AACR American Association for Cancer Research®
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Selectively targeting KRAS mutant alleles: contribution of both cell autonomous and pro-immunogenic MOAs in an expanded spectrum of human cancers

James G. Christensen, PhD
Mirati Therapeutics, San Diego, CA

Disclosure Information

James G Christensen

I have the following relevant financial relationships to disclose:

Employee and Shareholder of Mirati Therapeutics

I will be discussing investigational use of adagrasib

DO NOT POST

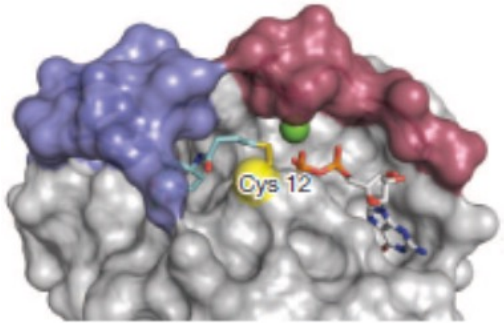
Progress Toward Discovery of Allele-Specific KRAS Inhibitors

AACR American Association for Cancer Research
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

2013

K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions

Jonathan M. Ostrem,[1,*] Ulf Peters,[1,*] Martin L. Sos,[1] James A. Wells,[2] and Kevan M. Shokat[1]



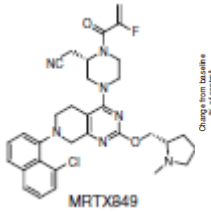
548 | NATURE | VOL 503 | 28 NOVEMBER 2013

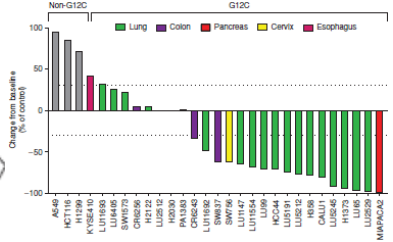
2013-2020

The KRAS^{G12C} Inhibitor MRTX849 Provides Insight toward Therapeutic Susceptibility of KRAS-Mutant Cancers in Mouse Models and Patients

Jill Hallin[1], Lars D. Engstrom[1], Lauren Hargis[1], Andrew Calinisan[1], Ruth Aranda[1], David M. Briere[1], Niranjan Sudhakar[1], Vickie Bowcut[1], Brian R. Baer[2], Joshua A. Ballard[2], Michael R. Burkard[2], Jay B. Fell[2], John P. Fischer[2], Guy P. Vigers[2], Yaohua Xue[3], Sole Gatto[4], Julio Fernandez-Banet[4], Adam Pavlicek[4], Karen Velastagui[1], Richard C. Chao[1], Jeremy Barton[1], Mariaelena Pierobon[5], Elisa Baldelli[5], Emanuel F. Patricoin III[5], Douglas P. Cassidy[6], Matthew A. Marx[1], Igor I. Rybkin[7], Melissa L. Johnson[8], Sai-Hong Ignatius Ou[9], Piro Lito[3], Kyriakos P. Papadopoulos[10], Pasi A. Jänne[6], Peter Olson[1], and James G. Christensen[1]

JANUARY 2020 CANCER DISCOVERY





…..also AMG510, JDQ443 GDC-6036 and friends

2015-2022

nature medicine

Article

https://doi.org/10.1038/s41591-022-02007-7

Anti-tumor efficacy of a potent and selective non-covalent KRAS^{G12D} inhibitor

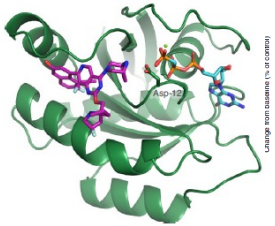
Received: 27 December 2021

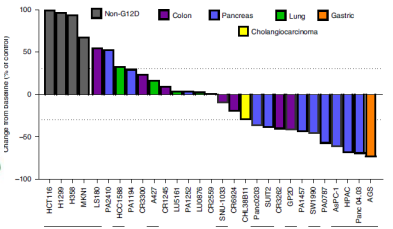
Accepted: 9 August 2022

Published online: 10 October 2022

Check for updates

Jill Hallin[1], Vickie Bowcut[1], Andrew Calinisan[1], David M. Briere[1], Lauren Hargis[1], Lars D. Engstrom[1], Jade Laguer[1], James Medwid[1], Darin Vanderpool[1], Ella Lifset[1], David Trinh[1], Natalie Hoffman[1], Xiaolun Wang[1], J. David Lawson[1], Robin J. Gunn[1], Christopher R. Smith[1], Nicole C. Thomas[1], Matthew Martinson[2], Alex Bergstrom[2], Francis Sullivan[2], Karyn Bouhana[2], Shannon Winski[2], Leo He[3], Julio Fernandez-Banet[3], Adam Pavlicek[3], Jacob R. Haling[1], Lisa Rahbaek[1], Matthew A. Marx[1], Peter Olson[1] and James G. Christensen[1]





DO NOT POST

Progress Toward Development of Allele-Specific and Broad-Spectrum RAS Family Inhibitors

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

2021/2022

FDA grants accelerated approval to sotorasib for KRAS G12C mutated NSCLC

On May 28, 2021, the Food and Drug Administration granted accelerated approval to sotorasib (Lumakras™, Amgen, Inc.), a RAS GTPase family inhibitor, for adult patients with *KRAS G12C* -mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA -approved test, who have received at least one prior systemic therapy.

FDA grants accelerated approval to adagrasib for KRAS G12C-mutated NSCLC

On December 12, 2022, the Food and Drug Administration (FDA) granted accelerated approval to adagrasib (Krazati, Mirati Therapeutics, Inc.), a RAS GTPase family inhibitor, for adult patients with KRAS G12C¬-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy

2022/2023

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Study of MRTX1133 in Patients With Advanced Solid Tumors Harboring a KRAS G12D Mutation

ClinicalTrials.gov Identifier: NCT05737706

A Study of ASP3082 in Adults With Previously Treated Solid Tumors

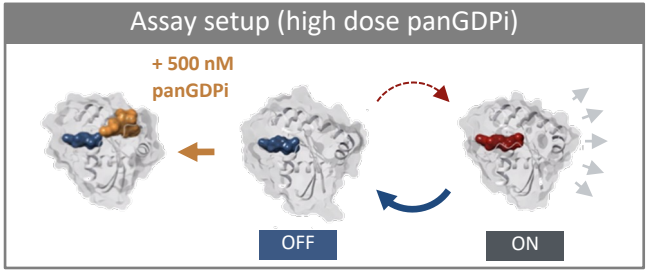
ClinicalTrials.gov Identifier: NCT05382559

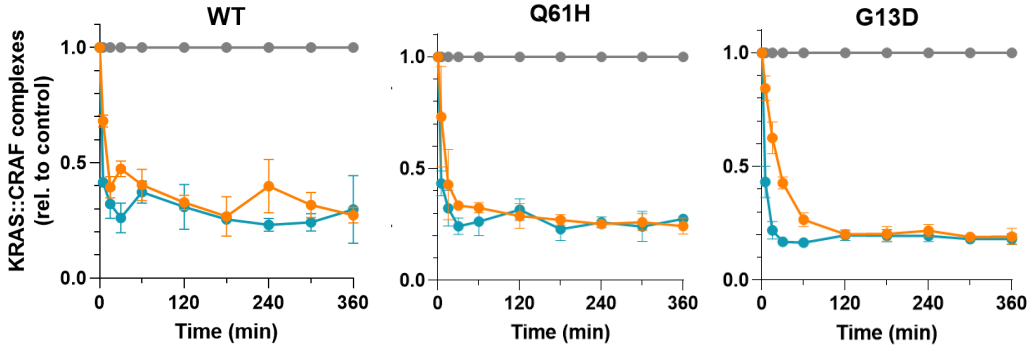
Evaluation of RMC-6236 in Subjects With Advanced Solid Tumors Harboring Specific Mutations in KRAS

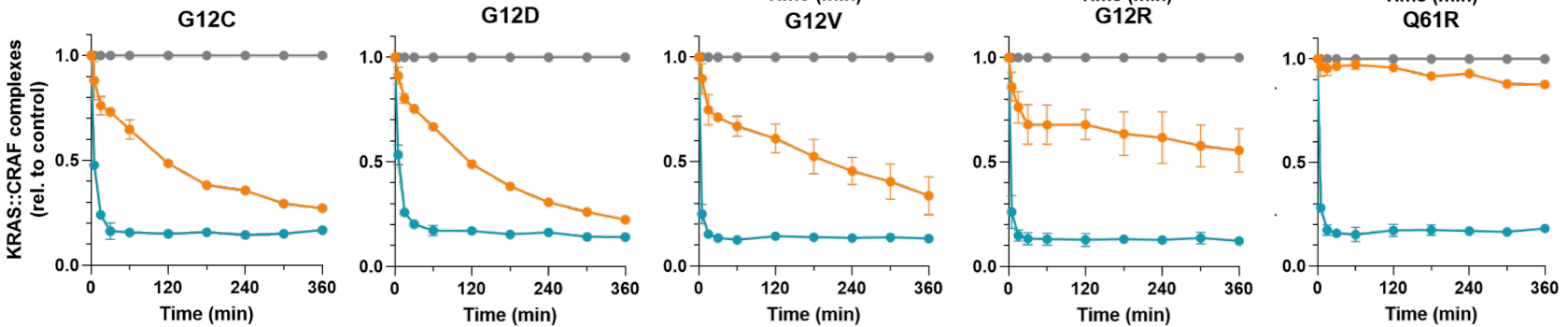
ClinicalTrials.gov Identifier: NCT05379985

A Subset of KRAS Mutants Appear Susceptible to SII Pocket Targeting with Reversible Inhibitors

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23







➔ Q61H and G13D have properties like KRAS WT

➔ G12D has near-identical cycling properties as G12C

➔ Other key KRAS mutants (G12V / G12R) are further pushed to the ON state

500 nM panGDP KRASi
Pos. Ctrl: 30 uM BI-2852

MRTX Pan-KRAS SII Inhibitors Targets Susceptible WT KRAS and Susceptible Mutant Variants

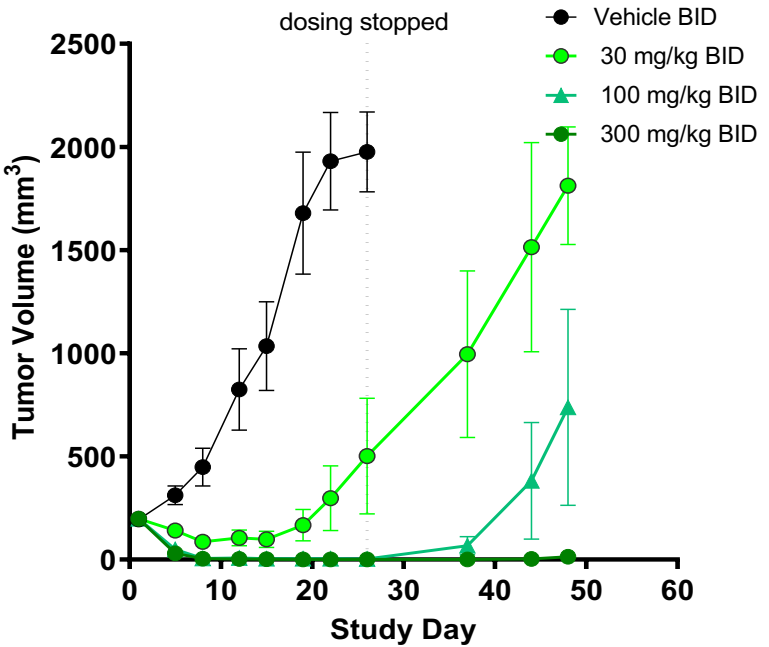
AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

KRAS mutant pathway inhibition selectivity spectrum

Cell Line	KRAS Mutation	MRTXB pERK IC_{50} (nM)
H358_Lung	G12C	4.1
MiaPaca2_Pancreas	G12C	4.4
NIH3T3 G12D	G12D	9.4
ASPC1_Pancreas	G12D	9.8
PSN1_Pancreas	G12R	533.8
HUPT3_Pancreas	G12R	3,807.0
A549_Lung	G12S	20.5
H727_Lung	G12V	28.6
RKN_Soft Tissue	G12V	47.8
HCT116_Large Intestine	G13D	22.6
H460_Lung	Q61H	8.3
MKN1_Stomach	WT AMP (dependent)	3.5

- IC_{50} values for NRAS and HRAS mut cell lines each >3,000 nM

Antitumor Activity of MRTXA in RKN Model (LMS, $KRAS^{G12V}$) In Vivo (PO Administration)



Covalent Technologies Enable Access To a Subset of Difficult to Target KRAS Mutants

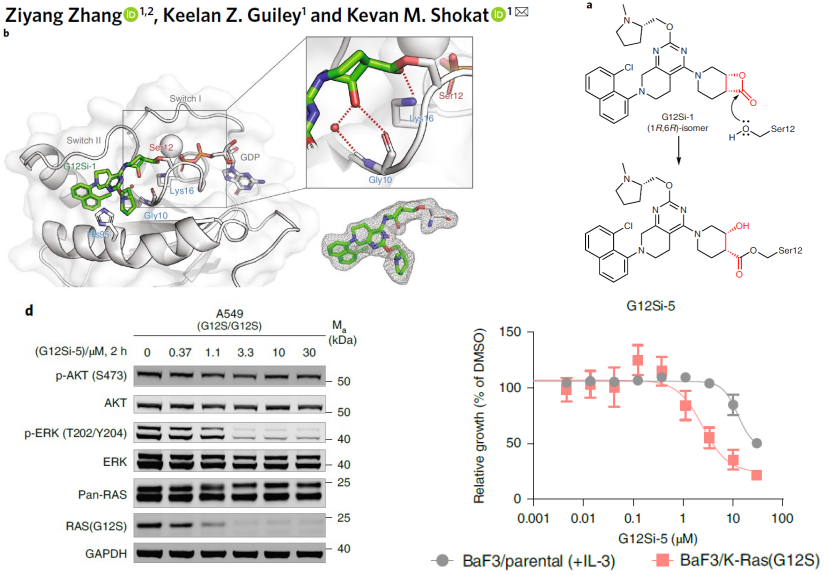
AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

nature chemical biology
ARTICLES
https://doi.org/10.1038/s41589-022-01065-9
Check for updates

OPEN

Chemical acylation of an acquired serine suppresses oncogenic signaling of K-Ras(G12S)

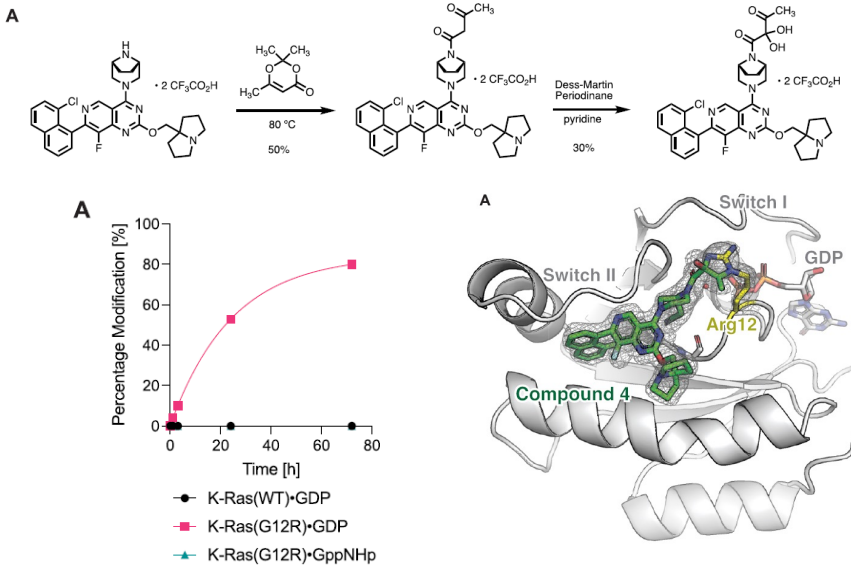
Ziyang Zhang[1,2], Keelan Z. Guiley[1] and Kevan M. Shokat[1]



JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

Chemoselective Covalent Modification of K-Ras(G12R) with a Small Molecule Electrophile

Ziyang Zhang,*[,§] Johannes Morstein,[§] Andrew K. Ecker,[§] Keelan Z. Guiley, and Kevan M. Shokat*

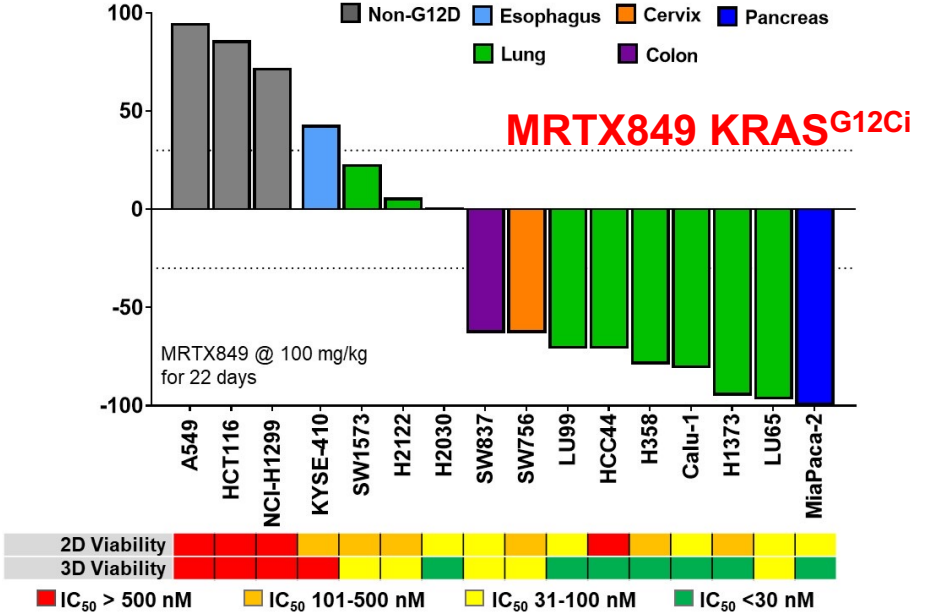


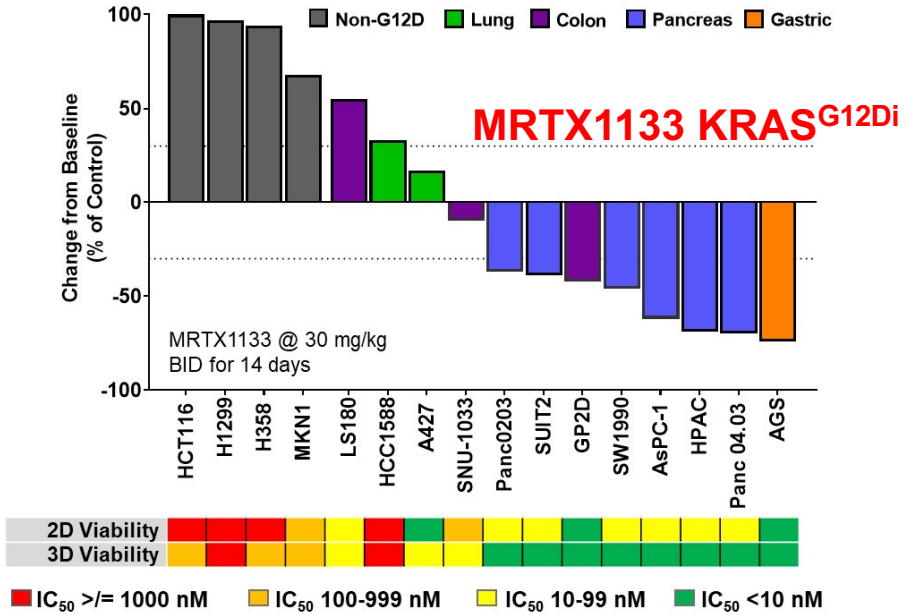
How can we apply learnings to facilitate rationale development of KRAS inhibitors?

KRAS$^{G12C/G12D}$ Inhibitor Cell Autonomous Antitumor Activity (In vitro/In vivo Correlation)

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Response to KRAS Inhibitors in Cell Viability Assays and in Immunocompromised Tumor Models



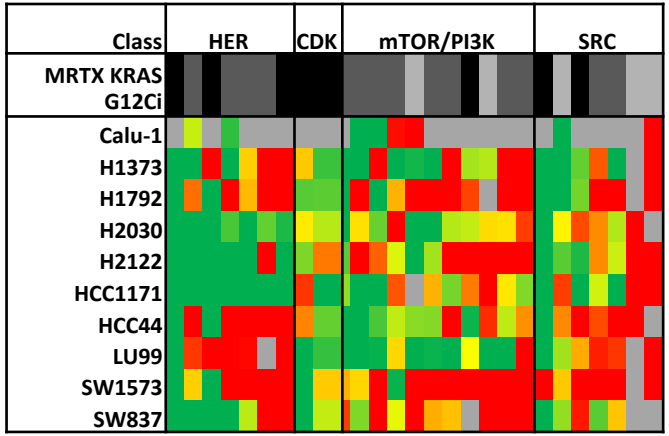


- Objective response observed in tumor models for KRAS$^{G12C/G12D}$ Inhibitors including 66% (6/9) KRAS^{G12C} NSCLC models for MRTX849 and all (6/6) KRAS^{G12D} PDAC models for MRTX1133
- In vivo response of tumor models exhibit strong correlation with 3D cell viability assays (not 2D)

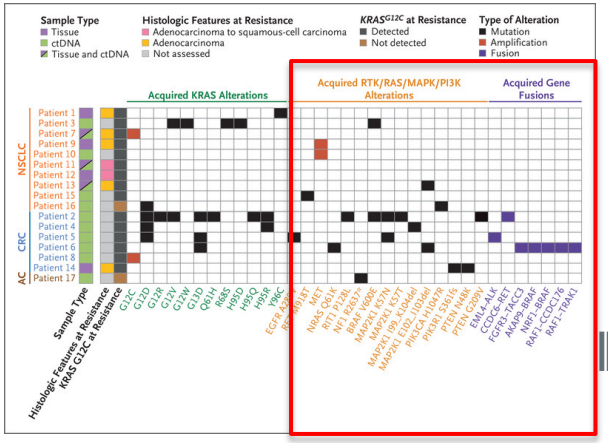
Rationale for Cell Autonomous Targeted Therapy Combinations

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Small Mol Combo Screen

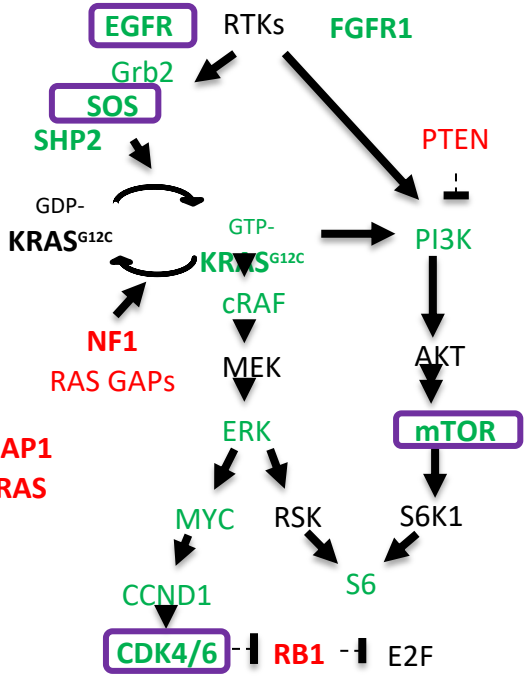


Acquired resistance



Awad et al., NEJM 2021

Adagrasib Combination Targets and Resistance Gene Map



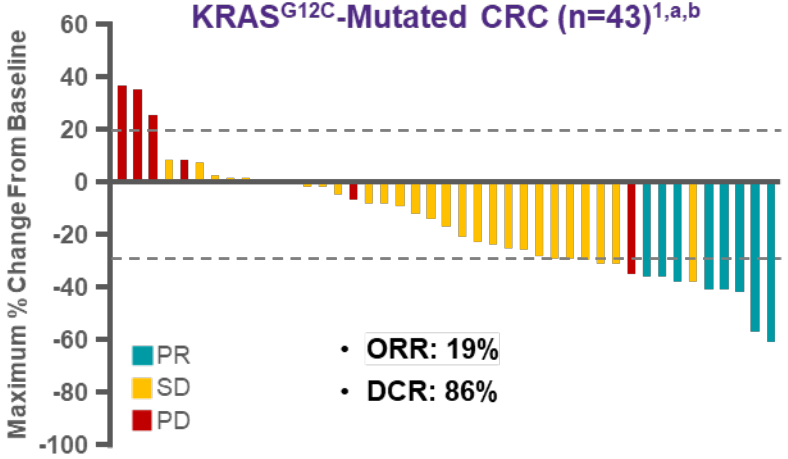
- Screened ~12 agents in combination with adagrasib across 8 lung cell lines *in vitro* that were partially adagrasib-resistant *in vivo*.
- Adagrasib-anchored CRISPR screens: ~1,000 genes, 6 $KRAS^{G12C}$ cell lines, *in vitro/in vivo*
- Clinical trial analysis of resistance mechanisms at progression in plasma/tumor
- Top combination targets: EGFR family, SOS1, mTOR, SHP2, CDK4/6.

DO NOT POST

Adagrasib Demonstrates Improved Antitumor Activity in KRAS^{G12C} CRC Pts in Combination with Cetuximab

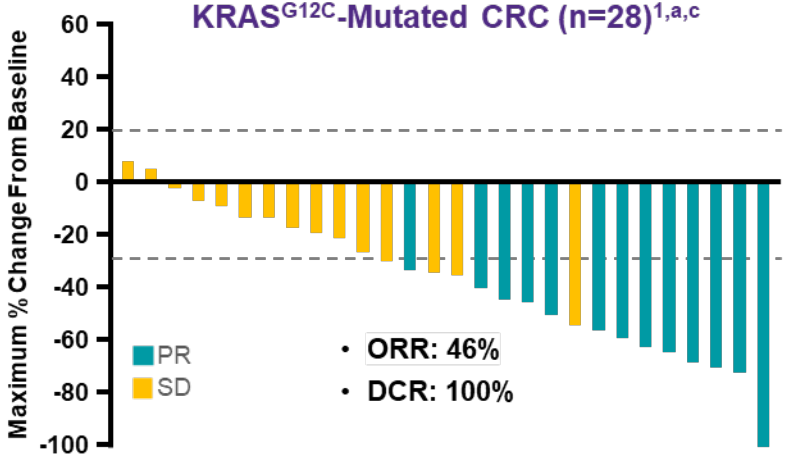
AACR American Association for Cancer Research
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Adagrasib Monotherapy Response in KRAS^{G12C}-Mutated CRC (n=43)[1,a,b]



- Median DOR: 4.3 months (95% CI, 2.3–8.3)
- Median PFS: 5.6 months (95% CI, 4.1–8.3)
- Median OS: 19.8 months (95% CI, 12.5–23.0)

Adagrasib + Cetuximab Response in KRAS^{G12C}-Mutated CRC (n=28)[1,a,c]



- Median DOR: 7.6 months (95% CI, 5.7–NE)
- Median PFS: 6.9 months (95% CI, 5.4–8.1)
- Median OS: 13.4 months (95% CI, 9.5–20.1)

[a]Data as of June 16, 2022 (median follow-up, 20.1 months). [b]Response per investigator assessment (n=43; one patient withdrew consent prior to the first scan). [c]Response per investigator assessment (n=28; four patients are not included due to no post-baseline assessment of target lesions)

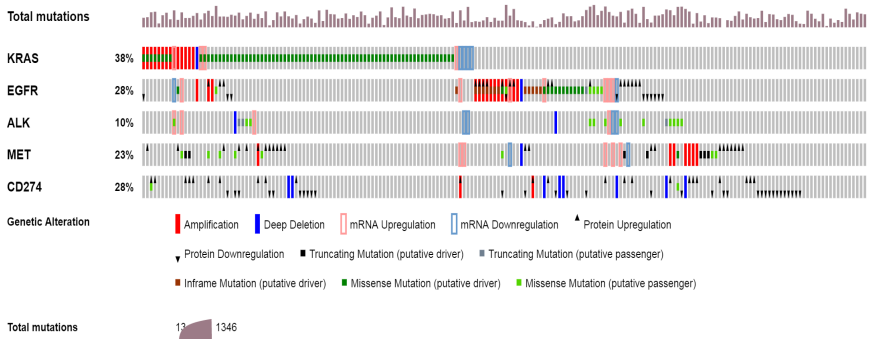
1. Yaeger R, et al. N Engl J Med 2022. 2. Fakih MG, et al. Lancet Oncol 2022

Considerations for Immunotherapy in KRAS^{G12C}-Mutant Tumors

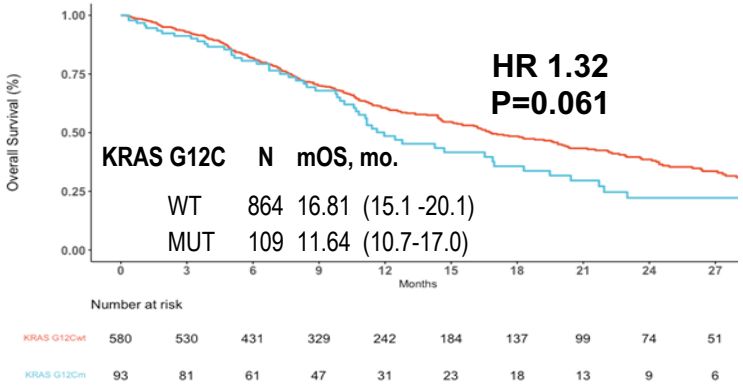
AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

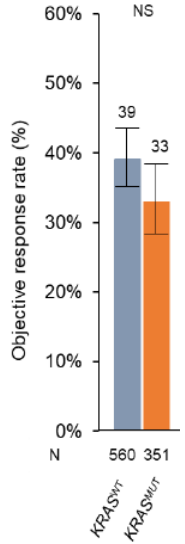
- KRAS^{G12C} are transversion mutations linked to smoking & high TMB which is correlated to CIT benefit
- Although PD-1/L1 Inhibitors demonstrate clinical activity in KRAS-mut NSCLC, there is a significant opportunity for improvement (esp. PD-L1 low: STK11, KEAP1, SMARCA4 subsets)
- KRAS is implicated in silencing antigen presentation and immune suppressed tumor microenvironment

TMB and PD-L1 in KRAS^{WT} and KRAS^{MUT} NSCLC Adeno (cBioPortal)



Chemoimmunotherapy outcomes in KRAS G12C^{MUT} vs KRAS G12C^{WT} for TPS low



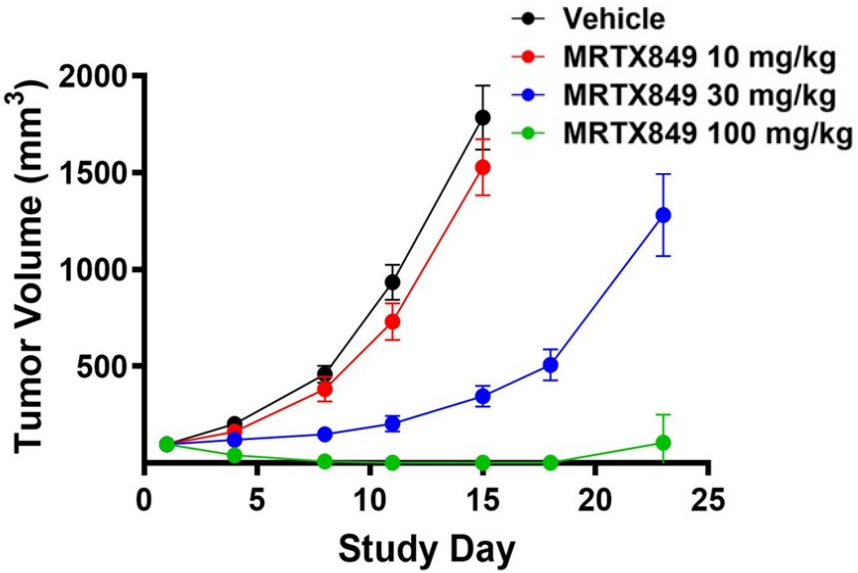


Borghaei H, et al. *N Engl J Med*. 2015; Garon EB, et al. *N Engl J Med*. 2015; Liao W, et al. *Cancer Cell*. 2019;.Coelho MA, et al. *Immunity*. 2017; Kortlever RM, et al. *Cell*. 2017; Ancrile BB, *Mol Interv*. 2008; 2014; Campbell JD, et al. *Nat Genet*. 2019; Alessi et al. J Thorac. Oncol. 2023; Aggrawal et al, SITC 2022

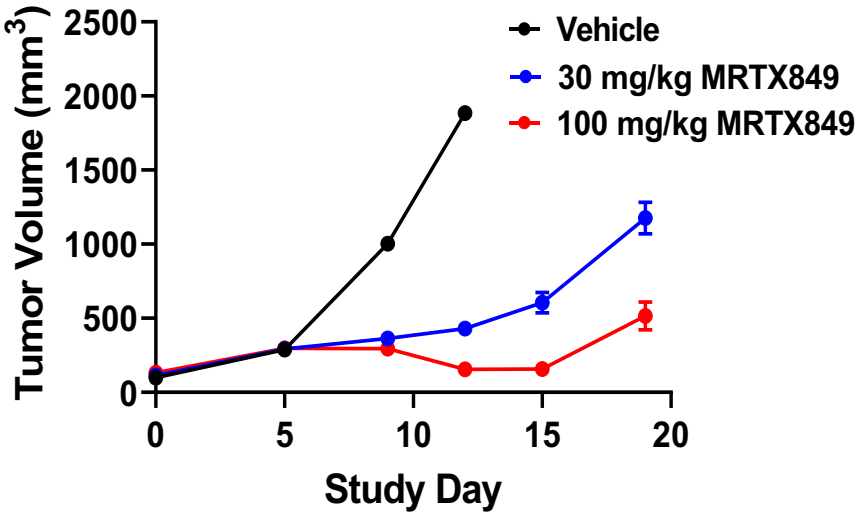
Response to Adagrasib is Enhanced in Immunocompetent Tumor Model Setting

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Antitumor activity of Adagrasib in CT26 KRAS^{G12C} xenografts implanted in immunocompetent mice



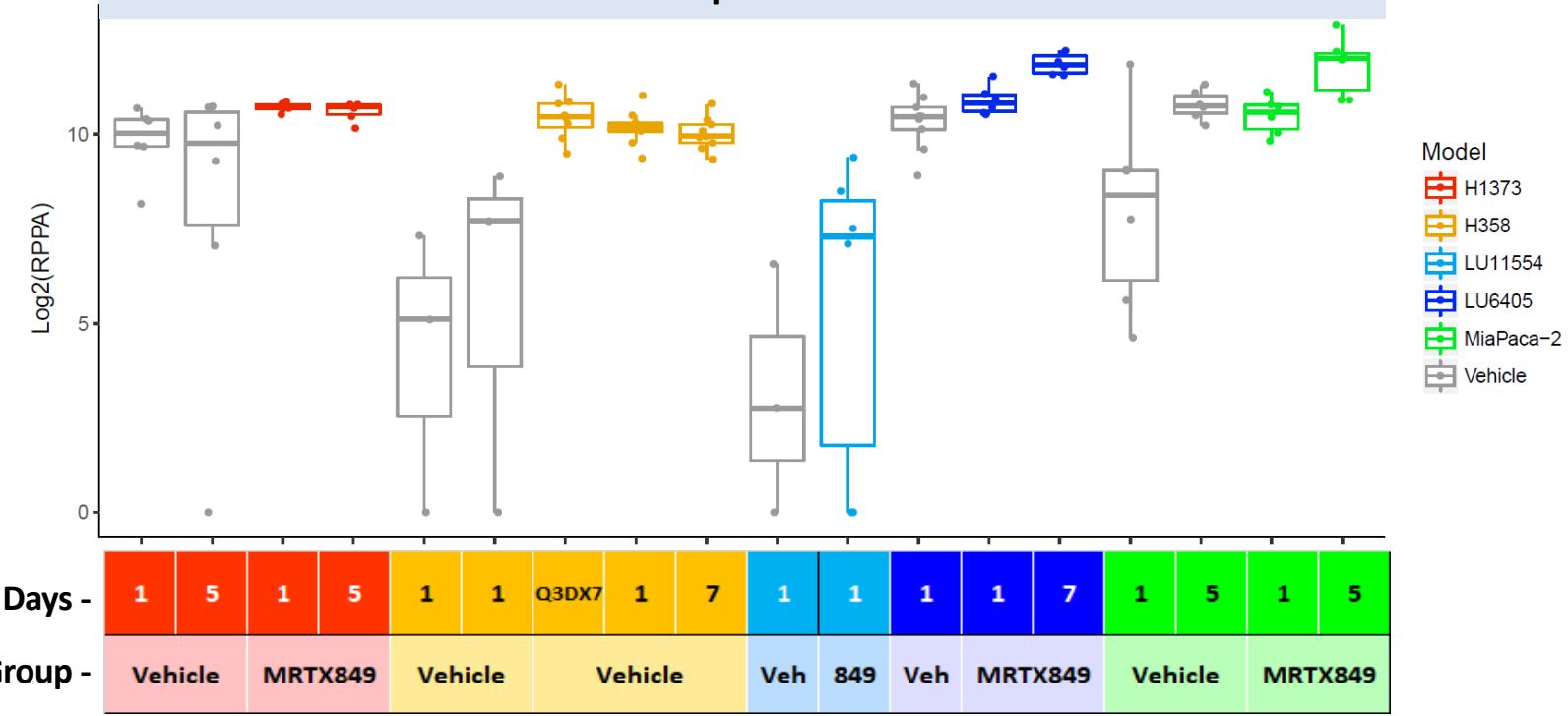
Antitumor activity of Adagrasib in CT26 KRAS^{G12C} xenografts implanted in immunocompromised mice (*nu/nu*)



Adagrasib Upregulates MHC Class I Protein Expression in KRAS^{G12C} Models

AACR American Association for Cancer Research
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Expression of MHC Class I protein by RPPA after MRTX849 Treatment in KRAS G12C-positive tumors



KRAS Regulates TME Cytokines Via Tumor Cell Intrinsic Mechanism and Facilitates IFN Response

AACR American Association for Cancer Research
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

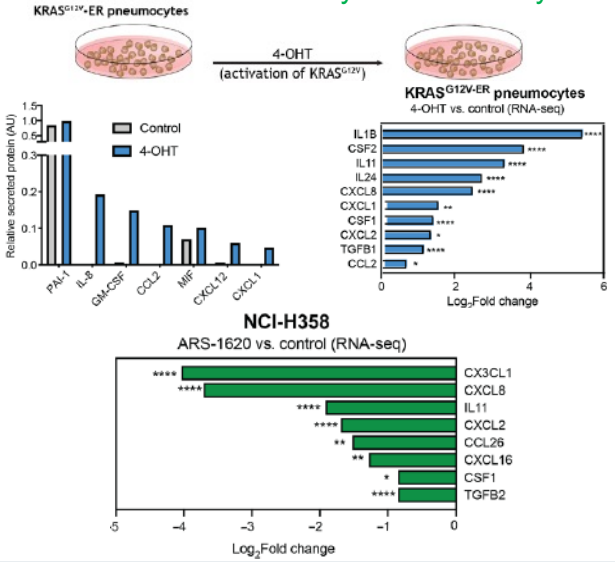
SCIENCE ADVANCES | RESEARCH ARTICLE

CANCER

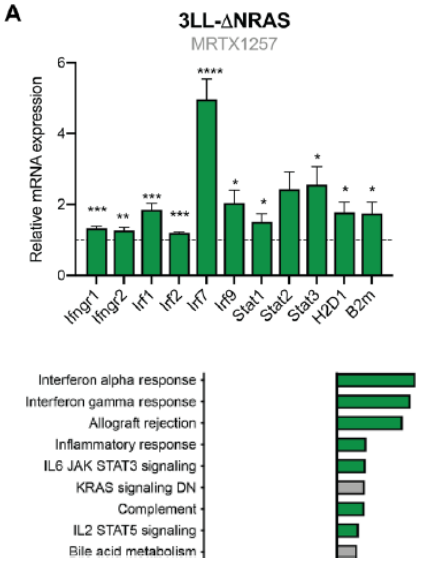
Therapeutic KRAS^{G12C} inhibition drives effective interferon-mediated antitumor immunity in immunogenic lung cancers

Edurne Mugarza[1]†, Febe van Maldegem[1]†‡, Jesse Boumelha[1]†, Christopher Moore[1], Sareena Rana[1], Miriam Llorian Sopena[2], Philip East[2], Rachel Ambler[1], Panayiotis Anastasiou[1], Pablo Romero-Clavijo[1], Karishma Valand[1], Megan Cole[1], Miriam Molina-Arcas[1]*, Julian Downward[1,3]*

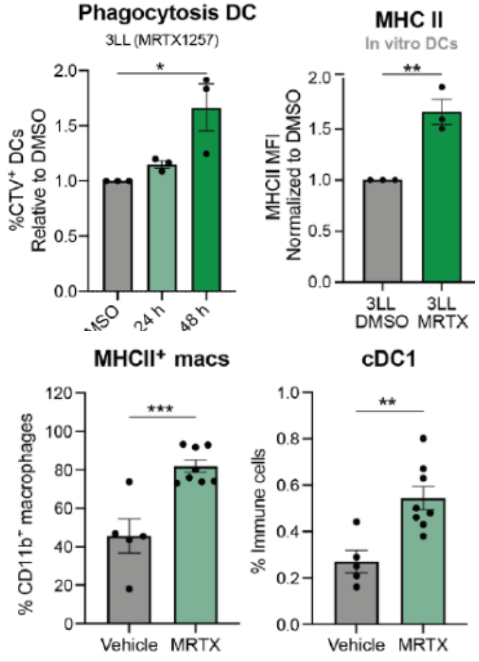
Regulation of immunomodulatory chemokines by KRAS



KRAS^{G12C} Inhibition Enhances Tumor Cell-Intrinsic IFN Response



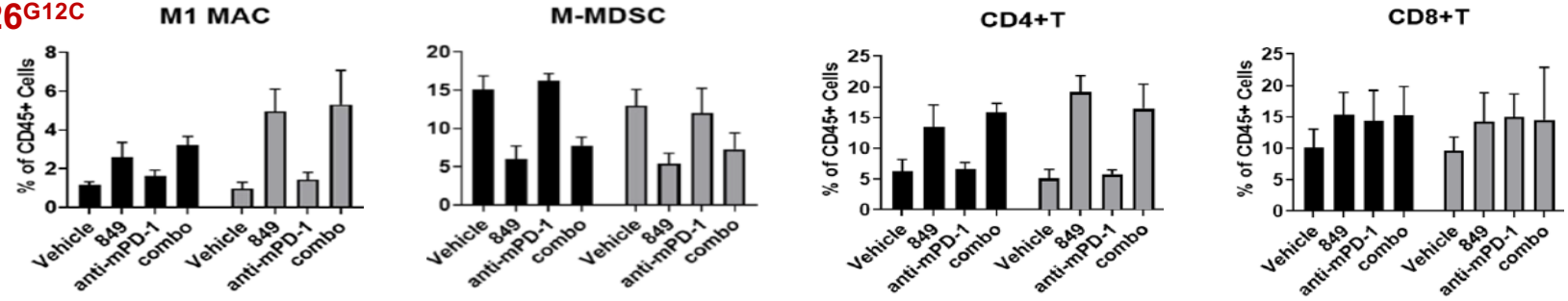
KRAS^{G12C} Inhibition Promotes APC Activation/Antigen Presentation



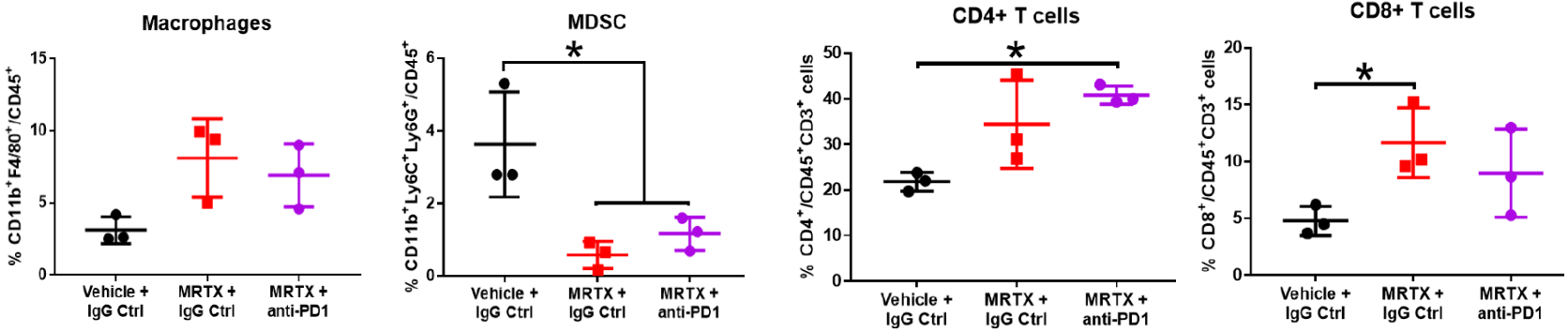
Adagrasib Impact on Innate & Adaptive Immune Cell Populations in Immunocompetent Tumor Models

AACR American Association for Cancer Research
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

CT26^{G12C}



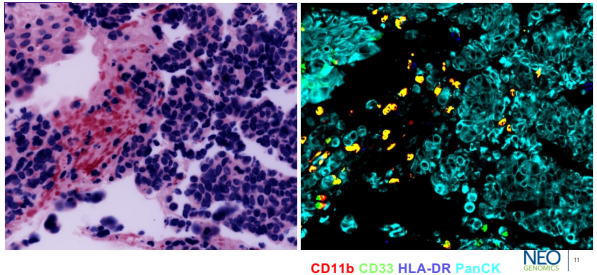
LSL-KRAS^{G12C}Trp53^{R270H} GEMM — Kwok Wong NYU

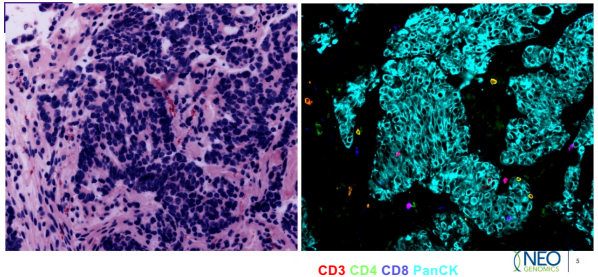


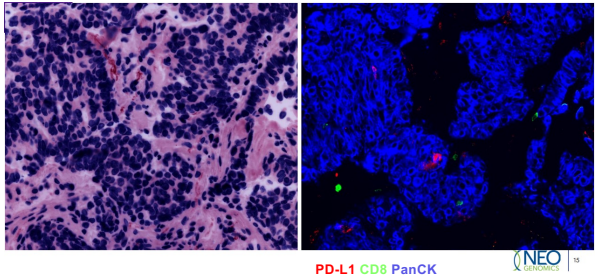
Adagrasib Demonstrates Pro-immunogenic Response in NSCLC Patient Tumor Samples

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

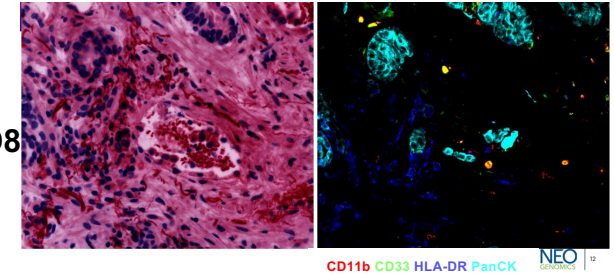
Pre

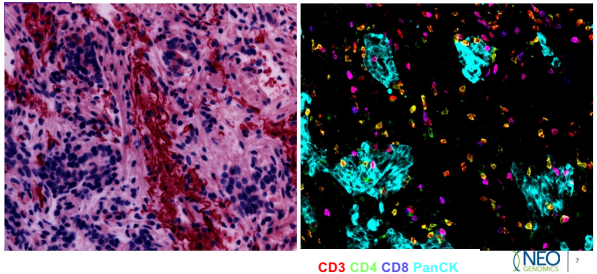


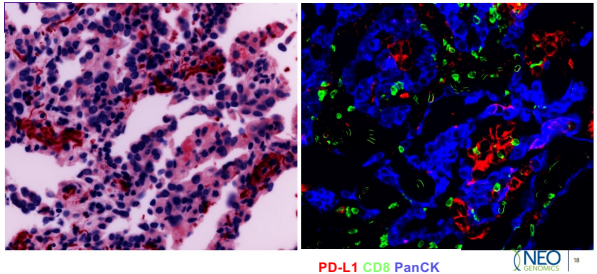




C1D8



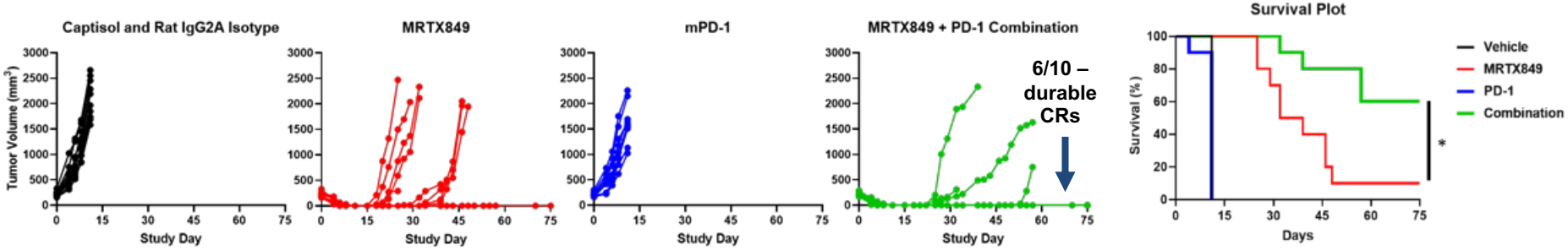




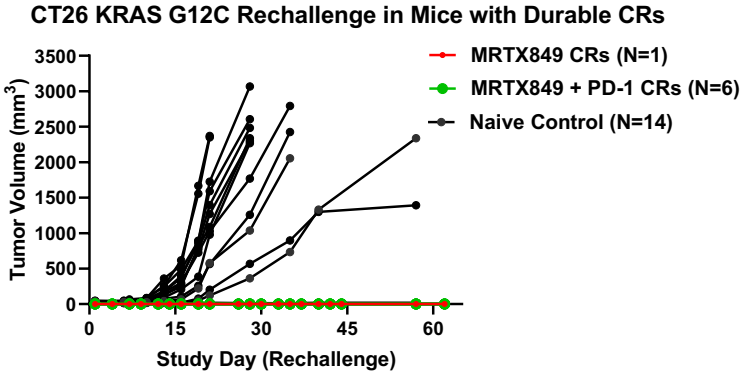
- CD11b/CD33/HLA-Dr^{low} signature of myeloid-derived suppressor cells (MDSC) markers are decreased in response to adagrasib treatment
- CD3+/CD4+ and CD8+ T-cell populations are increased in response to adagrasib treatment
- PD-L1+ and CD8+ cell populations are increased indicating an immune-related response to adagrasib treatment

Adagrasib / PD-1 Combination Elicits Durable Complete Responses in an KRAS^{G12C}-mutant Mouse Model

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23



- CT26 (KRAS^{G12D}) was engineered to replace the KRAS allele with KRAS^{G12C} utilizing a CRISPR/sgRNA approach
- CT26 KRAS^{G12C} is responsive to adagrasib
- Adagrasib increased the number of durable complete responses in combination with PD-1 surrogate mAb
- Re-challenge of treated mice with KRAS^{G12C} resulted in tumor rejection indicative of an adaptive memory immune response



DO NOT POST

Adagrasib + Pembrolizumab Clinical Trials — Phase 1b and Phase 2 Cohorts

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Key Eligibility Criteria

- Advanced, unresectable or metastatic NSCLC with $KRAS^{G12C}$ mutation[1]
- No prior systemic therapy for locally advanced/ metastatic disease
- Stable brain metastases allowed

KRYSTAL-1 Phase 1b

Adagrasib 400 mg[2] BID + Pembrolizumab
N=7

Key Study Objectives

- Primary endpoint: safety
- Secondary endpoints: ORR (RECIST v1.1), DOR, PFS, OS

KRYSTAL-7 Phase 2

Cohort 1a, PD-L1 TPS <1%[3,4]
Adagrasib 400 mg BID + Pembrolizumab
N=11

Cohort 2, PD-L1 TPS ≥1%[3]
Adagrasib 400 mg BID + Pembrolizumab
N=64

Key Study Objectives

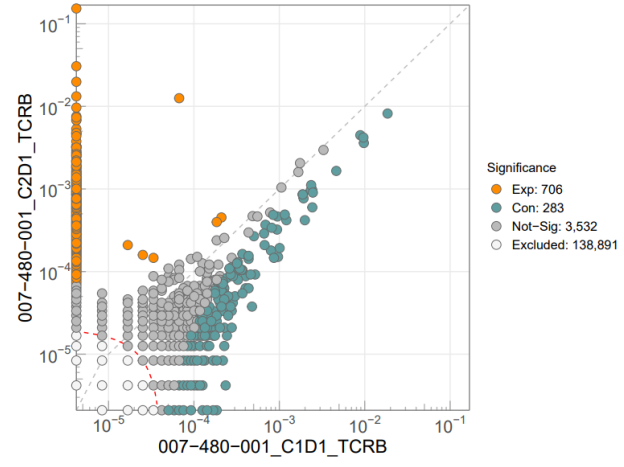
- Primary endpoint: ORR (RECIST v1.1)
- Secondary endpoints: DOR, PFS, OS, safety, PK

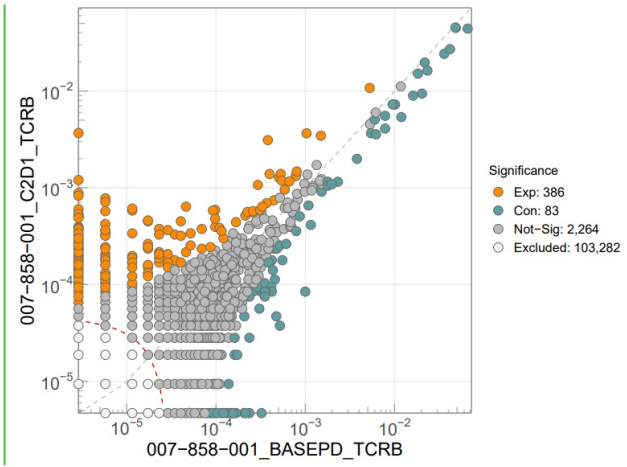
- We report preliminary safety and efficacy data from a phase 1b cohort of KRYSTAL-1 and the phase 2 KRYSTAL-7 studies, evaluating adagrasib[5] 400 mg BID + pembrolizumab 200 mg IV Q3W in treatment-naïve patients with NSCLC harboring a $KRAS^{G12C}$ mutation
- KRYSTAL-1 median follow-up, 19.3 months; KRYSTAL-7 median follow-up 3.5 months

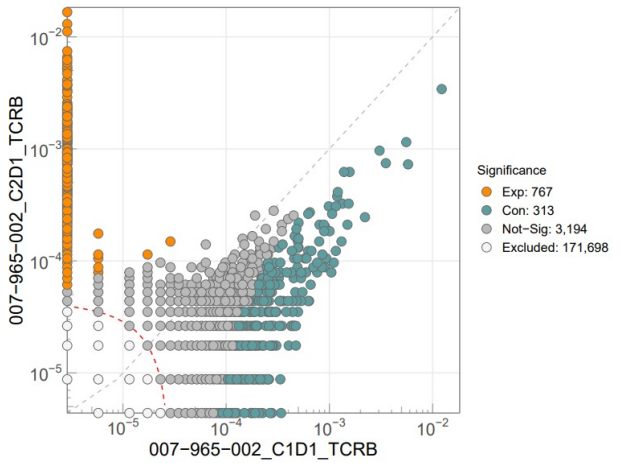
[1]$KRAS^{G12C}$ mutation detected in tumor tissue and/or ctDNA. [2]KRYSTAL-1 phase 1b cohort was initiated using 600 mg BID adagrasib dosing and switched to 400 mg BID dosing during study conduct. ClinicalTrials.gov. NCT04613596

Preliminary Data from Adagrasib + Pembrolizumab Treated Patients Indicates Effects on T-cell Repertoire Clonality

AACR American Association for Cancer Research
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23



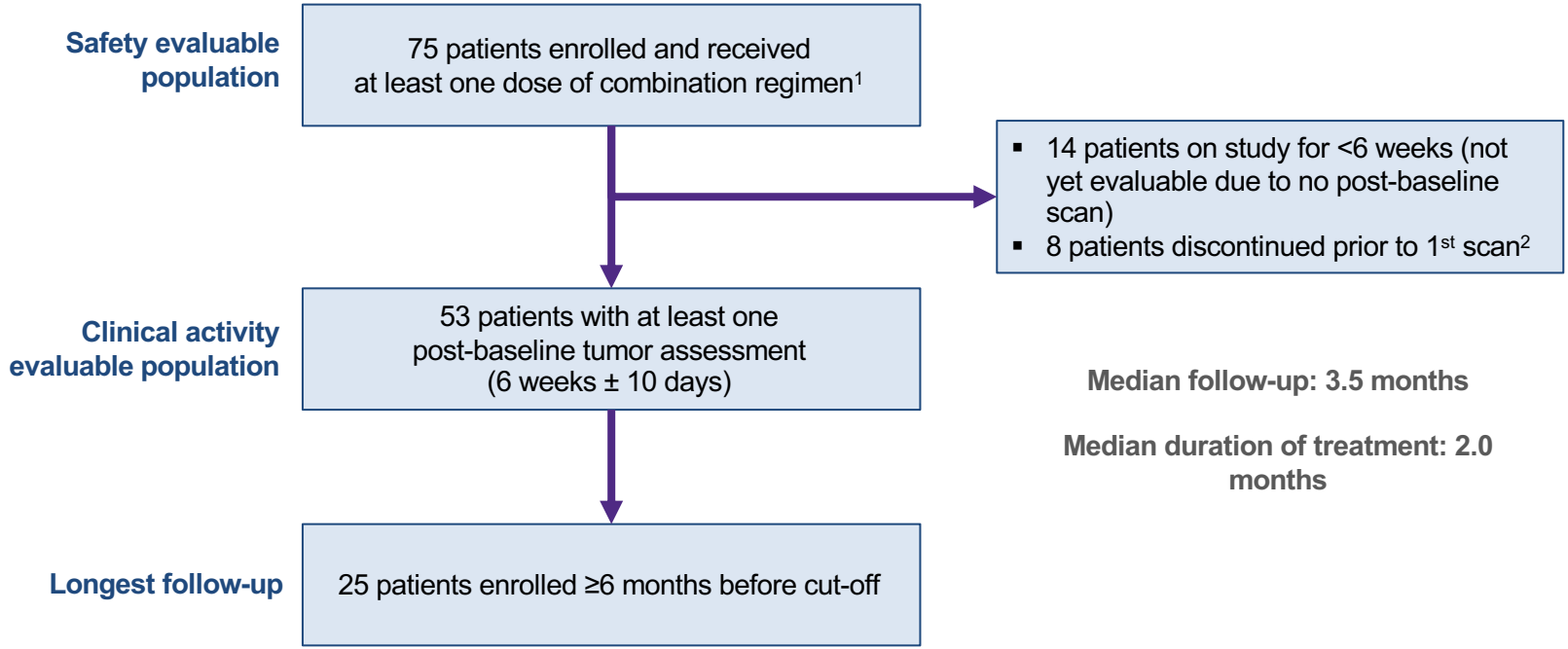




- Evidence of widespread expansion of novel TCR beta clones and elevated diversity in 3 patients with >98% of expanded clones undetected at C1D1 in 2 patients
- Orange points represent clones significantly more abundant in C2D1. Teal points represent clones significantly more abundant in C1D1
- Preliminary data indicates potential for effects on T-cell repertoire leading to heightened immune response and increased anti tumor response in combination

Adagrasib + Pembrolizumab in Treatment-Naïve KRAS^{G12C}-mutated NSCLC: KRYSTAL-7

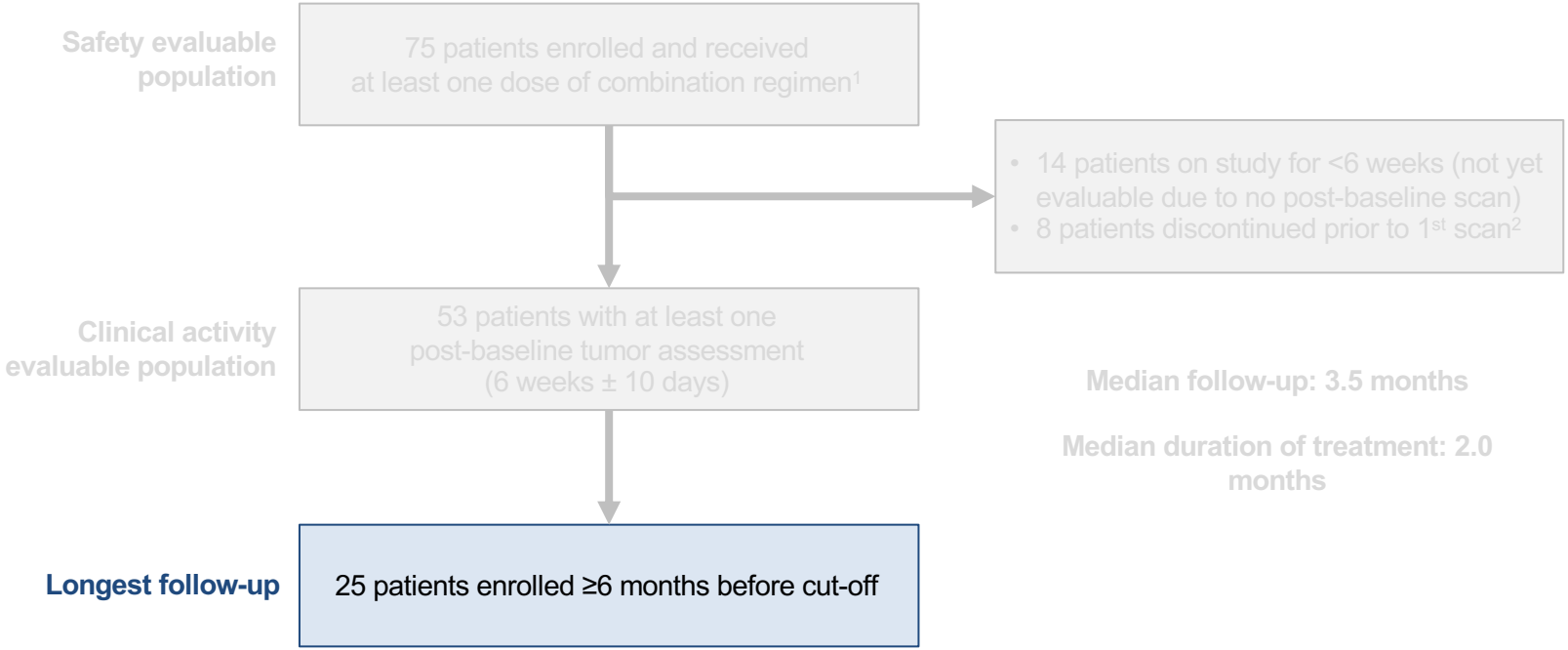
AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23



[1]Pooled patients from cohort 1a PD-L1 TPS <1% and cohort 2 PD-L1 TPS ≥1%. [2]Discontinued due to death not related to treatment (n=5), lost to follow-up (n=1), adverse event not related to treatment (n=1), global deterioration of health (n=1)
Data as of 30 August 2022; NSCLC = non-small cell lung cancer

Adagrasib + Pembrolizumab in Treatment-Naïve KRAS^{G12C}-mutated NSCLC: KRYSTAL-7

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23



[1]Pooled patients from cohort 1a PD-L1 TPS <1% and cohort 2 PD-L1 TPS ≥1%. [2]Discontinued due to death not related to treatment (n=5), lost to follow-up (n=1), adverse event not related to treatment (n=1), global deterioration of health (n=1)
Data as of 30 August 2022; NSCLC = non-small cell lung cancer

Adagrasib + Pembrolizumab in 1L KRAS^{G12C}-mutated NSCLC: Treatment-Related Adverse Events

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Most Frequent TRAEs	Concurrent 400 mg BID Adagrasib + Pembrolizumab (n=75)				
TRAEs, %	**Any grade**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Any TRAEs	83%	15%	24%	40%	4%[1]
Most frequent TRAEs[2], %					
Nausea	48%	24%	19%	5%	0%
Diarrhea	43%	33%	5%	4%	0%
Vomiting	24%	13%	9%	1%	0%
ALT increased	21%	7%	7%	8%	0%
AST increased	21%	7%	5%	9%	0%
Fatigue	21%	9%	8%	4%	0%
Decreased appetite	20%	11%	9%	0%	0%
Amylase increased	16%	5%	11%	0%	0%

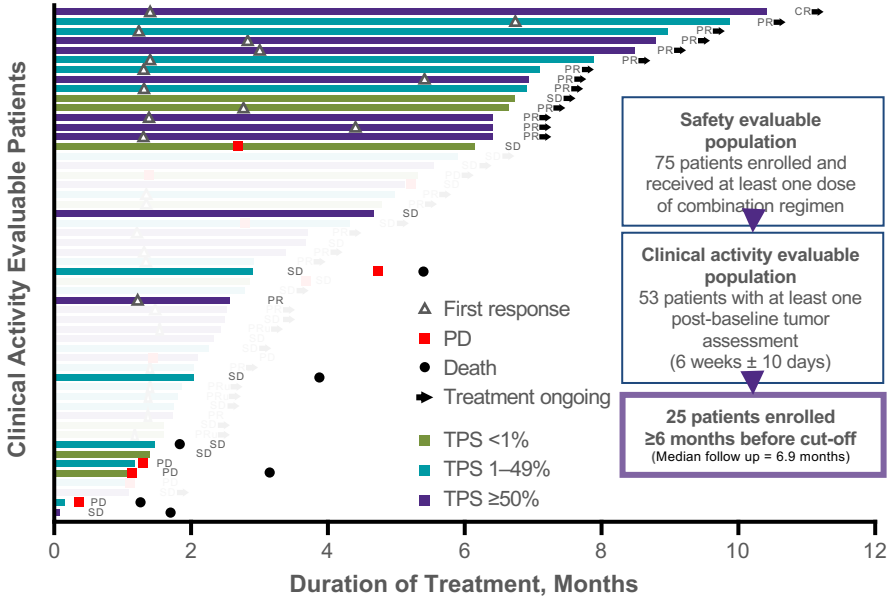
- No dose-limiting safety signal identified and no Grade 5 TRAEs
- ALT and AST 9% total incidence of Grade 3 LFT increase observed (no Grade 4 events, no Hy's law cases)
- TRAEs led to discontinuation of both drugs in 2/75 (3%) patients and only pembrolizumab in 2/75 (3%)[3] patients
- All causality discontinuation rate estimates are consistent with KN189, KN24, KN42

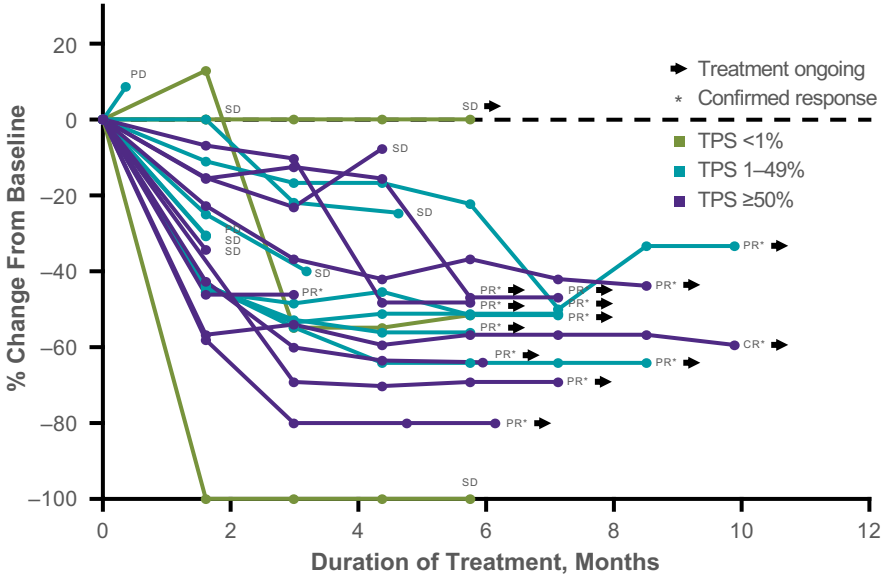
[1]Grade 4 TRAEs comprised 1 case each of pneumonitis, neutropenia and pulmonary embolism. [2]Occurring in >15% of patients (any grade). Additional TRAEs of interest include 1 (1%) patient with Grade 1 blood bilirubin increased, 1 (1%) with Grade 2 pancreatitis, 2 (3%) with Grade 3 hepatitis, 8 (11%) with Gr 3 lipase increased, 2 (3%) with Grade 3–4 pneumonitis, and 2 (3%) with Grade 1–2 QT prolongation. [3]No patients discontinued only adagrasib due to a TRAE
Data as of 30 August 2022. Median follow-up 3.5 months. Median duration of treatment 2.0 months; NSCLC = non-small cell lung cancer; TRAE = treatment related adverse event

Activity of Adagrasib & Pembrolizumab Combination in Patients Enrolled 6 Months Prior to Data Cutoff

AACR American Association for Cancer Research
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Adagrasib + Pembrolizumab in 1L KRAS^{G12C}-mutated NSCLC in Patients Enrolled for ≥6 months



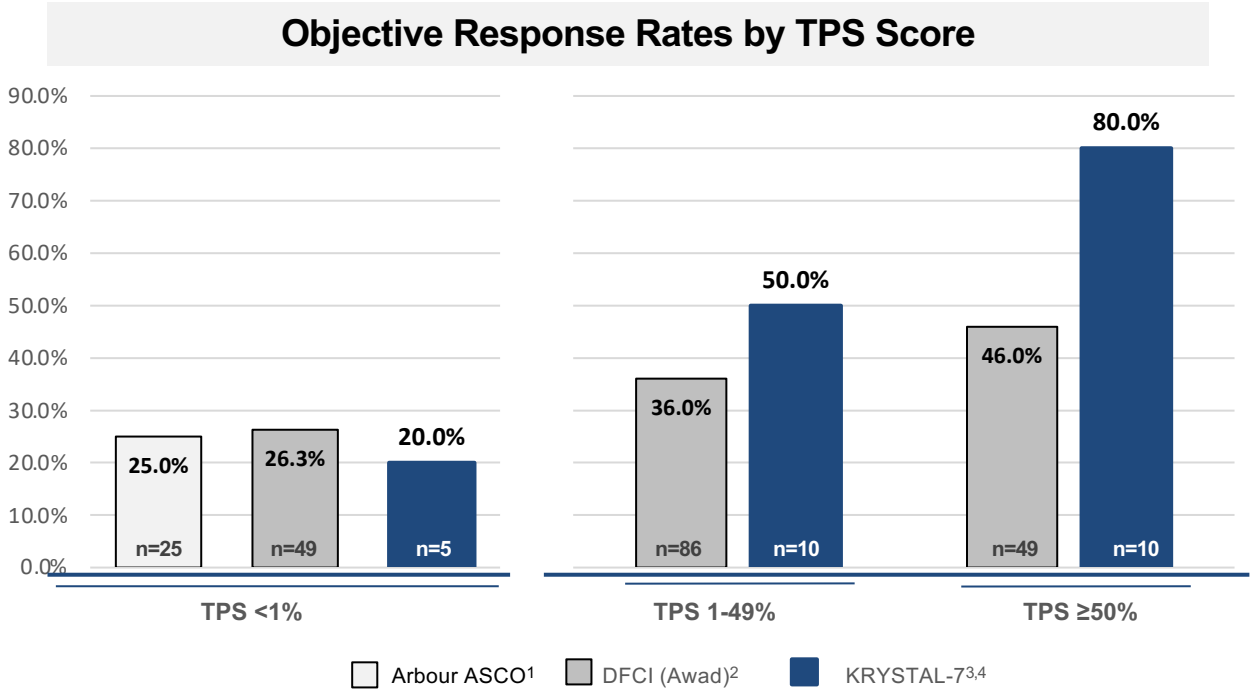


- For clinical activity evaluable patients who were enrolled ≥6 months before data cut-off, ORR was 56% (14/25)
- All partial responses shown are confirmed partial responses

Data as of 30 August 2022. Median follow-up 6.9 months; NSCLC = non-small cell lung cancer; 1L = first-line; ORR = objective response rate

Adagrasib + Pembrolizumab ORR in Pts Enrolled ≥6 Months Compared with Chemoimmunotherapy (in KRAS^{G12C})

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23



Adagrasib + Pembrolizumab

- Majority of patients remain ongoing beyond 6 months
- Experience in >6 months is limited in TPS <1%
- In 2L adagrasib monotherapy ORR of 47% in TPS <1%
  - Anticipate improved efficacy in 1L with more patient data and follow up

[1]MSKCC Institutional Experience - (Unpublished data courtesy of K. Arbour); [2]Dana-Farber Cancer Institute, Awad et al. personal communication/manuscript submitted; [3]Adagrasib clinical activity evaluable population who were enrolled ≥6 months before data cut-off (n=25); [4]Data as of 30 August 2022; median follow-up 3.5 months

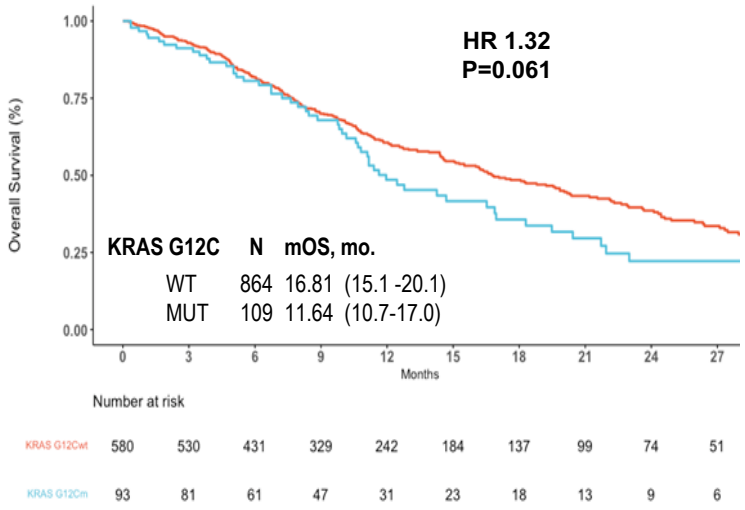
Poor Outcomes for Chemoimmunotherapy in 1L KRAS^{G12C} NSCLC TPS <50% or Harboring Selected Co-mutations

AACR American Association for Cancer Research
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Tempus Outcomes Database

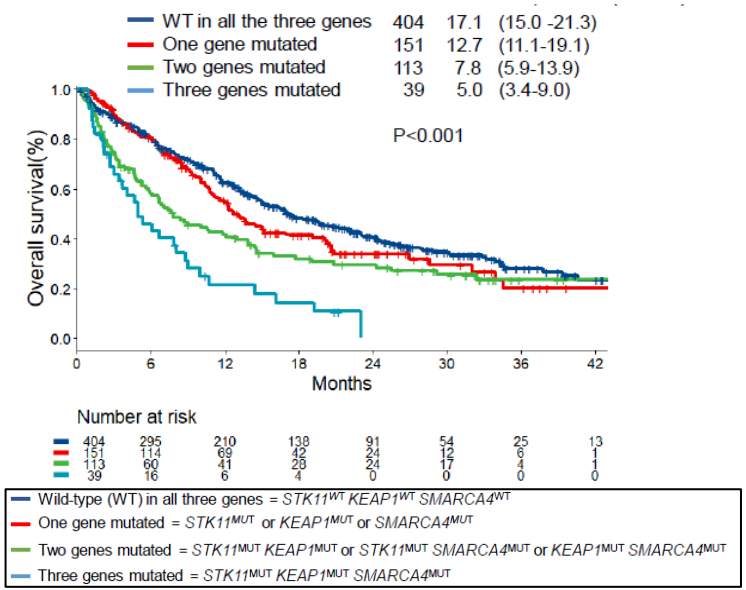
PD-L1 TPS <50%

(Patel et al. SITC 2023)



Outcomes in KRAS^{G12C} + Selected Co-mutations

(Alessi et al. J. Thoracic Oncol 2023 online)



- TPS <1% OS: ~11-15 months for KRAS^{G12C} vs ~17 months all NSCLC (KN189)
- TPS 1-49% OS: ~11-15 months for KRAS^{G12C} vs ~22 months all NSCLC (KN189)

Can KRAS Inhibitors Augment an Antitumor Immune Response in Malignancies with a Cold TME?

AACR American Association for Cancer Research
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

RESEARCH BRIEF | CANCER DISCOVERY FEBRUARY 2023

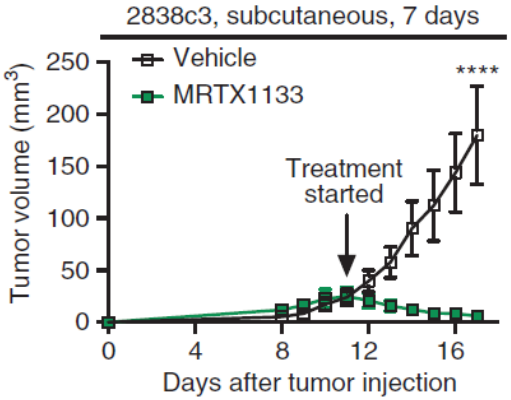
Efficacy of a Small-Molecule Inhibitor of Kras^{G12D} in Immunocompetent Models of Pancreatic Cancer

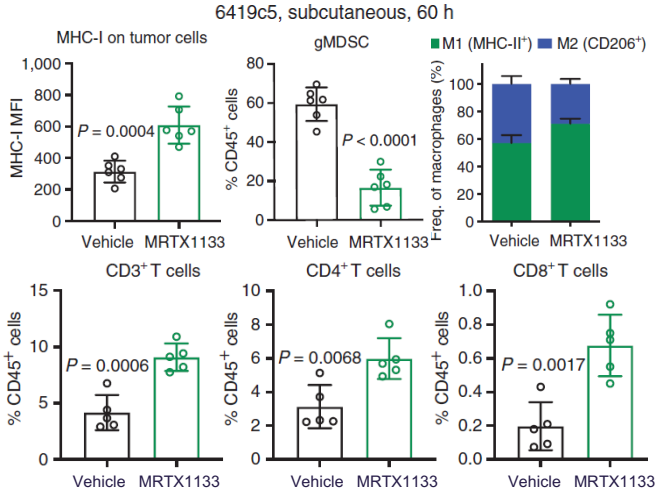
Samantha B. Kemp[1,2], Noah Cheng[1,2], Nune Markosyan[1,2], Rina Sor[1,2], Il-Kyu Kim[1,2], Jill Hallin[3], Jason Shoush[1,2], Liz Quinones[1,2], Natalie V. Brown[1,2], Jared B. Bassett[1,2], Nikhil Joshi[1,2], Salina Yuan[1,2], Molly Smith[1,2], William P. Vostrejs[1,2], Kia Z. Perez-Vale[1,2], Benjamin Kahn[1,2], Feiyan Mo[1,2], Timothy R. Donahue[4], Caius G. Radu[4], Cynthia Clendenin[1,2], James G. Christensen[3], Robert H. Vonderheide[1,2,5], and Ben Z. Stanger[1,2]

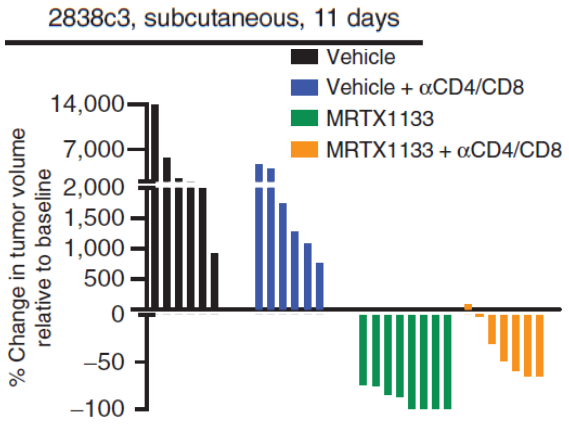
Clinical activity of immune checkpoint inhibitors as monotherapy in PDAC or CRC (MMR proficient) is limited

- PDAC: ipilimumab monotherapy ORR = 0% (0/27)
- PDAC: durvalumab monotherapy ORR = 0% (0/14)
- CRC: durvalumab monotherapy ORR = 0% (0/18)
- CRC (MMRp): pembrolizumab ORR = 0% % (0/18)

Brahmer et al. NEJM 2012;366(26):2455-65; Le DT, et al. NEJM. 2015; 372:2509-20; Royal et al. J Immunother. 2010; 33:828-33.







DO NOT POST

DO NOT POST

Acknowledgments

- Adagrasib/MRTX849 Project Team
- MRTX1133 Project Team
- Adagrasib Investigators and Patients
- KRAS collaborators including those featured in this presentation…..
  - Kwok Wong, Ben Neel et al. NYU Langone Cancer Center
  - Bob Vonderheide, Ben Stanger, et al. UPenn
  - Channing Der, Adrienne Cox et al. UNC Lineberger CC
  - Clinical Correlative Science: Pasi Jänne/Mark Awad/Andy Aguirre (DFCI), Alex Spira (UVA), Jun Zhang (KUMC), Greg Riely/Kathryn Arbour (MSKCC)
  - Julian Downward et al. Francis Crick Institute