elcc European Lung Cancer Congress 2023

Adagrasib (MRTX849) in Patients With Advanced/Metastatic KRAS^{G12C}-Mutated Non-Small Cell Lung Cancer (NSCLC): Preliminary Analysis of Mutation Allele Frequency

Pasi A. Jänne[1], Alexander I. Spira[2], Gregory J. Riely[3], Shirish M. Gadgeel[4], Rebecca S. Heist[5], Sai-Hong Ignatius Ou[6], Melissa L. Johnson[7], Joshua K. Sabari[8], Karen Velastegui[9], James G. Christensen[9], Wenjing Yang[9], Kenna Anderes[9], Richard C. Chao[9], Cloud P. Paweletz[1]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Virginia Cancer Specialists, Fairfax, VA, USA; US Oncology Research, The Woodlands, TX, USA; NEXT Oncology, Fairfax, VA, USA; [3]Thoracic Oncology Service, Division of Solid Tumor, Department of Medicine, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA; [4]Henry Ford Cancer Institute, Detroit, MI, USA; [5]Massachusetts General Hospital, Boston, MA, USA; [6]University of California, Irvine, Chao Family Comprehensive Cancer Center, Orange, CA, USA; [7]Sarah Cannon Research Institute Tennessee Oncology, Nashville, TN, USA; [8]Perlmutter Cancer Center, New York University Langone Health, New York, NY, USA; [9]Mirati Therapeutics, Inc., San Diego, CA, USA

Organisers

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

IASLC

Partners

ESTRO

ESTS

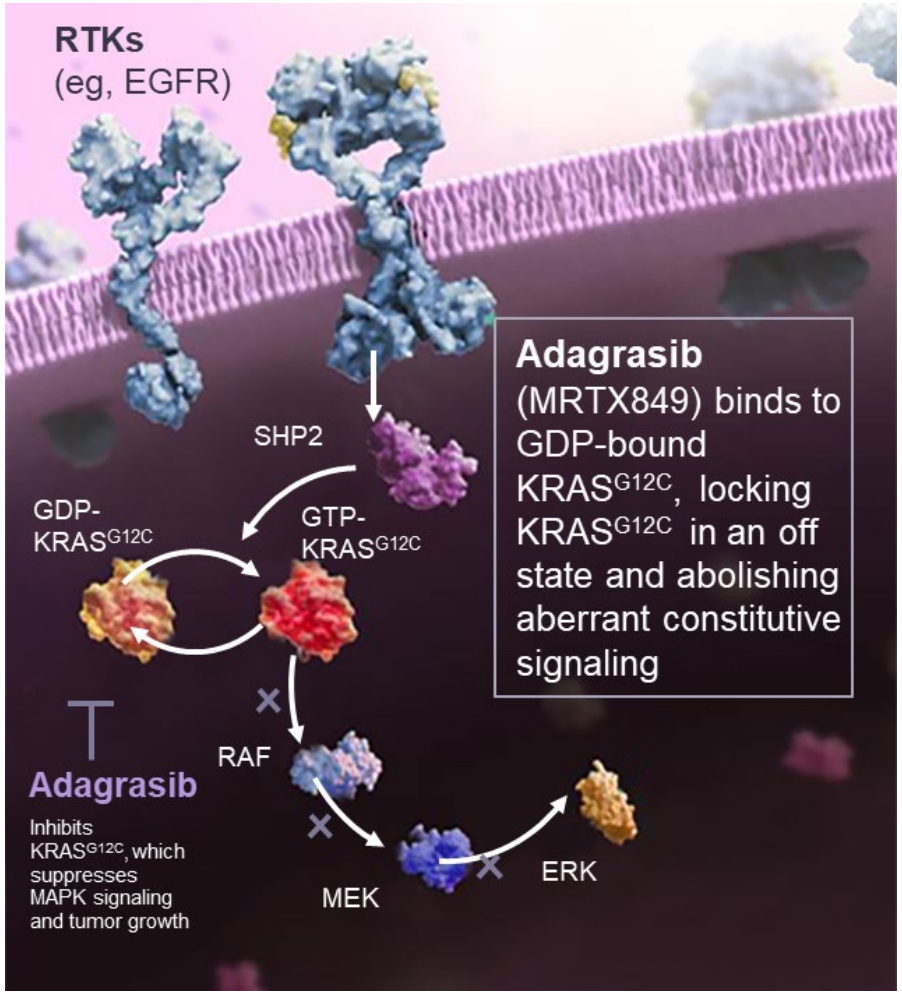
ETOP·IBCSG PARTNERS

Disclosures

- Dr Jänne declares the following conflicts of interest:
- Stocks/shares: Gatekeeper Pharmaceuticals
- Sponsored research: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Revolution Medicines, Takeda Oncology, Daiichi Sankyo
- Advisory role: AstraZeneca, Boehringer Ingelheim, Pfizer, Roche/Genentech, Eli Lilly, SFJ Pharmaceuticals, Voronoi, Daiichi Sankyo, Novartis, Biocartis, Takeda Oncology, Transcenta, Silicon Therapeutics, Syndax, Nuvalent, Allorion Therapeutics, Accutar Biotech, AbbVie, Bayer, Eisai, Monte Rosa, Scorpion Therapeutics, Merus, Frontier Medicines, Hongyun Biotechnology

Adagrasib (MRTX849) is a Differentiated KRAS^{G12C} Inhibitor

- Adagrasib, a selective KRAS^{G12C} inhibitor, was selected for desired properties, including a long half-life (23 hours), dose-dependent PK and CNS penetration[1,2]
- Adagrasib has been granted accelerated approval by the FDA and is under review by the EMA for use in patients with previously treated advanced/metastatic KRAS^{G12C}-mutated NSCLC[3]
- In the registrational Phase 2 cohort, adagrasib demonstrated promising clinical activity (ORR, 43%; DCR, 80%) as well as a manageable safety profile, in patients with previously treated NSCLC harboring a KRAS^{G12C} mutation[4]
- Clinical activity with adagrasib has been shown in patients across multiple KRAS^{G12C}-mutated solid tumors, including patients with NSCLC and treated/untreated CNS metastases[4–7]



KRYSTAL-1 (849-001) Phase 2 Cohort A Study Design

Phase 2
NSCLC Monotherapy Treatment

Key Eligibility Criteria

- NSCLC with KRAS^{G12C} mutation[a]
- Unresectable or metastatic disease
- Prior treatment with a PD-1/L1 inhibitor in combination or in sequence with chemotherapy
- Treated, stable CNS metastases were allowed

Adagrasib 600 mg BID (Capsule, Fasted)

N=116

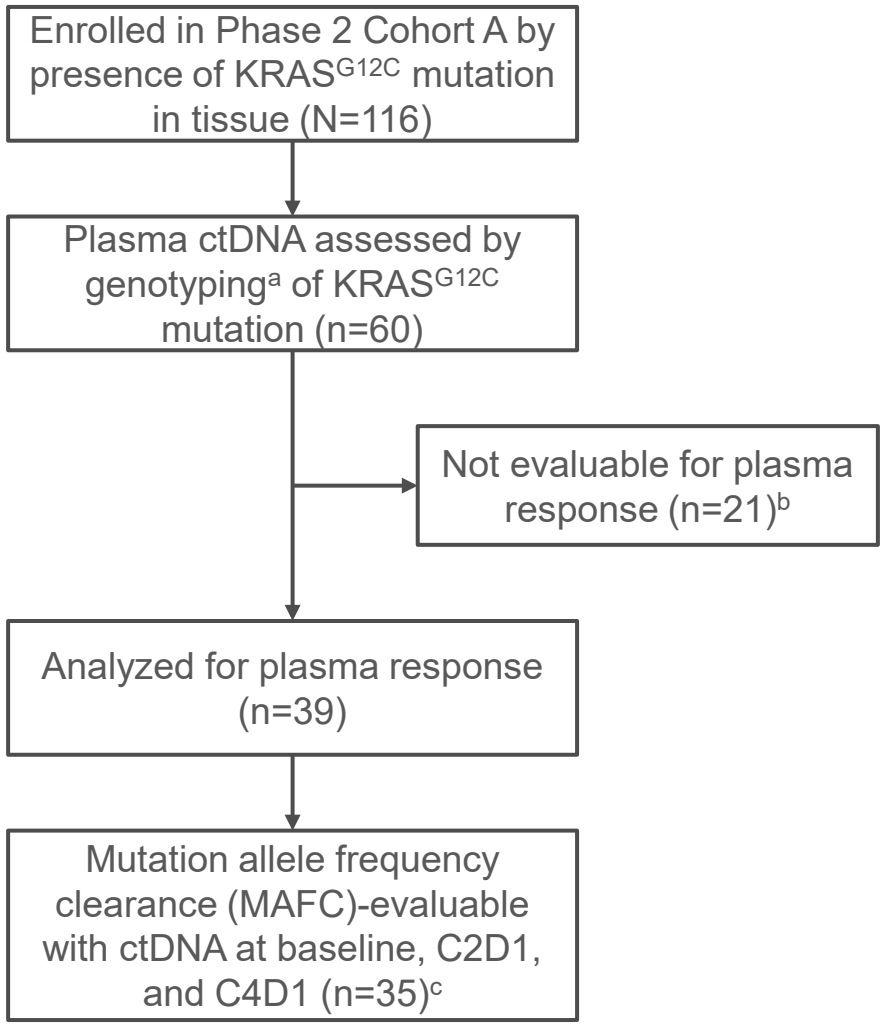
Study Objectives

- Primary endpoint: ORR (RECIST 1.1) per BICR
- Secondary endpoints: DOR, PFS, OS, safety
- Exploratory endpoints: correlative analyses, plasma ctDNA response[b]

Here we report an exploratory analysis of clinical response according to levels of KRAS^{G12C} ctDNA, in those patients with detectable plasma ctDNA (n=39)

[a]KRAS^{G12C} mutation detected in tumor tissue by sponsor-approved local laboratory testing. [b]Quantitative assessment was performed by ddPCR or by Agilent Resolution ctDx FIRST[8]
ClinicalTrials.gov. NCT03785249

Patient Flow, Demographics and Baseline Characteristics



	Adagrasib Monotherapy (N=116)[4,d]	Analyzed for Plasma Response (N=39)
Median age (range), years	64 (25–89)	63 (25-84)
Female sex, n (%)	65 (56%)	22 (56%)
Race, n (%)		
White	97 (84%)	32 (82%)
Black or African American	9 (8%)	2 (5%)
Asian / Other	5 (4%) / 5 (4%)	2 (5%) / 3 (8%)
ECOG PS, n (%)		
0 / 1	18 (16%) / 97 (84%)[e]	9 (23%) / 30 (77%)
Smoking history, n (%)		
Never smoker	5 (4%)	1 (3%)
Current smoker / former smoker	11 (10%) / 100 (86%)	1 (3%) / 37 (95%)
Prior lines of systemic therapy, n (%)		
1 / 2+	50 (43%) / 66 (57%)	16 (41%) / 23 (59%)
Clinical efficacy[f]		
ORR	43%[g]	56%
Median PFS	6.5 months[g]	6.9 months

[a]By ddPCR or Agilent Resolution ctDx FIRST. [b]Due to reasons of: missing specimens at baseline (n=14), non-detection of KRASG12C mutation at baseline (n=6), or missing specimens from C2D1 (n=1)
[c]Of 39 patients analyzed, four had missing C4D1 data and were therefore not evaluable for MAFC. [d]Among the enrolled patients, 113 (97%) had adenocarcinoma and 3 (3%) had squamous histology; 103 patients (89%) had metastatic disease and 13 (11%) had locally advanced disease. [e]Missing, n=1. [f]Data cutoff: 15 October 2021 (median follow-up: 12.9 months). [g]N=112

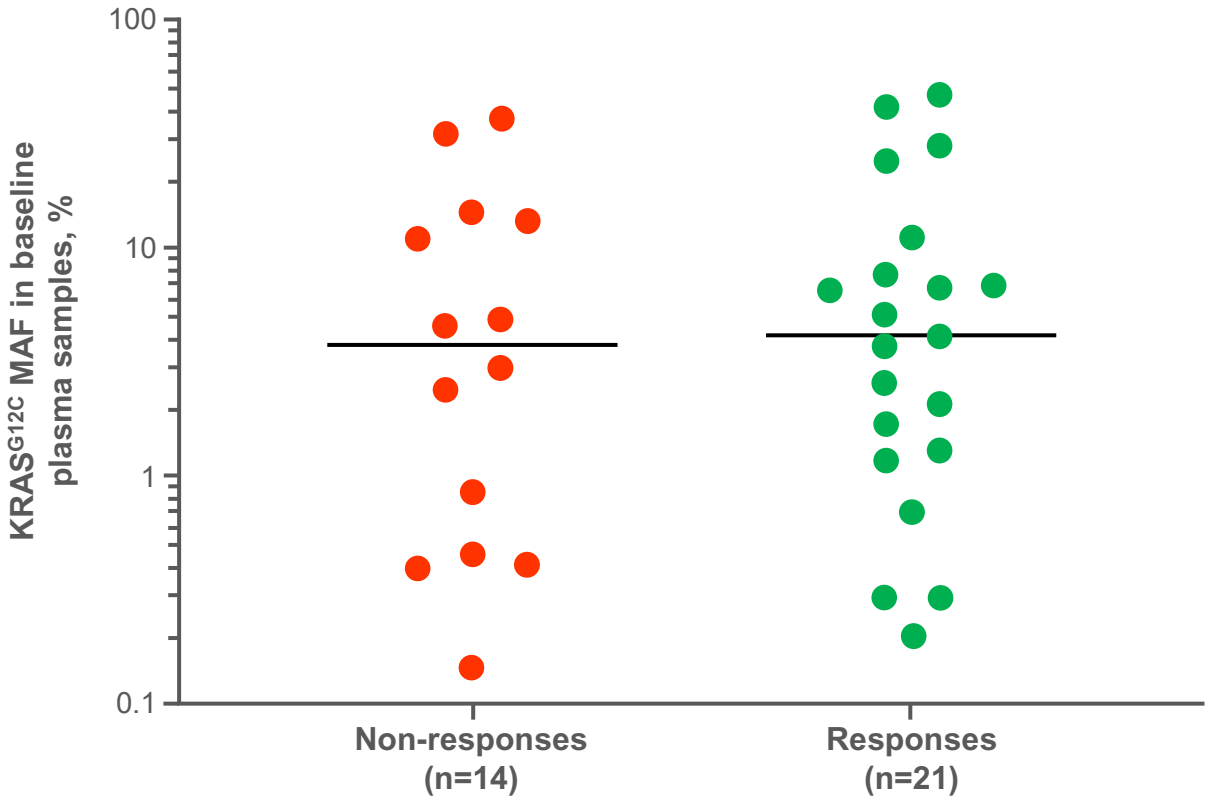
Exploratory Analysis: ORR by MAFC

	MAFC-Evaluable Patients, n (%) (N=35)[a]	Patients With Radiographic Response, n (%)
MAFC ≥90% by C4D1	31 (89%)	21 (68%)
MAFC <90% by C4D1	4 (11%)	0

- In MAFC-evaluable patients, 89% (31/35) had MAFC ≥90% by C4D1
- ORR was 68% (21/31) in patients with MAFC ≥90%; ORR was 0% (0/4) in patients with MAFC <90% by C4D1
- Complete clearance (–100%) of the KRAS^{G12C} mutant allele at both C2D1 and C4D1 was observed in 77% (27/35) of patients, with radiographic responses observed in 67% (18/27) of those patients

[a]ctDNA samples available at baseline, C2D1 and C4D1

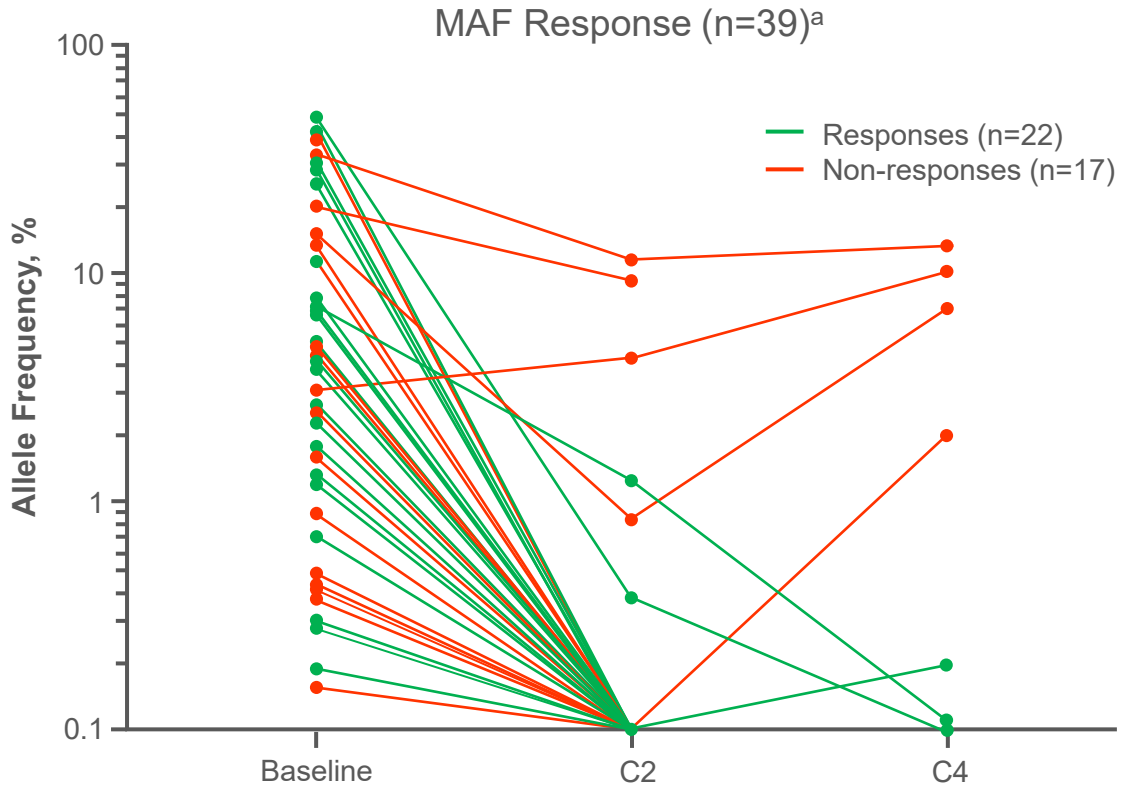
Exploratory Analysis: MAF at Baseline by Response

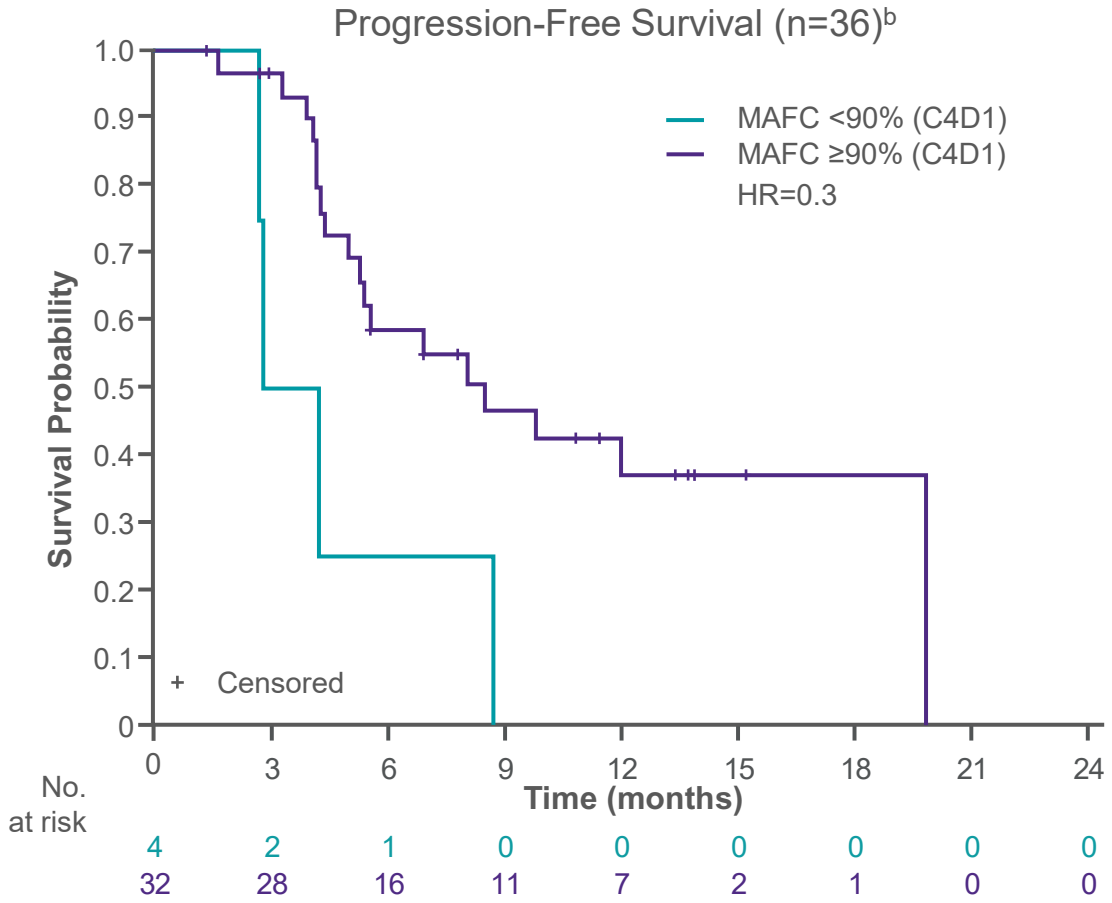


- In MAFC-evaluable patients, KRAS^{G12C} MAF at baseline did not appear to correlate with response (median MAF: 3.8 for non-responses, 4.2 for responses)

MAF ranged from 0.15% to 47.9% at baseline for the MAFC-evaluable population

Exploratory Analysis: Additional Efficacy Analyses by MAFC





- All responses corresponded with MAFC ≥90%
- MAFC-evaluable patients without a response had a BOR of SD (n=13) or PD (n=1) and MAFC range at C4D1 of complete clearance (–100%; n=9) to +235% (n=1)[c]
- MAFC ≥90% at C4D1 was associated with longer PFS versus MAFC <90% at C4D1

[a]All patients analyzed. [b]ctDNA samples available at baseline and C4D1. [c]ctDNA samples available at baseline, C2D1 and C4D1

Conclusions and Future Directions

- In this registrational Phase 2 cohort, adagrasib showed promising efficacy and manageable tolerability in previously treated patients with advanced/metastatic KRAS^{G12C}-mutated NSCLC
- This exploratory analysis of ctDNA MAFC suggests objective responses and increased PFS are associated with MAFC ≥90%; however, not all patients with MAFC ≥90% demonstrated clinical benefit
- A confirmatory Phase 3 study is enrolling, evaluating adagrasib monotherapy versus docetaxel in previously treated patients with advanced/metastatic KRAS^{G12C}-mutant NSCLC (KRYSTAL-12; NCT04685135)

For more information contact Mirati Medical Information at medinfo@mirati.com

Acknowledgments

- The patients and their families for making this trial possible
- The clinical study teams and investigators for their work and contributions
- This study is supported by Mirati Therapeutics, Inc.
- All authors contributed to and approved this presentation; writing and editorial assistance were provided by Rebecca Benatan, BSc, of Ashfield MedComms, an Inizio company, and was funded by Mirati Therapeutics, Inc.

Investigators

John Adams
USOR, Texas Oncology, Arlington

Scott Anderson
Goldschmidt Cancer Center

Minal Barve
Mary Crowley Cancer Research

Lyudmila Bazhenova[a]
University of California San Diego

David Berz
Beverly Hills Cancer Center

David Ellison
USOR, Charleston Hematology Oncology Associates

Shirish M. Gadgeel
Henry Ford Cancer Institute/ Henry Ford Health System

David Hakimian
USOR, Illinois Cancer Specialists

Rebecca S. Heist
Massachusetts General Hospital

Pasi A. Jänne[a]
Dana-Farber Cancer Institute

Melissa L. Johnson[a]
Sarah Cannon Research Institute

Scott Kruger
USOR, Virginia Oncology Associates

Nataliya Uboha
University of Wisconsin Carbone Cancer Center

Konstantinos Leventakos[a]
Mayo Clinic, Rochester

Yanyan Lou
Mayo Clinic, Jacksonville

Kristi McIntyre
USOR, Texas Oncology, Presbyterian Cancer Center Dallas

Jamal Misleh
USOR, Medical Oncology Hematology Consultants

Marcelo V. Negrao
MD Anderson Cancer Center

Sai-Hong Ignatius Ou[a]
University of California Irvine

Jose M. Pacheco[a]
University of Colorado

Kyriakos P. Papadopolous[a]
START San Antonio

Nathan A. Pennell[a]
Cleveland Clinic

Gregory J. Riely[a]
Memorial Sloan Kettering Cancer Center

Richard Rosenberg
USOR, Arizona Oncology Associates

Joshua Sabari[a]
Perlmutter Cancer Center

Alexander I. Spira[a]
Virginia Cancer Specialists

Anthony Van Ho
USOR, Compass Oncology

Jared Weiss[a]
University of North Carolina

Edwin Yau
Roswell Park Comprehensive Center

Jun Zhang[a]
University of Kansas

[a]Investigators recruiting patients with MAFC data