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A Phase II Study of Selective AXL Inhibitor Bemcentinib and Pembrolizumab in Patients with NSCLC Refractory to Anti-PD(L)1

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Background: The RTK AXL is implicated in epithelial-to-mesenchymal transition, negative regulation of anti-tumour immunity and resistance to multiple therapies including immune checkpoint inhibitors. Bemcentinib (BGB324) is a first-in-class, oral, highly selective and potent AXL inhibitor which has been demonstrated to enhance anti-PD1 therapy. The combination of bemcentinib and pembrolizumab was well tolerated and showed promising efficacy in previously treated IO-naïve NSCLC patients (Cohort A, NCT03184571), particularly in those with AXL positive disease, including PD-L1 negative patients. The novel combination is now being assessed in patients refractory to anti-PD-(L)1 therapy, considering the emerging need in this population and AXL's role as a mediator of resistance. **Method:** This is an open-label, single-arm, 2-stage phase II study (Cohort B, NCT03184571) to evaluate the safety and efficacy of bemcentinib (200mg/d) in combination with pembrolizumab (200mg/q3wk) in patients post anti-PD-(L)1 therapy. The primary endpoint is overall response rate (ORR), and additional endpoints include efficacy by biomarker expression, duration of response (DoR), disease control rate (DCR), progression free survival (PFS), overall survival (OS), and safety. Clinical efficacy endpoints are based on tumour imaging evaluable by RECIST v1.1. Eligible patients received a maximum of 2 prior lines of therapy, with the most recent course having included a PD-(L)1 inhibitor. To be eligible, patients must have exhibited disease control (CR/PR/SD) for at least 6 months on prior PD-(L)1 inhibitor therapy with disease progression occurring within 12 weeks since last dose. Bemcentinib will be administered as a loading dose of 400mg on days 1, 2 and 3 followed by a dose of 200mg once daily. A fixed dose of 200 mg pembrolizumab will be given by intravenous infusion over 30 minutes every 3 weeks. Bemcentinib and pembrolizumab will be given until disease progression, unacceptable dose toxicity, or for a maximum of 35 cycles. Tumour specimens will be analysed for PD-L1 expression (22C3 pharmDx), AXL by IHC, and infiltrating immune cells. The pre-specified efficacy threshold for continuation into the second stage is 1 objective response among the first 13 patients, at which point up to a further 16 patients may be evaluated, for a total of 29 patients. **Result:** Section not applicable **Conclusion:** Section not applicable
Keywords: bemcentinib, AXL, Pembrolizumab

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An Explorative Analysis of Pemetrexed +/- Pembrolizumab Maintenance from KEYNOTE-189 Versus PARAMOUNT, PRONOUNCE, and JVBL

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Background: Recently, the phase 3 KEYNOTE-189 study demonstrated improved progression-free survival (PFS) and overall survival (OS) when pemetrexed/platinum doublet was combined with pembrolizumab as first-line treatment in patients with non-squamous NSCLC. The specific benefits of maintaining pemetrexed in combination with pembrolizumab after the triplet with platinum has not been previously assessed. **Method:** Using patient level data, we selected patients who had ≥5 cycles of pemetrexed (including the induction phase with platinum) from 3 randomized non-pembrolizumab clinical trials (PARAMOUNT, PRONOUNCE, and JVBL; N=486). As such, patients in the KEYNOTE-189 trial who had ≥5 cycles of pemetrexed in both arms (placebo arm; N=135, versus pembrolizumab arm; N=310) were analyzed. PFS and OS were evaluated by Kaplan-Meier estimator and Cox proportional hazard model; treatment emergent adverse events (TEAEs) were compared by descriptive statistics. **Result:** Baseline characteristics of the selected population with ≥5 cycles of pemetrexed were comparable between the pooled trials and KEYNOTE-189. Median PFS for patients with ≥5 cycles of pemetrexed was 5.6 months (95% CI: 4.6-5.8) from the pooled non-pembrolizumab trials and 6.6 months (95% CI: 5.4-7.1) in the placebo plus pemetrexed/platinum arm in KEYNOTE-189 (un-stratified HR: 1.29; 95% CI: 1.02-1.62). Median PFS in the selected population with ≥5 cycles of pemetrexed in KEYNOTE-189 was 9.3 months (95% CI: 9.0-11.1) in the pembrolizumab plus pemetrexed/platinum arm, and when compared with the placebo plus pemetrexed/platinum arm in KEYNOTE-189, resulted in an un-stratified HR of 0.53 (95% CI: 0.42-0.68). Incidence rates of TEAEs were similar in those 3 selected populations (Table 1).

Table 1. PFS and TEAE Grade 3-5 in patients with pemetrexed treatment ≥5 cycles: descriptive comparison between the pooled data (PARAMOUNT, PRONOUNCE, JVBL) and KEYNOTE-189 trial

	Pooled historical data Pemetrexed ≥5 cycles (N = 486)	KEYNOTE-189	
		Placebo Arm Pemetrexed ≥5 cycles (N = 135)	Pembrolizumab Arm Pemetrexed ≥5 cycles (N = 310)
Median PFS, months (95% CI)	5.6 (4.6-5.8)	6.6 (5.4-7.1)	9.3 (9.0-11.1)
TEAE Grade 3-5, n (%)	284 (58.4)	86 (63.7)	200 (64.5)

CI, confidence interval; PFS, progression-free survival; TEAE, treatment emergent adverse event

Conclusion: In a selected population with pemetrexed maintenance in KEYNOTE-189, the placebo arm showed numerically comparable efficacy with historical data on pemetrexed maintenance. Pemetrexed/platinum in combination with pembrolizumab proved consistent clinical benefit in the same population with ≥5 cycles of pemetrexed, compared to the placebo arm in KEYNOTE-189 and historical controls.
Keywords: NSCLC, Pembrolizumab, pemetrexed

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A Retrospective Study Evaluating Clinical Predictors of Duration of Response to Immune Checkpoint Inhibitors in Advanced NSCLC

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