Supplemental Table 1. Mutation and Consensus Molecular Subtype (CMS) profile of patients with colorectal cancer classified by tumor site.

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| --- |
| Mutational Cohort (n=1876) |
|  | Cecum | Ascending Colon | Hepatic Flexure | Transverse Colon | Splenic Flexure | Descending Colon | Sigmoid Colon | Recto-sigmoid Junction | Rectum | Global P | Right P\* | Left P\* |
| Number | 313 (17) | 124 (7) | 51 (3) | 86 (5) | 36 (2) | 78 (4) | 521 (29) | 194 (11) | 422 (23) |  |  |  |
| TP53 | 170 (54) | 70 (57) | 34 (67) | 54 (63) | 19 (53) | 45 (58) | 360 (69) | 143 (74) | 291 (69) | **<0.0001** | 0.26 | **0.027** |
| KRAS | 205 (66) | 66 (53) | 22 (43) | 41 (48) | 18 (50) | 31 (40) | 197 (38) | 88 (45) | 215 (51) | **<0.0001** | **0.0008** | **0.0015** |
| APC | 142 (45) | 63 (51) | 18 (35) | 34 (40) | 20 (56) | 36 (46) | 245 (47) | 84 (43) | 186 (44)  | 0.49 | 0.20 | 0.61 |
| PIK3CA | 62 (20) | 31 (25) | 10 (20) | 14 (16) | 7 (20) | 20 (26) | 74 (14) | 17 (9) | 44 (10) | **<0.0001** | 0.46 | **0.0009** |
| SMAD4 | 55 (18) | 16 (13)  | 10 (20) | 12 (14) | 3 (8) | 11 (14) | 51 (10) | 18 (9) | 48 (11) | **0.034** | 0.54 | 0.70 |
| BRAF V600 | 30 (10) | 20 (16) | 11 (22) | 11 (13) | 2 (6) | 7 (9) | 19 (4) | 5 (3) | 5 (1) | **<0.0001** | **<0.0001** | **0.0033** |
| FBXW7 | 21 (7) | 8 (7) | 3 (6) | 9 (11) | 1 (3) | 7 (9) | 31 (6) | 18 (9)  | 41 (10) | 0.37 | 0.63 | 0.16 |
| NRAS | 15 (5) | 6 (5) | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 24 (5) | 9 (5) | 20 (5) | 0.24 | 0.23 | 0.23 |
| PTEN | 15 (5) | 7 (6) | 3 (6) | 3 (4) | 1 (3) | 2 (3) | 7 (1) | 2 (1) | 4 (1) | **0.002** | 0.89 | 0.71 |
| ATM | 5 (2) | 8 (7) | 1 (2) | 2 (2) | 0 (0) | 3 (4) | 11 (2) | 3 (2) | 8 (2) | 0.11 | **0.047** | 0.67 |
| CTNNB1 | 13 (4) | 1 (1)  | 1 (2) | 3 (4) | 2 (6) | 5 (6)  | 3 (1) | 0 (0) | 2 (1) | **<0.0001** | 0.31 | **<0.0001** |
| GNAS | 10 (3) | 4 (3) | 2 (4) | 1 (1) | 0 (0) | 2 (3) | 4 (1) | 2 (1) | 2 (1) | **0.028** | 0.75 | 0.40 |
| ERBB4 | 2 (1) | 3 (2) | 0 (0) | 0 (0)  | 0 (0) | 2 (3)  | 5 (1) | 3 (2) | 7 (2) | 0.55 | 0.18 | 0.68 |
| ERBB2 | 2 (1) | 1 (1) | 1 (1) | 1 (1) | 0 (0) | 2 (3) | 4 (1) | 1 (1) | 7 (2) | 0.69 | 0.80 | 0.38 |
| KDR | 1 (0) | 2 (2)  | 1 (2)  | 1 (1) | 0 (0) | 0 (0) | 7 (1) | 2 (1) | 5 (1) | 0.84 | 0.44 | 0.82 |
| RB1 | 5 (2) | 1 (1) | 1 (2) | 0 (0) | 1 (3) | 2 (3) | 3 (1) | 0 (0) | 3 (1) | 0.28 | 0.61 | 0.12 |
| RET | 3 (1) | 2 (2) | 0 (0) | 0 (0) | 0 (0) | 1 (1) | 4 (1) | 3 (2) | 3 (1) | 0.89 | 0.57 | 0.80 |
| SMO | 2 (1) | 2 (2) | 0 (0) | 2 (2) | 0 (0) | 0(0) | 2 (0.4) | 4 (2) | 4 (1) | 0.33 | 0.43 | 0.19 |
| SMARCB1 | 5 (2) | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 2 (3) | 2 (0) | 2 (1) | 3 (1) | 0.31 | 0.31 | 0.28 |
| AKT1 | 2 (2) | 4 (1) | 0 (0) | 1 (2)  | 0 (0) | 3 (1) | 3 (1) | 0 (0) | 1 (1) | 0.65 | 0.13 | **0.0017** |
| STK11 | 1 (0) | 3 (2) | 0 (0) | 0 (0) | 0 (0) | 1 (1) | 1 (0) | 3 (2) | 5 (1) | 0.17 | 0.074 | 0.28 |
| KIT | 2 (1) | 2 (2) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 4 (1) | 3 (2) | 2 (1) | 0.70 | 0.48 | 0.55 |
| CDKN2A | 3 (1) | 0 (0) | 0 (0) | 1 (1) | 0 (0) | 2 (3) | 0 (0) | 2 (1) | 4 (1) | 0.21 | 0.61 | 0.056 |
| MET | 3 (1) | 0 (0) | 2 (4) | 0 (0) | 0 (0) | 0 (0) | 5 (1) | 0 (0) | 2 (1) | 0.11 | 0.061 | 0.51 |
| FGFR3 | 3 (1) | 0 (0) | 0 (0) | (0) | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 6 (1) | 0.10 | 0.47 | **0.032** |
| Consensus Molecular Subtype Cohort (n=608) |
| Number  | 122 | 85 | 25 | 36 | 6 | 30 | 160 | 40 | 104 | **<0.0001** | 0.36 | 0.096 |
| CMS I | 36 (30) | 35 (41) | 13 (52) | 12 (33) | 1 (17) | 0 (0) | 5 (3) | 0 (0) | 4 (4) |  |  |  |
| CMS II | 33 (27) | 24 (28) | 8 (32) | 12 (33) | 3 (50) | 12 (40) | 104 (65) | 26 (65) | 58 (56) |  |  |  |
| CMS III | 25 (20) | 12 (14) | 2 (8) | 5 (14) | 1 (17) | 5 (17) | 9 (6) | 5 (13) | 14 (13) |  |  |  |
| CMS IV | 28 (23) | 14 (16) | 2 (8) | 7 (19) | 1 (17) | 13 (43) | 42 (26) | 9 (23) | 28 (27) |  |  |  |
| CpG Island Methylator Phenotype (CIMP) Cohort (n=457) |
| Number | 80 | 53 | 11 | 25 | 9 | 20 | 137 | 36 | 86 |  |  |  |
| CIMP-H | 22 (28) | 19 (36) | 0 (0) | 8 (32) | 3 (33) | 2 (10) | 25 (18) | 5 (14) | 20 (23) | **0.039** | 0.12 | 0.42 |

\*Only genes with a mutation in >10 patients in the cohort of 1876 are displayed. Global P represents a comparison of alteration prevalence across all tumor sites, while Right P and Left P represent a comparison within tumor sites classified as belonging to the same side, right or left.

Supplemental Table 2. Mutation profile of patients with stage IV colorectal cancer stratified by tumor side and site of biopsy.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Right Sided Colon | Left Sided Colon | Rectum |
|  | Primary | Metastasis | P | Primary | Metastasis | P | Primary | Metastasis | P |
| Number | 388 | 202 |  | 501 | 340  |  | 251 | 162 |  |
| TP53 | 211 (54) | 122 (60) | 0.16 | 334 (67) | 239 (70) | 0.27 | 167 (67) | 117 (72) | 0.22 |
| KRAS | 223 (57) | 124 (61) | 0.36 | 204 (41) | 132 (39) | 0.58 | 131 (52) | 79 (49) | 0.50 |
| APC | 179 (46) | 84 (42) | 0.29 | 233 (47) | 156 (46) | 0.86 | 116 (46) | 64 (40) | 0.18 |
| PIK3CA | 89 (23) | 33 (16) | 0.060 | 73 (15) | 48 (14) | 0.85 | 32 (13) | 9 (6) | 0.017 |
| SMAD4 | 63 (16) | 32 (16) | 0.90 | 34 (7) | 50 (15) | 0.0002 | 26 (10) | 20 (12) | 0.53 |
| BRAF V600 | 54 (14) | 16 (8) | 0.033 | 23 (5) | 11 (3) | 0.33 | 3 (1) | 2 (1) | 1 |
| NRAS | 17 (4) | 6 (3) | 0.4 | 22 (4) | 12 (4) | 0.53 | 14 (6) | 5 (3) | 0.24 |
| PTEN | 23 (6) | 5 (2) | 0.061 | 8 (2) | 5 (1) | 0.88 | 3 (1) | 1 (1) | 1 |
| CTNNB1 | 11 (3) | 6 (3) | 0.93 | 7 (1) | 3 (1) | 0.50 | 0 (0) | 2 (1) | 0.15 |
| MSI-H\* | 23 (7) | 7 (5) | 0.25 | 11 (3) | 4 (1) | 0.45 | 6 (3) | 1 (1) | 0.25 |

\*MSI status known for 1495 patients

Supplementary Table 3. Summary of univariate and multivariate models used to compare overall survival in metastatic colorectal cancer based on primary tumor location.

|  |  |  |
| --- | --- | --- |
| **Variable** | **Hazard Ratio (95% CI)** | **P-Value** |
| **Univariate Analysis of the Impact of Tumor Location on Overall Survival** |
| Location |  |  |
|  Rectum | Reference (1.00) |  |
|  Rectosigmoid Junction | 0.95 (0.75-1.20) | 0.64 |
|  Sigmoid Colon | 1.01 (0.85-1.21) | 0.88 |
|  Descending Colon | 1.30 (0.93-1.80) | 0.12 |
|  Splenic Flexure | 1.19 (0.75-1.91) | 0.46 |
|  Transverse Colon | 1.38 (1.02-1.88) | **0.038** |
|  Hepatic Flexure | 1.98 (1.38-2.85) | **<0.0001** |
|  Ascending Colon | 1.72 (1.34-2.21) | **<0.0001** |
|  Cecum | 1.69 (1.40-2.04) | **<0.0001** |
| **Multivariate Analysis of the Impact of Tumor Location on Overall Survival\*** |
| Location |  |  |
|  Rectum | Reference (1.00) |  |
|  Rectosigmoid Junction | 0.97 (0.74-1.27 | 0.83 |
|  Sigmoid Colon | 0.98 (0.80-1.20) | 0.87 |
|  Descending Colon | 1.13 (0.78-1.63) | 0.51 |
|  Splenic Flexure | 0.97 (0.55-1.70) | 0.91 |
|  Transverse Colon | 1.27 (0.91-1.81) | 0.18 |
|  Hepatic Flexure | 1.70 (1.13-2.57) | **0.011** |
|  Ascending Colon | 1.39 (1.03-1.87) | **0.029** |
|  Cecum | 1.33 (1.06-1.67) | **0.012** |
| Stage at Diagnosis |  |  |
|  Stage I-III | Reference (1.00) |  |
|  Stage IV  | 1.52 (1.30-1.77) | **<0.0001** |
| Histology |  |  |
|  Adenocarcinoma | Reference (1.00) |  |
|  Mucinous/Signet Histology | 1.49 (1.24-1.80) | **<0.0001** |
| BRAF V600 Mutation Status |  |  |
|  Wild-type | Reference (1.00) |  |
|  Mutated | 1.83 (1.36-2.46) | **<0.0001** |
| KRAS/NRAS Mutation Status |  |  |
|  Wild-type | Reference (1.00) |  |
|  Mutated | 1.32 (1.13-1.54) | **<0.0001** |

\*Variables selected for multivariate model using a forward likelihood ratio selection with P<0.1 for inclusion of each variable. Other variables considered for the model but where P>0.1 included gender, MSI status, age and mutations in *TP53, KRAS, PIK3CA, SMAD4, PTEN, GNAS, CTNNB1, FGFR3* and *AKT1.*