FIGURE 1

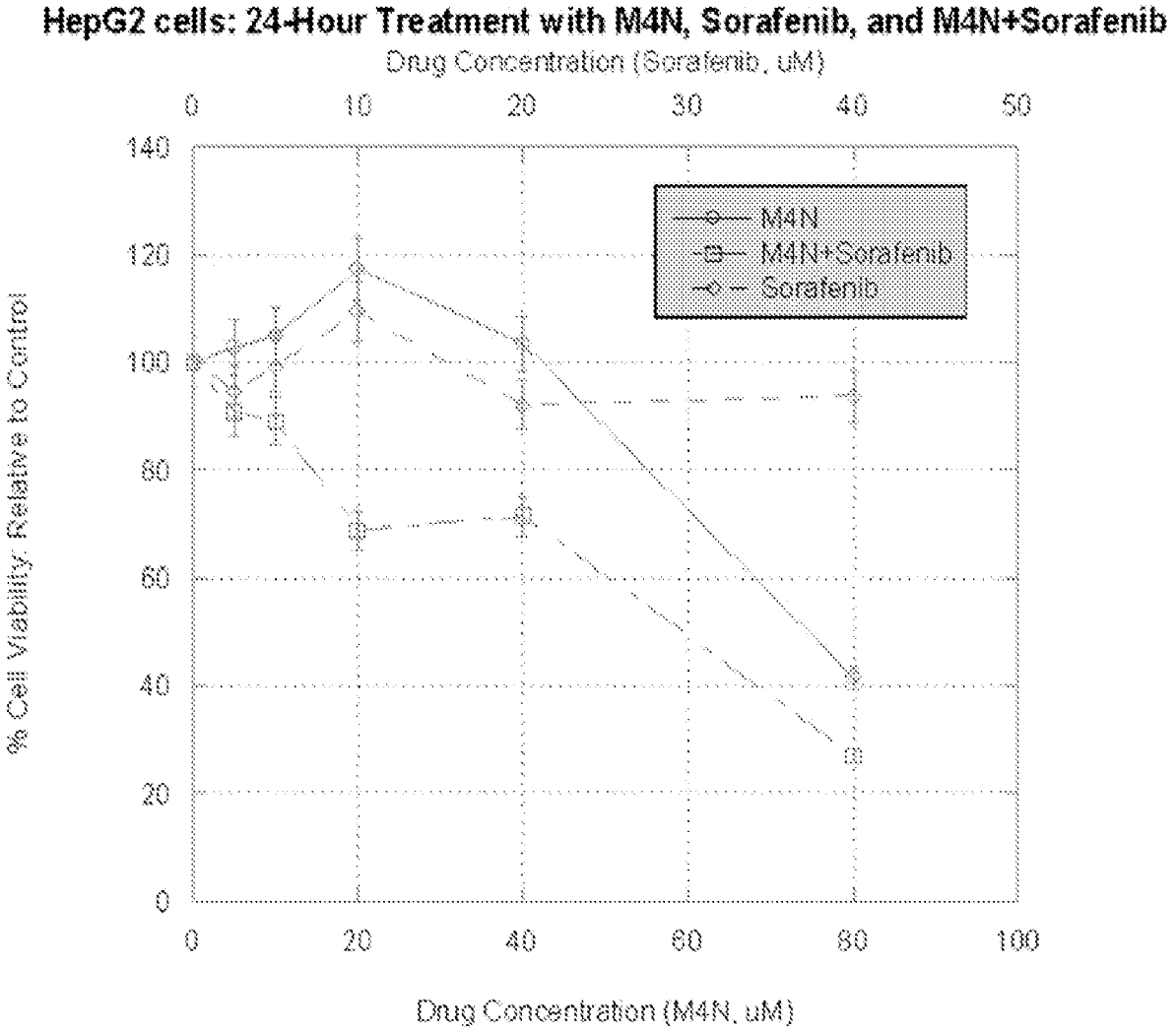

HepG2 cells: 24-Hour Treatment with M4N, Sorafenib, and M4N+Sorafenib
Drug Concentration (Sorafenib, uM)
0
10
20
30
40
50
140
120
100
80
60
40
20
0
% Cell Viability: Relative to Control
M4N
M4N+Sorafenib
Sorafenib
0
20
40
60
80
100
Drug Concentration (M4N, uM)

FIGURE 2

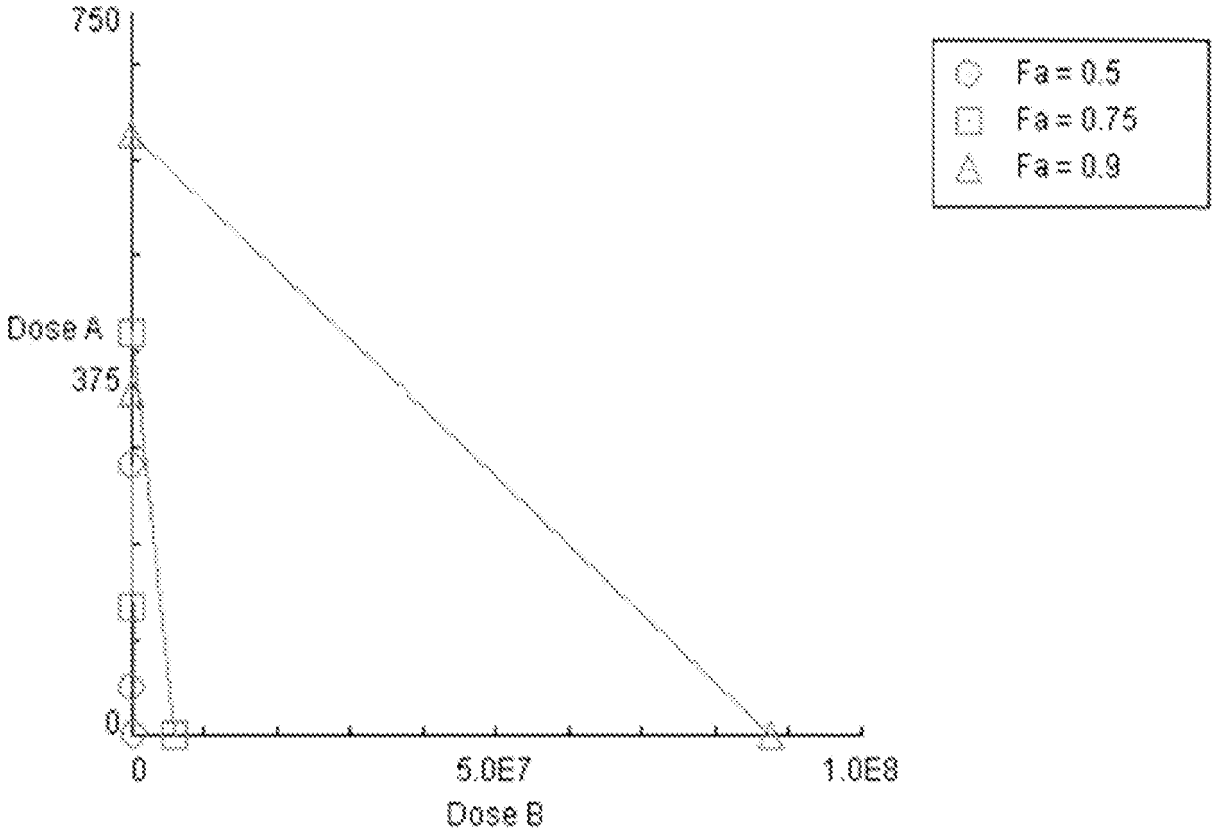


FIGURE 3

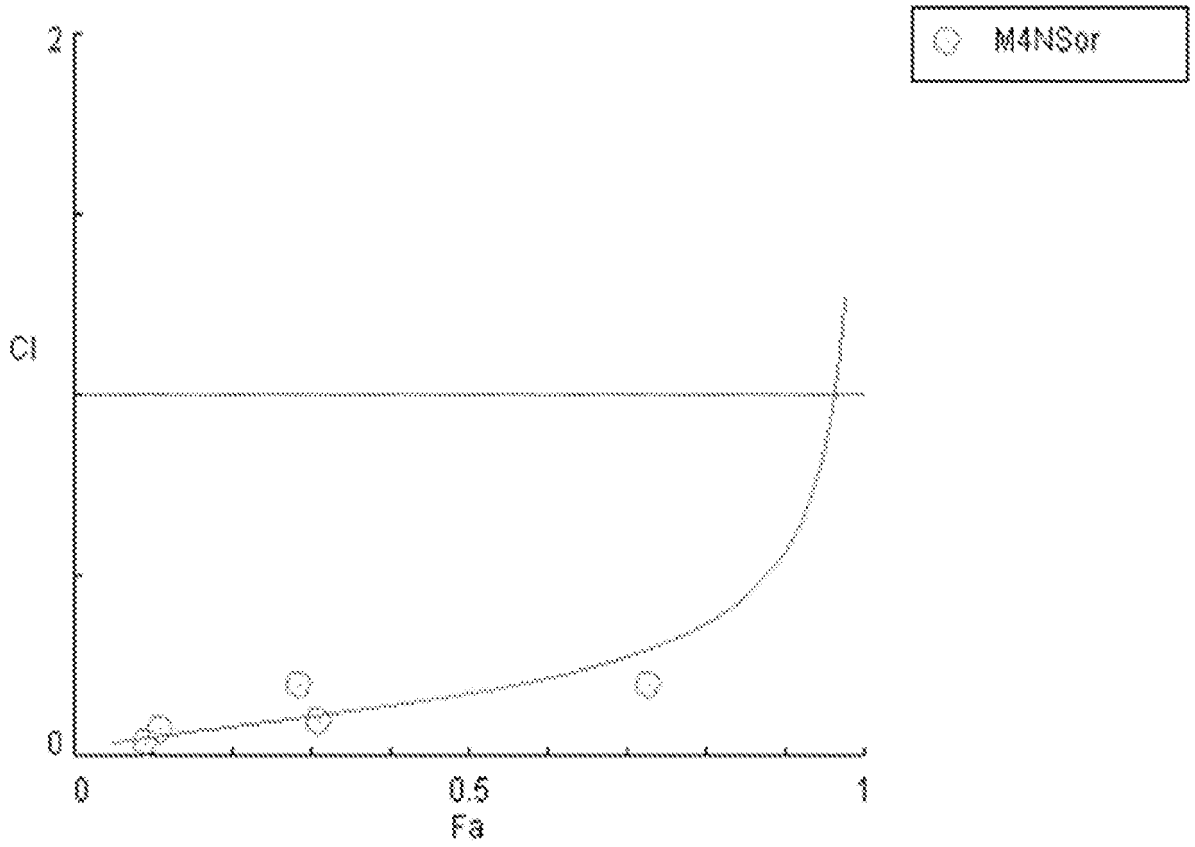


FIGURE 4

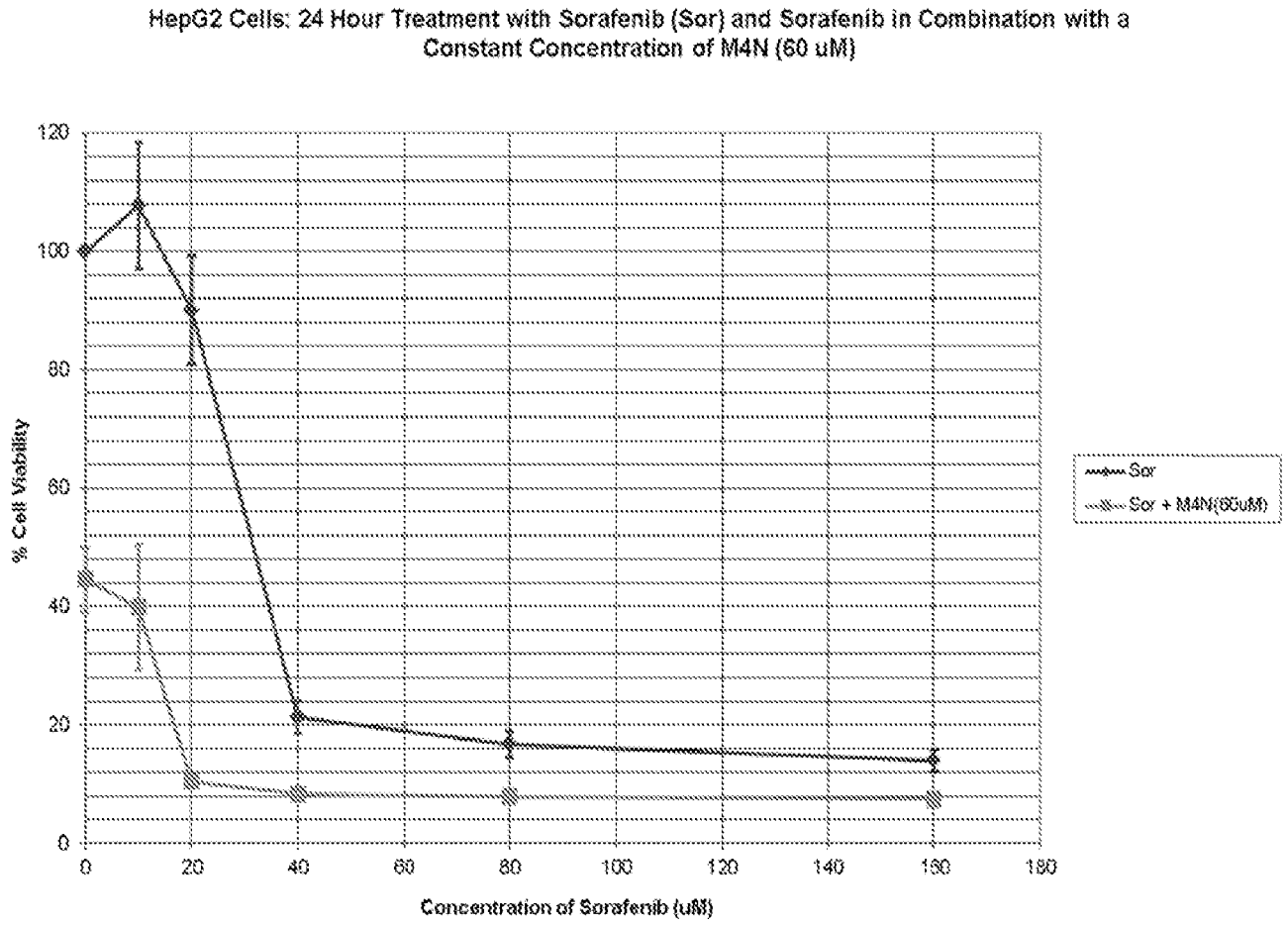

HepG2 Cells: 24 Hour Treatment with Sorafenib (Sor) and Sorafenib in Combination with a Constant Concentration of M4N (60 uM)
% Cell Viability
Concentration of Sorafenib (uM)
Sor
Sor + M4N(60uM)
0
20
40
60
80
100
120
140
160
180

FIGURE 5

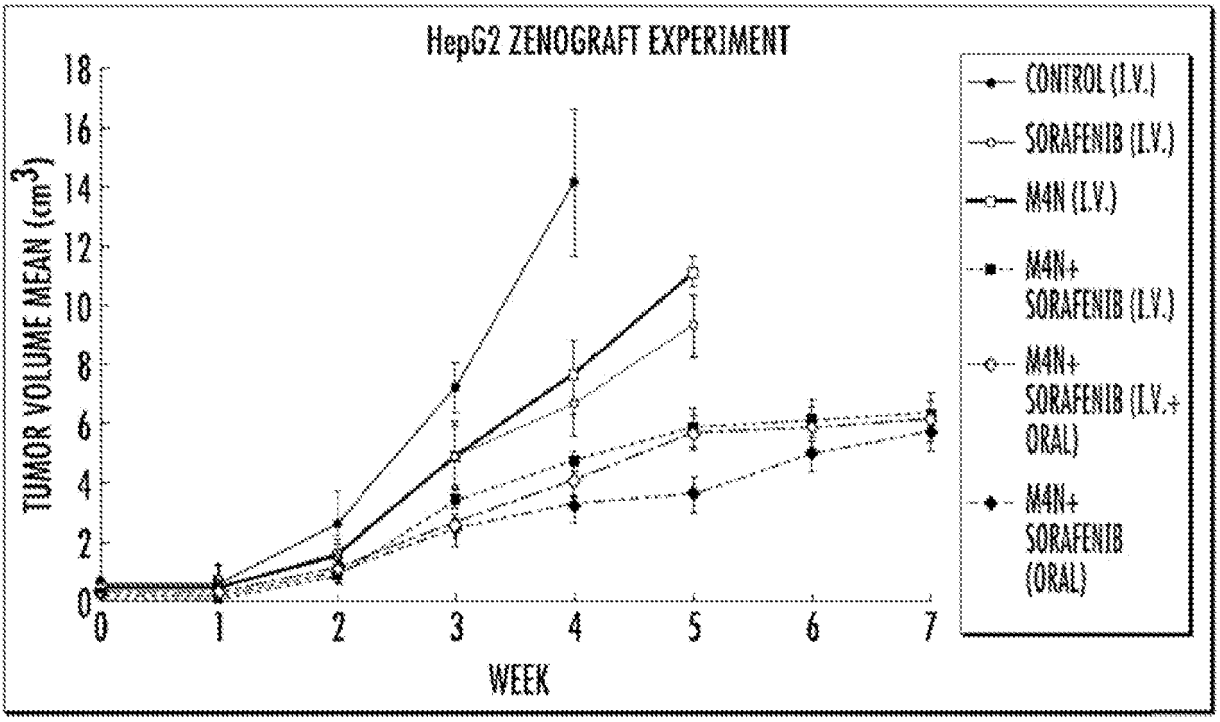

HepG2 ZENOGRAFT EXPERIMENT
TUMOR VOLUME MEAN (cm3)
WEEK
0
2
4
6
8
10
12
14
16
18
0
1
2
3
4
5
6
7
CONTROL (I.V.)
SORAFENIB (I.V.)
M4N (I.V.)
M4N+ SORAFENIB (I.V.)
M4N+ SORAFENIB (I.V.+ ORAL)
M4N+ SORAFENIB (ORAL)

FIGURE 6

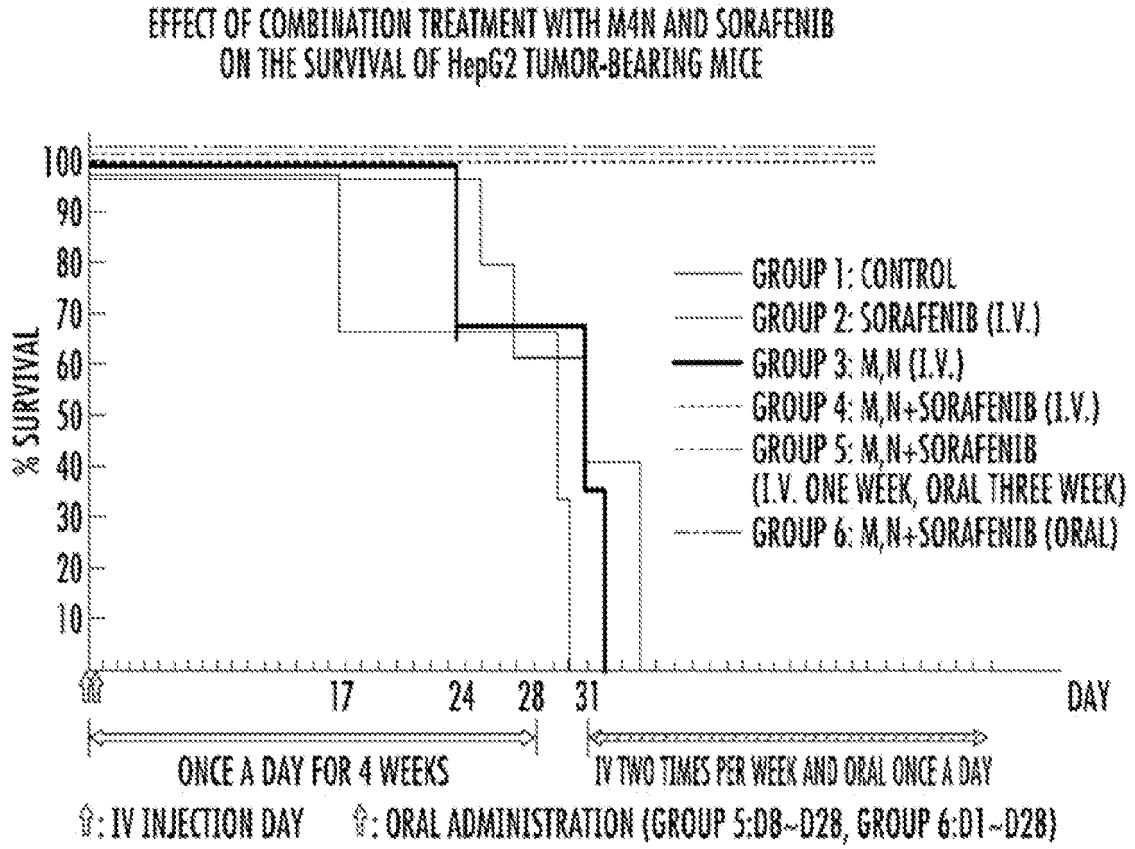

EFFECT OF COMBINATION TREATMENT WITH M4N AND SORAFENIB
ON THE SURVIVAL OF HepG2 TUMOR-BEARING MICE
% SURVIVAL
100
90
80
70
60
50
40
30
20
10
17
24
28
31
DAY
GROUP 1: CONTROL
GROUP 2: SORAFENIB (I.V.)
GROUP 3: M,N (I.V.)
GROUP 4: M,N+SORAFENIB (I.V.)
GROUP 5: M,N+SORAFENIB
(I.V. ONE WEEK, ORAL THREE WEEK)
GROUP 6: M,N+SORAFENIB (ORAL)
ONCE A DAY FOR 4 WEEKS
IV TWO TIMES PER WEEK AND ORAL ONCE A DAY
: IV INJECTION DAY
: ORAL ADMINISTRATION (GROUP 5:D8~D28, GROUP 6:D1~D28)

FIGURE 7

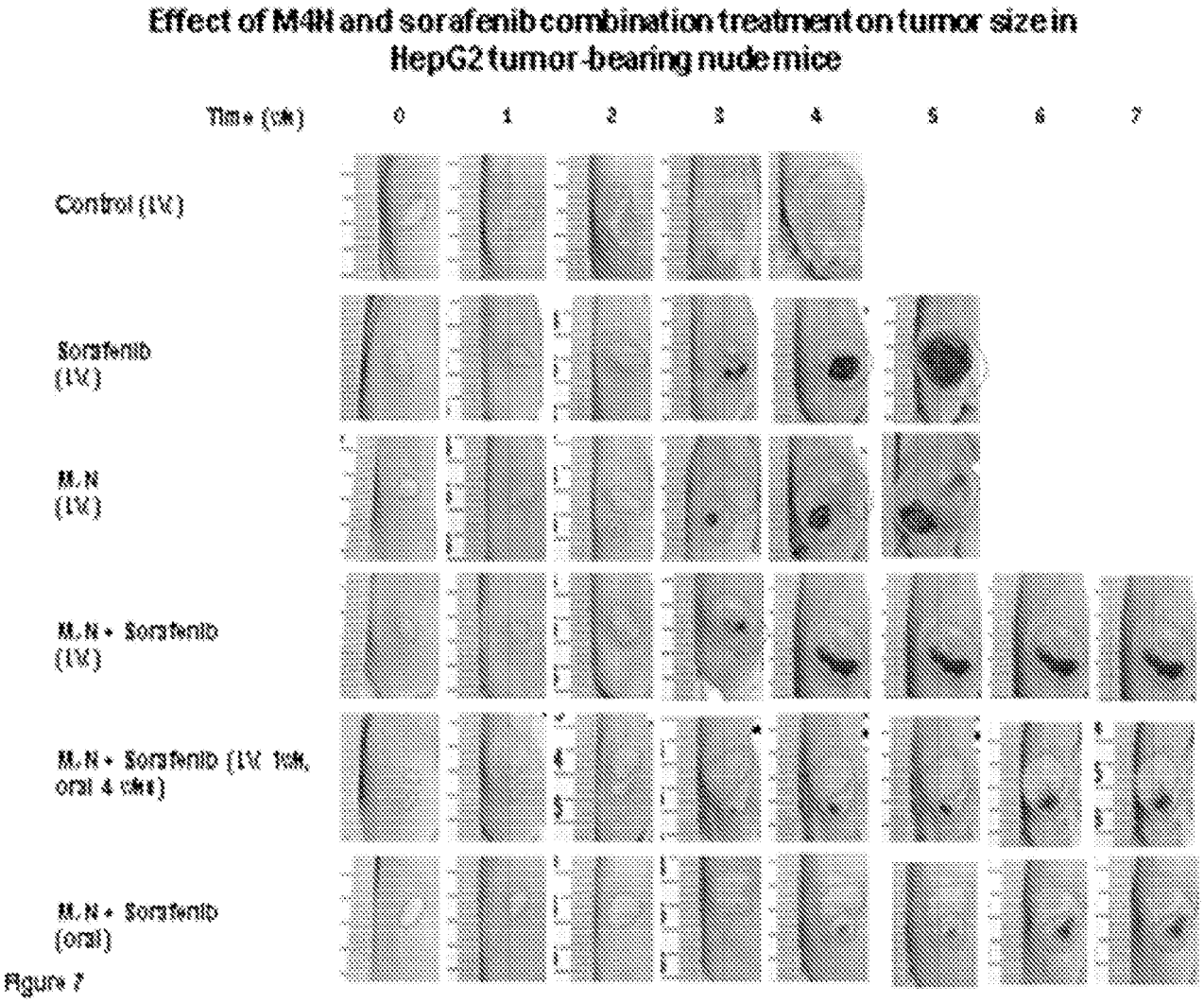


Figure 7

FIGURE 8

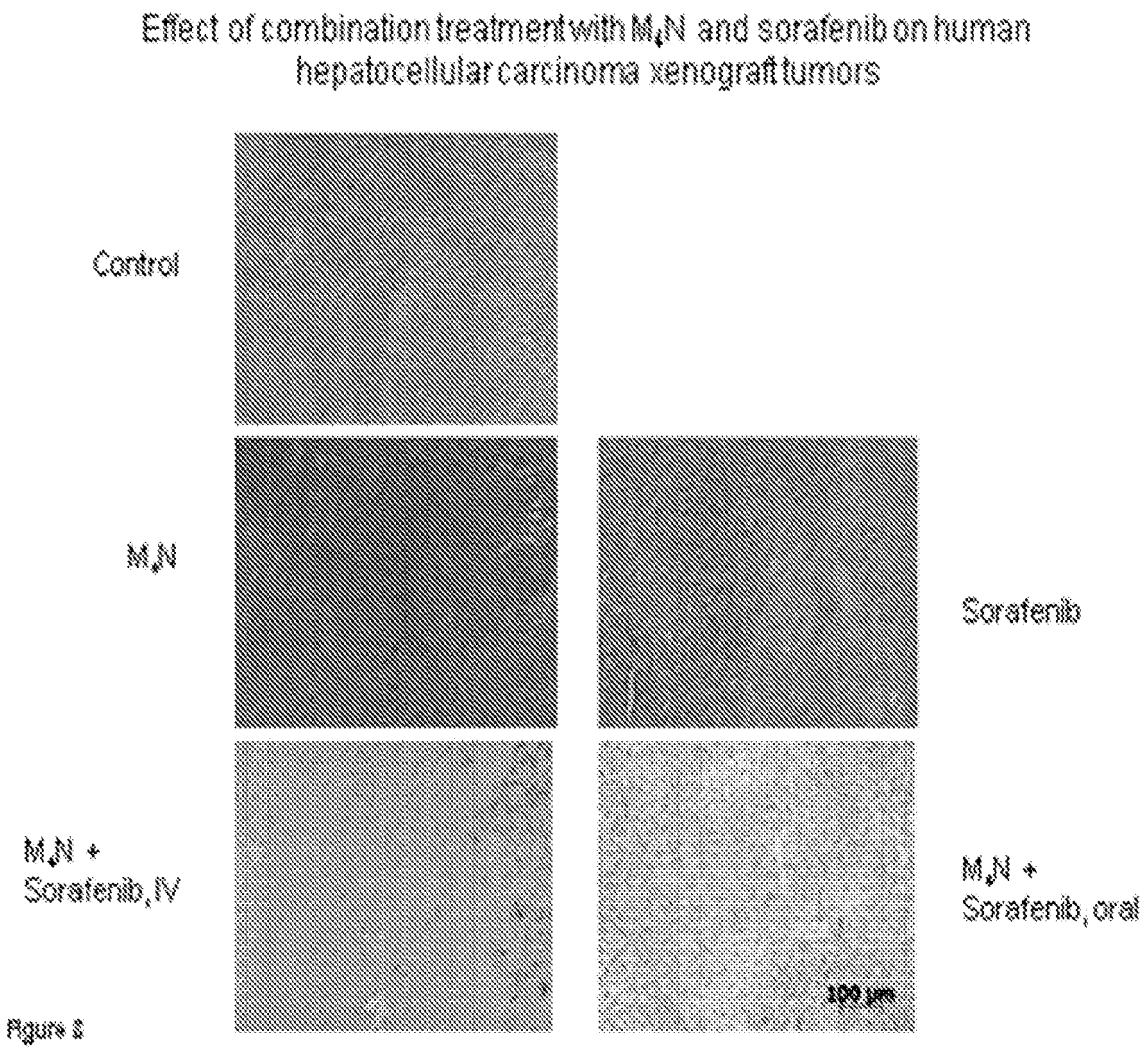


Figure 8

FIGURE 9

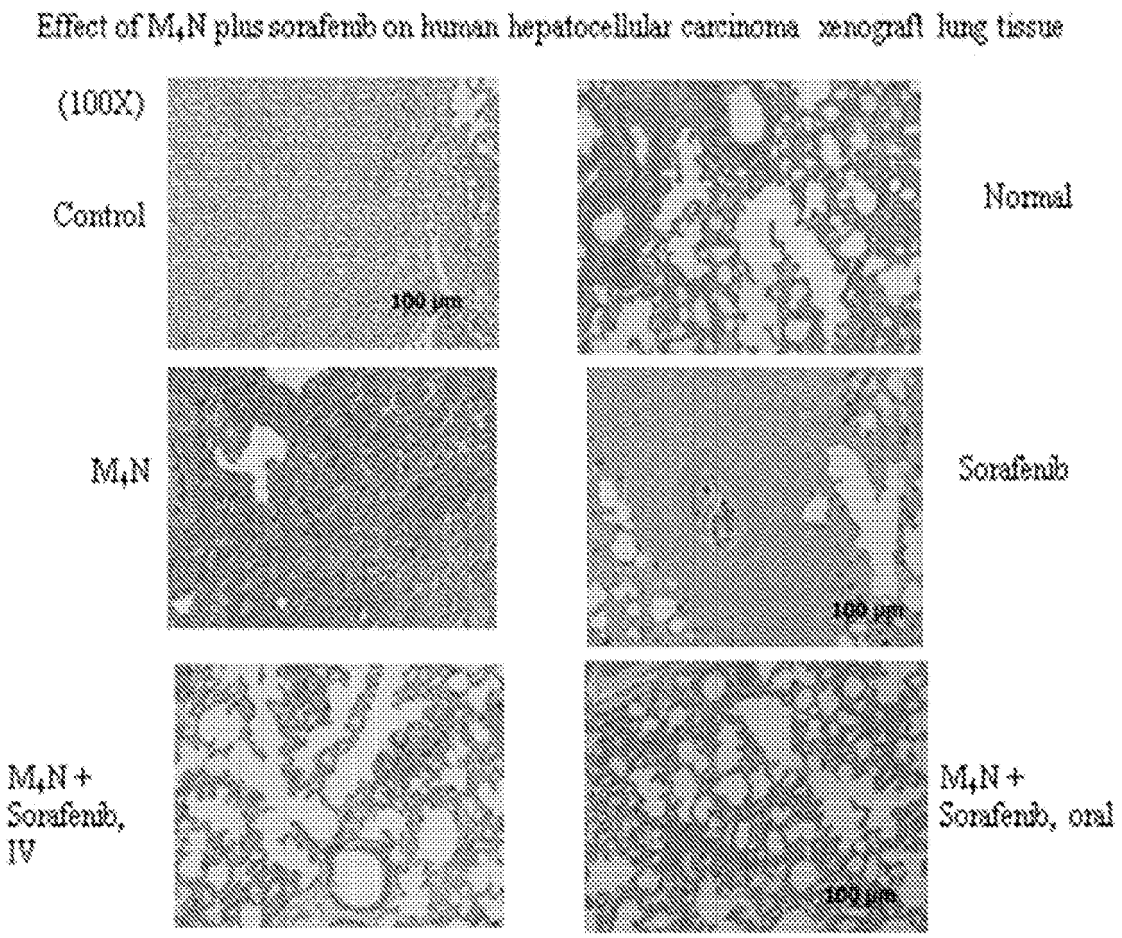

Effect of M4N plus sorafenib on human hepatocellular carcinoma xenograft lung tissue
(100X)
Control
100 µm
Normal
M4N
Sorafenib
100 µm
M4N + Sorafenib, IV
M4N + Sorafenib, oral
100 µm

FIGURE 10

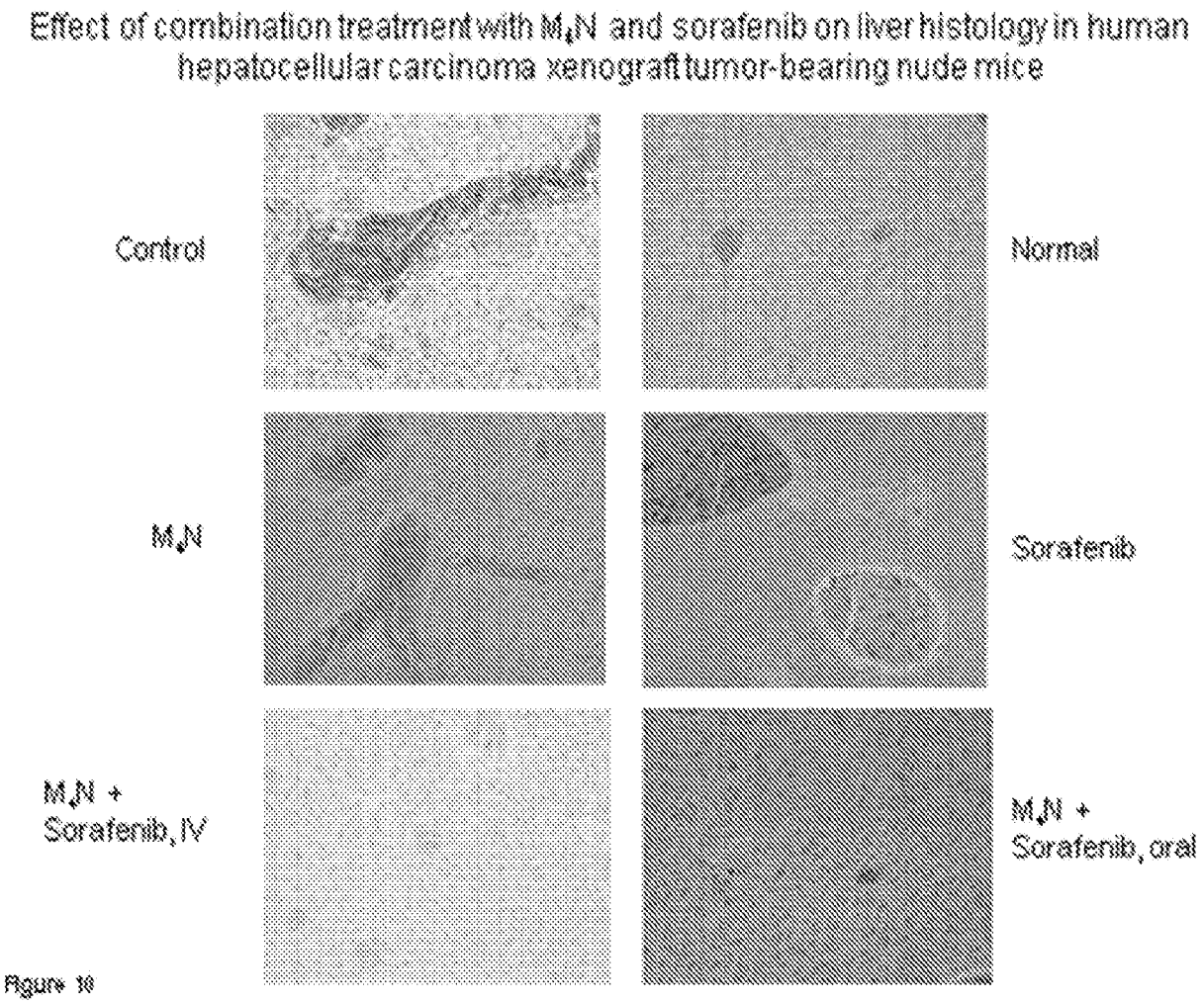

Effect of combination treatment with M4N and sorafenib on liver histology in human hepatocellular carcinoma xenograft tumor-bearing nude mice
Control
Normal
M4N
Sorafenib
M4N + Sorafenib, IV
M4N + Sorafenib, oral
Figure 10

FIGURE 11

Drugs	Parameters[a]			CI[b] value at				DRI[c] value at			
	D_m	m	r	ED_{50}	ED_{75}	ED_{90}	ED_{95}	ED_{50}	ED_{75}	ED_{90}	ED_{95}
M_4N	290.49	0.46	0.68					290.49	3158.66	34346.20	174086.00
Sor	29.10	4.05	0.96					29.10	38.16	50.05	60.18
M_4N + Sor	49.66	3.49	0.90	0.68	0.61	0.62	0.64				

FIGURE 12

Drugs	Parameters[a]			CI[b] value at				DRI[c] value at			
	D_m	m	r	ED_{50}	ED_{75}	ED_{90}	ED_{95}	ED_{50}	ED_{75}	ED_{90}	ED_{95}
M_4N	79.44	3.55	0.95					3.73	3.94	4.17	4.33
Sor	111.30	3.55	0.89					5.23	5.52	5.84	6.06
M_4N + Sor	42.59	4.32	0.87	0.46	0.43	0.41	0.40				

FIGURE 13

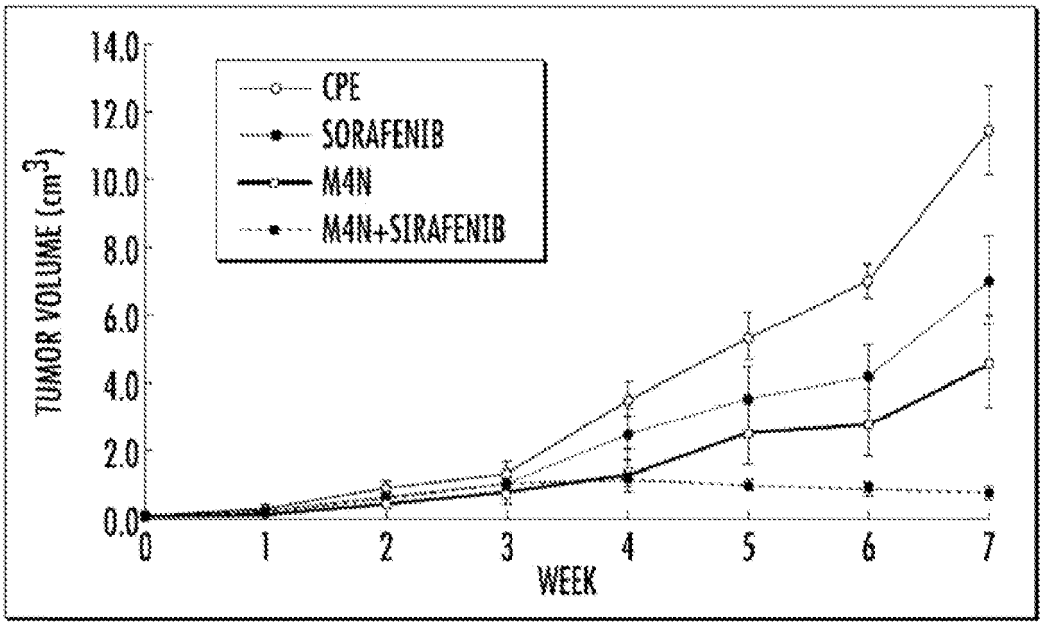

14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
TUMOR VOLUME (cm3)
0
1
2
3
4
5
6
7
WEEK
CPE
SORAFENIB
M4N
M4N+SIRAFENIB

FIGURE 14

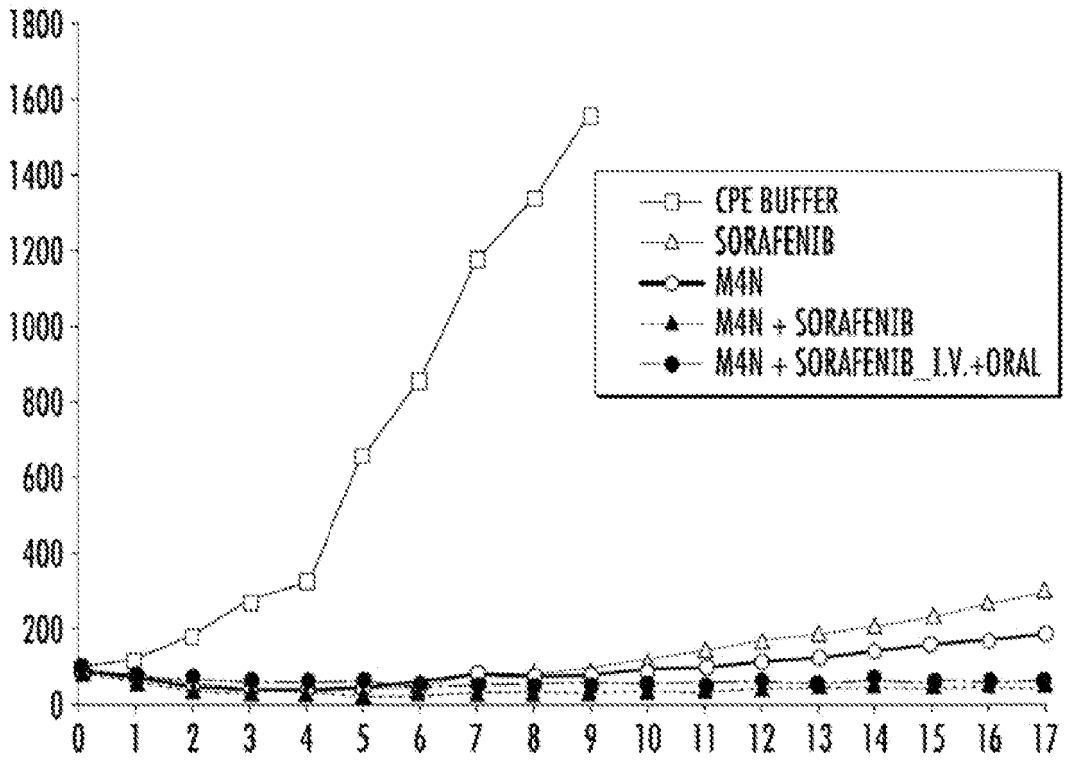

1800
1600
1400
1200
1000
800
600
400
200
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
CPE BUFFER
SORAFENIB
M4N
M4N + SORAFENIB
M4N + SORAFENIB_I.V.+ORAL

FIGURE 15

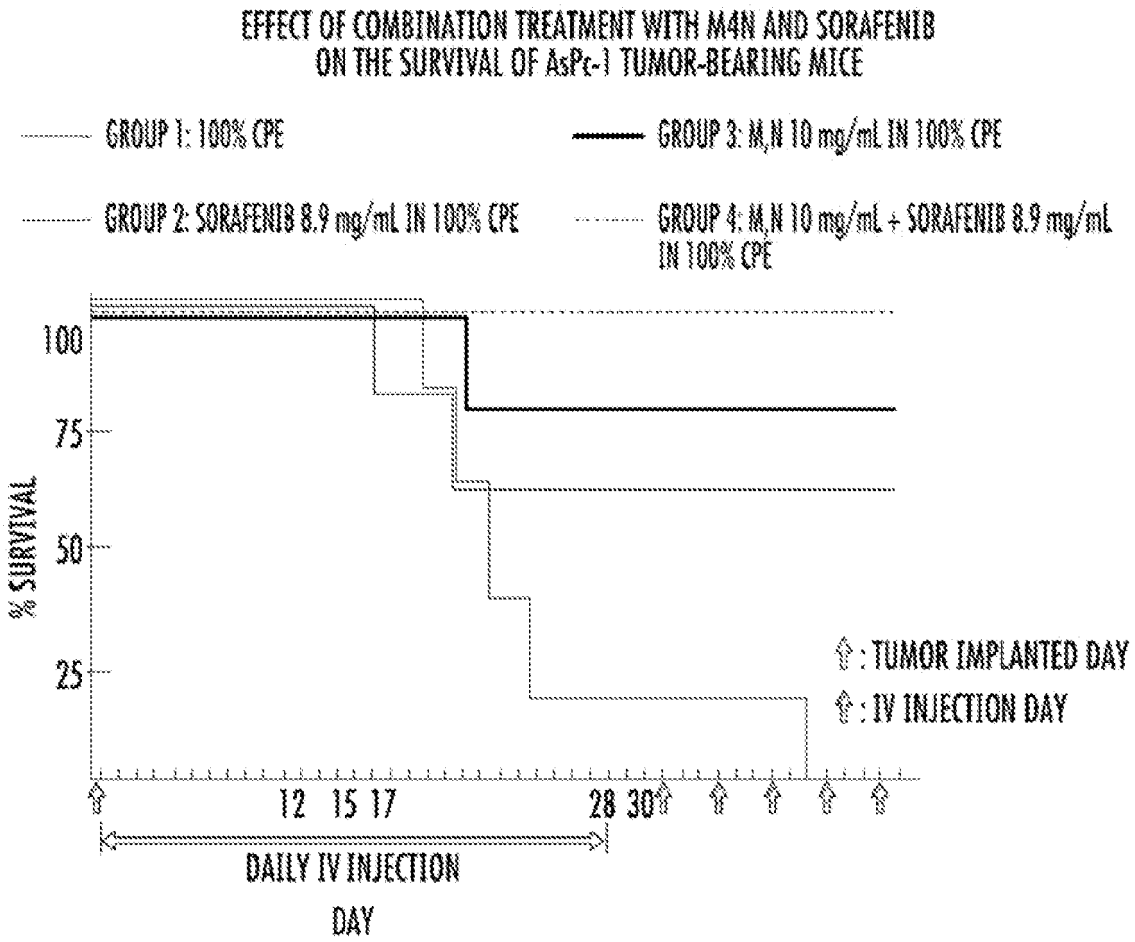

EFFECT OF COMBINATION TREATMENT WITH M4N AND SORAFENIB
ON THE SURVIVAL OF AsPc-1 TUMOR-BEARING MICE
GROUP 1: 100% CPE
GROUP 2: SORAFENIB 8.9 mg/mL IN 100% CPE
GROUP 3: M4N 10 mg/mL IN 100% CPE
GROUP 4: M4N 10 mg/mL + SORAFENIB 8.9 mg/mL IN 100% CPE
% SURVIVAL
100
75
50
25
⇧: TUMOR IMPLANTED DAY
⇧: IV INJECTION DAY
12 15 17
28 30
DAILY IV INJECTION DAY

FIGURE 16

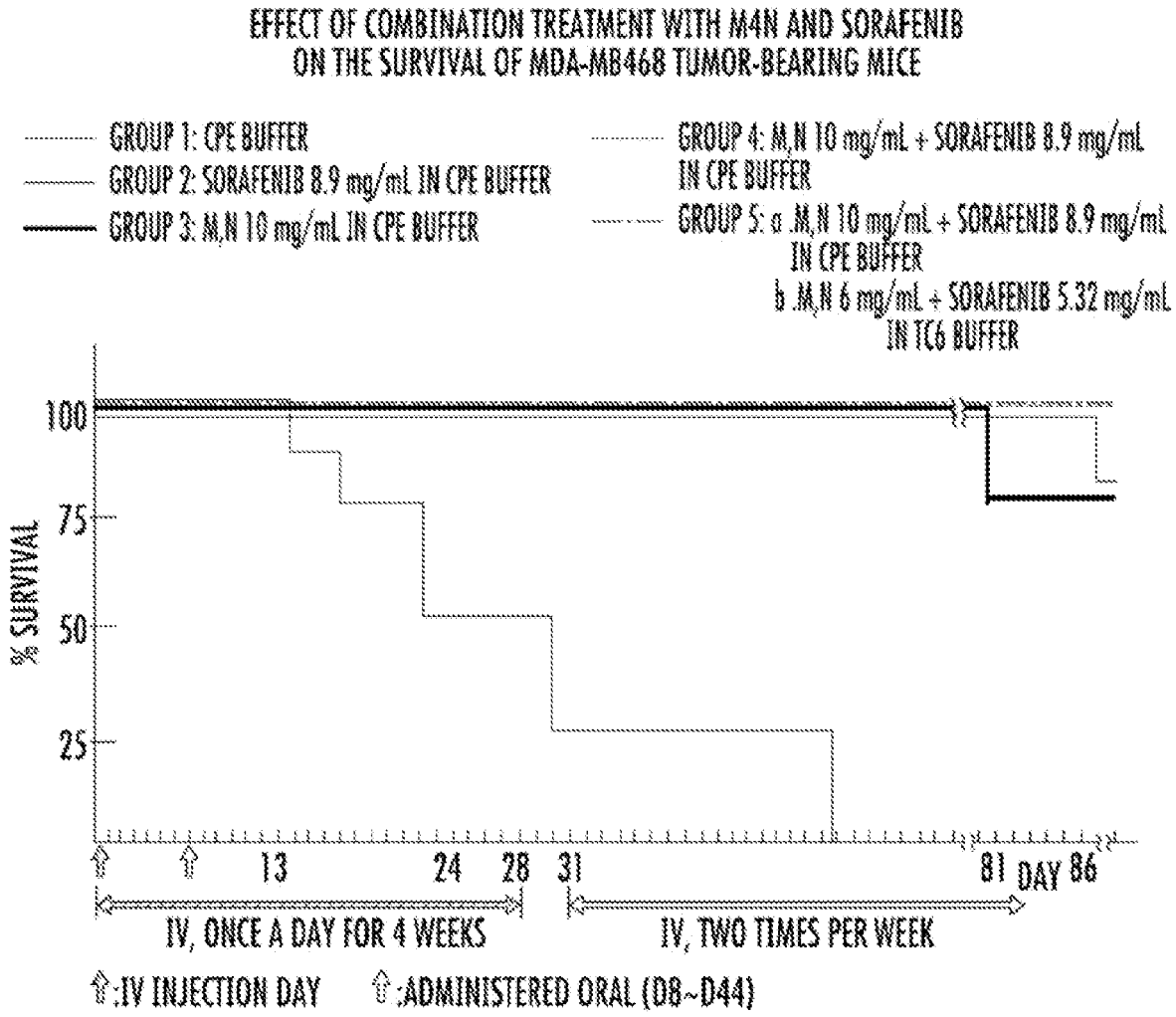
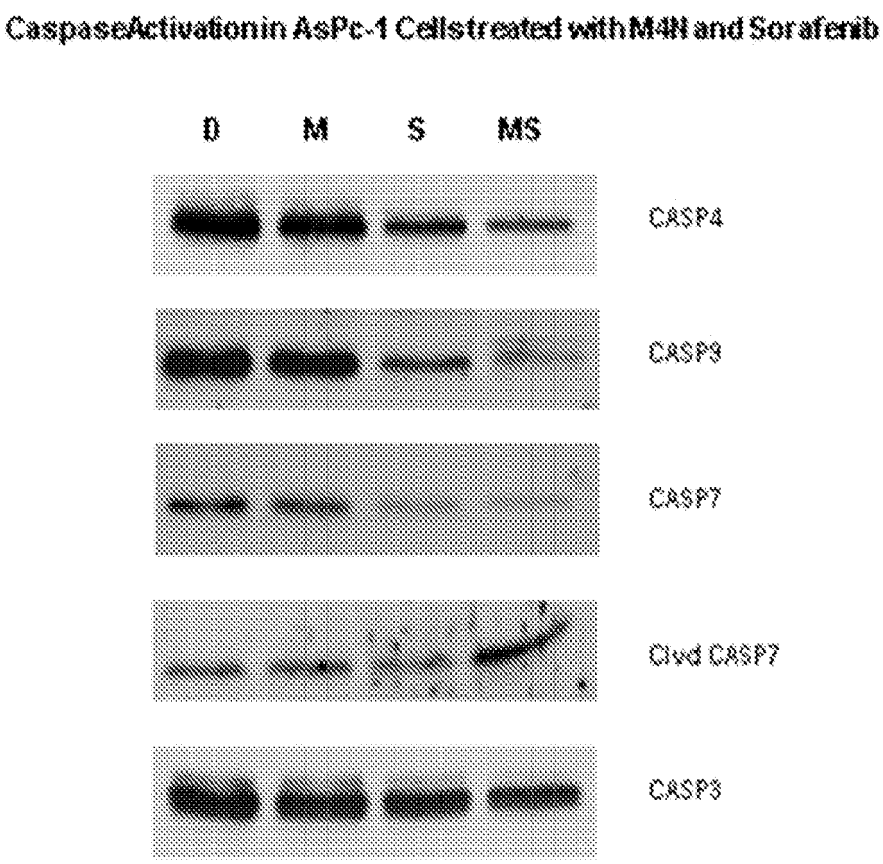

EFFECT OF COMBINATION TREATMENT WITH M4N AND SORAFENIB
ON THE SURVIVAL OF MDA-MB468 TUMOR-BEARING MICE
GROUP 1: CPE BUFFER
GROUP 2: SORAFENIB 8.9 mg/mL IN CPE BUFFER
GROUP 3: M,N 10 mg/mL IN CPE BUFFER
GROUP 4: M,N 10 mg/mL + SORAFENIB 8.9 mg/mL IN CPE BUFFER
GROUP 5: a .M,N 10 mg/mL + SORAFENIB 8.9 mg/mL IN CPE BUFFER
b .M,N 6 mg/mL + SORAFENIB 5.32 mg/mL IN TC6 BUFFER
% SURVIVAL
100
75
50
25
13
24
28
31
81
DAY 86
IV, ONCE A DAY FOR 4 WEEKS
IV, TWO TIMES PER WEEK
:IV INJECTION DAY
:ADMINISTERED ORAL (D8~D44)

FIGURE 17


Caspase Activation in AsPc-1 Cells treated with M4N and Sorafenib
D
M
S
MS
CASP4
CASP9
CASP7
Clvd CASP7
CASP3