Advances in the Optimal Choice of Therapeutic Strategies for Patients With R/R Myeloma

Faculty Presenters:
Jesús F. San-Miguel, MD, PhD

This activity is supported by educational grants from AbbVie; Amgen; Bristol-Myers Squibb; Celgene Corporation; Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC; and Takeda Oncology.

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Program Faculty

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Jesús F. San-Miguel, MD, PhD, has disclosed that he has received consulting fees from Amgen, Bristol-Myers Squibb, Celgene, Janssen, MSD, Novartis, Roche, Sanofi, and Takeda.
Therapeutic Strategies at Relapse in Multiple Myeloma

Jesus San-Miguel
Universidad Navarra
Patient Case Example

- A 66-year-old woman was diagnosed with IgG lambda R-ISS stage II myeloma
  - BM showed 60% PC with 1q gain plus t(4;14)
  - MC: 43 g/L; Hb: 10.3 g/dL, creatinine: 1.2 mg/dL; calcium: 9.2 mg/dL
  - She had extensive bony disease
- She was treated VTD + ASCT + lenalidomide for 2 years and achieved sCR
- After 4 years, she relapsed
How would you treat this patient?

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<td>Jesús F. San-Miguel, MD, PhD</td>
<td>Rescue treatment followed by second ASCT</td>
</tr>
</tbody>
</table>
Late relapse (> 3-4 years post ASCT)
- Aggressive relapse: Reinduction (VRD/KRD +/- Dara) + 2nd ASCT
- Biochemical relapse: Repeat the initial approach or same as above

Early relapse (< 1 year post ASCT)
- "Overcome drug resistance"
  Combination of non cross-resistant agents
  VRD (KRD)-PACE + Dara ➔ RIC-Allo/CAR-T

Intermediate relapse (1-3 years post ASCT)
- "Prolong survival until curative treatments are developed"
  Sequential novel agent combinations: Dara + PomDex.....KRD...
Patient Case Example, Continued

- A 66-year-old woman was diagnosed with IgG lambda R-ISS stage II MM
  - BM showed **1q gain plus t(4;14)** with extensive **bony disease**
  - She was treated VTD + ASCT + lenalidomide for 2 years and achieved sCR
  - After 4 years, she relapsed
- She refused 2nd ASCT (70 years, with hypertension) and was treated with **VCD x 8 cycles** and achieved CR
- She relapsed 10 months later
How would you treat this patient?

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## Lenalidomide-Based Regimens: Efficacy

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>POLLUX (n=569)</th>
<th>ASPIRE (n=792)</th>
<th>ELOQUENT-2 (n=646)</th>
<th>TOURMALINE-MM1 (n=722)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS HR ((\uparrow) m)</strong></td>
<td>DaraRd vs Rd (^1\text{-}^3)</td>
<td>KRd vs Rd (^4\text{-}^5)</td>
<td>ERd vs Rd (^6)</td>
<td>IRd vs Rd (^7)</td>
</tr>
<tr>
<td></td>
<td>0.44 ((\uparrow) 27)</td>
<td>0.67 ((\uparrow) 8.7 m)</td>
<td>0.71 ((\uparrow) 4.5 m)</td>
<td>0.74 ((\uparrow) 5.9 m)</td>
</tr>
<tr>
<td></td>
<td>44.5 vs 17.5 m</td>
<td>26.3 vs 17.6 m</td>
<td>19.4 vs 14.9 m</td>
<td>20.6 vs 14.7 m</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>93</td>
<td>87</td>
<td>79</td>
<td>78</td>
</tr>
<tr>
<td><strong>(\geq) CR, %</strong></td>
<td>51</td>
<td>32</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td><strong>OS HR (95% CI)</strong></td>
<td>0.63</td>
<td>0.79 ((\uparrow) 8 m)</td>
<td>0.78 ((\uparrow) 4.1 m)</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>48 vs 40 m</td>
<td>43.7 vs 39.6 m</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High Risk: m (HR)</strong></td>
<td>22.6 (0.64)</td>
<td>23 (0.70)</td>
<td>19 (0.60)</td>
<td>21 (0.54)</td>
</tr>
</tbody>
</table>

This table is provided for ease of viewing information from multiple trials with different patient populations. Direct comparison across trials is not intended and should not be inferred. DOR, duration of response; NE, not evaluated.

Patient Case Example

- A 66-year-old woman was diagnosed with IgG lambda R-ISS stage II MM
  - BM showed **1q gain plus t(4;14)** with extensive **bony disease**
  - She was treated VTD + ASCT + lenalidomide for 2 years and achieved sCR
  - After 4 years, she relapsed

- She refused 2nd ASCT (70 years, with hypertension) and was treated with VCD x 8 cycles and achieved CR

- She relapsed 10 months later

- She began tx with **lenalidomide/dexamethasone** until progression
  - On cycle 5, she was already in VGPR and maintained her response for 15 months before relapse
How would you treat this patient?

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# Proteasome Inhibitors-Based Regimens: Efficacy

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>ENDEAVOR (n=929)</th>
<th>CASTOR (n=499)</th>
<th>OPTIMISMM (n=559)</th>
<th>PANORAMA-1 (n=768)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS HR</td>
<td><strong>0.53 (▲ 9.3 m)</strong></td>
<td><strong>0.32 (▲ 9.6 m)</strong></td>
<td><strong>0.61 (▲ 4.1 m)</strong> *</td>
<td><strong>0.63 (▲ 4 m)</strong> *</td>
</tr>
<tr>
<td></td>
<td><strong>18.7 vs 9.4 m</strong></td>
<td><strong>16.7 vs 7.1 m</strong></td>
<td><strong>11.2 vs 7.1 m</strong></td>
<td><strong>12 vs 8 m</strong></td>
</tr>
<tr>
<td>ORR, %</td>
<td>77</td>
<td>85</td>
<td>82.2</td>
<td>60.7</td>
</tr>
<tr>
<td>≥ CR, %</td>
<td>13</td>
<td>30</td>
<td>15.7</td>
<td>27.6</td>
</tr>
<tr>
<td>OS HR (95% CI)</td>
<td><strong>0.79 (▲ 7.6 m)</strong></td>
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</tr>
<tr>
<td></td>
<td><strong>47.6 vs 40 m</strong></td>
<td></td>
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</tr>
<tr>
<td>Len Refract</td>
<td>24% (8.6m)</td>
<td>18% (9.3m)</td>
<td>71% (9.5m)</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>High Risk: m (HR)</td>
<td><strong>8.8 (0.73)</strong></td>
<td><strong>11.2 (0.45)</strong></td>
<td><strong>8.4 (0.56)</strong></td>
<td>NA</td>
</tr>
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Patient Case Example

- A 66-year-old woman was diagnosed with IgG lambda R-ISS stage II MM
  - BM showed **1q gain plus t(4;14)** with extensive **bony disease**
  - She was treated VTD + ASCT + lenalidomide for 2 years and achieved sCR but relapsed after 4 years

- She refused 2nd ASCT (70 years, with hypertension) and was treated with VCD x 8 cycles and achieved CR
  - She relapsed 10 months later

- She began tx with lenalidomide/dexamethasone until progression
  - She achieved VGPR but relapsed 15 months later

- **She received Dara-Vd and achieved PR on C2 but progressed with extramedullary disease on C8**
Let’s Vote!
How would you treat this patient now?

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<td>Philippe Moreau, MD</td>
<td>Clinical trial with BCMA CAR T-cell therapy</td>
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Treatment at 3rd/subsequent relapses

**Poma – Dexa** (backbone)
- ORR: 31%; PFS 4 m; OS: 13.1 m

**PCyDex** (ORR 65%; PFS 9.5 m)
- EloPom Dex (ORR:53%, PFS 10.2m)

**Daratumumab**
- ORR: 31%; PFS 4m; OS 20.1 m

**DaraCfzDex** *
- ORR: 86% (81% CR)
- PFS: 71% at 12m (14.1m)

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4. Voorhees PM, ASH 2015 Abst 375
Elotuzumab-Poma-Dexa vs Poma-Dex in RRMM: Phase 2 Randomized ELOQUENT-3 Trial – Efficacy (N = 117)

**KEY INCLUSION**

- ≥ 2 prior regimens
- Prior IMID and PI treatment
- Refractory to last line
- Refractory to Len and a PI

POM: 4 mg days 1-21; 40 mg (20 of >75y) weekly

ELO: 10 mg/kg/w C1&C2; >C3: 20mg/kg/ 4 w

**Median number of prior lines: 3 (2 – 8)**
- Prior exposure to: BORT (100%), CFZ (21%), LEN (99%)
- Refractory to: PI 80%, LEN 87%, double refractory (70%)

**Safety Epd vs Pd:** Grade 3-4 neutropenia: 13% vs 27% // Anemia: 10% vs 20% // Infections any grade: 65% vs 65%

**Safety was consistent with prior reports of ELO and POM**

Dimopoulos MA et al. NEJM 2018, 379:1811-22
XPO1-Inhibitor Selinexor in RRMM. Summary of Phase I data

First-in-class, oral Selective Inhibitor of Nuclear Export (SINE) that inhibits XPO1 and activates tumor suppressor proteins & reduces oncoproteins

- Cancer cells (and MM) overexpress XPO1, causing increased export of tumor suppressors and growth regulatory proteins from the nucleus
- Selinexor inhibit XPO1 mediated nuclear-cytoplasmic transport by transiently binding to XPO1 cargo binding site.
- Accumulation of Tumor suppressors in the nucleus amplifies the natural apoptotic function in cancer cells with damaged DNA.

Tai et al. Leukemia 2014

PHASE I OF SELINEXOR PLUS/MINUS DEX IN RRMM

- Single agent (oral:3-45 mg twice/ w).... 17% MR, Chen et al. ASH 2014

Main AEs: Anorexia, nausea/vomiting, fatigue, thrombocytopenia.

- +Dex (n=122) (STORM).............................. 26% ORR (Pent a-Refrc) PFS: 3,7m Vogl et al. JCO 2018, Chari ASH 2018 (Abs 598)

AEs: nausea 73%, vomiting 49%, anorexia 49%, thrombocytopenia 73% /59% gr 3-4)

- + Bortz/dex (n=42)................................. 63% (43% in Btz Rfct) (PFS: 9 (6,1)m ) Bahlis NJ, Blood 2018, (PH III BOSTON trial ongoing)

AEs: anorexia 33%, nausea 67%, Thrombocytopenia 17%

- + Pom/dex (n=24)................................. 65% % in Pom Naive/Len R (29% in Pom/Len Rft). Chen et al, ASH 2017)

- + Dara/dex (n=25)................................. 74% % in double Rft. Gasparetto et al, ASH 2018, Abs 599)
Venetoclax (bcl-2 inhibitor) in RRMM. Summary of Ph1 data

- Venetoclax is a selective, orally available small molecule BCL-2 inhibitor\(^1\), 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\(^1\).

- **Monotherapy (n=66)** (61% double Ref) .............. ORR 21% (40% in t(11;14)) DOR: 9.7m
  
  G 3-4 AEs: thrombocytopenia (26%) & neutropenia (21%)

- **+Btz/Dex (n=66)** ................................. ORR 67% (90% in BTz sensitive & 94% in BCL2 high)
  
  G3-4 AEs: Thrombocytopenia (29%), anemia (15%), neutropenia (14%),

- **+Cfz/Dex (n=42)** (33% double Ref).................. ORR 78% (PFS: 5.7m. The VGPR in t(11,14): 88%)

Melflufen

- Melflufen is a highly lipophilic alkylator, belonging to the novel class of Peptidase Enhanced Compounds, consisting of melphalan + 4-fluoro-L-phenylalanine.

- Intracellular amino-peptidases that are overexpressed in most malignant cells, will rapidly cleave melflufen releasing the hydrophilic, active metabolite melphalan.

- In vitro, equimolar treatment of tumor cells with melphalan and melflufen, results in a 20-50 fold higher intracellular concentration.

**Melflufen 40 mg iv every 28 days + Dex 40 mg weekly**

**Phase II O-12-M1 trial**

RRMM pts ≥ 2 lines and refr. to last line.

n = 45; 4 (2-14) lines; 64% double refr.; 53% Alkylator refr.

**ORR 31% .......... 5 VGPR & 9 PR 36% in Alkylator refr.**

PFS: 5,7m ; OS: 20M

G3/4 AEs: Thromboc. (58%), Neutrop(51%), Anemia: 42%

*Blood 2017, 130: 3150*

**Phase II Horizon trial**

RRMM pts ≥ 2 lines and 89% double Ref

n = 62 6 (3-11) lines; Alkylator refr. 58%;Pom & Dara Refr: 56%

**ORR 32% .......... PFS: 5,7M; OS: 20,7M**

G3/4 rel. TEAEs: Thromboc. (45%), Neutropenia (39%), Anemia: 21%

*Richardson P. ASH 2018 (Abst 600)*
Four Major Targets for Cancer Immunotherapy

Direct targeting of surface tumor antigens:
Monoclonal antibodies

Boosting immune effectors:
Adoptive cell therapy

Overcoming inhibitory immune suppression:
Immunomodulators: IMiDs, checkpoint inhibitors

Activating tumor specific immunity:
Vaccines

IMiD, immunomodulatory drugs.
Monoclonal Antibodies: Futures Perspectives

To overcome the limitations of an immunosuppressive tumor microenvironment by linking CTLs with the tumor cell.

Bispecific T-cell engagers: BCMA–CD3 Phase I trials

AMG 420: 35 pts: (Topp et al ASH 2018, 1010)
28% ORR (6CR). 83% ORR at MTD (including MRD-)
SAE: 49% (infections); CRS (3 cases).

Conjugated mAb:
GSK2857916: BCMA – MMAF*
AMG 224: BCMA – DM1
STRO-001: CD74-DBCO

*35 patients (Trudel S, et al. Blood 2017;130:741)
ORR: 60% (43% previous data) PFS: 7.9m
63% corneal events most G1-2

MMAF, monomethyl auristatin F; DM1, maytansinoid N(2')- deacetyl-N(2')-(3-mercaptop-1-oxopropyl)-maytansine.
Adoptive Cell Therapy: Genetically Modified T-Cell Therapy

TCR engineered T-cells

<table>
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<tr>
<th>HLA - restricted</th>
<th>Antigen recognition is independent of MHC molecule</th>
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<tbody>
<tr>
<td>Potential recognition of intracellular antigens</td>
<td>Only extracellular proteins can be recognized (like mAb)</td>
</tr>
<tr>
<td>TCR-mediated activation</td>
<td>Possibility to insert other genes</td>
</tr>
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HLA, human leukocyte antigen; mAb, monoclonal antibody; MHC, major histocompatibility complex; TCR, T-cell receptor; CAR, Chimeric antigen receptor (CAR) T-cells

## BCMA CAR T-Cells in MM

<table>
<thead>
<tr>
<th>Trial site</th>
<th>ScFv</th>
<th>Co-s domain</th>
<th>Gene transfer</th>
<th>Conditioning therapy</th>
<th>T-cell dose CAR+ T-cells/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI</td>
<td>11D5-3</td>
<td>CD28</td>
<td>Y- retroviral</td>
<td>Cy 300 mg/m² x3 + Flu 30 mg/m² x3</td>
<td>0.3–9.0 x 10⁶</td>
</tr>
<tr>
<td>Bluebird Celgene</td>
<td>NR, murine</td>
<td>4-1BB</td>
<td>Lentiviral</td>
<td>Cy 300 mg/m² x3 + Flu 30 mg/m² x3</td>
<td>50, 150, 450 and 800 x 10⁶</td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>NR, human</td>
<td>4-1BB</td>
<td>Lentiviral</td>
<td>None or Cy 1.5 g/m²</td>
<td>10–50 x 10⁶ or 100–500 x 10⁶</td>
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<tr>
<td>Nanjing Legend Biotech</td>
<td>NR</td>
<td>NR</td>
<td>Lentiviral</td>
<td>Cy 300 mg/m² x3</td>
<td>1.5–7.0 x 10⁶</td>
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<tr>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>NR, human</td>
<td>4-1BB</td>
<td>Y- retroviral</td>
<td>Cy 3000 mg/m² or Cy 300 mg/m² x3 + Flu 30 mg/m² x3</td>
<td>1x10⁶ 150, 450 and 800 x 10⁶</td>
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This slide is provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.

ScFv, single-chain fragment variable.
# BCMA CAR T-cell Therapies for MM

| Group/company | Anti-BCMA CAR<sup>1</sup> NCT02215967 | Bb2121<sup>2</sup> NCT02658929 | CART-BCMA<sup>3</sup> NCT02546167 | LCAR-B38M<sup>4</sup> NCT03090659 |
|---------------|----------------------------------------|---------------------------------|----------------------------------|--------------------------------||
| **Patients**  | 16 patients at 9x10<sup>6</sup>/kg dose level | 22 (>150 x 10<sup>6</sup> cells) | 21 (3 cohorts): 9 (10-500 x 10<sup>6</sup> No Cyt) 5 (10–50 x 10<sup>6</sup> Cyt) 7 (500–500 x 10<sup>6</sup> Cyt) | 57 |
| **BCMA expression required?** | Yes | Yes; ≥ 50% BCMA expression | No | Yes |
| **Median prior lines of therapy** | 7 | 7 | 7 (3–11) | 3 |
| **Reported efficacy** | ORR 14/16 (81%) 11/14 (79%) MRD-(50%) sCR/CR EFS: 7.2 months | 86.4% ≥VGPR | #1: 67% (1 sCR, 1VGPR) #2: (40%) 1 PR, 1 MR both PD #3: (83%) 1 CR, 3 PR, 1 MR PFS: 11.8 months | ORR: 88% CR: 74% MRD-: 93% of CR PFS:15m |
| **Safety data** | CRS all grades:100%, 37%G3-4 | CRS all grades: 63% 2 events of CRS grade ≥3 resolved within 24 hours | CRS: 17 pts (grade 3: 32%) Neurotoxicity: 3 (2 grade 4) 1 death – PD candidaemia | Transient CRS (5.7% G3) No neurotoxicity |


Abstracts ASH 2018: 488, 955-7, 959, 960, 1009, 1011-14
Safety Concerns Regarding CAR T-Cell Therapy

CRS is the most common toxicity triggered by the activation of T-cells and bystander immune cells → release of cytokines and chemokines: IFN-γ, soluble IL-2R, IL-6, etc.

- **Off target effects (B-cell aplasia)**
- **CRS 40–100% (severe ~20–30%)**
- **Tumour lysis syndrome**
- **Neurological toxicities (CRES)**
- **HLH/ MAS**
- **GVHD**

CRS, cytokine release syndrome, (Tocilizumab & Corticosteroids)  CRES, CAR T-cell-related encephalopathy syndrome,  GVHD, graft-versus-host disease, HLH, haemophagocytic lymphohistiocytosis, MAS, macrophage activation syndrome.
## Improvements of CAR T-Cell Therapies

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Potential Improvements</th>
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</table>
| Immunological rejection & safety  | • **Humanised** CARs to reduce immunogenicity  
• **Allogeneic CAR T**: Gene editing (CRISPR/Cas9) of normal donor T-cells to remove naive TCR (to avoid GVHD) and transfection with a CAR with post-conditioning vaccination to improve memory  
• **Safety marker gene** to extinguish the CAR-T activity. |
| Immune system limitations         | • **Rational combination strategies** : Checkpoint inhibitors, IMiDs, BTK inhibitors                                                                                                                                     |
| Efficacy & antigen escape          | • **Bi-specific CAR** (e.g. CD19, CD123, BCMA, SLAMF7)  
• Use of **specific T-cell subpopulations** (from naive to **central memory** and to terminal effector T-cells)  
• **APRIL** as the **natural** BCMA/TACI ligand instead of the Ab (anti-BCMA)  
• **Antibody-Coupled T-Cell Receptor (ACTR)**: engages antibody to direct T-cell attack against many different Ags  
• **Armored CAR** (2nd gene that generate a cytokine: i.e. IL12) |

AICD, activation-induced cell death, ScFv, single-chain fragment variable, TRAC, T-cell receptor α constant.  
Conclusions

• The discovery and development of new therapies addressing a variety of therapeutic targets is already changing the natural history of MM

• The understanding of the mechanisms of progression and immune-surveillance escape as well as the manipulation of autologous immune cells and gene editing are opening new frontiers in the treatment of advanced or difficult-to-treat MM

• The combination of different class of drugs with complementary immunological strategies and earlier in the natural history of the disease may offer the future possibility of long-term control or even disease eradication in some subsets of patients
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**Downloadable slides** from this symposium (IMF link below)

**Interactive Decision Support Tool** for myeloma, with personalized expert recommendations for your patients with myeloma

**Online programs** on caring for your patients with myeloma

myeloma.org/videos/new-strategies-multiple-myeloma-care-next-steps-future

clinicaloptions.com/MyelomaTool

clinicaloptions.com/oncology/topics/Multiple-Myeloma