NASDAQ: MRTX

MIRATI THERAPEUTICS

Targeting the genetic and immunological drivers of cancer

A phase 1 clinical trial evaluating the pharmacokinetics (PK), safety, and clinical activity of MRTX849, a mutant-selective small molecule KRAS G12C inhibitor, in advanced solid tumors

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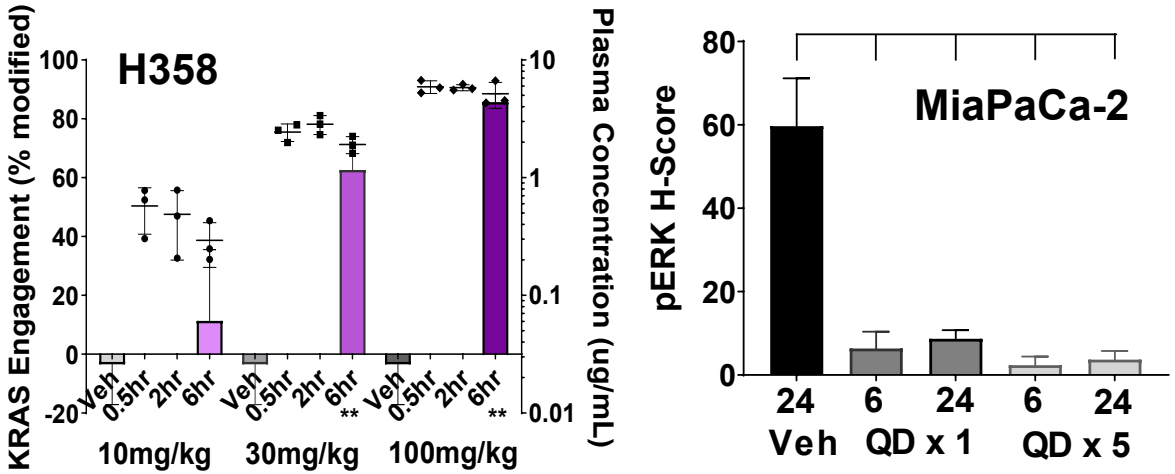
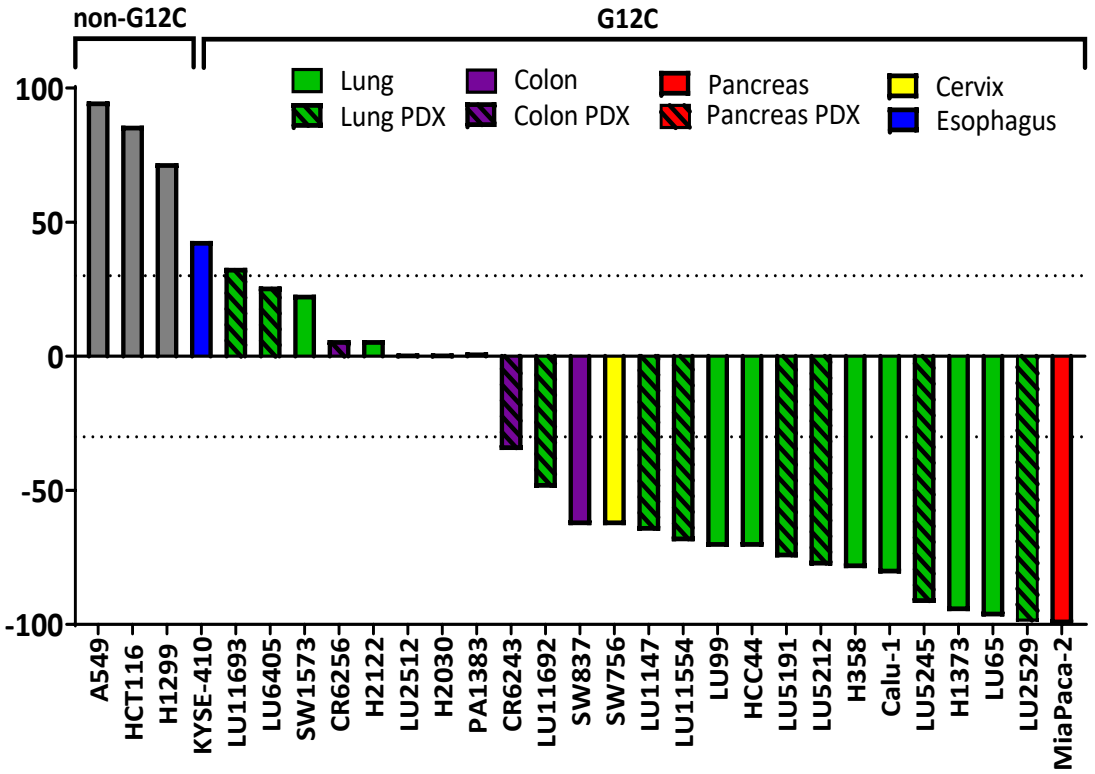
MRTX849 Demonstrates Near Complete Target Inhibition and Broad Spectrum Antitumor Activity In Nonclinical Models

Modification of KRAS^{G12C} Protein and Inhibition of pERK



- **MRTX849 demonstrates near-complete modification of KRAS^{G12C} protein and inhibition of pERK – and is well tolerated – at 100 mg/kg**
- **Protein binding-corrected plasma exposure in human exceeds levels in mouse at 100 mg/kg**
- **Response rate in nonclinical CDX and PDX models is 65% in all models and 75% in NSCLC models**

Antitumor Activity of MRTX849 in Cancer Models



Concomitant mutations in TP53, KEAP1, or STK11 do not predict MRTX849 therapeutic response

Phase 1/2 Study of MRTX849 in Patients with Advanced Solid Tumors with KRASG12C Mutation

Study Population

- Solid tumor with *KRAS* (p.G12C) mutation based on Sponsor-approved test
- Unresectable or metastatic disease
- No available treatment with curative intent
- No active brain metastases

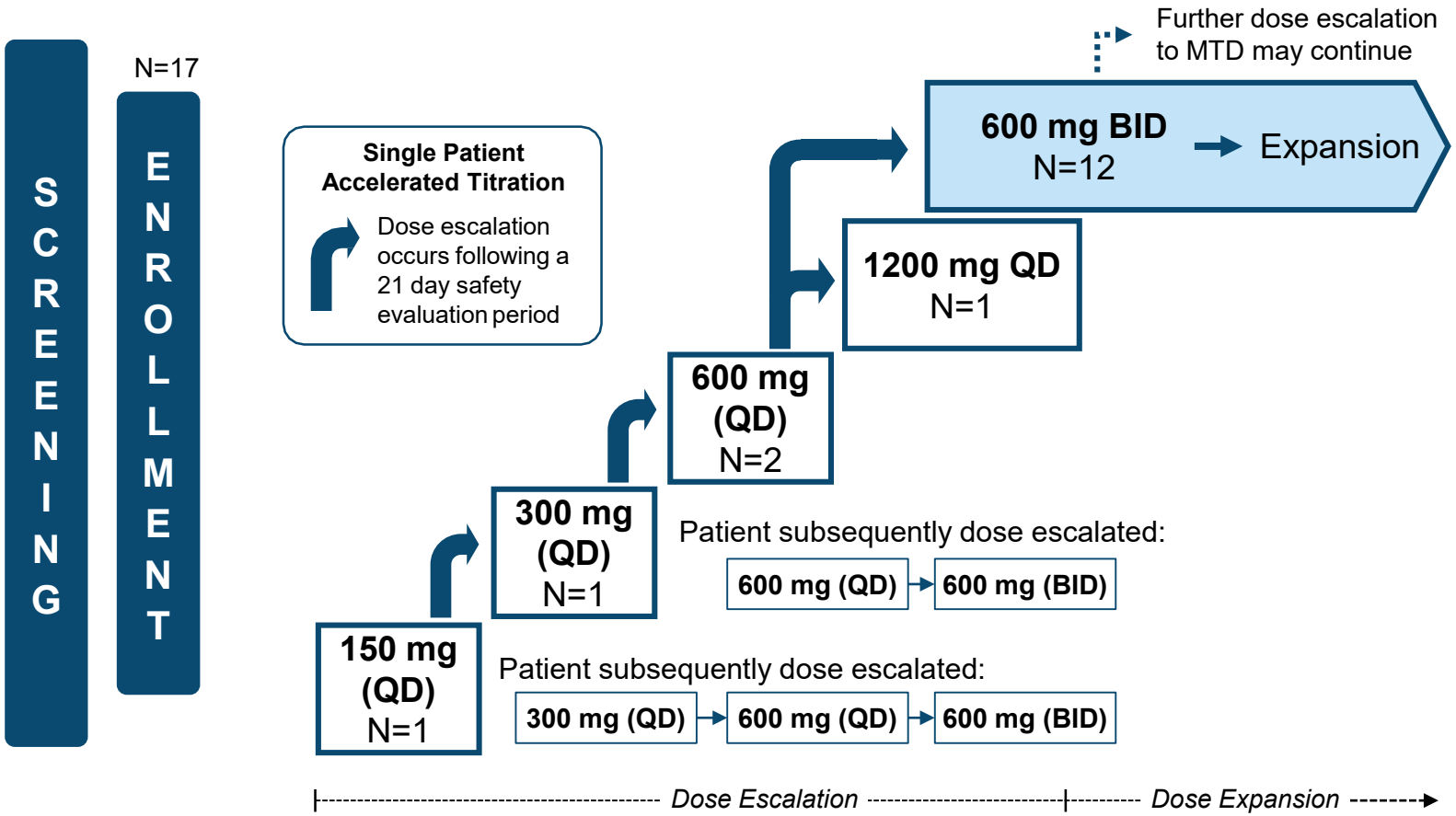
Study Endpoints

- Safety
- PK/PD
- Clinical Activity

Expansion Criteria

- Dose expansion decisions prior to MTD will be based on PK, PD, and safety

Doses Evaluated (as of 11-Oct-2019)



ClinicalTrials.gov Identifier: NCT03785249

Patient Disposition

Enrolled Patients
(received ≥ 1 dose MRTX849)

N=17
10 NSCLC, 4 CRC,
2 Appendiceal, 1 Duodenal

Evaluable Patients
(received ≥ 1 scan)

N=12
6 NSCLC, 4 CRC,
2 Appendiceal

Non-Evaluable Patients

Yet to have 1st scan
N=3

Off treatment prior to 1st scan
N=2*

* 1 patient withdrew consent prior to 1st scan (1200 mg QD);
1 patient discontinued treatment due to an unrelated AE prior to 1st scan (600 mg QD)

Data cut-off date: 11-Oct-2019

Patient Demographics and Baseline Characteristics

Baseline Characteristics	N=17
Age – median (range), years	60 (44-76)
Race	
White, n (%)	15 (88)
Black, n (%)	1 (6)
Asian, n (%)	1 (6)
Sex	
Male, n (%)	9 (53)
Female, n (%)	8 (47)
ECOG Performance Status	
0, n (%)	10 (59)
1, n (%)	7 (41)
Diagnosis	
Non-Small Cell Lung Cancer, n (%)	10 (59)
Colorectal Cancer, n (%)	4 (24)
Other Tumor Type, n (%)	3 (18)

Data cut-off date: 11-Oct-2019

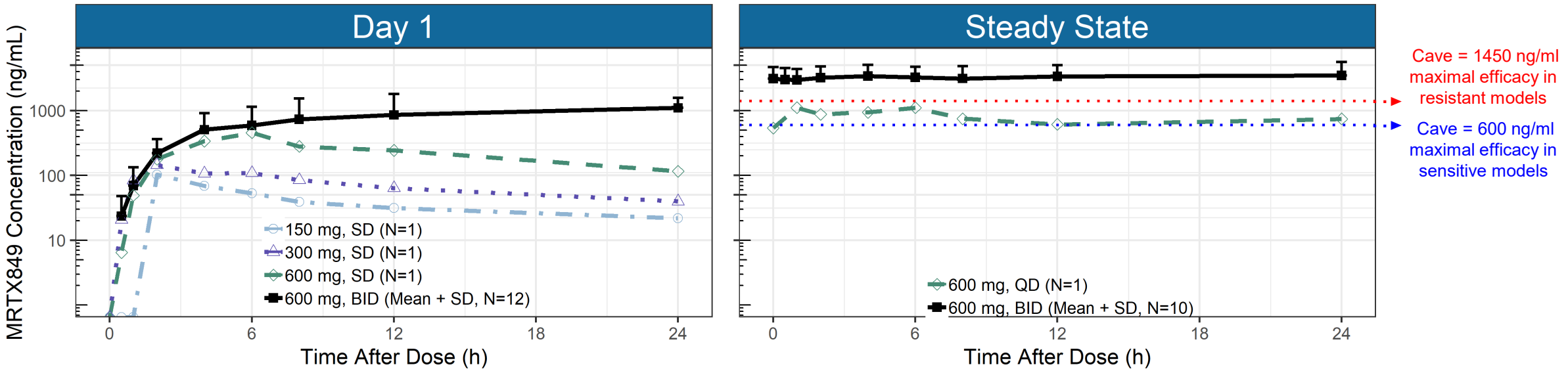
Patient Population

	All Patients N=17	NSCLC N=10	CRC N=4
Smoking History			
Lifetime Never Smoker	5 (29)	0	3 (75)
Former Smoker	12 (71)	10 (100)	1 (25)
Histology			
Adenocarcinoma	16 (94)	10 (100)	3 (75)
No. Prior Regimens			
1, n (%)	4 (24)	2 (20)	0
2, n (%)	1 (6)	1 (10)	0
≥3, n (%)	12 (71)	7 (70)	4 (100)
Median (Range)	3 (1-9)	3 (1-9)	4 (3-5)
Type of Prior Regimens			
Checkpoint Inhibitor[1], n (%)	10 (59)	9 (90)	1 (25)
Cisplatin or Carboplatin, n (%)	10 (59)	10 (100)	0
Oxaliplatin, n (%)	5 (29)	0	4 (100)
Irinotecan, n (%)	6 (35)	1 (10)	4 (100)

[1]Includes pembrolizumab, nivolumab, atezolizumab regimens

Data cut-off date: 11-Oct-2019

Mean MRTX849 Plasma Concentrations Following Single and Multiple Oral Dose Administration QD and BID



600 mg BID GeoMean (CV%)					
Period	**C_{max} (ng/mL)**	**AUC_{0-24} (ug*h/mL)**	**C_{ave} (ng/mL)**	**$t½$ (h)**	**$t½\_{eff}$ (h)**
Day 1 (N=12)	**513 (101.0)**	**12.1 (69.5)[a]**	**318 (79.8)**	**24.7[b]**	**-**
Steady State (N=10)	**3180 (50.4)**	**69.8 (58.6)[a]**	**2880 (51.4)**	**-**	**63.2 (76.6)**

Median (Min-Max); [a]N=9; [b]N=1 (Only 1 patient contributed to the lead-in 96 hours post-dose sampling);
Data Source: Interim Pharmacokinetic Data (14 October 2019)

The C_{ave} achieved at 600 mg BID at steady-state is:

- 2-fold above concentration associated with maximal efficacy in resistant models (1450 ng/ml)
- 5-fold above concentration associated with maximal efficacy in sensitive models (600 ng/ml)

Patient Incidence of Treatment Related AEs (>10%)
The MTD has not yet been established

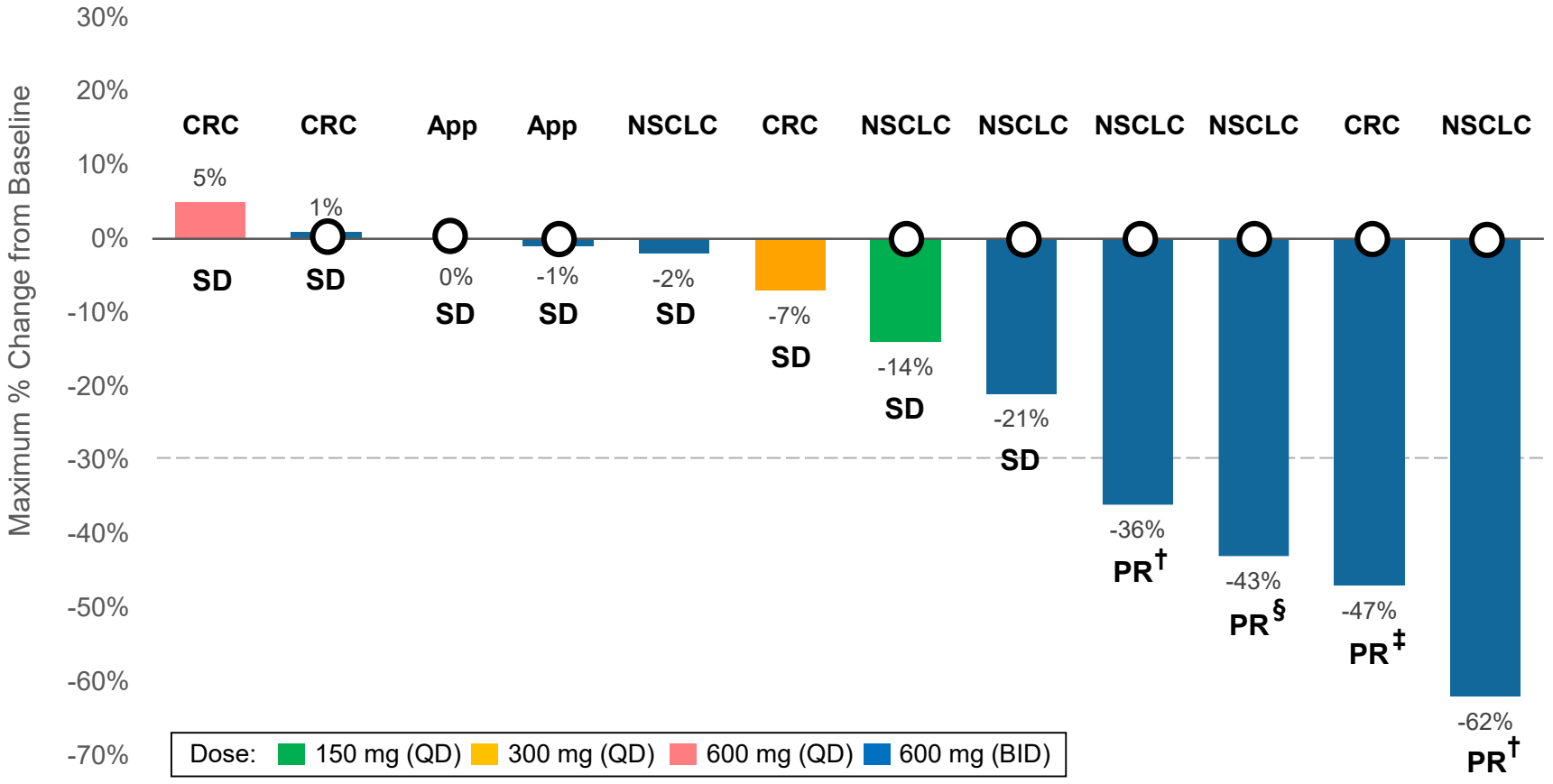
Treatment-Related AEs (N=17)	Grade 1 n	Grade 2 n	Grade 3 n
Diarrhea	6	6	0
Nausea	8	2	0
AST Increased	5	0	0
Vomiting	4	1	0
Fatigue	2	1	1
ALT Increased	3	0	0
Creatinine Increased	3	0	0
Abdominal Distension	2	0	0
Abdominal Pain	2	0	0
Alkaline Phosphatase Increased	1	1	0

Treatment-Related AEs (N=17)	Grade 1 n	Grade 2 n	Grade 3 n
Anemia	0	2	0
Decreased Appetite	2	0	1
Dehydration	0	2	0
Dry Mouth	2	0	0
Dysgeusia	0	2	0
Dyspnea	0	1	1
QT Prolonged	1	1	0
Hypomagnesemia	2	0	0
Rash	2	0	0

Dose limiting toxicities observed: 1200 QD capsule burden intolerable (12 capsules), limited dose exposure <80%;
600 mg BID grade 3/4 amylase/lipase increase, isolated enzyme elevation without pancreatitis (only treatment related Grade 4 AE observed)

Data cut-off date: 11-Oct-2019

All Evaluable Patients: Best Tumor Response* (N = 12)



Evaluable Patients at All Doses	
NSCLC	ORR: 3/6 DCR: 6/6
CRC	ORR: 1/4 DCR: 3/4
Append	ORR: 0/2 DCR: 2/2

DCR: Disease Control Rate (SD+PR at 6 weeks)

* Based on local radiographic scans every 6 weeks using RECIST 1.1 criteria

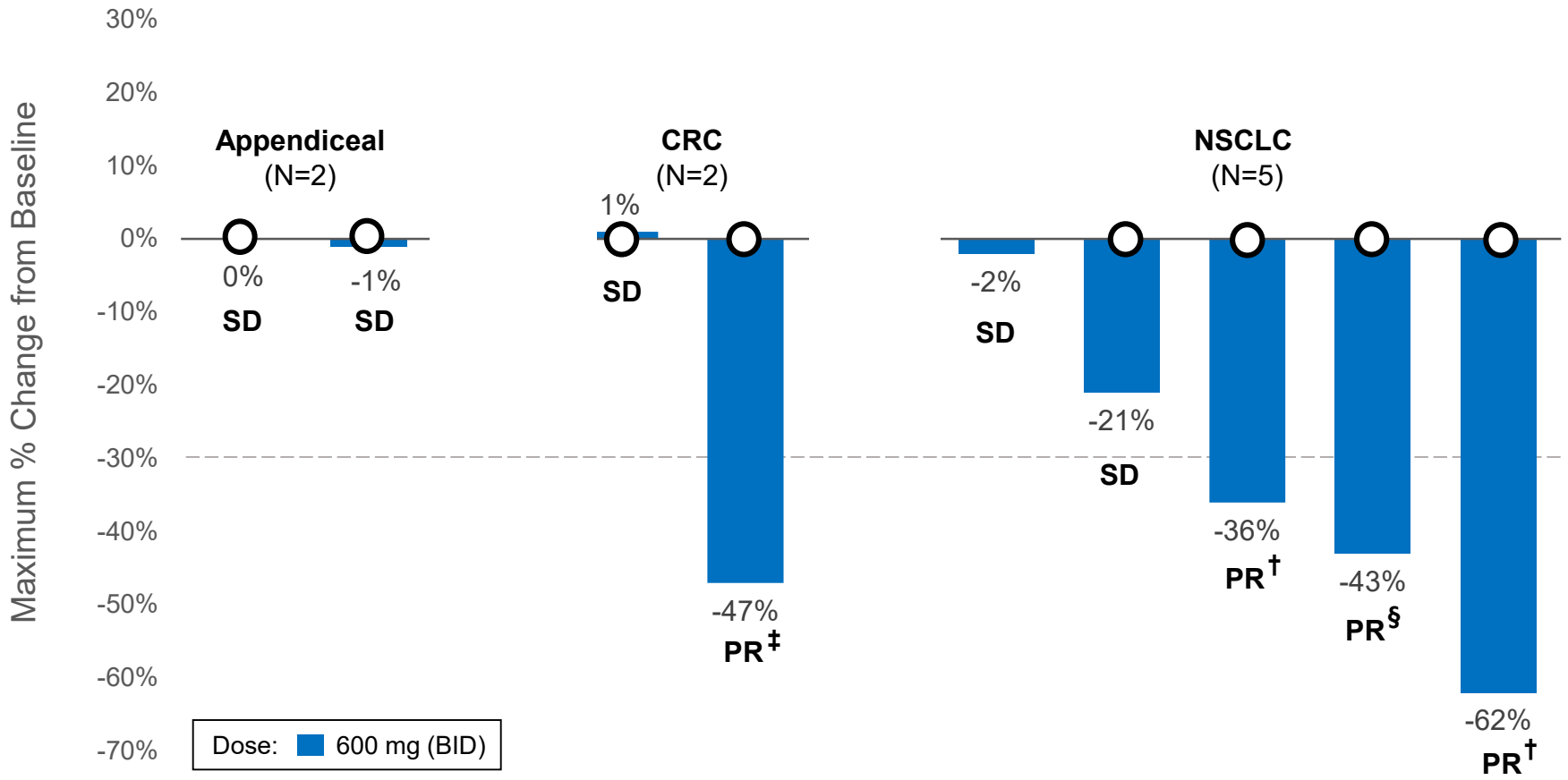
‡ Confirmed response (1st scan: -37%, 2nd scan: -47%); † Response yet to be confirmed (on study but only 1 scan)

§ Patient had confirmed PR post data cut-off (1st scan: -33%, 2nd scan: -43%)

O Patient on study (off study patients: 1 progressive disease, 1 global deterioration of health, 1 patient withdrawal of consent)

Data cut-off date: 11-Oct-2019

600 mg BID Dose Patients: Best Tumor Response* (N = 9)



Evaluable Patients at 600mg BID	
NSCLC	ORR: 3/5 DCR: 5/5
CRC	ORR: 1/2 DCR: 2/2
Append	ORR: 0/2 DCR: 2/2

ORR: Overall Response
DCR: Disease Control Rate (SD+PR at 6 weeks)

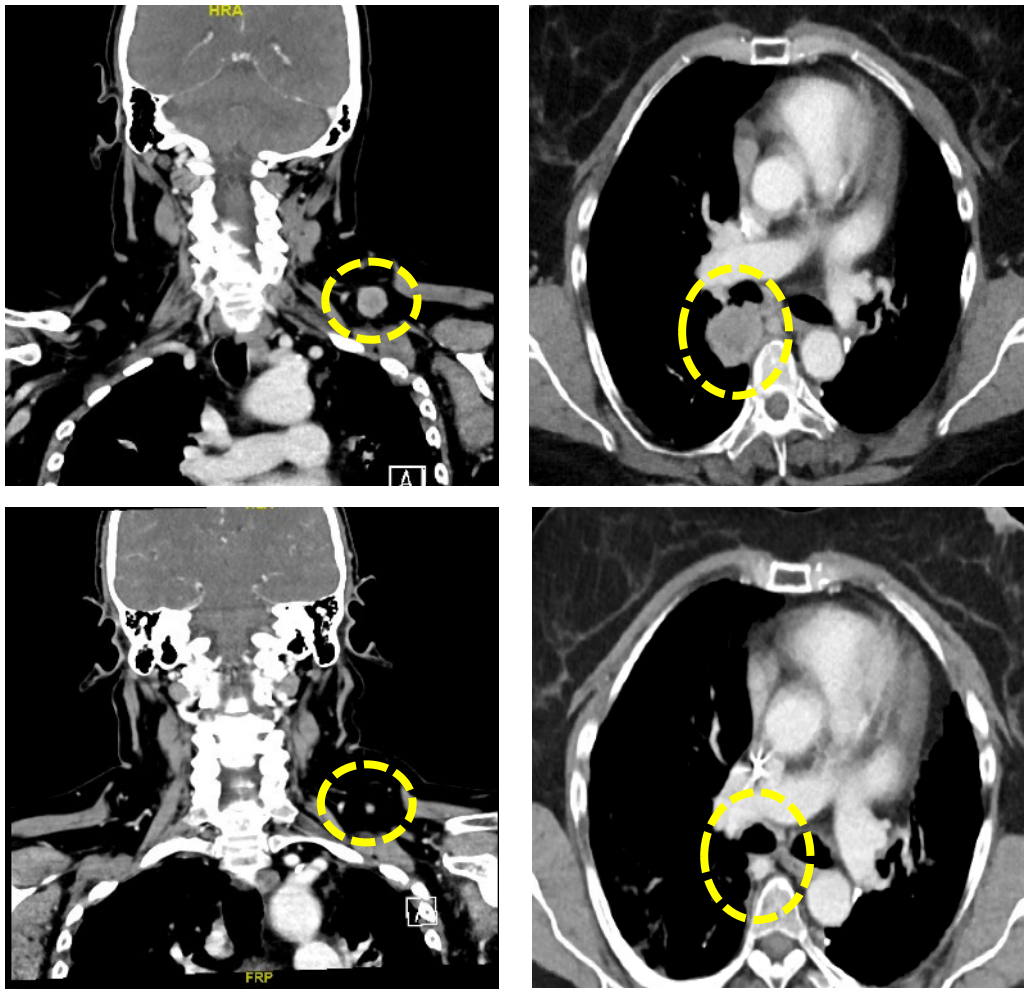
* Based on local radiographic scans every 6 weeks using RECIST 1.1 criteria
‡ Confirmed response (1st scan: -37%, 2nd scan: -47%); † Response yet to be confirmed (on study but only 1 scan);
§ Patient had confirmed PR post data cut-off (1st scan: -33%, 2nd scan: -43%)
O Patient on study (off study patient: 1 patient withdrawal of consent)

Data cut-off date: 11-Oct-2019

Case Study #1: NSCLC

Baseline

Post cycle 2



-62%

Demographics

61 year old female with metastatic NSCLC, former smoker

Molecular Characteristics

- *KRAS* G12C mutation (c.34G>T), High mutant allele freq
- High TMB: 16.7 mut/megabase, no additional notable mutations

Treatment History

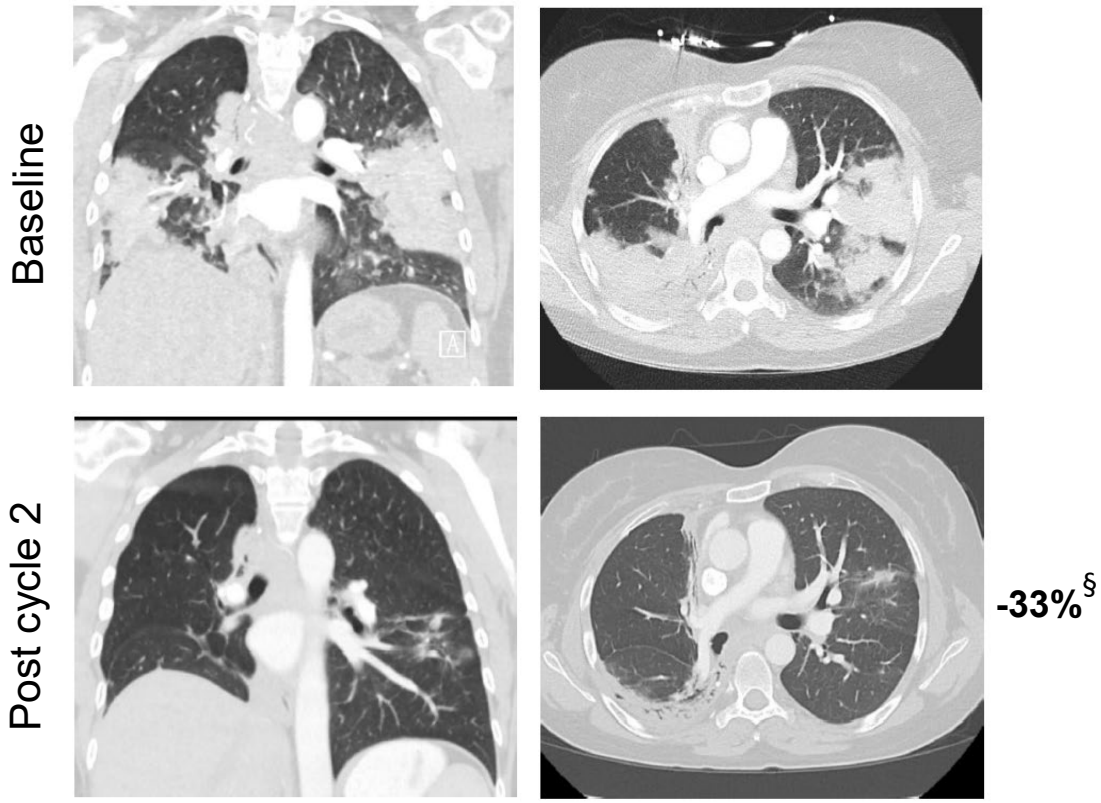
- Cisplatin/pemetrexed with concurrent chemoradiation
- RLL wedge resection and LLL lobectomy
- 8 chemotherapy regimens for recurrent disease, including carboplatin/pemetrexed, selumetinib, carboplatin/gemcitabine, gemcitabine monotherapy, pembrolizumab, vinorelbine, irinotecan, and paclitaxel, all without an objective response.

Best Response

PR: 62% reduction at first scan. The patient remains on study.

Prominent neck mass noted smaller by week 1 and no longer detectable by week 2. Notable increase in energy and activity during continued treatment.

Case Study #2: NSCLC



§ This patient had confirmed PR post data cut-off (1st scan: -33%, 2nd scan: -43%)

Demographics

45 year old female with metastatic lung adenocarcinoma, former smoker

Molecular Characteristics

- *KRAS* G12C mutation (c.34G>T)
- *KEAP1* (K97M)
- *STK11* (E223*)

Treatment History

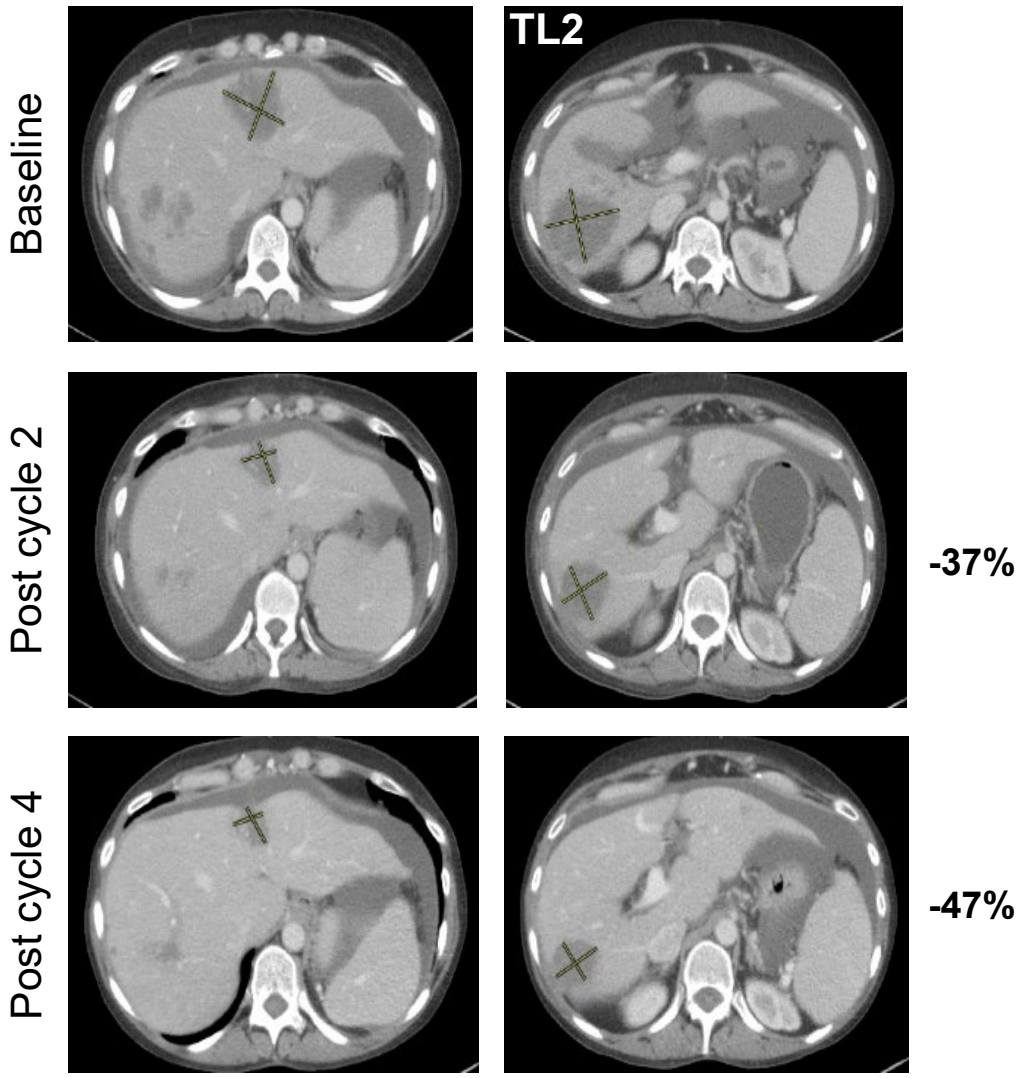
- Carboplatin/pemetrexed/pembrolizumab
- Docetaxel
- Investigational treatment with binimetinib plus palbociclib
- Best response on prior regimens is SD

Best Response

PR: 33% reduction at first scan. A 43% reduction was observed at the second scan, after the data cut-off. The patient remains on study.

Marked clinical improvement within 2 weeks, including complete resolution of baseline cough and oxygen dependency.

Case Study #3: CRC



Demographics

47 year old KRAS (p.G12C) female with adenocarcinoma of the left colon with extensive metastases involving the liver, peritoneum, ovaries and lymph nodes, never smokers

Treatment History

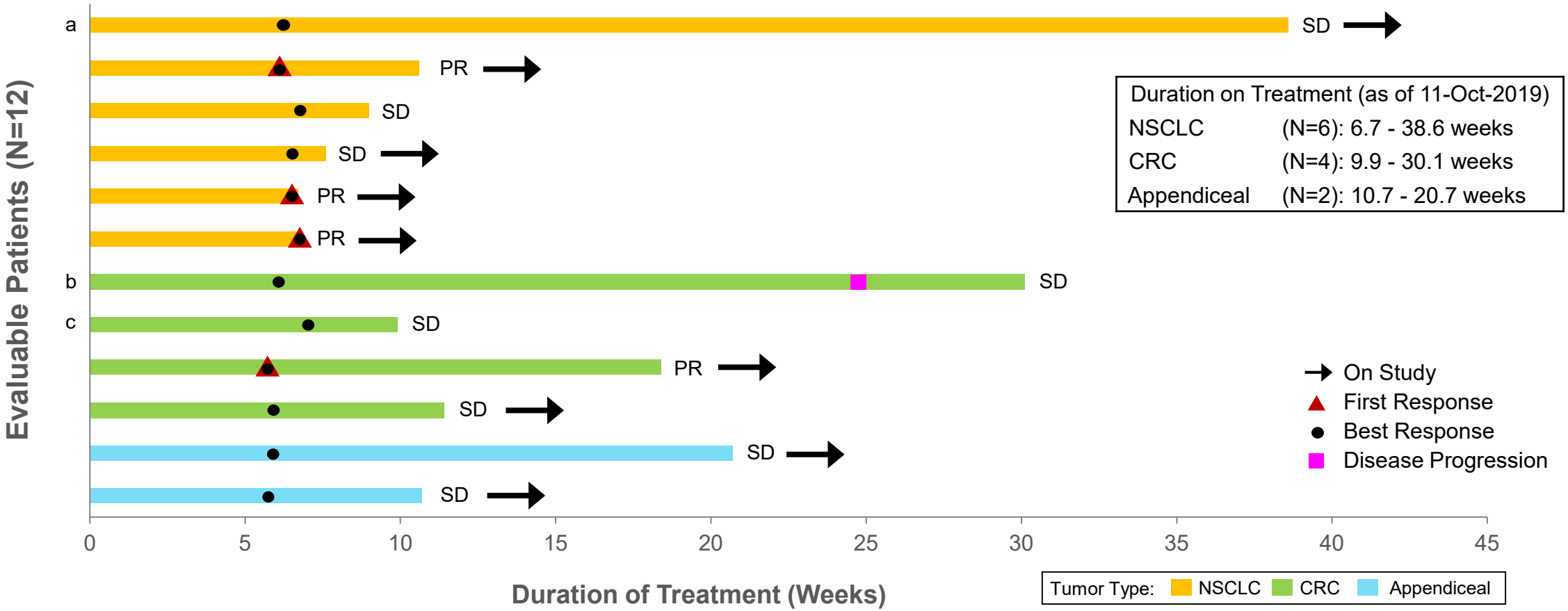
- FOLFOX/bevacizumab, partial response
- Capecitabine monotherapy, no response
- FOLFIRI/bevacizumab, no response
- Investigational antibody drug conjugate, no response

Best Response

PR: 37% reduction at first scan, confirmed PR with 47% reduction at second scan. The patient remains on study.

Marked clinical improvement within 3 weeks and a visible decrease in size of her umbilical Sister Mary Joseph's nodule

Duration of Treatment by Tumor Types and Responses (N=12)



Dose: a. 150 mg QD; b. 300 mg QD; c. 600 mg QD; all other patients received 600 mg BID

Data cut-off date: 11-Oct-2019

Conclusions

- MRTX849 is rationally designed, potent, mutant-selective inhibitor of $KRAS^{G12C}$ that irreversibly binds to and locks $KRAS^{G12C}$ in its inactive, GDP-bound state
- MRTX849 is orally bioavailable and demonstrates linear pharmacokinetics with extensive tissue distribution and a half-life of approximately 25 hours after a single dose (effective $t_{1/2}$ at SS is 63 h)
- MRTX849 is associated with a favorable safety profile and clinical expansion is being pursued at 600 mg BID
  - Expansion cohorts for NSCLC, CRC, and multi-tumor basket underway
- MRTX849 has demonstrated significant clinical activity in heavily pretreated patients, with objective responses observed in patients without responses to prior treatment regimens
- Clinical activity supports the role for inhibition of mutant KRAS in cancer treatment

With Thanks to Patients, Caregivers, Research Staff, and Investigators

趙 CHAO FAMILY
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