# Combination of bemcentinib (BGB324) – a first-in-class selective, oral AXL inhibitor – with pembrolizumab in patients with triple negative breast cancer and adenocarcinoma of the lung.

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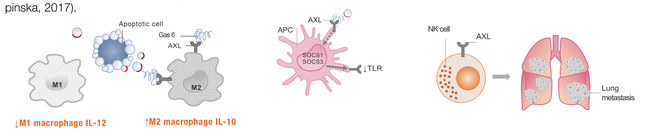
BerGenBio

In collaboration with: MSD

## Introduction & background

### RTK AXL in inate immunity and immune evasion

Activation of the receptor tyrosine kinase AXL has a profound suppressive effect on the innate immune system (Zagórska, 2014). AXL is overexpressed on multiple cell types in the tumour immune microenvironment including dendritic cells, NK cells and tumour-associated macrophages. AXL signalling in immune cells supports tumour immune escape by downregulating dendritic cell activity, modulating efferocytosis as well as favouring an immunosuppressive chemokine profile and M-MDSC expansion. AXL is prevalent in tumours resistant to anti-PD-1 therapy (Hugo, 2016). AXL expression in tumour cells confers resistance to effector T cell cytotoxicity (Wnuk-Lipinska, 2017).

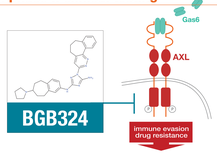



### Bemcentinib (BGB324): selective, oral small molecule inhibtor of AXL in phase II clinical testing

Bemcentinib (BGB324) is a first-in-class, orally bioavailable, highly selective AXL kinase inhibitor which is being evaluated as a therapy for solid tumours and myeloid malignancies. Phase II clinical trials are ongoing with bemcentinib in combination with pembrolizumab in adenocarcinoma of the lung (NCT03184571), TNBC (NCT03184558) and melanoma (NCT02872259) as well as in NSCLC in combination with erlotinib (NCT02424617) or docetaxel (NCT02922777) and as a single agent and in combination with low dose chemotherapy in AML & MDS (NCT02488408).

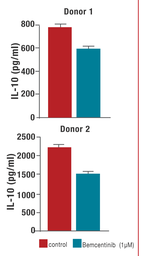
**Selectivity Profile**

| Kinase | Kinome Scan (Kd) | |
|---|---|---|
| | nM | Fold |
| Axl | 0.4 | 1 |
| Mer | 100 | 250 |
| Tyro | >1000 | >1000 |



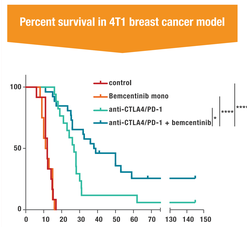

### Bemcentinib stimulates innate immunity & increases the effect of immune checkpoint inhibitors in vivo

**Bemcentinib stimulates innate immunity**



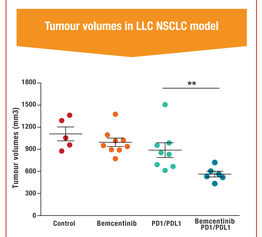

Monocytes isolated from PBMCs of HVs were cultured in the presence of 50 mg/ml M-CSF. M2s were pretreated for 2 hrs with bemcentinib then primed with 5 ng/ml IFN-g for 2 hrs followed by o/n stimulation with 100 ng/ml LPS. Supernatants were collected and IL-10 were determined by ELISA.

**Bemcentinib potentiates the effect of immune checkpoint inhibitors in TNBC animal model**



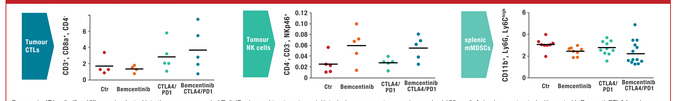

Transformed survival curves showing durable tumour clearance in 23 % of animals bearing orthotopic 4T1 mammary tumours treated with bemcentinib + anti-mCTLA4/anti-mPD-1. Treatment with anti-mCTLA4/ anti-mPD-1 alone resulted in tumour clearance in 5.6% of animals. Treatment was initiated when tumours were established and showed an average volume of 120 mm³. Statistical analysis was performed using log-rank (Mantel-Cox) test (*: p ≤ 0.05; ****: p < 0.0001). n = 4-18.

**Bemcentinib potentiates the effect of immune checkpoint inhibitors in NSCLC animal model**




Syngeneic LLC cells ($2.5 \times 10^5$) were implanted into the right flank of C57/BL6 mice. Treatment was initiated at the day of implantation. Animals were treated with anti-PD-L1 and anti-PD-1 (10 mg/kg each, at days 0, 2, 4, 6, 8, 14, IP), bemcentinib (50 mg/kg BID, oral gavage). Vehicle groups were injected with control IgG (10 mg/kg). Final tumor volumes are shown.

**Bemcentinib + immune checkpoint inhibitors modulate tumour immune infiltration**




Syngeneic 4T1 cells ($2 \times 10^6$) were implanted into the mammary pad of Balb/C mice and treatment was initiated when average tumour size reached 150 mm³. Animals were treated with control IgG or anti-CTLA4 and anti-PD-1 (10 mg/kg each at days 0, 2, 4, 6 IP) or bemcentinib (50 mg/kg BID, oral gavage). Tumours were harvested 10 d after treatment initiation and dissociated for flow cytometry analysis of immune cell infiltration.

## Phase II Studies of bemcentinib (BGB324) in combination with pembrolizumab in TNBC and adenocarcinoma of the lung

### Study designs

**2nd line advanced TNBC or TN-IBC**

- Prior taxane &/or anthracycline
- Measurable disease
- Fresh tissue biopsy
- PD-L1 +ve and -ve
- AXL +ve and -ve

→ **Single arm**
- Bemcentinib 200mg daily
- Pembrolizumab 200mg 3-weekly

→ **Interim analysis** n = 28 patients → **Final analysis** n = 56 patients

**2nd line advanced adeno NSCLC**

- Prior platinum
- Measurable disease
- Fresh tissue biopsy
- PDL1 +ve and -ve
- AXL +ve and -ve

→ **Single arm**
- Bemcentinib 200mg daily
- Pembrolizumab 200mg every

→ **Interim analysis** n = 22 patients → **Final analysis** n = 48 patients

### Key inclusion & exclusion criteria

**TNBC (NCT03184558)**

- 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 must have included a prior taxane and/or anthracycline-based therapy
- 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

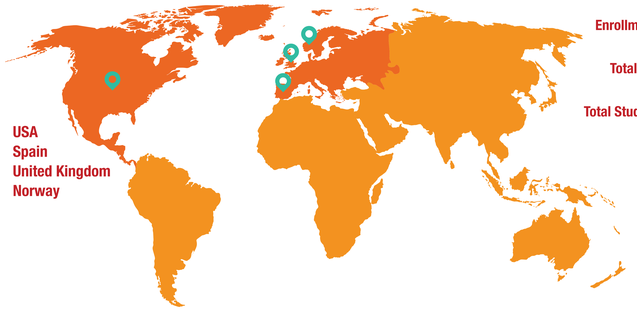
- Not received more than three previous lines of therapy in the metastatic setting
- No prior therapy with an immunomodulatory agent
- No known active central nervous system (CNS) metastases and/or carcinomatous meningitis
- No recent or ongoing systemic steroid therapy

**NSCLC (NCT03184571)**

- Histopathologically or cytologically documented Stage IV adenocarcinoma NSCLC
- Has disease progression on or after a prior platinum-containing chemotherapy
- Measurable disease as defined by RECIST 1.1
- Provision of suitable tumor tissue for the analysis of Axl kinase expression and PD- L1 expression
- Eastern Cooperative Oncology Group (ECOG) performance score 0 or 1

- Not received more than one prior line of chemotherapy for advanced or metastatic adenocarcinoma of the lung
- No prior therapy with an immunomodulatory agent
- No known active central nervous system (CNS) metastases and/or carcinomatous meningitis
- No recent or ongoing systemic steroid therapy

### Participating countries



USA
Spain
United Kingdom
Norway

**Enrollment opened:** July 2017

**Total Study Sites** 30

**Total Study Countries** 4

### Study objectives

**Primary objective:**

- Anti-tumor activity of bemcentinib and pembrolizumab in combination

**Secondary objectives:**

- Safety of bemcentinib and pembrolizumab when given in combination
- Anti-tumour activity of the combination of bemcentinib and pembrolizumab
- Pharmacokinetic profile of bemcentinib when given with pembrolizumab

**Explorative:**

- Assessment of relevant biomarkers

**Primary endpoint:**

- Objective Response Rate

**Secondary endpoints:**

- Duration of Response
- Disease Control Rate
- Time to progression
- Survival at 12 months
- Response by biomarker expression

### Translational analyses

**Target expression levels**

| Biomarker | Method |
|---|---|
| • PD-L1 expression levels | • IHC |
| • AXL expression levels | • IHC |

**Predictive & mechanism of action biomarkers (explorative)**

| Biomarker | Method |
|---|---|
| • Soluble protein biomarkers | • Myriad RBM Discovery Map (liquid biopsy) |
| • Transcriptome | • Gene expression signature |
| • Immune cell populations | • Multiplex IHC |
| • AXL signalling pathways | • EMT signature |

**Pharmacokinetics**

- Bemcentinib
- Pembrolizumab

**Stage 1 completion expected for H2 2018**

## Safety: Bemcentinib (BGB324) in combination with pembrolizumab

### Treatment emerging SAEs combining bemcentinib and pembrolizumab - status: Jan 15th '18

| | | TNBC NCT03184558 | NSCLC NCT03184571 | melanoma* NCT02872259 | total | |
|---|---|---|---|---|---|---|
| | | 19 | 9 | 6 | 34 | |
| SOC | preferred term | n | n | n | n | % |
| Skin and subcutaneous tissue disorders | | 4 | 0 | 0 | 4 | 12 |
| | Rash | 2 | | | | |
| | Maculo-papular rash | 1 | | | | |
| | Pruritus | 1 | | | | |
| General disorders and administration site conditions | | 3 | 0 | 1 | 4 | 12 |
| | Pyrexia | 2 | | | | |
| | Fatigue | | | 1 | | |
| | Fever | 1 | | | | |
| Gastrointestinal disorders | | 3 | 0 | 0 | 3 | 9 |
| | Diarrhea | 1 | | | | |
| | Nausea | 1 | | | | |
| | Vomiting | 1 | | | | |
| Investigations | | 3 | 0 | 0 | 3 | 9 |
| | Alanine aminotransferase | 1 | | | | |
| | Aspartate aminotransferase | 1 | | | | |
| | Blood Bilirubin Increased | 1 | | | | |
| Blood and lymphatic system disorders | | 1 | 0 | 0 | 1 | 3 |
| | Thrombocytopenia | 1 | | | | |
| Cardiac disorders | | 1 | 0 | 0 | 1 | 3 |
| | Dyspnoea | 1 | | | | |
| Hepatobiliary disorders | | 0 | 1 | 0 | 1 | 3 |
| | Immune hepatitis | | 1 | | | |
| Respiratory, thoracic and mediastinal disorders | | 1 | 0 | 0 | 1 | 3 |
| | Pneumonitis | 1 | | | | |

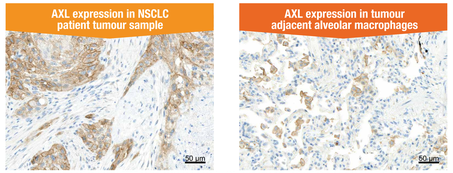
**Serious Adverse Events (SAEs) observed during treatment with bemcentinib (200mg qd) in combination with pembrolizumab (200mg/q3wk)**

Displayed are events categorised as possibly, likely and certainly related to either pembrolizumab or bemcentinib or both.

The most commonly reported drug reactions to pembrolizumab occur as a consequence of immune-mediated reactions and are listed as diarrhea, nausea, rash, pruritus and fatigue. To date a similar spectrum of events has been reported in patients receiving a combination of pembrolizumab with BGB324.

*NCT02872259 is an investigator sponsored, randomised comparison of the addition of BGB324 to systemic therapies for patients with unresectable or metastatic melanoma from diagnosis throughout the duration of therapy. The study design includes multiple efficacy endpoints including overall survival. One arm of the study includes the use of BGB324 in combination with pembrolizumab monotherapy - safety data from this arm of the study has been included here.
(Straume *et al*: World Congress of Melanoma, 2017).

## AXL IHC assay development




Shown are squamous cell carcinoma FFPE patient samples stained for AXL (brown) as per BerGenBio's proprietary AXL IHC assay

**Methods**

**Establishment of a validated, automated immunohistochemistry (IHC) assay for the detection of AXL in human formalin-fixed paraffin-embedded (FFPE) tissue:**

IHC was implemented on the Discovery XT staining platform (Roche Diagnostics/Ventana Medical Systems) using a rabbit monoclonal anti-AXL antibody. FFPE tissue samples and FFPE TMAs were sliced into 3-5 μm sections and mounted and the method was verified for linerity and precision using a semi-quantitative H-score performed by a pathologist.

Between 28 and 33 patient samples of TNBC, adenocarcinoma of the lung and squamous cell carcinoma, respectively, were pathologist scored for presence of AXL expression on either tumour tissue or tumour infiltrating immune cells.

## Conclusions

**SAE profile of combination compareable to that reported for pembrolizumab alone.**

**Combination studies with bemcentinib & pembrolizumab in TNBC & NSCLC ongoing and recruiting.**

**Parallel biomarker studies under way.**

**Stage 1 completion expected for 2018.**

## References

Graham *et al*: **Nature Reviews Cancer.** (2014)
Chui *et al*: **Oral Pathology.** (2015)
Hugo *et al*: **Cell.** (2016)
Wnuk-Lipinska *et al*: **Cancer Research.** (2017)
Zagórska *et al*: **Nature Immunology.** (2014)

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