20180ITC_Krebs-et-al_final-for-print.pdf 1 08/11/2018 18:58

A Phase II study of bemcentinib (BGB324), a first-in-class selective AXL inhibitor, in combination with pembrolizumab in patients with advanced NSCLC: Analysis of the first stage

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BerGenBio

In collaboration with:

Background and Objectives

NCT03184571: Phase II clinical trial of selective AXL inhibitor bemcentinib and pembrolizumab

Simon-like two stage design enroling up to 48 patients

2nd line advanced adeno NSCLC
- IO naïve
- Prior platinum doublet therapy
- Measurable disease
- Fresh tissue biopsy
- PD-L1 all comers

Single arm
bemcentinib, 200mg daily
+
pembrolizumab, 200mg q3wks

Stage 1 analysis (n=24)

Final analysis (n=48)

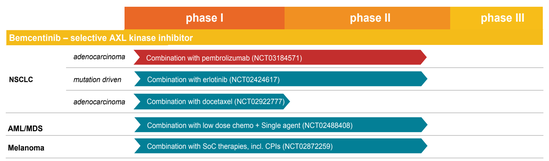
Key inclusion and exclusion criteria
- Histopathologically or cytologically documented Stage IV adenocarcinoma NSCLC
- Has disease progression on or after a prior platinum-containing chemotherapy
- Measurable disease as defined by RECIST v1.1
- Provision of suitable fresh tumour tissue for the analysis of AXL kinase and PD-L1 expression
- Eastern Cooperative Oncology Group (ECOG) performance score 0 or 1
- Not received more than one prior line of chemotherapy in advanced setting
- No prior therapy with an immunomodulatory agent
- No symptomatic central nervous system (CNS) metastases and/or carcinomatous meningitis
- No recent or ongoing systemic steroid therapy

Biomarker analysis
- PD-L1 and AXL expression per IHC
- Soluble protein biomarkers by liquid biopsy
- Immune cell populations by multi-spectral imaging

Endpoints
- Primary: ORR
- Secondary: DCR, DoR, PFS, Survival at 12 months, response by biomarker expression

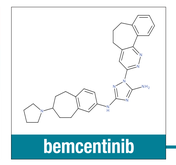
Bemcentinib (BGB324): selective, oral small molecule inhibitor of AXL in phase II clinical testing

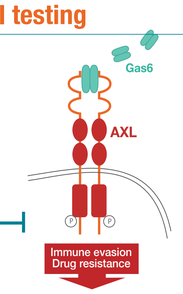
Bemcentinib is developed in combination with immunotherapy, targeted and chemotherapy in NSCLC, AML/MDS and melanoma.



Selectivity Profile

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





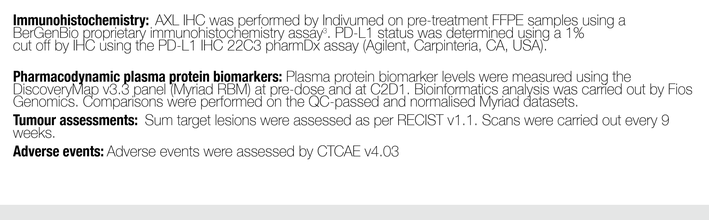
Study rationale

Anti PD-1 therapies in second line metastatic non-small cell lung cancer (NSCLC)
- Pembrolizumab as a single agent is indicated for the treatment of patients with metastatic NSCLC with disease progression on or after platinum-containing chemotherapy and whose tumours express ≥1% PD-L1[1]
- KEYNOTE-001[2], a multi-cohort phase I study designed to define and validate expression levels of PD-L1 associated with the likelihood of clinical benefit, showed that pembrolizumab monotherapy efficacy is correlated with PD-L1 levels
- **Novel combination treatment strategies are needed to improve efficacy of pembrolizumab particularly in patients with no or low PD-L1 while limiting additive toxicity**

AXL receptor tyrosine kinase and selective AXL inhibitor bemcentinib
- AXL is a receptor tyrosine kinase expressed on tumour and immune cells and a member of the TAM family (Tyro-AXL-Mer) of kinases
- AXL is overexpressed in response to a hostile tumour microenvironment and drives a tumour survival programme driving immune escape, anti-tumour therapy resistance & metastasis
- AXL is a negative prognostic factor in a multitude of cancers including NSCLC
- Bemcentinib, a first-in-class highly selective inhibitor of AXL, and has been shown to potently improve the efficacy of checkpoint blockade in murine pre-clinical models of NSCLC

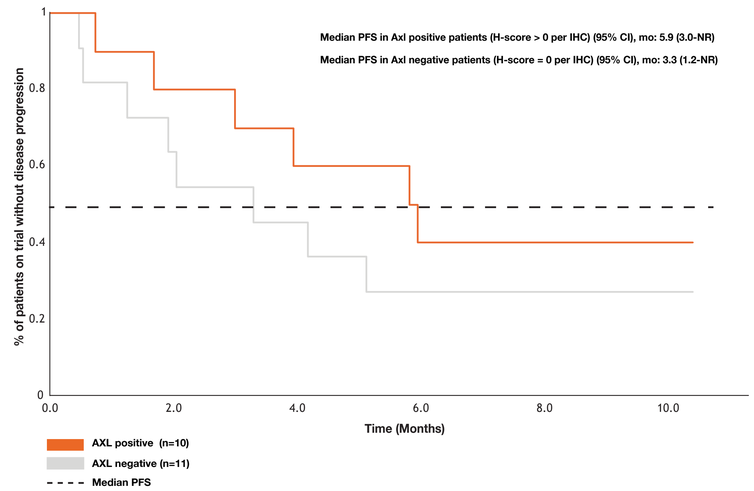
Stage 1 analysis: 40% ORR and 5.9 months median PFS in AXL positive disease

Patient disposition, stage 1: Intention-To-Treat (ITT) population

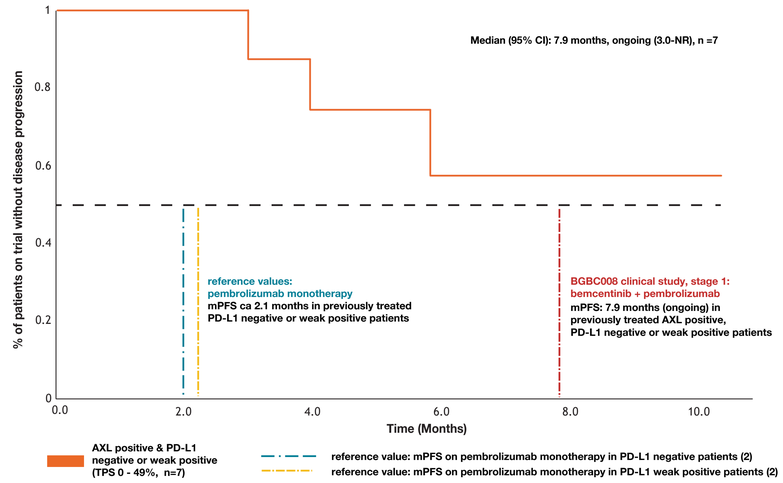


AXL positive disease is associated with improved outcomes in response to bemcentinib + pembrolizumab combination therapy

Median PFS in all AXL positive patients was 5.9 months: approximately 80% improvement over AXL negative disease (mPFS 3.3 months)

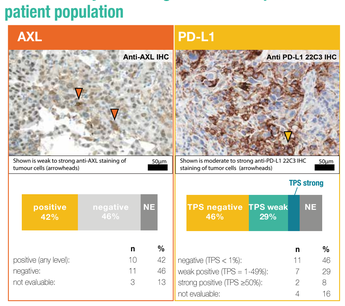


Median PFS in AXL positive patients with negative to weak PD-L1 expression (TPS 0-49%) is 7.9 months (ongoing): benefit in AXL positive patients not driven by high PD-L1 expression



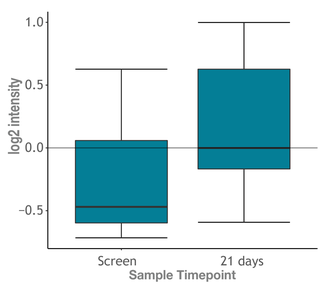
AXL & PD-L1 prevalence

Predominantly PD-L1 negative or weak positive patient population



Pharmacodynamics

Soluble AXL increases following bemcentinib treatment, indicating on-target activity



Demographics

Median age (range)	64 (39-76)
ECOG at screen	
0 (%)	8 (33)
1 (%)	16 (67)
Male (%)	14 (58)
Ethnicity	
Hispanic or Latino (%)	4 (17)
Not Hispanic or Latino (%)	20 (83)
Mutations	
KRAS (%)	4 (17)
TP53+ERBB2 (%)	1 (4)
None (%)	19 (79)
Other/Unknown (%)	0 (0)
Smoking status	
Smoker (%)	5 (21)
Ex-smoker (%)	12 (50)
Never smoked (%)	6 (25)
Unknown (%)	1 (4)

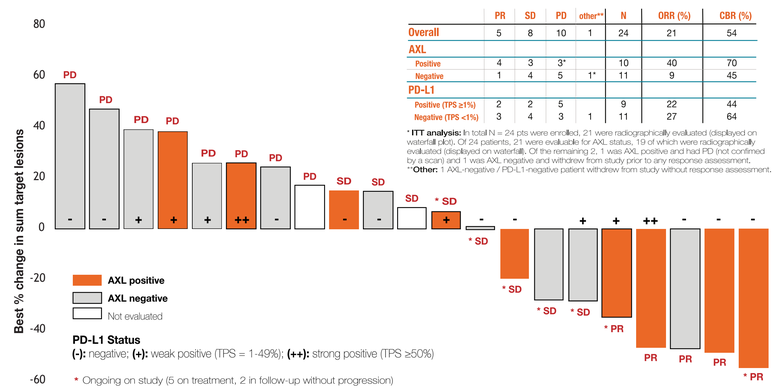
Safety, No grade 4 or 5 TRAEs reported

Treatment related adverse events (TRAEs)

	n = 24	
Preferred term, n (%) E	**Any grade**	**Grades ≥3**
Alanine aminotransferase increased	8 (33) 12	2 (8) 2
Diarrhoea	6 (25) 9	
Fatigue	5 (21) 9	1 (4) 1
Pruritus *	5 (21) 8	
Aspartate aminotransferase increased	5 (21) 8	1 (4) 1
Transaminases increased *	4 (17) 11	3 (13) 3
Asthenia	3 (13) 6	1 (4) 1
Gamma-glutamyltransferase increased	3 (13) 5	1 (4) 1
Rash maculo-papular *	3 (13) 5	1 (4) 1
Decreased appetite	3 (13) 4	
Autoimmune hepatitis *	3 (13) 3	2 (8) 2
Nausea	3 (13) 3	
Amylase increased	2 (8) 5	
Rash *	2 (8) 4	1 (4) 1
Electrocardiogram QT prolonged	2 (8) 2	1 (4) 1
Hypocalcaemia	2 (8) 2	
Hyperglycaemia	2 (8) 2	
Myalgia	2 (8) 2	

*Listed AEs have been reported as possibly, probably or definitely related to bemcentinib, pembrolizumab, or both. * Possibly immune-related AEs*

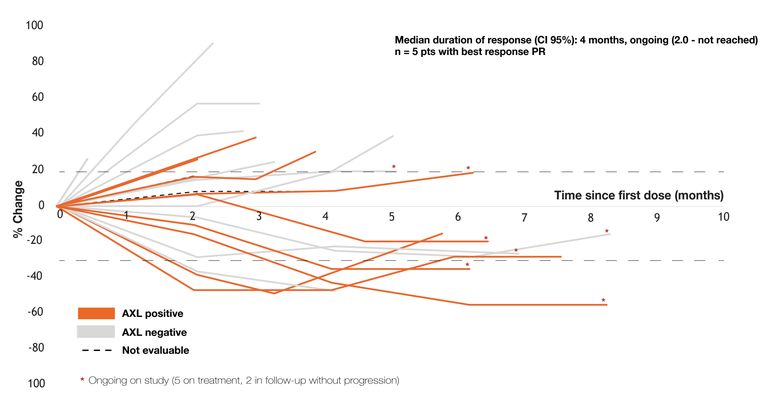
Best change in sum target lesions (n = 21 pts with at least 1 post-baseline scan) and best response by RECIST v1.1



	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.

Change in sum of target lesions over time, by patient



Conclusions

- The studied patient population contained a large proportion of PD-L1 negative (55% of patients evaluable for PD-L1) patients who are not expected to benefit from pembrolizumab monotherapy treatment.
- Among 21 patients evaluable for AXL status, approximately half were AXL positive.
- The combination treatment of bemcentinib and pembrolizumab was overall well tolerated.
- Median PFS in AXL positive patients was 5.9 months which represents an approximately 80% improvement over AXL negative patients (3.3 months)
- This benefit was not driven by high PD-L1 expressors. Median PFS in AXL positive and PD-L1 negative/weak positive patients was not mature at 7.9 months and thus much better than what is expected with pembrolizumab monotherapy, as per KEYNOTE 001 results.

Methods

Immunohistochemistry: AXL IHC was performed by Indivumed on pre-treatment FFPE samples using a BerGenBio proprietary immunohistochemistry assay[3]. PD-L1 status was determined using a 1% cut off by IHC using the PD-L1 IHC 22C3 pharmDx assay (Agilent, Carpinteria, CA, USA).

Pharmacodynamic plasma protein biomarkers: Plasma protein biomarker levels were measured using the DiscoveryMap v3.3 panel (Myriad RBM) at pre-dose and at C2D1. Bioinformatics analysis was carried out by Fios Genomics. Comparisons were performed on the QC-passed and normalised Myriad datasets.

Tumour assessments: Sum target lesions were assessed as per RECIST v1.1. Scans were carried out every 9 weeks.

Adverse events: Adverse events were assessed by CTCAE v4.03

References

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

(2) Garon *et al*. NEJM (2015) Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

(3) Davidsen *et al*. Springer Publishing (2017) The Role of Axl Receptor Tyrosine Kinase in Tumor Cell Plasticity and Therapy Resistance

Acknowledgements

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

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This poster was presented at SITC 2018, Washington, D.C. (November 7 - 11, 2018)