Effect of KRAS codon 12 or 13 mutations on survival with trifluridine/tipiracil in pretreated metastatic colorectal cancer: a meta-analysis

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Background: KRAS gene mutations can predict prognosis and treatment response in patients with metastatic colorectal cancer (mCRC).

Methods: We undertook a meta-analysis of three randomized, placebo-controlled trials (RECORESE, TERRA and J003) to investigate the impact of KRAS mutations in codons 12 or 13 on overall survival (OS) and progression-free survival in patients receiving trifluridine/tipiracil (FTD/TPI) for refractory mCRC.

Results: A total of 1375 patients were included, of whom 478 had a KRAS codon 12 mutation and 130 had a KRAS codon 13 mutation. In univariate analyses, the absence of a KRAS codon 12 mutation was found to significantly increase the OS benefit of FTD/TPI relative to placebo compared with the presence of the mutation (hazard ratio (HR), 0.62 [95% confidence interval (CI): 0.53-0.72] versus 0.86 (0.70-1.05), respectively; interaction P = 0.2006). Multivariate analyses showed that taking confounding factors into account reduced the difference in treatment effect between the presence and the absence of KRAS codon 12 mutations, confirming that treatment benefit was maintained in patients with [HR, 0.73 (95% CI: 0.59-0.89)] and without [HR, 0.63 (95% CI: 0.54-0.74)] codon 12 mutations (interaction P = 0.2939). KRAS mutations in codon 13 did not reduce the OS benefit of FTD/TPI relative to placebo, and, furthermore, KRAS mutations at either codon 12 or codon 13 did not affect the progression-free survival benefit.

Conclusions: Treatment with FTD/TPI produced a survival benefit, relative to placebo, regardless of KRAS codon 12 or 13 mutation status in patients with previously treated mCRC.

Key words: metastatic colorectal cancer, trifluridine/tipiracil, KRAS, survival, meta-analysis

INTRODUCTION

In patients with metastatic colorectal cancer (mCRC), KRAS mutations are associated with several negative outcomes.1-3 Patients with colorectal cancer who have a mutant KRAS gene have a significantly higher incidence of lung, bone and brain metastases compared with patients who have wild-type KRAS.1 In addition, the presence of mutant KRAS in patients with mCRC predicts a lack of response to drugs targeting epidermal growth factor receptors (anti-EGFRs), but does not preclude benefit from oxaliplatin or irinotecan.2,4

Codons 12 and 13 in exon 2 are the most common sites of KRAS gene mutation in patients with colorectal cancer, being found in ~40% of patients with the disease.5 Patients with KRAS codon 12 mutations have been reported to have poor overall survival (OS).6,7 In contrast, the prognostic value of KRAS codon 13 mutations is controversial.8-10

Therapeutic options for patients with mCRC and KRAS codon 12 or 13 mutations are limited.2 Trifluridine/tipiracil (FTD/TPI) is approved for the treatment of patients with mCRC who have been previously treated with, or are not considered to be candidates for, fluoropyrimidines-, oxaliplatin- and irinotecan-based chemotherapies, anti-vascular endothelial growth factor therapy or anti-EGFR therapy.11-13

In the phase III RECORESE trial, which included patients with refractory mCRC (n = 800), median OS was significantly longer in patients randomized to FTD/TPI than to placebo (7.1 versus 5.3 months; hazard ratio (HR), 0.68 [95% confidence interval (CI): 0.58-0.81]; P < 0.001).14

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There was no significant difference in OS in the cohort of 407 patients (51%) with mutant KRAS [HR, 0.80 (95% CI: 0.63–1.02)], justifying further study in a larger patient population by including patients from other studies and increasing the study population to 708 patients with mutant KRAS colorectal cancer (478 with KRAS codon 12 mutations and 130 with KRAS codon 13 mutations). At present, however, there are insufficient data to guide the use of FTD/TPI in patients with previously treated mCRC in whom KRAS codon 12 or 13 mutation status is known.

Therefore, we undertook a meta-analysis to determine whether the presence of mutations at KRAS codon 12 or 13 impacts the efficacy of FTD/TPI, in terms of survival benefits, in patients with previously treated mCRC.

MATERIALS AND METHODS

Included studies

We carried out a meta-analysis of data from three randomized, placebo-controlled trials of FTD/TPI in patients with previously treated mCRC in whom KRAS codon 12 and 13 mutation status was known. The three trials were: the phase III RECOURSE trial (NCT01607957), the phase III TERRA trial (NCT01955837) and the phase II J003 trial (JapicCTI-090880). The most up-to-date OS data were used for two of the trials (RECOURSE and J003). The most up-to-date PFS data were used for two of the trials (RECOURSE and TERRA). For the J003 trial, information on methodology used was not sufficiently detailed to support the use of different approaches. OS data from these trials were re-analyzed using two alternative ways of determining codon mutation status: a method-dependent approach. It should be noted that according to the literature and expert opinion, only some methods of measurement can differentiate between mutations in codons 12 and 13. Methods that allow discrimination between KRAS codon 12 and KRAS codon 13 are: allele-specific oligonucleotide probing; amplification-refractory mutation system (ARMS); direct sequencing; DxS Scorpion Technology; Scorpion ARMS; pyrosequencing; restriction endonuclease-mediated selective PCR (REMS-PCR); and cycleave PCR.

Sensitivity analysis

Sensitivity analyses were conducted using data from the RECOURSE and TERRA trials only. For the J003 trial, information on methodology used was not sufficiently detailed to support the use of different approaches. OS data from these trials were re-analyzed using two alternative ways of determining codon mutation status: a ‘method-dependent’ approach, and a ‘strict’ approach. It should be noted that according to the literature and expert opinion, only some methods of measurement can differentiate between mutations in codons 12 and 13. Methods that allow discrimination between KRAS codon 12 and KRAS codon 13 are: allele-specific oligonucleotide probing; amplification-refractory mutation system (ARMS); direct sequencing; DxS Scorpion Technology; Scorpion ARMS; pyrosequencing; restriction endonuclease-mediated selective PCR (REMS-PCR); and cycleave PCR.

In the ‘method-dependent’ analysis, patients were excluded if the KRAS status was unclear (i.e. the precise
mutation was not reported, or indicated the presence of mutations in both codon 12 and codon 13) and the method used was unable to differentiate between codons 12 and 13. In the ‘strict’ approach, patients were excluded if the KRAS status was unclear regardless of the analytic method used.

RESULTS

Study population

The meta-analysis included data from 1375 patients who participated in the J003, RECOURSE and TERRA trials. Baseline demographics and disease characteristics according to KRAS codon 12 mutation status are shown in Table 1 (for individual trial data, see Supplementary Tables S1 and S2, available at 10.1016/j.esmoop.2022.100511). In total, 917 patients were randomized to FTD/TPI and 458 patients were randomized to placebo; 736 patients had wild-type KRAS (492 FTD/TPI, 244 placebo) and 635 patients had mutant KRAS (422 FTD/TPI, 213 placebo). KRAS status was not known in four patients (all from the J003 trial). Among patients who received FTD/TPI, codon 12 mutations were present in 313 patients and absent in 604 patients, whereas codon 13 mutations were present in 85 patients and absent in 832 patients. Overall, KRAS codon 12 mutations were present in 34.8% (n = 478) of patients.

Analysis groups were generally well balanced with respect to baseline characteristics (Table 1), with most patients being male, aged <65 years, and of Asian ethnicity.

Wild-type versus mutant KRAS

In the meta-analysis of individual patient data, FTD/TPI was associated with a statistically significant OS prolongation compared with placebo, both in patients with wild-type

| KRAS codon 12 mutation status | No (FTD/TPI n = 604) | Placebo (n = 293) | Yes (FTD/TPI n = 313) | Placebo (n = 165) |
|-------------------------------|----------------------|------------------|----------------------|------------------|
| Age, years                    | 60.3 (10.8)          | 60.1 (10.5)      | 59.6 (10.2)          | 59.1 (12.1)      |
| Age <65 years                 | 365 (60.4)           | 184 (62.8)       | 201 (64.2)           | 101 (61.2)       |
| Age ≥65 years                 | 239 (39.6)           | 109 (37.2)       | 112 (35.8)           | 64 (38.8)        |
| Male                          | 381 (63.1)           | 185 (63.1)       | 179 (57.2)           | 93 (55.8)        |
| Race                          |                      |                  |                      |                  |
| Asian                         | 388 (64.2)           | 178 (60.8)       | 179 (57.2)           | 108 (65.5)       |
| Black/African-American        | 2 (0.3)              | 1 (0.3)          | 2 (0.6)              | 4 (2.4)          |
| Caucasian                     | 188 (31.1)           | 106 (36.2)       | 118 (37.7)           | 49 (29.7)        |
| Not collected                 | 26 (4.3)             | 8 (2.7)          | 14 (4.5)             | 4 (2.4)          |
| Region                        |                      |                  |                      |                  |
| Asia                          | 385 (63.7)           | 175 (59.7)       | 176 (56.2)           | 105 (63.6)       |
| Westerna                      | 219 (36.3)           | 118 (40.3)       | 137 (43.8)           | 60 (36.4)        |
| ECOG performance status      |                      |                  |                      |                  |
| 0                             | 279 (46.2)           | 127 (43.3)       | 158 (50.5)           | 85 (51.5)        |
| 1                             | 325 (53.8)           | 166 (56.7)       | 155 (49.5)           | 80 (48.5)        |
| Neutrophil-to-lymphocyte ratio n <3 | 595 (98.2) | 290 (97.6) | 308 (98.1) | 165 (96.4) |
| ≥3                           | 279 (46.9)           | 127 (43.8)       | 119 (38.6)           | 83 (50.3)        |
| Number of metastatic sites   |                      |                  |                      |                  |
| 1-2                          | 316 (53.1)           | 163 (56.2)       | 189 (61.4)           | 82 (49.7)        |
| ≥3                           | 223 (36.9)           | 133 (45.4)       | 136 (43.5)           | 59 (35.7)        |
| Number of prior treatment regimens 2 | 91 (15.1) | 36 (12.3) | 83 (26.5) | 47 (28.5) |
| 3                            | 150 (24.8)           | 67 (22.9)        | 89 (28.4)            | 39 (23.6)        |
| ≥4                           | 362 (59.9)           | 190 (64.8)       | 139 (44.4)           | 79 (47.9)        |
| Primary diagnosis             |                       |                  |                       |                  |
| Colon                        | 358 (59.3)           | 184 (62.8)       | 197 (62.9)           | 98 (59.4)        |
| Rectum                       | 246 (40.7)           | 109 (37.2)       | 116 (37.1)           | 67 (40.6)        |
| Prior use of regorafenib     |                       |                  |                       |                  |
| No                           | 547 (90.6)           | 253 (86.3)       | 274 (87.5)           | 151 (91.5)       |
| Time since first metastasis, months 18 months | 143 (23.7) | 56 (19.1) | 98 (31.3) | 50 (30.3) |
| ≥18 months                   | 383 (63.4)           | 203 (69.3)       | 181 (57.8)           | 92 (55.8)        |
| Unknown                      | 78 (12.9)            | 34 (11.6)        | 34 (10.9)            | 23 (13.9)        |
| BRAF mutation status          |                       |                  |                       |                  |
| Wild-type                    | 116 (19.2)           | 62 (21.2)        | 56 (17.9)            | 29 (17.6)        |
| Mutant                       | 9 (1.5)              | 6 (2.0)          | 1 (0.3)              | 1 (0.6)          |
| Unknown                      | 479 (79.3)           | 225 (76.8)       | 256 (81.8)           | 135 (81.8)       |

ECOG, Eastern Cooperative Oncology Group; FTD/TPI, trifluridine/tipiracil; SD, standard deviation.

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KRA S and with mutant KRA S [Figure 1; wild-type: HR, 0.66 (95% CI: 0.56-0.78) \( P < 0.0001 \); mutant: HR, 0.77 (95% CI: 0.64-0.91) \( P = 0.0026 \). For more details see Supplementary Figure S1A, available at 10.1016/j.esmoop.2022.100511].

**Codon 12 mutation status**

In meta-analysis of individual data from all three studies, a non-statistically significant prolongation of the OS of FTD/TPI was observed in patients with [HR, 0.86 (95% CI: 0.70-1.05) \( P = 0.1385 \)] and statistical significant prolongation was observed in patients with [HR, 0.62 (95% CI: 0.53-0.72) \( P < 0.0001 \)] KRA S codon 12 mutations (Table 2, Figure 2 and Supplementary Figure S1B, available at 10.1016/j.esmoop.2022.100511), although the effect size was more pronounced in the latter subgroup (interaction \( P = 0.0206 \)). For more details see Supplementary Figure S1B, available at 10.1016/j.esmoop.2022.100511.

FTD/TPI was associated with an OS benefit, versus placebo, in patients without a mutation in KRA S codon 12 in each of the individual trials (RE COURSE: HR, 0.57 (95% CI: 0.47-0.69); J003: HR, 0.59 (95% CI: 0.39-0.89); TERRA: HR, 0.76 (95% CI: 0.57-1.01)). In patients with a mutation in KRA S codon 12, an OS benefit of FTD/TPI over placebo was present but less evident in each of the individual trials. A significant quantitative interaction between treatment effect and KRA S codon 12 mutation status was detected in the RE COURSE trial [HR, 0.91 (95% CI: 0.71-1.17); interaction \( P = 0.007 \)] but not in the TERRA [HR, 0.85 (95% CI: 0.57-1.28); interaction \( P = 0.667 \)] or J003 [HR, 0.67 (95% CI: 0.39-1.15); \( P = 0.752 \)] trials (Figure 2).

In the multivariate analysis (Table 3), OS was longer with FTD/TPI than with placebo regardless of codon 12 status [with codon 12 mutation: HR, 0.73 (95% CI: 0.59-0.89); without codon 12 mutation: HR, 0.63 (95% CI: 0.54-0.74)]; no interaction between treatment effect and KRA S codon 12 mutation status was detected (\( P = 0.2939 \)). Prognostic factors retained in the multivariate analysis of OS were number of metastases, neutrophil-to-lymphocyte ratio, time since metastasis, ECOG performance status and number of prior treatment regimens.

Regardless of codon 12 mutation status, PFS was significantly longer with FTD/TPI than with placebo in each individual trial and in the meta-analysis of all three trials (see Supplementary Figure S2A and B, available at 10.1016/j.esmoop.2022.100511).

**Codon 13 mutation status**

There were 130 patients (9.5%) with and 1245 patients (90.5%) without a KRA S codon 13 mutation across the three trials.

In the meta-analysis of individual data, there is a statistically significant OS prolongation for patients with FTD/TPI

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**Table 2. Meta-analysis based on stratified, fixed-effects Cox model analysis of overall survival in patients receiving trifluridine/tipiracil (FTD/TPI) or placebo, according to KRA S codon 12 and 13 mutation status**

| KRA S mutation | FTD/TPI versus placebo & | Interaction P value & |
|----------------|--------------------------|---------------------|
|                | HR 95% CI  P value       |                     |
| Codon 12       |                          |                     |
| Yes            | 0.86 0.70-1.05 0.1385    | 0.0206              |
| No             | 0.62 0.53-0.72 <0.0001   |                     |
| Codon 13       |                          |                     |
| Yes            | 0.46 0.31-0.69 0.0001    | 0.0104              |
| No             | 0.74 0.65-0.84 <0.0001   |                     |

CI, confidence interval; HR, hazard ratio.
&:Stratified Cox model based on study level.
\$:Interaction between treatment arm and KRA S codon 12 or 13 mutation status (stratified Cox model based on study level).
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compared with placebo both in patients with [HR, 0.46 (95% CI: 0.31-0.69) \( P = 0.0001 \)] and without [HR, 0.74 (95% CI: 0.65-0.84) \( P < 0.0001 \)] KRAS codon 13 mutations (Table 2 and Figure 3) For more details see Supplementary Figure S1B, available at 10.1016/j.esmoop.2022.100511. There was a significant interaction between treatment arm and KRAS codon 13 mutation status \( (P = 0.0104) \). In the three individual trials, FTD/TPI was associated with longer median OS than placebo regardless of codon 13 mutation status; however, between-group differences did not consistently show statistical significance (Figure 3). In the TERRA and J003 trials, codon 13 mutation status did not significantly alter the effect of FTD/TPI on OS, relative to placebo; however, a difference in treatment effect was detected between those with and without the codon 13 mutation in the RECOURSE trial (interaction \( P = 0.023 \)). PFS was significantly longer with FTD/TPI than with placebo irrespective of codon 13 mutation status, both for the individual trials and in the meta-analysis (see

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### Table A

| Study    | Weight (%) | Codon 12 status | Events/N | Median OS (95% CI) | Events/N | Median OS (95% CI) | HR (95% CI) | P value | P val. inter. |
|----------|------------|-----------------|----------|-------------------|----------|-------------------|-------------|---------|--------------|
| RECOURSE | 62.4       | Y               | 174/201  | 6.3 (5.1-7.1)     | 92/101   | 5.7 (4.6-7.3)     | 0.91 (0.71-1.17) | 0.47    | 0.007        |
|          | 58.9       | N               | 289/333  | 7.7 (6.9-8.9)     | 157/165  | 4.9 (4.0-6.9)     | 0.57 (0.47-0.69) | 0.0001  |              |
| TERRA    | 24.2       | Y               | 6378     | 7.0 (5.8-8.4)     | 3741     | 6.3 (4.9-8.4)     | 0.85 (0.57-1.28) | 0.43    | 0.067        |
|          | 28.0       | N               | 142/193  | 8.6 (7.4-10.4)    | 74/94    | 7.3 (6.0-9.2)     | 0.76 (0.57-1.01) | 0.053   |              |
| J003     | 13.4       | Y               | 33/34    | 11.7 (7.8-15.4)   | 23/23    | 7.0 (5.4-11.1)    | 0.67 (0.39-1.15) | 0.144   | 0.752        |
|          | 13.1       | N               | 77/78    | 8.1 (7.1-10.6)    | 34/34    | 5.9 (3.7-9.3)     | 0.59 (0.39-0.89) | 0.011   |              |

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**Figure 2.** Overall survival according to KRAS codon 12 mutation status. (A) Forest plot. (B) Kaplan–Meier curves.

\( P \) value: \( P \) value from log-rank test. HR (FTD/TPI versus placebo) and 95% CI obtained from a distinct unstratified Cox model for each subgroup. P val. inter: \( P \) value from unstratified Cox model including arm treatment, subgroup and their interaction in the model. Ties handling method: Efron. CI, confidence interval; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; OS, overall survival.
Table 3. Multivariate analysis of overall survival

| Factor                           | Codon 12 mutation | Comparison              | HR<sup>a</sup> | 95% CI<sup>a</sup> | P value<sup>b</sup> | Interaction P value<sup>c</sup> | Missing values (n) |
|----------------------------------|-------------------|-------------------------|----------------|-----------------|-----------------|-----------------------------|-------------------|
| Treatment effect                  | —                 | FTD/TPI versus placebo  | 0.68           | 0.60-0.77       | <0.0001         | 0                           | 0                 |
| Treatment effect by codon         | —                 | FTD/TPI versus placebo  | 0.73           | 0.59-0.89       | 0.0018          | 0.2939                      | 0                 |
| 12 mutation status<sup>d</sup>   | Yes               | FTD/TPI versus placebo  | 0.63           | 0.54-0.74       | <0.0001         | 0                           | 0                 |
| Number of metastases             | —                 | 1-2 versus ≥3           | 0.56           | 0.50-0.63       | <0.0001         | 0                           | 0                 |
| Neutrophils-lymphocytes ratio    | <3 versus ≥3      | 0.56                    | 0.49-0.63      | <0.0001         | 17              | 0                           | 0                 |
| Time since metastasis (months)    | ≥18 versus ≥18    | 0.66                    | 0.56-0.77      | <0.0001         | 0               | 0                           | 0                 |
| ECOG performance status          | 0 versus >1       | 0.74                    | 0.65-0.84      | <0.0001         | 0               | 0                           | 0                 |
| Number of prior treatment        | 2 versus >4       | 1.20                    | 1.01-1.43      | 0.0340          | 3               | 0                           | 0                 |
| regimens                         | 3 versus >4       | 1.15                    | 1.00-1.33      | 0.0524          | 0               | 0                           | 0                 |

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio.

<sup>a</sup>HR and 95% CI from the full Cox regression model, stratified by study, and including terms for treatment arm, codon 12 mutation status, interaction between treatment arm and codon 12 mutation status; all factors were retained from stepwise selection (entry and stay α = 0.1).

<sup>b</sup>P value for interaction with treatment arm from the full model, plus the two-way interaction with only the factor shown (i.e. separate models including only one factor crossed with treatment).

<sup>c</sup>For interaction factor, the HR corresponds to the treatment effect adjusted to all significant factors.

Supplementary Figure S3A and B, available at 10.1016/j.esmoop.2022.100511.

Sensitivity analysis

Similar results to the main analyses were obtained when the data from the RECOURSE and TERRA trials were reanalyzed using method-dependent and strict criteria to determine mutation status (see Supplementary Figure S4A-D, available at 10.1016/j.esmoop.2022.100511).

DISCUSSION

This meta-analysis was conducted to determine the effect of KRAS codon 12 and 13 mutations on the efficacy of FTD/TPI in previously treated patients with mCRC. The analysis was carried out using data from the RECOURSE<sup>,14</sup> TERRA<sup>,15</sup> and J003 trials. Although the results of the univariate analysis showed that the effect of FTD/TPI on OS, relative to placebo, was reduced in the presence of mutant KRAS codon 12, the multivariate analysis showed that treatment with FTD/TPI produced an OS benefit over placebo regardless of KRAS codon 12 mutation status. The significant interaction that we observed in the univariate analysis was strongly driven by the RECOURSE trial, since no effect of KRAS codon 12 mutation status was detected in the TERRA and J003 trials. With respect to PFS, FTD/TPI was associated with similar benefits in patients with and without mutations in KRAS codon 12.

KRAS mutations are reportedly associated with a poor response to treatment of mCRC. Mutations in KRAS codon 12 have been associated with poor outcomes and negatively affecting the antitumor effectiveness of some therapies in early mCRC. In contrast with previously published analyses, we were not able to confirm the prognostic value of KRAS codon 12 mutations using survival data from placebo recipients. In our multivariate analysis, a benefit of FTD/TPI on OS was shown in patients with and without KRAS codon 12 mutations.

In early mCRC, KRAS codon 13 mutations appear to predict worse OS in Chinese patients in comparison with wild-type KRAS, whereas KRAS codon 12 mutations do not. Little is known about the prognostic significance of KRAS mutations in later mCRC. Our analysis showed that survival outcomes were very poor in placebo-treated patients with KRAS codon 13 mutations, and that FTD/TPI was associated with a survival benefit regardless of KRAS codon 13 mutation status. Fewer than 10% of patients in the meta-analysis had mutant KRAS codon 13, however, and these findings should therefore be interpreted with caution.

Previous analyses of clinical trial data have found that the efficacy of FTD/TPI in mCRC is unaffected by KRAS mutation status. In both an exploratory analysis of the RECOURSE trial<sup>27</sup> and a previously published meta-analysis of the RECOURSE, TERRA and J003 trials,<sup>25</sup> OS was found to be similar in patients with wild-type and mutant KRAS. By contrast, a real-world study of patients with refractory mCRC treated with FTD/TPI as part of a compassionate use program found that the presence of a KRAS mutation was associated with shorter OS.<sup>26</sup>

Effective options for the third- or fourth-line treatment of mCRC are limited. The results of our meta-analysis therefore suggest that treatment with FTD/TPI is beneficial for patients with KRAS wild-type disease and in those with KRAS codon 12 or 13 mutations.

Our analysis has several limitations. First, only three trials were available for inclusion in the meta-analysis, which has implications for the strength of the findings, particularly with respect to codon 13 mutations; additionally, most of the patients came from one of the trials (RECOURSE). Second, the individual trials were not designed to assess the effect of KRAS codon 12 and 13 mutations on treatment effects. Third, data on specific KRAS point mutations were not available for all patients. Fourth, only one strategy of covariate selection was used for the multivariate model (stepwise approach is a standard practice in clinical trial). Fifth, our analysis was limited to KRAS mutational status, meaning that the NRAS status was not examined.

Accordingly, our findings require confirmation, in prospective controlled trials and real-world studies, before definitive conclusions about the effects of KRAS codon 12 and 13 mutations on the effectiveness of FTD/TPI can be made.

In conclusion, this meta-analysis of three randomized, placebo-controlled trials provides preliminary evidence that...
treatment with FTD/TPI produced a survival benefit, relative to placebo, regardless of KRAS codon 12 or 13 mutation status in patients with previously treated mCRC.

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