A Phase II Study of BGB324 in Combination with Pembrolizumab in Patients with Previously Treated Advanced Lung Adenocarcinoma

In collaboration with: MSD

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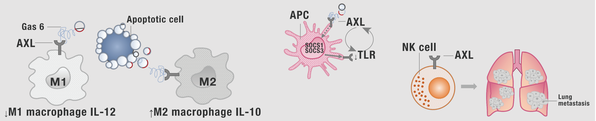
Introduction & Background

RTK AXL in innate immunity and immune evasion

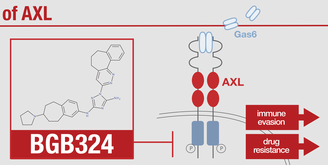
Activation of the receptor tyrosine kinase AXL has a profound suppressive effect on the innate immune system. AXL is overexpressed on multiple cell types in the tumour immune microenvironment including dendritic cells, NK cells and tumour-associated macrophages. AXL signalling in immune cells supports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



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

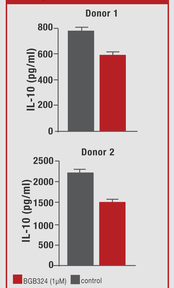
TNBC NCT03184558: BGB324 + pembrolizumab

Melanoma NCT02872259: BGB324 + pembrolizumab or dabrafenib/trametinib

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

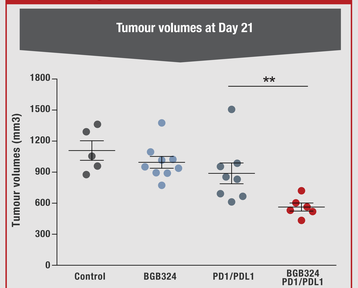
BGB324 stimulates innate immunity & increases effect of immune checkpoint inhibitors *in vivo*

BGB324 stimulates innate immunity



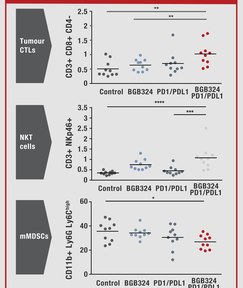
Monocytes isolated from PBMCs of HVs were cultured in the presence of 50 mg/ml M-CSF. MΦs were pretreated for 2 hrs with BGB324 then primed with 5 ng/ml IFN-g for 2 hrs followed by o/n stimulation with 100 ng/ml LPS. Supernatants were collected and IL-10 were determined by ELISA.

BGB324 potentiates the effect of immune checkpoint inhibitors in the Lewis Lung carcinoma model



Syngeneic LLC cells (2.5 x 105) were implanted into the right flank of C57/BL6 mice. Treatment was initiated at the day of implantation. Animals were treated with anti-PDL1 and anti-PD1 (10 mg/kg each, at days 0, 2, 4, 6, 8, 14, IP). BGB324 (50 mg/kg BID, oral gavage). Vehicle groups were injected with control IgG (10 mg/kg). Final tumor volumes are shown.

BGB324 + anti-PD1/PDL1 modulates tumour immune infiltration



Syngeneic LLC cells (2.5 × 10⁵) were implanted into the right flank of C57/BL6 mice and treatment was initiated. Animals were treated with anti-PDL1 and anti-PD1 (10 mg/kg at d 0, 2, 4, 6, 8, 14, IP). BGB324 (50 mg/kg BID, oral gavage). Control IgG (10 mg/kg). Tumours were harvested 15 days after treatment initiation (n=10). Tumours were dissociated for flow cytometry analysis of immune cell infiltration.

Phase II Study of BGB324 in Combination with Pembrolizumab

Study Design

2nd line advanced adeno NSCLC
- Prior platinum
- measurable disease
- fresh tissue biopsy
- PDL1 +ve and -ve
- AXL +ve and -ve

Single arm
- BGB324 200mg daily
- pembrolizumab 200mg every 3wks

Interim analysis
n = 22 patients

Final analysis
n = 48 patients

Participating Countries

USA
Spain
United Kingdom
Norway

Enrollment opened: August 2017

Total Study Sites 20

Total Study Countries 4

Study Objectives & Endpoints

Primary objective:
- Anti-tumor activity of BGB324 and pembrolizumab in combination

Secondary objectives:
- Safety of BGB324 and pembrolizumab when given in combination
- Anti-tumor 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

Statistical Considerations

The trial will follow a k-stage single arm design with k=2, being an extension of Simon's 2- stage design.

- With p_0=0.15 and p_1=0.30, the interim will be conducted with n = 22 evaluable patients who have the potential for at least 24 weeks (and at least 2 on treatment scans) of follow-up.

  If 3 or fewer responses are observed in up to 22 patients, the trial will be terminated in favor of the null for futility; however, if 8 or more responses are observed, then the trial will be stopped in favor of the alternative for demonstration of activity. Otherwise, up to a further 26 patients may be evaluated, for a maximum total of 48 evaluable patients.

- The full study population will have the potential to have at least 24 weeks of follow-up. If a total of 12 or more responses are seen in up to 48 patients, then the null will have been rejected in favor of the alternative.

Major Inclusion & Exclusion Criteria

Key Inclusion Criteria
- Histopathologically or cytologically documented Stage IV adenocarcinoma NSCLC
- Has disease progression on or after a prior platinum-containing chemotherapy
- Renal and hepatic and cardiac function within normal ranges
- 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

Key Exclusion Criteria
- Has disease suitable for local therapy administered with curative intent
- Has received more than one prior line of chemotherapy for advanced or metastatic adenocarcinoma of the lung
- 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

Immunohistochemistry
- PDL1
- AXL

Liquid biomarkers / PBMCs
- AXL signalling pathway
- soluble AXL
- MAP Kinase pathway signalling
- Immune cell populations
- AKT signalling pathway
- SLFN-11

Pharmacokinetics
- BGB324
- Pembrolizumab

References

- Graham et al: The TAM family: phosphatidylserine-sensing receptor tyrosine kinases gone awry in cancer. **Nature Reviews Cancer**. 14: 769 (2014)
- Hugo et al: Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma. **Cell**. 165: 35 (2016)

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