Phase 1 dose escalation and expansion study of bemcentinib (BGB324), a first-in-class selective AXL inhibitor, with docetaxel in patients with previously treated advanced NSCLC

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INTRODUCTION

- AXL, a transmembrane receptor tyrosine kinase, is overexpressed and associated with poor prognosis and treatment resistance in non-small cell lung cancer (NSCLC)
- Bemcentinib (BGB324) is a selective orally bioavailable small molecule inhibitor of AXL, currently in phase 2 clinical development, that has demonstrated synergistic activity with docetaxel in *in vivo* models of NSCLC
- This phase I dose escalation trial assessed the safety, tolerability, and preliminary efficacy of bemcentinib in combination with docetaxel in previously treated advanced NSCLC, and is now closed to recruitment

STUDY DESIGN

Primary and Secondary Objectives:

- Determine safety and tolerability
- Determine preliminary efficacy
- Determine pharmacokinetic profile and pharmacodynamic effects of bemcentinib alone and in combination with docetaxel

Methods:

- A modified 3+3 design was followed to determine the optimal dose of bemcentinib and docetaxel (Table 1)
- Bemcentinib monotherapy was administered for one week prior to docetaxel initiation to assess pharmacodynamic effects alone and in combination
- Dose-limiting toxicities (DLTs) were assessed during the first cycle of treatment (7-day lead-in plus 21 days of combination therapy)
- Prophylactic G-CSF support was added for all patients starting cohort 2

Table 1: Bemcentinib and docetaxel dose cohorts

	Bemcentinib dose (mg)			Docetaxel dose (mg/m^2 IV on Day 1 of each cycle)
	Cycle 1 Day -7, -6, -5	Cycle 1 Day -4 to 21	Cycles ≥ 2 All days	
Cohort -1	200 daily	100 daily	100 daily	60
Cohort 1	200 daily	100 daily	100 daily	75
Cohort 2	400 daily	200 daily	200 daily	75
Cohort 2A	400 daily	200 daily	200 daily	60

Key Eligibility Criteria:

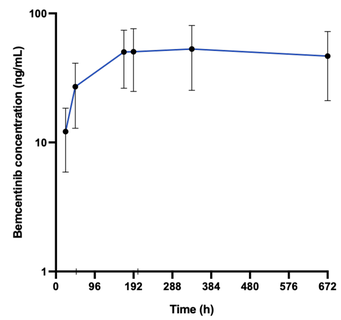
- Histopathologically or cytologically documented stage IV NSCLC
- Up to three previous lines of therapy for advanced NSCLC, of which one must have been a platinum-doublet therapy and no more than two were cytotoxic chemotherapy
- Measurable or evaluable disease per RECIST v1.1
- ECOG performance status 0 or 1
- Previously treated brain metastases (surgery and/or radiation therapy) were eligible, provided that patients were asymptomatic and not requiring corticosteroids

RESULTS

Table 2: Baseline characteristics (N=21)

Characteristic	Number (%) or median (range)
Age (year)	62 (39-84)
Sex	
Male	14 (67)
Female	7 (33)
Race	
White	19 (90)
Asian	2 (10)
Histology	
Adenocarcinoma	16 (76)
Squamous	4 (19)
Other	1 (5)
ECOG performance status score	
0	1 (5)
1	20 (95)
Lines of prior systemic therapy	2 (1-3)

Figure 1: Pharmacokinetics of Bemcentinib



Patients received a 200 mg loading dose of bemcentinib for 3 days followed by a 100 mg maintenance dose. The geometric mean plasma trough concentration ranged from 46.72 to 52.97 ng/mL between C1D1 to C4D1. The mean AUC over 24 hours at steady state was calculated to be 2824 ± 420 ng.h/mL, which is similar to monotherapy values for bemcentinib (3100 ± 1370 ng.h/mL). Docetaxel values (data not shown) were similar to historical monotherapy docetaxel concentrations.

Table 3: AXL expression by immunohistochemistry (IHC) in patient tumor samples

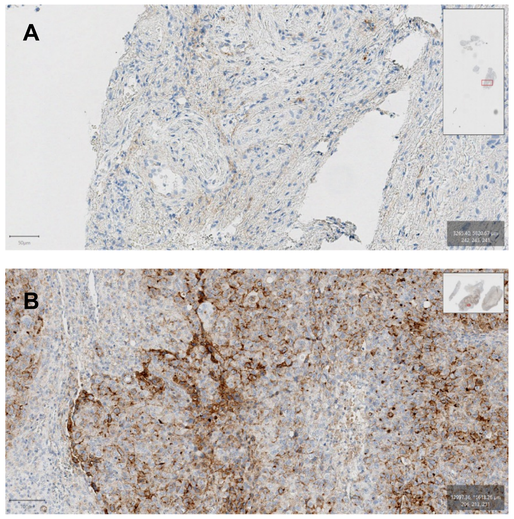
Patient	H Score tumor cell		Peritumoral stromal	Stromal intensity
	Membranous	Cytoplasmic		
A	0	0	Yes	2+
B	0	20	Yes	2+
C	0	0	Yes	2+
D	0	0	Yes	2+
E	0	0	Yes	1+
F	0	0	Yes	1+
G	0	0	Yes	1+
H	0	0	Yes	2+
I	40	55	Yes	2+
J	15	75	Yes	2+
K	0	0	No	0

Table 4: Treatment-related adverse effects (>10% of patients)

Adverse event	All grades, n (%)	Grades ≥ 3, n (%)
Neutropenia	18 (86)	16 (76)
Diarrhea	12 (57)	0 (0)
Fatigue	11 (52)	1 (5)
Nausea	11 (52)	0 (0
Neuropathy	8 (38)	1 (5)
Alopecia	7 (33)	0 (0)
Edema	7 (33)	0 (0)
Myalgia	7 (33)	0 (0)
Neutropenic fever	N/A	7 (33)
Leukopenia	6 (29)	5 (24)
Dyspnea	5 (24)	0 (0)
Mucositis	5 (24)	0 (0)
Hyponatremia	4 (19)	1 (5)
Dysgeusia	4 (19)	0 (0)
LFT abnormalities	4 (19)	0 (0)
Vomiting	4 (19)	0 (0)
Abdominal discomfort	3 (14)	0 (0)
Arthralgias	3 (14)	0 (0)
Dyspepsia	3 (14)	0 (0)
Elevated creatinine	3 (14)	0 (0)
Fever	3 (14)	0 (0)
QTc Prolongation	3 (14)	1 (5)

Figure 2: AXL expression by IHC

Examples of negative AXL staining (2A) and positive AXL staining, H-score 55 (2B)



EFFICACY RESULTS

Figure 3: Best RECIST Response

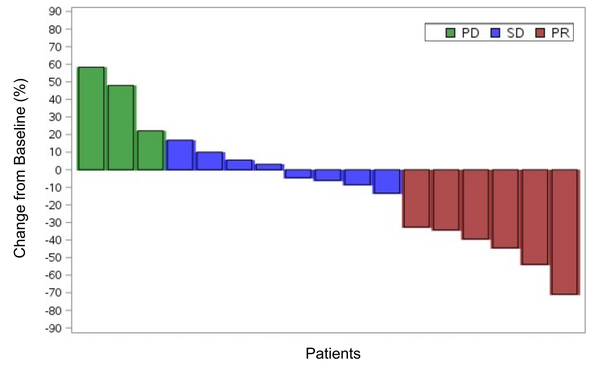
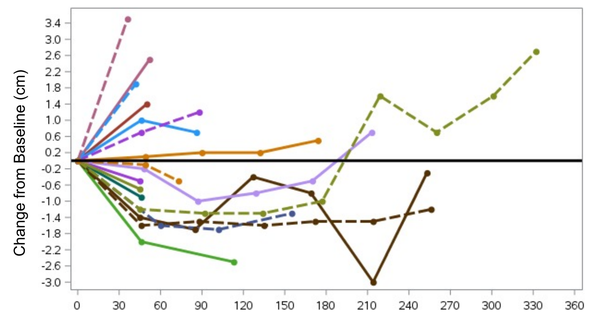


Figure 4: Tumor Response by Days



SUMMARY

- Maximum tolerated dose was docetaxel 60mg/m^2 plus bemcentinib 400mg loading dose followed by 200mg daily with prophylactic G-CSF support
- Most common treated-related adverse effects included neutropenia, diarrhea, fatigue, and nausea, and non-hematological grade ≥3 toxicities were rare
- PK parameters for bemcentinib and docetaxel when given in combination were similar to those determined for monotherapy, suggesting that the potential for PK drug-drug interaction in combination is low
- Among 17 evaluable patients, 6 (35%) patients had partial response and 8 (47%) patients had stable disease as the best radiographic response

CONCLUSIONS

- Bemcentinib in combination with docetaxel and prophylactic G-CSF support has a manageable safety profile and demonstrates evidence of anti-tumor activity in previously treated, advanced NSCLC
- Further studies to identify the patient population most likely to benefit from this regimen are warranted

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