Beyond the horizon
New treatment strategies for multiple myeloma

Dominik Dytfeld

March the 14th 2019
## Disclosures for Dominik Dytfeld

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support</td>
<td>Janssen, Celgene, Amgen</td>
</tr>
<tr>
<td>Employee</td>
<td>N/A</td>
</tr>
<tr>
<td>Consultant</td>
<td>N/A</td>
</tr>
<tr>
<td>Major Stockholder</td>
<td>N/A</td>
</tr>
<tr>
<td>Speakers’ Bureau/Scientific Advisory</td>
<td>Janssen, Amgen, Novartis, Celgene, Takeda,</td>
</tr>
<tr>
<td>Board</td>
<td>Abbvie</td>
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</tbody>
</table>
**Improved outcome** after introduction of bortezomib and lenalidomide

Kumar, 2014
….. but still the there is a gap...
Further improvement can be achieved by bringing the most **effective** treatment upfront....

RD vs MPT vs MP frontline

RVD vs RD frontline

Benboubker, 2014

Durie, 2017
... and by **intensifying** it and keep it continuously.

**Double vs single transplant**

**R maintenance**

MacCarthy, 2017
Cavo, 2017
...and by introduction of new generations of existing drugs

Carfilzomib 2\textsuperscript{nd} generation PI prolongs survival

Ixasomib first oral PI breaks high risk

Pomalidomid 3\textsuperscript{rd} generation IMID works in advanced disease

Dimopoulos, 2014 and 2017
San Miquel, 2013
...and monoclonal antibodies expected for soooo long

**Daratumumab** works in monotherapy and in combination with lenalidomide and bortezomib

![Graphs and charts showing patient progression-free and alive data over time.]

- **Dara mono**
- **Dara VD vs VD**
- **Dara RD vs VD**

**Elotuzumab** is active in combination only...

Lonial, 2016  
Bahlis, 2018  
Mateos, 2018  
Dimopoulos, 2017
The best results in refractory myeloma are seen in **daratumumab**-based chemotherapies....

\[
\begin{array}{cccccccc}
\text{Vd} & \text{Kd} & \text{Rd} & \text{KRd} & \text{Rd} & \text{IRd} & \text{Vd} & \text{ERd} \\
\text{HR}=0.53 & \text{HR}=0.66 & \text{HR}=0.74 & \text{HR}=0.62 & \text{HR}=0.73 & \text{HR}=0.39 & \text{HR}=0.44 \\
\end{array}
\]

*Results extrapolated from published data to estimate median PFS
What holds even more in frontline setting

Dara VMP vs VMP

Dara RD vs RD

Dimopoulos, 2018
Facon 2018
Looks like daratumumab is the winner but the game will be lost sooner or later
Newer molecules might be a solution

Selinexor

Melflufen
Selinexor
first-in-class oral XPO-1 inhibitor

Rosebeck, 2015
Results of the Pivotal STORM Study (Part 2) in Penta-Refractory Multiple Myeloma (MM): Deep and Durable Responses With Oral Selinexor Plus Low Dose Dexamethasone in Patients with Penta Exposed and Triple Class-Refractory MM


Oral presentation at the 60th Annual Meeting of the American Society of Hematology December 1–4, 2018

Monday, December 3, 2018 at 07:45 hours
Phase 2 STORM (Part 2)
Penta-refractory MM (N = 122) previously treated with BORT, CFZ, LEN, POM, DARA, an alkylator, and glucocorticoids
- Refractory to ≥ 1 PI, ≥ 1 IMiD, DARA, glucocorticoid, and last therapy

Primary endpoint:
ORR

Secondary endpoints:
response duration, CBR, OS, PFS, safety

28-day cycle

Patient Characteristics N = 122

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 122</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>65 (40–86)</td>
</tr>
<tr>
<td>Median time from diagnosis (range), years</td>
<td>6.6 (1.1–23.4)</td>
</tr>
<tr>
<td>High risk cytogenetics, n (%)</td>
<td>65 (53)</td>
</tr>
<tr>
<td>Median prior treatment regimens (range), n</td>
<td>7 (3–18)</td>
</tr>
<tr>
<td>CFZ, POM, DARA refractory, n (%)</td>
<td>117 (96)</td>
</tr>
<tr>
<td>Prior DARA-based therapy n (%)</td>
<td>86 (70)</td>
</tr>
<tr>
<td>Prior stem cell transplant, n (%)</td>
<td>102 (84)</td>
</tr>
<tr>
<td>Prior CAR T therapy, n (%)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

Efficacy Outcomes N = 122

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N = 122</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>26.2</td>
</tr>
<tr>
<td>Stringent CR</td>
<td>1.6</td>
</tr>
<tr>
<td>VGPR</td>
<td>4.9</td>
</tr>
<tr>
<td>PR</td>
<td>19.7</td>
</tr>
<tr>
<td>≥ SD, %</td>
<td>78.0</td>
</tr>
<tr>
<td>Median response duration, months</td>
<td>4</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>6</td>
</tr>
<tr>
<td>PFS, months</td>
<td>3</td>
</tr>
</tbody>
</table>

AUTHORS’ CONCLUSIONS:
- SEL is the first oral agent with activity in very heavily pretreated, penta-exposed, triple class-refractory MM patients

AE, adverse event; BORT, bortezomib; CAR T, chimeric antigen receptor T-cell; CBR, clinical benefit rate; CFZ, carfilzomib; CR, complete response; DARA, daratumumab; DEX, dexamethasone; IMiD, immunomodulatory drug; LEN, lenalidomide; MR, minimal response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; POM, pomalidomide; PR, partial response, Sd, selinexor + low-dose dexamethasone; SEL, selinexor; SD, stable disease.

ABSTRACT

OP-106 HORIZON – Melflufen Therapy for RRMM Patients Refractory to Daratumumab and/or Pomalidomide: Updated Results and

Paul Richardson, Enrique Ocio, Albert Oriol, Alessandra Larocca, Paula Rodriguez Otero, Jan Moreb, Joan Bladé, Hani Hassoun, Michele Cavo, Adrián Alegre, Amitabha Mazumder, Christopher Maisel, Agne Paner, Nashat Gabrail, Jeffrey A. Zonder, Dharminder Chauhan, Johan Harmenberg, Sara Thuresson, Hanan Zubair, Maria-Victoria Mateos

Oral presentation at the 60th Annual Meeting of the American Society of Hematology

December 1–4, 2018

Monday, December 3, 2018 at 08:15 hours
MELF IN RRMM PATIENTS REFRACTORY TO DARA AND/OR POM STUDY DESIGN AND UPDATED RESULTS

• Ongoing, single-arm, open-label, multicentre, phase 2 trial to evaluate MELF in pts who have progressed on IMiD and PI and are refractory to POM and/or DARA

• Primary endpoint: ORR (N = 83) (at data cutoff October 22 2018, 82 patients were response evaluable)

• Secondary endpoints: OS, PFS, duration of response, CBR, TTR, TTP, safety, and tolerability

MELF IN RRMM PATIENTS REFRACTORY TO DARA AND/OR POM

OP-106 HORIZON
• Refractory to POM and/or DARA
• Measurable disease (≥ 1 of the following):

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>N = 83</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>27 (33)</td>
</tr>
<tr>
<td>sCR</td>
<td>1 (1)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>VGPR</td>
<td>9 (11)</td>
</tr>
<tr>
<td>PR</td>
<td>17 (21)</td>
</tr>
<tr>
<td>MR</td>
<td>5 (6)</td>
</tr>
<tr>
<td>SD</td>
<td>37 (45)</td>
</tr>
<tr>
<td>PD</td>
<td>12 (15)</td>
</tr>
</tbody>
</table>

Most Common (> Grade 3 or n (%))

- Any treatment-related grade 3 or 4 AE in ≥ 2 patients
- Neutropenia | 51 (61)
- Thrombocytopenia | 49 (59)
- Anemia | 21 (25)

- Incidence of non-haematological AEs was low (7.2% infection)
- No treatment-related deaths

AUTHORS’ CONCLUSIONS:

• MELF shows promising activity in patients with multi-resistant RRMM
• Response was observed irrespective of refractory status
• Treatment was generally well tolerated with a manageable safety profile

Richardson et al. ASH 2018: Abstract 600. Oral presentation.
...or totally different approach involving **immunology** of the patient?

- **ELOTUZUMAB**
- **POMALIDOMIDE**
- **BiTE**
- **CAR-T**
Stimulation of NKs by (forgotten?) elotuzumab and pomalidomide

Mechanisms of Immune Activation by Elotuzumab

- Elotuzumab
  - SLAMF7
  - CD16
  - Nkp46
  - Ligands for Nkp46
  - Primary signaling (ITAM)
  - Co-stimulation (ITSM)

- Myeloma Cell
  - Natural Cytotoxicity

- Macrophage
  - ADCP

- NK Cell
  - Natural Cytotoxicity

ELO POM DEX vs POM DEX

- Hazard ratio for disease progression or death, 0.54 (95% CI, 0.34–0.86)
- P = 0.008

- Probability of Progression-free Survival
- Months since Randomization

Dimopoulos, 2018
AMG 420, an Anti-BCMA BiTE®, Induces MRD-Negative CRs in Relapsed/Refractory MM Patients: Results of a Dose Escalation FIH Phase 1 Study

Max S Topp, 1 Johannes Duell, 1 Gerhard Zugmaier, 2 Michel Attal, 3 Philippe Moreau, 4 Christian Langer, 5 Jan Krönke, 6 Thierry Facon, 7 Hermann Einsele, 1* Gerd Munzert 8*

1 Department of Internal Medicine II, University Hospital Würzburg, Würzburg, Germany,
2 Amgen Research (Munich), Munich, Germany,
3 University of Toulouse, Toulouse, France,
4 Hematology Department Chair, University Hospital Center of Nantes, Nantes, France,
5 Kempten Clinic, Kempten, Germany,
6 Ulm University, Ulm, Germany,
7 Regional University Hospital of Lille, Lille, France,
8 Boehringer Ingelheim, Ingelheim am Rhein, Germany

* Contributed equally
Background

- B-Cell Maturation Antigen (BCMA), or TNFRSF17, is expressed on multiple myeloma (MM) cells, plasma cells, and mature B cells.1-4

- AMG 420* binds BCMA on tumor cells and plasma cells and CD3 on T cells, resulting in T-cell mediated lysis of BCMA+ cells5 at least in part through a Fas-mediated mechanism.6

Most patients did not receive an active dose of AMG 420.

### CRS AEs and Serious AEs (SAEs)

<table>
<thead>
<tr>
<th></th>
<th>N=42</th>
<th># Gr 1</th>
<th># Gr 2</th>
<th># Gr 3</th>
<th># Gr 4</th>
<th># Gr 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS</td>
<td>All treatment-related</td>
<td>16 (38%)</td>
<td>13</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>SAEs in ≥2 patients</td>
<td>Infections</td>
<td>12 (29%)</td>
<td>-</td>
<td>3</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Peripheral polyneuropathy</td>
<td>2 (5%)</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Treatment-related SAEs</td>
<td>Peripheral polyneuropathy</td>
<td>2 (5%)</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Edema</td>
<td>1 (2%)</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

*One patient died of aspergillus / flu and one of liver failure secondary to adenovirus infection.

- Of those with serious AEs (n=20, 48%), 17 patients were hospitalized and 4 had prolonged hospitalization (one patient had both on separate occasions).
- No grade 3 or 4 central nervous system toxicities were observed.
- Regarding any neurologic AEs, except for 1 case of worsening asthenia and 2 of peripheral polyneuropathy, all AEs were grade 1 and 2 and were generally nonspecific (e.g., headache, fatigue).
Conclusions

In this FIH dose escalation study, AMG 420, a short half-life BiTE® targeting BCMA, demonstrated clinical activity in patients with heavily pretreated multiple myeloma:

- No major toxicities prior to DLTs at 800 µg/d of CRS and polyneuropathy; a patient in the subsequent 400 µg/d dose expansion also had a DLT of polyneuropathy, which resolved.
- Careful evaluation of infections should be conducted in future clinical trials to enable development of optimal management guidelines.
- Of doses tested in this study, 400 µg/d was the MTD; other doses may be tested in the future.
- There was encouraging evidence of activity, with 13 responders overall
  - 7/10 (70%) of patients dosed with 400 µg/d had responses, 4 of which were MRD-negative sCRs
  - 3 patients at lower doses attained CRs, one of which was also an MRD-negative sCR
- These data warrant further clinical investigation of AMG 420; a phase 1b trial will be starting in Q1 2019.

31% ORR (n=42)
bb2121: AN OPTIMAL BCMA CAR T CELL DESIGN

- Autologous T cells transduced with a lentiviral vector encoding a CAR specific for human BCMA
- State of the art lentiviral vector system
- Optimal 4-1BB costimulatory signaling domain: associated with less acute toxicity and more durable CAR T cell persistence than CD28 costimulatory domain

TUMOR RESPONSE: DOSE-RELATED; INDEPENDENT OF TUMOR BCMA EXPRESSION

**Tumor Response By Dose**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Objective Response Rate</th>
<th>mDOR (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR/C</td>
<td>33.3%</td>
<td>1.9</td>
</tr>
<tr>
<td>CR</td>
<td>57.1%</td>
<td>10.8</td>
</tr>
<tr>
<td>VGPR</td>
<td>95.5%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Response By BCMA Expression</th>
</tr>
</thead>
</table>

**ORR=100%**

<table>
<thead>
<tr>
<th>BCMA Expression Level</th>
<th>Objective Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low BCMA (n=11)</td>
<td>37.5%</td>
</tr>
<tr>
<td>High BCMA (n=11)</td>
<td>54.5%</td>
</tr>
</tbody>
</table>

Data cutoff: March 29, 2018. CR, complete response; mDOR, median duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; sCR, stringent CR; VGPR, very good partial response. *Patients with ≥2 months of response data or PD/death within <2 months. ORR is defined as attaining sCR, CR, VGPR, or PR, including confirmed and unconfirmed responses. Low BCMA is <50% bone marrow plasma cells expression of BCMA; high BCMA is defined as ≥50%.

• mPFS of 11.8 months at active doses (≥150 x 10^6 CAR+ T cells) in 18 subjects in dose escalation phase
• mPFS of 17.7 months in 16 responding subjects who are MRD-negative

Data cutoff: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable. *PFS in dose escalation cohort.

LEGEND-2 Study

- **LCAR-B38M** is a chimeric antigen receptor (CAR) T cell therapy with 2 BCMA targeting domains
  - Confers high avidity binding and distinguishes LCAR-B38M from other BCMA-targeted CAR T cell therapies

- **LEGEND-2 (N=74):** Phase 1 investigator-initiated study in R/R multiple myeloma (MM) conducted at 4 sites in China
  - Variable preconditioning regimens (Cy-Flu vs. Cy)
  - Variable CAR T infusion methods (split vs. single infusion)

- **LEGEND-2 results previously presented**
  - First 35/57 patients at the Xi’an site at ASCO and EHA 2017
  - First 11/17 patients at the 3 other sites at ASH 2017

- **57 patient experience at Xi’an site as of 25 June 2018** are presented here, with a 12-month (0.7–25.1) follow-up
# Adverse Events

<table>
<thead>
<tr>
<th>AEs (≥20% in All Patients)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total (N=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>14 (25)</td>
<td>27 (47)</td>
<td>10 (18)</td>
<td>1 (2)</td>
<td>52 (91)</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>27 (47)</td>
<td>20 (35)</td>
<td>4 (7)</td>
<td>0</td>
<td>51 (90)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8 (14)</td>
<td>7 (12)</td>
<td>3 (5)</td>
<td>10 (18)</td>
<td>28 (49)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3 (5)</td>
<td>7 (12)</td>
<td>15 (26)</td>
<td>2 (4)</td>
<td>27 (47)</td>
</tr>
<tr>
<td>Increased AST</td>
<td>7 (12)</td>
<td>3 (5)</td>
<td>12 (21)</td>
<td>0</td>
<td>22 (39)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (4)</td>
<td>5 (9)</td>
<td>9 (16)</td>
<td>1 (2)</td>
<td>17 (30)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>7 (12)</td>
<td>2 (4)</td>
<td>3 (5)</td>
<td>0</td>
<td>12 (21)</td>
</tr>
<tr>
<td>Other AE of interest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity$^1$</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

*Apnevahia, seizure-like activity, and agitation reported in one patient dosed at 1×10⁵ cells/kg
Efficacy

Best Overall Response (N=57)

ORR = 88%

- mDOR = 16 mo (95% CI, 12–NR)
- mDOR for MRD-neg CR = 22 mo (95% CI, 14–MRD-neg CR)
- Median time to initial response = 1 mo (0.4–3.6)

Best Overall Response by Dose

- N=57
- n=25
- n=32

All Doses

<0.5x10^6 cells/kg

≥0.5x10^6 cells/kg

BCMA <40% (n=26/53)^k = 92% ORR

BCMA ≥40% (n=27/53)^k = 82% ORR

*8-color flow cytometry with cell count up to 500,000 cells; ^BCMA expression data available for 53 patients

CR=complete response; mDOR=median duration of response; MRD-neg=minimal residual disease-negative; NE=not evaluable; ORR=overall response rate; PD=progressive disease; PR=partial response; SD=stable disease; VGPR=very good partial response

Zhao et al; ASH2018, Abs#955, oral presentation
Progression-Free Survival

Patients Achieving MRD-neg CR
mPFS: 24 mo
(95% CI, 15–NR)
12-mo PFS: 87%

Patients Not Achieving MRD-neg CR
mPFS: 6 mo
(95% CI, 3–8)
12-mo PFS: 6%

All Patients
mPFS: 15 mo
(95% CI, 11–NR)
12-mo PFS: 61%

 Patients at risk:
 All Patients 57 53 48 37 21 11 7 4 1 0
 Patients Achieving MRD-neg CR 39 39 38 33 20 10 7 4 1 0
 Patients Not Achieving MRD-neg CR 18 14 10 4 1 1 0 0 0 0

*30/39 patients still in remission
JCARH125—DESIGN AND MANUFACTURING FEATURES

- **JCARH125 CAR construct**
  - Fully human binder with low affinity for sBCMA
  - Modified spacer to enhance binding to BCMA on target cells
  - Minimized tonic signaling to reduce antigen-independent exhaustion
  - Active on target cells that express low BCMA density

- **Manufacturing process**
  Optimized to deliver a defined cell product comprised of purified CD4 and CD8 CAR+ T cells enriched for central memory phenotype cells, potentially increasing persistence and durability

To date, JCARH125 has been successfully manufactured for all patients

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BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; sBCMA, soluble B-cell
BEST OVERALL RESPONSE

**ORR 82%, with 48% ≥VGPR**

One patient was not evaluable for efficacy (no postbaseline response evaluation at Day 29).

CAR, chimeric antigen receptor; CR, complete response; ORR, objective response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

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**CAR+ T Cell Dose**

- **Patients, n:**
  - 50 × 10^6: 14
  - 150 × 10^6: 28
  - 450 × 10^6: 2
  - Total: 44

- **Median follow-up, weeks:**
  - 1
  - 9
  - 7
  - 11

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\(^a\)One patient was not evaluable for efficacy (no postbaseline response evaluation at Day 29).
Old drugs
Dexamethasone
Prednisone
Melphalan
Vinca alkaloids

PIs
Bortezomib
Carfilzomib
Ixazomib

MoAbs
Daratumumab
Elotuzumab

Stromal cell

NEW
Alkylating agent
Melflufen

XPO-1 inhibitors
Selinexor

Biclonal antibodies
AMG 420

Microenviorment

NEW
Stromal cell

CAR-T cell

PIs
Bortezomib
Carfilzomib
Ixazomib

Immids
Thalidomide
Lenalidomide
Pomalidomide

Microenviorment
..this is a team game where every player counts and new players will show up in the pitch soon
Beyond the horizon
New treatment strategies for multiple myeloma

Dominik Dytfeld

March the 14th 2019