1266P: Update on the randomised Phase Ib/II study of the selective small molecule AXL inhibitor bemcentinib (BGB324) in combination with either dabrafenib/trametinib or pembrolizumab in patients with metastatic melanoma

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Haukeland University Hospital

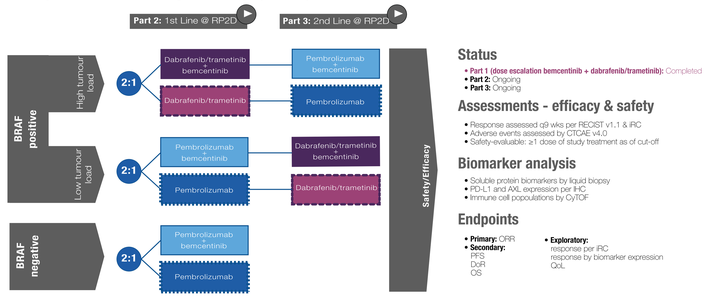
Centre for Cancer Biomarkers
Norwegian Centre of Excellence

In collaboration with: BerGenBio

Background & objective

NCT02872259: Ph I/II randomised trial of selective AXL inhibitor bemcentinib in metastitic melanoma patients

Three part randomised design enrolling up to 92 patients



Status

- **Part 1 (dose escalation bemcentinib + dabrafenib/trametinib):** Completed
- **Part 2:** Ongoing
- **Part 3:** Ongoing

Assessments - efficacy & safety

- Response assessed q9 wks per RECIST v1.1 & iRC
- Adverse events assessed by CTCAE v4.0
- Safety-evaluable: ≥1 dose of study treatment as of cut-off

Biomarker analysis

- Soluble protein biomarkers by liquid biopsy
- PD-L1 and AXL expression per IHC
- Immune cell populations by CyTOF

Endpoints

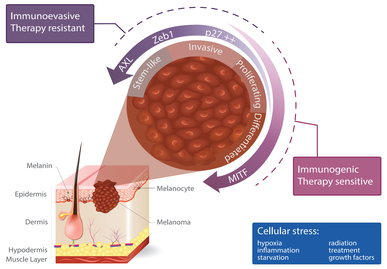
- **Primary:** ORR
- **Secondary:** PFS, DoR, OS
- **Exploratory:** response per iRC, response by biomarker expression, QoL

Key inclusion and exclusion criteria

- Histologically confirmed advanced cutaneous non-resectable (Stage IIIc) or metastatic (Stage IV) melanoma
- Measurable disease as defined by RECIST 1.1 & documented progression of ≥1 measurable lesion
- Availability of fresh or archival tumour tissue sample suitable for evaluation of predictive biomarkers of response
- ECOG score 0 to 2 at screening
- No prior treatment for Stage IIIb or Stage IIIc melanoma
- No history of or current active autoimmune diseases
- No symptomatic central nervous system metastatic lesions
- No recent or ongoing systemic treatment with immunosuppressive or immunomodulating agents

Study rationale

The drug resistant low MITF/ high Axl melanoma phenotype is associated with an immune suppressive microenvironment.

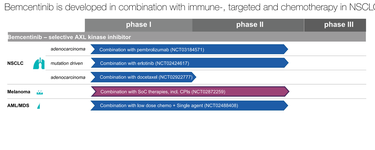


Upregulation of the Axl kinase has been associated with reduced response to anti-PD-1 therapy. The drug resistant low MITF/ high Axl melanoma phenotype has been associated with an immune suppressive micro-environment. Axl is a key negative feedback regulator of the innate immune response and attenuates macrophage, dendritic and natural killer (NK) cell activity. Hence, AXL signaling contributes to both tumor intrinsic and microenvironmental immune suppression mechanisms.

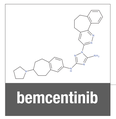
Axl dependent cell plasticity signaling pathways confer resistance to inhibitors of BRAF/MEK. Melanomas display either a high E-cadherin/high MITF-M expression on the one hand, or high N-cadherin/high Axl expression on the other. The low MITF/high AXL phenotype is linked to drug-resistance and common among mutant BRAF and NRAS melanoma cell lines. Interestingly, Axl-mediated resistance to BRAF and MEK targeting agents could be predicted by soluble Axl receptor in patient blood samples.

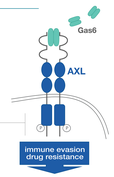
Bemcentinib (BGB324): selective, oral small molecule inhibitor of AXL in phase II clinical testing

Bemcentinib is developed in combination with immune-, targeted and chemotherapy in NSCLC, AML/MDS and melanoma



Selectivity Profile		
Kinase	Kinome Scan (Kd)	
	nM	Fold
Axl	0.4	1
Mer	100	250
Tyro	>1000	>1000





Dose escalation completed, preliminary results for patients receiving first line treatment

Baseline demographics, n=27

Age, median (range)	66 (34 - 79)
LDH (U/L), median (range)	235 (67 - 3523)
≥ ULN	13 (48%)
< ULN	11 (41%)
Unknown	3 (11%)
Gender, n (%)	
female	12 (44%)
male	15 (56%)
Mutations, n (%)	
BRAF	16 (59%)

Treatment related adverse events

Preferred term, n (%)	Grade 2	Grade 3	Grade 4
Pyrexia	2 (8)		
Fatigue	1 (4)		
Diarrhoea	3 (12)		
Rash	3 (12)	3 (12)	
Increased liver enzymes	1 (4)	3 (12)	
Increased creatinine	1 (4)		
Nausea	1 (4)		
Orchitis	1 (4)		
Necrotising myopathy			1 (4)

Conclusions

- **Part 1 of the study (dose escalation of bemcentinib + dabrafenib / trametinib) has been successfully completed.**
- **Significant positive response was observed in the majority of patients.**
- **Blood based biomarkers that predict response are under investigation.**
- **All treatment combinations were well tolerated.**
- **Safety, efficacy & biomarker performance will continue to be explored.**

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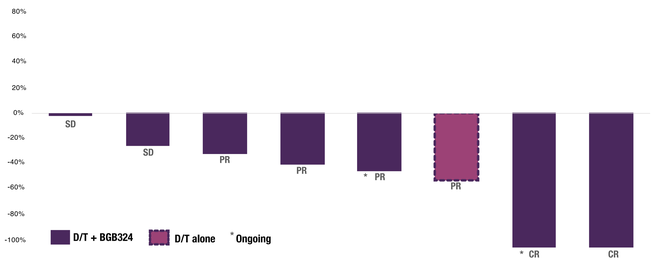
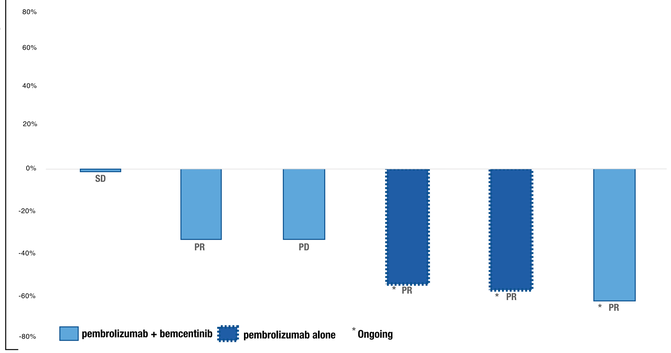
Preliminary efficacy assessment in RECIST evaluable patients to date - includes patients receiving first line treatment

Best % change from baseline in target lesions (high tumour load)



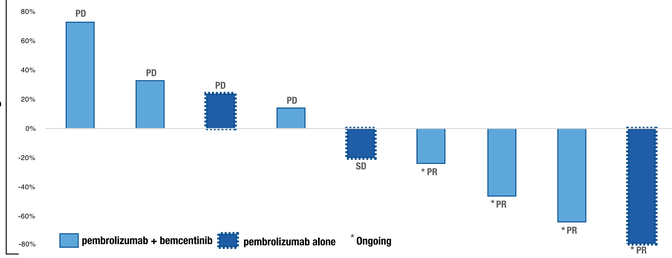
Best % change from baseline in target lesions (low tumour load)

BRAF positive

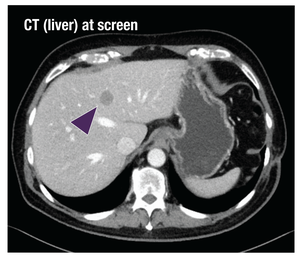


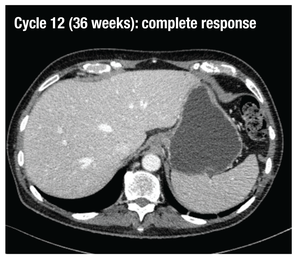
Best % change from baseline in target lesions (low tumour load)

BRAF negative



Example CR on bemcentinib + dabrafenib/trametinib

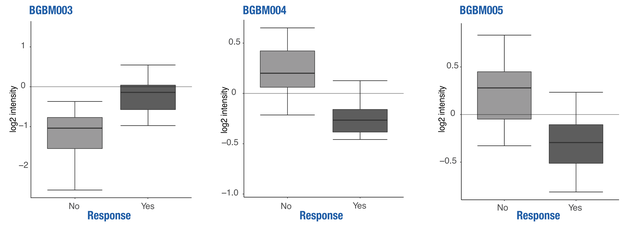




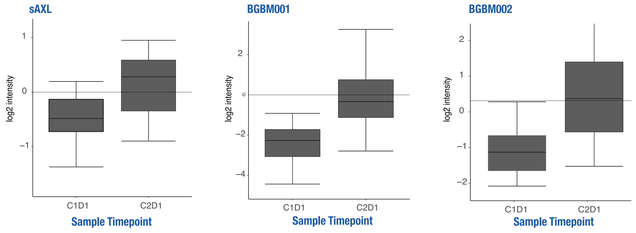
A 68-year-old male was randomised to receive 200 mg/daily bemcentinib + standard dabrafenib/trametinib.
PET in June 2017 showed distant metastases to liver and possibily lung. Screen LDH normal. Treatment with BRAF/MEK inhibition because of rapid progression from localised to stage IV disease. Treatment started 03 July 2017.
At cycle 12, he had a complete response in line with RECIST v1.1.

Biomarkers

Predictive biomarker candidates: Serum biomarkers BGBM003, BGBM004 & BGBM005 are predictive for patient benefit from combination treatment with bemcentinib



Pharmacodynamics: Serum AXL (sAXL), serum biomarkers BGBM001 & BGBM002 levels increase upon treatment with bemcentinib



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This poster was presented at the ESMO 2018 Congress, Munich, Germany (October 19 - 23, 2018)