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Exploring outcomes of *RAS* mutant (*RAS* mut) advanced colorectal cancer (aCRC) treated with chemotherapy: Analysis from 2254 patients (pts) in randomised clinical trials (RCTs).

### **Introduction:**

*RAS* mut status predicts lack of benefit from anti-EGFR agents in aCRC, but its impact on prognosis and chemotherapy outcomes is less clear. Previously we have reported that the poor outcomes of *BRAF* mut cancer aCRC are due to accelerated decline following 1<sup>st</sup>-line progression, not chemoresistance. In the same dataset we perform a detailed analysis of outcomes of *RAS* mut pts throughout the aCRC treatment pathway to help guide clinical decision-making in this underserved population.

### **Methods:**

*RAS* was assessed in tumors of 2254 *BRAF* wild-type (wt) pts in 3 RCTs: COIN (n=1158), FOCUS (n=706, *KRAS* only) and PICCOLO (n=390). End-points were progression free survival (PFS), response rate (RR), and OS. Treatments received were 1<sup>st</sup> line OxFU (COIN), 1<sup>st</sup> line OxFU or IrFU (FOCUS) or 2<sup>nd</sup> line Irinotecan (Ir) (PICCOLO). Analyses were adjusted for known negative prognostic markers: poor performance status, primary tumour in-situ, right tumour location, peritoneal mets and high platelet count, and were performed using Cox proportional hazards models and logistic regression.

### **Results:**

1101 pts (48.8%) were *RAS* mut. *RAS* mut status conferred worse OS in both 1<sup>st</sup>-line studies (COIN adj HR=1.38, p<0.001; FOCUS adj HR=1.33, p<0.001), and at the point of starting 2<sup>nd</sup>-line treatment (adj HR=1.33, p=0.014).

Compared with wt, *RAS* mut pts treated with 1<sup>st</sup>-line combination chemotherapy had inferior treatment outcomes (RR 42.2% vs 51.7%; adj OR=0.69, p<0.001) and PFS (6.4 vs 8.0 mths, adj HR=1.24, p<0.001).

*RAS* mut pts were just as likely as wt to receive 2<sup>nd</sup>-line treatment after 1<sup>st</sup>-line progression in COIN (51.4% vs 51.7%) and were well represented in PICCOLO (53.6%). *RAS*-mut pts treated with 2<sup>nd</sup>-line Ir had inferior outcomes than wt (RR 7.7% vs 12.7%; PFS 3.1 vs 4.9 months) but neither were statistically significant (p=0.10 and p=0.42, respectively).

### **Conclusions:**

*RAS*-mut status is an independent poor prognostic marker in aCRC. This is partly driven by relative chemoresistance in both the 1<sup>st</sup> and 2<sup>nd</sup>-line settings, observed

following adjustment for known poor prognostic factors. New approaches in treating *RAS* mut aCRC are urgently required.