Figure 1

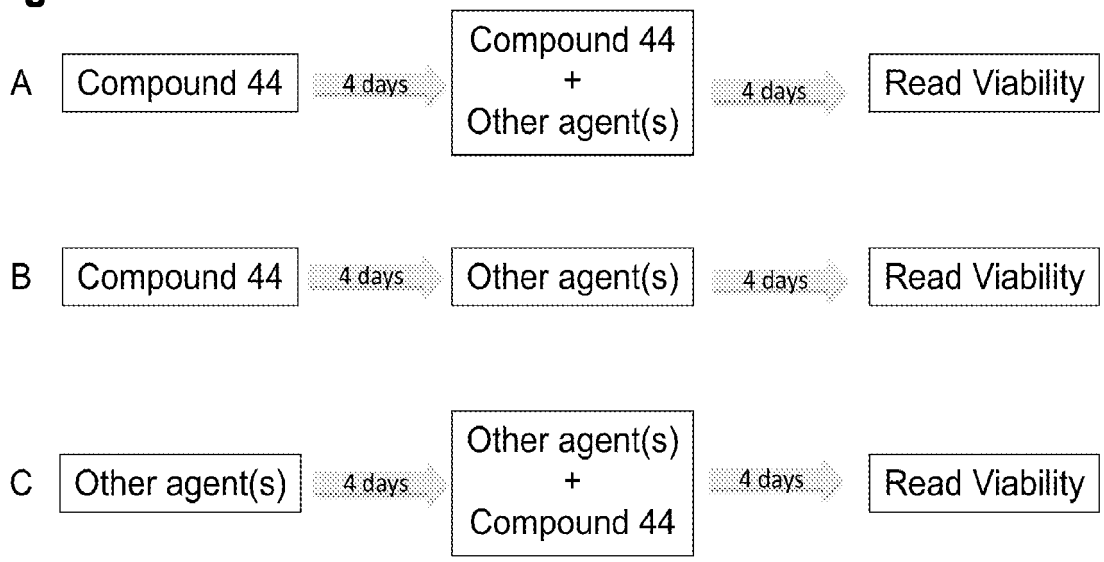
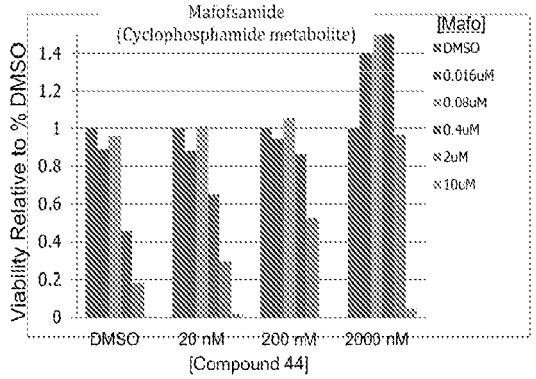
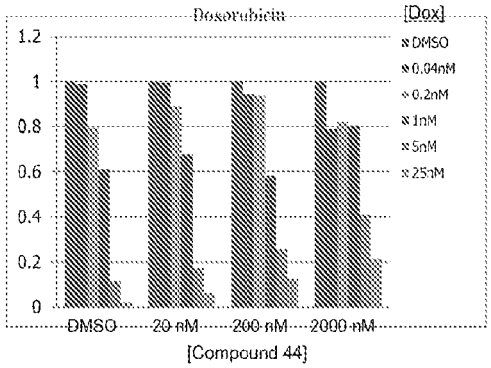

A
Compound 44
4 days
Compound 44
+
Other agent(s)
4 days
Read Viability
B
Compound 44
4 days
Other agent(s)
4 days
Read Viability
C
Other agent(s)
4 days
Other agent(s)
+
Compound 44
4 days
Read Viability

Figure 2

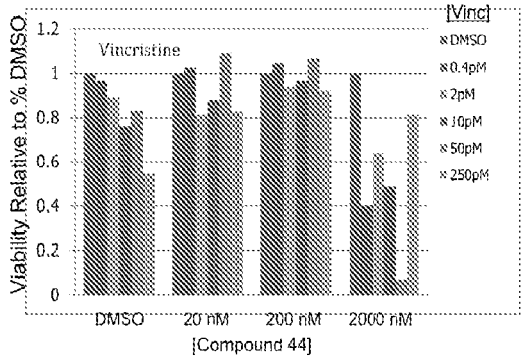
A



B



C



D

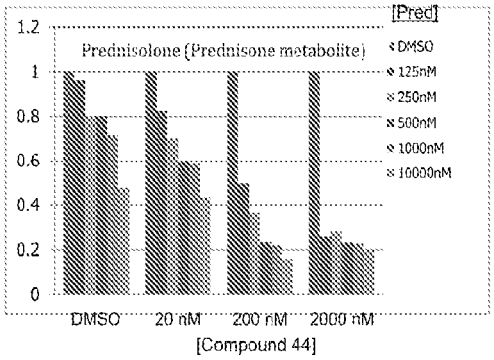
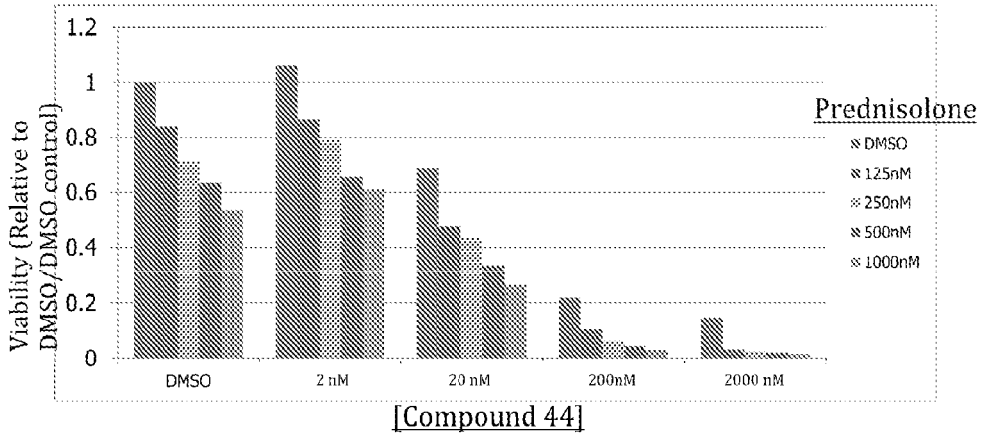


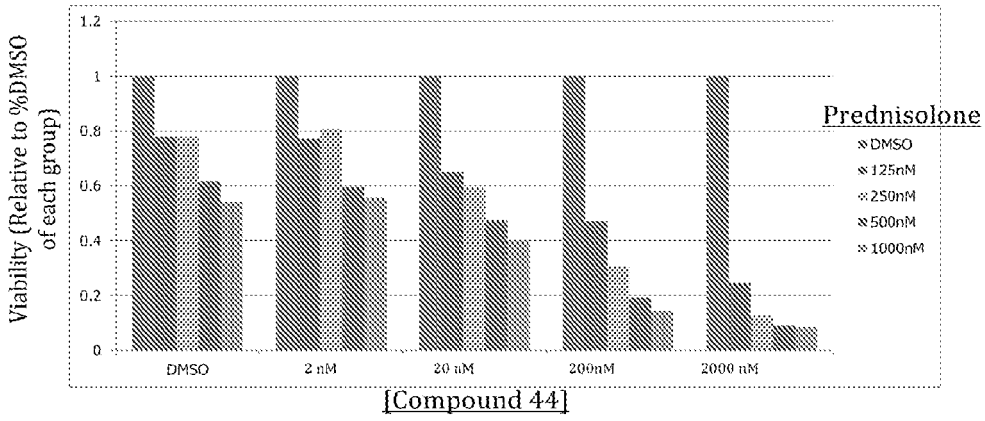
Figure 3

A



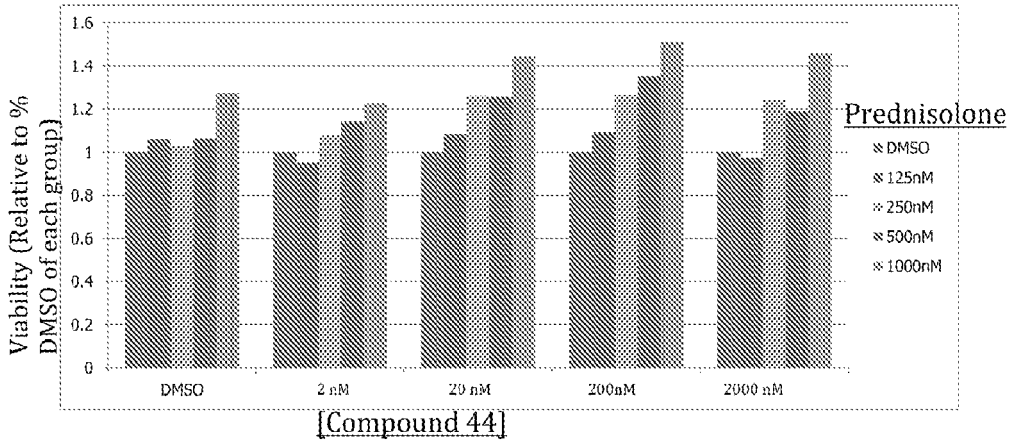
[Compound 44]

B



[Compound 44]

C

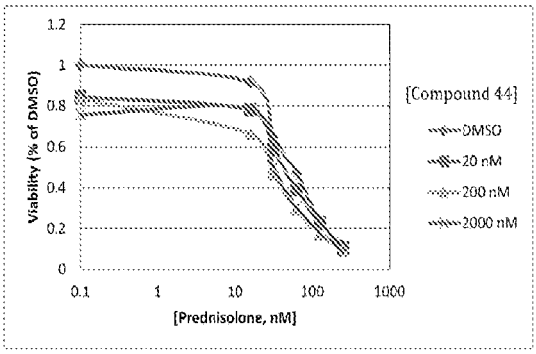


[Compound 44]

Figure 4

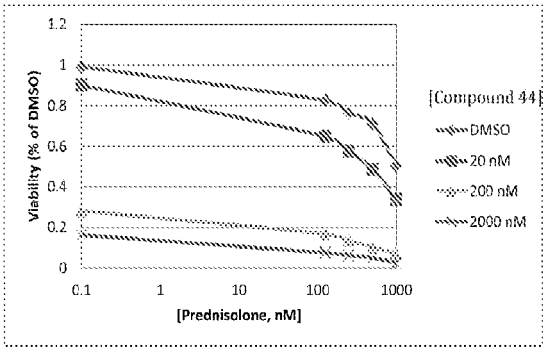
A

OCI-LY19 cells (EZH2 WT)
Resistant to EZH2i



B

WSU-DLCL2 cells (Y641F)
Sensitive to EZH2i



C

RL cells (Y641N)
Resistant to EZH2i

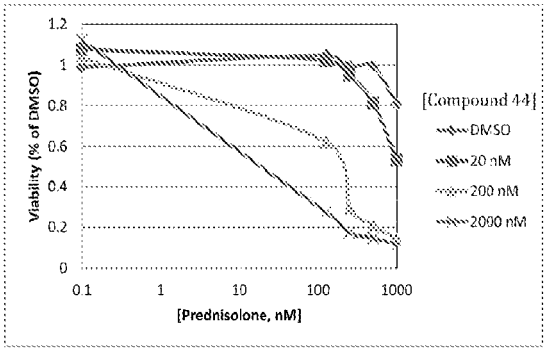
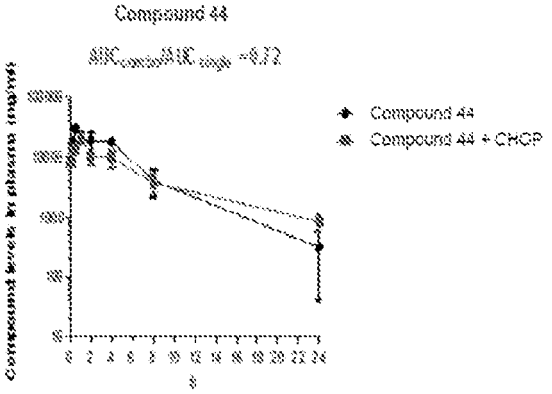
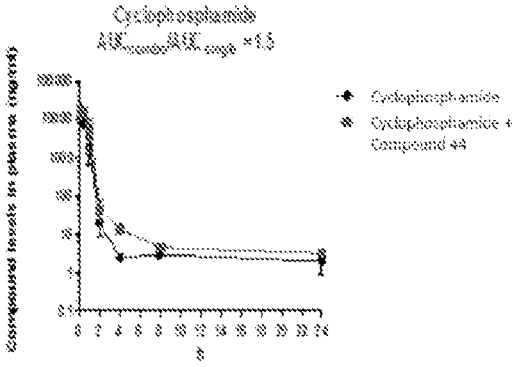
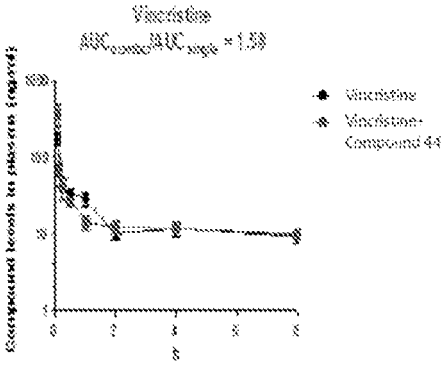


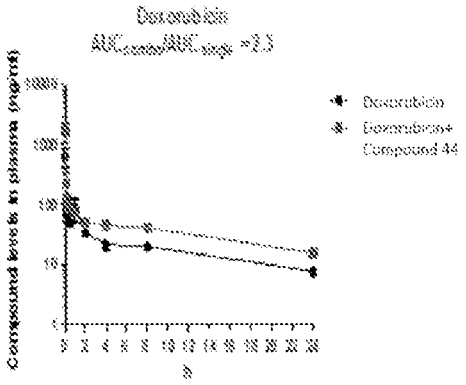
Figure 5

Cyclophosphamide	30 mg/kg i.p.
Vincristine	0.375 mg/kg i.v.
Doxorubicin	2.475 mg/kg i.v.
Prednisolone	0.15 mg/kg p.o.
Compound 44	225 mg/kg p.o.









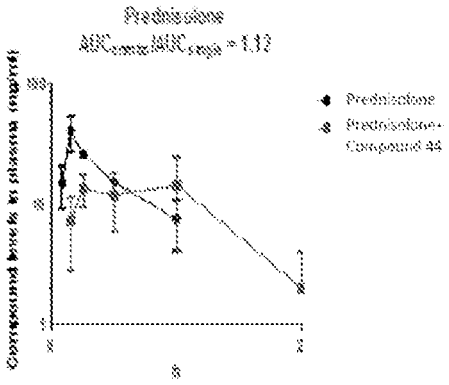


Figure 6

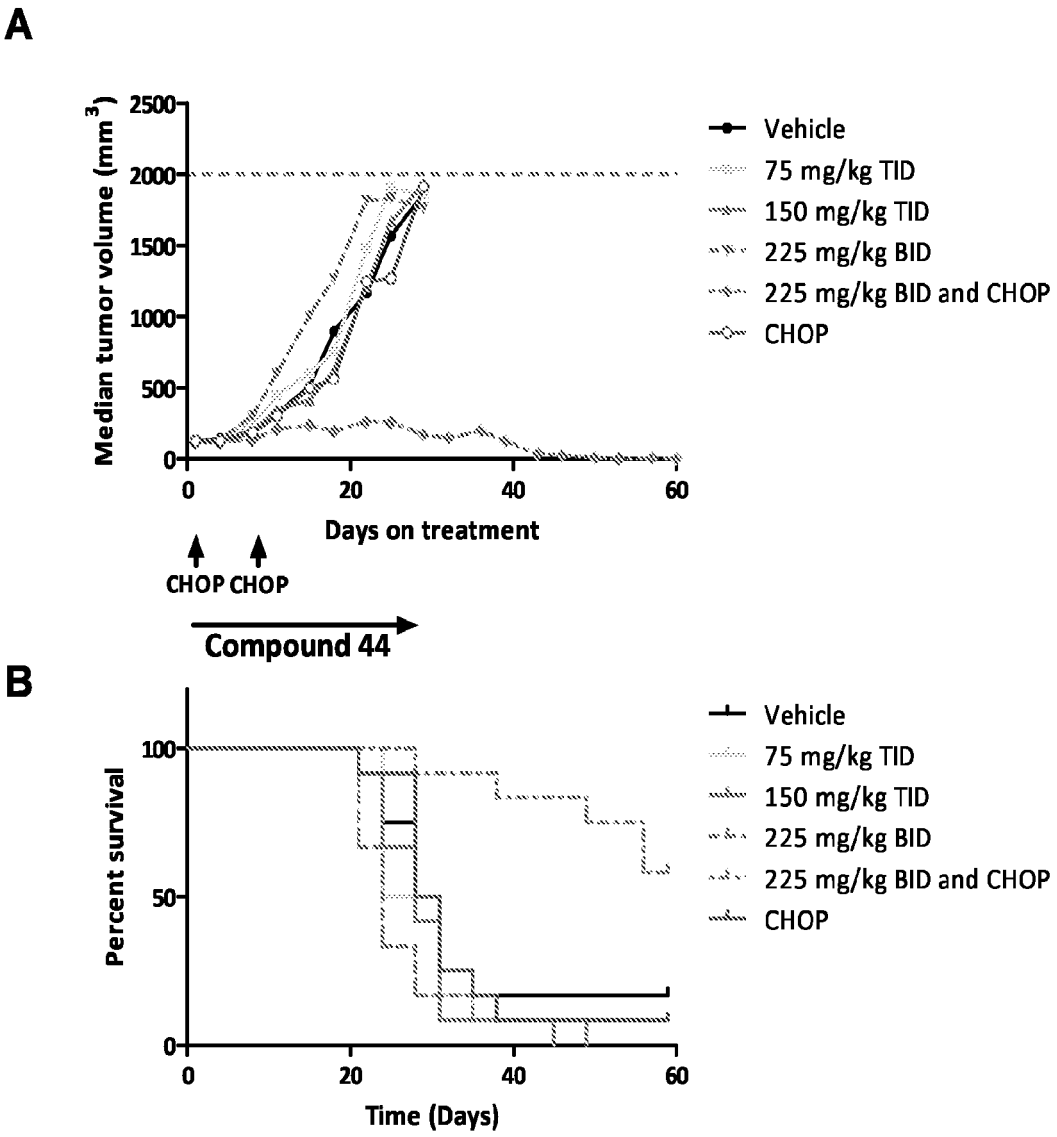

A
Median tumor volume (mm3)
2500
2000
1500
1000
500
0
0
20
40
60
Days on treatment
CHOP CHOP
Compound 44
Vehicle
75 mg/kg TID
150 mg/kg TID
225 mg/kg BID
225 mg/kg BID and CHOP
CHOP
B
Percent survival
100
50
0
0
20
40
60
Time (Days)
Vehicle
75 mg/kg TID
150 mg/kg TID
225 mg/kg BID
225 mg/kg BID and CHOP
CHOP

Figure 7

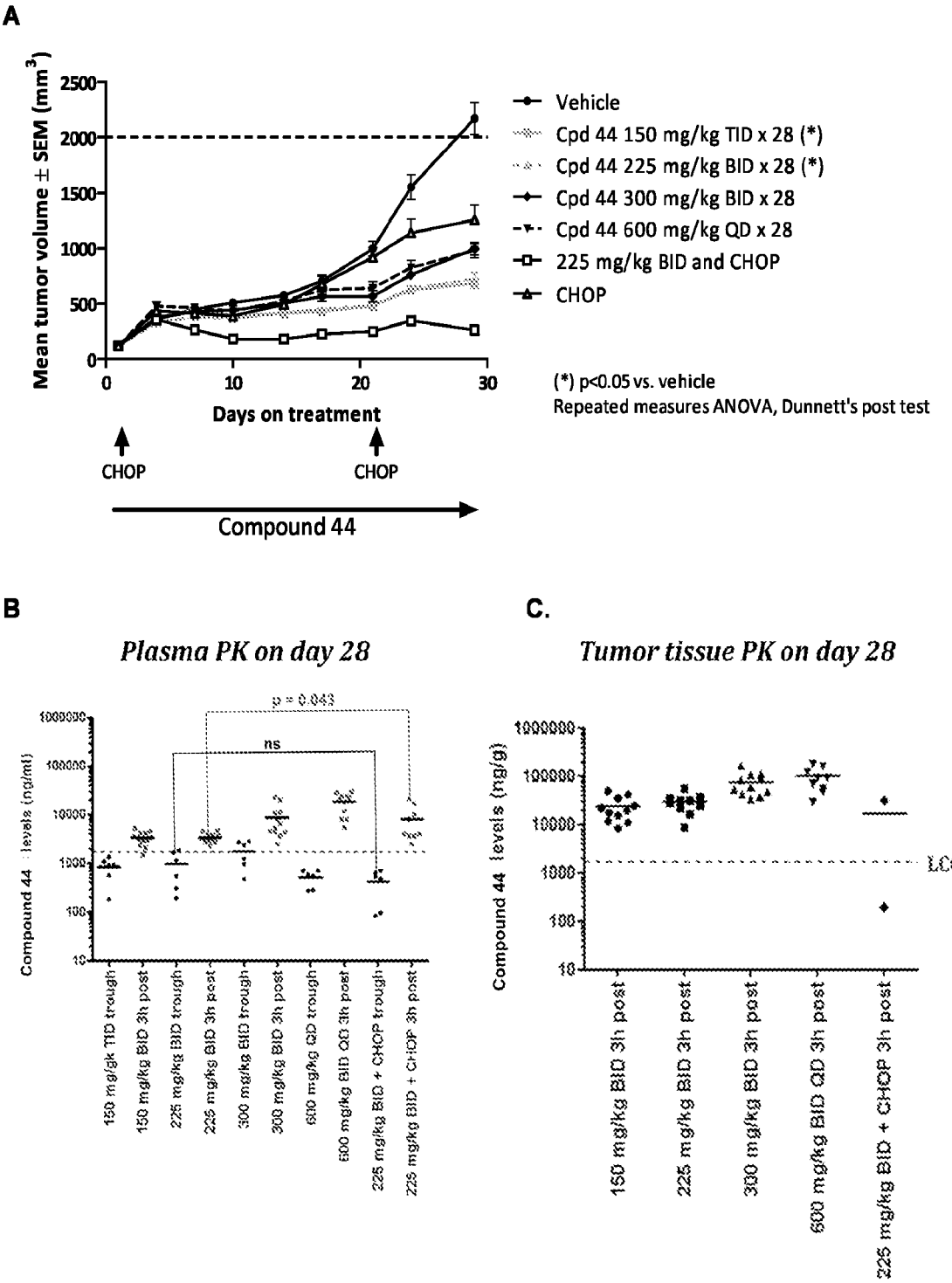
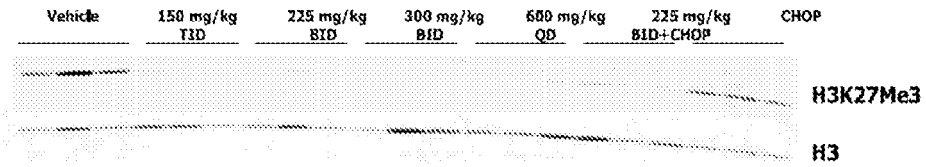

A
Mean tumor volume ± SEM (mm3)
2500
2000
1500
1000
500
0
0
10
20
30
Days on treatment
CHOP
CHOP
Compound 44
Vehicle
Cpd 44 150 mg/kg TID x 28 (*)
Cpd 44 225 mg/kg BID x 28 (*)
Cpd 44 300 mg/kg BID x 28
Cpd 44 600 mg/kg QD x 28
225 mg/kg BID and CHOP
CHOP
(*) p<0.05 vs. vehicle
Repeated measures ANOVA, Dunnett's post test
B
Plasma PK on day 28
p = 0.043
ns
Compound 44 levels (ng/ml)
150 mg/gk TID trough
150 mg/kg BID 3h post
225 mg/kg BID trough
225 mg/kg BID 3h post
300 mg/kg BID trough
300 mg/kg BID 3h post
600 mg/kg QD trough
600 mg/kg BID QD 3h post
225 mg/kg BID + CHOP trough
225 mg/kg BID + CHOP 3h post
C.
Tumor tissue PK on day 28
Compound 44 levels (ng/g)
LOQ
150 mg/kg BID 3h post
225 mg/kg BID 3h post
300 mg/kg BID 3h post
600 mg/kg BID QD 3h post
225 mg/kg BID + CHOP 3h post

Figure 8

A


Vehicle
150 mg/kg TID
225 mg/kg BID
300 mg/kg BID
600 mg/kg QD
225 mg/kg BID+CHOP
CHOP
H3K27Me3
H3

B

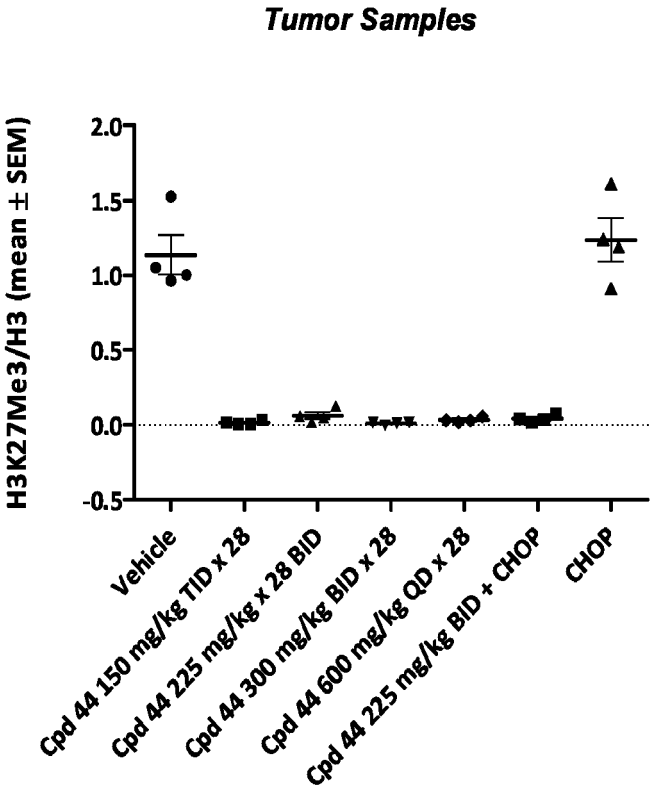
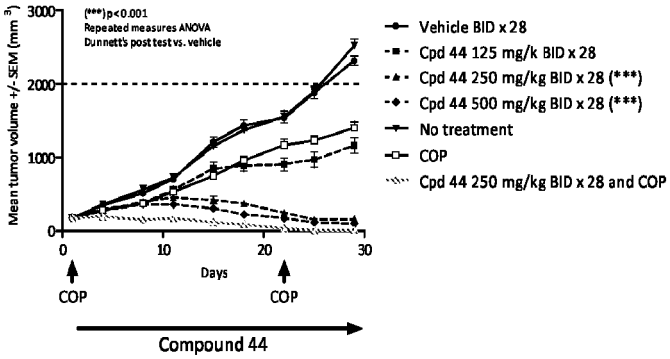
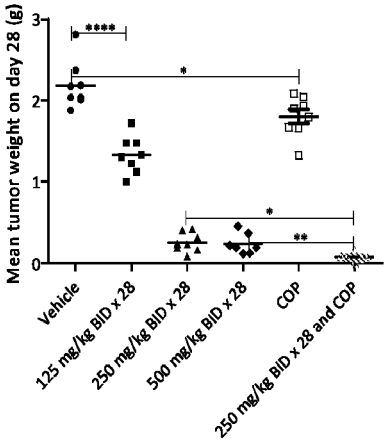

Tumor Samples
H3K27Me3/H3 (mean ± SEM)
2.0
1.5
1.0
0.5
0.0
-0.5
Vehicle
Cpd 44 150 mg/kg TID x 28
Cpd 44 225 mg/kg x 28 BID
Cpd 44 300 mg/kg BID x 28
Cpd 44 600 mg/kg QD x 28
Cpd 44 225 mg/kg BID + CHOP
CHOP

Figure 9

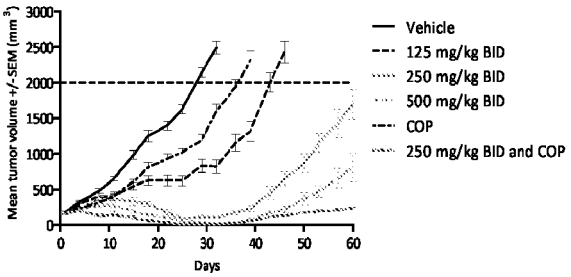
A



B



C



D

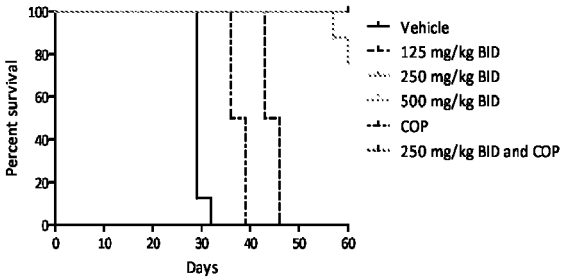
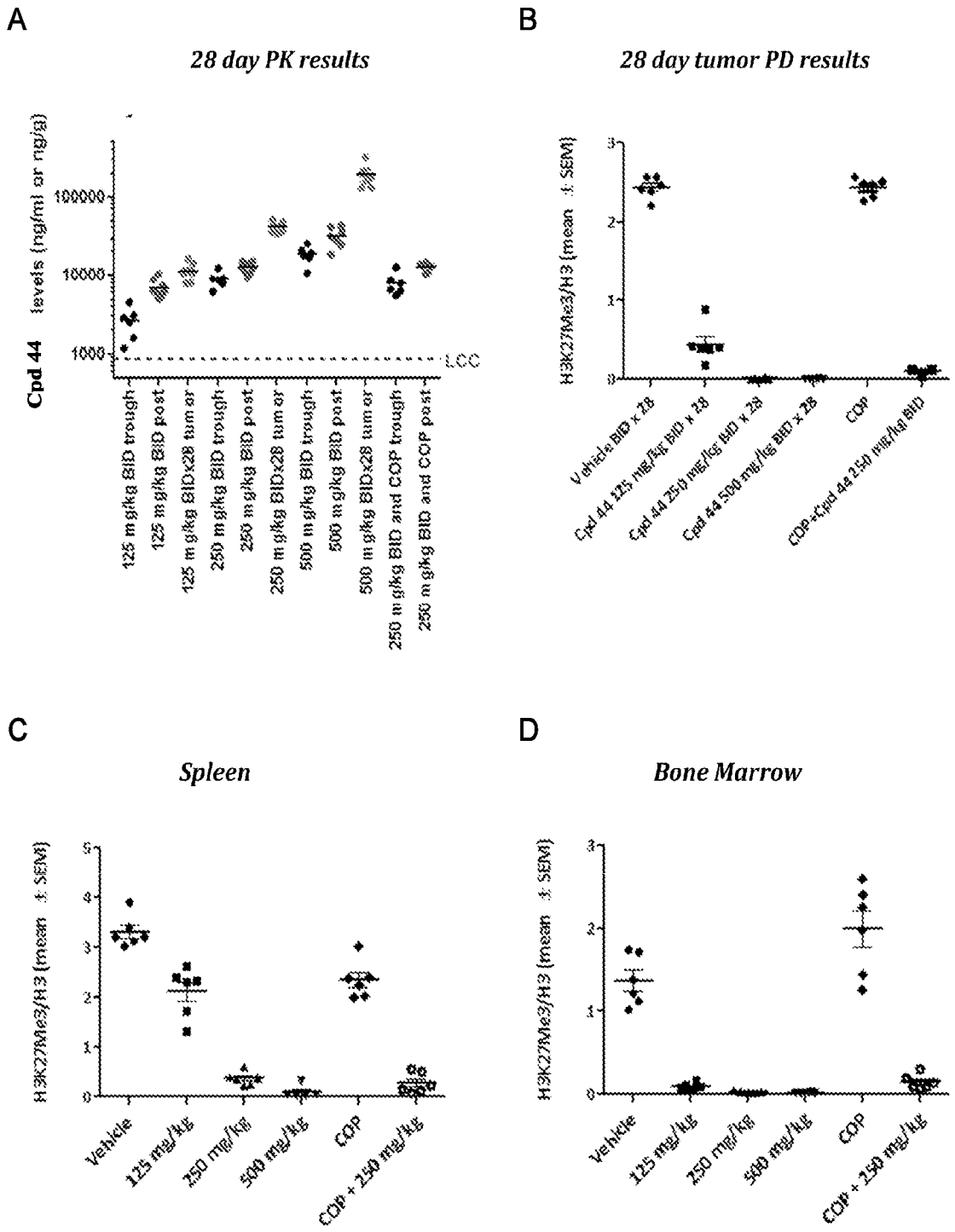


Figure 10


A
28 day PK results
Cpd 44 levels (ng/ml or ng/g)
100000
10000
1000
LLOQ
125 mg/kg BID trough
125 mg/kg BID post
125 mg/kg BIDx28 tumor
250 mg/kg BID trough
250 mg/kg BID post
250 mg/kg BIDx28 tumor
500 mg/kg BID trough
500 mg/kg BID post
500 mg/kg BIDx28 tumor
250 mg/kg BID and COP trough
250 mg/kg BID and COP post
B
28 day tumor PD results
H3K27Me3/H3 (mean ± SEM)
Vehicle BID x 28
Cpd 44 125 mg/kg BID x 28
Cpd 44 250 mg/kg BID x 28
Cpd 44 500 mg/kg BID x 28
COP
COP+Cpd 44 250 mg/kg BID
C
Spleen
H3K27Me3/H3 (mean ± SEM)
Vehicle
125 mg/kg
250 mg/kg
500 mg/kg
COP
COP + 250 mg/kg
D
Bone Marrow
H3K27Me3/H3 (mean ± SEM)
Vehicle
125 mg/kg
250 mg/kg
500 mg/kg
COP
COP + 250 mg/kg