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A phase II study of bemcentinib (BGB324), a first-in-class selective AXL inhibitor, in combination with pembrolizumab in patients with advanced NSCLC: Updated analysis

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Disclosures

Personal financial interests:

- Advisory boards/consultancy: Roche, Achilles, Octimet, Janssen,
- Travel expenses: AstraZeneca, BerGenBio (incl. SITC 2019)
- Research funding: BerGenBio, Roche

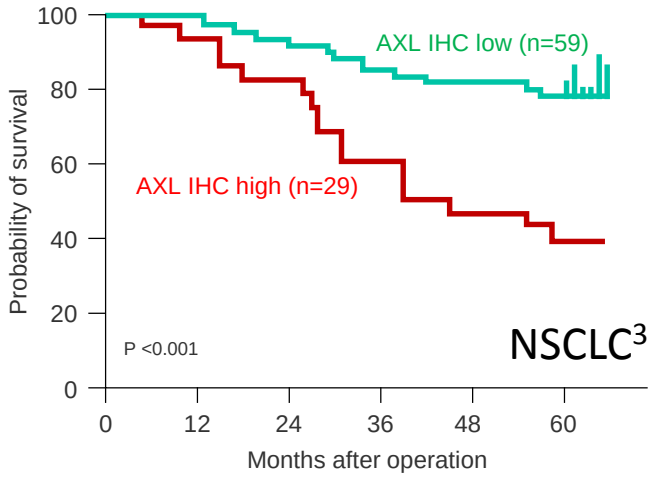
Institutional financial interests:

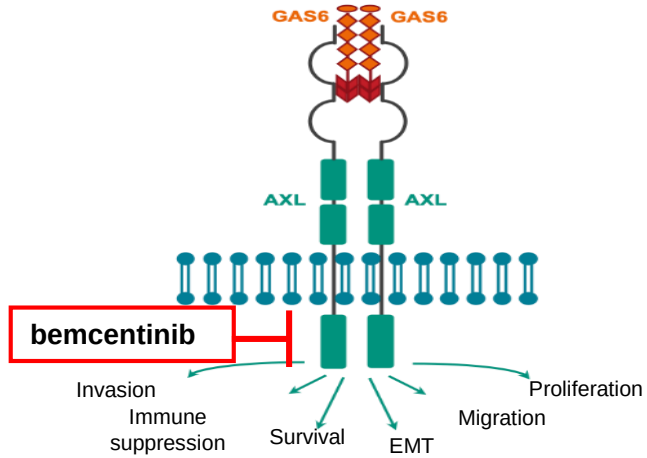
- AstraZeneca, Bayer, BerGenBio, Blueprint, Carrick, Chugai, Immutep, Incyte, Janssen, Lilly, Merck, MSD, Octimet, Roche, Sierra

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

Study Rationale

- AXL drives tumor **EMT and resistance to cytotoxic lymphocyte-mediated cell killing**[1]
- AXL receptor tyrosine kinase is a **negative prognostic factor** for many cancers including NSCLC[2]
- AXL expression is associated with **anti-PD-1 therapy failure** in melanoma patients[3]
- AXL is expressed by suppressive **tumor-associated M2 macrophages and dendritic cells**[4]
- Bemcentinib is a first-in-class highly **selective, potent, and orally bioavailable, small molecule AXL kinase inhibitor**
- Bemcentinib **reverses EMT, repolarizes TAMs and potentiates efficacy of immunotherapy** in murine cancer models[4]





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

NCT03184571: Study design

BGBC008
Phase II 2-stage study of bemcentinib (BGB324) in combination with pembrolizumab

Inclusion criteria
- Adenocarcinoma histology
- Measurable disease
- Fresh tumor tissue
- AXL and PD-L1 All comers

Assessments
Efficacy
- **Primary endpoint**
  - Objective Response Rate
- **Secondary endpoints**
  - Duration of Response
  - Disease Control Rate
  - Time to Progression
  - Survival at 12 months
  - Response by Biomarker expression

Safety
PK

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

Cohort A

- **Previously treated with a platinum containing chemotherapy**
- 2nd line advanced adeno NSCLC

Interim Analysis

Stage 1

N=24 patients
(each patient has the potential for at least 24 weeks follow-up)

Stop at this stage for:
Futility (H0:15% if ≤3 responses)
Or unfavourable risk/benefit

Final Analysis

Stage 2

N=50 patients total
(each patient has the potential for at least 24 weeks follow-up)

Cohort B

- **Previously treated with a checkpoint inhibitor (PD-L1 or PD-1 inhibitor)**
- No more than 2 previous lines of treatment
- Must have had disease control for ≥12 weeks followed by progression
- 2nd or 3rd line advanced adeno NSCLC

Cohort C

- **Previously treated 1st line with a checkpoint inhibitor- containing regimen in combination with a platinum-containing chemotherapy**
- Disease control on 1st line therapy for ≥12 weeks followed by progression
- 2nd line advanced adeno NSCLC

Interim Analysis Cohorts B & C

Stage 1

N=13 patients/cohort

(each patient has the potential for at least 24 weeks follow-up)

Stop at this stage for
Futility (H0:15% if 0 responses)
Or unfavourable risk/benefit

Final Analysis Cohorts B & C

Stage 2

N=29 patients/cohort

(each patient has the potential for at least 24 weeks follow-up)

Ref. BGBC008 / NCT03184571 – clinical trial collaboration with Merck & Co., Inc.

Cohort A Patient Disposition and Demographics*

Patient disposition

Screened
n = 74

Received at least 1 dose of combination:
n = 50

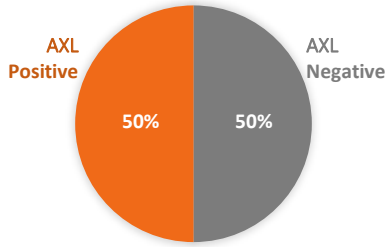
44 had at least 1 post-baseline radiological assessment
6 with no evaluable post-baseline scan:
- 1 withdrawal of consent after 1 dose
- 1 lost to follow-up before first scan
- 1 with unevaluable scan showing new lesions (TLs not measurable), and shortly after taken off study
- 3 died before first scan

Discontinued
n = 41
- 20 PD
- 8 AE
- 7 death
- 4 investigator's decision
- 2 withdrawal of consent/ lost to follow-up

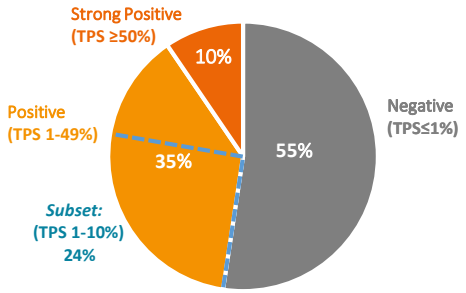
Ongoing
n = 9

Biomarker

AXL composite status
n = 30



PD-L1 status
n = 37



Patient demographics

		N (%)
Age	Median	65
	Range	39-82
ECOG at screen	0	22 (44%)
	1	28 (56%)
Sex	Female	20 (40%)
	Male	30 (60%)
Race	White	47 (94%)
	Asian	2 (4%)
	Other	1 (2%)
Smoking Status	Smoker	10 (20%)
	Ex-smoker	29 (58%)
	Never smoked	10 (20%)
	Unknown	1 (2%)

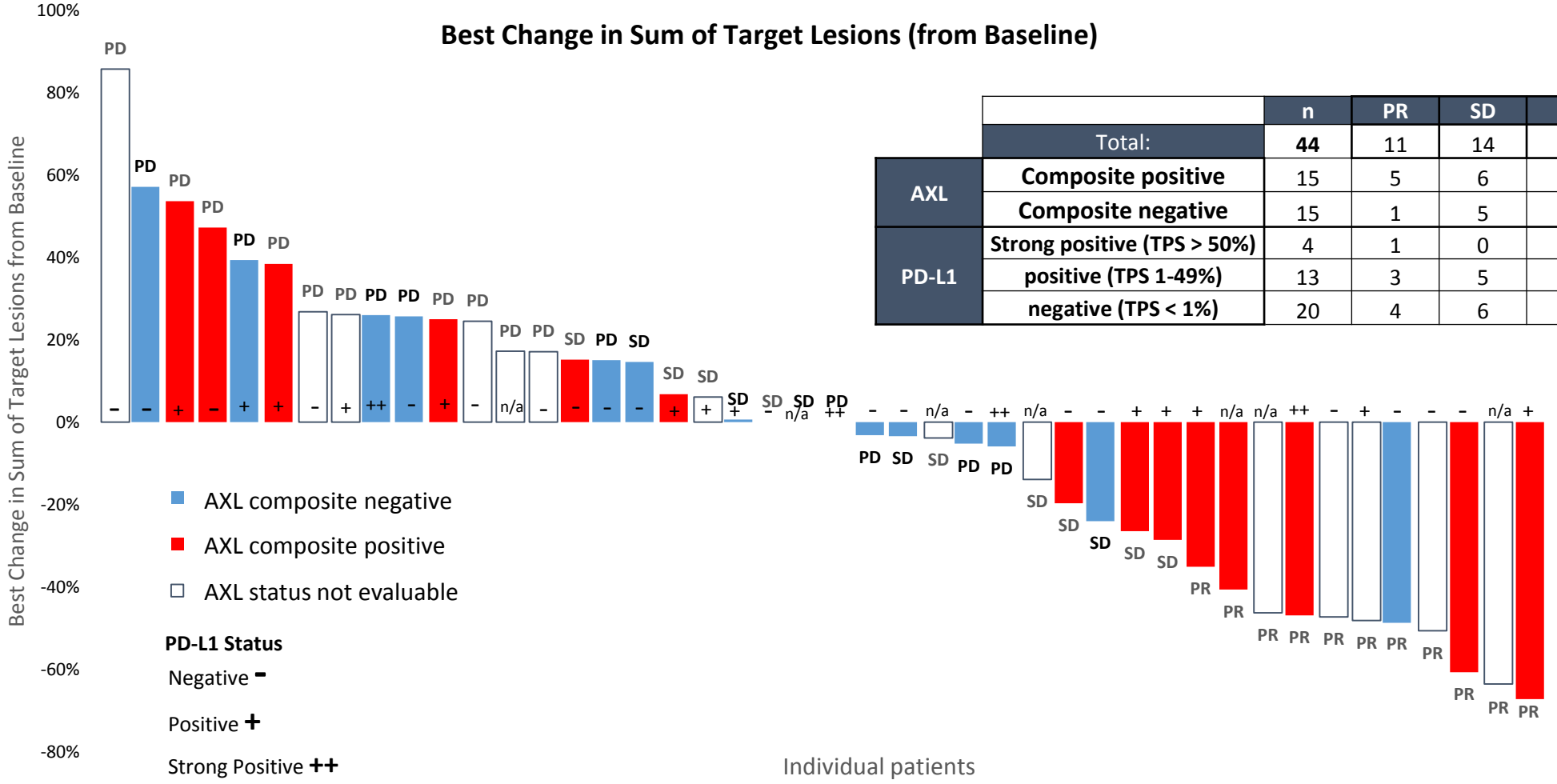
Patient disease characteristics

Disease Characteristics (n=50)		
Mutations*	**n**	**%**
None	36	72%
KRAS	7	14%
TP53	2	4%
ERBB2	1	2%
EGFR	3	6%
ALK	1	2%
Other/Unknown	2	4%

*Evaluable: ≥1 dose of study treatment as of data cutoff (30 Sep 2019)

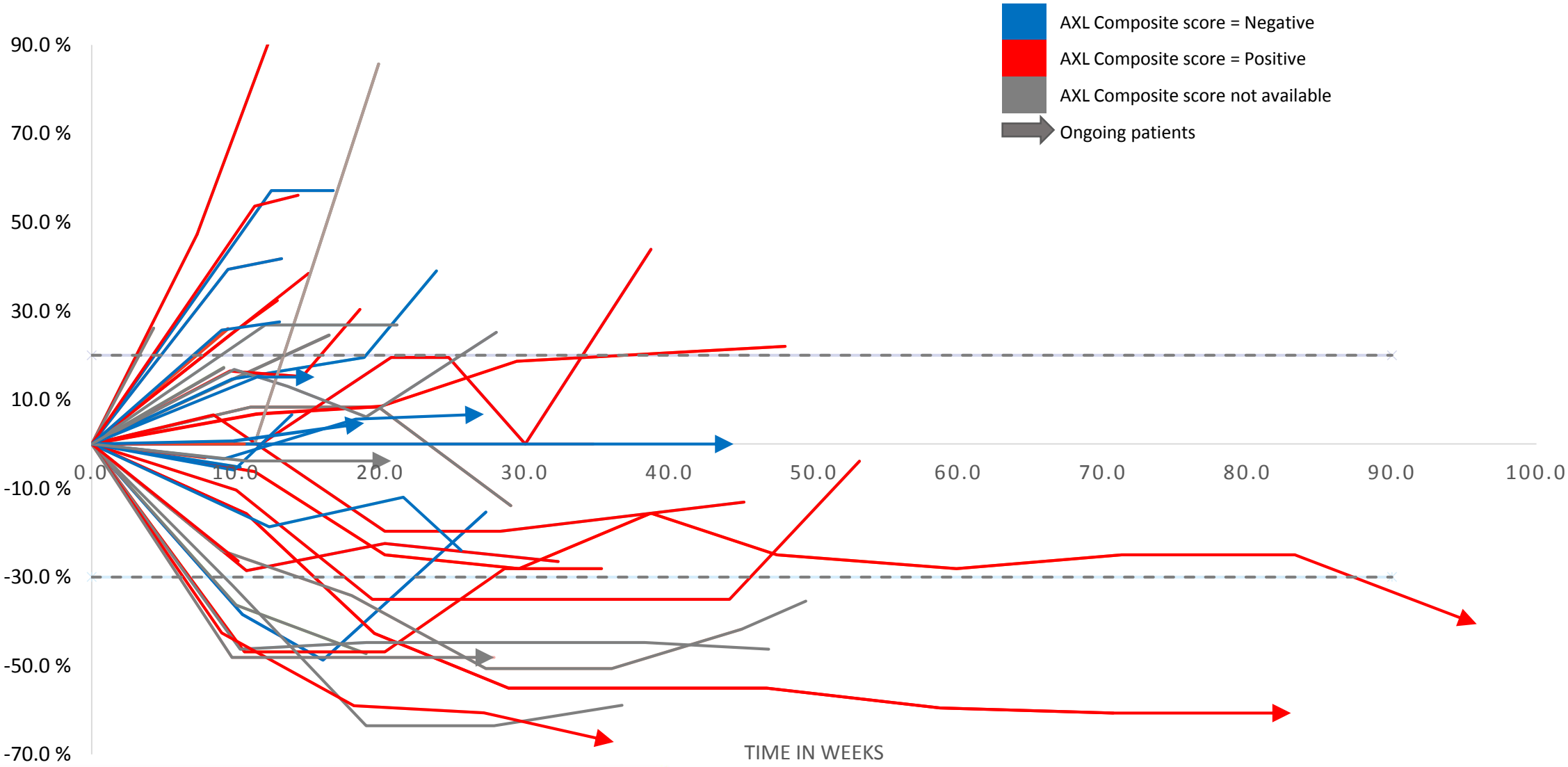
* May be overlap between individual patients

Antitumour activity of Bemcentinib in combination with pembrolizumab: Change in tumour size from baseline

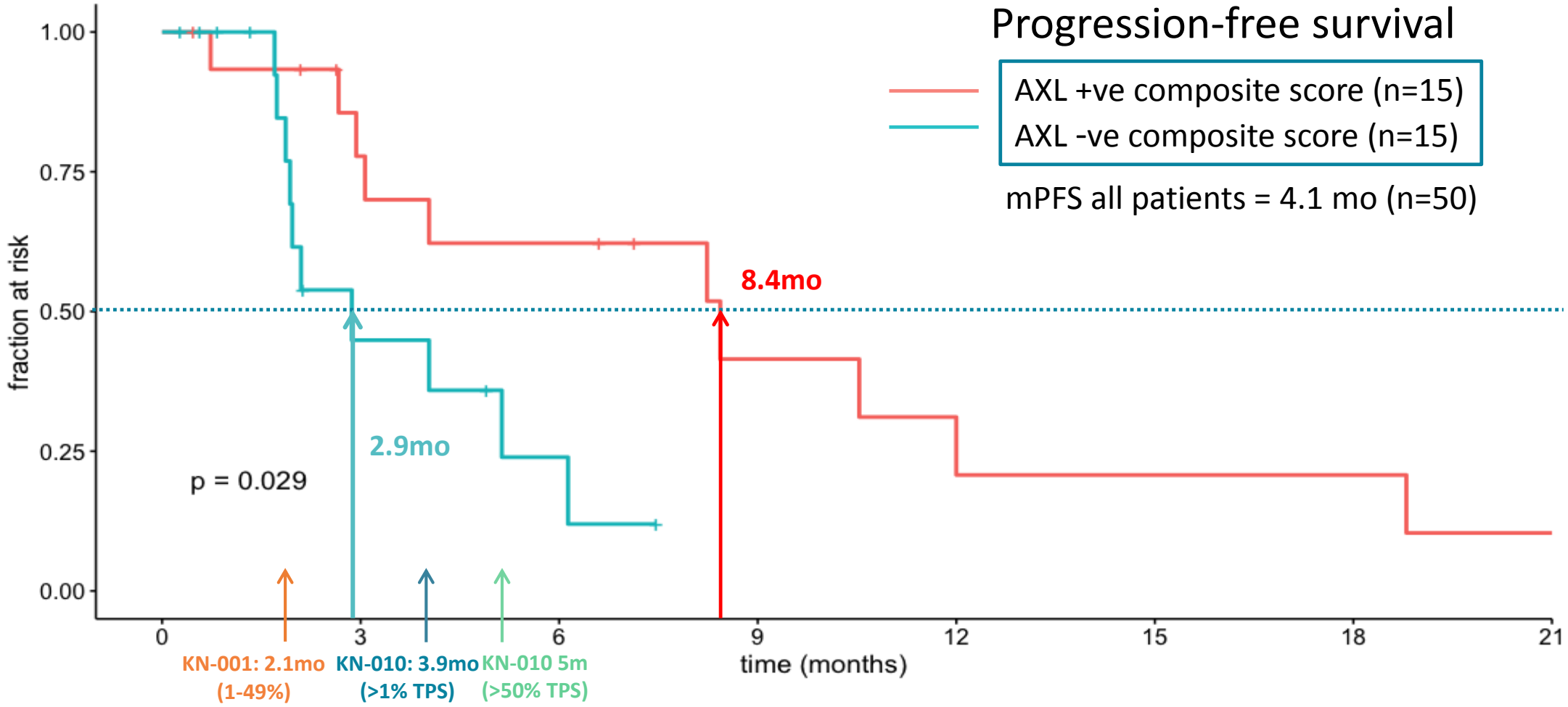


		n	PR	SD	PD	ORR%	DCR%
	Total:	**44**	11	14	19	25	57
AXL	**Composite positive**	15	5	6	4	33	73
	Composite negative	15	1	5	9	7	40
PD-L1	**Strong positive (TPS > 50%)**	4	1	0	3	25	25
	positive (TPS 1-49%)	13	3	5	5	23	62
	negative (TPS < 1%)	20	4	6	10	20	50

Change in sum of target lesions over time, by patient



Significant mPFS improvement in composite AXL tumor-immune score positive patients



Safety

Most frequent TRAEs (≥10% dosed pts) **

Event Terms	All Grades		Grade≥3	
	n	%	n	%
Transaminase increased*	19	38 %	7	14%
Asthenia / Fatigue	15	30 %	4	8%
Diarrhoea	12	24 %	0	0%
Nausea	7	14 %	0	0%
Anaemia	6	12 %	1	2%
Blood creatinine increased	6	12 %	0	0%
Decreased appetite	6	12 %	0	0%
Pruritus	5	10 %	0	0%

* Preferred terms include: Alanine aminotransferase increased, Aspartate aminotransferase increased, and Transaminases increased.
** cut-off date: 18 Jul19

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)

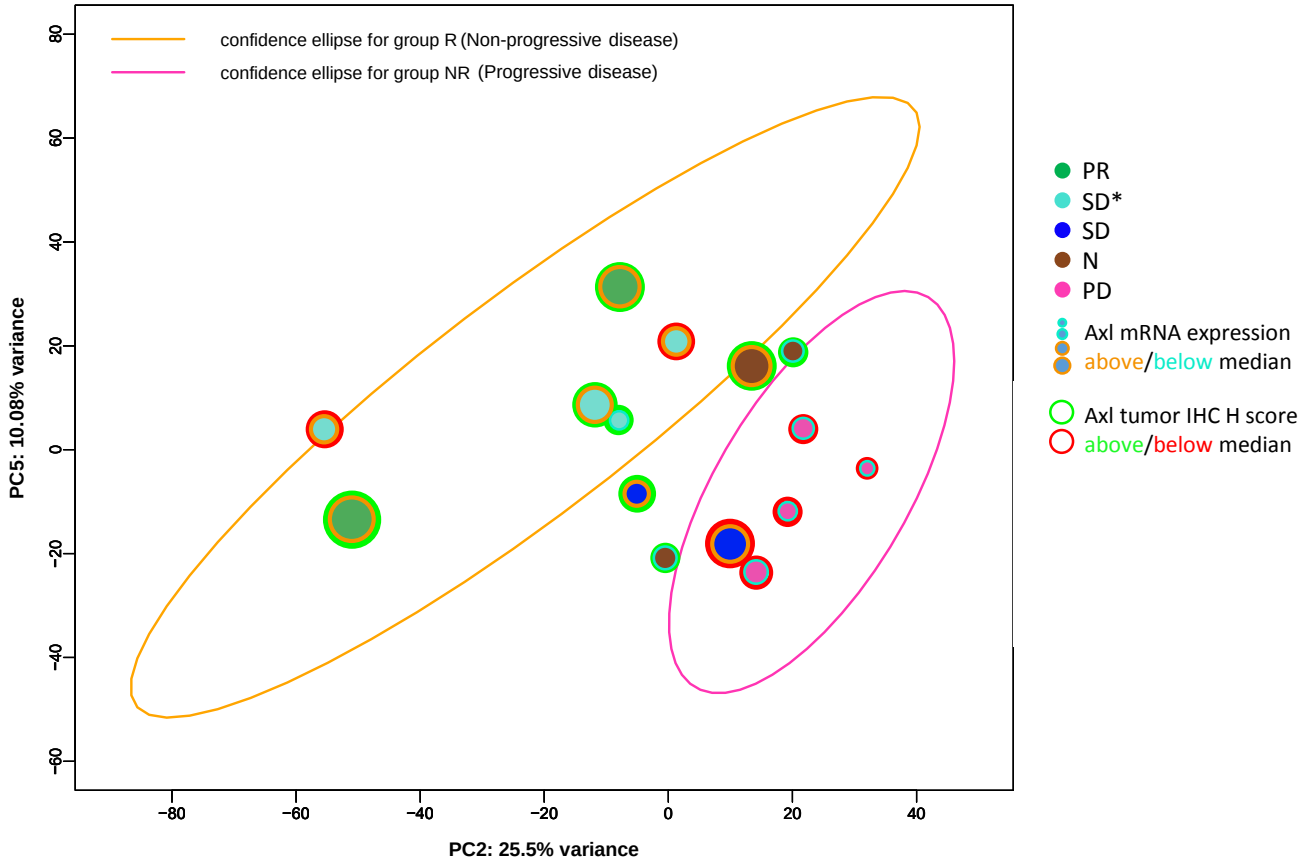
AST increased (1 x grade 3)

Pneumonia (1 x grade 4)

Safety Summary

- The safety profile of combination treatment is consistent with that of each individual drug
- Treatment related adverse events were generally mild and reversible
- Treatment related adverse events were considered to be less severe and better tolerated than for other TKIs or CPI combinations used in NSCLC

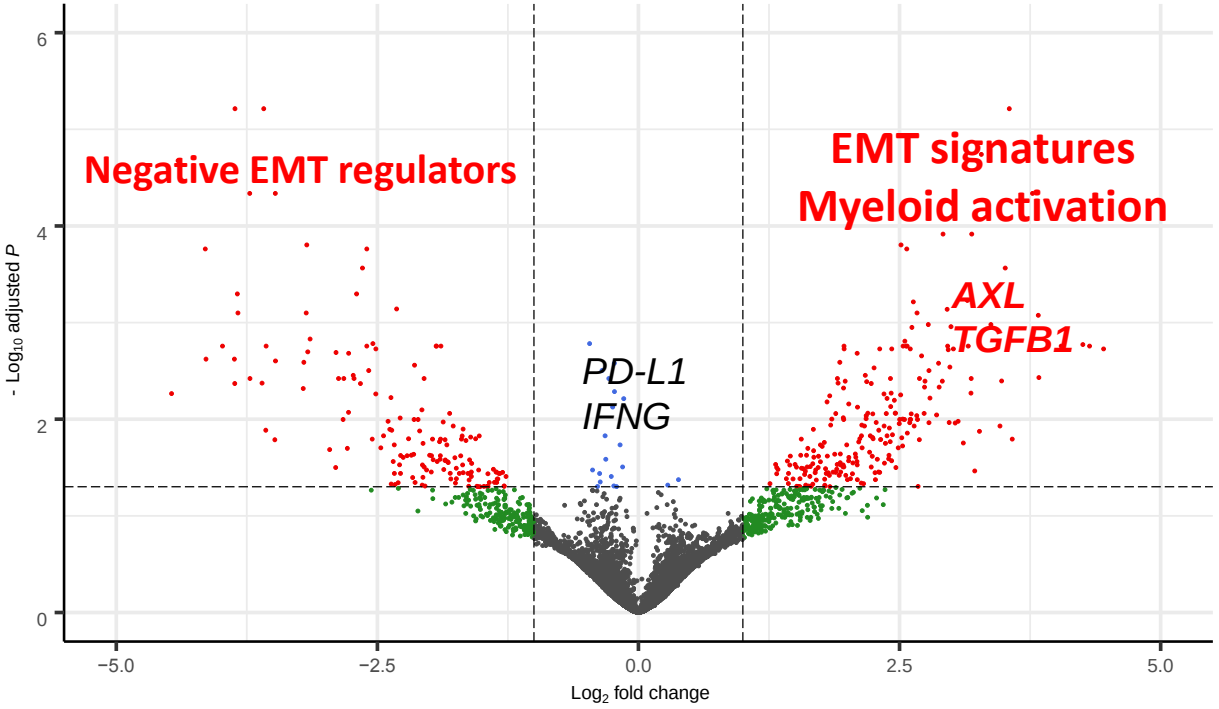
Clinical benefit from bemcentinib-pembrolizumab correlates with AXL expression



Unsupervised Principal Component Analysis

- Unbiased clustering of patients based on pretreatment biopsy RNAseq analysis separates patients into clinical benefit and progressive disease groups
- Patient benefit correlates with total AXL expression in tumors
- IHC-based tumor cell H-scoring does not capture overall patient benefit from combination therapy

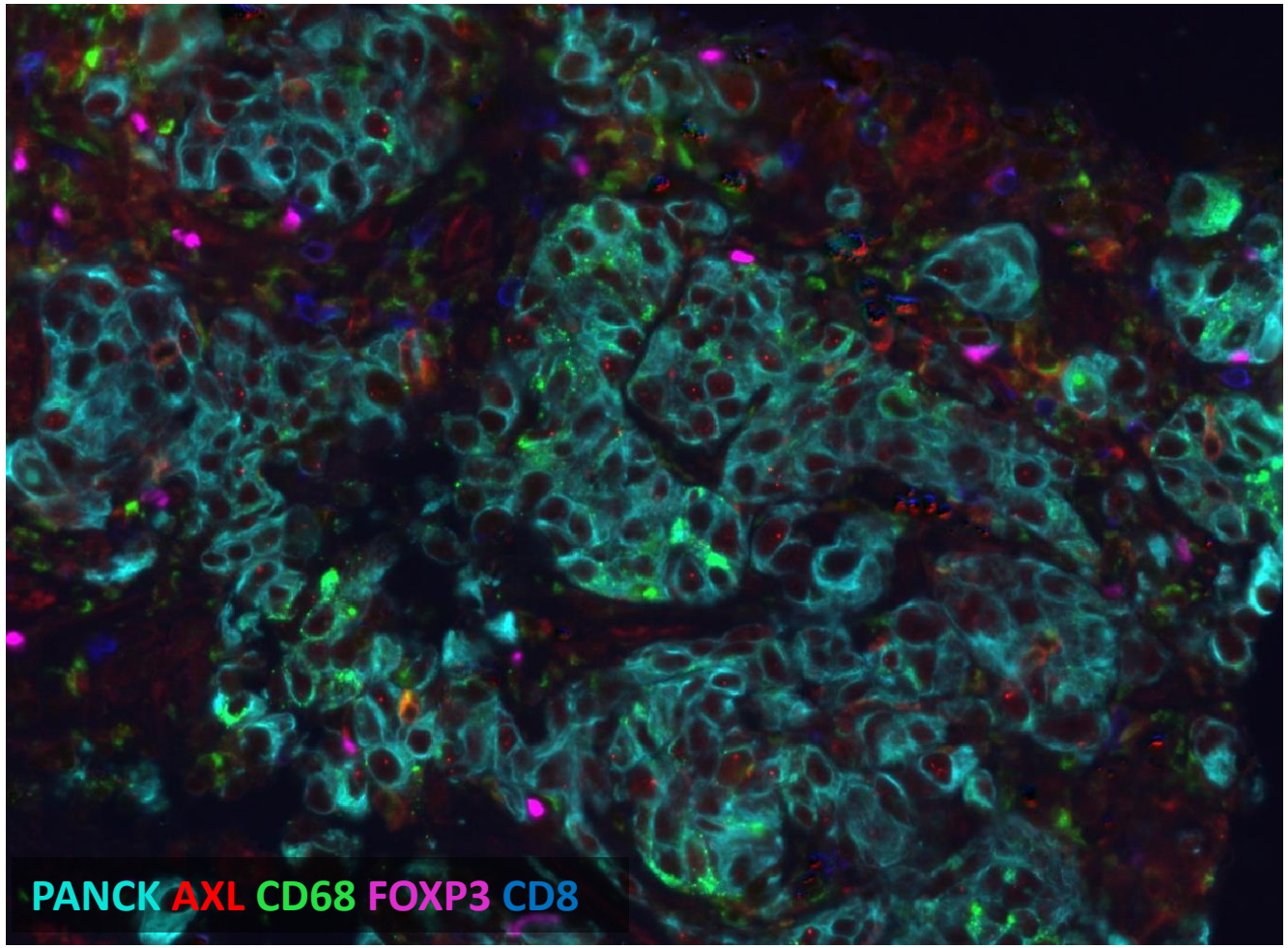
Novel gene signature predicts patients that benefit from bemcentinib-pembrolizumab combination therapy

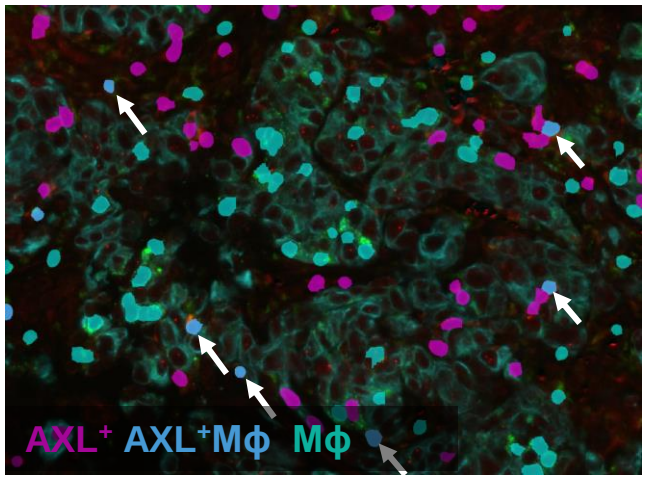


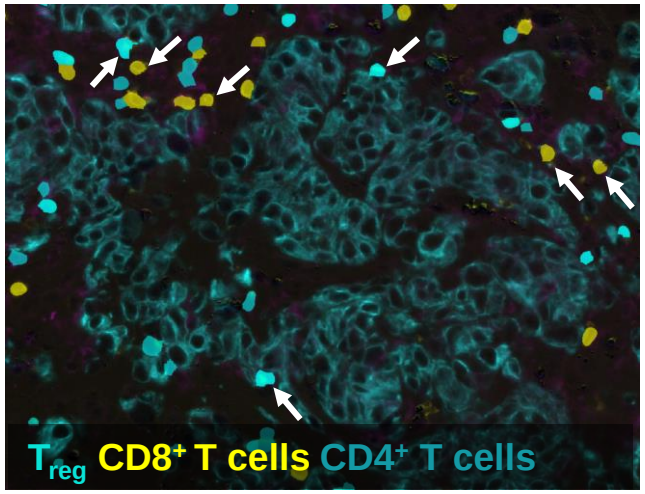
Volcano Plot: Differential gene expression analysis of patients showing most benefit (n=3) vs patients with PD (n=3)

- Responding patient gene expression matches signatures that predict poor outcome, lack of response to pembrolizumab, and are enriched for EMT and myeloid activation
- PD-L1 and IFNγ expression do not predict response
- AXL expression in tumor and immune cells (composite score) is associated with response to combination treatment

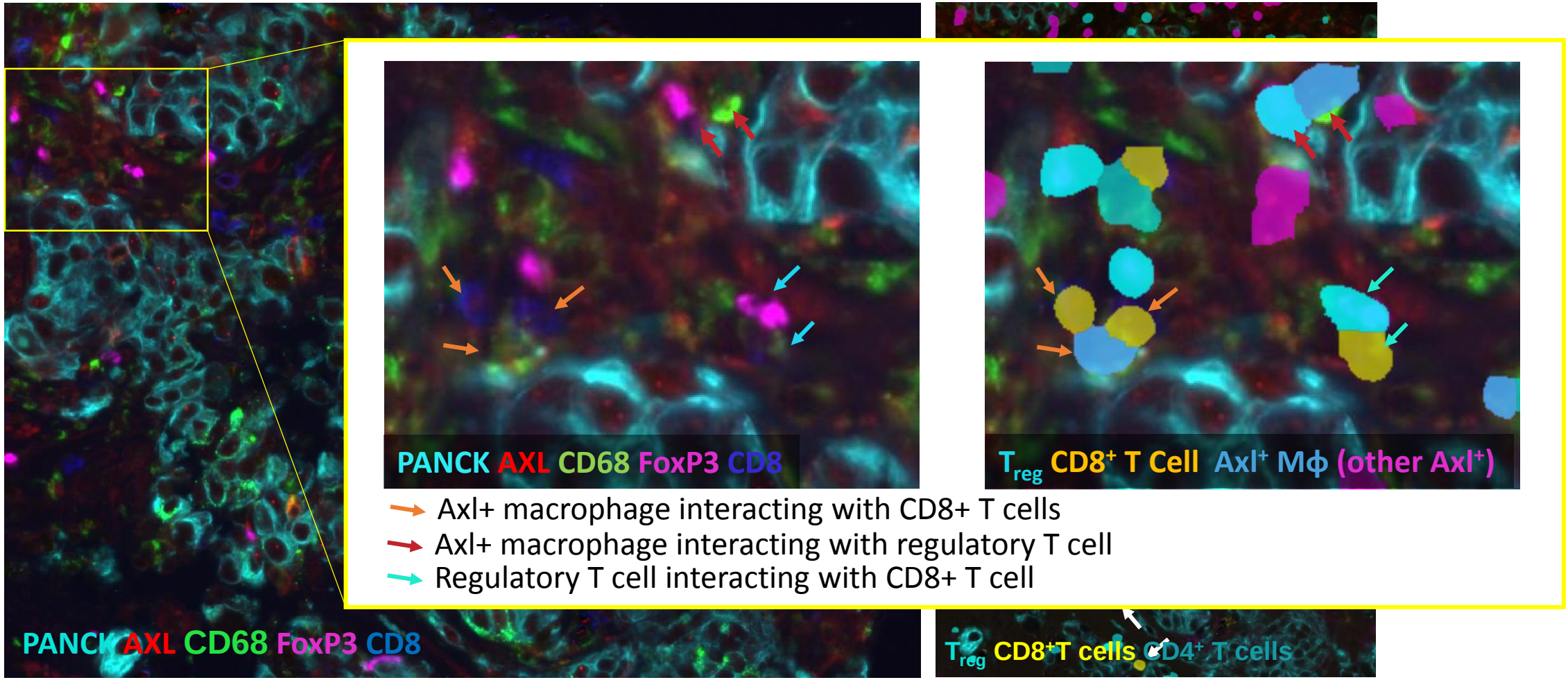
Tumor infiltrating AXL+ macrophages interact with CD8+ T cells and T_{regs} in pre-treatment biopsy from responding patient







Tumor infiltrating AXL+ macrophages interact with CD8+ T cells and T_{regs} in pre-treatment biopsy from responding patient



Conclusions

- Primary endpoint of ORR in cohort A met in PD-L1 low/negative NSCLC patients
- mPFS of 8.4mo in composite AXL positive patients (secondary endpoint)
- OS for Stage 2 patients is still maturing
- The combination treatment of bemcentinib and pembrolizumab is well-tolerated
- Patients benefiting from the combination show pretreatment AXL, EMT and myeloid gene expression.
- Tumor infiltrating AXL+ M2 macrophages observed to interact with Tregs and CD8+ T cells in responding patient pretreatment biopsy
- Conditioning the tumor microenvironment with bemcentinib in AXL positive patients optimizes pembrolizumab response in previously treated patients

Acknowledgements

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