Corporate Presentation
May 2020
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BerGenBio corporate overview

World leaders in understanding AXL biology

- AXL tyrosine kinase mediates aggressive disease: immune evasion, therapy resistance & metastatic cancer, fibrosis and viral infection
- Selective AXL inhibitors have the potential to treat many serious unmet medical needs
- Pipeline opportunities in multiple cancers and fibrosis

3 selective AXL inhibitors in clinical development

- Bemcentinib (oral once a day pill)
- Tilvestamab (mAb), ADCT601* (ADC)
- Phase II: Monotherapy and combos with, CPI, targeted & chemo
- Biomarker correlation, parallel CDx development
- Bemcentinib phase II trials: AML (monotherapy), AML (chemo-combo) NSCLC (KEYTRUDA combo) COVID19 (mono)

Resourced to deliver milestones

- Listed on Oslo Børs: BGBIO
- Clinical trial collaborations with Merck and leading academic centres EU & USA
- 38 staff at two locations: HQ & R&D in Bergen, Norway; Clinical Development in Oxford, UK

*AXL antibody out licensed to ADC Therapeutics SA
Senior Management Team

Richard S. Godfrey, Chief Executive Officer
- Pharmacist / MBA – joined BerGenBio in 2008 as CEO
- Formerly CEO Aenova Inc., USA
- Previously Managing Director DCC Healthcare, earlier Eli Lilly, Reckitt Benckiser, Catalent
- 28 years industry experience, led and managed multiple international drug development and commercialization partnerships

Prof. James Lorens, Founder and Chief Scientific Officer
- Professor University of Bergen Medical School
- 30 years biotech research experience, academic biomedical research positions at Stanford University and University of Bergen
- Former Director Oncology R&D, Rigel Inc. (San Francisco, CA)
- The first to recognize that Axl kinase is an essential mediator of cancer development (EMT)

Prof. Hani Gabra MD, PhD, Chief Medical Officer
- MD Oncologist – joined BerGenBio in 2019
- Former VP Clinical Development Astra Zeneca UK.
- Professor of Medical Oncology at Imperial College London and Honorary Consultant in Medical Oncology at Imperial College Healthcare NHS Trust
- 20 years clinical / cancer biology research at Imperial College London.

Rune Skeie, Chief Financial Officer
- 20 years of financial management, corporate development, corporate governance and advisory experience across multiple industry sectors. – Joined BerGenBio in 2018
- Previously Executive Director at EY and CFO of REMA Franchise Norge AS, the multinational supermarket business.
- Registered Accountant and a State Authorized Public Auditors
Recent highlights

**Oct 2019**
FDA Fast Track designation received for bemcentinib in relapse AML

**Nov 2019**
Primary & Secondary endpoint of ORR met in Phase II 2L NSCLC (cohort A) in combination with KEYTRUDA®
Four-fold improvement over Keytruda monotherapy**

CDX: Proprietary composite AXL tumor-immune (cAXL) score developed to diagnose patients with clinical benefit
Five-fold improvement in ORR and four-fold mPFS improvement for cAXL +ve patients

**Dec 2019**
Presented preliminary clinical data from Ph II combination trial of bemcentinib and LDAC in AML patients at ASH conference
Durable responses reported with long duration

**Jan 2020**
Met Primary end point of ORR in phase II clinical trial in NSCLC (cohort B) in 2L IO refractory patients
Bemcentinib in combination with KEYTRUDA® meets primary end point and progress to stage 2 of the study cohort

**May 2020**
FPI COVID19 rPhII ACCORD trial
Uk Govt selected bemcentinib as first experimental compound to enter fully funded seamless platform trial for efficacy and safety

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AXL drives aggressive disease
**AXL Biology**

- AXL a receptor tyrosine kinase that is important for regulating innate immune cells.\(^1\)
- AXL levels are elevated by cellular stress and is strongly associated with inflammatory diseases including cancer and fibrosis.\(^2\)
- It functions as a homeostatic regulator in adult tissues and organ systems that are subject to continuous challenge and renewal throughout life – immune, nervous, vascular and reproductive
- AXL drives cancer progression, immune evasion, and resistance to targeted therapies.\(^3\)
- AXL is a key suppressor of the type I interferon response and is targeted by viruses to block the antiviral immunity.\(^4\)
- AXL is used by several different enveloped viruses (e.g. Ebola, Zika) to enter cells.\(^5\)
- Bemcentinib potently inhibits SARS-CoV-2 infection of cells.\(^6\)
- A lung cancer patient currently under treatment with bemcentinib who was high risk for COVID19 reported a mild Covid-19 infection.\(^7\)

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**Very low expression under healthy physiological conditions**

**Elevated AXL signaling strongly associated with cancer progression, immune evasion, drug resistance and metastasis**

**AXL mediates viral entry to cells and dampening of viral immune response**
AXL is independent negative prognostic factor in a broad variety of cancers

**Strong AXL expression correlates with poor survival rate**

1. Breast carcinoma
   - Weak AXL (60/5)
   - Strong AXL (64/11)

2. Lung adenocarcinoma (NSCLC)
   - AXL expression
   - Log Rank Test, P=0.035

3. Acute Myeloid Leukaemia
   - AXL < median
   - AXL > median

4. Pancreatic ductal adenocarcinoma
   - AXL IHC high (n=29)
   - AXL IHC low (n=59)

**Broad evidence of AXL linked with poor prognosis**

- Astrocytic brain tumours
- Melanoma
- Breast cancer
- Mesothelioma
- Gallbladder cancer
- NSCLC
- Gastric cancer
- Pancreatic cancer
- Colon cancer
- Sarcomas
- Oesophageal cancer
- Ewing Sarcoma
- Gastric cancer
- Kaposis sarcoma
- Gastric cancer
- Liposarcoma
- Gastric cancer
- Osteosarcoma
- Gynaecological
- Skin SCC
- Ovarian cancer
- Thyroid cancer
- Uterine cancer
- Urological
- Ovarian cancer
- Bladder cancer
- Osteosarcoma
- 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 is a key survival mechanism ‘hijacked’ by aggressive cancers and drives drug 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 increases on the tumor cell and causes cancer escape and survival

- AXL is a unique type I interferon (IFN) response checkpoint
- Acquired drug resistance
- Immune cell death resistant
- Metastasis

AXL increases 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

AXL is targeted by enveloped viruses to enter cells and dampen the viral immune response

Enveloped viruses display phosphatidylserine that is recognized by GAS6, the AXL receptor ligand, that mediates viral entry through “apoptotic mimicry”.

bemcentinib blocks AXL-dependent viral entry and enhances antiviral interferon response

Viral-mediated AXL receptor activation dampens type I interferon responses, a key anti-viral defence mechanism for all cells.

Bemcentinib
Bemcentinib, a first-in-class, potent, oral, highly selective AXL inhibitor

- IC$_{50}$ = 14 nM
- Uniquely selective for AXL
  - 50-100 fold selective cf. TAM kinases
- CMC scaled for regulatory filing
- Size 0 100mg HPMC capsules
- 3 years stability confirmed

- Once daily oral dosing
- Already trailed in >300 patients
- Favourable safety profile supports use in first line, high risk fragile patients
- Safety and tolerability profile supports use in combination with other drugs
- MOA is synergistic with other therapies enhancing response
- Global regulatory exposure with Fast Track Designation by FDA
- IMP available in stock for immediate clinical trial use
## BerGenBio pipeline - 3 selective AXL inhibitors in clinical development
### Multiple attractive opportunities in cancer and viral infection

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Targeted Indication</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>Bemcentinib</td>
<td>&gt;2L AML</td>
<td></td>
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<td>Ph II safety and POC efficacy demonstrated in 39 patient trial</td>
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<tr>
<td>Bemcentinib</td>
<td>(combination with LDAC)</td>
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<td>Ph Ib Safety demonstrated, efficacy POC expansion study - 28 pts.</td>
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<tr>
<td>Bemcentinib</td>
<td>2L AML</td>
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<td>Ph II safety and POC efficacy demonstrated in 50 patient trial, end points met</td>
<td>Ph II POC study on going 29 pts – stage 1 met end point</td>
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<tr>
<td>Bemcentinib (combination with Keytruda)</td>
<td>2L NSCLC (chemo refractory)</td>
<td>Ph II safety and POC efficacy demonstrated in 39 patient trial</td>
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<tr>
<td>Bemcentinib (combination with Keytruda)</td>
<td>2L NSCLC (CPI+chemo refractory)</td>
<td>Ph II PO study ongoing 29 pts</td>
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<tr>
<td>Bemcentinib</td>
<td>COVID19</td>
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<td>Ph II Efficacy &amp; Safety study ongoing 120 pts</td>
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<tr>
<td>Tilvestamab (BGB149)</td>
<td>TBA</td>
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<td>Ph I Healthy volunteer study ongoing</td>
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<tr>
<td>BGB601</td>
<td>Various solid tumors</td>
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<td></td>
<td>Ph I safety study ongoing</td>
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**CPI** – checkpoint inhibitor
# Broad phase II clinical development plan with bemcentinib

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Clinical Proof-of-concept</th>
<th>Late stage Opportunities</th>
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<tr>
<td>Selected, biomarker directed patients</td>
<td></td>
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<tr>
<td>AML / MDS</td>
<td>Completed</td>
<td></td>
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<tr>
<td>Glioblastoma (IIT)</td>
<td>Ongoing</td>
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<tr>
<td>COVID19</td>
<td>Ongoing</td>
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<table>
<thead>
<tr>
<th>Chemotherapy Combinations</th>
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<tr>
<td>Improve responses in hard to treat settings</td>
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<tr>
<td>AML + LDCT (LDAC)</td>
<td>Complete. -EXPANSION</td>
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<tr>
<td>Pancreatic, (IIT)</td>
<td>Ongoing</td>
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<tr>
<td>NSCLC (IIT)</td>
<td>Ongoing</td>
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<tr>
<th>Immunotherapy Combinations</th>
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<tr>
<td>Target resistance, enlarge addressable patient population</td>
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<tr>
<td>NSCLC (PD-L1 / AXL all comers)</td>
<td>Cohort A Complete Cohort B ongoing - EXPANSION Cohort C ongoing</td>
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<tr>
<td>Melanoma, (IIT)</td>
<td>Ongoing</td>
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<tr>
<td>Mesothelioma (IIT)</td>
<td>In set-up</td>
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<tr>
<th>Targeted Therapy Combinations</th>
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<tr>
<td>Target resistance, enlarge addressable patient population</td>
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<td></td>
</tr>
<tr>
<td>NSCLC + EGFRi</td>
<td>Completed</td>
<td></td>
</tr>
<tr>
<td>Melanoma, (IIT)</td>
<td>Ongoing</td>
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Companion Diagnostic (CDx)
- Developed a proprietary duplex IHC method with composite AXL tumor-immune Score (cAXL)
- A proprietary diagnostic algorithm using IHC scoring of AXL on tumor cells and on immune cells to identify solid tumour (NSCLC) patients that will respond / benefit from bemcentinib + CPI

AXL mediates aggressive cancer traits through EMT and Immune suppression in the tumour microenvironment:

Patient A: AXL +ve staining on lung tumour cells
- AXL mediated EMT in tumour cells
- AXL+ve Mesenchymal tumour cells are drug resistant & immune evasive

Patient B: AXL +ve staining on lung macrophages
- AXL is required to stabilize M2 macrophages
- M2 microphages are immune suppressive
- Bemcentinib inhibits AXL and macrophages switch to M1
- M1 macrophages are immune promoting
AXL inhibitors – emerging competitive landscape

Benefits of a selective AXL inhibitor:
1. Safety
2. Biomarker directed treatment
3. Combination with other drugs
Bemcentinib clinical development in COVID19

**ACCORD-2 trial**

To evaluate the efficacy and safety in hospitalized COVID19 patients

First compound selected by UK Govt. COVID19 Therapeutic Task Force

Trial funded by UK Govt.

A multicentre, randomised Phase II (120 patients) seamless Phase III transition option
BerGenBio’s bemcentinib selected to be fast-tracked as a potential treatment for COVID-19

- Preclinical data suggest that bemcentinib is potentially useful for the treatment of early SARS-CoV-2 infection, as it selectively inhibits AXL kinase activity.

- Bemcentinib selected as the first candidate to be fast-tracked in a new UK national multi-centre randomised Phase II clinical trial initiative to investigate potential treatments for hospitalised COVID-19 patients.

- ACCORD (ACcelerating COVID-19 Research & Development platform) study is funded by the UK Department of Health and Social Care and UK Research and Innovation.

- Study is a collaboration between the UK Government Scientific Office, the NIHR’s Biomedical Research centres and clinical research company IQVIA.

- Professor Tom Wilkinson is the academic lead of ACCORD-2, based at the National Institute for Health Research (NIHR) Southampton Biomedical Research Centre.

- The study will test 120 patients across 6 UK NHS hospital trusts, with the first patients due to be treated imminently.
Protocol title: A Multicentre, Seamless, Phase 2 Adaptive Randomisation Study to Assess the Efficacy and Safety of Multiple Candidate Agents for the Treatment of COVID-19 in Hospitalised Patients

Rationale:
There are currently no approved therapeutic agents available to treat coronaviruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19 disease, and there is an urgent public health need for rapid development of such interventions. This adaptive platform study is designed to rapidly assess multiple candidate agents as treatments for COVID-19. Candidate drugs that are initially assessed as being efficacious will be moved from an evaluation (pilot) stage to a confirmatory stage, with candidate agents being added to and removed from the study on an ongoing basis, depending on the results of their evaluation. Patients to be included in the study will be hospitalised and may require either supplemental oxygen, noninvasive ventilation or high flow oxygen devices, or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

Objectives:
Stage 1: To evaluate the efficacy of candidate agents as add-on therapies to standard of care (SoC) in patients hospitalised with COVID-19 in a screening stage.

Stage 2: To confirm the efficacy of identified efficacious candidate agents in patients hospitalised with COVID-19 in an expansion stage.

Endpoints:
- Time to clinical improvement of at least 2 points (from randomisation) of patients stage 3, 4 or 5 on a 9-point category ordinal scale, or live discharge from the hospital, whichever comes first (this will also define the “responder” for the response rate analyses).

9-Point Category Ordinal Scale:
0. Uninfected, no clinical or virological evidence of infection
1. Ambulatory, no limitation of activities
2. Ambulatory, limitation of activities
3. Hospitalised – mild disease, no oxygen therapy
4. Hospitalised – mild disease, oxygen by mask or nasal prongs
5. Hospitalised – severe disease, noninvasive ventilation or high flow oxygen
6. Hospitalised – severe disease, intubation and mechanical ventilation
7. Hospitalised – severe disease, ventilation and additional organ support – pressors, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO)
8. Death
**ACCORD Study overview**

**Figure 1  Study Schema**

Study dimensions:

- 6 NHS sites across UK
- Randomized Phase II
- 120 patients (60 receive bemcentinib, 60 in SoC control group)
- IQVIA are the CRO
- Standard bemcentinib dosing
- 15 day dosing schedule
- Independent Data monitoring Committee
- Seamless transition to stage 2 (phase III)

- Hospitalised adults (>18 years) with laboratory-confirmed SARS-CoV-2 infection
- Clinical status as defined Grades 3-5 on the 9 point Ordinal Scale

IA=interim analysis; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SoC=standard of care.

Note: This figure shows a hypothetical situation, where in Stage 1 of the study there are 4 candidate agents being compared with the SoC, of which 2 candidate agents progress to Stage 2.
Objective: to evaluate the safety and efficacy of bemcentinib in AML and MDS

Bemcentinib monotherapy in patients relapsed AML or MDS

Bembentinib in combination with low-dose cytarabine (LDAC) in 1L newly diagnosed or relapsed patients with AML

Bembentinib in combination with LDAC in 2L relapsed patients with AML
Acute Myeloid Leukaemia (AML)

Most common type of acute leukaemia in adults\(^1\)

AML is a rare aggressive cancer of the blood and bone marrow characterised by difficult to treat malignancies.

~ 21,000 new cases diagnosed and >11,000 deaths in the US in 2018\(^2\)

AML makes up 32% of all adult leukaemia cases.

Occurs in a predominantly elderly, frail patient population; 68% of patients diagnosed with AML were aged >60 years \(^6\)

5 year survival rates of 3-8% in patients over 60 years old \(^7\)

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\(^1\) Cancer.gov; \(^2\) SEER; \(^3\) https://www.who.int/selection_medicines/committees/expert/20/applications/AML_APL.pdf?ua=1ble
\(^4\) https://www.cancer.net/cancer-types/leukemia-acute-myeloid-aml/statistics
\(^6\) http://asheducationbook.hematologylibrary.org/content/2010/1/62.long
\(^7\) https://www.ncbi.nlm.nih.gov/books/NBK65996/
Acute Myeloid Leukaemia: Standard of Care & Bemcentinib Positioning

Standard of Care

**Fit for Intensive Chemotherapy**
- Goal is complete remission

- **Induction chemotherapy**
  - +/- FLT3 inhibitor*
  - +/- CD33 antibody*

- **Consolidation chemotherapy**

- **Haematopoietic Stem Cell Transplant (HPSCT)**

**Unfit for Intensive Chemotherapy (~70% pts)**
- Goal is to extend survival

- **Low dose chemotherapy or hypomethylating agents**
  - +/- novel targeted drugs*

- **Best supportive care**

*A small number of patients may be eligible for targeted therapy
Current Approach to AML in Elderly Patients Unfit for Intensive Chemotherapy

Newly Diagnosed AML: Choice of Low Intensity Induction Therapy:
• Hypomethylating agent (HMA) +/- venetoclax (approved in US only)
• LDAC alone or in combination with venetoclax or glasdegib (approved in US only)
• Future direction: AML with mutation of FLT3, IDH1/2

1st Relapse
• Clinical trial
• No approved therapy, but options may include HMA, LDAC or single agent venetoclax dependent on funding
• Best supportive care (BSC) or palliative care

2nd Relapse
• Clinical trial
• BSC or palliative care

Opportunity for Bemcentinib + LDAC
Opportunity for Single Agent Bemcentinib
Bemcentinib clinical development in Acute Myeloid Leukemia, (BGBC003)

Phase 1 n=36

- Single agent bemcentinib dose-finding in r/r AML/MDS

Established safety and recommended Phase 2 dose in this population

- Recommended Phase 2 dose of bemcentinib in AML or MDS is 400/200 mg as single agent OR in combination. **No dose adjustment required.**

Phase 2 Expansion Cohorts

- Cohort B1 n=14 Monotherapy AML
- Cohort B2 n=16 Combination with LDAC in newly diagnosed or relapsed AML
- Cohort B3 n=14 Combination with decitabine in ND or relapsed AML
- Cohort B4 n=14 Monotherapy MDS
- Cohort B5 expansion Combination with LDAC relapsed AML (ongoing)

LDAC = Low Dose Cytarabine
Results Bemcentinib monotherapy in relapsed/refractory ≥2L r/r AML.

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=27)</th>
<th>sAXL low (n=14)</th>
<th>sAXL high (n=11)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
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<tr>
<td>CR/CRi/CRp</td>
<td>6</td>
<td>22%</td>
<td>6</td>
</tr>
<tr>
<td>SD</td>
<td>8</td>
<td>30%</td>
<td>3</td>
</tr>
<tr>
<td>PD*</td>
<td>13</td>
<td>48%</td>
<td>5</td>
</tr>
<tr>
<td>ORR</td>
<td>5</td>
<td>22%</td>
<td>6</td>
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Biomarker: Soluble AXL (sAXL) at screen: Inversely correlated with AXL receptor activity

≥2L Relapse patients >75yrs
No approved SoC
Bemcentinib Monotherapy

AXL +ve* patients
14/27
54%
CR/Cri/CRp
6/14
43%
Stable Disease
3/14
21%
mDOR 3.1mo. (5.5*mo.)

Safety profile was well tolerated

* including 2 patients with low dose decitabine, one remains in CR after 20 months
Bemcentinib + LDAC combination is active and effective in 1L newly diagnoses unfit/elderly AML patients
- 4/6 patients with ORR
- mDoR immature >12months and all 4 responding patients ongoing
- Responding patients have poor risk factors
Bemcentinib + LDAC in r/r AML patients

Clinical Activity in Relapsed/Refractory Patients

Time on treatment

- 7 months: Ongoing
- 8 months: PR reported
- 9 months: Documented progression
- 10 months: Death (on study)
- 11 months: Secondary AML
- 12 months: Previous cancer history unknown

Treatment Response History:
- Newly-diagnosed: Patient has not been treated for AML prior to study
- Relapsed: Patient had response on most recent AML treatment regimen prior to study
- Refractory: Patient had no response to most recent AML treatment regimen prior to study

Event-free Survival (Relapsed/Refractory Patients)

- LDAC mono therapy mEFS: 1.3 months
- LDAC + vedoxorbin mEFS: 1.9 months
- LDAC + bemcentinib mEFS: 1.7 months

2L r/r AML LDAC combo expansion cohort 28pts ongoing
Registration strategies for bemcentinib in AML under consideration

Bemcentinib has FAST TRACK DESIGNATION by FDA in AML.

3 possible registration paths are apparent, in slightly different patient populations

Scientific advice will be sort early 2020, route to registration to be discussed

1. **2L Bemcentinib + LDAC combination**
   - relapse patients >60 years, patients having failed HMA or HMA+Venetoclax
   - rPh II / III, to receive bem+LDAC or LDAC alone
   - End points: ORR and DoR
   - Anticipated sample size 200 with 6 month f/u

2. **≥2L bemcentinib mono therapy**
   - Heavily pre-treated, ≥2L relapse patients >75yrs, with low sAXL
   - sAXL assay is a CLSI validate Clinical Trial Assay method performed at a CLIA lab.
   - Possible single arm or comparator being best supportive care (BSC) or palliative care
   - End points: ORR and DoR
   - Anticipated sample size 100 with 6 month f/u

3. **1L Bemcentinib + LDAC combination**
   - 1L patients >60 yrs, unsuitable for HMA+Venetoclax
   - rPh II / III
   - End points: ORR and DoR/OS
   - Anticipated sample size 200 with 12 month f/u
Bemcentinib clinical development in Non Small Cell Lung Cancer (NSCLC)

Objective: to improve the effectiveness of immune check point inhibitor (CPI) (pembrolizumab/Keytruda) refractory NSCLC patients, with a well tolerated, effective, and convenient drug

Chemotherapy refractory patients

CPI +/- chemotherapy refractory patients

CPI+Chemotherapy refractory patients
Rationale for AXL inhibitor bemcentinib as an immuno-oncology agent in combination with check point inhibitor (CPI)

- AXL drives tumor EMT and resistance to cytotoxic lymphocyte-mediated cell killing\(^1\)
- AXL receptor tyrosine kinase is a negative prognostic factor for many cancers including NSCLC\(^2\)
- AXL expression is associated with anti-PD-1 therapy failure in melanoma patients\(^3\)
- AXL is expressed by suppressive tumor-associated M2 macrophages and dendritic cells\(^4\)
- 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\(^4\)

\(^1\)Terry, 2019; \(^2\)Hugo, 2016; \(^3\)Ishikawa, 2012, Davidsen, 2017; \(^4\)Ludwig, 2018, Davidsen, submitted
NSCLC causes more cancer related deaths than breast, colon, pancreas and prostate combined

The largest cancer killer, most patients depend on drug therapy

The most common type of cancer

2.09 million new cases of lung cancer diagnosed/yr worldwide, making up 11.6% of all cancer cases¹

1.76 million lung cancer deaths/yr worldwide¹

5-year survival rate is 3.5% in patients with PD-L1 <1%, and 12.6% in patients PD-L1 1-49%

NSCLC Market:

2018 $16bn

14% annual growth rate

2026 $24 billion

¹ fortunebusinessinsights.com/industry-reports/non-small-cell-lung-cancer-therapeutics-market-100484
Non-Small Cell Lung Cancer (NSCLC)
Rapidly evolving SoC creates opportunities for novel effective, chemo free well tolerated regimens

US market
(non mutation)

1st Line
101,000 pts**
$4.5bn

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<thead>
<tr>
<th>PD-L1 expression</th>
<th>Platinum doublet chemotherapy +/- checkpoint inhibitor</th>
<th>Checkpoint inhibitor monotherapy</th>
<th>Targeted therapy</th>
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</thead>
<tbody>
<tr>
<td>&lt;1%</td>
<td>Platinum doublet chemotherapy</td>
<td>Checkpoint inhibitor monotherapy</td>
<td>Targeted therapy</td>
</tr>
<tr>
<td>1-49%</td>
<td>Platinum doublet chemotherapy</td>
<td>Checkpoint inhibitor monotherapy</td>
<td>Targeted therapy</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>Platinum doublet chemotherapy</td>
<td>Checkpoint inhibitor monotherapy</td>
<td>Targeted therapy</td>
</tr>
</tbody>
</table>

2nd Line
61,000 pts **
$3bn

Checkpoint refractory:
SoC: Docetaxel or clinical trial

Bemcentinib + Keytruda
(BGBC008)

Effective and well tolerated
2L therapies

Deepening 1L responses,
particularly PD-L1 negative/low

* Mutations / rearrangements with available targeted therapies such as EGFR and ALK
** Evaluate Pharma:USA only
BGBC008
Phase II 2-stage study of bemcentinib (BGB324) in combination with pembrolizumab

Inclusion criteria
• Adenocarcinoma histology
• Measurable disease
• Fresh tumor tissue
• AXL and PD-L1 All comers

Assessments
Efficacy
• Primary endpoint
  • Objective Response Rate

Secondary endpoints
• Duration of Response
• Disease Control Rate
• Time to Progression
• Survival at 12 months
• Response by Biomarker expression

Safety
PK

Regimen
• Pembrolizumab 200mg fixed
• Bemcentinib 400mg loading dose, then 200mg OD

Cohort A
• Previously treated with a platinum containing chemotherapy
• 2nd line advanced adeno NSCLC

Cohort B
• Previously treated with a checkpoint inhibitor (PD-L1 or PD-1 inhibitor)
• No more than 2 previous lines of treatment
• Must have had disease control for ≥12 weeks followed by progression
• 2nd or 3rd line advanced adeno NSCLC

Cohort C
• Previously treated 1st line with a checkpoint inhibitor-containing regimen in combination with a platinum-containing chemotherapy
• Disease control on 1st line therapy for ≥12 weeks followed by progression
• 2nd line advanced adeno NSCLC

Interim Analysis
Stage 1
N=24 patients
(each patient has the potential for at least 24 weeks follow-up)
Stop at this stage for:
Futility (H0:15% if ≤3 responses)
Or unfavorable risk/benefit

Final Analysis
Stage 2
N=50 patients total
(each patient has the potential for at least 24 weeks follow-up)

Interim Analysis
Stage 1
N=13 patients/cohort
(each patient has the potential for at least 24 weeks follow-up)
Stop at this stage for:
Futility (H0:15% if 0 responses)
Or unfavorable risk/benefit

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

Ref. BGBC008 / NCT03184571 – clinical trial collaboration with Merck & Co., Inc.
Cohort A 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>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient demographics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>65</td>
</tr>
<tr>
<td>Range</td>
<td>39-82</td>
</tr>
<tr>
<td>ECOG at screen</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>22 (44%)</td>
</tr>
<tr>
<td>1</td>
<td>28 (56%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>10 (20%)</td>
</tr>
<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>

<table>
<thead>
<tr>
<th>Disease mutations</th>
<th>N (=50)</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>

Safety Summary

The safety profile of combination treatment is consistent with that of each individual drug.

Treatment related adverse events were generally mild and reversible.

Treatment related adverse events were considered to be less severe and better tolerated than for other TKIs or CPI combinations used in NSCLC.

<table>
<thead>
<tr>
<th>Event Terms</th>
<th>All Grades</th>
<th>Grade≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transaminase increased*</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>Asthenia / Fatigue</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

Biomarker

<table>
<thead>
<tr>
<th>cAXL status</th>
<th>n = 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>AXL Positive</td>
<td>50%</td>
</tr>
<tr>
<td>AXL Negative</td>
<td>50%</td>
</tr>
</tbody>
</table>

PD-L1 status | n = 37 |

- Strong Positive (TPS ≥50%): 10%
- Positive (TPS 1-49%): 35%
- Subset: (TPS 1-10%) 24%
- Negative (TPS<1%) 55%

*Data cutoff (30 Sep 2019)
Cohort A: Anti-tumor activity of bemcentinib in combination with pembrolizumab
Change in tumour size from baseline by RECIST 1.1

Primary endpoint met: Overall Response Rate
cAXL^+ve 5X > cAXL^-ve

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>ORR%</th>
<th>DCR%</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>11</td>
<td>14</td>
<td>19</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Composite positive</td>
<td>15</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>Composite negative</td>
<td>15</td>
<td>1</td>
<td>5</td>
<td>9</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Strong positive (TPS &gt; 50%)</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Positive (TPS 1-49%)</td>
<td>13</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>Negative (TPS &lt; 1%)</td>
<td>20</td>
<td>4</td>
<td>6</td>
<td>10</td>
<td></td>
<td>20</td>
</tr>
</tbody>
</table>

Best Change in Sum of Target Lesions (from Baseline)

- AXL composite negative
- AXL composite positive
- AXL status not evaluable

PD-L1 Status
- Negative -
- Positive +
- Strong Positive ++

Individual patients
Cohort A: >4 X improvement in mPFS* in composite AXL positive patients

- 4-fold improvement in cAXL +ve vs. cAXL –ve patients.
- 4-fold improvement in what might be expected in the same patient population with Keytruda monotherapy

Source: KN001; Garon et al NEJM 2015; KN-010 Herbst et al, Lancet 2016

*Progression-free survival
BerGenBio’s proprietary novel gene signature predicts patients that benefit from bemcentinib - pembrolizumab combination therapy

SITC 2019: BerGenBio & Merck independently published related gene signatures that predict response or resistance to pembrolizumab.

Merck reported a gene signature from patients that did not respond to Keytruda monotherapy in many cancers, this was similar to the BerGenBio gene signature EXCEPT these patients did respond to Keytruda + bemcentinib.
Cohort B: Bemcentinib + KEYTRUDA in CPI refractory patients

CHECK POINT INHIBITOR REFRACTORY PATIENTS: precise and specific definition

Patients must have reported an initial clinical benefit (CR, PR or SD) for at least 12 weeks and subsequently progressed on treatment with an anti-PD1/L1 monoclonal antibody (mAb) administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. PD-1 treatment progression is defined by meeting all of the following criteria:

a) Has received at least 2 doses of an approved anti-PD-1/L1 mAb.

b) Has demonstrated disease progression after PD-1/L1 as defined by RECIST v1.1. The initial evidence of disease progression (PD) is to be confirmed by a second assessment no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression.

c) Progressive disease has been documented within 12 weeks from the last dose of anti-PD-1/L1 mAb. Seymour et al; iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 18: e143-52

This determination is made by the investigator. Once PD is confirmed, the initial date of PD documentation will be considered the date of disease progression.

a) Other therapies not to be administered between last dose of anti PD-1/L1 mAb and commence of clinical trial agent
## Development strategy for Bemcentinib in NSCLC (ad. & Sc.)

<table>
<thead>
<tr>
<th>Clinical Position</th>
<th>Patient Population</th>
<th>Concept</th>
<th>Development Plan – target conditional approval / BT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2L IO(chemo) refractory</td>
<td>Stage III/IV Ad. PD-L1 all comor cAXL +ve.</td>
<td>Randomised Phase IIb / III Bemcentinib + CPI vs. docetaxol 1º endpoints: Interim mPFS, (for C/A A) 6 &amp; 12mn OS, OS (for full approval) 2º endpoints: ORR, DoR, Safety, tolerability.</td>
<td>1. Pending BGBC008 cohort B + C 2. SA advice from FDA &amp; EMA 3. cAXL assay validation in BGBC008 B&amp;C</td>
</tr>
<tr>
<td>1L</td>
<td></td>
<td>TBA</td>
<td></td>
</tr>
</tbody>
</table>
BGB149
anti-AXL monoclonal antibody
BGB149: Anti-AXL monoclonal antibody
Phase I clinical trial ongoing

- Functional blocking fully-humanised IgG1 monoclonal antibody
- Binds human AXL, blocks AXL signalling
- High affinity (KD: 500pM), Anti-tumour efficacy demonstrated *in vivo*
- Robust manufacturing process established, 18 months stability
- Phase Ia healthy volunteer SAD study complete
  - Safety – no dose limiting toxicity seen up to 3mg/kg dose
  - Pharmacokinetics - exposure predictable with dose proportional Cmax increase
  - Confirmatory evidence of *in vivo* target engagement with sAXL -- stabilisation in circulation
- Phase I safety trial ongoing
The role of AXL in fibrosis

- AXL Regulates and modulates key fibrogenic pathways
  - TGFβ signaling\(^1,2\)
  - Mechanosensing Hippo pathway\(^3\)
  - Peroxisome proliferator-activated receptor\(^4\)
- Axl regulates cellular plasticity implicated in fibrotic pathologies e.g. EMT, EndMT, Macrophage polarity
- AXL is a negative regulator of epithelial cell barrier integrity\(^5\)
- Axl is required for hepatic stellate cell (HSC) activation and ECM deposition\(^6\)
- Pharmacological modulation of Axl inhibits pre-clinical development of Liver (CCl4/HighFatDiet\(_6\)), Renal (UUO\(_6\)) and Pulmonary (Asthma\(^9\), Bleo\(^10\), IPF\(^10\)) fibrosis

FIBROGENESIS
- fibroblast activation
- ECM deposition
- Proliferation and migration
- Inflammatory signals
- Enhanced sAXL

INFLAMMATION
- Cytokines
- Chemokines
- Immune cell infiltration

---

AXL inhibition prevents fibrosis in a panel of pre-clinical models

**Lung**

Bemcentinib reduces fibrosis in a human xenograft model of IPF 1

Bemcentinib reduces bleomycin induced fibrosis 2

**Liver**

Bemcentinib reduces fibrosis in the CCL4-induced model of liver fibrosis 3

Bemcentinib reduces fibrosis in a diet induced model of NASH 4

**Kidney**

Bemcentinib reduces kidney fibrosis following Unilateral Ureteral Obstruction (UOO) 5

Bemcentinib ameliorates anti-GBM induced lupus like nephritis and improved kidney function 6

1 Espindola et al., 2018; 2 BerGenBio ASA; 3 Barcena et al., 2015; 4 Tutsaus et al., unpublished; 5 Landolt et al., 2019 6 Zhen et al., 2018
Corporate
## BerGenBio pipeline – near term news flow

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Targeted Indication</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Next expected news</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bemcentinib</td>
<td>&gt;2L AML</td>
<td>Ph II safety and POC efficacy demonstrated in 39 patient trial</td>
<td></td>
<td></td>
<td></td>
<td>ASH 2020 Update clinical &amp; translational data</td>
</tr>
<tr>
<td>Bemcentinib (combination with LDAC)</td>
<td>2L AML</td>
<td>Ph Ib Safety demonstrated, efficacy POC expansion study- 28 pts.</td>
<td></td>
<td></td>
<td></td>
<td>SITC 2020 Updated mOS</td>
</tr>
<tr>
<td>Bemcentinib (combination with Keytruda)</td>
<td>2L NSCLC. (chemo refractory)</td>
<td>Ph II POC efficacy demonstrated in 50 patient trial, end points met</td>
<td></td>
<td></td>
<td></td>
<td>SITC 2020 Stage 1 interim clinical and translational data</td>
</tr>
<tr>
<td>Bemcentinib (combination with Keytruda)</td>
<td>2L NSCLC (CPI refractory)</td>
<td>Ph II POC study ongoing 29 pts – stage 1 met end point</td>
<td></td>
<td></td>
<td></td>
<td>SITC 2020 Stage 1 interim clinical and translational data</td>
</tr>
<tr>
<td>Bemcentinib (combination with Keytruda)</td>
<td>2L NSCLC (CPI+chemo refractory)</td>
<td>Ph II POC study ongoing 29 pts</td>
<td></td>
<td></td>
<td></td>
<td>SITC 2020 Stage 1 interim clinical and translational data / WCLCL 2021</td>
</tr>
<tr>
<td>Bemcentinib</td>
<td>COVID19</td>
<td>Ph II Efficacy &amp; Safety study ongoing 120 pts</td>
<td></td>
<td></td>
<td></td>
<td>Q2/3 2020 Top line clinical data</td>
</tr>
<tr>
<td>Tilvestamab (BGB149)</td>
<td>TBA</td>
<td>Ph I Healthy volunteer study ongoing</td>
<td></td>
<td></td>
<td></td>
<td>Q4 2020 Top line clinical data</td>
</tr>
<tr>
<td>BGB601</td>
<td>Various solid tumors</td>
<td>Ph I safety study Terminated (change in clinical plan and drug supply)</td>
<td></td>
<td></td>
<td></td>
<td>Update by collaborators</td>
</tr>
</tbody>
</table>

**Notes:**
- CPI – checkpoint inhibitor
- mOS – median overall survival
- ASH – American Society of Heamatology (Dec 5-8)
- SITC – Society of Immunotherapy of Cancer (Nov10-15)
- WCLC – World Congress of Lung Cancer (Jan 26-29 2021)
Select Company Financials

<table>
<thead>
<tr>
<th>Oslo Børs</th>
<th>BGBIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cash (YE'19 + Q1'20 - PIPE)</td>
<td>$45m</td>
</tr>
<tr>
<td>Shares Outstanding</td>
<td>73,3m</td>
</tr>
</tbody>
</table>
Board of Directors

Sveinung Hole, Chairman of the board
- Non-Executive director of BerGenBio since 2010, chairman from 2019.
- Master of International Management.
- Representative of lead shareholder.

Prof. Stener Kvinnsland, MD, PhD, Non-Executive Director
- Non-Executive director of BerGenBio since 2015.
- More than 30 years of experience in oncology, Chair Oslo University Hospital, CEO of the Bergen Hospital Trust, Head of the Department of Oncology and Professor of Medicine (Oncology) at the University of Bergen and Director Clinical R&D, Oncology for Pharmacia & Upjohn in Milan.

Grunde Eriksen, Non-Executive Director
- Non-Executive director of BerGenBio since 2019.
- Experienced capital markets advisor and investor.
- 18 years international experience in corporate finance and equity sales with SEB & Arctic Securities.

Dr. Debra Barker MD, Non-Executive Director
- Non-Executive director of BerGenBio since 2019.
- Diploma in Pharmaceutical Medicine and MSc in immunology.
- Executive experience with Novartis, Roche, Smithkline Beecham and Knoll and served until recently as the Chief Medical and Development Officer at Polyphor Ltd.

Dr. Pamela Trail, Noe-Executive Director
- Non-Executive director of BerGenBio since 2015.
- More than 30 years of experience in oncology, Chair Oslo University Hospital, CEO of the Bergen Hospital Trust, Head of the Department of Oncology and Professor of Medicine (Oncology) at the University of Bergen and Director Clinical R&D, Oncology for Pharmacia & Upjohn in Milan.

- Non executive director of BerGenBio since 2019.
- PhD from the University of Connecticut.
- Strategic oncology leadership roles at Regeneron, MedImmune, Bayer Healthcare and BMS and served as CSO at Seattle Genetics.
Analyst coverage

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Sponsored research:
Link to reports from Trinity Delta:
https://www.bergenbio.com/investors/analyst-coverage/
Background published data on AXL role in viral infection
AXL mediates viral entry through “apoptotic mimicry” and suppresses the anti-viral type I interferon (IFN) response


Viral particle binding via GAS6-AXL potently activates signal transduction through its tyrosine kinase domain to suppress type I interferon (IFN) signaling and facilitate viral replication (Bhattacharyya 2013, Meertens 2017).

AXL increases viral infection through two mechanisms:
1) enhanced viral entry through “apoptotic mimicry”; and
2) suppression of anti-viral type I interferon (IFN) responses
AXL mediates viral entry through “apoptotic mimicry” and suppresses the anti-viral type I interferon (IFN) response

AXL signaling suppresses viral-induced IFN responses via SOCS1/3, leading to increased viral replication in infected cells and decreased anti-viral defenses of neighboring cells (Huang 2015, Chen 2018, Strange 2019).

Therapeutic AXL receptor inhibition ameliorated pulmonary pathology resulting from primary viral infection in experimental models, indicating an important role for AXL within the lung (Shibata 2014).

During primary respiratory syncytial virus (RSV) infection, AXL inhibition increased the number of IFNg–producing T cells and NK cells, suppressed RSV replication and whole lung levels of IL-4 and IL-13.

The lethal effect of intrapulmonary H1N1 infection inflammation was reduced by AXL inhibition. AXL inhibition in infected mice increased the number of IFN-b–producing macrophages and dendritic cells and suppressed neutrophil infiltration.

Axl-null mice are resistant to ZIKA pathogenesis likely due to a combination of reduced virus entry and enhanced IFN responses (Hastings 2019), indicating a potential role for AXL inhibitors as therapeutics during viral infection.
**AXL is a unique type I interferon (IFN) response checkpoint**

- IFNR signaling induces AXL expression\(^4,5\).
- AXL is a critical negative feedback regulatory mechanism for TLR-induced type I interferon (IFN) responses in myeloid (dendritic cells, macrophage), NK and tumor cells\(^1-4\).
- AXL is an IFN checkpoint: AXL signaling blocks IFNR signaling via SOCS1/3 and TBK1\(^5,6\).
- AXL on dendritic cells is targeted by viruses (e.g. Zika) to abrogate IFN responses and inhibit anti-viral immunity\(^7\).

AXL inhibition enhances type I interferon gene response to viral infection

6. Cruz et al JCI Insight. 2019 Apr 2
Bemcentinib showed effect against lethal EBOV infection in animal models conducted by PHE

Abstract: In light of the recent outbreak of Ebola virus (EBOV) disease in West Africa, there have been renewed efforts to search for effective antiviral countermeasures. A range of compounds currently available with broad antimicrobial activity have been tested for activity against EBOV. Using live EBOV, eighteen candidate compounds were screened for antiviral activity in vitro. The compounds were selected on a rational basis because their mechanisms of action suggested that they had the potential to disrupt EBOV entry, replication or exit from cells or because they had displayed some antiviral activity against EBOV in previous tests. Nine compounds caused no reduction in viral replication despite cells remaining healthy, so they were excluded from further analysis (zidovudine; didanosine; stavudine; abacavir sulphate; entecavir; JB1a; Aimspro; celgosivir; and castanospermine). A second screen of the remaining compounds and the feasibility of appropriateness for in vivo testing removed six further compounds (ouabain; omeprazole; esomeprazole; Gleevec; D-LANA-14; and Tasigna). The three most promising compounds (17-DMAG; BGB324; and NCK-8) were further screened for in vivo activity in the guinea pig model of EBOV disease. Two of the compounds, BGB324 and NCK-8, showed some effect against lethal infection in vivo at the concentrations tested, which warrants further investigation. Further, these data add to the body of knowledge on the antiviral activities of multiple compounds against EBOV and indicate that the scientific community should invest more effort into the development of novel and specific antiviral compounds to treat Ebola virus disease.
References
References

Non-Oncology

Viruses

Best SM. Viruses Play Dead to TAMe Interferon Responses. Cell Host Microbe 2013 14:117

- Thoughtful editorial on the role of AXL in viral infection accompanying Bhattacharyya 2013


- Demonstration that GAS6-AXL complexes tether enveloped viruses to cells, activating AXL and dampening type I interferon responses.

Chen J et al. AXl promotes Zika virus infection in astrocytes by antagonizing type I interferon signalling. Nat Microbiol 2018 3:302

- Key article showing that Zika virus targets AXl on dendritic cells to block type I interferon responses including several type I interferon genes and IFN-stimulating genes.

Dowall SD et al. Antiviral Screening of Multiple Compounds against Ebola Virus. Viruses 2016, 8:27


Hastings et al. Loss of the TAM Receptor Axl Ameliorates Severe Zika Virus Pathogenesis and Reduces Apoptosis in Microglia iScience 2019 13:339

- Report showing that Axl knockout mice are resistant to ZIKV pathogenesis.


- Axl silencing decreased HBV clearance of adult mice whereas enhanced HBV clearance. IFN-β signaling induced Axl regulatory pathway and facilitated Treg-cell differentiation.


- Demonstration that AXL mediates Ebola virus infection via micropinocytosis.


- Report detailing the role of GAS6-AXL in Dengue viruses (DVs) infection.


- Demonstration that bemcentinib blocks ZIKA virus infection of glial cells but blocking AXL-mediated viral entry and dampened innate immunity.

Moller-Tank, S, Maury W. Phosphatidylserine receptors: Enhancers of enveloped virus entry and infection Virolgy 2014 :468-70:565

- Review of receptors driving apoptotic mimicry.


- Therapeutic AXL receptor inhibition ameliorated pulmonary pathology resulting from primary viral infection in experimental models, indicating an important role for AXL within the lung.


- First demonstration of AXL in Ebola cell entry.

Strange DP et al. Axl promotes Zika virus entry and modulates the antiviral state of human Sertoli cells. mBio 2019 10:e01372.

- Demonstration that bemcentinib blocks Zika virus infection in multicellular organoids by attenuating both viral entry and type I interferon antagonism.
Published papers in 2019 registered on Pubmed for AXL and Fibrosis: 8

Tutusaus et al., (2019) Axl targeting abrogates experimental non-alcoholic steatohepatitis (NASH) progression, Cellular and Molecular Gastroenterology and Hepatology, In Press
- Bemcentinib reduces inflammation and fibrosis in a diet induced model of Non Alcoholic Steato Hepatitis (NASH)
- Patients with advanced fibrosis and cirrhosis have elevated sAXL in circulation and AXL expression in liver biopsies.

Landolt et al., (2019) AXL targeting reduces fibrosis development in experimental unilateral ureteral obstruction. Physiol Rep
- Unilateral ureteric obstruction by ligation in mice, induced tubulointerstitial fibrosis with enhanced expression of AXL on cells of the interstitium, tubules and glomeruli
- Bemcentinib reduced development of fibrosis and inflammation in obstructed kidneys

Reviews

COPD
- Continued AXL signaling results in basal cell hyperplasia and a dysfunctional epithelial barrier in trachea with pathology typical of chronic inflammatory pulmonary diseases.
- Genetic depletion of AXL allows resolution of inflammation with differentiation to ciliated epithelium
Published papers in 2019 registered on Pubmed for AXL and Cancer: 122

• Inhibition of AXL with Bemcentinib preferentially kills early hemopoietic stem cells from patients with JAK2 mutated driven MPN.

Terry et al., (2019 Cancer Immunology Research) AXL Targeting Overcomes Human Lung Cancer Cell Resistance to NK- and CTL-Mediated Cytotoxicity, Cancer Immunology Research.
• AXL drives tumor EMT and resistance to cytotoxic lymphocyte-mediated cell killing.
• Bemcentinib sensitizes NSCLC tumor cells to lymphocyte mediated cell killing.

• AXL drives an epithelial plasticity program enhancing invasive and metastatic capacity via TBK1 in KRAS-mutant PDA.

• AXL contributes to platinum and taxane resistance in ovarian cancer, and inhibition of AXL improves chemoresponse and accumulation of chemotherapy drugs.

Tanaka et al., (2019) Axl signaling is an important mediator of tumor angiogenesis, Oncotarget.
• Bemcentinib decreases the secretion of pro-angiogenic factors and impairs functional properties of endothelial cells in vitro and in vivo.

• AXL positively correlates expressions of PD-L1 and CXCR6.
• Bemcentinib decreased mRNA expressions of PD-L1 and CXCR6 in EGFR mutation-positive cell lines.

Reviews
• Arner EN et al., Behind the Wheel of Epithelial Plasticity in KRAS-Driven Cancers. Front Oncol.
• Myers KV et al., Targeting Tyro3, Axl and MerTK (TAM receptors): implications for macrophages in the tumor microenvironment. Mol Cancer.
• Niu ZS et al., Role of the receptor tyrosine kinase Axl in hepatocellular carcinoma and its clinical relevance. Future Oncol.
References

**Bemcentinib:**
- Axl associated with poor outcomes in pancreatic cancer uniquely links drug resistance and immune evasion.
- Bemcentinib blocks aggressive traits of pancreatic cancer uniquely links drug resistance and immune evasion.
- Bemcentinib drives tumour cell differentiation and provokes an immune stimulatory microenvironment. Treatment reduces expression of Arginase-1 a key player in immune-suppression.
Guo et al (2017) Axl inhibition induces the antitumor immune response which can be further potentiated by PD-1 blockade in the mouse cancer models, Oncotarget
- Axl inhibition via bemcentinib reprograms immunological microenvironmentIncreased proliferation and activation of CD4 and CD8
- Bemcentinib and PD-1 blockade act synergistically

**Mode of Action & Biomarkers**
- Warfarin inhibits Axl signalling and Axl-mediated biological response at doses lower than those which mediate anti-coagulation effects.
- Retrospective analysis of a large population cohort demonstrates that patients on low dose Warfarin had a significantly lower incidence of cancer.

- Immune checkpoint inhibitors are most effective against T-cell inflamed tumors. Non-T-cell or T-cell excluded tumors remain a significant barrier to treatment.
- Axl identified as a key mediator of immune evasion and experimental evidence demonstrates Axl targeting leads to greater anti-tumour immune response post radiotherapy.

- Proteases known as sheddases cleave the extracellular domain of several receptor tyrosine kinases such as Axl generating soluble Axl (sAxl).
- Plasma levels of sAxl are predictive of patient response to standard of care BRAF&MEKinhibitor therapy and could be used for patient stratification strategies.

- Axl particularly abundant in ovarian cancer subtype designated as mesenchymal (Mes)
- Axl co-clustered cMET, EGFR, and HER2, producing sustained extracellular signal–regulated kinase (ERK) activation in Mes cells
- Bemcentinib reduced tumor growth in chick chorioallantoic membrane model.

**Reviews**
Chouabi et al (2014) Tumor Plasticity Interferes with Anti-Tumor Immunity. Critical RevImmunology
Resistance


- Renal cell carcinoma (RCC) represents 2-3% of all cancers in the Western world.
- First line therapy is sunitinib (PDGF/VEGF TK inhibitor).
- 47% of RCC patients treated with sunitinib were +ve for Axl.
- Axl expression in sunitinib treated patients correlated with worse clinical outcome (13 months Vs 43 months survival).


- Patient treated with EGFR based therapies develop resistance via multiple mechanisms.
- Resistant metastatic lung cancers exhibit increased AXL, EMT and PDL1 expression.

Elkabet et al (2015) AXL Mediates Resistance to PI3Ka Inhibition by Activating theEGFR/PKC/mTOR Axis in Head and Neck and Esophageal Squamous Cell Carcinomas. *Cancer Cell*

- Axl mediates persistent mTOR activation and upregulated in resistant tumors
- Combined treatment with PI3Ka and either EGFR, AXL, or PKC inhibitors reverts this resistance


- EMT signature was developed based on 11 tumor types
- Axl frequently overexpressed in EMT tumors along with PD-L1, PD1, CTLA4, OX40L, and PDL2
- highlights the possibility of utilizing EMT status—independent of cancer type—as an additional selection tool to select patients who may benefit from immune checkpoint blockade


Mueller et al (2014) Low MITF/AXL ratio predicts early resistance to multiple targeted drugs in melanoma

- high Axl in melanoma cells correlates with drug resistance
- BRAF and ERK inhibitors are more effective when using Axl inhibition
References

Non-Oncology

Pulmonary fibrosis
• Axl was activated in hyperplasia of epithelial cells in idiopathic pulmonary fibrosis patients where the epithelial barrier integrity was lost
• In vitro, Axl inhibition or downregulation by small interfering RNA led to increase in epithelial surfactant protein expression and promotion of an epithelial cell phenotype.
• IPF patients with high expression of Axl are rapid (declining lung function) progressors.
• Bemcentinib inhibited the fibrogenic phenotype of IPF patient derived fibroblasts.
• GAS6 knockout animals were protected from Bleomycin induced lung fibrosis (Gold standard model of pulmonary fibrosis).
• Bemcentinib inhibited the development of fibrosis in the IPF SCID mouse model (Human IPF fibroblasts induce pulmonary fibrosis in the SCID mouse).

Chronic Obstructive Pulmonary Disease
• Basal epithelial cells in the trachea, express AXL and are activated by Gas6 ligand interaction with apoptotic cells in airway inflammation.
• AXL signaling is critical for expansion of the pool of basal cells, but needs to be silenced to allow differentiation of basal epithelium ciliated cell regeneration.
• Continued AXL signaling results in basal cell hyperplasia and a dysfunctional epithelial barrier with abnormal differentiation to squamous (not ciliated) epithelium and continued cell turnover, typical of the pathology of chronic inflammatory pulmonary diseases.
• Genetic depletion of AXL allows resolution of inflammation with differentiation to ciliated epithelium.

Liver Fibrosis
• sAxl confirmed to be accurate biomarker of liver fibrosis and cirrhosis.
• sAxl/albumin demonstrated to be further enhancing as a cheap and accurate biomarker.
• Axl levels paralleled HSC activation
• Axl knock out mice displayed decreased HSC activation in vitro and liver fibrogenesis after chronic damage by CCl4 administration
• Bemcentinib reduced collagen deposition and CCl4-induced liver fibrosis in mice

Kidney fibrosis
• Progressive chronic kidney disease is typified by kidney fibrosis, typified by activated myofibroblast accumulation and deposition of extracellular matrix.
• Unilateral ureteric obstruction by ligation, in mice, induced tubulointerstitial fibrosis with enhanced detection of AXL on cells of interstitium, tubules and glomeruli
• Bemcentinib reduced development of fibrosis and inflammation in obstructed kidneys compared to treatment with an ACE-inhibitor

Polycthemia Vera, Myelofibrosis (MyeloProliferative Neoplasms - MPN)
• AXL is upregulated and activated in JAK2 associated MPNs
• Inhibition of AXL with Bemcentinib preferentially kills early hemopoietic stem cells from patients and, as such represents a promising therapeutic approach for JAK2 driven MPN

Reviews