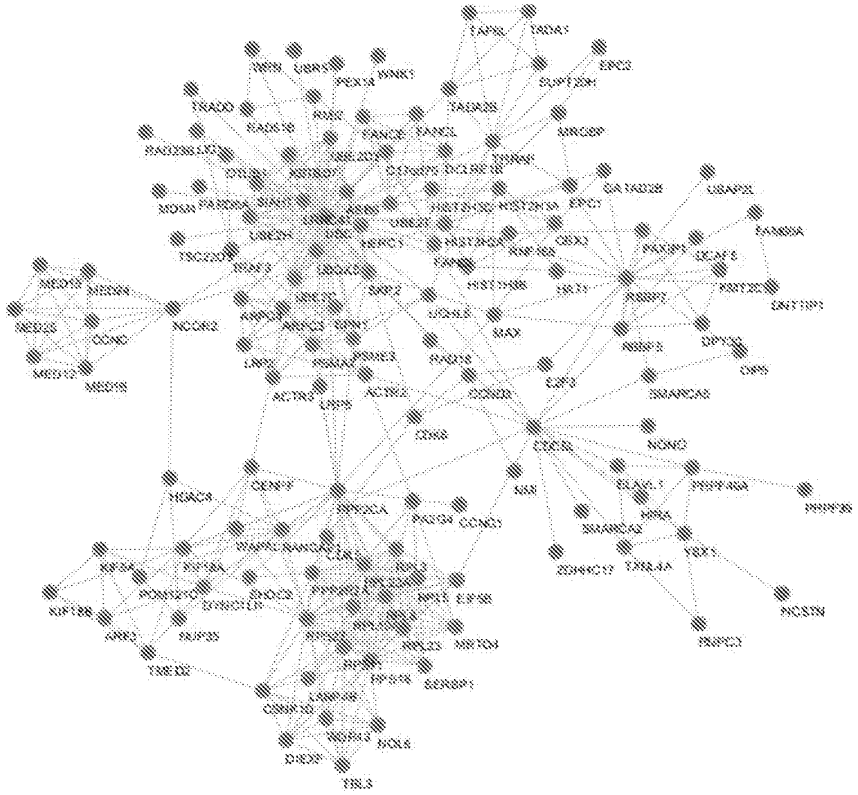
A.



B.

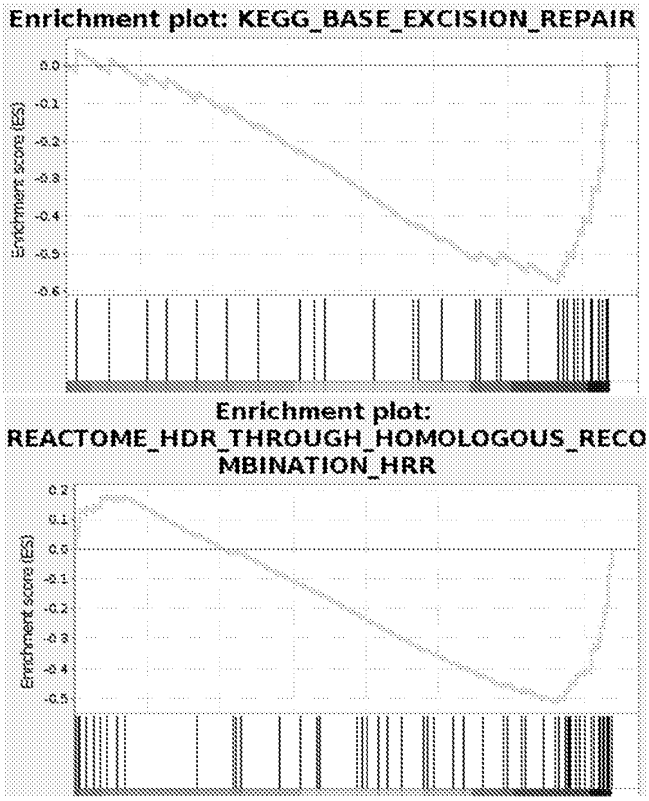

Enrichment plot: KEGG_BASE_EXCISION_REPAIR
Enrichment score (ES)
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
Enrichment plot:
REACTOME_HDR_THROUGH_HOMOLOGOUS_RECOMBINATION_HRR
Enrichment score (ES)
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5

Figure 1

C.

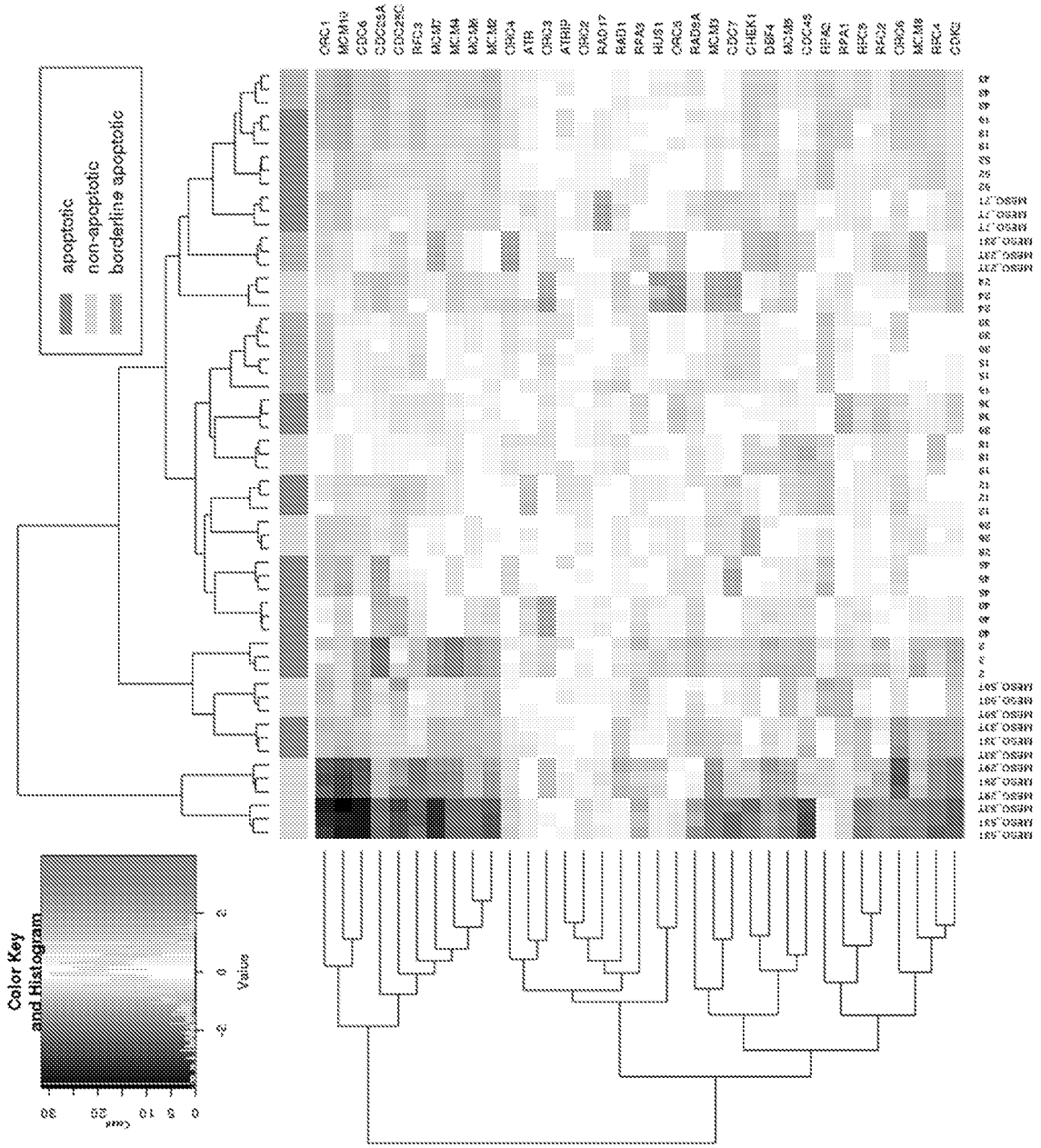
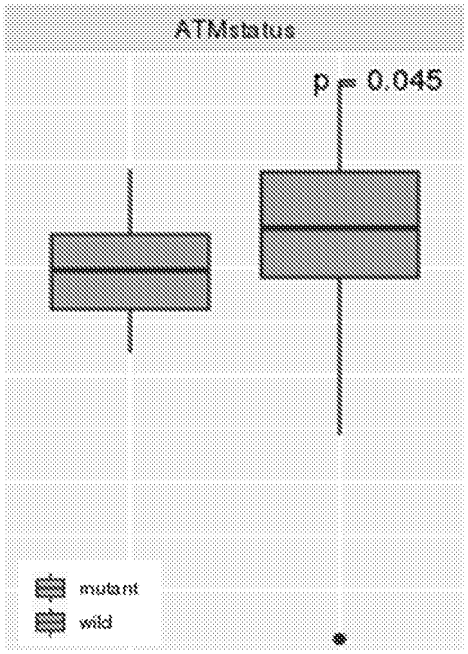

apoptotic
non-apoptotic
borderline apoptotic
ORC1
MCM10
CDC6
CDC25A
CDC28C
RFC3
RCM7
MCM4
MCM6
MCM2
ORC4
ATR
ORC3
ATRIP
ORC2
RAD17
RAD1
RPA2
HUS1
ORC5
RAD9A
MCM3
CDC7
CHEK1
DBF4
MCM5
CDC45
RPA3
RPA1
RFC5
RFC2
ORC6
MCM8
RFC4
CDKE
Color Key and Histogram
Value
Count

Figure 1

A.



B.

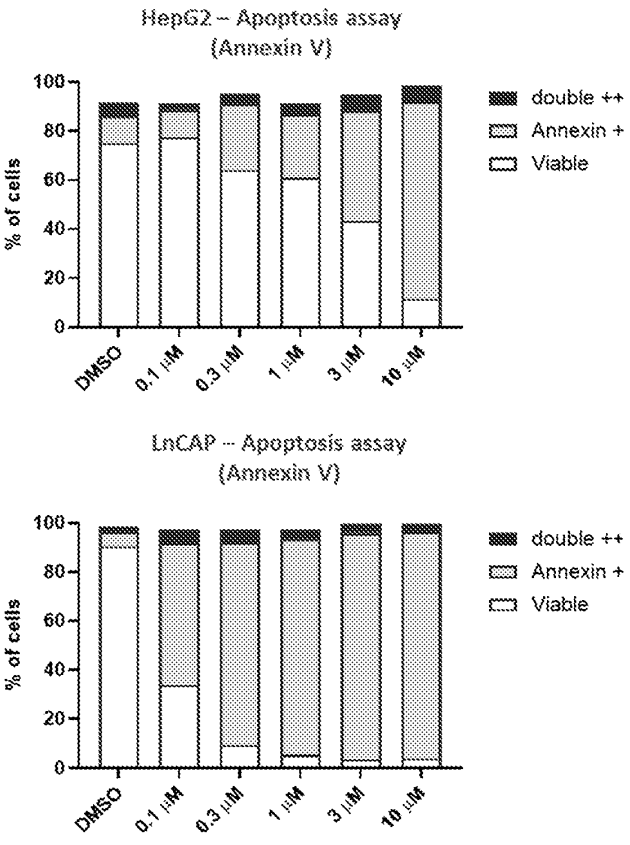
Samples	Type	ATM mutation
12	apoptotic	mutant
19	apoptotic	mutant
2	apoptotic	mutant
36	apoptotic	mutant
40	apoptotic	mutant
45	apoptotic	wild
52	apoptotic	mutant
MESO7T	apoptotic	wild
MESO33T	apoptotic	Wild
18	non-apoptotic	wild
24	non-apoptotic	wild
26	non-apoptotic	wild
MESO29T	non-apoptotic	wild
MESO50T	non-apoptotic	wild
MESO53T	non-apoptotic	wild
15	Borderline apoptotic	wild
30	Borderline apoptotic	wild
43	Borderline apoptotic	mutant
MESO23T	Borderline apoptotic	mutant

Figure 2

C. Cell proliferation

Cell line	Indication	Compound-1 IC50 (µM)
HCC1500	Breast	0.1673
LnCAP	Prostate	0.019
HT-144	Melanoma	0.2636
HepG2	Liver	0.054

D. Apoptosis



E. Modulation of DDR signaling

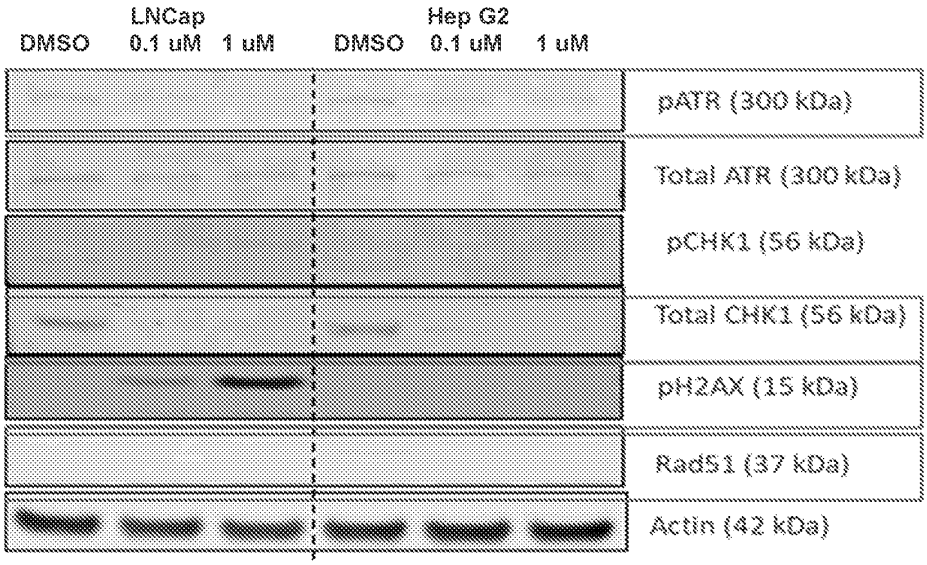


Figure 2

F.

Organoid ID	Tissue origin	*TP53* status	*BRCA1* Alteration	*BRCA2* Alteration	*ATM* Alteration	Compound #1 IC_{50} (µM)
BR9457B	Breast	WT		Yes		0.05
GA6894B	Gastric	WT			Yes	0.075
PA20069B	Pancreas	WT		Yes	Yes	0.07
PA20081B	Pancreas	WT			Yes	0.063
BR5337B	Breast	WT				27
GA0119B	Gastric	WT				12
GA0098B	Gastric	WT				12
PA20079B	Pancreas	WT				20

5

G.

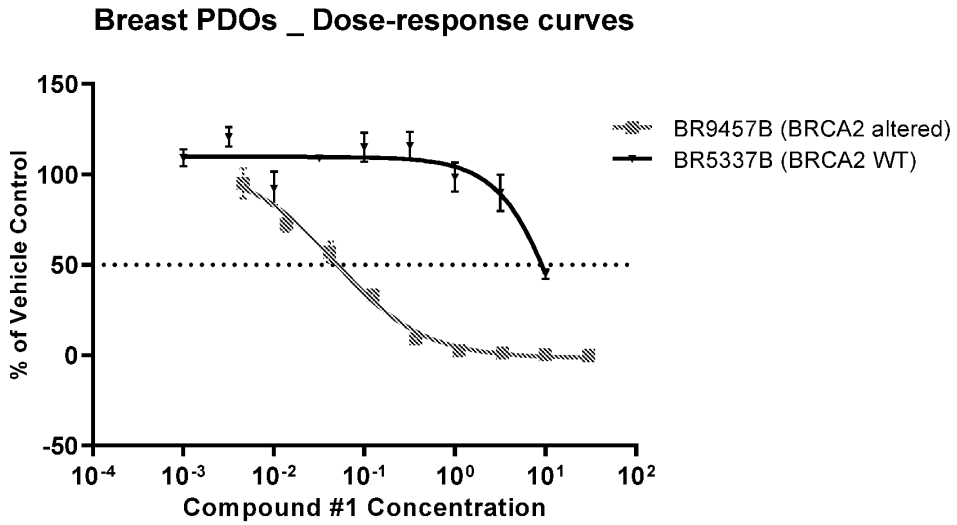
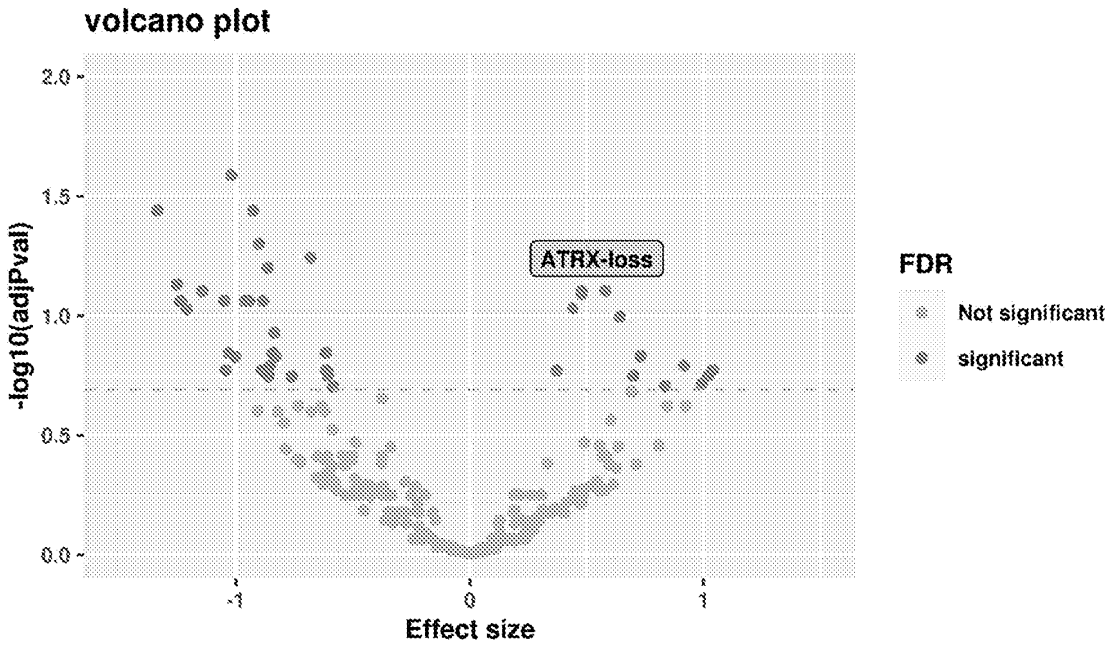


Figure 2

A.


volcano plot
-log10(adjPval)
2.0
1.5
1.0
0.5
0.0
ATRX-loss
-1
0
1
Effect size
FDR
Not significant
significant

B.

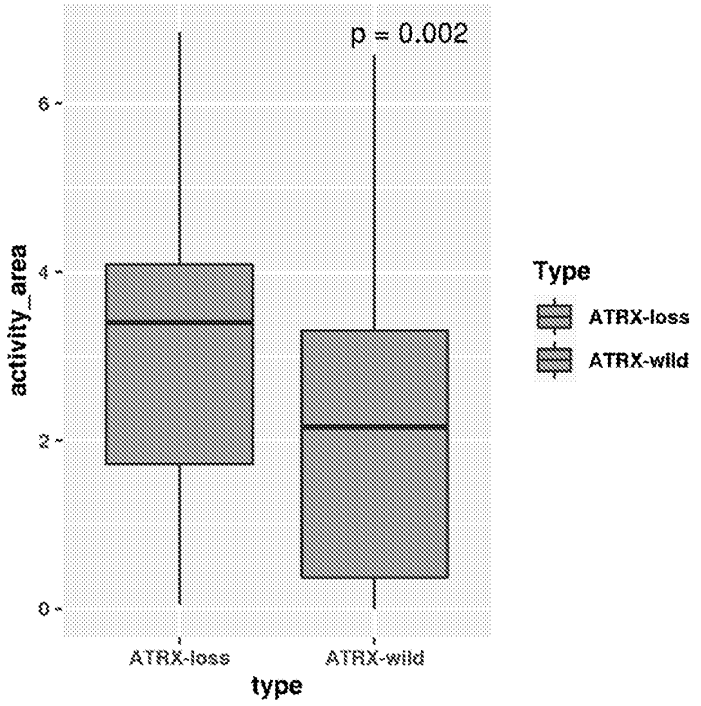

p = 0.002
activity_area
6
4
2
0
ATRX-loss
ATRX-wild
type
Type
ATRX-loss
ATRX-wild

Figure 3

A.

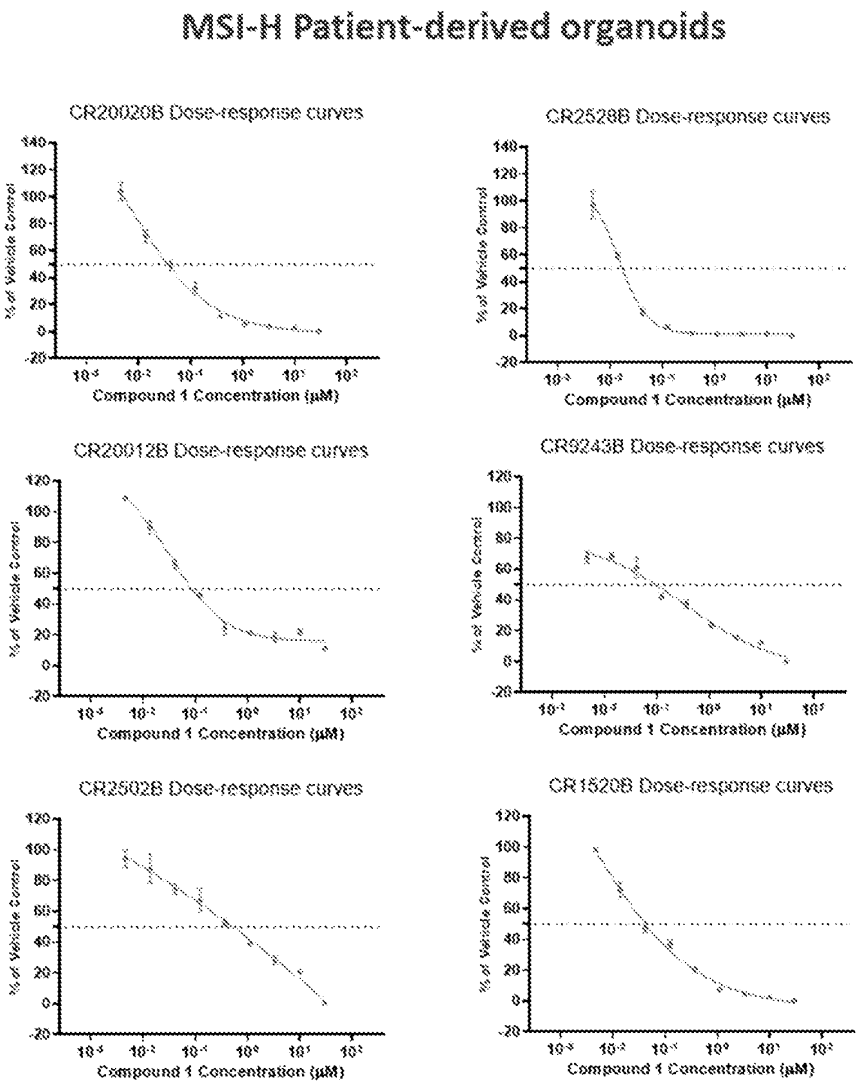
Cell Line	Activity area	Microsatellite status	Tumor mutation burden (Mutations/Mb)	POLD1
HCT116	3.55	MSI-H	70.63	mutant
LOVO	3.41	MSI-H	56.07	mutant
LS180	3.39	MSI-H	66.53	mutant
RKO	3.00	MSI-H	81.4	wild
SW48	2.99	MSI-H	66.07	mutant
CW2	2.81	MSI-H	237.83	mutant
GP2D	2.68	MSI-H	-	mutant
SNU-1	3.51	MSI-H	51.53	mutant
SNGM	6.58	MSI-H	58.77	wild

B.

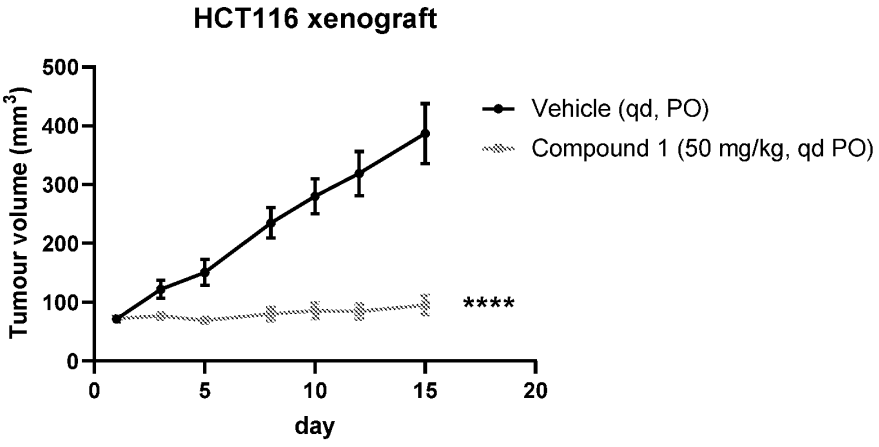
MSI-H Cell lines	Indication	Compound #1 IC50
CW2	CRC	0.5824 µM
SW48	CRC	0.5682 µM
RKO	CRC	0.5970 µM
LS180	CRC	0.1550 µM
LOVO	CRC	0.4329 µM
HCT116	CRC	0.1022 µM
SNU-1	Gastric	0.0858 µM
SNGM	Endometrial	0.1106 µM

Figure 4

C.



D.



**** p-value < 0.0001 vs vehicle by 2way ANOVA

Figure 4

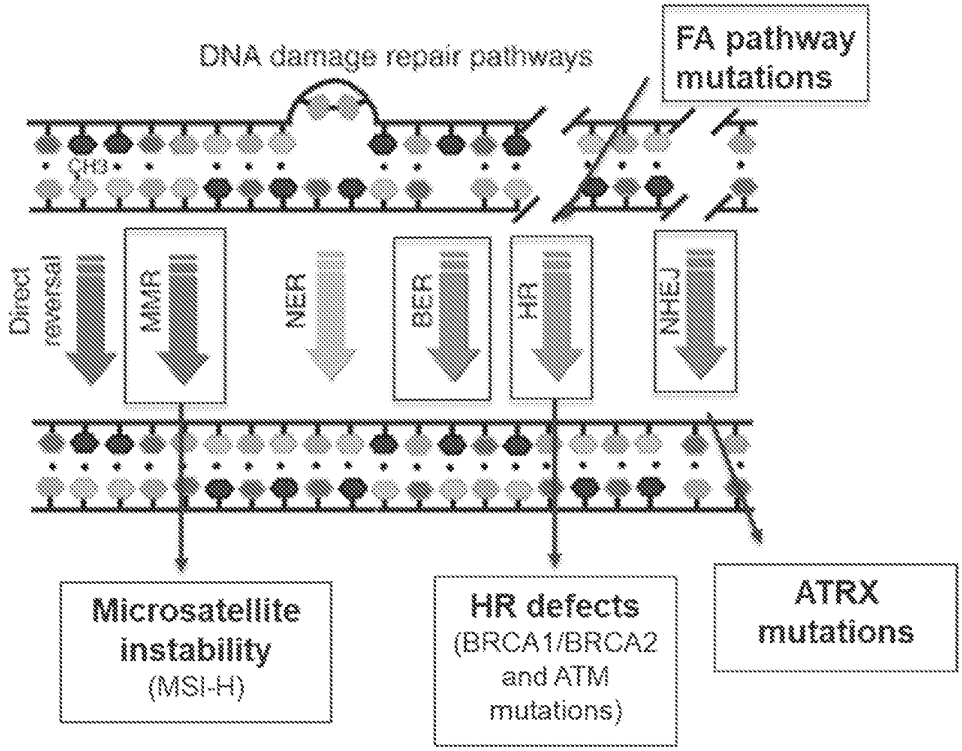

DNA damage repair pathways
FA pathway mutations
CH3
Direct reversal
MMR
NER
BER
HR
NHEJ
Microsatellite instability (MSI-H)
HR defects (BRCA1/BRCA2 and ATM mutations)
ATRX mutations

Figure 5

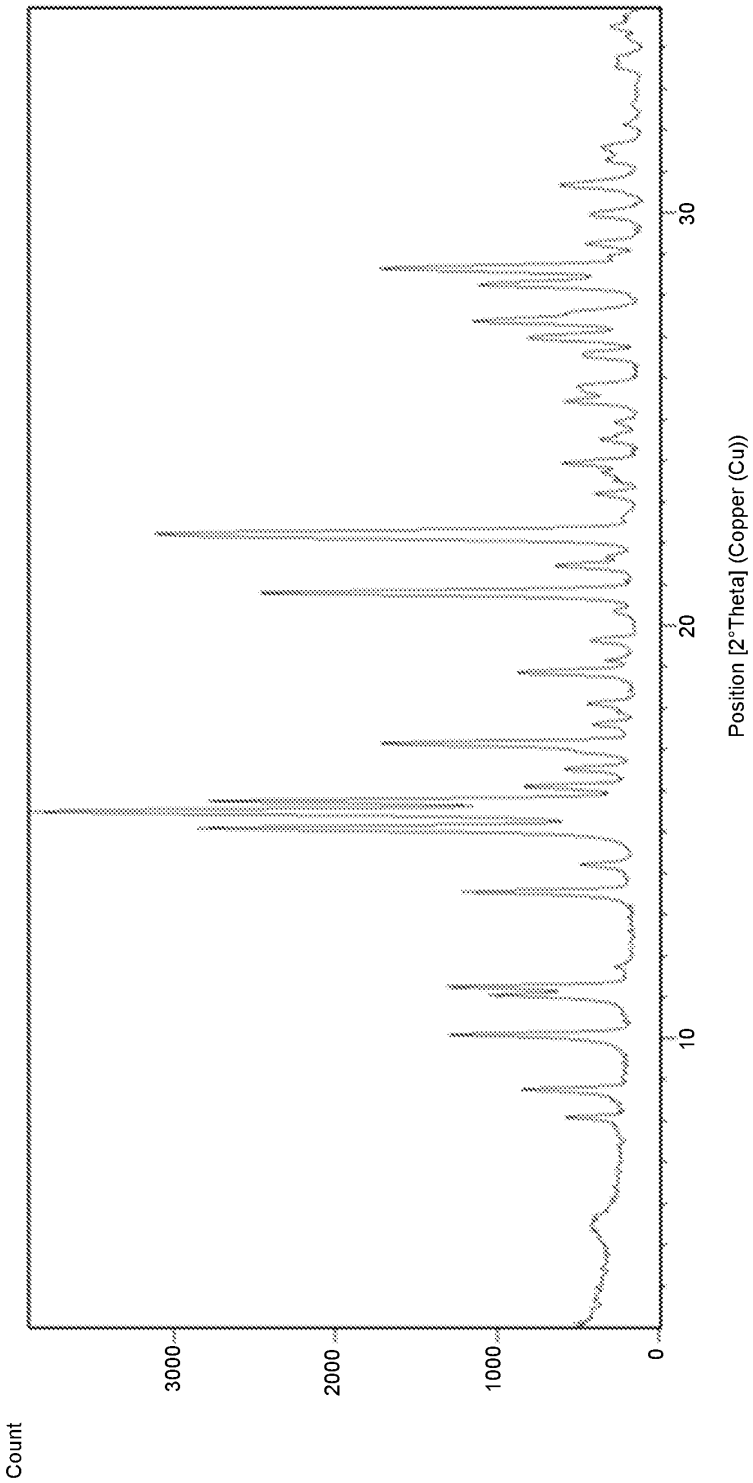


Figure 6

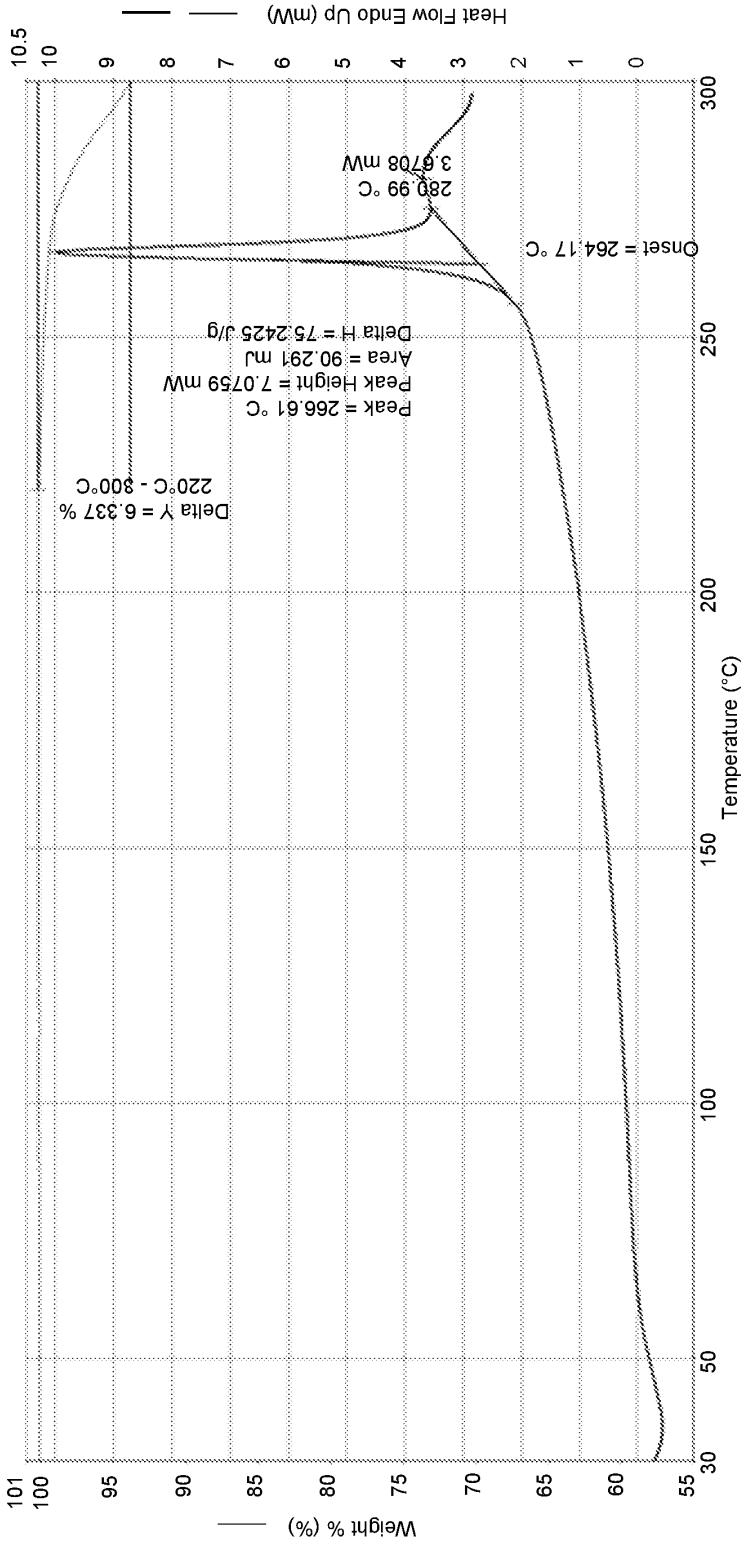

Heat Flow Endo Up (mW)
Weight % (%)
Temperature (°C)
Onset = 264.17 °C
280.99 °C
3.6708 mW
Peak = 266.61 °C
Peak Height = 7.0759 mW
Area = 90.291 mJ
Delta H = 75.2425 J/g
Delta Y = 6.337 %
220°C - 800°C

Figure 7