THE RELATIONSHIP BETWEEN EGFR AND KRAS MUTATION STATUS AND OVERALL SURVIVAL (OS) IN THE NCIC CTG BR.26 RANDOMIZED TRIAL OF DACOMITINIB (D) VERSUS PLACEBO (P) IN PATIENTS WITH PREVIOUSLY TREATED NON SMALL CELL LUNG CANCER (NSCLC)


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Aim: Dacomitinib (D) is an irreversible, pan Her inhibitor with activity in NSCLC previously treated with an EGFR TKI.

Methods: BR26 was a randomized placebo controlled trial of D (45mg orally daily) versus P in NSCLC patients previously treated with chemotherapy and an EGFR TKI. The primary outcome was OS. Secondary outcomes included PFS and OS in patients with KRAS wild type (WT) and EGFR mutated (mut) tumors, response rate (RR), toxicity and quality of life.

Results: Patients were randomized 2:1 to D (n = 480), or P (n = 240). Baseline characteristics were well balanced. D improved PFS compared with P (2.7m v 1.4m, HR 0.66, 95%CI 0.55 – 0.79, p < 0.0001), but did not improve OS (6.8m v 6.3m, HR 1.0, 95%CI 0.83-1.21, p = 0.99). Tumor mutation data were available for KRAS in 418 patients and EGFR in 531. Similar proportions of patients allocated to D and P had mutations of KRAS (11.9% v 8.8%) or EGFR (23.8% v 28.3%). The effect of D on OS was similar in EGFR mut (7.2 v 7.5m, HR 0.98, 95%CI 0.67-1.44) and EGFR WT subgroups (6.9 v 5.6m, HR 0.93, 95%CI 0.71-1.21, interaction (int) p = 0.69). However, the effect of D on OS appeared to differ in KRAS WT compared to D (7.0 v 5.2m, HR 0.79, 95%CI 0.61-1.03) and KRAS mut subgroups (5.8 v 8.3m, HR 2.10, 95%CI 1.05-4.22, int p = 0.08). RR in KRAS WT was 9.1% v 8.0%, with no responses in KRAS mut. A higher RR was observed with D in EGFR mut (11.4% v 1.0%) than EGFR WT (4.3% v 0%). For PFS, there was a significant interaction between treatment and both EGFR status (HR 0.56 mut v 0.83 WT, int p = 0.049), and KRAS status (HR 1.87 mut v 0.58 WT, int p = 0.011). An exploratory analysis showed this difference was only partly explained by EGFR status (KRAS/EGFR WT HR 0.71 v KRAS WT/EGFR mut HR 0.54). The rate of systemic therapy after disease progression was similar (37% vs 41%).

Conclusions: The effect of D on OS did not differ according to EGFR status. However, there was a trend suggesting a qualitative interaction between D and KRAS status and OS. D was associated with shorter OS in patients with KRAS mut, but longer OS in patients with KRAS WT. These results require validation in future studies.

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