Aim: Subset analyses from 9 randomized trials report conflicting results concerning the ability of KRAS mutation (M+) status to predict benefit from E-TKIs. This pooled analysis of 4 trials of E-TKI v placebo was conducted to clarify the prognostic/predictive roles of KRAS M+ and to explore the importance of M+ subtype.

Methods: Data were pooled for patients with known KRAS status from 4 trials of E-TKI v placebo (NCIC CTG BR.21 & TOPICAL - erlotinib in advanced NSCLC; BR.26 - dacomitinib in advanced NSCLC; BR.19 - postoperative gefitinib). Exploratory analyses were performed to identify relationships between M status/subtype, overall (OS), disease-free & progression-free survival (DFS, PFS) with an adjusted Cox model.

Results: KRAS status was known in 1366 patients (787 E-TKI, 579 placebo); 275 (20%) had M+ (252 codon 12; 15 codon 13). In the placebo arm there was no OS difference for patients with KRAS M+ or wild-type (WT) tumors (HR 1.04, CI .82-1.33), nor between M+ codon 12 & 13. Patients with G12C/G12V M+ had significantly longer OS than those with G12D/G12S or G12A/G12R (med OS 9.2, 1.7, 3.9 m, respectively, p = .015). Patients with KRAS WT tumors receiving E-TKIs had significantly improved PFS and a trend for OS (PFS HR .73, CI .63-0.83, p = .001; OS HR .91, CI .79-1.04, p = .09) and higher ORR (9.1 v 1.3%, p = .02). Patients with KRAS M+ had no benefit (OS HR 1.13, CI .85-1.51; PFS (HR 1.02, CI .76-1.36). The interaction was significant for PFS (p = .04), but not OS (p = .17). There was significant OS benefit from E-TKIs in patients with advanced WT adenocarcinoma (HR 0.74, CI 0.6-0.93, p = .008), but not KRAS M+ (HR 1.14, CI 0.77-1.69, interaction p = .06). For G12C/G12V M+, treatment with E-TKIs potentially was harmful (OS HR 1.41, CI 0.97-2.05, p = .07) but not G12D/G12S (OS HR 0.49, CI 0.24-1.00, p = .05).

Conclusions: KRAS M+ is not homogenous in terms of prognosis or prediction of benefit from E-TKIs. G12C/G12V subtypes are associated with better prognosis but potentially worse outcome with E-TKIs. While G12D/G12S subtypes have poorer prognosis, patients with these mutations appear to benefit from E-TKIs. These observations require validation.

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