Supplementary Material

These document contains supplementary tables with detailed survival data respective to molecular subgroups of trials analysed in this meta-analysis.
### Online resource 1. PREDICTIVE RESULTS OF THERAPEUTIC ESCALATION ACCORDING TO RAS STATUS IN FIRST LINE THERAPY

| Parameter | TRIBE | AVG2107g | FOCUS | ML22011 | AGITG-MAX |
|-----------|-------|----------|-------|---------|-----------|
|           |       |          |       |         |           |
|           | RAS WT | RAS MUT | RAS WT | RAS MUT | RAS WT | RAS MUT | RAS WT | RAS MUT | RAS WT | RAS MUT | RAS WT | RAS MUT |
|           | FOLFIRI | FOLFIRI | FOLFIRI | FOLFIRI | FOLFIRI | FOLFIRI | FOLFIRI | FOLFIRI | FOLFIRI | FOLFIRI | FOLFIRI | FOLFIRI |
|           | + Bev | + Bev | + Bev | + Bev | + Bev | + Bev | + Bev | + Bev | + Bev | + Bev | + Bev | + Bev |
|           | IFL | IFL | IFL | IFL | IFL | IFL | IFL | IFL | IFL | IFL | IFL | IFL |
|           | S-FU | S-FU | S-FU | S-FU | S-FU | S-FU | S-FU | S-FU | S-FU | S-FU | S-FU | S-FU |
|           | IrFU | IrFU | IrFU | IrFU | IrFU | IrFU | IrFU | IrFU | IrFU | IrFU | IrFU | IrFU |
|           | OxFU | OxFU | OxFU | OxFU | OxFU | OxFU | OxFU | OxFU | OxFU | OxFU | OxFU | OxFU |
| OS        |       |          |       |         |           |
| Median, months | 26.8 | 37.1 | 23.9 | 27.3 | 17.6 | 27.7 | 13.6 | 19.9 | n/a | n/a | 32.2 | 25.2 |
| HR (95% CI) | 0.78 (0.51 – 1.20) | 0.88 (0.65 – 1.18) | 0.58 (0.30 – 1.00) | 0.69 (0.40 – 1.30) | 1.00 | 1.01 | 0.86 | 1.00 | 0.92 | 0.82 | 0.58 (0.38 – 0.89) | 0.92 (0.65 – 1.29) | 0.99 (0.67 – 1.45) | 0.91 (0.58 – 1.44) |
| P value   | 0.66 | 0.04 | 0.26 | 0.87 | 0.01 | 0.62 | 0.95 | 0.70 |
| PFS       |       |          |       |         |           |
| Median, months | 11.0 | 12.8 | 9.5 | 12.0 | 7.4 | 13.5 | 5.5 | 9.3 | n/a | n/a | 12.6 | 8.4 |
| HR (95% CI) | 0.84 (0.58 – 1.21) | 0.78 (0.60 – 1.02) | 0.44 (0.30 – 0.70) | 0.41 (0.20 – 0.70) | 1.00 | 0.73 | 0.67 | 1.00 | 0.77 | 0.63 | 0.49 (0.35 – 0.69) | 0.87 (0.65 – 1.17) | 0.69 (0.49 – 0.97) | 0.56 (0.37 – 0.86) |
| P value   | 0.77 | < 0.0001 | 0.0008 | 0.92 | < 0.001 | 0.34 | 0.03 | 0.007 |

**Legend:** RAS: rat sarcoma; WT: wildtype; MUT: mutated; FOLFIRI: 5-fluorouracil/folinic acid/irinotecan; FOLFOXIRI: 5-fluorouracil/folinic acid/oxaliplatin/irinotecan; IFL: irinotecan/5-fluorouracil/folinic acid; Bev: bevacizumab; 5-FU: 5-fluorouracil; IrFU: irinotecan/5-fluorouracil; OxFU: oxaliplatin/5-fluorouracil; FP: fluoropyrimidine, Cape: capecitabine; Mito: mitomycin; OS: overall survival; PFS: progression free survival; HR: hazard ratio; 95% CI: 95% confidence interval
### Online resource 2. PREDICTIVE RESULTS OF THERAPEUTIC ESCALATION ACCORDING TO RAS STATUS IN SECOND LINE THERAPY

| Parameter | ML18147 RAS WT | ML18147 RAS MUT | RAISE RAS WT | RAISE RAS MUT | VELOUR RAS WT | VELOUR RAS MUT |
|-----------|----------------|-----------------|--------------|--------------|---------------|---------------|
| OS        | Chemotherapy + Bev | Chemotherapy + Bev | FOLFIRI + Bev | FOLFIRI + Bev | FOLFIRI + Ramucirumab | FOLFIRI + Ramucirumab |
| Median, months | 11.1 | 15.4 | 10.0 | 10.4 | 11.9 | 14.4 | 11.3 | 12.7 | 11.7 | 16.0 | 11.2 | 12.6 |
| HR (95% CI) | 0.69 (0.53 – 0.90) | 0.92 (0.71 – 1.18) | 0.82 (0.67 – 1.00) | 0.89 (0.73 – 1.09) | 0.70 (0.50 – 0.97) | 0.93 (0.70 – 1.23) |
| P value | 0.0052 | 0.4969 | 0.049 | 0.263 | n/a | n/a |
| PFS | Chemotherapy + Bev | Chemotherapy + Bev | FOLFIRI + Bev | FOLFIRI + Bev | FOLFIRI + Ramucirumab | FOLFIRI + Ramucirumab |
| Median, months | 4.5 | 6.4 | 4.1 | 5.5 | 4.7 | 5.7 | 4.3 | 5.6 | 4.5 | 7.7 | 4.2 | 6.5 |
| HR (95% CI) | 0.61 (0.49 – 0.77) | 0.70 (0.56 – 0.89) | 0.77 (0.65 – 0.92) | 0.84 (0.70 – 1.00) | 0.67 (0.49 – 0.93) | 0.80 (0.60 – 1.07) |
| P value | < 0.0001 | 0.0027 | 0.004 | 0.056 | n/a | n/a |

Legend: RAS: rat sarcoma; WT: wildtype; MUT: mutated; FOLFIRI: 5-fluorouracil/folinic acid/irinotecan; Bev: bevacizumab; OS: overall survival; PFS: progression free survival; HR: hazard ratio; 95% CI: 95% confidence interval
### Online resource 3. PREDICTIVE RESULTS OF THERAPEUTIC ESCALATION ACCORDING TO RAS STATUS IN LATER LINE THERAPY

| Parameter | CORRECT | | CONCUR | | RECOUSE |
|-----------|---------| |---------| |---------|
|           | RAS WT | RAS MUT | RAS WT | RAS MUT | RAS WT | RAS MUT |
|           | Placebo | Regorafenib | Placebo | Regorafenib | Placebo | Regorafenib |
| OS        |         |         |         |         |         |         |
| Median, months | n/a | n/a | n/a | n/a | n/a | n/a | n/a | 5.7 | 8.0 | 4.9 | 6.5 |
| HR (95% CI) | 0.65 (0.48 – 0.90) | 0.87 (0.67 – 1.12) | 0.59 (0.34 – 1.01) | 0.65 (0.36 – 1.15) | 0.58 (0.45 – 0.74) | 0.80 (0.63 – 1.02) |
| P value | n/a | n/a | n/a | n/a | < 0.0001 | 0.0712 |
| PFS       |         |         |         |         |         |         |
| Median, months | n/a | n/a | n/a | n/a | n/a | n/a | n/a | 1.7 | 2.1 | 1.8 | 1.9 |
| HR (95% CI) | 0.48 (0.36 – 0.62) | 0.53 (0.43 – 0.65) | 0.43 (0.26 – 0.71) | 0.15 (0.08 – 0.30) | 0.48 (0.38 – 0.60) | 0.49 (0.39 – 0.61) |
| P value | n/a | n/a | n/a | n/a | 0.0001 | < 0.0001 |

**Legend:** RAS: rat sarcoma; WT: wildtype; MUT: mutated; TAS102: trifluridine/tipiracil; OS: overall survival; PFS: progression free survival; HR: hazard ratio; 95% CI: 95% confidence interval
### Online resource 4. PREDICTIVE RESULTS OF THERAPEUTIC ESCALATION ACCORDING TO RAS STATUS IN MAINTENANCE THERAPY

| Parameter | AIOKR0207 | CAIRO3 | PRODIGE9 |
|-----------|-----------|--------|----------|
|           | RAS/BRAF WT | RAS/BRAF MUT | RAS WT | RAS MUT | RAS WT | RAS MUT |
| No treatment | Bevacizumab | Fluoropyrimidine | No treatment | Bevacizumab | Fluoropyrimidine | No treatment | Bevacizumab | No treatment | Bevacizumab | No treatment | Bevacizumab |
| **OS** | | | | | | | | | | | |
| Median, months | | | | | | | | | | | |
| Control | 27.8 | 28.6 | 27.0 | 20.0 | 18.8 | 19.4 | 19.0 | 25.7 | 18.7 | 20.9 | n/a | n/a | n/a | n/a |
| HR (95% CI) | 1.01 (0.56 – 1.81) | 1.15 (0.64 – 2.08) | Control | 0.97 (0.64 – 1.44) | 1.05 (0.69 – 1.61) | 0.68 (0.46 – 1.00) | 0.98 (0.73 – 1.30) | 0.92 (0.72 – 1.31) | 1.13 (0.82 – 1.55) |
| P value | n/a | n/a | 0.047 | 0.867 | 0.499 |

| **PFS** | | | | | | | | | | | |
| Median, months | | | | | | | | | | | |
| Control | 3.9 | 5.3 | 8.1 | 3.7 | 4.1 | 6.4 | 9.0 | 13.3 | 8.9 | 11.2 | n/a | n/a | n/a | n/a |
| HR (95% CI) | 0.45 (0.28 – 0.72) | 0.33 (0.21 – 0.53) | Control | 0.84 (0.58 – 1.19) | 0.53 (0.36 – 0.78) | 0.57 (0.39 – 0.84) | 0.74 (0.55 – 0.89) | 0.72 (0.54 – 0.95) | 1.07 (0.79 – 1.44) |
| P value | n/a | n/a | 0.004 | 0.038 | 0.072 |

**Legend:** RAS: rat sarcoma; WT: wildtype; MUT: mutated; OS: overall survival; PFS: progression free survival; HR: hazard ratio; 95% CI: 95% confidence interval
| Section/topic | Checklist item | Reported on page |
|---------------|----------------|-----------------|
| **ABSTRACT**  | Provide a structured summary, including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **METHODS**   | Specify study characteristics (e.g., PICOS, length of follow-up and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4 |
|               | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 5-6 |
|               | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 6-7 |
| **RESULTS**   | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 5 |
| Study selection | State the principal summary measures (e.g., risk ratios, difference in means). | 5 |
|                | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis. | 6-7 |
| Risk of bias across studies | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 5-6 |
| Additional analyses | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 6-7 |
| **DISCUSSION** | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 10-13 |
| Limitations | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 10-13 |
| Conclusions | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 10-13 |
| **FUNDING**   | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 14 |