Safety, pharmacokinetics, and antitumor activity findings from a phase 1b, open-label, dose-escalation and expansion study investigating RAF dimer inhibitor lifirafenib in combination with MEK inhibitor mirdametinib in patients with advanced or refractory solid tumors

Benjamin Solomon, MBBS, PhD, FRACP

On behalf of Bo Gao, Vivek Subbiah, Michael Millward, Lee Rosen, Jayesh Desai, Eric I Sbar, Neal Collins, Thuy Hoang, Xi Song, Wenlin Shao, Jaspreet Jaggi, Badreddin Edris, Paraneedharan Ramachandran, Lusong Luo, Michael Friedlander

1Peter MacCallum Cancer Centre, East Melbourne, Australia; 2Blacktown Cancer and Hematology Centre, Sydney, Australia; 3MD Anderson, Houston, TX, USA; 4Linear Clinical Research, Perth, Australia; 5UCLA, Santa Monica, CA, USA; 6SpringWorks Therapeutics, Inc., Stamford, CT, USA; 7BeiGene, San Mateo, CA, USA; 8Prince of Wales Clinical School UNSW and Prince of Wales Hospital, Sydney, Australia
Disclosure Information

Benjamin Solomon

I have the following relevant financial relationships to disclose:

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Vertical Inhibition is a Validated Strategy to Target MAPK Aberrant Tumors

Excessive cell proliferation and survival

GEFs

GAPs (eg, NF)

RAS-GTP

RAS-GDP

lifirafenib

encorafenib
dabrafenib
vemurafenib

B-RAF V600E

trametinib
binimetinib
cobimetinib

mirdametinib

MEK

ERK

MEK

ERK

RAF

RAF

RAS-GTP

RAS-GDP

Lifirafenib + Mirdametinib Lead to Sustained Inhibition of MAPK Pathway Signaling and Significant Tumor Regression

Combination led to rapid MAPK inhibition with durable and sustained pERK inhibition after multiple doses and achieved synergistic antitumor response, resulting in a 100% ORR at 1.25 mpk lifi + 5 mpk mirda in the Calu-6 model.

Lifi, lifirafenib; Mirda, mirdametinib; mpk, mg/kg.
Dose-Escalation/Dose-Finding Study Design/Schema

9 dose levels, with a DLT window in Cycle 1 of 28 days, with and without lifirafenib lead-in dosing, as follows:

- Continuous dosing
  - Level 1: **M 2 mg QD + L 15 mg QD**
  - Level 2: **M 2 mg QD + L 20 mg QD**

- 5 days on, 2-day off (5/2-day intermittent)
  - Level 3a: **M 3 mg QD + L 20 mg QD**
  - Level 4a: **M 4 mg QD + L 20 mg QD**

- Lead-in dosing (5/2-day intermittent) for 14 days, then 5/2-day intermittent dosing for each 28-day cycle
  - Level 3b: (lead-in dose of M 3 mg QD + L 10 mg QD) **M 3 mg QD + L 20 mg QD**
  - Level 3c: (lead-in dose of M 2 mg BID + L 10 mg QD) **M 2 mg BID + L 15 mg QD**
  - Level 4b: (lead-in dose of M 2 mg BID + L 10 mg QD) **M 2 mg BID + L 20 mg QD**
  - Level 4c: (lead-in dose of M 3 mg BID + L 10 mg QD) **M 3 mg BID + L 15 mg QD**
  - Level 5c: (lead-in dose of M 4 mg BID + L 10 mg QD) **M 4 mg BID + L 15 mg QD**

Objectives for Dose Escalation/Dose Finding
- Establish MTD and/or RP2D
- Evaluate PK of mirdametinib (and its active metabolite PD 0315209) in combination with lifirafenib

Study Population
- Patients with a known mutation in the MAPK pathway and a histologically or cytologically confirmed advanced tumor

BID, twice a day; DLT, dose-limiting toxicity; **L, lifirafenib; M, mirdametinib; MTD, maximum tolerated dose; PK, pharmacokinetic(s); QD, once a day; RP2D, recommended phase 2 dose.\n
### Demographics and Baseline Characteristics (N=71)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>55.9 (23-78)</td>
</tr>
<tr>
<td>Sex, male/female, n (%)</td>
<td>18 (25)/53 (75)</td>
</tr>
<tr>
<td>Race, white/other, n (%)</td>
<td>56 (79)/15 (21)</td>
</tr>
<tr>
<td>ECOG PS 0/PS 1, n (%)</td>
<td>42 (59)/29 (41)</td>
</tr>
<tr>
<td>Prior lines of therapy, median (range)</td>
<td>1 (1-8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary cancer type, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian cancer</td>
<td>31 (44)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>13 (18)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (16)</td>
</tr>
</tbody>
</table>

### Mutation Type (N=71)

<table>
<thead>
<tr>
<th>Mutation type, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>41 (57.7)</td>
</tr>
<tr>
<td>BRAF</td>
<td>13 (18.3)</td>
</tr>
<tr>
<td>BRAF-V600E</td>
<td>10 (14.1)</td>
</tr>
<tr>
<td>Non-V600</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>NRAS</td>
<td>8 (11.3)</td>
</tr>
<tr>
<td>NF1</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>CRAF/RAF1</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>RASA1</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>CIC</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>PAK2</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>H-RAS</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>

Data cutoff date: 20 January 2023. ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung carcinoma; PS, performance status.
## Treatment-Emergent Adverse Events (≥ 10% of All Events) Related to Lifirafenib and/or Mirdametinib

Data cutoff date: 20 January 2023.

<table>
<thead>
<tr>
<th>Condition</th>
<th>All TEAEs</th>
<th>Grade ≥ 3 TEAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis acneiform</td>
<td>42.3%</td>
<td>0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32.4%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>26.8%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Thrombocytopenia/Platelet count</td>
<td>18.3%</td>
<td>5.6%</td>
</tr>
<tr>
<td>decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>18.3%</td>
<td>0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>16.9%</td>
<td>0%</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>15.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>14.1%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td>14.1%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Rash</td>
<td>14.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>14.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Ejection fraction decreased</td>
<td>11.3%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Constipation</td>
<td>11.3%</td>
<td>0%</td>
</tr>
</tbody>
</table>
# Overall Summary of Safety

Data cutoff date: 20 January 2023. DLT, dose limiting toxicity; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

## Lead-in dosing occurred for 14 days as follows:
- DL 3b (M 3 mg QD + L 10 mg QD), DL 3c (M 2 mg BID + L 10 mg QD), DL 4b (M 2 mg BID + L 10 mg QD), and DL 4c (M 3 mg BID + L 10 mg QD).

## Number (%) of Patients

<table>
<thead>
<tr>
<th></th>
<th>Without Lead-In Dosing (n=31)</th>
<th>With Lead-In Dosing (^a) (n=40)</th>
<th>Overall (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE</td>
<td>31 (100)</td>
<td>40 (100)</td>
<td>71 (100)</td>
</tr>
<tr>
<td>TEAE related to lifirafenib</td>
<td>28 (90.3)</td>
<td>34 (85.0)</td>
<td>62 (87.3)</td>
</tr>
<tr>
<td>TEAE related to mirdametinib</td>
<td>28 (90.3)</td>
<td>35 (87.5)</td>
<td>63 (88.7)</td>
</tr>
<tr>
<td>SAE</td>
<td>17 (54.8)</td>
<td>13 (32.5)</td>
<td>30 (42.3)</td>
</tr>
<tr>
<td>SAE related to lifirafenib</td>
<td>7 (22.6)</td>
<td>3 (7.5)</td>
<td>10 (14.1)</td>
</tr>
<tr>
<td>SAE related to mirdametinib</td>
<td>4 (12.9)</td>
<td>4 (10.0)</td>
<td>8 (11.3)</td>
</tr>
<tr>
<td>TEAE of Grade ≥ 3</td>
<td>17 (54.8)</td>
<td>15 (37.5)</td>
<td>32 (45.1)</td>
</tr>
<tr>
<td>DLT TEAE</td>
<td>6 (19.4)</td>
<td>1 (2.5)</td>
<td>7 (9.9)</td>
</tr>
<tr>
<td>TEAE leading to dose modification</td>
<td>22 (71.0)</td>
<td>19 (47.5)</td>
<td>41 (57.7)</td>
</tr>
<tr>
<td>TEAE leading to treatment discontinuation</td>
<td>2 (6.5)</td>
<td>2 (5.0)</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>TEAE leading to death (^b)</td>
<td>1 (3.2)</td>
<td>3 (7.5)</td>
<td>4 (5.6)</td>
</tr>
</tbody>
</table>

\(^a\) Lead-in dosing occurred for 14 days as follows: DL 3b (M 3 mg QD + L 10 mg QD), DL 3c (M 2 mg BID + L 10 mg QD), DL 4b (M 2 mg BID + L 10 mg QD), and DL 4c (M 3 mg BID + L 10 mg QD).

\(^b\) These TEAEs leading to death were considered by the investigator to be not related to study treatment.
Clinical Activity During Dose Escalation in All Evaluable Patients

According to RECIST v1.1

Data cutoff date: 20 January 2023.

Best Overall Response \(^a\)
(n=62)

- 14 patients (22.6%) had confirmed objective responses

Changes in Tumor Response Over Time \(^a\)
(n=62)

\(^a\) According to RECIST v1.1
Data cutoff date: 20 January 2023.
Clinical Activity During Dose Escalation in All Evaluable Patients By Tumor Types

Best Overall Response $^a$  
($n=62$)

- LGSOC
- NSCLC
- Endometrial Cancer
- CRC
- Other tumor types

$^a$ According to RECIST v1.1  
Data cutoff date: 20 January 2023.
Clinical Activity During Dose Escalation in All Evaluable Patients By Mutation Types

Best Overall Response \(^a\)  
(n=62)

According to RECIST v1.1  
Data cutoff date: 20 January 2023.

Best Response in Target Lesion %

-100% -80% -60% -40% -20%  0%  20%  40%  60%  80%

-20% -40% -60% -80% -100%

BRAF V600E  
BRAF fusions  
KRAS Mutations  
NRAS mutations  
Other MAPK aberrations

\(^a\) According to RECIST v1.1  
Data cutoff date: 20 January 2023.
Clinical Activity During Dose Escalation in Evaluable Patients With LGSOC

**Best Overall Response by Mutation Type in Patients With LGSOC**
(n=17)

- 10 patients with LGSOC (58.8%) had objective responses; median duration of treatment ~26 months; 14/17 pts still on treatment as of 20 Jan 2023.

**Changes From Baseline in Tumor Response Over Time**
(n=17)

Data cutoff date: 20 January 2023. LGSOC, low-grade serous ovarian carcinoma.

* According to RECIST v1.1
* Pts still on treatment at DCO
Clinical Activity During Dose Escalation in Evaluable Patients with NSCLC and Endometrial Cancer

**NSCLC (n=11)**

- BRAF V600E
- HRAS G12D
- KRAS Mutations
- NRAS Q61K

2/11 patients with NSCLC (18%) had objective responses

**Endometrial Cancer (n=4)**

- BRAF fusion
- KRAS Mutations

2/4 patients with endometrial cancer (50.0%) had objective responses

Data cutoff date: 20 January 2023.
NSCLC, non-small cell lung cancer.

\* According to RECIST v1.1.
75-year-old Endometrial Cancer Patient With KRAS G12A Mutation

Diagnosis:
Metastatic endometrial cancer (KRAS G12A mutation)

Prior Treatment:
11/2017 – 01/2018: neoadjuvant carboplatin + paclitaxel x 3 - PR
02/2018 – 03/2018: adjuvant carboplatin + paclitaxel x 3 - CR
04/2020 – 08/2020: carboplatin + liposomal doxorubicin - PR
01/2021 – 03/2021: OX40 inhibitor - PD
04/2021 – 05/2021: OX40 inhibitor + PD-1 - PD
05/2021 – 06/2021: PARPi + TMZ, discontinued due to Grade 4 thrombocytopenia
11/2021 - now: lifirafenib + mirdametinib – PR
continue on treatment as of Jan 20, 2023
Conclusions

• Lifirafenib in combination with mirdametinib demonstrated a favorable safety profile, with limited DLTs and discontinuations.

• Lifirafenib plus mirdametinib showed antitumor activity in patients with various KRAS, NRAS, and BRAF mutations across several solid tumor types:
  ➢ LGSOC appears to be very sensitive to this combination treatment, with BRAF mutations seeming to have deeper and faster responses compared with other MAPK pathway aberrations;
  ➢ Other sensitive tumor types included NSCLC (especially with NRAS and BRAF mutations) and endometrial cancer with KRAS and BRAF mutations

• The combination of lifirafenib and mirdametinib demonstrated a desirable risk-benefit profile and warrants further clinical investigation; the dose-expansion portion of the study is planned to start in the second half of 2023 with a focus on biomarker selected patient population with a tumor agnostic approach.
Acknowledgments

We thank the patients and their families, investigators, and site staff for participating in this study, which is sponsored by BeiGene.

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Backup Slides
### Serious Adverse Events (≥ 2 Patients) by Preferred Term

Data cutoff date: 20 January 2023. 5/2, days dosing followed by a 2-day break; BID, twice a day; L, lifirafenib; M, mirdametinib; QD, once a day; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

**Preferred Term** | **Without Lead-In Dosing (n=31)** | **With Lead-In Dosing a (n=40)** | **Overall N=71**
---|---|---|---
**Patients with at least 1 SAE** | | | |
Pyrexia | 2 (33.3) | 5 (62.5) | 6 (54.5) | 4 (66.7) | 3 (25.0) | 1 (33.3) | 4 (50.0) | 4 (36.4) | 1 (14.3) | 30 (42.3)
Thrombocytopenia/Platelet count decreased | 1 (16.7) | 1 (12.5) | 0 | 0 | 2 (33.3) | 0 | 0 | 0 | 0 | 0 | 4 (5.6)
Small intestinal obstruction | 0 | 1 (12.5) | 1 (9.1) | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | 0 | 3 (4.2)
Fibrile neutropenia | 1 (16.7) | 0 | 0 | 0 | 1 (8.3) | 0 | 0 | 0 | 0 | 0 | 2 (2.8)
Urinary tract infection | 0 | 0 | 1 (9.1) | 0 | 0 | 0 | 0 | 0 | 1 (9.1) | 0 | 2 (2.8)
Constipation | 0 | 0 | 0 | 0 | 0 | 1 (33.3) | 0 | 0 | 2 (2.8)
Large intestinal obstruction | 0 | 0 | 0 | 0 | 1 (16.7) | 1 (8.3) | 0 | 0 | 0 | 2 (2.8)
Biliary tract infection | 0 | 1 (12.5) | 1 (9.1) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.8)
COVID-19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.8)

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a Lead-in dosing occurred for 14 days as follows: DL 3b (M 3 mg QD + L 10 mg QD), DL 3c (M 2 mg BID + L 10 mg QD), DL 4b (M 2 mg BID + L 10 mg QD), and DL 4c (M 3 mg BID + L 10 mg QD).
Most commonly reported (incidence > 3%) SAEs included pyrexia (8.5%), thrombocytopenia/platelet count decreased (5.6%), and small intestinal obstruction (4.2%)

Of the 30 patients who had SAEs, serious events related to lifirafenib were reported for 10 (14.1%) patients and serious events related to mirdametinib were reported for 8 (11.3%) patients

Most commonly reported treatment-related SAEs were thrombocytopenia (4 [5.6%]; 3 related to lifirafenib, 1 to both drugs; 0 after lead-in dose) and pyrexia (4 [5.6%]; all related to both study drugs; 1 after lead-in dose)
67-Year-Old Patient With NSCLC (adenocarcinoma)  
**NRAS Q61K Mutation**

**Diagnosis:**
67 year old male, Stage IV at presentation - Aug 2021

**Treatment:**
Prior therapy – Aug 2021 - Dec 2021; carboplatin/paclitaxel/atezolizumab/bevacizumab  
  Best response – PD  
  RT to bone metastases – skull/sternum/spine/rib

Referred for BGB283-PD0325901-AU-001 trial in February 2022

Currently at Cycle 13; best response as of 20 Jan 2023 - PR
67-Year-Old Patient With NSCLC (adenocarcinoma) NRAS Q61K Mutation (continued)

Screening 23 Feb 2022

Prior to C13D1 22 Feb 2023
## Overall Summary of Safety

Data cutoff date: 20 January 2023. 5/2, 5 days dosing followed by a 2-day break; BID, twice a day; DLT, dose limiting toxicity; L, lifirafenib; QD, once a day; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Without Lead-in Dosing</th>
<th>Number (%) of Patients</th>
<th>With Lead-in Dosing</th>
<th>Number (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DL 1 M 2 mg QD L 15 mg QD n=6</td>
<td></td>
<td>DL 3b M 3 mg QD L 20 mg QD n=12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DL 2 M 2 mg QD L 20 mg QD n=8</td>
<td></td>
<td>DL 3c M 2 mg BID L 15 mg QD n=3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DL 3a M 3 mg QD L 20 mg QD 5/2 n=11</td>
<td></td>
<td>DL 4b M 2 mg BID L 20 mg QD n=7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DL 4a M 4 mg QD L 20 mg QD 5/2 n=6</td>
<td></td>
<td>DL 4c M 3 mg BID L 15 mg QD n=11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DL 5c M 4 BID L 15 mg QD</td>
<td></td>
<td>Overall N=71</td>
<td></td>
</tr>
<tr>
<td>TEAE</td>
<td>6 (100) 8 (100) 11 (100) 6 (100)</td>
<td></td>
<td>12 (100) 3 (100) 7 (100) 11 (100) 7 (100)</td>
<td>71 (100)</td>
</tr>
<tr>
<td>TEAE related to lifirafenib</td>
<td>5 (83.3) 8 (100) 10 (90.9) 5 (83.3)</td>
<td></td>
<td>10 (83.3) 3 (100) 5 (71.4) 9 (81.8) 7 (100)</td>
<td>62 (87.3)</td>
</tr>
<tr>
<td>TEAE related to mirdametinib</td>
<td>5 (83.3) 7 (87.5) 10 (90.9) 6 (100)</td>
<td></td>
<td>10 (83.3) 3 (100) 6 (85.7) 9 (81.8) 7 (100)</td>
<td>63 (88.7)</td>
</tr>
<tr>
<td>SAE</td>
<td>2 (33.3) 5 (62.5) 6 (54.5) 4 (66.7)</td>
<td></td>
<td>3 (25.0) 1 (33.3) 4 (57.1) 4 (36.4) 1 (14.3)</td>
<td>30 (42.3)</td>
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<tr>
<td>SAE related to lifirafenib</td>
<td>2 (33.3) 2 (25.0) 1 (9.1) 2 (33.3)</td>
<td></td>
<td>1 (8.3) 0 1 (14.3) 1 (9.1) 0</td>
<td>10 (14.1)</td>
</tr>
<tr>
<td>SAE related to mirdametinib</td>
<td>2 (33.3) 1 (12.5) 1 (9.1) 0</td>
<td></td>
<td>1 (8.3) 1 (8.3) 1 (8.3) 1 (8.3) 0</td>
<td>8 (11.3)</td>
</tr>
<tr>
<td>TEAE of Grade ≥ 3</td>
<td>1 (16.7) 6 (75.0) 5 (45.5) 5 (83.3)</td>
<td></td>
<td>2 (16.7) 1 (33.3) 4 (57.1) 5 (45.5) 3 (42.9)</td>
<td>32 (45.1)</td>
</tr>
<tr>
<td>DLT TEAE</td>
<td>1 (16.7) 1 (12.5) 2 (18.2) 2 (33.3) 1 (8.3) 0 0 0 0</td>
<td></td>
<td>7 (9.9)</td>
<td></td>
</tr>
<tr>
<td>TEAE leading to dose modification</td>
<td>2 (33.3) 6 (75.0) 9 (81.8) 5 (83.3) 5 (41.7) 1 (33.3) 3 (42.9) 6 (54.5) 4 (57.1)</td>
<td></td>
<td>41 (57.7)</td>
<td></td>
</tr>
<tr>
<td>TEAE leading to treatment discontinuation</td>
<td>0 1 (12.5) 1 (9.1) 0</td>
<td></td>
<td>0 1 (33.3) 1 (14.3) 0 0</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>TEAE leading to death</td>
<td>0 0 1 (9.1) 0</td>
<td></td>
<td>1 (8.3) 0 1 (14.3) 1 (9.1) 0</td>
<td>4 (5.6)</td>
</tr>
</tbody>
</table>

aData cutoff date: 20 January 2023. 5/2, 5 days dosing followed by a 2-day break; BID, twice a day; DLT, dose limiting toxicity; L, lifirafenib; QD, once a day; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

a Lead-in dosing occurred for 14 days as follows: DL 3b (M 3 mg QD + L 10 mg QD), DL3c (M 2 mg BID + L 10 mg QD), DL 4b (M 2 mg BID + L 10 mg QD), and DL 4c (M 3 mg BID + L 10 mg QD).

b These TEAEs leading to death were considered by the investigator to be not related to study treatment.