BerGenBio

BGB324 - first-in-class, selective, potent and orally available small molecule AXL kinase inhibitor in clinical development

Precision: Lung Cancer, July 25-26 2017

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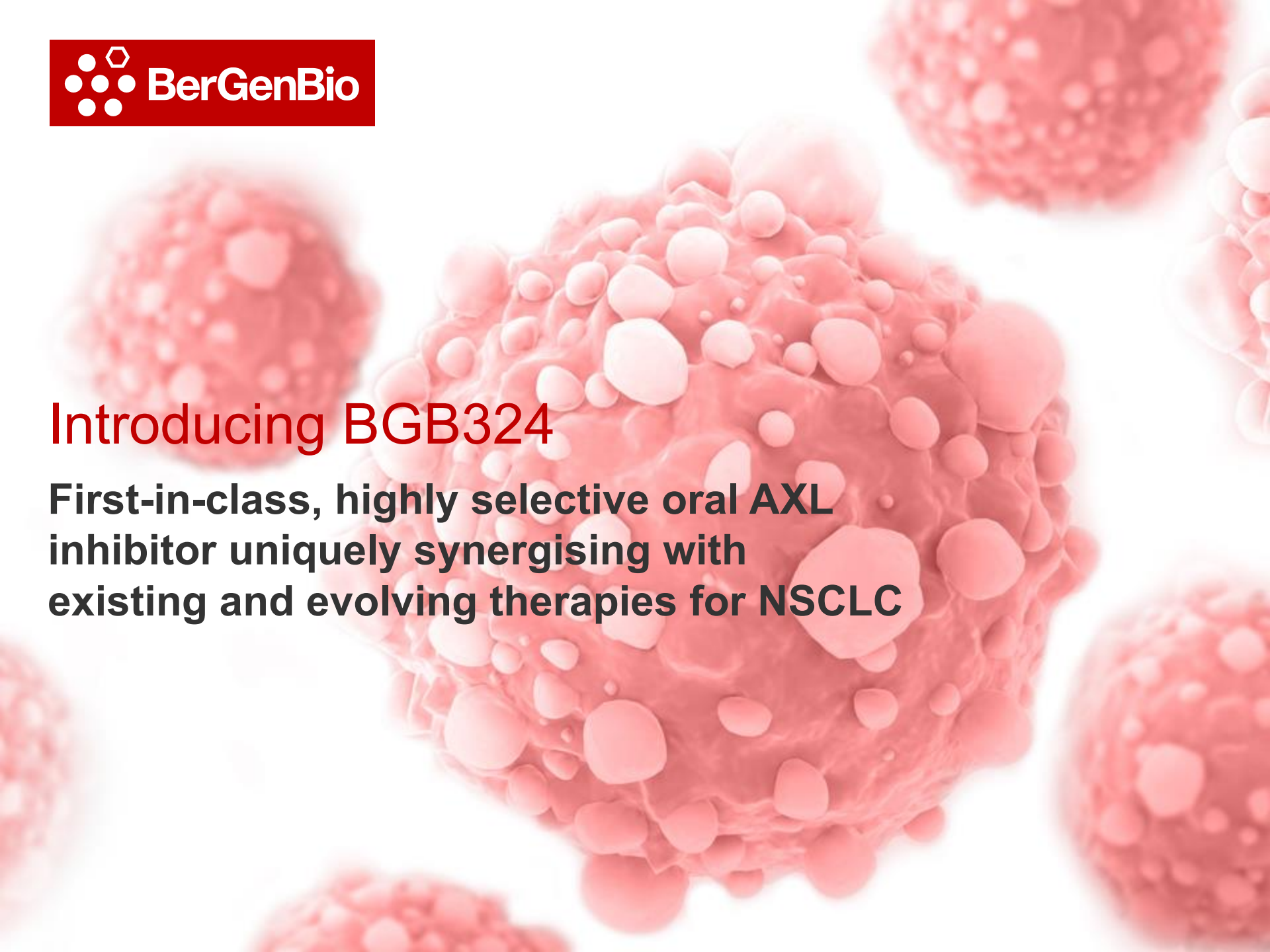
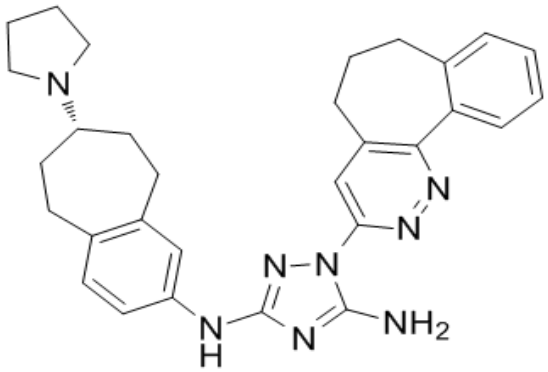


Introducing BGB324

First-in-class, highly selective oral AXL inhibitor uniquely synergising with existing and evolving therapies for NSCLC

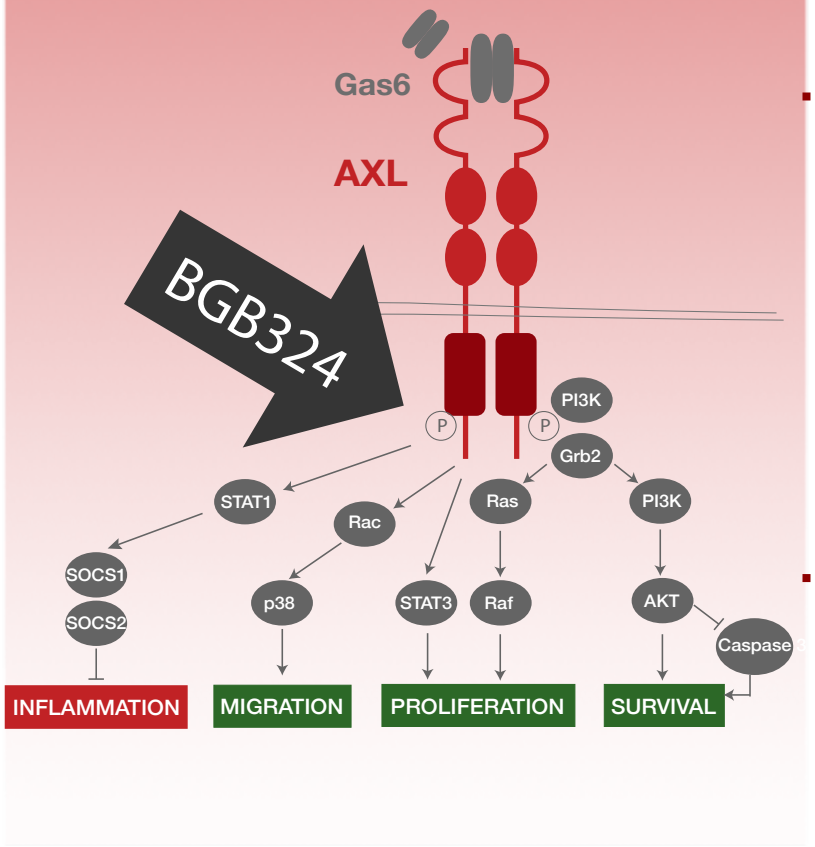
BGB324 – First-in-class, highly selective oral AXL inhibitor

1. First-in-class, highly selective, potent AXL inhibitor
2. Orally bioavailable: One a day pill, supports compliance
3. Well tolerated
4. Wide therapeutic index: highly suitable for combination with existing drugs
5. Pre-clinical evidence suggests wide clinical utility



Complementary mechanisms of BGB324

Mode of Action



AXL inhibition via BGB324 blocks:

- Therapy resistance
- Proliferation, survival, migration
- Metastasis
- Immune evasion

AXL inhibition via BGB324 increases anti-tumour immunity:

- Increased CTL & NK cell infiltration
- Reduces immunosuppressive M2 macrophages
- Reduces immunosuppr. cytokines
- Reduces mMDSCs

Broad Phase II Programme exploring BGB324 safety and efficacy

	Discovery	Preclinical	Phase I	Phase II	Phase III
BGB324 – Axl kinase inhibitor					
AML / MDS			Phase Ib / II – Single agent / Combination		
NSCLC *(mutation driven)*			Phase Ib / II – Combination with TARCEVA® (erlotinib)		
NSCLC *(adenocarcinoma)*			Phase II Combination with KEYTRUDA® (pembrolizumab)		
TNBC			Phase II Combination with KEYTRUDA® (pembrolizumab)		
Investigator-sponsored trials					
NSCLC			Phase II BGB324 in combination with Docetaxel		
Melanoma			Phase II BGB324 in combination with current standard therapies, incl. CPIs		
AXL antibody programmes					
BGB149 – Oncology			Anti-Axl mAb		
BGB601 – Metastatic cancer (Partnered)			ADC		

Clinical development plan in NSCLC addresses drug combinations based on unique synergies of BGB324 with respective MOAs

1 Chemo combination

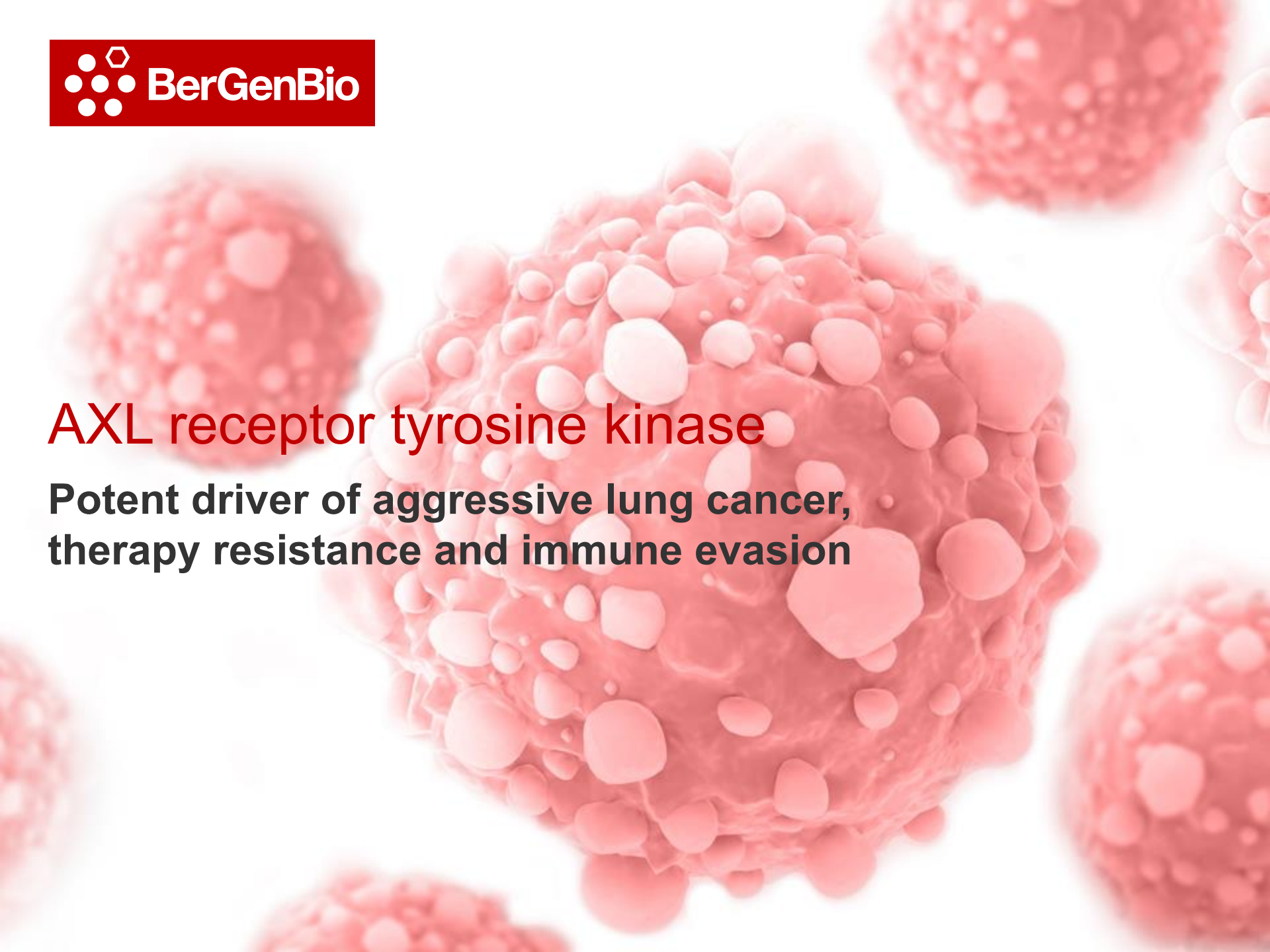
- **Reversal of resistance to chemotherapy in NSCLC**
  - Stage IV NSCLC
  - Up to three lines of previous therapy, including a platinum-based doublet therapy
  - **BGB324 + docetaxel**

2 Combination with targeted therapy

- **Reversal and prevention of resistance to targeted therapy in EGFR driven NSCLC**
  - Stage IV NSCLC w/ known EGFR mutation status
  - Patients who received 1st or 2nd gen EGFR inhibitors and progressed / experienced disease stabilisation
  - **BGB324 + erlotinib**

3 Immunotherapy combination

- **Prevention of acquired resistance to and increase of efficacy of immunotherapy**
  - Stage IV NSCLC
  - Patients who have progressed on chemo- or targeted therapy
  - **BGB324 + pembrolizumab**



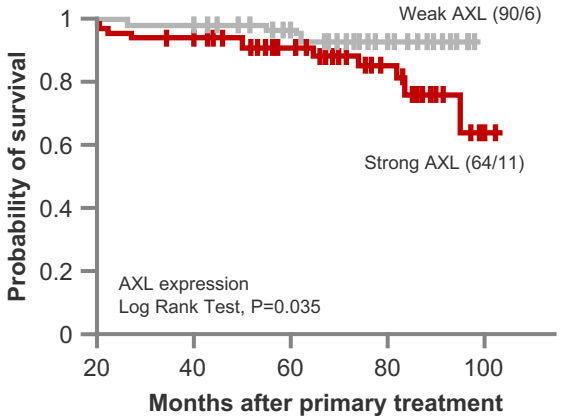
AXL receptor tyrosine kinase

Potent driver of aggressive lung cancer, therapy resistance and immune evasion

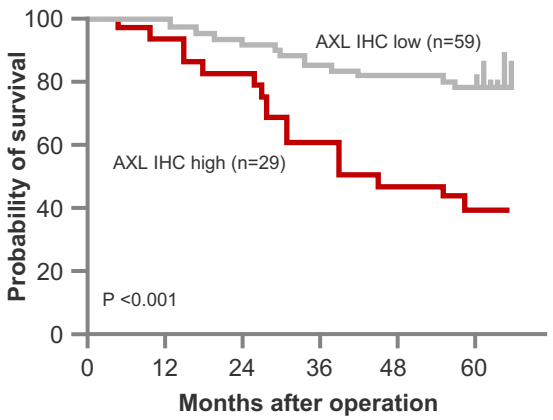
High Axl expression correlates with poor overall survival in most cancers

Strong AXL expression correlates with poor survival rate

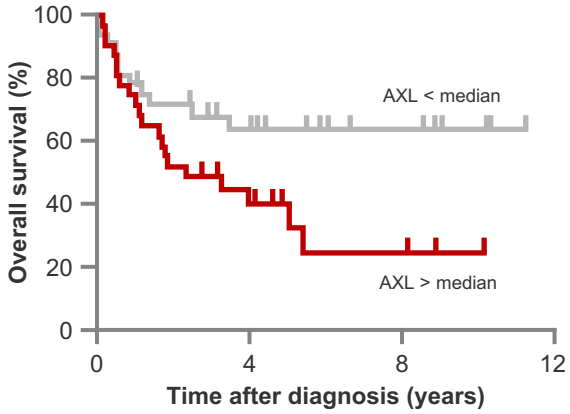
Breast carcinoma[1]



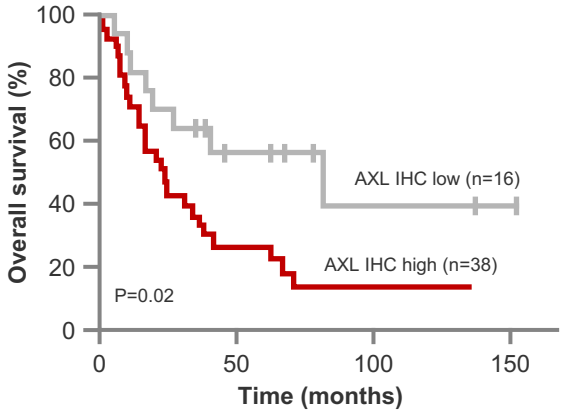
Lung adenocarcinoma (NSCLC)[2]



Acute Myeloid Leukaemia[3]



Pancreatic ductal adenocarcinoma[4]



Broad evidence of AXL linked with poor prognosis[5]

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

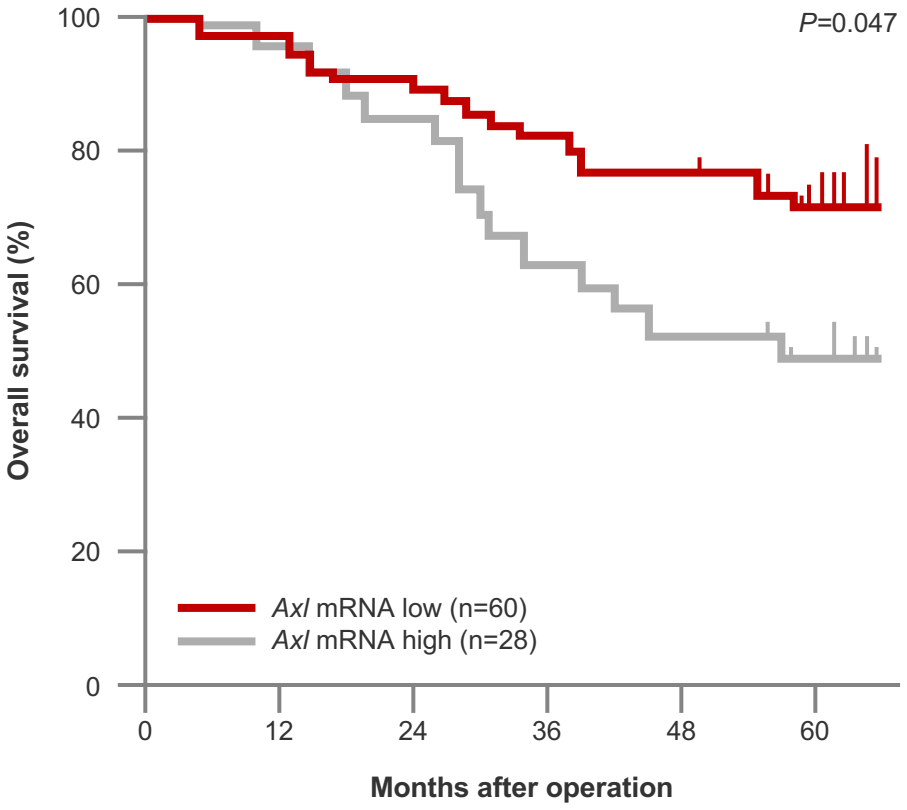
1 Gjerdrum, 2010; 2 Ishikawa, 2012; 3 Ben-Battala, 2013; 4 Song, 2010, 5 supported by > 100 publications

High AXL expression correlates with NSCLC aggressiveness and poorer overall survival

Higher AXL expression correlates with less favourable clinical characteristics[1]

Variable	Patients, n	Expression of AXL, n -	Expression of AXL, n +	Positive Rate, %	P-value
Total	257				
Histological type					1.000
Adenocarcinoma	143	66	77	53.85	
Squamous cell carcinoma	114	51	63	55.26	
Differentiation					0.001
Well	44	33	11	25.00	
Moderate	140	71	69	49.29	
Poor	73	13	60	82.19	
TNM stage					0.005
Stage 1	47	35	12	25.53	
>Stage 1	210	83	127	60.48	
Lymph node metastasis					0.091
YES	115	44	71	61.74	
NO	142	73	69	48.59	
Tumor size					0.166
<3 cm	92	50	42	45.65	
>3 cm	165	67	98	59.39	

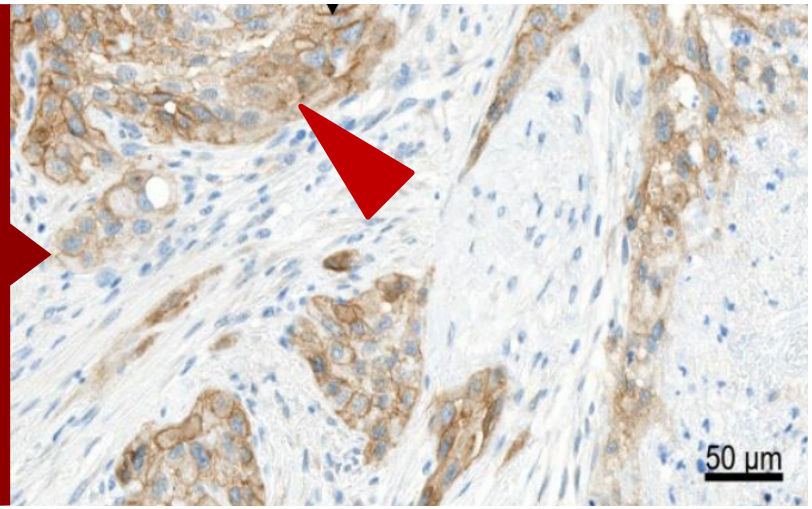
Higher AXL gene expression correlates with reduced Overall Survival[2]



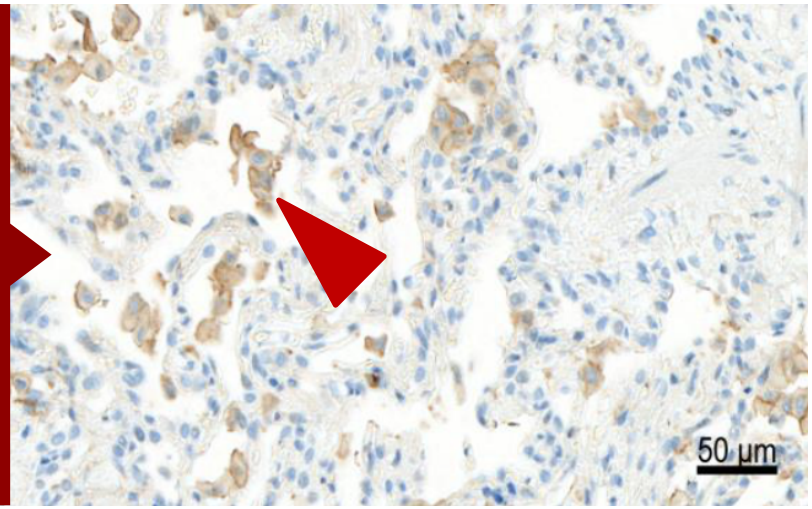
(1) Qu et al: Oncol Lett. 2016 Dec; 12(6): 5085–5091. (2) Ishikawa et al: Ann Surg Oncol. 2013; 20(Suppl 3): 467–476.

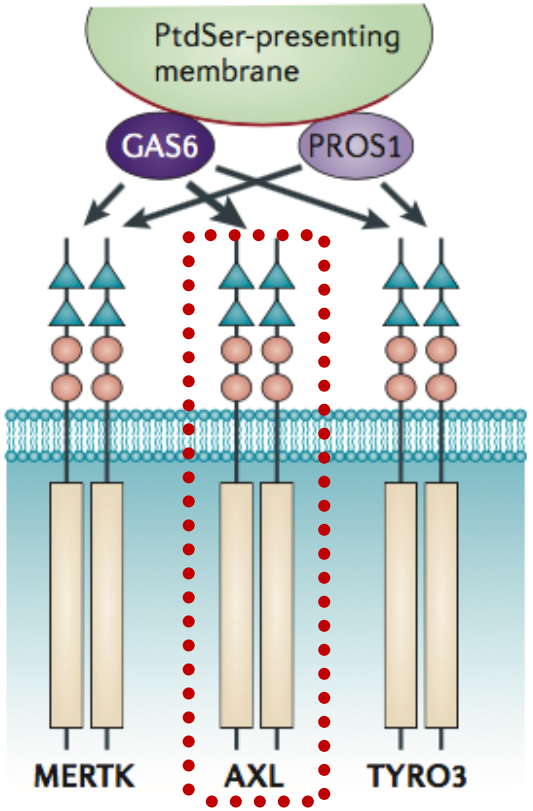
AXL is a TAM family receptor tyrosine kinase expressed on tumour and immune cells

AXL is expressed on lung cancer patient samples[1]



AXL is expressed on tumour adjacent alveolar macro-phages[1]





Tyro-AXL-Mer (TAM) family:

- Activated by Gas6 (and PROS1)
- Implicated in tumour progression, innate & adaptive immunity

(1) BerGenBio internal data. Graham DK et al, Nat Rev Cancer 2014

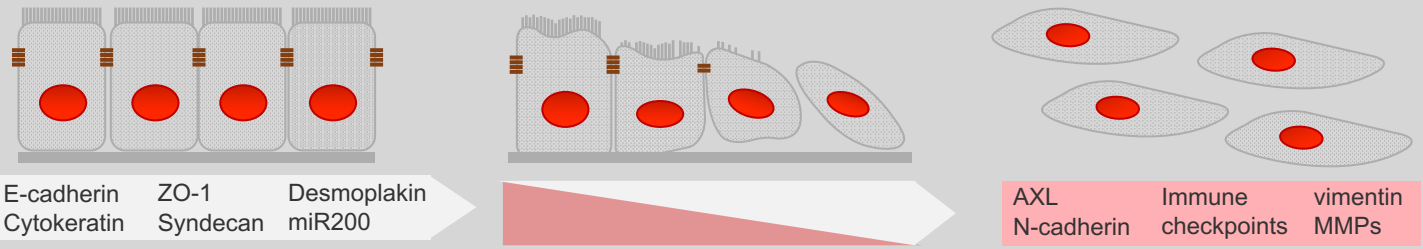
Ig-like domian | FNIII domain | Kinase domain

AXL is a key driver of Epithelial-to-Mesenchymal Transition & tumour aggressiveness

Inflammation
Hypoxia
Drug Treatment

↓

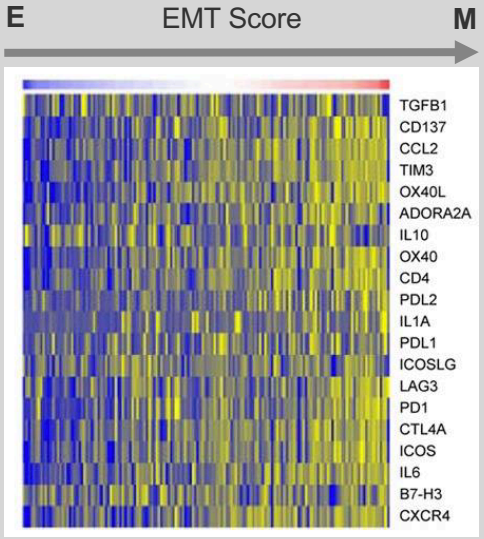
EMT ⇄ **AXL**



AXL is a novel target driving aggressive tumour plasticity mechanisms

AXL driven mesenchymal tumours are highly aggressive

- Express multiple **immune checkpoints**
- **Resistant** to therapy
- **Insensitive** to CTL Killing
- **Immunosuppressive** cytokine profile
- Exhibit **stemlike** properties
- **Invasive**

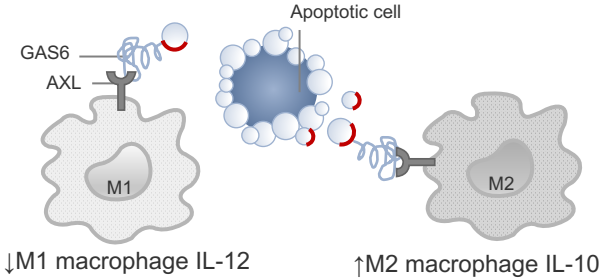


mRNA expression in lung Ad. shows upregulation of immune checkpoints[1]

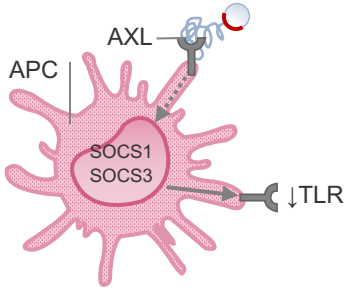
(1) Mak et al Clin Cancer Res (2016)

AXL is an immune checkpoint suppressing innate immune activation

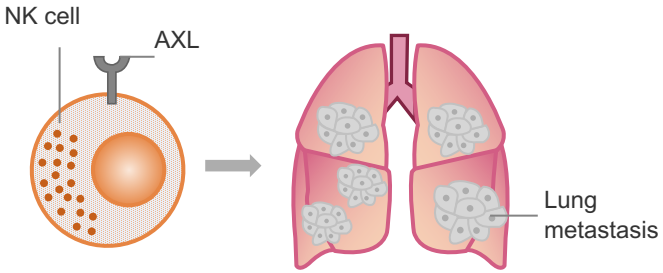
AXL is upregulated by pro-inflammatory stimuli and suppresses innate immune activation



Axl polarises M1 macrophages towards immunosuppressive M2



AXL suppresses dendritic cell inflammatory responses and antigen presentation



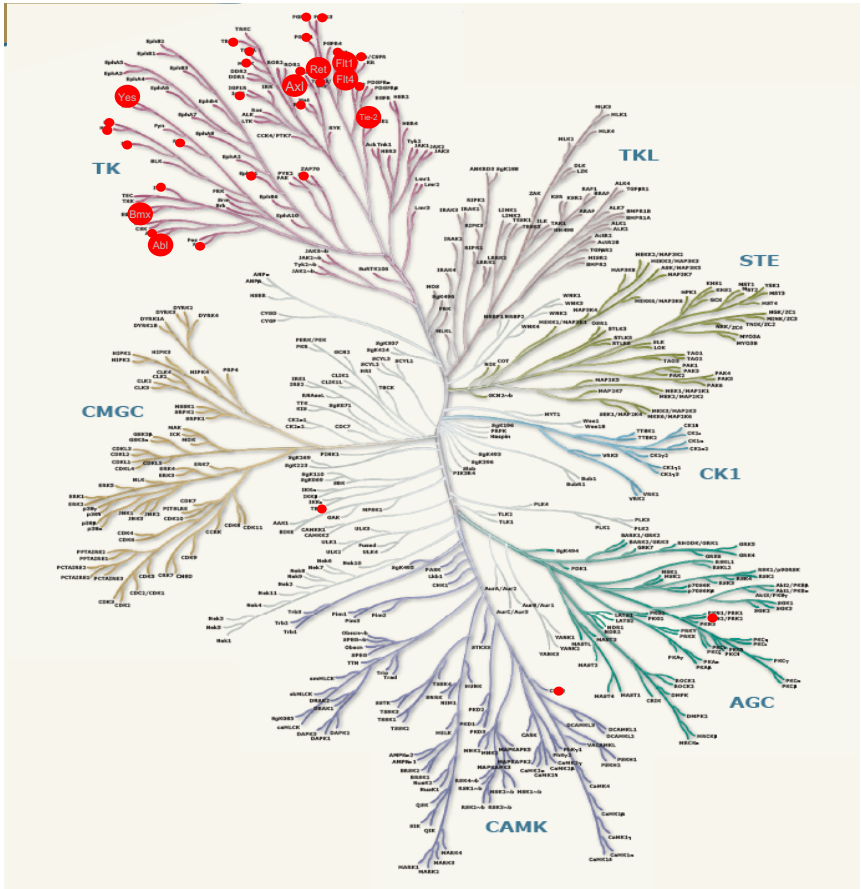
AXL negatively regulates NK cell differentiation and activity

Graham DK et al, Nat Rev Cancer 2014; Zagórska et al, Nat Immunol 2014,

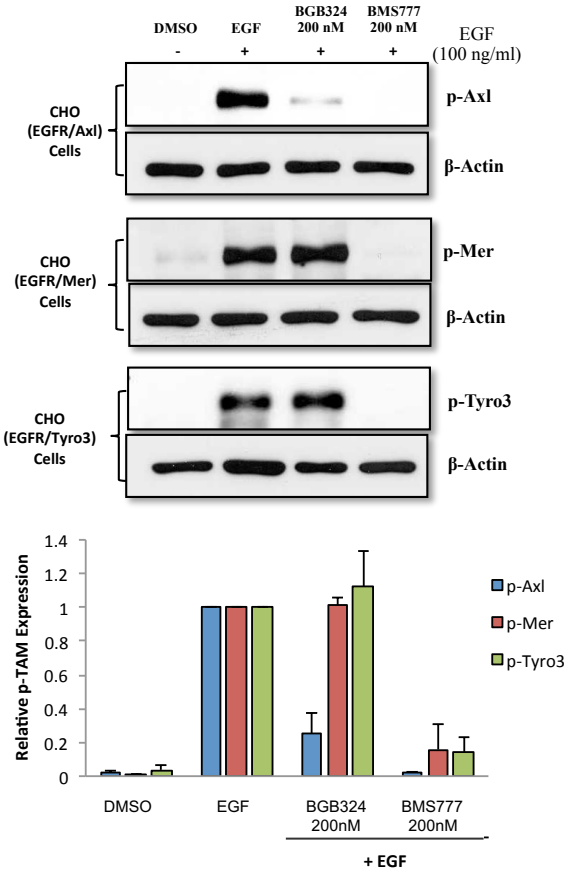
BerGenBio
BGB324
Only selective AXL inhibitor in clinical development
First-in-class, orally bioavailable, highly potent and highly selective AXL inhibitor

BGB324 - a highly selective oral Axl kinase inhibitor

ATP competitive and reversible inhibitor
Very selective in a 450 kinase panel
Selective over Tyro3 and Mer



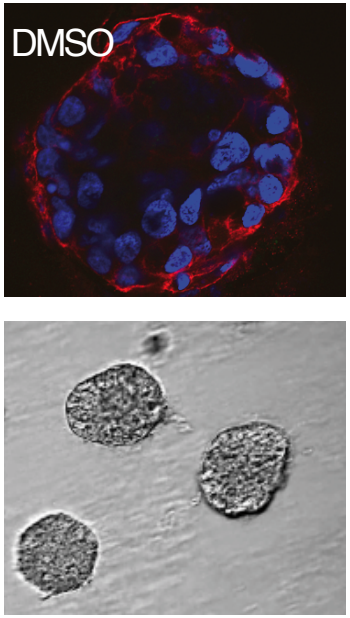
Cellular reporter assay confirms that BGB324 is uniquely AXL kinase specific[1]



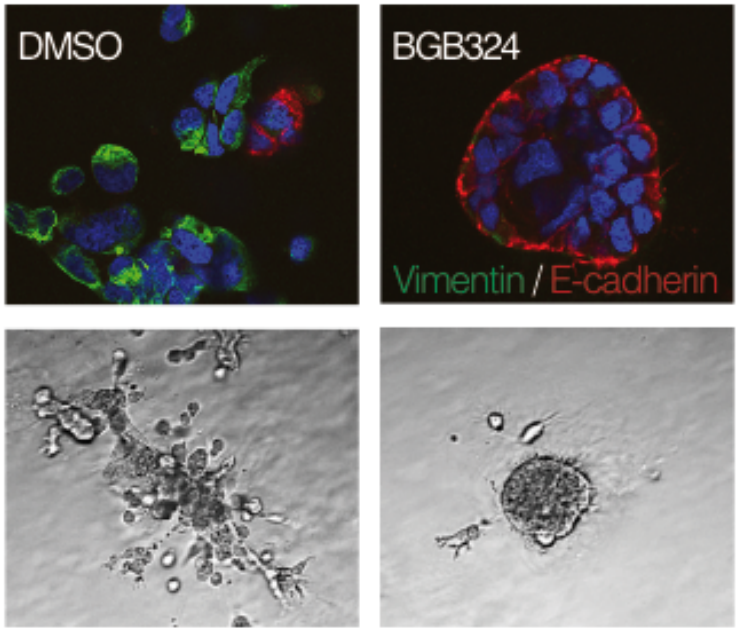
Ray Birge, Rutgers

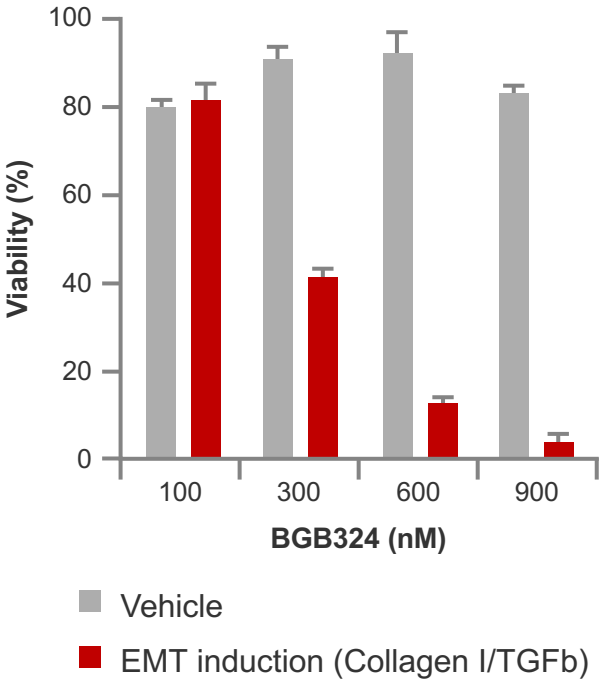
BGB324 prevents EMT and targets mesenchymal NSCLC cells *in vitro*

Laminin rich matrix
EPITHELIAL

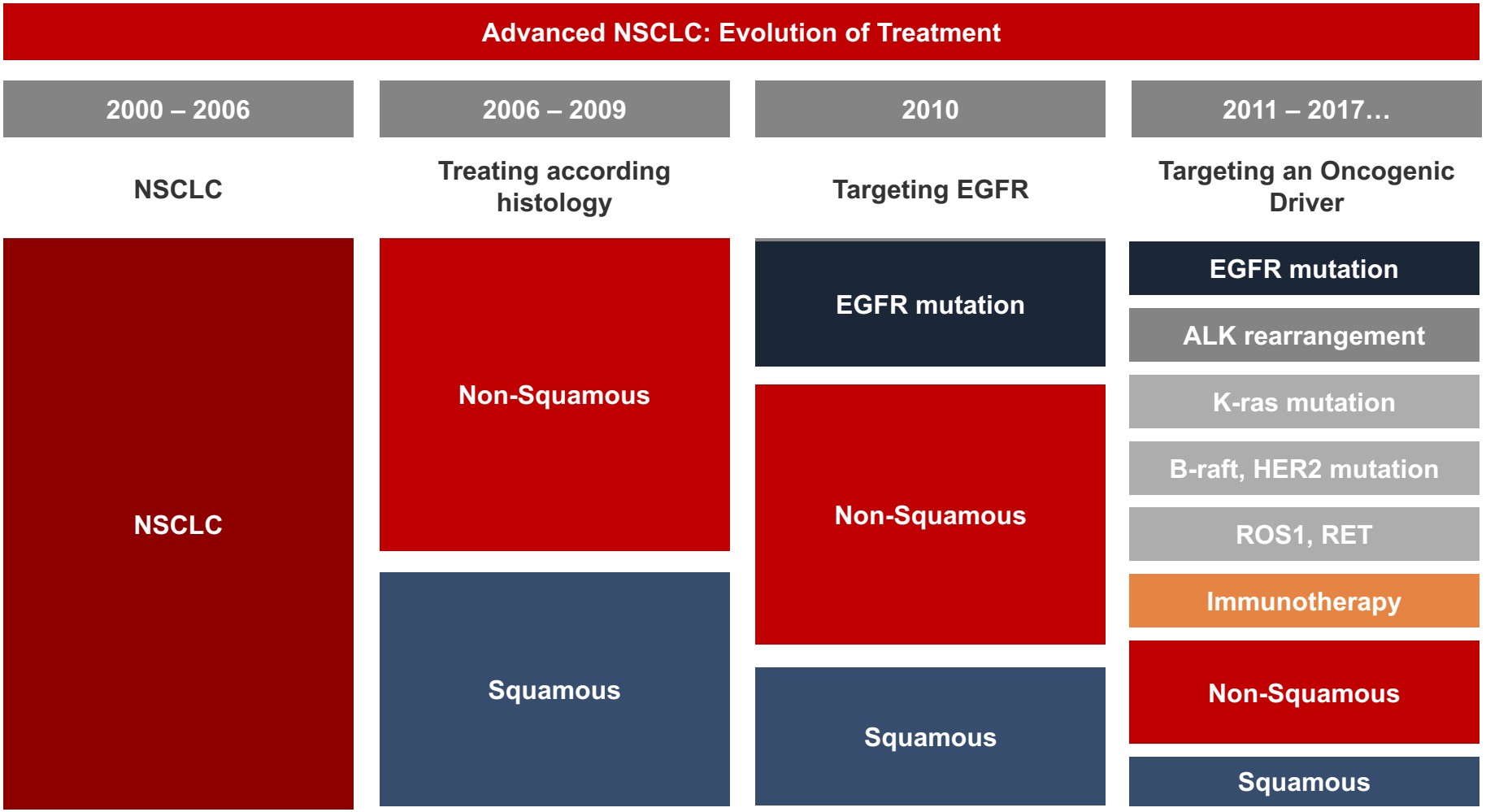


Laminin/Collagen I/TGFb/Gas6
INDUCED EMT





Segmentation of NSCLC – BGB324 is uniquely placed to synergise with and enhance current as well as emerging therapies in NSCLC



BGBIL005

Ph I/II Trial of BGB324 in Combination with Docetaxel in Previously Treated Non-small Cell Lung Cancer

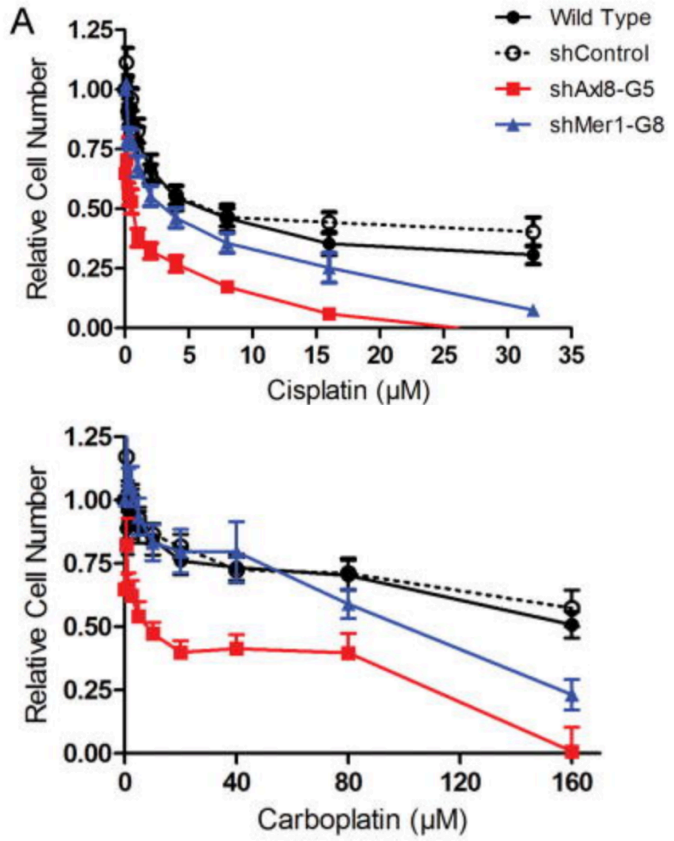
NCT02922777

AXL/EMT is a major mechanism of resistance to cytotoxic therapy

AXL drives resistance to cytotoxic therapy in a variety of cancers[1]

Treatment	Malignancy
Radiation:	HNC (SCC)
	Pancreatic cancer
Platinum compounds: ▪ Cisplatin ▪ Carboplatin	AML
	Astrocytoma
	Esophageal adenocarcinoma
	HNC (SCC)
	Neuroblastoma
	NSCLC
	Ovarian cancer
Anthracyclins: ▪ Doxorubicin	AML
	Breast cancer
	CML
	NSCLC
	Skin cancer (SCC)
Alkylating agents: ▪ Temozolomide	Astrocytoma
Tubulin inhibitors: ▪ Taxanes: ▪ Paclitaxel ▪ Docetaxel	Breast cancer (TNBC and BCSC)
	CML
	▪ NSCLC
Vinca alkaloids: ▪ Vincristine	Breast cancer
	▪ CML
	▪ Neuroblastoma
	▪ NSCLC
Topoisomerase inhibitors: ▪ Etoposide	AML
	Breast cancer (BCSC)
	NSCLC
	Skin cancer (SCC)
Antimetabolites: ▪ Fluorouracil	Breast cancer (TNBC)
	Colon cancer

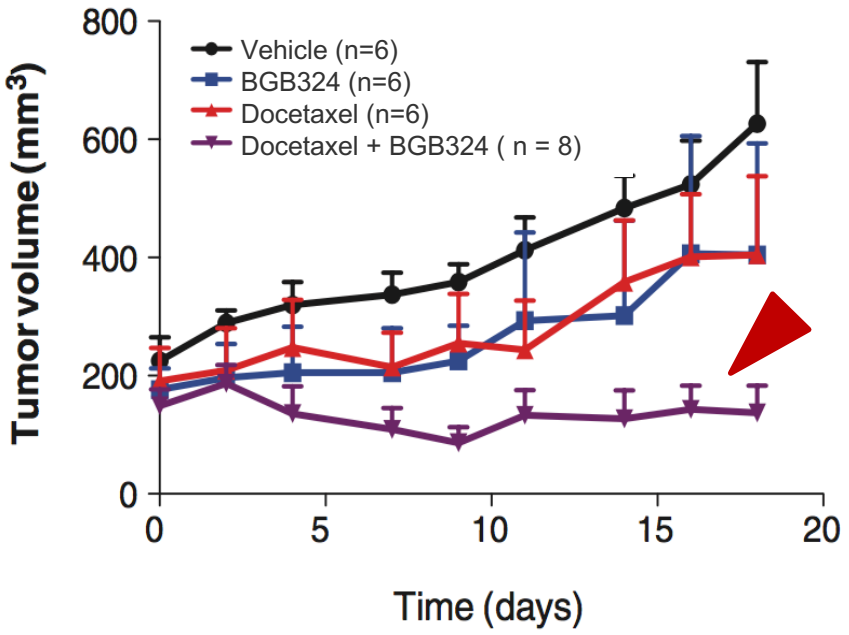
AXL gene knockdown enhances sensitivity to chemotherapy increased cell death and apoptotic pathway activation in A549 cells[2]



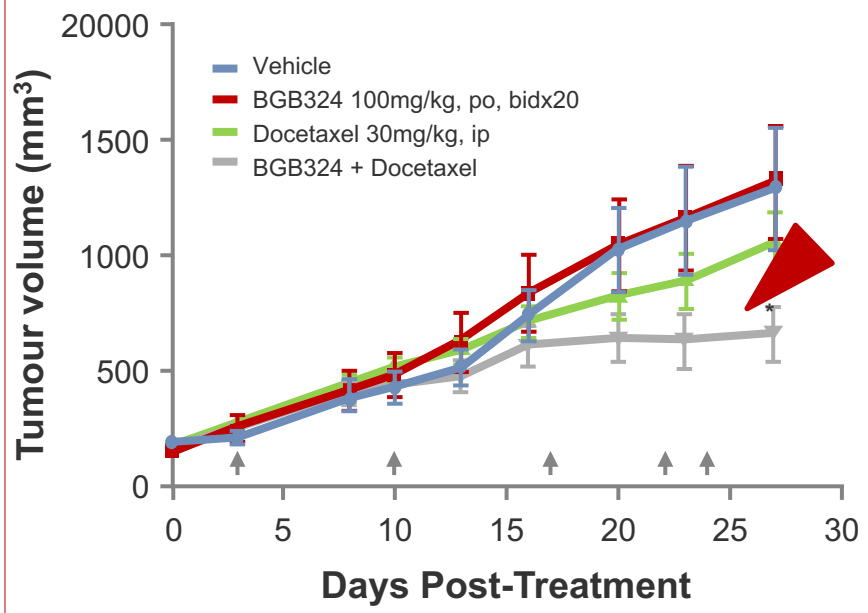
(1) Supported by > 35 publications, (2) Linger *et al* Oncogene (2013)

Treatment with BGB324 prevents resistance to to docetaxel *in vivo*

HeLa xenograft[1]



NCI-H1299 xenograft[2]



(1) Wilson et al. Cancer Res (2014) (2) Wnuk-Lipinska et al. in prep

BGBIL005: Trial of Dose Escalated BGB324 in Previously Treated Non-small Cell Lung Cancer

Patient population

Patients previously treated advanced non-small cell lung cancer (NSCLC)

Dose Escalation Phase

Group 1 (200/100mg)
Group 2 (400/200mg)
6 ≤ patients ≥ 12

RP2D

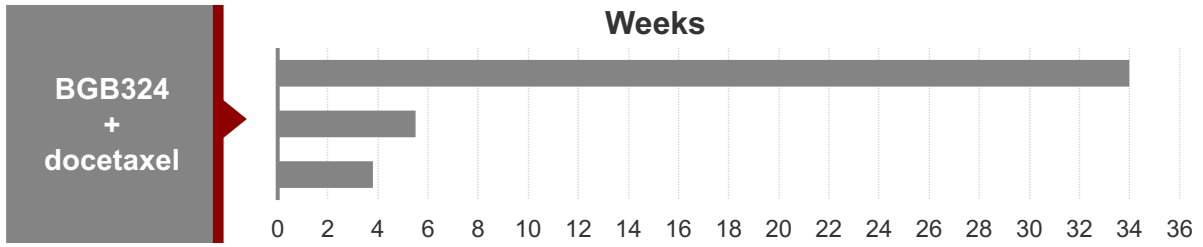
Treatment Phase

Treatment up to PD
Up to 30 pts

Overview

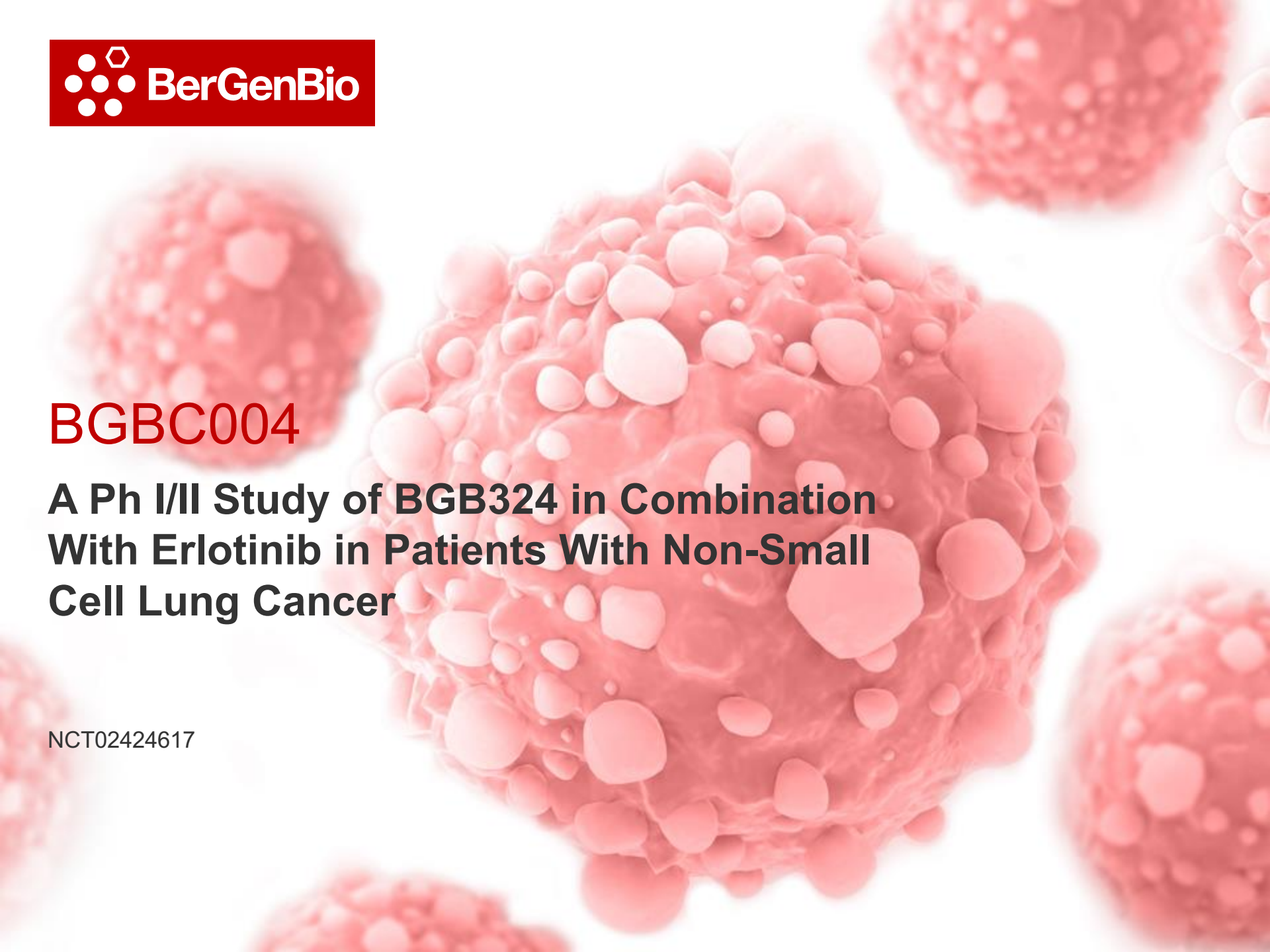
- One patient on treatment for 13 cycles
- 1 partial response (Recist 1.1)

1 pt on treatment for more than 13 cycles



Part of BerGenBio's Investigator Initiated Trial programme.
Sponsor Investigator: Dr David Gerber, UTSW Dallas

UT Southwestern Medical Center



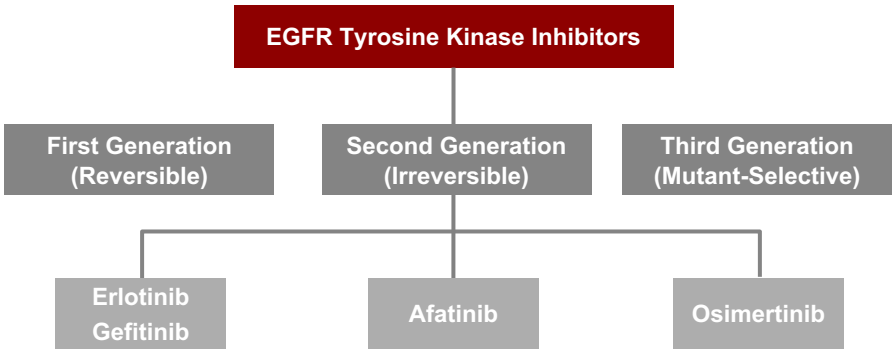
BGBC004

A Ph I/II Study of BGB324 in Combination With Erlotinib in Patients With Non-Small Cell Lung Cancer

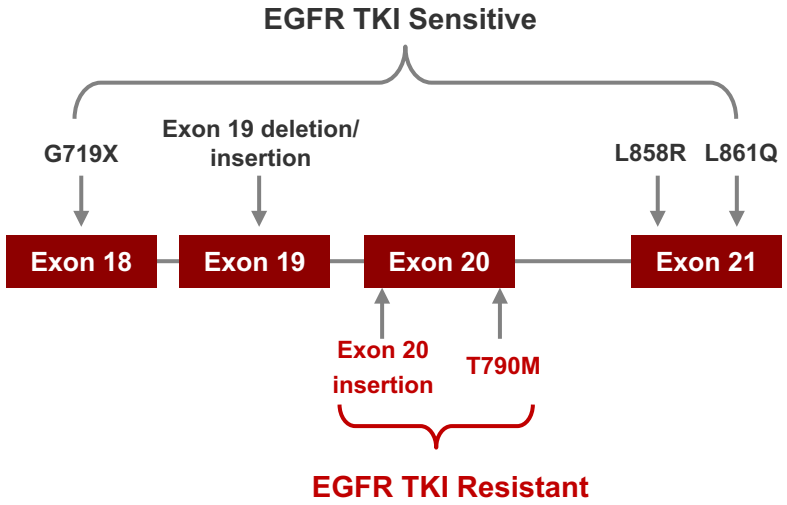
NCT02424617

EGFR inhibition in NSCLC

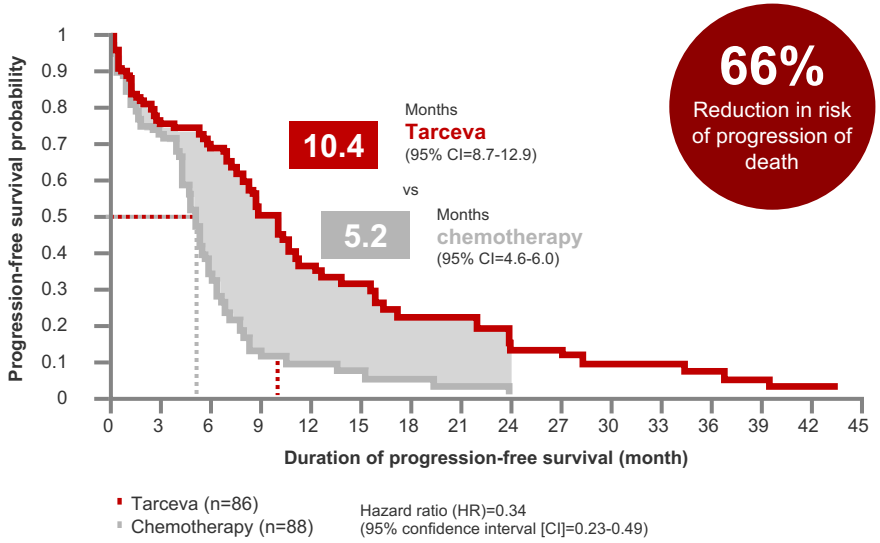
The evolution of EGFR tyrosine kinase inhibitors



First line therapy with erlotinib is superior to a Platinum doublet in NSCLC with an activating mutation



PFS in the EURTAC intent-to-treat (ITT) Population



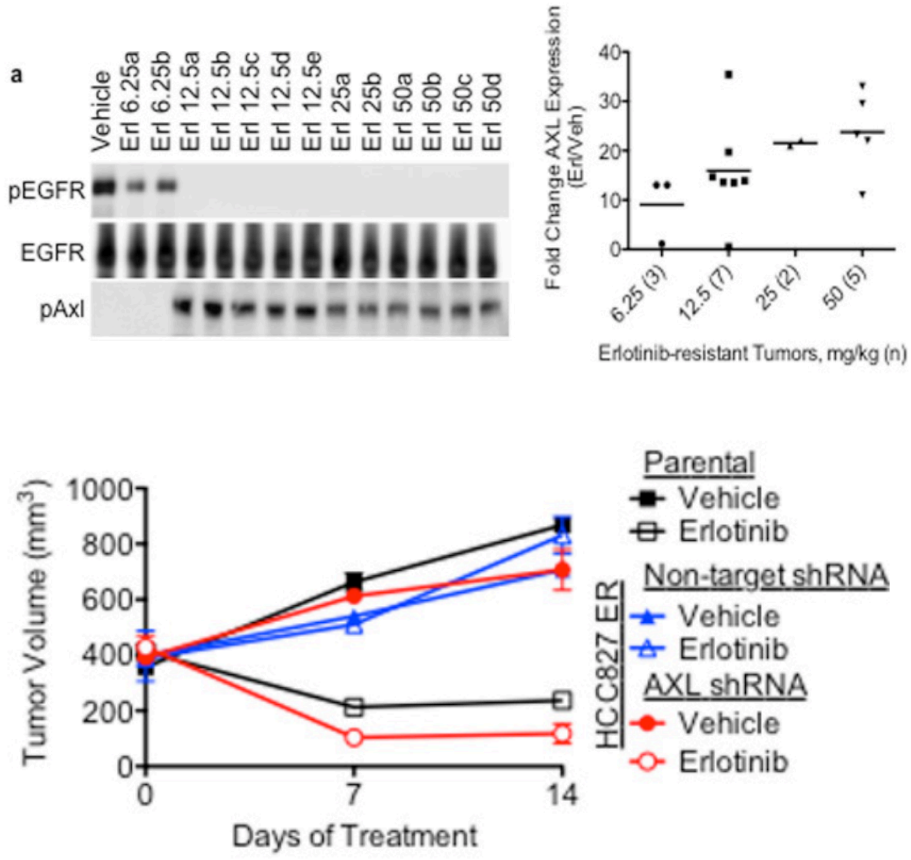
*As assessed by investigator

AXL/EMT is a major mechanism of resistance to targeted therapy

AXL is implicated in resistance to targeted therapy in a variety of cancers[1]

Target	Drug	Malignancy
ALK	Crizotinib	NSCLC
ALK^{F1174L}	TAE684, ceritinib	Neuroblastoma
Bcr-Abl	Imatinib, nilotinib	CML
c-Kit	Imatinib	GIST
EGFR	EGFR-TKI (erlotinib, gefitinib)	NSCLC (EGFR mutated)
		NSCLC (EGFR wildtype)
		Breast cancer (TNBC)
		HNC(SCC)
		Colon cancer
		Liver cancer
		Tongue cancer
	Irreversible EGFR-TKI (CO-1686)	NSCLC
	Cetuximab	HNC(SCC)
		NSCLC
FLT3	PKC412, AC220	AML
HER2	Lapatinib, trastuzumab	Breast cancer, incl TNBC
		Ovarian cancer
	AZD8931 (EGFR/HER2/HER3- inhibitor)	Breast cancer
IGF-IR	MAB39 (IGF-IR-blocking Ab)	Rhabdomyosarcoma
MAPK pathway in BRAFV600E	BRAF inhibitors (PLX4720, vemurafenib, dabrafenib) MEK inhibitors (AZD6244/selumetinib, trametinib) ERK inhibitor (SCH772684)	Melanoma
MEK	MEK1 inhibitor	Pancreatic cancer
PI3Kα	BYL719	Esophageal SCC
		HNC (SCC)
TRAIL	Recombinant TRAIL	Esophageal adenocarcinoma
VEGF	Bevacizumab	Colon cancer
	Anti- VEGF	Breast cancer
		NSCLC
	Sunitinib	RCC

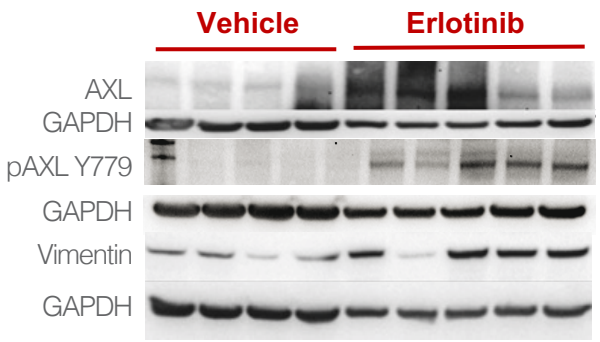
AXL is overexpressed in erlotinib resistant HCC827 xenografts and AXL gene knockdown restores sensitivity[2]

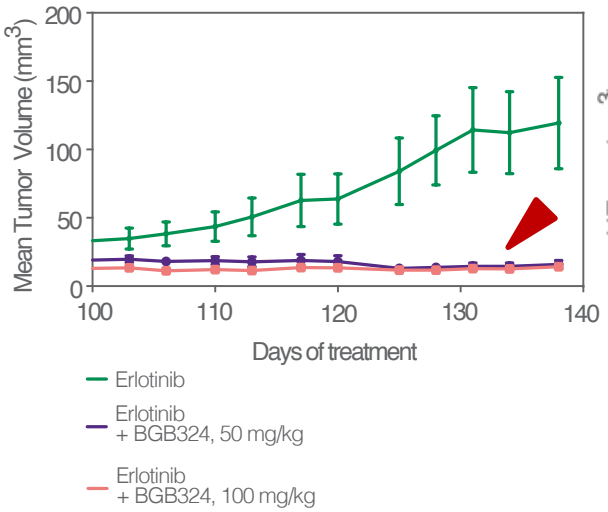


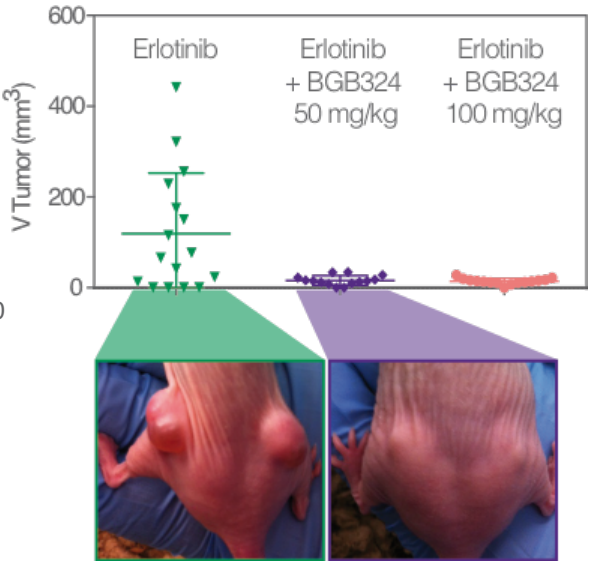
(1) Supported by > 40 publications (2) Zhang *et al* Nat Genet (2012)

BGB324 prevents acquired resistance to erlotinib *in vivo*

HCC827 model: Tumours of erlotinib treated mice become mesenchymal and develop resistance at day 67







HCC827 (EGFRmut NSCLC)/Nude mice
Wnuk-Lipinska et al. in prep

BGBC004: A Study of BGB324 in Combination With Erlotinib in Patients With Non-Small Cell Lung Cancer

Completed

BGBC004 Phase Ib – Study design part A1 & A2

Patient population

Part A1
- 8 stage IV metastatic patients
- Heavily pretreated
  - Exhausted all licensed drugs

Part A2
- 8 stage IV metastatic patients with EGFR mutation
  - 2nd mutation in ca. 50%
- Heavily pretreated
  - Second line setting

Dose escalation

Part A1: 3 +3 dose escalation
- Single agent
- Loading and daily maintenance dose

Part A2: 3 + 3 dose escalation
- Combination with erlotinib
- Loading and daily maintenance dose

Biomarker
- Tissue sample collection and processing
- Assay development and qualification

Read out

1 year PFS in 25% patients

50% CBR

→ RP2D

Ongoing

BGBC004 Phase II – Study design part B

Patient population

- Previously treated unresectable NSCLC
- Known activating EGFR mutation

Phase II

Part B
- Combination with erlotinib

Biomarker
- Tissue sample collection and processing
- Assay development and qualification

Read out

- ORR
- PFS
- Circulating Axl levels
- Safety

BGBC004 Phase Ib – Study design part A1 & A2

BGBC004: A Study of BGB324 in Combination With Erlotinib in Patients With Non-Small Cell Lung Cancer

Completed

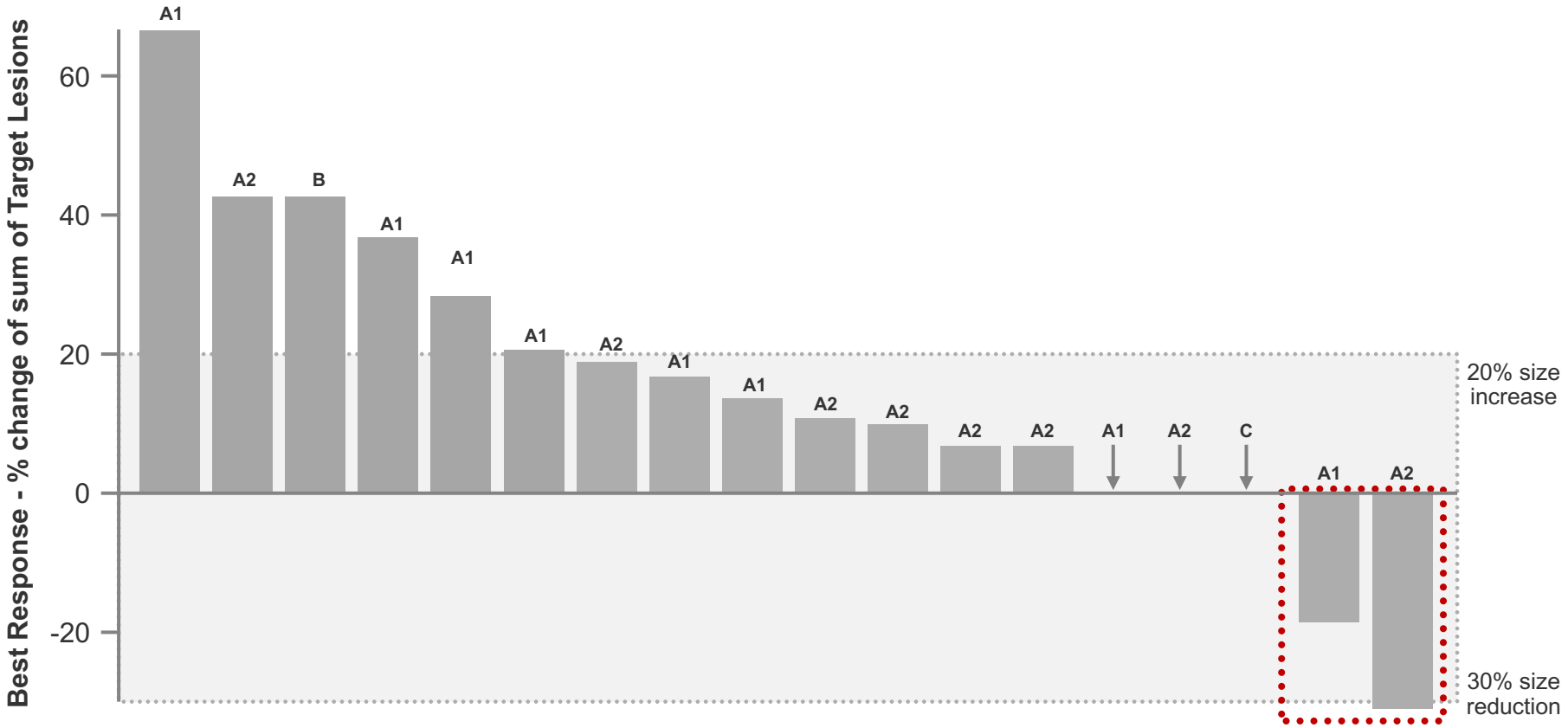
BGBC004 Phase Ib – Study design part A1 & A2 Demographic

	Part A1: BGB324 Monotherapy	Part A2: BGB324 + erlotinib
n	8	8
Gender		
Female	5	5
Male	3	3
Average (range)	64 (58 - 77)	58 (38 - 68)
Stage		
IIIB	2	0
IV	6	8
ECOG		
0	4	1
1	4	7
# pts with activating mutations	3	8
Median # lines of previous treatment (range)	5 (2 - 10)	1 (1 – 3)
Ethnicity		
African American	1	0
Asian	1	3
Caucasian	5	5
Other	1	0

Maximum Percentage Change from Baseline (RECIST 1.1)

Median # prior therapies:
Part A1 (Monotherapy): 5 (2-10)
Part A2 (BGB324 + erlotinib): 1 (1-3)

CBR (SD+PR>4m)
Monotherapy: 37%
Arm A: 50%



NSCLC Phase Ib: BGB324 monotherapy – clear clinical benefit

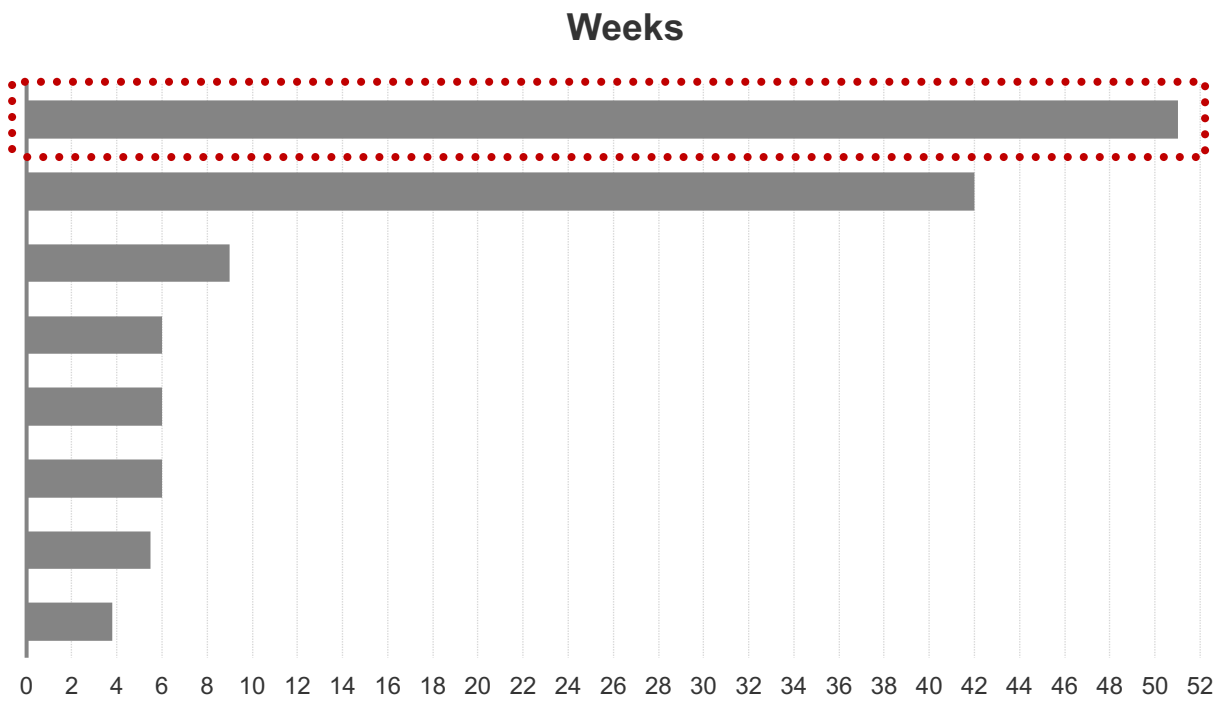
Overview

1 year PFS in 25% patients

- 1 minor response
- 1 stable disease

- Two patients treated for approximately 12 months
- Very well tolerated, patients discontinued due to disease progression
- Recommended Phase II Dose

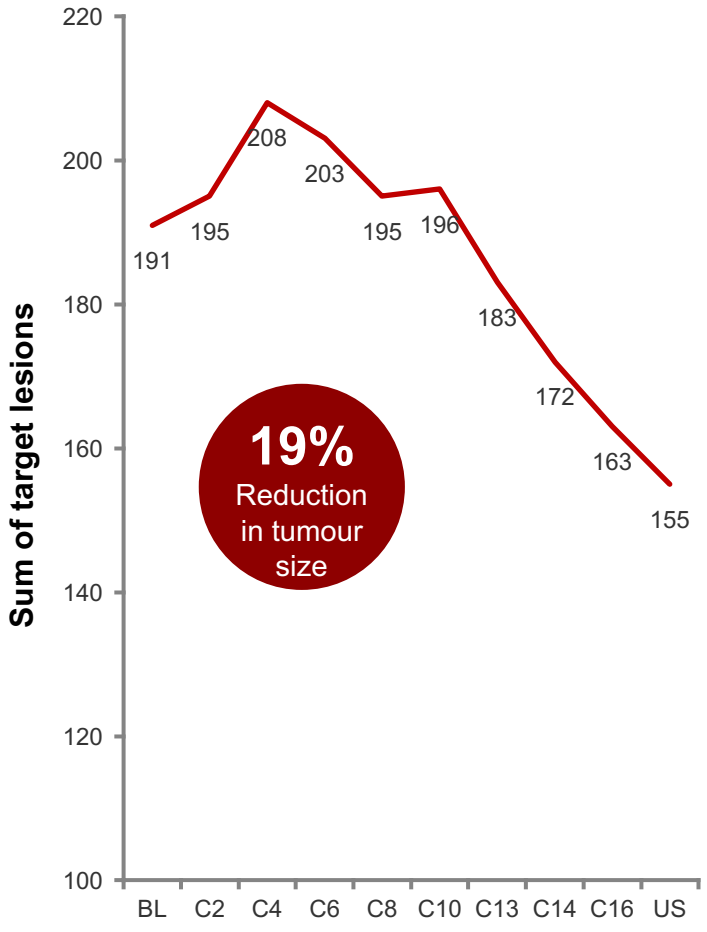
~1 year Progression Free Survival in 25% of patients



NSCLC Phase Ib: BGB324 monotherapy – clear clinical benefit

Patient 310 - 107

Age, ethnicity & sex	57 year old white female
ECOG	1
Histologic diagnosis	Adenocarcinoma of the lung
Stage at initial diagnosis at screening	 IV IV
Sites	Lung, bone, CNS/brain
Mutations	Negative for EGFR, KRAS, BRAF, ALK Positive for STK1
Previous treatments Nov 2010 – Jan 2011 Jan 2011 – Apr 2011 Nov 2010 – Jan 2011 May 2011 – Nov 2011 Jan 2012 – May 2013 Jan 2012 – May 2013 Sep 2013 – Jun 2014 Sep 2013 – Mar 2014 May 2014 – May 2014 Jul 2014 – Feb 2015 Jul 2014 – Feb 2015 Jul 2014 – Feb 2015 Oct 2014 – Oct 2014 Mar 2015 – Jun 2015 Jul 2015 – Nov 2015 Dec 2015 – Dec 2015	 CARBOPLATIN PEMETREXED TAXOL ERLOTINIB MEK INHIBITOR AKT INHIBITOR METFORMIN TEMSIROLIMUS PALLIATIVE RADIATION THERAPY DASATINIB AVASTIN TAXOL PALLIATIVE RADIATION THERAPY PEGYLATED IL-10 NIVOLUMAB PALLIATIVE RADIATION THERAPY



BL= Baseline measurement
SD = Stable Disease according to RECIST1-1
US = unscheduled scan

NSCLC Phase Ib: Combination with erlotinib – 50% clinical benefit rate

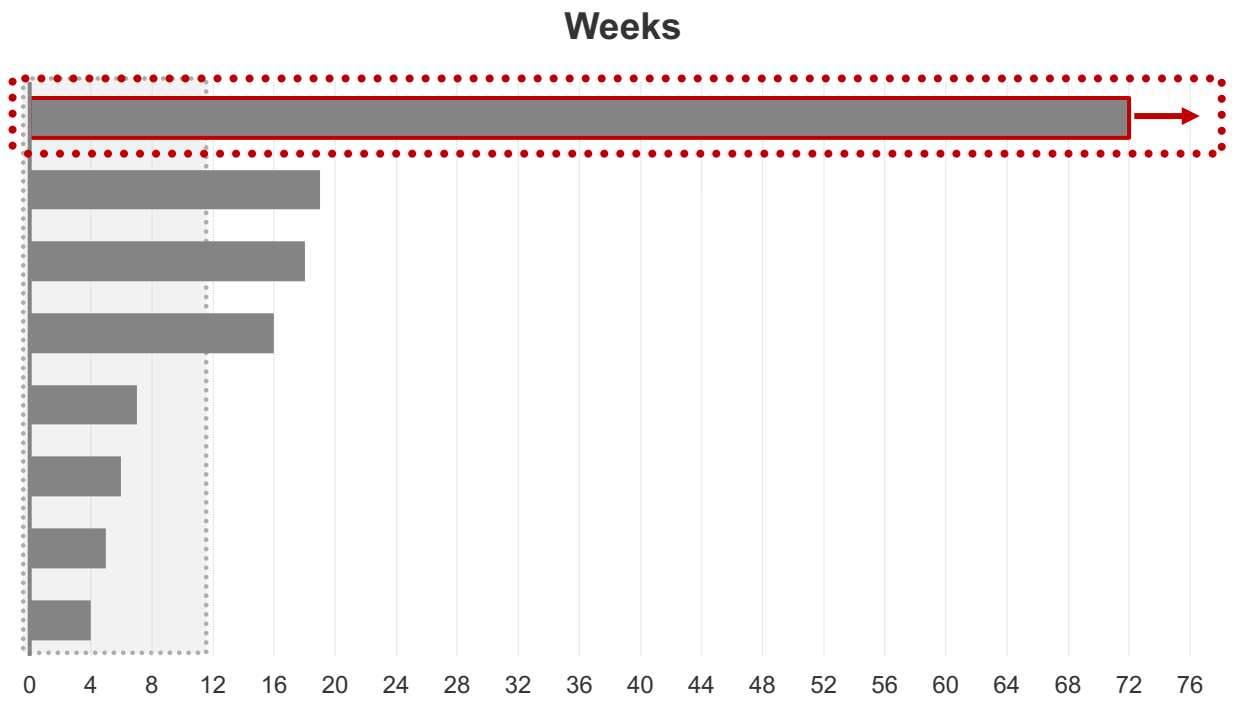
Overview

50% CBR

- 3 SD > 4 months
- 1 stable disease

- One patient ongoing > 15 months
- Very well tolerated
- Recommended Phase II Dose

> 4 months Progression Free Survival in 50% of patients

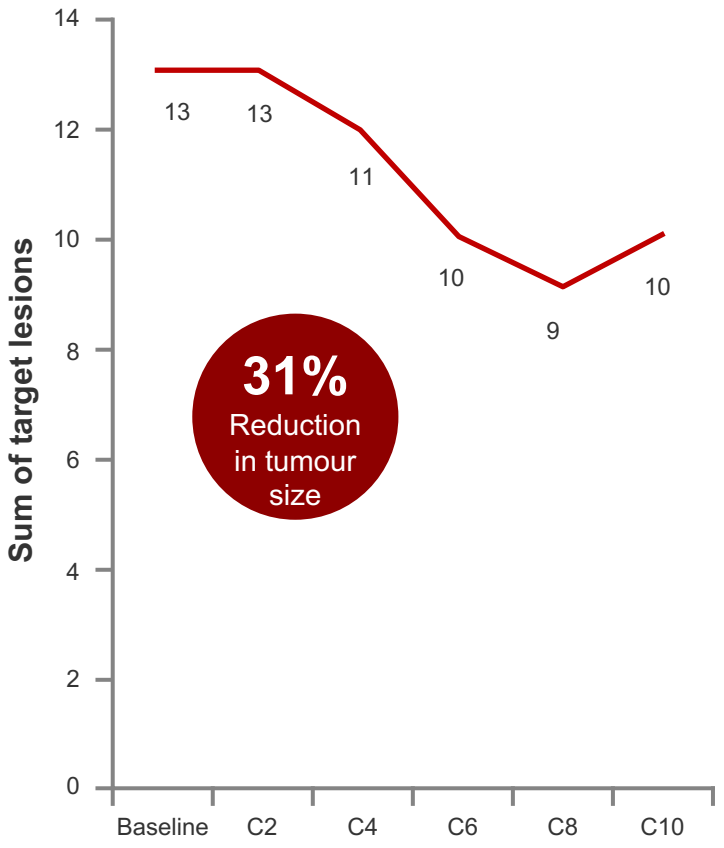


Source: Byers, EORTC Nov 2016

NSCLC Phase Ib: Combination with erlotinib – 50% clinical benefit rate

Patient 311 - 210

Age, ethnicity & sex	68 year old white female
ECOG	1
Histologic diagnosis	Adenocarcinoma of the lung
Stage **at initial diagnosis** **at screening**	 IV IV
Sites	Lung, bone
Mutations	EGFR: exon 21 L858R substitution mutation
Previous lines of therapy **Feb 2015 – Oct 2015** **Oct 2015 – Feb 2016**	 DACOMITINIB ERLOTINIB
Current status	Ongoing, C24



Source: Byers, EORTC Nov 2016

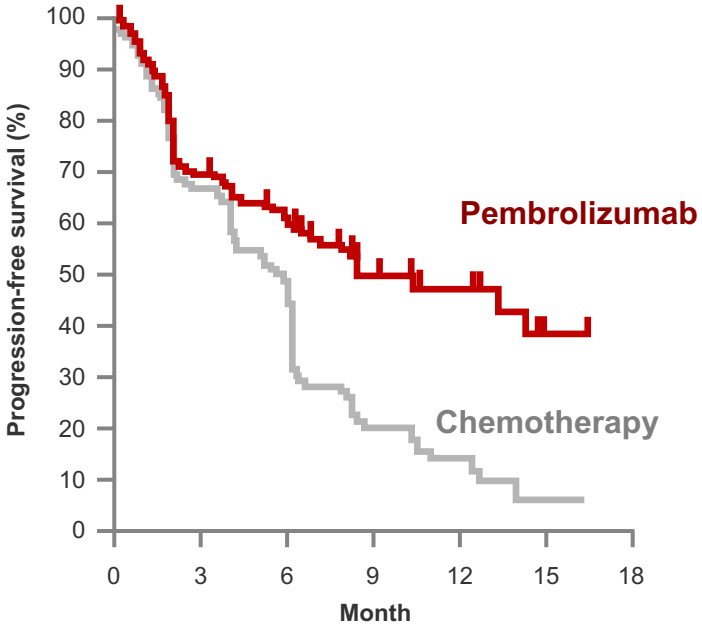
BGBC008

Ph II Trial of BGB324 in Combination With Pembrolizumab in Patients With Advanced NSCLC

NCT03184571

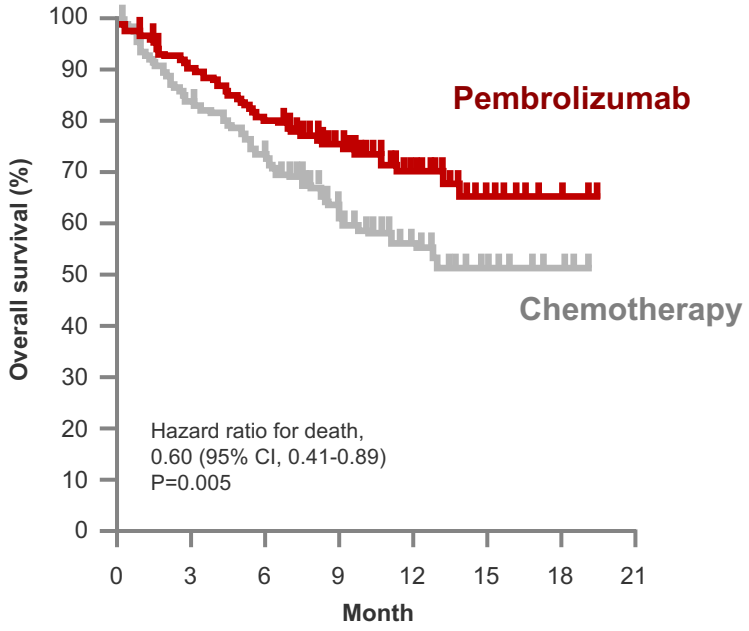
Pembrolizumab enhances PFS & OS compared to chemotherapy in NSCLC

In patients with high levels of PD-L1 overexpression (> 50%)



No.at Risk							
Pembrolizumab	154	134	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0

Hazard ratio for disease progression or death,
0.50 (95% CI, 0.37-0.68)
P<0.001



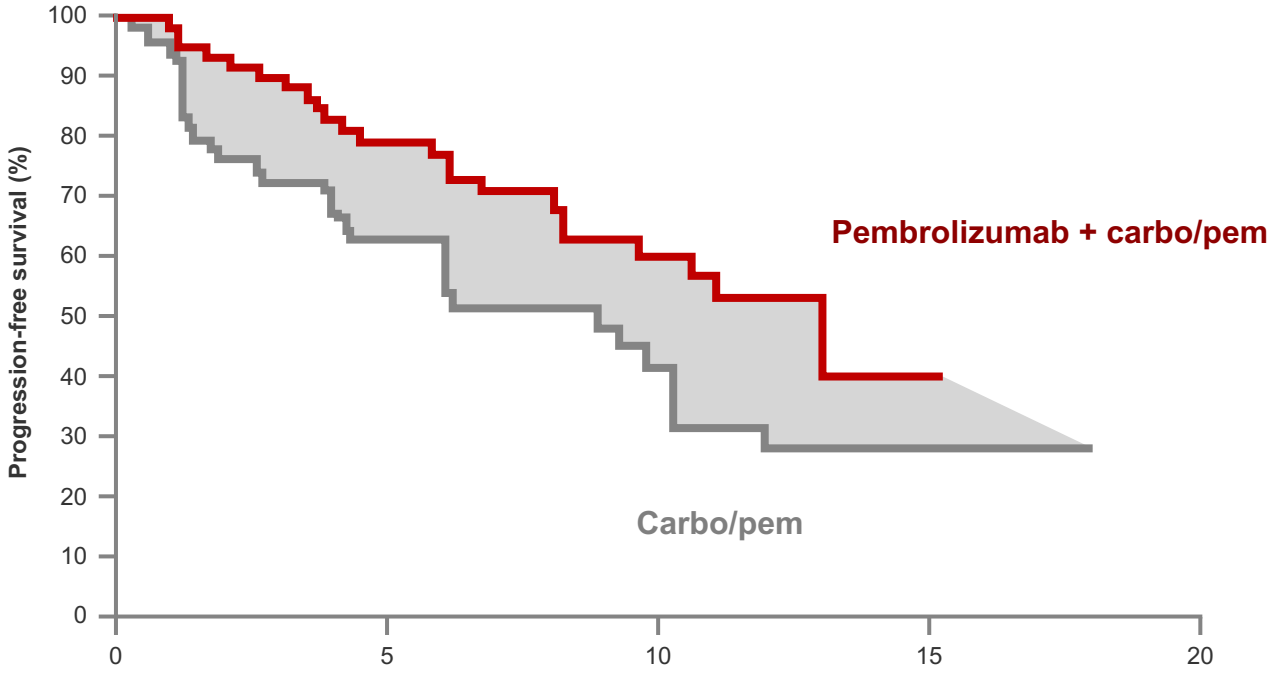
No.at Risk								
Pembrolizumab	154	136	121	82	39	11	2	0
Chemotherapy	151	123	106	64	34	7	1	0

Pembrolizumab combination with chemotherapy in Non-Small Lung Cancer

Adenocarcinoma Histology

13.0 Month Median PFS

with KEYTRUDA carbo/pem vs 8.9 months with carbo/pem alone irrespective of PD-L1 expression



Number at risk					
KEYTRUDA + carbo/pem	60	40	20	5	0
Carbo/pem	68	32	13	3	0

AXL/EMT and PD-L1-mediated immunosuppression are tightly interlinked

Clinical Cancer Research

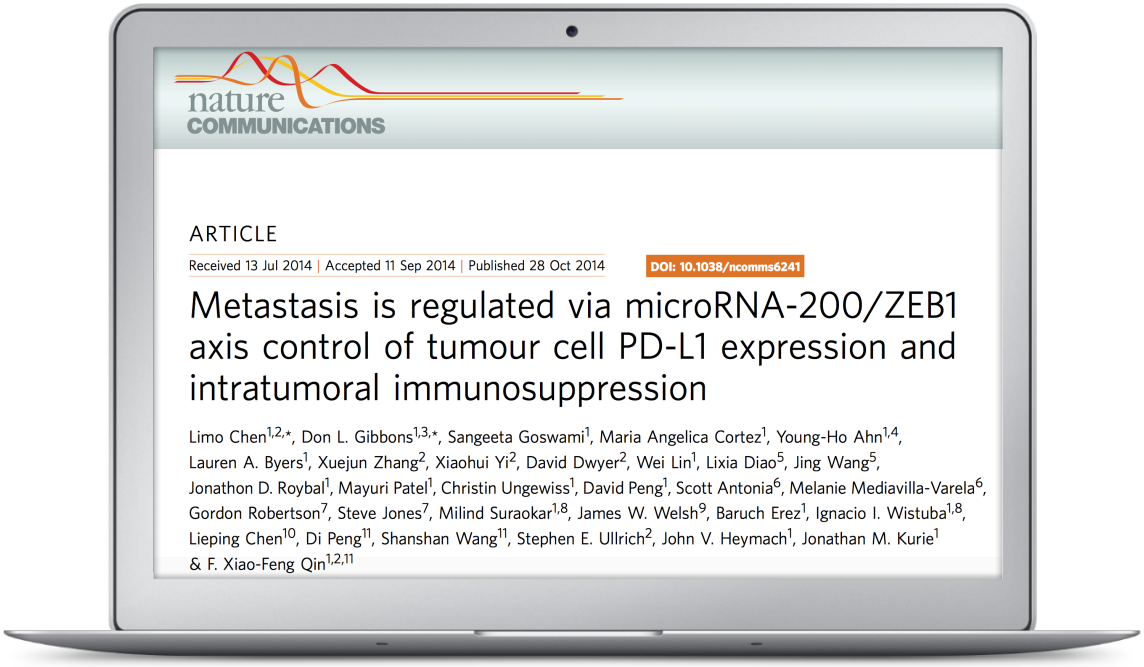
Integrative Analysis Identifies a Novel AXL–PI3 Kinase–PD-L1 Signaling Axis Associated with Radiation Resistance in Head and Neck Cancer

Heath D. Skinner, Uma Giri, Liang P. Yang, Manish Kumar, Ying Liu, Michael D. Story, Curtis R. Pickering, Lauren A. Byers, Michelle D. Williams, Jing Wang, Li Shen, Suk Y. Yoo, You Hong Fan, David P. Molkentine, Beth M. Beadle, Raymond E. Meyn, Jeffrey N. Myers, and John V. Heymach

Clinical Cancer Research

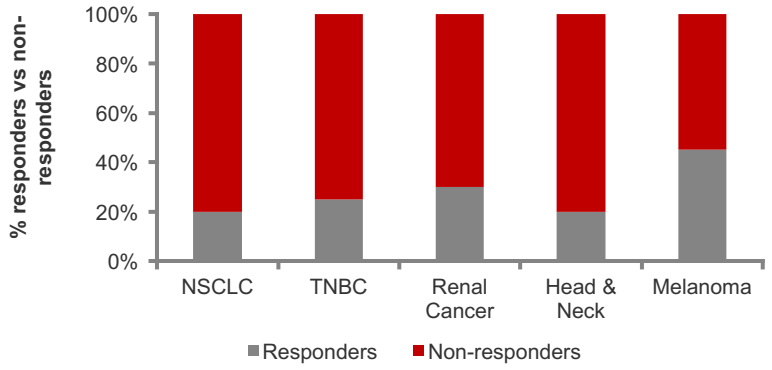
Epithelial–Mesenchymal Transition Is Associated with a Distinct Tumor Microenvironment Including Elevation of Inflammatory Signals and Multiple Immune Checkpoints in Lung Adenocarcinoma

Yanyan Lou, Lixia Diao, Edwin Roger Parra Cuentas, Warren L. Denning, Limo Chen, You Hong Fan, Lauren A. Byers, Jing Wang, Vassiliki A. Papadimitrakopoulou, Carmen Behrens, Jaime Canales Rodriguez, Patrick Hwu, Ignacio I. Wistuba, John V. Heymach, and Don L. Gibbons

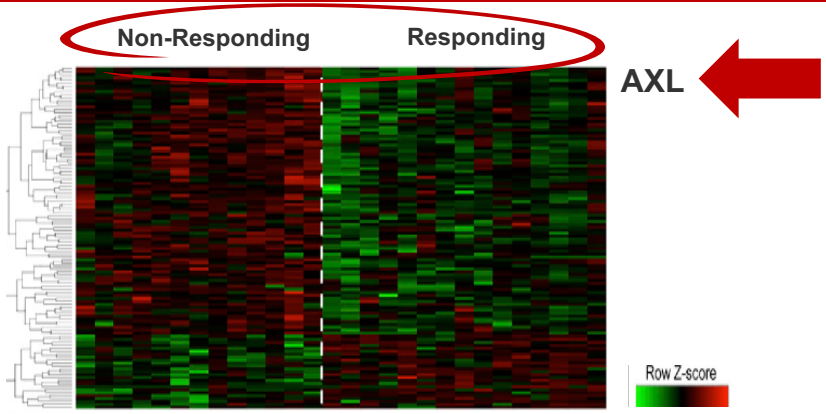


AXL/EMT is a major mechanism of resistance to Immunotherapy

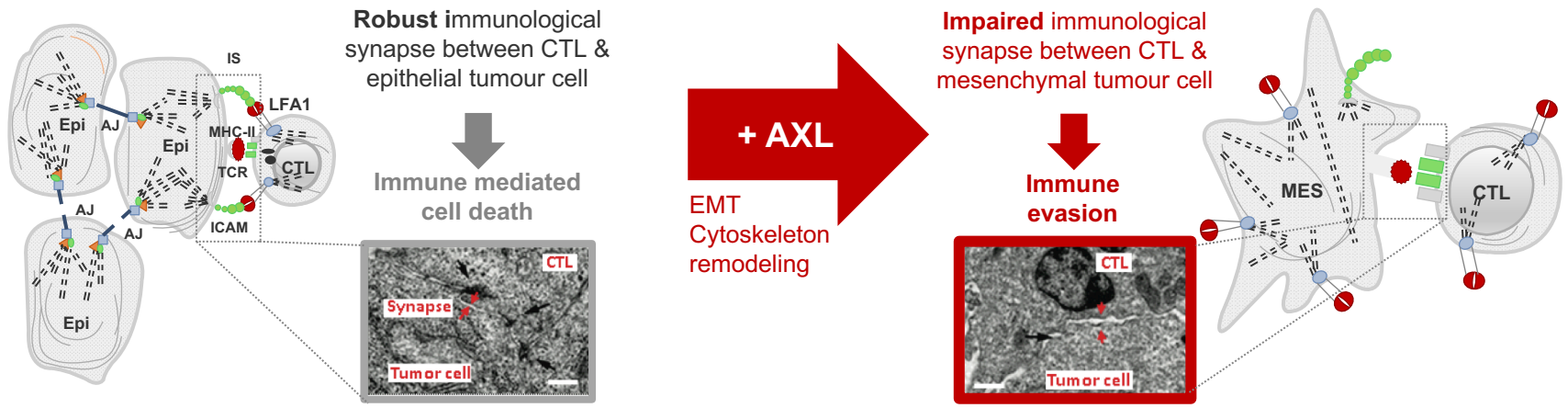
Checkpoint inhibitors work for only a few patients



Axl is upregulated in checkpoint inhibitor resistant melanoma



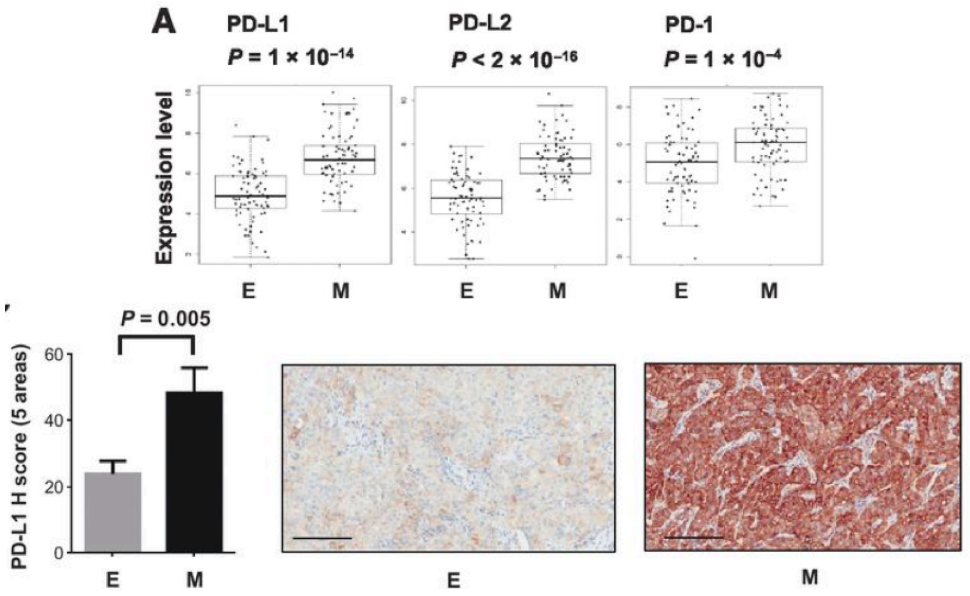
Activation of cytotoxic T-lymphocytes (CTL) is the key mechanism of immune checkpoint inhibitors
Tumor EMT prevents CTL killing of cancer cell



Source: Chouaib, 2014; Hugo, 2016

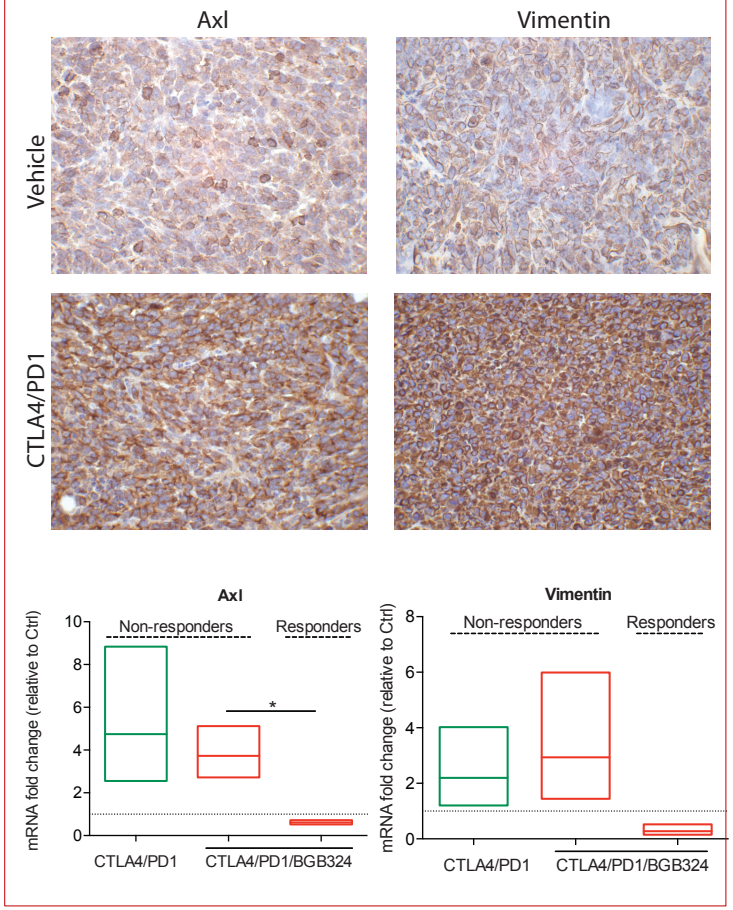
BGB324 potentiates the effect of immune checkpoint inhibitors *in vivo*

EMT status associated with inflammatory tumour microenvironment & elevation of multiple targetable immune checkpoints in patient samples[1]



The strong association between EMT status and an inflammatory tumor microenvironment with elevation of multiple targetable immune checkpoint molecules warrants further investigation of **using EMT as a predictive biomarker for immune checkpoint blockade agents** and other immunotherapies in NSCLC and possibly a broad range of other cancers.

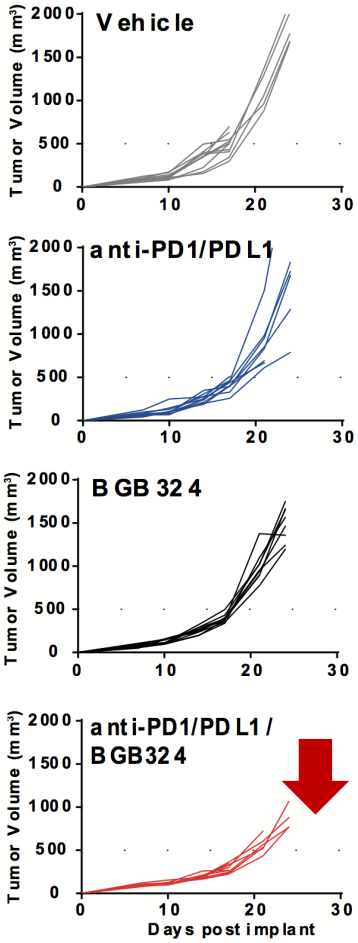
Treatment with Immune Checkpoint Inhibitors induces AXL/EMT *in* vivo, reversed by BGB324[2]



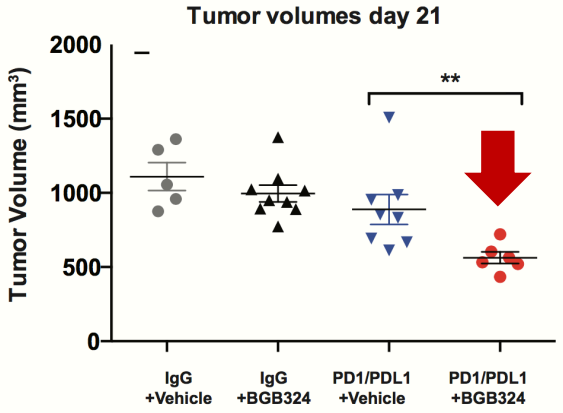
(1) Lou *et al.* Clin Can Res (2016)
(2) Wnuk Lipinska *et al* AACR Annual Meeting 2017

BGB324 potentiates the effect of immune checkpoint inhibitors *in vivo*[1]

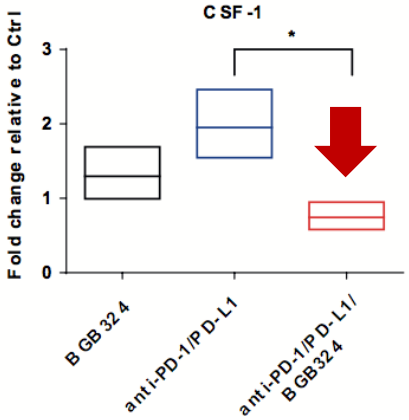
Tumour volumes over time



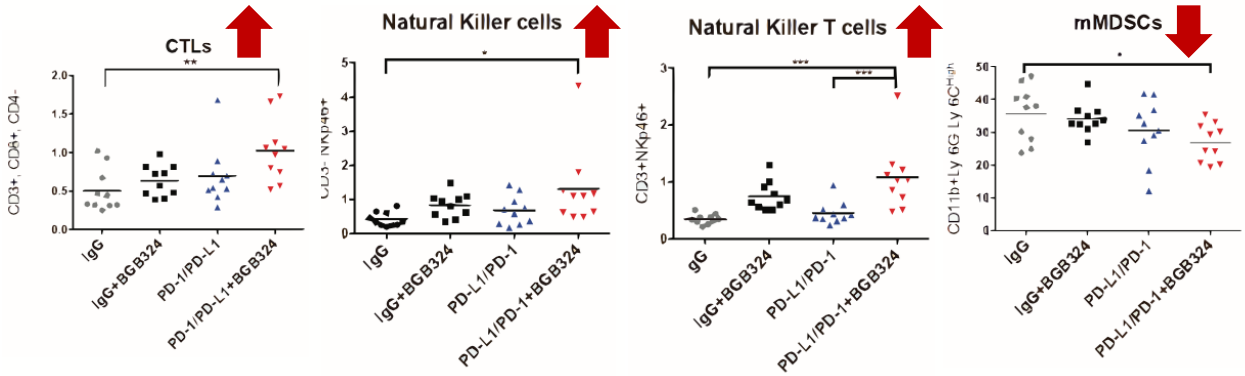
Decreased tumour volumes



Decrease in immune suppressive cytokines



Increased anti-tumour immunity



Wnuk Lipinska *et al* AACR Annual Meeting 2017

BGBC008: BGB324 in Combination With Pembrolizumab in Patients With Advanced NSCLC

BGBC008 Phase II – Adenocarcinoma of the lung

MERCK

Patient Population

- Previously treated unresectable adenocarcinoma of the lung
- Measurable disease
- Fresh tissue biopsy

Parameters

- Continuous treatment with BGB324 in combination with KEYTRUDA

Biomarker:

- Tissue sample and blood based biomarker collection and processing
- Assay development and qualification
- PD-L1 assay to be performed by Merck

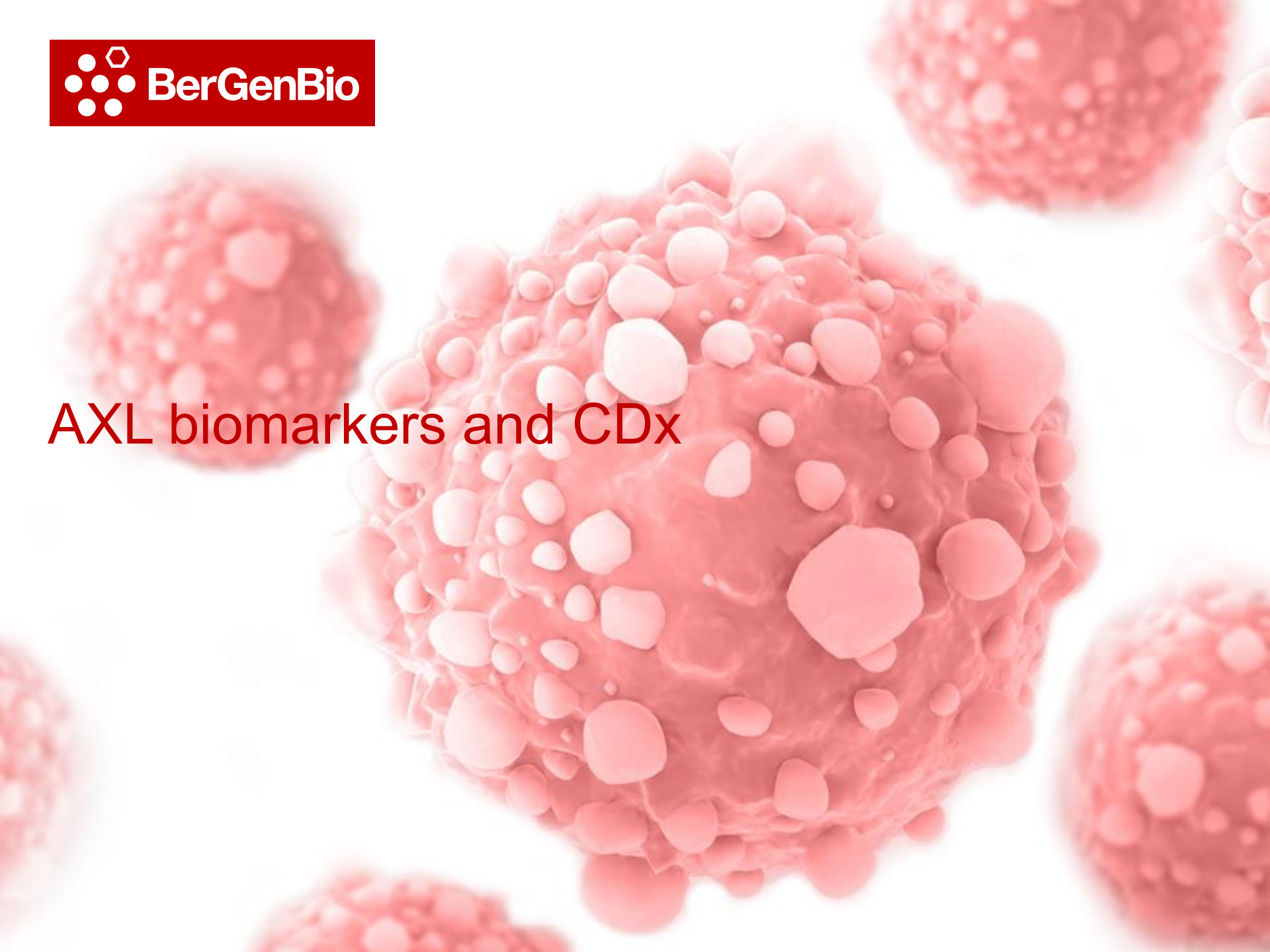
Read out

1^0 Endpoint:

- Objective response rate

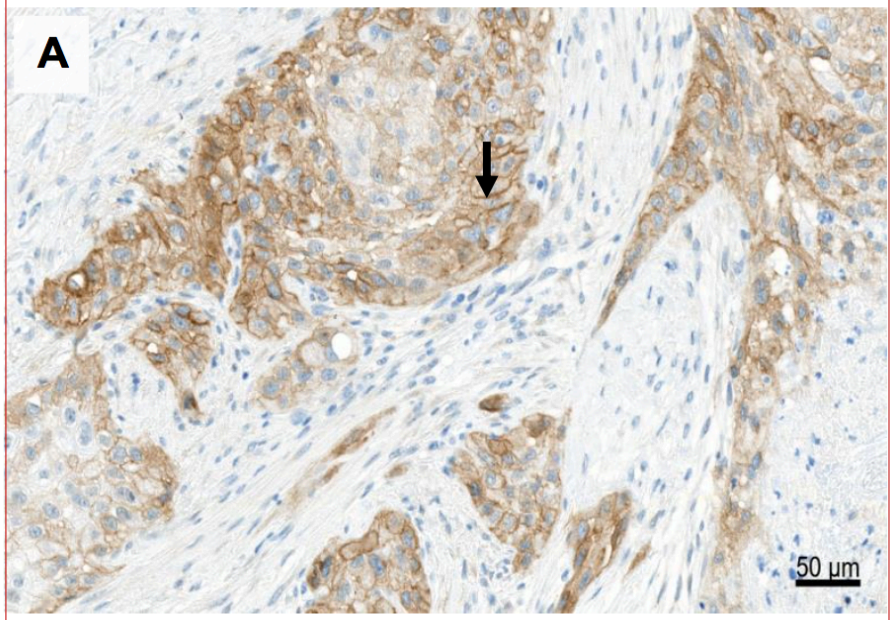
2^0 Endpoint:

- Safety
- Duration of response
- Progression free survival
- Survival at 12 months
- Response by biomarker expression


BerGenBio
AXL biomarkers and CDx

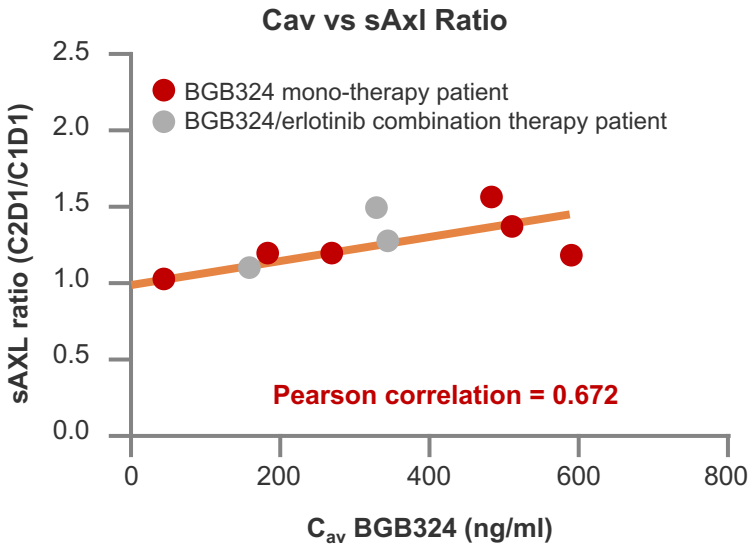
Parallel Development of Companion Diagnostic & Biomarkers

Immunohistochemistry assay for AXL expression in development



Anti-AXL IHC of human FFPE lung squamous cell carcinoma tissue sample

Soluble AXL increases in response to treatment with BGB324

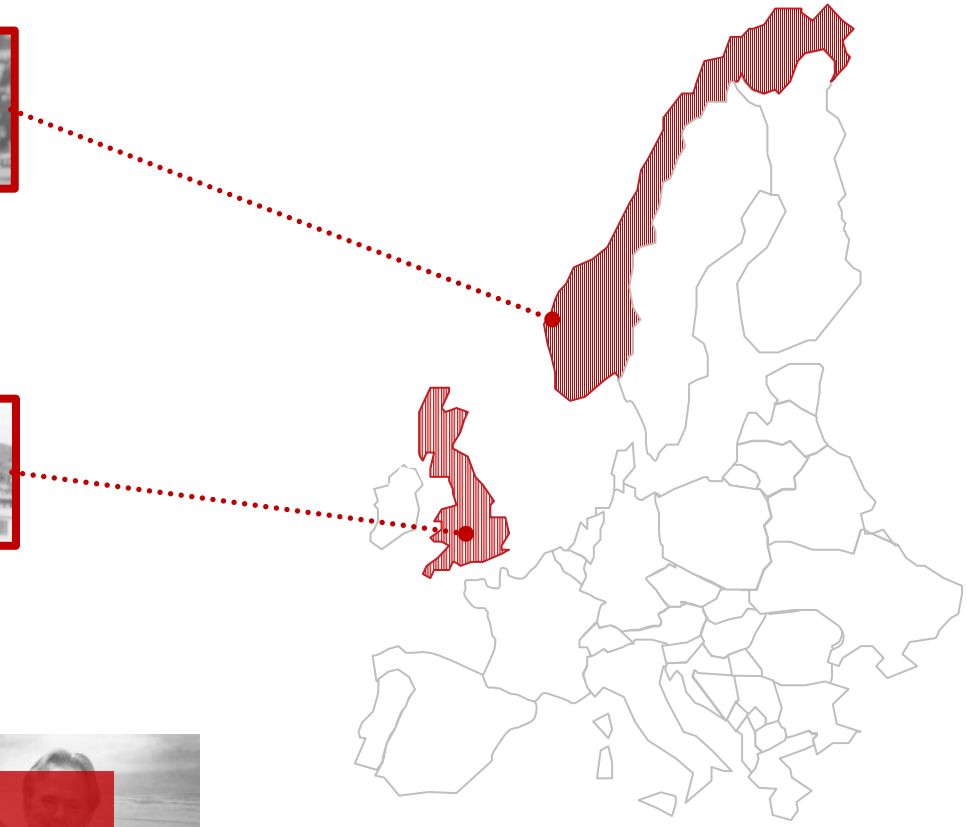


Blood plasma based assay testing for soluble AXL which increases in exposure dependent manner

Thank you

- Listed on Oslo Børs : '*BGBIO*'
- HQ and Administration
- Research

- Clinical trial management
- Drug discovery programs



Contact:
partnering@bergenbio.com