Reprogramming of the Lung Cancer Tumor Microenvironment With The AXL Inhibitor Bemcentinib

Session: Immunotherapy Strategy For NSCLC

Non-Small Cell Lung Cancer Drug Development Summit 2021
15th July 2021

Presenter:
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Chief Medical Officer, BerGenBio

On behalf of BerGenBio
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Copyright of all published material, including photographs, drawings and images in this presentation remain with BerGenBio and relevant third parties, as appropriate. Consequently, no reproduction in any form of the presentation, or parts thereof, is permitted without the prior written permission, and only with appropriate acknowledgements.
AXL drives “aggressive” cancer, as a maladaptation of a coordinated micro-environmental apoptosis programme
**AXL expression is an independent adverse prognostic factor in a broad variety of cancers**

- **Strong AXL expression correlates with poor survival rate**
  - **Breast carcinoma**
  - **Acute Myeloid Leukaemia**
  - **Lung adenocarcinoma (NSCLC)**
  - **Pancreatic ductal adenocarcinoma**

- **Broad evidence of AXL linked with poor prognosis**
  - **Astrocytic brain tumours**
  - **Breast cancer**
  - **Gallbladder cancer**
  - **GI**
    - Colon cancer
    - Oesophageal cancer
    - Gastric cancer
  - **Gynaecological**
    - Ovarian cancer
    - Uterine cancer
  - **Haematological**
    - AML
    - CLL
    - CML
  - **Melanoma**
  - **Mesothelioma**
  - **NSCLC**
  - **Pancreatic cancer**
  - **Sarcomas**
    - Ewing Sarcoma
    - Kaposis sarcoma
    - Liposarcoma
    - Osteosarcoma
  - **Skin SCC**
  - **Thyroid cancer**
  - **Urological**
    - Bladder cancer
    - Prostate cancer
    - RCC

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1 Gjerdrum, 2010; 2 Ishikawa, 2012; 3 Ben-Battala, 2013; 4 Song, 2010, 5 supported by > 100 publications
AXL activation is a key survival mechanism ‘hijacked’ by aggressive cancers: drives therapy resistance, immune-suppression & metastasis

very low expression under healthy physiological conditions

overexpressed in response to hypoxia, inflammation, cellular stress & drug treatment

overexpression correlates with worse prognosis in most cancers

AXL upregulated and activated on immune cells and suppresses the innate immune response
- M1 to M2 macrophage polarisation\(^1\)
- Decreased antigen presentation by DCs\(^2\)
- Prevent CD8+ T cell mediated cell death\(^3\)
- Activates Treg cells through DCs and macrophages\(^4\)

AXL upregulated and activated on the tumour cell and causes cancer escape and survival
- Acquired drug resistance
- Immune cell death resistant
- Metastasis
- AXL is a unique type I interferon (IFN) response checkpoint

DC - dendritic cells  Treg – Regulatory T Cell
Bemcentinib – Oral small molecule TKI, highly selective for AXL

- Highly selective, orally bioavailable small molecule, administered once a day, in phase II clinical trials
- Clinical PoC in NSCLC & AML, broad ILS support
- Excellent safety and biomarker correlation reported

Bemcentinib was formerly known as BGB324
AXL modulates innate immuno-suppression, as well as tumor cell aggression.
The role of AXL in Cancer I/O resistance

**AXL is prevalent in TAMs**
Pro-tumoural, immune-suppressive tumour associated macrophages (TAMs) are rich in AXL but not Mer (Jim Lorens lab, unpublished data).

**↓ antigen presentation by DCs, NK cell activity**
Paolino 2014 et al (2014) found that inhibition of AXL increased NK cell activity and their ability to eliminate metastases.
Kurowska-Stolarska et al (2017) demonstrate that AXL acts as off-switch for DCs.

**↓ T-cell mediated killing**
Pre-treatment of mesenchymal tumour cells with bemcentinib increase T-cell mediated killing due to more efficient immunological synapse (Chouaib lab, unpublished data).
Sakemura et al reported at ASH 2018 that AXL targeting increases CAR-T therapy efficacy.

**Resistance to PD-1 inhibitors in patients**
Hugo et al Cell 2016: Identified a transcriptional signature related to innate anti-PD-1 resistance in melanoma: AXL is one of top differentially expressed genes in non-responders.

Axl-activity associated with decreased activation of TAMs (Paolino et al 2014)
Increased Axl-expression associated with de-novo resistance to PD-1 inhibitors (Hugo et al 2016)
Axl-inhibition may increase antigen presentation from dendritic cells and increase efficacy of PD-1/L1 blockade (Hugo et al 2016)
Tumours mobilise AXL in immune-suppressive myeloid cells

AXL is expressed on tumour microenvironment resident suppressive myeloid cells

Source: Davidsen et al – in preparation
AXL acts as off-switch for dendritic cells (DCs)

1. Innate immune activation through toll-like receptor (TLR) signalling triggers AXL upregulation in DCs
   - miR-34a downregulates AXL
   - ↓miR-34a → ↑AXL

2. AXL signalling in DCs, via INF/STAT pathway, leads to expression of DC negative regulators SOCS1/3

Antigen presentation by DCs (red) to T-cells (green) is reduced when AXL is active

AXL is off-switch for DCs

AXL drives tumour cell escape from checkpoint inhibitors

Source: Chouaib, 2014; Hugo, 2016
Executing a Broad Development Program for Bemcentinib

- **Relapsed MDS**
- **Relapsed NSCLC**
- **1L Metastatic Melanoma**
- **1L Metastatic Mesothelioma**
- **1L COVID19**
- **1L Pancreas**
- **1L Melanoma**
- **1L & Relapsed NSCLC**
- **r/r AML**

Bemcentinib foundation for cancer therapy

Monotherapy

- + checkpoint inhibitors
- + chemotherapy
- + targeted therapy
- + epigenetic therapy (HMA)
NSCLC: AXL and the role of Bemcentinib in facilitating the response to checkpoint inhibition
• AXL is a recognized adverse prognostic factor and resistance mechanism in NSCLC\(^1\)

• Bemcentinib is a first-in-class highly selective, potent, and orally bioavailable, small molecule AXL kinase inhibitor

• Bemcentinib reverses EMT, repolarizes TAMs and potentiates efficacy of immunotherapy in murine cancer models\(^2\)

\(^1\)Hugo, 2016 \(^2\)Ludwig, 2018
Bemcentinib and NSCLC: opportunities

- Monotherapy
- Pembrolizumab Combination
- Docetaxel Combination
- Erlotinib Combination
Non-small cell lung cancer: not one disease, but many

Then

Histology-Based Subtyping

Now


Slide credit: clinicaloptions.com
Treatment landscape for non-small cell lung cancer *

Non-squamous non-small cell lung cancer 2020

Molecular driver positive

Targeted therapy
EGFR
ALK
ROS1
BRAF
TRK
RET
MET
KRAS G12C

1st line

2nd line +

Non-molecular driven NSCLC

PD-L1 <50%

Platinum/
Pemetrexed/
Pembrolizumab

• Atezo/carbo/nab-P
• Carbo/taxol/bev/atezo
• Nivo/ipi/platinum/pem

Maintenance

2L UNMET NEED

PD-L1 ≥ 50%

Pembrolizumab

2L UNMET NEED

Platinum/pemetrexed

3L UNMET NEED

* ESMO guidelines Sep 2020
Composite AXL score (cAXL)

High AXL expression on *tumour* cells

Examples of positively-stained *tumor* and *immune* cells, respectively

High AXL expression on *immune* cells
Tumour infiltrating AXL+ macrophages interact with CD8+ T cells and T\textsubscript{regs} in pre-treatment biopsy from responding patient

\[\text{PANCK AXL CD68 FoxP3 CD8}\]

\[\text{\downarrow Axl+ macrophage interacting with CD8+ T cells}\]

\[\text{\downarrow Axl+ macrophage interacting with regulatory T cell}\]

\[\text{\rightarrow Regulatory T cell interacting with CD8+ T cell}\]

Krebs et al SITC 2019
# NCT03184571 /BGBC008: Phase II clinical trial of selective AXL inhibitor Bemcentinib in combination with Pembrolizumab:
Open-label multi-center single arm phase II study

<table>
<thead>
<tr>
<th>Cohort A</th>
<th>Interim Analysis</th>
<th>Final Analysis</th>
</tr>
</thead>
</table>
| • Previously treated with a platinum containing chemotherapy  
• CPI-naïve  
• Has PD at screening | Cohort A  
Stage 1  
N=22 patients  
(each patient has the potential for at least 24 weeks follow-up) | Cohort A  
Stage 2  
N=48 patients  
(each patient has the potential for at least 24 weeks follow-up) |

<table>
<thead>
<tr>
<th>Cohort B</th>
<th>Interim Analysis</th>
<th>Final Analysis</th>
</tr>
</thead>
</table>
| • Previously treated with a mono therapy PD-L1 or PD-1 inhibitor  
• Must have had disease control on most recent treatment  
• Has PD at screening | Cohort B  
Stage 1  
N=16 patients  
(each patient has the potential for at least 24 weeks follow-up) | Cohorts B  
Stage 2  
N=29 patients  
(each patient has the potential for at least 24 weeks follow-up) |

<table>
<thead>
<tr>
<th>Cohort C</th>
<th>Interim Analysis</th>
<th>Final Analysis</th>
</tr>
</thead>
</table>
| • Previously treated 1st line with a combination of checkpoint inhibitor + platinum-containing chemotherapy  
• Must have had disease control on 1st line therapy  
• Has PD at screening | Cohorts C  
Stage 1  
N=13 patients  
(each patient has the potential for at least 24 weeks follow-up) | Cohorts C  
Stage 2  
N=29 patients  
(each patient has the potential for at least 24 weeks follow-up) |
Patient Disposition and Demographics

Patient disposition  N
---
Screened          74
Enrolled          50
Evaluable         44
Ongoing           4

Patient demographics  N (%)
---
Age
Median    65
Range     39-82

ECOG at screen
0          22 (44)
1          28 (56)

Sex
Female    20 (40)
Smoker    10 (20)
Ex-smoker 29 (58)
Never smoked 10 (20)
Unknown  1 (2)

Disease mutations  N (%)
---
None             36 (72)
KRAS             7 (14)
TP53             2 (4)
EGFR             3 (6)
Other            4 (8)

Biomarkers

cAXL status
n = 30
- cAXL Positive
- cAXL Negative

PD-L1 status
n = 37
- Negative (TPS <1%)
- Positive (TPS 1-49%)
- Subset: (TPS 1-10%) 24%
- Strong Positive (TPS ≥50%)

*Data cutoff: 17 Apr 2020*
Time on treatment in patients evaluable for cAXL

Responses in cAXL positive patients
- Partial Response: 27%
- Stable Disease: 33%
- Progressive Disease: 40%

Responses in cAXL negative patients
- Partial Response: 7%
- Stable Disease: 33%
- Progressive Disease: 60%
Enhanced survival in cAXL +ve patients with addition of Bemcentinib to Pembrolizumab

AXL is an adverse prognostic biomarker

mPFS 8.4 months in cAXL+ patients

- 4-fold improvement in PFS in cAXL +ve vs. cAXL -ve patients.
- 12 mo OS in cAXL positive patients 79% vs 60% in cAXL negative patients
- Clinical benefit reflected in mOS of cAXL +ve patients vs. cAXL -ve
- cAXL -ve patient survival data is comparable to historic controls

Data cut-off: 17-April-2020

CheckMate-057: Borghaei et al, NEJM 2015

Cohort | mOS | 12-mo OS
--- | --- | ---
Cohort A – cAXL +ve pts** | 17.3 mo* | 79%
Cohort A – cAXL -ve pts** | 12.4 mo* | 60%
BGB Cohort A – all pts** | 12.6 mo* | 64%* (up to 67%)
CheckMate-057 (Opdivo) | 12.2 mo | 51%
KEYNOTE-010 (Keytruda) | 10.4 mo | 43.2%

*OS data still maturing, current calculation (cut-off survival: 28-May-2020)
**pts who have been on study treatment for at least 1 cycle (n=42)
# BGB08: Study Design

Open-label multi-center single arm phase II study

## Cohort A
- Previously treated with a platinum containing chemotherapy
- CPI-naïve
- Has PD at screening

## Cohort B
- Previously treated with a mono therapy PD-L1 or PD-1 inhibitor
- Must have had disease control on most recent treatment
- Has PD at screening

## Cohort C
- Previously treated 1st line with a combination of checkpoint inhibitor + platinum-containing chemotherapy
- Must have had disease control on 1st line therapy
- Has PD at screening

### Interim Analysis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cohort</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cohort A</td>
<td>N=22 patients</td>
</tr>
<tr>
<td>2</td>
<td>Cohort A</td>
<td>N=48 patients</td>
</tr>
<tr>
<td>1</td>
<td>Cohort B</td>
<td>N=16 patients</td>
</tr>
<tr>
<td>2</td>
<td>Cohort B</td>
<td>N=29 patients</td>
</tr>
<tr>
<td>1</td>
<td>Cohort C</td>
<td>N=13 patients</td>
</tr>
<tr>
<td>2</td>
<td>Cohort C</td>
<td>N=29 patients</td>
</tr>
</tbody>
</table>

(Each patient has the potential for at least 24 weeks follow-up)
CHECK POINT INHIBITOR REFRACTORY PATIENTS: precise and specific definition

**Initial clinical benefit on prior anti-PD(L)1 therapy**
- Anti-PD(L)1 monoclonal antibody as monotherapy or combination therapy
- **Clinical benefit** (CR, PR, SD) lasting for at least 12 weeks
- At least 2 doses of anti-PD(L)1

**Progression**
- Confirmed PD (RECIST v1.1)
- Progression occurred within 12 weeks of last dose of anti-PD(L)1 therapy

**IO-refractory patient enters trial**
- Enrolment within 12 weeks of initial PD
- No administration of other therapy between last dose of anti PD-1/L1 mAb and commencement of clinical trial agent
### Patient disposition and demographics

**Cohort B (stage 1)**

**Patient demographics**

<table>
<thead>
<tr>
<th></th>
<th>n=16</th>
</tr>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
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<tr>
<td>Median</td>
<td>64.5</td>
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<tr>
<td>Range</td>
<td>40-76</td>
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<tr>
<td><strong>ECOG at screen</strong></td>
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</tr>
<tr>
<td>0</td>
<td>6 (38%)</td>
</tr>
<tr>
<td>1</td>
<td>10 (63%)</td>
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<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>Male</td>
<td>13 (81%)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>8 (50%)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>8 (50%)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>0</td>
</tr>
</tbody>
</table>

**Biomarkers**

**cAXL status**

- cAXL positive: 58%
- cAXL negative: 42%

**PD-L1 status**

- TPS >50%: 33%
- TPS 1-49%: 25%
- TPS <1%: 42%

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

Spicer SITC 2020
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
SD
SD
PD

Previous therapies
Spicer SITC 2020
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
Composite AXL score (cAXL) as a companion diagnostic predictive biomarker

The “composite AXL score” forms the basis for our proposed CDx for both chemo-refractory / CPI-naïve and CPI-refractory NSCLC patients

- Clinical benefit is enriched in patients with cAXL +ve status in both naïve and refractory patients
- cAXL –ve status defines a group with PD and low probability of clinical benefit in both chemo-refractory/CPI-naïve and CPI-refractory patients

CPI-naïve

Responses in cAXL positive patients

- PR: 27%
- SD: 33%
- PD: 40%

Responses in cAXL negative patients

- PR: 60%
- SD: 33%

CPI-refractory

Responses in cAXL positive group

- PR: 14%
- SD: 71%
- PD: 100%

Responses in cAXL negative group

- PR: 33%
- SD: 60%
- PD: 100%
AXL expression defines a poor prognosis subgroup of NSCLC

cAXL+ patients have significantly enhanced survival with bemcentinib + pembrolizumab in CPI-naïve and -refractory patients

In NSCLC, the AXL expression encodes poor-prognosis\(^1\): defines expectations of the control arm

---

**Cohort A PFS : CPI-naïve**

- **AXL IHC low (n=59)**
- **AXL IHC high (n=29)**

**Cohort B1 PFS: CPI-refractory**

- **cAXL+ve**
- **cAXL-ve**

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\(^1\)Ishikawa, 2012
Safety
Bemcentinib + pembrolizumab combination offers an excellent safety profile - not dissimilar to pembrolizumab alone

Safety profile of 008 cohorts A + B1

Most frequently reported TRAEs†† (>10% of patients) in 008 cohorts A and B1

<table>
<thead>
<tr>
<th>Preferred term (ungrouped)</th>
<th>All Grades n (%)</th>
<th>Grades &gt;3 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>20 (30%)</td>
<td>0</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>19 (29%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>18 (27%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>11 (17%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged</td>
<td>10 (15%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>9 (14%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>9 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (14%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (14%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Preferred term (ungrouped)

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<tr>
<th>Preferred term</th>
<th>All Grades n (%)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>678 (24%)</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>467 (17%)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>386 (14%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>343 (12%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>304 (11%)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>281 (10%)</td>
<td></td>
</tr>
</tbody>
</table>

Expected safety profile of Pembrolizumab

Most frequently reported TRAEs (>10% of patients), of any grade, in patients treated with pembrolizumab monotherapy††

<table>
<thead>
<tr>
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</table>

Treatment combination was well tolerated

- No grade 5 TRAEs reported
- Of the most frequent TRAEs, one grade 4 TRAE reported (AST increase), which resolved upon interruption of study treatment

† Cross-study, reference safety dataset: Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase); KN006, and KN010.

†† Definitely, probably or possibly related to bemcentinib or pembrolizumab.
FDA Fast-Track Designation for Bemcentinib defines an addressable AXL positive population:

• Bemcentinib in combination with a checkpoint inhibitor is indicated for 2L treatment of **AXL positive** advanced/metastatic NSCLC patients without actionable mutations who have progressed following initial checkpoint inhibitor therapy with or without chemotherapy in their first line of treatment.
RNA Seq Analysis identifies immunosuppressive innate immune populations predictive of response
RNA Seq identifies biomarkers predictive of clinical benefit in second line NSCLC for patients who are either CPI naïve or CPI refractory

- Enriched for EMT activation
- PD-L1 and IFNg expression do not predict response
- AXL expression in tumour and immune cells (composite score) is associated with response to combination treatment
- Enriched for Myeloid suppressor activation
  - In immuno-refractory patients there is specific identification of
    - CCR7+ AXL+ mreg DC1
    - TREM2+ AXL+ Macrophages

Krebs SITC 2019
Spicer SITC 2020
AXL+ myeloid cells drive T cell dysfunction

The data are consistent with a mechanistic model where AXL+ myeloid cell-mediated T cell dysfunction drives acquired resistance to CPI and can be reversed by bemcentinib treatment.
Conclusions: Cohort A (CPI-naïve / PD-L1 low)

- Updated analysis confirms clinically and statistically significant PFS advantage for cAXL+ patients receiving bemcentinib with pembrolizumab

- mPFS of 8.4mo in cAXL+ patients compared with 1.9mo for cAXL- patients

- mOS still maturing 17.3mo for cAXL+ (despite prognostically adverse biology) v 12.4mo for cAXL-
Conclusions: Cohort B1 (CPI-refractory)

- New data presented for cohort B1 (CPI-refractory) suggests clinically significant effect for cAXL+ patients receiving bemcentinib and pembrolizumab reminiscent of cohort A

- In stage 1, mPFS of 4.7mo in cAXL+ patients compared with 1.9mo for cAXL- patients

- Cohort B, stage 2 now recruiting – focusing on second line patients who received CPI monotherapy in the first line
Conclusions – General considerations

- cAXL+ patients in cohorts A and B1 show analogous clinical biology in both groups with significant benefit for bemcentinib + pembrolizumab

- cAXL biomarker/companion diagnostic is being developed for patient selection in second line NSCLC

- Bemcentinib sensitises to checkpoint inhibitor therapy by targeting AXL+ TREM2+ macrophages and AXL+ CCR7+ regulatory DCs, as seen with RNAsseq analysis of pretreatment biopsies

- These findings support a rationale for further development of AXL-targeting to extend immunotherapy efficacy in biomarker-selected relapsed NSCLC patients
Acknowledgements

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BGBC008 Investigators

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