The role of AXL in immuno-oncology: A translational perspective

Session: Immunotherapy Strategy For NSCLC

Next-Gen Immuno-Oncology Conference 2021
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Chief Medical Officer, BerGenBio

On behalf of BerGenBio
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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\(^1\)
- Lung adenocarcinoma (NSCLC)\(^2\)
- Acute Myeloid Leukaemia\(^3\)
- Pancreatic ductal adenocarcinoma\(^4\)

**Broad evidence of AXL linked with poor prognosis\(^5\)**

- Astrocytic brain tumours
- Breast cancer
- Gallbladder cancer
- GI
  - Colon cancer
  - Oesophageal cancer
  - Gastric cancer
- Gynaecological
  - Ovarian cancer
  - Uterine cancer
- HCC
- HNC
- Haematological
  - AML
  - CLL
  - CML
- Melanoma
- Mesothelioma
- Pancreatic cancer
- Sarcomas
  - Ewing Sarcoma
  - Kaposi sarcoma
  - Liposarcoma
  - Osteosarcoma
- Skin SCC
- Thyroid cancer
- Urological
  - Bladder cancer
  - Prostate cancer
  - RCC

\(^1\) 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

**AXL upregulated and activated on immune cells and suppresses the innate immune response**

- M1 to M2 macrophage polarisation
- Decreased antigen presentation by DCs
- Prevent CD8+ T cell mediated cell death
- Activates Treg cells through DCs and macrophages

**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

**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**
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
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.
Tumours mobilise AXL in immune-suppressive myeloid cells

AXL is expressed on tumour microenvironment resident suppressive myeloid cells

UMAPs of single immune cells in tumours showing AXL, PD-L1, arginine and Mer.
UMAP = Uniform Manifold Approximation and Projection method

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 DCs¹
   - miR-34a downregulates AXL
   - ↓miR-34a → ↑AXL

2. AXL signalling in DCs, via INF/STAT pathway, leads to expression of DC negative regulators SOCS1/3²

Antigen presentation by DCs (red) to T-cells (green) is reduced when AXL is active¹

AXL is off-switch for DCs

AXL drives tumour cell escape from checkpoint inhibitors

AXL upregulated in CPI resistant melanoma

AXL driven tumour EMT prevents CTL killing of cancer cells

Bemcentinib leads to increased CTL mediated tumour cell killing

AXL inhibition via bemcentinib = effective immunological synapse

CTL + mesenchymal tumour cell = inefficient immunological synapse

Source: Chouaib, 2014; Hugo, 2016  E:T = Effector:Target ratio
Executing a Broad Development Program for Bemcentinib

Bemcentinib foundation for cancer therapy

- Relapsed MDS
- Recurrent Glioblastoma
- 1L COVID19
- 1L Metastatic Melanoma
- 2L Metastatic Mesothelioma
- 1L Pancreas
- 1L Melanoma
- 1L & Relapsed NSCLC
- Relapsed AML
- r/r AML

Monotherapy + checkpoint inhibitors

+ chemotherapy

+ targeted therapy

+ epigenetic therapy (HMA)
Targeting AXL in AML: Both AML blasts and Innate immune compartment
BGBC003 phase 2 clinical trial in AML and MDS

Cohort expansion phase in four disease-specific cohorts

- **AML**
  - bemcentinib + LDAC
  - bemcentinib + decitabine
- **MDS**
  - bemcentinib

**Part B**

ongoing
Bemcentinib + LDAC in BGBC003 phase 2 trial

- 76 year-old male patient with newly-diagnosed secondary AML
- FAB classification of M7: acute megakaryoblastic leukemia (AMKL, only 1% of adult AML, poor prognosis)
- Intermediate cytogenetic risk
- Patient is ongoing

Loges et al ASH 2019
Loges et al EHA 2021

Bem monotherapy treatment led to T- and B-cell repertoire (TCR/BCR) diversification indicative of an immune response in 7/11 patients
Single cell RNA (scRNA) sequencing analysis indicates distinct gene expression patterns in NK- and T cell compartment predicting response

- 10X sc RNASeq analysis of pre-treatment bone marrow samples
- Data indicate differences in the T- and NK cell compartment according to treatment response (CR/C Ri/PR = Response; SD = No Response)

Loges et al ASH 2020
Proposed mechanism

Loges et al ASH 2020
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 NSCLC¹

• 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 models²

¹Hugo, 2016 ²Ludwig, 2018
Non-small cell lung cancer: not one disease, but many

Then

Histology-Based Subtyping

Now

Treatment landscape for non-small cell lung cancer *

Non-squamous non-small cell lung cancer 2020

1st line
- Targeted therapy
  - EGFR
  - ALK
  - ROS1
  - BRAF
  - TRK
  - RET
  - MET
  - KRAS G12C

Molecular driver positive

2nd line +
- PD-L1 <50%
  - Platinum/Pemetrexed/Pembrolizumab
  - Atezo/carbo/nab-P
  - Carbo/taxol/bev/atezo
  - Nivo/ipi/platinum/pem

- Maintenance

Non-molecular driven NSCLC

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

Spicer et al SITC 2020
Tumour infiltrating AXL+ macrophages interact with CD8+ T cells and T\textsubscript{regs} in pre-treatment biopsy from responding patient

PANCK AXL CD68 FoxP3 CD8

→ Axl+ macrophage interacting with CD8+ T cells
→ Axl+ macrophage interacting with regulatory T cell
→ 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 | Cohorts 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

<table>
<thead>
<tr>
<th>Patient disposition</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened</td>
<td>74</td>
</tr>
<tr>
<td>Enrolled</td>
<td>50</td>
</tr>
<tr>
<td>Evaluable</td>
<td>44</td>
</tr>
<tr>
<td>Ongoing</td>
<td>4</td>
</tr>
</tbody>
</table>

### Patient demographics

<table>
<thead>
<tr>
<th>Age</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>65</td>
<td>39-82</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG at screen</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>22 (44)</td>
</tr>
<tr>
<td>1</td>
<td>28 (56)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>20 (40)</td>
</tr>
<tr>
<td>Smoker</td>
<td>10 (20)</td>
</tr>
</tbody>
</table>

### Smoking Status

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex-smoker</td>
<td>29 (58)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

### Disease mutations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>36 (72)</td>
</tr>
<tr>
<td>KRAS</td>
<td>7 (14)</td>
</tr>
<tr>
<td>TP53</td>
<td>2 (4)</td>
</tr>
<tr>
<td>EGFR</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (8)</td>
</tr>
</tbody>
</table>

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*Data cutoff: 17 Apr 2020*

## Biomarkers

### cAXL status

- Negative: 50%
- Positive: 50%

### PD-L1 status

- Negative (TPS <1%): 55%
- Positive (TPS 1-49%): 35%
- Strong Positive (TPS ≥50%): 10%
- Subset: (TPS 1-10%): 24%
Time on treatment in patients evaluable for cAXL

**PD-L1**
- 0 +
- NE +
- 1 +
- 1 +
- 1 +
- 95 +
- 15 +
- 0 +
- 15 +
- 3 +
- 1 +
- 0 +
- 0 +
- 40 +
- 0 +
- NE -
- 0 -
- 0 -
- 0 -
- 0 -
- 30 -
- 0 -
- 0 -
- 100 -
- 0 -
- 0 -
- 1 -
- 0 -
- 55 -
- 0 -
- 0 -
- 90 -

**cAXL**
- positive
- negative

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

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

AXL is an adverse prognostic biomarker

- 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

### Cohort

<table>
<thead>
<tr>
<th></th>
<th>mOS</th>
<th>12-mo OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort A – cAXL +ve pts**</td>
<td>17.3 mo*</td>
<td>79%</td>
</tr>
<tr>
<td>Cohort A – cAXL -ve pts**</td>
<td>12.4 mo*</td>
<td>60%</td>
</tr>
<tr>
<td>BGB Cohort A – all pts**</td>
<td>12.6 mo*</td>
<td>64%* (up to 67%)</td>
</tr>
<tr>
<td>CheckMate-057 (Opdivo)</td>
<td>12.2 mo</td>
<td>51%</td>
</tr>
<tr>
<td>KEYNOTE-010 (Keytruda)</td>
<td>10.4 mo</td>
<td>43.2%</td>
</tr>
</tbody>
</table>

*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)

mPFS 8.4 months in cAXL+ patients

Data cut-off: 17-April-2020

CheckMate-057: Borghaei et al, NEJM 2015

Gabra  Next Gen IO 2020
# BGB008: Study Design

**Open-label multi-center single arm phase II study**

## Cohort A
- Previously treated with a platinum containing chemotherapy
- CPI-naive
- 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

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

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

- **Cohort C**
  - Stage 1
  - **N=13 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**
  - Stage 2
  - **N=29 patients**
  - (each patient has the potential for at least 24 weeks follow-up)

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

---

**Spicer SITC 2020**
### Patient disposition and demographics

**Cohort B (stage 1)**

<table>
<thead>
<tr>
<th>Patient demographics</th>
<th>n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>64.5</td>
</tr>
<tr>
<td>Range</td>
<td>40-76</td>
</tr>
<tr>
<td><strong>ECOG at screen</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (38%)</td>
</tr>
<tr>
<td>1</td>
<td>10 (63%)</td>
</tr>
<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**

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

**PD-L1 status**

- **n = 12**
  - TPS >50%: 33%
  - TPS 1-49%: 42%
  - TPS <1%: 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 lines: 2
Prior therapies: PltCT: platinum-based chemotherapy D: docetaxel P: pembrolizumab; A: atezolizumab; N: nivolumab; I: ipilimumab; O: other

Response first achieved

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

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

Median: 1.87 mo
Median: 4.73 mo
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: 27% PR, 33% SD, 40% PD
- Responses in cAXL negative patients: 60% PR, 33% SD, 10% PD

### CPI-refractory

- Responses in cAXL positive group: 14% PR, 71% SD, 15% PD
- Responses in cAXL negative group: 100% PD
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: defines expectations of the control arm

**AXL IHC high (n=29)**

**AXL IHC low (n=59)**

**Cohort A PFS: CPI-naïve**

**Cohort B1 PFS: CPI-refractory**

---

**BIOLOGY**

**RATIONALE**

**OUTCOME**

---

Ishikawa, 2012
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

Cohort A – Immunotherapy-naïve relapse

- Enriched for EMT activation
- PD-L1 and IFNγ 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

Cohort B – Immunotherapy-refractory relapse

- Enriched for EMT activation
- PD-L1
- MyeloidSuppressor activation
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

- AXL expression defines a dynamic microenvironment – wide alteration affecting immune and tumor cells

- AXL expression defines an immunosuppressed microenvironment harboring aggressive, therapy resistant, immunoevasive tumor cells with enhanced metastatic capability

- Bemcentinib, the highly specific, orally bioavailable AXL inhibitor reprograms and reverses this adverse state, targeting AXL+ CCR7 mregDC1 and TREM2 macrophages

- In particular, bemcentinib reverses the profound immunosuppression associated with AXL+ innate immunity

- This has created opportunities in clinical development for:
  - Bemcentinib monotherapy (MDS and Glioblastoma)
  - Bemcentinib combination with chemotherapy (pancreatic cancer and AML)
  - Bemcentinib combination with checkpoint inhibitor pembrolizumab (NSCLC, melanoma, mesothelioma)
Acknowledgements

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BerGenBio ASA