Best of ASH 2019
What Patients and Caregivers Need to Know

Brian G.M. Durie, MD
Thursday, January 9th, 2020
• 2020 is the 30 year anniversary

• This year will be pivotal for key projects for:
  • CURE
  • PREVENTION
• IMF at ASH 2019
• Dr. Durie’s Blog
  • Takeaways from ASH 2019
  • ASH 2019 Update: Late-Breaking Abstracts
  • ASH Top 10 for 2019: Immune therapies again dominate news
• Satellite Symposium: Approaches to Achieve the Best Possible Outcomes in Myeloma
• Support Group Leaders at ASH: Tweets/Blogs
• ASH Doctor Interviews
• IMWG Conference Series
KEY TAKEAWAYS FOR ASH 2019

• Smoldering myeloma

• Frontline therapy

• Potential precision medicine approaches

• CAR T therapy/Bispecific T Cell Engagers/MoAbs

• Novel agents/combinations
• What is HR-SMM?

• How should it be managed?
## IMWG Classification of HR SMM

Progression by Risk Group (n = 1151 pts)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Coefficient</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FLC Ratio</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-10 (reference)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>&gt;10-25</td>
<td>0.69</td>
<td>1.99 (1.15, 3.45)</td>
<td>0.014</td>
<td>2</td>
</tr>
<tr>
<td>&gt;25-40</td>
<td>0.96</td>
<td>2.61 (1.36, 4.99)</td>
<td>0.004</td>
<td>3</td>
</tr>
<tr>
<td>&gt;40</td>
<td>1.56</td>
<td>4.73 (2.88, 7.77)</td>
<td>&lt;0.0001</td>
<td>5</td>
</tr>
<tr>
<td><strong>M protein (g/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1.5 (reference)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>&gt;1.5-3</td>
<td>0.95</td>
<td>2.59 (1.56, 4.31)</td>
<td>0.0002</td>
<td>3</td>
</tr>
<tr>
<td>&gt;3</td>
<td>1.30</td>
<td>3.65 (2.02, 6.61)</td>
<td>&lt;0.0001</td>
<td>4</td>
</tr>
<tr>
<td><strong>BMPC%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-15 (reference)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>&gt;15-20</td>
<td>0.57</td>
<td>1.77 (1.03, 3.06)</td>
<td>0.04</td>
<td>2</td>
</tr>
<tr>
<td>&gt;20-30</td>
<td>1.01</td>
<td>2.74 (1.6, 4.68)</td>
<td>0.0002</td>
<td>3</td>
</tr>
<tr>
<td>&gt;30-40</td>
<td>1.57</td>
<td>4.82 (2.5, 9.28)</td>
<td>&lt;0.0001</td>
<td>5</td>
</tr>
<tr>
<td>&gt;40</td>
<td>2.00</td>
<td>7.42 (3.23, 17.02)</td>
<td>&lt;0.0001</td>
<td>6</td>
</tr>
<tr>
<td><strong>FISH abnormality</strong></td>
<td></td>
<td>0.83</td>
<td>2.28 (1.53, 3.42)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### 2/20/20 Model

- **FLC Ratio**: 20
- **Serum M Protein**: 2 g/dl
- **Bone Marrow Plasma Cell %**: 20%

**Low Risk**

**High Risk**

**New SMM Risk Score Tool**
Rationale for Early Intervention

To treat the disease early: to achieve cure

Numerous clinical trials in SMM (~51 in clinicaltrials.gov)

TO DELAY THE DISEASE PROGRESSION:
- Len-Dex vs observation: +PFS & OS
- Len vs observation: +PFS
- Elo-Rd: *Positive results*
- Ixaz-Rd: *Positive results*
- Daratumumab: *Positive results*
- **KRd: Positive results (12 cases MRD- 92%)**
- Pembrolizumab; Nivolumab-Rd; Isatuximab

TO CURE THE DISEASE:
- KRD + ASCT + Consol + Maint (CESAR)
- KRD + Dara +/- ASCT...... (ASCENT)
- iSTOPMM protocols

Black Swan Trials
# Improvement in the quality of response over the treatment

<table>
<thead>
<tr>
<th></th>
<th>Induction (KRdx6) N = 77</th>
<th>HDT/ASCT N = 77</th>
<th>Consolidation (KRdx2) N = 77</th>
<th>Maintenance (Rdx1y) N = 77</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥CR</td>
<td>43%</td>
<td>63%</td>
<td>75%</td>
<td>81%</td>
</tr>
<tr>
<td>VGPR</td>
<td>43%</td>
<td>24%</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>PR</td>
<td>13%</td>
<td>13%</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>PD</td>
<td></td>
<td></td>
<td></td>
<td>1%*</td>
</tr>
<tr>
<td>MRD-negative</td>
<td>33%</td>
<td>49%</td>
<td>62%</td>
<td>62%</td>
</tr>
</tbody>
</table>

* Progressive disease was biological at the end of maintenance and the MRD was positive
CESAR TRIAL: PFS AND OS RESULTS

**PFS**
- Proportion of pts alive and free of progression
- 92% at 35m

**OS**
- Proportion of pts alive
- 96% at 35m

6 pts did progress and in 5 pts PD was biological and 4 pts were at ultra high risk

3 pts died and in only one was treatment-related death
• Molecular mass defines clonality
• Intensity indicates amount of monoclonal protein

The result is a highly sensitive and specific approach to monitor M-proteins

Noemi Puig, MD, PhD, et. al.
MONITORING IN THE CESAR TRIAL

SPEP/IFE vs QIP-MS: Sensitivity

POST-IND

POST-ASCT

POST-CONSOL

SPEP

QIP-MS

MASS SPEC MORE SENSITIVE

Noemi Puig, MD, PhD, et. al.
COMPARISON OF QiP-MS AND NGF-MRD

NGF-MRD vs QIP-MS: Sensitivity

POST-IND

POST-ASCT

POST-CONSOL

Only relapse was NGF -, but QiP-MS +

Noemi Puig, MD, PhD, et. al.
EXPLANATIONS FOR BONE MARROW MRD NEGATIVE BUT QiP-MS POSTIVE

NGF-MRD - vs QIP-MS+

PATCHY DISEASE

EXTRAMEDULLARY LESIONS

Noemi Puig, MD, PhD, et. al.
WHEN SHOULD TREATMENT BE STARTED

Potential New Myeloma or Smoldering Myeloma

Any Myeloma Defining Events?
- CRAB
- $\geq 60\%$ PC
- FLC $\geq 100$
- MRI $>1$ focal lesion

No Myeloma Defining Events (SMM)

High-Risk SMM (Median TTP $\sim 2$ years)

Intermediate or Low-Risk SMM

Treat as Myeloma
Observation
Early Therapy With Len or Rd
Clinical Trials
Observation
• What is best?

• Are dara* + triplet regimens the way forward?

*or isatuximab...
TRIPLE RESULTS: VRd + ASCT: IFM 2009 STUDY

**PFS**

- RVD
- Transplantation

**OS**

- MRD Negative
- MRD Positive

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<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVD</td>
<td>350 294 228 157 32 0</td>
</tr>
<tr>
<td>Transplantation</td>
<td>350 308 264 196 50 0</td>
</tr>
</tbody>
</table>

**S1B**

- MRD Negative
- MRD Positive

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<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD Negative</td>
<td>311 379 347 119 0</td>
</tr>
<tr>
<td>MRD Positive</td>
<td>358 259 227 65 0</td>
</tr>
</tbody>
</table>
TRIPLET RESULTS: VRD x 6 for induction
458 Patients in GEM2012 trial

Bortezomib, lenalidomide, and dexamethasone as induction therapy prior to autologous transplantation in multiple myeloma

Laura Rosiñol, Albert Oriol, Rafael Rios, Anna Sureda, María-Jesús Blanchard, Miguel Teodoro Hernández, Rafael Martínez-Martínez, Jose M Moraleda, Isidro Jarque, Juan Bargay, Mercedes Gironella, Felipe de Arriba, Luis Palomera, Yolanda González-Montes, Josep Martí, Isabel Krsnik, Jose M Arguiñano, María-Esther Gonzalez, Ana Pilar Gonzalez, Luis Felipe Casado, Lucia Lopez-Anglada, Bruno Paiva, Maria-Victoria Mateos, Jesus San Miguel, Juan-José Lahuerta and Joan Bladé

VELCADE
• 2x each week SQ for 2 weeks
• Q4 week cycles
PFS by Double-negativity Rate for MRD (MFC; $10^{-5}$) and PET/CT Post-consolidation
ASH Abstract #691: Dara plus VRd v VRd: Griffin Study Update

PFS

OS

Median PFS and OS not reached for D-RVd and RVd

Peter M. Voorhees, MD, et. al.
ASH Abstract #860: Dara KRd + ASCT

IMWG

- CR/sCR
- VGP
- PR
- PD

INCREASING

CR/sCR

NGS-MRD

- MRD Neg @ ≥10⁻⁵ level
- Maximum benefit = 65% @ ≥10⁻⁶ level
Will dara* + triplet become the “standard of care”? OR will we stick with?

- dara-VRd (Griffin)
- dara-KRd (for high risk MM)
- dara-VTd or VCd (if R not available)
- dara-VMP (for non-transplant)

OR will we stick with?

- dara Rd (MAIA)
- VRd (modified)
- Other triplets

...and save quadruplets for later?

*or isatuximab...
MYELOMA: FRONTLINE TREATMENT

Newly Diagnosed MM

Not Transplant Candidate
- Rd or VMP
- VMP-Dara or VRD followed by Len or DRd following approval

Transplant Candidate
- VRd or VTd or VCD if VRd not available or Dara-based quadruplet induction following approval

Auto-SCT Maintenance (Len for std risk; Len+Pl-based for high risk)

No Delayed Transplant Outside clinical trials
Potential Precision Medicine Approaches

New Data at ASH

• 1q21 gain

• t(11;14)

• Role of ASCT and VENETOCLAX

• Therapy for primary systemic amyloidosis

• Unfit/frail patients with NDMM: HOVON 143 IXA/Dara/Dex
4343 1q21 Gain May Challenge the Role of t(4;14) As an Adverse Prognostic Marker of Multiple Myeloma

PFS

B

OS

1q+ plus t(4;14)
Overall Survival
ASH Abstract #1888: Bortezomib and dexamethasone +/- VENETOCLAX: Update of BELLINI Phase 3 Trial

PFS

\[ t(11;14) \text{ or } \text{BCL2}^{\text{HIGH}} \]

PFS

\[ \text{NON } t(11;14) \text{ or } \text{BCL2}^{\text{LOW}} \]

Philippe Moreau, MD, et. al.
ASH Abstract #139: Primary Results from the Phase 3 Tourmaline-AL1 Trial of Ixazomib-Dexamethasone Versus Physician’s Choice of Therapy in Patients (Pts) with Relapsed/Refractory Primary Systemic AL Amyloidosis (RRAL)

Figure. Time to vital organ deterioration/death and efficacy outcomes (PA)

- Hazard ratio (95% CI): 0.525 (0.316, 0.873)
- Median: Ixa-Dex: 34.8 mos, Physician’s choice: 26.1 mos
- No. of events: Ixa-Dex: 37, Physician’s choice: 40
- P=0.0116
WILL THERE BE “PRECISION MEDICINE” APPROACHES FOR t(11;14), 1q+ AND OTHERS?

• 1q+ plus t(4;14): clear high risk group!

• t(11;14): treat incorporating:
  • ASCT
  • Venetoclax

• IXA oral combinations for amyloid and unfit/frail
• CAR T Therapy

• Bispecific T Cell Engagers (BiTEs [Amgen]; BEATs; TCEs [BMS])

• GSK 2857916 ("belamaf": MoAb/drug conjugate)
Is CAR T Therapy a Game Changer in MM?

BCMA sequence inserted into DNA

Chimeric Antigen Receptor (CAR) Therapy for Multiple Myeloma

### CARTITUDE-1: Safety

#### Hematologic AEs (≥25% All Grade)

<table>
<thead>
<tr>
<th>AE</th>
<th>All Grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>27 (93%)</td>
<td>27 (93%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>25 (86%)</td>
<td>16 (55%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>25 (86%)</td>
<td>20 (69%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>15 (52%)</td>
<td>15 (52%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>13 (45%)</td>
<td>9 (31%)</td>
</tr>
</tbody>
</table>

#### Non-Hematologic AEs (≥25% All Grade)

<table>
<thead>
<tr>
<th>AE</th>
<th>All Grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased AST</td>
<td>9 (31%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>8 (28%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (28%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>8 (28%)</td>
<td>0</td>
</tr>
</tbody>
</table>

#### CAR-T-associated AEs

<table>
<thead>
<tr>
<th>AE</th>
<th>All Grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurotoxicity consistent with ICANSb</td>
<td>3 (10%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

#### Maximum CRS Grade (N = 29)

- Grade 0: 2 (7%)
- Grade 1: 14 (48%)
- Grade 2: 11 (38%)
- Grade 3: 1 (3%)
- Grade 4: 1 (3%)
577 Results from CARTITUDE-1: A Phase 1b/2 Study of JNJ-4528, a CAR-T Cell Therapy Directed Against B-Cell Maturation Antigen (BCMA), in Patients with Relapsed and/or Refractory Multiple Myeloma (R/R MM)

Deepu Madduri, MD, et. al.
TIME FOR A PAUSE TO CONSIDER 100% RESPONSES!

CARTITUDE-1 Efficacy: Tumor Burden Reduction

100% of patients achieved a reduction in paraprotein

Percent Maximum Change in Paraprotein

*Serum M-protein, urine M-protein, or difference between involved and uninvolved free light chain (dFLC). *Bence-Jones proteinuria at baseline, with a transient response during bridging therapy; output represents dFLC value.

Deepu Madduri, MD, et. al.
## IND Approvals for BCMA-CAR T Therapy in China

<table>
<thead>
<tr>
<th>No.</th>
<th>Company</th>
<th>Product</th>
<th>Indication</th>
<th>Approved time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nanjing Legend Biotech Co.,Ltd.</td>
<td>LCAR-B38M Chimeric Antigen Receptor T Cell (LCAR-B38M CAR-T)</td>
<td>R/R MM</td>
<td>2018.03</td>
</tr>
<tr>
<td>2</td>
<td>Shanghai HRAIN Biotechnology Co.,Ltd.</td>
<td>Human BCMA Targeted T Cells Injection (BCMA-CART)</td>
<td>R/R MM (BCMA+)</td>
<td>2018.12</td>
</tr>
<tr>
<td>3</td>
<td>Shanghai CARsgen therapeutics Co.,Ltd.</td>
<td>CT053(Human anti-BCMA CAR-T) Cell Infusion</td>
<td>R/R MM</td>
<td>2019.03</td>
</tr>
<tr>
<td>4</td>
<td>Nanjing IASO Biotherapeutics Co.,Ltd.</td>
<td>Fully human BCMA CAR T-cell Injection (humanized BCMA-CART)</td>
<td>R/R MM</td>
<td>2019.09</td>
</tr>
</tbody>
</table>
3154 Efficacy and Safety of CAR-T Therapy with Safety Switch Targeting Bcma for Patients with Relapsed/Refractory Multiple Myeloma in a Phase 1 Clinical Study

Hospital 1

HRAIN Product with Safety Switch

ORR: 38/49 (77.55%), ≥CR 43%

ECOG ≥3 ORR: 15/20 (75.00%)

ECOG 0~2 ORR: 23/29 (79.31%)

Hospital 2 & 3

ZHZN-05-021 Pt17
HDZ-WZ-013 Pt16
CHXM-03-101 Pt15
TAXP-03-077 Pt14
NUC-03-076 Pt13
ZHUM-03-075 Pt12
LIZH-03-073 Pt11
WAYR-03-069 Pt10
WETL-03-063 Pt9
GUNI-03-062 Pt8
CHCL-03-059 Pt7
WWF-02-055 Pt6
HKR-02-049 Pt5
LKH-02-047 Pt4
HWB-02-034 Pt3
ZJY-02-027 Pt2
ZJ-02-026 Pt1

Ongoing response
- Death
- PD
- sCR
- CR
- VGPR
- PR
- MR
- SD
- MRD-
- MRD+

Post infusion (month)

**RESPONSE OVER TIME**

- Median time to first response was 4.1 weeks (range 4.0–13.1)
- 5 of 30 (16.7%) patients achieved an MRD-negative sCR/CR
  - Of 13 responding patients, 92.3% achieved MRD negativity (≤1/10^5) in the bone marrow on or before C4D1 by Euroflow

**Key Events**

- Time on Study (months)
- PD: Progressive Disease
- VGPR: Very Good Partial Response
- PR: Partial Response
- Ongoing
- MR: Minimal Response
- Death
- CC-93259 dose
- MRD-negative

Data as of October 29, 2019.

*MRD negativity by Euroflow analysis was reported only if a minimum sensitivity of ≤1 tumor cell in 10^6 nucleated cells was achieved and in patients who had ≥1 baseline and ≥1 post-baseline MRD assessment. HTB: high tumor burden (defined as >50% bone marrow plasma cells or >5 extramedullary lesions). LTB: low tumor burden (defined as ≤50% bone marrow plasma cells and ≤5 extramedullary lesions). MR: minimal response.*

Luciano J. Costa, MD, PhD, et. al.
Belatamab Mafodotin (GSK2857916): a BCMA-Targeted Antibody Drug Conjugate

Mechanisms of Action:
1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death

Fc region of the Antibody
- Target specific
- Enhanced ADCC

Linker
- Stable in circulation

Drug
- MMAF (non cell permeable, highly potent auristatin)

Efficacy in refractory populations

Patients refractory to IMID and PI (n = 32)
ORR: 56.3%
(95% CI: 37.7-73.6)

Patients previously treated with dara AND refractory to IMID and PI (n = 13)
ORR: 38.5%
(95% CI: 13.9-68.4)

DREAMM – 1: single agent dose expansion results
Dose 3.4 mg/kg every 3 weeks, 1hr infusion

Overall ORR = 60% (95% CI: 42.1-76.1); n = 35

[sCR: 2 (6%), CR: 3 (9%), VGPR: 14 (40%), PR: 2 (6%)]

Heavily pretreated - 89% double refractory;
- 34% double + dara refractory

29% with high-risk cytogenetics
How should BCMA targeted therapy be used and sequenced?

Is earlier use the best approach?
  • For consolidation?
  • At first relapse?

Clearly active in relapsed patient population
NOVEL AGENTS OR COMBINATION AT RELAPSE

- dara/Kyprolis/dex (CANDOR): LBA-6 (ASH 2019)
- dara/Pom/dex
- Kyprolis/Pom/dex
- iberdomide (CC-220)
- melflufen
- I\(^{131}\) CLR 1404 (lipid rafts target)
Treatment with KdD resulted in a 37% reduction in the risk of progression or death vs Kd in patients with RRMM.
Daratumumab-Pom-Dex: Phase II Trial (n = 103)

IBERDOMIDE (CC-220): Cohort B Response Results

- **ORR 32.2%**
  - CBR: 17 (28.8)
  - DCR: 10 (16.9)
  - ORR: 2 (3.4)

- **ORR 35.3%**
  - CBR: 17 (33.3)
  - DCR: 9 (17.7)
  - ORR: 1 (2.0)

- **ORR 29.6%**
  - CBR: 7 (25.9)
  - DCR: 4 (14.8)
  - ORR: 1 (3.7)

**Response, n (%):**
- **All Evaluable (n = 59):**
  - CBR 49.2%
  - DCR 84.7%
  - ORR 32.2%

- **IMiD-Refractory* (n = 51 evaluable):**
  - CBR 33.3%
  - DCR 17.7%
  - ORR 13.7%

- **DARA + POM-Refractory (n = 27 evaluable):**
  - CBR 25.9%
  - DCR 14.8%
  - ORR 37.0%

*aIncludes Len or Pom

MYELOMA: FIRST RELAPSE

First Relapse

Not Refractory to Lenalidomide
- DRd or KRd
- Alternatives including If Dara Refractory: KRd, IRd, Kd, ERd; Kd-dara after approval

Refractory to Lenalidomide
- PVd or DVd (DPd, DKd or KPd after approval)
- Alternatives including If Dara Refractory: KPd, PVd, or EPd Frail: Pd, IPd
### MYELOMA: SECOND OR HIGHER RELAPSE

**First Relapse Options**

- Any first relapse options that have not been tried
  
  (2 new drugs; triplet preferred)

  **Isa-Pd, or DPd, or DKd, or KPd after approval**

**Additional Options**

- VDT-PACE like anthracycline containing regimens
- Melphalan/melflufen
- Adding Panobinostat
- Quadruplet regimens
- CART
- Bispecific
- Conjugated BCMA
- Selinexor
- Referral for clinical trials always if available
Thank you for watching!
Thank you to our sponsors!