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NOVEMBER 9–14
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A PhII study of bemcentinib, a first-in-class selective AXL kinase inhibitor, in combination with pembrolizumab, in pts with previously-treated advanced NSCLC: Updated clinical & translational analysis

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Disclosures

Personal financial interests:

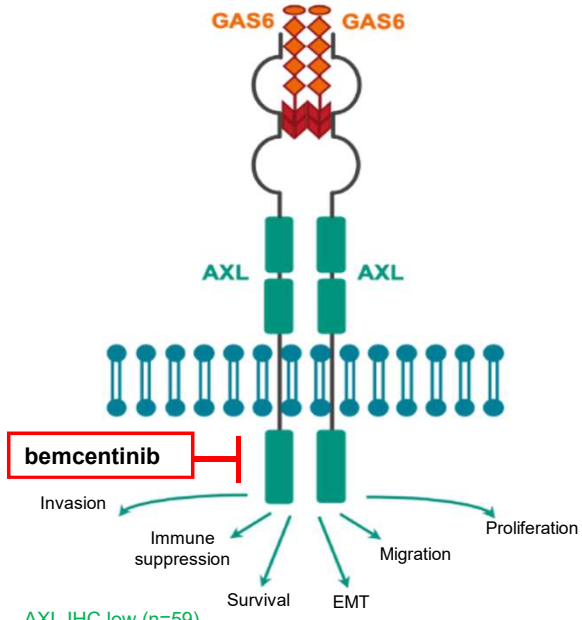
- Travel expenses: BerGenBio

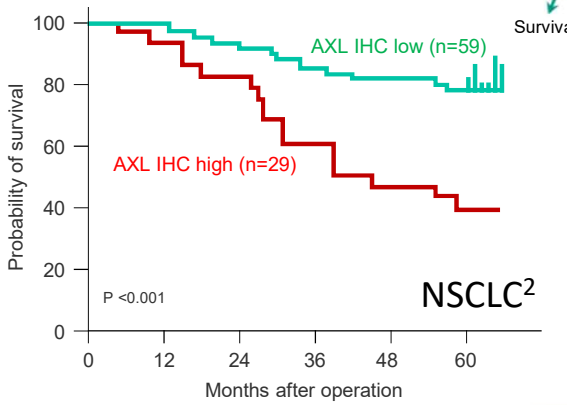
Institutional financial interests: BerGenBio, AstraZeneca, BMS, Genmab, GSK, Lilly, Roche

Study rationale

Multi-arm study in 2L NSCLC of selective AXL inhibitor bemcentinib in combination with pembrolizumab

- AXL drives tumor **EMT and resistance to CTL-mediated tumor cell killing**[1]
- AXL receptor tyrosine kinase is **negatively prognostic** in many cancers including NSCLC[2]
- AXL expression is associated with **anti-PD-1 therapy failure** in melanoma patients[3]
- AXL is expressed by immuno-suppressive **tumor-associated M2 macrophages and dendritic cells**[4]
- Bemcentinib is a first-in-class highly **selective, potent oral small molecule AXL kinase inhibitor**
- Bemcentinib **reverses EMT, repolarizes TAMs and potentiates immunotherapy** in mouse models[4]





[1]Terry, 2019; [2]Ishikawa, 2012, [3]Hugo, 2016; Davidsen,2017; [4]Ludwig, 2018, Davidsen, submitted

Study design

Multi-arm study in 2L NSCLC of selective AXL inhibitor bemcentinib in combination with pembrolizumab

Cohort A
- Previously treated with a platinum-containing chemotherapy
- CPI-naïve
- Demonstrable PD

Interim Analysis
Cohort A
Stage 1
N=22 patients
(each patient has the potential for at least 24 weeks follow-up)

Final Analysis
Cohort A
Stage 2
N=48 patients
(each patient has the potential for at least 24 weeks follow-up)

Cohort B
- Previously treated with PD-L1 or PD-1 inhibitor mono-therapy
- ≥12 weeks clinical benefit followed by PD

Interim Analysis
Cohorts B
Stage 1
N=16 patients
(each patient has the potential for at least 24 weeks follow-up)

Final Analysis
Cohorts B
Stage 2
N=29 patients
(each patient has the potential for at least 24 weeks follow-up)

Cohort C
- Previous 1st line combination checkpoint inhibitor + platinum doublet
- ≥12 weeks clinical benefit on 1st line therapy followed by PD

Interim Analysis
Cohorts C
Stage 1
N=13 patients
(each patient has the potential for at least 24 weeks follow-up)

Final Analysis
Cohorts C
Stage 2
N=29 patients
(each patient has the potential for at least 24 weeks follow-up)

Previously-reported survival data in Cohort A[1]

Cohort	mOS	12-mo OS
Cohort A – cAXL +ve	17.3 mo	79%
Cohort A – cAXL -ve	12.4 mo	60%

[1] Gabra, *et al*. Next Gen Immuno-Oncology Congress, June 2020

Safety profile of combination across all cohorts

Most frequently occurring treatment-related* AEs (≥10% dosed patients) n=73

Preferred term	All Grades n (%)	Grades ≥3 n (%)
Alanine aminotransferase increased	24 (33%)	8 (11%)
Diarrhea	23 (32%)	1 (1%)
Aspartate aminotransferase increased	22 (30%)	5 (7%)
Asthenia	12 (16%)	4 (5%)
Pruritus	12 (16%)	0
Blood creatinine increased	10 (14%)	0
Anemia	9 (12%)	2 (3%)
QT prolonged	9 (12%)	1 (1%)
Fatigue	9 (12%)	1 (1%)
Nausea	9 (12%)	0

- AEs were reported as possibly, probably or definitely related to bemcentinib and/or pembrolizumab.
- Safety cut-off: July 2020

Safety Summary

- Treatment combination was well tolerated
- Safety profile of combination treatment consistent with that of individual drugs
- Treatment-related AEs generally mild and reversible
- Two patients reported grade 4 and no patients reported grade 5 TRAEs

Study design

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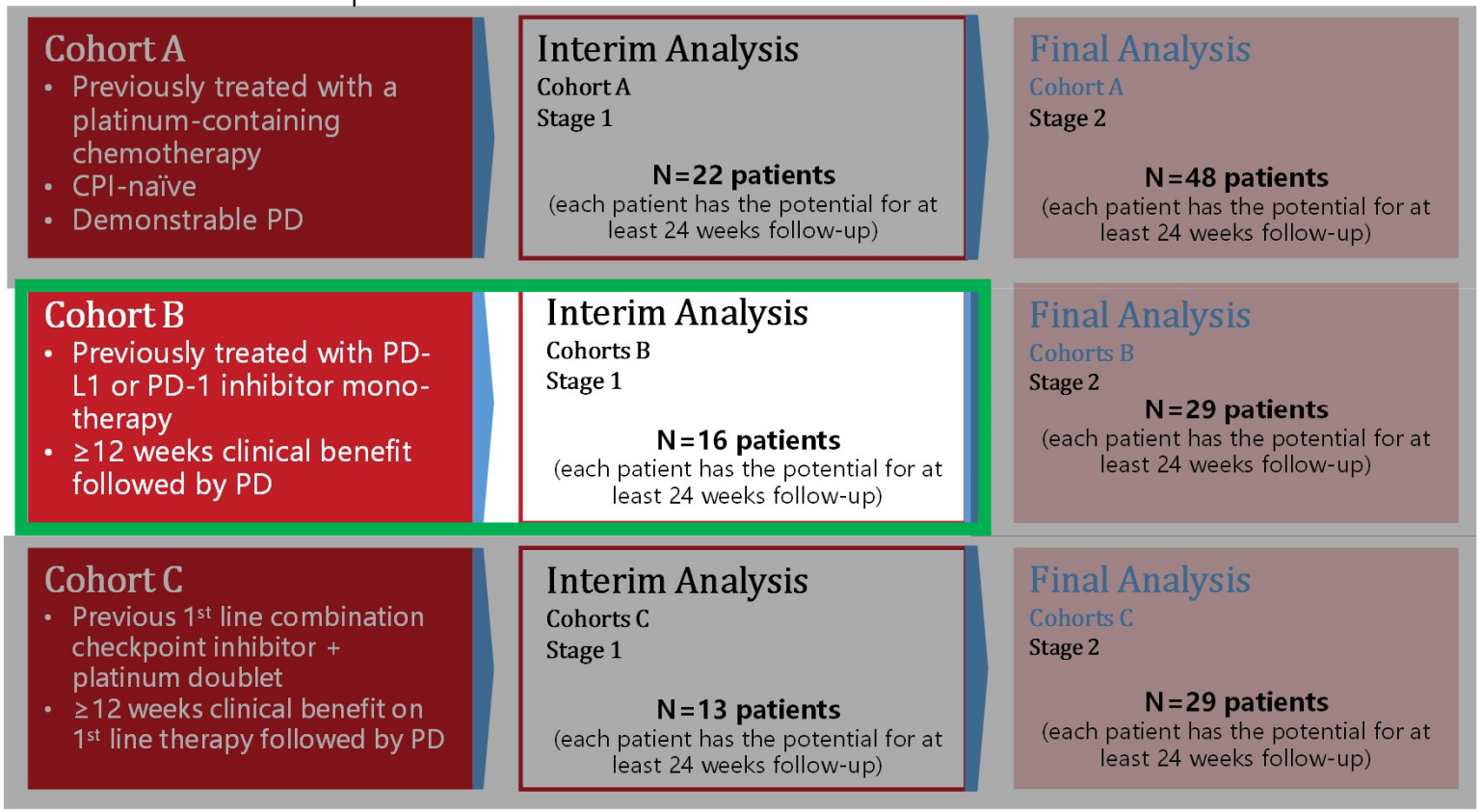
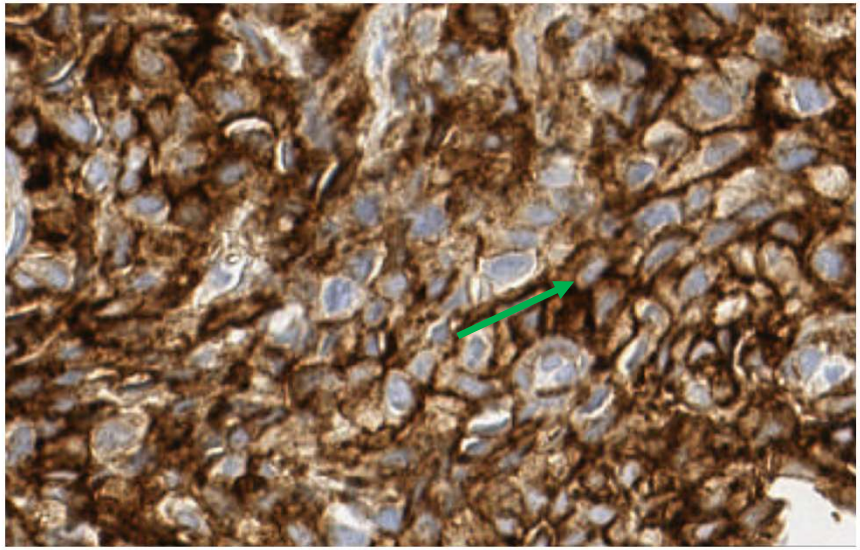
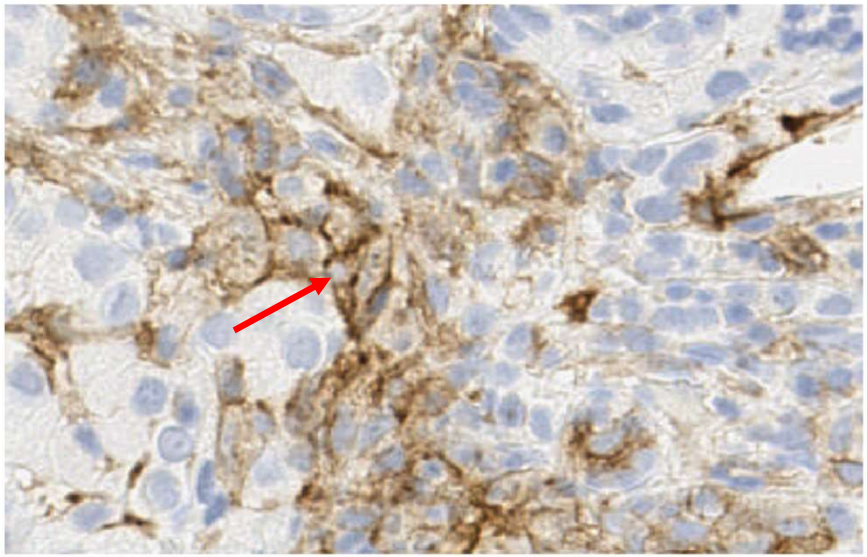


Composite AXL score (cAXL)

High AXL expression on *tumour* cells



High AXL expression on *immune* cells



Examples of positively-stained **tumor** and **immune** cells, respectively

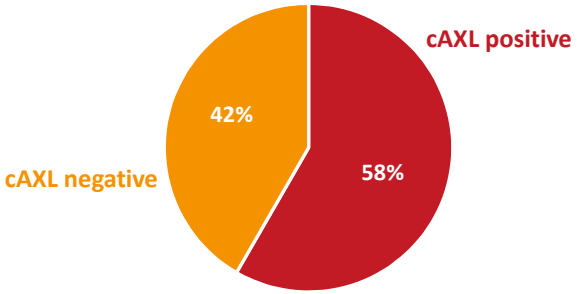
Patient disposition and demographics

Cohort B (stage 1)

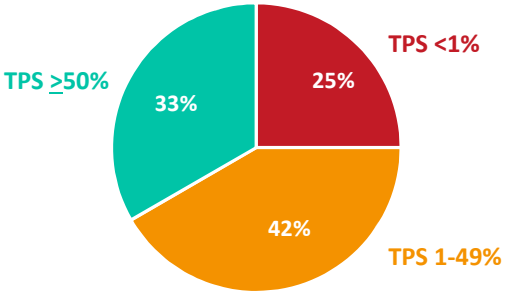
Patient demographics		n=16
Age	Median	64.5
	Range	40-76
ECOG at screen	0	6 (38%)
	1	10 (63%)
Sex	Female	3 (19%)
	Male	13 (81%)
Smoking status	Smoker	8 (50%)
	Ex-smoker	8 (50%)
	Never smoked	0

Biomarkers

cAXL status
n = 12*



PD-L1 status
n = 12*

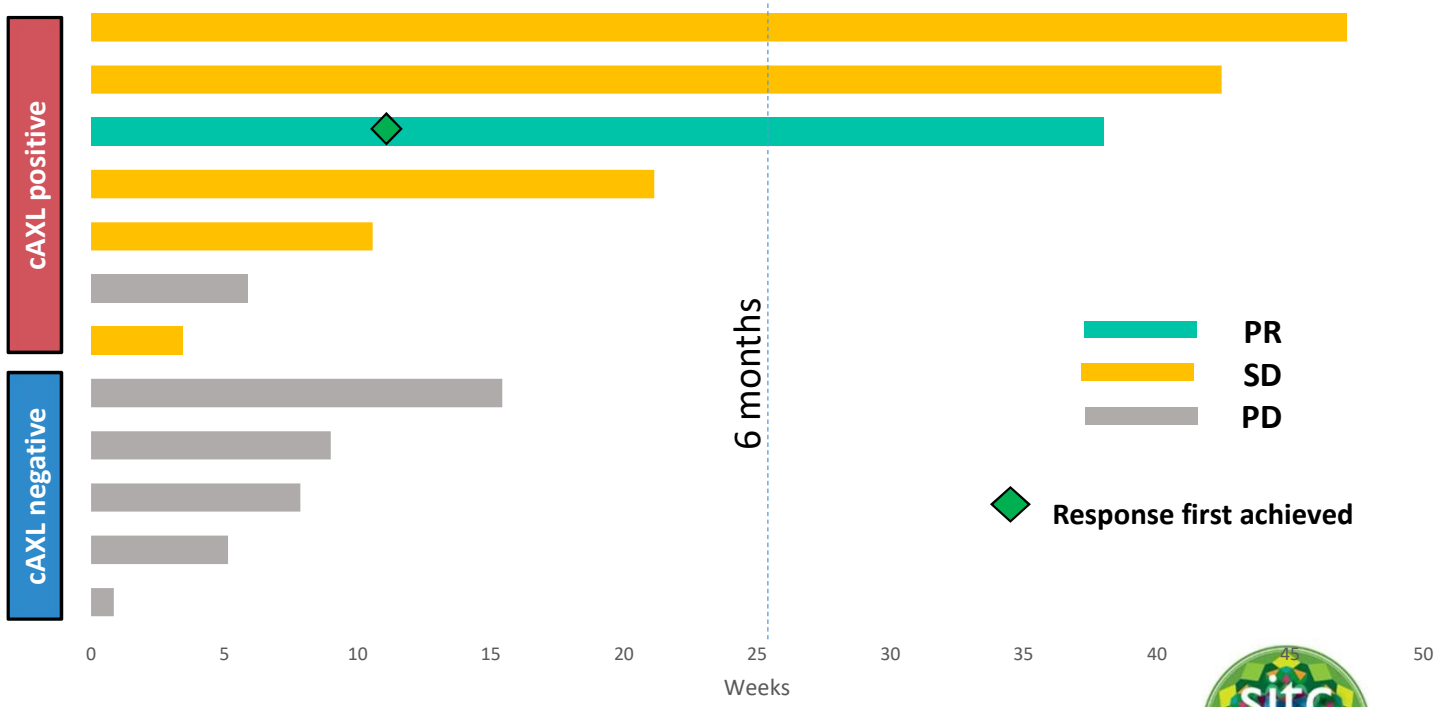


** Of 15 radiologically evaluable patients, 3 not evaluable for AXL or PDL1*

Patient outcomes

Activity and time on treatment Cohort B1 patients evaluable for cAXL

Prior lines	Prior therapies	PD-L1 (%)	cAXL status
2	PltCT, A/O	65	+
1	P	20	+
1	A	95	+
2	PltCT, P	15	+
2	PltCT, N	100	+
2	PltCT, P	95	+
1	I/N	2	+
2	PltCT, P	35	-
3	PltCT/D, PltCT, N	30	-
2	PltCT, A	0	-
2	PltCT, O	NE	-
2	PltCT, O	0	-

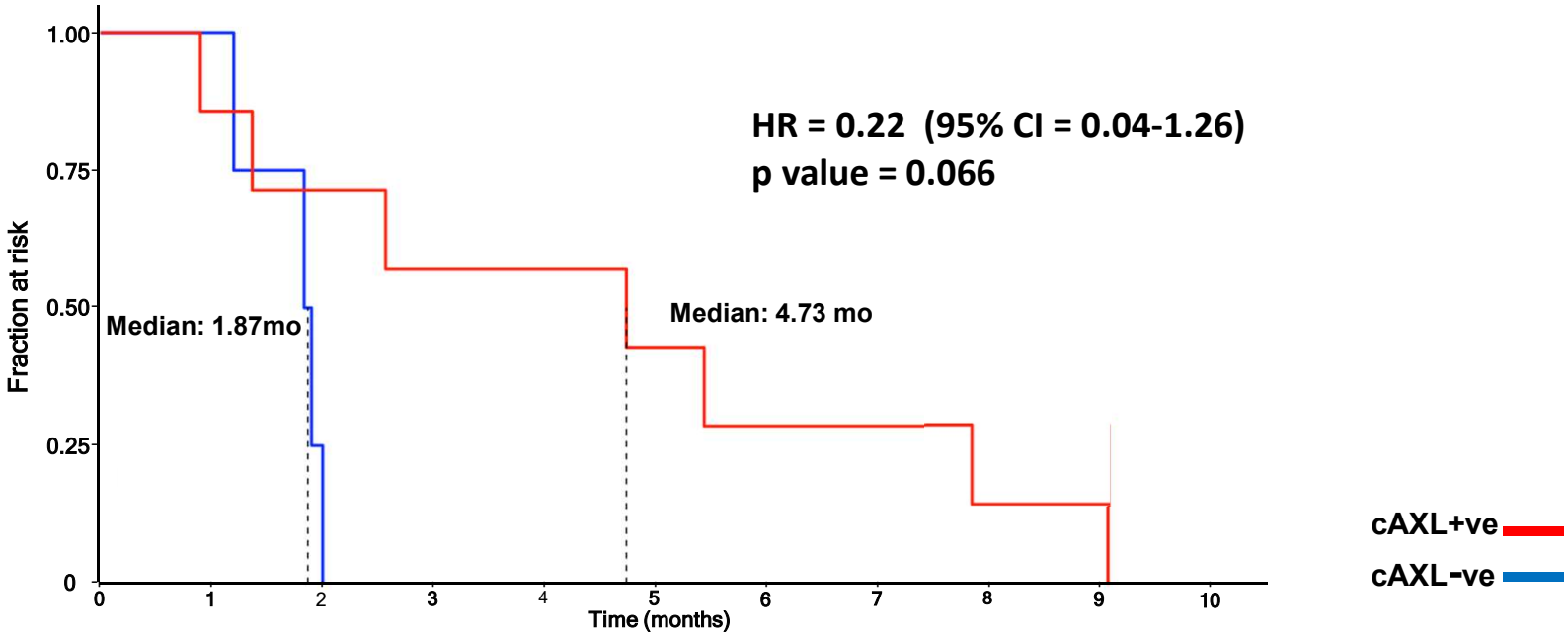


Previous therapies

PltCT: platinum-based chemotherapy **D**: docetaxel **P**: pembrolizumab; **A**: atezolizumab; **N**: nivolumab; **I**: ipilumimab; **O**: other

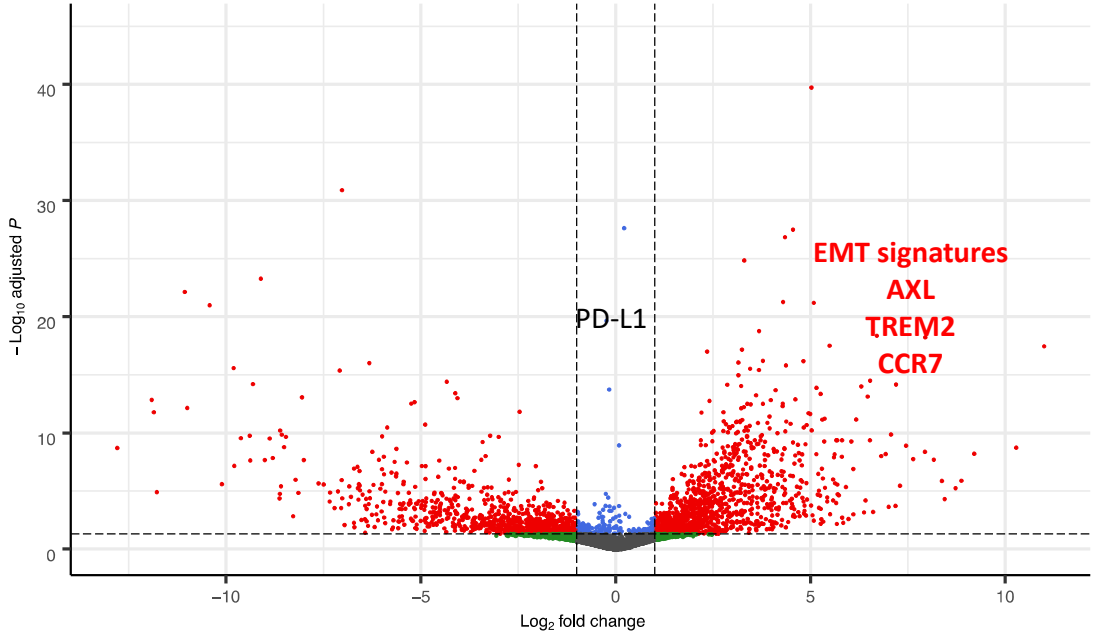
Patient outcomes

Progression-free survival in Cohort B1 patients evaluable for cAXL



Clinical translational findings

Whole tumor gene expression of Cohort B1 patients benefiting from bemcentinib-pembrolizumab



Volcano Plot: Differential gene expression analysis of patients showing benefit (n=5) vs patients with PD (n=3)

RNAseq analysis identifies gene signatures from benefiting patients:

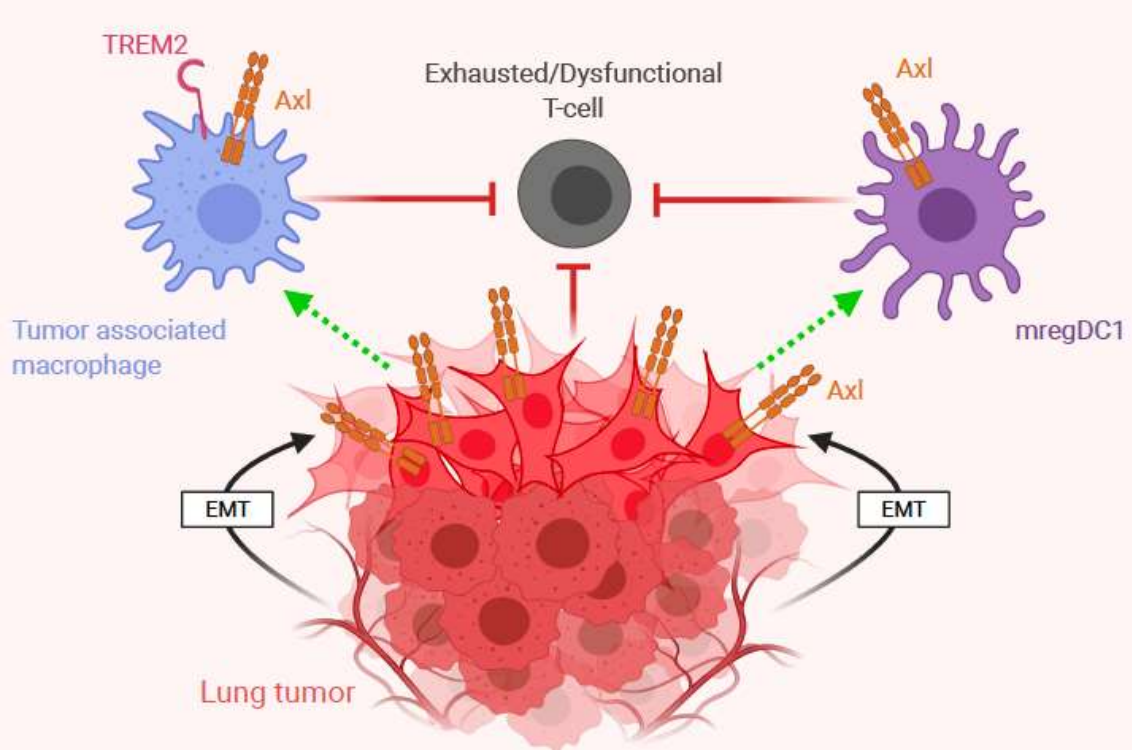
- Increased AXL expression
- Genes associated with tumor cell EMT[1]
- Presence of TREM2+ TAMs[#,2]
- Presence of CCR7+ mregDC1[##,3]

[#] tumor-associated macrophages
[##]regulatory dendritic cells

[1]Liberzon, Cell Systems 2015;[2]Katzenelenbogen *Cell* 2020, Molgora *Cell* 2020; [3]Maier *Nature* 2020

Proposed mechanism

AXL+ suppressive myeloid cells drive T cell dysfunction



- AXL promotes tumor-cell EMT and recently-described regulatory myeloid cells:
  - AXL+ TREM2+ TAM[1,2]
  - AXL+ CCR7+ mregDC1[3]
- AXL expression in these cells promotes T cell dysfunction/exhaustion[2]
- Bemcentinib inhibition of AXL reverses this state of immune suppression in the microenvironment, and promotes checkpoint inhibitor re-engagement

1. Katzenelenbogen *Cell* 2020; 2. Molgora *Cell* 2020; 3. Maier. et al. *Nature* 2020

Conclusions

- Bemcentinib-pembrolizumab combination well tolerated and clinically active in CPI-refractory cAXL+ NSCLC
- Recruitment ongoing in CPI-refractory and chemo-CPI-refractory patient populations
- Bemcentinib may reverse acquired resistance to checkpoint inhibition by targeting AXL+ TREM2 macrophages and regulatory DCs
- Findings support further development of AXL inhibition with bemcentinib to extend efficacy of immunotherapy in biomarker-selected NSCLC

Acknowledgements

The patients and their families

All BGBC008 investigators
- Arriola, E. - Hospital del Mar, Spain
- Carcereny, E.- Hospital Universitari Germans trias i Pujol-ICO, Spain
- Felip, E. - Hospital Universitario Vall d'Hebron (VHIR), Spain
- Gómez, M. - Hospital Universitario Fundación Jiménez Díaz, Spain
- Helland, A. - Oslo University Hospital / The Norwegian Radium Hospital, Norway
- Krebs, M. - The Christie NHS Foundation Trust, Manchester, UK
- Ortega, A. - Hospital Universitario de Jaen, Spain
- Strauss, J. - Mary Crowley Cancer Research, Dallas, USA
- Thompson, J. - Medical College of Wisconsin, USA
- Trigo Perez, J. - Hospital Universitario Virgen de la Victoria, Spain

BerGenBio ASA

Merck & Co., Inc.