Treatment of Multiple Myeloma: current challenges and future perspectives

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What should be the treatment goal in Symptomatic MM patients?

To search for an appropriate balance between treatment efficacy, toxicity & costs

- In frail patients (> 85y) ………to ensure QoL & avoid additional costs of expensive treatments

- In fit elderly patients (65-85y) & young ones with severe co-morbidities ………. treatment goal should be to prolong survival and ensure QoL

- In young patients (<65y) …In reference centers & large cooperative groups ………to investigate therapeutic schemes with a cure in the horizon
MRD techniques will contribute to both a better definition of response and to monitoring the efficacy of intensification and maintenance therapies… to tailor treatment & to avoid both under & over treatments.
## IMWG criteria for MRD in multiple myeloma

<table>
<thead>
<tr>
<th>IMWG MRD negativity criteria (Requires CR as defined below)</th>
<th>Response subcategory</th>
<th>Response criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained MRD-negative</td>
<td>MRD negative in the bone marrow (by next-generation flow cytometry or next-generation sequencing) and by imaging as defined below, confirmed 1 year apart; subsequent evaluations can be used to further specify the duration of negativity (e.g. MRD negative at 5 years)</td>
<td></td>
</tr>
<tr>
<td>Imaging MRD-negative</td>
<td>MRD negative as defined below (by next-generation flow cytometry or next-generation sequencing) PLUS Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT</td>
<td></td>
</tr>
<tr>
<td>Flow MRD-negative</td>
<td>Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or a validated equivalent method), with a minimum sensitivity of 1 in $10^5$ nucleated cells or higher</td>
<td></td>
</tr>
<tr>
<td>Sequencing MRD-negative</td>
<td>Absence of clonal plasma cells by next-generation sequencing on bone marrow aspirates in which the presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the Lymphosight® platform (or a validated equivalent method) with a minimum sensitivity of 1 in $10^5$ nucleated cells or higher</td>
<td></td>
</tr>
</tbody>
</table>

IMWG, International Myeloma Working Group
Myeloma treatment in the last century

- **1846**
  - Mr McBean
    - Chest brace, blood letting
    - Quinine and iron
    - Dover powder (opium)

- **1958**
  - Melphalan (Blokhin, Ann NY Acad Sci)

- **1960**
  - Alkylating glucocorticoids (1969)

- **1970**
  - Combination chemotherapy
    - Vincristine
    - Doxorubicin
    - Dexamethasone
    - Ara-C

- **1980**
  - High-dose chemotherapy
  - Stem-cell transplantation

- **1990**
  - New IMiDs: pomalidomide
  - New PIs: carfilzomib; ixazomib; oprozomib
  - mAbs: elotuzumab, daratumumab, isatuximab
  - HDACs: panobinostat

- **2000**
  - Bortezomib

- **2003**
  - Lenalidomide

- **2004**
  - Thalidomide

HDACs, Histone deacetylases; IMiDs, immunomodulatory drugs; mAbs, monoclonal antibodies; PIs, proteasome inhibitors
Young “Symptomatic/active” MM Patients: “Old” Transplant candidate approach

Induction (VAD or TD) → ASCT (Mel 200) → Maintenance (IFN +/- Predn)
Have the new induction regimens improved outcome as compared to VAD or TD?: Response to induction

This translates into prolonged PFS: VTD or PAD > VAD or TD

The Debate...ASCT: Up-Front or at Relapse

Len-Bz-Dex ×3

Stem collection

ASCT

Len-Bz-Dex ×2

Lenalid ×12m

Len-Bz-Dex ×3

Stem collection

Len-Bz-Dex ×5

Lenalid ×12m

ASCT at relapse

NCI Clinical Trial Identifier NCT01191060.
IFM 2009: PFS and OS

RVD arm vs Transplant arm

- **CR:** 49% vs 59%
- **≥ VGPR:** 78% vs 88%

**PFS**

<table>
<thead>
<tr>
<th>Months of follow-up</th>
<th>HDT</th>
<th>no HDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>24</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>36</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>48</td>
<td>60</td>
<td>50</td>
</tr>
</tbody>
</table>

**OS**

<table>
<thead>
<tr>
<th>Months of follow-up</th>
<th>HDT</th>
<th>no HDT</th>
</tr>
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<tbody>
<tr>
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</tr>
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<td>48</td>
<td>60</td>
<td>50</td>
</tr>
</tbody>
</table>

Attal M. ASH 2015
**EMN02/HO95 MM trial: study design (n= 1192)**

- **VCD x three-four 21-d cycles**
  - Bort 1.3 mg/sm twice weekly; CTX 500 mg/sm d1-8; Dex 40 mg on day of and after bort
  - CTX (2-4 g/sm) + G-CSF + PBSC collection

- **R1**
  - VMP x 4 cycles
  - VRD x two 28-d cycles
    - Bort 1.3 mg/sm, twice weekly; len 25 mg d1-21; dex 20 d1-2-4-5-8-9-11-12

- **R2**
  - HDM x 1-2 courses
  - No consolidation therapy

- **Lenalidomide 10 mg/day, d1-21/28**

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- Upfront ASCT was associated with a significant improvement in PFS vs VMP in the overall patient population (Median PFS: NR vs 46m)
- Superior PFS with ASCT vs VMP was retained across prespecified subgroups of patients at low (NR vs 46m) and high risk (42 vs 32m)

*Cavo ASCO 2016*
## Comparison of early vs. late ASCT

Pooled analysis of two trials (n=529)

- GIMEMA MM-RV-209……. Rd-MPR vs. Rd-Mel200 (2nd rand: +/- maintenance)
- EMN MM-RV-441………. Rd-CRD vs. Rd-Mel200 (2nd rand: R vs RP Maint.)

<table>
<thead>
<tr>
<th></th>
<th>Early ASCT</th>
<th>Late ASCT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (months)</td>
<td>42</td>
<td>24</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>4-year OS</td>
<td>84%</td>
<td>70%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Only 53% of CCT patients received ASCT at relapse

Gay et al et al. EHA 2016; Palumbo et al NEJM 371:895-905, 2014;

Gay (EHA 2016): (benefit in all subgroups, but higher in good prognosis (Stage I and low risk cytog)
The Debate...ASCT: Up-Front or at Relapse

Len-Bz-Dex ×3

<table>
<thead>
<tr>
<th>Stem collection</th>
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</thead>
<tbody>
<tr>
<td>Len-Bz-Dex ×2</td>
</tr>
<tr>
<td><strong>ASCT</strong></td>
</tr>
<tr>
<td>Lenalid ×12m</td>
</tr>
</tbody>
</table>

winner

Len-Bz-Dex ×3

<table>
<thead>
<tr>
<th>Stem collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Len-Bz-Dex ×5</td>
</tr>
<tr>
<td>Lenalid ×12m</td>
</tr>
<tr>
<td><strong>ASCT at relapse</strong></td>
</tr>
</tbody>
</table>

NCI Clinical Trial Identifier NCT01191060.
Options after ASCT

Consolidation

- **Improve** response/deeper following therapy
  - By administration of treatment for a limited period

Maintenance

- **Maintain** response achieved following therapy
  - By administration of treatment for prolonged period

VTD: Upgrade to CR post-consolidation by 30% (molecular and PFS)

- Thalidomide (6 trials)… PFS: + 6/6 OS: +3/6
- Bortezomib (2 Trials)…. PFS: + 2/2 OS: +1/2
- Lenalidomide (3 trials)… PFS: +3/3 OS: + 1/3

Cavo et al Blood 2012

BMT CTN 0702: SCHEMA

Register and randomize

MEL 200 mg/m²

VRD × 4*

MEL 200 mg/m²

Lenalidomide maintenance*

Lenalidomide maintenance†

Lenalidomide maintenance†

* Bortezomib 1.3 mg/m² days 1, 4, 8, 11
Lenalidomide 15 mg days 1–15
Dexamethasone 40 mg days 1, 8, 15
† Lenalidomide 15 mg daily × 3 years

Options after ASCT

**Consolidation**

- **Improve** response/deeper following therapy
  - By administration of treatment for a limited period

**Maintenance**

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  - By administration of treatment for prolonged period

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Cavo et al. Blood 2012

- Thalidomide (6 trials)… PFS: + 6/6 OS: +3/6
- Bortezomib (2 Trials)…. PFS: + 2/2 OS: +1/2
- Lenalidomide (3 trials)… PFS: +3/3 OS: + 1/3

Lenalidomide maintenance: OS meta-analysis

26% reduction in risk of death, representing an estimated 2.5-year increase in median survival

Overall survival (months)

Patients at risk

Median follow-up: 80 months

N = 1,209

Median OS (95% CI), months

LEN

CONTROL

86.0 (79.8–96.0)

HR (95% CI)

p value

0.74 (0.62–0.89)

0.001

The OS benefit was observed in all investigated subgroups of patients (except high-risk CA and ISS stage III)

LEN maintenance after ASCT can be considered a standard of care

*Median for LEN treatment arm was extrapolated to be 116 months based on median of the control arm and HR (median 86 months; HR = 0.74).

CA, cytogenetic abnormality; ISS, International Staging System; NE, not estimable.

# Bortezomib maintenance therapy

<table>
<thead>
<tr>
<th>Study details</th>
<th>n</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS</td>
</tr>
<tr>
<td>HOVON 65 MM/</td>
<td>413</td>
<td>PAD x 3 → HDM → bortezomib every 2 weeks for 2 years</td>
<td>34 months</td>
</tr>
<tr>
<td>GMMG-HD4¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median follow-up: 91 months</td>
<td>414</td>
<td>VAD x 3 → HDM → thalidomide daily for 2 years</td>
<td>28 months</td>
</tr>
<tr>
<td>PETHEMA/GEM²</td>
<td>89</td>
<td>VT (1 cycle bortezomib every 3 months, thalidomide daily) for 3 years</td>
<td>Significant PFS benefit for VT p &lt; 0.0009</td>
</tr>
<tr>
<td>Median follow-up: 34.9 months</td>
<td>87</td>
<td>Thalidomide (daily for 3 years)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>Interferon-α2b (3 x per week for 3 years)</td>
<td></td>
</tr>
</tbody>
</table>

HOVON 65 MM → PAD x3 → tandem HDM → bortezomib maintenance: benefit for patients with del(17p)

Bortezomib maintenance after double ASCT is effective in patients with del(17p)

Bortezomib administered at 1.3 mg/m² i.v. in both studies

HDM, high-dose melphalan; i.v., intravenous; PAD, bortezomib, doxorubicin, dexamethasone; RMS<sub>8y</sub>, restricted mean survival time at 8 years; VAD, vincristine, doxorubicin, dexamethasone.

## Maintenance therapy after ASCT: future

<table>
<thead>
<tr>
<th>Sponsor/cooperative group</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lenalidomide-based</strong></td>
<td></td>
</tr>
<tr>
<td>IFM/DFCI 2009</td>
<td>Lenalidomide x 1 year vs lenalidomide until DP</td>
</tr>
<tr>
<td>Myeloma XI</td>
<td>Lenalidomide vs lenalidomide + vorinostat vs no maintenance</td>
</tr>
<tr>
<td>GEM14MAIN</td>
<td>Lenalidomide vs lenalidomide + ixazomib for up to 2 years Patients with MRD will continue 3 additional years</td>
</tr>
<tr>
<td>GMMHD6</td>
<td>Lenalidomide-dexamethasone vs lenalidomide-dexamethasone + elotuzumab</td>
</tr>
<tr>
<td>GIMEMA</td>
<td>Lenalidomide vs lenalidomide + carfilzomib</td>
</tr>
<tr>
<td>SWOG</td>
<td>Lenalidomide vs lenalidomide + ixazomib until DP</td>
</tr>
<tr>
<td>US Cooperative group trials (pick the winner)</td>
<td>Lenalidomide vs lenalidomide + vaccination/lenalidomide x 2 years vs lenalidomide until DP Lenalidomide vs lenalidomide + ixazomib</td>
</tr>
<tr>
<td>AFT-40</td>
<td>Lenalidomide vs lenalidomide + durvalumab vs lenalidomide + daratumumab vs lenalidomide + ACY241</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>C16019 Takeda Millennium</td>
<td>Ixazomib for up to 2 years vs placebo</td>
</tr>
<tr>
<td>HOVON-IFM</td>
<td>Daratumumab vs placebo</td>
</tr>
<tr>
<td>CCT-PNK-004-mmy001</td>
<td>Human cord blood derived, cultured and expanded NK cells</td>
</tr>
</tbody>
</table>

Developing early endpoints as surrogate markers for long-term outcomes and OS is critically important; otherwise, trials may continue for 10 years or longer.
Elderly MM: bortezomib + MP (VMP) vs. MP (682 patients)


* Weekly and/or subcutaneous administration reduced PN (grade 3) from 14% to 5–3%³

** TTP¹ **
- VMP: 24.0 months
- MP: 16.6 months, p<0.000001

** OS: 13.3 months benefit² **
- Median follow-up 60.1 months
- VMP: 56.4 months
- MP: 43 months, p=0.0004

MP, melphalan and prednisone; PN, peripheral neuropathy; VMP, bortezomib, melphalan, and prednisone
FIRST trial: LEN–DEX (18 cycles or continuous) vs. MPT

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients (n)</th>
<th>Median PFS</th>
<th>Hazard ratio (vs. MPT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd</td>
<td>535</td>
<td>25.5 months</td>
<td>0.72; p=0.0006</td>
</tr>
<tr>
<td>Rd18</td>
<td>541</td>
<td>20.7 months</td>
<td>0.70; p=0.0001</td>
</tr>
<tr>
<td>MPT</td>
<td>547</td>
<td>21.2 months</td>
<td>1.03; p=0.70349</td>
</tr>
</tbody>
</table>

**OS**

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients (n)</th>
<th>4-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd</td>
<td>535</td>
<td>59.4%</td>
</tr>
<tr>
<td>Rd18</td>
<td>541</td>
<td>55.7%</td>
</tr>
<tr>
<td>MPT</td>
<td>547</td>
<td>51.4%</td>
</tr>
</tbody>
</table>

MPT, melphalan+prednisone+thalidomide; Rd, continuous lenalidomide+dexamethasone; Rd18, 18 cycles lenalidomide+dexamethasone

Symptomatic newly diagnosed MM patients >65 years

Sequential scheme

VMP × 9 cycles
LEN–DEX × 9 cycles

Alternating scheme*

VMP, Rd, VMP, Rd, VMP, Rd, VMP, Rd, VMP, Rd, VMP, Rd, VMP, Rd, VMP, Rd

Hypothesis:
— higher efficacy for the alternating scheme
— less probability of cell scape
— lower cumulative toxicity

74 weeks

*Half of the patients will start with VMP and half with Rd

N=240 patients

VMP, bortezomib+melphalan+prednisone
Outcomes in terms of PFS and OS

Median follow-up: 30 months (9–43 months)

PFS
- Alternating: 34 months
- Sequential: 32 months

OS
- Alternating: 71% at 3 years
- Sequential: 73% at 3 years

VISTA: 21 months
FIRST: 25 months (cont Rd); 21 months (Rd18)

VISTA: 68% at 3 years
FIRST: 59% (cont Rd) and 56% (Rd18) at 4 years

Mateos MV, Blood 2016
Outcome in terms of PFS and OS on ITT analysis (n=233)

Median follow-up: 37 (9-50)

VISTA: 21m
FIRST: 25m (cont Rd); 21m (Rd18)

PFS
- 65-75y: 35m
- 75-80y: 32m
- ≥80y: 25m

4 yrs-OS
- 65-75y: 75%
- 75-80y: 61%
- ≥80y: 30%

65-75 vs 75-80 → p = 0.8
65-75 vs ≥ 80 → p = 0.01
75-80 vs ≥ 80 → p = 0.04

65-75 vs 75-80 → p = 0.05
65-75 vs ≥ 80 → p < 0.0001
75-80 vs ≥ 80 → p = 0.003

Mateos MV et al. ASH2015
Future of the treatment for elderly MM patients

Alkylators-based regimens
- MP
- VMP

Alkylators-free regimens
- IMiD’s
- Len-dex

Spanish standard of care for ”fit” elderly NDMM patients

It is necessary to individualize the treatment in elderly patients according to the frailty
Future of the treatment for elderly MM patients

Alkylators-based regimens
- MP

Alkylators-free regimens
- IMiD’s
  - Len-dex

Six randomized trials: Benefit in PFS&OS...6m

One randomized trial: Benefit in PFS&OS

KMP = VMP
VMP-Dara vs VMP
CyBorD-SAR

One randomized trial: Benefit in PFS&OS vs MPT

Benboubker L, et al. NEJM 2014; 371: 906-17
Rd as continuous therapy as backbone for different new regimens for elderly NDMM

- Elotuzumab plus Rd
  - Daratumumab plus Rd
    - Bortezomib plus Rd
  - Ixazomib plus Rd
    - Clarytromycin plus Rd
- Carfilzomib plus Rd
Strategies at relapse:
How to make the right choice?

Type of relapse

Efficacy of previous treatments

Toxicity of previous treatments

Further options
Novel drugs in MM

- Derivatives from already approved
  - Novel PIs
  - Novel IMiDs

- Immuno-oncologic approaches

- Novel drugs with different MoA
  - Deacetylase inhibitors
  - CDK inhibitors
  - Akt inhibitors
  - Kinesin spindle protein inhibitors

CDK, cyclin-dependent kinase
Doublets & Triplets with new Proteasome inhibitors in relapsed MM: survival on Phase III trials

- **ASPIRE trial (KRd vs. Rd)**:
  - PFS 26.3 vs. 17.6 months (HR 0.69, p=0.0001) …… ▲ 9 months
  - OS at 2 years: 73% vs. 65% (HR 0.79, p=0.01)

- **ENDEAVOR trial (Kd vs. Vd)**:
  - PFS 18.7 vs. 9.4 months (HR 0.53, p=0.0001) …… ▲ 9.3 months
  - OS NE vs. 24 months (HR 0.79, p=0.06)

- **TOURMALINE–MM1 trial (IRd vs. Rd)**:
  - PFS 20.6 vs. 14.7 months (HR 0.74, p=0.01) …… ▲ 5.9 months

KRd/Kd/IRd are new standards of care for patients after 1 prior line of therapy

IRd, ixazomib+lenalidomide+dexamethasone; Kd, carfilzomib+dexamethasone; KRd, carfilzomib+lenalidomide+dexamethasone; Vd, bortezomib+dexamethasone
## Pomalidomide-Dex in Refractory MM (& combinations)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MM-003&lt;sup&gt;1&lt;/sup&gt;</th>
<th>STRATUS (MM-010)&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Pom-Dex vs Pom-Cyclo-Dex&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Pom-Btz-Dex&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failed Bort &amp; Len &amp; refr to last line</td>
<td>PD (302)</td>
<td>PD (604)</td>
<td>PD (36)</td>
<td>PD (36)</td>
</tr>
<tr>
<td>At least 2 prior lines &amp; Len-refractory</td>
<td></td>
<td></td>
<td>At least 2 prior lines &amp; Len-refractory</td>
<td></td>
</tr>
<tr>
<td>1-4 prior lines &amp; Len-refractory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>31</td>
<td>35</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>≥ VGPR, %</td>
<td></td>
<td></td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>PFS, months</td>
<td>4.0</td>
<td>4.2</td>
<td>4.4</td>
<td>4.4</td>
</tr>
<tr>
<td>OS, months</td>
<td>13.1</td>
<td>11.9</td>
<td>16.8</td>
<td>NR</td>
</tr>
</tbody>
</table>

*EFS at 12 months

OPTIMISMM (MM-007) Phase 3 study: Pom+Btz+Dex vs Btz+Dex
1 – 3 prior treatments

Randomization
N = 450

Arm A (N = 225)
POM + BTZ + LoDex
21 day treatment cycle

Arm B (N = 225)
BTZ + LoDex
21 day treatment cycle

Ongoing Treatment and evaluation every 21-days until PD or unacceptable toxicity

Discontinuation follow-up for OS, subsequent treatment and SPM

End Points
1: PFS
2: OS, ORR, duration of response

I/E Criteria
• At least 1 but no greater than 3 prior anti-myeloma regimens
• All subjects must have received prior treatment with a lenalidomide-containing regimen for at least 2 consecutive cycles
• Pts with BTZ exposure are eligible but BTZ exposure not required. Must not be BTZ refractory

N = 450

Novel drugs in MM

- Derivatives from already approved
  - Novel PIs
  - Novel IMiDs

- Immuno-oncologic approaches

- Novel drugs with different MoA
  - Deacetylase inhibitors
  - CDK inhibitors
  - Akt inhibitors
  - Kinesin spindle protein inhibitors

CDK, cyclin-dependent kinase
Immune-therapies under investigation in MM

Immunotherapy\textsuperscript{1,2}

**Active**

*Designed to act on the immune system itself*

- I-O therapies
  - Immune effector cell modulators
    - Checkpoint Inhibitors
    - Co-stimulatory agonists
  - Cell-based
    - DC-based cancer vaccines
  - Single antigen/peptide-based

- Therapeutic cancer vaccines
  - Cytokines
    - Interleukins
    - Interferons
  - IMiDs

- Unspecific
  - Tumor-directed mAbs
  - Ab-drug Conjugates (ADC)

**Passive**

*Designed to act on the tumor*

- Adoptive
  - Cell therapies
    - Adoptive T-cell therapy

---

DC, dendritic cell; IMiD, immunomodulatory agent; I-O, immuno-oncology; mAb, monoclonal antibody.

Immune-therapies under investigation in MM

Immunotherapy

Active
(Designed to act on the immune system itself)

- I-O therapies
  - Immune effector cell modulators
  - Checkpoint Inhibitors
  - Co-stimulatory agonists

- Therapeutic cancer vaccines
  - Cell-based
    - DC-based cancer vaccines
  - Single antigen/peptide-based

- Unspecific
  - Cytokines
    - Interleukins
    - Interferons
  - IMiDs

Passive
(Designed to act on the tumor)

- Antitumor mAbs
  - Tumor-directed mAbs
  - Ab-drug Conjugates (ADC)

- Adoptive
  - Cell therapies
  - Adoptive T-cell therapy

DC, dendritic cell; IMiD, immunomodulatory agent; I-O, immuno-oncology; mAb, monoclonal antibody.
Targets for monoclonal antibody therapy in MM

Adapted from: Anderson KC. J Clin Oncol 2012;30:445-452

Cell surface targets

- IL-6
- RANKL
- DKK1
- VEGF
- IGF-1
- SDF-1α
- BAFF, APRIL

Signaling molecules

- C56
- CD40
- FGFR3
- SLAMF7
- CD138
- IGF1R
- VEGFR
- CD38

Adhesion

- ICAM-1
- VCAM-1
- LFA-1
- MUC-1
- Fibronectin
- VLA-4

BMSC
Future for mAbs: Bispecific Antibodies

BiTE® Antibodies
Designed to Bridge T Cells to Cancer Cells
Bispecific T cell engagers (BiTEs)

Double specificity by targeting: the tumor cell & T-cell (CD3). Overcome the limitations of an immunosuppressive tumor microenvironment by linking CTLs with the tumor cell.

- B-Cell Maturation Antigen (BCMA) expression was observed in malignant PCs in 99.5% MGUS and MM patients, and also in normal PC and plasmablasts.

- EM801 effectively binds myeloma cells and T-cells

- In vitro, EM801 induced concentration dependent cell death in mPCs in primary BM-samples of NDMM (75%) and RRMM (80%) & tumor regression in a Xenograft model

Seckinger A et al, ASH 2015 oral presentation 117
Immune-therapies under investigation in MM

Immunotherapy\(^1,2\)

Active
*(Designed to act on the immune system itself)*

- **I-O therapies**
  - Immune effector cell modulators
    - Checkpoint Inhibitors
    - Co-stimulatory agonists
  - Cell-based
    - DC-based cancer vaccines
  - Single antigen/peptide-based

- **Therapeutic cancer vaccines**
  - Cytokines
    - Interleukins
    - Interferons
  - IMiDs

- **Unspecific**
  - Tumor-directed mAbs
  - Ab-drug Conjugates (ADC)
  - Cell therapies
    - Adoptive T-cell therapy

Passive
*(Designed to act on the tumor)*

DC, dendritic cell; IMiD, immunomodulatory agent; I-O, immuno-oncology; mAb, monoclonal antibody.

Adoptive T cell therapy: CAR-T cells

- CAR T or NK cells are engineered anti-tumor immune cells with high affinity chimeric antigen receptors specific for tumor antigens\(^1\)

**Chimeric Antigen Receptor Structure\(^1\)**

- Single-chain antibody able to recognize tumor-associated antigens in a non-MHC-specific manner
- Molecular hinge region derived from CD8 to provide flexibility to allow reorientation to bind antigen
- Cytoplasmic domain of CD28 and additional signaling domains, including CD137, were added to later generation CARs to enhance cytokine secretion and tumor growth inhibition
- Cytoplasmic signaling domain of CD3\(\zeta\)


Adoptive T cell therapy: CAR-T cells in MM (CD19)

Additional regimens including...
- carfilzomib
- pomalidomide
- vorinostat
- elotuzomab

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

Stadtmauer, NEJM 2015
**First-in-human clinical trial of T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor:** 4/12 Pts (2PR, 1 VGPR; 1sCR)

Patient 10 obtained SCR of chemotherapy-resistant IgA myeloma after **CAR-BCMA T**-cell infusion

- Serum and urine IFE-negative

**BCMA:** B-cell maturation Ag
**a member of the TNF superfamily**

- Patient 10 experienced cytokine release syndrome including fever, tachycardia, hypotension, elevated liver enzymes, and elevated creatinine kinase-all resolved in 2 weeks or less

*Abbas, & Kochenderfer, ASH 2015 (LBA1)*
Immune-therapies under investigation in Cancer

Immunotherapy\(^1,2\)

**Active**
*Designed to act on the immune system itself*
- I-O therapies
  - Immune effector cell modulators
    - Checkpoint Inhibitors
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  - Cell-based cancer vaccines
    - DC-based cancer vaccines
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  - Therapeutic cancer vaccines
  - Unspecific
    - Cytokines
      - Interleukins
      - Interferons
    - IMiDs
- Adoptive
  - Cell therapies
    - Adoptive T-cell therapy

**Passive**
*Designed to act on the tumor*
- Antitumor mAbs
  - Tumor-directed mAbs
  - Ab-drug Conjugates (ADC)
- Adoptive
  - Cell therapies

DC, dendritic cell; IMiD, immunomodulatory agent; I-O, immuno-oncology; mAb, monoclonal antibody.

**Immuno-oncology Activating/Inhibitory Pathways**

**Activating**
- NK cell
  - SLAMF7
  - CD137
- T cell
  - CD137
  - CD40L
  - CD28
  - OX40

**Inhibitory**
- NK cell
  - KIR
- T cell
  - LAG-3
  - CTLA-4
  - PD-1
  - B7-H3 receptor

SLAMF7, signaling lymphocytic activation molecule family member 7.

KIR, killer cell immunoglobulin-like receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; LAG-3, lymphocyte-activation gene 3; PD-1, programmed cell death protein 1.
Elotuzumab (Anti-SLAM F7 MoAb) in MM

- **SLAMF7**: Signaling Lymphocyte Activation Molecule-1. Also called CS1

- Elotuzumab is a humanized IgG1 mAb targeting human CS1, a cell surface glycoprotein\(^1,2\)

- **CS1** is highly expressed on >95% of MM cells\(^1-3\)
  - Also on NK cells
  - Little to no expression on normal tissues

**Dual mechanism of action**

Binding to SLAMF7 directly activates Natural Killer cells\(^4\) but not myeloma cells\(^5\)

When bound to myeloma via SLAMF7, Elo activates Natural Killer cells via a CD16 mediated pathway, enabling selective killing via antibody-dependent cellular cytotoxicity (ADCC) with minimal effects on normal tissue

**Phase I**  
\(n=25 \rightarrow 26\%\) SD

3. Van Rhee F et al. Mol Cancer Ther. 2009;  
Elotuzumab synergizes with Lenalidomide in MM

Lenalidomide
Induces myeloma cell injury and lowers threshold for NK cell–mediated killing of myeloma cells by elotuzumab

Lenalidomide
Enhances adaptive and innate immune system, including production of IL-2, to increase NK cell activity

ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; SLAMF7, signaling lymphocytic activation molecule family member 7
Eloquent-2: Elo + Ld vs Ld
Co-Primary End Point: PFS

Median (95% CI) PFS:
E-Ld 19.4 (16.6–22.2) months
Ld 14.9 (12.1–17.2) months
Hazard ratio: 0.70
(95% CI: 0.57–0.85; P=0.0004)

E-Ld-treated patients had a 30% reduction in the hazard of PFS; treatment difference at 1 and 2 years was 11% and 14%, respectively

Lonial et al. NEJM 2015
**Immuno-oncology Activating/Inhibitory Pathways**

### Activating

- **NK cell**: SLAMF7
- **T cell**: CD137

**SLAMF7**, signaling lymphocytic activation molecule family member 7.

### Inhibitory

- **NK cell**: KIR
- **T cell**: LAG-3, CTLA-4, PD-1, B7-H3 receptor

Check-Point Inhibitors
## RR of Nivolumab (Anti-PD1) in Haem Malignancies

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th># pts</th>
<th>ORR</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Myeloma</td>
<td>27</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>0</td>
<td>17 (63)</td>
</tr>
<tr>
<td>B-Cell Non-Hodgkin Lymphoma</td>
<td>31</td>
<td>8 (26)</td>
<td>3 (10)</td>
<td>5 (16)</td>
<td>16 (52)</td>
</tr>
<tr>
<td>Diffuse Large B-Cell</td>
<td>11</td>
<td>4 (36)</td>
<td>2 (18)</td>
<td>2 (18)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Follicular NHL</td>
<td>10</td>
<td>4 (40)</td>
<td>1 (10)</td>
<td>3 (30)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Mantle Cell Lymphoma</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Primary Mediastinal B-Cell</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Other B-NHL</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (50)</td>
</tr>
<tr>
<td>T-Cell Non-Hodgkin Lymphoma</td>
<td>23</td>
<td>4 (17)</td>
<td>0</td>
<td>4 (17)</td>
<td>10 (43)</td>
</tr>
<tr>
<td>CTCL/MF</td>
<td>13</td>
<td>2 (15)</td>
<td>0</td>
<td>2 (15)</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Peripheral T-Cell</td>
<td>5</td>
<td>2 (40)</td>
<td>0</td>
<td>2 (40)</td>
<td>0</td>
</tr>
<tr>
<td>Other T-NHL</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>23</td>
<td>20 (87)</td>
<td>6 (26)</td>
<td>14 (61)</td>
<td>3 (13)</td>
</tr>
</tbody>
</table>

*includes other B-cell lymphoma (n=8)
†includes other cutaneous T-cell lymphoma (n=3) and other non-cutaneous T-cell lymphoma (n=2)  

Lesokhin. EHA 2015
**Pembrolizumab + LD Antitumor Activity in RRMM patients**

**Best Response (n (%))**

<table>
<thead>
<tr>
<th></th>
<th>Efficacy Population† (n = 40)</th>
<th>Len-Refr (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>20 (50)</td>
<td>11 (38)</td>
</tr>
<tr>
<td><strong>sCR</strong></td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td><strong>VGPR</strong></td>
<td>5 (13)</td>
<td>3 (10)</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>14 (35)</td>
<td>7 (24)</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>19 (48)</td>
<td>17 (59)</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

†11 patients NE by central review
3 discontinued within cycle 1 for reasons other than PD (2 no treatment assessments and 1 SD by investigator)
8 inadequate myeloma data for response assessment (5 PD and 3 SD by investigator)

**Treatment Exposure & Response Duration**

- Median follow-up: 9 months (range, 1-25)
- Median DOR: 11.3 months
- Median time to achieve first objective response: 1.5 months (range, 1.0-6.6)
- 4 patients who responded (20%) upgraded the quality of response
- 75% of patients were still alive

---

Pembro plus Pom-dex has shown also significant activity in RRMM patients (Badros, ASH 2015)
Immune-therapies under investigation in Cancer

Immunotherapy\textsuperscript{1,2}

**Active**
\textit{(Designed to act on the immune system itself)}

- I-O therapies
  - Immune effector cell modulators
    - Checkpoint Inhibitors
    - Co-stimulatory agonists
    - Other mAbs
  - Cell-based
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    - Interferons
  - IMiDs

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RANKL
DKK1
VEGF
IGF-1
SDF-1α
BAFF, APRIL

Adhesion

BMSC

ICAM-1
VCAM-1
Fibronectin
LFA-1
MUC-1
VLA-4
Anti CD38 antibodies: Mechanisms of Action

Daratumumab binds to CD38

Direct ON-TUMOR Actions
- CDC (Complement-dependent cytotoxicity)
- ADCC (Antibody-dependent cell-mediated cytotoxicity)
- ADCP (Antibody-dependent cellular phagocytosis)
- Apoptosis

IMMUNOMODULATORY Actions
- Modulation of tumor microenvironment
- Depletion of immunosuppressive cells
- Increase in cytotoxic & helper T cells

Myeloma cell death
Anti CD38 in MM: single agent activity in RRMM

<table>
<thead>
<tr>
<th></th>
<th>Daratumumab</th>
<th>Isatuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study details</td>
<td>3 studies: GEN501¹, SIRIUS² &amp; combined analysis⁴</td>
<td>First in-human, phase 1 dose escalation³</td>
</tr>
<tr>
<td>Patients</td>
<td>Pts with rel/ref MM n=148 (SIRIUS n=42 and GEN501 n=106)</td>
<td>Pts with rel/ref MM n=40</td>
</tr>
<tr>
<td>Dose</td>
<td>16 mg/kg</td>
<td>Dose is not yet defined</td>
</tr>
<tr>
<td>Results</td>
<td>• ORR 31% (36% GEN501 &amp; 29% SIRIUS)</td>
<td>• At ≥ 10 mg/kg: 29%</td>
</tr>
<tr>
<td></td>
<td>• Median DOR: 7.6 m</td>
<td>• At 20 mg/kg: 24%⁵</td>
</tr>
<tr>
<td></td>
<td>• Median OS: 20 months</td>
<td>• Infusion-reactions mainly grade 1/2, only with first dose</td>
</tr>
<tr>
<td></td>
<td>• Median PFS: 4m, Infusion-related reactions gr 1-2</td>
<td></td>
</tr>
</tbody>
</table>

Dara/SAAR are CD38 MoAB showing activity as single agents in RRMM patients

The 18-month and 24-month OS rates were 56.5% (95% CI, 47.9%-64.2%) and 45.0% (95% CI, 35.5%-54.1%), respectively.

**DVd vs Vd in Relapsed MM - Phase III CASTOR trial**

**Efficacy data:** ORR, PFS and TTP

### ORR (DVd vs Vd): 83% vs 63%

### CR (DVd vs Vd): 20% vs 9%

**PFS**

- **HR:** 0.39 (95% CI, 0.28-0.53); *P* < 0.0001
- **Median PFS:** NR
- **Median PFS:** 7.2 months

**TTP**

- **HR:** 0.30 (95% CI, 0.21-0.43); *P* < 0.0001
- **Median TTP:** NR
- **Median TTP:** 7.3 months

**AE:** 45% infusion reactions (most during the first & Gr ½); PN: 4.5 vs 6.8%

Treatment discontinuation due to AE 7.4% vs 9.3%

Daratumumab significantly improved PFS (63% reduction in risk of progression/death)

DRd was associated with a manageable safety profile consistent with the profile of D and Rd.

Dimopoulos M, et col. NEJM 2016
Novel drugs in MM

- Derivatives from already approved
  - Novel PIs
  - Novel IMiDs

- Immuno-oncologic approaches

- Novel drugs with different MoA
  - Deacetylase inhibitors
  - CDK inhibitors
  - Akt inhibitors
  - Kinesin spindle protein inhibitors

CDK, cyclin-dependent kinase
PANORAMA 1: Panobinostat+BTZ+Dex vs. PBO+BTZ+Dex

**ORR 60.7% vs. 54.6%**

**CR: 27.6% vs. 15.7%**

**PFS**

<table>
<thead>
<tr>
<th></th>
<th>PAN-BTZ-Dex</th>
<th>PBO-BTZ-Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>12 (10.3–12.9)</td>
<td>8.1 (7.6–9.2)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.63 (0.52–0.76)</td>
<td></td>
</tr>
</tbody>
</table>

Subgroup analysis by prior treatment:

**PFS prior BTZ + IMiDs with ≥2 prior lines**

<table>
<thead>
<tr>
<th></th>
<th>PAN-BTZ-Dex</th>
<th>PBO-BTZ-Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>12.5 (7.3–14.0)</td>
<td>4.7 (3.7–6.1)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.47 (0.31–0.72)</td>
<td></td>
</tr>
</tbody>
</table>

Novel drugs in MM

- Derivatives from already approved
  - Novel PIs
  - Novel IMiDs

- Immuno-oncologic approaches

- Novel drugs with different MoA
  - Deacetylase inhibitors
  - CDK inhibitors
  - Akt inhibitors
  - Kinesin spindle protein inhibitors
  - Exportin-1 inhibitor: selinexor

CDK, cyclin-dependent kinase
Management of relapsed and refractory MM: Summary

New agents activity show promise

The best the first will be the inversion we have to do to cure the MM

New combinations are emerging for the treatment of RRMM

Antibodies and immunotherapy are on the way, and may be game changers
Early Intervention
According to the heterogeneity in the risk of progression to MM, we have to identify the individual risk for each new SMM patient.
Smoldering multiple myeloma: Risk of transformation into symptomatic MM

Based on the % of aberrant PCs by immunophenotype plus immunoparesis

- >95% aPC/ BMPC + paresis: n=39 (28 progr.)
- No adverse factors: n=28 (1 progr.)

120
96
72
48
24
0

<table>
<thead>
<tr>
<th>Months</th>
<th>TTP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>24</td>
<td>0.0</td>
</tr>
<tr>
<td>48</td>
<td>0.0</td>
</tr>
<tr>
<td>72</td>
<td>0.0</td>
</tr>
<tr>
<td>96</td>
<td>0.0</td>
</tr>
<tr>
<td>120</td>
<td>0.0</td>
</tr>
</tbody>
</table>

p=0.003

High Risk
Median 23 months
82%

Low Risk
Median not reached
8%

>95% aPC/ BMPC: n=22 (10 progr.)
Median 73 months
42%

p=0.003

aPC, aberrant plasma cell; progresion.
QuiRedex: Study Design

- Multicenter, open-label, randomized phase III trial

Patients with high-risk smouldering MM (N = 125)

**Induction**
9 x 28-day cycles

- Lenalidomide 25 mg/day on Days 1-21 +
- Dexamethasone 20 mg/day on Days 1-4, 12-15

**Maintenance**
28-day cycles

- Lenalidomide 10 mg/day on Days 1-21
- (Low-dose dexamethasone added at time of biologic progression)

**No Treatment**

In both arms, blood counts, biochemical analysis (including creatinine and calcium) and serum/urine levels of MC were performed monthly. Skeletal survey was performed during the screening phase and thereafter only if clinical symptoms emerged.

High-risk was defined according to the Mayo and/or Spanish models

**Len-dex vs no treatment: TTP to active disease (n = 119)**

**Per-protocol Patients population**

 Mateos MV, et al. NEJM 2013

Median follow-up: 40 m

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>57</td>
</tr>
<tr>
<td>Observation group</td>
<td>62</td>
</tr>
</tbody>
</table>

Hazard ratio for progression: 0.18, p<0.001

Mateos MV, et al. Lancet Oncology 2016: accepted for publication

Median follow-up: 75 m

Hazard ratio for progression: 0.24, p<0.0001
Len-dex vs no treatment: OS from inclusion (n = 119)

Median follow-up: 40 m

Median follow-up: 75 m

Hazard ratio for death: 0.43, p=0.024

Mateos MV, et al. NEJM 2013

Mateos MV, et al. Lancet Oncology 2016: accepted for publication
**Curative Estrategia Smouldering Alto Riesgo (CESAR trial) (n:90)**

**Induction** 6 cycles of KRd

- MRD

**ASCT** (melphalan 200)

- MRD

**Consolidation** (2 cycles of KRd)

- MRD

**Maintenance** (Len-dex for 2yrs)

- MRD

**Primary objective:** To evaluate the proportion of patients in sustained immunophenotypic response at 5 years

**Hypothesis:** At least 50% of patients will achieve the objective

20 centers
Multiple myeloma: A model for scientific and clinical progress
From biology to therapeutics

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

Discovery of New Drugs
- Singular mechanism of action

Individualised and tailored treatment

*MM should not be considered a single entity.
Acknowledgments: Investigators of GEM
Acknowledgments: GEM/Pethema

Support from Arturo Touchard & LLA
Acknowledgments: Patients

Asociaciones locales de cada ciudad/region por el soporte
Acknowledgments: pharmaceutical companies

- Velcade
- Darzalex
- SAR650984
- Isatuximab
- Ixazomib
- Ninlaro®
- Elotuzumab
- Empliciti™
- Panobinostat
- Farydak®
- Daratumumab
- Pembrolizumab
- Keytruda
- Durvalumab
- Grupo Zeitia
- AstraZeneca
- MEDI4736
- Novartis
- Panobinostat
- Nivolumab
- Celgene
- Millennium
- Ixazomib
- Ninlaro®
- AMGEN
- Takeda
- Bristol-Myers Squibb