AXL inhibitors as cornerstone of combination cancer therapy

First-in-class medicines to treat aggressive cancers

Third Annual Immuno-Oncology Summit Europe March 22nd 2018
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Corporate snapshot

Background

Leaders in developing therapeutics that target AXL, a protein that makes cancers and their environment highly aggressive and which is associated with poorer outcomes across many cancers

Diversified pipeline. Lead drug is tested in several indications of high unmet medical need and large market potential

Promising efficacy with sustained treatment benefit and confirmed favourable safety

Companion diagnostic supported by biomarker tests

Bemcentinib (BGB324)

First-in-class highly selective small molecule AXL inhibitor

Broad phase II proof of concept clinical trials ongoing in NSCLC, TNBC, AML/MDS, melanoma.

OSE:BGBIO

Raised $50m in IPO on OSE in April '17

$320m market cap (Feb 18th 2018)

Pipeline

Bemcentinib (BGB324)

AXL antibody

AXL ADC (partnered)

Immunomodulatory small molecules

Corporate

35 staff

Headquarters and research in Bergen, Norway; Clinical Trial Management in Oxford, UK
## Advancing a broad development pipeline of innovative drugs

### Bemcentinib – Axl kinase inhibitor

<table>
<thead>
<tr>
<th>Stage</th>
<th>Disease Type</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preclinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>adenocarcinoma (mutation driven)</td>
<td>Phase II Combination with KEYTRUDA® (pembrolizumab)</td>
</tr>
<tr>
<td>Phase II</td>
<td></td>
<td>Phase II bemcentinib in combination with Docetaxel</td>
</tr>
<tr>
<td>Phase III</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **NSCLC**
  - Phase Ib / II – Combination with TARCEVA® (erlotinib)

- **TNBC**
  - Phase II Combination with KEYTRUDA® (pembrolizumab)

- **Melanoma**
  - Phase II bemcentinib in combination with current standard therapies, incl. CPIs

- **AML / MDS**
  - Phase Ib / II – Single agent / Combination

### Antibody programs

<table>
<thead>
<tr>
<th>Program</th>
<th>Type</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>BGB149</td>
<td>Oncology</td>
<td>Anti-Axl mAb</td>
</tr>
<tr>
<td>BGB601 (Partnered)</td>
<td>Metastatic cancer</td>
<td>ADC</td>
</tr>
</tbody>
</table>

### Discovery Pipeline – small molecule inhibitors

<table>
<thead>
<tr>
<th>Program</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>BGB002/ BGB003</td>
<td>Small molecule</td>
</tr>
</tbody>
</table>

*Investigator-sponsored trials

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>350 Patients

>50 sites in Europe & US.

2018 Key read-outs:
### Three combination trials of bemcentinib with KEYTRUDA

#### Bemcentinib – Axl kinase inhibitor

<table>
<thead>
<tr>
<th>Disease</th>
<th>Phase II Combination</th>
<th>Investigator-sponsored trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC  adenocarcinoma</td>
<td>Phase II Combination with KEYTRUDA® (pembrolizumab)</td>
<td>Merck</td>
</tr>
<tr>
<td>TNBC</td>
<td>Phase II Combination with KEYTRUDA® (pembrolizumab)</td>
<td>Merck</td>
</tr>
<tr>
<td>Melanoma*</td>
<td>Phase II bemcentinib in combination with current standard therapies, incl. CPIs</td>
<td></td>
</tr>
</tbody>
</table>
Successful anti-cancer therapies depend on both tumour antigenicity and immune system adjuvanticity

- Interferon mediated - anti-tumour immune reaction

Tumour clearance
Successful anti-cancer therapies depend on both tumour antigenicity and immune system adjuvanticity.
AXL is a negative feedback mechanism: drives cancer immune escape via tumour intrinsic survival programme & suppression of immune adjuvanticity.

Survival programme (EMT):
- Therapy resistance
- Metabolic programming
- Reduced immunogenicity:
  - Biophysical
  - PD-L1
  - Autophagy

Immune suppression:
- SOCS → ↓DC
- M2 macrophages
- Tregs
- ↓MHC
Successful cancer drug combination strategies...

Boost tumour antigenicity

Boost immune adjuvanticity and concomitantly

Effectively address feedback inhibition

AXL driven tumour cell plasticity and immune suppression is a negative feedback mechanism
AXL receptor tyrosine kinase

AXL is a surface receptor tyrosine kinase

- Member of the TAM (Tyro-AXL-Mer) family
- Ubiquitously expressed at low levels
- Epigenetically upregulated upon immune reaction or cellular damage (e.g. anti-cancer therapy, hypoxia)
  - Innate immune checkpoint
  - Tumour cell pro-survival programme:
    - Therapy resistance
    - Metabolic reprogramming
    - Reduced immunogenicity
- Only TAM member that correlates with aggressive cancers

AXL antibody BGB149 binds IG domain

bemcentinib binds the internal kinase domain

Immunosuppression & therapy resistance
AXL is an innate immune checkpoint facilitating immune escape

1. Innate immune activation through toll-like receptor (TLR) signalling triggers AXL upregulation in DCs\(^1\)
   - 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\(^2\)

Antigen presentation by DCs (red) to T-cells (green) is reduced when AXL is active\(^1\)

AXL is off-switch for DCs

AXL drives tumour cell escape from checkpoint inhibitors

Checkpoint inhibitors (CPIs) work only in a small proportion of patients

<table>
<thead>
<tr>
<th>Disease</th>
<th>Responders (%)</th>
<th>Non-responders (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>TNBC</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>Renal</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Melanoma</td>
<td>60</td>
<td>40</td>
</tr>
</tbody>
</table>

AXL upregulated in CPI resistant melanoma

AXL driven tumour EMT prevents CTL killing of cancer cells

- Effective synapse
- Immune mediated cell death

Robust immunological synapse between CTL and epithelial tumour cell

- Impaired synapse
- Immune evasion

Source: Chouaib, 2014; Hugo, 2016
AXL is detected in patient tumour and immune cells (BerGenBio) IHC assay

Shown are squamous cell carcinoma FFPE patient samples stained for AXL (brown) as per BerGenBio’s proprietary AXL IHC assay
AXL is independent negative 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 tumors
- Breast cancer
- Gallbladder cancer
- GI
  - Colon cancer
  - Esophageal cancer
- Gastric cancer
- Gynaecological
  - Ovarian cancer
  - Uterine cancer
- HCC
- HNC
- Haematological
  - AML
  - CLL
  - CML
- Melanoma
- Mesothelioma
- NSCLC
- Pancreatic cancer
- Sarcomas
  - Ewing Sarcoma
  - Kaposi sarcoma
  - Liposarcoma
  - Osteosarcoma
- Skin SCC
- Thyroid cancer
- Urological
  - Bladder cancer
  - Prostate cancer
  - RCC

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Bemcentinib, first in class highly selective AXL inhibitor
Bemcentinib is active throughout the complete cancer immunity cycle reversing immune suppression

1. **Antigen presentation**
   - AXL is inhibitory regulator of dendritic cells (DCs) (Rusholme-Stemmer, Nature Comm, 2017)
   - Treatment with bemcentinib enhances DC tumour-infiltration and activation (Guo, Oncol Target, 2017)

2. **Release of cancer antigen**
   - Bemcentinib leads to immunogenic cell death in lung cancer cells (Byers et al, EORTC 2016)

3. **Priming & activation**
   - Treatment with bemcentinib reduces APC inhibitory cytokine IL-10 (Guo, ASCO/STC Clinical IO, 2018)

4. **T-cell trafficking to tumours**
   - Treatment with bemcentinib increases T-cell recruiting cytokines (CXCL9, CXCL10 and CXCL11) (Guo, Oncol Target, 2017)

5. **T-cell infiltration**
   - Treatment with bemcentinib increases tumour infiltration of CTLs (Nanak-Lopmee, AACR, 2017)

6. **Recognition by T-cells**
   - AXL suppresses MHC-I expression (Agulina, Nature Comm, 2016)

7. **T-cell mediated killing**
   - AXL suppresses MHC-I expression (Agulina, Nature Comm, 2016)

8. **Reversal of immune suppression**
   - Bemcentinib is active throughout the complete cancer immunity cycle reversing immune suppression
Bemcentinib is an immune modulator that enhances anti-tumour immunity

Cytokines that mediate immune suppression

- Recruitment (CCL2, CCL3, CCL4, CCL5)
- Activity (CCL11, IL-7, IL-1β, and IL-6)

Bemcentinib decreases immune suppression

- Recruitment (CXCL9, CXCL10, and CXCL11)
- Functionality (IFN-γ, IL-12p40, T-bet)

T cell activity increased

Myeloid Suppression decreased

Source: Ludvig, Cancer Research, 2017; Guo, OncoTarget, 2017
Bemcentinib is an immune modulator that enhances anti-tumour immunity

Increased T Cell infiltration

- Increased CD4⁺ T cells
- Increased CD8⁺ T cells
- Increased NK cells
- Increased cDC
- Increased Mono/Mo
- Increased Gran.
- Increased Treg

Decreased myeloid suppressors

Increased dendritic cells

ID8 ovarian carcinoma, 5 day bemcentinib monotherapy

Increased T cell proliferation

- Increased % of CD8 or NK cells

Decreased CD69⁺CD4⁺ T
- Increased CD69⁺CD8⁺ T
- Increased Ki67⁺CD4⁺ T
- Increased Ki67⁺CD8⁺ T

Increased T cell activity

- Increased % IFN-γ expression

Vehicle

Vehicle

Vehicle
Bemcentinib therapy targets immune suppressive M-MDSC and tumor associated macrophages

**M-MDSC**
Monocytic myeloid-derived suppressor cell
- Immature myeloid cells with pathologic activation, immune suppressive

**TAM**
Tumour associated macrophage
- Pro-tumoural macrophage, promote proliferation, invasion, and metastasis of tumour cells, and inhibit T cell response

**Arg1**
Arginase
- Metabolises L-arginine to L-ornithine and urea - myeloid cell arginase-mediated L-arginine depletion suppresses T cell responses

*Source: Ludvig, Cancer Research, 2017*
Bemcentinib promotes dendritic cell tumour-infiltration and activation

**CD103**^+ DC
- Peripheral, cross-presenting dendritic cell (DC)

**CD40**^+CD86**+ DC**
- Mature DC

**IL-12p40**^+ DC
- IL-12 secreting DC

ID8 ovarian carcinoma, 5 day bemcentinib monotherapy

Source: Guo, OncoTarget, 2017
Bemcentinib enhances immune checkpoint inhibitor efficacy

Checkpoints inhibitor treatment induces aggressive tumour AXL programme

Durable response to bemcentinib + CPI treatment

Abrogation of metastases in responders

Source: Davidsen, Wnup-Lipinska, et al, in prep
Bemcentinib phase II PoC programme:

designed to evaluate potential of bemcentinib to increase efficacy of anti-cancer therapies
Bemcentinib recently reported interim PoC Phase II data

BGBC008: NSCLC
BGBC007: TNBC
BGBIL006: Melanoma
BGBC004: NSCLC
BGBIL005: NSCLC
BGBIL006: Melanoma
BGBC003: AML
BGBC003: AML/MDS

+ checkpoint inhibitors
+ targeted therapy
+ chemotherapy
monotherapy

Bemcentinib (BGB324) foundation therapy
AXL inhibition to increase efficacy of anti-PD-1 therapy

BGBC007, BGBC008, BGBIL006
Combination with bemcentinib to increase efficacy of anti-PD1 therapy

- A significant proportion (up to 95% in 2L TNBC) of patients do not respond to checkpoint inhibitor therapy.
- Non-responders to checkpoint therapy have been shown to express AXL at higher rates.
- Inhibiting AXL may increase the number of patients responding to checkpoint therapy.
- Comprehensive biomarker programme analysing AXL, PD-L1 and immune signature.
ASCOSITC Clinical IO Symposium 2018
Favourable safety reported for bemcentinib / pembro combo across all three trials

<table>
<thead>
<tr>
<th></th>
<th>TNBC NCT03184558</th>
<th>NSCLC NCT03184571</th>
<th>Melanoma NCT02872259</th>
<th>total</th>
</tr>
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<tbody>
<tr>
<td><strong>SOC</strong></td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>34</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>3</td>
<td>0</td>
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<td>Investigations</td>
<td>3</td>
<td>n</td>
<td>n</td>
<td>3</td>
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<td>Blood and lymphatic system disorders</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Cardiac disorders</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

- 34 patients evaluable for safety
- SAE profile of combination similar to pembro alone

Source: Yule et al ASCO-SITC Clinical IO Symposium (January 2018)
BGBC008 trial in NSCLC

Keytruda monotherapy showed 18% response rate in previously treated NSCLC patients. PD-L1 negative patients remain particularly challenging.

The BGBC008 trial is designed to test the hypothesis whether AXL inhibition can

- **Enhance** responses to immunotherapy

when given in combination with pembrolizumab in previously treated, immunotherapy-naïve NSCLC patients.
Bemcentinib increases immune checkpoint inhibitor efficacy in NSCLC models *in vivo*

**Bemcentinib reverses CPI induced EMT**

Vimentin

N-cadherin

**Bemcentinib increases CPI efficacy**

**Bemcentinib reverses immunosuppression in tumour microenvironment**

**BGBC008: Phase II trial in NSCLC of bemcentinib in combination with KEYTRUDA**

<table>
<thead>
<tr>
<th>BGBC008 Phase 2 – NSCLC Adenocarcinoma of the lung</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously treated, unresectable adenocarcinoma of the lung</td>
<td></td>
</tr>
<tr>
<td>up to 48 pts</td>
<td></td>
</tr>
<tr>
<td>any PD-L1 expression</td>
<td></td>
</tr>
<tr>
<td>any AXL expression</td>
<td></td>
</tr>
<tr>
<td>no prior IO</td>
<td></td>
</tr>
</tbody>
</table>

**Single arm**
- Bemcentinib 200mg/d
- Keytruda 200mg/3w

**Simon two stage (interim after 22 pts)**
- **ORR**
  - Safety, DoR, TtP, OS at 12 mo, response by biomarker expression

**Expected readout**
- Initial read-out expected 2H 2018

**Mandatory pre-treatment biopsies**
BGBC007 trial in TNBC

KEYTRUDA monotherapy showed 4% response rate in previously treated TNBC patients.

The BGBC007 trial is designed to test the hypothesis whether AXL inhibition with bemcentinib can

✔️ **Enhance responses** to immunotherapy

when given in combination with pembrolizumab in previously treated, immunotherapy-naïve TNBC patients.

Clinical collaboration with Merck & Co. (MSD)
Bemcentinib increases immune checkpoint inhibitor efficacy in TNBC models in vivo

Bemcentinib reverses CPI induced EMT – correlates with response

Bemcentinib reverses immunosuppression in tumour microenvironment

Source: Wnuk-Lipinska et al. AACR 2017 – 4T1 model
BGBC007: Phase II trial in TNBC of bemcentinib in combination with KEYTRUDA

<table>
<thead>
<tr>
<th>BGBC007 Phase 2 – TNBC</th>
<th>Simon two stage (interim after 28 pts)</th>
<th>Expected readout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously treated, unresectable or metastatic TNBC</td>
<td>Single arm</td>
<td>Initial read-out expected 2H 2018</td>
</tr>
<tr>
<td>up to 56 pts any PD-L1 expression any AXL expression no prior IO</td>
<td>bemcentinib 200mg/d Keytruda 200mg/3w</td>
<td>Safety, DoR, TtP, OS at 12 mo, response by biomarker expression</td>
</tr>
</tbody>
</table>

Mandatory pre-treatment biopsies
Although responses to TKIs are rapid, resistance ultimately emerges. Monotherapy checkpoint inhibitor responses can be further improved.

The BGBIL006 trial is designed to test the hypothesis whether AXL inhibition can

- **Enhance** responses to immunotherapy
- **Enhance** responses to targeted therapy

when given in combination with pembrolizumab or dabrafenib/trametinib in treatment naïve melanoma patients
**BGBIL006 : Randomised Phase II trial of BGB324 in combination with targeted and I/O therapies in Melanoma**

| BGBIL006 Phase II – Melanoma, randomised SoC (Keytruda or BRAF/MEKi) +/- BGB324 |
|----------------------------------|------------------|------------------|------------------|
| **First Line**                  | **Second Line**  | **Endpoints**    | **Expected readout** |
| Treatment naïve, BRAF mutant (high tumour burden) | Dabrafenib+trametinib +/- bemcentinib 200mg/d | Dabrafenib+trametinib +/- bemcentinib 200mg/d | ORR Safety, DoR, TiP, OS at 12 mo, response by biomarker expression | Initial read-out expected 2H 2019 |
| up to 40 pts BRAF mutation driven any AXL expression | Pembrolizumab 200mg/3w +/- bemcentinib 200mg/d | Pembrolizumab 200mg/3w +/- bemcentinib 200mg/d | |
| Treatment naïve, BRAF mutant (low tumour burden), BRAF- | | | |
| up to 40 pts any AXL expression any PD-L1 expression | | | |

*Only BRAF mutant pts will be allowed to cross-over at progression on first line KEYTRUDA +/- bemcentinib)
Summary

AXL drives tumour immune evasion & immune suppression = negative feedback

Bemcentinib is a first-in-class selective AXL inhibitor in phase II clinical development

Interim PoC clinical data available for bemcentinib monotherapy and in combination with targeted- and chemotherapy

Bemcentinib synergises with ICB in preclinical models

The potential of bemcentinib to enhance efficacy of KEYTRUDA is being explored in three phase II trials in NSCLC, TNBC and melanoma with interim readouts expected during the coming months
Thank you.

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