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Conquering Thoracic Cancers Worldwide

Preliminary efficacy results of selective AXL inhibitor bemcentinib with pembrolizumab as 2L in patients with NSCLC

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DISCLOSURES

Advisory role or speaker's bureau: AbbVie, AstraZeneca, BerGenBio, Blueprint medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Guardant Health, Janssen, Medscape, Merck KGaA, Merck Sharp & Dohme, Novartis, Pfizer, priME Oncology, Roche, Samsung, Springer, Takeda, Touchtime

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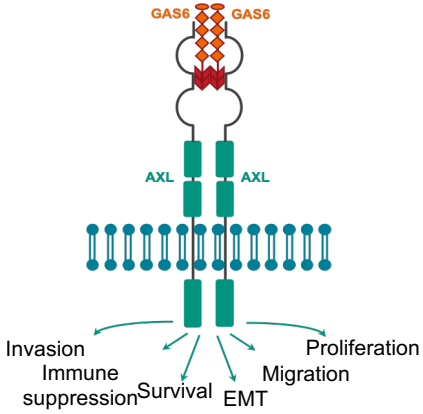
NCT03184571: Phase II clinical trial of selective AXL inhibitor bemcentinib in combination with pembrolizumab

Study Rationale

- AXL receptor tyrosine kinase is expressed on tumour and suppressive immune cells, and drives immune evasion, therapy resistance and metastasis[1]
- AXL is a negative prognostic factor in many cancers including NSCLC[2]
- Bemcentinib is a first-in-class highly selective, potent, and orally bioavailable, small molecule AXL kinase inhibitor[3]
- Bemcentinib potentiates efficacy of targeted, chemo- and immunotherapy, and prevents acquired resistance in murine models[4,5]



Study overview

2nd line advanced NSCLC
- Adenocarcinoma histology
- IO naïve
- Progressed on a platinum based chemotherapy in 1L
- AXL and PD-L1 All comers
- Fresh tissue biopsy

Single arm
Bemcentinib 200mg daily
+
Pembrolizumab 200mg q3weeks

Interim Analysis
N=24 patients

Final Analysis
N=48 patients

Endpoints
- **Primary –** ORR
- **Secondary –** DCR, DoR, TtP 12mth OS, Response by biomarker expression

Biomarker analysis
- PD-L1 and AXL expression by IHC
- Soluble protein biomarkers by liquid biopsy
- Tumor immune cell characterization

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

[1]Davidsen, et al. Springer Publishing (2017). The Role of Axl Receptor Tyrosine Kinase in Tumor Cell Plasticity and Therapy Resistance. [2]Shieh, et al. Neoplasia (2005). Expression of axl in lung adenocarcinoma and correlation with tumor progression. [3]Ludwig et al. Cancer Res. (2018) Small molecule inhibition of Axl targets tumor immune suppression and enhances chemotherapy in pancreatic cancer [4]Byers et al. EORTC (2016). A Phase I/II and pharmacokinetic study of BGB324, a slective AXL inhibitor as monotherapy and combination with erlotinib in patients with advanced Non-Small Cell Lung Cancer (NSCLC) [5]Davidsen et al. AACR (2018). Bemcentinib (BGB324) a selective small molecule inhibitor of receptor tyrosine kinase AXL, targets tumor immune suppression and enhances immune checkpoint inhibitor efficacy

Patient analysis *

Patient disposition, stages I + II

Screened
n = 74

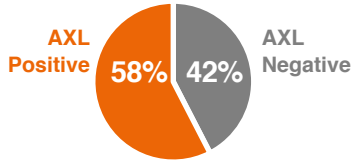
Received at least 1 dose of combination:
n = 46

35 had radiological assessment
3 progressed without radiological assessment
8 with no response assessment

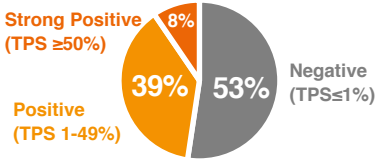
Discontinued
n = 30
- 15 PD
- 7 AE
- 3 death
- 3 investigator's decision
- 2 withdrawal of consent/ lost to follow-up

Ongoing
n = 16

AXL status
n = 33
(28 with at least 1 response assessment



PD-L1 status
n = 38
(29 with at least 1 response assessment)



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Patient demographics

		N (%)
Age	Median	64.5
	Range	39-82
ECOG at screen	0	22 (48%)
	1	24 (52%)
Sex	Female	18 (39%)
	Male	28 (61%)
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%)

Patient disease characteristics

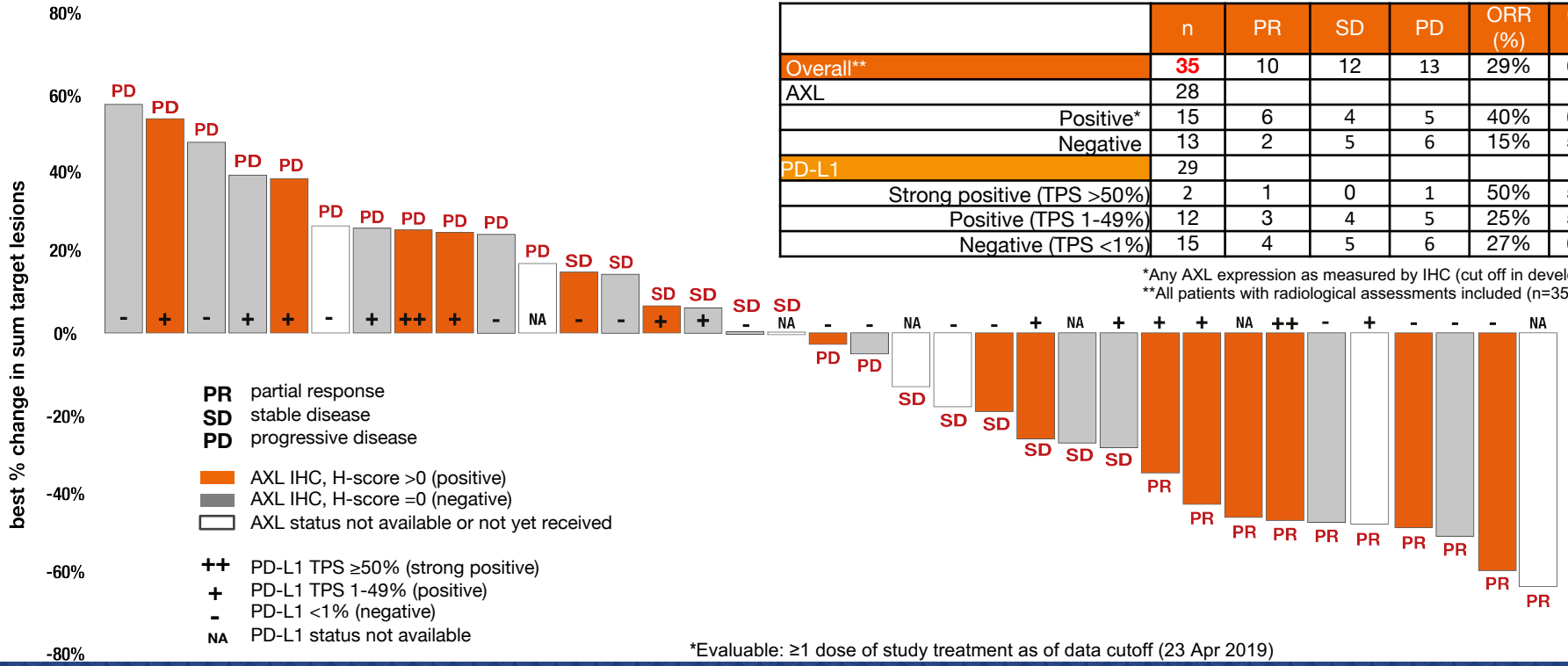
Mutations*	n	%
None	35	76%
KRAS	6	13%
TP53	2	4%
ERBB2	1	2%
EGFR	1	2%
Other/Unknown	2	4%

Best response to 1st line of treatment	n	%
CR	2	4%
PR	17	37%
SD	10	22%
PD	12	26%
Unknown	5	11%

* May be overlap between individual patients

Analysis of evaluable patients*

Antitumour activity: Change in tumour size from baseline (by AXL IHC)



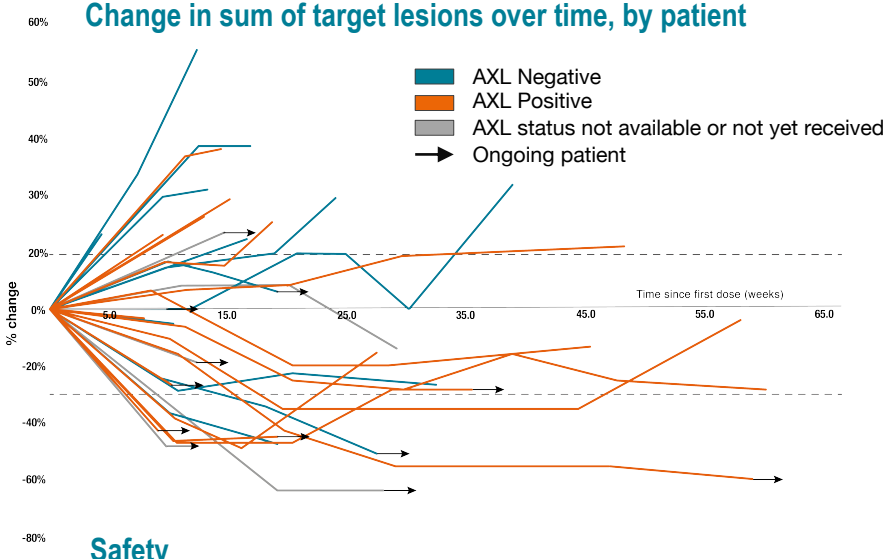
	n	PR	SD	PD	ORR (%)	CBR (%)
Overall**	35	10	12	13	29%	63%
AXL	28					
Positive*	15	6	4	5	40%	67%
Negative	13	2	5	6	15%	54%
PD-L1	29					
Strong positive (TPS >50%)	2	1	0	1	50%	50%
Positive (TPS 1-49%)	12	3	4	5	25%	58%
Negative (TPS <1%)	15	4	5	6	27%	60%

*Any AXL expression as measured by IHC (cut off in development)
**All patients with radiological assessments included (n=35)

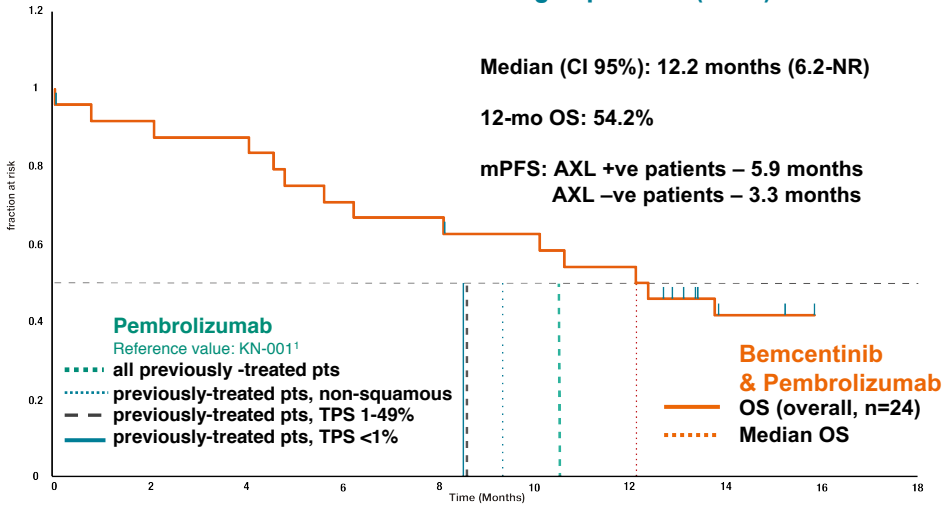
*Evaluable: ≥1 dose of study treatment as of data cutoff (23 Apr 2019)

Interim analysis of evaluable patients

Change in sum of target lesions over time, by patient



Median overall survival in stage I patients (n=24)



Safety

Most frequent TRAEs (occurring in >10% of dosed patients) n = 46

Preferred term	All grades		Grades ≥3		Preferred term	All grades		Grades ≥3	
	n	%	n	%		n	%	n	%
Transaminase increase*	16	35%	6	13%	Nausea	6	13%	0	0%
Asthenia / Fatigue	14	30%	2	4%	Anaemia	5	11%	1	2%
Diarrhoea	12	26%	0	0%	Decreased appetite	5	11%	0	0%

AEs leading to discontinuation of treatment

Transaminitis (1 x grade 2, 2 x grade 3)
Fatigue (1 x grade 2)
Asthenia (1 x grade 3)
AST increased (1 x grade 3)
Pneumonia (1 x grade 4)

* Preferred terms include: Alanine aminotransferase increase, Aspartate aminotransferase increase and Transaminases increase.All events were reversible

Summary

- Promising clinical activity seen overall, particularly in patients with AXL positive tumours including those with low or no PD-L1 expression
- The studied population was predominantly PD-L1 negative (53%) patients, who are less likely to benefit from pembrolizumab monotherapy treatment
- The studied population was predominantly AXL positive (58%) patients
- The combination treatment of bemcentinib and pembrolizumab was overall well-tolerated; the most common treatment related adverse events included transaminase increase (35%), asthenia/fatigue (30%), and diarrhoea (26%)
- Transaminase increases were reversible and managed with the administration of systemic corticosteroids and interruption of study treatments

Take home message…

The combination therapy of pembrolizumab and bemcentinib is well tolerated and is benefitting AXL positive/PD-L1 low/negative patients