FIG. 1A

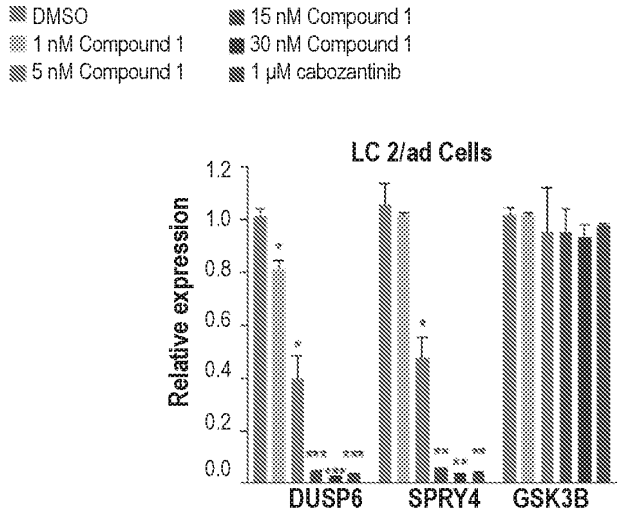


FIG. 1B

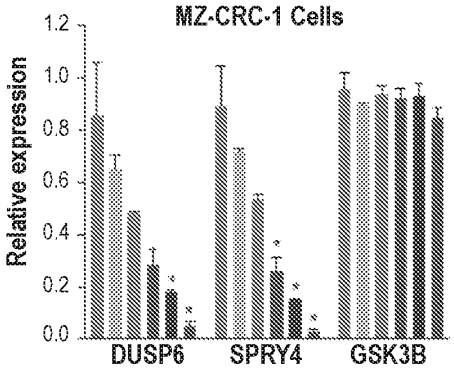


FIG. 1C

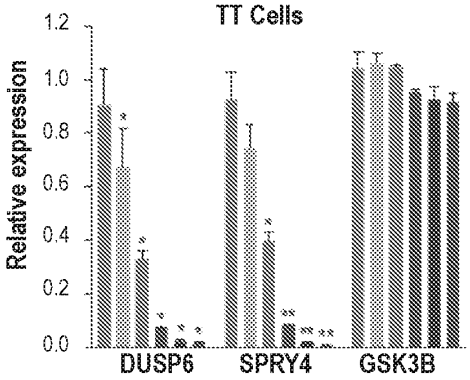


FIG. 2

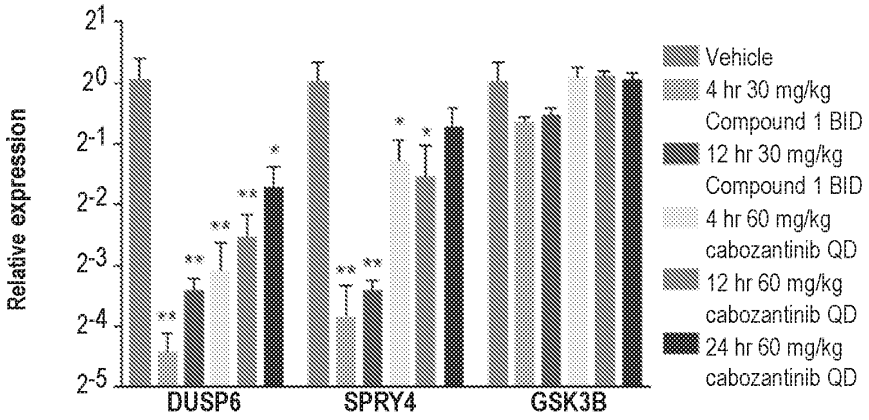

Relative expression
2^1
2^0
2^-1
2^-2
2^-3
2^-4
2^-5
DUSP6
SPRY4
GSK3B
Vehicle
4 hr 30 mg/kg Compound 1 BID
12 hr 30 mg/kg Compound 1 BID
4 hr 60 mg/kg cabozantinib QD
12 hr 60 mg/kg cabozantinib QD
24 hr 60 mg/kg cabozantinib QD

FIG. 3

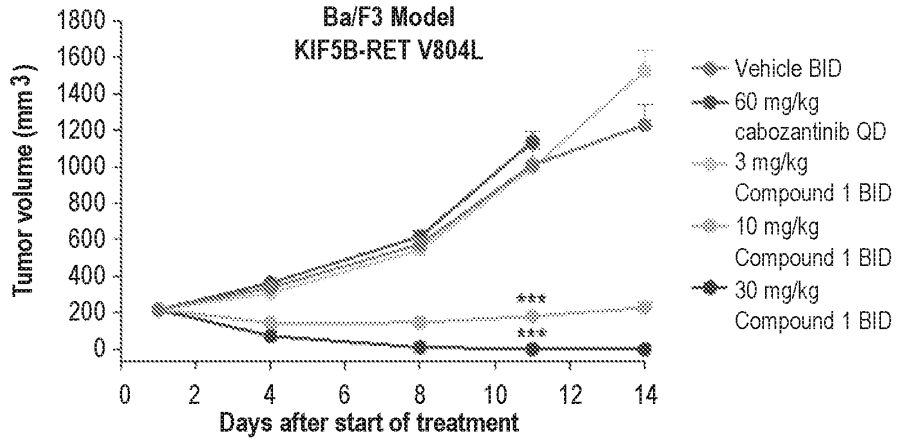

Ba/F3 Model
KIF5B-RET V804L
Tumor volume (mm3)
1800
1600
1400
1200
1000
800
600
400
200
0
0
2
4
6
8
10
12
14
Days after start of treatment
Vehicle BID
60 mg/kg cabozantinib QD
3 mg/kg Compound 1 BID
10 mg/kg Compound 1 BID
30 mg/kg Compound 1 BID

FIG. 4A

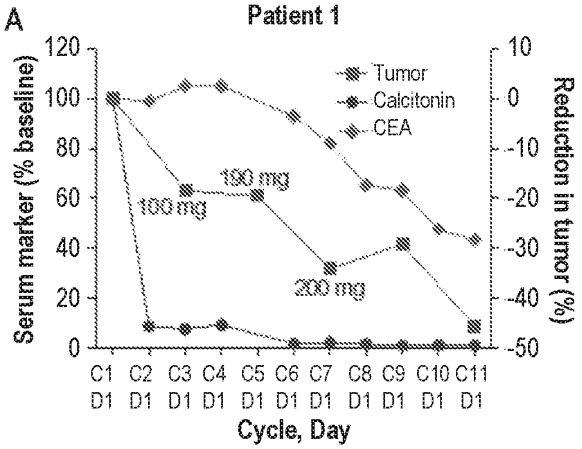

A
Patient 1
Serum marker (% baseline)
Reduction in tumor (%)
120
100
80
60
40
20
0
10
0
-10
-20
-30
-40
-50
Tumor
Calcitonin
CEA
100 mg
150 mg
200 mg
C1 D1
C2 D1
C3 D1
C4 D1
C5 D1
C6 D1
C7 D1
C8 D1
C9 D1
C10 D1
C11 D1
Cycle, Day

FIG. 4B

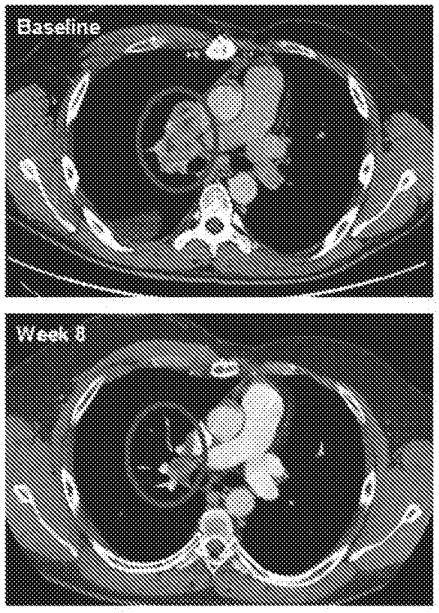

Baseline
Week 8

FIG. 4C

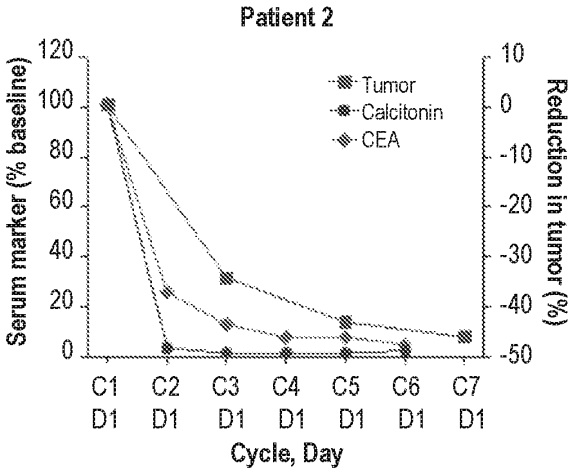

Patient 2
Serum marker (% baseline)
120
100
80
60
40
20
0
Tumor
Calcitonin
CEA
10
0
-10
-20
-30
-40
-50
Reduction in tumor (%)
C1 D1
C2 D1
C3 D1
C4 D1
C5 D1
C6 D1
C7 D1
Cycle, Day

FIG. 4D

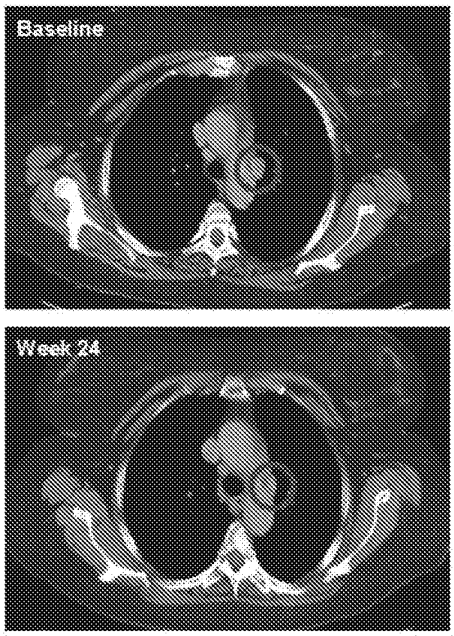

Baseline
Week 24

FIG. 4E

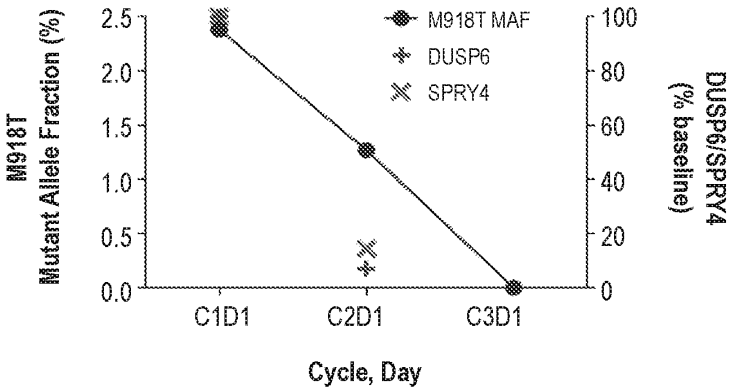

M918T
Mutant Allele Fraction (%)
2.5
2.0
1.5
1.0
0.5
0.0
M918T MAF
DUSP6
SPRY4
100
80
60
40
20
0
DUSP6/SPRY4
(% baseline)
C1D1
C2D1
C3D1
Cycle, Day

FIG. 5A

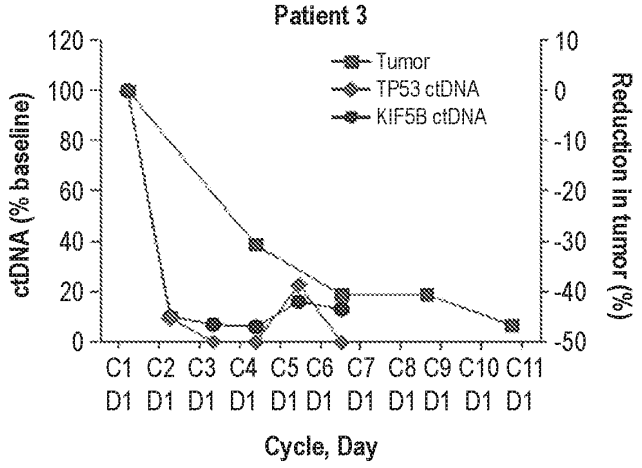

Patient 3
ctDNA (% baseline)
120
100
80
60
40
20
0
Tumor
TP53 ctDNA
KIF5B ctDNA
10
0
-10
-20
-30
-40
-50
Reduction in tumor (%)
C1 D1
C2 D1
C3 D1
C4 D1
C5 D1
C6 D1
C7 D1
C8 D1
C9 D1
C10 D1
C11 D1
Cycle, Day

FIG. 5B

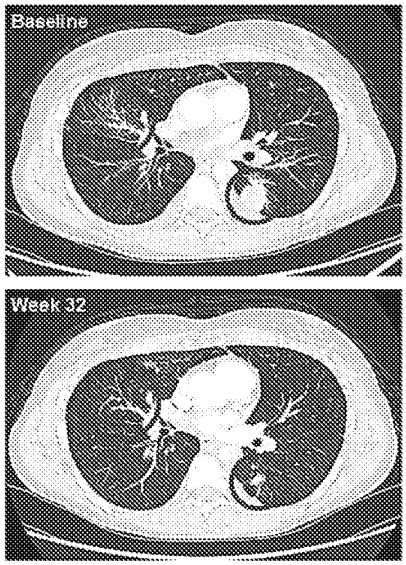


FIG. 6A

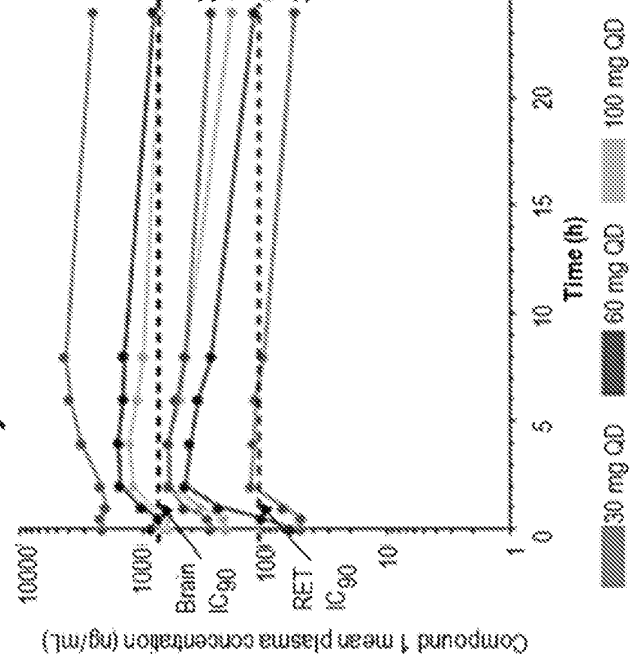

Steady-State Pharmacokinetics
Compound 1 mean plasma concentration (ng/mL)
Time (h)
600 mg QD
400 mg QD
300 mg QD
200 mg QD
100 mg QD
60 mg QD
30 mg QD
Brain IC90
RET IC90

FIG. 6B

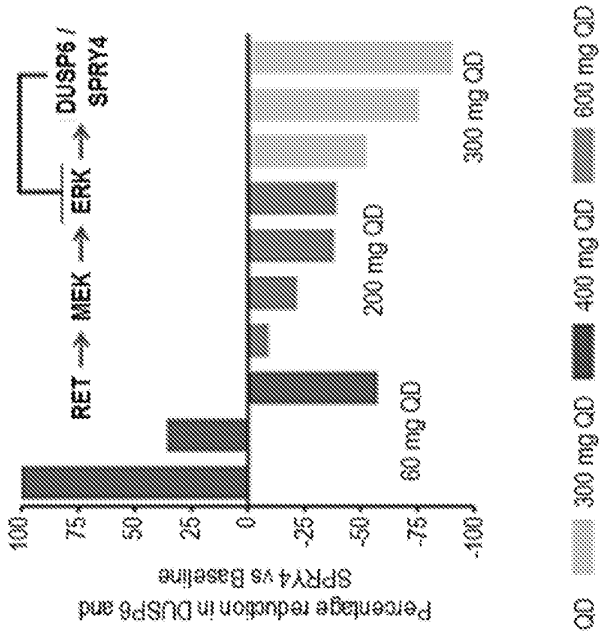

Tumor Pharmacokinetics
RET → MEK → ERK → DUSP6 / SPRY4
Percentage reduction in DUSP6 and SPRY4 vs Baseline
60 mg QD
200 mg QD
300 mg QD
30 mg QD
60 mg QD
100 mg QD
200 mg QD
300 mg QD
400 mg QD
600 mg QD

FIG. 7A

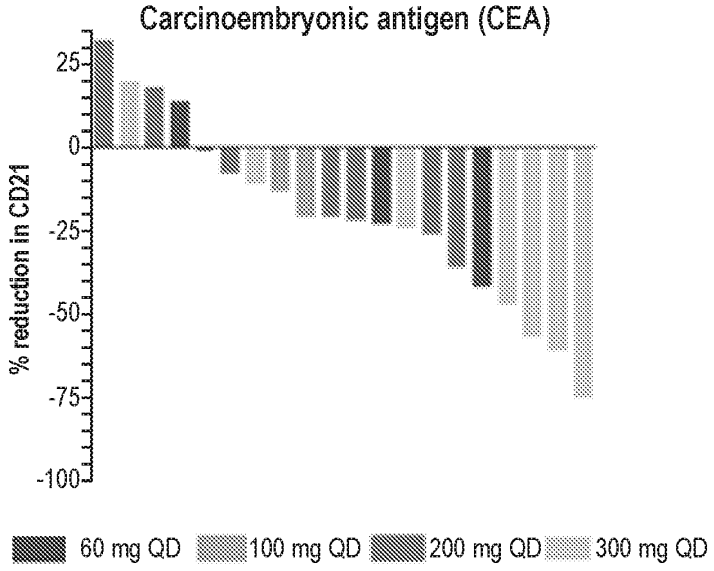

Carcinoembryonic antigen (CEA)
% reduction in CD21
25
0
-25
-50
-75
-100
60 mg QD
100 mg QD
200 mg QD
300 mg QD

FIG. 7B

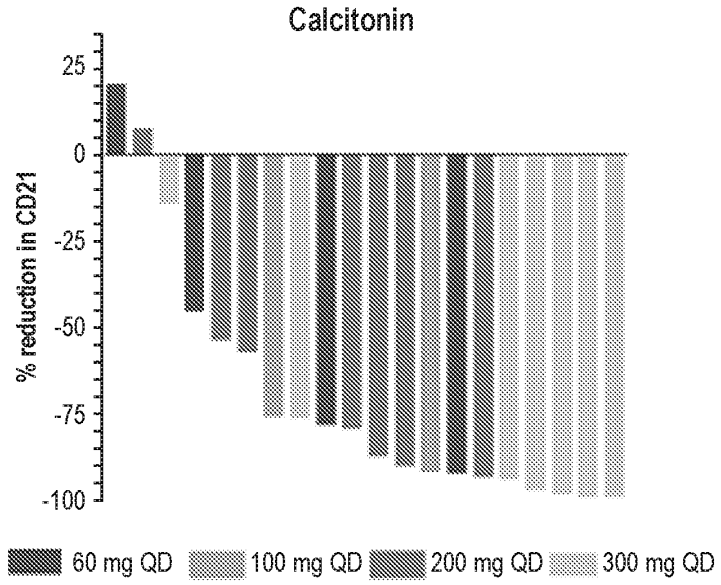
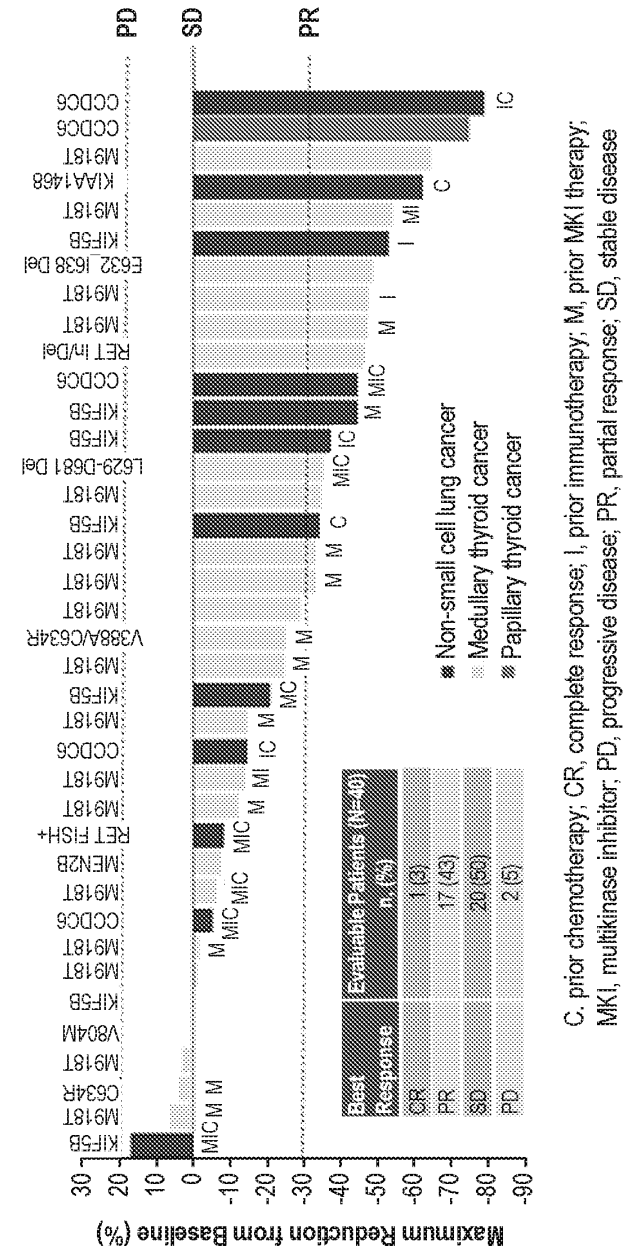

Calcitonin
% reduction in CD21
25
0
-25
-50
-75
-100
60 mg QD
100 mg QD
200 mg QD
300 mg QD

FIG. 8



C, prior chemotherapy; CR, complete response; I, prior immunotherapy; M, prior MKI therapy; MKI, multikinase inhibitor; PD, progressive disease; PR, partial response; SD, stable disease

FIG. 9A

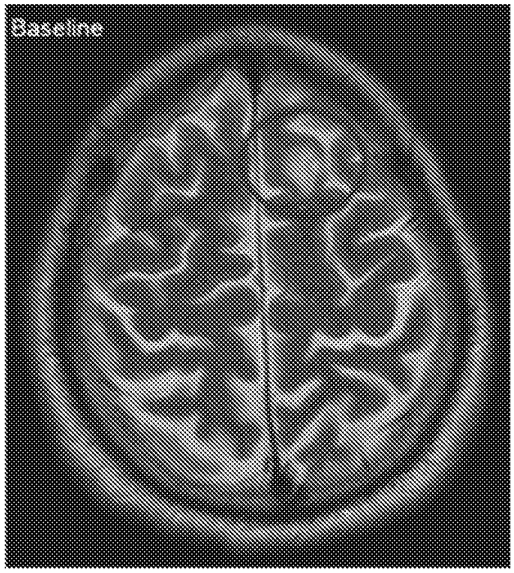


FIG. 9B



FIG. 10

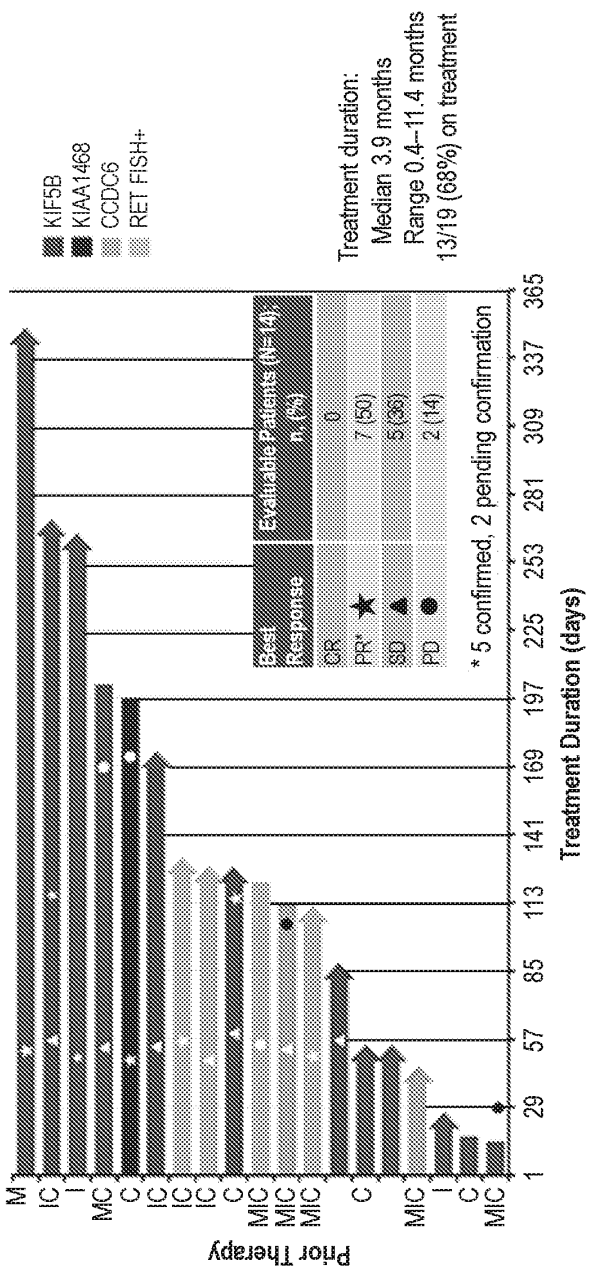

KIF5B
KIAA1468
CCDC6
RET FISH+
Best Response
Evaluable Patients (N=19) n (%)
CR 0
PR* 7 (50)
SD 5 (36)
PD 2 (14)
* 5 confirmed, 2 pending confirmation
Treatment duration:
Median 3.9 months
Range 0.4–11.4 months
13/19 (68%) on treatment
Prior Therapy
M
IC
I
MC
C
IC
IC
IC
C
MIC
MIC
MIC
C
MIC
I
C
MIC
1 29 57 85 113 141 169 197 225 253 281 309 337 365
Treatment Duration (days)

FIG. 11A

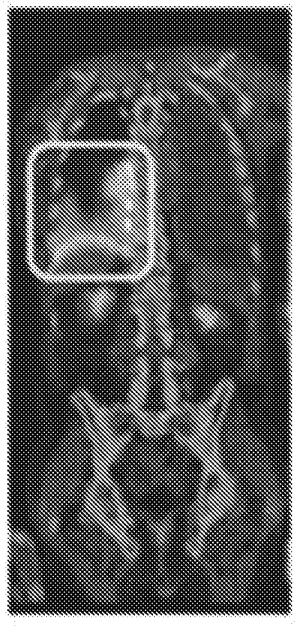


FIG. 11B

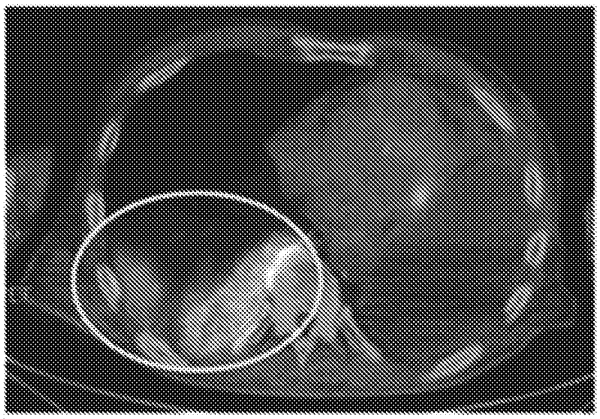


FIG. 11C

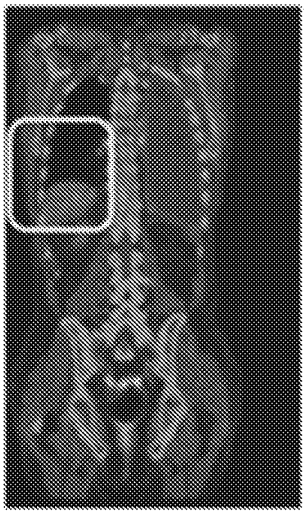


FIG. 11D

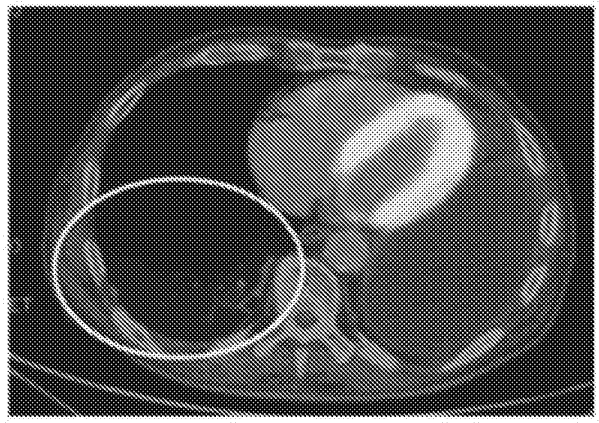


FIG. 12

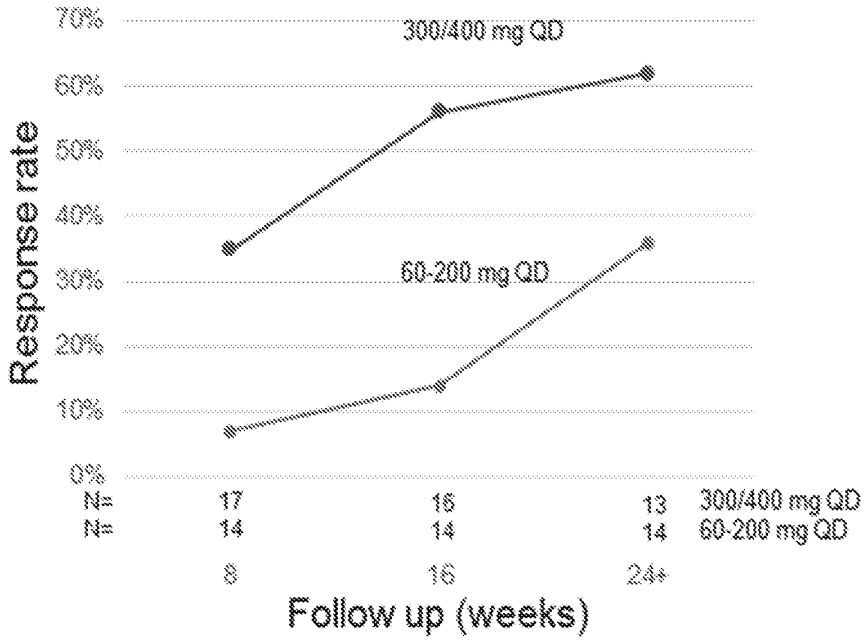

70%
60%
50%
40%
30%
20%
10%
0%
Response rate
300/400 mg QD
60-200 mg QD
N= 17 16 13 300/400 mg QD
N= 14 14 14 60-200 mg QD
8 16 24+
Follow up (weeks)

FIG. 13

