How to Treat Relapsed/Refractory Multiple Myeloma in 2020
Disclosures

Jesús F. San-Miguel, MD, PhD, has disclosed that he has received consulting fees from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Karyopharm, Merck Sharpe & Dohme, Novartis, Roche, Sanofi, and Takeda.
Case Discussion 3:
Managing a patient with relapsed disease after ≥ 1 line of therapy
Patient Case Example

- A 66-year-old man was diagnosed with IgA lambda R-ISS Stage-III myeloma
  - BM showed 60% PC with t (4;14) plus 1q gain
  - MC: 25 g/L; Hb: 10 g/dL, creatinine: 1.2 mg/dL; calcium: 9.2 mg/dL
  - Extensive bony disease
- He received Dara-VTD + ASCT achieving sCR but MRD+, planned maintenance with lenalidomide for 2 years
- After 23 months, he relapsed (18 months from ASCT)
Presurvey 3: In your current clinical practice, how would you treat this patient?

1. PI / lenalidomide / dexamethasone
2. PI / pomalidomide / dexamethasone
3. Anti-CD38 mAb / lenalidomide / dexamethasone
4. Anti-CD38 mAb / pomalidomide / dexamethasone
5. Anti-CD38 mAb / PI / dexamethasone
6. Rescue treatment followed by second ASCT
7. Uncertain
## Expert Recommendations

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Patient Case Example, Continued

- He was treated with **Dara-Vd x 8 cycles** and **achieved VGPR**
- He progressed 3 months later
Presurvey 4: In your current clinical practice, what approach would you recommend for this patient now?

1. PI / pomalidomide / dexamethasone
2. Anti-CD38 mAb or elotuzumab / pomalidomide / dexamethasone
3. Anti-CD38 mAb / carfilzomib / dexamethasone
4. Selinexor or selinexor combinations
5. Belantamab or belantamab combinations
6. Venetoclax or venetoclax combinations
7. Melflufen or melflufen combinations
8. Bispecific antibodies or CAR T-cell therapy
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Strategies at Relapse: How to Make the RIGHT CHOICE?

Disease-related Factors
Type of relapse, cytogenetic risk, extramedullary disease

Efficacy and Toxicity of previous treatments

Further options

Patient-related factors
Age (Trx eligibility), comorbidities, frailty
Response to Therapy is the Key Element to Evaluate Treatment Efficacy and Critical For Survival

The definition of CR is suboptimal: ……The term CR is confusing for the patient
Who wouldn't want to know with precision the quality of patients’ response to therapy?

Is MRD relevant in the relapse setting?
Positive vs Negative MRD: Two Different Myelomas

Results from an expanded meta-analysis (8,114 patients)

NDMM (transplant-eligible)  NDMM (transplant-ineligible)  RR MM

Progressive improvement in MRD technologies

MRD Assessment in Pollux and Castor: Impact of Achieving MRD-Negativity (10^{-5})

Pollux (Rd +/- Dara)

Castor (Vd +/- Dara)

Bahlis. Leukemia. 2020;34:1875.

Should We Treat Biochemical Relapses?
PFS and OS According to Biochemical vs Clinical Relapses
Endeavor study (n = 211 relapsing after ASCT)

### Biochemical Relapse

<table>
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<th>Kd56 (n = 61)</th>
<th>Vd (n = 57)</th>
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<td>Progression/Death, n (%)</td>
<td>14 (23.0)</td>
<td>20 (35.1)</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>NE</td>
<td>13.7</td>
</tr>
<tr>
<td>HR (Kd56/Vd) (95% CI)</td>
<td>0.462 (0.232-0.922)</td>
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### Clinical Relapse

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<th>Kd56 (n = 403)</th>
<th>Vd (n = 408)</th>
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<tr>
<td>Progression/Death, n (%)</td>
<td>157 (39.0)</td>
<td>223 (54.7)</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>17.7</td>
<td>8.8</td>
</tr>
<tr>
<td>HR (Kd56/Vd) (95% CI)</td>
<td>0.539 (0.439-0.652)</td>
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Should We Perform a Second ASCT at Relapse?  
66-Year-Old Man Relapsing after VTD + ASCT + Len x 2y:

Decisions based on the **duration of the previous response**

**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 (2-3 years post ASCT)**
- **“Prolong survival until curative treatments are developed”**
  - Sequential novel agent combinations: Dara + PomDex.....KRD...
1st Relapse After Bortezomib-Based Induction (Len Naive or Exposed but Not Refractory)

Lenalidomide-Based Regimens: Efficacy (Rd vs triplets with Rd backbone)

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>POLLUX[^1] (N = 569)</th>
<th>ASPIRE[^2] (N = 792)</th>
<th>ELOQUENT-2[^3] (N = 646)</th>
<th>TOURMALINE-MM1[^4] (N = 722)</th>
</tr>
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<tr>
<td>DaraRd vs Rd</td>
<td>0.44 (▲ 27 mos) 44.5 mos vs 17.5 mos</td>
<td>0.66 (▲ 9.5 mos) 26.1 mos vs 16.6 mos</td>
<td>0.72 (▲ 4.5 mos) 19.4 mos vs 14.9 mos</td>
<td>0.74 (▲ 5.9 mos) 20.6 mos vs. 14.7 mos</td>
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<td>KRd vs Rd</td>
<td>0.66 (▲ 9.5 mos) 26.1 mos vs 16.6 mos</td>
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**Economical constrains:** RD + Cyclophosphamide, VTD (if TFI > 12 mos)

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First relapse following continuous Lenalidomide/Dex, Len maintenance, VRD-Rd ... will be considered Len-Refrac.

Proteasome Inhibitors-Based Regimens: Efficacy

First relapse after IMiD-based induction

Doublets
Kd or Vd

Triplets based on PI
DaraVd, PomVd
Or Dara-KD

<table>
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<tr>
<th>Efficacy</th>
<th>ENDEAVOR (N = 929)</th>
<th>KCyDex (N = 198)</th>
<th>CASTOR (N = 498)</th>
<th>CANDOR (N = 466)</th>
<th>IKEMA (N = 302)</th>
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<tr>
<td>Kd vs Vd</td>
<td>0.53 (▲ 9)</td>
<td>1 (▲ 5)</td>
<td>0.31 (▲ 9)</td>
<td>0.63 (▲ NE)</td>
<td>0.53 (▲ NE)</td>
</tr>
<tr>
<td>PFS HR (▲ mos)</td>
<td>18.7 vs 9.4 mos</td>
<td>20.7 vs 15.2 mos</td>
<td>16.7 vs 7.1 mos</td>
<td>NE vs 15.8 mos</td>
<td>NE vs 19.2 mos</td>
</tr>
<tr>
<td>Len Refract, experimental arm, % (mPFS)</td>
<td>24% (8.6 mos)</td>
<td>36% (26 mos)</td>
<td>18% (9.3 mos)</td>
<td>31.7% (NA)</td>
<td>32% (NA)</td>
</tr>
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**PANORAMA-1 PanoVD vs VD (n=768)**: mPFS 12 mos vs 8 mos (HR: 0.63 (▲ 4 m); 27.6% CR rate; Only 19% Lena Refractory

**Economical Constrains. VMP/VCD (16 m; 83% at 1 Yr)**

# Relapse/Refractory to Lenalidomide: Pomalidomide-based Regimens

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>OPTIMISM (N = 559) PVd vs Vd(^1)</th>
<th>ICARIA (N = 307) IsaPd vs Pd(^2)</th>
<th>ELOQUENT (N = 117) EloPd vs Pd(^3)</th>
<th>APOLLO (N= 304) DPd vs Pd(^4)</th>
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<tr>
<td>PFS HR ((\uparrow) mos)</td>
<td>0.61 ((\uparrow) 4.1)</td>
<td>0.59 ((\uparrow) 5.0)</td>
<td>0.54 ((\uparrow) 5.6)</td>
<td>0.63 ((\uparrow) 5.5)</td>
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<tr>
<td>11.2* vs 7.1m</td>
<td>11.5 vs 6.5m</td>
<td>10.3 vs 4.7m</td>
<td>12.4 vs 6.9m</td>
<td></td>
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<tr>
<td>ORR, %</td>
<td>82 vs 50</td>
<td>60 vs 35</td>
<td>53 vs 26</td>
<td>51 vs 19.6 ≥ VGPR</td>
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*17.8 m in Len-Ref 1st
- PomCyDex (n = 100): mPFS 7.6 m (10.4 m in PR)\(^5\)
- KPomDex (EMN-011; n= 60): mPFS 18 m\(^6\)

- **Dara-Kd (CANDOR) in Lena Ref HR 0.45**\(^7\)
- **Isa-Kd (IKEMA) in Lena Ref HR 0.59**\(^8\)

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Next-generation IMiDs, CELMoDs™ (Cereblon E3 Ligase Modulation Drugs) in Multiple Myeloma

CC-220 (iberdomide)...ORR:32%¹
CC-92480.....ORR: 54%²

Iber combinations:³
+ Dara (65% Dara Ref)....35% ORR
+ Btz (100% Btz Ref)....50% ORR

- Melflufen is a highly lipophilic alkylating peptide, belonging to the novel class of Peptidase Enhanced Compounds.

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

- In vitro, treatment of tumor cells with melflufen results in 50-fold higher intracellular concentration of alkylating metabolite than those treated with equimolar melphalan alone. In vivo, human xenograft mouse models treated with melflufen showed prolonged survival.

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

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

RR MM pts ≥ 2 lines and refr. to last line.
N = 45 in combination cohort.
Median 4 (2-14) lines; 64% double refr.; 53% Alkylator refr.

**ORR 31% .......... 5 VGPR & 9 PR patients**

**PFS: 5.7m ..........DOR 8.4m; OS: 20.7m**

G3/4 AEs: Thromboc. (62%), Neutrop. (58%), Anemia: 42%


**Phase II Horizon trial**

- 125 RRMM pts. Median 5 (2-12) prior lines; 38% patients had high-risk cytogenetics; 88% double refr; 71% triple refractory (PI + IMiD + anti-CD38)

**ORR 29% .**

**PFS: 4.2 mos. OS: 11.6 mos**

G3/4AEs: Neutopenia (66%), Thromboc. (69%), Anemia: (37%)

Selinexor Combination in Relapsed/Refractory MM

- **Exportin 1 (XPO1) is the major nuclear export protein for Tumor suppressor proteins (TSPs, e.g., p53, IkB and FOXO). XPO1 is overexpressed in MM**
- **Selinexor is an oral selective XPO1 inhibitor**

**Phase IIb STORM Trial: Selinexor + Dex (N = 122)**
- 7 median prior lines of therapy (range: 3-18)
- 96% refractory to Btz, Len, carf, pom, dara

**AEs:**
- thrombocytopenia (73%, 58% G3-4), anemia (67%, 44% G3-4),
- fatigue (73%; 25% G3-4); GI: nausea (72%, 10% G3/4),
- anorexia (56%; 5% G3/4), weight loss (50%; 1% G3/4)

**Median PFS, Mos**
- ORR: 26%
- ≥ MR 39%; ≥ SD 79%
- mDOR: 4.4 months
- mOS: 8.6 months

**Phase III BOSTON Trial: Selinexor + Vd (N = 402)**
- 1-3 prior lines of therapy (median: 2; 19% had 3 lines)
- 76% exposed to prior PI, 38% prior len

**Median PFS, Mos**
- ORR: 26% vs 62% (28% VGPR (17% sCR/CR))
- mDOR: 20.3 v 12.9 mos
- mOS: NR vs 25 mos
- HR: 0.70 (P = .0075)

**PN G ≥ 2: 21% vs 34%, p=0.001**

Seli-Pd (STOMP): 52 Pts: 58% ORR; 12m PFS. Chen. ASH 2020. Abs 726.
Venetoclax is a small molecule BCL-2 inhibitor that induces cell death in MM cell, particularly t(11;14) & high BCL2. ORR: 21%...60%.

**VENETOCLAX+ BortDex vs BortDex (291 patients, 2:1 random)** BELLINI Study

**PFS in all patients**

- 23.2 m (VenBd)
- 11.4 m (PboBd)
- HR: 0.60; \( P = .001 \)

**PFS in patients with t(11;14)**

- NR vs 9.3; HR: 0.09; \( P = .003 \)

**PFS by t(11;14) and BCL2 status**

- NR vs 9.9; HR: 0.30; \( P < .001 \)

Venetoclax: 800mg QD; BtzDex: C1-8/21d...C9/35d...until progression
Belantamab Mafodotin (DREAMM-2 Study) in Refractory MM

- **Belantamab mafodotin** (GSK2857916): humanized, afucosylated, IgG1 BCMA-targeted ADC that neutralizes soluble BCMA

N = 196, after ≥ 3 prior lines of therapy; refractory or intolerant to IMiDs, PI, and CD38 antibodies

Median 7 (3-21) prior lines in 2.5 mg/kg cohort and 6 (3-21) in 3.4 mg/kg cohort

**ORR:** 32-35% (by dose)

- 18% VGPR, 5% CR or sCR at 3.4 mg/kg
- ≥ MR 40%; ≥ SD 57% at 3.4 mg/kg

Median DOR: 6.2 months

**Main AEs:** Corneal events: 72% to 77%; Thrombocytopenia: 36% to 57%; Infusion-related reaction: 16% to 21%

- **OS**

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<th>Treatment</th>
<th>Median, Mos (95% CI)</th>
<th>Bela maf 2.5 mg/kg (n = 97)</th>
<th>Bela maf 3.4 mg/kg (n = 99)</th>
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<td></td>
<td>OS</td>
<td>14.9 (9.9-NR)</td>
<td>14.0 (10.0-NR)</td>
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<tr>
<td></td>
<td>PFS</td>
<td>2.8 (1.6-3.6)</td>
<td>3.9 (2.0-5.8)</td>
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DREAMM-6: Bela Maf + Vd (ORR: 78%)  

DREAMM-5: Bela Maf Combinations  
NCT04126200

DREAMM-7: Bela Maf + Vd vs DaraVd  
NCT04246047

DREAMM-9: Bela Maf + SoC in ND MM  
NCT04091126

DREAMM-8: Bela Maf + Pd  
NCT04484623  29 Pts (penta Ref)….86% ORR  
(Trudel. ASH 2020. Abs 725)
MULTIPLE MYELOMA
A model for scientific and clinical progress from biology to therapeutics

Progress in MM Cell Biology
- Prognostic factors
- Myeloma subtypes*

Discovery of New Drugs
- Singular mechanism of action

Individualised and tailored treatment

*MM should not be considered a single entity.
Now, let’s return to our patient case
Patient Case Example

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