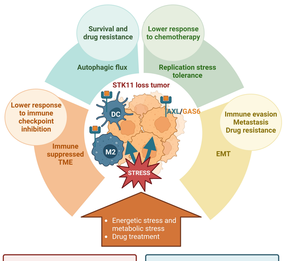
Bemcentinib + Pembrolizumab show promising efficacy in metastatic NSCLC patients harboring mutations associated with poor prognosis: exploratory sub-analysis from the BGBC008 trial

Gro Gausdal[1], David Micklem[1], Magnus Blø[1], Austin Rayford[1,2], Michael Chisamore[3], Claudia Gorcea-Carson[4], Cristina Oliva[4], Nigel McCracken[4]

[1]BerGenBio ASA, Bergen, Norway; [2]Department of Biomedicine, University of Bergen, Norway; [3]Merck & Co., Inc., Rahway, NJ, US; [4]BerGenBio Ltd, Oxford, UK

Introduction

- Non-small cell lung cancer (NSCLC) is a heterogeneous disease with genetic mutations impacting treatment outcomes. Mutations in LKB1/STK11, KEAP1, SMARCA4, and KRAS are associated with unfavorable responses to treatment[1-3,14,29]. These mutations influence tumor survival, stress tolerance, and the tumor microenvironment (TME), resulting in reduced efficacy and immune suppression[6-8,15]. Loss of STK11 activity (STK11^{Loss}) can be caused by direct mutation or by other mechanisms and can be detected using a gene-signature[5]. This gene signature is strongly associated with KEAP1 mutations[24].
- AXL, a receptor tyrosine kinase, serves as a biomarker for poor prognosis in NSCLC[33]. Activated in response to cellular stress, AXL promotes drug resistance, metastasis, and an immune-suppressive TME[16-18,22]. Targeting AXL with the selective oral inhibitor bemcentinib (BEM) has shown promise when combined with immune-checkpoint inhibition (ICI) in pre-clinical NSCLC models harboring mutations in STK11, KEAP1, SMARCA4 and KRAS[22].



STK11 inactivation characterized by:
- Immunosuppressive TME with ⇩ CD8+ T cells and ⇧ neutrophil infiltration[14,15]
- Loss of PDL1 expression[14]
- Aberrant metabolism[9]
- ⇧ oxidative stress and ROS[12]
- ⇩ autophagic flux[8]
- ⇧ replication stress[10,11]
- ⇧ EMT and metastasis[13]

AXL expression/activation characterized by:
- Immunosuppressive TME[17,23]
- Drug resistance[16]
- EMT and metastasis[17]
- Immune evasion[6]
- Suppression of apoptosis[18]
- ⇧ autophagic flux[18]
- Replication stress tolerance[19,21]
- Oxidative stress tolerance[18]

Abbreviations: EMT=Epithelial-mesenchymal transition; ROS=Reactive oxygen species; DC=Dendritic cell; TME=Tumor microenvironment

- BGBC008 phase 2 study investigated BEM+ pembrolizumab (PEM) as a second-line therapy for NSCLC patients after platinum-based chemotherapy and/or ICI, reporting favorable tolerability and efficacy[4].
- Top-line mOS/mPFS 13/6.2 months, independent of PD-L1 status[4].

Here we present exploratory mutational sub-analyses, focusing on patients with mutations and gene signatures (STK11 loss[5]) associated with poor response.

BGBC008 Study (NCT03184571)

Phase 2 study

Bemcentinib 400mg loading dose, 200mg QD + Pembrolizumab (200mg fixed dose every 3 weeks for up to 2 years)

2L+ advanced non-squamous NSCLC

90 efficacy evaluable patients, 56 with whole exome sequencing

Cohort A (n=44)
Prior 1L platinum chemotherapy treatment

Cohort B (n=27)
Prior 1L anti-PD-1/L1 treatment
- Disease control on 1L for ≥12 weeks before progression

Cohort C (n=19)
Prior 1L anti-PD-1/L1 + platinum-chemotherapy treatment
- Disease control on 1L for ≥12 weeks before progression

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

Methods

Patients provided their informed consent

IRB/IEC approval obtained for each study center

- Tumor material obtained from FFPE biopsy samples taken pre-treatment
- PD-L1 expression assessed using immunohistochemistry (IHC, 22C3 assay)

  PD-L1 negativity defined as IHC tumor proportion score (TPS) <1
- AXL expression assessed by IHC (Roche/Ventana assay)

  Tumor scored using H-score =
  1 * % cells with low expression +
  2 * % with moderate expression +
  3 * % with high expression

  Immune cells scored as percent AXL^{+ve} immune cells/tumor area

  AXL positive defined as H-score >5 and/or immune score ≥ 1%
- Mutations analyzed through whole exome sequencing (WES) of biopsies
- STK11^{LOSS} analyzed via RNA sequencing of biopsies
- Kaplan-Meier analysis and Cox Proportional Hazard ratios were calculated in R using the Survival package[28]

Comparator Study for expected effects of STK11/KEAP1/KRAS/SMARCA4:

MSK-MIND Dataset available from cBioPortal[25-27]

Anti-PD-(L)1 therapeutics alone or in combination with anti-CTLA-4 in mixed 1L-7L

Subset to PD-(L)1 alone, 2L+ adenocarcinoma with time on treatment >1d)

Results

Expected result based on published data | **Results from BGBC008**

Effect of STK11/KEAP1 mutations on 2L treatment outcomes

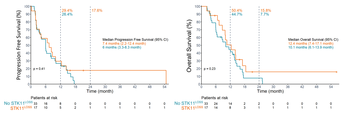
STK11 and KEAP1 mutations are associated with reduced survival compared to wild-type patients in 1L and 2L+

Gene	Mutation frequency n/N (%)	PD-L1 status mutated vs wt	(MSK-MIND) 2L+ PD-(L)1 inhibitors mutated vs wild-type	
		% pts TPS<1	OS	PFS
KEAP1	19/94 (20%)	89 vs 63	4.3 vs 17.2 [HR 3, p<0.001]	1.8 vs 4.3 [HR 1.8, p=0.03]
STK11	30/93 (32%)	87 vs 60	5.2 vs 19.4 [HR 3, p<0.001]	2 vs 4.6 [HR 1.8, p=0.02]

STK11 and KEAP1 mutations are prognostic and associated with poor survival outcomes across multiple therapeutic classes[29]

BEM + PEM in 2L+ NSCLC has similar activity when STK11/KEAP1 mutations are present and absent

Gene	Mutation frequency n/N (%)	AXL status mutated vs wt	PD-L1 status mutated vs wt	(BGBC008) 2L+ BEM + PEM mutated vs wild-type	
		% +ve	% pts TPS<1	OS	PFS
KEAP1	10/56 (18%)	89 vs 88	56 vs 36	11.5 vs 12.4 [HR 1.0, p=0.96]	4.8 vs 6.0 [HR 1.2, p=0.68]
STK11	5/56 (9%)	100 vs 87	80 vs 35	9.9 vs 13.0 [HR 1.4, p=0.43]	8.7 vs 6.0 [HR 1.2, p=0.70]
STK11^{LOSS}	17/50 (34%)	87 vs 93	56 vs 29	12.4 vs 10.1 [HR 0.7, p=0.23]	7.4 vs 6.0 [HR 0.8, p=0.41]



Effect of KRAS mutations on 2L treatment outcomes

Patients with KRASm alone respond well to checkpoint inhibitors

Gene	Mutation frequency n/N (%)	PD-L1 status mutated vs wt	(MSK-MIND) 2L+ PD-(L)1 inhibitors mutated vs wildtype	
		% pts TPS<1	OS	PFS
KRAS	48/97 (49%)	62 vs 71	16.6 vs 11.3 [HR 0.9, p=0.62]	4.7 vs 2.9 [HR 0.9, p=0.57]

STK11 and KRAS co-mutations shorten survival compared with STK11m and KRAS^{wt} with current treatments[3,30-32]

KRASm alone has no impact on survival, but significantly improves PFS in patients treated with BEM + PEM

Gene	Mutation frequency n/N (%)	AXL status mutated vs wt	PD-L1 status mutated vs wt	(BGBC008) 2L+ BEM + PEM mutated vs wild-type	
		% +ve	% pts TPS<1	OS	PFS
KRAS	21/56 (38%)	89 vs 88	39 vs 40	14.1 vs 10.0 [HR 0.8, p=0.50]	9.8 vs 3.8 [HR 0.5, p=0.01]

STK11^{Loss} in combination with KRASm has better survival than STK11^{Loss} in combination with KRAS^{wt} in patients treated with BEM + PEM

Effect of SMARCA4 mutations on 2L treatment outcomes

Although SMARCA4m patients have worse survival with 1L chemo-immunotherapy[2], they do not appear to with 2L+ immunotherapy

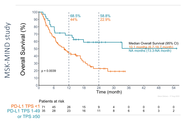
Gene	Mutation frequency n/N (%)	PD-L1 status mutated vs wt	(MSK-MIND) 2L+ PD-(L)1 inhibitors mutated vs wildtype	
		% pts TPS<1	OS	PFS
SMARCA4	21/95 (22%)	76 vs 65	9.1 vs 14.8 [HR 1.3, p=0.45]	4.1 vs 2.8 [HR 1.0, p=0.91]

SMARCA4m does not appear to negatively impact survival on 2L+ treatment with BEM + PEM

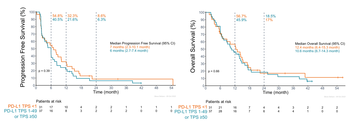
Gene	Mutation frequency n/N (%)	AXL status mutated vs wt	PD-L1 status mutated vs wt	(BGBC008) 2L+ BEM + PEM mutated vs wild-type	
		% +ve	% pts TPS<1	OS	PFS
SMARCA4	9/56 (16%)	100 vs 87	33 vs 41	14.1 vs 12.1 [HR 1.0, p=0.96]	7.4 vs 6.0 [HR 1.3, p=0.50]

2L treatment outcomes in PD-L1 negative patients

Lack of PD-L1 expression widely associated with reduced survival in 2L+



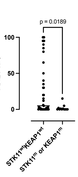
BEM + PEM treatment is equally effective in PD-L1-negative population



	(MSK-MIND) 2L+ PD-(L)1 inhibitors mutated pts. vs wt pts. median PD-L1 TPS score [Interquartile range]	
STK11	0% [0-0]	0% [0-25]
KEAP1	0% [0-0]	0% [0-15]
KEAP1 or STK11	0% [0-4]	5% [0-70]

PD-L1 TPS <1% are significantly enriched in the KEAP1 and STK11 mutant populations (Fisher's exact test p=0.0075) (MSK-MIND)

	(BGBC008) 2L+ BEM + PEM mutated pts. vs wt pts. median PD-L1 TPS score [Interquartile range]	
STK11	0% [0-7.5]	3% [0-40]
KEAP1	0% [0-1.5]	5% [0-65]
KEAP1 or STK11	0% [0-1.75]	5% [0-58]



STK11m or KEAP1m have significantly lower PD-L1 TPS scores in the BGBC008 trial

References

1. Garassino MC., JTO Clin Res Rep, 2022, 4(1):100431.
2. Alessi JV., J Thorac Oncol, 2023, 18(6):731-743.
3. Ricciuti B., J Thorac Oncol, 2022, 17(3):399-410.
4. Felip E., Annals Oncol, 2023, poster:5343.
5. Kaufman JM., J Thorac Oncol, 2014, 9(6):794-804.
6. Watterson A., Cell Commun Signal, 2023, 21(1):45.
7. Pons-Tostivint E., Cells, 2021, 10(11):3129.
8. Tian Y., Cancer Lett, 2023, 554:216022.
9. Momcilovic M., Br J Cancer, 2015, 113(4):574-84.
10. Takahashi N., Cancer Res Commun, 2022, 2(6):503–517.
11. Wang Y., Oncotarget, 2016, 7(45):73389–73401.
12. Bonanno L., Int J Mol Sci., 2019, 20(8):1874.
13. Tzavlaki K., J Cell Physiol., 2023, 238(4):790-812.
14. Skoulidis F., Cancer Discov., 2015, 5:860–77.
15. Koyama S., Cancer Res., 2016, 76(5):999–1008.
16. Wu F., Int. J. Clin. Exp. Pathol., 2014, 7:6653–6661.
17. Byers LA., Clin Cancer Res, 2013, 19(1):279-90.
18. Liang Z., Apoptosis, 2023, 28(3-4):485-497.
19. Lotsberg ML., J Thorac Oncol, 2020, 15(6):973-999.
20. Balaji K., Mol Cancer Res, 2017, 15(1):45-58.
21. Ramkumar K., Mol Cancer Res., 2021, 19(3):485-497.
22. Li H., Cell Rep Med., 2022, 3(3):100554.
23. Ludwig KF., Cancer Res., 2018, 78(1):246-255.
24. Blø M., Cancer Res, 2023, 83 7_Supplement: 3245.
25. Vanguri RS., Nat Cancer, 2022, 3(10),1151-1164.
26. Cerami E., Cancer Discov, 2012 2(5):401-404.
27. Gao J., Sci Signal, 2013, 6(269):pl1.
28. Therneau T., https://CRAN.R-project.org/package=survival, 2023.
29. Papillon-Cavanagh S., ESMO Open, 2020, 5:e000706.
30. Skoulidis F., Cancer Discov, 2018, 8, 822-835.
31. Manolakos P., J Pers Med, 2023, 13(6):1010.
32. Arbour KC., Clin Cancer Res, 2018, 24(2):334-340.
33. Ishikawa M., Ann Surg Oncol, 2013, 20(Suppl 3):S467–S476.

Acknowledgements

Thank you to all the patients and their families, investigators and study coordinators who participated in and supported this study. The study was performed in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Conclusions

Mutations in STK11 and KEAP1 have previously been associated with reduced survival irrespective of treatment regimen or line of therapy[29]

In 2L, BEM+PEM appears to reduce/eliminate the liability of STK11 and/or KEAP1 mutations, demonstrating approximately equal survival benefit across mutational classes

Lack of PD-L1 expression has previously been associated with poor survival

In 2L, BEM+PEM appears to reduce/eliminate the liability of lack of PD-L1 expression, demonstrating approximately equal survival benefit in PD-L1^{neg} (TPS <1%) vs PD-L1^{pos} (TPS ≥1%)

Co-mutations in STK11 and KRAS have previously been associated with poor survival[2]

In 2L, BEM+PEM enhances the survival of patients with STK11^{Loss} and KRAS mutation compared with STK11^{Loss} without KRAS mutation.

Despite evidence that SMARCA4 mutations result in poorer outcomes in 1L[2], data presented here (BGBC008, MSK-MIND) indicate that SMARCA4 may not be a negative prognostic factor in 2L+

Although this is a small dataset, the promising results in the context of hard-to-treat mutations warrant further investigation.

Contact

BerGenBio ASA
Møllendalsbakken 9,
5009 Bergen, Norway

David Micklem, PhD
Director of Biomarkers and Research

David.Micklem@bergenbio.com
+47 559 61 159
www.bergenbio.com