An expert panel discussion recorded in June 2020

**touchPANEL DISCUSSION**

Current management of relapsed/refractory multiple myeloma and the future integration of BCMA-targeting agents

This educational activity is supported by an educational grant from GlaxoSmithKline

BCMA, B-cell maturation antigen.
Disclaimer

Unapproved products or unapproved uses of approved products may be discussed by the faculty; these situations may reflect the approval status in one or more jurisdictions.

The presenting faculty have been advised by touchIME to ensure that they disclose any such references made to unlabelled or unapproved use.

No endorsement by touchIME of any unapproved products or unapproved uses is either made or implied by mention of these products or uses in touchIME activities. touchIME accepts no responsibility for errors or omissions.
Expert panel

Dr Rakesh Popat (Chair)
Consultant Haematologist and Associate Professor, University College Hospital, London, UK

Dr Paula Rodríguez-Otero
Haematology specialist and Medical Coordinator of the Clinical Trials Unit, University of Navarra, Pamplona, Spain

Prof. Katja Weisel
Deputy Director and Associate Professor of Haematology/Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
Agenda

How should patients be managed with the current treatment options?
*Presentation:* Rakesh Popat
*Panel discussion:* Paula Rodríguez-Otero and Katja Weisel; moderated by Rakesh Popat

Why is BCMA a target for new treatments and what agents are in development?
*Presentation:* Rakesh Popat
*Panel discussion:* Paula Rodríguez-Otero and Katja Weisel; moderated by Rakesh Popat

What are the latest clinical data for BCMA-targeting agents and how might they be incorporated into future clinical practice?
*Presentation:* Rakesh Popat
*Panel discussion:* Paula Rodríguez-Otero and Katja Weisel; moderated by Rakesh Popat

BCMA, B-cell maturation antigen.
How should patients be managed with the current treatment options?

Dr Rakesh Popat (Chair)

Consultant Haematologist and Associate Professor, University College Hospital, London, UK
Patient and disease characteristics for treatment selection in multiple myeloma

**Patient characteristics**
- Age, comorbidities and performance status
- Eligibility for first or salvage ASCT
- Efficacy/tolerance to prior therapies
- Patients’ views and wishes

**Disease characteristics**
- Aggressiveness of relapse
- Time since relapse: retreatment after 6–9 months?

**Subgroup considerations**
- Elderly/frail patients:
  - preservation of QoL over deep remission?
  - use of geriatric assessment scores
- High-risk disease by FISH, EMD; intensive treatment to prolong PFS and OS?

ASCT, autologous stem cell transplant; EMD, extramedullary disease; FISH, fluorescence in situ hybridization; OS, overall survival; PFS, progression-free survival; QoL, quality of life.
ESMO guidelines: relapsed multiple myeloma

First relapse¹

- **IMiD-based induction**
  - Doublets: Kd/Vd
  - Triplet based on
    - DaraVd
    - EloVd
    - PanoVd
    - VCd

- **Bortezomib-based induction**
  - Rd
  - Triplets (Rd backbone)
    - DaraRd
    - IxaRd
    - EloRd

Subsequent relapse¹

- Pom-d backbone plus
  - Bortezomib
  - Cyclo
  - Dara
  - Elo
  - Ixa

- Dara (single-agent or combination)

- Clinical trial

Ongoing developments

- Frontline lenalidomide
- Lenalidomide-refractory subgroup efficacy data²
  - Kd vs Dara-Kd
  - Kd vs Isa-Kd
  - Pom-d vs Isa-Pom-d
  - Pom-d vs Dara-Pom-d
  - Vd vs Vd-selinexor
  - Vd vs Vd-venetoclax

- Selinexor combinations³,⁴
  - Isa-Pom-d – approved by EC in June 2020⁵

---

Cyclo, cyclophosphamide; Dara, daratumumab; EC, European Commission; Elo, elotuzumab; ESMO, European Society of Medical Oncology; IMiD, immunomodulatory drug; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; Kd, carfilzomib, low-dose dexamethasone; PanoVd, panobinostat, bortezomib, dexamethasone; Pom-d, pomalidomide dexamethasone; Rd, lenalidomide, low-dose dexamethasone; VCd, bortezomib, cyclophosphamide, dexamethasone; Vd, bortezomib, low-dose dexamethasone.

Why is BCMA a target for new treatments and what agents are in development?

Dr Rakesh Popat (Chair)

Consultant Haematologist and Associate Professor, University College Hospital, London, UK
BCMA signalling in healthy cells and MM

BCMA activation by APRIL (and BAFF to a lesser extent) in normal PCs
- Supports survival of long-lived PCs
- Antibody production
- Class switch of immunoglobulin

BCMA in MM
- Promotes proliferation and survival of MM
- Immunosuppressive bone marrow environment
- γ-secretase causes shedding of soluble BCMA units, associated with poor outcomes

APRIL, a proliferation-inducing ligand; BAFF, B-cell-activating factor; BCMA, B-cell maturation antigen; Elk-1, ETS Like-1; JNK, c-Jun N-terminal kinase; MM, multiple myeloma; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B-cells; p38, a mitogen-activated protein kinase; PC, plasma cell.

Different approaches to BCMA targeting

**Antibody-drug conjugate**
BCMA mAb with linked cytotoxic payload

**CAR T-cell**
Patient’s own T-cell with added BCMA-targeting mAb

**Bispecific T-cell engager**
Two linked mAbs targeting BCMA and T-cells

MM cell lysis/apoptosis

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; mAb, monoclonal antibody; MM, multiple myeloma.

What are the latest clinical data for BCMA-targeting agents and how might they be incorporated into future clinical practice?

Dr Rakesh Popat (Chair)
Consultant Haematologist and Associate Professor, University College Hospital, London, UK
Antibody-drug conjugate: Belantamab mafodotin

**DREAMM-2**

≥3L RRMM Refractory to IMs, PIs and/or intolerant to an anti-CD38 mAb

<table>
<thead>
<tr>
<th>Belamaf 2.5 mg/kg*</th>
<th>ORR (97.5% CI)</th>
<th>32% (21.7–43.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Q3W (n=97)</td>
<td>mDoR (95% CI)</td>
<td>11 mo (4.2–NR)</td>
</tr>
<tr>
<td></td>
<td>mPFS (95% CI)</td>
<td>2.8 mo (1.6–3.6)</td>
</tr>
<tr>
<td></td>
<td>mOS (95% CI)</td>
<td>14.9 mo (9.9–NR)</td>
</tr>
</tbody>
</table>

**Grade ≥3 AEs (=>10%)**

- Keratopathy (MECs): 46%
- Thrombocytopenia: 22%
- Anaemia: 21%
- Lymphocyte count decreased: 13%
- Neutropenia: 11%

*3.4 mg/kg also explored in this study

**DREAMM-6**

N=18 RRMM ≥1 prior line of therapy

<table>
<thead>
<tr>
<th>Belamaf 2.5 mg/kg D1/Q3W</th>
<th>Bortezomib 1.3 mg/m² D1,4,8,11/Q3W</th>
<th>Dexamethasone 20 mg D1,2,4,5,8,9,11,12/Q3W</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>78% (52.4–93.6)</td>
<td>VGPR 50%</td>
</tr>
<tr>
<td>mDoR NR</td>
<td></td>
<td>mDoR NR</td>
</tr>
</tbody>
</table>

**Belamaf has a manageable toxicity profile with deep and durable clinically meaningful responses**

- Efficacy not impacted by mild–moderate renal impairment
- Comparable responses in patients with high-risk cytogenetics
- Clinical trial data are supported by real-world evidence
- Combination data are promising; Belamaf is also under investigation with lenalidomide/dexamethasone, pomalidomide/dexamethasone, and pembrolizumab

• Dose delays and interruptions due to AEs were common (54%) and did not impact efficacy
• Most dose delays/interruptions were due to keratopathy (MECs)
• Changes in visual acuity were temporary and manageable with dose modification

• Dose delays and interruptions due to AEs were common (54%) and did not impact efficacy
• Most dose delays/interruptions were due to keratopathy (MECs)
• Changes in visual acuity were temporary and manageable with dose modification

AEs, adverse events; Belamaf, belantamab mafodotin; CI, confidence interval; D, day; DoR, duration of response; IM, immunomodulatory agent; IV, intravenous; m, median; mAb, monoclonal antibody; MEC, microcyst-like epithelial change; mo, months; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; Q3W, every 3 weeks; RRMM, relapsed/refractory multiple myeloma; VGPR, very good partial response.


≥3L RRMM refractory to IMs, PIs and/or intolerant to an anti-CD38 mAb

Phase 1 dose escalation

0.3–720 µg/kg weekly step-up dosing (N=78)

<table>
<thead>
<tr>
<th>Most common AEs</th>
<th>All grade, %</th>
<th>Grade ≥3, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>58</td>
<td>36</td>
</tr>
<tr>
<td>CRS</td>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>45</td>
<td>38</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>40</td>
<td>24</td>
</tr>
</tbody>
</table>

Other AEs of interest

<table>
<thead>
<tr>
<th></th>
<th>All grade, %</th>
<th>Grade ≥3, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurotoxicity</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>9</td>
<td>NR</td>
</tr>
<tr>
<td>Tx-related infections</td>
<td>19</td>
<td>3</td>
</tr>
</tbody>
</table>

Two grade 4 DLTs: delirium (20 µg/kg), thrombocytopenia (180 µg/kg)

- Safety profile manageable across all doses
- CRS events all grade 1 or 2
- Response rates increased at higher doses
- Responses appeared to be durable
- No DLT at 720 µg/kg (efficacy data not mature)
- Further evaluation in expansion cohorts ongoing

AEs, adverse events; CRS, cytokine-release syndrome; DLT, dose-limiting toxicity; DoR, duration of response; IM, immunomodulatory agent; mAb, monoclonal antibody; NR, not reached; ORR, overall response rate; PFS, progression-free survival; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; Tx, treatment.

**CAR T-cell therapies**

All patients had disease progression with IMs, PIs and an anti-CD38 mAb

---

### Idecabtagene vicleucel
**KarMMa**\(^1\)

- **N=128**
- 150–450 x 10\(^6\) CAR+ T-cells
- **mFU 13.3 mo**

#### Efficacy

<table>
<thead>
<tr>
<th>ORR, % (95% CI)</th>
<th>73 (65.8–81.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS, mo (95% CI)</td>
<td>8.8 (5.6–11.6)</td>
</tr>
<tr>
<td>mOS, mo (95% CI)</td>
<td>19.4 (18.2–NR)</td>
</tr>
</tbody>
</table>

#### Safety

| CRS, % | 84 | ≤6 |
| Neurotoxicity, % | 18 | 3 |
| Neutropenia, % | 91 | 89 |

---

### JNJ-4528
**CARTITUDE-1**\(^2\)

- **N=29**
- Target 0.75 x 10\(^6\) CAR+ T-cells/kg
- **mFU 11.5 mo**

#### Efficacy

| ORR, % | 100 |
| 9-month PFS, % (95% CI) | 86 (67–95) |
| 6-month MRD negative at 10\(^{-6}\), % | 70 (n=14/20 evaluable) |

#### Safety

| CRS, % | 93 | 7 |
| Neurotoxicity, % | 10 | 3 |
| Neutropenia, % | 100 | 100 |

---

### Orvacabtagene autoleucel
**EVOLVE**\(^3\)

- **N=62**
- 300–600 x 10\(^6\) CAR+ T-cells
- **mFU for ORR 6.9 mo**

#### Efficacy

| ORR, % | 92 |
| PFS | Not yet evaluable overall |
| 3-month MRD negative | 21/25 |

#### Safety

| CRS, % | 89 | 3 |
| Neurotoxicity, % | 13 | 3 |
| Neutropenia, % | 90 | 90 |

---

- High response rates with deep and durable responses in heavily pretreated patients
- CRS was generally managed with tocilizumab and, less frequently, corticosteroids

---

CAR, chimeric antigen receptor; CI, confidence interval; CRS, cytokine release syndrome; FU, follow-up; Gr, grade; IM, immunomodulatory agent; m, median; mAb, monoclonal antibody; mo, months; MRD, minimal residual disease; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma.

Thank you for watching this on-demand event

touchoncology.com/education-zone