63PD: Predictive and Pharmacodynamic Biomarkers Associated with the Selective and Orally Bioavailable AXL Inhibitor Bemcentinib Across Multiple Clinical Trials

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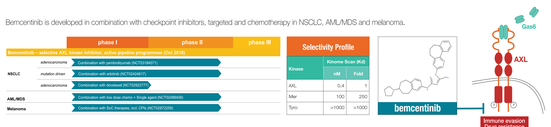
BerGenBio

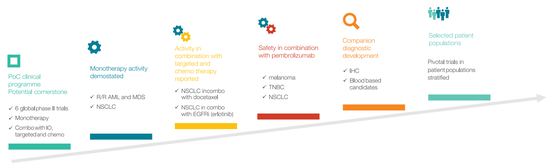
Bemcentinib & AXL Biology

Bemcentinib: Selective, oral small molecule inhibitor of AXL in Phase II clinical testing

Bemcentinib is developed in combination with checkpoint inhibitors, targeted and chemotherapy in NSCLC, AML/MDS and melanoma.



Selectivity Profile		
Kinase	Kinome Scan (Kd)	
	nM	Fold
AXL	0.4	1
Mer	100	250
Tyro	>1000	>1000



Membrane AXL is down-regulated by receptor shedding

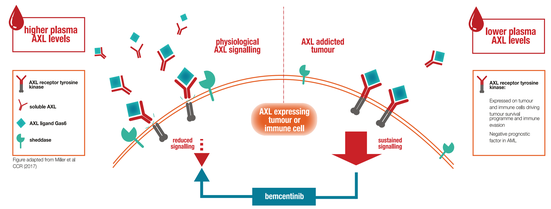
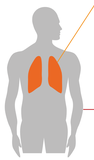


Figure adapted from Miller et al. CCR (2017)

Materials & Methods



Tumour tissue biopsy – detect membrane AXL and other biomarker candidates

Methods and materials

- **All analyses were carried out on fresh pre-treatment FFPE tumour biopsies.**
- **A panel of biomarkers including AXL, CD68, and tumour segmentation marker PanCK was analysed using multiplexing methodology (MultiOmyx™, NeoGenomic Fort Myers, FL) coupled with deep learning to identify individual cells and perform cell classification for all individual markers.**
- **AXL Immunohistochemistry (IHC) was performed using a proprietary method (Indivumed, Hamburg, Germany) and PD-L1 IHC using the Dako 22C3 pharmDx kit (NeoGenomics).**

BGBIL006
BGBC007
BGBC008

Liquid biopsy – emerging technology

Methods and materials

- **Plasma protein biomarker levels were measured using the DiscoveryMap v3.3 panel (Myriad RBM, Austin, TX) at pre-dose and C2D1 across six clinical trials (see above).**
- **Bioinformatics analysis was carried out by Fios Genomics. Comparisons were performed on the QC-passed and normalised Myriad datasets; including (i) pre-dose (C1D1) Responders vs Non-Responders and (ii) Paired Timepoint comparison, C1D1 vs C2D1 for all patients.**

BGBC003
BGBC004
BGBIL005
BGBIL006
BGBC007
BGBC008

References

(1) NCT03184571: Bemcentinib in combination with pembrolizumab in advanced adenocarcinoma of the lung (BGBC008). Data presented at WCLC 2018 (Lorens et al)

Acknowledgements

The authors wish to thank patients, their families and caretakers, investigators and site staff.

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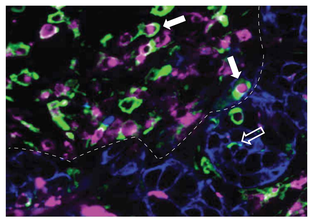
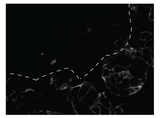
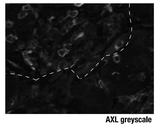
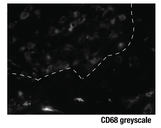
Predictive biomarker candidates to bemcentinib monotherapy and combination therapy with immuno- & targeted therapy have been identified in tissue and plasma

AXL is present in both tumour and tumour infiltrating immune cells







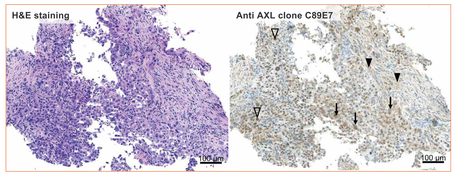


PanCK+
AXL+
CD68+

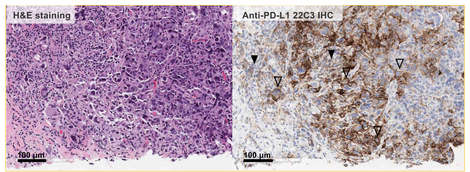
Closed arrows indicate examples of AXL positive macrophages, open arrow indicate example of AXL positive tumour cell

- A significant proportion of AXL expressing cells are macrophages and NK cells
- Investigation of correlation of AXL on immune cells with response is ongoing

AXL IHC identifies subset of NSCLC patients with increased response to bemcentinib + pembrolizumab (incl. PD-L1 negative patients)[1]



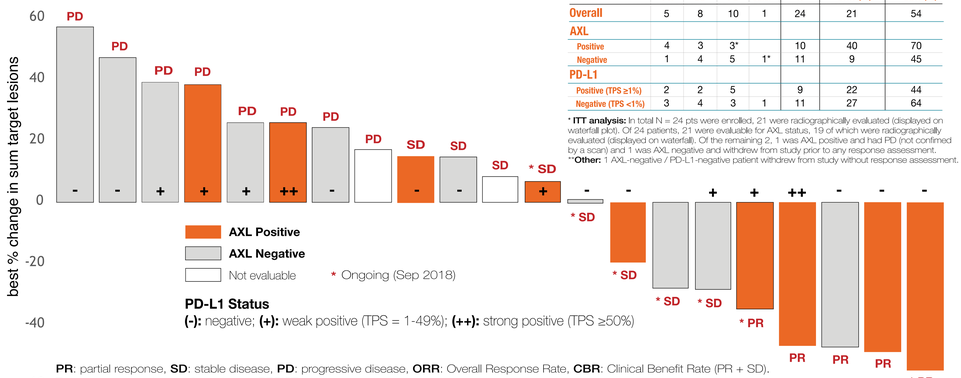
Weak to moderate predominantly nuclear anti-AXL staining (open arrowheads) as well as weak to strong cytoplasmic anti-AXL staining of tumour cells (arrows) was observed. Additionally a mainly weak cytoplasmic staining of stromal cells was seen (arrowheads).



A predominantly moderate to strong membranous anti-PD-L1 22C3 IHC staining of tumour cells was observed (open arrowheads) as well as a weak to moderate membranous/cytoplasmic anti-PD-L1 22C3 IHC staining of immune cells (filled arrowheads).

Phase II trial exploring bemcentinib in combination with pembrolizumab in advanced NSCLC (NCT03184571): approximately half of patients found to be positive for tumour AXL staining, 7 of 10 AXL positive patients show clinical benefit incluing 4 PRs (ORR = 40%)[1]

Waterfall plot: Best % change sum target lesions n = 21 pts with radiographic evaluation following treatment



Best overall response: Intention-to-treat (ITT) & biomarker status analysis*

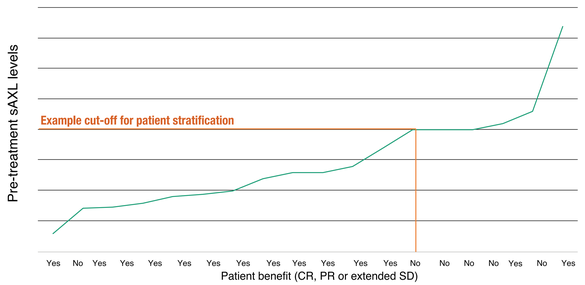
	PR	SD	PD	other**	N	ORR (%)	CBR (%)
Overall	5	8	10	1	24	21	54
AXL							
Positive	4	3	3*		10	40	70
Negative	1	4	5	1*	11	9	45
PD-L1							
Positive (TPS ≥1%)	2	2	5		9	22	44
Negative (TPS <1%)	3	4	3	1	11	27	64

***ITT analysis:** In total N = 24 pts were enrolled, 21 were radiographically evaluated (displayed on waterfall plot). Of 24 patients, 21 were evaluable for AXL status, 19 of which were radiographically evaluated (displayed on waterfall). Of the remaining 2, 1 was AXL positive and had PD (not confirmed by a scan) and 1 was AXL negative and withdrew from study prior to any response assessment.
**Other: 1 AXL-negative / PD-L1-negative patient withdrew from study without response assessment.

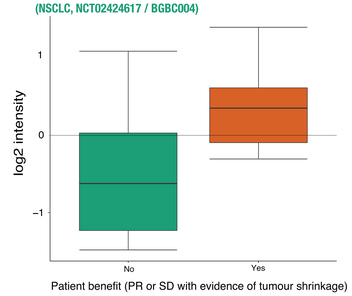
PR: partial response, **SD**: stable disease, **PD**: progressive disease, **ORR**: Overall Response Rate, **CBR**: Clinical Benefit Rate (PR + SD).
Tumours assessed every 9 weeks per RECIST v1.1

Pre-treatment levels of soluble AXL (sAXL) and other soluble biomarkers are predictive of patient benefit in AML/MDS and NSCLC

Pre-treatment sAXL plasma levels correlate with bemcentinib monotherapy clinical benefit (relapsed/refractory AML and MDS, NCT02488408 / BGBC003)



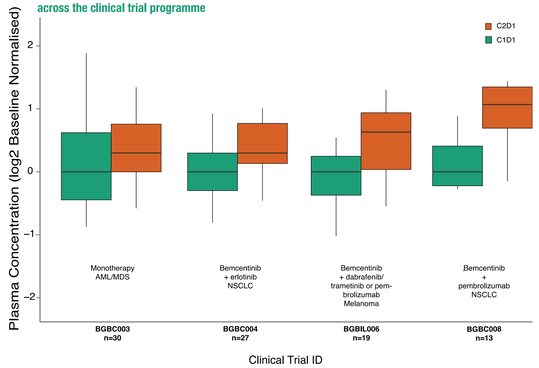
Pre-treatment BGBM014* levels correlate with clinical benefit from bemcentinib + erlotinib combination treatment (NSCLC, NCT02424617 / BGBC004)



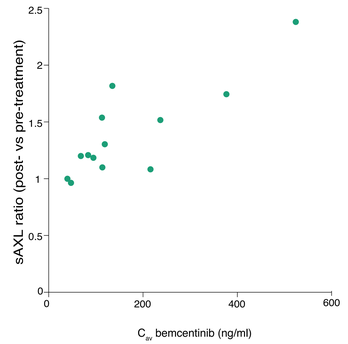
*BGBM014 is a transmembrane protein overexpressed in a wide variety of tumour types and induced by hypoxia.

Pharmacodynamics: Soluble AXL (sAXL) levels in plasma samples increase following monotherapy and combination treatment

sAXL levels increase following 1 cycle of bemcentinib monotherapy or combination treatment across the clinical trial programme



Change in sAXL plasma level over 1 cycle of bemcentinib monotherapy treatment is correlated with bemcentinib exposure



Conclusions

- **Predictive biomarker candidates have been identified across multiple phase II monotherapy and combination trials:**
  1. Plasma sAXL is predictive of patient benefit from bemcentinib monotherapy in AML/MDS
  2. Tissue AXL IHC identifies a subgroup of NSCLC patients with increased response to bemcentinib + pembrolizumab combination treatment
  3. Plasma BGBM014 is predictive of NSCLC patient benefit from bemcentinib combination treatment with erlotinib
- **Tissue AXL is found on tumour cells and tumour infiltrating immune cells (macrophages and NK cells)**
- **Plasma sAXL is also a pharmacodynamic marker across trials indicating bemcentinib on-target activity:**
  1. Plasma sAXL levels correlate with bemcentinib exposure
  2. Plasma sAXL increases following bemcentinib treatment in all indications following monotherapy as well as combination treatment

This poster was presented at the ESMO 2018 Congress, Munich, Germany (October 19 - 23, 2018)