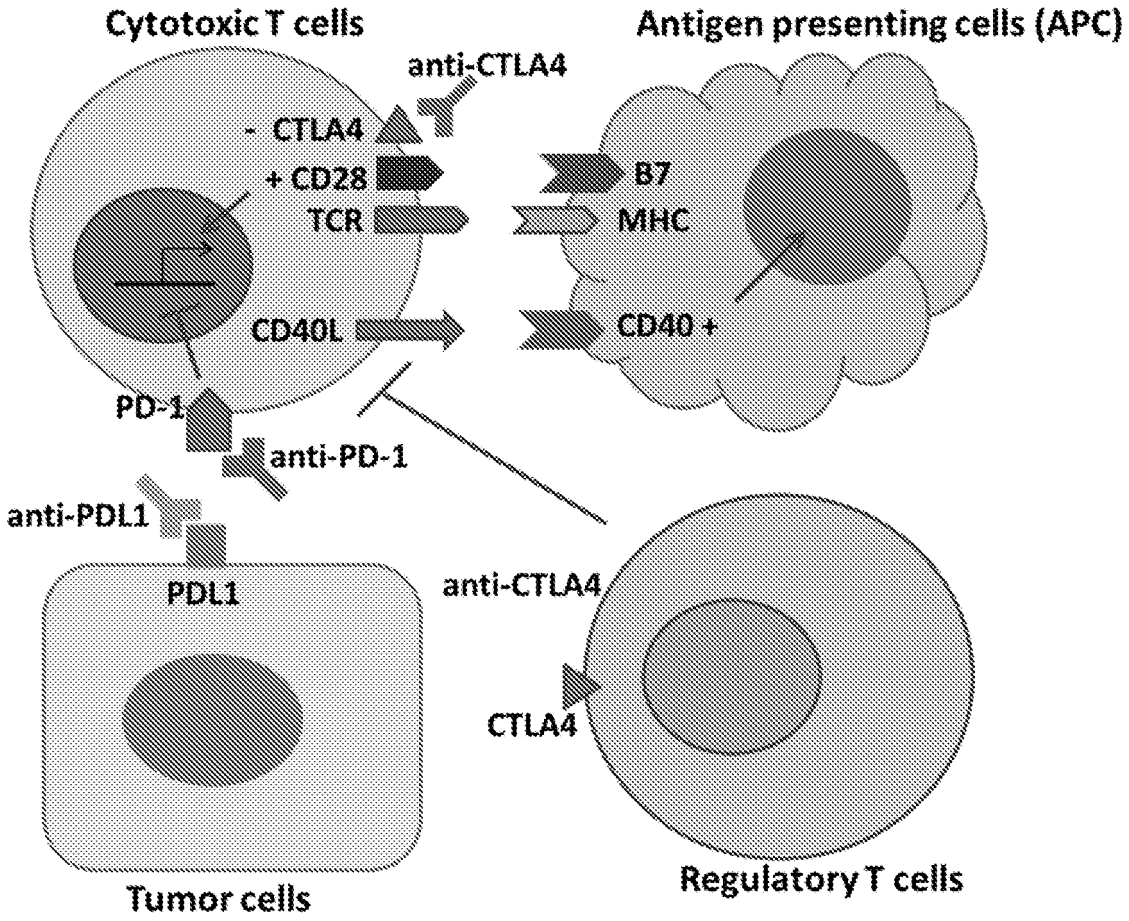

Cytotoxic T cells
Antigen presenting cells (APC)
anti-CTLA4
- CTLA4
+ CD28
TCR
B7
MHC
CD40L
CD40 +
PD-1
anti-PD-1
anti-PDL1
PDL1
anti-CTLA4
CTLA4
Tumor cells
Regulatory T cells

FIG. 1

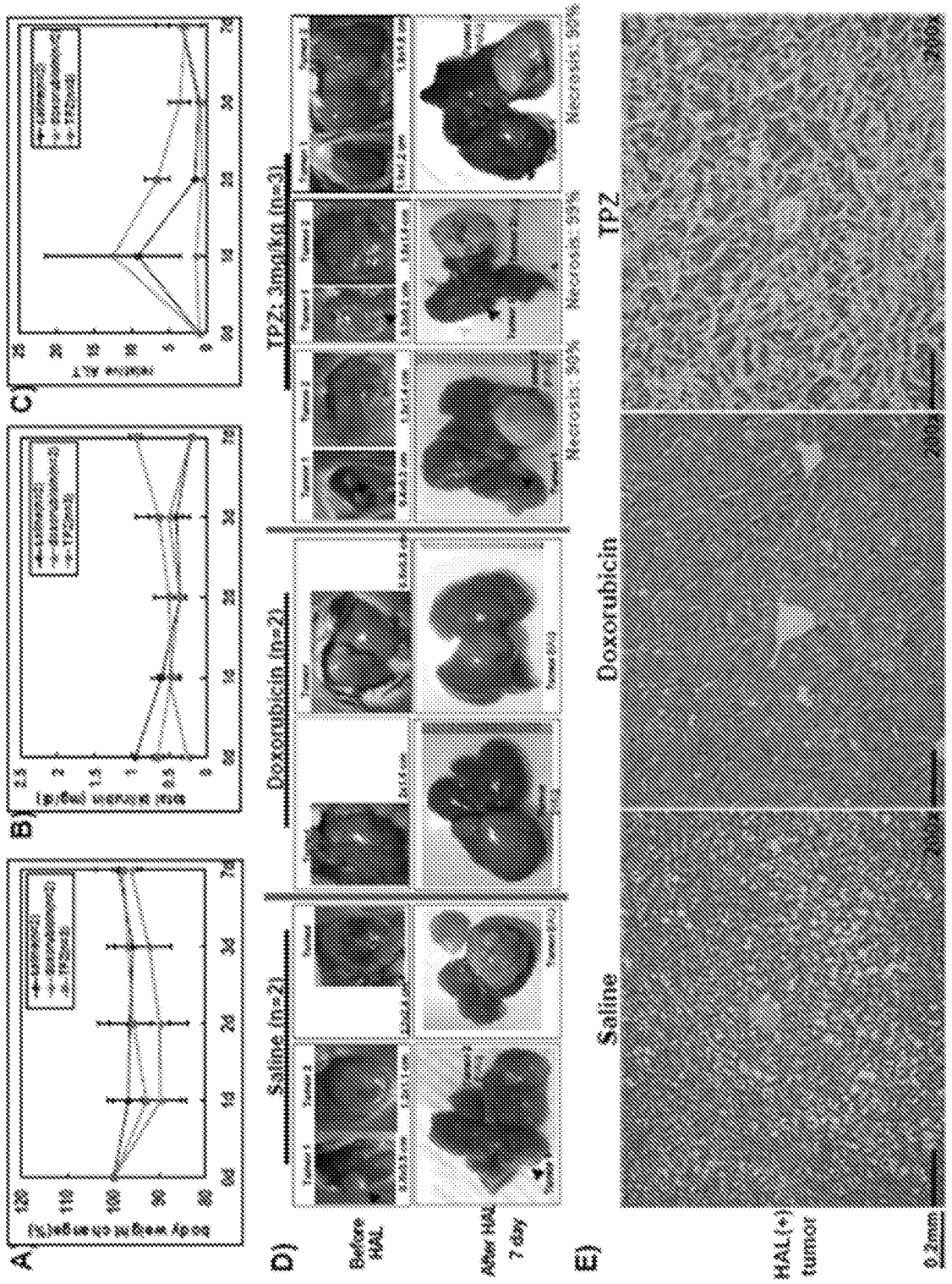

A)
B)
C)
D)
Saline (n=2)
Doxorubicin (n=2)
TPZ: 3mg/kg (n=3)
Before HAL
After HAL 7 day
E)
Saline
Doxorubicin
TPZ
HAL(+) tumor
0.2cm
200μ

FIG. 2

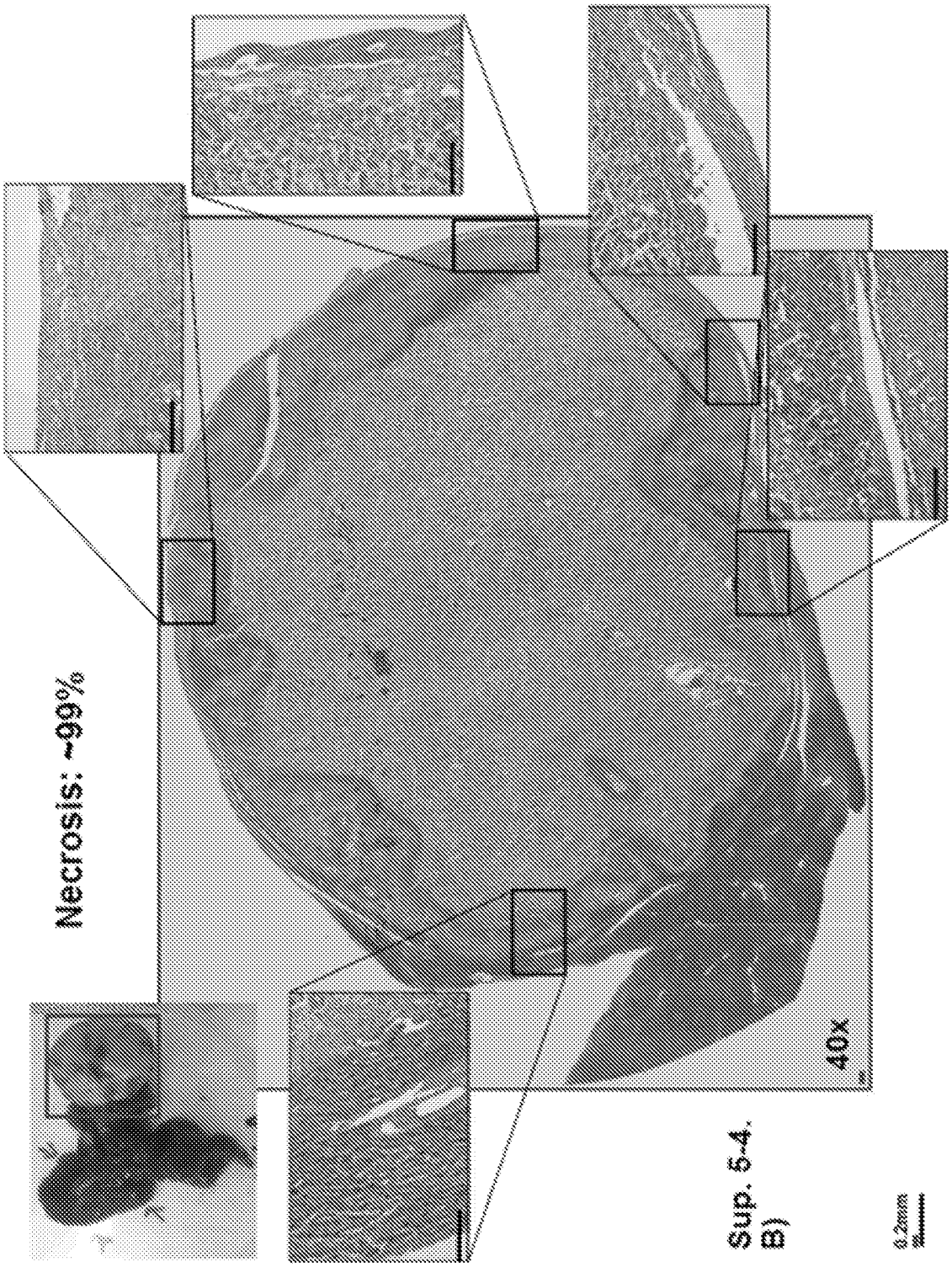


FIG. 3

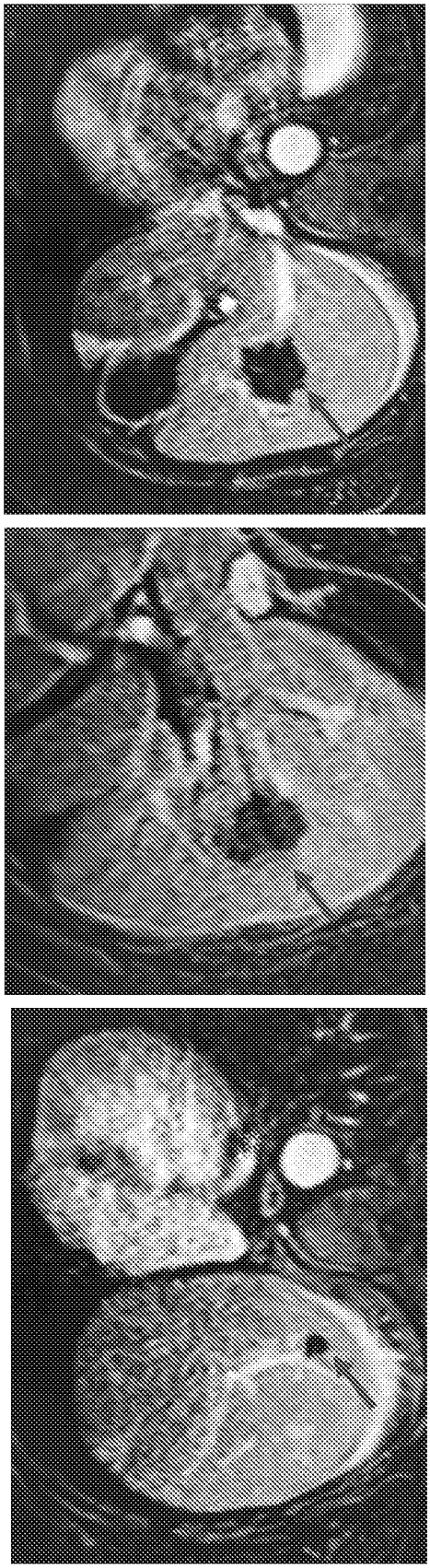


FIG. 4

N
VT
VT
N
control treated with normal saline
N
VT
IN
N
after treatment with tirapazamine and combretastatin A4
N
IN
N
IN
after treatment with tirapazamine and DMXAA
VT: viable tumor
N: necrosis
IN: inflammatory infiltrates

FIG. 5

Group	N	Treatment	Dose (mg/kg)	Dosing Route	Schedule
1	6	Vehicle Control	0	*i.p.*	Q2d, Day 4 – Day 14
2	6	Anti-m-PD 1	10 mg/kg	*i.p.*	Q2d, Day 4 – Day 14
3	6	TPZ	30 mg/kg	*i.p.*	Day 0 and Day 2
4	6	DMXAA	10 mg/kg	*i.p.*	Day 0 and Day 2
5	6	Combretastatin A-4 P	10 mg/kg	*i.v.*	Day 0 and Day 2
6	6	TPZ	30 mg/kg	*i.p.*	Day 0 and Day 2
		Combretastatin A-4 P	10 mg/kg	*i.v.*	Day 0 and Day 2, 2 min after TPZ injection
7	6	TPZ	30 mg/kg	*i.p.*	Day 0 and Day 2
		DMXAA	10 mg/kg	*i.p.*	Day 0 and Day 2, 2 min after TPZ injection
8	6	TPZ	30 mg/kg	*i.p.*	Day 0 and Day 2
		Combretastatin A-4 P	10 mg/kg	*i.v.*	Day 0 and Day 2, 2 min after TPZ injection
		Anti-m-PD 1	10 mg/kg	*i.p.*	Q2d, Day 4 – Day 14
9	6	TPZ	30 mg/kg	*i.p.*	Day 0 and Day 2
		DMXAA	10 mg/kg	*i.p.*	Day 0 and Day 2, 2 min after TPZ injection
		Anti-m-PD 1	10 mg/kg	*i.p.*	Q2d, Day 4 – Day 14

FIG. 6

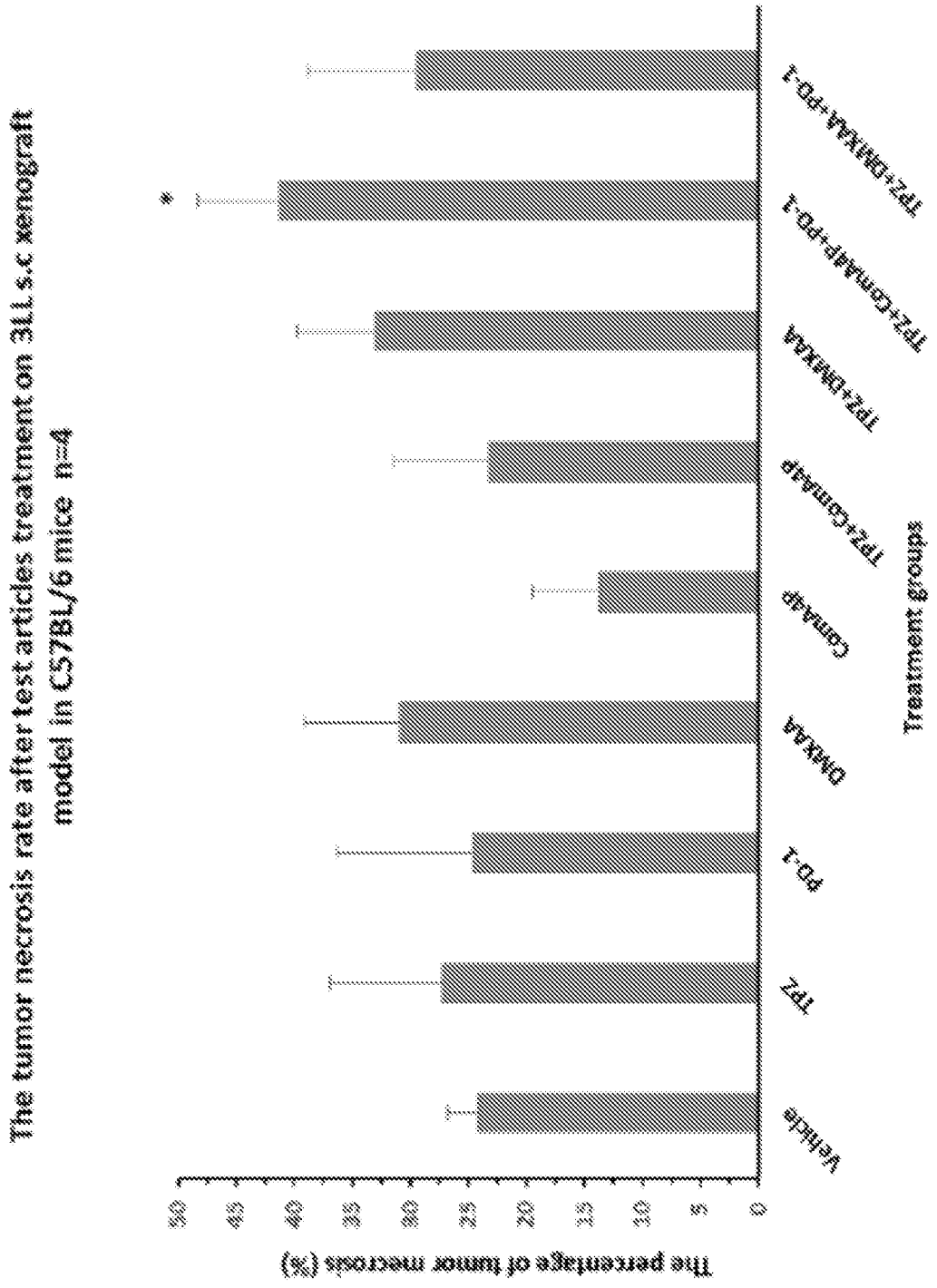

The tumor necrosis rate after test articles treatment on 3LL s.c xenograft model in C57BL/6 mice n=4
The percentage of tumor mecrosis (%)
0
5
10
15
20
25
30
35
40
45
50
*
Vehicle
TPZ
PD-1
DMXAA
ComA4P
TPZ+ComA4P
TPZ+DMXAA
TPZ+ComA4P+PD-1
TPZ+DMXAA+PD-1
Treatment groups

FIG. 7

Vehicle	24.22±2.59
TPZ	27.32±9.56
PD-1	24.68±11.72
DMXAA	31.01±8.17
ComA4P	13.73±5.79
TPZ+ComA4P	23.28±8.15
TPZ+DMXAA	33.14±6.59
TPZ+ComA4P+PD-1	41.36±6.96*
TPZ+DMXAA+PD-1	29.61±9.29

FIG. 8