**Supplementary data**

**Supplementary Tables**

**Suppl. Table 1: Mutational profiling of PDX by Illumina TruSequ Amplicon Cancer Panel.** In this profiling 212 amplicons of 48 oncogenes were analyzed. The table summarizes the mutational status of the most relevant oncogenes in CRC assessed by this analysis.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **PDX** | **APC** | **BRAF** | **EGFR** | **KRAS** | **NRAS** | **PIK3CA** | **PTEN** | **TP53** |
| ***AA mutation*** | | | | | | | |
| **Co 5676** |  |  |  |  |  |  |  | Indel*HO* |
| **Co 5677** |  |  |  |  |  |  |  | Indel*HO* |
| **Co 5679** | E1451X*HE* |  |  | G13D*HO* |  |  |  | R273H*HO* |
| **Co 5682** | Indel*HO* |  |  | G12S*HO* |  |  |  | G206C*HO* |
| **Co 5734** |  |  |  |  |  |  |  | V172F*HO* |
| **Co 5735** | Indel*HE* |  |  |  |  |  |  | L194R*HO* |
| **Co 5736** | Indel*HO* |  |  | G12V*HE* |  |  |  |  |
| **Co 5771** | S1392X*HE* |  |  | Q61H*HE* |  | Q546K*HE* |  |  |
| **Co 5776** | E1306X*HO* |  |  | A146T*HE* |  |  |  | V173F*HO* |
| **Co 5841** | Q1123X*HE* |  |  | G12D*HE* |  |  |  | R196X*HO* |
| **Co 5854** | E1538X*HO* | V600E*HE* |  |  |  | E542K*HE* | G293V*HO* |  |
| **Co 5896** | Indel*HE* |  |  | G12S*HE* |  |  |  | P278L*HO* |
| **Co 6044** | S1356X*HO* |  |  |  |  |  |  |  |
| **Co 6228** |  |  |  |  |  |  |  | R175H*HO* |
| **Co 72711** | Indel*HO* |  |  | G12A*HO* |  |  |  | R175H*HO* |
| **Co 7475** | Indel*HO* |  |  | A146T*HE* |  | E545K*HE* |  |  |
| **Co 7515** | Indel*HO* |  |  |  |  |  | R335X*HO* | R267X*HO* |
| **Co 7523** |  | G466R*HE* |  |  | G12E*HE* |  |  |  |
| **Co 7553A2** |  |  |  |  |  |  |  |  |
| **Co 7553B2** |  |  |  |  |  |  |  |  |
| **Co 7567** | Q1406X*HO* |  |  | G12A*HE* |  |  |  | R175H*HO* |
| **Co 7596** | R876X*HO* |  |  |  |  |  |  | R243W*HO* |
| **Co 76601** | Indel*HO* |  |  | G12A |  |  |  | R175H*HO* |
| **Co 7689** |  |  |  | G12D*HE* |  |  |  |  |
| **Co 7809** | Indel*HO* |  |  | G12D*HE* |  |  |  | R273C*HO* |
| **Co 7818** |  | G469V*HE* |  |  |  |  |  | R248Q*HO* |
| **Co 7835** | K1308X*HO* |  |  | G12D*HE* |  | E545G*HE* |  | R273C*HO* |
| **Co 7888** |  |  |  | A146V*HO* |  |  |  | R248Q*HO* |
| **Co 7935** | E1322X*HO* |  |  |  |  |  |  |  |
| **Co 9587** | R876X*HE* |  |  | G12D*HE* |  | del104*HE* |  |  |
| **Co 9634** |  |  |  | Q61H*HO* |  | C420R*HE*; R88Q*HE* |  |  |
| **Co 9689A3** | Q1378X*HE* |  |  |  |  |  |  | R248W*HO* |
| **Co 9689B3** | Q1378X*HE* |  |  |  |  |  |  | R248W*HO* |
| **Co 9729** | E1397X*HE* |  |  | G12V*HO* |  |  |  |  |
| **Co 9775** |  |  |  | G12D*HE* |  |  |  | G245S*HO* |
| **Co 9946** | ins1414*HE* |  |  |  | Q61R*HO* | N345I*HO* |  | R306X*HO* |
| **Co 9978** | E1322X*HE* |  |  | G12V*HE* |  |  |  |  |
| **Co 99974** | Q1429X*HE*; del904*HE* |  |  | G12A*HE* |  |  |  |  |
| **Co 10158** | 99, Q1429X |  |  | A146T*HO* |  |  |  |  |
| **Co 10194** | A876X*HE*; E1306X*HE* |  |  |  |  |  |  |  |
| **Co 103004** | Q1429X*HE*; del904*HE* |  |  | G12A*HE* |  |  |  |  |
| **Co10302A5** | E1521V*HE* | V600E*HE* |  |  |  |  |  |  |
| **Co10302B5** |  | V600E*HE* |  |  |  |  |  |  |
| **Co 10377** | Q1406X*HO* |  |  | A146T*HE* |  | del106*HE* |  | R248W*HO* |
| **Co 10383** |  |  |  | G12C*HE* |  |  |  |  |
| **Co 10588** |  |  |  | G12V*HO* |  |  |  | E211X*HE* Y163X*HE* |
| **Co 10764** |  |  |  | G13D*HO* |  |  |  | R196X*HO* |
| **Co 10925** | E1379X*HO* |  |  |  |  |  |  |  |
| **Co 11061** | del1412*HE* |  |  |  |  |  | del321*HE* |  |
| **%*mut*PDX** | **67.3** | **10.2** | **0.0** | **55.1** | **4.1** | **16.3** | **6.1** | **53.1** |

1 -5 PDX models were derived from the same patient

**Suppl. Table 2: Sensitivity of the PDX towards standard of care drugs.** The table summarizes the chemosensitivity data by tumor response scores basd on the optimal treated to control values (optT/C): (-) negative, optT/C value 50-100%; (+), optT/C value 25-50%; (++), optT/C value 10-25%; (+++), optT/C value 5-10%; (++++), optT/C value 0-5%.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **PDX** | **5-FU** | | |  | **Irinotecan** | | |  | **Oxaliplatin** | | |  |
| **opt T/C**  **[%]** | **score** | **RTV** |  | **opt T/C**  **[%]** | **score** | **RTV** |  | **opt T/C**  **[%]** | **score** | **RTV** |  |
| **Co 5676** | 47.6 | + | 1.9 |  | 16.6 | +++ | 0.6 |  | 60.61 | - | 2.03 |  |
| **Co 5677** | 64.5 | - | 2 |  | 18.8 | +++ | 0.3 |  | 107.3 | - | 8.9 |  |
| **Co 5679** | 35.5 | + | 2.1 |  | 14.8 | +++ | 0.8 |  | 95.3 | - | 10.2 |  |
| **Co 5682** | 43.6 | + | 1.4 |  | 49.1 | + | 1.2 |  | 60.3 | - | 1.7 |  |
| **Co 5734** | 31 | ++ | 1.1 |  | 30.9 | ++ | 1.1 |  | 57.8 | - | 4.8 |  |
| **Co 5735** | 21.6 | ++ | 1.4 |  | 9.9 | +++ | 0.7 |  | 9.8 | +++ | 1.8 |  |
| **Co 5736** | 73.1 | - | 2 |  | 46.2 | + | 1.3 |  | 60.8 | - | 6.2 |  |
| **Co 5771** | 54 | - | 3.1 |  | 11.5 | +++ | 0.6 |  | 59.2 | - | 3.6 |  |
| **Co 5776** | 47.6 | + | 1.9 |  | 6.37 | +++ | 1.25 |  | 18.5 | +++ | 3 |  |
| **Co 5841** | 47.1 | + | 2.32 |  | 34.1 | ++ | 2 |  | 22.6 | ++ | 3.6 |  |
| **Co 5854** | 93.7 | - | 5.2 |  | 31.8 | ++ | 1.6 |  | 25.9 | ++ | 5.3 |  |
| **Co 5896** | 74.32 | - | 2.85 |  | 47.46 | + | 1.6 |  | 44.7 | + | 4.9 |  |
| **Co 6044** | 21.3 | ++ | 1.7 |  | 5.6 | +++ | 0.5 |  | 14.2 | +++ | 1.5 |  |
| **Co 6228** | 74.14 | - | 3.9 |  | 22.41 | ++ | 1.46 |  | 43.8 | (+) | 5.4 |  |
| **Co 72711** | 21.2 | ++ | 1.6 |  | 6.1 | +++ | 0.7 |  | 86.6 | - | 9.1 |  |
| **Co 7475** | 12.38 | +++ | 1.53 |  | 1.9 | ++++ | 0.27 |  | 88.1 | - | 8.8 |  |
| **Co 7515** | 50.53 | - | 3.05 |  | 25.26 | ++ | 1.21 |  | 34.6 | ++ | 3.5 |  |
| **Co 7523** | 41.8 | + | 1.56 |  | 24.59 | ++ | 1.09 |  | 55.8 | - | 3.6 |  |
| **Co 7553A2** | 42.86 | + | 3.28 |  | 11.43 | +++ | 0.75 |  | 58.8 | - | 6.6 |  |
| **Co 7553B2** | 55.71 | - | 3.58 |  | 18.45 | +++ | 0.93 |  | 63.5 | - | 1 |  |
| **Co 7567** | 54.39 | - | 1.22 |  | 31.34 | ++ | 1 |  | 80.2 | - | 3.1 |  |
| **Co 7596** | 52.38 | - | 4 |  | 7.14 | +++ | 0.47 |  | 138.7 | - | 8.9 |  |
| **Co 76601** | n.a. | n.a. | n.a. |  | n.a. | n.a. | n.a. |  | 75.1 | - | 2.4 |  |
| **Co 7689** | 77.12 | - | 5.37 |  | 12.14 | +++ | 1.42 |  | 19.1 | +++ | 1.2 |  |
| **Co 7809** | 88.75 | - | 7.87 |  | 2.1 | ++++ | 0.28 |  | 26.3 | ++ | 1.3 |  |
| **Co 7818** | 71.43 | - | 10.33 |  | 10.22 | +++ | 1 |  | 41.4 | + | 4.2 |  |
| **Co 7835** | 33.59 | ++ | 5.95 |  | 3.98 | ++++ | 0.6 |  | 42 | + | 5.7 |  |
| **Co 7888** | 52 | - | 2.63 |  | 11.11 | +++ | 0.38 |  | 60.7 | - | 2.6 |  |
| **Co 7935** | 82.73 | - | 3.37 |  | 27.85 | ++ | 1 |  | 63.1 | - | 2.1 |  |
| **Co 9587** | 54.9 | - | 1.3 |  | 74.8 | - | 1.6 |  | 58.4 | - | 1.2 |  |
| **Co 9634** | 39.3 | + | 10.7 |  | 12.4 | +++ | 1.6 |  | 48.1 | + | 10.8 |  |
| **Co 9689A3** | 64.9 | - | 4.2 |  | 31.7 | ++ | 2.2 |  | 54.3 | - | 3.6 |  |
| **Co 9689B3** | 103.8 | - | 5.5 |  | 9.1 | +++ | 0.6 |  | 67.2 | - | 4.8 |  |
| **Co 9729** | 106.1 | - | 2.1 |  | 118.3 | - | 2.1 |  | 94.5 | - | 1.7 |  |
| **Co 9775** | 30.4 | ++ | 2 |  | 18.5 | +++ | 1.5 |  | 51.8 | - | 3.9 |  |
| **Co 9946** | 86.9 | - | 2 |  | 71.1 | - | 1.4 |  | 79.1 | - | 1.5 |  |
| **Co 9978** | 20.6 | ++ | 15.8 |  | 13 | +++ | 3.6 |  | 38.2 | + | 19.5 |  |
| **Co 99974** | 52.4 | - | 3 |  | 27.4 | ++ | 1.6 |  | 97.6 | - | 6.6 |  |
| **Co 10158** | 18.3 | +++ | 3.1 |  | 11.1 | +++ | 2 |  | 20.6 | ++ | 3.5 |  |
| **Co 10194** | 85.7 | - | 4.9 |  | 9.6 | +++ | 0.7 |  | 38.9 | + | 1.9 |  |
| **Co 103004** | 56.3 | - | 2 |  | 26.2 | ++ | 1.3 |  | 97.2 | - | 3.6 |  |
| **Co10302A5** | 46.9 | + | 2.1 |  | 37.4 | + | 1.7 |  | 72.4 | - | 3.6 |  |
| **Co10302B5** | 44.6 | (+) | 1.9 |  | 25.7 | ++ | 1.5 |  | 72.7 | - | 1.9 |  |
| **Co 10377** | 126.4 | - | 32.1 |  | 2.2 | ++++ | 1.5 |  | 69.6 | - | 15.7 |  |
| **Co 10383** | 8.8 | +++ | 1.2 |  | 5.6 | +++ | 1 |  | 70 | - | 9.8 |  |
| **Co 10588** | 188.4 | - | 12.2 |  | 53.3 | - | 3.5 |  | 133 | - | 4.4 |  |
| **Co 10764** | 40.7 | + | 3.4 |  | 28.8 | ++ | 2.2 |  | 48.5 | + | 3.6 |  |
| **Co 10925** | 17.8 | +++ | 0.8 |  | 11.6 | +++ | 0.5 |  | 25.2 | ++ | 1.2 |  |
| **Co 11061** | 21.9 | ++ | 1.8 |  | 24 | ++ | 2.3 |  | 42.5 | + | 4.1 |  |

1 -5 PDX models were derived from the same patient

**Suppl. Table 3:Sensitivity of the PDX towards targeted drugs.** The table summarizes the chemosensitivity data by tumor response scores basd on the optimal treated to control values (optT/C): (-) negative, optT/C value 50-100%; (+), optT/C value 25-50%; (++), optT/C value 10-25%; (+++), optT/C value 5-10%; (++++), optT/C value 0-5%.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **PDX** | **Bevacizumab** | | |  | **Cetuximab** | | |  | **Erlotinib** | | |  |
| **opt T/C**  **[%]** | **score** | **RTV** |  | **opt T/C**  **[%]** | **score** | **RTV** |  | **opt T/C**  **[%]** | **score** | **RTV** |  |
| **Co 5676** | 48.8 | + | 4.1 |  | 0.57 | ++++ | 0.12 |  | 53.1 | - | 4.7 |  |
| **Co 5677** | 79.2 | - | 5.2 |  | 96.9 | - | 5.7 |  | 103.8 | - | 8 |  |
| **Co 5679** | 44.8 | + | 6.6 |  | 38.6 | + | 6.2 |  | 151.2 | - | 8.7 |  |
| **Co 5682** | 21.5 | ++ | 0.9 |  | 45.2 | + | 1.3 |  | 78.1 | - | 3.7 |  |
| **Co 5734** | 33.8 | ++ | 1.8 |  | 12.1 | +++ | 1.4 |  | 29.6 | ++ | 1.2 |  |
| **Co 5735** | 15.9 | +++ | 2.6 |  | 22.5 | ++ | 3.0 |  | 39.9 | + | 3.8 |  |
| **Co 5736** | 107.3 | - | 12.2 |  | 92.4 | - | 12 |  | 51.4 | - | 6 |  |
| **Co 5771** | 14.7 | +++ | 1.1 |  | 25.5 | ++ | 1.7 |  | 36.6 | + | 2.6 |  |
| **Co 5776** | 30.1 | ++ | 3.3 |  | 72.3 | - | 7.1 |  | 72.2 | - | 6.7 |  |
| **Co 5841** | 23 | ++ | 1.5 |  | 44.2 | + | 1.6 |  | 27.4 | ++ | 3.6 |  |
| **Co 5854** | 38.9 | + | 8.2 |  | 73.7 | - | 16.8 |  | 34 | ++ | 7.2 |  |
| **Co 5896** | 39.6 | + | 3.6 |  | 44.3 | + | 4.2 |  | 92.9 | - | 7.3 |  |
| **Co 6044** | 75.5 | - | 6.4 |  | 102.4 | - | 12.2 |  | 81.6 | - | 5.7 |  |
| **Co 6228** | 27.8 | ++ | 5.2 |  | 74.4 | - | 3.6 |  | 78 | - | 12.7 |  |
| **Co 72711** | 45.7 | + | 4 |  | 15.9 | +++ | 1.6 |  | 56.1 | - | 5.8 |  |
| **Co 7475** | 15.9 | +++ | 5.7 |  | 38.5 | + | 7.7 |  | 97.1 | - | 5.5 |  |
| **Co 7515** | 40.4 | + | 2.9 |  | 20.5 | ++ | 2.2 |  | 42.2 | + | 4.3 |  |
| **Co 7523** | 57.8 | - | 3.8 |  | 20.8 | ++ | 1.2 |  | 73.7 | - | 5.7 |  |
| **Co 7553A2** | 36.9 | + | 3.8 |  | 8.3 | +++ | 0.8 |  | 26.9 | ++ | 2.4 |  |
| **Co 7553B2** | 36.5 | + | 1.2 |  | 8.7 | +++ | 0.8 |  | 36 | + | 0.7 |  |
| **Co 7567** | 72.5 | - | 2 |  | 94.5 | - | 2.2 |  | 141.4 | - | 3.3 |  |
| **Co 7596** | 31.2 | ++ | 2.2 |  | 0.7 | ++++ | 0.2 |  | 29.2 | ++ | 1.6 |  |
| **Co 76601** | 26.9 | ++ | 0.7 |  | 28.8 | ++ | 0.7 |  | 76.9 | - | 1.7 |  |
| **Co 7689** | 63.7 | - | 4 |  | 58.2 | - | 4.6 |  | 73.4 | - | 3.5 |  |
| **Co 7809** | 11.7 | +++ | 2.2 |  | 60.3 | - | 8.4 |  | 85.3 | - | 10.9 |  |
| **Co 7818** | 37.9 | + | 3.7 |  | 36.4 | + | 3.6 |  | 38.9 | + | 3.2 |  |
| **Co 7835** | 24.5 | ++ | 2.9 |  | 44.4 | + | 6.4 |  | 45.5 | + | 5.8 |  |
| **Co 7888** | 59.5 | - | 1.9 |  | 29.1 | ++ | 1.1 |  | 63.9 | - | 3.4 |  |
| **Co 7935** | 67.4 | - | 1.5 |  | 21.1 | ++ | 0.9 |  | 23 | ++ | 1 |  |
| **Co 9587** | 65.9 | - | 1.5 |  | 75.4 | - | 2 |  | 42.7 | + | 1 |  |
| **Co 9634** | 41.9 | + | 5.2 |  | 64.1 | - | 7.8 |  | 72.6 | - | 8.2 |  |
| **Co 9689A3** | 33 | ++ | 1.9 |  | 14.5 | +++ | 0.8 |  | 51.9 | - | 2.9 |  |
| **Co 9689B3** | 25 | ++ | 2.3 |  | 8.4 | +++ | 0.9 |  | 32.7 | ++ | 2.7 |  |
| **Co 9729** | 109.7 | - | 2.3 |  | 103.9 | - | 2 |  | 119.6 | - | 2.2 |  |
| **Co 9775** | 25.1 | ++ | 1.7 |  | 49.7 | (+) | 3.3 |  | 47.5 | + | 3.7 |  |
| **Co 9946** | 50.2 | - | 1 |  | 57.2 | - | 1.1 |  | 72.3 | - | 1.6 |  |
| **Co 9978** | 20.2 | ++ | 9.2 |  | 14.7 | +++ | 10.6 |  | 18 | +++ | 8.8 |  |
| **Co 99974** | 55.8 | - | 3.3 |  | 42.2 | + | 2.2 |  | 52.8 | - | 3.2 |  |
| **Co 10158** | 24 | ++ | 3.6 |  | 42.1 | + | 6.1 |  | 40.2 | + | 6.1 |  |
| **Co 10194** | 64.2 | - | 3.1 |  | 0.6 | ++++ | 0.1 |  | 33.5 | ++ | 2 |  |
| **Co 103004** | 71.3 | - | 2.7 |  | 55 | - | 2.3 |  | 65.8 | - | 2.8 |  |
| **Co10302A5** | 100.7 | - | 4.7 |  | 190.4 | - | 9.5 |  | 88.5 | - | 4.2 |  |
| **Co10302B5** | 108.8 | - | 2.3 |  | 87.7 | - | 3.7 |  | 53.4 | - | 2.2 |  |
| **Co 10377** | 44.3 | + | 8.5 |  | 69.3 | - | 13.6 |  | 106 | - | 23.3 |  |
| **Co 10383** | 16.3 | +++ | 1.9 |  | 15.9 | +++ | 2.1 |  | 60.5 | - | 8.4 |  |
| **Co 10588** | 100.2 | - | 6.9 |  | 171.8 | - | 10.7 |  | 206 | - | 14.8 |  |
| **Co 10764** | 38.1 | + | 2.8 |  | 39.5 | + | 2.8 |  | 51.6 | - | 3.6 |  |
| **Co 10925** | 21.9 | ++ | 1.1 |  | 6.8 | +++ | 0.4 |  | 32.2 | ++ | 1.5 |  |
| **Co 11061** | 33.6 | ++ | 3.1 |  | 15.2 | +++ | 1.6 |  | 22.9 | ++ | 2.3 |  |

1 -5 PDX models were derived from the same patient

**Suppl. Table 4: Gene copy number (GCN) of all PDX.** The GCN was determined by real-time PCR.

|  |  |  |  |
| --- | --- | --- | --- |
| PDX | Gene copy number | | |
| **BRAF** | **EGFR** | **KRAS** |
| Co 5676 | 2 | 3 | 3 |
| Co 5677 | 1 | 1 | 2 |
| Co 5679 | 2 | 2 | 6 |
| Co 5682 | 2 | 2 | 2 |
| Co 5734 | 2 | 2 | 2 |
| Co 5735 | 2 | 2 | 2 |
| Co 5736 | 1 | 1 | 2 |
| Co 5771 | 2 | 2 | 4 |
| Co 5776 | 1 | 1 | 2 |
| Co 5841 | 2 | 2 | 3 |
| Co 5854 | 2 | 2 | 2 |
| Co 5896 | 1 | 1 | 2 |
| Co 6044 | 1 | 1 | 2 |
| Co 6228 | 1 | 2 | 3 |
| Co 72711 | 2 | 2 | 2 |
| Co 7475 | 1 | 1 | 2 |
| Co 7515 | 1 | 1 | 1 |
| Co 7523 | 1 | 1 | 2 |
| Co 7553A2 | 2 | 2 | 3 |
| Co 7553B2 | 4 | 4 | 6 |
| Co 7567 | 2 | 3 | 4 |
| Co 7596 | 23 | 4 | 9 |
| Co 76601 | 1 | 1 | 1 |
| Co 7689 | 1 | 1 | 2 |
| Co 7809 | 1 | 2 | 3 |
| Co 7818 | 6 | 5 | 7 |
| Co 7835 | 2 | 2 | 3 |
| Co 7888 | 3 | 6 | 3 |
| Co 7935 | 3 | 4 | 4 |
| Co 9587 | 1 | 1 | 2 |
| Co 9634 | 2 | 2 | 2 |
| Co 9689A3 | 3 | 5 | 4 |
| Co 9689B3 | 3 | 4 | 4 |
| Co 9729 | 1 | 1 | 2 |
| Co 9775 | 4 | 3 | 4 |
| Co 9946 | 2 | 2 | 3 |
| Co 9978 | 2 | 2 | 4 |
| Co 99974 | 3 | 3 | 5 |
| Co 10158 | 1 | 1 | 3 |
| Co 10194 | 2 | 2 | 4 |
| Co 103004 | 2 | 3 | 4 |
| Co10302A5 | 1 | 1 | 3 |
| Co10302B5 | 1 | 1 | 2 |
| Co 10377 | 1 | 1 | 2 |
| Co 10383 | 2 | 3 | 3 |
| Co 10588 | 1 | 1 | 1 |
| Co 10764 | 2 | 2 | 2 |
| Co 10925 | 2 | 4 | 4 |
| Co 11061 | 1 | 1 | 3 |

1 -5 PDX models were derived from the same patient

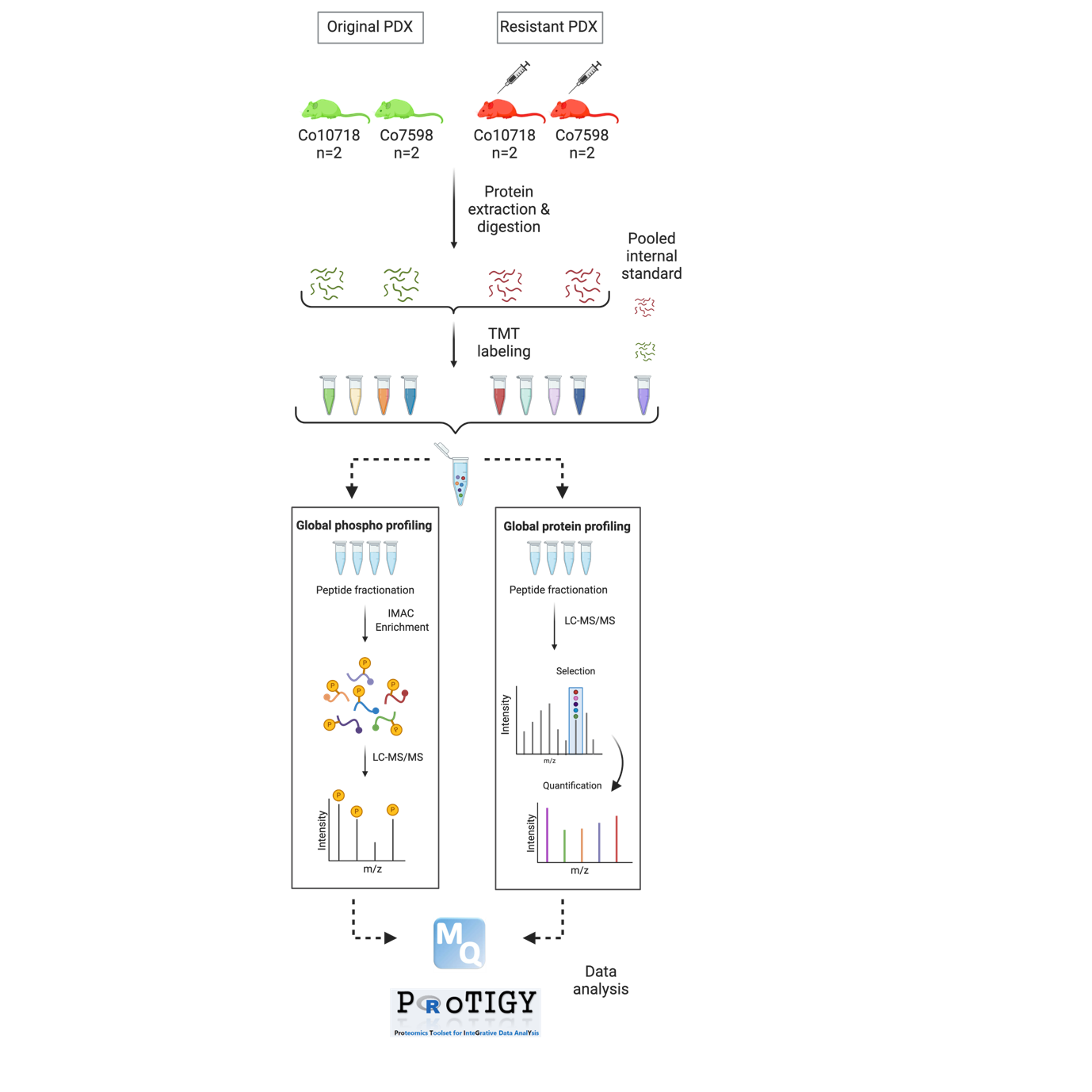
**Suppl. Table 5: Comparison of gene copy numbers (GCN) in cetuximab resistant PDX.** GCN of BRAF, EGFR and KRAS was compared in Co7596\_orig vs. Co5796\_cetux and in Co10718\_orig vs. Co10718\_cetux. The GCN were determined by real-time PCR analysis using samples of PDX of same in vivo passage numbers to ensure best comparability.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Gene copy number** | | |
|  | **BRAF** | **EGFR** | **KRAS** |
| **Co 7596** | 21.25±4.24 | 4.00±0.00 | 2.00±0.00 |
| **Co 7596\_cetux** | 9.42±2.90 | 5.00±1.41 | 2.00±0.00 |
|  | **BRAF** | **EGFR** | **KRAS** |
| **Co 10718** | 3.05±0.69 | 4.67±1.15 | 2.00±0.00 |
| **Co 10718\_cetux** | 2.35±0.42 | 4.40±0.89 | 2.00±0.00 |

**Supplementary Table 6:** TMT labelling scheme of all samples used in this study.

|  |  |
| --- | --- |
| **Channels** | **Randomized samples** |
| 126 | Empty |
| 127N | Co7596\_orig Replicate 2 |
| 127C | Co10718\_cetux Replicate 2 |
| 128N | Co7596\_cetux Replicate 1 |
| 128C | Co10718\_orig Replicate 1 |
| 129N | Co7596\_cetux Replicate 2 |
| 129C | Co10718\_orig Replicate 2 |
| 130N | Co7596\_orig Replicate 1 |
| 130C | Co10718\_cetux Replicate 1 |
| 131 | Pooled internal standard |

**Supplementary Figures**



**Supplementary Figure 1:** Schematic representation of the proteomic analysis workflow.



**Supplementary Figure 2:** Principal component analysis of all samples used in this study. PCA analysis is performed on subset of high variant proteins ( sd > 0.5). Samples are color-coded by model name and acquired resistance status. PC1 and PC2 accounted for 31.31% and 17.3% of the contribution to the variance, respectively. Note that acquired resistance status can be explained by second highest variance



**Suppl. Fig 3: Proteins and phosphosites significantly regulated in cetuximab resistant model Co10718\_cetux**. **A.** Volcano plot illustrates [-10Log10(p-value)] vs. the log fold change, with proteins outside the significance lines colored in red (adj. p-value < 0.05). p values are calculated from the resistant models and their sensitive counterparts. **B.** Volcano plot shows significantly regulated phosphosites in cetuximab resistant model Co10718\_cetux.

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**Suppl. Fig 4: GO analysis of significantly regulated proteins and phosphosites in cetuximab resistant model Co10718\_cetux**. **A.** GO terms are grouped according to KEGG pathways and biological process analysis of the significantly regulated proteins in cetuximab resistant model Co10718\_cetux (adj. p-value<0.05) and top 20 groups are shown, if available. Red and blue colors indicate up and downregulation, respectively. **B.** Top20 biological processes and KEGG pathways enriched in the significantly regulated phosphosites of cetuximab resistant model Co10718\_cetux (adj. p-value<0.05).