018 (1-sided)</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>75</td>
<td>64</td>
<td>0.709; .025 (2-sided)</td>
</tr>
<tr>
<td>ORR, %</td>
<td>82</td>
<td>72</td>
<td>-</td>
</tr>
<tr>
<td>CR, %</td>
<td>16</td>
<td>8</td>
<td>-</td>
</tr>
</tbody>
</table>

*VRd showed better PFS in patients with high- or standard-risk vs Rd†*

- *All patients received aspirin (325 mg/d). †Patients received HSV prophylaxis. ‡High-risk cytogenetics included: t(4;14), t(14;16), or del(17p); preliminary data from 316 patients.
### Does Age Matter with Triplet: NO

<table>
<thead>
<tr>
<th>Patients (N=471)*</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Patients given bortezomib with lenalidomide and dexamethasone (VRd group)</td>
<td>242 (51%)</td>
<td>0.73 (0.58–0.92)</td>
</tr>
<tr>
<td>International Staging System stage III</td>
<td>157 (33%)</td>
<td>1.58 (1.16–2.13)</td>
</tr>
<tr>
<td>International Staging System stage II</td>
<td>184 (39%)</td>
<td>1.16 (0.86–1.57)</td>
</tr>
<tr>
<td>Intent to transplant</td>
<td>324 (69%)</td>
<td>0.98 (0.74–1.28)</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>202 (43%)</td>
<td>1.32 (1.03–1.71)</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise stated. *N=471 patients with valid data for factor.

**Table 2: Multivariate age-adjusted progression-free survival and overall survival**
Three Drugs with new agent: KRD:
Carfilzomib, lenalidomide, and dexamethasone

AJ Jakubowiak,1 K Griffith,2 D Dytfeld,3 DH Vesole,4 S Jagannath,5 T Anderson,2 B Nordgren,2 K Detweiler-Short,2 D Lebovic,2 K Stockerl-Goldstein,6 T Jobkar,2 S Wear,7 A Al-Zoubi,2 A Ahmed,2 M Mietzel,2 D Couriel,2 M Kaminski,2 M Hussein,8 H Yeganegi,9 R Vij6

1University of Chicago, Chicago, IL; 2University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; 3Poznan University of Medical Sciences, Poznan, Poland; 4John Theurer Cancer Center, Hackensack, NJ; 5Mount Sinai Medical Center, New York, NY; 6Washington University School of Medicine, St. Louis, MO; 7Multiple Myeloma Research Consortium, Norwalk, CT; 8Celgene, Inc, Summit, NJ; 9Onyx Pharmaceuticals, South San Francisco, CA
KRD for newly diagnosed Myeloma

**K Rd w/o ASCT**
- 4 cycles: n=49, ≥VGPR 69, ≥nCR 43, ≥CR 18, sCR 8
- 8 cycles: n=44, ≥VGPR 89, ≥nCR 66, ≥CR 34, sCR 30
- 18 cycles: n=41, ≥VGPR 90, ≥nCR 80, ≥CR 59, sCR 51

**K Rd + ASCT**
- 4 cycles: n=73, ≥VGPR 73, ≥nCR 22, ≥CR 15, sCR 11
- 8 cycles: n=52, ≥VGPR 96, ≥nCR 85, ≥CR 73, sCR 69
- 18 cycles: n=28, ≥VGPR 93, ≥nCR 93, ≥CR 82, sCR 82

Response after ASCT (n=64)
- 92% ≥VGPR
- 45% ≥nCR
- 27% ≥CR
- 20% sCR

nCR, near complete response; VGPR, very good partial response
KRD in the older (median age 72)

<table>
<thead>
<tr>
<th>Cycles</th>
<th>≥ nCR (%)</th>
<th>sCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>45</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>35</td>
</tr>
<tr>
<td>12</td>
<td>82</td>
<td>62</td>
</tr>
<tr>
<td>16</td>
<td>100</td>
<td>78</td>
</tr>
</tbody>
</table>
MRD Evaluation

- Multiparameter Flow Cytometry (MFC)
  - 10 color
  - Sensitivity: $10^{-4}$ – $10^{-5}$

- Next generation sequencing (NGS)
  - Adaptive Biotechnologies
  - Sensitivity: $10^{-6}$

**KRd w/o ASCT**

At CR

<table>
<thead>
<tr>
<th>MRD negative, %</th>
<th>KRd w/o ASCT</th>
<th>KRd + ASCT ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=26</td>
<td>51*</td>
<td>82</td>
</tr>
<tr>
<td>8 cycles</td>
<td>39†</td>
<td>66</td>
</tr>
</tbody>
</table>

**KRd + ASCT ‡**

At landmark time points

<table>
<thead>
<tr>
<th>MRD negative, %</th>
<th>KRd + ASCT ‡</th>
<th>n=20</th>
<th>n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 cycles</td>
<td>89</td>
<td>71</td>
<td></td>
</tr>
</tbody>
</table>

*Estimated rate based on 23 of 26 evaluated pts assessed for MRD by flow cytometry at CR/ suspected CR
†Estimated rate based on percentage of 13 pts in CR/sCR negative by NGS
‡Actual MRD rates in subgroup of pts evaluated for MRD at the end of 8 and 18 cycles as per new IMWG MRD criteria (pts were considered MRD – negative only if in CR/sCR)
Targets on the Myeloma Cell Surface and Therapeutic Antibodies

**Antibody Drug: Dacetuzumab, Lucatumumab**

**Antibody Drug: Elotuzumab ABBV-838**

**Antibody Drug: Daratumumab**
- B-B4, nBT062 DL101

**Antibody Drug: Isatuximab Mor202**

**Antibody Drug: CAR-T**

**Targets on the Myeloma Cell Surface:**
- CD40
- CD138
- CD38
- SLAMF7
- BCMA
Elotuzumab (HuLuc63) is an IV humanized monoclonal antibody targeting human SLAMF7, a cell surface glycoprotein.

# Performance of Elotuzumab

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Phase</th>
<th>Patient Population</th>
<th>Number of patients</th>
<th>Outcomes</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elotuzumab Single Agent Therapy (Zonder et al, 2012)</td>
<td>I</td>
<td></td>
<td>35</td>
<td>RRMM</td>
<td>No objective response seen</td>
</tr>
<tr>
<td>Elotuzumab + Lenalidomide+ Dexamethasone (ELOQUENT-2, Lonial et al, 2015)</td>
<td>III</td>
<td></td>
<td>646 ERD:32 1 RD:325</td>
<td>RRMM 1 to 3 prior regimens</td>
<td>EloRD vs. RD Response rate: EloRD:79% vs RD:66% Median Duration of response: Elo RD:19.4 vs RD:14.9 months</td>
</tr>
<tr>
<td>Elotuzumab + Velcade + Dexamethasone (Palumbo et al, 2015)</td>
<td>II</td>
<td></td>
<td>152 Ebd:77 Bd: 75</td>
<td>RRMM 1 to 3 prior regimens</td>
<td>EloVD vs. VD Response rate: Elo VD:65% vs VD: 63% Median Duration of response: EloVD:9.9 vs VD:6.8 months</td>
</tr>
<tr>
<td>Elotuzumab + Lenalidomide+ Bortezomib+ Dexamethasone (Laubach J, et al. ASCO 2017)</td>
<td>II</td>
<td></td>
<td>40</td>
<td>Newly diagnosed, MM</td>
<td>Response rate after 4 cycles: Overall Response was 97%, VGPR or better of 65% CR or stringent CR of 15%</td>
</tr>
</tbody>
</table>
Daratumumab’s Mechanisms of Action

**DIRECT ON-TUMOR** actions may contribute to **RAPID** response

**IMMUNOMODULATORY** actions may contribute to **DEEP & DURABLE** response

- **CDC**
  - C1q complex

- **ADCC**
  - NK cell

- **ADCP**
  - Macrophage

- **Apoptosis**
  - Daratumumab

**Rapid**
- Myeloma cell death
- Increase in CD8+ granzyme B+ cells
- Depletion of CD38+ immunosuppressive cells
- Increase in helper T cells
- Clonal expansion of cytotoxic T cells
- Modulation of tumor microenvironment

**Deep and durable**
- Clonal expansion of cytotoxic T cells
- Increase in helper T cells
- Modulation of tumor microenvironment

**Daratumumab**
- Human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action

**Approved**
- As monotherapy in many countries for heavily pretreated RRMM
- In combination with standard of care regimens in RRMM after ≥1 prior therapy in many countries

**Efficacy**
- Daratumumab induces rapid, deep, and durable responses in combination with a PI (bortezomib) or an IMiD (lenalidomide) in RRMM

RRMM, relapsed or refractory multiple myeloma; CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; ADCP, antibody-dependent cellular phagocytosis; PI, proteasome inhibitor; IMiD, immunomodulatory drug.

Daratumumab Combination: Study Design

Multicenter, randomized (1:1), open-label, active-controlled, phase 3 study

DRd (n = 286)
Daratumumab 16 mg/kg IV
• Qw in Cycles 1 to 2, q2w in Cycles 3 to 6, then q4w until PD
• R 25 mg PO
  • Days 1 to 21 of each cycle until PD
• d 40 mg PO
• 40 mg weekly until PD

Rd (n = 283)
R 25 mg PO
• Days 1 to 21 of each cycle until PD
• d 40 mg PO
• 40 mg weekly until PD

Cycles: 28 days

Key eligibility criteria
• RRMM
• ≥1 prior line of therapy
• Prior lenalidomide exposure, but not refractory
• Creatinine clearance ≥30 mL/min

Stratification factors
• No. of prior lines of therapy
• ISS stage at study entry
• Prior lenalidomide

Primary endpoint
• PFS

Secondary endpoints
• TTP
• OS
• ORR, VGPR, CR
• MRD
• Time to response
• Duration of response

Statistical analyses
• Primary analysis: ~177 PFS events

Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg, a acetaminophen, and an antihistamine

ISS, international staging system; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; qw, weekly; q2w, every 2 weeks; q4w, every 4 weeks; PD, progressive disease; R, lenalidomide; PO, oral; d, dexamethasone; Rd, lenalidomide/dexamethasone; PFS, progression-free survival; TTP, time to progression; OS, overall survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.

aOn daratumumab dosing days, dexamethasone 20 mg was administered as pre-medication on Day 1 and Day 2.
Updated Efficacy

- Median (range) follow-up: 17.3 (0-24.5) months

Responses continue to deepen in the DRd group with longer follow-up

HR, hazard ratio; CI, confidence interval; sCR, stringent complete response; PR, partial response.

Note: PFS = ITT population; ORR = response-evaluable population.

\(^{a}\)Kaplan-Meier estimate;

\(^{b}\)P <0.0001 for DRd vs Rd.
MRD-negative Rate

MRD-negative rates were >3-fold higher at all thresholds

Intent-to-treat population. P values are calculated using likelihood-ratio chi-square test.

*P < 0.0001.
Can Daratumumab Help Upfront?

Phase 3 Randomized Study of Daratumumab Plus Bortezomib, Melphalan, and Prednisone (D-VMP) Versus Bortezomib, Melphalan, and Prednisone (VMP) in Newly Diagnosed Multiple Myeloma (NDMM) Patients (Pts) Ineligible for Transplant (ALCYONE)
**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

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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: Prolong Progression Free Survival

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

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

HR, hazard ratio; CI, confidence interval.

*Kaplan-Meier estimate.
Efficacy: Better Response Rate

- Median duration of response: 21.3 months in VMP versus not reached in D-VMP

Significantly higher ORR, ≥VGPR rate, and ≥CR rate with D-VMP; >2-fold increase in rate of sCR with D-VMP

<table>
<thead>
<tr>
<th></th>
<th>VMP (n = 263)c</th>
<th>D-VMP (n = 318)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) time to first response, months</td>
<td>0.82 (0.7-12.6)</td>
<td>0.79 (0.4-15.5)</td>
</tr>
<tr>
<td>Median (range) time to best response, months</td>
<td>4.11 (0.7-20.5)</td>
<td>4.93 (0.5-21.0)</td>
</tr>
</tbody>
</table>

PR, partial response; sCR, stringent complete response.

aITT population, bP <0.0001; P value was calculated with the use of the Cochran–Mantel–Haenszel chi-square test.

cResponders in response-evaluable population.
Efficacy: MRD (NGS; $10^{-5}$ Sensitivity Threshold)

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

\[ P < 0.0001 \]
\[ 3.6X \]

>3-fold higher MRD-negative rate with D-VMP; Lower risk of progression or death in all MRD-negative patients

*Assessed at time of confirmation of CR/sCR and, if confirmed, at 12, 18, 24, and 30 months after first dose.
CAR – T Immune Therapy
CAR-T cell therapy 101
Chimeric antigen receptors (CARs) help T-cells recognize and destroy cancer cells

1. T cells are collected from the patient. A machine removes the desired cells from the blood, then returns the rest back to the patient.

2. A modified virus (blue) is used to transfer DNA to the patient's T cells so they will produce CAR proteins.

3. CARs have two ends: a binding site (blue) specific to the tumor cells, and a signaling engine that activates the T cell to kill the tumor it binds to.

4. Once designed, millions of engineered CAR T cells are grown in the laboratory.

5. The expanded population of CAR T cells is infused into the patient through a standard blood transfusion.
MM Patient #1: Response to CD19 CAR Therapy

- IgA (mg/dl) over time:
  - MEL 200
  - LEN
  - LEN/BTZ
  - DEX/CLR
  - CY
  - CY
  - MEL 140
  - CTL019

- Additional regimens including:
  - carfilzomib
  - pomalidomide
  - vorinostat
  - elotuzumab

- CTL019 first undetectable MRD-negative

- Days (ASCT #1)

- Days (ASCT #2)

- sCR, MRD neg
- Now d +307
- TTP after ASCT #1 d190
- Remission inversion

Garfall et al, NEJM 2015; 373: 1040-7
CAR-BCMA T Cells in Myeloma: Background

- B-cell maturation antigen (BCMA) is expressed by normal and malignant plasma cells.
  - BCMA 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 proteins associated with cancer.

- The patient’s own T-cells are stimulated, transduced with CD-28/BCMA retroviruses, and cultured for 9 days before re-infusion.


J Clin Oncol 35, 2017 (suppl; abstr LBA3001); 22nd EHA Congress; June, 2017; Abstract S142
LCAR-B38M CAR-BCMA T Cells in Relapsed Myeloma Response

- A study from The Second Affiliated Hospital of Xi’an Jiaotong University in Xi’an, China using LCAR-B38M CAR-T cell therapy from Legend Biotech.
- 33 out of 35 patients (94%) with relapsed or refractory multiple myeloma experienced clinical response after CAR T cell BCMA treatment.

<table>
<thead>
<tr>
<th>Response 4 months after BCMA Therapy</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>14</td>
</tr>
<tr>
<td>Very good partial response VGPR</td>
<td>4</td>
</tr>
<tr>
<td>Partial response</td>
<td>1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>0</td>
</tr>
</tbody>
</table>

After 1 year the first 5 patients have maintained their responses. There was a single incidence of disease progression from very good Partial remission.
BB-2121 anti-BCMA CAR T-cell therapy for relapsed/refractory multiple myeloma

Response to Therapy

- Stringent complete response (sCR)
- Very good partial response (VGPR)
- Partial response
- Stable disease
- Progressive disease

Patent Responses; Cohort (dose) #

- Dose Cohort #1: 33%
- Dose Cohort #2&3: 100%

Lin Y et al; 22nd EHA Congress; June, 2017; Abstract S142
After CAR-BCMA T cell infusion, the patient may experience cytokine release syndrome (CRS)!

- Fever
- Low Blood pressure (hypotension)
- High heart rate (tachycardia)
- High creatinine kinase (muscle damage) and liver enzymes (liver damage).
- Acute kidney damage
- Shortness of breath

In the LCAR-B38M CAR-T study
- This was observed in 14 (74%) patients who received treatment.
  - Most (11) were grade 1 (mild) or grade 2 (moderate).

In the bb2121 CAR-T study
- Mild to moderate CRS had been reported in 8/11 (73%) treated patients
Today’s Car T cells…long way to Ferrari
BCMA-BiTE-based Immunotherapies

- CD3
- BCMA
- Cytotoxic granule

- T cell proliferation
- BCMA-BiTE

- MM cell lysis

Tai et al 2016
Pembrolizumab in Combination with Pomalidomide and Dexamethasone for Relapsed/Refractory Multiple Myeloma (RRMM)

Ashraf Z Badros, et al.
Blood 2016 128:490
Pembrolizumab

- A humanized (Ig) G4 directed against surface receptor PD-1 with potential immune checkpoint inhibitory and antineoplastic activities.
- Pembrolizumab binds to PD-1, an inhibitory signaling receptor expressed on the surface of activated T cells, and blocks the binding to and activation of PD-1 by its ligands, which results in the activation of T-cell-mediated immune responses against tumor cells.
**Pembrolizumab, Pomalidomide, Dexamethasone for R/R MM: Prior Therapy**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pts (N = 48)</th>
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<tbody>
<tr>
<td>Median time from diagnosis to study, yrs (range)</td>
<td>4 (1.2-26)</td>
</tr>
<tr>
<td>Median lines of earlier therapy (range)</td>
<td>3 (2-5)</td>
</tr>
<tr>
<td>▪ 2 lines, %</td>
<td>35</td>
</tr>
<tr>
<td>▪ 3 lines, %</td>
<td>38</td>
</tr>
<tr>
<td>▪ &gt; 3 lines, %</td>
<td>27</td>
</tr>
<tr>
<td>Previous therapy, %</td>
<td></td>
</tr>
<tr>
<td>▪ ASCT</td>
<td>72</td>
</tr>
<tr>
<td>▪ Bortezomib</td>
<td>100</td>
</tr>
<tr>
<td>▪ Carfilzomib</td>
<td>50</td>
</tr>
<tr>
<td>▪ Lenalidomide</td>
<td>98</td>
</tr>
<tr>
<td>▪ Thalidomide</td>
<td>2</td>
</tr>
<tr>
<td>Refractory, %</td>
<td></td>
</tr>
<tr>
<td>▪ Proteasome inhibitors</td>
<td>79</td>
</tr>
<tr>
<td>▪ Lenalidomide</td>
<td>90</td>
</tr>
<tr>
<td>▪ IMiDs + proteasome inhibitors</td>
<td>73</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 Improves Response and Survival

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

<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 PFS</td>
<td>17.4 (11.7-18.8)</td>
</tr>
<tr>
<td>Median OS</td>
<td>Not reached (18.8-not reached)</td>
</tr>
</tbody>
</table>

Can We Use Checkpoint Inhibitors with Allograft

- Patients do relapse after allografting.
- Donor lymphocyte infusions lead to unfavorable results in the majority of patients.
- Donor lymphocytes are readily available and potentially activated by PD-1 blockade.
Donor lymphocyte infusion followed by Nivolumab

Before Allo  3 months after Allo  1 month after Nivo
Is this the Furfure

DKRD  SCT  IMIDs +/- Elotuzumab
DVRD  CART  IMIDs +/- Nivolumab

Front line treatment

Induction  Consolidation  Post consolidation  Cure

Maintenance
Conclusions

- Survival is improving due to better combinations.
- Combination therapy provide higher rates of negative minimal residual disease and improve survival.
- Immune therapy is very promising. Total therapy approach including these drugs may prove curative.