A Ph II study of the selective AXL inhibitor BGB324 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-IBC)

BerGenBio

In collaboration with: MSD

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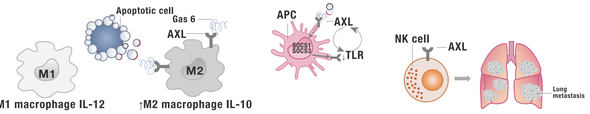
Introduction & Background

RTK AXL in innate immunity and immune evasion

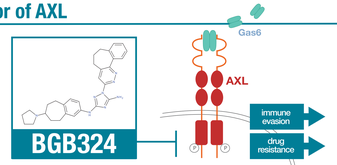
Activation of the receptor tyrosine kinase AXL has a profound suppressive effect on the innate immune system (Zagórska, 2014). AXL is overexpressed on multiple cell types in the tumour immune microenvironment including dendritic cells, NK cells and tumour-associated macrophages. AXL signalling in immune 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).



BGB324 - selective, oral small molecule inhibitor of AXL

BGB324 selectivity profile

	Kinome Scan (Kd)		Kinase Profiler (IC50)		Fluorescence Polarization (IC_{50})		Receptor Cross-Linking (IC_{50})	
Kinase	nM	Fold	nM	Fold	nM	Fold	nM	Fold
Axl	0.4	1	4.6	1	14	1	14	1
Mer	100	250	12.5	2.7	220	16		50
Tyro	>1000	>1000	413	89				>100



BGB324 is in phase II development in solid tumours and heamatological malignancies:

NSCLC NCT03184571: BGB324 + pembrolizumab
NCT02922777: BGB324 + docetaxel
NCT02424617: BGB324 + erlotinib

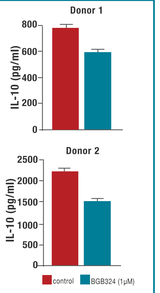
TNBC NCT03184558: BGB324 + pembrolizumab

Melanoma NCT02872259: BGB324 + pembrolizumab or dabrafenib/trametinib

AML/MDS NCT02488408: BGB324 single agent or + decitabine or cytarabine

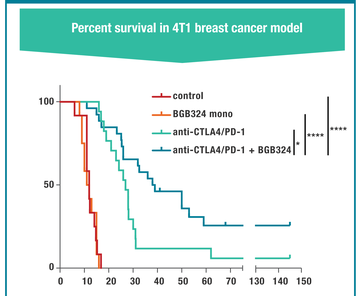
BGB324 stimulates innate immunity & increases effect of immune checkpoint inhibitors *in vivo*

BGB324 stimulates innate immunity



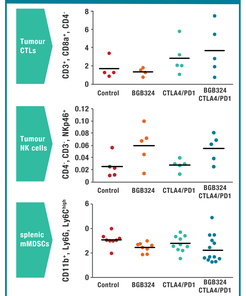
Monocytes isolated from PBMCs of HVs were cultured in the presence of 50 ng/ml M-CSF. M2s were pre-treated for 2 hrs with BGB324 then primed with 5 ng/ml IFN-g for 2 hrs followed by o/n stimulation with 100 ng/ml LPS. Supernatants were collected and IL-10 were determined by ELISA.

BGB324 potentiates the effect of immune checkpoint inhibitors



Transformed survival curves showing durable tumour clearance in 23 % of animals bearing orthotopic 4T1 mammary tumours treated with BGB324 + 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 mm^3. Statistical analysis was performed using log-rank (Mantel-Cox) test (*: $p \leq 0.05$; ****: $p < 0.0001$). n = 4-18.

BGB324 + immune checkpoint inhibitors modulate tumour immune infiltration



Syngeneic 4T1 cells (2×10^5) were implanted into the mammary pad of Balb/C mice and treatment was initiated when average tumour size reached 150 mm^3. 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 BGB324 (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 Study of the selective AXL inhibitor BGB324 in Combination with Pembrolizumab: NCT03184558

Study Design

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

- BGB324 200mg daily
- Pembrolizumab 200mg 3-weekly

Interim analysis

n = 28 patients

Final analysis

n = 56 patients

Participating Countries

Enrollment opened: July 2017

Total Study Sites 20

Total Study Countries 4

Study Objectives & Endpoints

Primary objective:

- Anti-tumour activity of BGB324 and pembrolizumab in combination

Secondary objectives:

- Safety of BGB324 and pembrolizumab when given in combination
- Anti-tumour activity of the combination of BGB324 and pembrolizumab
- Pharmacokinetic profile of BGB324 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

Major Inclusion & Exclusion Criteria

Key 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

Key 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
- Indigestion remedies
- Recent or ongoing systemic steroid therapy

Translational Analyses

Target expression levels

Biomarker	Method
PD-L1 expression levels	Immunohistochemistry
AXL expression levels	Immunohistochemistry

Predictive & mechanism of action biomarkers (explorative)

Biomarker	Method
Soluble protein biomarkers	Liquid biopsy
Differentially expressed genes	Nanostring / gene expression analysis
Immune cell populations	Multispectral IHC, transcriptome analysis
AXL signalling pathways	EMT phenotyping

Pharmacokinetics

- BGB324
- Pembrolizumab

Primary completion expected in 2H 2018

References

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Chui *et al*: Polarization of tumor-associated macrophages and Gas6/Axl signaling in oral squamous cell carcinoma. **Oral Pathology.** 51:683 (2015)

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This poster was presented at the San Antonio Breast Cancer Symposium 2017 (December 5 - 9, 2017); San Antonio, TX