**Supplementary Table 1.** Molecular genomic alterations on tissue and ctDNA.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient** | **Gene** | **c.DNA** | **p.Prot** | **COSMIC** | **Tissue** | **Consult A** | **Consult B** | **Consult C** | **Consult D** | **Consult E** | **Consult F** | **Consult G** | **Consult H** | **Consult I** | **Consult J** |
| **1631** | *KRAS* | c.35G>T | p.(Gly12Val) | COSM520 |  | 11.9% | 11.4% | 22.2% | 2.3% | 1.1% | 7.5% | 28.2% | 19.9% | 23.6% | 23.3% |
| *TP53* | c.916C>T | p.Arg306\* | COSM10663 |  | 27.7% | 21.7% | 34.5% | 3.2% | 2.0% | 15.7% | 64.7% | 51.6% | 57.9% | 70.8% |
| **1624** | *TP53* | c.517G>A | p.(Val173Met) | COSM11084 |  | 55.5% | 6.2% | 18.0% | 75.4% | 68.2% | 64.0% |  |  |  |  |
| **1574** | *CARD11* | c.269T>C | p.(Val90Ala) | - |  | 0.0% | 0.0% | 4.0% | 4.7% | 4.7% | 3.3% |  |  |  |  |
| *TP53* | c.508A>C | p.Thr170Pro | COSM45480 |  | 5.8% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |  |  |  |  |
| *TP53* | c.560-3\_573del | p.(?) | - |  | 0.0% | 0.0% | 3.3% | 2.9% | 3.2% | 3.7% |  |  |  |  |
| **1776** | *SMAD4* | c.1051G>A | p.(Asp351Asn) | COSM32910 | 82.1% | 67.0% | 8.0% | 92.0% | 86.0% |  |  |  |  |  |  |
| *TP53* | c.376-2A>G | p.(?) | COSM45672 | 73.6% | 52.8% | 4.4% | 85.3% | 79.6% |  |  |  |  |  |  |
| *RB1* | c.277C>T | p.(Gln93\*) | COSM1477249 | 79.5% | 0.0% | 0.0% | 0.0% | 0.0% |  |  |  |  |  |  |
| **1704** | *CTNNB1* | c.121A>G | p.(Thr41Ala) | COSM5664 | 94.0% | 0.0% | 0.0% | 0.0% | 0.0% | 1.7% |  |  |  |  |  |
| *JAK1* | c.1582A>T | p.(Lys528\*) | - | 93.0% | 0.0% | 0.0% | 0.0% | 0.0% | 1.8% |  |  |  |  |  |
| *CDKN2A* | c.79G>T | p.(Glu27\*) | COSM28676 | 90.7% | 0.0% | 26.9% | 5.6% | 3.7% | 1.9% |  |  |  |  |  |
| *SMAD4* | c.1508T>G | p.(Met503Arg) | - |  | 2.0% | 0.0% | 2.1% | 1.7% | 2.0% |  |  |  |  |  |
| **1636** | *BRAF* | c.1799T>A | p.Val600Glu | COSM476 | 23.5% | 21.9% | 20.1% | 24.0% | 32.5% |  |  |  |  |  |  |
| *TP53* | c.640\_641delCA | p.His214\*fs\*1 | - | 30.9% | 21.1% | 14.8% | 14.9% | 24.0% |  |  |  |  |  |  |
| *KRAS* | c.\*29G>C |  | - |  | 0.0% | 0.0% | 1.9% | 0.0% |  |  |  |  |  |  |
| *TP53* | c.\*7G>A |  | - |  | 0.0% | 0.0% | 3.5% | 0.0% |  |  |  |  |  |  |
| **1505** | *TP53* | c.216dupC | p.(Val73Argfs\*76) | - |  | 54.8% | 0.0% | 5.7% | 59.1% |  |  |  |  |  |  |
| **1546** | *APC* | c.3949G>C | p.Glu1317Gln | COSM19099 |  | 85.9% | 50.6% | 0.0% |  |  |  |  |  |  |  |
| *APC* | c.4666dupA | p.Thr1556Asnfs\*3 | - |  | 70.6% | 0.0% | 0.0% |  |  |  |  |  |  |  |
| *EGFR* | c.2452T>G | p.Cys818Gly | - |  | 0.0% | 10.9% | 0.0% |  |  |  |  |  |  |  |
| *KDR* | c.889G>A | p.Val297Ile | COSM1131107 |  | 11.4% | 48.9% | 0.0% |  |  |  |  |  |  |  |
| *PIK3CA* | c.2119G>A | p.Glu707Lys | COSM5030972 |  | 2.8% | 1.9% | 0.0% |  |  |  |  |  |  |  |
| *TP53* | c.508A>C | p.Thr170Pro | COSM45480 |  | 0.0% | 5.2% | 0.0% |  |  |  |  |  |  |  |
| *TP53* | c.406C>T | p.Gln136\* | COSM11166 |  | 0.0% | 0.0% | 82.6% |  |  |  |  |  |  |  |
| **1763** | *TP53* | c.841G>T | p.(Asp281Tyr) | COSM3820706 | 0.0% | 0.0% | 0.0% | 12.0% |  |  |  |  |  |  |  |
| **1790** | *TP53* | c.722C>T | p.(Ser241Phe) | COSM10812 |  | 82.0% | 73.5% | 91.5% |  |  |  |  |  |  |  |
| **1551** | *TP53* | c.818G>T | p.Arg273Leu | COSM3675521 |  | 65.1% | 15.0% | 65.2% |  |  |  |  |  |  |  |
| **1848** | *ATRX* | c.6392G>A | p.(Arg2131Gln) | COSM3973883 | 16.4% | 0.0% | 0.0% | 0.0% |  |  |  |  |  |  |  |
| *BAP1* | c.295G>A | p.(Val99Met) | COSM4119066 | 24.0% | 0.0% | 0.0% | 0.0% |  |  |  |  |  |  |  |
| *HIST1H3B* | c.325A>G | p.(Asn109Asp) | COSM6941791 | 41.8% | 0.0% | 0.0% | 0.0% |  |  |  |  |  |  |  |
| *BRAF* | c.1799T>A | p.(Val600Glu) | COSM476 | 53.0% | 19.6% | 0.0% | 0.0% |  |  |  |  |  |  |  |
| *TP53* | c.844C>T | p.(Arg282Trp) | COSM10704 | 79.4% | 27.3% | 0.0% | 0.0% |  |  |  |  |  |  |  |
| **1387** | *RB1* | c.763C>T | p.Arg255\* | COSM943 |  | 31.8% | 65.6% |  |  |  |  |  |  |  |  |
| *TP53* | c.535C>T | p.His179Tyr | COSM129848 |  | 19.9% | 48.4% |  |  |  |  |  |  |  |  |
| **1705** | *TP53* | c.767C>A | p.Thr256Lys | COSM44429 |  | 72.9% | 56.2% |  |  |  |  |  |  |  |  |
| *ERBB2* | c.2033G>A | p.Arg678Gln | COSM436498 |  | 43.1% | 35.0% |  |  |  |  |  |  |  |  |
| **1288** | *KRAS* | c.35G>T | p.Gly12Val | COSM520 |  | 40.7% | 26.2% |  |  |  |  |  |  |  |  |
| *TP53* | c.733G>A | p.Gly245Ser | COSM6932 |  | 70.2% | 35.3% |  |  |  |  |  |  |  |  |
| **1390** | *APC* | c.2626C>T | p.Arg876\* | COSM18852 |  | 30.2% | 25.0% |  |  |  |  |  |  |  |  |
| *KRAS* | c.35G>A | p.Gly12Asp | COSM521 |  | 45.4% | 41.2% |  |  |  |  |  |  |  |  |
| *APC* | c.4120G>A | p.Glu1374Lys | COSM18737 |  | 56.2% | 46.3% |  |  |  |  |  |  |  |  |
| *TP53* | c.524G>A | p.Arg175His | COSM10648 |  | 80.6% | 66.2% |  |  |  |  |  |  |  |  |
| *KDR* | c.889G>A | p.Val297Ile | COSM1131107 |  | 9.4% | 16.0% |  |  |  |  |  |  |  |  |
| **1616** | *TP53* | c.637C>T | p.Arg213\* | COSM99618 |  | 89.7% | 85.0% |  |  |  |  |  |  |  |  |
| **1680** | *TP53* | c.817C>T | p.Arg273Cys | COSM10659 |  | 74.0% | 52.9% |  |  |  |  |  |  |  |  |
| **1894** | *RB1* | c.2084T>A | p.(Met695Lys) | COSM3955643 | 83.8% | 0.0% |  |  |  |  |  |  |  |  |  |
| *TP53* | c.724T>C | p.(Cys242Arg) | COSM11738 | 91.0% | 55.8% |  |  |  |  |  |  |  |  |  |
| **1864** | *TP53* | c.807C>G | p.(Ser269Arg) | - |  | 1.1% | 0.0% |  |  |  |  |  |  |  |  |
| *TP53* | c.812A>G | p.(Glu271Gly) | COSM43879 |  | 0.9% | 0.0% |  |  |  |  |  |  |  |  |
| *BRAF* | c.1799T>A | p.(Val600Glu) | COSM476 |  | 0.8% | 0.0% |  |  |  |  |  |  |  |  |
| **1893** | *CDKN2A* | c.203C>T | p.Ala68Val | COSM13440 |  | 12.7% |  |  |  |  |  |  |  |  |  |
| *PTEN* | c.955\_958delACTT | p.Thr319\*fs\*1 | - |  | 26.1% |  |  |  |  |  |  |  |  |  |
| *RB1* | c.1981C>T | p.Arg661Trp | COSM861 |  | 16.1% |  |  |  |  |  |  |  |  |  |
| *TP53* | c.833C>G | p.Pro278Arg | COSM10887 |  | 41.7% |  |  |  |  |  |  |  |  |  |
| **1230** | *TP53* | c.524G>A | p.Arg175His | COSM10648 |  | 1.2% |  |  |  |  |  |  |  |  |  |
| **1445** | / | - | - | - |  | / | / |  |  |  |  |  |  |  |  |
| **1677** | / | - | - | - |  | / | / | / | / |  |  |  |  |  |  |

**Supplementary Table 2.** Factors associated with overall survival (OS) in univariate analysis for platinum-etoposide chemotherapy and Folfiri-based chemotherapy.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variables | Platinum-etoposide chemotherapy | | | | | Folfiri-based chemotherapy | | | | |
| n | Median OS [95%CI] in months | Hazard Ratio | [95%CI] | p-value | n | Median OS [95%CI] in months | Hazard Ratio | [95%CI] | p-value |
| Small-cell  vs Large-cell NEC | 14  9 | 14.8 [9.8; 19.9]  9.9 [9.2; 10.5] | 0.63 | [0.24; 1.66] | 0.36 | 10  8 | 5.9 [0.9; 10.9]  3.6 [3.0; 4.3] | 0.80 | [0.29; 2.16] | 0.66 |
| Ki67, <80%  vs ≥80% | 8  16 | 12.6 [4.9; 20.3]  10.1 [9.4; 10.8] | 0.93 | [0.37; 2.35] | 0.88 | 6  13 | 4.4 [0.8; 8.0]  3.8 [0.1; 7.7] | 0.82 | [0.30; 2.45] | 0.70 |
| *TP53* mutation in ctDNA, yes  vs no | 20  4 | 10.1 [5.8; 14.4]  10.2 [4.6; 15.9] | 0.82 | [0.26; 2.53] | 0.73 | 15  4 | 5.9 [1.7; 10.1]  3.7 [2.8; 4.6] | 0.57 | [0.18; 186] | 0.36 |
| *RB1* mutation in ctDNA, yes  vs no | 2  22 | 14.8 [-]  10.1 [9.1; 11.1] | 0.86 | [0.20; 3.79] | 0.84 | 2  17 | 2.6 [-]  4.4 [1.4; 7.4] | 1.79 | [0.39; 8.13] | 0.45 |
| *KRAS* mutation in ctDNA, yes  vs no | 4  20 | 8.0 [4.6; 11.5]  12.6 [6.3; 18.9] | 1.80 | [0.59; 5.52] | 0.30 | 4  15 | 3.3 [2.5; 4.1]  5.9 [2.0; 9.8] | 1.58 | [0.50; 5.00] | 0.44 |
| *BRAF* mutation in ctDNA, yes  vs no | 3  21 | -  10.3 [6.2; 14.3] | 1.15 | [0.15; 9.01] | 0.89 | 2  17 | 3.6 [-]  4.4 [1.4; 7.4] | 0.55 | [0.07; 4.24] | 0.57 |
| “Adenocarcinoma-like”, yes  vs no | 10  14 | 8.7 [6.7; 10.7]  12.6 [4.2; 21.0] | 2.04 | [0.81; 5.18] | 0.13 | 7  12 | 3.6 [2.7; 4.5]  4.4 [0.8; 8.0] | 1.18 | [0.42; 3.27] | 0.75 |

n, number of patients for OS analysis.

CI, confidence interval; NEC, neuroendocrine carcinoma.