Preliminary efficacy results of selective AXL inhibitor bemcentinib with pembrolizumab following chemo in patients with NSCLC

Poster 1576P

J. Trigo Perez[1], E. Felip[2], P. Brunsvig[3], A. Helland[4], N. Viñolas[5], S. Ponce Aix[6], E. Carcereny Costa[7], M. Domine Gomez[8], E. Arriola[9], R. Garcia Campelo[10], J. Spicer[11], J. Thompson[12], A.L. Ortega Granados[13], J. Lorens[14], M. Shoaib[14], A. Siddiqui[14], E. Schmidt[15], M. Chisamore[15], M. Krebs[16]

[1]Hospital Universitario Virgen de la Victoria, Málaga, Spain; [2]Vall d'Hebron University Hospital, Barcelona, Spain; [3]Oslo University Hospital, Oslo, Norway; [4]University of Oslo, Institute of Clinical medicine, Oslo, Norway; [5]Hospital Clinic y Provincial de Barcelona, Barcelona, Spain; [6]University Hospital 12 De Octubre, Madrid, Spain; [7]Catalan Institute of Oncology (ICO Badalona), Hospital Germans Trias i Pujol, Badalona, Spain; [8]University Hospital "Fundacion Jimenez Diaz", Madrid, Spain; [9]Hospital del Mar, Barcelona, Spain; [10]CHUAC - Complexo Hospitalario Universitario A Coruña, A Coruña, Spain; [11]King's College London, Guy's Hospital, London, United Kingdom; [12]Medical College of Wisconsin Affiliated Hospitals, Menomonee Falls, WI, USA; [13]Complejo Hospitalario de Jaen Universidad de Jaen, Jaen, Spain [14]BerGenBio ASA, Bergen, Norway; [15]Merck & Co., Inc., Kenilworth, NJ, USA; [16]The Christie NHS Foundation Trust and The University of Manchester, Manchester, United Kingdom

Background & objective

NCT03184571: Phase II clinical trial of selective AXL inhibitor bemcentinib in combination with pembrolizumab

Simon-like two stage design enrolling up to 48 patients

Patients
- Advanced adeno NSCLC
- Measurable disease
- Fresh tissue biopsy
- PD-L1 +ve and –ve
- AXL +ve and –ve

Regimen
- Pembrolizumab 200mg fixed
- Bemcentinib 400mg loading dose, then 200mg qd

Chemo Refractory
- Previously treated with platinum containing chemotherapy
- 1 line previous therapy
- PD-L1/PD-1 naive

Stage 1 n = 24 patients — COMPLETE

Stage 2 n = 24 patients — COMPLETE

Key inclusion and exclusion criteria

- Histopathologically or cytologically documented Stage IV adenocarcinoma of the lung
- Has disease progression on or after a prior platinum-containing chemotherapy
- Measurable disease as defined by RECIST 1.1
- Provision of suitable fresh tumour tissue for the analysis of AXL kinase expression and PD-L1 expression
- Eastern Cooperative Oncology Group (ECOG) performance score 0 or 1
- Not received more than one prior line of chemotherapy for advanced or metastatic adenocarcinoma of the lung
- No prior therapy with an immunomodulatory agent
- No known active central nervous system (CNS) metastases and/or carcinomatous meningitis
- No recent or ongoing systemic steroid therapy

Assessments - efficacy & safety

- Response was assessed every 9 weeks per RECIST v1.1
- Adverse events were assessed by CTCAE v4.03
- Evaluable: ≥1 dose of study treatment as of data cutoff (Apr 2019)
- Radiologically evaluable: having at least 1 evaluable post-baseline scan

Biomarker analysis

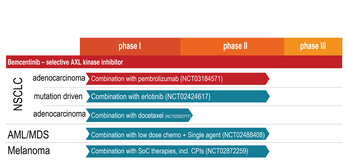
- Immunohistochemistry analysis of PD-L1 and AXL expression in tumour biopsies
- Comprehensive liquid biopsy analysis of soluble protein biomarkers in blood samples
- High dimensional multi-spectral immunofluorescence imaging of tumour microenvironment immune cell populations in tumour biopsies
- Peripheral TCR/BCR repertoire sequencing of PBMCs
- Gene expression analysis of tumour biopsies

Endpoints

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

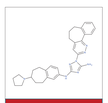
Bemcentinib is a highly selective, potent, orally available, AXL kinase inhibitor

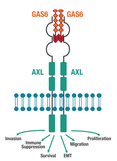
Bemcentinib is being developed as monotherapy and in combination with immune, targeted and chemotherapy in NSCLC, AML/MDS and melanoma.



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)

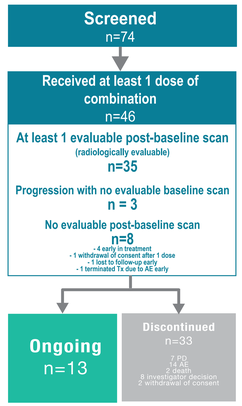
- Pembrolizumab as a single agent is indicated for the treatment of patients with metastatic NSCLC with disease progression on or after platinum-containing chemotherapy[1,2]
- KEYNOTE-001[3], a multi-cohort phase I study designed to define and validate expression levels of PD-L1 associated with the likelihood 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 while limiting additive toxicity

AXL receptor tyrosine kinase and selective AXL inhibitor bemcentinib

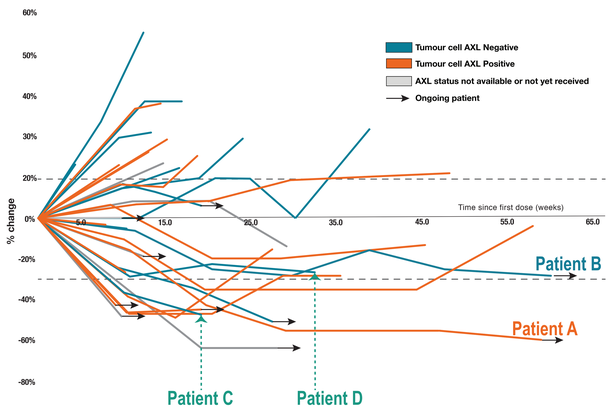
- AXL is a receptor tyrosine kinase expressed on tumour and immune cells and a member of the TAM family (Tyro-AXL-Mer) of kinases
- AXL is overexpressed in response to a hostile tumour micro-environment and drives a tumour survival programme including immune escape, anti-tumour therapy resistance & metastasis[3]
- AXL is a negative prognostic factor in a multitude of cancers including NSCLC[4]
- Bemcentinib, a first-in-class highly selective, potent, and orally bioavailable inhibitor of AXL, has been shown to potently improve the efficacy of checkpoint blockade in murine pre-clinical models of NSCLC

Promising clinical activity, particularly in patients with AXL positive tumour mocro-environment, independent of PD-L1 expression

Patient disposition (stages I + II)



Change in sum of target lesions over time, by patient

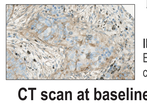


Of the 46 patients who have been dosed, 35 had a radiological assessment (shown above).
Of the 11 patients not shown, 3 had PD without evaluable radiological assessment, and 8 patients either had no response assessment or were early in treatment.

Patient A

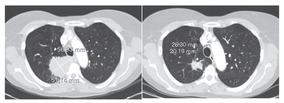
Age: 64
Sex: Female
Race: white
Smoking Status: ex-smoker
(pack years) (unknown)

PD-L1 (TPS%)	-ve (0%)
AXL expression	
Tumour cells (H-Score)	+ve (55)
Immune Cells	Strong +ve
Stromal Cells	Weak +ve

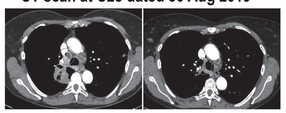


IHC evaluation of AXL: Expression of AXL both on cancer cells and cells in the stroma (right).

CT scan at baseline dated 31 Jan 2018



CT scan at C28 dated 30 Aug 2019

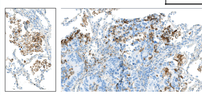


Patient A has received 4 cycles of cisplatin and pemetrexed with disease progression after 4th cycle prior to study entry. She started study treatment (pembrolizumab and bemcentinib) in Feb 2018 and her target lesions have shrunk from 57mm to 35mm with partial radiological response as per RECIST 1.1.

Patient B

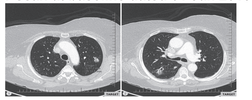
Age: 76
Sex: Female
Race: white
Smoking Status: ex-smoker
(pack years) (28.5)

PD-L1 (TPS%)	Non-Evaluable
AXL expression	
Tumour cells (H-Score)	-ve (0)
Immune Cells	+ve
Stromal Cells	-ve

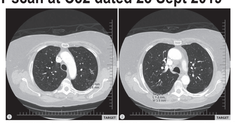


IHC evaluation of AXL. Strong expression of AXL on alveolar macrophages (left). cancer cells stained negative for AXL expression (right)

CT scan at baseline dated 31 Jan 2018



CT scan at C32 dated 23 Sept 2019



Prior to study entry Patient B received 6 cycles of carboplatin and pemetrexed from April 2015 to Jun 2015 with disease progression in Sep 2017. She started study treatment (pembrolizumab and bemcentinib) in Dec 2017 and her target lesions have shrunk from 32mm to 19mm with partial radiological response as per RECIST 1.1

Patient C

Age: 64
Sex: Male
Race: white
Smoking Status: never smoker

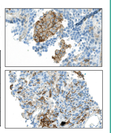
PD-L1 (TPS%)	-ve (0%)
AXL expression	
Tumour cells (H-Score)	-ve (0)
Immune Cells	Weak +ve
Stromal Cells	Weak +ve

IHC evaluation of AXL: Weak to moderate cytoplasmic staining of **inflammatory cells** and **macrophages.** Few single tumour cells with minimal to weak cytoplasmic staining.

Patient D

Age: 62
Sex: Female
Race: white
Smoking Status: Smoker
(pack years) (49)

PD-L1 (TPS%)	+ve (15%)
AXL expression	
Tumour cells (H-Score)	-ve (0)
Immune Cells	Strong +ve
Stromal Cells	Weak +ve



IHC evaluation of AXL: Positive staining on alveolar macrophages (top figure). Weak to moderate cytoplasmic staining of stromal cells, moderate to strong staining of macrophages, very few tumour cells staining positive (bottom figure).

Patient demographics

Median Age (range)		64.5 (39-82)
ECOG at screen		
	0 (%)	22 (48%)
	1 (%)	24 (52%)
	≥2 (%)	0
Sex		
	Female (%)	18 (39%)
	Male (%)	28 (61%)
Ethnicity		
	Hispanic or Latino (%)	9 (20%)
	Not Hispanic or Latino (%)	37 (80%)
Race		
	White (%)	43 (94%)
	Asian (%)	2 (4%)
	Other (%)	1 (2%)
Smoking status		
	Smoker (%)	8 (17%)
	Ex-smoker (%)	27 (59%)
	Never smoked (%)	10 (22%)
	Unknown (%)	1 (2%)
Pack years		
	Median	36.5
	Range	0.5-100

Disease Characteristics

Mutations*	**n**	**%**
None	35	76%
KRAS	6	13%
TP53	2	4%
ERBB2	1	2%
EGFR	1	2%
Other/Unknown	2	4%
Best response to most recent treatment	**n**	**%**
CR	2	4%
PR	17	37%
SD	10	22%
PD	12	26%
Unknown	5	11%

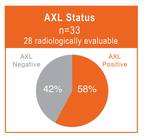
* May be overlap between individual patients

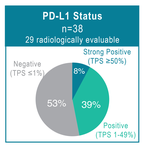
Safety

Most frequent TRAEs (occurring in >10% dosed pts)	All Grades	
	n	**%**
Any TRAE	35	76%
Transaminase increased*	16	35%
Asthenia / Fatigue	14	30%
Diarrhoea	12	26%
Nausea	6	13%
Anaemia	5	11%
Decreased appetite	5	11%

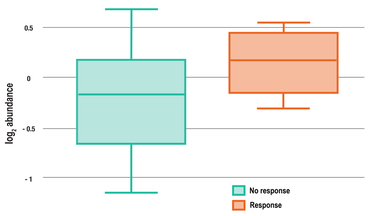
* Preferred terms include: Alanine aminotransferase increased, Aspartate aminotransferase increased and Transaminases increased.

Biomarkers





Novel predictive biomarker candidate



Methods

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.

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

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References

[1]**Herbst, et al.** The Lancet (2016). Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial.
[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.
[4]**Shieh, et al.** Neoplasia (2005). Expression of axl in lung adenocarcinoma and correlation with tumor progression.
[5]**Leighl, et al.** Lancet (2019). Pembrolizumab in patients with advanced non-small-cell lung cancer (KEYNOTE-001): 3-year results from an open-label, phase 1 study.

Contact

BerGenBio ASA
Jonas Lies vei 91
5009 Bergen
NORWAY

www.bergenbio.com
@BGenBio

BerGenBio Ltd
1 Robert Robinson Ave
OX4 4GA
Oxford, UK

post@bergenbio.com
+47 559 61 159

Conclusions

- The combination therapy of bemcentinib and pembrolizumab is well-tolerated.
- The combination therapy of bemcentinib and pembrolizumab is benefitting AXL positive and PD-L1 low/negative 2nd Line NSCLC patients
- Durable clinical benefit observed in patients with upregulated AXL expression in tumour, immune, or stromal cells.
- New novel predictive plasma protein biomarker candidate identified

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