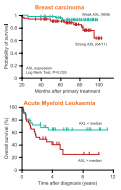
BerGenBio

AXL receptor tyrosine kinase

Key driver of tumour plasticity, heterogeneity and immune evasion

High AXL expression is correlated with poor survival in most cancers

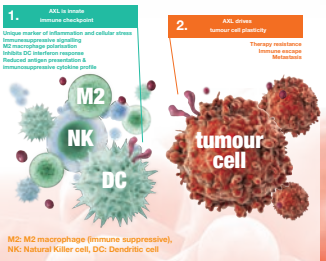
Strong AXL expression correlates with poor survival rate



Broad evidence of AXL linked with poor prognosis

Astrocytic brain tumors	Melanoma
Breast cancer	Mesothelioma
Gallbladder cancer	NSCLC
GI	Pancreatic cancer
- Colon cancer	Sarcomas
- Esophageal cancer	- Ewing Sarcoma
- Gastric cancer	- Kaposis sarcoma
Gynaecological	- Liposarcoma
- Ovarian cancer	- Osteosarcoma
- Uterine cancer	Skin SCC
HCC	Thyroid cancer
HNC	Urological
Haematological	- Bladder cancer
- AML	- Prostate cancer
- CLL	- RCC
- CML	

AXL is an innate immune checkpoint & drives tumour intrinsic cell plasticity



M2: M2 macrophage (immune suppressive), NK: Natural Killer cell, DC: Dendritic cell

AXL is a receptor tyrosine kinase

- Gas6, single high affinity ligand
- Low expression in normal tissues; upregulated by inflammation and cellular stress
- Unique signal transduction drives
  - Survival
  - Drug resistance
  - Immune suppression / evasion
  - Metastasis
- Interest in AXL as a key target for aggressive disease is increasing rapidly

Benefits of selective AXL inhibition with bemcentinib

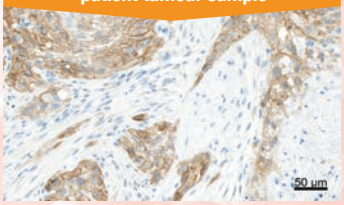
Selectivity
- Selective over other kinases and other TAM family members (MerTK, Tyro) specifically
- Allows for rational combinations while reducing the risk of additive toxicity

Safety
- AXL knockout mice are phenotypically normal
- AXL is the TAM receptor that is specifically upregulated in aggressive disease
- bemcentinib is well tolerated across BerGenBio combination studies

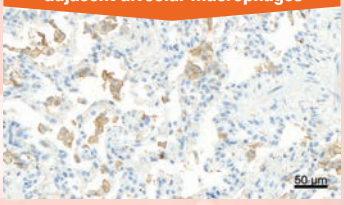
Efficacy
- Single agent activity in AML and NSCLC
- Increased clinical benefit in combination with chemo in NSCLC
- Reverses acquired resistance to erlotinib in NSCLC
- Increases efficacy of checkpoint inhibitors in NSCLC

AXL is detected on patient tumour tissue and adjacent immune cells by BerGenBio proprietary immunohistochemistry method (IHC)

AXL expression in NSCLC patient tumour sample



AXL expression in tumour adjacent alveolar macrophages



BerGenBio

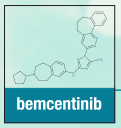
Bemcentinib

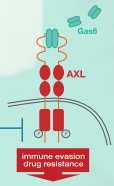
First-in-class, highly selective and orally bioavailable AXL inhibitor

- **Once a day capsule**
- **Most advanced selective oral AXL inhibitor in clinical development, PoC data in:**
  - monotherapy AML/MDS
  - KEYTRUDA combo NSCLC
  - EGFR inhibitor combo NSCLC
  - chemo combo NSCLC
- **Wide therapeutic index, well tolerated**
- **25 kg API manufactured, 100 mg capsule, shelf life > 3 years at RT confirmed**

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

Selectivity Profile		
Kinase	Kinome Scan (Kd)	
	nM	Fold
Axl	0.4	1
Mer	100	250
Tyro	>1000	>2,500 fold





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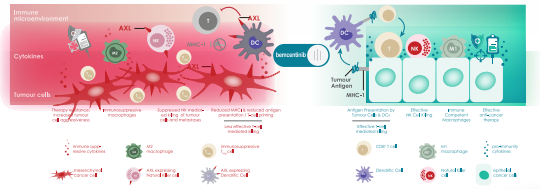
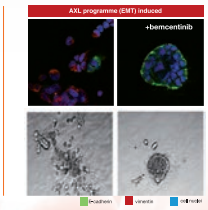
Bemcentinib preclinical data

Selective AXL inhibition to enhance immune cell attack, anti-tumour therapy and prevent spread

Bemcentinib acts on tumour and immune cells

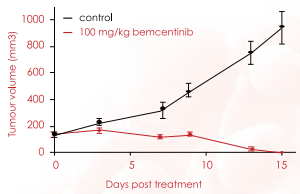


Reverses AXL programme *in vitro*



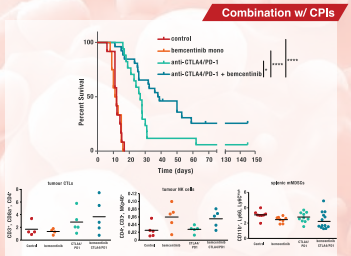
Bemcentinib is active as a monotherapy and in combination with immune- targeted and chemotherapy *in vivo*

Single agent activity



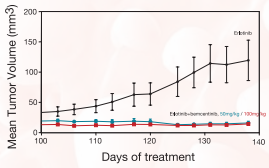
AML model

Combination w/ CPIs



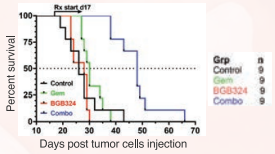
TNBC model

Combination w/ targeted therapy



NSCLC model

Combination w/ chemo



Pancreatic model

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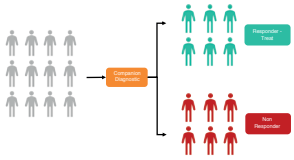
Companion Diagnostic

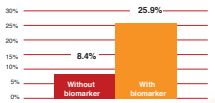
for personalised medicine

What is Precision Medicine?



Why Precision Medicine?

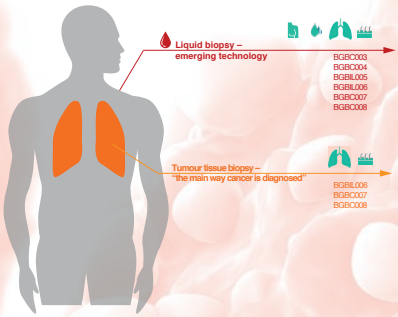
Likelihood of success (Phase I to approval)



- Selecting patients most likely to benefit from treatment
- Improving probability of approval
- Increase reimbursement rates

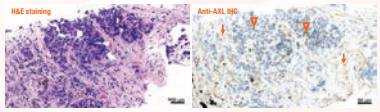
BerGenBio biomarker programme

Designed in line with established and emerging techniques: Standard (tissue) and emerging (blood) pathology techniques are used to diagnose cancer and determine optimal, personalised treatment.



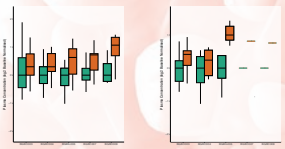
Pre-treatment soluble AXL levels in plasma are predictive of patient benefit in AML/MDS

Tissue AXL levels correlate with response in bemcentinib/pembrolizumab combo trial



Shown is a fresh tissue biopsy from a partial responder to bemcentinib + pembrolizumab. Anti-AXL staining of tumour cells was observed (open arrowheads). Additionally a mainly weak to moderate cytoplasmic staining of stromal cells was seen (arrows).

Pharmacodynamics



sAxl levels C1D1 vs C2D1 in all samples log2 baseline normalised

sAXL levels C1D1 vs C2D1 in patients showing clinical benefit (log2 baseline normalised). Patients not demonstrating treatment benefit show no significant alteration of sAxl levels following treatment.

AXL drives a tumour survival programme that is increased by reduced receptor shedding

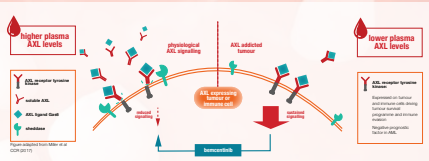


Figure adapted from Miller et al CCR (2017)

BerGenBio

In collaboration with MSD

Bemcentinib and KEYTRUDA® in NSCLC

Keytruda® monotherapy showed 10% response rate in previously treated NSCLC patients (Keynote 010).

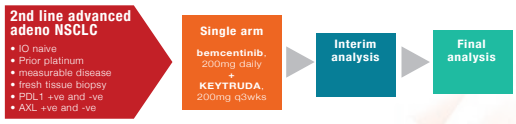
The BGBC008 trial is designed to test the hypothesis whether AXL inhibition can

- Enhance responses to immunotherapy

when given in combination with KEYTRUDA in previously treated, immunotherapy-naïve NSCLC patients.

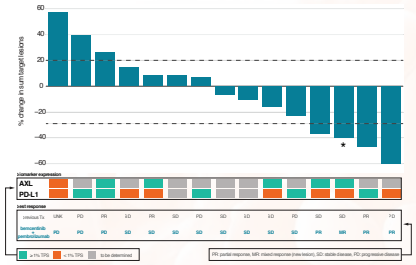
Clinical collaboration with Merck & Co. (MSD)

BGBC008: Phase II trial in NSCLC, bemcentinib with KEYTRUDA



BGBC008: Interim clinical data Phase II trial in NSCLC of bemcentinib with KEYTRUDA

Best response

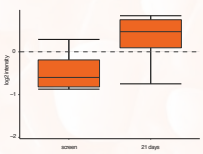


Best overall response according to biomarker expression at time of data cut-off (analysis includes ongoing patients)

	PR	SD	PD	N	ORR (%)	DCR (%)
All	3	9	3	15	20	80
PD-L1 < 1%	2	4	1	7	29	86
AXL ≥ 1%	1	3	1	5	20	80

Biomarkers

Plasma soluble AXL levels increase upon treatment with bemcentinib + KEYTRUDA

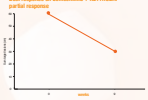


Patient case study: AXL biomarker correlated with patient benefit.

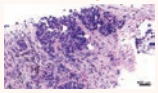
Patient characteristics

71 year old white male
screen ECOG of 2
no known mutations
1 line of previous therapy with best response of SD
liver metastases present
biomarker expression, TPS (%)
AXL: 25%
PD-L1: 0%

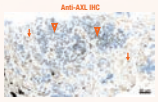
Best response on bemcentinib + KEYTRUDA: partial response



H&E staining



Anti-AXL IHC



Anti-AXL staining of tumour cells was observed (open arrowheads). Additionally a mainly weak to moderate cytoplasmic staining of stromal cells was seen (arrows).

BerGenBio

In collaboration with MSD

Bemcentinib and KEYTRUDA® in TNBC

A Ph II study of the selective AXL inhibitor bemcentinib in combination with pembrolizumab in patients with previously treated, locally advanced and unresectable or metastatic triple negative breast cancer (TNBC) or triple negative inflammatory breast cancer (TN-IB)

The BGBC007 trial is designed to test the hypothesis whether AXL inhibition with bemcentinib can

- enhance responses to immunotherapy

when given in combination with pembrolizumab in previously treated, immunotherapy-naïve TNBC patients.

Clinical collaboration with Merck & Co. (MSD)

Phase II Study of the selective AXL inhibitor bemcentinib in combination with KEYTRUDA

2nd line advanced TNBC or TN-IBC

- Prior taxane &/or anthracycline
- measurable disease
- fresh tissue biopsy
- PDL1 +ve and -ve
- AXL +ve and -ve

Single arm

- bemcentinib 200mg daily
- pembrolizumab 200mg 3-weekly

→ **Interim analysis** → **Final analysis**

Study Objectives & Endpoints

Primary objective:
- Anti-tumour activity of bemcentinib and pembrolizumab in combination

Secondary objectives:
- Safety of bemcentinib and pembrolizumab when given in combination
- Anti-tumour activity of the combination of bemcentinib and pembrolizumab
- Pharmacokinetic profile of bemcentinib when given with pembrolizumab

Explorative:
- Assessment of relevant biomarkers

Primary endpoint:
- Objective Response Rate

Secondary endpoints:
- Duration of Response
- Disease Control Rate
- Time to progression
- Survival at 12 months
- Response by biomarker expression

Major Inclusion & Exclusion Criteria

Key Inclusion Criteria
- Histopathologically or cytologically documented TNBC or TN-IBC
- Locally advanced and unresectable or metastatic TNBC or triple negative inflammatory breast cancer.
- Received one or more prior therapies for TNBC or inflammatory breast cancer in the metastatic setting
- Prior treatment (metastatic or (neo) adjuvant) must have included a prior taxane and/or anthracycline-based therapy
- Renal and hepatic and cardiac function within normal ranges
- Measurable disease as defined by RECIST 1.12
- Provision of suitable tumour tissue for the analysis of AXL kinase expression and PD-L1 expression
- Eastern Cooperative Oncology Group (ECOG) performance score 0 or 1

Key Exclusion Criteria
- Has disease suitable for local therapy administered with curative intent
- Has received more than three previous lines of therapy in the metastatic setting
- Has received prior therapy with an immunomodulatory agent
- Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis
- Indigestion remedies
- Recent or ongoing systemic steroid therapy

Translational Analyses

Immunohistochemistry
- PD-L1
- AXL

Liquid biomarkers / PBMCs
- AXL signalling pathway
- Soluble AXL
- MAP Kinase pathway signalling
- Immune cell populations
- AKT signalling pathway

Pharmacokinetics
- bemcentinib
- pembrolizumab

Participating Countries

Conclusion

14 out of 18 patients analysed were negative for AXL

12 out of 15 patients analysed were negative for PD-L1

Of 18 patients analysed, 1 had a partial response

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Bemcentinib as monotherapy and combination in R/R AML and MDS

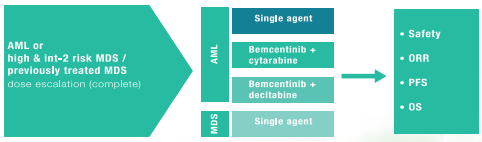
AML and high-risk MDS patients unfit for high intensity chemotherapy remain a very challenging patient population with limited treatment options

The BGBC003 trial is designed to test the hypothesis whether AXL inhibition with bemcentinib can

- Elicit single agent effect and / or
- Enhance responses to chemotherapy

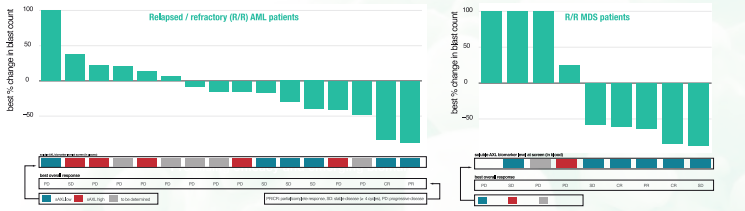
when given as a single agent in relapsed / refractory AML and high risk MDS or in combination with cytarabine or decitabine in treatment naïve AML patients

BGBC003: Phase II trial of bemcentinib in AML/MDS



Interim clinical data Phase II trial of bemcentini in AML/MDS

Best response

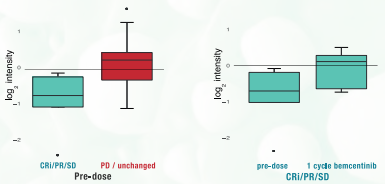


Response assessment per soluble AXL biomarker (measured at screen in plasma)

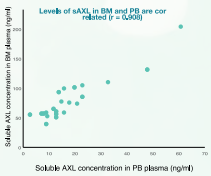
		PD	SD	PR	CR	N	ORR (%)	CBR (%)
AML+ MDS	sAXL high	6	1			7	0	17
	sAXL low	1	6	3	3	13	46	92
AML	sAXL high	5	1			6	0	17
	sAXL low	1	3	2	1	7	43	86
MDS	sAXL high	1				1	0	0
	sAXL low		3	1	2	6	50	100

Blood plasma levels of soluble AXL (sAXL) predict response to bemcentinib monotherapy in R/R AML & MDS patients

Blood plasma levels of sAXL are decreased at prescreen in patients experiencing benefit, levels increase in response to treatment with bemcentinib



Blood and BM plasma levels of sAXL are correlated & sAXL levels are elevated in BM plasma upon treatment



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Bemcentinib in combination with SoC in metastatic melanoma

Although responses to TKIs are rapid, resistance ultimately emerges. Monotherapy checkpoint inhibitor responses can be further improved.

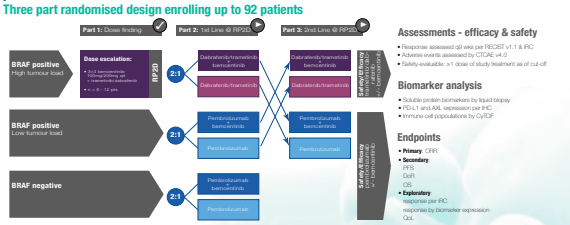
The BGBIL006 trial is designed to test the hypothesis whether AXL inhibition can

- Enhance responses to immunotherapy
- Enhance responses to targeted therapy

when given in combination with pembrolizumab or dabrafenib/trametinib in treatment naïve melanoma patients

Ph I/II randomised trial of selective AXL inhibitor bemcentinib in melanoma patients

Three part randomised design enrolling up to 92 patients



Assessments - efficacy & safety

- Response assessed q9 wks per RECIST v1.1 & iRC
- Adverse events assessed by CTCAE v4.0
- Safety evaluable: ≥1 dose of study treatment as of cut-off

Biomarker analysis

- Soluble protein biomarkers by liquid biopsy
- PD-L1 and AXL expression per IHC
- Immune cell populations by CyTOF

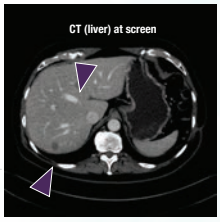
Endpoints

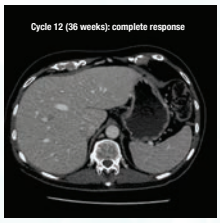
- **Primary**: ORR
- **Secondary**
  - PFS
  - DoR
  - OS
- **Exploratory**
  - responses per iRC
  - response by biomarker expression
  - QoL

Interim clinical data Phase II trial in metastatic melanoma

Example CR on bemcentinib + dabrafenib/trametinib

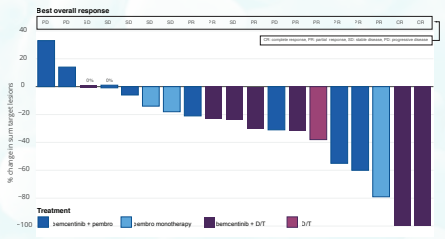
- A 68 year old male was randomised to receive 200 mg/daily bemcentinib + standard dabrafenib/trametinib.
- At screening the patient had multiple metastases to the liver and the lungs.
- At cycle 12, he had a complete response.





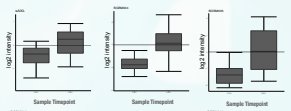
Best response

Best percentage change from baseline in target lesions in RECIST evaluable patients to date

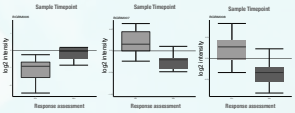


Biomarkers

Pharmacodynamics:
Serum AXL, serum biomarker BGBM004 and serum biomarker BGBM005 levels increase upon treatment with bemcentinib



Predictive:
Pre-treatment levels of soluble AXL serum biomarker BGBM007 and serum biomarker BGBM008 associated with benefit from treatment



BerGenBio

Bemcentinib + TARCEVA® in NSCLC

Patients with EGFR driven NSCLC develop resistance to targeted therapy.

The BGBC004 trial is designed to test the hypothesis whether AXL inhibition can

- Reverse and / or
- Prevent resistance to EGFRm targeted therapies

when given in combination with erlotinib in EGFRm NSCLC patients who have either progressed on or have just started EGFRm targeted therapy

BGBC004: Phase II trial in NSCLC of bemcentinib with TARCEVA (erlotinib)

BGBC004 Phase II – NSCLC EGFR-mutation driven

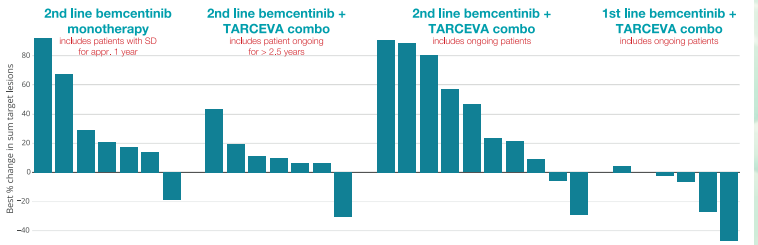
Stage IIIb or IV disease EGFR mutation positive

up to 66 pts

Dose escalation (completed) & expansion (ongoing)		Expected readout
Arm A: safety run-in & expansion	Safety	Initial read-out expected 2H 2018
Arm B: 2nd line bemcentiinib 200mg/d + TARCEVA	Efficacy, PK, biomarkers	
Arm C: 1st line bemcentinib 200mg/d + TARCEVA		

BGBC004: Interim clinical data Phase II trial in NSCLC of bemcentinib with TARCEVA (erlotinib)

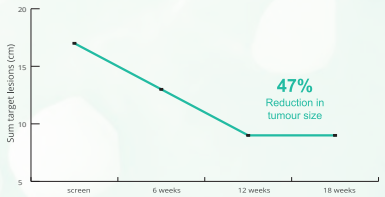
Best response



First line combo with TARCEVA, partial responder

Age, ethnicity & sex	58 year old white male
ECOG	1
Histologic diagnosis	Adenocarcinoma of the lung
Stage at initial diagnosis	IV
at screening	IV
Sites	Lung, pleura
Mutations	EGFR
Previous lines of therapy	Tarceva, 14 Weeks
Current status	Ongoing

First line combo with TARCEVA: Partial response



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Bemcentinib + docetaxel in NSCLC

Docetaxel is standard second line chemo in NSCLC patients. Response rates in this disease setting are typically 7-10%.

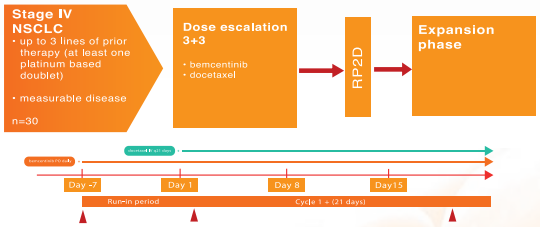
The BGBIL005 trial is designed to investigate

- safety and tolerability

and test the hypothesis of whether AXL inhibition can

- enhance responses to chemotherapy

when given in combination with docetaxel in previously treated (last line) NSCLC patients



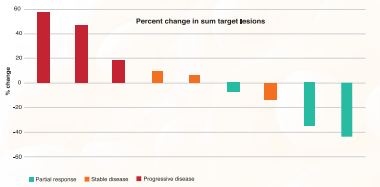
Sponsor Investigator: Dr David Gerber, UTSW Dallas

"While it is still early, to date 3 of 7 evaluable cases have demonstrated radiographic partial responses, which we cautiously hope may represent a real improvement over the 7-10% response rate seen with docetaxel chemotherapy in this disease setting"

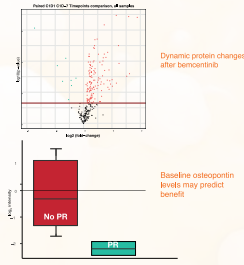
BGBIL005: Interim clinical data Phase I/II trial in NSCLC of bemcentinib with docetaxel

Best response on study

Pt	010	003	007	005	009	011	002	006	004
Last treatment	B1 (investigational)	Pembrolizumab	Pembrolizumab	Carboplatin/ pemetrexed	Nivolumab	Gemcitabine	Nivolumab	Nivolumab	Pembrolizumab
Best response on last Tx	SD	PD	PD	PD	PD	PD	SD	SD	PD
Best response on study	PD	PD	PD	SD	SD	PR	SD	PR	PR



Promising efficacy and emerging biomarkers



Dynamic protein changes after bemcentinib

Baseline osteopontin levels may predict benefit

Pt 004 characteristics

Gender, age	Female, 64 years old
Ethicity	Caucasian
Histologic diagnosis	NSCLC
Stage	IV
Mutations	EGFR wild-type, ALK negative
Previous lines of treatment	1. Carboplatin / Paclitaxel – SD 2. Carboplatin / pemetrexed – PD 3. Pembrolizumab – PD
Dose	Starting dose 75mg/m^2 docetaxel, 100mg bemcentinib. Cycle 2 day 1 docetaxel reduced to 60mg/m^2

Pt 004 tumour shrinkage (weeks)

BerGenBio

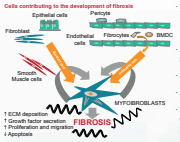
AXL in fibrosis

Pre-clinical evidence suggests a promising role for selective AXL inhibition in fibrotic diseases

Background

- Fibrosis –45% of all morbidity and mortality of NCDs
- Contributes to a broad range of fibrotic diseases and remodeling pathologies
- Fibrosis can affect all organs
- Fibrotic pathologies remain diseases of unmet medical need

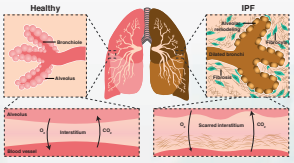
The importance of AXL in fibrosis



- Regulates and modulates key fibrogenic pathways
  - TGFb signaling[2]
  - Mechanosensing Hippo pathway[3]
  - PPARγ[4]
- AXL regulates cellular plasticity implicated in fibrotic pathologies[1]
- AXL required for hepatic stellate cell (HCS) activation
- AXL required for HCS ECM expression[5]
- Pharmacological modulation of AXL inhibits development of fibrosis several pre-clinical models

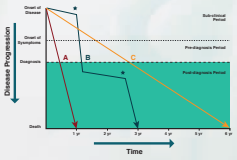
1 Gilbane ART 2015; 2 Reichl Hep. 2015; 3 Gibault ChemMed 2017; 4 Zhu AJTR 2016; 5 Barcena J. Hep 2015

Idiopathic Pulmonary Fibrosis (IPF)



- Rare disease
- Only two licensed anti-fibrotic therapies:
  - Nintedanib
  - Pirfenidone
- Market size estimated to grow to $3.5B by 2025

IPF splits into fast and slower progressors

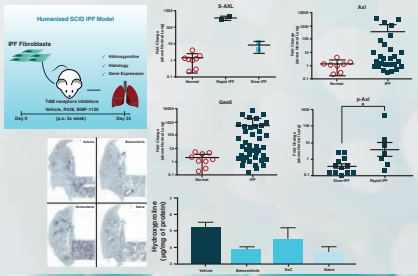


- Axl expression predicts rapid decliners
- Bemcentinib modulates the IPF fibroblast fibrogenic phenotype
- GAS6 -/- mice protected from lung fibrosis

Bemcentinib is active in a humanised mouse model of IPF, and is significantly more active than nintedanib[6]

(6) Espindola 2018

AXL & Gas6 expression is increased in IPF, levels of activated AXL (pAXL) increased in rapid IPF

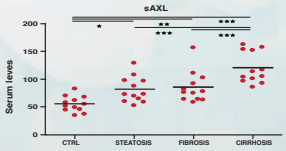


AXL in Non Alcoholic Steatohepatitis (NASH)

- Non-alcoholic fatty liver disease (NAFLD) affects 75-100 million Americans
- Approximately 5% (16 million) Americans currently believed to have NASH
- Market: >$25B in 2026
- Patients with advanced fibrosis (F3 and F4) or cirrhosis sAxl and GAS6 in circulation[7]
- sAxl accurate biomarker for liver fibrosis and cirrhosis[7]

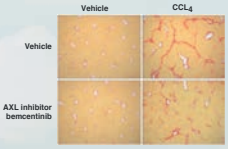
AXL is biomarker for liver fibrosis and cirrhosis, bemcentinib inhibits NASH *in vivo*

(7) Ramirez ESSL 2016



Serum AXL elevated in NASH, selective AXL inhibition active *in vivo*[7]

Bemcentinib reduces fibrosis in a CCL4-induced model of NASH



Bemcentinib reduces fibrosis in a diet induced model of NASH