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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 1st-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 1st line OxFU (COIN), 1st line OxFU or IrFU (FOCUS) or 2nd 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 1st-line studies (COIN adj HR=1.38, p<0.001; FOCUS adj HR=1.33, p<0.001), and at the point of starting 2nd-line treatment (adj HR=1.33, p=0.014).

Compared with wt, *RAS* mut pts treated with 1st-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 2nd-line treatment after 1st-line progression in COIN (51.4% *vs* 51.7%) and were well represented in PICCOLO (53.6%). *RAS*-mut pts treated with 2nd-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 1st and 2nd-line settings, observed

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