

Supplementary figure and table legends

Supplementary Figure 1: Consort diagram of BRAF-BeCool population.

Supplementary Figure 2: Kaplan-Meier curves of progression-free survival (panel A) and overall survival (panel B) according to sidedness in BRAF-BeCool population.

Supplementary Figure 3: Kaplan-Meier curves of progression-free survival and overall survival according to sidedness and treatment in the MSS/pMMR subgroup of BRAF-BeCool population.

Supplementary Figure 4: Kaplan-Meier curves of progression-free survival (panel A) and overall survival (panel B) according to ECOG-PS in BRAF-BeCool population.

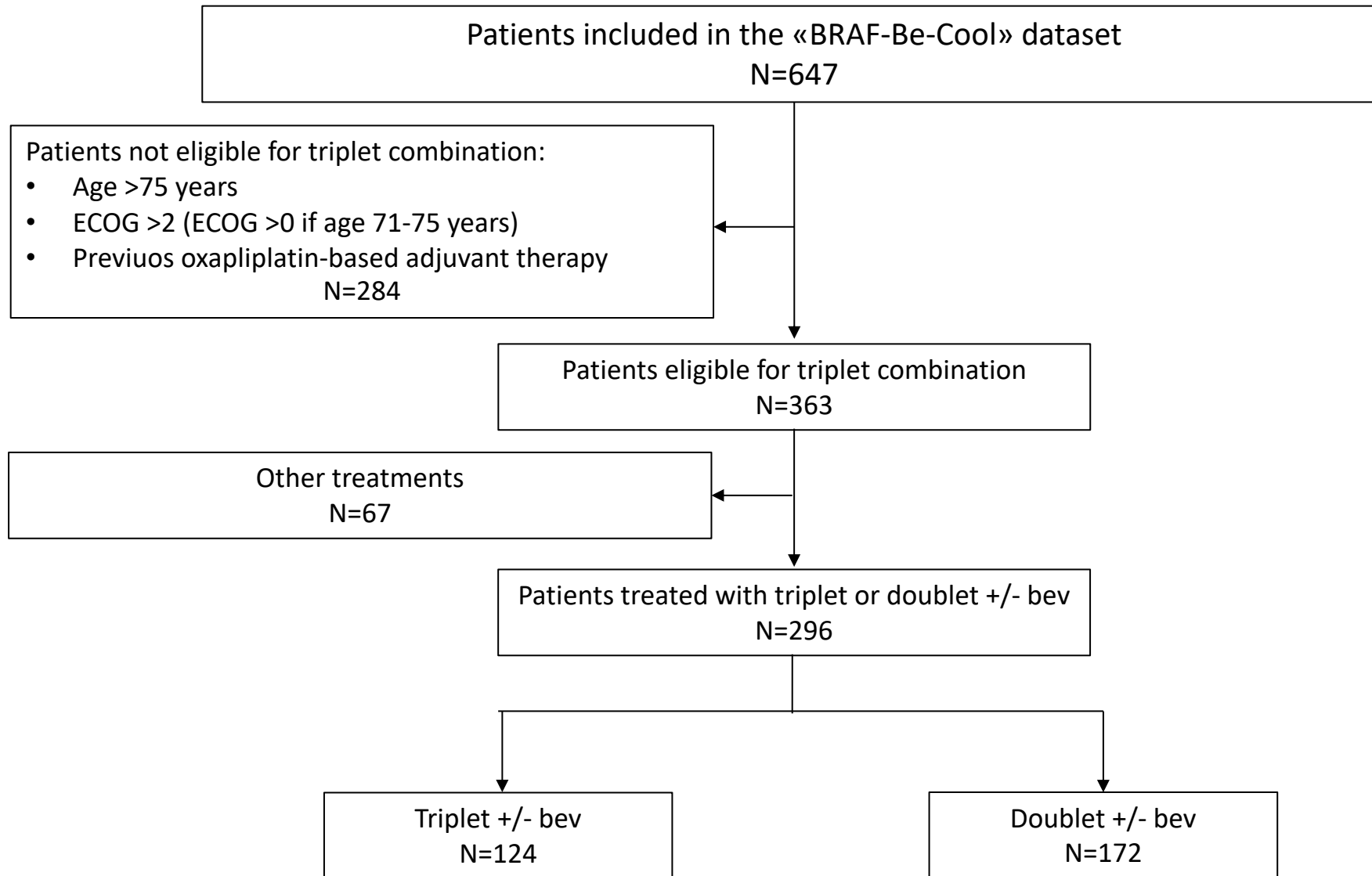
Supplementary Figure 5: Expression of TOP2A, ERCC1 and ERCC2 genes based on sidedness in both MSS/pMMR and MSI-H/dMMR cohorts of CGP population.

Supplementary Figure 6: Distribution of immune/stromal cells of tumour microenvironment based on sidedness in both MSS/pMMR (panel A) and MSI-H/dMMR (panel B) cohorts of CGP population.

Supplementary Figure 7: BM1/BM2 classification of CGP tumour samples according to the simplified Barras classifier (panel A). Distribution of BM subtypes based on sidedness in both MSS/pMMR and MSI-H/dMMR cohorts of CGP population (panel B).

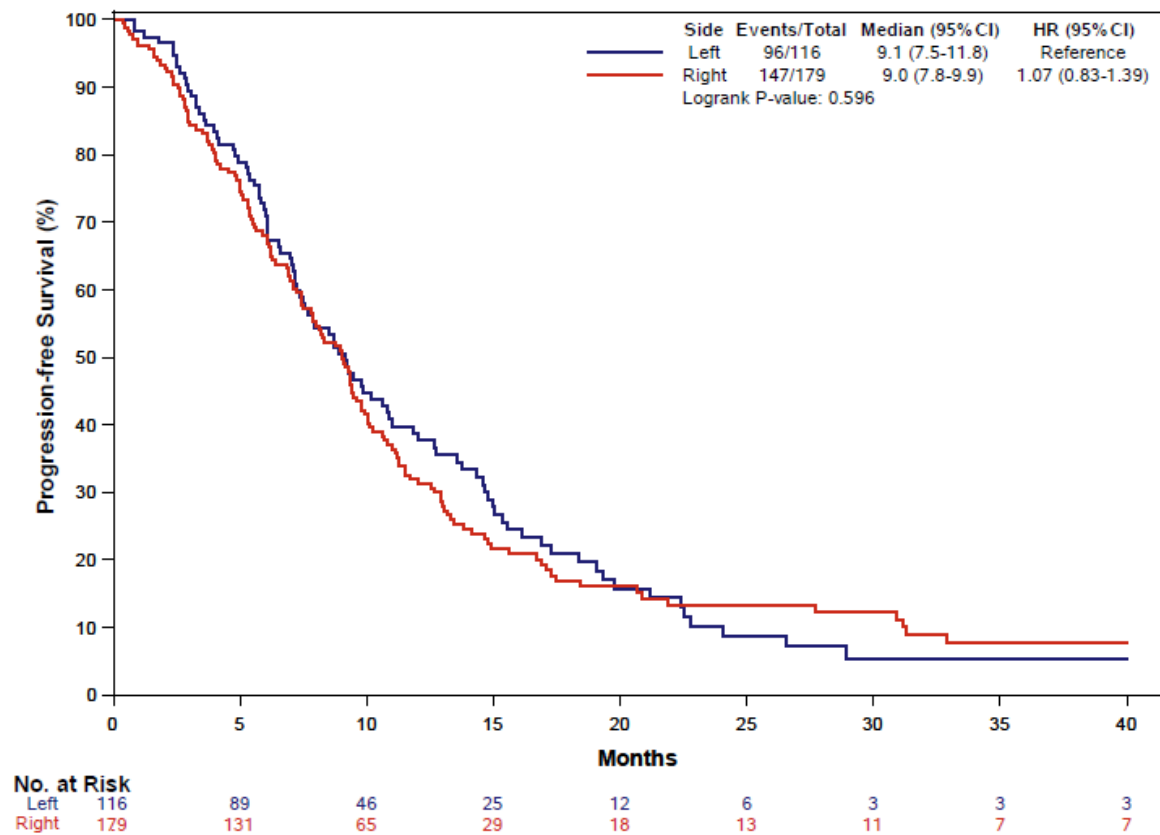
Supplementary Figure 8: Distribution and mutual exclusivity/co-occurrence of WNT pathway alterations in both MSS/pMMR (panel A) and MSI-H/dMMR (panel B) cohorts of CGP population.

Supplementary Figure 9: Frequency of most common mutations (panel A), amplifications (panel B) and fusions (panel C) in MSI-H/dMMR cohort of the CGP population.

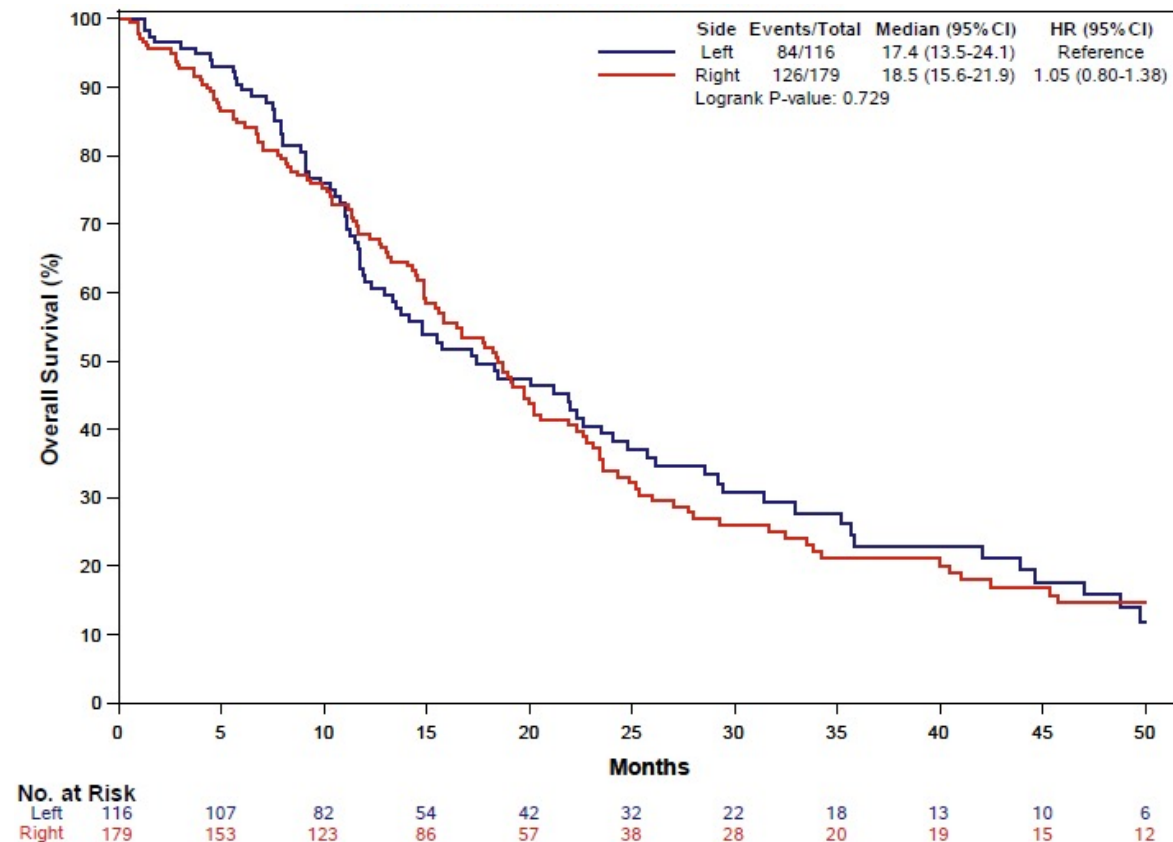


Supplementary Figure 1

Panel A

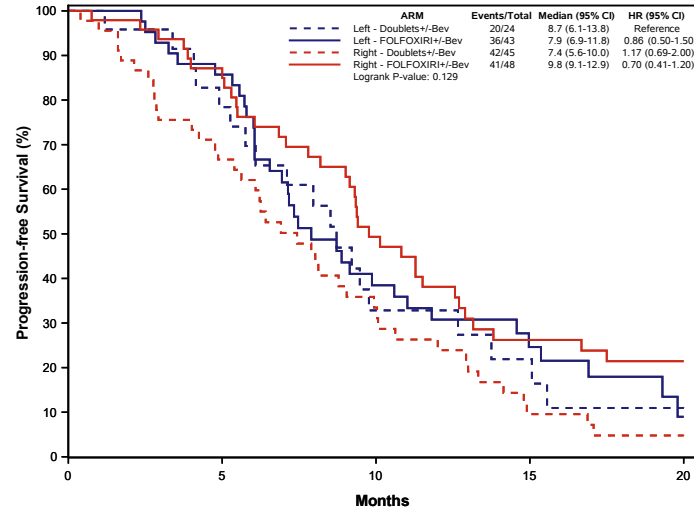


Panel B



Supplementary Figure 2

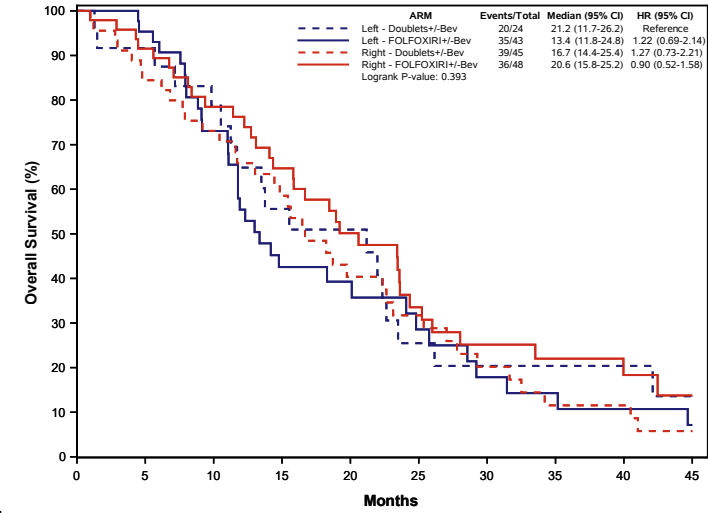
Panel A



No. at Risk

| | | | | | |
|-------------------------|----|----|----|----|---|
| Left - Doublets+/-Bev | 24 | 18 | 7 | 4 | 1 |
| Left - FOLFOXIRI+/-Bev | 43 | 36 | 15 | 8 | 2 |
| Right - Doublets+/-Bev | 45 | 30 | 14 | 4 | 2 |
| Right - FOLFOXIRI+/-Bev | 48 | 40 | 22 | 11 | 8 |

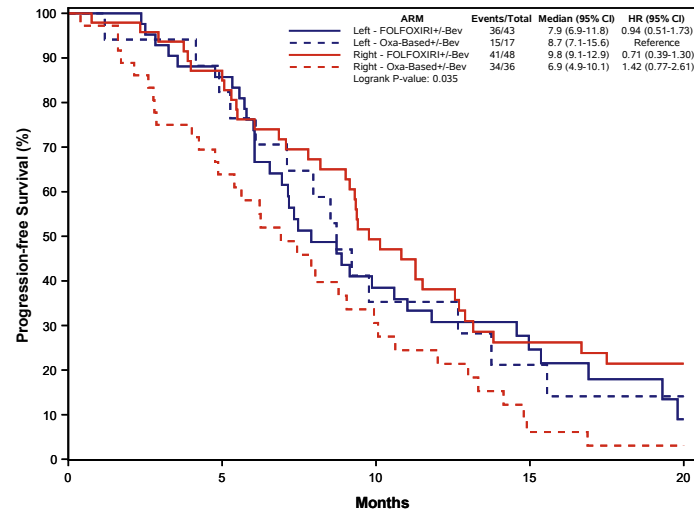
Panel B



No. at Risk

| | | | | | | | | | | |
|-------------------------|----|----|----|----|----|----|---|---|---|---|
| Left - Doublets+/-Bev | 24 | 22 | 18 | 12 | 10 | 5 | 4 | 3 | 3 | 2 |
| Left - FOLFOXIRI+/-Bev | 43 | 41 | 29 | 16 | 11 | 8 | 5 | 4 | 3 | 2 |
| Right - Doublets+/-Bev | 45 | 38 | 32 | 24 | 15 | 11 | 7 | 4 | 4 | 2 |
| Right - FOLFOXIRI+/-Bev | 48 | 43 | 35 | 28 | 19 | 12 | 8 | 6 | 5 | 3 |

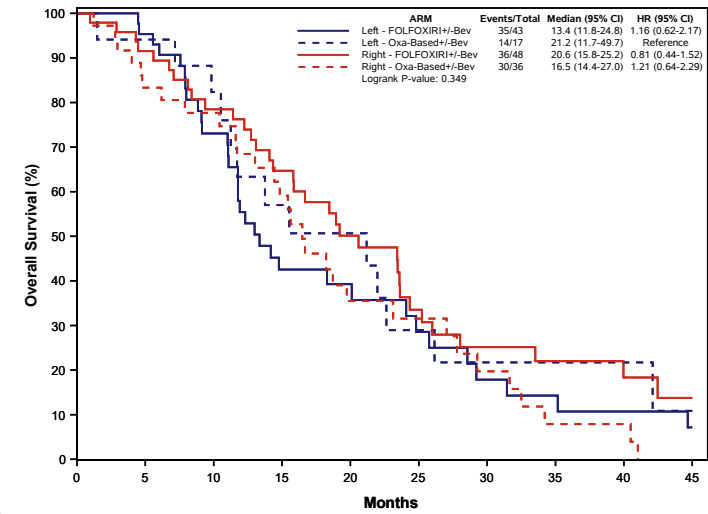
Panel C



No. at Risk

| | | | | | |
|-------------------------|----|----|----|----|---|
| Left - FOLFOXIRI+/-Bev | 43 | 36 | 15 | 8 | 2 |
| Left - Oxa-Based+/-Bev | 17 | 14 | 6 | 3 | 1 |
| Right - FOLFOXIRI+/-Bev | 48 | 40 | 22 | 11 | 8 |
| Right - Oxa-Based+/-Bev | 36 | 23 | 10 | 2 | 1 |

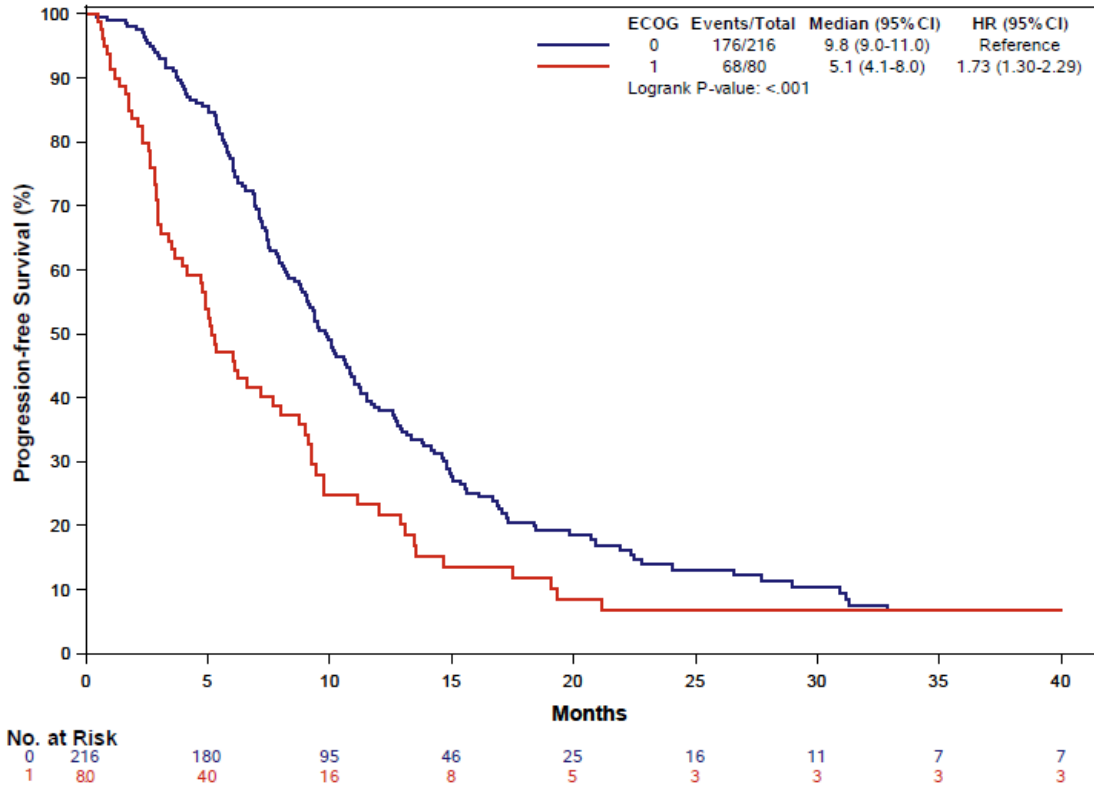
Panel D



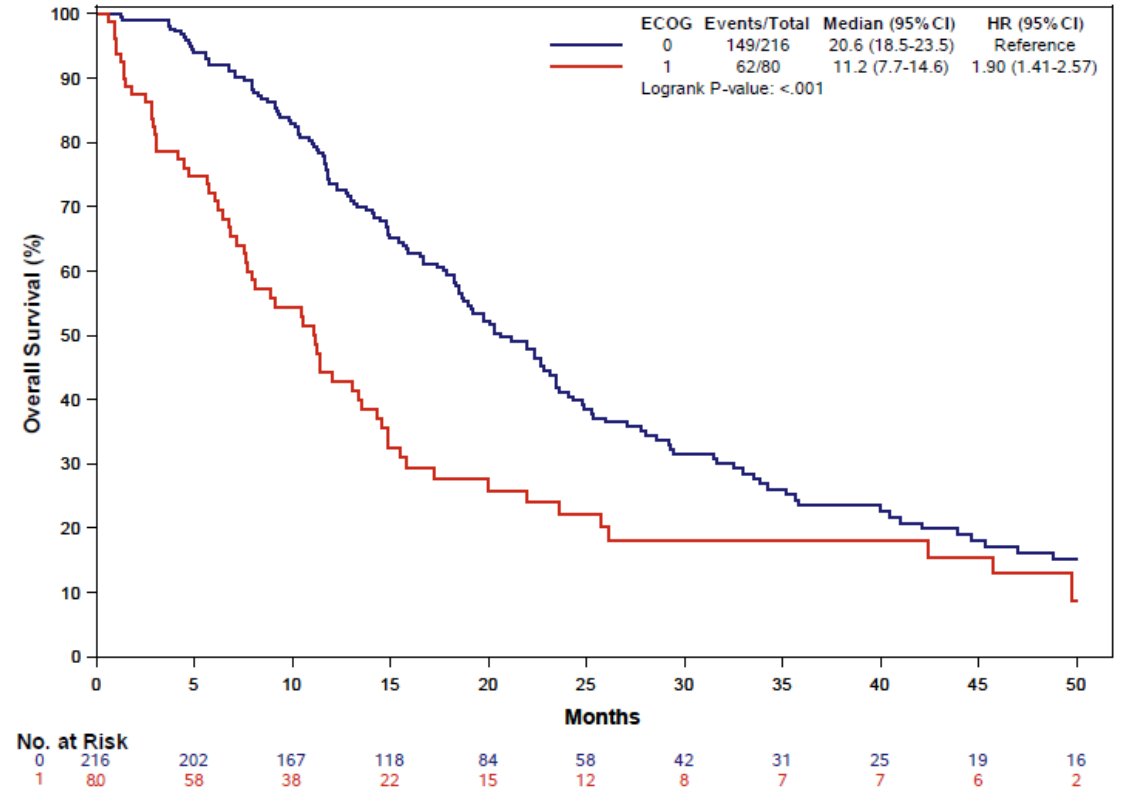
No. at Risk

| | | | | | | | | | | |
|-------------------------|----|----|----|----|----|----|---|---|---|---|
| Left - FOLFOXIRI+/-Bev | 43 | 41 | 29 | 16 | 11 | 8 | 5 | 4 | 3 | 2 |
| Left - Oxa-Based+/-Bev | 17 | 16 | 14 | 9 | 7 | 4 | 3 | 2 | 2 | 1 |
| Right - FOLFOXIRI+/-Bev | 48 | 43 | 35 | 28 | 19 | 12 | 8 | 6 | 5 | 3 |
| Right - Oxa-Based+/-Bev | 36 | 30 | 27 | 19 | 10 | 8 | 5 | 2 | 2 | 0 |

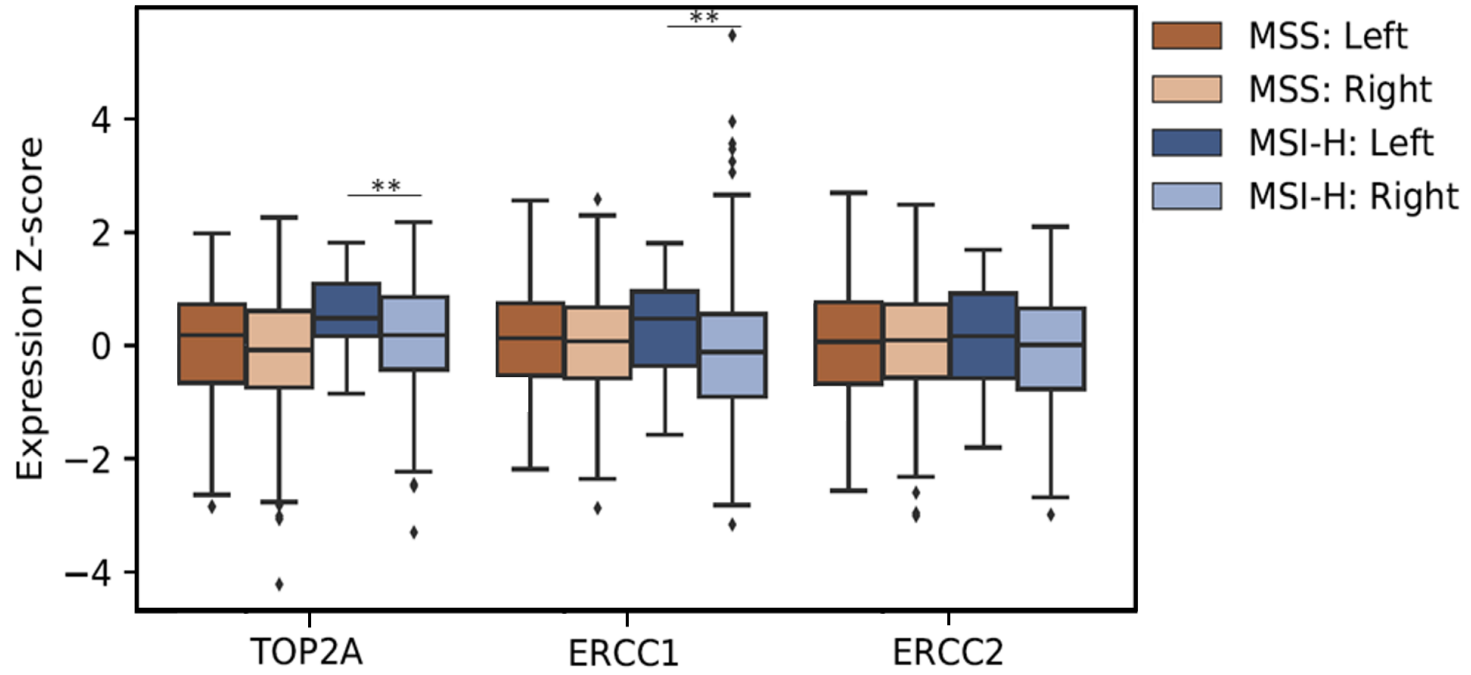
Panel A



Panel B



Supplementary Figure 4

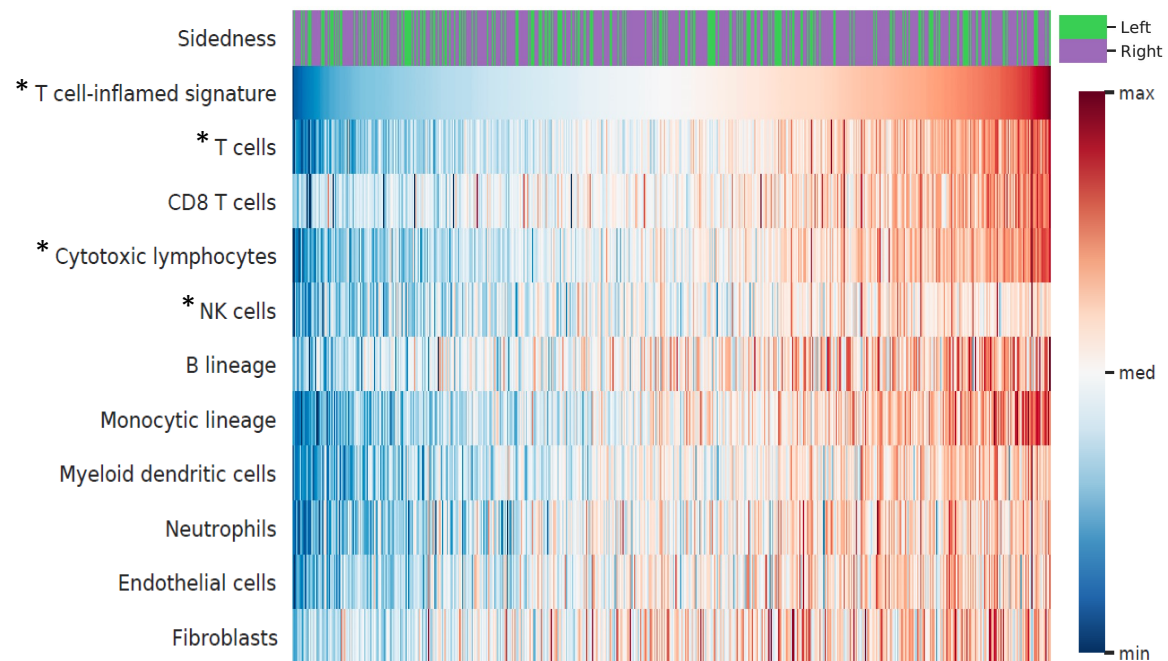


| Gene | Subgroup | Median expression (TPM) | | Fold change (Left/Right) | p-value | q-value |
|-------|----------|-------------------------|-------|--------------------------|---------------|--------------|
| | | Left | Right | | | |
| TOP2A | MSS | 35.2 | 28.7 | 1.2 | 0.067 | 0.15 |
| | MSI-H | 44.8 | 35.3 | 1.3 | 0.0066 | 0.030 |
| ERCC1 | MSS | 9.2 | 8.9 | 1.0 | 0.27 | 0.31 |
| | MSI-H | 11.2 | 8.0 | 1.4 | 0.0049 | 0.030 |
| ERCC2 | MSS | 5.7 | 5.8 | 1.0 | 0.42 | 0.42 |
| | MSI-H | 6.0 | 5.5 | 1.1 | 0.087 | 0.16 |

Supplementary Figure 5

Panel A

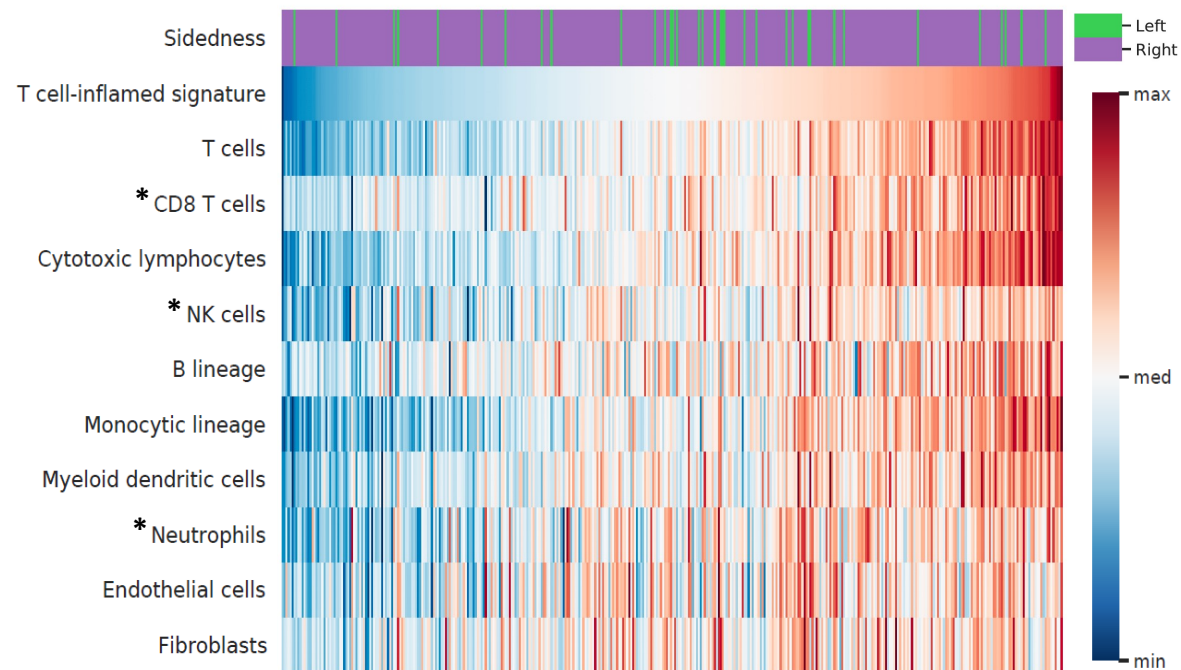
MSS/pMMR



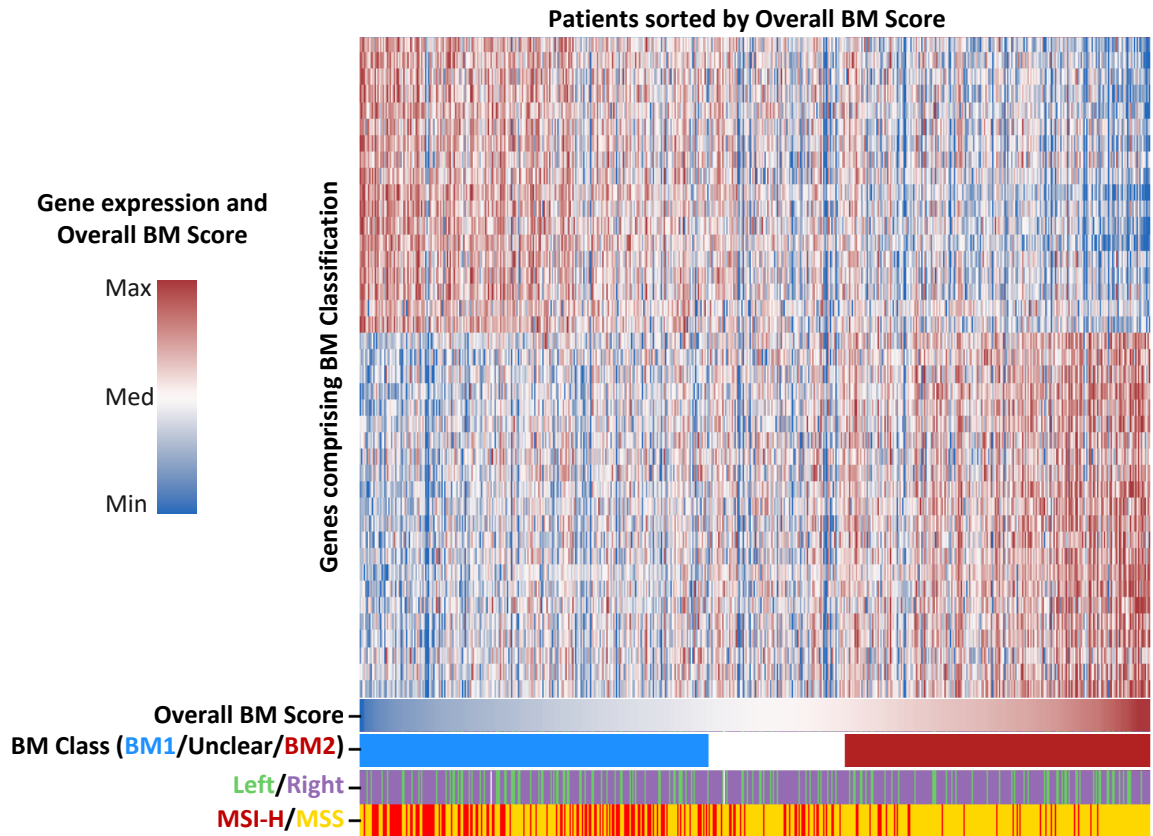
*p<0.05 (raw p-value)

Panel B

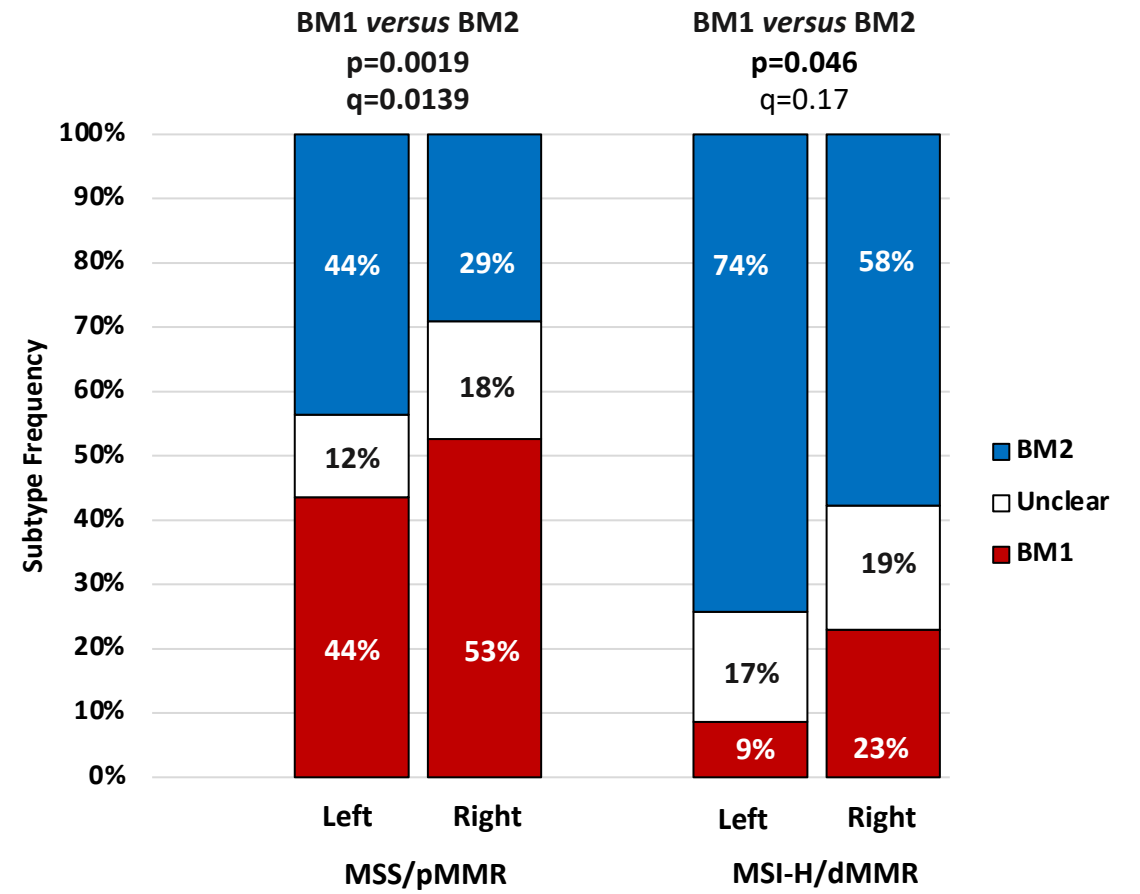
MSI-H/dMMR



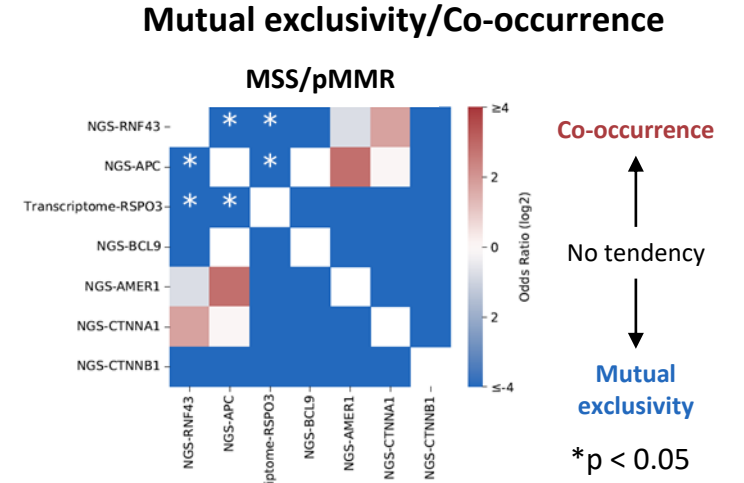
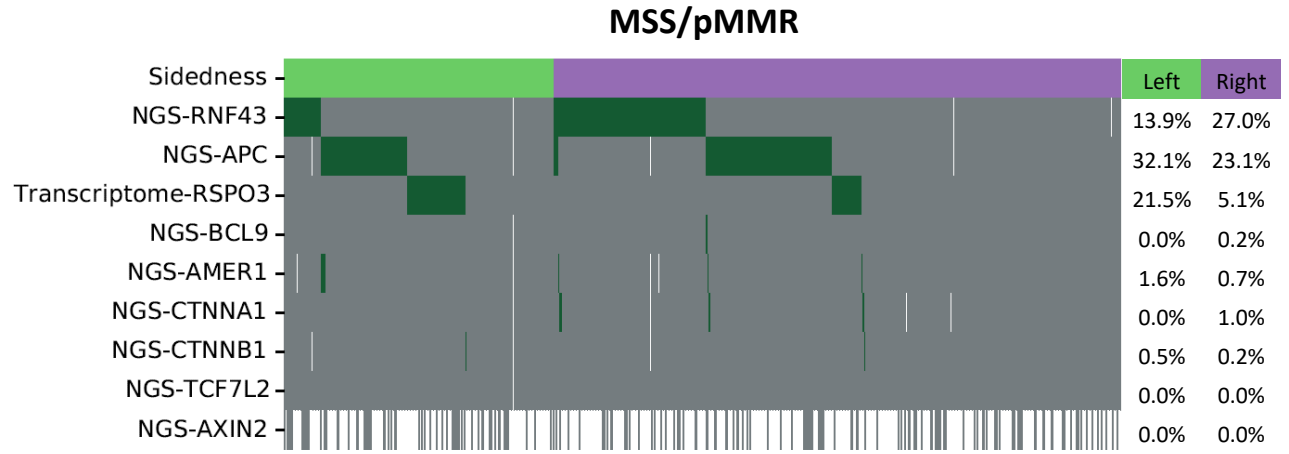
Panel A



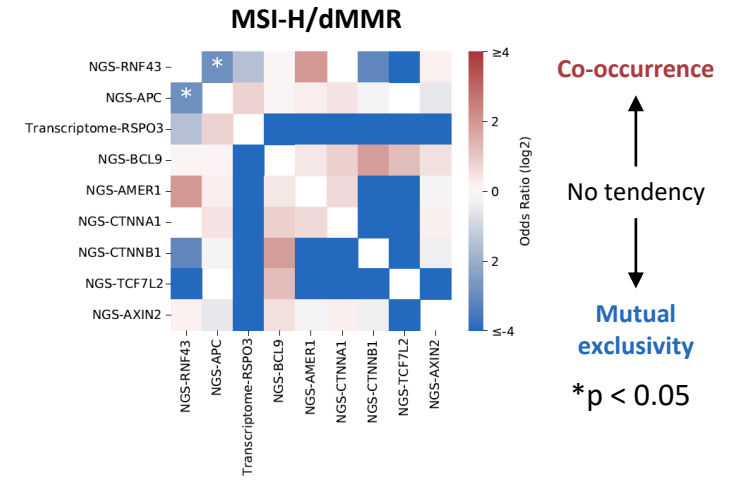
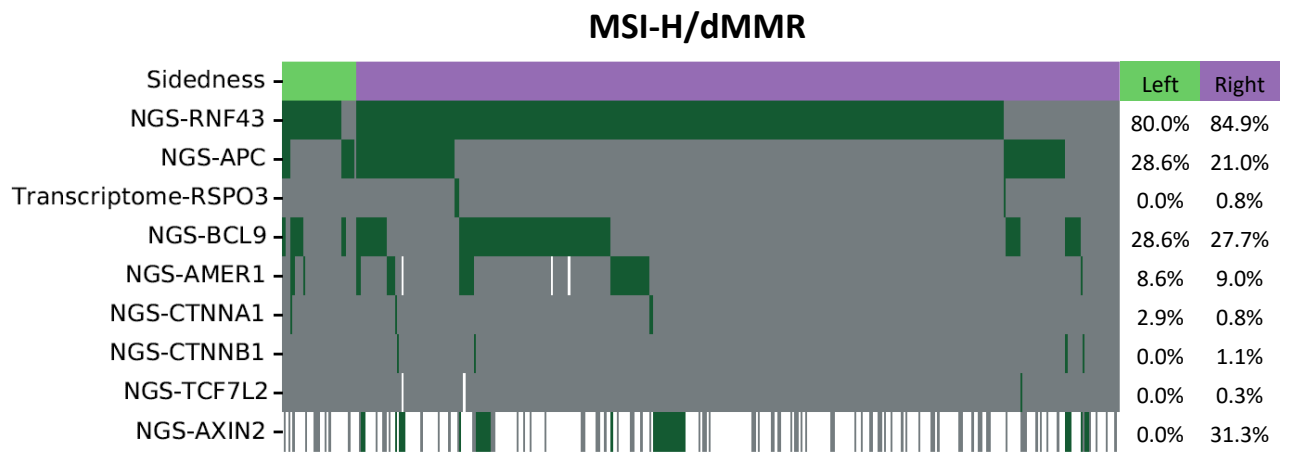
Panel B



Panel A

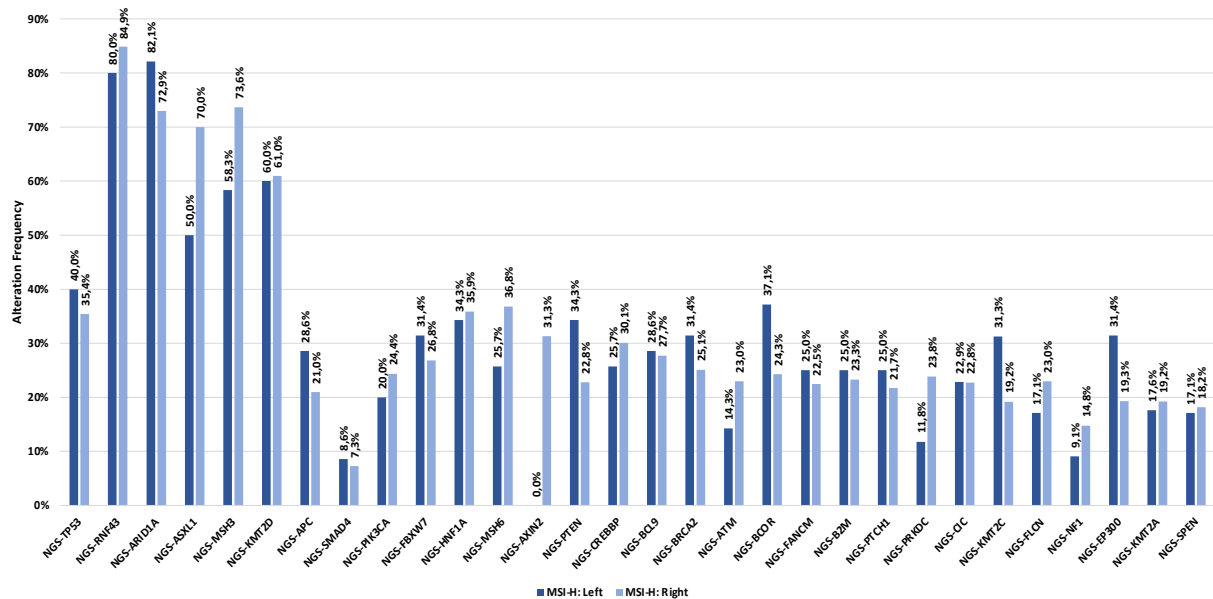


Panel B

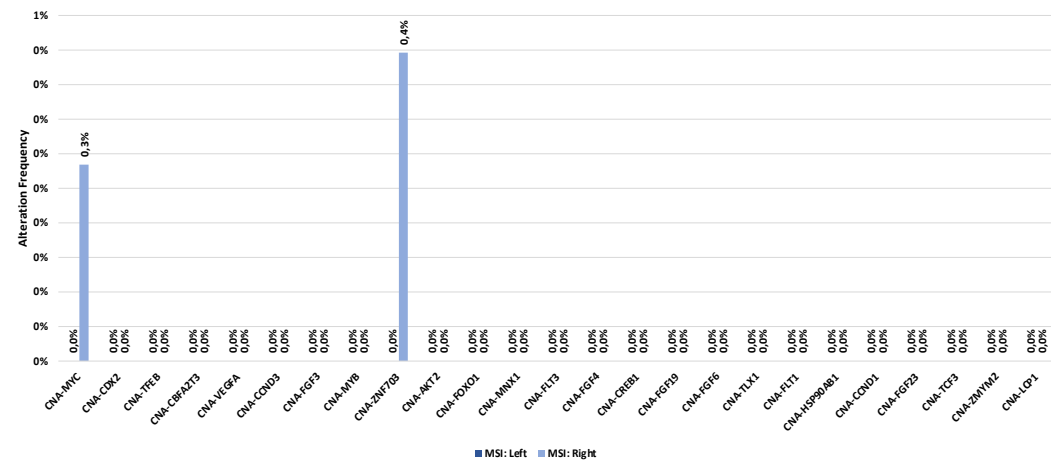


Mutation/Fusion ■ Positive ■ Negative □ Indeterminate Note: AXIN2 only available on WES panel

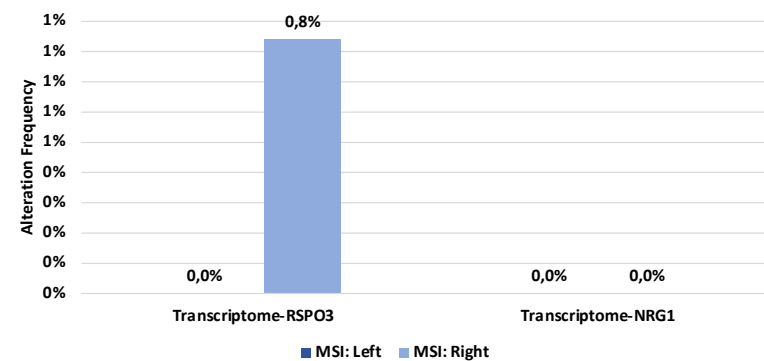
Panel A



Panel B



Panel C



Supplementary Table 1. Patients' characteristics of BRAF-BeCool population

| | Overall population N=296 n (%) |
|--------------------------------------|--------------------------------------|
| Age (years) | |
| Median | 61 |
| Range (min – max) | 24 - 75 |
| Sex | |
| Male | 138 (47%) |
| Female | 158 (53%) |
| ECOG-PS | |
| 0 | 216 (73%) |
| 1-2 | 80 (27%) |
| Site of Primary Tumor | |
| Right | 179 (61%) |
| Left and rectum | 116 (39%) |
| NA | 1 |
| Microsatellite status | |
| pMMR/MSS | 160 (83%) |
| dMMR/MSI-H | 32 (17%) |
| NA | 104 |
| Resected Primary Tumor | |
| Yes | 215 (73%) |
| No | 81 (27%) |
| Liver Only Disease | |
| Yes | 75 (25%) |
| No | 221 (75%) |
| Number of metastatic sites | |
| 1 | 144 (49%) |
| >1 | 152 (51%) |
| R0/R1 Resection of metastases | |
| Yes | 54 (18%) |
| No | 242 (82%) |

| | | |
|-------------------------------------|---|-----------|
| Time to Metastases | | |
| | Synchronous | 264 (89%) |
| | Metachronous | 32 (11%) |
| Simplified risk score | | |
| | High | 61 (21%) |
| | Intermediate | 100 (34%) |
| | Low | 132 (45%) |
| | NA | 3 |
| Treatment arm | | |
| | Doublet +/- bev | 172 (58%) |
| | Triplet +/- bev | 124 (42%) |
| Bevacizumab-based treatment | | |
| | Yes | 237 (80%) |
| | No | 59 (20%) |
| Chemotherapy-based treatment | | |
| | Oxaliplatin-based | 134 (45%) |
| | Irinotecan-based | 38 (13%) |
| | Oxaliplatin and irinotecan-based | 124 (42%) |

Legend: N=number, ECOG-PS=Eastern Cooperative Oncology Group Performance Status, NA=not available, pMMR= proficient mismatched repair, MSS=microsatellite stable, dMMR=deficient mismatched repair, MSI-H=microsatellite instability high; Simplified score as described by Loupakis et al.¹².

Supplementary Table 2. Uni- and multivariate analyses for progression-free survival and overall survival in BRAF-BeCool population

| | | Progression-free survival | | | | Overall survival | | | |
|--------------------------------------|-----------|---------------------------|------------------|-----------------------|------------------|---------------------|------------------|-----------------------|------------------|
| Characteristics | N (%) | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| | | HR (95% CI) | <i>p</i> | HR (95% CI) | <i>P</i> | HR (95% CI) | <i>p</i> | HR (95% CI) | <i>p</i> |
| ECOG PS | | | | | | | | | |
| 0 | 216 (73%) | 1 | <0.001 | 1 | 0.12 | 1 | <0.001 | 1 | 0.13 |
| 1-2 | 80 (27%) | 1.73 (1.30-2.29) | | 1.53 (0.89-2.61) | | 1.91 (1.41-2.57) | | 1.50 (0.89-2.51) | |
| Simplified risk score | | | | | | | | | |
| Low | 132 (44%) | 1 | | 1 | | 1 | | - | |
| Intermediate | 100 (34%) | 1.12 (0.84-1.50) | 0.44 | 0.61 (0.40-0.94) | 0.023 | 1.40 (1.02-1.92) | 0.036 | 0.89 (0.56-1.43) | 0.64 |
| High | 61 (21%) | 2.29 (1.63-3.21) | <0.001 | 1.14 (0.58-2.21) | 0.71 | 2.75 (1.93-3.92) | <0.001 | 1.58 (0.79-3.13) | 0.19 |
| NA | 3 | | | | | | | | |
| Time to Metastases | | | | | | | | | |
| Metachronous | 32 (11%) | 1 | 0.41 | - | - | 1 | 0.15 | - | - |
| Synchronous | 264 (89%) | 1.18 (0.79-1.76) | | - | | 1.37 (0.88-2.13) | | - | |
| Resected Primary Tumour | | | | | | | | | |
| No | 81 (27%) | 1 | <0.001 | 1 | 0.049 | 1 | <0.001 | 1 | <0.001 |
| Yes | 215 (73%) | 0.49 (0.37-0.66) | | 0.66 (0.43-0.99) | | 0.34 (0.25-0.46) | | 0.47 (0.30-0.73) | |
| Liver Only Disease | | | | | | | | | |
| No | 221 (75%) | 1 | 0.80 | - | - | 1 | 0.09 | 1 | 0.74 |
| Yes | 75 (25%) | 0.96 (0.73-1.28) | | - | | 0.77 (0.56-1.05) | | 1.09 (0.66-1.78) | |
| Number of metastatic sites | | | | | | | | | |
| 1 | 144 (49%) | 1 | <0.001 | 1 | 0.046 | 1 | <0.001 | 1 | 0.41 |
| >1 | 152 (51%) | 1.61 (1.25-2.08) | | 1.50 (1.01-2.22) | | 1.60 (1.22-2.10) | | 1.23 (0.76-2.01) | |
| R0/R1 Resection of metastases | | | | | | | | | |
| Yes | 54 (18%) | 1 | <0.001 | 1 | <0.001 | 1 | <0.001 | 1 | 0.026 |
| No | 242 (82%) | 2.00 (1.42-2.81) | | 2.13 (1.36-3.32) | | 2.08 (1.44-3.00) | | 1.70 (1.06-2.72) | |

| | | | | | | | | | |
|------------------------------------|-----------|------------------|-------|------------------|--------|------------------|--------|------------------|--------|
| Site of Primary Tumour | | | | | | | | | |
| Right | 179 (60%) | 1 | 0.60 | - | - | 1 | 0.73 | - | - |
| Left and rectum | 116 (39%) | 0.93 (0.72-1.21) | | - | | 0.95 (0.72-1.26) | | - | |
| NA | 1 (1%) | | | | | | | | |
| Microsatellite status | | | | | | | | | |
| pMMR/MSS | 160 (54%) | 1 | 0.057 | 1 | 0.0050 | 1 | <0.001 | 1 | <0.001 |
| dMMR/MSI-H | 32 (11%) | 0.66 (0.42-1.03) | | 0.50 (0.31-0.81) | | 0.34 (0.20-0.60) | | 0.30 (0.17-0.55) | |
| NA | 104 (35%) | | | | | | | | |
| Treatment arm | | | | | | | | | |
| Doublet +/- bev | 172 (58%) | 1 | 0.023 | 1 | 0.0012 | 1 | 0.75 | - | - |
| Triplet +/- bev | 124 (42%) | 0.75 (0.58-0.96) | | 0.57 (0.41-0.80) | | 0.96 (0.73-1.26) | | - | |
| Bevacizumab-based treatment | | | | | | | | | |
| Yes | 237 (80%) | 1 | 0.094 | 1 | 0.40 | 1 | 0.41 | - | - |
| No | 59 (20%) | 1.32 (0.96-1.82) | | 1.21 (0.77-1.91) | | 1.15 (0.83-1.61) | | - | |

Legend: HR=hazard ratio, CI=confidence interval, N=number, ECOG-PS=Eastern Cooperative Oncology Group Performance Status, NA=not available, pMMR=proficient mismatched repair, MSS=microsatellite stable, dMMR=deficient mismatched repair, MSI-H=microsatellite instability high; Simplified score as described by Loupakis et al.¹².