**Supplementary tables**

**Table S1: pmCRC patient cohort characteristics**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **CRC-05A / B** | **CRC-06** | **CRC-09** | **CRC-13** | **CRC-19A / D** | **CRC-21B** | **CRC-28A / B** | **CRC-39** | **CRC-55A / B** | **CRC-69A** |
| **Age** | 76 | 59 | 44 | 69 | 47 | 53 | 53 | 49 | 57 | 76 |
| **Sex** | f | m | f | m | f | m | m | m | m | f |
| **Primary colon site** | right | right | left | right | left | left | right | left | left | n.a. |
| **Pathology** | mucAC | AC | mucAC | mucAC | AC | AC | AC | AC | AC | AC |
| **Differentiation** | G2 | G3 | G2 | G2 | G2 | G3 | G2 | - | G3 | G3 |
| **UICC stage** | 4b | 4b | 4 | 4 | 4 | 3b | 4 | 2a | 4 | n.a. |
| **T/N/M stage** | 4a/2a/1b | 4b/2b/1 | 2/2b/1a | 2/0/1 | 4a/1c/1 | 4a/1a/0 | 4b/2b/1b | 3/0/0 | 4/2b/0 | 3/2b/0 |
| **Chemotherapy** | FOLFOXIRI bevac | FOLFOX pani | FOLFOXIRI cape | FOLFOX bevac | FOLFOX bevac | FOLFOXIRI pani | FOLFOX | FOLFIRI | FOLFOXIRI bevac | FOLFOX |
| **Ki-67** | n.a. | 80 % | n.a. | 60 % | n.a. | 40 % | 70 % | 60 % | 60 % | 90 % |
| **MSS/MSI** | MSS | MSS | MSS | MSS | MSS | MSS | MSS | MSS | MSS | MSS |
| **KRAS status** | mut. | w.t. | mut | mut | n.a. | w.t. | mut | mut | w.t. | mut |
| **Metastasis** | syn | syn | syn | syn | syn | meta | syn | meta | meta | meta |
| **PCI** | 15 | 9 | 16 | 39 | 13 | 14 | 21 | 2 | 20 | 4 |
| **Metastasis site** | per / om | per | per | per | per / om | om | per / om | per | per / om | per |
| **KRAS mutation** | G13D | A146T | G12D | G12C | G12D | Q61K | G12D | G12S | none | G12A |
| **CMS class** | CMS4 | CMS4 | CMS4 | CMS4 | CMS4 | CMS4 | CMS4 | CMS2 | CMS4 | CMS4 |

**f,m** – female, male; **(muc)AC** – (mucinous) adenocarcinoma; **bevac** – bevacizumab; **pani** – panitumumab; **cape** – capecitabine; **w.t.** – wild type; **syn, meta** – synchronous, metachronous; **PCI** – peritoneal cancer index; **per, om** – peritoneum, omentum; **CMS** – consensus molecular subtype

**Table S2: Compound concentrations and application for preclinical treatment**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Treatment** | | **PDX** | | | **PD3D** | | | |
| **Compound** | **Target** | **dose [mg/kg]** | **application** | **sequence** | **Cmax\*5 [μM]** | **Cmax [μM]** | **Cmax/5 [μM]** | **Cmax/25 [μM]** |
| **5-FU** | DNA/RNA synth. | 100 | i.p. | q7dx4 | 2000 | 400 | 80 | 16 |
| **Oxaliplatin** | DNA/RNA synth. | 5 | i.p. | qdx5 | 18 | 3.6 | 0.72 | 0.144 |
| **Irinotecan/SN38** | Topoisomerase | 15 | i.p. | qdx5 | 0.3 | 0.06 | 0.012 | 0.0024 |
| **Regorafenib** | multi-kinase | 10 | p.o. | qd | 40 | 8 | 1.6 | 0.32 |
| **Cetuximab** | EGFR | 50 | i.p. | q7dx2 | 3 | 0.6 | 0.12 | 0.024 |
| **Dabrafenib** | BRAF | 75 | p.o. | qdx28 | 14 | 2.8 | 0.56 | 0.112 |
| **Trametinib** | MEK1/2 | 3 | p.o. | qdx28 | 0.2 | 0.04 | 0.008 | 0.0016 |
| **LY294002** | PI3K | 75 | i.p. | q4d | 100 | 20 | 4 | 0.8 |
| **Copanlisib** | PI3K | 10 | i.v. | qdx5 (5on/2off) | 5 | 1 | 0.2 | 0.04 |
| **Afatinib** | EGFR/ErbB | 10 | p.o. | qdx28 | 0.05 | 0.01 | 0.002 | 0.0004 |
| **Ruxolitinib** | JAK1/2 | 50 | p.o. | b.i.d. | 6 | 1.2 | 0.24 | 0.048 |
| **Everolimus** | mTOR | 5 | p.o. | qdx5 (5on/2off) | 0.1 | 0.02 | 0.004 | 0.0008 |
| **Crizotinib** | ALK, c-MET | 50 | p.o. | qdx28 | 1 | 0.2 | 0.04 | 0.008 |
| **Docetaxel** | microtubules | 12 | i.v. | q7dx4 | 18 | 3.6 | 0.72 | 0.144 |
| **Erlotinib** | EGFR | 50 | p.o. | qdx5 | 16 | 3.2 | 0.64 | 0.128 |
| **Bevacizumab** | VEGF | 5 | i.p. | b.i.w. | n.a. | n.a. | n.a. | n.a. |
| **Selumetinib** | MEK1/2 | 50 | i.p. | b.i.d. | n.a. | n.a. | n.a. | n.a. |
| **Olaparib** | PARP | n.a. | n.a. | n.a. | 87.34 | 17.47 | 3.49 | 0.7 |

**i.p.** – intraperitoneal; **p.o.** – per os; **i.v.** – intravenous; **qd** – daily; **q4d** – every fourth day; **q7d** – weekly; **b.i.d.** – twice a day; **b.i.w.** – twice a week; **n.a.** – not applied

**Table S3: PDX treatment response (T/C)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **CRC-05A** | **CRC-05B** | **CRC-06** | **CRC-09** | **CRC-13** | **CRC-19A** | **CRC-19D** | **CRC-21** | **CRC-28A** | **CRC-28B** | **CRC-39** | **CRC-55A** | **CRC-55B** | **CRC-69A** |
| **5-FU** | - | ++ | + | ++ | ++ | + | - | +++ | + | - | ++ | - | - | + |
| **Oxaliplatin** | +++ | + | - | + | + | + | - | +++ | - | - | + | - | - | - |
| **Irinotecan** | ++ | +++ | ++ | + | ++ | ++ | - | ++ | ++ | + | ++ | ++ | +++ | - |
| **Regorafenib** | - | ++ | + | + | + | ++ | - | ++ | + | + | ++ | + | ++ | - |
| **Cetuximab** | - | ++ | + | + | + | ++ | - | + | - | - | ++ | - | - | + |
| **Dabrafenib** | - | + | - | + | - | - | - | - | + | - | - | - | - | ++ |
| **Trametinib** | ++ | + | + | ++ | - | + | ++ | + | + | + | ++ | - | - | +++ |
| **LY294002** | + | - | - | + | - | - | + | + | + | - | + | - | - | ++ |
| **Copanlisib** | - | + | - | + | - | - | + | - | - | - | - | - | - | +++ |
| **Afatinib** | - | + | - | + | - | - | + | + | - | - | - | - | - | ++ |
| **Ruxolitinib** | - | - | - | + | + | - | + | + | - | + | + | - | - | +++ |
| **Everolimus** | - | ++ | - | + | - | - | ++ | + | + | + | + | - | - | ++ |
| **Crizotinib** | - | - | - | + | - | - | - | - | - | - | - | - | - | + |
| **Docetaxel** | + | + | + | ++ | + | ++ | - | + | + | + | ++ | - | - | + |
| **Erlotinib** | - | ++ | - | + | ++ | + | - | ++ | + | - | ++ | - | - | + |
| **Bevacizumab** | + | ++ | + | + | + | ++ | - | + | + | - | ++ | + | + | + |
| **Selumetinib** | - | ++ | + | + | + | ++ | - | ++ | + | + | ++ | - | + | + |

Response categories (T/C): **+++/dark green** – 0%-10% (strong response), **++/olive** –11%-25% (moderate response), **+/yellow** – 26%-50% (minor response), **-/orange** – >50% (resistance)

**Table S4: PD3D treatment response (viability at Cmax)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **CRC-06** | **CRC-19A** | **CRC-21** | **CRC-28A** | **CRC-28B** | **CRC-39** | **CRC-55A** | **CRC-55B** | **CRC-69A** |
| **5-FU** | ++ | ++ | - | ++ | ++ | - | + | + | ++ |
| **Oxaliplatin** | + | - | - | - | - | - | + | - | + |
| **SN38** | ++ | - | - | ++ | ++ | - | - | ++ | + |
| **Regorafenib** | - | + | ++ | + | + | - | - | + | ++ |
| **Cetuximab** | - | - | - | - | - | - | - | - | - |
| **Dabrafenib** | - | - | - | - | - | - | - | - | + |
| **Trametinib** | + | ++ | ++ | + | + | - | + | + | +++ |
| **LY294002** | - | + | +++ | - | + | - | + | ++ | ++ |
| **Copanlisib** | + | +++ | +++ | + | + | - | ++ | +++ | + |
| **Afatinib** | - | - | - | - | - | - | - | - | + |
| **Ruxolitinib** | - | - | - | - | - | + | - | - | - |
| **Everolimus** | - | - | - | - | - | - | - | + | - |
| **Crizotinib** | - | - | - | - | - | - | - | - | + |
| **Docetaxel** | +++ | + | + | + | - | - | + | ++ | + |
| **Erlotinib** | - | + | + | - | + | - | + | ++ | ++ |

Response categories (viability@Cmax):**+++/dark green** – 0%-30% (strong response), **++/olive** – 31%-60% (moderate response), **+/yellow** – 61%-80% (minor response), **-/orange** – >80% (resistance)

**Table S5: PD3D treatment response (IC50)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Cmax** | **CRC-06** | **CRC-19A** | **CRC-21B** | **CRC-28A** | **CRC-28B** | **CRC-39** | **CRC-55A** | **CRC-55B** | **CRC-69A** |
| **5-FU** | **400** | 10.08 | 17.08 | 2960.00 | 4.30 | 5.11 | 1032.00 | 132.20 | 59.48 | 34.68 |
| **Oxaliplatin** | **3,6** | 5.09 | 36.53 | 46.04 | 301.00 | - | - | 17.07 | 161.90 | 3.65 |
| **SN38** | **0,06** | 0.01 | 0.11 | 3.85 | 0.02 | 0.03 | 10.13 | 0.17 | 0.02 | 0.02 |
| **Regorafenib** | **8** | 12.29 | 7.90 | 0.67 | 6.81 | 1.52 | 9.10 | 9.72 | 4.38 | 5.99 |
| **Cetuximab** | **0,6** | - | - | 34.32 | 14.22 | 4.58 | 5.01 | 153.20 | 10.60 | 2.84 |
| **Dabrafenib** | **2,8** | 233.10 | 44.71 | 7.49 | 46.03 | 36.90 | 24.90 | 43.23 | 10.01 | 15.49 |
| **Trametinib** | **0,04** | 0.03 | 0.01 | 0.01 | 0.04 | 0.01 | - | 0.03 | 0.02 | 0.00 |
| **LY294002** | **20** | 54.20 | 19.70 | 5.06 | 66.66 | 23.13 | 367.70 | 20.34 | 4.92 | 4.32 |
| **Copanlisib** | **1** | 0.26 | 0.04 | 0.02 | 1.20 | 0.21 | - | 0.04 | 0.04 | 0.14 |
| **Afatinib** | **0,01** | 2.90 | 0.68 | 0.37 |  | 0.12 | 0.07 | 1.28 | 0.10 | 0.02 |
| **Ruxolitinib** | **1,2** | - | - | 104.10 | - | - | 2.00 |  | 19.17 | 14.15 |
| **Everolimus** | **0,02** | - | 0.13 | 0.15 | - | 0.23 | 7.67 | 1.32 | 0.06 | 0.08 |
| **Crizotinib** | **0,2** | 11.68 | 2.48 | 2.49 | 39.58 | 11.74 | 1.11 | 3.78 | 1.38 | 0.32 |
| **Docetaxel** | **3,6** | 0.04 | 1.38 | 0.92 | 7.82 | 17.98 | - | 4.27 | 0.51 | 2.45 |
| **Erlotinib** | **3,2** | 110.70 | 5.66 | 3.99 | 6.58 | 2.57 | - | 2.58 | 0.70 | 0.37 |

IC50 values below Cmax are highlighted in green

**Table S6: Ratios and correlations of pmCRC sample types**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **CRC-05A** | **CRC-05B** | **CRC-06** | **CRC-09** | **CRC-13** | **CRC-19A** | **CRC-19D** | **CRC-21** | **CRC-28A** | **CRC-28B** | **CRC-39** | **CRC-55A** | **CRC-55B** | **CRC-69A** |
| **RNA** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| %PDX/Pat | 89 | n.a. | 94 | 93 | 86 | 90 | 91 | 89 | 91 | 90 | 93 | 83 | 84 | 86 |
| %PD3D/Pat | n.a. | n.a. | 91 | n.a. | n.a. | 93 | n.a. | 92 | 92 | 94 | 97 | 87 | 91 | n.a. |
| %PD3D/PDX | n.a. | n.a. | 97 | n.a. | n.a. | 100 | n.a. | 100 | 100 | 100 | 100 | 100 | 100 | n.a. |
| **PDX RNA** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| %Human | 98 | 96 | 97 | 90 | 67 | 93 | 90 | 90 | 91 | 94 | 97 | 96 | 94 | 52 |
| **PDX Prot** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| %Human | 78 | 79 | 83 | 79 | 48 | 63 | 73 | 63 | 84 | 78 | 81 | 83 | 79 | 36 |
| **RNA/Prot** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pearson r | 0.404 | 0.669 | 0.719 | 0.689 | 0.536 | 0.669 | 0.683 | 0.623 | 0.699 | 0.556 | 0.708 | 0.723 | 0.718 | 0.375 |
| **PD3D RNA** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| %Human | n.a. | n.a. | 100 | n.a. | n.a. | 100 | n.a. | 83 | 100 | 99 | 100 | 100 | 100 | n.a. |
| **PD3D Prot** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| %Human | n.a. | n.a. | 97 | n.a. | n.a. | 97 | n.a. | 2\* | 96 | 96 | 96 | 97 | 79 | n.a. |
| **RNA/Prot** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pearson r | n.a. | n.a. | 0.681 | n.a. | n.a. | 0.623 | n.a. | 0.016\* | 0.613 | 0.666 | 0.648 | 0.649 | 0.585 | n.a. |

**RNA** – transcripts after mRNA sequencing; **Prot** – proteins after MS proteomics; **\*** - matrigel contamination

**Table S7: Comparison of identified CRC-related polymorphisms in the transcriptome of patient metastases and derived models**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | ***APC*** | ***AXIN2*** | ***TP53*** | ***SMAD*** | ***KRAS*** | ***EGFR*** | ***ERBB2*** | ***ERBB3*** | ***FGFR4*** | ***MAPK3*** | ***PIK3CA*** | ***BRCA2*** | ***FBXW7*** | ***KMT2D*** | ***ATM*** | ***RNF43*** | ***NOTCH1*** | ***NOTCH3*** | ***GNAS*** | ***EP300*** |
| **CRC-05A** | **P** | **R1450\*** V1822D |  | P72R **R175H** | C499R **L533R** | **G13D** |  | I655V | G284R S1234F | V10I P136L |  |  | **T2125fs** V2466A |  |  |  | I47V L418M |  | A2223V |  |  |
| **X** | **R1450\*** V1822D |  | P72R **R175H** | **L533R** | **G13D** |  | I655V | G284R S1234F | V10I P136L |  |  | S131fs S384F **N863fs** **N1784fs** V2466A **E2981fs** **T3033fs** |  |  | **E2304fs** | I47V L418M |  | A2223V |  |  |
| **CRC-05B** | **X** | **R1450\*** **T1556fs** V1822D |  | P72R **R175H** | **L533R** | **G13D** | L480fs | I655V P1170A | G284R  S413fs S1234F | V10I P136L |  |  | S384F **I605fs** **N863fs** **N986fs** V2466A **T3033fs** |  | A3552fs | **E2304fs** | I47V L418M |  |  |  |  |
| **CRC-06** | **P** | **Y953\*** V1822D | P50S | P72R | **D52fs** | A146T | T477\* | P1170A |  | P136L G388R |  |  | Y2884F **T3033fs** |  | R1918H G2493E |  | I47V L418M |  | V1952M A2223V |  |  |
| **X** | **Y953\*** P1549L V1822D | P50S | P72R |  | A146T | L480fs | P1170A |  | P136L G388R |  |  | V2466A Y2884F **T3033fs** |  | R1687fs R1918H G2493E |  | I47V L418M |  |  |  |  |
| **3** | **Y953\*** V1822D | P50S | P72R |  |  |  | P1170A |  | P136L G388R |  |  | V2466A Y2884F |  | R1918H G2493E | **S214fs** | I47V L418M |  | V1952M A2223V |  |  |
| **CRC-09** | **P** | V1822D K2051fs | P50S | P72R | **D52fs** |  | R521K | P1170A |  |  |  | R38H | V2466A |  |  | D1853N | L418M |  | A2223V |  |  |
| **X** | I495V P1549L V1822D | P50S | P72R F134C |  | **G12D** | A202G R521K I1165M |  |  |  |  | R38H | **N986fs** K1690N V2466A |  |  | I1581fs **L1814fs** | I47V L418M |  | A2223V |  |  |
| **CRC-13** | **P** | V1822D | P50S | P72R |  | **G12C** | R521K | I655V P1170A |  | V10I P136L |  |  | **I605fs** **N1766fs** V2466A **T3033fs** E3316fs |  |  |  |  | R1279H | A2223V |  | I997V **N1236fs** |
| **X** | P429Q |  | Q165K | I347V | **G12C** | R521K | F55Y I655V P1170A |  | V10I P136L | S58fs |  |  |  |  |  |  | R1279H | A2223V |  | N251S P261S I997V |
| **CRC-19A** | **P** | V1822D | P50S N412S | **R282W** | **D52fs** | **G12D** |  | P1170A | S413fs |  | E323K |  | L1390fs V2466A |  | P813L |  | I47V **R113\*** |  | A2223V |  |  |
| **X** | K1543E V1822D | P50S | **R282W** | **G352E** | **G12D** |  | P8T P1170A |  |  | E323K |  | T1692fs V2466A |  | P813L |  | I47V **R113\*** |  |  |  |  |
| **3** | V1822D | P50S | **R282W** | **G352E** | **G12D** |  | P8T P1170A |  |  | E323K |  | **T3033fs** V2466A |  | P813L |  | I47V **R113\*** |  |  |  |  |
| **CRC-19D** | **P** | **T1556fs** V1822D | P50S N412S | **R282W** | **G352E** | **G12D** |  | P1170A |  |  | E323K |  | V2466A |  | P813L |  | I47V **R113\*** |  | A2223V |  |  |
| **X** | A59T P429Q V1822D | P50S | **R282W** | **G352E** | **G12D** |  | P1170A |  |  | E323K |  | V2466A |  | P813L | **I1581fs** | I47V **R113\*** |  |  |  |  |
| **CRC-21** | **P** | E19Q | P50S | P72R |  | **Q61K** | R521K | I655V |  | P136L A174T |  |  | N372H |  |  | S49C |  |  | A2223V |  |  |
| **X** | E19Q P429Q K1543E P1549L V1822D | P50S |  |  | **Q61K** | R521K | I655V |  | P136L |  |  | N372H **N1784fs** V2466A **E2981fs** **T3033fs** |  |  | S49C |  |  |  |  |  |
| **P3D** |  | P50S | Q165K |  | **G12C** | R521K | I655V P1170A |  | V10I P136L |  |  | V2466A |  |  |  |  | R1279H | A2223V |  |  |
| **CRC-28A** | **P** | I495V T838M **R1450\*** V1822D | P50S S762N | P72R **R175H** |  | **G12D** | R521K | I655V P1170A |  | P136L G388R |  |  | V2466A Y3098H |  |  | **L1176fs** | I47V L418M |  | A2223V |  | I997V |
| **X** | **R805**\* **R1450\*** V1822D | P50S S762N | P72R **R175H** | K428E | **G12D** | L480fs R521K | I655V P1170A |  | P136L G388R |  |  | V2466A **T3033fs** Y3098H | R479Q |  |  | I47V L418M |  | A2223V |  | I997V |
| **P3D** | **R805\*** **R1450\*** V1822D | P50S S762N | P72R **R175H** |  | **G12D** | R521K | I655V P1170A |  | P136L G388R |  |  | N372H V2466A Y3098H | R479Q |  |  | I47V L418M |  | A2223V |  |  |
| **CRC-28B** | **P** | **R805\*** **R1450\*** V1822D | P50S S762N | P72R **R175H** |  | **G12D** | R521K | P8T I655V P1170A |  | P136L G388R |  |  | V2466A Y3098H |  |  |  | I47V L418M |  | A2223V |  | I997V |
| **X** | **R1450\*** | P50S S762N | P72R **R175H** | K428E | **G12D** | R521K | I655V P1170A |  | P136L G388R |  |  | **L3045fs** | R479Q |  |  | I47V L418M |  | A2223V |  |  |
| **3** | **R805\*** **R1450\*** V1822D | P50S S762N | P72R **R175H** |  | **G12D** | R521K | I655V P1170A | S413fs | P136L G388R |  |  | N372H V2466A Y3098H | R479Q |  |  | I47V L418M |  | A2223V |  |  |
| **CRC-39** | **P** | **E1353\*** V1822D |  | P72R **E258K** |  | **G12S** |  | P1170A | S413fs S1119C | P136L G388R |  |  | V2466A **T3033fs** |  |  |  | I47V L418M |  | H1133Q A2223V |  |  |
| **X** | I495V I983V **E1353**\* S1620A V1822D |  | P72R **E258K** |  | **G12S** |  | P1170A | S1119C | P136L G388R |  |  | V2466A **T3033fs** |  | R1687fs |  | I47V L418M |  |  |  |  |
| **P3D** | **E1353\*** V1822D |  | P72R **E258K** |  | **G12S** |  | P1170A | S1119C | P136L G388R |  |  | V2466A |  |  |  | I47V L418M |  | A2223V |  |  |
| **CRC-55A** | **P** | E1317Q **T1556fs** |  | P72R **P151S** | **D52fs** |  | R521K | P8T P1170A |  | P136L G388R |  |  | N372H V2466A **T3033fs** |  | R1687fs | **S214fs** F858L P1054R | I47V L418M | E848K | A2223V |  |  |
| **X** | V1822D |  | P72R **P151S** |  |  | R521K | P8T P1170A |  | P136L D184G G388R |  |  | V2466A **T3033fs** |  |  |  | I47V L418M | E848K |  |  |  |
| **3** | E1317Q **T1556fs** V1822D |  | P72R **P151S** A189V Q634H |  |  | R521K | P8T P1170A |  | P136L |  |  | N372H G1529E V2466A |  |  | F858L | I47V L418M | E848K |  |  |  |
| **CRC-55B** | **P** | V1822D |  | P72R **P151S** |  |  | L480fs R521K | P8T P1170A | S413fs | P136L G388R |  |  | **V726fs** V2466A **T3033fs** |  |  | F858L | I47V L418M | E848K | A2223V |  |  |
| **X** | M701I **T1556fs** V1822D |  | P72R **P151S** |  |  | R521K | P8T P1170A |  | P136L G388R |  |  |  |  |  |  | I47V L418M | E848K |  |  |  |
| **3** | E1317Q **T1556fs** V1822D K1156R |  | P72R **P151S** A189V Q634H |  |  | R521K | P8T P1170A |  | P136L G388R |  |  | V2466A |  |  | F858L | I47V L418M | E848K |  |  |  |
| **CRC-69A** | **P** | P429Q **L1302fs** V1822D | P50S | P72R | **D52fs** | **G12A** | L480fs | I655V P1170A |  | P136L | E323K | I391M | V2466A **E2981fs** **T3033fs** |  |  |  |  |  | A2223V | **R844C** | M289V |
| **X** | A59T A61T S296G I495V R1171H P1188S **L1302fs** K1543E P1549L V1822D A2650P | P50S | P72R |  | **G12A** | I966fs | I655V E967fs A1181T S1190P |  | P136L | M30V S58fs R67S E323K | I347V M1040T M1040I | V2466A |  |  | **E2304fs** F2799I |  |  |  | **R844C** | P261S M289V N301S F1487L |

**P** – patient metastasis; **X** – PDX model; **3** – PD3D model; **bold** – pathogenic (ClinVar)

**Table S8: *In silico* analysis of transcribed polymorphisms in patient metastases for prediction of therapy response**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Therapy** | **Gene** | **CRC-05** | **CRC-06** | **CRC-09** | **CRC-13** | **CRC-19** | **CRC-21** | **CRC-28** | **CRC-39** | **CRC-55** | **CRC-69** |
| **WNTi** | *APC* | E761\* **R1450\*** **T1556fs** V1822D K2051fs | **Y935\*** V1822D | K2051fs V1822D | V1822D | **T1556fs** R1788fs V1822D K2051fs | E19Q | **R805\* R1450\*** P1594fs V1822D K2051fs | **E1353\*** V1822D K2051fs | E1317Q **T1556fs** P1594fs V1822D | P429Q **L1302fs** V1822D |
| *RSPO2* |  |  | L186P |  |  |  |  |  |  |  |
| **PORCUPINEi** | *RNF43* | I47V R343H L418M | I47V R343H L418M | L418M | P231L | I47V **R113\*** | R117H R337\* | I47V L418M | I47V P231L L418M | I47V L418M | R117H P686R |
| *ZNRF3* |  |  | A725fs |  |  | S557delta |  |  |  |  |
| **ERBBi** | *EGFR* |  | T477\* | R521K | R521K |  | R521K | R521K | R521K | L480fs | L480fs |
| *ERBB2* | I655V | P1170A | P1170A | I655V P1170A | P1170A | I655V | P8T I655V P1170A | P1170A | P8T P1170A | I655V P1170A |
| *ERBB3* | G284R S1234F |  |  |  | S413fs |  |  | S413fs S1119C | S413fs |  |
| *ERBB4* |  |  |  | S418fs |  |  |  |  |  |  |
| *ERRFI1* | S273F |  |  | R247K |  |  |  |  |  |  |
| **FGFRi** | *FGFR2* |  |  |  |  |  |  |  | I654fs |  |  |
| **KDRi** | *KDR* | N511fs G539R | Q472H | Q472H | Q472H | V297I Q472H N511fs |  | Q472H |  | Q472H |  |
| **Sorafenib** | *RET* |  |  |  | W543\* |  |  |  |  |  | R897L |
| **Sunitinib** | *FLT3* |  |  |  | T227M |  | T227M | R311W |  | T227M | T227M |
| **JAKi** | *JAK2* |  |  | N457fs |  |  |  |  |  |  |  |
| *GNAS* |  |  |  |  |  |  | R99K K100E |  |  | **R844C** |
| **Imatinib** | *PDGFRA* |  |  |  |  | S478P |  |  |  |  |  |
| *PDGFRB* | E485K |  |  |  |  |  |  |  |  | E485K |
| *KIT* | V409\* |  | M541L |  | K236fs |  | Y846fs |  |  |  |
| *ABL1* |  |  |  |  |  |  |  | S972L |  |  |
| **RAFi** | *MITF* |  |  |  |  |  |  |  |  | E291D E291V |  |
| *NRAS* |  |  |  |  | L171fs |  |  |  |  |  |
| **MEKi** | *KRAS* | **G13A** | A146T |  | **G12C** | **G12D** | **Q61L** | **G12D** | **G12S** | C186fs | **G12A** |
| **PI3K/AKTi** | *PIK3CA* |  |  | R38H |  |  |  | C604R H1065Y |  | L99fs | L99fs I391M |
| *PIK3R1* |  |  |  |  | S460fs | M326I |  |  | I82fs |  |
| **MTORi** | *MTOR* |  |  |  |  |  |  | R624H |  |  |  |
| *TSC1* |  | M322T | M322T | M322T | **N891fs** | M322T | V178I |  | **N891fs** | L627V |
| *TSC2* |  |  |  |  |  | **V299fs** R367Q | **V299fs** L826M | **V299fs** | **V299fs** | R1369T |
| **Crizotinib** | *ALK* |  |  | I1461V |  | I1461V | I1461V | Y1239C | P1370L |  |  |
| *ROS1* |  |  |  |  |  |  |  |  |  | S1109L |
| **Cisplatin** | *ERCC2* | D312N | D312N K751Q | A182V D312N K751Q | D312N K751Q |  | D312N K751Q |  | D312N K751Q | D312N K751Q |  |
| **AURKAi** | *AURKA* | F31I P57V M373V | F31I | P57V | F31I P57V | M373V | P57V | F31I P57V | P57V | P57V | P57V |
| **WEE1i / CHK1i** | *TP53* | P72R **R175H** | P72R S94\* | P72R | P72R | **R282W** | P72R | P72R **R175H** | P72R **E258K** | P72R **P151S** | P72R |
| **MDM4i** | *MDM4* |  |  |  |  |  |  | L203fs |  |  |  |
| **PARPi** | *BRCA1* | S1613G | P871L E1038G K1183R S1613G |  |  |  |  | P871L E1038G K1183R S1613G | P871L | P871L E1038G K1183R S1613G | D693N P871L E1038G K1183R S1613G |
| *BRCA2* | **T2125fs** V2466A | Y2884F **T3033fs** | V2466A | **I605fs** **N1766fs** V2466A **T3033fs** E3316fs | L1390fs V2466A | N372H | N854fs V2466A Y3098H | F1216fs **T3033fs** | N372H **V726fs** V2466A **T2607fs T3033fs** | V2466A **E2981fs T3033fs** |
| *ATM* |  |  | D1853N | I2233T | N619fs | S49C | **L1176fs** | E594A E594fs | **S214fs** F858L P1054R |  |
| *ATR* | R1814fs | M211T S927fs R1814fs H2437Y H2437L | M211T F929L R1814fs | M211T S271fs | R1814fs | M211T R2425Q H2437Y H2437L E2438V E2438D E2438\* T2439L T2439C | M211T S271fs | M211T R1814fs R2425Q | M211T S271fs V316I V959M | M211T R1814fs |
| *TMPRSS2* | V160M | V160M |  |  | V160M |  | V160M |  | V160M | V160M |
| *CDK12* | S133fs | S133fs | S133fs | S133fs | S133fs |  | S133fs | S133fs | S133fs | S133fs |
| **IFG1-Ri** | *IGFR1* |  |  |  |  | C230Y C231S C231Y H232Y | S24fs |  |  |  |  |
| **NOTCHi** | *NOTCH1* |  |  |  | R1279H |  |  | N2248K |  | E848K |  |
| *NOTCH2* |  |  |  | D1327G |  |  |  |  |  |  |
| **HHi** | *SMO* |  |  |  |  |  |  |  |  | G29R |  |
| *PTCH1* | P1315L | P1315L |  |  |  |  | P1315L | P1315L | E53K P1315L |  |
| **HDACi** | *KTM2A* | A930fs I3105fs | I3105fs | I3105fs | I3105fs | G156fs I3105fs | A930fs G1746E I3105fs | A383fs K929fs P3668fs I3105fs | A930fs S1325N | I256fs A383fs I3105fs | A383fs I3105fs |
| *BAP1* | G624R |  |  |  |  |  |  |  |  |  |
| *BRD3* |  | K435Q |  |  |  | K435Q |  |  |  |  |
| *BRD4* |  |  |  |  |  |  |  |  | R12K H1145Y |  |
| **IDHi** | *IDH1* | V178I |  |  | V178I |  |  |  |  |  |  |
| **EPHi** | *EPHA3* | S548fs |  | R580fs | R580fs | P845H | K142fs T924R |  |  | R580fs R914H T924R | T924R |
| **EZH2i** | *EZH2* | D185H |  |  |  |  |  |  |  |  |  |
| **Enzalutamide** | *AR* |  |  | **N849fs** |  |  |  |  |  |  |  |
| **CDKi** | *CDKN1A* |  |  |  |  |  |  | S31R |  | S31R |  |
| *CDKN1B* | V109G |  |  | V109G | V109G |  |  |  | V109G | V109G |
| *CDKN2A* |  | A148T |  |  |  |  | A148T | A148T |  |  |
| *CDK6* |  |  |  |  |  |  | D110N |  |  |  |
| *CCND3* | S259A | S259A | S259A | E253D S259A | S259A | S259A | S259A | S259A | S259A | S259A |

**\*i** – inhibitor; **bold** – pathogenic (ClinVar)

**Table S9: Comparison of commonly mutated genes in CRC and its metastases**

|  |  |  |  |
| --- | --- | --- | --- |
| **Gene** | **Yaeger *et al.* (11)**  **(m)CRC [pT+M]** | **El-Deiry *et al.* (12)**  **(m)CRC [pT]** | **this report**  **pmCRC[M]** |
| *APC* | 79% | 67.9% | 57% |
| *TP53* | 78% | 58.3% | 57% |
| *KRAS* | 44% | 44.0% | 64% |
| *PTEN* | 20% | 2–5% | 0% |
| *PIK3CA* | 18% | 14.1% | 7% |
| *BRAF* | 16% | 9.60% | 0% |
| *SMAD4* | 16% | 12.9% | 50% |
| *BRCA2* | 16% | n.p. | 85% |
| *PIK3R1* | 14% | n.p. | 0% |
| *NF1* | 13% | n.p. | 0% |
| *ERBB3* | 10% | n.p. | 7% |
| *RNF43* | 9% | n.p. | 14% |
| *CTNNB1* | 8% | 1–2% | 0% |
| *ERBB2* | 8% | 1–2% | 0% |
| *BRCA1* | 8% | n.p. | 0% |
| *FBXW7* | n.p. | 7.10% | 0% |
| *TSC1* | 4% | n.p. | 7% |
| *AKT1* | 3% | 1–2% | 0% |
| *EGFR* | 2% | 1–2% | 0% |
| *GNAS* | n.p. | 2–5% | 7% |
| *ATM* | n.p. | 2–5% | 14% |
| *MAP2K1* | 2% | n.p. | 0% |
| *TSC2* | 1% | n.p. | 29% |
| *NTRK2* | 1% | n.p. | 0% |
| *MET* | 1% | n.p. | 0% |
| *MTOR* | 1% | n.p. | 0% |
| *RAF1* | 1% | n.p. | 0% |
| *HRAS* | 1% | n.p. | 0% |

**(m)CRC** – metastasized and non-metastasized colorectal cancer;

**pT** – primary tumors ; **M** – metastases; **n.p.** – data not published

**Table S10: Matched predictive biomarkers of respective drug treatment**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **5-FU** | | | | | | | | |
| Gene | log2.Pat | log2.PDX | Sens.Pat | Spec.Pat | Sens.PDX | Spec.PDX | Prediction | Description |
| *PCDHGB2* | 1.9 | 4.8 | 100% | 78% | 75% | 100% | Response | Protocatherin gamma-B2 |
| *EPOP* | -1.4 | -1.8 | 100% | 100% | 78% | 100% | Resistance | Elongin BC and Polycomb repressive complex 2-associated protein |
| *ATP6V1C2* | -2.3 | -1.7 | 89% | 100% | 89% | 100% | Resistance | V-type proton ATPase subunit C2 |
| *SLC7A5* | -2.7 | -2.2 | 89% | 100% | 89% | 100% | Resistance | Large neutral amino acids transporter small subunit |
| *SFTA2* | -7.4 | -3.3 | 100% | 100% | 78% | 100% | Resistance | Surfactant-associated protein-2 |
|  |  |  |  |  |  |  |  |  |
| **Trametinib** | | | | | | | | |
| Gene | log2.Pat | log2.PDX | Sens.Pat | Spec.Pat | Sens.PDX | Spec.PDX | Prediction | Description |
| *CYP4X1* | 2.3 | 5.6 | 100% | 88% | 100% | 88% | Response | Cytochrome P450 4X1 |
| *ERP27* | -1.4 | -3.0 | 75% | 100% | 75% | 100% | Resistance | Endoplasmic reticulum resident protein 27 |
| *H2AFY2* | -1.9 | -6.0 | 88% | 100% | 75% | 100% | Resistance | Core histone macro-H2A.2 |
| *ADGRF4* | -2.1 | -1.7 | 88% | 100% | 100% | 100% | Resistance | Adhesion G protein-coupled receptor F4 |
| *BAMBI* | -2.3 | -1.5 | 75% | 100% | 88% | 80% | Resistance | BMP and activin membane-bound inhibitor homolog |
| *FOXH1* | -4.2 | -2.8 | 75% | 100% | 50% | 100% | Resistance | Forkhead box protein H1 |
| *IL36RN* | -5.6 | -2.5 | 75% | 100% | 75% | 100% | Resistance | Interleukin-36 receptor antagonist protein |
| *SLC30A10* | -5.7 | -5.1 | 75% | 100% | 75% | 100% | Resistance | Zinc transporter 10 |
| *TMPRSS11E* | -6.8 | -4.5 | 88% | 100% | 75% | 100% | Resistance | Transmembrane protease serine 11E |
|  |  |  |  |  |  |  |  |  |
| **Erlotinib** | | | | | | | | |
| Gene | log2.Pat | log2.PDX | Sens.Pat | Spec.Pat | Sens.PDX | Spec.PDX | Prediction | Description |
| *CITED4* | -1.8 | -2.6 | 100% | 100% | 100% | 100% | Resistance | Cbp/p300-interacting transactivator 4 |
| *ATP6V1C2* | -2.3 | -2.9 | 80% | 100% | 90% | 100% | Resistance | V-type proton ATPase subunit C2 |
| *BMP7* | -3.2 | -4.3 | 90% | 100% | 90% | 100% | Resistance | Bone morphogenic protein 7 |
| *SLITRK6* | -3.8 | -8.3 | 100% | 100% | 80% | 100% | Resistance | SLIT and NTRK-like protein 6 |
| *FOLR1* | -6.2 | -5.7 | 100% | 100% | 90% | 100% | Resistance | Folate receptor alpha |
| *VGLL1* | -6.7 | -6.2 | 90% | 100% | 90% | 100% | Resistance | Transcription cofactor vestigial-like protein 1 |
| *SFTA2* | -6.9 | -5.2 | 90% | 100% | 100% | 100% | Resistance | Surfactant-associated protein 2 |
| *MUC15* | -7.3 | -7.1 | 80% | 100% | 80% | 100% | Resistance | Mucin-15 |
| *IGFL* | -9.5 | -5.6 | 90% | 100% | 70% | 100% | Resistance | Insulin growth factor-like family member 1 |
|  |  |  |  |  |  |  |  |  |
| **Bevacizumab / Cetuximab** | | | | | | | | |
| Gene | log2.Pat | log2.PDX | Sens.Pat | Spec.Pat | Sens.PDX | Spec.PDX | Prediction | Description |
| *CLDN10* | 4.6 | 6.9 | 100% | 91% | 100% | 73% | Response | Claudin-10 |
| *CGLN* | 3.8 | 5.1 | 100% | 91% | 100% | 100% | Response | Calmegin |
| *PTK7* | -1.9 | -5.8 | 100% | 100% | 91% | 100% | Resistance | Inactive tyrosine-protein kinase 7 |
| *KLK7* | -4.9 | -5.2 | 82% | 100% | 82% | 100% | Resistance | Kallikrein-7 |
| *OTX1* | -5.3 | -3.4 | 91% | 100% | 91% | 100% | Resistance | Homeobox protein OTX1 |
| *KRT17* | -7.2 | -3.1 | 91% | 100% | 82% | 100% | Resistance | Keratin, type I cytoskeletal 17 |
| *CYP2W1* | -9.0 | -6.1 | 82% | 100% | 82% | 100% | Resistance | Cytochrome P450 2W1 |
| *KRT6A* | -10.8 | -8.1 | 91% | 100% | 82% | 100% | Resistance | Keratin, type II cytoskeletal 6A |
|  |  |  |  |  |  |  |  |  |
| **Oxaliplatin** | | | | | | | | |
| Gene | log2.Pat | log2.PDX | Sens.Pat | Spec.Pat | Sens.PDX | Spec.PDX | Prediction | Description |
| *DMBT1* | 7.0 | 5.7 | 100% | 91% | 100% | 91% | Response | Deleted in malignant brain tumors 1 protein |
| *HSD3B1* | 4.5 | 6.5 | 100% | 100% | 100% | 100% | Response | 3 beta-hydroxysteroid dehyfrogenase/Delta 5-->4isomerase type 1 |
| *FRMPD1* | 3.8 | 5.0 | 100% | 100% | 100% | 82% | Response | FERM and PDZ domain-containing protein 1 |
| *HACD1* | -2.7 | -5.2 | 100% | 100% | 100% | 100% | Resistance | Very-long-chain (3R)-3-hydroxyacyl-CoA dehydrogenase 1 |
| *SOSTDC1* | -8.8 | -7.6 | 91% | 100% | 91% | 100% | Resistance | Sclerosin domain-containing protein 1 |
|  |  |  |  |  |  |  |  |  |
| **Selumetinib** | | | | | | | | |
| Gene | log2.Pat | log2.PDX | Sens.Pat | Spec.Pat | Sens.PDX | Spec.PDX | Prediction | Description |
| *GPC2* | -1.6 | -2.6 | 100% | 100% | 90% | 100% | Resistance | Glypican-2 |
| *PALM3* | -3.5 | -3.4 | 80% | 100% | 70% | 100% | Resistance | Paralemmin-3 |
| *FAM3B* | -5.2 | -6.3 | 70% | 100% | 80% | 100% | Resistance | Protein FAM3B |
| *C6orf15* | -6.0 | -5.3 | 70% | 100% | 80% | 100% | Resistance |  |
| *ABHD12B* | -7.0 | -9.2 | 80% | 100% | 60% | 100% | Resistance | Protein ABHD12B |
| *CYP2W1* | -9.7 | -6.3 | 90% | 100% | 90% | 100% | Resistance | Cytochrome P450 2W1 |
|  |  |  |  |  |  |  |  |  |
| **Docetaxel** | | | | | | | | |
| Gene | log2.Pat | log2.PDX | Sens.Pat | Spec.Pat | Sens.PDX | Spec.PDX | Prediction | Description |
| *DSG3* | -4.9 | -4.2 | 90% | 100% | 70% | 100% | Resistance | Desmoglein-3 |
| *MYH4* | -5.2 | -4.4 | 70% | 100% | 80% | 100% | Resistance | Myosin-4 |
|  |  |  |  |  |  |  |  |  |
| **Everolimus** | | | | | | | | |
| Gene | log2.Pat | log2.PDX | Sens.Pat | Spec.Pat | Sens.PDX | Spec.PDX | Prediction | Description |
| *UNC93A* | -6.9 | -5.4 | 91% | 100% | 91% | 100% | Resistance | Protein unc-93 homolog A |
| *IGF2BP1* | -8.9 | -10.1 | 73% | 100% | 73% | 100% | Resistance | Insulin-like growth factor 2 mRNA-binding protein 1 |

**log2.Pat** – log2-fold change in patient tissue, **log2.PDX** – log2-fold change in PDX tumor, **Sens.Pat** – sensitivity in patient tissue, **Spec.Pat** – specificity in patient tissue, **Sens.PDX** – sensitivity in PDX tumor, **Spec.Pat** – specificity in PDX tumor

**Table S11: Matched predictive sequence variants for treatment response in pmCRC**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **5-FU** | | **Resp:Res** | **PDX** | **Pat** | **PD3D** |  |  | **Trametinib** | | **Resp:Res** | **PDX** | **Pat** | **PD3D** |  |
| 5:9 | 4:9 | 4:4 |  |  | 5:9 | 4:9 | 2:6 |  |
| **SYMBOL** | **Protein Position** | **Amino Acids** | **p-val PDX** | **p-val Pat** | **p-val PD3D** | **Existing Variation** |  | **SYMBOL** | **Protein Position** | **Amino Acids** | **p-val PDX** | **p-val Pat** | **p-val PD3D** | **Existing Variation** |
| PGM3 | 344 | D/N | 0.0005 | 0.0014 | 0.0357 | rs473267 |  | UNC50 | 1 | M/K | 0.002997 | 0.004662 | 0.03571 | rs1062847 |
| USP31 | 205 | I/T | 0.0005 | 0.0014 | 0.0357 | rs13339649 |  | SEMA4D | 592 | G/D | 0.002997 | 0.004662 | 0.03571 | rs45464494 |
| TBRG4 | 57 | P/L | 0.0030 | 0.0070 | 0.0357 | rs2304693 |  | ZNF638 | 1215 | V/M | 0.004995 | 0.006993 | 0.02777 | rs1804020 |
| TBRG4 | 22 | A/S | 0.0030 | 0.0070 | 0.0357 | rs2304694 |  | GPN2 | 264 | R/G | 0.02298 | 0.03186 | 0.03571 | rs3170660 |
| CLRN3 | 75 | F/I | 0.0050 | 0.0140 | 0.0357 | rs35070529 |  | POLL | 306 | L/P | 0.02298 | 0.03186 | 0.03571 | rs3730476 |
| DHX37 | 96 | M/I | 0.0050 | 0.0014 | 0.0357 | rs11558556 |  | NOB1 | 231 | R/Q | 0.02298 | 0.03497 | 0.03571 | rs3811348 |
| GSDMA | 128 | V/L | 0.0050 | 0.0014 | 0.0357 | rs7212938 |  | ARFGAP2 | 274 | S/N | 0.02747 | 0.03497 | 0.02777 | rs3740691 |
| GSDMB | 282 | G/R | 0.0050 | 0.0140 | 0.0357 | rs2305479 |  | INPP4A | 249 | T/A | 0.03097 | 0.004662 | 0.03571 | rs2278206 |
| GSDMB | 289 | P/S | 0.0050 | 0.0140 | 0.0357 | rs2305480 |  |  |  |  |  |  |  |  |
| METTL2B | 169 | E/K | 0.0050 | 0.0140 | 0.0357 | rs1065267 |  | **Oxaliplatin** | | **Resp:Res** | **PDX** | **Pat** | **PD3D** |  |
| TMPRSS2 | 160 | V/M | 0.0050 | 0.0014 | 0.0357 | rs12329760 |  | 2:12 | 2:11 | 0:8 |  |
| NAA40 | 42 | V/I | 0.0210 | 0.0210 | 0.0357 | rs3740637 |  | **SYMBOL** | **Protein Position** | **Amino Acids** | **p-val PDX** | **p-val Pat** | **p-val PD3D** | **Existing Variation** |
| PODXL | 194 | S/L | 0.0210 | 0.0210 | 0.0357 | rs12670788 |  | AGFG2 | 115 | M/T | 0.03297 | 0.01282 |  | rs17855473 |
| PODXL | 112 | G/S | 0.0210 | 0.0210 | 0.0357 | rs3735035 |  | C2CD2L | 264 | R/W | 0.03297 | 0.01282 |  | rs2239896 |
| TLDC1 | 145 | D/E | 0.0210 | 0.0210 | 0.0357 | rs436278 |  | FREM1 | 1203 | V/M | 0.03297 | 0.01282 |  | rs10961700 |
| TBC1D16 | 73 | T/I | 0.0230 | 0.0210 | 0.0357 | rs4889804 |  | LAMC2 | 733 | S/T | 0.03297 | 0.01282 |  | rs2296303 |
| CCDC50 | 258 | I/N | 0.0275 | 0.0140 | 0.0357 | rs2028574 |  | MRPS2 | 294 | H/R | 0.03297 | 0.01282 |  | rs3748199 |
| CCDC50 | 303 | K/R | 0.0275 | 0.0140 | 0.0357 | rs4677728 |  | SLC25A27 | 197 | I/T | 0.03297 | 0.01282 |  | rs35884480 |
| GSDMA | 130 | E/K | 0.0275 | 0.0140 | 0.0357 | rs7212944 |  | TBC1D8 | 926 | G/R | 0.03297 | 0.01282 |  | rs1062062 |
| NRBP2 | 468 | R/C | 0.0275 | 0.0140 | 0.0357 | rs72693365 |  | TNS3 | 1050 | T/A | 0.03297 | 0.01282 |  | rs61731308 |
| SART3 | 23 | D/E | 0.0275 | 0.0014 | 0.0357 | rs2072579 |  | WWOX | 153 | S/I | 0.03297 | 0.01282 |  | rs383362 |
|  |  |  |  |  |  |  |  | ERICH1 | 219 | T/I | 0.03297 | 0.03846 |  | rs61741834 |
| **Erlotinib** | | **Resp:Res** | **PDX** | **Pat** | **PD3D** |  |  | HSD3B1 | 367 | T/N | 0.03297 | 0.03846 |  | rs45609334 rs1047303 |
| 4:10 | 3:10 | 2:6 |  |  | NDFIP2 | 135 | A/V | 0.03297 | 0.03846 |  | rs11549502 |
| **SYMBOL** | **Protein Position** | **Amino Acids** | **p-val PDX** | **p-val Pat** | **p-val PD3D** | **Existing Variation** |  | PLEKHM2 | 32 | I/T | 0.03297 | 0.03846 |  | rs12091750 |
| CLRN3 | 75 | F/I | 0.001 | 0.0035 | 0.0357 | rs35070529 |  | TAF11 | 2 | E/K | 0.03297 | 0.03846 |  | rs13198340 |
| GSDMB | 282 | G/R | 0.001 | 0.0035 | 0.0357 | rs2305479 |  | TAF11 | 24 | T/R | 0.03297 | 0.03846 |  | rs15922 |
| GSDMB | 289 | P/S | 0.001 | 0.0035 | 0.0357 | rs2305480 |  | VSIG10 | 239-241 | EEE/E | 0.03297 | 0.03846 |  | rs72125532 |
| ASCC3 | 146 | L/F | 0.001 | 0.03497 | 0.0357 | rs9390698 |  | VSIG10 | 202 | H/Y | 0.03297 | 0.03846 |  | rs7307331 |
| FBXO3 | 221 | V/I | 0.005 | 0.01399 | 0.0357 | rs1402954 |  | ZC3HC1 | 103 | T/A | 0.03297 | 0.03846 |  | rs1464890 |
| HELZ2 | 1447 | P/L | 0.005 | 0.01399 | 0.0357 | rs3810485 |  |  |  |  |  |  |  |  |
| MUC20 | 671 | S/C | 0.005 | 0.01399 | 0.0357 | rs3762739 |  | **Everolimus** | | **Resp:Res** | **PDX** | **Pat** | **PD3D** |  |
| PGM3 | 344 | D/N | 0.005 | 0.01399 | 0.0357 | rs473267 |  | 3:11 | 2:11 | 0:8 |  |
| STK40 | 395 | A/T | 0.005 | 0.01399 | 0.0357 | rs3795498 |  | **SYMBOL** | **Protein Position** | **Amino Acids** | **p-val PDX** | **p-val Pat** | **p-val PD3D** | **Existing Variation** |
| USP31 | 205 | I/T | 0.005 | 0.01399 | 0.0357 | rs13339649 |  | EML3 | 14 | A/V | 0.01099 | 0.03846 |  | rs12808829 |
| WASHC2C | 162 | T/M | 0.005 | 0.01399 | 0.0357 | rs199748321 |  | SUMF1 | 398 | F/L | 0.03297 | 0.03846 |  | rs795734 |
| LRR1 | 96 | I/N | 0.005 | 0.03497 | 0.0357 | rs17121605 |  | ZNF333 | 11 | E/A | 0.03297 | 0.03846 |  | rs75269766 |
| LRR1 | 229 | R/W | 0.005 | 0.03497 | 0.0357 | rs7148147 |  |  |  |  |  |  |  |  |
| CCDC50 | 258 | I/N | 0.01099 | 0.0035 | 0.0357 | rs2028574 |  | **Docetaxel** | | **Resp:Res** | **PDX** | **Pat** | **PD3D** |  |
| CCDC50 | 303 | K/R | 0.01099 | 0.0035 | 0.0357 | rs4677728 |  | 3:11 | 3:10 | 2:6 |  |
| GSDMA | 130 | E/K | 0.01099 | 0.0035 | 0.0357 | rs7212944 |  | **SYMBOL** | **Protein Position** | **Amino Acids** | **p-val PDX** | **p-val Pat** | **p-val PD3D** | **Existing Variation** |
| NRBP2 | 468 | R/C | 0.01099 | 0.0035 | 0.0357 | rs72693365 |  | ALDH3A1 | 134 | S/A | 0.01099 | 0.01399 | 0.03571 | rs887241 |
| SART3 | 23 | D/E | 0.01099 | 0.01399 | 0.0357 | rs2072579 |  | GPN2 | 264 | R/G | 0.02747 | 0.03497 | 0.03571 | rs3170660 |
| AFMID | 36 | Q/R | 0.01099 | 0.03846 | 0.0357 | rs72897838 |  | KIF16B | 1207 | G/C | 0.02747 | 0.03497 | 0.03571 | rs2328020 |
| CCDC50 | 156 | M/T | 0.01099 | 0.03846 | 0.0357 | rs293813 |  |  |  |  |  |  |  |  |
| DHX57 | 308 | S/F | 0.01099 | 0.03846 | 0.0357 | rs11893062 |  | **Selumetinib** | | **Resp:Res** | **PDX** | **Pat** | **PD3D** |  |
| FARP1 | 593 | H/Y | 0.01099 | 0.03846 | 0.0357 | rs61730892 |  | 4:10 | 3:10 | n.t. |  |
| IQCK | 132 | L/P | 0.01099 | 0.03846 | 0.0357 | rs7191155 |  | **SYMBOL** | **Protein Position** | **Amino Acids** | **p-val PDX** | **p-val Pat** | **p-val PD3D** | **Existing Variation** |
| KLC2 | 320 | P/S | 0.01099 | 0.03846 | 0.0357 | rs2276036 |  | DEF8 | 197 | M/I | 0.004995 | 0.01399 |  | rs8166 |
| KRAS | 12 | G/C | 0.01099 | 0.03846 | 0.0357 | rs121913530 |  | BRD8 | 384 | T/M | 0.004995 | 0.03497 |  | rs11750814 |
| MIIP | 142 | P/S | 0.01099 | 0.03846 | 0.0357 | rs11588712 |  | FAM160A2 | 619 | R/L | 0.004995 | 0.03846 |  | rs3750943 |
| QRICH1 | 771 | N/S | 0.01099 | 0.03846 | 0.0357 | rs61729488 |  | NOL10 | 485 | D/N | 0.01099 | 0.03497 |  | rs2287059 |
| RLF | 1296 | Q/E | 0.01099 | 0.03846 | 0.0357 | rs34141181 |  | BAZ2B | 1145 | S/N | 0.01099 | 0.03846 |  | rs415793 |
| RNF123 | 854 | R/H | 0.01099 | 0.03846 | 0.0357 | rs34823813 |  | BBS12 | 467 | D/N | 0.01099 | 0.03846 |  | rs13135778 |
| RNF43 | 104 | P/L | 0.01099 | 0.03846 | 0.0357 | rs2680701 |  | CCPG1 | 196 | A/G | 0.01099 | 0.03846 |  | rs117236526 |
| SH3BP1 | 587 | A/V | 0.01099 | 0.03846 | 0.0357 | rs12483880 |  | CKAP2 | 435 | E/K | 0.01099 | 0.03846 |  | rs41292820 |
| SLC38A10 | 477 | K/R | 0.01099 | 0.03846 | 0.0357 | rs35546507 |  | CLCN7 | 360 | V/M | 0.01099 | 0.03846 |  | rs12926089 |
| SLC38A10 | 594 | E/D | 0.01099 | 0.03846 | 0.0357 | rs55872261 |  | CROCC | 1038 | V/M | 0.01099 | 0.03846 |  | rs41272737 |
| TP53I3 | 230 | T/A | 0.01099 | 0.03846 | 0.0357 | rs10209238 |  | CROCC | 1672 | S/G | 0.01099 | 0.03846 |  | rs56278097 |
| TRAF3IP1 | 276 | M/L | 0.01099 | 0.03846 | 0.0357 | rs3739070 |  | CROCC | 1399 | G/R | 0.01099 | 0.03846 |  | rs78888579 |
| UBE3D | 192 | V/M | 0.01099 | 0.03846 | 0.0357 | rs7739323 |  | IL17RC | 297 | P/L | 0.01099 | 0.03846 |  | rs115419420 |
| USP19 | 36 | D/H | 0.01099 | 0.03846 | 0.0357 | rs11552724 |  | LAMA5 | 1626 | H/Y | 0.01099 | 0.03846 |  | rs875379 |
| ZCCHC14 | 112 | Y/H | 0.01099 | 0.03846 | 0.0357 | rs78839939 |  | LIG4 | 3 | A/V | 0.01099 | 0.03846 |  | rs1805389 |
| ZNF417 | 168 | P/S | 0.01099 | 0.03846 | 0.0357 | rs142466487 |  | MATN2 | 717 | T/M | 0.01099 | 0.03846 |  | rs2255317 |
| TBRG4 | 57 | P/L | 0.01499 | 0.03497 | 0.0357 | rs2304693 |  | MROH1 | 483 | I/V | 0.01099 | 0.03846 |  | rs112996909 |
| TBRG4 | 22 | A/S | 0.01499 | 0.03497 | 0.0357 | rs2304694 |  | NCEH1 | 71 | K/Q | 0.01099 | 0.03846 |  | rs2302815 |
| DHX37 | 96 | M/I | 0.04096 | 0.01399 | 0.0357 | rs11558556 |  | PATJ | 303 | G/R | 0.01099 | 0.03846 |  | rs3762321 |
| GSDMA | 128 | V/L | 0.04096 | 0.01399 | 0.0357 | rs7212938 |  | PCSK9 | 14-15 | -/L | 0.01099 | 0.03846 |  | rs371488778 |
| TMPRSS2 | 160 | V/M | 0.04096 | 0.01399 | 0.0357 | rs12329760 |  | PCSK9 | 53 | A/V | 0.01099 | 0.03846 |  | rs11583680 |
| TTC3 | 118 | M/T | 0.04096 | 0.01399 | 0.0357 | rs1053808 |  | PTPN12 | 576 | E/K | 0.01099 | 0.03846 |  | rs2230602 |
| TTC3 | 1029 | D/H | 0.04096 | 0.01399 | 0.0357 | rs1053966 |  | RFX5 | 238 | P/R | 0.01099 | 0.03846 |  | rs2233854 |
| BCAS1 | 491 | S/P | 0.04096 | 0.03846 | 0.0357 | rs1055246 |  | SEL1L | 691 | V/I | 0.01099 | 0.03846 |  | rs1051193 |
| PPP1R15A | 597 | T/A | 0.04096 | 0.03846 | 0.0357 | rs500079 |  | SUCLG2 | 425 | V/I | 0.01099 | 0.03846 |  | rs902320 |
| STK31 | 232 | G/E | 0.04096 | 0.03846 | 0.0357 | rs4722266 |  | THAP12 | 355 | I/V | 0.01099 | 0.03846 |  | - |
| WWC1 | 772-773 | VE/V | 0.04096 | 0.03846 | 0.0357 | rs111457550 |  | TMF1 | 798 | D/H | 0.01099 | 0.03846 |  | rs1532918 |
|  |  |  |  |  |  |  |  | TUBGCP3 | 428 | R/H | 0.01099 | 0.03846 |  | rs41288616 |
| **Cetuximab** | | **Resp:Res** | **PDX** | **Pat** | **PD3D** |  |  | CCSER2 | 84 | N/S | 0.01499 | 0.03497 |  | rs3814205 |
| 3:10 | 2:10 | 0:8 |  |  | COG2 | 738 | \* | 0.01499 | 0.03497 |  | rs1051038 |
| **SYMBOL** | **Protein Position** | **Amino Acids** | **p-val PDX** | **p-val Pat** | **p-val PD3D** | **Existing Variation** |  | NAAA | 356 | I/N | 0.01499 | 0.03497 |  | rs7686066 |
| SUCLG2 | 425 | V/I | 0.00275 | 0.01282 |  | rs902320 |  | SPOUT1 | 130 | T/R | 0.01499 | 0.03497 |  | rs6478854 |
| FANCA | 1045 | S/F | 0.01099 | 0.01282 |  | rs17233497 |  | STOX1 | 498 | E/D | 0.01499 | 0.03497 |  | rs10509305 |
| ABCB1 | 21 | N/D | 0.01099 | 0.03846 |  | rs9282564 |  | TBC1D13 | 114 | V/A | 0.01499 | 0.03497 |  | rs1572912 |
| FANCA | 1285 | T/A | 0.01099 | 0.03846 |  | rs9282681 |  | TOPBP1 | 1037 | N/S | 0.01499 | 0.03497 |  | rs10935070 |
| IRAK4 | 225 | A/T | 0.01099 | 0.03846 |  | rs4251545 |  | ZFP91 | 207 | S/G | 0.01499 | 0.03497 |  | rs8373 |
| MAVS | 93 | Q/E | 0.01099 | 0.03846 |  | rs17857295 |  | ADGRG1 | 106 | S/R | 0.04096 | 0.01399 |  | rs1801257 |
| MC1R | 92 | V/M | 0.01099 | 0.03846 |  | rs2228479 |  | ASCC3 | 146 | L/F | 0.04096 | 0.03497 |  | rs9390698 |
| NDOR1 | 257 | V/I | 0.01099 | 0.03846 |  | rs62587579 |  | ARHGEF10L | 1175 | I/V | 0.04096 | 0.03846 |  | rs2270976 |
| PUS7L | 264 | K/E | 0.01099 | 0.03846 |  | rs1057190 |  | EFHB | 57-58 | -/P | 0.04096 | 0.03846 |  | rs878999429 |
| SENP7 | 46 | K/Q | 0.01099 | 0.03846 |  | rs6809436 |  | ERCC6L2 | 7 | P/S | 0.04096 | 0.03846 |  | rs56108623 |
| SKAP2 | 202 | A/S | 0.01099 | 0.03846 |  | rs1129771 |  | FANCA | 1045 | S/F | 0.04096 | 0.03846 |  | rs17233497 |
| SLC28A2 | 22 | P/L | 0.01099 | 0.03846 |  | rs11854484 |  | UTP6 | 69 | Q/R | 0.04096 | 0.03846 |  | rs3760454 |
| TCF25 | 391 | R/Q | 0.01099 | 0.03846 |  | rs57940434 |  |  |  |  |  |  |  |  |
| TMEM132A | 824 | E/K | 0.01099 | 0.03846 |  | rs55920775 |  |  |  |  |  |  |  |  |
| TOMM34 | 185 | H/R | 0.01099 | 0.03846 |  | rs1804644 |  |  |  |  |  |  |  |  |
| SMPD2 | 204 | S/X | 0.03297 | 0.01282 |  | rs35444917 |  |  |  |  |  |  |  |  |
| AKIP1 | 143 | T/M | 0.03297 | 0.03846 |  | rs2016844 |  |  |  |  |  |  |  |  |
| FBXO7 | 6 | G/E | 0.03297 | 0.03846 |  | rs9621461 |  |  |  |  |  |  |  |  |
| MICAL1 | 12 | A/T | 0.03297 | 0.03846 |  | rs4946977 |  |  |  |  |  |  |  |  |
| MTERF4 | 151 | L/V | 0.03297 | 0.03846 |  | rs2240539 |  |  |  |  |  |  |  |  |
| MTERF4 | 45 | T/A | 0.03297 | 0.03846 |  | rs3796093 |  |  |  |  |  |  |  |  |
| RILPL1 | 2 | T/A | 0.03297 | 0.03846 |  | - |  |  |  |  |  |  |  |  |
| RMND5B | 5 | S/G | 0.03297 | 0.03846 |  | - |  |  |  |  |  |  |  |  |
| TRIM47 | 187 | R/W | 0.03297 | 0.03846 |  | rs4600514 |  |  |  |  |  |  |  |  |
| ZACN | 281 | Q/\* | 0.03297 | 0.03846 |  | rs1043149 |  |  |  |  |  |  |  |  |
| ZNF285 | 381 | G/R | 0.03297 | 0.03846 |  | rs12610859 |  |  |  |  |  |  |  |  |
| ZNF358 | 119 | K/Q | 0.03297 | 0.03846 |  | rs78214445 |  |  |  |  |  |  |  |  |
| ZNF721 | 730 | R/L | 0.03297 | 0.03846 |  | rs61793704 |  |  |  |  |  |  |  |  |
| ZWILCH | 230 | S/G | 0.03297 | 0.03846 |  | rs11071896 |  |  |  |  |  |  |  |  |

**Resp:Res** – number of responding vs. resistant models used for prediction analysis;

**Table S12: Validation of improved response of pmCRC models to combination therapy with PARP inhibitors**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Biomarker (Pat, TPM)** | **5-FU** | **CRC-05A** | **CRC-09** | **CRC-19A** | **CRC-28B** | **CRC-55A** | **CRC-55B** |
| PCDHGB2 | ROC cut-off = 3.40 | 0.52 | 5.14 | 1.21 | 0.95 | 0.76 | 0.61 |
| EPOP | ROC cut-off = 2.69 | 3.52 | 1.31 | 3.23 | 3.38 | 6.5 | 5.62 |
| ATP6V1C2 | ROC cut-off = 1.44 | 3.12 | 0.92 | 2.25 | 2.03 | 4.48 | 3.12 |
| SLC7A5 | ROC cut-off = 21.96 | 50.00 | 2.6 | 26.69 | 130.02 | 187.59 | 161.38 |
| SFTA2 | ROC cut-off = 7.40 | 80.98 | 0.34 | 11.84 | 538.57 | 241.38 | 233.42 |
| **Monotherapy response** | PDX *in vivo* | low | high | low | low | low | low |
|  | PDX cells *in vitro* | low | high | low | low | (high) | (high) |
| **Improvement in**  **combination with Olaparib** | | **yes** | no | **yes** | **yes** | (no) | (no) |
| **Monotherapy response** | PD3D (1st exp) |  |  | high | high | low | low |
|  | PD3D (2nd exp) |  |  | n.t. | high | low | n.t. |
| **Improvement in**  **combination with Olaparib** | |  |  |  | no | **yes** |  |
|  |  |  |  |  |  |  |  |
| **Biomarker (Pat, TPM)** | **Trametinib** | **CRC-05A** | **CRC-09** | **CRC-21** | **CRC-28B** | **CRC-55A** | **CRC-55B** |
| CYP4X1 | ROC cut-off = 2.43 | 21.34 | 5.19 | 1.93 | 1.17 | 1.79 | 1.53 |
| ERP27 | ROC cut-off = 2.54 | 0.86 | 1.3 | 2.06 | 6.44 | 4.14 | 6.73 |
| H2AFY2 | ROC cut-off = 12.80 | 2.08 | 12.46 | 13.13 | 25.53 | 38.94 | 27.24 |
| ADGRF4 | ROC cut-off = 2.69 | 2.41 | 0.22 | 2.97 | 10.84 | 14.13 | 10.09 |
| BAMBI | ROC cut-off = 19.78 | 18.59 | 7.22 | 14.52 | 22.46 | 91.61 | 66.88 |
| FOXH1 | ROC cut-off = 0.23 | 0.11 | 0.03 | 0.91 | 3.33 | 2.23 | 1.49 |
| IL36RN | ROC cut-off = 0.37 | 0.26 | 0.04 | 0.47 | 0.80 | 9.01 | 8.33 |
| SLC30A10 | ROC cut-off = 0.04 | 0.03 | 0.03 | 0.18 | 1.03 | 0.13 | 0.08 |
| TMPRSS11E | ROC cut-off = 0.20 | 0.09 | 0.05 | 1.14 | 2.98 | 0.56 | 0.77 |
| **Monotherapy response** | PDX *in vivo* | high | high | low | low | low | low |
|  | PDX cells *in vitro* | high | high | low | n.t. | low | low |
| **Improvement in**  **combination with Olaparib** | | no | no | **yes** |  | **yes** | **yes** |
| **Monotherapy response** | PD3D (1st exp) |  |  | low | low | low | low |
|  | PD3D (2nd exp) |  |  | low | low | low | n.t. |
| **Improvement in**  **combination with Olaparib** | |  |  | **yes** | **yes** | **yes** |  |

**Pat** – pmCRC patient metastasis; **TPM** – transcripts per million; **ROC** – receiver operator curve based; **exp** – experiment;

**n.t.** – not tested