A PhII study of bemcentinib, a first-in-class selective AXL kinase inhibitor, in combination with pembrolizumab, in pts with previously-treated advanced NSCLC: Updated clinical & translational analysis

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Disclosures

**Personal financial interests:**
• Travel expenses: BerGenBio

**Institutional financial interests:** BerGenBio, AstraZeneca, BMS, Genmab, GSK, Lilly, Roche
Study rationale
Multi-arm study in 2L NSCLC of selective AXL inhibitor bemcentinib in combination with pembrolizumab

- AXL drives tumor **EMT and resistance to CTL-mediated tumor cell killing**\(^1\)
- AXL receptor tyrosine kinase is **negatively prognostic** in many cancers including NSCLC\(^2\)
- AXL expression is associated with **anti-PD-1 therapy failure** in melanoma patients\(^3\)
- AXL is expressed by immuno-suppressive **tumor-associated M2 macrophages and dendritic cells**\(^4\)
- Bemcentinib is a first-in-class highly **selective, potent oral small molecule AXL kinase inhibitor**
- Bemcentinib reverses EMT, repolarizes TAMs and potentiates **immunotherapy** in mouse models\(^4\)

\(^1\)Terry, 2019; \(^2\)Ishikawa, 2012, \(^3\)Hugo, 2016; Davidsen, 2017; \(^4\)Ludwig, 2018, Davidsen, submitted
Study design
Multi-arm study in 2L NSCLC of selective AXL inhibitor bemcentinib in combination with pembrolizumab

Cohort A
- Previously treated with a platinum-containing chemotherapy
- CPI-naïve
- Demonstrable PD

Interim Analysis
Cohort A
Stage 1
N=22 patients
(each patient has the potential for at least 24 weeks follow-up)

Final Analysis
Cohort A
Stage 2
N=48 patients
(each patient has the potential for at least 24 weeks follow-up)

Cohort B
- Previously treated with PD-L1 or PD-1 inhibitor mono-therapy
- ≥12 weeks clinical benefit followed by PD

Interim Analysis
Cohort B
Stage 1
N=16 patients
(each patient has the potential for at least 24 weeks follow-up)

Final Analysis
Cohort B
Stage 2
N=29 patients
(each patient has the potential for at least 24 weeks follow-up)

Cohort C
- Previous 1st line combination checkpoint inhibitor + platinum doublet
- ≥12 weeks clinical benefit on 1st line therapy followed by PD

Interim Analysis
Cohort C
Stage 1
N=13 patients
(each patient has the potential for at least 24 weeks follow-up)

Final Analysis
Cohort C
Stage 2
N=29 patients
(each patient has the potential for at least 24 weeks follow-up)

Previously-reported survival data in Cohort A¹

<table>
<thead>
<tr>
<th>Cohort</th>
<th>mOS</th>
<th>12-mo OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort A – cAXL +ve</td>
<td>17.3 mo</td>
<td>79%</td>
</tr>
<tr>
<td>Cohort A – cAXL -ve</td>
<td>12.4 mo</td>
<td>60%</td>
</tr>
</tbody>
</table>

¹ Gabra, et al. Next Gen Immuno-Oncology Congress, June 2020
Safety profile of combination across all cohorts

Most frequently occurring treatment-related* AEs (≥10% dosed patients) n=73

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>All Grades n (%)</th>
<th>Grades ≥3 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine aminotransferase increased</td>
<td>24 (33%)</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23 (32%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>22 (30%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>12 (16%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12 (16%)</td>
<td>0</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>10 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>9 (12%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>QT prolonged</td>
<td>9 (12%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (12%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (12%)</td>
<td>0</td>
</tr>
</tbody>
</table>

* AEs were reported as possibly, probably or definitely related to bemcentinib and/or pembrolizumab.

Safety Summary

- Treatment combination was well tolerated
- Safety profile of combination treatment consistent with that of individual drugs
- Treatment-related AEs generally mild and reversible
- Two patients reported grade 4 and no patients reported grade 5 TRAEs

Safety cut-off: July 2020
## Study design

Multi-arm study in 2L NSCLC of selective AXL inhibitor bemcentinib in combination with pembrolizumab

### Cohort A
- Previously treated with a platinum-containing chemotherapy
- CPI-naïve
- Demonstrable PD

### Cohort B
- Previously treated with PD-L1 or PD-1 inhibitor mono-therapy
- ≥12 weeks clinical benefit followed by PD

### Cohort C
- Previous 1st line combination checkpoint inhibitor + platinum doublet
- ≥12 weeks clinical benefit on 1st line therapy followed by PD

### Interim Analysis

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Stage</th>
<th>Patients</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>N=22</td>
<td>≥24 weeks</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
<td>N=16</td>
<td>≥24 weeks</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>N=13</td>
<td>≥24 weeks</td>
</tr>
</tbody>
</table>

### Final Analysis

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Stage</th>
<th>Patients</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2</td>
<td>N=48</td>
<td>≥24 weeks</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td>N=29</td>
<td>≥24 weeks</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>N=29</td>
<td>≥24 weeks</td>
</tr>
</tbody>
</table>
Composite AXL score (cAXL)

High AXL expression on *tumour* cells

High AXL expression on *immune* cells

Examples of positively-stained *tumor* and *immune* cells, respectively
# Patient disposition and demographics

**Cohort B (stage 1)**

<table>
<thead>
<tr>
<th>Patient demographics</th>
<th>n=16</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>64.5</td>
<td>40-76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG at screen</th>
<th>0</th>
<th>6 (38%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>10 (63%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Female</th>
<th>3 (19%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>13 (81%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Smoker</th>
<th>8 (50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ex-smoker</td>
<td>8 (50%)</td>
</tr>
<tr>
<td></td>
<td>Never smoked</td>
<td>0</td>
</tr>
</tbody>
</table>

**Biomarkers**

- **cAXL status**
  - n = 12*
  - cAXL positive 58%
  - cAXL negative 42%

- **PD-L1 status**
  - n = 12*
  - TPS \( \geq 50\% \) 33%
  - TPS <1% 42%
  - TPS 1-49% 25%

* Of 15 radiologically evaluable patients, 3 not evaluable for AXL or PDL1
## Patient outcomes

### Activity and time on treatment Cohort B1 patients evaluable for cAXL

<table>
<thead>
<tr>
<th>Prior lines</th>
<th>Prior therapies</th>
<th>PD-L1 (%)</th>
<th>cAXL status</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>PltCT, A/O</td>
<td>65</td>
<td>+</td>
</tr>
<tr>
<td>1</td>
<td>P</td>
<td>20</td>
<td>+</td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>95</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>PltCT, P</td>
<td>15</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>PltCT, N</td>
<td>100</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>PltCT, P</td>
<td>95</td>
<td>+</td>
</tr>
<tr>
<td>1</td>
<td>I/N</td>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>PltCT, P</td>
<td>35</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>PltCT/D, PltCT, N</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>PltCT, A</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>PltCT, O</td>
<td>NE</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>PltCT, O</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

**Prior therapies**

PltCT: platinum-based chemotherapy  
D: docetaxel  
P: pembrolizumab  
A: atezolizumab  
N: nivolumab  
I: ipilimumab  
O: other

**Response first achieved**

- **PR**: Positive Response  
- **SD**: Stable Disease  
- **PD**: Progression Disease
Patient outcomes
Progression-free survival in Cohort B1 patients evaluable for cAXL

HR = 0.22 (95% CI = 0.04-1.26)
p value = 0.066
Clinical translational findings
Whole tumor gene expression of Cohort B1 patients benefiting from bemcentinib-pembrolizumab

RNAseq analysis identifies gene signatures from benefiting patients:

- Increased AXL expression
- Genes associated with tumor cell EMT
- Presence of TREM2+ TAMs
- Presence of CCR7+ mregDC1

Volcano Plot: Differential gene expression analysis of patients showing benefit (n=5) vs patients with PD (n=3)

1 Liberzon, Cell Systems 2015; 2 Katzenelenbogen Cell 2020, Molgora Cell 2020; 3 Maier Nature 2020

#tumor-associated macrophages
##regulatory dendritic cells
Proposed mechanism
AXL+ suppressive myeloid cells drive T cell dysfunction

• AXL promotes tumor-cell EMT and recently-described regulatory myeloid cells:
  - AXL+ TREM2+ TAM$^{1,2}$
  - AXL+ CCR7+ mregDC$^{1}$

• AXL expression in these cells promotes T cell dysfunction/exhaustion$^{2}$

• Bemcentinib inhibition of AXL reverses this state of immune suppression in the microenvironment, and promotes checkpoint inhibitor re-engagement

Conclusions

- Bemcentinib-pembrolizumab combination well tolerated and clinically active in CPI-refractory cAXL+ NSCLC
- Recruitment ongoing in CPI-refractory and chemo-CPI-refractory patient populations
- Bemcentinib may reverse acquired resistance to checkpoint inhibition by targeting AXL+ TREM2 macrophages and regulatory DCs
- Findings support further development of AXL inhibition with bemcentinib to extend efficacy of immunotherapy in biomarker-selected NSCLC
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