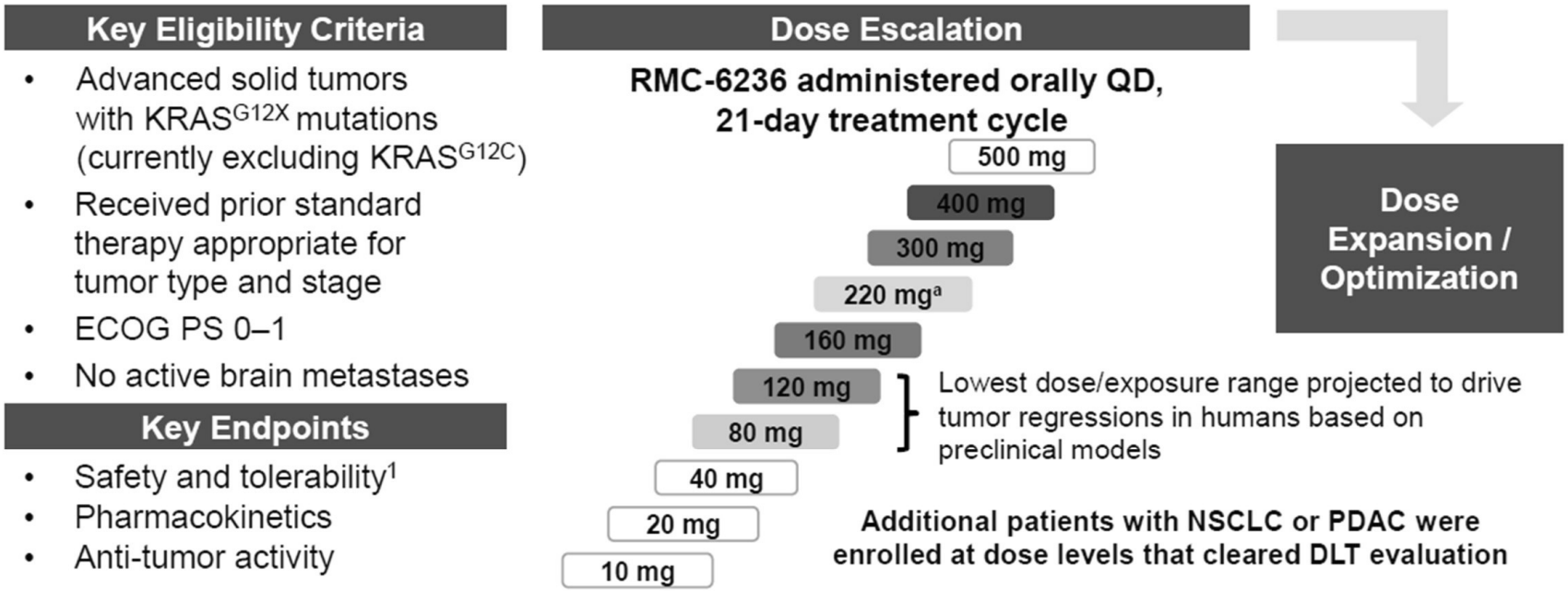


[a]220 mg cleared DLT evaluation and a dose of 200 mg was selected for further expansion/optimization.
KRAS^{G12X} defined as mutation at codon 12 which encodes glycine (G) to X where X = A, D, R, S, or V.

FIG. 1

	Total N=131
Age, median (range), years	64 (30–86)
Male, n (%)	69 (53)
Tumor type, n (%)	
PDAC	69 (53)
NSCLC	47 (36)
CRC	10 (7)
Other*	5 (4)
ECOG PS, n (%)	
0	40 (31)
1	91 (69)
Number of prior anti-cancer therapies, median (range)	2 (1–7)

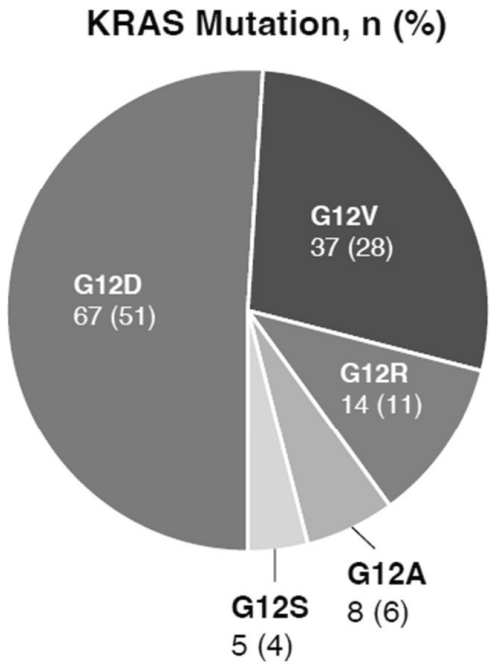


FIG. 2A

	NSCLC[a] N = 46	PDAC[a] N = 65
Age, median (range), years	65 (31–83)	64 (30–86)
Female, n (%)	25 (54)	31 (48)
ECOG PS, n (%)		
0	11 (24)	20 (31)
1	35 (76)	45 (69)
Smoking status, n (%)		
Current	2 (4)	2 (3)
Past	28 (61)	14 (22)
Never	16 (35)	49 (75)
Number of prior anti-cancer therapies, median (range)	2 (1–6)	3 (1–7)
Select type of prior anti-cancer therapy/regimens, n (%)		
Checkpoint inhibitor[b]	44 (96)	–
Platinum-based chemotherapy	46 (100)	–
FOLFIRINOX	–	45 (69)
Gemcitabine + nab-paclitaxel	–	49 (75)

[a]Includes patients with NSCLC or PDAC treated at 80 mg or above.
[b]Two patients enrolled in the expansion/optimization cohort received platinum-based chemotherapy and targeted therapy (checkpoint inhibitor not required).

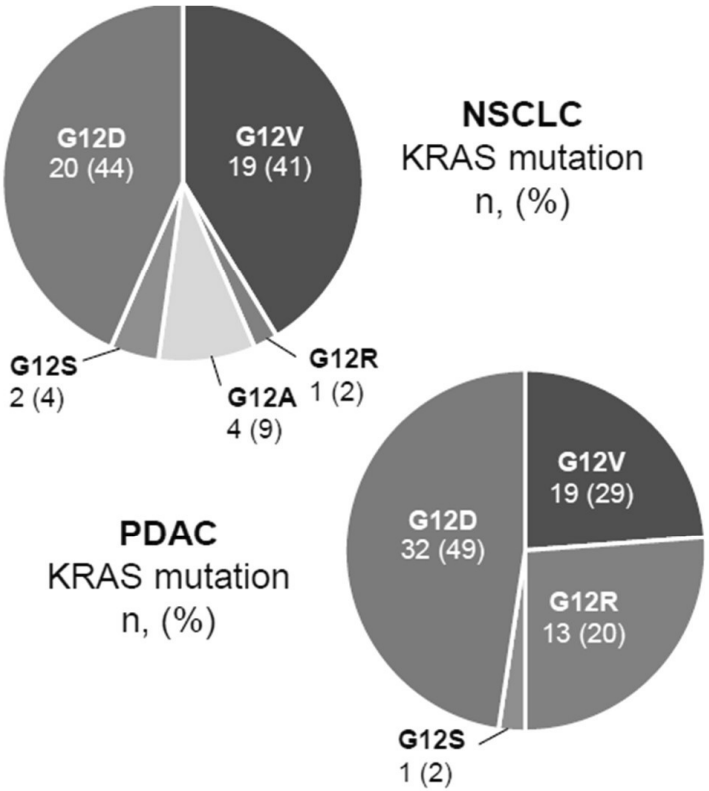


FIG. 2B

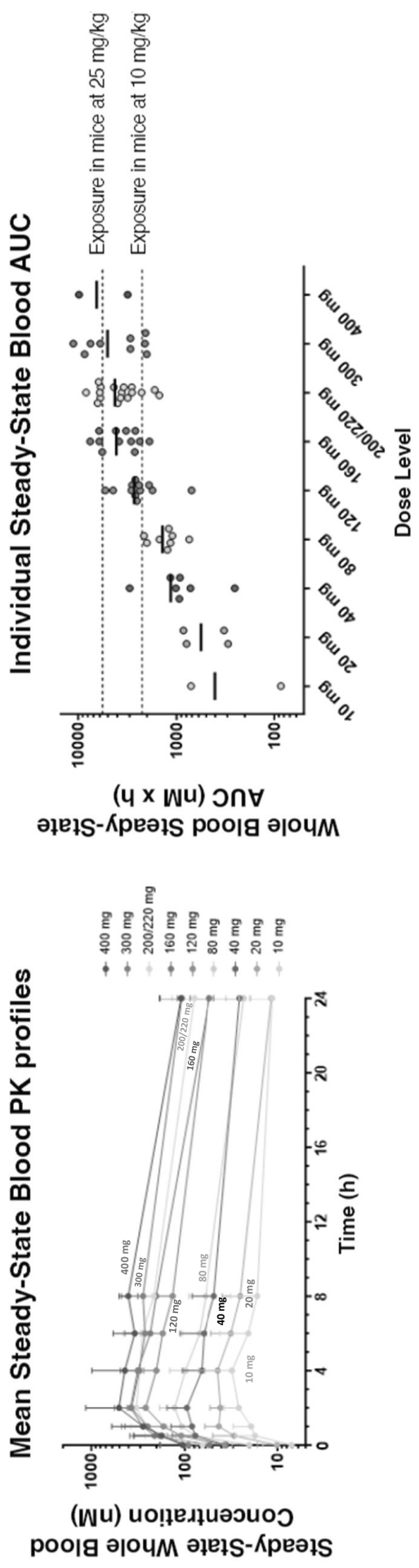

Individual Steady-State Blood AUC
Exposure in mice at 25 mg/kg
Exposure in mice at 10 mg/kg
Whole Blood Steady-State AUC (nM x h)
10000
1000
100
10 mg
20 mg
40 mg
80 mg
120 mg
160 mg
200/220 mg
300 mg
400 mg
Dose Level
Mean Steady-State Blood PK profiles
Steady-State Whole Blood Concentration (nM)
1000
100
10
0
4
8
12
16
20
24
Time (h)
400 mg
300 mg
200/220 mg
160 mg
120 mg
80 mg
40 mg
20 mg
10 mg

FIG. 3

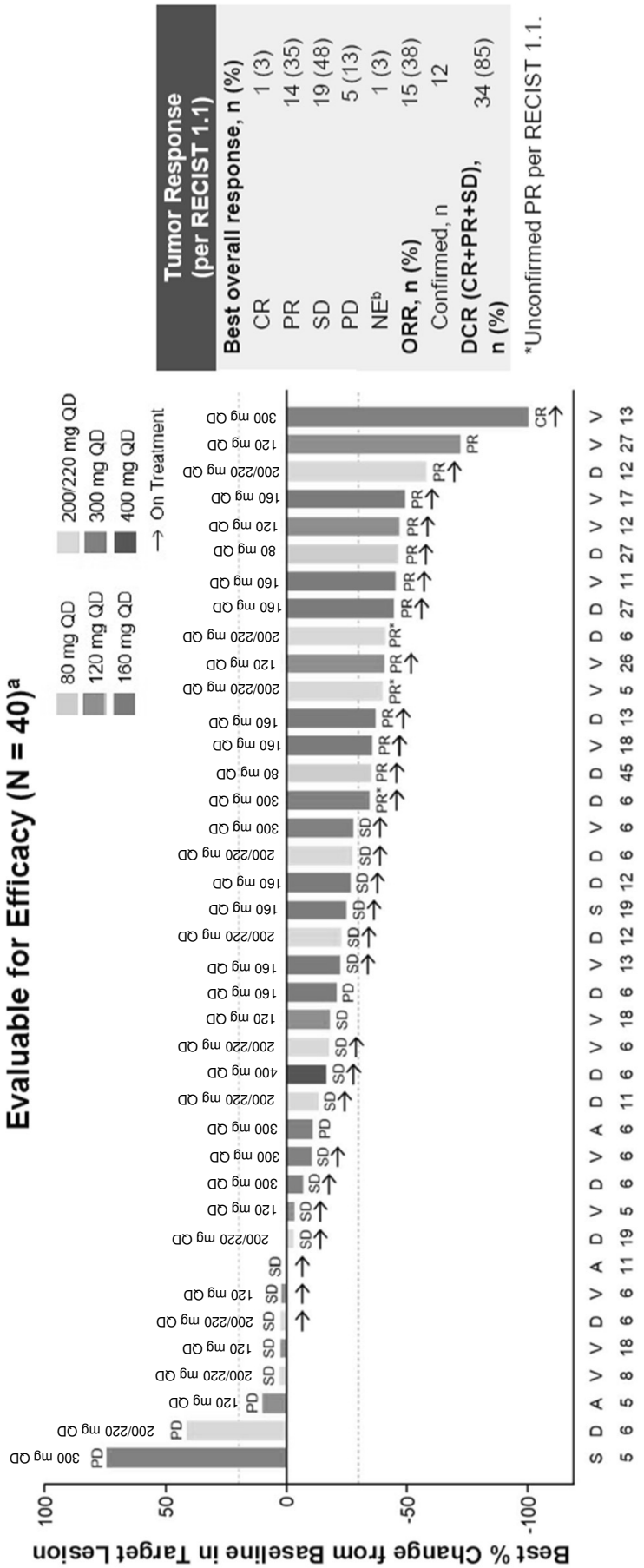
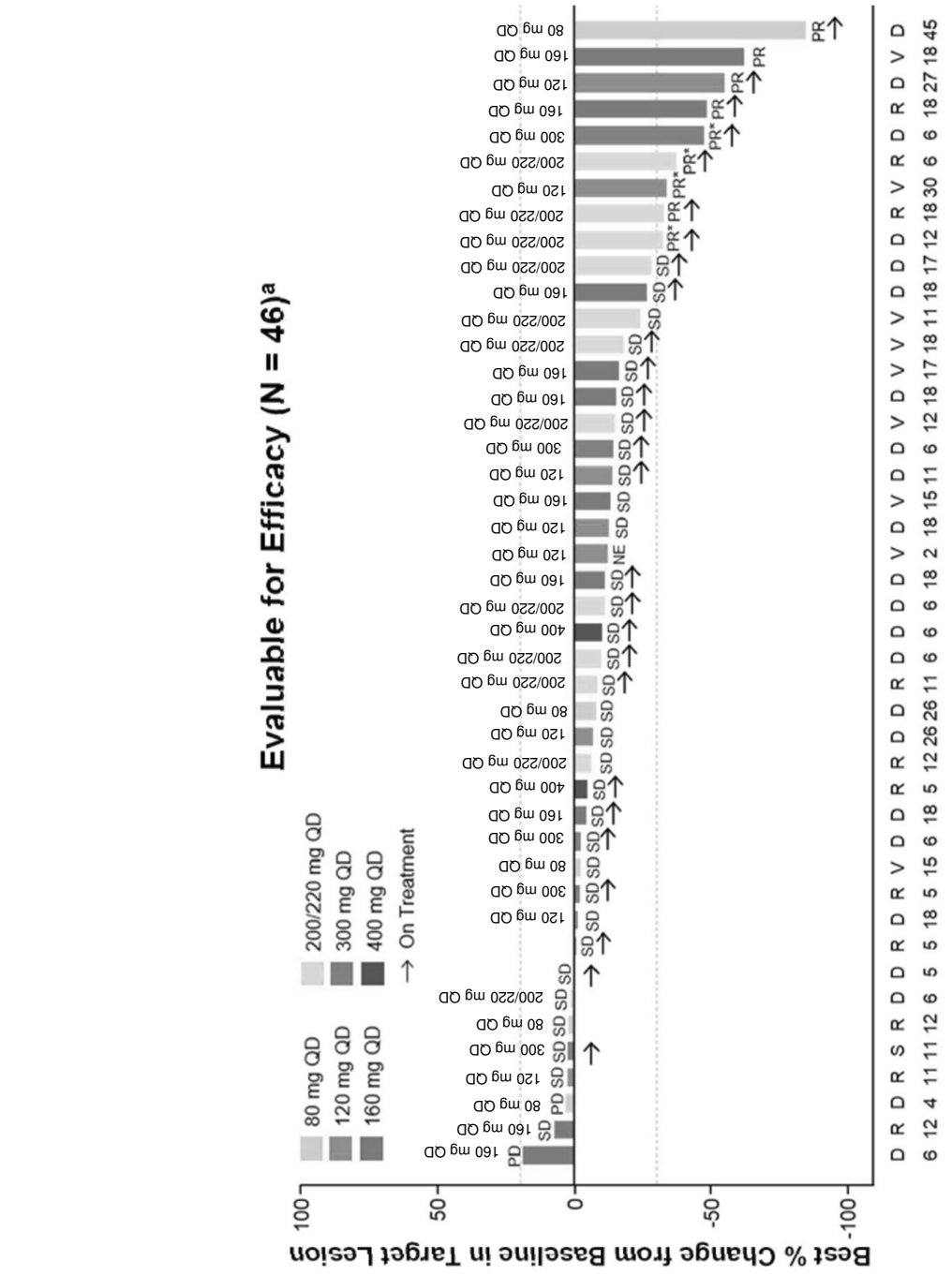

Evaluable for Efficacy (N = 40)a
Best % Change from Baseline in Target Lesion
100
50
0
-50
-100
80 mg QD
120 mg QD
160 mg QD
200/220 mg QD
300 mg QD
400 mg QD
→ On Treatment
Tumor Response (per RECIST 1.1)
Best overall response, n (%)
CR 1 (3)
PR 14 (35)
SD 19 (48)
PD 5 (13)
NEb 1 (3)
ORR, n (%) 15 (38)
Confirmed, n 12
DCR (CR+PR+SD), n (%) 34 (85)
*Unconfirmed PR per RECIST 1.1.

FIG. 4



Tumor Response (per RECIST 1.1)	
Best overall response, n (%)	
PR	9 (20)
SD	31 (67)
PD	3 (7)
NE[b]	3 (7)
ORR, n (%)	9 (20)
Confirmed, n	5
DCR (CR+PR+SD), n (%)	40 (87)

*Unconfirmed PR per RECIST 1.1.

FIG. 5

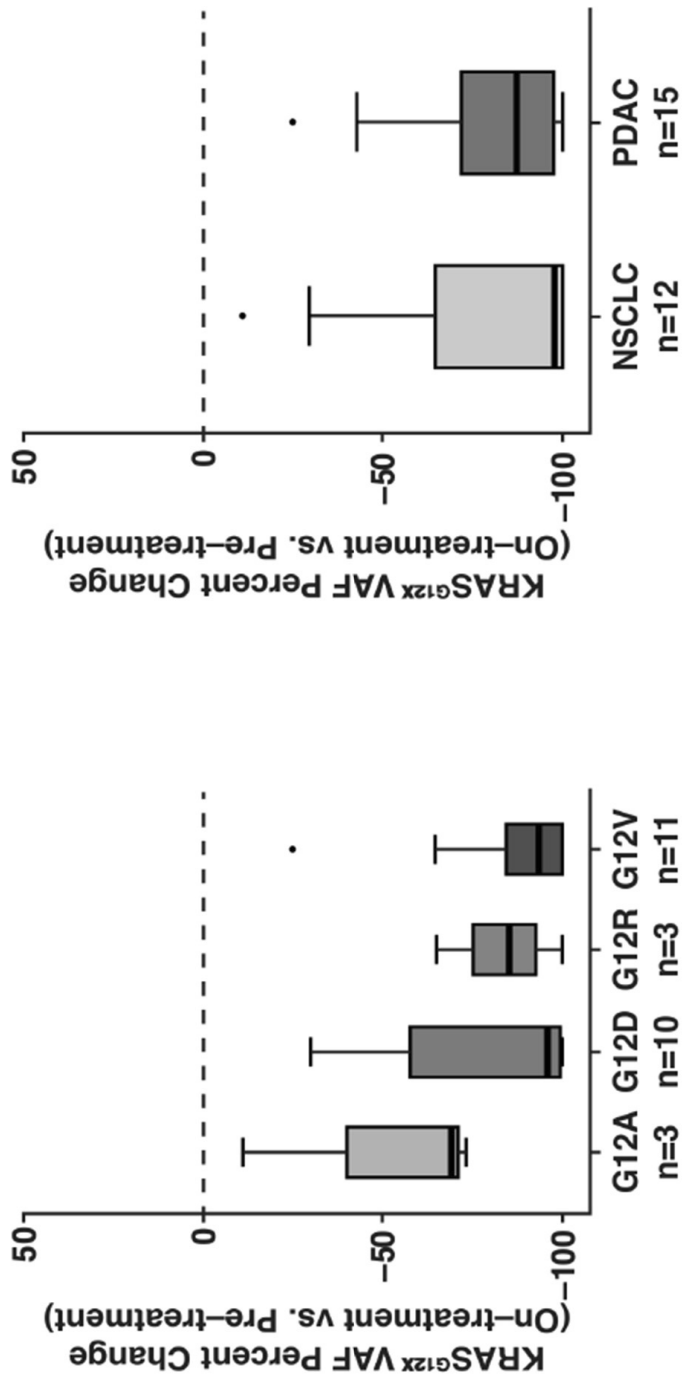

KRAS^{G12x} VAF Percent Change
(On–treatment vs. Pre–treatment)
50
0
−50
−100
G12A
n=3
G12D
n=10
G12R
n=3
G12V
n=11
NSCLC
n=12
PDAC
n=15

FIG. 6

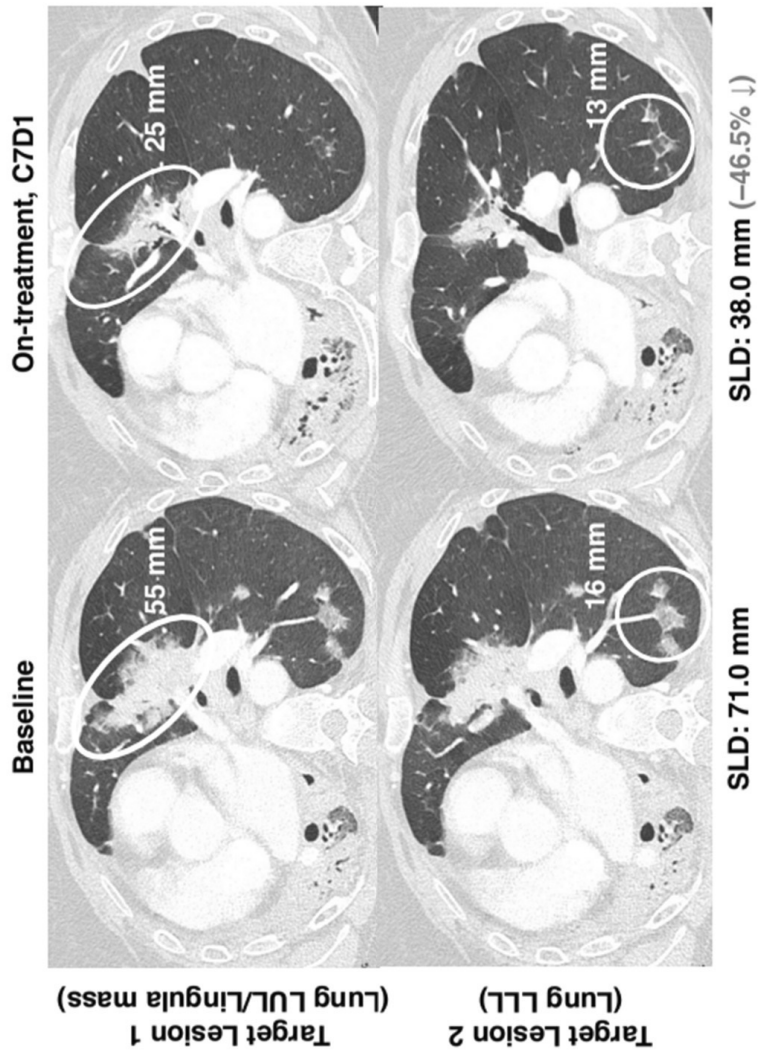

Baseline
On-treatment, C7D1
55 mm
25 mm
16 mm
13 mm
Target Lesion 1
(Lung LUL/Lingula mass)
Target Lesion 2
(Lung LLL)
SLD: 71.0 mm
SLD: 38.0 mm (–46.5% ↓)

FIG. 7

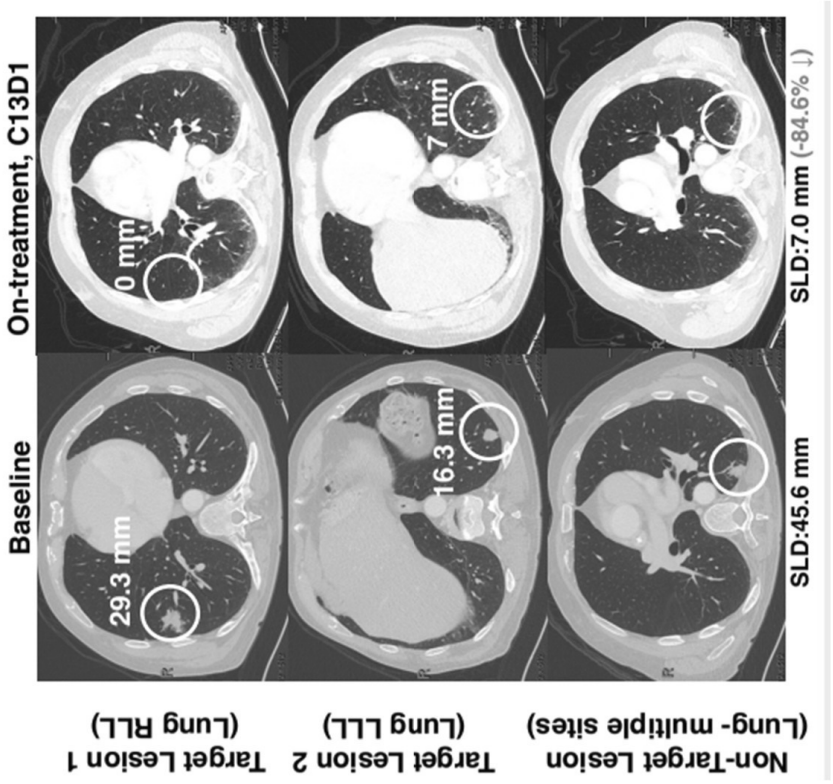

Baseline
On-treatment, C13D1
29.3 mm
0 mm
16.3 mm
7 mm
SLD:45.6 mm
SLD:7.0 mm (-84.6% ↓)
Target Lesion 1 (Lung RLL)
Target Lesion 2 (Lung LLL)
Non-Target Lesion (Lung- multiple sites)

FIG. 8

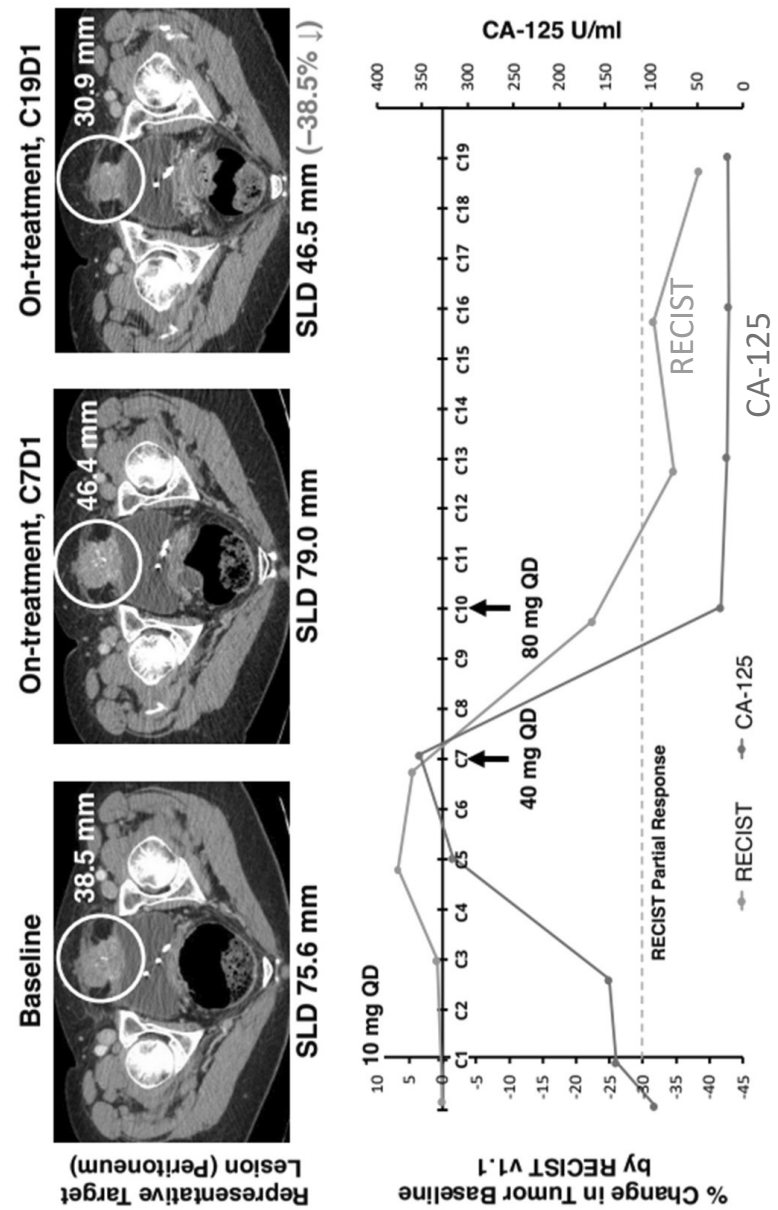
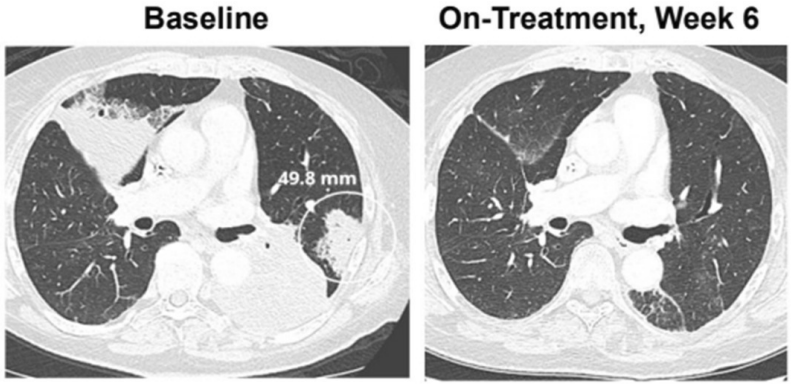

Baseline
On-treatment, C7D1
On-treatment, C19D1
38.5 mm
46.4 mm
30.9 mm
SLD 75.6 mm
SLD 79.0 mm
SLD 46.5 mm (–38.5% ↓)
Representative Target Lesion (Peritoneum)
% Change in Tumor Baseline by RECIST v1.1
CA-125 U/ml
10 mg QD
40 mg QD
80 mg QD
RECIST Partial Response
RECIST
CA-125

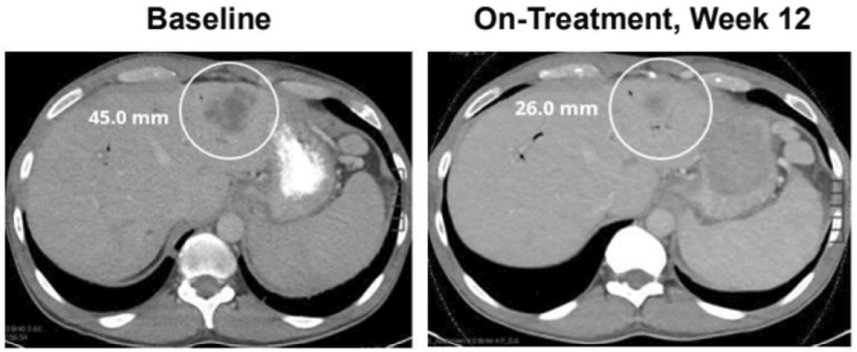
FIG. 9



Target Lesion: Lung, Left Lower Lobe

Target Lesion	Baseline	On Treatment
1. Lung (left upper lobe)	11.6 mm	0 mm
2. Lung (left lower lobe)	49.8 mm	0 mm
Sum of Diameters	61.4 mm	**0 mm (−100% ↓)**
Overall Response (RECIST 1.1)	--	**CR**

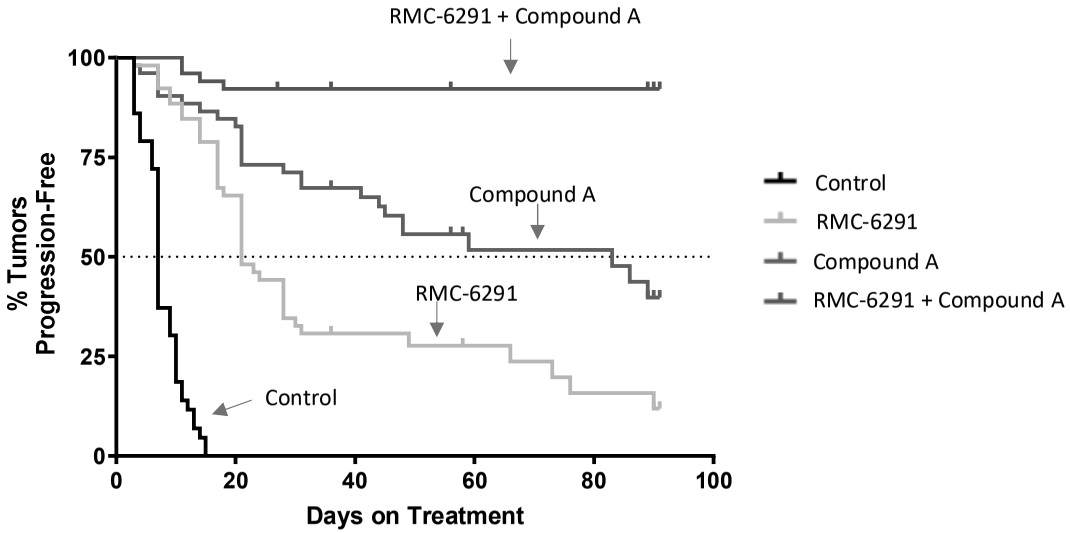
FIG. 10



Target Lesion: Segment 2 Liver

Target Lesion	Baseline	On Treatment
1. Segment 2 liver	45 mm	26 mm
2. Lung (medial basilar left lower lobe nodule)	17 mm	6 mm
3. Lung (right lower lobe nodule)	10 mm	6 mm
Sum of Diameters	72 mm	38 mm **(−47% ↓)**
Overall Response (RECIST 1.1)	--	**PR**

FIG. 11



- RAS(ON) Inhibitor doublet evaluated across seven models, including five identified as resistant to RMC-6291 monotherapy

(1) RVMD preclinical research; NSCLC = non-small cell lung cancer; Compound A dosed at 25 mg/kg po qd (n=52); RMC-6291 dosed at 100 or 200 mg/kg po qd (n=52); Combination (n=51). For each group, n = total number of animals from the seven models that comprise the dataset. Progression defined as tumor doubling from baseline.

FIG. 12