

FIGURE 1

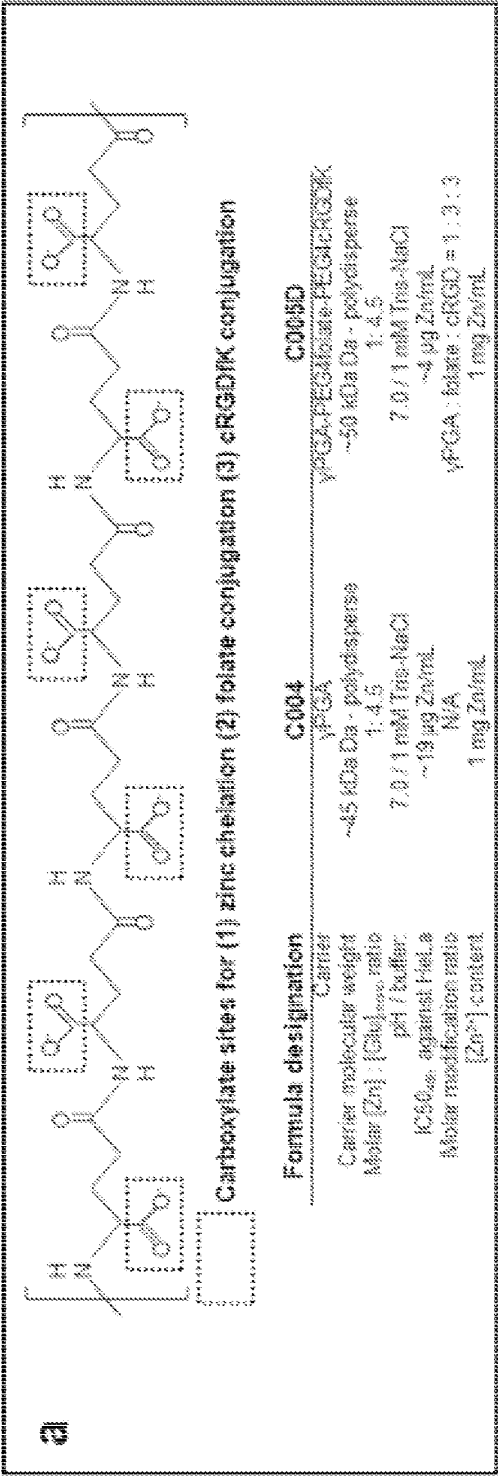


FIGURE 2

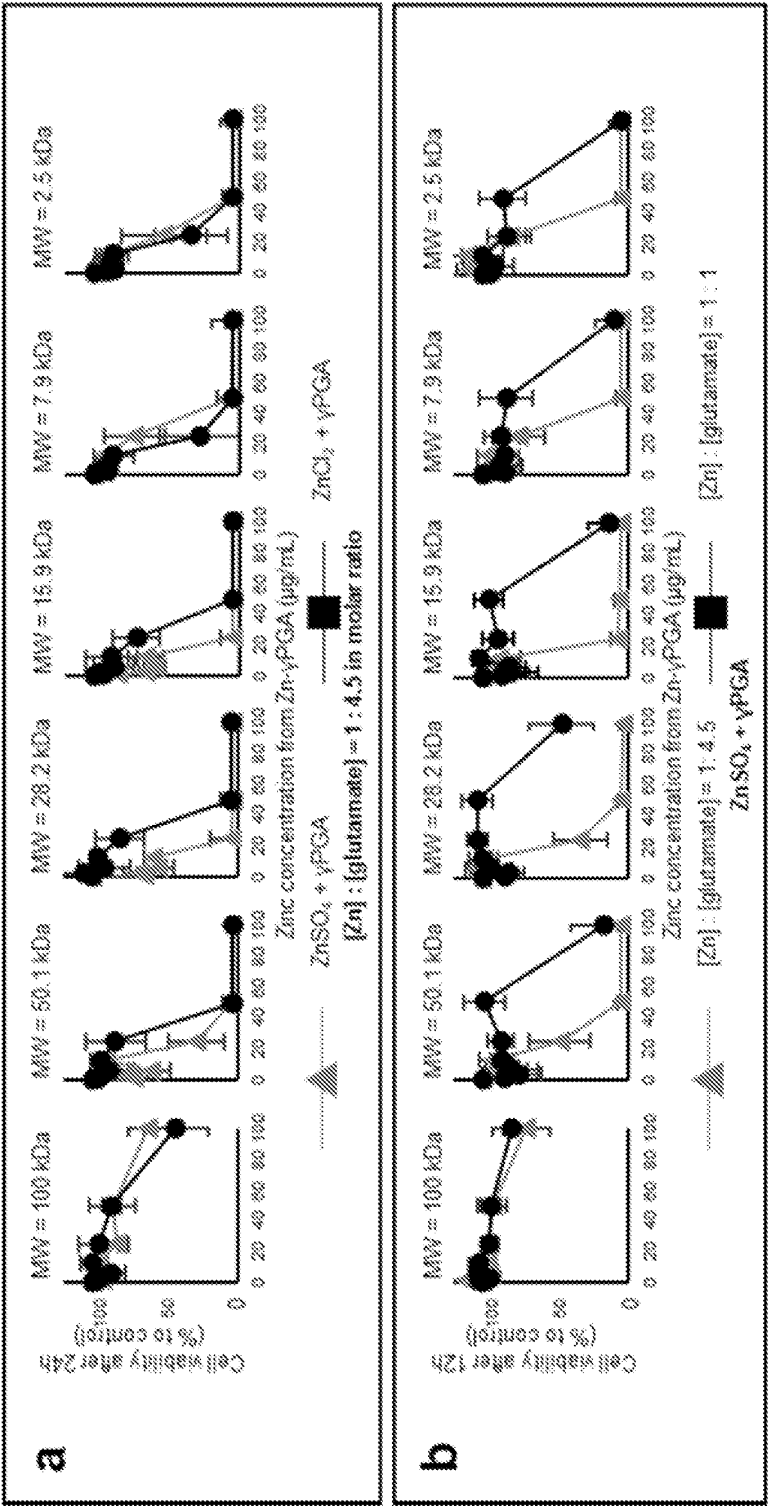


FIGURE 3A

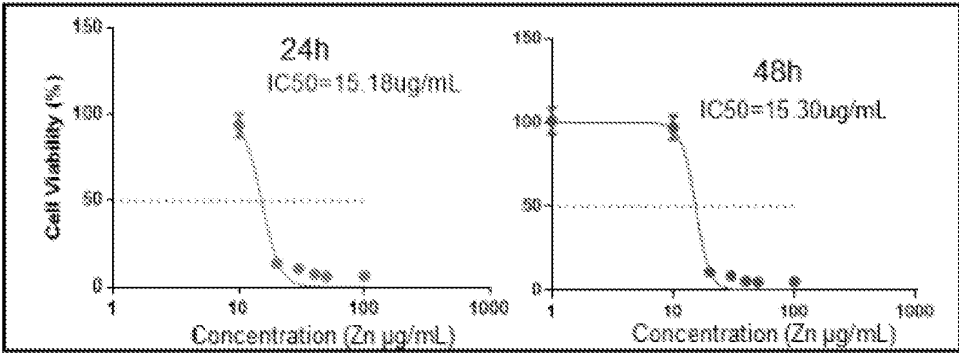
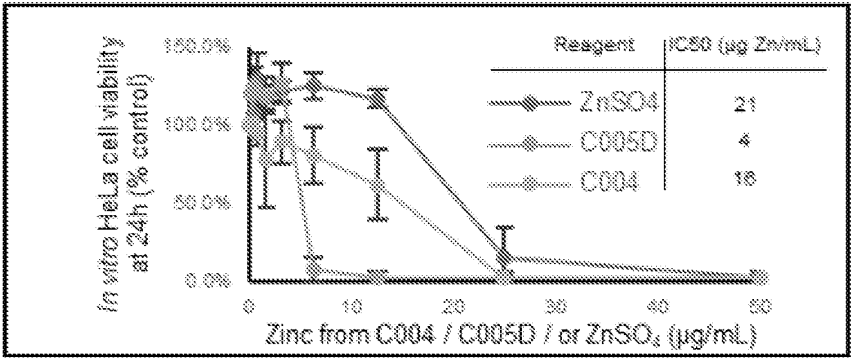


FIGURE 3B



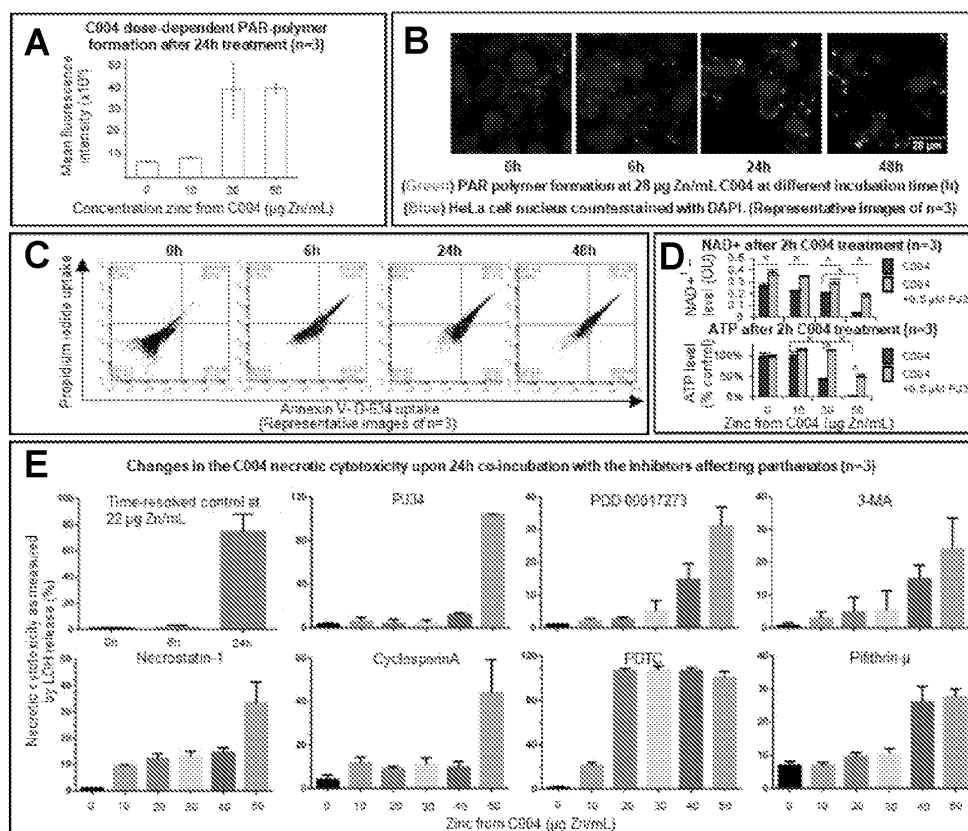


FIGURE 5A

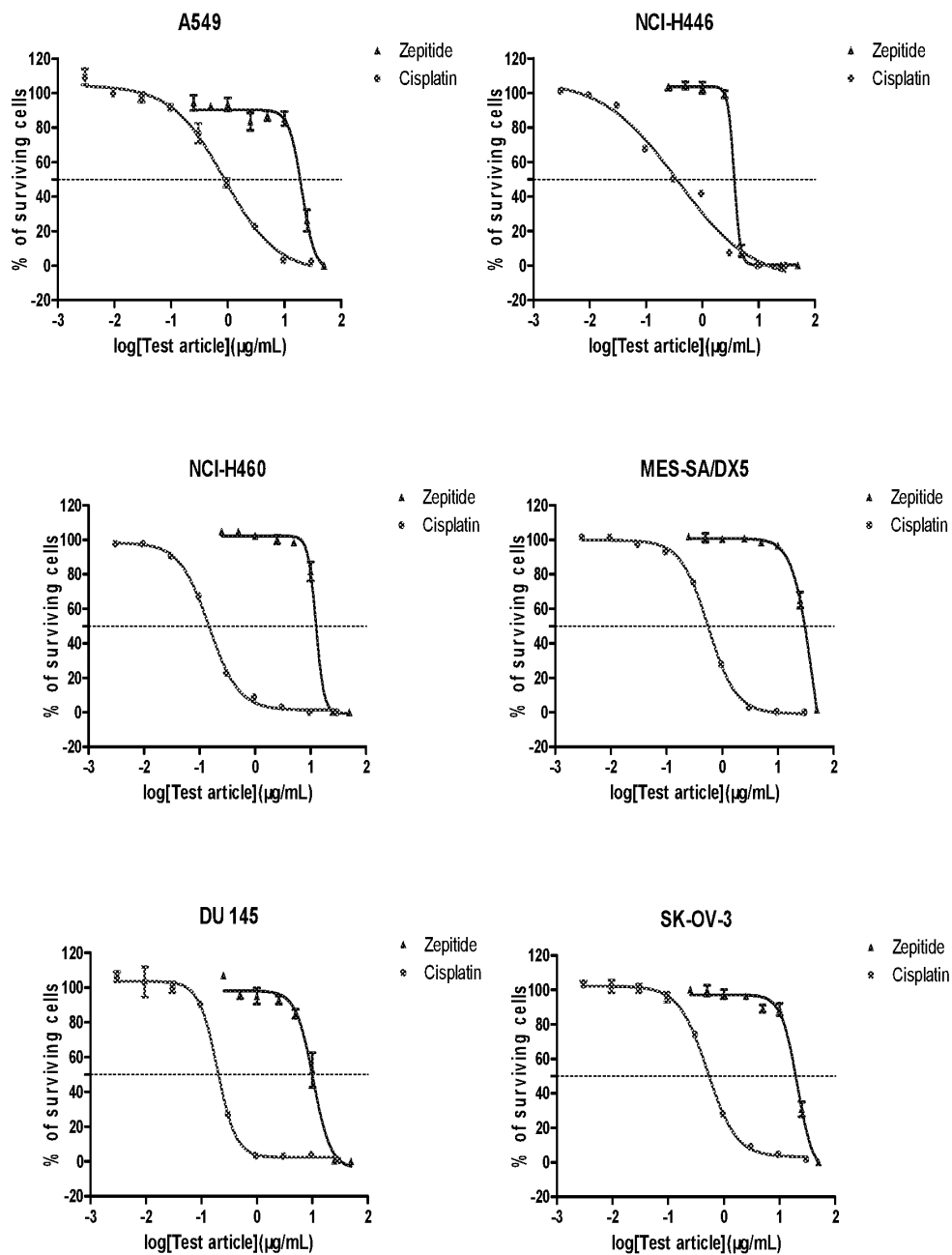


FIGURE 5B

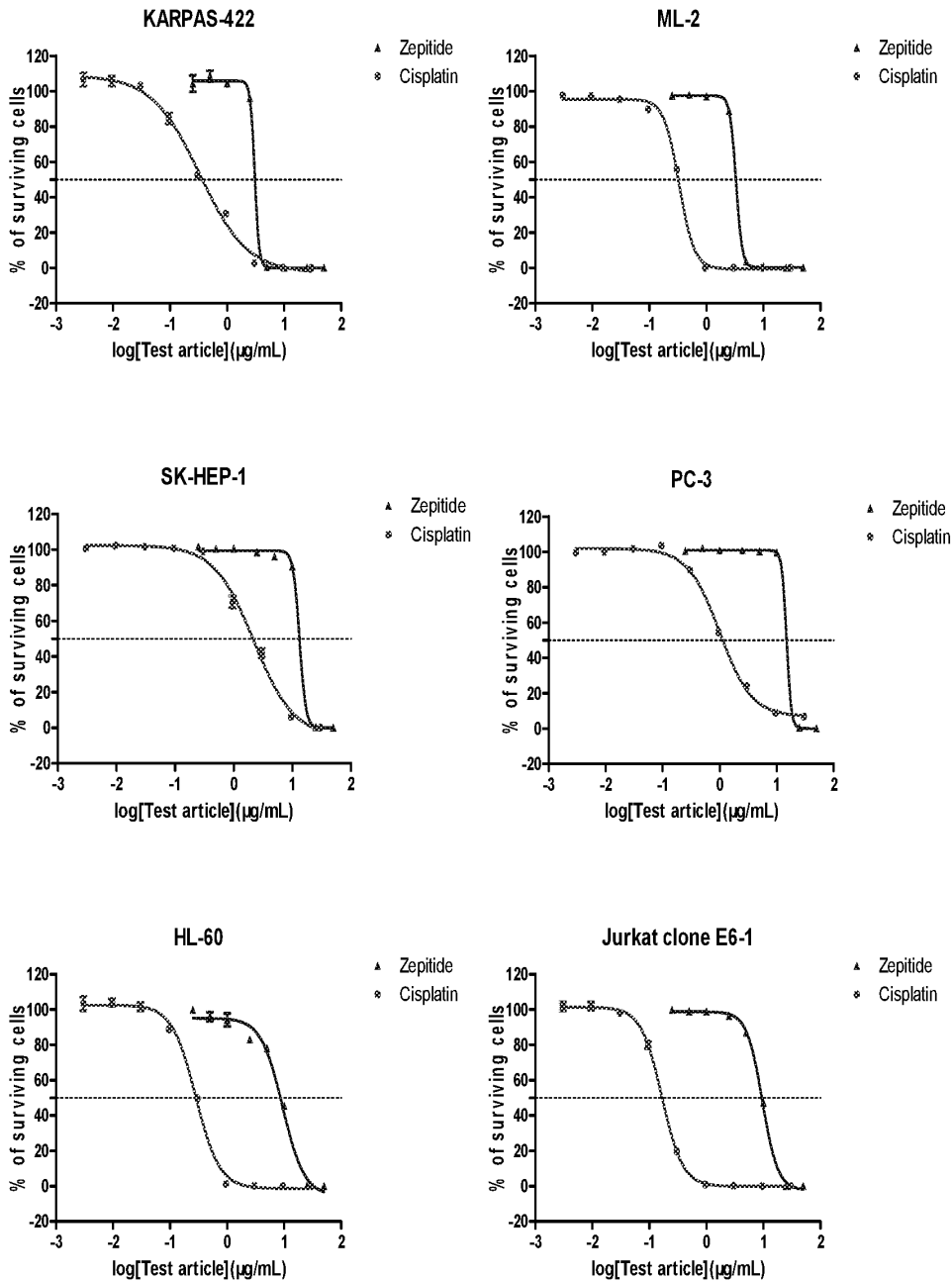


FIGURE 5C

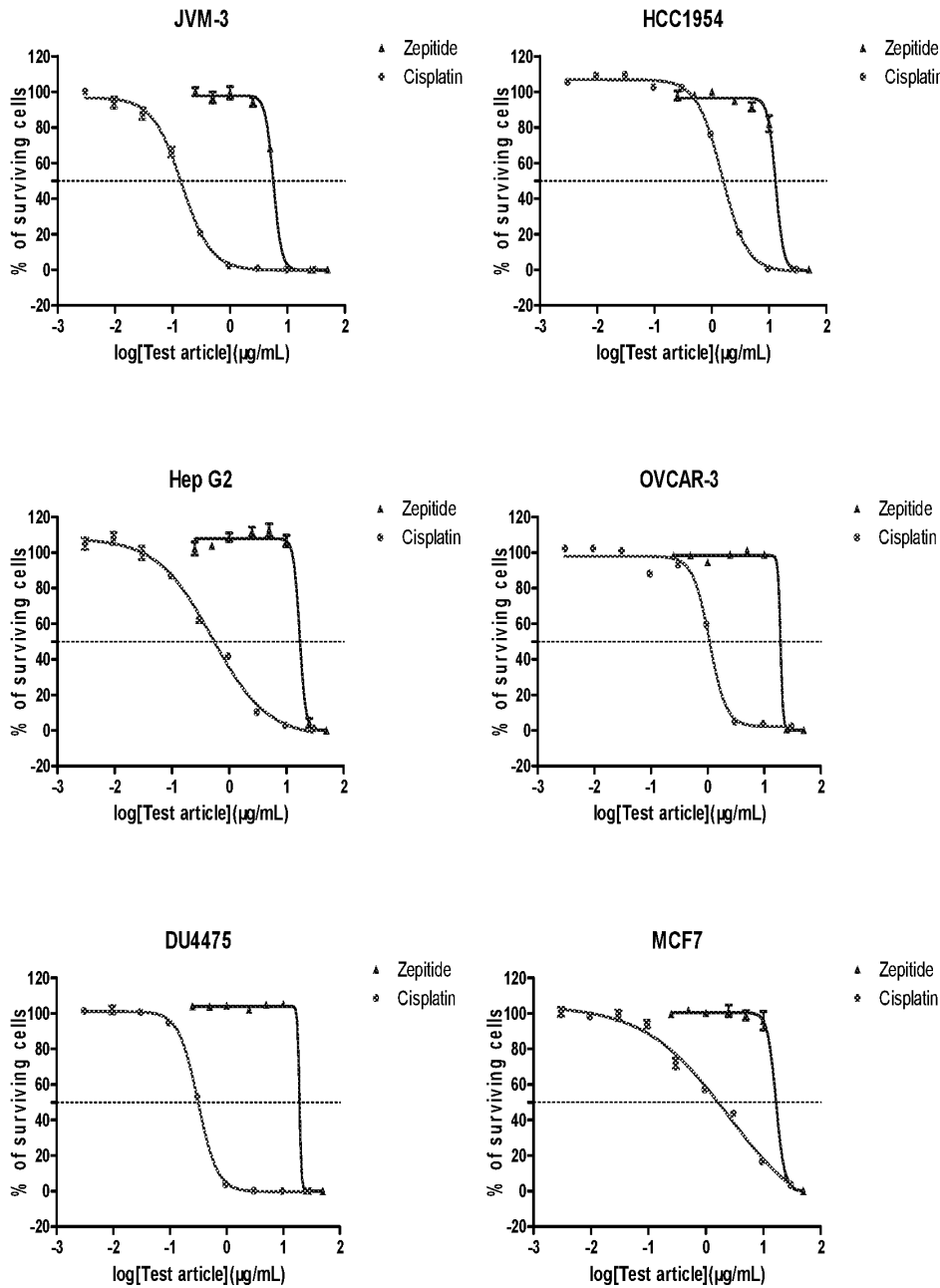


FIGURE 5D

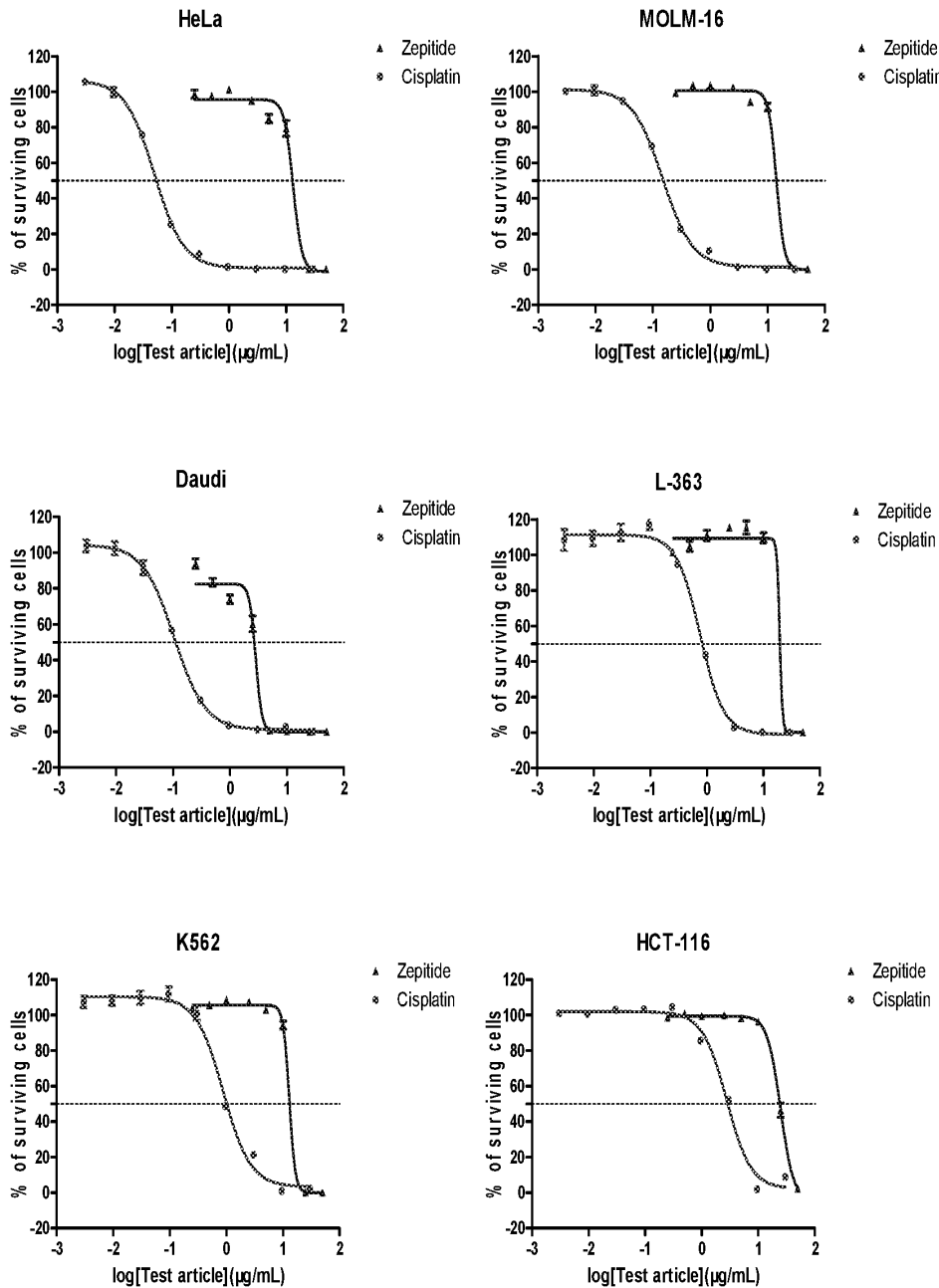


FIGURE 5E

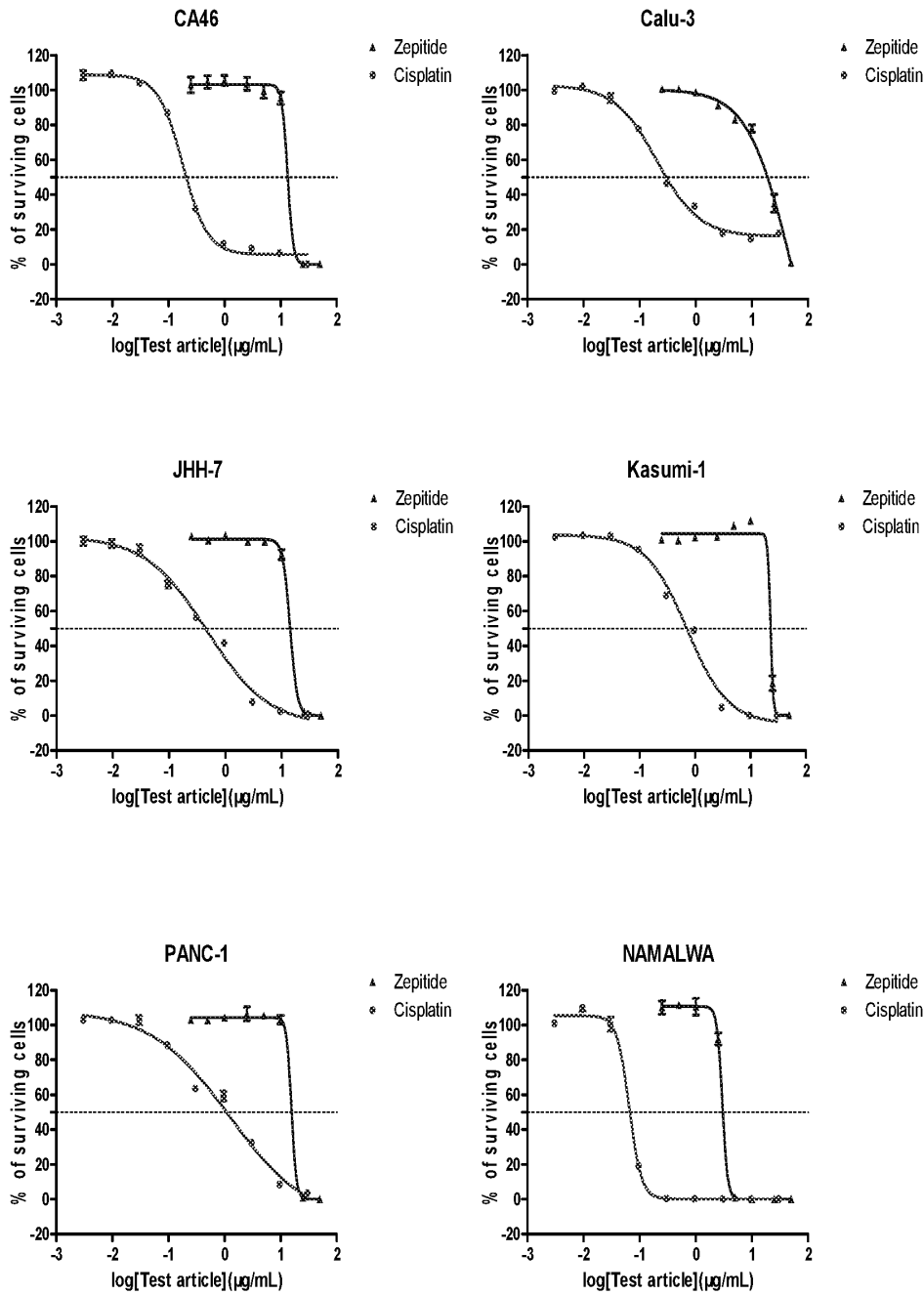


FIGURE 5F

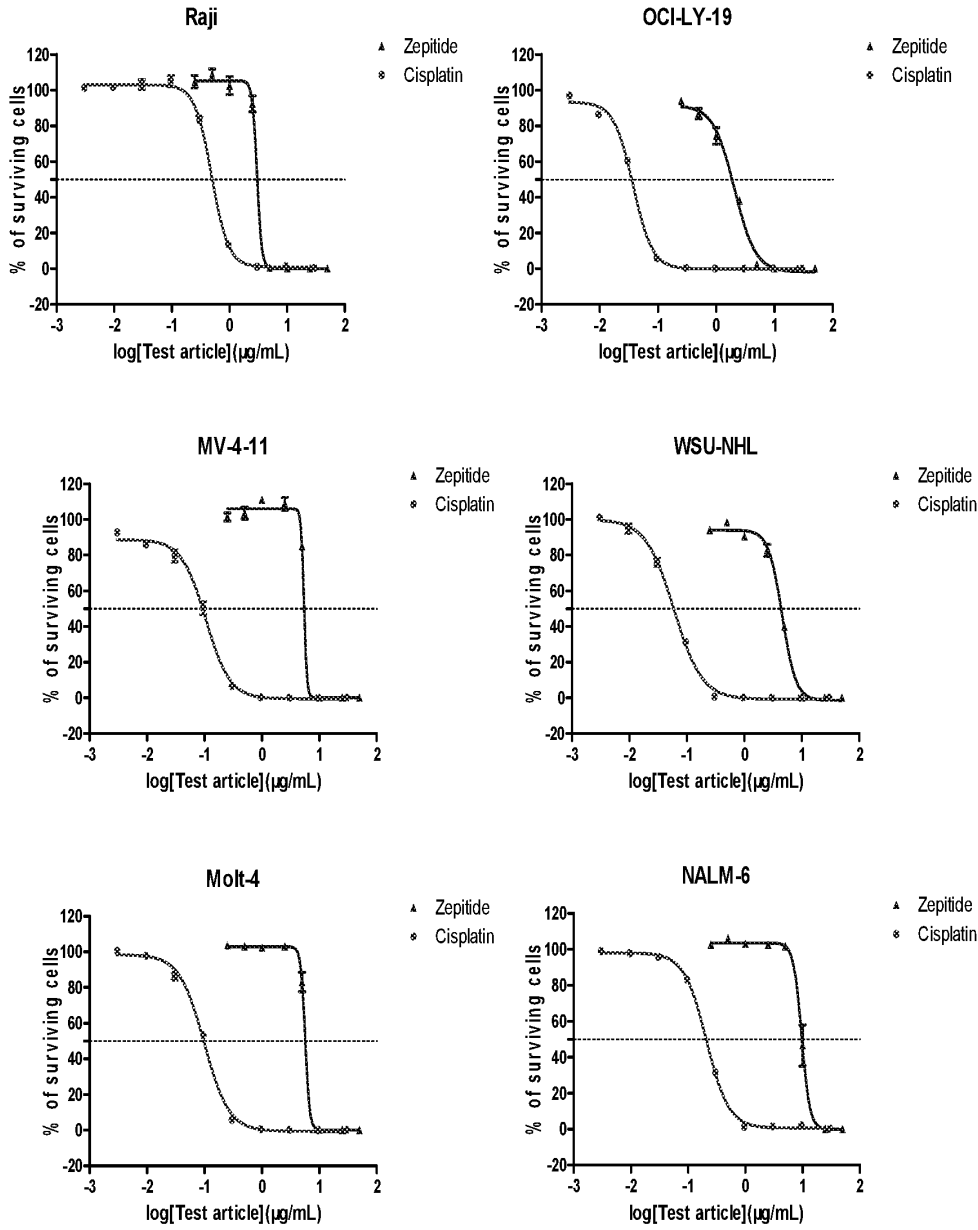


FIGURE 5G

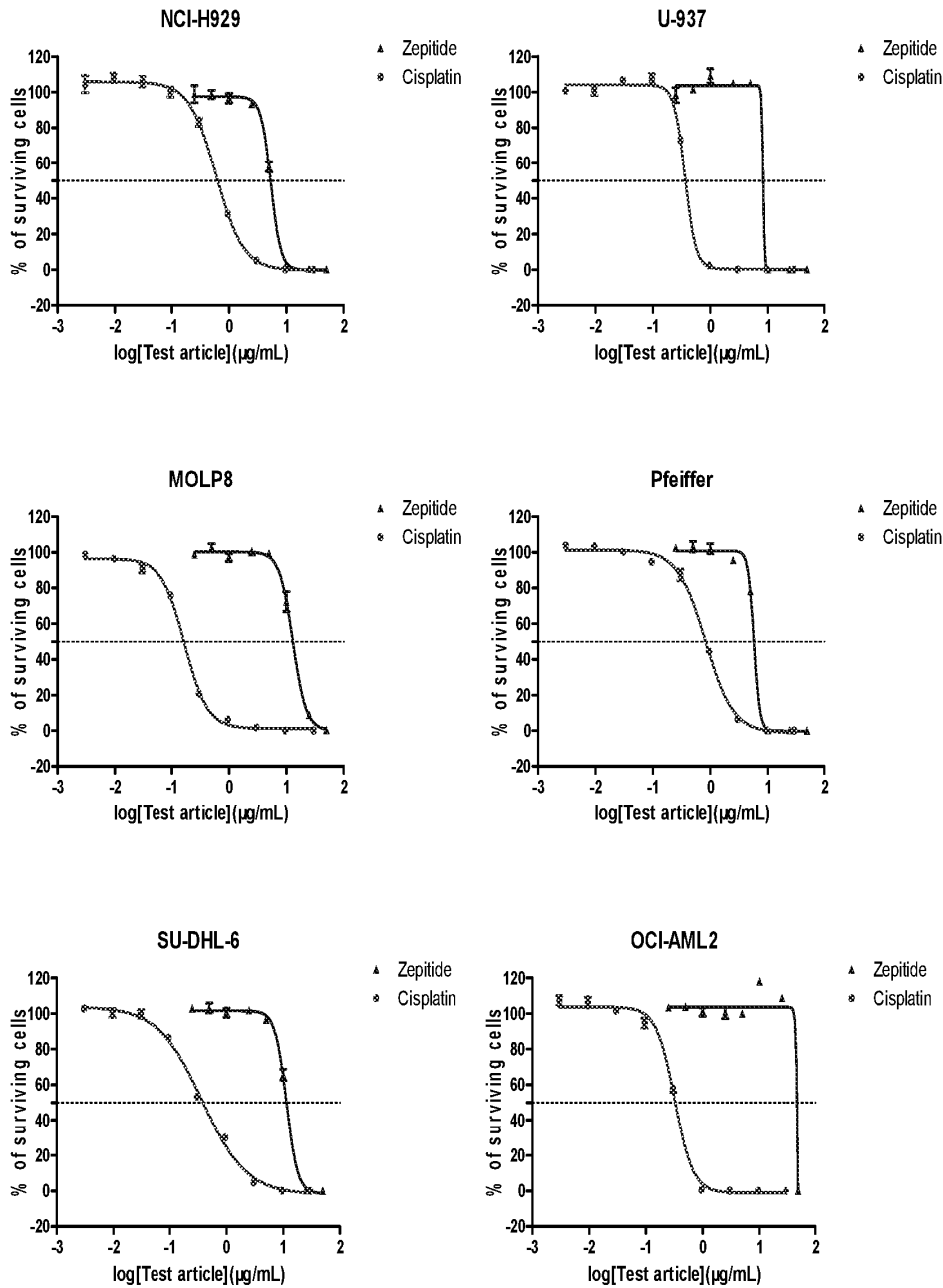


FIGURE 5H

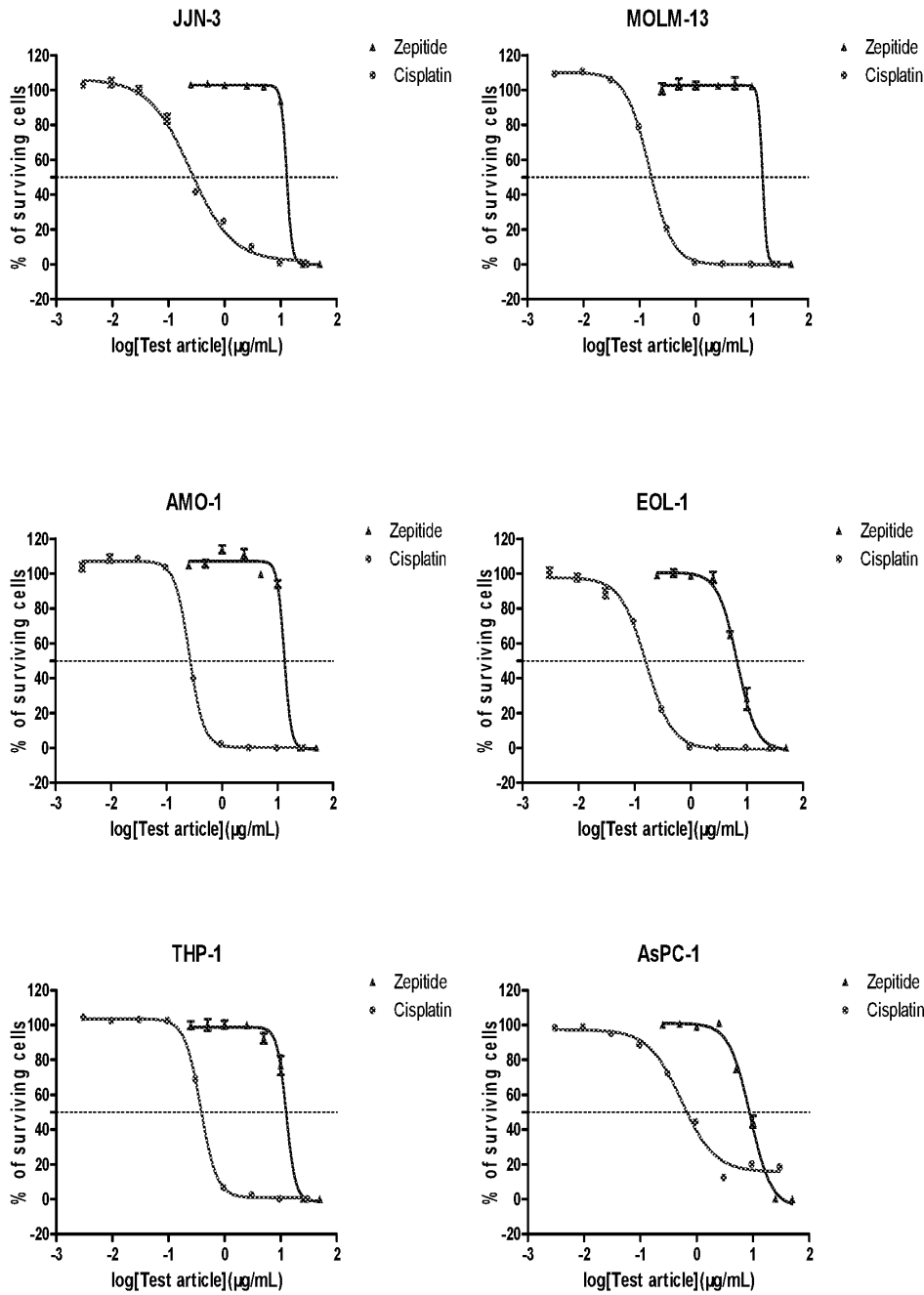
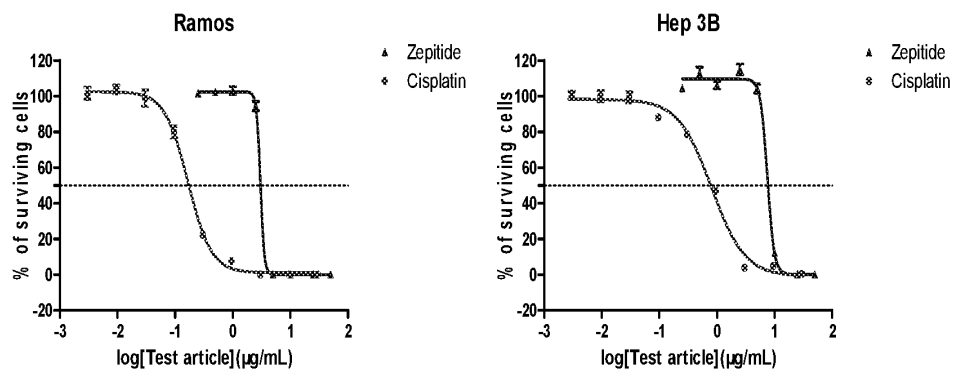


FIGURE 5I



## FIGURE 6

| Cell Line Name    | Tissue Origin | Zepitide IC50 (ug Zn/mL) | Cisplatin IC50 (ug/m) | MLH1/MSH2 mutation | PMS2 mutation | PARP1 mutation | BRCA1/2 mutation | P53 mutation | Classification                        |
|-------------------|---------------|--------------------------|-----------------------|--------------------|---------------|----------------|------------------|--------------|---------------------------------------|
| A549              | Lung          | 18.99                    | 0.88                  | yes                | K541E         | V762A          | yes              | WT           |                                       |
| AMO-1             | Blood         | 13.46                    | 0.27                  | yes                | K541E         | V762A          | yes              | WT           | Plasmacytoma                          |
| AsPC-1            | Pancreas      | 8.67                     | 0.67                  |                    |               |                |                  | mt           |                                       |
| CA46              | Blood         | 13.41                    | 0.21                  | yes                | K541E         | V762A          | yes              | mt           | Burkitt lymphoma                      |
| Calu-3            | Lung          | 18.99                    | 0.3                   | yes                | K541E         | K352K          | yes              | mt           |                                       |
| Daudi             | Blood         | 2.68                     | 0.11                  | yes                | K541E         | V762A          | yes              | mt           | Burkitt lymphoma                      |
| DU145             | Prostate      | 9.99                     | 0.2                   | yes                | K541E         | K352K          | yes              | mt           | Prostate cancer                       |
| DU4475            | Breast        | 19.44                    | 0.31                  | yes                |               |                |                  | WT           |                                       |
| EOL-1             | Blood         | 6.68                     | 0.16                  | yes                | K541E         | K352K          | yes              | WT           | Acute Myeloid (eosinophilic) leukemia |
| HCC1954           | Breast        | 12.94                    | 1.59                  |                    |               |                |                  | mt           |                                       |
| HCT 116           | Colorectum    | 24.1                     | 2.89                  | yes                | K541E         | K352K          | yes              | WT           |                                       |
| HeLa              | Cervix        | 12.96                    | 0.05                  |                    |               |                |                  | WT           |                                       |
| Hep G2            | Liver         | 17.32                    | 0.55                  |                    | K541E         | V762A          | yes              | WT           |                                       |
| Hep3B             | Liver         | 7.69                     | 0.78                  | yes                | K541E         | K352K          | yes              | mt           |                                       |
| HL-60             | Blood         | 8.61                     | 0.29                  |                    | K541E         | K352K          | yes              | mt           | B-cell lymphoma                       |
| JHH-7             | Liver         | 14.2                     | 0.44                  |                    | K541E         | V762A          | yes              | mt           |                                       |
| JHU-3             | Blood         | 12.93                    | 0.28                  |                    | K541E         | M411I          | yes              | WT           | Plasma cell leukemia                  |
| Jurkat clone E6-1 | Blood         | 9.4                      | 0.17                  | yes                | K541E         | V762A          |                  | mt           | Acute T cell leukemia                 |
| JVM-3             | Blood         | 5.67                     | 0.14                  |                    | K541E         | V762A          | yes              | WT           | Chronic B-cell leukemia               |
| K-562             | Blood         | 13.11                    | 1.02                  |                    | K541E         |                | yes              | mt           | Chronic myeloid leukemia              |
| KARPAS-422        | Blood         | 3.08                     | 0.37                  | yes                | K541E         | K352K          | yes              | mt           | B-NHL lymphoma                        |
| Kasumi-1          | Blood         | 23.07                    | 0.71                  |                    | K541E         | V762A          | yes              | mt           | Acute myeloid leukemia                |
| L-263             | Blood         | 19.63                    | 0.83                  | yes                | K541E         | K352K          | yes              | mt           | Plasma cell leukemia                  |
| MCF7              | Breast        | 16.75                    | 1.64                  |                    | K541E         | V762A          | yes              | WT           |                                       |
| MES-SA/DX5        | Uterus        | 30.4                     | 0.56                  |                    |               |                |                  | WT           |                                       |
| ML-2              | Blood         | 3.3                      | 0.32                  | yes                | K541E         | K352K          | yes              | WT           | Acute myeloid leukemia                |
| MOLM-13           | Blood         | 15.57                    | 0.16                  | yes                | K541E         | V762A          | yes              | mt           | Acute myeloid leukemia                |
| MOLM-16           | Blood         | 14.31                    | 0.15                  |                    | K541E         | V762A          | yes              | mt           | Acute myeloid leukemia                |
| MOLP8             | Blood         | 13.02                    | 0.16                  | yes                | K541E         | V762A          | yes              | WT           | Multiple myeloma                      |
| Molt-4            | Blood         | 5.7                      | 0.1                   | yes                | K541E         | K352K          | yes              | mt           | Acute lymphoblastic leukemia          |
| MY-4-11           | Blood         | 9.45                     | 0.09                  | yes                | K541E         | V762A          | yes              | WT           | Acute myeloid leukemia                |
| NALM-6            | Blood         | 9.78                     | 0.21                  |                    |               |                |                  | WT           | B-cell precursor leukemia             |
| NAMALWA           | Blood         | 3.04                     | 0.07                  | yes                | K541E         | K352K          | yes              | mt           | Burkitt lymphoma                      |
| NCI-H446          | Lung          | 3.72                     | 0.35                  |                    | K541E         | K352K          | yes              | mt           | SCLC                                  |
| NCI-H460          | Lung          | 12.6                     | 0.15                  |                    | K541E         | V762A          | yes              | WT           | NSCLC                                 |
| NCI-H929          | Blood         | 5.32                     | 0.64                  | yes                |               | K352K          | yes              | WT           | Multiple myeloma                      |
| OCI-AML2          | Blood         | 48.08                    | 0.33                  |                    |               |                |                  | WT           | Acute myeloid leukemia                |
| OCI-LY-19         | Blood         | 1.87                     | 0.04                  | yes                | K541E         | V762A          | yes              | WT           | B-cell Non-Hodgkin lymphoma (B-NHL)   |
| OVCA8-3           | Ovary         | 19.46                    | 1.08                  |                    | K541E         | K352K          |                  | mt           |                                       |
| PANC-1            | Pancreas      | 15.74                    | 1.08                  |                    |               |                |                  | mt           |                                       |
| PC-3              | Prostate      | 14.96                    | 1.13                  | yes                | K541E         | V762A          | yes              | mt           |                                       |
| Pfeiffer          | Blood         | 5.77                     | 0.83                  |                    | K541E         | V762A          | yes              | mt           | Acute T cell leukemia                 |
| Raji              | Blood         | 3.04                     | 0.5                   | yes                | K541E         | K352K          | yes              | mt           | Burkitt lymphoma                      |
| Ramos             | Blood         | 3.04                     | 0.17                  |                    | K541E         | V762A          | yes              | mt           | Burkitt lymphoma                      |
| SK-HEP-1          | Liver         | 13.26                    | 2.13                  | yes                | K541E         | K352K          | yes              | WT           |                                       |
| SK-OV-3           | Ovary         | 19.56                    | 0.54                  |                    | K541E         | K352K          | yes              | mt           |                                       |
| SU-DHL-6          | Blood         | 11.46                    | 0.38                  | yes                | K541E         | K352K          | yes              | mt           | B-cell Non-Hodgkin lymphoma (B-NHL)   |
| THP-1             | Blood         | 12.53                    | 0.39                  |                    | K541E         | V762A          | yes              | mt           | Acute Monocytic Leukemia              |
| U-937             | Blood         | 8.28                     | 0.37                  | yes                | K541E         | K352K          | yes              | mt           | histiocytic lymphoma                  |
| WSU-NHL           | Blood         | 4.37                     | 0.06                  | yes                | K541E         | E12G           | yes              | mt           | B-cell lymphoma                       |

FIGURE 7A

Median-normalized IC50 distribution

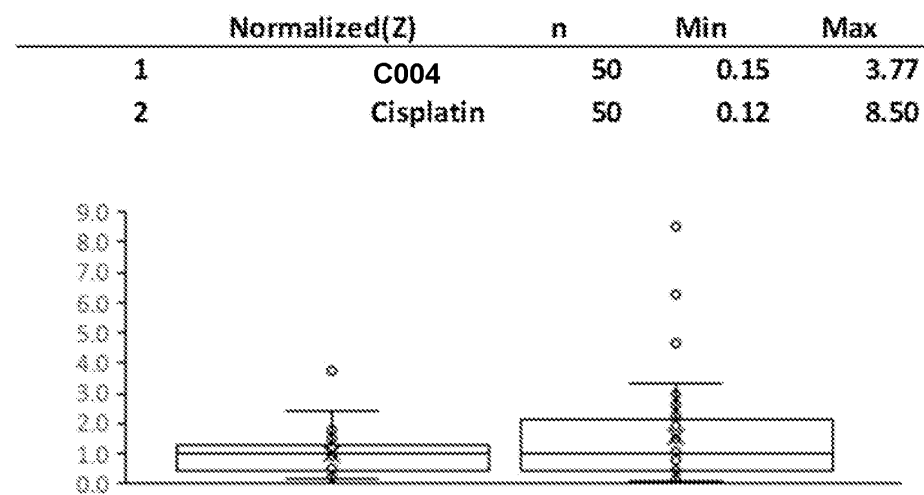


FIGURE 7B

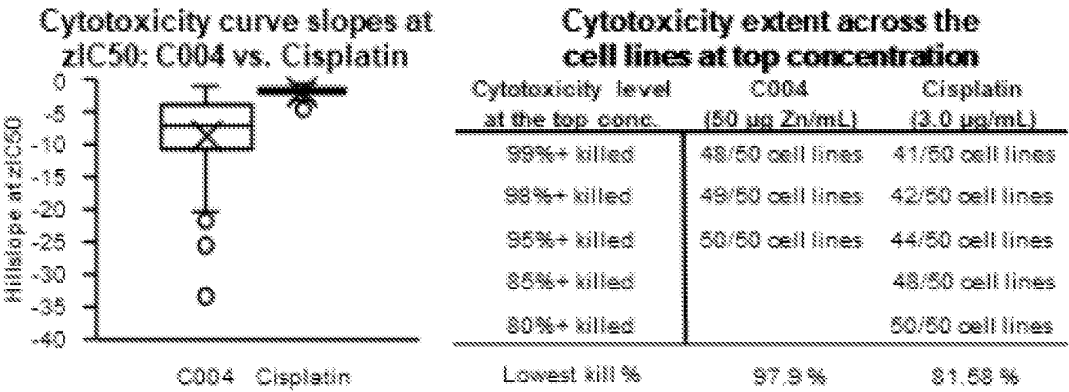


FIGURE 8

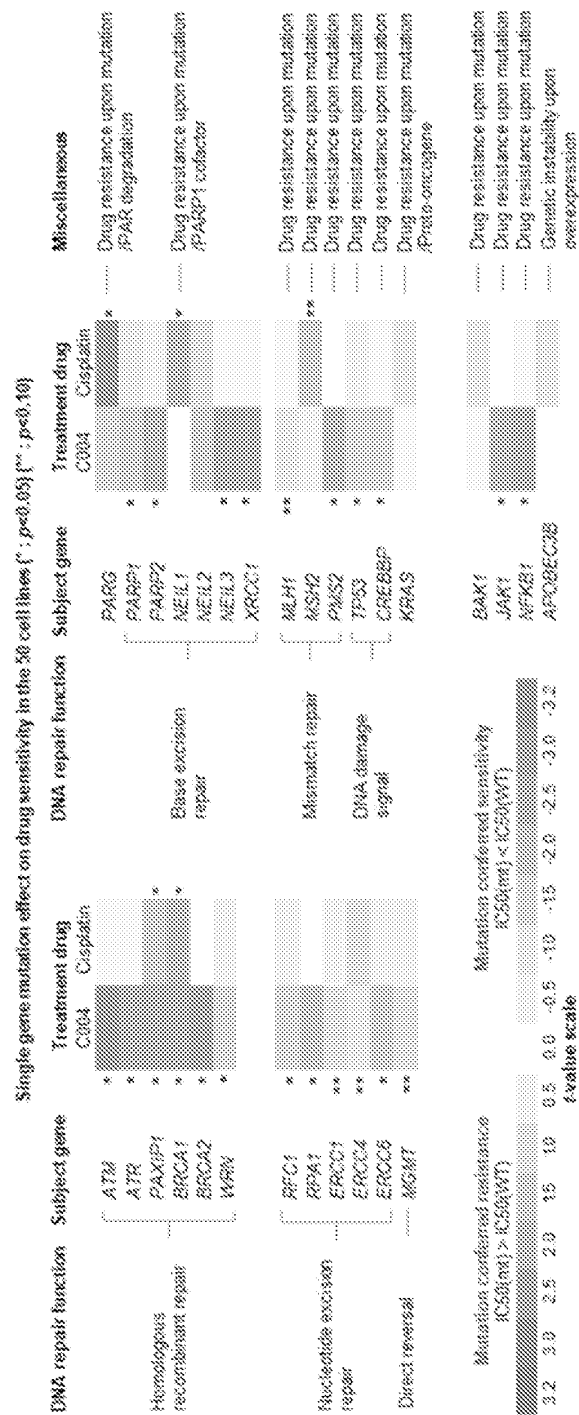
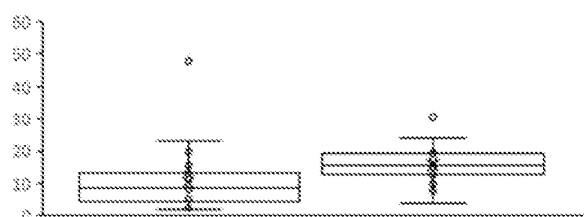


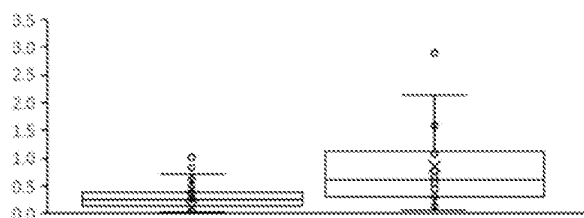
FIGURE 9A

## Blood cancer vs. solid cancer

|   | Zn-γPGA      | n  | Average | Compare | p        |
|---|--------------|----|---------|---------|----------|
| 1 | Blood cancer | 30 | 10.188  | 1<2     | 0.011075 |
| 2 | Solid cancer | 20 | 15.587  |         |          |



|   | Cisplatin    | n  | Average  | Compare | p       |
|---|--------------|----|----------|---------|---------|
| 1 | Blood cancer | 30 | 0.317667 | 1<2     | 0.07734 |
| 2 | Solid cancer | 20 | 0.866    |         |         |

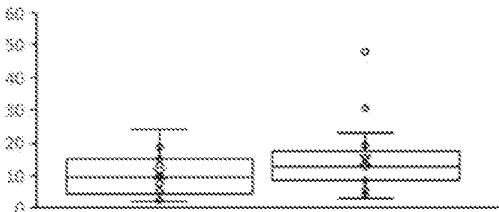


- Zn-γPGA is significantly more effective against blood cancer types than solid cancers ( $p=0.011$ ). However the IC50 difference itself is small (10.2 vs. 15.6  $\mu\text{g Zn/mL}$ , respectively). This is primarily due to more frequent GIM found in the blood cancer cell lines, as the following genetic analyses in the next slides show.
- Cisplatin, on the other hand, is insignificantly more effective against blood cancer types than solid cancers ( $p=0.07734$ )

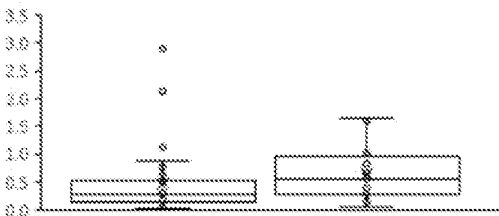
FIGURE 9B

Effect of MLH1/MSH2 mutations

|   | Zn-yPGA      | n  | Average | Compare | p        |
|---|--------------|----|---------|---------|----------|
| 1 | MLH1/MSH2 mt | 27 | 10.23   | 1<2     | 0.024278 |
| 2 | MLH1/MSH2 WT | 23 | 14.84   |         |          |



|   | Cisplatin    | n  | Average | Compare | p       |
|---|--------------|----|---------|---------|---------|
| 1 | MLH1/MSH2 mt | 27 | 0.50    | 1<2     | 0.33288 |
| 2 | MLH1/MSH2 WT | 23 | 0.57    |         |         |

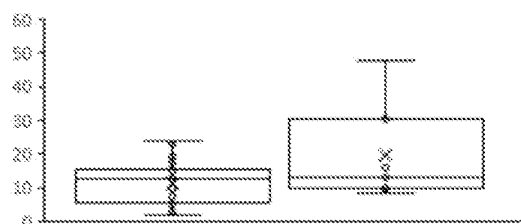


- Zn-yPGA is significantly more effective against cancer types that carry MLH1 or MSH2 mutations ( $p=0.0243$ )
- Cisplatin does not show similar sensitivity enhancement ( $p=0.333$ )

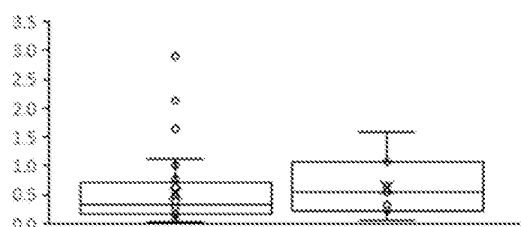
FIGURE 9C

## Effect of dMMR(MLH1/MSH2/PMS2) mutations

|   | Zn-γPGA           | n  | Average | Compare | p        |
|---|-------------------|----|---------|---------|----------|
| 1 | MLH1/MSH2/PMS2 mt | 43 | 11.14   | 1<2     | 0.004379 |
| 2 | MLH1/MSH2/PMS2 WT | 7  | 19.80   |         |          |



|   | Cisplatin         | n  | Average | Compare | p        |
|---|-------------------|----|---------|---------|----------|
| 1 | MLH1/MSH2/PMS2 mt | 43 | 0.52    | 1<2     | 0.300775 |
| 2 | MLH1/MSH2/PMS2 WT | 7  | 0.64    |         |          |

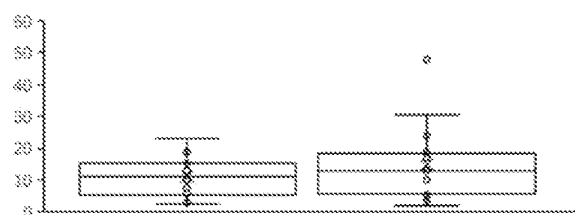


- Zn-γPGA is significantly more effective against cancer types that carry MLH1 or MSH2 or PMS2 mutations ( $p=0.0044$ ). The gap between the two average IC50 is wider as well (11.14 vs 19.80  $\mu\text{g Zn/mL}$ )
- Cisplatin does not show similar sensitivity enhancement ( $p=0.3008$ )

FIGURE 9D

## Effect of TP53 mutations

|   | Zn-γPGA | n  | Average | Compare | p        |
|---|---------|----|---------|---------|----------|
| 1 | p53mt   | 30 | 10.87   | 1<2     | 0.061078 |
| 2 | p53WT   | 20 | 14.57   |         |          |



|   | Cisplatin | n  | Average | Compare | p       |
|---|-----------|----|---------|---------|---------|
| 1 | p53mt     | 30 | 0.50    | 1<2     | 0.29586 |
| 2 | p53WT     | 20 | 0.59    |         |         |



- At a weaker significance level, Zn-γPGA is more effective against cancer types that carry TP53 mutations ( $p=0.061$ ).
- Cisplatin does not show similar sensitivity enhancement ( $p=0.2959$ )

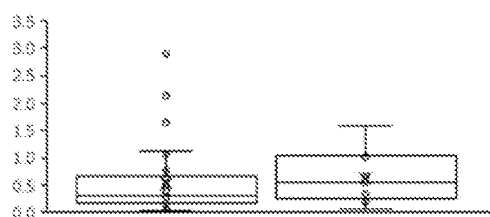
## FIGURE 9E

## Effect of PARP1 mutations

|   | Zn-γPGA  | n  | Average | Compare | p        |
|---|----------|----|---------|---------|----------|
| 1 | PARP1 mt | 41 | 10.88   | 1<2     | 0.003142 |
| 2 | PARP1 WT | 9  | 19.01   |         |          |



|   | Cisplatin | n  | Average | Compare | p        |
|---|-----------|----|---------|---------|----------|
| 1 | PARP1 mt  | 41 | 0.51    | 1<2     | 0.261992 |
| 2 | PARP1 WT  | 9  | 0.65    |         |          |

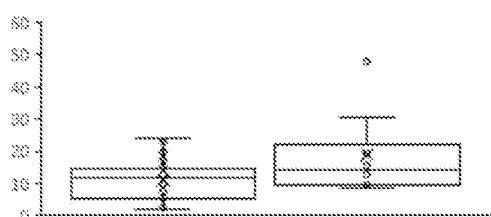


- Zn-γPGA is significantly more effective against cancer types that carry PARP1 mutations ( $p=0.00031$ ). The gap between the average IC50 values is also wider (10.88 vs 19.01).
- It is notable that most BRCA1 or BRCA2 mutants also carry PARP1 mutations, and vice versa
- Cisplatin does not show similar sensitivity enhancement ( $p=0.2620$ )

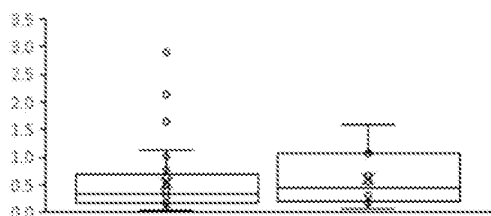
FIGURE 9F

## Effect of BRCA1/BRCA2 mutations

|   | Zn-γPGA        | n  | Average | Compare | p        |
|---|----------------|----|---------|---------|----------|
| 1 | BRCA1/BRCA2 mt | 40 | 10.76   | 1<2     | 0.002744 |
| 2 | BRCA1/BRCA2 WT | 10 | 18.69   |         |          |

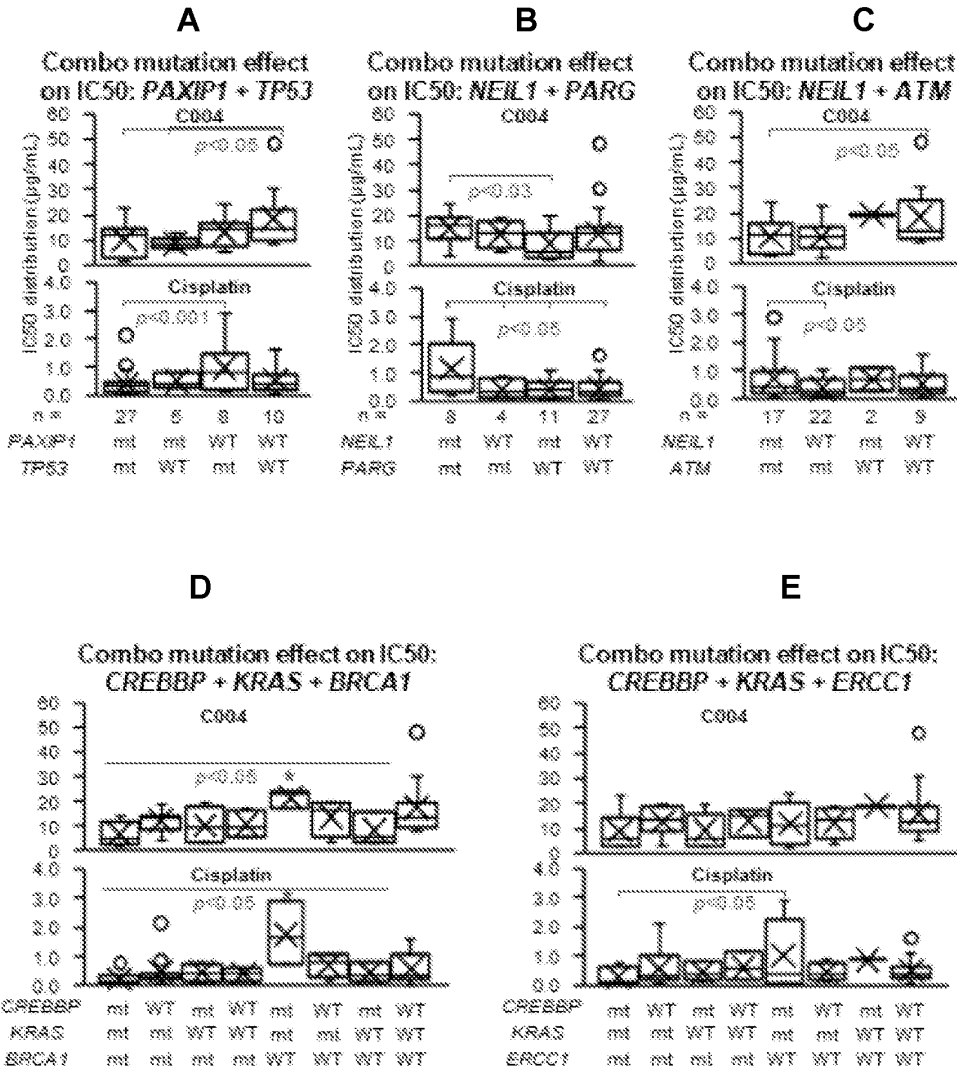


|   | Cisplatin      | n  | Average | Compare | p        |
|---|----------------|----|---------|---------|----------|
| 1 | BRCA1/BRCA2 mt | 40 | 0.52    | 1<2     | 0.336822 |
| 2 | BRCA1/BRCA2 WT | 10 | 0.61    |         |          |



- Zn-γPGA is significantly more effective against cancer types that carry BRCA1 or BRCA2 mutations ( $p=0.00027$ ). The gap between the average IC50 values is also wider (10.76 vs 18.69).
- It is notable that most BRCA1 or BRCA2 mutants also carry PARP1 mutations, and vice versa.
- Cisplatin does not show similar sensitivity enhancement ( $p=0.3368$ )

FIGURES 10A-10E



FIGURES 10F-10L

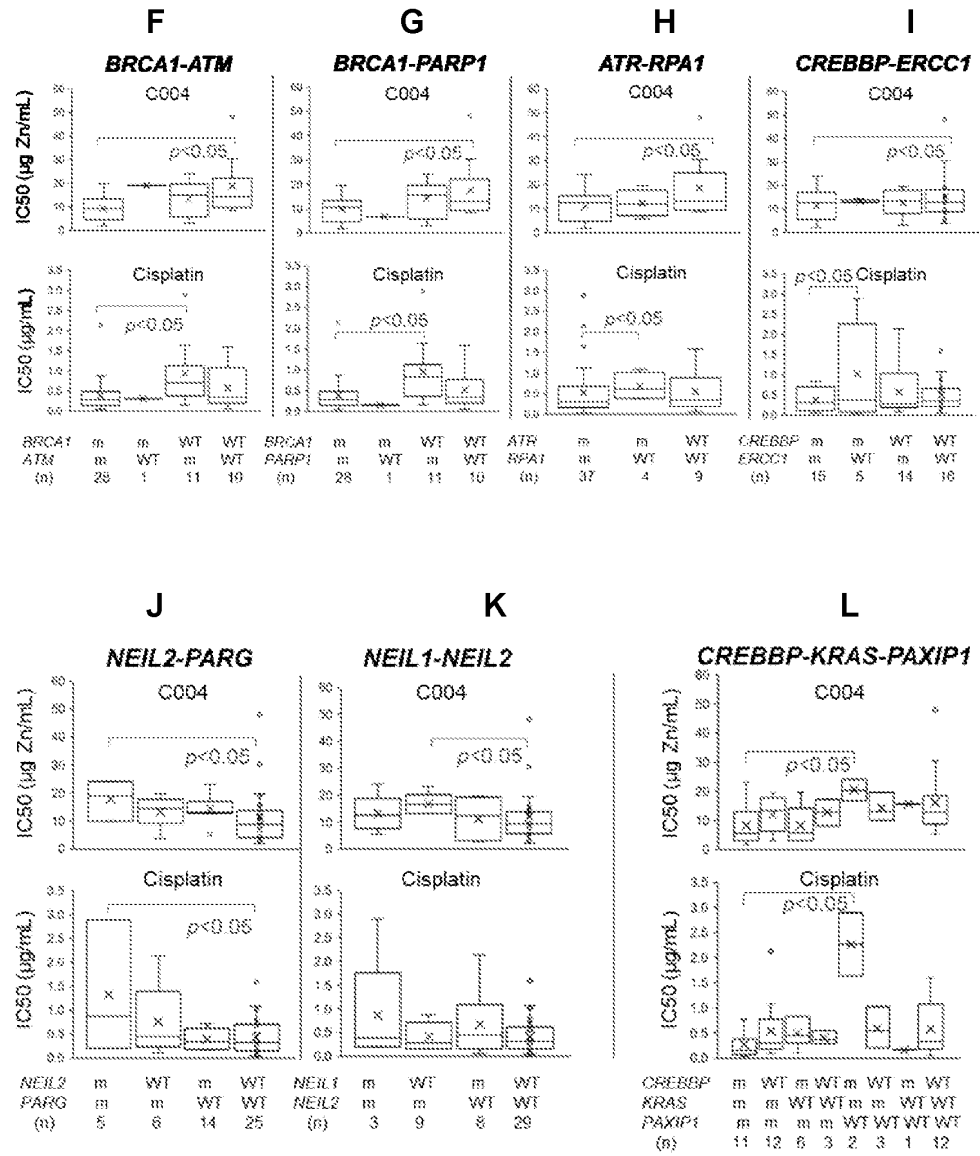
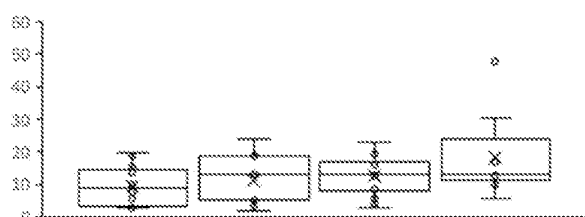


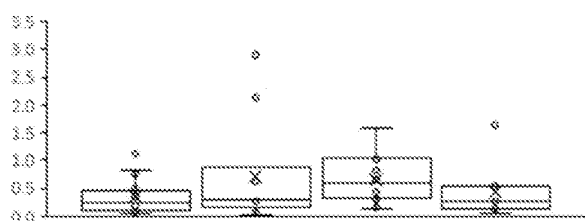
FIGURE 10M

## Combination effect: TP53+MLH1/MSH2 mutations

|   | Zn-γPGA           | n  | Average | Compare | p        |
|---|-------------------|----|---------|---------|----------|
| 1 | MLH1/MSH2mt+p53mt | 16 | 9.45    | 1<2     | 0.229629 |
| 2 | MLH1/MSH2mt+p53WT | 11 | 11.35   | 1<3     | 0.084907 |
| 3 | MLH1/MSH2WT+p53mt | 14 | 12.48   | 2<3     | 0.338712 |
| 4 | MLH1/MSH2WT+p53WT | 9  | 18.50   | 3<4     | 0.072957 |
|   |                   |    |         | 2<4     | 0.069747 |
|   |                   |    |         | 1<4     | 0.011967 |



|   | Cisplatin         | n  | Average | Compare | p        |
|---|-------------------|----|---------|---------|----------|
| 1 | MLH1/MSH2mt+p53mt | 16 | 0.36    | 1<2     | 0.082    |
| 2 | MLH1/MSH2mt+p53WT | 11 | 0.72    | 1<3     | 0.014337 |
| 3 | MLH1/MSH2WT+p53mt | 14 | 0.67    | 3<2     | 0.426396 |
| 4 | MLH1/MSH2WT+p53WT | 9  | 0.43    | 4<3     | 0.118593 |
|   |                   |    |         | 4<2     | 0.211785 |
|   |                   |    |         | 1<4     | 0.318662 |

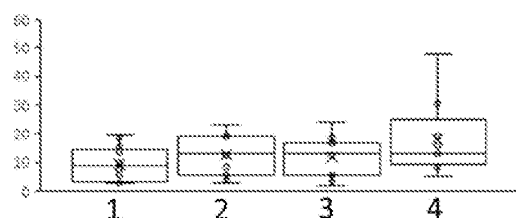


- Zn-γPGA is significantly more effective when more GIM mutations are accumulated ( $p=0.01197$ ).
- A clear trend of increasing Zn-γPGA sensitivity is observed as more GIM mutations are combined among the TP53, MLH1, and MSH2 genes.
- Cisplatin, on the other hand, only displayed a significant improvement in sensitivity in the absence of genetic mutations to TP53. ( $1<3, p=0.01439$ )

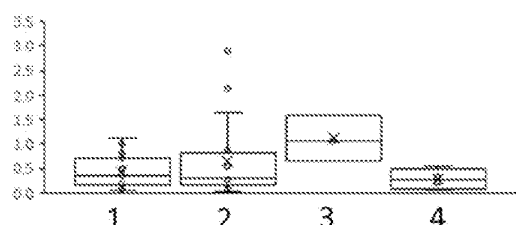
FIGURE 10N

# Combination effect: TP53+MMR(MLH1/MSH2/PMS2) mutations

|   | Zn-γPGA    | n  | Average | Compare | p        |
|---|------------|----|---------|---------|----------|
| 1 | dMMR+p53mt | 27 | 10.69   | 1<2     | 0.276424 |
| 2 | dMMR+p53WT | 16 | 11.89   | 1<3     | 0.918207 |
| 3 | nMMR+p53mt | 3  | 12.45   | 1<4     | 0.001165 |
| 4 | nMMR+p53WT | 4  | 25.31   | 2<4     | 0.013103 |
|   |            |    |         | 3<4     | 0.139738 |



|   | Cisplatin  | n  | Average | Compare | p        |
|---|------------|----|---------|---------|----------|
| 1 | dMMR+p53mt | 27 | 0.43    | 1<2     | 0.100745 |
| 2 | dMMR+p53WT | 16 | 0.67    | 1<3     | 0.001212 |
| 3 | nMMR+p53mt | 3  | 1.11    | 2<3     | 0.192794 |
| 4 | nMMR+p53WT | 4  | 0.29    | 4<3     | 0.011716 |
|   |            |    |         | 4<2     | 0.199449 |
|   |            |    |         | 4<1     | 0.195856 |

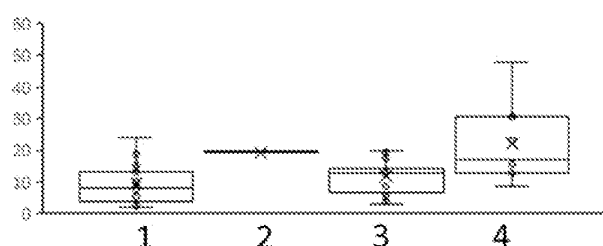


- Zn-γPGA is, again, even more significantly effective when the full dMMR and p53 mutations are combined. (1<4:  $p=0.0012$ , 2<4:  $p=0.0131$ )
- An clearer trend of increasing Zn-γPGA sensitivity is observed as more GIM mutations are combined among the TP53, and the full dMMR panels, compared with MLH1/MSH2 only.
- Cisplatin, doesn't appear to show any significant sensitivity enhancement under the same setting. (n is too small on nMMR+p53mt group for reliable analysis).

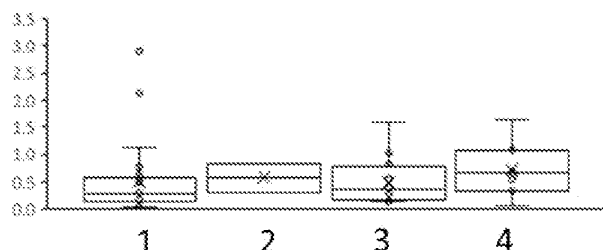
FIGURE 100

## Combination effect: PARP1+MLH1/MSH2 mutations

|   | Zn-yPGA            | n  | Average | Compare | p        |
|---|--------------------|----|---------|---------|----------|
| 1 | MLH1/MSH2+PARP1 mt | 25 | 9.48    | 1<2     | 0.014724 |
| 2 | MLH1/MSH2mt only   | 2  | 19.54   | 3<2     | 0.024698 |
| 3 | PARP1 mt only      | 16 | 11.60   | 1<4     | 0.000438 |
| 4 | MLH1/MSH2+PARP1 WT | 7  | 22.24   | 3<4     | 0.00533  |



|   | Cisplatin          | n  | Average | Compare | p        |
|---|--------------------|----|---------|---------|----------|
| 1 | MLH1/MSH2+PARP1 mt | 25 | 0.50    | 1<4     | 0.215328 |
| 2 | MLH1/MSH2mt only   | 2  | 0.57    | 2<4     | 0.359312 |
| 3 | PARP1 mt only      | 16 | 0.51    | 3<4     | 0.157627 |
| 4 | MLH1/MSH2+PARP1 WT | 7  | 0.72    |         |          |

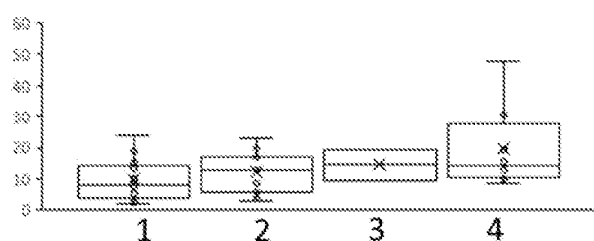


- Zn-yPGA is, again, even more significantly effective when PARP1 mutations are combined with MLH1/MSH2 mutation. (1<4:  $p=0.000438$ ). Also the game between 1 and 4 groups is quite wide (9.48 vs 22.24).
- Discounting MLH1/MSH2 mt only group (n=2 only), there is a clear trend in increasing sensitivity with more combined mutations between PARP1 and MLH1/MSH2.
- Cisplatin, doesn't show any significant sensitivity enhancement under the same setting.

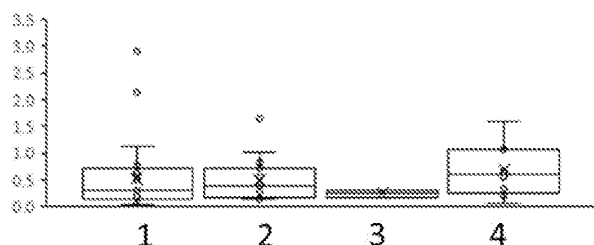
FIGURE 10P

# Combination effect: BRCA1/BRCA2+MLH1/MSH2 mutations

|   | Zn-γPGA              | n  | Average | Compare | p        |
|---|----------------------|----|---------|---------|----------|
| 1 | MLH1/MSH2+BRCA1/2 mt | 25 | 9.89    | 1<4     | 0.003692 |
| 2 | MLH1/MSH2mt only     | 15 | 12.21   | 2<4     | 0.035735 |
| 3 | BRCA1/2 mt only      | 2  | 14.42   | 3<4     | 0.30531  |
| 4 | MLH1/MSH2+BRCA1/2 WT | 8  | 19.75   |         |          |



|   | Cisplatin            | n  | Average | Compare | p    |
|---|----------------------|----|---------|---------|------|
| 1 | MLH1/MSH2+BRCA1/2 mt | 25 | 0.53    | 3<1     | n.s. |
| 2 | MLH1/MSH2mt only     | 15 | 0.51    | 3<2     | n.s. |
| 3 | BRCA1/2 mt only      | 2  | 0.24    | 3<4     | n.s. |
| 4 | MLH1/MSH2+BRCA1/2 WT | 8  | 0.70    | 1<4     | n.s. |
|   |                      |    |         | 2<4     | n.s. |



- Zn-γPGA is, again, even more significantly effective when BRCA1/BRCA2 mutations are combined with MLH1/MSH2 mutation. (1<4;  $p=0.00369$ )
- Discounting BRCA1/BRCA2 mt only group (n=2 only), there is a clear trend in increasing sensitivity with more combined mutations between BRCA1/BRCA2 and MLH1/MSH2.
- Cisplatin, doesn't show any significant sensitivity enhancement under the same setting.

FIGURE 11

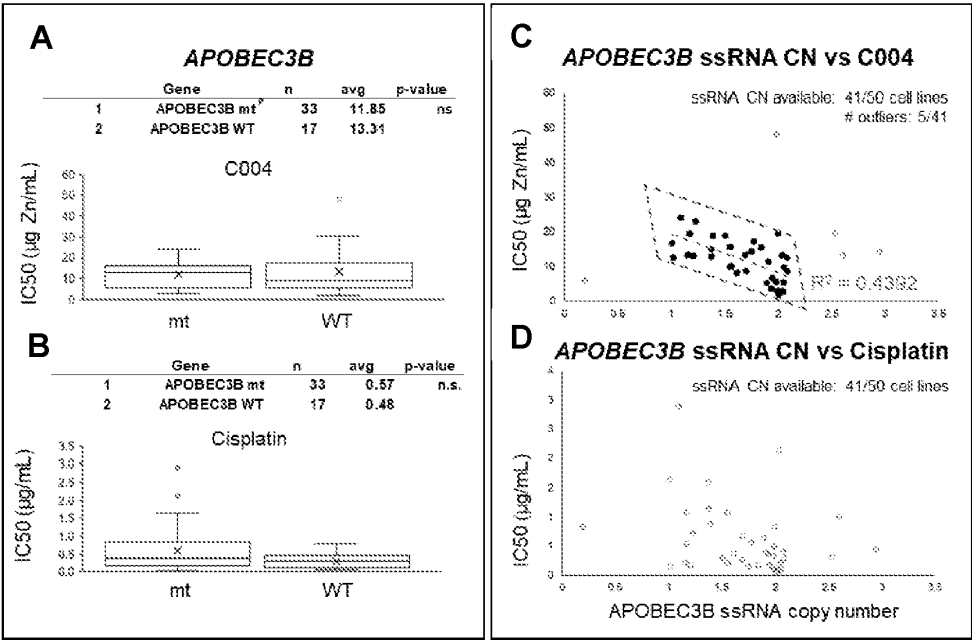


FIGURE 12A

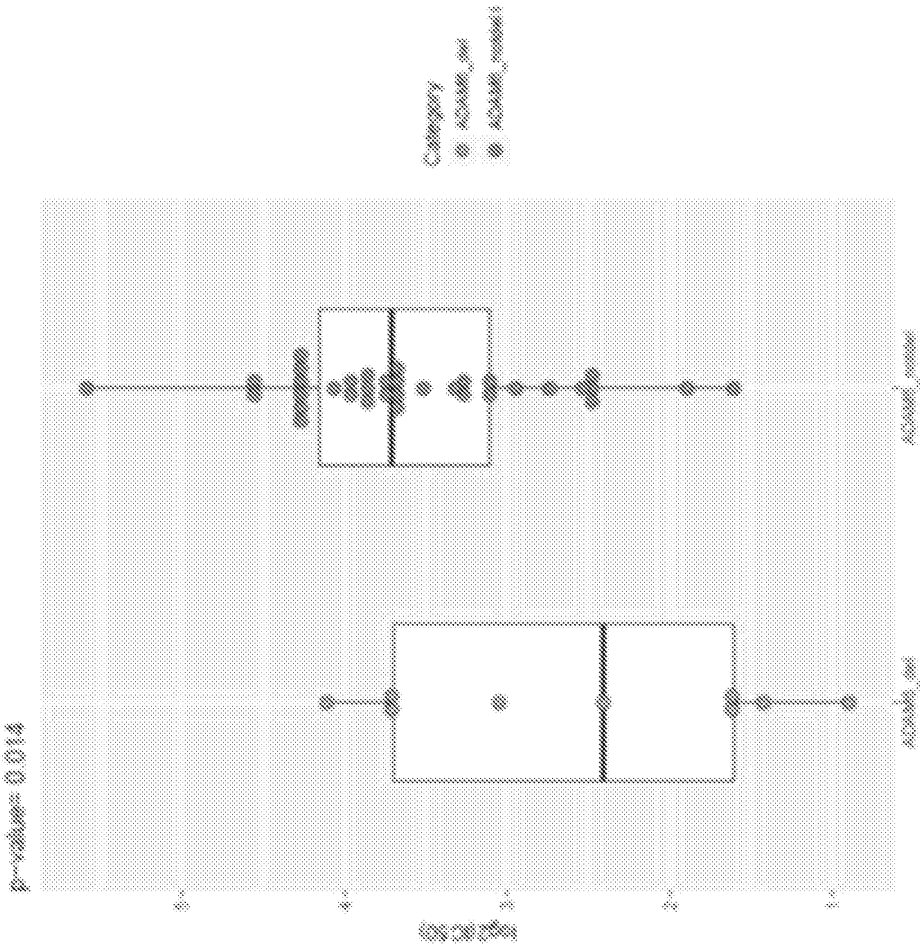


FIGURE 12B

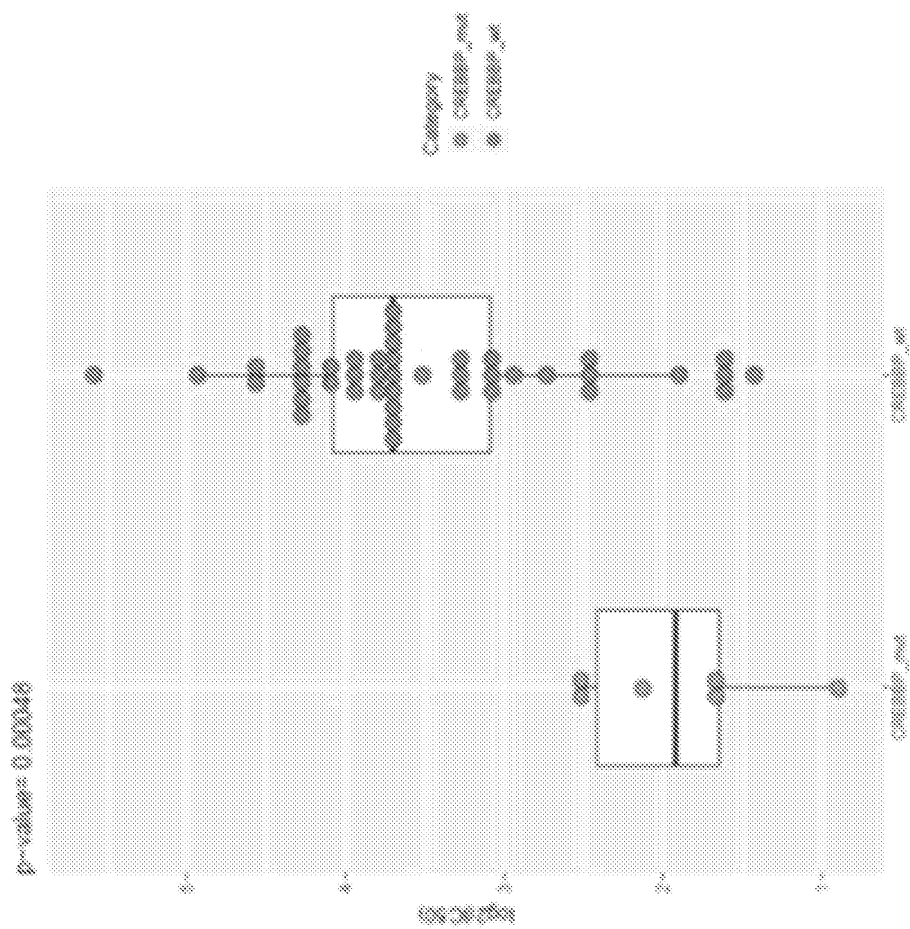


FIGURE 12C

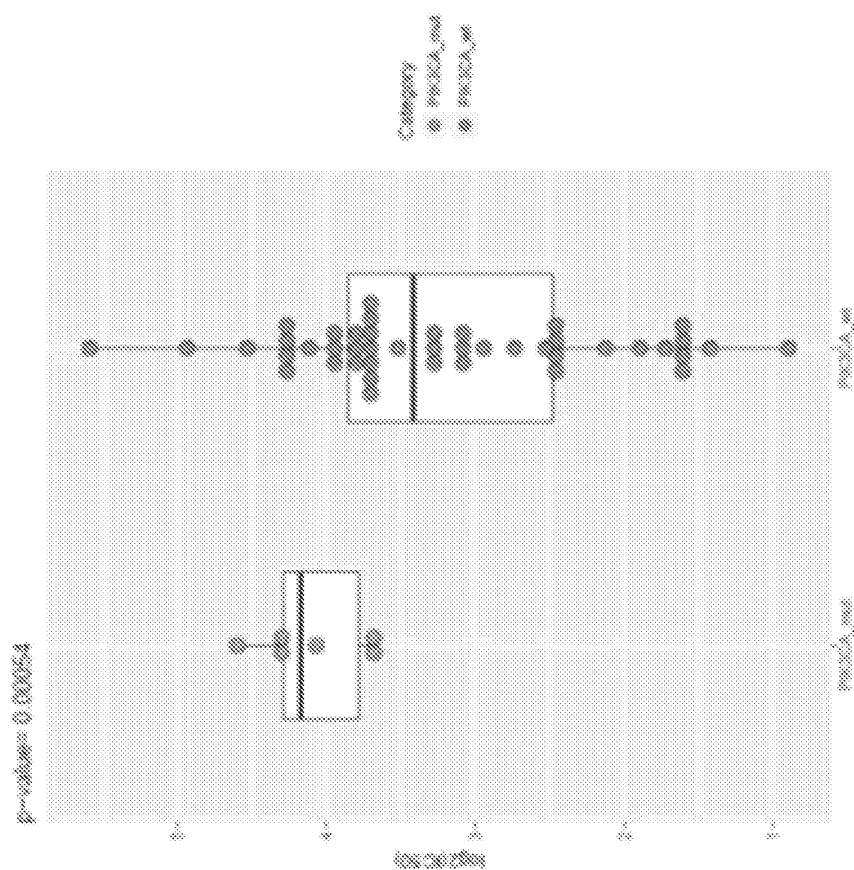


FIGURE 13

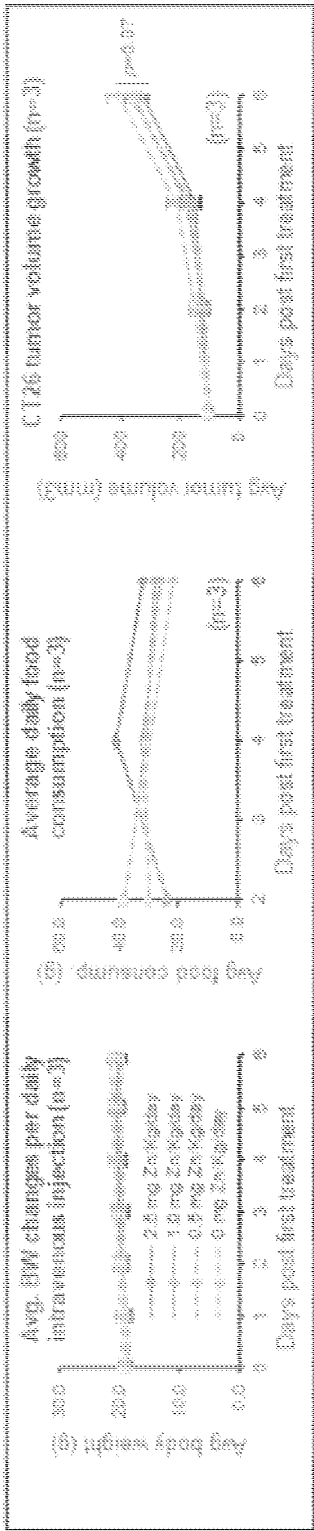


FIGURE 14A

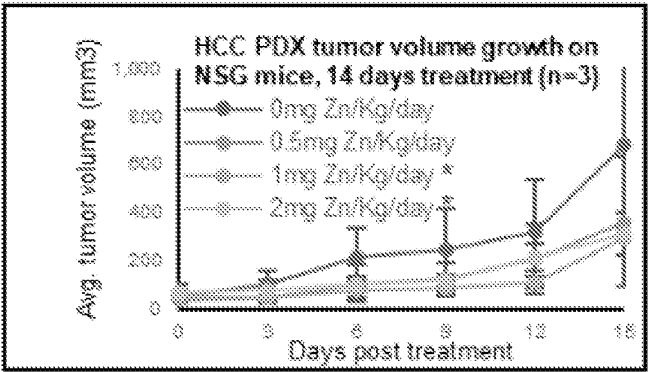


FIGURE 14B

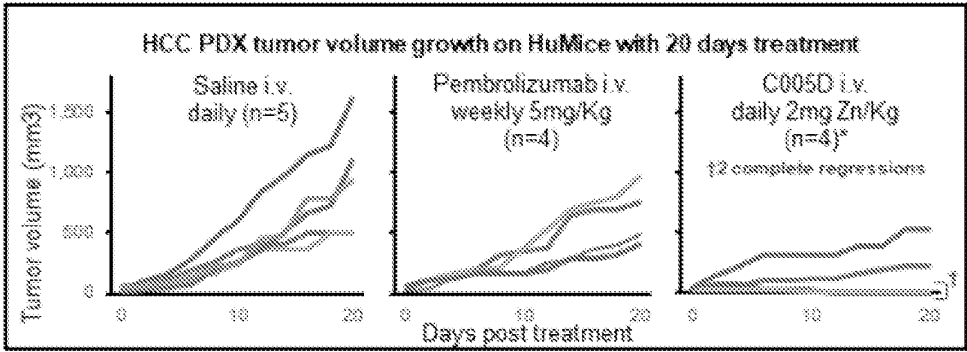


FIGURE 15

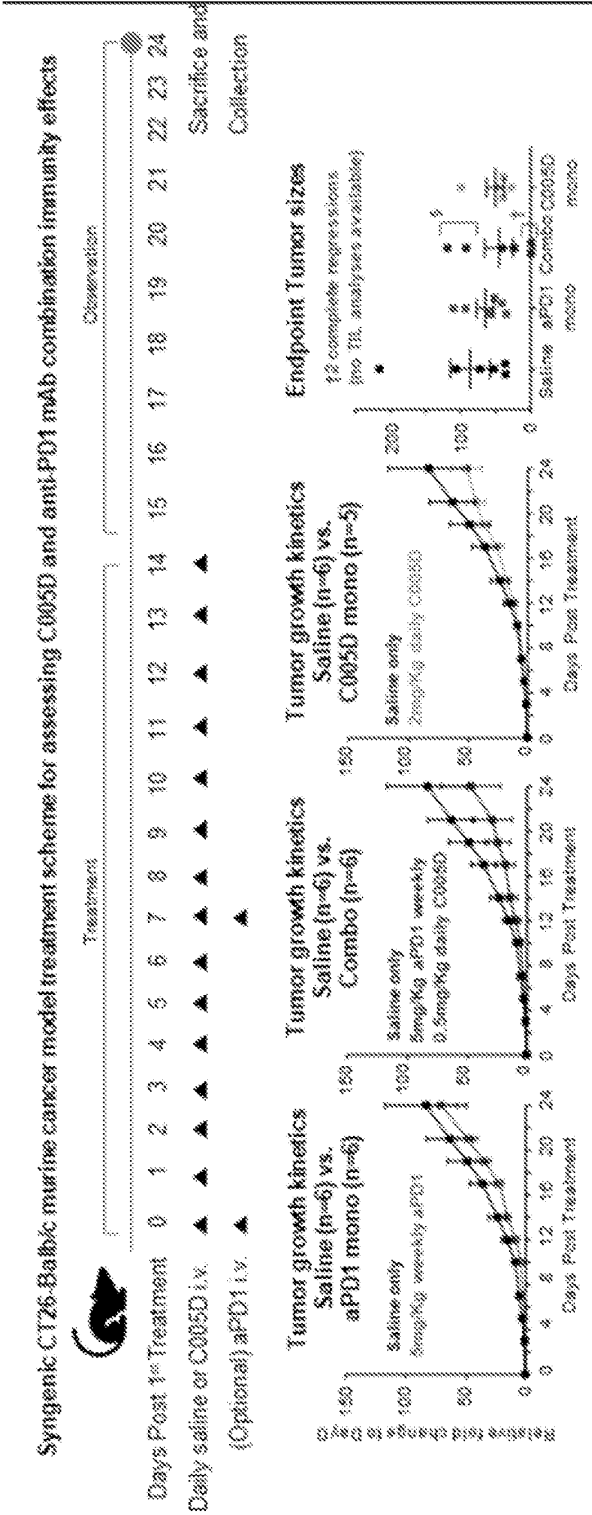


FIGURE 16

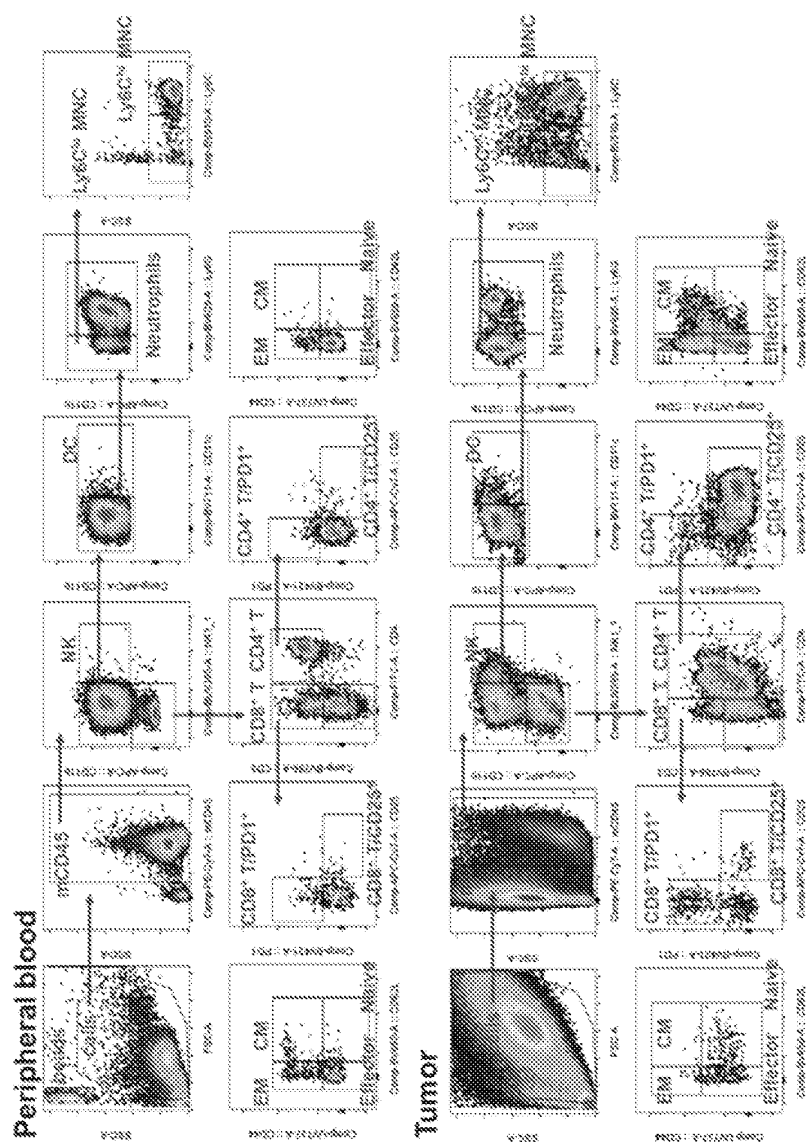


FIGURE 17A

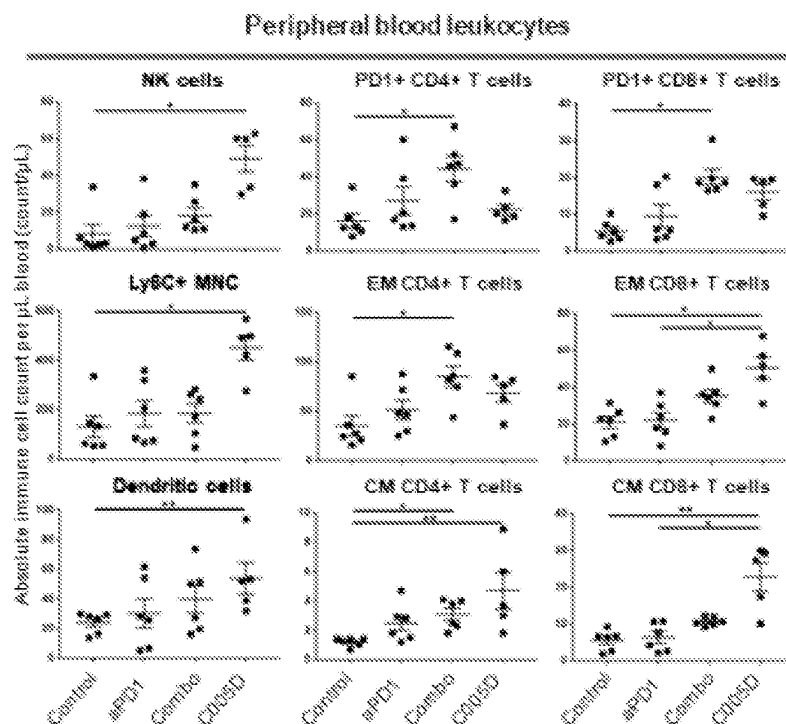


FIGURE 17B

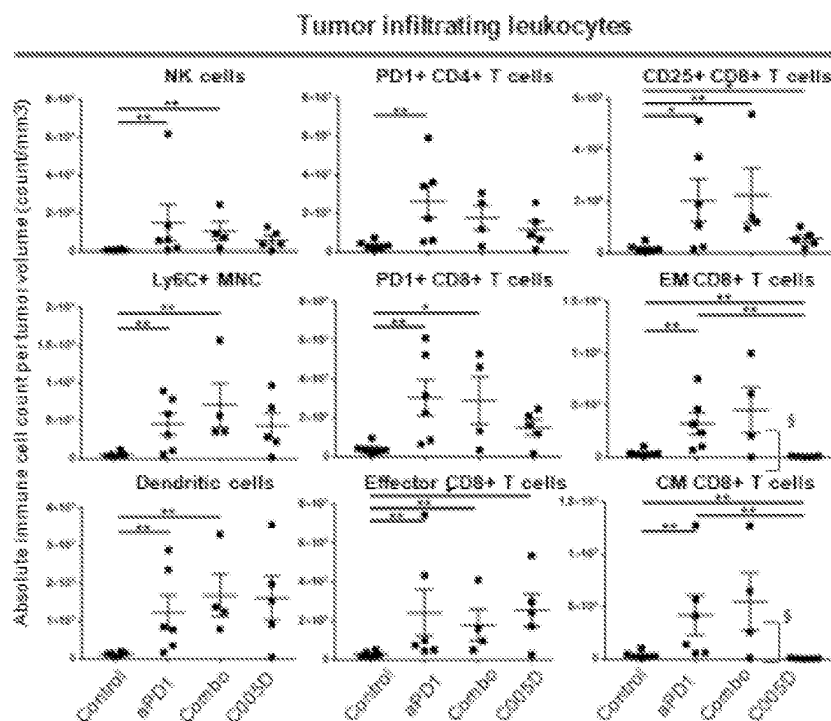


FIGURE 17C

Immune cell number per tumor volume (mm<sup>3</sup>)

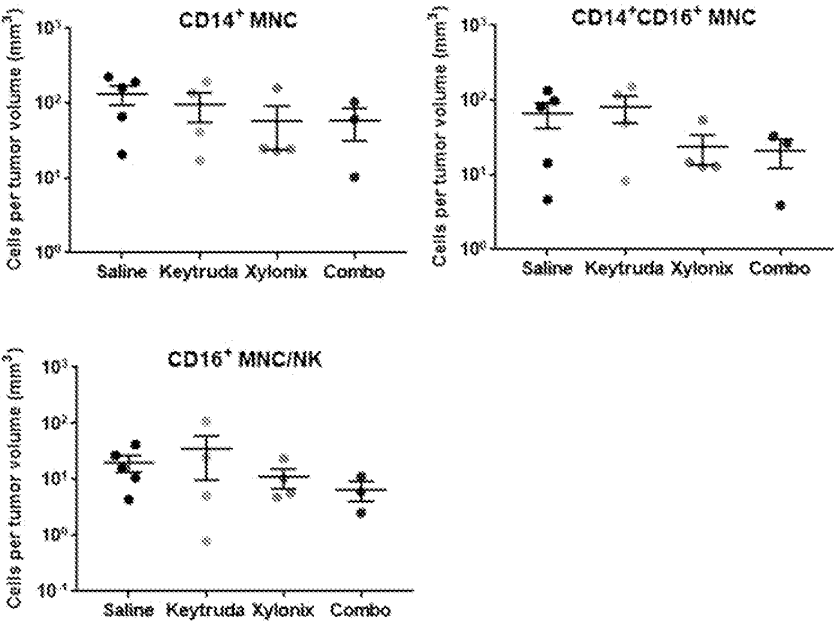


FIGURE 17D

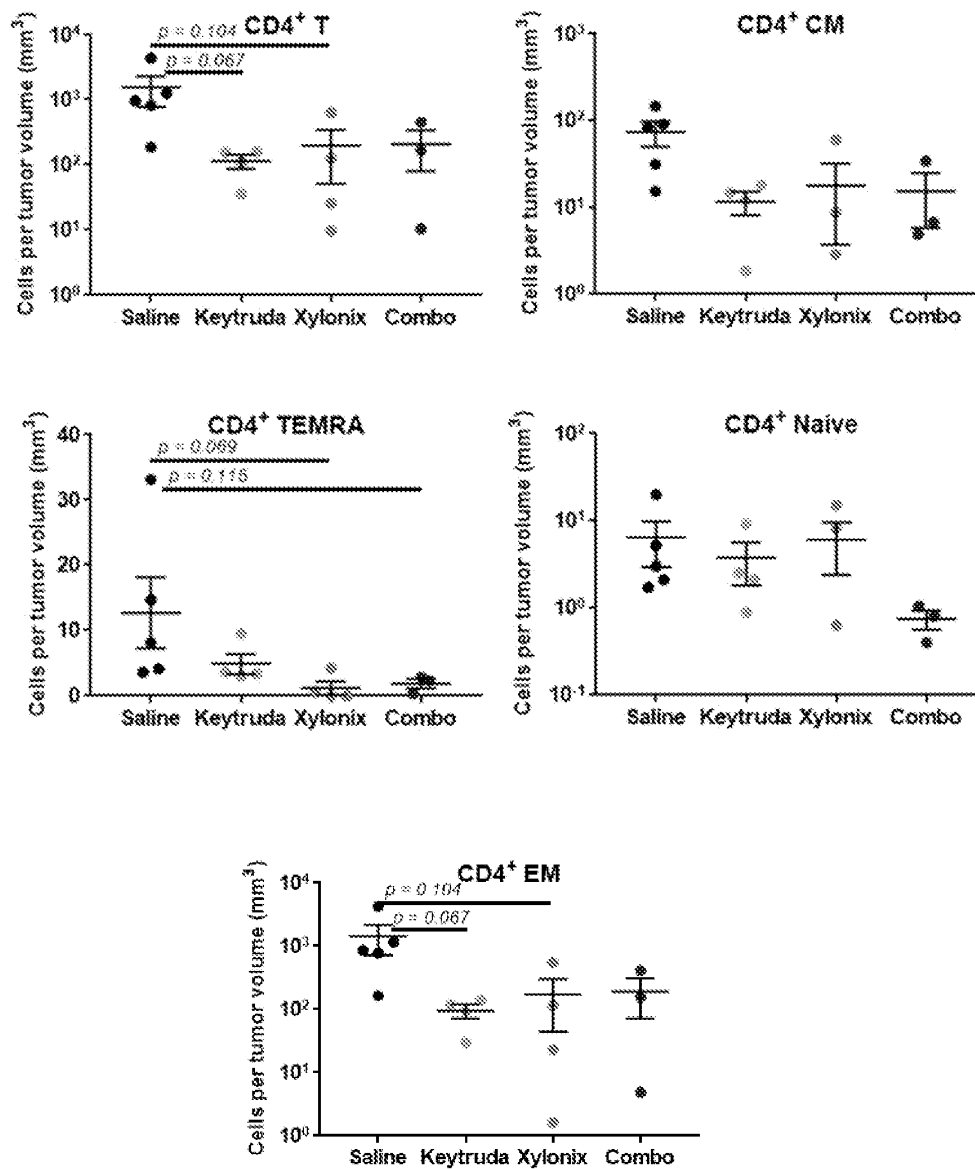
Immune cell number per tumor volume (mm<sup>3</sup>)

FIGURE 17E

Immune cell number per tumor volume (mm<sup>3</sup>)

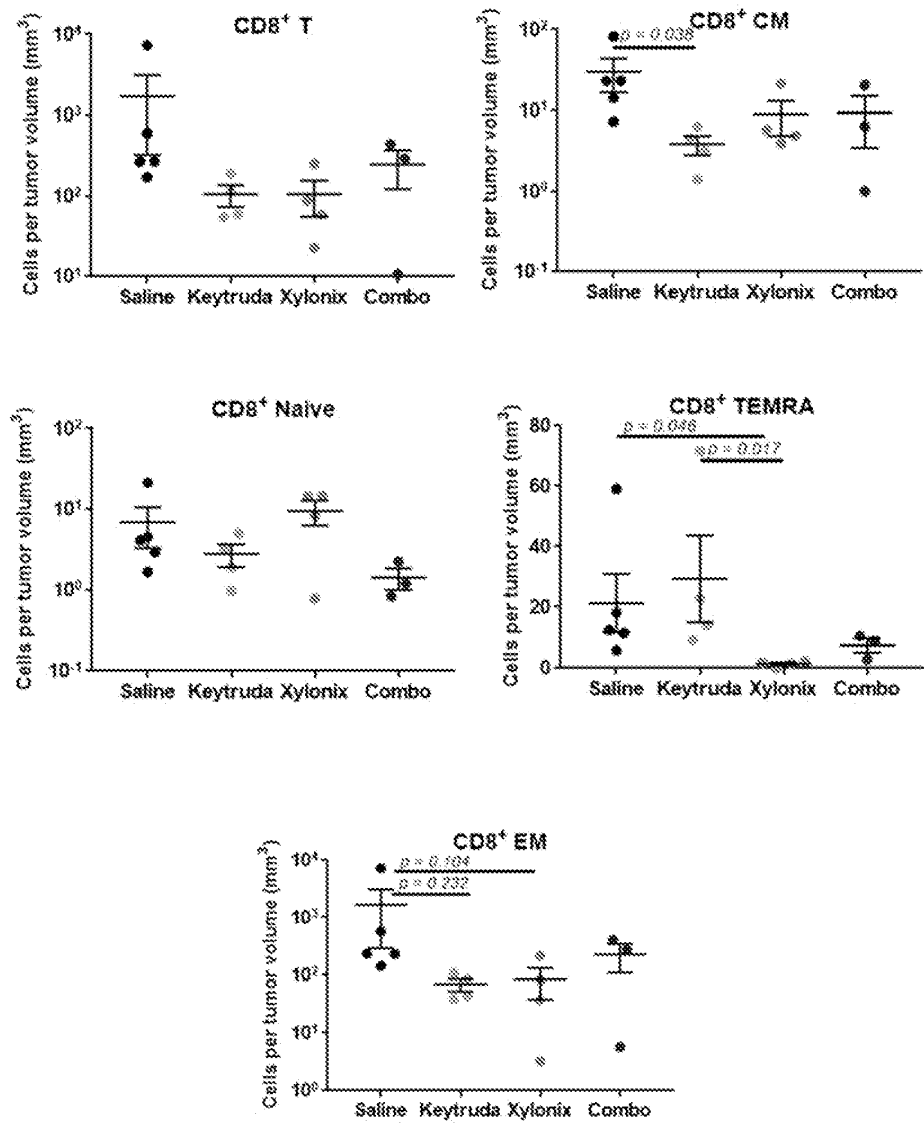


FIGURE 17F

Percent Immune cell / hCD45 per tumor volume (mm<sup>3</sup>)

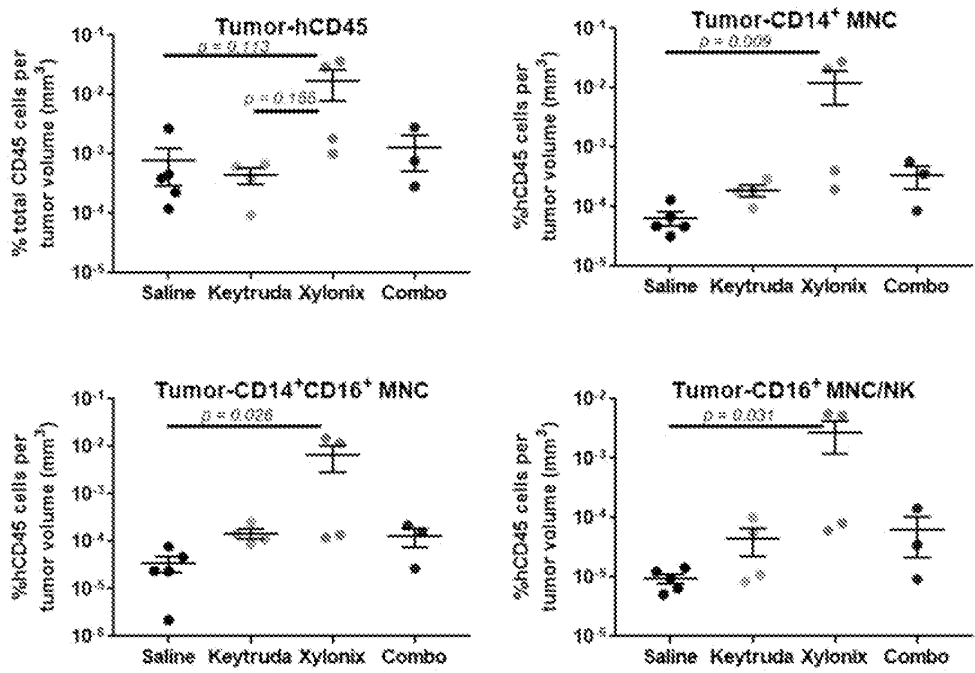


FIGURE 17G

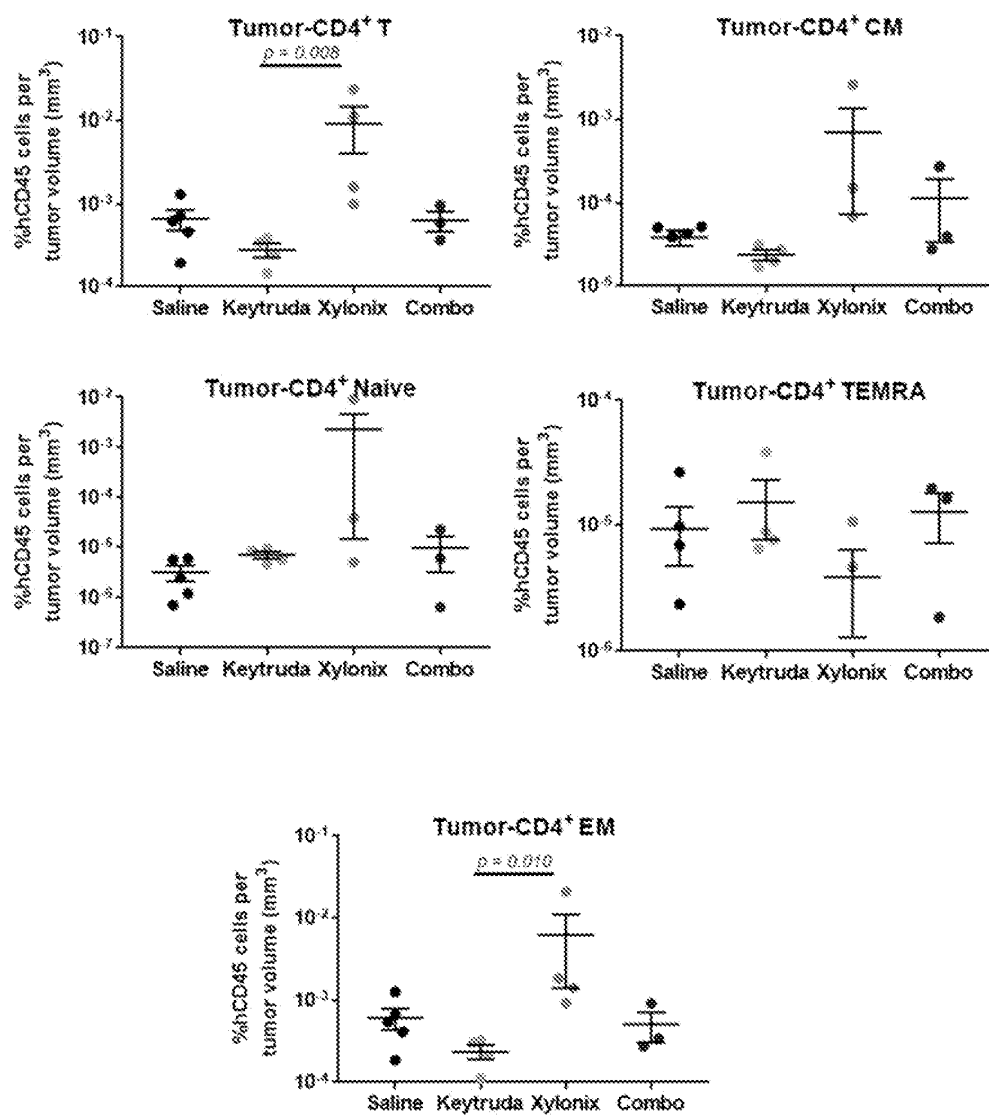
Percent Immune cell / hCD45 per tumor volume (mm<sup>3</sup>)

FIGURE 18

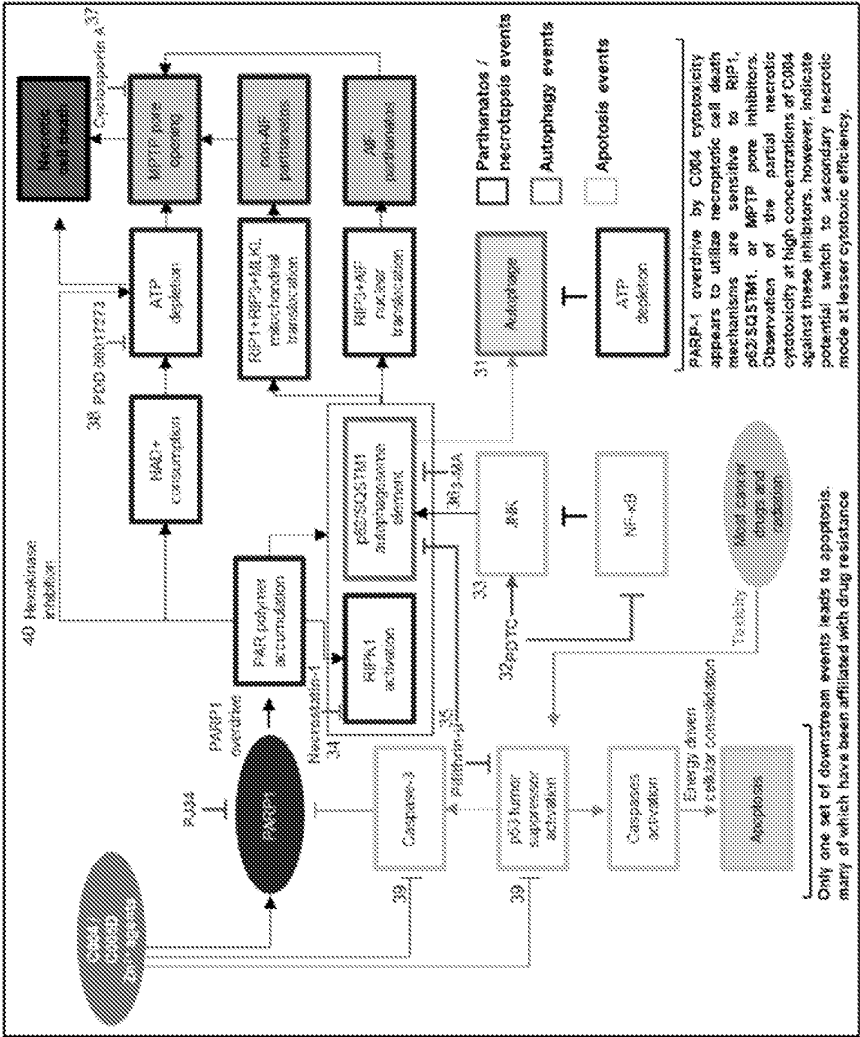


FIGURE 19

