Bemcentinib (BGB324) – a selective small molecule inhibitor of the receptor tyrosine kinase AXL, targets tumour immune suppression and enhances immune checkpoint inhibitor efficacy

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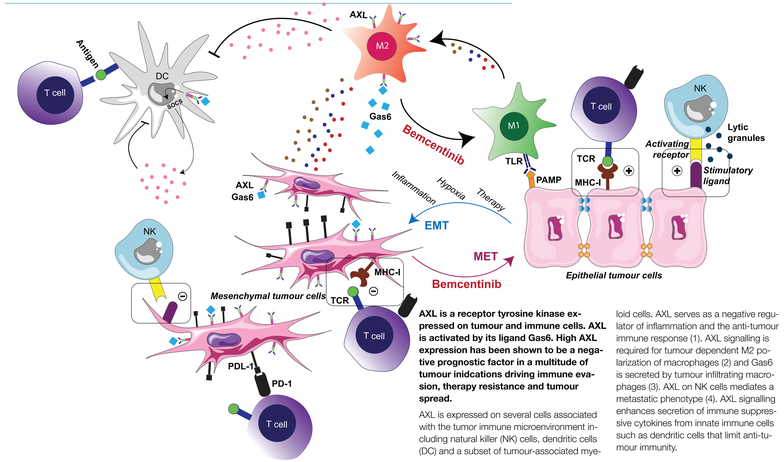
Introduction & background

AXL is expressed on tumour and immune cells driving tumour aggressiveness



AXL is a receptor tyrosine kinase expressed on tumour and immune cells. AXL is activated by its ligand Gas6. High AXL expression has been shown to be a negative prognostic factor in a multitude of tumour inidcations driving immune evasion, therapy resistance and tumour spread.

AXL is expressed on several cells associated with the tumor immune microenvironment including natural killer (NK) cells, dendritic cells (DC) and a subset of tumour-associated myeloid cells. AXL serves as a negative regulator of inflammation and the anti-tumour immune response (1). AXL signalling is required for tumour dependent M2 polarization of macrophages (2) and Gas6 is secreted by tumour infiltrating macrophages (3). AXL on NK cells mediates a metastatic phenotype (4). AXL signalling enhances secretion of immune suppressive cytokines from innate immune cells such as dendritic cells that limit anti-tumour immunity.

Bemcentinib (BGB324): first-in-class selective, oral small molecule inhibitor of AXL in phase II clinical testing

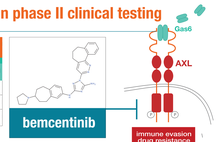
Bemcentinib (BGB324) is a first-in-class, orally bioavailable, highly selective AXL kinase inhibitor which is being evaluated as a therapy for solid tumours and myeloid malignancies.

A comprehensive cell-based counter screen profiling approach was used for bemcentinib SAR ensuring high selectivity over other kinases including members of the TAM (Tyro3-AXL-Mer) family of kinases.

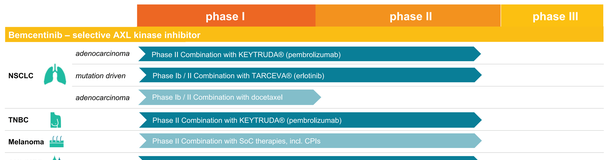
Bemcentinib has a wide therapeutic index and has been shown to be well tolerated. It is administrated as a once-a-day pill.

Selectivity Profile

	nM	Fold
AXL	0.4	1
Mer	100	250
Tyro3	>1000	>1000



Clinical development as a potential cornerstone of combination therapy across several solid & liquid tumour indications



Bemcentinib is developed as a potential cornerstone of therapy in combination with immune-, targeted and chemotherapy.

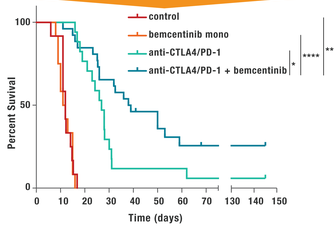
Six phase II trials are ongoing across non-small cell lung cancer (NSCLC), melanoma, triple negative breast cancer (TNBC) and acute myeloid leukaemia (AML) & high risk myelodysplastic syndrome (MDS).

References: (1) Zagorska, A., et al. (2014) Nat immun; (2) Chlu, K. C., et al. (2015) J Oral Path Med; (3) Loges, S., et al. (2010) Blood; (4) Paolino, M., et al. (2014) Nature; (5) Rothlin, CV., et al. (2007) Cell.

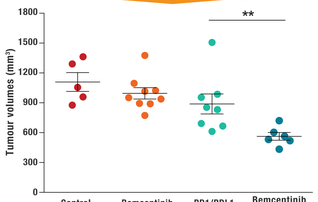
Bemcentinib enhances innate and adaptive immunity

Bemcentinib potentiates ICP blockade

Percent survival in 4T1 breast cancer model



Tumour volumes in LLC NSCLC model

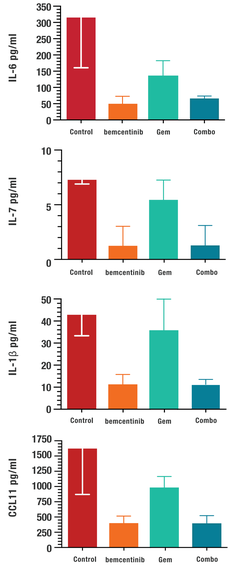


Transformed survival curves showing durable tumour clearance in 23 % of animals bearing orthotopic 4T1 mammary tumours treated with bemcentinib + anti-mCTLA4/anti-mPD-1. Treatment with anti-mCTLA4/ anti-mPD-1 alone resulted in tumour clearance in 5.6% of animals. Treatment was initiated when tumours 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.

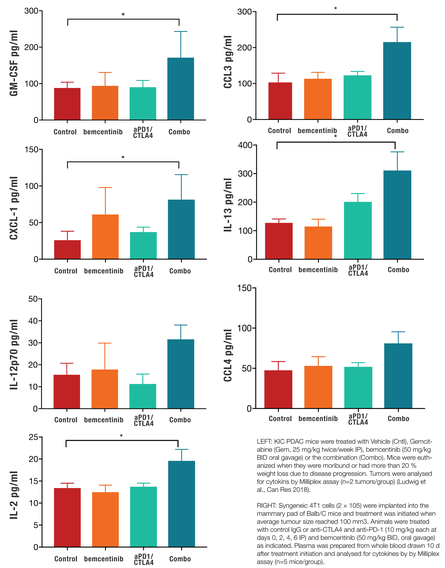
Syngeneic LLC cells (2.5 × 105) were implanted into the right flank of C57/BL6 mice. Treatment was initiated at the day of implantation. Animals were treated with anti-PDL1 and anti-PD1 (10 mg/kg each, at days 0, 2, 4, 6, 8, 14, IP), bemcentinib (50 mg/kg BID, oral gavage). Vehicle groups were injected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

Bemcentinib promotes an inflammatory microenvironment

Bemcentinib affects cytokine profile in PDAC GEMM model



Bemcentinib affects cytokine profile in TNBC model

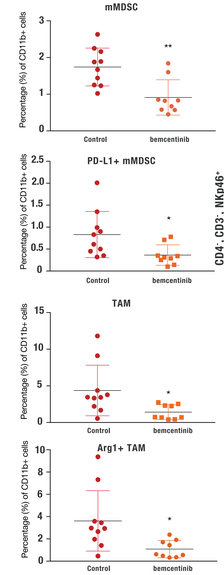


LEFT: KIC PDAC mice were treated with Vehicle (Crtl), Gemcitabine (Gem, 25 mg/kg twice/week IP), bemcentinib (50 mg/kg BID oral gavage) or the combination (Combo). Mice were euthanized when they were moribund or had more than 20 % weight loss due to disease progression. Tumors were analysed for cytokins by Milliplex assay (n=2 tumors/group) (Ludwig et al., Can Res 2018).

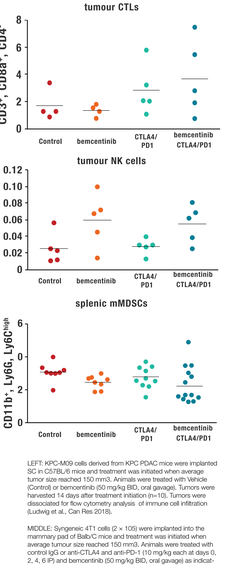
RIGHT: Syngeneic 4T1 cells (2 × 105) were implanted into the mammary pad of Balb/C mice and treatment was initiated when average tumour size reached 100 mm3. Animals were treated with control IgG or anti-CTLA4 and anti-PD-1 (10 mg/kg each at days 0, 2, 4, 6 IP) and bemcentinib (50 mg/kg BID, oral gavage) as indicated. Plasma was prepared from whole blood drawn 10 d after treatment initiation and analysed for cytokines by by Milliplex assay (n=5 mice/group).

Bemcentinib promotes immune cell infiltration in a variety of tumour models

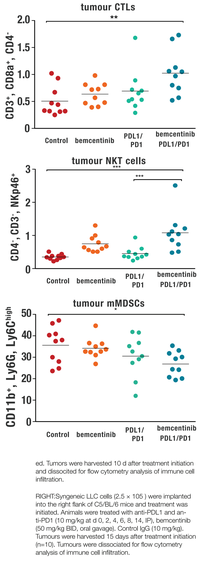
Bemcentinib reverses immune suppression in PDAC model



Bemcentinib modifies immune cell infiltration in 4T1 breast model



Bemcentinib modifies immune cell infiltration in LLC lung model



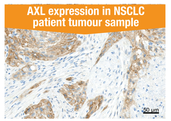
LEFT: KPC-M09 cells derived from KPC PDAC mice were implanted SC in C57BL/6 mice and treatment was initiated when average tumor size reached 150 mm3. Animals were treated with Vehicle (Control) or bemcentinib (50 mg/kg BID, oral gavage). Tumors were harvested 14 days after treatment initiation (n=10). Tumors were dissociated for flow cytometry analysis of immune cell infiltration (Ludwig et al., Can Res 2018).

MIDDLE: Syngenic 4T1 cells (2 × 105) 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) and bemcentinib (50 mg/kg BID, oral gavage) as indicated. Tumors were harvested 10 d after treatment initiation and dissociated for flow cytometry analysis of immune cell infiltration.

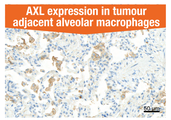
RIGHT:Syngenic LLC cells (2.5 × 105) were implanted into the right flank of C5/BL/6 mice and treatment was initiated. Animals were treated with anti-PDL1 and anti-PD1 (10 mg/kg at d 0, 2, 4, 6, 8, 14, IP), bemcentinib (50 mg/kg BID, oral gavage). Control IgG (10 mg/kg). Tumours were harvested 15 days after treatment initiation (n=10). Tumours were dissociated for flow cytometry analysis of immune cell infiltration.

AXL IHC assay development

AXL expression in NSCLC patient tumour sample



AXL expression in tumour adjacent alveolar macrophages



AXL in TNBC & NSCLC patient samples

	TNBC	NSCLC (adeno)	NSCLC (squamous)	total
Number	28	31	33	92
AXL positive	54 %	68 %	86 %	70 %

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.

Conclusion

Bemcentinib suppressed the levels of CCL11, IL-7, IL-1b and IL-6 which can activate MDSCs and strongly inhibit reactivity of DCs, macrophages, T- and NK cells.

Targeting AXL signalling uniquely abrogates microenvironmental immune suppression mechanisms and increases immune cell tumour infiltration.

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