A Phase Ib dose-escalation trial of SAR650984 (anti-CD38 mAb) in combination with lenalidomide and dexamethasone in relapsed/refractory multiple myeloma

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Introduction to CD38 and SAR650984

- CD38 is a 45 kD type II transmembrane glycoprotein which functions as a receptor and an ectoenzyme
- Widely expressed in many hematologic malignancies including multiple myeloma, NHL, AML, and CLL
- SAR650984 is a humanized IgG1 monoclonal antibody that binds selectively to a unique epitope on the human CD38 receptor
  - Four potential modes of action

Combination of SAR650984 and lenalidomide in the RPMI-8226 MM xenograft model

- Lenalidomide is an immunomodulatory drug (IMiD) with potential for synergy with SAR650984 through:
  - Direct anti-myeloma activity\(^1\)
  - Increased IL-2 production leading to enhanced ADCC\(^2\)

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Phase I trial SAR/Len/Dex (TCD11863): Study objectives

Primary objective

- Determine the maximum tolerated dose of SAR650984 in combination with lenalidomide and dexamethasone (Len/Dex) in patients with relapsed or relapsed and refractory multiple myeloma (RRMM)

Secondary objectives

- Evaluate the safety, including immunogenicity, of SAR650984 in combination with Len/Dex in RRMM
- Evaluate the pharmacokinetic (PK) profile of the combination
- Assess pharmacodynamics, disease response and progression free survival (PFS)
TCD11863: Eligibility and study design

ELIGIBILITY

- Adults with RRMM
- Confirmed progression or refractory to salvage therapy
- At least 2 prior therapies
  - Prior IMiD therapy permitted
  - Prior autologous transplant permitted
  - No upper limit on number of prior therapies
- Adequate bone marrow and organ function

STUDY DESIGN

- Phase I: standard 3 + 3 dose escalation
- DLT period: first 28-day cycle
- Prophylaxis against infusion reactions†
- Disease assessment every cycle
- Data cut off: Sept 30, 2014
  - 9 months follow-up after last patient in

<table>
<thead>
<tr>
<th>Standard dose escalation (3 + 3 design)</th>
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<tbody>
<tr>
<td>3–6 patients per cohort</td>
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<tr>
<td>SAR650984 iv, Days 1 and 15 per 28 day cycle</td>
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<tr>
<td>Cohort 1</td>
</tr>
<tr>
<td>3 mg/kg</td>
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<tr>
<td>Cohort 2</td>
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<tr>
<td>5 mg/kg</td>
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<td>Cohort 3</td>
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<td>10 mg/kg</td>
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*MTD not reached

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<tr>
<th>Expansion cohort</th>
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<tbody>
<tr>
<td>18 patients</td>
</tr>
<tr>
<td>10 mg/kg*</td>
</tr>
</tbody>
</table>

- Lenalidomide 25 mg on days 1–21 per 28-day cycle
- Dexamethasone 40 mg qW (Days 1, 8, 15, and 22)

†Methylprednisolone 100 mg iv, diphenhydramine 50 mg iv, ranitidine 50 mg iv, and acetaminophen 650–1000 mg po (or equivalents)
## Demographics and disease characteristics

<table>
<thead>
<tr>
<th>SAR650984 dose, mg/kg q2W</th>
<th>Overall (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 (n=4)</td>
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<tr>
<td>Median age, years (range)</td>
<td>60 (48–69)</td>
</tr>
<tr>
<td>Median time since initial diagnosis, years (range)</td>
<td>7 (3–11)</td>
</tr>
<tr>
<td>Type of myeloma at diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>3 (75)</td>
</tr>
<tr>
<td>IgA</td>
<td>1 (25)</td>
</tr>
<tr>
<td>IgE</td>
<td>0</td>
</tr>
<tr>
<td>Light chain</td>
<td>0</td>
</tr>
<tr>
<td>Staging at diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>0</td>
</tr>
<tr>
<td>Stage II</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Stage III</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (25)</td>
</tr>
<tr>
<td>% Bone marrow plasma cells</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>34.0 (6.7)</td>
</tr>
<tr>
<td>Median</td>
<td>32.5</td>
</tr>
<tr>
<td>Range</td>
<td>28–43</td>
</tr>
</tbody>
</table>
Prior anti-myeloma treatments

<table>
<thead>
<tr>
<th>SAR650984 dose, mg/kg q2W</th>
<th>Overall (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg/kg (n=4)</td>
<td>10 (3–14)</td>
</tr>
<tr>
<td>5 mg/kg (n=3)</td>
<td>7 (6–7)</td>
</tr>
<tr>
<td>10 mg/kg (n=24)</td>
<td>6 (2–12)</td>
</tr>
</tbody>
</table>

- **Median prior regimens (range):**
  - Overall (n=31): 7 (2–14)
  - 3 mg/kg (n=4): 10 (3–14)
  - 5 mg/kg (n=3): 7 (6–7)
  - 10 mg/kg (n=24): 6 (2–12)

- **Median prior lines (range):**
  - Overall (n=31): 4 (1–11)
  - 3 mg/kg (n=4): 6 (2–11)
  - 5 mg/kg (n=3): 6 (4–6)
  - 10 mg/kg (n=24): 4 (1–9)

- **Median time on last LEN, months (range):**
  - Overall (n=31): 9 (1–54)
  - 3 mg/kg (n=4): 7 (3–17)
  - 5 mg/kg (n=3): 3 (3–10)
  - 10 mg/kg (n=24): 10 (1–54)

- **Rel + refr to IMiD:**
  - Overall (n=31): 26 (84)
  - 3 mg/kg (n=4): 3 (75)
  - 5 mg/kg (n=3): 2 (67)
  - 10 mg/kg (n=24): 21 (88)

Rel + refr definition according to IMWG criteria.
Treatment-emergent adverse events occurring in ≥30% of patients (all grades) and ≥5% (grade 3/4)

*Anemia, neutropenia, and thrombocytopenia are based on laboratory evaluations

URTI, upper respiratory tract infection
Infusion reactions

- Universal prophylaxis†

- Discontinued treatment: 2
  - Serious G3 anaphylactic reaction in cycle 1 (3 mg/kg cohort)
  - Non-serious G3 maculopapular rash in cycle 2 (10 mg/kg cohort)
  - AEs resolved in both patients

- All others were grade 1/2, and did not lead to treatment discontinuation
  - None reported after cycle 2
  - 12/478 (3%) SAR650984 administrations were temporarily interrupted

†methylprednisolone 100 mg iv, diphenhydramine 50 mg iv, ranitidine 50 mg iv, and acetaminophen 650–1000 mg po (or equivalents).

AE, adverse event
Pharmacokinetics

Effect of lenalidomide on SAR650984 PK
- Similar SAR650984 exposure was observed compared with monotherapy
- Single agent half-life was 9.8 days\(^1\)

Effect of SAR650984 on lenalidomide PK
- Similar lenalidomide exposure and CL/F were observed compared with monotherapy\(^2\)
  - Geometric mean ratio of AUC\(_{0–24}\) was 1.08

<table>
<thead>
<tr>
<th>SAR650984 + lenalidomide</th>
<th>n</th>
<th>C(_{\text{max}}) (ng/mL)</th>
<th>AUC(_{0–24}) (ng.h/mL)</th>
<th>CL/F (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>295 (41)</td>
<td>2420 (n=2)</td>
<td>172 (n=2)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>522 (14)</td>
<td>2231 (22)</td>
<td>184 (24)</td>
<td></td>
</tr>
</tbody>
</table>

Lenalidomide 25 mg po; Cycle 1 Day 1 (escalation phase only)

1. Presentation of Abstract 8512 at ASCO Annual Meeting 2014; 2. Lenalidomide prescribing information.
## Response summary (IMWG criteria)

<table>
<thead>
<tr>
<th>All treated patients (n=31)</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>58 (18)</td>
</tr>
<tr>
<td>Stringent complete response</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>23 (7)</td>
</tr>
<tr>
<td>Partial response</td>
<td>29 (9)</td>
</tr>
<tr>
<td>Clinical benefit rate</td>
<td>65 (20)</td>
</tr>
<tr>
<td>Minimal response</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>19 (6)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

All responses were confirmed by a subsequent assessment.

**CBR, clinical benefit rate (MR or better); MR, minimal response; ORR, overall response rate (PR or better); PR, partial response; sCR, stringent complete response; VGPR, very good partial response**
Maximum change in paraprotein

No post-baseline assessment of paraprotein for three patients: clinical progression at cycle 1 (N=2) and treatment discontinuation due to AE at Cycle 1-Day 1 (N=1)
Time on treatment by best response

DOR was 9.13 months (range, 1.2-15.2)
Response rate by prior anticancer treatment

- **Lenalidomide rel + refr (n=25)**
  - sCR: 28
  - VGPR: 20
  - PR: 8
  - MR: 0
  - ORR: 48%

- **Lenalidomide non-rel + refr (n=6)**
  - sCR: 33
  - VGPR: 67
  - ORR: 100%

- **Bortezomib rel + refr (n=18)**
  - sCR: 22
  - VGPR: 22
  - PR: 11
  - MR: 0
  - ORR: 44%

- **Bortezomib non-rel + refr (n=13)**
  - sCR: 15
  - VGPR: 23
  - PR: 38
  - ORR: 77%

- **Carfilzomib rel + refr (n=15)**
  - sCR: 7
  - VGPR: 33
  - PR: 13
  - ORR: 40%

- **Carfilzomib non-rel + refr (n=16)**
  - sCR: 13
  - VGPR: 38
  - PR: 25
  - ORR: 75%

- **Pomalidomide rel + refr (n=9)**
  - sCR: 11
  - VGPR: 22
  - PR: 11
  - ORR: 33%

- **Pomalidomide non-rel + refr (n=22)**
  - sCR: 9
  - VGPR: 27
  - PR: 32
  - MR: 5
  - ORR: 68%

Rel + refr, relapsed and refractory
Treatment exposure and patient disposition

- Three patients discontinued treatment due to AEs
  - In two patients the events were consistent with infusion reactions
  - One patient discontinued due to non study drug-related bacterial sepsis

- Deaths: 6
  - Five due to disease progression and 1 to non study drug-related bacterial sepsis
  - Deaths occurred 11–50 days after the last dose of SAR650984

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**SAR650984 dose, mg/kg q2W**

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Overall (n=31)</th>
<th>3 (n=4)</th>
<th>5 (n=3)</th>
<th>10 (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of dosing, weeks (range)</td>
<td>26 (2–84)</td>
<td>52 (2–84)</td>
<td>63 (4–71)</td>
<td>26 (4–55)</td>
</tr>
<tr>
<td>Median number of cycles(^a) administered, n (range)</td>
<td>7 (1–19)</td>
<td>8 (1–19)</td>
<td>16 (1–16)</td>
<td>26 (4–55)</td>
</tr>
<tr>
<td>Ongoing treatment(^b)</td>
<td>10 (32)</td>
<td>1 (25)</td>
<td>1 (33)</td>
<td>8 (33)</td>
</tr>
<tr>
<td>Discontinued treatment</td>
<td>21 (68)</td>
<td>3 (75)</td>
<td>2 (67)</td>
<td>16 (67)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>18 (58)</td>
<td>2 (50)</td>
<td>2 (67)</td>
<td>14 (58)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>3 (10)</td>
<td>1 (25)</td>
<td>0</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

\(^a\)1 cycle = 4 weeks
\(^b\)At least SAR650984 and lenalidomide; two patients discontinued dexamethasone due to adverse events
Progression free survival: Overall and by prior lines of therapy

Median PFS = NR (95% CI, 6.2─NR)

Median PFS = 6.2 months (95% CI, 4.80─13.33)

Median PFS = 5.8 months (95% CI, 2.10─10.30)
Conclusions

- SAR650984 with len/dex has a manageable safety profile
  - Safety findings consistent with those of individual agents
  - PK of SAR650984 and LEN appear independent
  - MTD was not reached

- SAR650984 with LEN/dex showed encouraging activity in this heavily-pretreated population
  - ORR was 58%; 63% at the SAR650984 10 mg/kg dose level
  - ORR was 50% in IMiD-rel + refr patients (n=26)
  - ORR was 40% (6/15) in CAR-rel + refr and 33% (3/9) in POM-rel + refr pts

- At 9 months follow-up, overall median PFS was 6.2 months
  - Median PFS not reached in patients who received 1–2 lines of prior therapy
Acknowledgments

- The authors would like to thank the participating patients and their families
- The authors would also like to acknowledge the work of all the research personal including the collaboration with Celgene and with the MMRC
- This study was funded by Sanofi
Response summary by prior lines of therapy

Number of prior lines of therapy

- **1–2 (n=7)**
  - sCR: 29%
  - VGPR: 57%
  - PR: 14%
  - MR: 8%
  - ORR 100%
  - CBR 100%

- **≥3 (n=24)**
  - sCR: 33%
  - VGPR: 13%
  - PR: 29%
  - MR: 6%
  - ORR 46%
  - CBR 54%

- **Overall (n=31)**
  - sCR: 6%
  - VGPR: 23%
  - PR: 29%
  - MR: 6%
  - ORR 58%
  - CBR 65%
Response summary by prior IMiD therapy

<table>
<thead>
<tr>
<th>Number of prior lines of therapy</th>
<th>IMiD rel + refr (n=26)</th>
<th>IMiD non-rel + refr (n=5)</th>
<th>Overall (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR (8%)</td>
<td>40%</td>
<td>60%</td>
<td>6%</td>
</tr>
<tr>
<td>VGPR (27%)</td>
<td>23%</td>
<td>23%</td>
<td>29%</td>
</tr>
<tr>
<td>PR (23%)</td>
<td>6%</td>
<td></td>
<td>6%</td>
</tr>
<tr>
<td>MR (8%)</td>
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ORR 50% CBR 58%

ORR 100% CBR 100%

ORR 58% CBR 65%
## Response kinetics

<table>
<thead>
<tr>
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<th>Median (range)</th>
</tr>
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<tbody>
<tr>
<td>Time to first response, weeks</td>
<td>4.14 (4.0–10.0)</td>
</tr>
<tr>
<td>Time to best response, weeks</td>
<td>8.29 (4.0–32.6)</td>
</tr>
<tr>
<td>Duration of response, months</td>
<td>9.13 (1.2–15.2)</td>
</tr>
</tbody>
</table>