**SUPPLEMENTARY MATERIAL**

**Supplementary Table 1**. Patient characteristics according to study and treatment arm

**Supplementary Table 2.** Median PFS1, PFS2, OS and 6-month / 1-year / 2-year PFS1, PFS2 and OS rates

**Supplementary Table 3.** Individual study results - Adjusted treatment effects for PFS1 in subgroups

**Supplementary Table 4.** Individual study results - Adjusted treatment effects for PFS2 in subgroups

**Supplementary Table 5.** Individual study results - Adjusted treatment effects for OS in subgroups

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| **Supplementary Table 1. Patient characteristics according to study and treatment arm** | | | | | | |
|  | **CAIRO3** | | | **AIO 0207**  **d** | | |
|  | **Obs (n=279)** | **FP+Bev (n=278)** | **Total (n=557)** | **Obs (n=158)** | **FP+Bev (n=156)** | **Total (n=314)** |
| **Age** | | | |  |  |  |
| ≥ 70 | 76 (27) | 61 (22) | 137 (25) | 54 (34) | 40 (26) | 94 (30) |
| **Sex** | | | |  |  |  |
| Male | 179 (64) | 182 (66) | 361 (65) | 99 (63) | 106 (68) | 205 (65) |
| **WHO/ECOG performance status** | | | |  |  |  |
| 0 | 173 (62) | 172 (62) | 345 (62) | 62 (43) | 77 (53) | 140 (48) |
| 1 | 106 (38) | 106 (38) | 212 (38) | 72 (49) | 64 (44) | 136 (47) |
| 2 | 0 (0) | 0 (0) | 0 (0) | 11 (8) | 5 (3) | 16 (6) |
| **Best response to induction treatment** | | | |  |  |  |
| Complete or partial response | 184 (66) | 182 (66) | 366 (66) | 106 (67) | 100 (64) | 206 (66) |
| Stable disease | 95 (34) | 96 (35) | 191 (34) | 52 (33) | 56 (36) | 108 (34) |
| **Prior adjuvant chemotherapy** | | | |  |  |  |
| Yes | 95 (34) | 93 (34) | 188 (34) | 16 (10) | 19 (12) | 35 (11) |
| **Primary tumour location** | | | |  |  |  |
| Colon | 143 (51) | 134 (48) | 277 (50) | 100 (63) | 102 (65) | 202 (64) |
| Rectum | 77 (28) | 84 (30) | 161 (29) | 58 (37) | 54 (35) | 112 (36) |
| Rectosigmoid | 59 (21) | 60 (22) | 119 (21) | 0 (0) | 0 (0) | 0 (0) |
| **Number of metastatic sites** | | | |  |  |  |
| 1 | 111 (42) | 118 (44) | 229 (43) | 60 (38) | 70 (45) | 130 (42) |
| >1 | 152 (58) | 150 (56) | 302 (57) | 97 (62) | 85 (55) | 182 (58) |
| **Stage of disease and primary tumour resection status** | | | |  |  |  |
| Synchronousa, resection | 84 (30) | 96 (35) | 180 (32) | 87 (55) | 86 (55) | 173 (55) |
| Synchronous, no resection | 107 (38) | 123 (44) | 230 (41) | 47 (30) | 40 (26) | 87 (27) |
| Metachronous | 88 (32) | 59 (21) | 147 (26) | 24 (15) | 30 (19) | 54 (17) |
| **LDH elevated at randomisation** | | | |  |  |  |
| Yes | 157 (56) | 155 (56) | 312 (56) | 55 (39) | 69 (51) | 124 (44) |
| **Platelets at start induction treatment** | | | |  |  |  |
| < 400 x 109/L | 167 (66) | 179 (70) | 346 (68) | 98 (63) | 108 (70) | 206 (67) |
| ≥ 400 x 109/L | 87 (34) | 76 (30) | 163 (32) | 57 (37) | 46 (30) | 103 (33) |
| **CEA at start induction treatment** | | | |  |  |  |
| ≤ 20 ng/mL | 78 (38) | 91 (43) | 169 (41) | 43 (30) | 51 (37) | 94 (33) |
| > 20 ng/mL | 126 (62) | 120 (57) | 246 (59) | 101 (70) | 88 (63) | 189 (67) |
| ***RAS/BRAF*****mutation status** | | | |  |  |  |
| *RAS /* V600E*BRAF* wild-type | 63 (31) | 81 (39) | 144 (35) | 47 (41) | 48 (44) | 95 (42) |
| *RAS* mutant | 128 (62) | 113 (54) | 241 (58) | 61 (53) | 54 (49) | 115 (51) |
| V600E*BRAF*mutant | 15 (7) | 15 (7) | 30 (7) | 7 (6) | 8 (7) | 15 (7) |
| Data are n (%) unless otherwise stated. Due to rounding, not all percentages total 100. a Synchronous disease was defined as distant metastases discovered ≤ 6 months of the primary CRC diagnosis. Bev = bevacizumab. FP = fluoropyrimidine. Obs = observation. | | | | | | |

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| **Supplementary Table 2. Median PFS1, PFS2, OS and 6-month / 1-year / 2-year PFS1, PFS2 and OS rates** | | | | | | |
|  | **CAIRO3** | | **AIO 0207** | | **Pooled study population** | |
|  | **n=557** | | **n=314** | | **n=871** | |
|  | **Obs**  **(n=279)** | **FP+Bev**  **(n=278)** | **Obs**  **(n=158)** | **FP+Bev**  **(n=156)** | **Obs**  **(n=437)** | **FP+Bev**  **(n=434)** |
| **PFS1** | | | | | | |
| Events | 275 | 268 | 150 | 131 | 425 | 399 |
| Median (months) | 4.1 | 8.5 | 3.5 | 6.3 | 4.0 | 7.3 |
| 95% CI | 3.9-4.2 | 6.6-10.3 | 2.7-4.3 | 5.4-7.3 | 3.8-4.2 | 6.3-8.3 |
| Log-rank P-value | <0.001 | | <0.001 | | <0.001 | |
| **PFS2** | | | | | | |
| Events | 274 | 266 | 145 | 129 | 419 | 395 |
| Median (months) | 8.6 | 11.6 | 6.4 | 6.9 | 7.6 | 9.9 |
| 95% CI | 7.0-10.1 | 10.0-13.3 | 4.9-7.9 | 5.8-8.0 | 6.7-8.5 | 8.5-11.2 |
| Log-rank P-value | <0.001 | | 0.056 | | <0.001 | |
| **OS** | | | | | | |
| Events | 268 | 263 | 124 | 134 | 392 | 397 |
| Median (months) | 18.2 | 21.6 | 22.4 | 20.2 | 19.0 | 21.4 |
| 95% CI | 16.1-20.3 | 19.5-23.7 | 19.3-25.5 | 16.9-23.5 | 17.1-20.8 | 19.6-23.1 |
| Log-rank P-value | 0.118 | | 0.431 | | 0.444 | |
| **PFS1 rate** | | | | | | |
| 6-month | 30.1% | 62.2% | 26.0% | 51.7% | 28.6% | 58.6% |
| 1-year | 6.5% | 34.5% | 3.9% | 23.1% | 5.5% | 30.6% |
| 2-year | 2.5% | 14.0% | 0.6% | 4.1% | 1.8% | 10.6% |
| **PFS2 ratea** | | | | | | |
| 6-month | 88.8% | 91.1% | 75.3% | 76.7% | 84.7% | 88.5% |
| 1-year | 52.7% | 60.7% | 39.7% | 30.0% | 48.8% | 55.2% |
| 2-year | 8.3% | 17.0% | 4.1% | 3.3% | 7.0% | 14.5% |
| **OS rate** | | | | | | |
| 6-month | 90.0% | 92.8% | 91.8% | 86.5% | 90.6% | 90.6% |
| 1-year | 72.0% | 74.1% | 72.2% | 73.1% | 72.1% | 73.7% |
| 2-year | 36.6% | 43.2% | 39.2% | 40.4% | 37.5% | 42.2% |

CI= confidence interval. Bev = bevacizumab. FP = fluoropyrimidine. Obs= observation. a Only patients that received reintroduction of the induction treatment regimen were assessed in the calculation of PFS2 rates.

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| **Supplementary Table 3. Individual study results - Adjusted treatment effects for PFS1 in subgroups** | | | | | | | | | | |
|  | **CAIRO3** | | | | | **AIO 0207** | | | | |
| **Subgroup** | **Obs** | **FP+Bev** | **HR** | ***P*-value** | ***P*interaction** | **Obs** | **FP+Bev** | **HR** | ***P*-value** | ***P*interaction** |
| **Sex** | | | | | | | | | | |
| Male | 168/169 | 170/174 | 0.36 (0.29-0.46) | <0.001 | 0.882 | 79/82 | 77/85 | 0.48 (0.34-0.69) | <0.001 | 0.776 |
| Female | 92/94 | 87/93 | 0.37 (0.27-0.51) | <0.001 |  | 47/48 | 33/37 | 0.44 (0.27-0.72) | 0.001 |  |
|  | (16) | (12) |  |  |  | (28) | (34) |  |  |  |
| **Age** | | | | | | | | | | |
| < 70 | 188/189 | 199/209 | 0.37 (0.29-0.46) | <0.001 | 0.979 | 80/84 | 82/92 | 0.44 (0.32-0.62) | <0.001 | 0.527 |
| ≥ 70 | 72/74 | 57/57 | 0.37 (0.25-0.53) | <0.001 |  | 46/46 | 28/30 | 0.54 (0.31-0.93) | 0.026 |  |
|  | (16) | (12) |  |  |  | (28) | (34) |  |  |  |
| **WHO/ECOG performance status** | | | | | | | | | | |
| 0 | 163/164 | 158/166 | 0.38 (0.30-0.48) | <0.001 | 0.405 | 55/57 | 54/63 | 0.37 (0.24-0.56) | <0.001 | 0.109 |
| 1-2 | 97/99 | 98/100 | 0.33 (0.24-0.44) | <0.001 |  | 71/73 | 56/59 | 0.58 (0.40-0.84) | 0.004 |  |
|  | (16) | (12) |  |  |  | (28) | (34) |  |  |  |
| **Response to induction treatment** | | | | | | | | | | |
| Complete or partial response | 165/168 | 163/173 | 0.35 (0.28-0.45) | <0.001 | 0.583 | 86/89 | 75/81 | 0.48 (0.34-0.67) | <0.001 | 0.671 |
| Stable disease | 95/95 | 93/93 | 0.39 (0.29-0.53) | <0.001 |  | 40/41 | 35/41 | 0.43 (0.26-0.70) | 0.001 |  |
|  | (16) | (12) |  |  |  | (28) | (34) |  |  |  |
| **Primary tumour location** | | | | | | | | | | |
| Colon | 136/137 | 120/127 | 0.34 (0.26-0.45) | <0.001 | 0.502 | 84/86 | 69/79 | 0.43 (0.30-0.62) | <0.001 | 0.453 |
| Rectum / rectosigmoid | 124/126 | 136/139 | 0.39 (0.30-0.51) | <0.001 |  | 42/44 | 41/43 | 0.54 (0.34-0.85) | 0.008 |  |
|  | (16) | (12) |  |  |  | (28) | (34) |  |  |  |
| **Number of metastatic sites** | | | | | | | | | | |
| 1 | 109/111 | 112/117 | 0.45 (0.34-0.59) | <0.001 | 0.058 | 44/45 | 46/53 | 0.41 (0.26-0.66) | <0.001 | 0.522 |
| >1 | 151/152 | 144/149 | 0.31 (0.24-0.40) | <0.001 |  | 82/85 | 64/69 | 0.50 (0.35-0.72) | <0.001 |  |
|  | (16) | (12) |  |  |  | (28) | (34) |  |  |  |
| **Stage of disease and primary tumour resection status** | | | | | | | | | | |
| Synchronous, resection | 76/77 | 84/91 | 0.28 (0.20-0.39) | <0.001 | 0.090 | 71/74 | 59/69 | 0.48 (0.33-0.70) | <0.001 | 0.971 |
| Synchronous, no resection | 103/103 | 115/117 | 0.38 (0.28-0.50) | <0.001 |  | 36/36 | 31/31 | 0.47 (0.28-0.79) | 0.004 |  |
| Metachronous | 81/83 | 57/58 | 0.48 (0.33-0.68) | <0.001 |  | 19/20 | 20/22 | 0.43 (0.21-0.90) | 0.025 |  |
|  | (16) | (12) |  |  |  | (28) | (34) |  |  |  |
| **LDH elevated at randomisation** | | | | | | | | | | |
| No | 114/117 | 113/116 | 0.34 (0.25-0.45) | <0.001 | 0.416 | 75/77 | 53/60 | 0.58 (0.40-0.86) | 0.006 | 0.095 |
| Yes | 146/146 | 143/150 | 0.39 (0.30-0.50) | <0.001 |  | 51/53 | 57/62 | 0.35 (0.23-0.55) | <0.001 |  |
|  | (16) | (12) |  |  |  | (28) | (34) |  |  |  |
| **Platelet count at start induction treatment** | | | | | | | | | | |
| < 400 x 109/L | 155/156 | 164/171 | 0.39 (0.31-0.50) | <0.001 | 0.144 | 78/80 | 78/85 | 0.52 (0.37-0.75) | <0.001 | 0.353 |
| ≥ 400 x 109/L | 84/86 | 69/72 | 0.29 (0.20-0.41) | <0.001 |  | 47/49 | 32/37 | 0.40 (0.25-0.64) | <0.001 |  |
|  | (37) | (35) |  |  |  | (29) | (34) |  |  |  |
| **CEA at start induction treatment** | | | | | | | | | | |
| ≤ 20 ng/mL | 69/71 | 79/85 | 0.36 (0.25-0.52) | <0.001 | 0.989 | 34/35 | 37/41 | 0.48 (0.28-0.82) | 0.007 | 0.902 |
| > 20 ng/mL | 119/120 | 112/114 | 0.36 (0.27-0.48) | <0.001 |  | 80/82 | 64/70 | 0.47 (0.32-0.67) | <0.001 |  |
|  | (88) | (79) |  |  |  | (41) | (45) |  |  |  |
| **Mutation status** | | | | | | | | | | |
| *RAS /* V600E*BRAF* wild-type | 58/58 | 74/77 | 0.32 (0.22-0.47) | <0.001 | 0.456 | 39/41 | 32/36 | 0.37 (0.21-0.65) | 0.001 | 0.605 |
| *RAS* mutant | 122/123 | 108/110 | 0.38 (0.28-0.51) | <0.001 |  | 52/53 | 36/43 | 0.53 (0.33-0.85) | 0.009 |  |
| V600E*BRAF* mutant | 13/14 | 11/14 | 0.22 (0.10-0.52) | <0.001 |  | 5/6 | 7/7 | 0.46 (0.13-1.66) | 0.234 |  |
|  | (84) | (77) |  |  |  | (58) | (70) |  |  |  |
| Numbers between brackets: number of patients with missing values per analysis. *P*interaction= *P*-value for heterogeneity across subgroups. Analyses performed using a mixed effect Cox model with study as random intercept and treatment (and any co-variables) as fixed effects. Subgroup analyses were stratified for prior adjuvant chemotherapy, response to induction treatment, WHO/ECOG PS, and adjusted for age, sex, stage, primary tumour location, primary tumour resection, number of metastatic sites, LDH at randomisation, and interval between primary diagnosis and randomisation. Subgroup analyses for ‘stage of disease and primary tumour resection status’ were not adjusted for stage and primary tumour resection. Bev = bevacizumab. FP = fluoropyrimidine. Obs = observation. | | | | | | | | | | |

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| **Supplementary Table 4. Individual study results - Adjusted treatment effects for PFS2 in subgroups** | | | | | | | | | | |
|  | **CAIRO3** | | | | | **AIO 0207** | | | | |
| **Subgroup** | **Obs** | **FP+Bev** | **HR** | ***P*-value** | ***P*interaction** | **Obs** | **FP+Bev** | **HR** | ***P*-value** | ***P*interaction** |
| **Sex** | | | | | | | | | | |
| Male | 168/169 | 169/174 | 0.64 (0.51-0.80) | <0.001 | 0.936 | 75/82 | 75/85 | 0.81 (0.57-1.16) | 0.251 | 0.934 |
| Female | 91/94 | 85/92 | 0.63 (0.46-0.86) | 0.004 |  | 47/48 | 33/37 | 0.83 (0.52-1.34) | 0.446 |  |
|  | (16) | (12) |  |  |  | (28) | (34) |  |  |  |
| **Age** | | | | | | | | | | |
| < 70 | 188/189 | 197/209 | 0.63 (0.51-0.79) | <0.001 | 0.989 | 77/84 | 81/92 | 0.80 (0.57-1.12) | 0.186 | 0.765 |
| ≥ 70 | 71/74 | 57/57 | 0.64 (0.44-0.91) | 0.014 |  | 45/46 | 27/30 | 0.88 (0.51-1.51) | 0.640 |  |
|  | (16) | (12) |  |  |  | (28) | (34) |  |  |  |
| **WHO/ECOG performance status** | | | | | | | | | | |
| 0 | 162/164 | 157/166 | 0.70 (0.56-0.88) | 0.002 | 0.174 | 53/57 | 52/63 | 0.59 (0.38-0.90) | 0.015 | 0.028 |
| 1-2 | 97/99 | 97/100 | 0.54 (0.41-0.73) | <0.001 |  | 69/73 | 56/59 | 1.11 (0.77-1.60) | 0.584 |  |
|  | (16) | (12) |  |  |  | (28) | (34) |  |  |  |
| **Response to induction treatment** | | | | | | | | | | |
| Complete or partial response | 164/168 | 162/173 | 0.57 (0.45-0.71) | <0.001 | 0.134 | 83/89 | 73/81 | 0.85 (0.61-1.20) | 0.358 | 0.606 |
| Stable disease | 95/95 | 92/93 | 0.75 (0.56-1.01) | 0.061 |  | 39/41 | 35/41 | 0.73 (0.45-1.19) | 0.210 |  |
|  | (16) | (12) |  |  |  | (28) | (34) |  |  |  |
| **Primary tumour location** | | | | | | | | | | |
| Colon | 136/137 | 119/127 | 0.58 (0.45-0.75) | <0.001 | 0.322 | 81/86 | 67/79 | 0.76 (0.53-1.09) | 0.136 | 0.507 |
| Rectum / rectosigmoid | 123/126 | 135/139 | 0.70 (0.54-0.90) | 0.006 |  | 41/44 | 41/43 | 0.93 (0.58-1.50) | 0.771 |  |
|  | (16) | (12) |  |  |  | (28) | (34) |  |  |  |
| **Number of metastatic sites** | | | | | | | | | | |
| 1 | 108/111 | 110/117 | 0.68 (0.51-0.89) | 0.006 | 0.566 | 41/45 | 45/53 | 0.63 (0.39-1.02) | 0.061 | 0.190 |
| >1 | 151/152 | 144/149 | 0.61 (0.48-0.77) | <0.001 |  | 81/85 | 63/69 | 0.95 (0.66-1.37) | 0.786 |  |
|  | (16) | (12) |  |  |  | (28) | (34) |  |  |  |
| **Stage of disease and primary tumour resection status** | | | | | | | | | | |
| Synchronous, resection | 75/77 | 83/91 | 0.49 (0.36-0.69) | <0.001 | 0.129 | 68/74 | 57/69 | 0.74 (0.50-1.11) | 0.142 | 0.557 |
| Synchronous, no resection | 103/103 | 115/117 | 0.66 (0.50-0.88) | 0.004 |  | 35/36 | 31/31 | 1.04 (0.62-1.74) | 0.896 |  |
| Metachronous | 81/83 | 56/58 | 0.81 (0.57-1.16) | 0.256 |  | 19/20 | 20/22 | 0.71 (0.35-1.43) | 0.335 |  |
|  | (16) | (12) |  |  |  | (28) | (34) |  |  |  |
| **LDH elevated at randomisation** | | | | | | | | | | |
| No | 113/117 | 112/116 | 0.60 (0.46-0.79) | <0.001 | 0.611 | 71/77 | 51/60 | 1.02 (0.69-1.50) | 0.923 | 0.106 |
| Yes | 146/146 | 142/150 | 0.66 (0.52-0.85) | 0.001 |  | 51/53 | 57/62 | 0.62 (0.40-0.96) | 0.033 |  |
|  | (16) | (12) |  |  |  | (28) | (34) |  |  |  |
| **Platelet count at start induction treatment** | | | | | | | | | | |
| < 400 x 109/L | 15/156 | 162/171 | 0.69 (0.54-0.87) | 0.002 | 0.065 | 75/80 | 76/85 | 0.89 (0.63-1.26) | 0.512 | 0.666 |
| ≥ 400 x 109/L | 83/86 | 69/72 | 0.47 (0.33-0.66) | <0.001 |  | 46/49 | 32/37 | 0.78 (0.49-1.26) | 0.312 |  |
|  | (37) | (35) |  |  |  | (29) | (34) |  |  |  |
| **CEA at start induction treatment** | | | | | | | | | | |
| ≤ 20 ng/mL | 69/71 | 79/85 | 0.62 (0.44-0.88) | 0.007 | 0.783 | 32/35 | 37/41 | 0.67 (0.39-1.17) | 0.158 | 0.297 |
| > 20 ng/mL | 119/120 | 112/114 | 0.58 (0.44-0.77) | <0.001 |  | 78/82 | 62/70 | 0.95 (0.67-1.35) | 0.782 |  |
|  | (88) | (79) |  |  |  | (41) | (45) |  |  |  |
| **Mutation status** | | | | | | | | | | |
| *RAS /* V600E*BRAF* wild-type | 57/58 | 73/77 | 0.50 (0.35-0.73) | <0.001 | 0.096 | 36/41 | 30/36 | 0.61 (0.34-1.10) | 0.100 | 0.461 |
| *RAS* mutant | 122/123 | 107/110 | 0.72 (0.54-0.95) | 0.021 |  | 52/53 | 36/43 | 0.83 (0.51-1.36) | 0.470 |  |
| V600E*BRAF* mutant | 13/14 | 11/14 | 0.32 (0.14-0.73) | 0.007 |  | 4/6 | 7/7 | 1.33 (0.35-5.01) | 0.675 |  |
|  | (84) | (77) |  |  |  | (58) | (70) |  |  |  |
| Numbers between brackets: number of patients with missing values per analysis. *P*interaction= *P*-value for heterogeneity across subgroups. Analyses performed using a mixed effect Cox model with study as random intercept and treatment (and any co-variables) as fixed effects. Subgroup analyses were stratified for prior adjuvant chemotherapy, response to induction treatment, WHO/ECOG PS, and adjusted for age, sex, stage, primary tumour location, primary tumour resection, number of metastatic sites, LDH at randomisation, and interval between primary diagnosis and randomisation. Subgroup analyses for ‘stage of disease and primary tumour resection status’ were not adjusted for stage and primary tumour resection. Bev = bevacizumab. FP = fluoropyrimidine. Obs = observation. | | | | | | | | | | |

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| **Supplementary Table 5. Individual study results - Adjusted treatment effects for OS in subgroups** | | | | | | | | | | |
|  | **CAIRO3** | | | | | **AIO 0207** | | | | |
| **Subgroup** | **Obs** | **FP+Bev** | **HR** | ***P*-value** | ***P*interaction** | **Obs** | **FP+Bev** | **HR** | ***P*-value** | ***P*interaction** |
| **Sex** | | | | | | | | | | |
| Male | 165/169 | 167/174 | 0.92 (0.74-1.15) | 0.470 | 0.035 | 64/84 | 78/90 | 1.51 (0.96-2.16) | 0.026 | 0.130 |
| Female | 90/94 | 84/92 | 0.61 (0.45-0.84) | 0.002 |  | 42/49 | 37/40 | 0.95 (0.59-1.52) | 0.829 |  |
|  | (16) | (12) |  |  |  | (25) | (26) |  |  |  |
| **Age** | | | | | | | | | | |
| < 70 | 184/189 | 195/209 | 0.82 (0.67-1.02) | 0.074 | 0.629 | 68/87 | 87/97 | 1.20 (0.86-1.68) | 0.280 | 0.552 |
| ≥ 70 | 71/74 | 56/57 | 0.74 (0.52-1.06) | 0.105 |  | 38/46 | 28/33 | 1.46 (0.86-2.48) | 0.166 |  |
|  | (16) | (12) |  |  |  | (25) | (26) |  |  |  |
| **WHO/ECOG performance status** | | | | | | | | | | |
| 0 | 159/164 | 156/166 | 0.93 (0.74-1.17) | 0.525 | 0.070 | 44/58 | 55/67 | 1.03 (0.67-1.58) | 0.909 | 0.166 |
| 1-2 | 96/99 | 95/100 | 0.66 (0.49-0.88) | 0.005 |  | 62/75 | 60/63 | 1.54 (1.06-2.22) | 0.023 |  |
|  | (16) | (12) |  |  |  | (25) | (26) |  |  |  |
| **Response to induction treatment** | | | | | | | | | | |
| Complete or partial response | 162/168 | 159/173 | 0.69 (0.55-0.86) | 0.001 | 0.024 | 71/90 | 72/83 | 1.27 (0.90-1.78) | 0.168 | 0.843 |
| Stable disease | 93/95 | 92/93 | 1.05 (0.78-1.41) | 0.752 |  | 35/43 | 43/47 | 1.34 (0.84-2.15) | 0.217 |  |
|  | (16) | (12) |  |  |  | (25) | (26) |  |  |  |
| **Primary tumour location** | | | | | | | | | | |
| Colon | 134/137 | 117/127 | 0.68 (0.52-0.89) | 0.004 | 0.088 | 72/89 | 73/85 | 1.08 (0.76-1.54) | 0.651 | 0.131 |
| Rectum / rectosigmoid | 121/126 | 134/139 | 0.94 (0.72-1.21) | 0.607 |  | 34/44 | 42/45 | 1.74 (1.06-2.85) | 0.029 |  |
|  | (16) | (12) |  |  |  | (25) | (26) |  |  |  |
| **Number of metastatic sites** | | | | | | | | | | |
| 1 | 105/111 | 108/117 | 0.89 (0.67-1.18) | 0.408 | 0.361 | 31/47 | 51/58 | 1.35 (0.84-2.16) | 0.219 | 0.763 |
| >1 | 150/152 | 143/149 | 0.75 (0.58-0.95) | 0.018 |  | 75/86 | 64/72 | 1.23 (0.85-1.77) | 0.272 |  |
|  | (16) | (12) |  |  |  | (25) | (26) |  |  |  |
| **Stage of disease and primary tumor resection status** | | | | | | | | | | |
| Synchronous, resection | 74/77 | 81/91 | 0.48 (0.34-0.67) | <0.001 | 0.001 | 57/75 | 65/75 | 1.34 (0.92-1.95) | 0.130 | 0.574 |
| Synchronous, no resection | 103/103 | 114/117 | 0.99 (0.75-1.31) | 0.951 |  | 32/38 | 31/32 | 1.39 (0.83-2.33) | 0.208 |  |
| Metachronous | 78/83 | 56/58 | 1.02 (0.71-1.45) | 0.930 |  | 17/20 | 19/23 | 0.89 (0.42-1.86) | 0.754 |  |
|  | (16) | (12) |  |  |  | (25) | (26) |  |  |  |
| **LDH elevated at randomisation** | | | | | | | | | | |
| No | 113/117 | 110/116 | 0.76 (0.58-1.00) | 0.048 | 0.606 | 63/80 | 56/63 | 1.35 (0.92-1.99) | 0.124 | 0.636 |
| Yes | 142/146 | 141/150 | 0.84 (0.65-1.08) | 0.165 |  | 43/53 | 59/67 | 1.17 (0.76-1.81) | 0.473 |  |
|  | (16) | (12) |  |  |  | (25) | (26) |  |  |  |
| **Platelet count at start induction treatment** | | | | | | | | | | |
| < 400 x 109/L | 151/156 | 160/171 | 0.84 (0.67-1.07) | 0.158 | 0.500 | 64/82 | 80/91 | 1.58 (1.10-2.26) | 0.012 | 0.119 |
| ≥ 400 x 109/L | 83/86 | 68/72 | 0.73 (0.52-1.03) | 0.073 |  | 41/50 | 34/38 | 0.99 (0.61-1.59) | 0.956 |  |
|  | (37) | (35) |  |  |  | (26) | (27) |  |  |  |
| **CEA at start induction treatment** | | | | | | | | | | |
| ≤ 20 ng/mL | 66/71 | 77/85 | 0.73 (0.51-1.04) | 0.082 | 0.691 | 23/35 | 35/43 | 1.37 (0.76-2.46) | 0.289 | 0.760 |
| > 20 ng/mL | 119/120 | 111/114 | 0.80 (0.61-1.05) | 0.107 |  | 72/85 | 68/74 | 1.23 (0.87-1.76) | 0.244 |  |
|  | (88) | (77) |  |  |  | (38) | (39) |  |  |  |
| **Mutation status** | | | | | | | | | | |
| *RAS /* V600E*BRAF* wild-type | 56/58 | 71/77 | 0.64 (0.44-0.93) | 0.020 | 0.032 | 30/42 | 31/39 | 1.51 (0.86-2.56) | 0.150 | 0.367 |
| *RAS* mutant | 120/123 | 107/110 | 0.94 (0.71-1.25) | 0.681 |  | 46/54 | 38/45 | 0.96 (0.59-1.56) | 0.867 |  |
| V600E*BRAF* mutant | 13/14 | 11/14 | 0.32 (0.14-0.76) | 0.010 |  | 5/6 | 8/8 | 1.80 (0.54-5.97) | 0.336 |  |
|  | (84) | (77) |  |  |  | (56) | (64) |  |  |  |
| Numbers between brackets: number of patients with missing values per analysis. *P*interaction= *P*-value for heterogeneity across subgroups. Analyses performed using a mixed effect Cox model with study as random intercept and treatment (and any co-variables) as fixed effects. Subgroup analyses were stratified for prior adjuvant chemotherapy, response to induction treatment, WHO/ECOG PS, and adjusted for age, sex, stage, primary tumour location, primary tumour resection, number of metastatic sites, LDH at randomisation, and interval between primary diagnosis and randomisation. Subgroup analyses for ‘stage of disease and primary tumour resection status’ were not adjusted for stage and primary tumour resection. Bev = bevacizumab. FP = fluoropyrimidine. Obs = observation. | | | | | | | | | | |