The Evolving Role of Novel and Next Generation Therapy in the Management of Multiple Myeloma: Focus on Selected Agents in RR MM

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Treating Multiple Myeloma Is a Marathon, Not a Sprint

MGUS or smoldering myeloma

M protein (g/L)

Asymptomatic | Symptomatic | Relapsing | Refractory

First-line therapy | Induction Remission +/- ASCT | Plateau remission | 2nd RELAPSE

1st RELAPSE

Adapted from Borrello I. Leuk Res. 2012;36:S3.
Key Targets in MM 2020

Genomic abnormalities:
- Target and overcome mutations
- Critical Role of Combination and Continuous Therapy
- Evolving Position and Timing of ASCT

Excess Protein Production:
- Target Protein Degradation

Immune Suppression:
- Restore anti-MM immunity
Venetoclax Targets BCL-2 and Induces Apoptosis in MM Cells

Venetoclax (Ven) targets BCL-2 and induces apoptosis in MM cells. BCL-2 is inhibited by Venetoclax, and in combination with Dexamethasone (Dex), Proteasome inhibitor (PI), and NOXA, it targets MCL-1 and BCL-XL, leading to apoptosis.

Ven had encouraging clinical efficacy in t(11;14) MM as monotherapy and in a broader patient population in combination with Bd, with a tolerable safety profile in phase 1 studies.

CR, complete response; mono, monotherapy; ORR, objective response rate; PI, proteasome inhibitor; PR, partial response; sCR, stringent CR; VGPR, very good partial response.
BELLINI Study Design

Stratification factors
- Bortezomib sensitive vs naïve
- Prior lines of therapy: 1 vs 2–3

Nonranked secondary endpoints
- PFS in BCL-2 high (IHC), DOR, TTP, MRD negativity rate, other PROs (GHS, fatigue)

Key subgroup analyses
- t(11;14), high/standard-risk cytogenetics, and BCL2 gene expression

Cycles 1-8: 21-day, bortezomib 1.3 mg/m² days 1, 4, 8, 11 and dexamethasone 20 mg days 1, 2, 4, 5, 8, 9, 11, 12
Cycles 9+: 35-day, bortezomib 1.3 mg/m² days 1, 8, 15, 22 and dexamethasone 20 mg days 1, 2, 8, 9, 15, 16, 22, 23

DOR, duration of response; GHS, global health status; IHC, immunohistochemistry; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; PRO, patient reported outcome; QD, daily; QoL, quality of life; RRMM, relapsed/refractory multiple myeloma; TTP, time to progression; VGPR, very good partial response.
PFS and OS in All Patients (ITT)
Clinical Data Cutoff: 15 Jul 2019

Investigator-Assessed PFS

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>194</th>
<th>163</th>
<th>140</th>
<th>118</th>
<th>101</th>
<th>89</th>
<th>84</th>
<th>75</th>
<th>58</th>
<th>27</th>
<th>9</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ven+Bd</td>
<td>97</td>
<td>83</td>
<td>69</td>
<td>57</td>
<td>39</td>
<td>30</td>
<td>22</td>
<td>19</td>
<td>17</td>
<td>8</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pbo+Bd</td>
<td>161</td>
<td>150</td>
<td>137</td>
<td>117</td>
<td>100</td>
<td>87</td>
<td>82</td>
<td>73</td>
<td>56</td>
<td>25</td>
<td>10</td>
<td>0</td>
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</tbody>
</table>

**PFS**

<table>
<thead>
<tr>
<th></th>
<th>Ven+Bd</th>
<th>Pbo+Bd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months</td>
<td>23.2</td>
<td>11.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.60 (0.44, 0.83)</td>
<td></td>
</tr>
<tr>
<td>(P) value</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

**OS**

<table>
<thead>
<tr>
<th></th>
<th>Ven+Bd</th>
<th>Pbo+Bd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months</td>
<td>32.5(^a)</td>
<td>Not reached</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.32 (0.82, 2.12)</td>
<td></td>
</tr>
<tr>
<td>(P) value</td>
<td>0.256</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Because of a large number of patients who were censored before reaching the median, the estimated median could change when longer follow-up data are available.
PFS is Significantly Prolonged with Venetoclax in Patients With t(11;14) or \( BCL2^{\text{high}} \), but not in Patients With Non-t(11;14), \( BCL2^{\text{low}} \) MM

High \( BCL2 \) gene expression was determined by qPCR.
Melflufen Is a Lipophilic Peptide-Conjugated Alkylator That Rapidly Delivers a Highly Cytotoxic Payload Into Myeloma Cells

Peptidase-enhanced activity in multiple myeloma cells

1. Peptidases are expressed in several cancers, including multiple myeloma\(^1^3\)
2. Melflufen is rapidly taken up by myeloma cells due to its high lipophilicity\(^4^5\)
3. Once inside the myeloma cell, melflufen is immediately cleaved by peptidases\(^5^7\)
4. The hydrophilic alkylator payloads are entrapped\(^5^7\)
5. Melflufen rapidly induces irreversible DNA damage, leading to apoptosis of myeloma cells\(^1^8\)

Melflufen is 50-fold more potent than melphalan in myeloma cells in vitro due to increased intracellular alkylator activity\(^4^5\)

Inclusion Criteria
• Pts with RR MM refractory to pom or dara or both
• ≥2 prior lines of therapy including an IMiD and a PI
• ECOG PS ≤2

Phase 2, Single-Arm, Open-Label, Multicenter Study

• With a median follow-up of 10.8 months, 29% of pts are on ongoing treatment (data cutoff 06 May 2019)

Primary endpoint
• ORR

Secondary endpoints
• PFS
• DOR
• OS
• CBR
• TTR
• TTP
• Safety

ClinicalTrials.gov Identified: NCT02963493.
CBR, clinical benefit rate; dara, daratumumab; dex, dexamethasone; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EoT, end of treatment; IMiD, immunomodulatory agent; mAbs, monoclonal antibodies; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; pom, pomalidomide; RR MM, relapsed/refractory multiple myeloma; TTP, time to progression; TTR, time to response.

Pts aged >75 years received dex 20 mg.
Best M-Protein Change (n=112)$^a$

Disease stabilization rate/disease control rate [DCR] (≥SD) was 86%

$^a$M-protein data for 9 pts missing at time of data cut-off.
Best Response

- Median time to response 1.2 months
- 13 of ongoing pts have follow-up time of 4 weeks

sCR was confirmed MRD negative (10^{-6} sensitivity) with current ongoing progression-free period of 13.6 months.

\(^8\) 8, 1, 7 and 6 pts, respectively, did not have any available response data or end of treatment data. At time of data cutoff 1 VGPR, 2 PRs and 4 MRs were unconfirmed. \(^a\)Not anti-CD38 refractory.

Data cutoff 06 May 2019.
Lonial et al, ASCO 2019
IBERDOMIDE Mechanism of Action

- IBER enhances in vitro immune stimulatory activity versus LEN and POM

<table>
<thead>
<tr>
<th>EC_{50}, nM</th>
<th>Ikaros</th>
<th>Aiolos</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEN</td>
<td>67</td>
<td>87</td>
</tr>
<tr>
<td>POM</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>IBER</td>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

DSMO, dimethylsulfoxide; EC_{50}, half maximal effective concentration; IL, interleukin; NK, natural killer; PBMC, peripheral blood mononuclear cell.

Iberdomide MM-001 Phase 1b/2a trial: Study Design

Phase 1
- RRMM
- Prior LEN or POM
- Prior proteasome inhibitor
- Documented PD during or within 60 days of last antimyeloma therapy

Phase 2

Cohort A: IBER
Cohort B: IBER + DEX
Cohort E: IBER + DARA + DEX
Cohort F: IBER + BORT + DEX
Cohort G: IBER + CFZ + DEX

Cohort C: IBER (RP2D)
Cohort D: IBER (RP2D) + DEX

Study objective: Determine the MTD / RP2D and efficacy of IBER in RRMM

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a DEX given at a dose of 40 mg (20 mg in patients aged > 75 years) on Days 1, 8, 15, and 22 of each 28-day cycle. b CFZ dosed once weekly (Cohort G1) or twice weekly (Cohort G2). CFZ, carfilzomib; DEX, dexamethasone; MTD, maximum tolerated dose; PD, progressive disease; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma.
Response

Evaluable patients include patients who have received ≥ 1 dose of IBER, had measurable disease at baseline, and ≥ 1 post-baseline response assessment.

a Includes LEN and POM.

CBR, clinical benefit rate; DCR, disease control rate; MR, minimal response; ORR, overall response rate; PR, partial response; SD, stable disease; VGPR, very good partial response.
**Antibody Drug Conjugates (ADC) – BCMA Auristatin Immunotoxin Induces Strong Anti-MM Effects**

- **Apoptosis**: MMAF released at lysosome to induce G2/M arrest followed by apoptosis.
- **Inhibition of NFκB signaling**: APRIL, BAFF.
- **ADCC**:
  - NK, Monocyte
  - GSK2857916
  - MM cell lysis
- **ADPC**:
  - Macrophage (Mφ)
  - FcRII
  - Mφ engulfing MM
  - MM cell lysis

DREAMM-2 Study Design

A phase II, open label, randomized 2-dose study in RRMM who were refractory to an immunomodulatory drug, proteasome inhibitor and refractory/intolerant to an anti-CD38 monoclonal antibody.

N=293

SCREENING

RANDOMIZE 1:1

Stratified by prior lines of therapy (≤4 vs. >4) and high-risk cytogenetic features*

N=99

Belantamab mafodotin
3.4 mg/kg Q3W frozen liquid configuration

N=97

Belantamab mafodotin
2.5 mg/kg Q3W frozen liquid configuration

N=25

Additional cohort treated with lyophilized configuration†

At the start of infusion, cooling eye masks could be applied and topical corticosteroids and preservative-free artificial tears were administered in both eyes

Ocular sub-study

Treatment until disease progression or unacceptable toxicity

N=30

Median duration of follow-up was 6.3 months in the 2.5 mg/kg cohort and 6.9 months in 3.4 mg/kg cohort

PRIMARY ENDPOINT

- ORR (IRC)

SECONDARY ENDPOINTS

- DoR, PFS, OS, CBR
- Safety
- ORR assessed by investigator†, TTR†, TTP†
- ADA activities†
- PK profiles†
- PFOs†
- HR-QoL‡

Efficacy Data: Overall Response Rate (IRC)

Efficacy Data: Clinical Benefit Rate

CBR = clinical benefit rate; CI = confidence interval; CR = complete response; IRC = independent review committee; ORR, overall response rate; MR = minimal response; NE, not evaluable; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Efficacy Data: Progression-Free Survival by Response

CI = confidence interval; IQR = interquartile range; MR = minimal response; NE = not evaluable; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease


The median PFS was not reached in patients with a partial response or better
Safety Data: Treatment Discontinuation, Dose Reductions, Dose Interruptions/Delays and Adverse Events of Special Interest

As of data cut-off (June 21, 2019)

Median dose intensity was
- 2.47 mg/kg (IQR: 1.56–2.50) in the 2.5 mg/kg cohort
- 2.95 mg/kg (IQR: 1.85–3.40) in the 3.4 mg/kg cohort

However, because of the higher incidence of dose modifications, the dose intensity was lower than the intended dose for the 3.4 mg/kg dose group

<table>
<thead>
<tr>
<th>Events</th>
<th>Belantamab Mafodotin 2.5-mg/kg Cohort (N=95)</th>
<th>Belantamab Mafodotin 3.4-mg/kg Cohort (N=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events leading to treatment</td>
<td>Percentage of patients</td>
<td></td>
</tr>
<tr>
<td>discontinuation</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Adverse events leading to dose reduction</td>
<td>29</td>
<td>41</td>
</tr>
<tr>
<td>Adverse events leading to dose interruption/delay</td>
<td>54</td>
<td>62</td>
</tr>
</tbody>
</table>

Keratopathy was the most common reason for permanent treatment discontinuation in both the 2.5 mg/kg and 3.4 mg/kg cohorts (1% and 3%, respectively)

<table>
<thead>
<tr>
<th>Adverse Event of Special Interest</th>
<th>Belantamab Mafodotin 2.5-mg/kg Cohort (N=95)</th>
<th>Belantamab Mafodotin 3.4-mg/kg Cohort (N=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>35</td>
<td>59</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Keratopathy</td>
<td>71</td>
<td>75</td>
</tr>
</tbody>
</table>

IQR = interquartile range

Conclusions – Continued Integration and Impact of Novel Agents in ND MM and RR MM, including Immune Therapies:

• Innovations (PIs, IMiDs, MoAbs, HDACs) to date have produced significant improvements in PFS and OS; recent approvals will augment this

• 10 Novel Drugs and > 26 new FDA-approved drugs/combos/indications in last 18 yrs

• Next wave of immune therapies: crucially, are they agnostic to mutational thrust?

• Baseline immune function is a key barrier to success and appears to be targetable

• mAbs (including ADCs, BiTEs) represent true new novel mechanisms, as well as other immuno-therapeutics (e.g. CAR –T, cellular therapies, vaccines)

• New insights to mechanisms of drug action are further expanding treatment/immuno-therapeutic opportunities with combinations

• Next generation small molecules also show great promise – e.g. VENETOCLAX, SELINEXOR, MELFLUFEN, CeLMoDS

• Further refinement of prognostics, immune profiling, and MRD will guide therapy