Supplemental Figure legends

Supplemental Figure 1. The total number of SNV mutations in 148 tumor samples.

A-E. The total number of SNV mutations was analyzed in relation to clinical characteristics such as age, gender, metastasis, pathological type and patient current status (P>0.05).

Supplemental Figure 2. Tumor percentage and the somatic copy number alteration landscape in each mutation type.

A. Tumor stage as a percentage of each mutation type. B. Tumor location as a percentage of each mutation type. C-N. The somatic copy number alteration landscape in each mutation type.

Supplemental Figure 3. **The expression of differentiated signature genes between several mutation organoids.**

A-C. Heatmap showing expression of differentiated signature genes between A mutation type and AKSP mutation organoids, AP mutation type and AKSP mutation organoids, ASP mutation type and AKSP mutation organoids.

Supplemental Figure 4. A/K/S/P mutation colorectal cancer organoids serve as a platform for preclinical drug screening.

A-B. Heatmap showing the IC50 values and corresponding percentage of 18 chemotherapy drugs for colorectal cancer in 29 PDOs. They were divided into five groups according to A/P/AP/ASP/AKSP mutation type at the top graph. The tested drugs and their targets are listed on the left. Dose–response graph is indicated on the right. The tested drugs are listed on the right.

C-D. Heatmap showing the IC50 values and corresponding percentage of 31 target drugs for colorectal cancer in 29 PDOs. They were divided into five groups according to A/P/AP/ASP/AKSP mutation type at the top graph. The tested drugs and their targets are listed on the left. Dose–response graph is indicated on the right. The tested drugs are listed on the right.

E. Representative drugs (docetaxel, paclitaxel and vincristine) response curves for PDO002(A), PDO057(A), PDO118(AP), PDO163(AP) PDO162(ASP), PDO164(ASP), PDO022(AKSP), PDO038(AKSP). The results are expressed as the mean ± standard error of the mean (S.E.M.).

F. Heatmap showing the IC50 values and corresponding percentage of 49 drugs for colorectal cancer in 9 PDOs. They were different mutation type at the right graph. The tested drugs are listed on the bottom. Dose–response graph is indicated on the right.
G. Representative drugs (topotecan hcl,eriotinib hcl, TAS-102 and gefitinib) response curves for PDO002(A), PDO057(A), PDO118(AP), PDO163(AP) PDO162(ASP), PDO164(ASP), PDO022(AKSP), PDO038(AKSP). The results are expressed as the mean ± standard error of the mean (S.E.M.).

Supplemental Figure 5. PDOs retain the previous treatment responses of colorectal cancer patients. **A.** Treatment procedure and responses of patient T198 from surgery. Each round of treatment received by the patient is displayed here. The blue arrow tips indicate the images taking time points in (B). PD indicates disease. **B.** Tumor CT scan images show that the metastatic liver of patient T198 continued to increase during the clinical treatment. The red arrows indicate tumors. **C.** IC50 values of various drugs for PDO197. **D.** Treatment procedure and responses of patient.

Fig S1

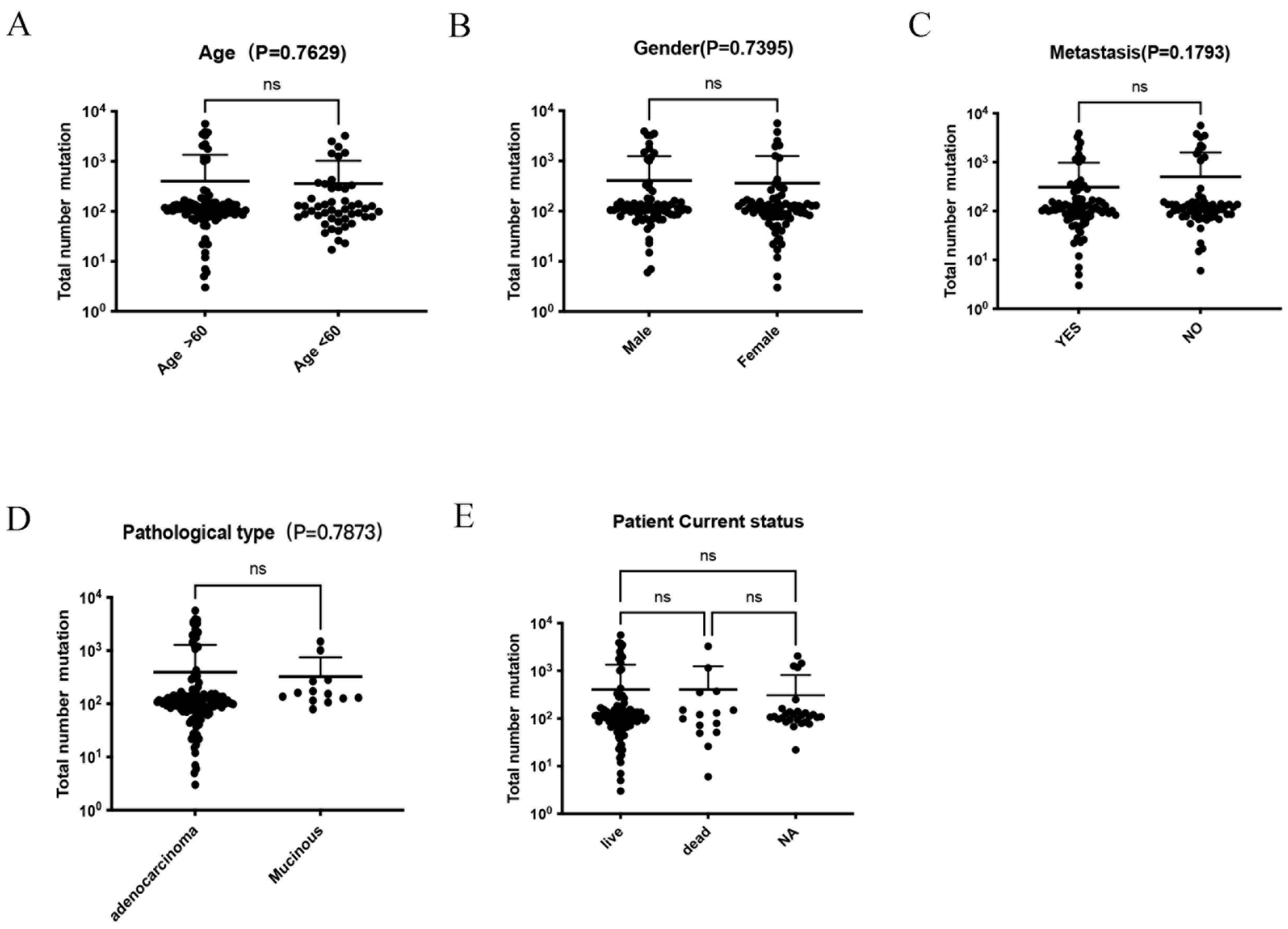
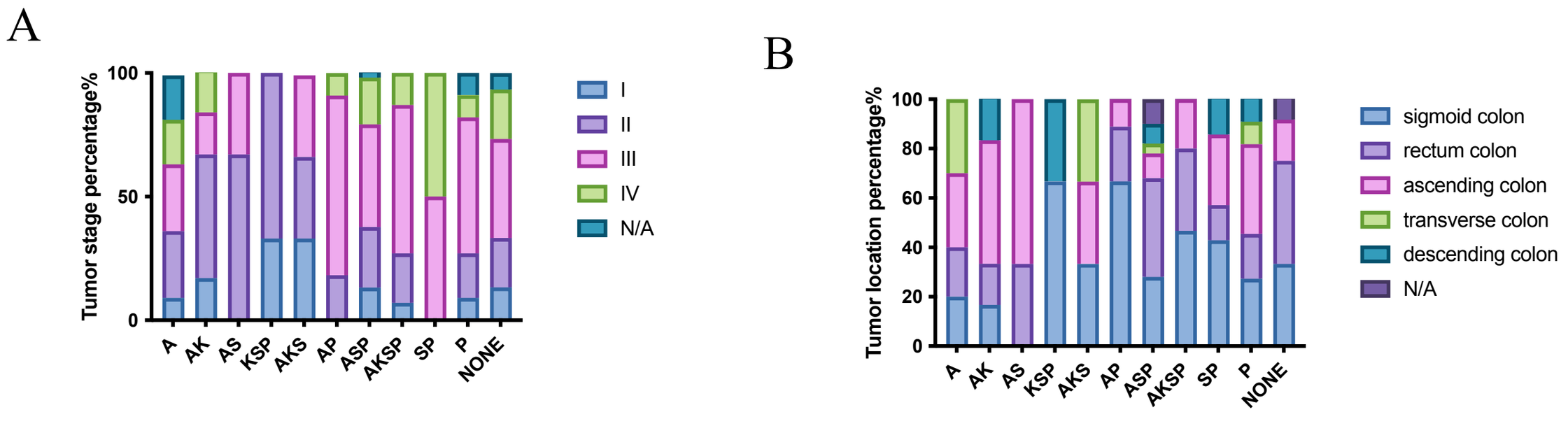
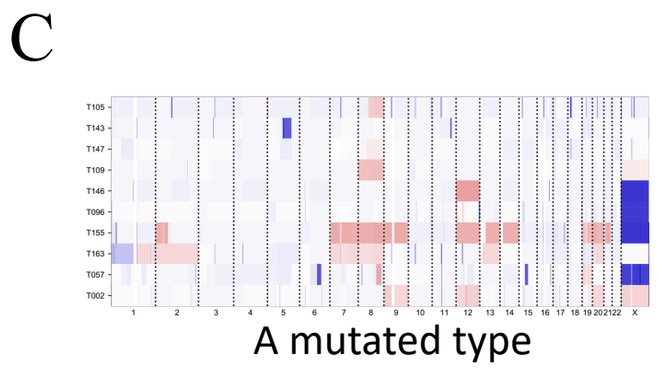
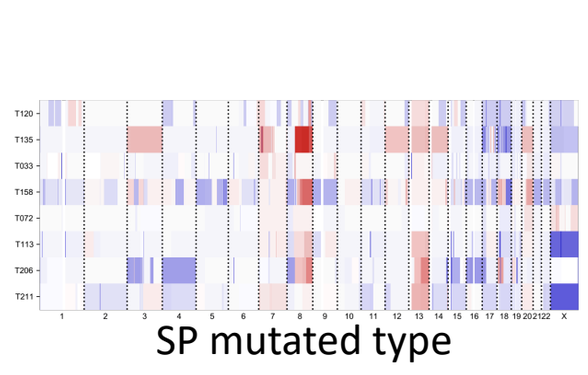
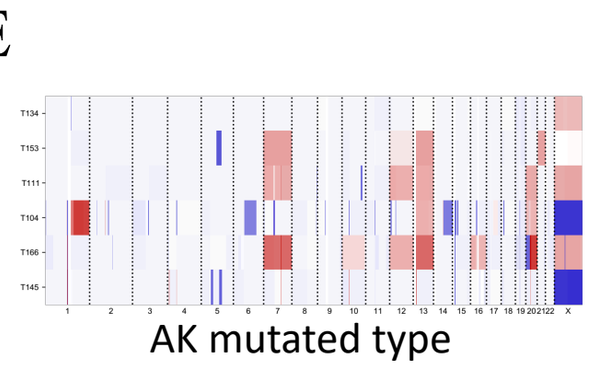

A
Age (P=0.7629)
ns
Total number mutation
Age >60
Age <60
B
Gender(P=0.7395)
ns
Male
Female
C
Metastasis(P=0.1793)
ns
YES
NO
D
Pathological type (P=0.7873)
ns
adenocarcinoma
Mucinous
E
Patient Current status
ns
ns
ns
live
dead
NA

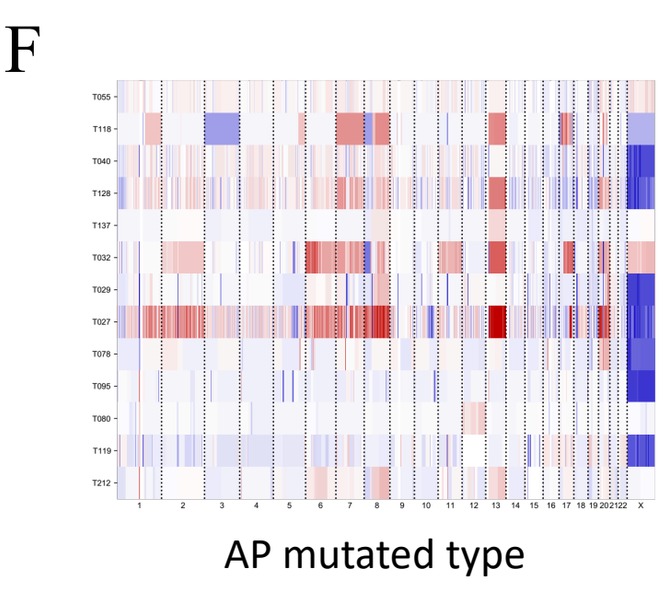
Fig S2

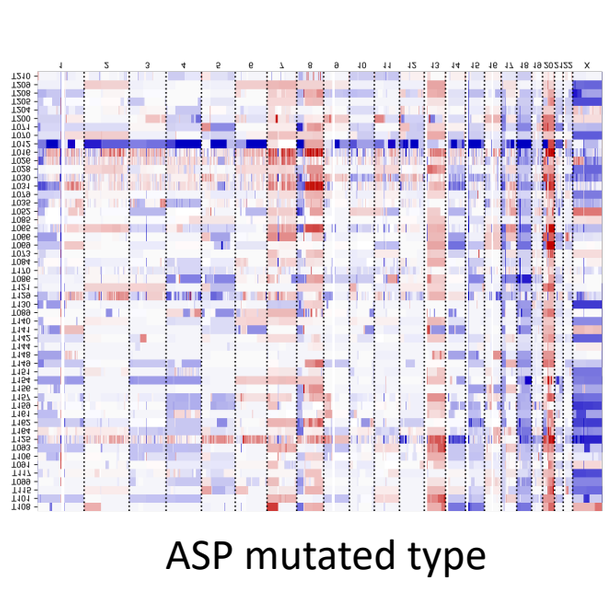


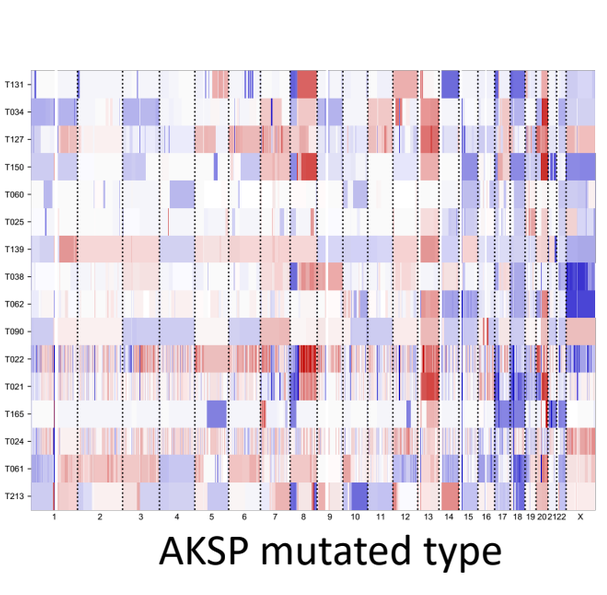

C
A mutated type

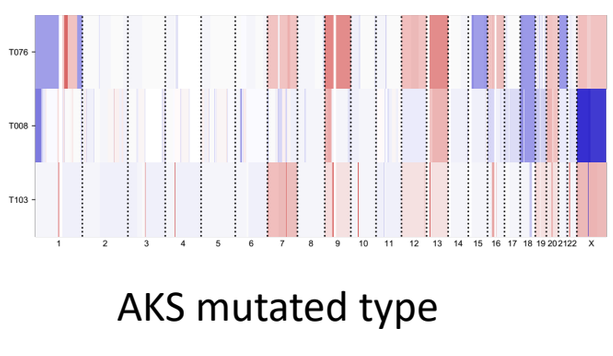

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SP mutated type

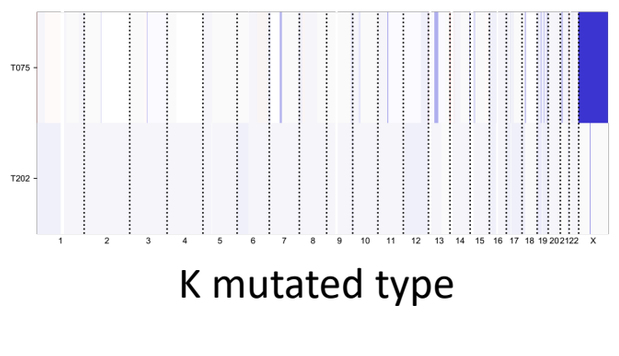

E
AK mutated type

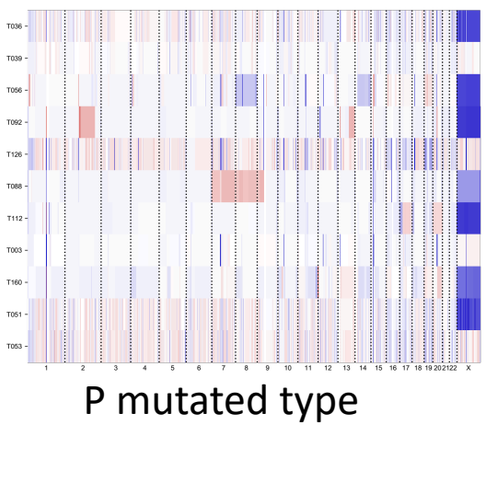

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AP mutated type

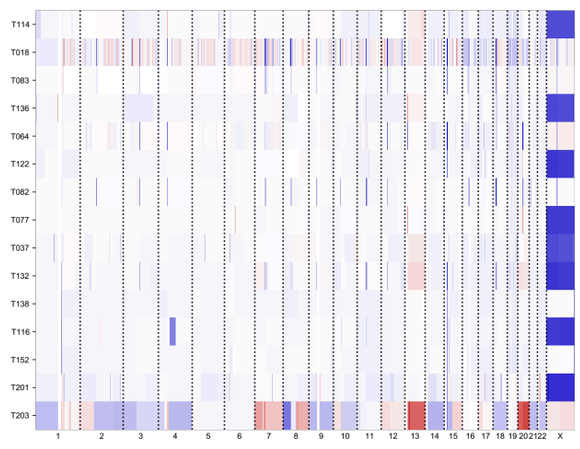

G
ASP mutated type

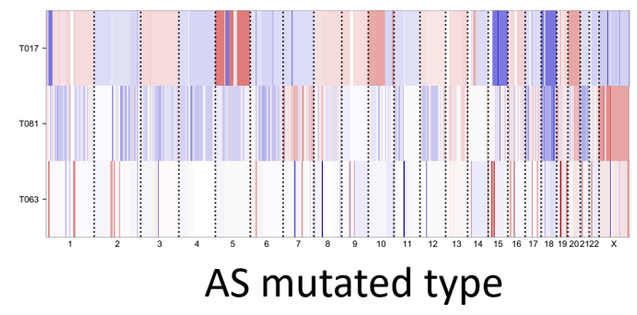

H
AKSP mutated type


I
AKS mutated type


J
K mutated type


K
P mutated type


L
NONE AKSP mutated type


M
AS mutated type

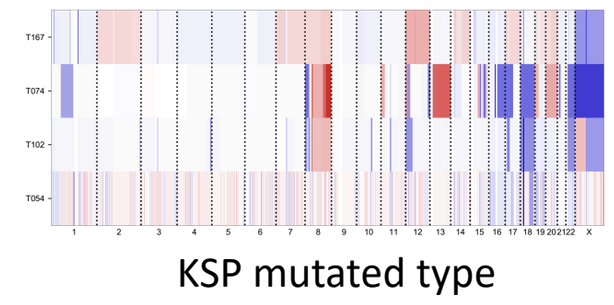

N
KSP mutated type

Fig S3

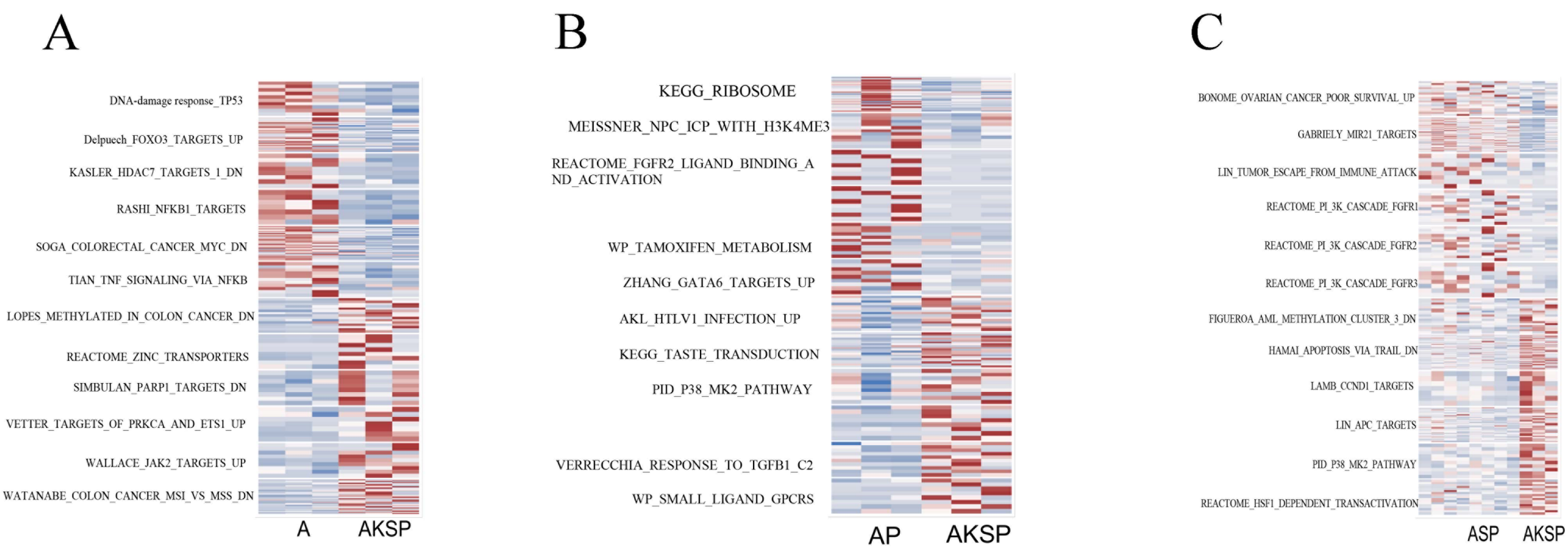
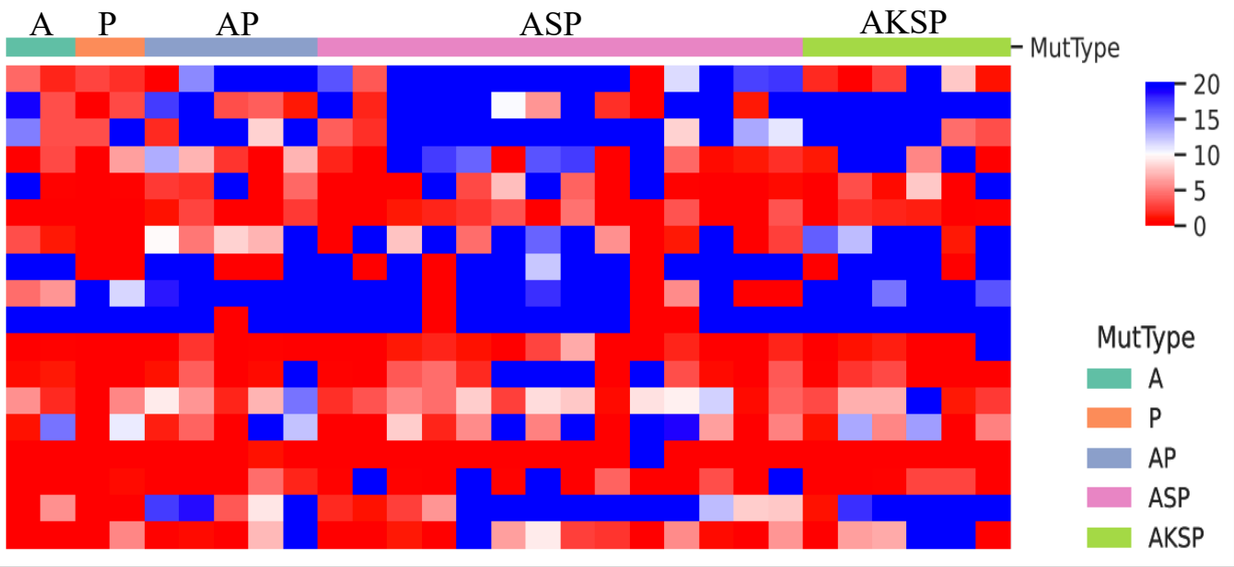

A
DNA-damage response_TP53
Delpuech_FOXO3_TARGETS_UP
KASLER_HDAC7_TARGETS_1_DN
RASHI_NFKB1_TARGETS
SOGA_COLORECTAL_CANCER_MYC_DN
TIAN_TNF_SIGNALING_VIA_NFKB
LOPES_METHYLATED_IN_COLON_CANCER_DN
REACTOME_ZINC_TRANSPORTERS
SIMBULAN_PARP1_TARGETS_DN
VETTER_TARGETS_OF_PRKCA_AND_ETS1_UP
WALLACE_JAK2_TARGETS_UP
WATANABE_COLON_CANCER_MSI_VS_MSS_DN
A
AKSP
B
KEGG_RIBOSOME
MEISSNER_NPC_ICP_WITH_H3K4ME3
REACTOME_FGFR2_LIGAND_BINDING_AND_ACTIVATION
WP_TAMOXIFEN_METABOLISM
ZHANG_GATA6_TARGETS_UP
AKL_HTLV1_INFECTION_UP
KEGG_TASTE_TRANSDUCTION
PID_P38_MK2_PATHWAY
VERRECCHIA_RESPONSE_TO_TGFB1_C2
WP_SMALL_LIGAND_GPCRS
AP
AKSP
C
BONOME_OVARIAN_CANCER_POOR_SURVIVAL_UP
GABRIELY_MIR21_TARGETS
LIN_TUMOR_ESCAPE_FROM_IMMUNE_ATTACK
REACTOME_PI_3K_CASCADE_FGFR1
REACTOME_PI_3K_CASCADE_FGFR2
REACTOME_PI_3K_CASCADE_FGFR3
FIGUEROA_AML_METHYLATION_CLUSTER_3_DN
HAMAI_APOPTOSIS_VIA_TRAIL_DN
LAMB_CCND1_TARGETS
LIN_APC_TARGETS
PID_P38_MK2_PATHWAY
REACTOME_HSF1_DEPENDENT_TRANSACTIVATION
ASP
AKSP

Fig S4

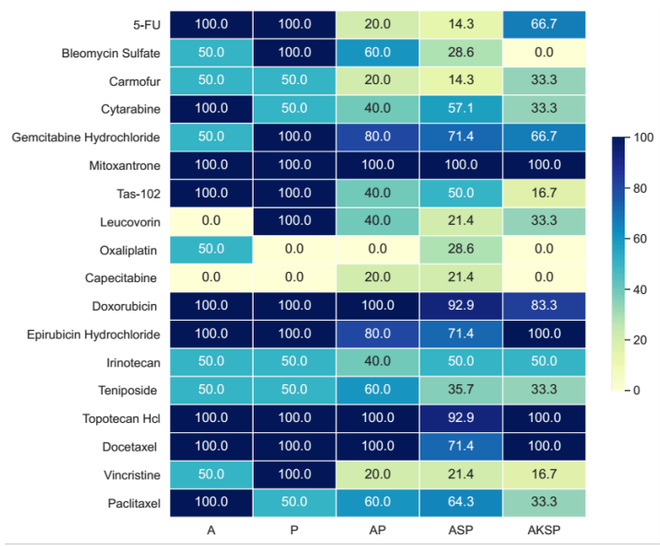
A

Chemotherapy drugs

Drug	Target
5-FU	DNA/RNA Synthesis
Bleomycin Sulfate	DNA/RNA Synthesis
Carmofur	DNA/RNA Synthesis
Cytarabine	DNA/RNA Synthesis
Gemcitabine Hydrochloride	DNA/RNA Synthesis
Mitoxantrone	DNA/RNA Synthesis
Tas-102	DNA Synthesis
Leucovorin calcium pentahydrate	DNA/RNA Synthesis
Oxaliplatin	DNA/RNA Synthesis
Capecitabine	DNA/RNA Synthesis
Doxorubicin	Topoisomerase
Epirubicin Hydrochloride	Topoisomerase
Irinotecan	Topoisomerase
Teniposide	Topoisomerase
Topotecan Hcl	Topoisomerase
Docetaxel	Microtubule
Vincristine	Microtubule
Paclitaxel	Microtubule



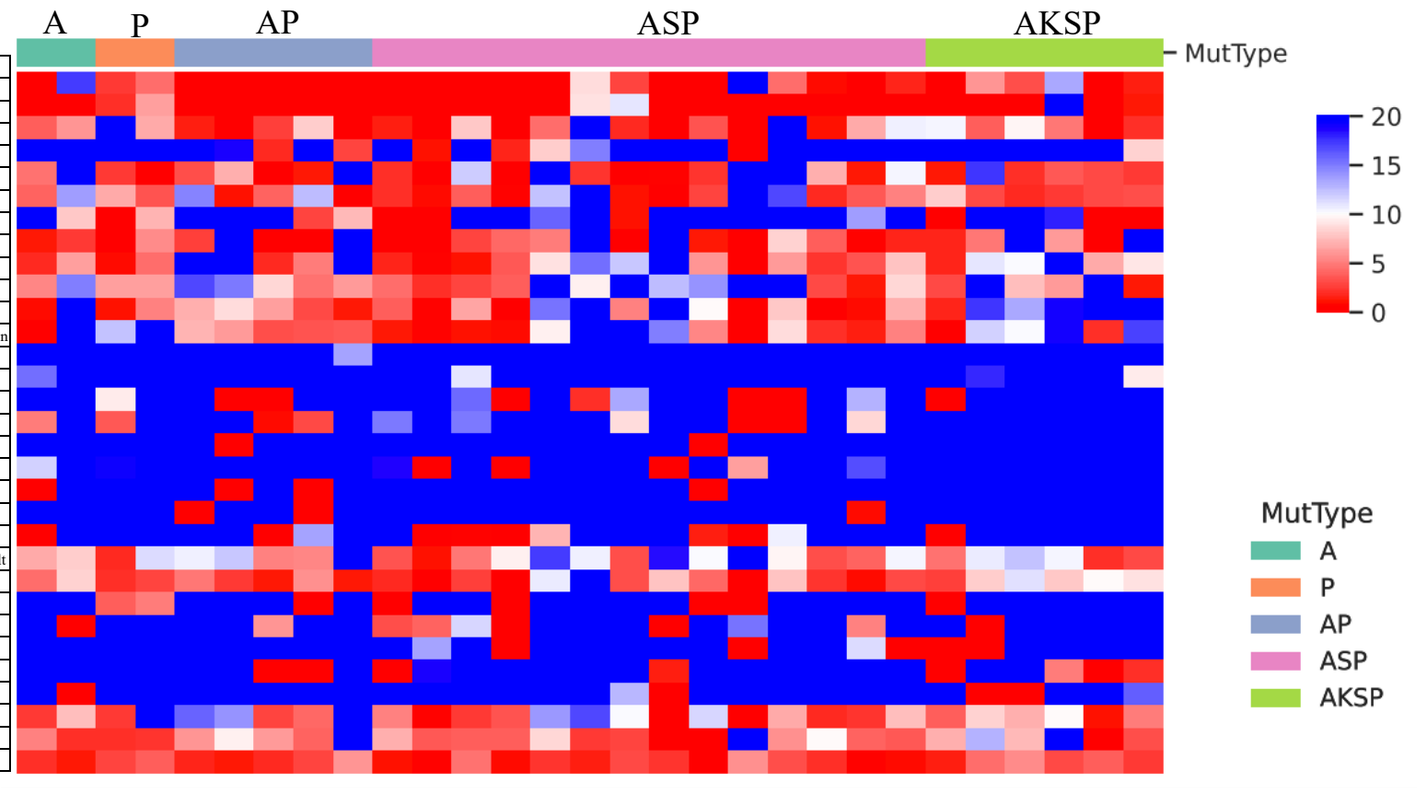
B



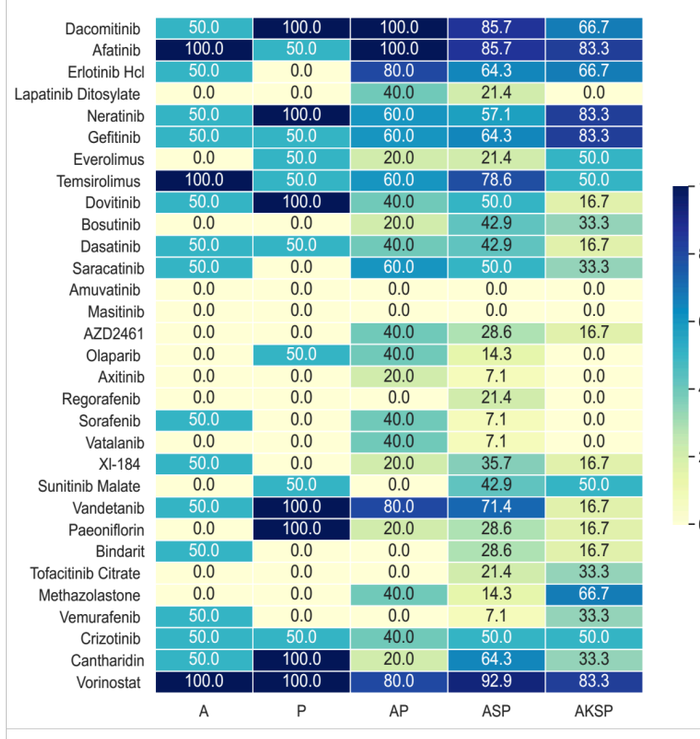
C

Target drugs

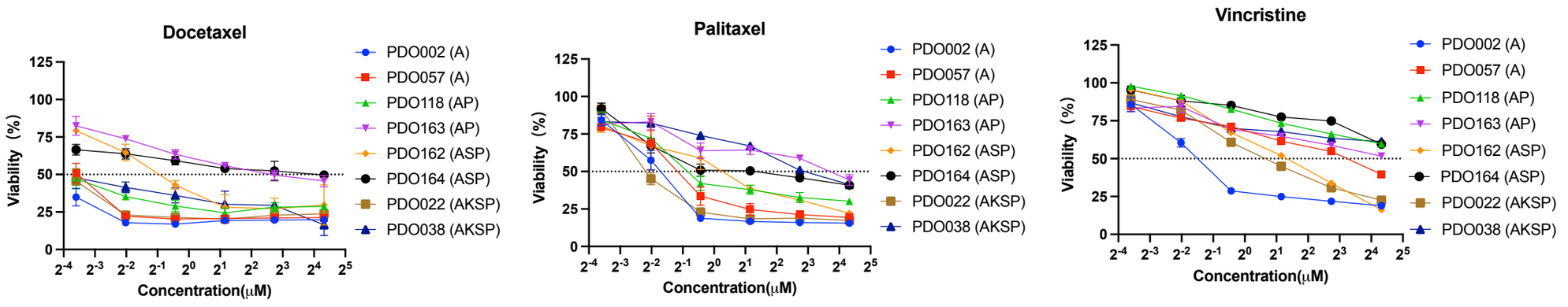
Drug	Target
Dacomitinib	EGFR
Afatinib	EGFR, HER2
Erlotinib Hcl	EGFR
Lapatinib Ditosylate	EGFR, HER2
Neratinib	EGFR
Gefitinib	EGFR
Everolimus	mTOR, fkbp12
Temsirolimus	mTOR
Dovitinib	FGFR
Bosutinib	Src,Abl
Dasatinib	Src, Abl, c-Kit
Saracatinib	Src,lck, c-yes, egfr, lyn
Amuvatinib	c-Kit, PDGFR, FLT3
Masitinib	c-Kit, PDGFR, FGFR
AZD2461	PARP
Olaparib	PARP
Axitinib	VEGFR, PDGFR, c-Kit
Regorafenib	VEGFR
Sorafenib	VEGFR, Raf
Vatalanib	VEGFR, PDGFR, c-Kit
Xl-184	c-Met, vegfr
Sunitinib Malate	VEGFR, PDGFR, c-Kit, Flt
Vandetanib	VEGFR
Paeoniflorin	NF-kB
Bindarit	NF-kB
Tofacitinib Citrate	JAK
Methazolastone	AKT
Vemurafenib	B-Raf
Crizotinib	c-Met
Cantharidin	PP2A
Vorinostat	HDAC



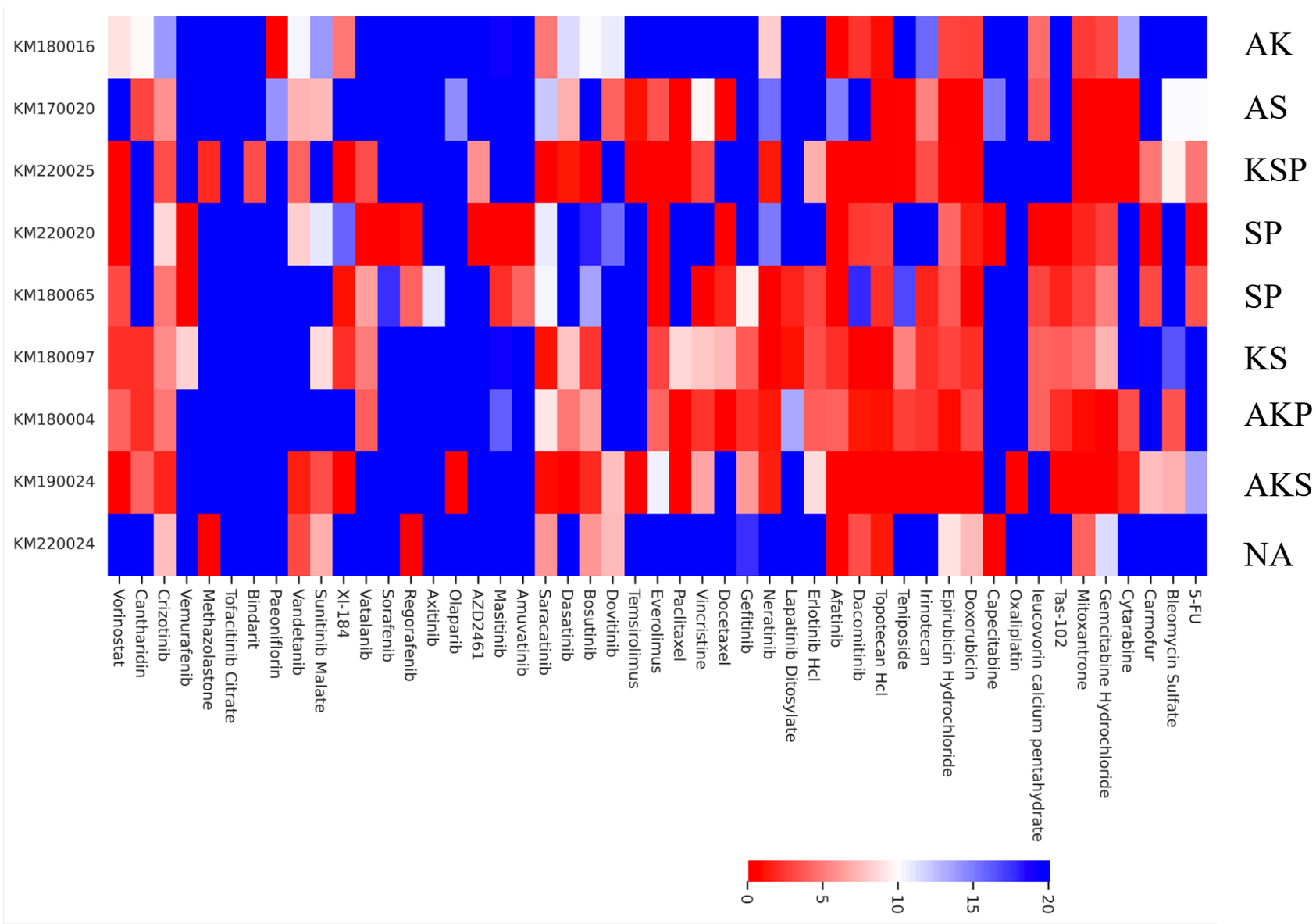
D



E



F



G

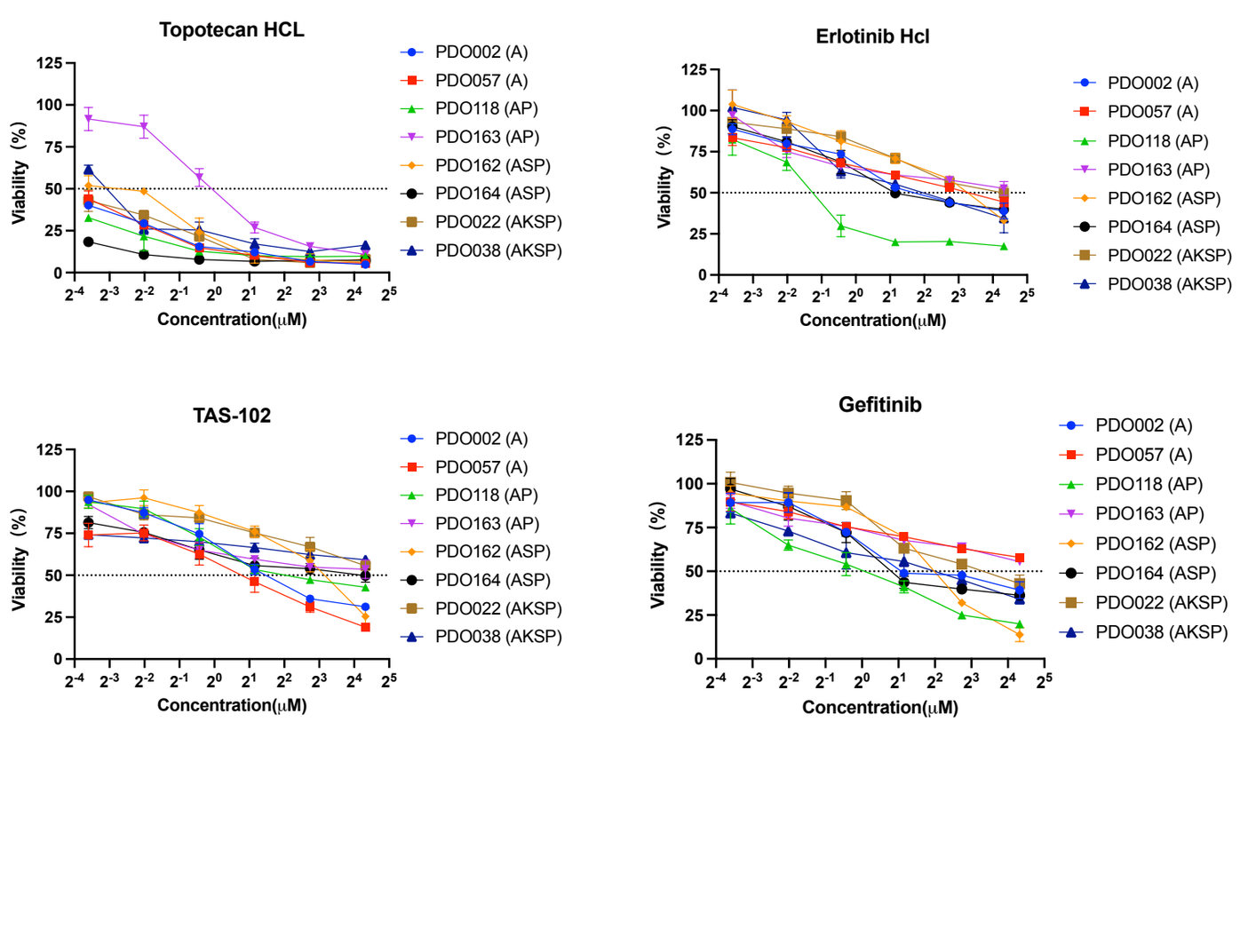
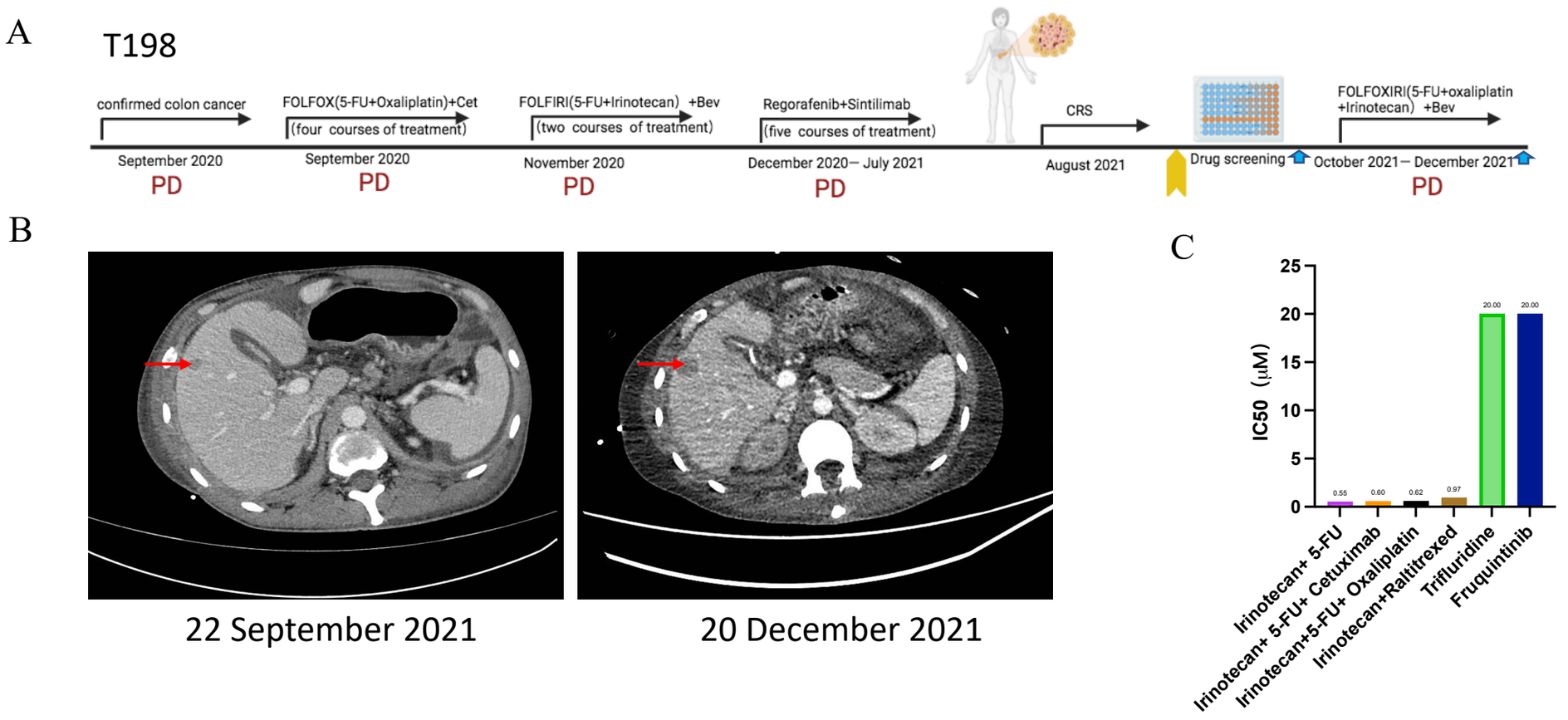


Fig S5


A
T198
confirmed colon cancer
September 2020
PD
FOLFOX(5-FU+Oxaliplatin)+Cet
(four courses of treatment)
September 2020
PD
FOLFIRI(5-FU+Irinotecan) +Bev
(two courses of treatment)
November 2020
PD
Regorafenib+Sintilimab
(five courses of treatment)
December 2020– July 2021
PD
CRS
August 2021
Drug screening
FOLFOXIRI(5-FU+oxaliplatin
+Irinotecan) +Bev
October 2021– December 2021
PD
B
22 September 2021
20 December 2021
C
IC50 (μM)
25
20
15
10
5
0
0.55
0.60
0.62
0.97
20.00
20.00
Irinotecan+ 5-FU
Irinotecan+ 5-FU+ Cetuximab
Irinotecan+5-FU+ Oxaliplatin
Irinotecan+Raltitrexed
Trifluridine
Fruquintinib