Predictive and pharmacodynamic biomarkers associated with treatment with the oral selective AXL inhibitor bemcentinib in combination with pembrolizumab in patients with advanced NSCLC and Melanoma

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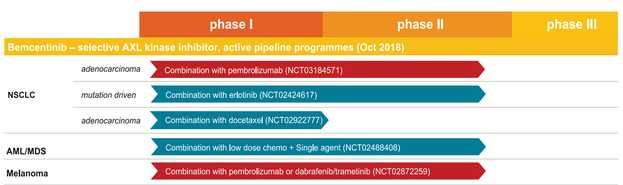
BerGenBio

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.

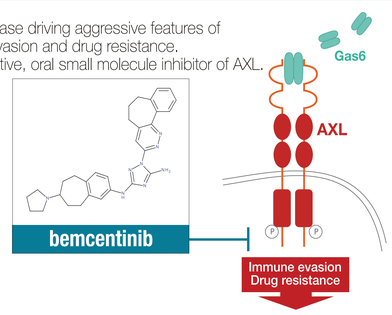


This biomarker analysis focuses on two combination trials of bemcentinib with pembrolizumab in NSCLC and melanoma (NCT03184571 and NCT02872259, respectively).

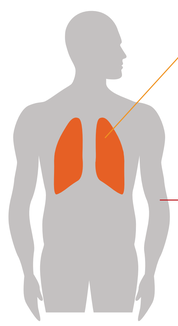
AXL is a receptor tyrosine kinase driving aggressive features of tumours including immune evasion and drug resistance. Bemcentinib is a highly selective, oral small molecule inhibitor of AXL.

Selectivity Profile

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



Materials & Methods



Tumour tissue biopsy – detect tissue AXL and other biomarker candidates

- **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) assigning a H-score for AXL expression on tumour cells, cut-off in development. PD-L1 IHC was done using the Dako 22C3 pharmDx kit (NeoGenomics).**

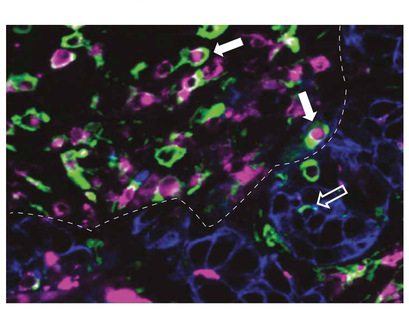
Liquid biopsy

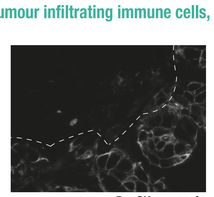
- **Plasma protein biomarker levels were measured using the DiscoveryMap v3.3 panel (Myriad RBM, Austin, TX) at pre-dose and C2D1.**
- **Bioinformatics analysis was carried out by Fios Genomics. Comparisons were performed on the QC-passed and normalised Myriad datasets to yield a paired timepoint comparison (C1D1 vs C2D1) for NSCLC and melanoma patients.**

Predictive and pharmacodynamic biomarker candidates to bemcentinib combination therapy with pembrolizumab have been identified in tissue and plasma

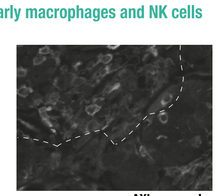
AXL associated disease is associated with improved outcomes in response to bemcentinib/pembrolizumab combination therapy in previously treated advanced NSCLC

Multispectral imaging reveals AXL is present in both tumour and tumour infiltrating immune cells, particularly macrophages and NK cells

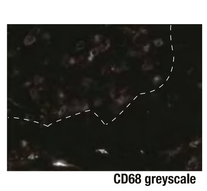




PanCK greyscale



AXL greyscale



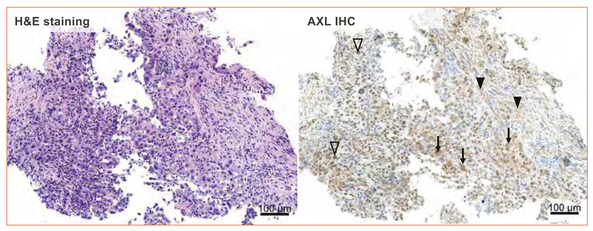
CD68 greyscale

PanCK+
AXL+
CD68+

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

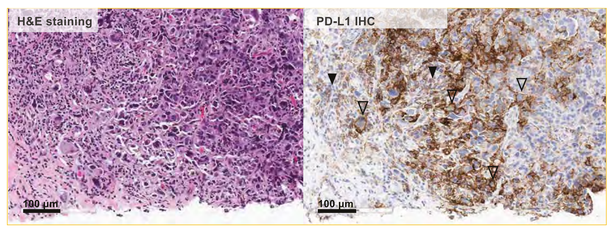
- A proportion of AXL expressing cells are macrophages and NK cells
- Investigation of correlation of AXL on immune cells with response is ongoing

10 of 21 patients evaluable for AXL status stained positive for tumour AXL in a phase II trial of bemcentinib + pembrolizumab in advanced previously treated NSCLC



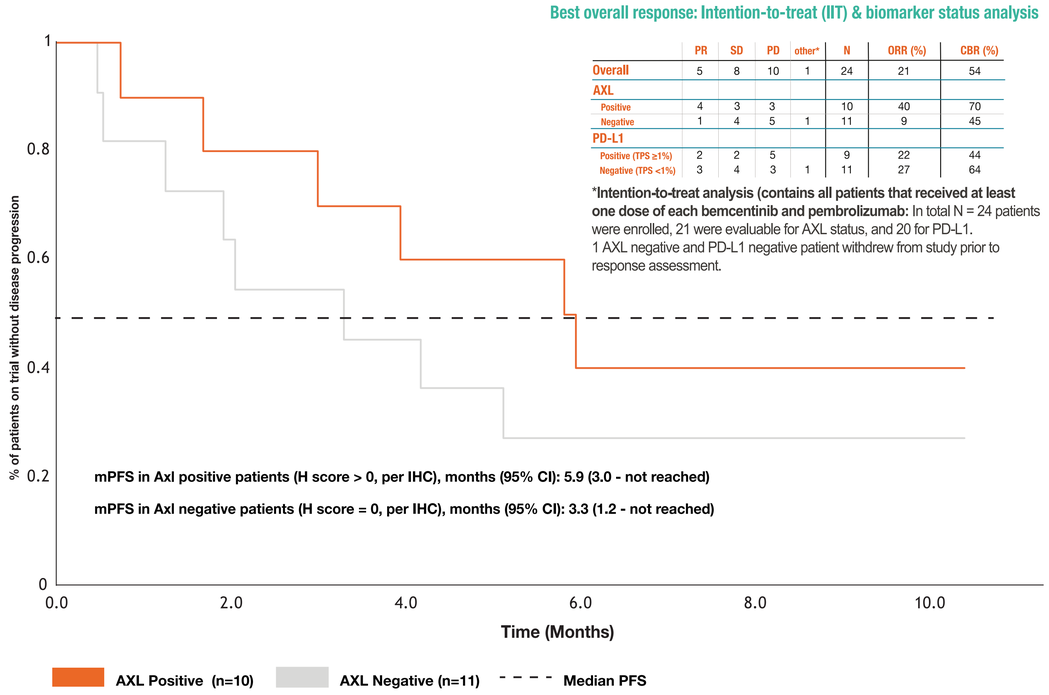
Example AXL IHC: Weak to moderate predominantly nuclear anti-AXL staining (open arrowheads) as well as weak to strong cytoplasmic anti-AXL staining of tumour cells (arrows) was observed. Additionally a mainly weak cytoplasmic staining of stromal cells was seen (arrowheads).

The studied patient population was predominantly PD-L1 negative (TPS < 1%) or weak positive (TPS = 1 - 49%) (11 and 7 of 20 patients evaluable for PD-L1 status, respectively)



Example PD-L1 IHC: 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).

Median progression-free-survival (mPFS) is approximately 80% increased in AXL positive vs negative patients



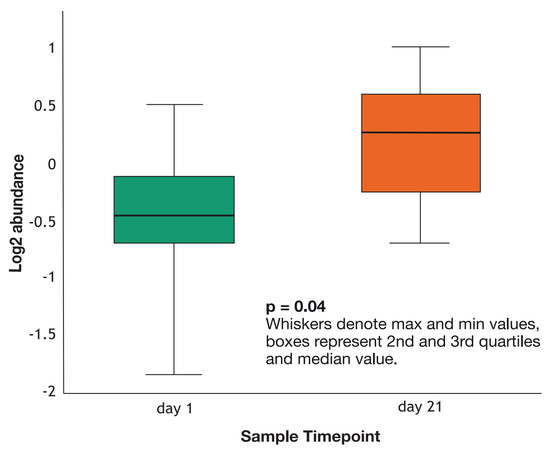
Best overall response: Intention-to-treat (IIT) & biomarker status analysis

	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

***Intention-to-treat analysis (contains all patients that received at least one dose of each bemcentinib and pembrolizumab:** In total N = 24 patients were enrolled, 21 were evaluable for AXL status, and 20 for PD-L1.
1 AXL negative and PD-L1 negative patient withdrew from study prior to response assessment.

Plasma levels of soluble AXL are increased following bemcentinib + pembrolizumab combination treatment in advanced NSCLC and melanoma

Soluble AXL (sAXL) in NSCLC and melanoma patients at beginning of treatment and after 1 cycle of bemcentinib + pembrolizumab



p = 0.04
Whiskers denote max and min values, boxes represent 2nd and 3rd quartiles and median value.

AXL receptor tyrosine kinase is a target for ADAM sheddases that downregulate AXL signalling by proteolytic cleavage of the AXL extracellular domain in response to AXL kinase inhibition (2).

This soluble form of the AXL receptor (sAXL) is thus measurable in blood plasma.

A correlation between sAXL increase in blood plasma and bemcentinib exposure has been previously reported indicating dose-dependent on target activity of bemcentinib (3).

Conclusions

Previously treated advanced NSCLC patients with AXL positive disease show improved outcomes to bemcentinib + pembrolizumab combination treatment compared to AXL negative patients

The studied patient population was predominantly PD-L1 negative or weakly positive (55% and 35% of patients evaluable for PD-L1 status, respectivey). Approximately half of the patients were found to have AXL positive disease.

Median PFS in AXL positive vs AXL negative patients was 5.9 vs 3.3 months.

An ORR of 40% vs 9% was observed in AXL positive vs AXL negative patients.

AXL is present on tumour and tumour infiltrating immune cells

Both tumour and NK cells as well as macrophages were found to stain positive for AXL by multispectral imaging.

Soluble AXL (sAXL) inreases in response to bemcentinib + pembrolizumab combination treatment

AXL signalling is downregulated in response to kinase inhibition by shedding of the extracellular domain of the AXL receptor tyrosine kinase. Increase of sAXL in response to bemcentinib treatment indicates on target activity of selective AXL inhibitor bemcentinib.

References

(1) Krebs *et al*, SITC (2018)
(2) Miller *et al*, CCR (2017)
(3) Holt *et al*, ESMO (2018)

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