AXL receptor tyrosine kinase
Key driver of tumour plasticity, heterogeneity and immune evasion

High AXL expression is correlated with poor survival in most cancers

Strong AXL expression correlates with poor survival rate. Broad evidence of AXL linked with poor prognosis.

AXL is an innate immune checkpoint & drives tumour intrinsic cell plasticity

AXL drives tumour cell plasticity 2.

AXL is innate immune checkpoint & drives tumour intrinsic cell plasticity

Unique marker of inflammation and cellular stress

Immune-suppressive signalling

M2 macrophage polarisation

Inhibits DC interferon response

Reduced antigen presentation & immunosuppressive cytokine profile

AXL expression in NSCLC

Patient tumour sample

AXL expression in tumour adjacent alveolar macrophages

AXL is detected on patient tumour tissue and adjacent immune cells

by BerGenBio proprietary immunohistochemistry method (IHC)

AXL expression in NSCLC patient tumour sample

AXL expression in tumour adjacent alveolar macrophages

AXL is a receptor tyrosine kinase

- Gi protein, single high affinity ligand
- Low expression in normal tissues; upregulated by inflammation and cellular stress
- Unique signal transduction drives survival
- Drug resistance
- Immune-suppressive
- Metastasis

AXL is detected on patient tumour tissue and adjacent immune cells

Selectivity

Selective over other kinases and other TAM family members specifically

(merT, tyro) specifically

Allows for rational combinations while reducing the risk of additive toxicity

Efficacy

- Increased clinical benefit in combination with chemo in NSCLC

- Reverses acquired resistance to erlotinib in NSCLC

- Increases efficacy of checkpoint inhibitors in NSCLC

- AXL knockout mice are phenotypically normal

- AXL is the TAM receptor that is specifically upregulated in aggressive disease

- bemcentinib is well tolerated across BerGenBio combination studies

Benefits of selective AXL inhibition with bemcentinib
Bemcentinib
First-in-class, highly selective and orally bioavailable AXL inhibitor

- Once a day capsule
- Most advanced selective oral AXL inhibitor in clinical development. PoC data in:
  - monotherapy AML/MDS
  - KEYTREDA combo NSCLC
  - EGFR inhibitor combo NSCLC
  - chemo combo NSCLC
- Wide therapeutic index, well tolerated
- 25 kg API manufactured, 100 mg capsule, shelf life > 3 years at RT confirmed

Bemcentinib is developed in combination with immune-targeted and chemotherapy in NSCLC, AML/MDS, melanoma and TNBC.
Bemcentinib preclinical data

Selective AXL inhibition to enhance immune cell attack, anti-tumour therapy and prevent spread

Bemcentinib acts on tumour and immune cells

Reverses AXL programme in vitro

Bemcentinib is active as a monotherapy and in combination with immune-targeted and chemotherapy in vivo

**AML model**

**组合 w/ targeted therapy**

**NEDCLC model**

**组合 w/ chemotherapy**

**Pancreatic model**

**组合 w/ CPAs**

**TNBC model**
Companion Diagnostic for personalised medicine

What is Precision Medicine?

- Tissue biopsy - "the main way cancer is diagnosed"
- Liquid biopsy - emerging technology

Why Precision Medicine?

- Likelihood of success (Phase I to approval):
  - Without biomarker: 8.4%
  - With biomarker: 25.9%

BerGenBio biomarker programme

- Designed in line with established and emerging techniques:
  - Standard (tissue) and emerging (blood) pathology techniques are used to diagnose cancer and determine optimal, personalised treatment.

Pharmacodynamics

- AXL drives a tumour survival programme that is increased by reduced receptor shedding.

Tissue AXL levels correlate with response in bemcentinib/pembrolizumab combo trial.

- Pre-treatment soluble AXL levels in plasma are predictive of patient benefit in AML/MDS.
Bemcentinib and KEYTRUDA® in NSCLC

Keytruda® monotherapy showed 10% response rate in previously treated NSCLC patients (Keynote 010).

The BGBC008 trial is designed to test the hypothesis whether AXL inhibition can enhance responses to immunotherapy when given in combination with KEYTRUDA in previously treated, immunotherapy-naïve NSCLC patients.

Clinical collaboration with Merck & Co. (MSD)

BGBC008: Phase II trial in NSCLC, bemcentinib with KEYTRUDA

2nd line advanced adenocarcinoma NSCLC

- IO naive
- Prior platinum
- Measurable disease
- Fresh tissue biopsy
- PD-L1 +ve and -ve
- AXL +ve and -ve

Single arm bemcentinib, 200mg daily + KEYTRUDA, 200mg q3wks

Interim analysis Final analysis

<table>
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<th>% change in sum target lesions</th>
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<th>40</th>
<th>60</th>
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<tr>
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<td>4</td>
<td>1</td>
<td>5</td>
</tr>
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<td>1</td>
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<td>6</td>
</tr>
<tr>
<td>PD</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>3</td>
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</table>

Best overall response according to biomarker expression at time of data cut-off (analysis includes ongoing patients).

Best response on bemcentinib + KEYTRUDA: partial response

Plasma soluble AXL levels increase upon treatment with bemcentinib + KEYTRUDA

Biomarker expression, TPS (%)

AXL: 25%

PD-L1: 0%

AXL biomarker correlated with patient benefit.

Patient case study: AXL biomarker correlated with patient benefit.

74 year old white male screen ECOG of 2 no known mutations

1 line of previous therapy with best response of SD liver metastases present biomarker expression

H&E staining Anti-AXL staining of tumour cells was observed (open arrowheads). Additionally a mainly weak to moderate cytoplasmic staining of stromal cells was seen (arrows).

Anti-AXL IHC

Patient characteristics

PD PD PD SD SD SD SD SD SD SD PR MR PR PR

previous Tx bemcentinib + pembrolizumab
Bemcentinib and KEYTRUDA®
in TNBC

A Phase II study of the selective AXL inhibitor bemcentinib in combination with pembrolizumab in patients with previously treated, locally advanced and unresectable or metastatic triple negative breast cancer (TNBC) or triple negative inflammatory breast cancer (TN-IB).

Clinical collaboration with Merck & Co. (MSD)

Study Objectives & Endpoints

- **Main Objective:** 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.

- **Secondary Objectives:**
  - Objective Response Rate
  - Duration of Response
  - Disease Control Rate
  - Time to progression
  - Survival at 12 months
  - Response by biomarker expression

- **Primary Objective:**
  - Anti-tumour activity of bemcentinib and pembrolizumab in combination

- **Secondary Objectives:**
  - Safety of bemcentinib and pembrolizumab in combination
  - Pharmacokinetic profile of bemcentinib and pembrolizumab
  - Assessment of biomarkers

Translational Analyses

- **Biomarkers:**
  - PD-L1
  - AXL

- **Translational Analyses:**
  - AXL signaling pathway
  - PD-L1 expression
  - Immune cell populations
  - AKT signaling pathway
  - Pharmacokinetic profile of bemcentinib when given with pembrolizumab

Major Inclusion & Exclusion Criteria

**Inclusion Criteria:**
- Histopathologically or cytologically documented TNBC or TN-IBC
- Locally advanced and unresectable or metastatic TNBC or triple negative inflammatory breast cancer.
- Received one or more prior therapies for TNBC or inflammatory breast cancer in the metastatic setting
- Prior treatment (metastatic or (neo) adjuvant) must have included a prior taxane and/or anthracycline-based therapy
- Renal and hepatic and cardiac function within normal ranges
- Measurable disease as defined by RECIST 1.12
- Provision of suitable tumour tissue for the analysis of AXL kinase expression and PD-L1 expression
- Eastern Cooperative Oncology Group (ECOG) performance score 0 or 1

**Exclusion Criteria:**
- Has disease suitable for local therapy administered with curative intent
- Has received more than three previous lines of therapy in the metastatic setting
- Has received prior therapy with an immunomodulatory agent
- Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis
- Has received prior therapy with pembrolizumab
- Has received any other investigational agent within 30 days of first dose of study drug
- Has undergone any major surgery within 28 days of first dose of study drug
- Has ongoing systemic steroid therapy
- Is pregnant or breastfeeding

Participating Countries

- USA
- Spain
- United Kingdom
- Norway

Enrollment opened: July 2017

Total Study Sites: 20
Total Study Countries: 4

Conclusion

14 out of 16 patients analyzed were negative for AXL
12 out of 15 patients analyzed were negative for PD-L1
Of 18 patients analyzed, I had a partial response
Bemcentinib as monotherapy and combination in R/R AML and MDS
AML and high-risk MDS patients unfit for high intensity chemotherapy remain a very challenging patient population with limited treatment options.

The BGBC003 trial is designed to test the hypothesis whether AXL inhibition with bemcentinib can:
- Directly enhance drug efficacy and/or
- Enhance responses to chemotherapy
when given as a single agent or in combination with disease-specific chemotherapeutic agents.

**BGBC003: Phase II trial of bemcentinib in AML/MDS**

**Interim clinical data Phase II trial of bemcentinib in AML/MDS**

**Best response**

**Blood plasma levels of soluble AXL (sAXL) predict response to bemcentinib monotherapy in R/R AML & MDS patients**

**Response data presented as number (%) of patients achieving complete or partial response.**

**Blood plasma levels of sAXL are decreased in patients experiencing benefit, i.e., increase in response to treatment with bemcentinib.**

**Blood and RBC plasma levels of sAXL are correlated with sAXL levels are elevated in RBC plasma upon treatment.**
Bemcentinib in combination with SoC in metastatic melanoma

Although responses to TKIs are rapid, resistance ultimately emerges. Monotherapy checkpoint inhibitor responses can be further improved.

A Ph I/II randomised trial of selective AXL inhibitor bemcentinib in melanoma patients

Interim clinical data Phase II trial in metastatic melanoma

The BGBIL006 trial is designed to test the hypothesis whether AXL inhibition can:
- Enhance response to immunotherapy
- Enhance response to targeted therapy

when given in combination with pembrolizumab or dabrafenib/trametinib in treatment naïve melanoma patients.

**Response assessment**

<table>
<thead>
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<th>Best response</th>
<th>PD</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Biomarkers**

- Soluble protein biomarkers by liquid biopsy
- PD-L1 and AXL expression per IHC
- Immune cell populations by CyTOF

**Endpoints**

- **Primary:** ORR
- **Secondary:** PFS, DoR, OS
- **Exploratory:** response per iRC, response by biomarker expression, QoL

**Treatment**

- **BRAF positive**
  - High tumour load: Dose escalation
    - 3+3 bemcentinib: 100mg/200mg qd + trametinib/dabrafenib
    - n = 6 - 12 pts
  - Low tumour load: 2:1
- **BRAF negative**
  - 2:1
  - Dabrafenib/trametinib
  - Pembrolizumab
  - Pembrolizumab
  - Pembrolizumab
  - Pembrolizumab

**Safety/Efficacy**

- trametinib/dabrafenib +/- bemcentinib
- pembrolizumab +/- bemcentinib

**Best overall response**

<table>
<thead>
<tr>
<th>PD</th>
<th>SD</th>
<th>PR</th>
<th>CR</th>
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<tbody>
<tr>
<td>31</td>
<td>31</td>
<td>31</td>
<td>31</td>
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</table>
Bemcentinib + TARCEVA® in NSCLC

Patients with EGFR driven NSCLC develop resistance to targeted therapy.

The BGBC004 trial is designed to test the hypothesis whether AXL inhibition can:
- Reverse and/or prevent resistance to EGFR-directed therapies
when given in combination with erlotinib in EGFRm NSCLC patients who have either progressed on or have developed resistance to EGFR-targeted therapy.

BGBC004: Phase II trial in NSCLC of bemcentinib with TARCEVA (erlotinib)

**Trial Design**
- Stage IIIb or IV disease EGFRm patients enrolled up to ECOG 1
- Arm A: daily bemcentinib + TARCEVA
- Arm B: 2nd Line bemcentinib + TARCEVA + TARCEVA
- Arm C: 1st Line bemcentinib + TARCEVA + TARCEVA

**Study Results**

- **QoL**
  - Safety
  - Tolerability
- **Outcomes**
  - PFS
  - OS

**Clinical Data**

- **2nd line bemcentinib monotherapy**
  - Includes patients with 1st line failure from any cause
- **2nd line bemcentinib + TARCEVA combo**
  - Includes patients ongoing for > 12 months
- **2nd line bemcentinib + TARCEVA combo**
  - Includes ongoing patients
- **1st line bemcentinib + TARCEVA combo**
  - Includes ongoing patients

**First line combo with TARCEVA: Partial response**

- **First line combo with TARCEVA: Partial response**

**47%** Reduction in Cancer Risk
Bemcentinib + docetaxel in NSCLC

Docetaxel is standard second line chemo in NSCLC patients. Response rates in this disease setting are typically 7-10%.

The BG-BL016 trial is designed to investigate:
- safety and tolerability
- and test the hypothesis of whether Axl inhibition can enhance response to chemotherapy when given in combination with docetaxel in previously treated (at least 3x) NSCLC patients

Initial read-out expected 2H 2018

**Pt 004 characteristics**
- Gender, age: Female, 64 years old
- Histologic diagnosis: NSCLC
- Stage: IV
- Starting dose: 75mg/m² docetaxel, 100mg bemcentinib
- Cycle 2 day 1 docetaxel reduced to 60mg/m² IV
- Ethnicity: Caucasian
- EGFR wild-type, ALK negative

**Sponsor Investigator:** Dr David Gerber, UTSW Dallas

“While it is still early, to date 3 of 7 evaluable cases have demonstrated radiographic partial responses, which we cautiously hope may represent a real improvement over the 7-10% response rate seen with docetaxel chemotherapy in this disease setting.”
AXL in fibrosis
Pre-clinical evidence suggests a promising role for selective AXL inhibition in fibrotic diseases

Background

**Idiopathic Pulmonary Fibrosis (IPF)**

- IPF splits into fast and slower progressors
- Bemcentinib is active in a humanised mouse model of IPF, and is significantly more active than nintedanib

**AXL in Non Alcoholic Steatohepatitis (NASH)**

- AXL is biomarker for liver fibrosis and cirrhosis, bemcentinib inhibits NASH in vivo
- AXL is required for HCS ECM expression
- Pharmacological modulation of AXL inhibits fibrosis in a diet induced model of NASH

The importance of AXL in fibrosis

- AXL regulates cellular plasticity implicated in fibrotic development of fibrosis several pre-clinical models
- AXL is biomarker for liver fibrosis and cirrhosis sAxl and GAS6 in circulation
- Patients with advanced fibrosis (F3 and F4) currently believed to have NASH
- Approximately 5% (16 million) Americans currently believed to have NASH
- Non-alcoholic fatty liver disease (NAFLD)
- Leads to NASH in animal models
- HFCD = high-fat, choline deficient diet

**AXL & Gas6 expression is increased in IPF, levels of activated AXL (pAXL) increased in rapid IPF**

- Bemcentinib is active in a humanised mouse model of IPF, and is significantly more active than nintedanib

**Disease Progression**

- IPF splits into fast and slower progressors
- Blood vessel selective AXL inhibition in fibrotic diseases
- Pre-clinical evidence suggests a promising role for AXL inhibitors in fibrotic diseases

**Symptoms**

- Onset of IPF: typified by dyspnoea, and atypical chest symptoms
- Diagnosis: typical symptoms are slowly progressive, with radiographic evidence of fibrosis

**Death**

- Investigative tools are under development to predict risk of rapid IPF progression
- The 12-month mortality rate of IPF is 30% in fast progressors

**Observed in**

- COPD
- Asthma
- IPF
- RA-ILD
- ARDS
- COPD
- Asthma

**Some fibrotic diseases**

- 1. Systemic sclerosis
- 2. Radiation therapy
- 3. Eosinophilic fasciitis
- 4. Idiopathic portal hypertension
- 5. Lupus nephritis
- 6. RA-ILD
- 7. Autoimmune hepatitis
- 8. HCV/HBV
- 9. Congenital hepatic fibrosis
- 10. Asthma
- 11. Chronic obstructive pulmonary disease (COPD)
- 12. RA-ILD

**TAM receptors inhibitors**

- Vehicle, R428, BIBF-1120

**LCAT**

- Liver
- Heart
- Eyes

**Sytemic sclerosis**

- 1. Systemic sclerosis
- 2. Radiation therapy
- 3. Eosinophilic fasciitis
- 4. Idiopathic portal hypertension
- 5. Lupus nephritis
- 6. RA-ILD
- 7. Autoimmune hepatitis
- 8. HCV/HBV
- 9. Congenital hepatic fibrosis
- 10. Asthma
- 11. Chronic obstructive pulmonary disease (COPD)
- 12. RA-ILD

**Nephrogenic systemic fibrosis**

- 1. Nephrogenic systemic fibrosis
- 2. Radiation therapy
- 3. Eosinophilic fasciitis
- 4. Idiopathic portal hypertension
- 5. Lupus nephritis
- 6. RA-ILD
- 7. Autoimmune hepatitis
- 8. HCV/HBV
- 9. Congenital hepatic fibrosis
- 10. Asthma
- 11. Chronic obstructive pulmonary disease (COPD)
- 12. RA-ILD

**Lofoten fibrosis**

- 1. Lofoten fibrosis
- 2. Radiation therapy
- 3. Eosinophilic fasciitis
- 4. Idiopathic portal hypertension
- 5. Lupus nephritis
- 6. RA-ILD
- 7. Autoimmune hepatitis
- 8. HCV/HBV
- 9. Congenital hepatic fibrosis
- 10. Asthma
- 11. Chronic obstructive pulmonary disease (COPD)
- 12. RA-ILD

**Onset of fibrosis**

- Onset of IPF: typified by dyspnoea, and atypical chest symptoms
- Diagnosis: typical symptoms are slowly progressive, with radiographic evidence of fibrosis

**Post-diagnosis Period**

- Normal IPF
- Normal Rapid IPF
- Vehicles Bemcentinib

**Histology**

- Normal IPF
- Normal Rapid IPF
- Vehicles Bemcentinib

**Nash**

- Non-alcoholic fatty liver disease (NAFLD)
- Leads to NASH in animal models
- HFCD = high-fat, choline deficient diet

**Hydroxyproline (μg/mg of protein)**

- 0.1
- 1
- 10
- 100
- 1000
- 10000

**Pirfenidone**

- Rare disease therapeutics:
  - Market size estimated to grow to $3.5B by 2025
  - Market: >$25B in 2026
  - Approximately 5% (16 million) Americans currently believed to have NASH
  - Approximately 5% (16 million) Americans currently believed to have NASH

**CO2O2**

- 0
- 50
- 100
- 150
- 200

**SoC**

- Bemcentinib modulates the IPF decliners
- Axl expression predicts rapid IPF progression

**· Axl expression predicts rapid IPF progression
**· Bemcentinib modulates the IPF decliners

**· AXL regulates cellular plasticity implicated in fibrotic development of fibrosis several pre-clinical models
**· Pharmacological modulation of AXL inhibits fibrosis in a diet induced model of NASH

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