**SUPPLEMENTARY MATERIALS**

**Supplementary Table 1.** 54 to 73 gene panels of ctDNA (*Guardant, Inc*.)

**Supplementary Table 1a.** 54 gene panel (N=3 samples).

|  |  |
| --- | --- |
| **POINT MUTATIONS** | **AMPLIFICATIONS** |
| *ABL1* | *AKT1* | ***ALK*** | ***APC*** | *EGFR* |
| ***AR*** | *ATM* | ***BRAF*** | ***CDKN2A*** | *ERBB2* |
| *CDH1* | *CSF1R* | *CTNNB1* | ***EGFR*** | *MET* |
| ***ERBB2*** | *ERBB4* | *EZH2* | ***FBXW7*** |  |
| *FGFR1* | *FGFR2* | *FGFR3* | *FLT3* |  |
| *GNA11* | *GNAQ* | *GNAS* | *HNF1A* |  |
| *HRAS* | *IDH1* | *IDH2* | *JAK2* |  |
| *JAK3* | *KDR* | *KIT* | ***KRAS*** |  |
| ***MET*** | *MLH1* | *MPL* | ***MYC*** |  |
| ***NOTCH1*** | *NPM1* | ***NRAS*** | *PDGFRA* |  |
| ***PIK3CA*** | ***PTEN*** | *PTPN11* | ***PROC*** |  |
| ***RB1*** | *RET* | *SMAD4* | *SMARCB1* |  |
| *SMO* | *SRC* | *STK11* | *TERT* |  |
| ***TP53*** | *VHL* |  |  |  |

All exons were sequenced in genes in ***bold***.

**Supplementary Table 1b.** 68 gene panel (N=18 samples).

|  |  |  |  |
| --- | --- | --- | --- |
| **POINT MUTATIONS** | **AMPLIFICATIONS** | **FUSIONS** | **INDELS** |
| *AKT1* | *ALK* | ***APC*** | ***AR*** | *AR* | *ALK* | *EGFR* exon 19 deletions |
| *AFAR* | ***ARID1A*** | *ATM* | ***BRAF*** | *BRAF* | *NTRK1* | *EGFR* exon 20 insertions |
| ***BRCA1*** | ***BRCA2*** | ***CCDN1*** | ***CCDN2*** | *CCNE1* | *RET* |  |
| ***CCNE1*** | *CDH1* | ***CDK4*** | ***CDK6*** | *CDK4* | *ROS1* |  |
| ***CDKN2A*** | ***CDKN2B*** | *CTNNB1* | ***EGFR*** | *CDK6* |  |  |
| ***ERBB2*** | *ESR1* | *EZH2* | *FBXW7* | *EGFR* |  |  |
| ***FGFR1*** | ***FGFR2*** | *FGFR3* | *GATA3* | *ERBB2* |  |  |
| *GNA11* | *GNAQ* | *GNAS* | *HNF1A* | *FGFR1* |  |  |
| ***HRAS*** | *IDH1* | *IDH2* | *JAK2* | *FGFR2* |  |  |
| *JAK3* | ***KIT*** | ***KRAS*** | *MAP2K1* | *KIT* |  |  |
| *MAP2K2* | ***MET*** | *MLH1* | *MPL* | *KRAS* |  |  |
| ***MYC*** | ***NF1*** | *NFE2L2* | *NOTCH1* | *MET* |  |  |
| *NPM1* | ***NRAS*** | *NTRK1* | ***PDGFRA*** | *MYC* |  |  |
| ***PIK3CA*** | ***PTEN*** | *PTPN11* | ***RAF1*** | *PDGFRA* |  |  |
| *RET* | *RHEB* | *RHOA* | *RIT1* | *PIK3CA* |  |  |
| *ROS1* | *SMAD4* | *SMO* | *SRC* | *RAF1* |  |  |
| *STK11* | *TERT* | ***TP53*** | *VHL* |  |  |  |

Complete exon coverage for genes in ***bold***.

**Supplementary Table 1c.** 70 gene panel (N=27 samples).

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| --- | --- | --- | --- |
| **POINT MUTATIONS** | **AMPLIFICATIONS** | **FUSIONS** | **INDELS** |
| *AKT1* | *ALK\** | ***APC*** | ***AR*** | *AR* | *ALK* | *EGFR* exon 19 deletions |
| *ARAF* | ***ARID1A*** | *ATM* | ***BRAF*** | *BRAF* | *FGFR2* | *EGFR* exon 20 insertions |
| ***BRCA1*** | ***BRCA2*** | ***CCND1*** | ***CCND2*** | *CCND1* | *FGFR3* | *ERBB2* exon 19 deletions |
| ***CCNE1*** | *CDH1* | ***CDK4*** | ***CDK6*** | *CCND2* | *NTRK1* | *ERBB2* exon 20 insertions |
| ***CDKN2A*** | ***CDKN2B*** | *CTNNB1* | ***EGFR*** | *CCNE1* | *RET* |  |
| ***ERBB2*** | *ESR1* | *EZH2* | *FBXW7* | *CDK4* | *ROS1* |  |
| ***FGFR1*** | ***FGFR2\**** | *FGFR3\** | *GATA3* | *CDK6* |  |  |
| *GNA11* | *GNAQ* | *GNAS* | *HNF1A* | *EGFR* |  |  |
| ***HRAS*** | *IDH1* | *IDH2* | *JAK2* | *ERBB2* |  |  |
| *JAK3* | ***KIT*** | ***KRAS*** | *MAP2K1* | *FGFR1* |  |  |
| *MAP2K2* | ***MET*** | *MLH1* | *MPL* | *FGFR2* |  |  |
| ***MYC*** | ***NF1*** | *NFE2L2* | *NOTCH1* | *KIT* |  |  |
| *NPM1* | ***NRAS*** | *NTRK1\** | ***PDGFRA*** | *KRAS* |  |  |
| ***PIK3CA*** | ***PTEN*** | *PTPN11* | ***RAF1*** | *MET* |  |  |
| ***RB1*** | *RET\** | *RHEB* | *RHOA* | *MYC* |  |  |
| *RIT1* | *ROS1\** | *SMAD4* | *SMO* | *PDGFRA* |  |  |
| *SRC* | *STK11* | *TERT* | ***TP53*** | *PIK3CA* |  |  |
| *TSC1* | *VHL* |  |  | *RAF1* |  |  |

Complete exon and partial intron coverage for genes in ***bold***. \*Genes with asterisk include rearrangements. *MET* includes exon 14 skipping.

**Supplementary Table 1d.** 73 gene panel (N=64 samples).

|  |  |  |  |
| --- | --- | --- | --- |
| **POINT MUTATIONS** | **AMPLIFICATIONS** | **FUSIONS** | **INDELS** |
| *AKT1* | *ALK* | *APC* | *AR* | *AR* | *ALK* | *APC* | *ARID1A* |
| *ARAF* | *ARID1A* | *ATM* | *BRAF* | *BRAF* | *FGFR2* | *ATM* | *BRCA1* |
| *BRCA1* | *BRCA2* | *CCND1* | *CCND2* | *CCND1* | *FGFR3* | *BRCA2* | *CDH1* |
| *CCNE1* | *CDH1* | *CDK4* | *CDK6* | *CCNE1* | *NTRK1* | *CDKN2A* | *EGFR* |
| *CDKN2A* | *CTNNB1* | *DDR2* | *EGFR* | *CDK4* | *RET* | *GATA3* | *KIT* |
| *ERBB2* | *ESR1* | *EZH2* | *FBXW7* | *CDK6* | *ROS1* | *MET* | *MLH1* |
| *FGFR1* | *FGFR2* | *FGFR3* | *GATA3* | *EGFR* |  | *MTOR* | *NF1* |
| *GNA11* | *GNAQ* | *GNAS* | *HNF1A* | *ERBB2* |  | *PDGFRA* | *PTEN* |
| *HRAS* | *IDH1* | *IDH2* | *JAK2* | *FGFR1* |  | *RB1* | *SMAD4* |
| *JAK3* | *KIT* | *KRAS* | *MAP2K1* | *FGFR2* |  | *STK11* | *TP53* |
| *MAP2K2* | *MAPK1* | *MAPK3* | *MET* | *KIT* |  | *TSC1* | *VHL* |
| *MLH1* | *MPL* | *MTOR* | *MYC* | *KRAS* |  |  |  |
| *NF1* | *NFE2L2* | *NOTCH1* | *NPM1* | *MET* |  |  |  |
| *NRAS* | *NTRK1* | *NTRK3* | *PDGFRA* | *MYC* |  |  |  |
| *PIK3CA* | *PTEN* | *PTPN11* | *RAF1* | *PDGFRA* |  |  |  |
| *RB1* | *RET* | *RHEB* | *RHOA* | *PIK3CA* |  |  |  |
| *RIT1* | *ROS1* | *SMAD4* | *SMO* | *RAF1* |  |  |  |
| *STK11* | *TERT* | *TP53* | *TSC1* |  |  |  |  |
| *VHL* |  |  |  |  |  |  |  |

All clinically relevant exons for 73 genes are sequenced. *TERT* includes alterations in the promoter region. *MET* includes exon 14 skipping.

**Supplementary Table 2.** Genomic alteration and its potential targeted therapies with FDA-approved agents (either on/off-label) or with investigational agents in clinical trials.

|  |  |  |
| --- | --- | --- |
| ***Genes*** | **Potential targeted therapies** | **Supplemental References** |
| ***Potentially actionable with FDA approved agents (on- or off-label)*** |
| ***AR*** | *AR* alteration is potentially targetable with AR inhibitor enzalutamide and anti-androgens (e.g., abiraterone, bicalutamide) | S1-6 |
| ***ATM*** | *ATM* alteration is potentially targetable with PARP inhibitors (e.g., olaparib, niraparib, rucaparib). | S7-10 |
| ***BRAF*** | *BRAF* alteration can be targeted with BRAF inhibitors (e.g. dabrafenib, vemurafenib), MEK inhibitors (e.g. trametinib, cobimetinib), and multiple tyrosine kinase inhibitors (e.g., sorafenib, regorafenib) | S11-20 |
| ***BRCA1/2*** | *BRCA* alteration is targetable with platinum-based chemotherapy and PARP inhibitors (e.g., olaparib, niraparib, rucaparib). | S21-25 |
| ***CCND2*** | *CCND2* may be sensitive to CDK4/6 inhibitors (e.g., palbociclib, abemaciclib, ribociclib). | S26-28 |
| ***CDK4/6*** | *CDK6* and its functional homolog, *CDK4* mutations are theoretically targetable with CDK4/6 inhibitors (e.g., palbociclib, abemaciclib, ribociclib). | S27-30 |
| ***CDKN2A*** | *CDKN2* alterations may be sensitive to CDK4/6 inhibitors (e.g., palbociclib, abemaciclib, ribociclib). | S27, 28, 31, 32 |
| ***EGFR*** | Erlotinib, in combination with gemcitabine, has also been approved by the FDA for the treatment of locally advanced, unresectable, or metastatic pancreatic cancer.  | S33, 34 |
| ***ERBB2*** | *ERBB2* alteration is targetable with Her-targeted drugs (e.g., afatinib, lapatinib, neratinib, pertuzumab, trastuzumab).  | S35-40 |
| ***FBXW7*** | Although there are conflicting data, *FBXW7* aberration stabilizes the mTOR signaling which is potentially targetable with mTOR inhibitors (e.g., everolimus, temsirolimus). | S41-43 |
| ***FGFR1*** | *FGFR1* alteration is targetable with multi-kinase inhibitors (e.g., pazopanib, ponatinib, regorafenib, nintedanib, lenvatinib).  | S13, 14, 44-48 |
| ***GNAS*** | *GNAS* alteration is potentially targetable with MEK inhibitors (e.g., trametinib, cobimetinib). | S18, 19, 49-51 |
| ***IDH1*** | *IDH1* alteration is targetable with IDH1 inhibitors (e.g., ivosidenib).  | S52-54 |
| ***KRAS*** | *KRAS* alteration is potentially targetable with MEK inhibitors (e.g., trametinib, cobimetinib).  | S50, 55-63 |
| ***MET*** | *MET* alteration is targetable with multi-kinase inhibitors (e.g., cabozantinib, crizotinib). | S64-68 |
| ***MPL*** | *MPL* alterations is associated with increased Jak/Stat signaling. Thus, it may be targetable with JAK inhibitors (e.g., ruxolitinib). | S69-72 |
| ***MTOR*** | *MTOR* alteration is potentially targetable with mTOR inhibitors (e.g., everolimus, temsirolimus).  | S73-79 |
| ***NF1*** | *NF1* alteration is associated with activation of RAS and downstream pathways. Thus, it may be targetable with MEK inhibitors (e.g., trametinib, cobimetinib). | S18, 19, 80, 81 |
| ***PIK3CA*** | *PIK3CA* alteration is targetable with mTOR inhibitors (e.g., everolimus, temsirolimus). | S78, 79, 82-86 |
| ***PTEN*** | *PTEN* alteration is targetable with mTOR inhibitors (e.g., everolimus, temsirolimus).  | S78, 79, 87 |
| ***TP53*** | Retrospective data suggest patients with *TP53* mutation had longer progression-free survival with bevacizumab containing regimen when compared to non-bevacizumab containing regimen (median 11.0 vs. 4.0 months, p<0.0001). *TP53* alteration status was also predictive of longer progression-free survival among sarcoma patients treated with pazopanib (multi-kinase inhibitor including VEGF) (hazard ratio: 0.38, p = 0.036). Interestingly, multiple regression analysis of transcriptomic data revealed *TP53* mutations are associated with higher VEGFA expression (p = 0.0006) suggesting the TP53 as a marker to predict bevacizumab response. | S88-91 |
| ***Potentially actionable with investigational agents*** |
| ***MYC*** | *MYC* alteration is potentially targetable with BET inhibitors (e.g., GSK-525762). | S92-94 |

**Supplementary Table 3.** Assessment of genomic uniqueness in ctDNA among patients with pancreatic ductal adenocarcinoma.

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| **Altered gene** | **Study ID** | **Characterized alterations** |
| *TP53*, *KRAS, and CDKN2A* | 7 | *TP53* E56\*, *KRAS* G12V, *CDKN2A* G23V |
| 51 | *TP53* C124\*, *KRAS* G12R, *CDKN2A* R103fs |
| *TP53* and *KRAS* | 3 | *TP53* R175H, *KRAS* G12D  |
| 14 | *TP53* Splice Site SNV, *KRAS* G12D |
| 31 | *TP53* C275F, *KRAS* G12V |
| 74 | *TP53* R248W, *KRAS* Q61H |
| 76 | *TP53* R196\*, *KRAS* Q61H,  |
| 87 | *TP53* R248W, *TP53* R213\*, *TP53* P222L, *KRAS* G12C |
| 95 | *TP53* R273C, *KRAS* G12D |
| 96 | *TP53* S127F, *TP53* A189T, *KRAS* G12D |
| 101 | *TP53* C135G, *KRAS* G12V  |
| 108 | *TP53* R158fs, *KRAS* G12V |
| *TP53* | 24 | *TP53* V216M |
| 28 | *TP53* Q100R |
| 29 | *TP53* H214R |
| 40 | *TP53* Y220C |
| 41 | *TP53* E285K, *TP53* E221K |
| 42 | *TP53* I195T |
| 53 | *TP53* L93M |
| 55 | *TP53* R213\* |
| 59 | *TP53* R196P |
| 68 | *TP53* R196\* |
| 71 | *TP53* R175H |
| 86 | *TP53* R273H |
| 93 | *TP53* V218E |
| 102 | *TP53* V216M |
| 106 | *TP53* Q100fs |
| *KRAS* | 8 | *KRAS* G12R |
| 43 | *KRAS* Q61H |
| 50 | *KRAS* G12D |
| 60 | *KRAS* G12V, *KRAS* Amplification |
| 64 | *KRAS* G12V |
| 70 | *KRAS* G12V |
| 85 | *KRAS* G12R |
| 88 | *KRAS* G12V, *KRAS* Amplification |

**Supplementary Table 4**. Complete list of ctDNA alterations found in patients with pancreatic ductal adenocarcinoma (N=112).

|  |  |  |
| --- | --- | --- |
| **ID** | **Characterized alteration in ctDNA** | **Disease status at the time of ctDNA analysis****(all treatment regimens prior to ctDNA)** |
| 1 | no characterized alteration detectable | Surgically resectable \*blood obtained after surgery |
| 2 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease (capecitabine; gemcitabine + abraxane; FOLFIRINOX) |
| 3 | *KRAS* G12D, *TP53* R175H | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 4 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease (FOLFIRINOX; gemcitabine + abraxane) |
| 5 | no characterized alteration detectable | Surgically resectable \*blood obtained before surgery |
| 6 | *KRAS* G12D, *SMAD4* R361C, *TP53* H214P, *GNAS* R201C, *ATM* R3047Q | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 7 | *CDKN2A* G23V, *KRAS* G12V, *TP53* E56\* | Metastatic, locally advanced, or recurrent disease (gemcitabine; capecitabine) |
| 8 | *KRAS* G12R | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 9 | no characterized alteration detectable | Surgically resectable \*blood obtained before surgery |
| 10 | no characterized alteration detectable | Surgically resectable \*blood obtained after surgery |
| 11 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 12 | *TERT* Promoter SNV | Metastatic, locally advanced, or recurrent disease (gemcitabine + abraxane) |
| 13 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 14 | *TP53* Splice Site SNV, *KRAS* G12D | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 15 | *PIK3CA* E545K | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 16 | *GNAS* R201H, *KRAS* G12V, *TP53* L265P | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 17 | no characterized alteration detectable | Surgically resectable \*blood obtained before surgery |
| 18 | *AR* R775H | Metastatic, locally advanced, or recurrent disease (FOLFIRINOX) |
| 19 | *KRAS* G12V, *TP53* R306\*, *PIK3CA* E545K, *NF1* K1444E | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 20 | no characterized alteration detectable | Surgically resectable \*blood obtained after surgery |
| 21 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 22 | *KRAS* G12D, *TP53* C176F, *PTEN* R13Q | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 23 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 24 | *TP53* V216M | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 25 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 26 | *MPL* W515L, *TP53* C141Y | Surgically resectable \*blood obtained before surgery |
| 27 | *NF1* I679fs, *GNAS* R201C | Metastatic, locally advanced, or recurrent disease (gemcitabine + abraxane) |
| 28 | *TP53* Q100R | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 29 | *TP53* H214R | Surgically resectable \*blood obtained after surgery |
| 30 | *CCND2* amplification | Surgically resectable \*blood obtained before surgery |
| 31 | *TP53* C275F, *KRAS* G12V | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 32 | no characterized alteration detectable | Surgically resectable \*blood obtained after surgery |
| 33 | *TP53* R213L, *FBXW7* R385H | Metastatic, locally advanced, or recurrent disease (5FU+ abraxane + oxaliplatin + bevacizuamb; gemcitabine + abraxane; 5FU) |
| 34 | *KRAS* G12V, *MYC* amplification | Metastatic, locally advanced, or recurrent disease (gemcitabine) |
| 35 | *TP53* S215R, *MYC* amplification | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 36 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 37 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease (FOLFIRINOX; gemcitabine + abraxane) |
| 38 | *RB1* E282\*, *TP53* R273C, *KRAS* G12D | Surgically resectable \*blood obtained before surgery |
| 39 | *TP53* R282W, *KRAS* G12R, *CDKN2A* W15\*, *ERBB2* amplification, *CDK4* amplification, *KRAS* amplification | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 40 | *TP53* Y220C | Metastatic, locally advanced, or recurrent disease (gemcitabine + carboplatin) |
| 41 | *TP53* E285K, *TP53* E221K | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 42 | *TP53* I195T | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 43 | *KRAS* Q61H | Metastatic, locally advanced, or recurrent disease (FOLFIRINOX; gemcitabine + abraxane) |
| 44 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease (capecitabine) |
| 45 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 46 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 47 | *CDKN2A* R80\*, *KRAS* G12D | Metastatic, locally advanced, or recurrent disease (abraxane + palbociclib; gemcitabine + erlotinib; palbociclib + trametinib + anakinra; palbociclib + trametinib + afatinib) |
| 48 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease (capecitabine) |
| 49 | *KRAS* G12R, *SMAD4* R361G, *CDK6* amplification, *EGFR* amplification | Metastatic, locally advanced, or recurrent disease (gemcitabine + abraxane) |
| 50 | *KRAS* G12D | Metastatic, locally advanced, or recurrent disease (gemcitabine + capecitabine; abraxane) |
| 51 | *KRAS* G12R, *TP53* C124\*, *CDKN2A* R103fs | Metastatic, locally advanced, or recurrent disease (FOLFIRINOX) |
| 52 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 53 | *TP53* L93M | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 54 | *TP53* V172F, *CCNE1* amplification, *BRAF* amplification, *EGFR* amplification, *CDK6* amplification | Metastatic, locally advanced, or recurrent disease (gemcitabine) |
| 55 | *TP53* R213\* | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 56 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease (FOLFIRINOX) |
| 57 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease (gemcitabine) |
| 58 | *KRAS* G12L, *FGFR1* amplification | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 59 | *TP53* R196P | Surgically resectable \*blood obtained before surgery |
| 60 | *KRAS* G12V, *KRAS* amplification | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 61 | *KRAS* G12R, *TP53* P223L, *MYC* amplification | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 62 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease (gemcitabine + abraxane; capecitabine) |
| 63 | *GNAS* R201H | Metastatic, locally advanced, or recurrent disease (FOLFIRINOX; gemcitabine + abraxane) |
| 64 | *KRAS* G12V | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 65 | *KRAS* G12D, *TP53* G105V, *GNAS* R201C, *KRAS* Amplification, *MYC* Amplification, *MET* Amplification | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 66 | no characterized alteration detectable | Surgically resectable \*blood obtained before surgery |
| 67 | *IDH1* R132C | Metastatic, locally advanced, or recurrent disease (gemcitabine + abraxane) |
| 68 | *TP53* R196\* | Metastatic, locally advanced, or recurrent disease (capecitabine) |
| 69 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease (gemcitabine + abraxane; capecitabine + irinotecan) |
| 70 | *KRAS* G12V | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 71 | *TP53* R175H | Metastatic, locally advanced, or recurrent disease (gemcitabine + abraxane; FOLFOX) |
| 72 | *KRAS* G12R, *TP53* Y220C, *TP53* K132E, *PIK3CA* amplification, *CCND2* amplification, *CCNE1* amplification | Metastatic, locally advanced, or recurrent disease (capecitabine + oxaliplatin; capecitabine) |
| 73 | *KRAS* G12V, *TP53* C176W, *FBXW7* R465C, *FGFR1* amplification, *BRAF* amplification | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 74 | *TP53* R248W, *KRAS* Q61H | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 75 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease (FOLFIRINOX) |
| 76 | *KRAS* Q61H, *TP53* R196\* | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 77 | *KRAS* G12D, *MYC* Amplification, *CCNE1* Amplification, *PIK3CA* Amplification, *KRAS* Amplification | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 78 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease (FOLFIRINOX) |
| 79 | *KRAS* Q61R, SMAD4 D537Y, *TP53* Y163C, *KRAS* Amplification | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 80 | *KRAS* G12V, *TP53* Y220H, *CCNE1* amplification, *PIK3CA* R401\* | Metastatic, locally advanced, or recurrent disease (gemcitabine + abraxane) |
| 81 | no characterized alteration detectable | Surgically resectable \*blood obtained after surgery |
| 82 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 83 | *KRAS* G12R, *TP53* R282W, *KRAS* Amplification, MYC Amplification, *PIK3CA* Amplification | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 84 | *BRAF* G469V | Metastatic, locally advanced, or recurrent disease (gemcitabine + abraxane + momelotinib; FOLFIRINOX; cediranib + olaparib) |
| 85 | *KRAS* G12R | Metastatic, locally advanced, or recurrent disease (gemcitabine + abraxane) |
| 86 | *TP53* R273H | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 87 | *KRAS* G12C, *TP53* R248W, *TP53* R213\*, *TP53* P222L | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 88 | *KRAS* G12V, *KRAS* Amplification | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 89 | *KRAS* G12D, KRAS amplification, *TP53* C242fs, *TP53* H168fs, *BRCA2* T3033fs, *IDH1* R132H | Metastatic, locally advanced, or recurrent disease (FOLFIRINOX; gemcitabine + abraxane) |
| 90 | *KRAS* G12D, *TP53* R273P, *NF1* N1652K | Metastatic, locally advanced, or recurrent disease (FOLFIRINOX; capecitabine) |
| 91 | *ATM* R337H, *KRAS* G12D | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 92 | *BRCA1* Splice Site SNV, *KRAS* G12V, *TP53* S149fs | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 93 | *TP53* V218E | Surgically resectable \*blood obtained after surgery |
| 94 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 95 | *TP53* R273C, *KRAS* G12D | Metastatic, locally advanced, or recurrent disease (gemcitabine + abraxane; FOLFIRINOX) |
| 96 | *TP53* S127F, *KRAS* G12D, *TP53* A189T | Metastatic, locally advanced, or recurrent disease (gemcitabine) |
| 97 | *GNAS* R201H, *CDKN2A* E27\*, *TP53* splice Site SNV, *KRAS* G12D | Metastatic, locally advanced, or recurrent disease (FOLFIRINOX) |
| 98 | *KRAS* G12D, *GNAS* R201H, *ATM* Splice Site SNV | Metastatic, locally advanced, or recurrent disease (capecitabine; gemcitabine + abraxane; FOLFOX; 5FU + irinotecan) |
| 99 | *KRAS* G12D, *TP53* P177\_C182del, *SMAD4* S232fs, *CDKN2A* H83Y, *NF1* Y489C, *TP53* R181fs | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 100 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 101 | *KRAS* G12V, *TP53* C135G | Metastatic, locally advanced, or recurrent disease (capecitabine + oxaliplatin; gemcitabine + abraxane) |
| 102 | *TP53* V216M | Surgically resectable \*blood obtained before surgery |
| 103 | *ARID1A* W588fs | Surgically resectable \*blood obtained after surgery |
| 104 | *KRAS* G12V, *CDKN2A* R80\*, *CDK6* amplification, *SMAD4* V341Fs, *TP53* Q331H1 | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 105 | *NF1* Splice Site SNV, *NF1* I2078fs | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 106 | *TP53* Q100fs | Metastatic, locally advanced, or recurrent disease (gemcitabine + abraxane; FOLFIRINOX) |
| 107 | *CDKN2A* Splice Site SNV, *KRAS* G12D, *TP53* Y236C, *SMAD4* H305fs | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 108 | *TP53* R158fs, *KRAS* G12V | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 109 | no characterized alteration detectable | Surgically resectable \*blood obtained before surgery |
| 110 | *ATM* R3008H, *CDK6* amplification, *KRAS* G12R | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 111 | *GNAS* R201C, *NF1* D1976fs, *KRAS* G12D, *EGFR* G1022S, *MTOR* D258fs | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |
| 112 | no characterized alteration detectable | Metastatic, locally advanced, or recurrent disease(no prior chemotherapy) |

**Supplementary Table 5**. Comparisons of ctDNA parameters between refractory and treatment naïve cases (N=94 with advanced pancreatic ductal adenocarcinoma).

|  |  |  |  |
| --- | --- | --- | --- |
| ***Parameters*** | ***Patients with ≥1 chemotherapy regimen prior to blood draw for ctDNA******(N=40)*** | ***Patients with no chemotherapy regimen prior to blood draw for ctDNA******(N=54)*** | ***P-*value** |
| **Number of characterized alterations** Median (range) |  1 (0-6) |  2 (0-6) |  0.27 |
| **≥1 characterized ctDNA alteration detected** *TP53* alteration *KRAS* alteration | 29 (73%) 16 (40.0%) 17 (43%) | 41 (76%)29 (54%)31 (57%) | 0.810.220.21 |
| **Maximum %ctDNA per patient** Median (range) (%) |  0.3 (0.0-62.5) |  0.6 (0.0-64.6) |  0.29 |
| **Total %ctDNA per patient** Median (range) (%) |  0.5 (0.0-92.5) |  0.9 (0.0--86.6) |  0.34 |

**Supplementary Table 6**. Patients who had full concordant results between ctDNA and tissue DNA analyses.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **ID** | **All characterized alterations in ctDNA** | **Disease status and intervention at the time of ctDNA analysis** | **All characterized alterations in tissue DNA** | **Disease status and intervention at the time of ctDNA analysis** | **Tissue biopsy site** | **Time between blood draw and tissue biopsy** |
| 51 | *CDKN2A* R103fs, *KRAS* G12R, *TP53* C124\* | Metastatic Blood obtained after disease progression from 1st line therapy | *CDKN2A* p16INK4a R103fs\*40 and p14ARF A117fs\*52, *KRAS* G12R, *TP53* C124\* | Metastatic  Tissue obtained before 1st line therapy | Metastatic site (liver) | 5.9 month |
| 61 | *KRAS* G12R, *MYC* Amplification, *TP53* P223L | Metastatic Blood obtained before 1st line therapy | *KRAS* G12R, *MYC* amplification, TP53 P223fs\*24 | Metastatic Tissue obtained before 1st line therapy | Metastatic site (liver) | 0.4 months |
| 79 | *KRAS* Amplification, *KRAS* G61R, *SMAD4* D537Y, *TP53* Y163C | Metastatic Blood obtained before 1st line therapy | *KRAS* Q61R, *SMAD4* D537Y, *TP53* Y163C | Metastatic Tissue obtained before 1st line therapy | Metastatic site (liver) | 1.0 months |
| 97 | *CDKN2A* E27\*, *GNAS* R201H, *KRAS* G12D, *TP53* splice Site SNV | Metastatic Blood obtained before 2nd line therapy | *CDKN2A* p16INK4a E27\*, *GNAS* R201H, *KRAS* G12D, *TP53* splice site 919+2T>G | Metastatic  Tissue obtained during 1st line therapy | Metastatic site (liver) | 4.6 months |

**Supplementary Figure 1**. Consort diagram for tumors assessed by next-generation sequencing of DNA.



**Supplementary Figure 2**. Kaplan-Meier curve for overall survival from advanced disease depending on %ctDNA dichotomized at median (for total %ctDNA for all alterations) among patients with advanced PDAC (N=94).



**Supplementary Figure 3**. Kaplan-Meier curve for overall survival from ctDNA analysis stratified by ctDNA sequencing panel.

**Supplementary Figure 3a**. 73-gene panel [N=52].



**Supplementary Figure 3b**. 54-70-gene panels [N=42].

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