ONCONOVA THERAPEUTICS

Preliminary Phase 1/2a Data with Rigosertib and Nivolumab in Advanced KRAS+ NSCLC Featuring Expert Overview

September 22, 2021

NASDAQ: ONTX

FORWARD-LOOKING STATEMENTS

This presentation contains forward-looking statements about Onconova Therapeutics based on management's current expectations, which are subject to known and unknown uncertainties and risks. Onconova has attempted to identify forward-looking statements by terminology including "believes," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "should," "approximately," "preliminary," "promising," "encouraging" or other words that convey uncertainty of future events or outcomes. This presentation assumes the Company raises capital for disclosed product development plans. Our actual results could differ materially from those discussed due to a number of factors including, but not limited to, our ability to raise additional financing on favorable terms, the success of our and investigator-initiated clinical trials, our ability to obtain regulatory approvals and other risk factors outlined in our annual and quarterly reports filed with the Securities and Exchange Commission. We are providing this information as of the date of this presentation and do not undertake any obligation to update any forward-looking statements, whether written or oral, that may be made from time to time, as a result of new information, future events or otherwise except as required by law.

AGENDA

- **Introductions**
- **Treatment Landscape and Unmet Need in KRAS+ NSCLC**
  - Rajwanth Veluswamy, M.D., MSCR, Assistant Professor, Medicine, Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai
- **Phase 1/2a Data: Rigosertib-Nivolumab Combination in Advanced KRAS+ NSCLC**
  - Rajwanth Veluswamy, M.D., MSCR
  - Clinical trial Principal Investigator
- **Conclusions and Next Steps: The Onconova Perspective**
  - Steven M. Fruchtman, M.D., President and Chief Executive Officer of Onconova
- **Question & Answer Session**
  - Rajwanth Veluswamy, M.D., MSCR
  - Scott Antonia, M.D., Ph.D., Professor of Medicine, Duke Cancer Institute; Director of the Duke Cancer Institute's Center for Cancer Immunotherapy
  - Onconova management

KRAS+ NSCLC: KRAS mutated non-small cell lung cancer

Scott Antonia, M.D., Ph.D.

Duke Cancer Institute

- Professor of Medicine
- Director of the Duke Cancer Institute's Center for Cancer Immunotherapy
- Global leader in the development of immunotherapy for lung cancer
- Global principal investigator of practice-changing Pacific Study in NSCLC

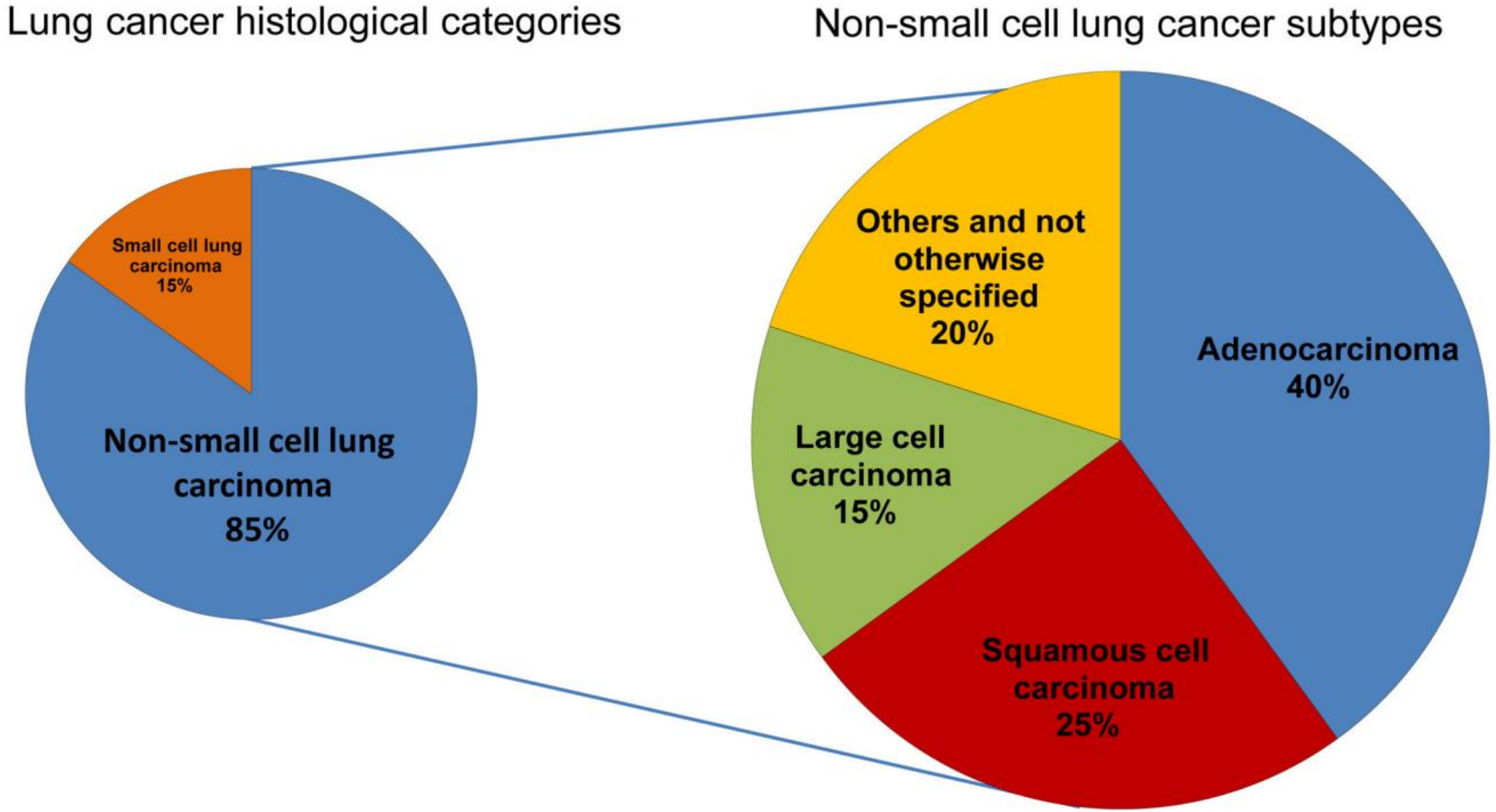
Rajwanth Veluswamy, M.D., MSCR

Icahn School of Medicine at Mount Sinai

- Assistant Professor of Medicine, Hematology and Medical Oncology
- Board-certified Medical Oncologist
- Specializes in the treatment of lung cancer and other thoracic malignancies
- Research focus: factors responsible for clinical outcomes in lung cancer

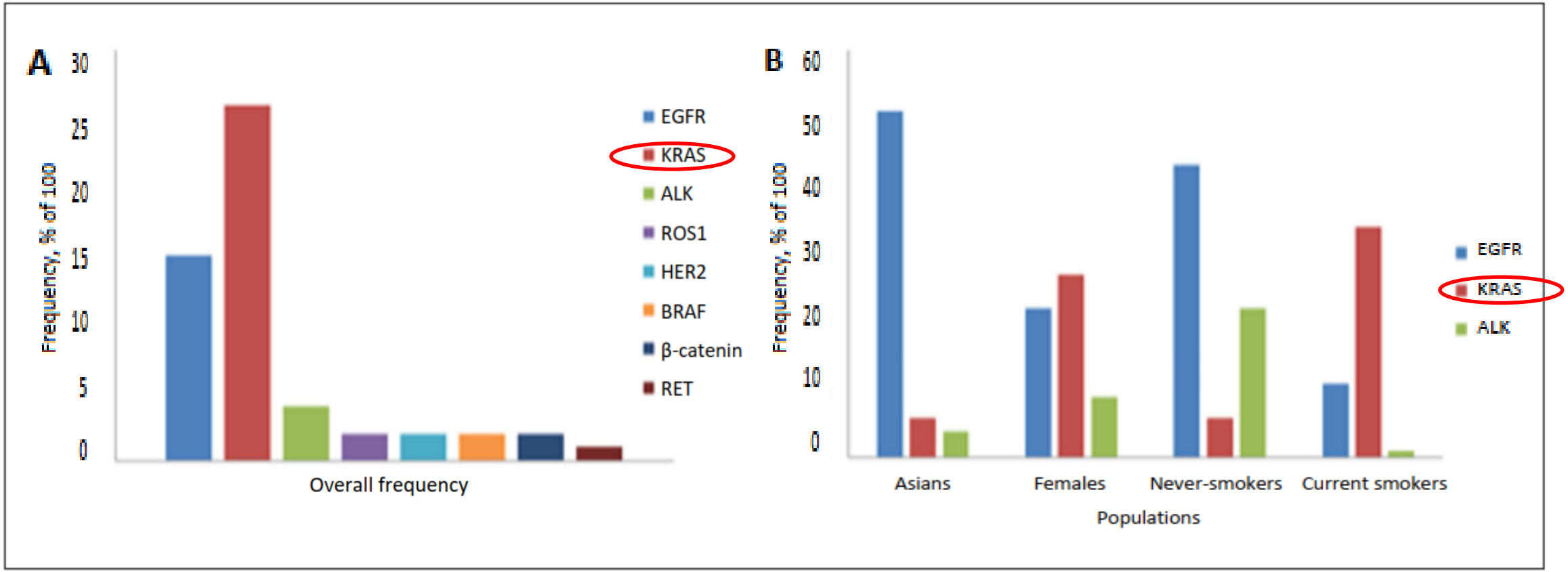
Treatment Landscape and Unmet Need in KRAS+ NSCLC

LUNG CANCER OVERVIEW



M B SCHABATH, M L COTE; CANCER EPIDEMIOL BIOMARKERS PREV. 2019 OCTOBER ; 28(10): 1563–1579

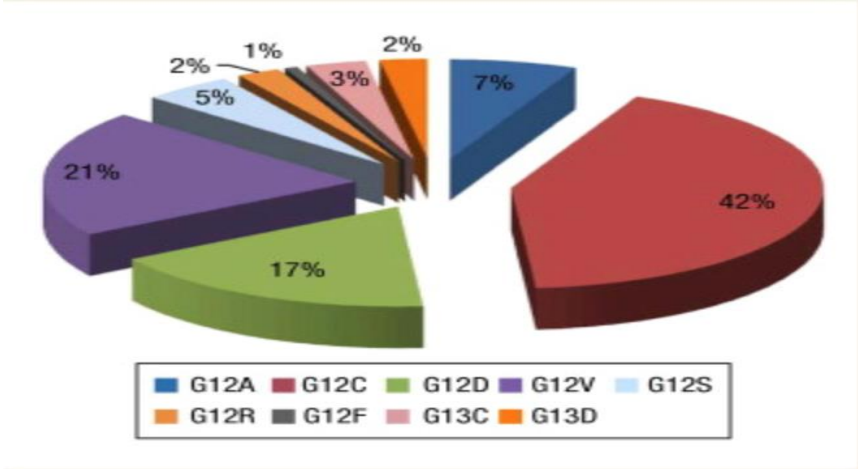
COMMON DRIVER MUTATIONS IN LUNG ADENOCARCINOMA IN THE US AND EUROPE

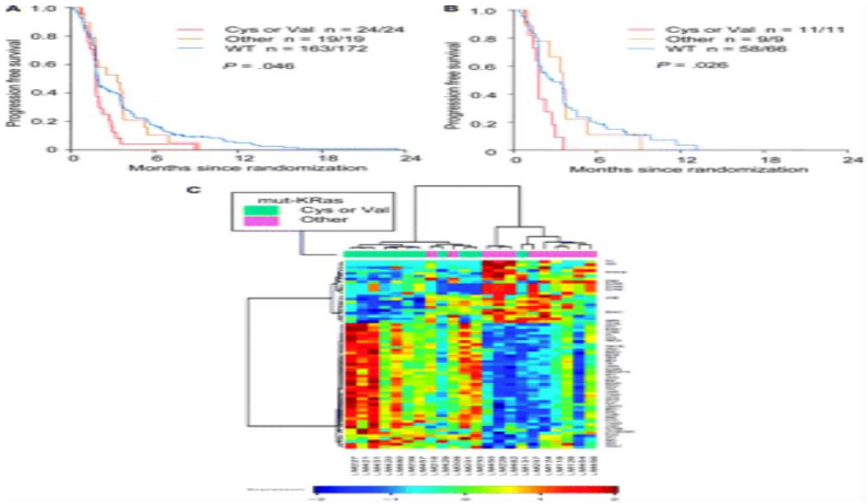


BARTA JA, ET AL. GLOBAL EPIDEMIOLOGY OF LUNG CANCER. ANNALS OF GLOBAL HEALTH. 2019; 85(1): 8, 1–16. DOI: HTTPS://DOI. ORG/10.5334/AOGH.2419

GENOMIC VARIABILITY OF KRAS MUTATIONS

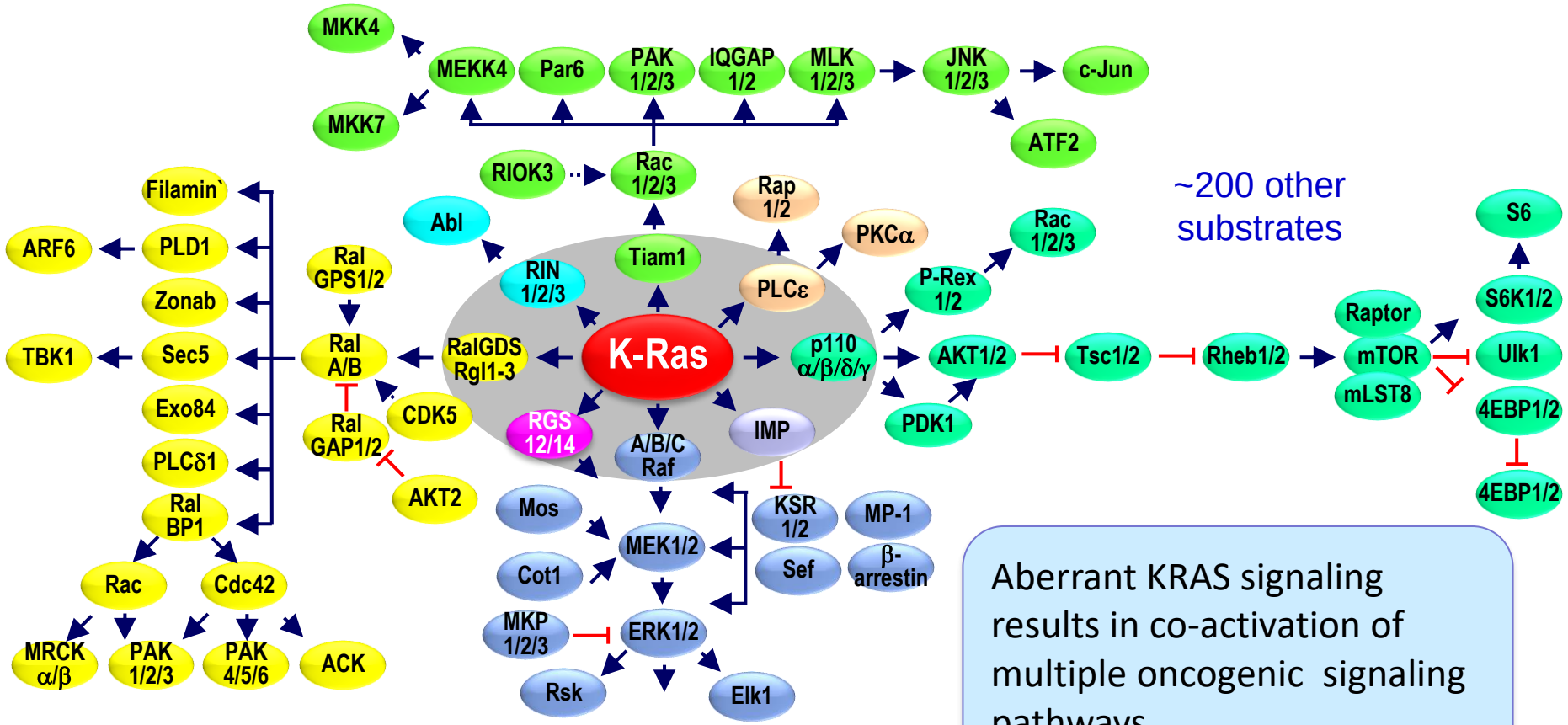
- Not all KRAS mutations the same
  - Different mutations
  - Different phenotypes (Epithelial vs Mesenchymal)
  - Overlap with other genetic alterations (i.e., TP53, STK11, CDKN2A/B)





Neil Vasan et al. Clin Cancer Res 2014
Karachaliu N et al., Clin Lung Cancer 2013

RAS EFFECTOR SIGNALING IS COMPLEX



Aberrant KRAS signaling results in co-activation of multiple oncogenic signaling pathways

SOTORASIB (LUMAKRAS)

- First KRAS inhibitor recently approved (G12C)
- On May 28, 2021, the Food and Drug Administration granted accelerated approval to sotorasib (Lumakras™, Amgen, Inc.) 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
- Approval was based on CodeBreaK 100, a multicenter, single-arm, open label clinical trial (NCT03600883) which included patients with locally advanced or metastatic NSCLC with KRAS G12C mutations
  - Efficacy was evaluated in 124 patients whose disease had progressed on or after at least one prior systemic therapy
  - The main efficacy outcome measures were objective response rate (ORR) according to RECIST 1.1, as evaluated by blinded independent central review and response duration
    - The ORR was 36% (95% CI: 28%, 45%)
    - Median response duration of 10 months (range 1.3+, 11.1)
- FDA also approved the QIAGEN therascreen® KRAS RGQ PCR kit (tissue) and the Guardant360® CDx (plasma) as companion diagnostics for Lumakras

Phase 1/2a Data: Rigosertib-Nivolumab Combination in Advanced KRAS+ NSCLC

Rajwanth Veluswamy, MD MSCR
Assistant Professor of Medicine
Icahn School of Medicine at Mount Sinai

Icahn School of Medicine at Mount Sinai

Disclosures

RRV has served on advisory boards for Bristol-Myers Squibb, Astrazeneca, Merck, Novocure, on unbranded speaker's bureau of Astrazeneca, received consulting honorarium from Beigene, and research grants from Bristol-Myers Squibb, Onconova, Astrazeneca and EMD Serono.

Rigosertib Mechanisms of Action

- RAS is the most commonly mutated gene accounting for ~25% of cancers

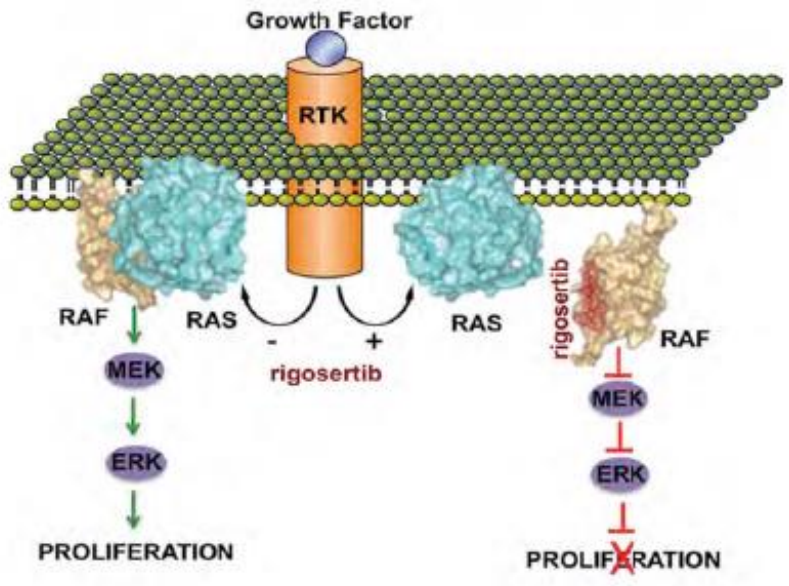
Proposed Mechanisms of Action

- Disruption of RAS effectors[1]
- Inhibition of Ras/Raf/MEK/ERK pathway signaling by a stress-induced phospho-regulatory circuit[2]
- Microtubule-destabilizing agent[3]
- Immunomodulator with promotion of immune effector cell tumor infiltration[4]

Clinical Studies

- Over 1,300 patients have been treated with established safety profile

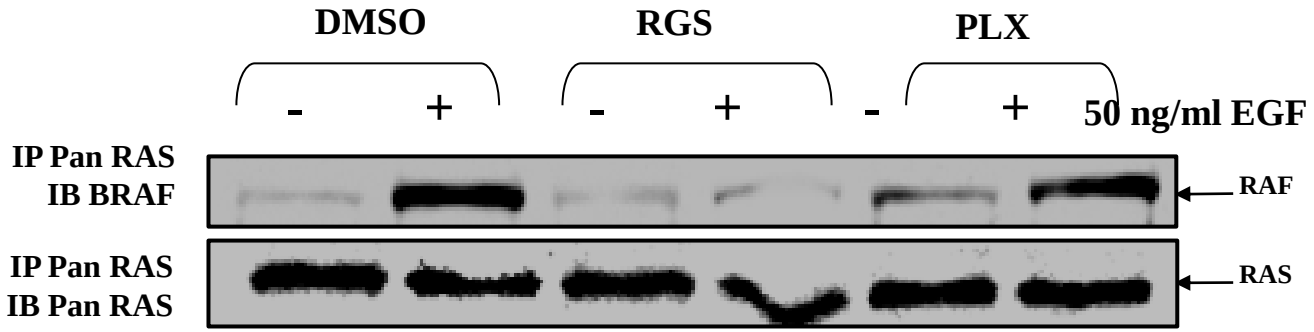
RAS-targeted novel mode of action**

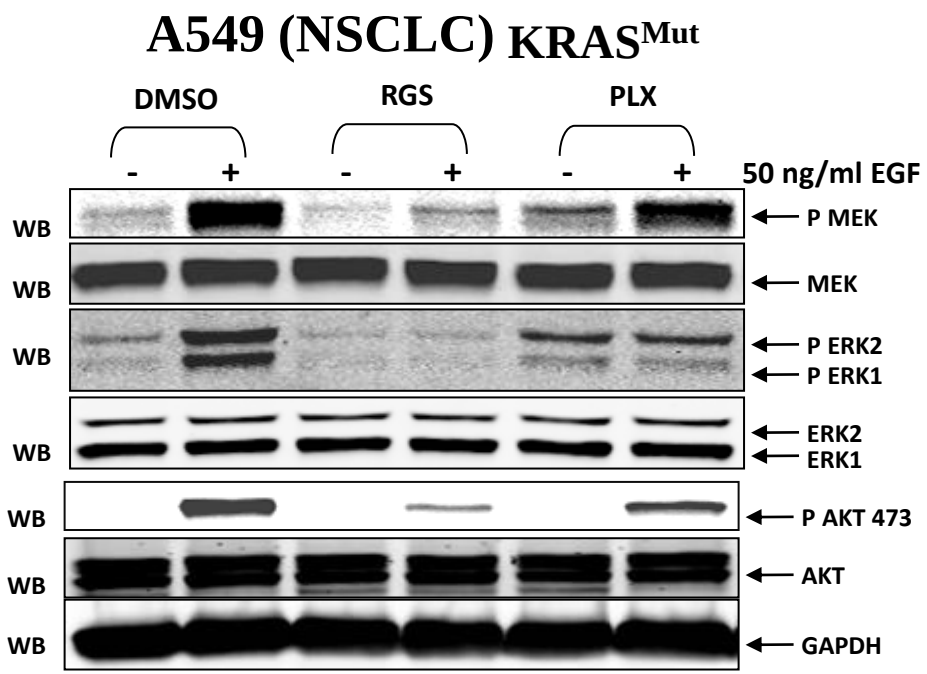


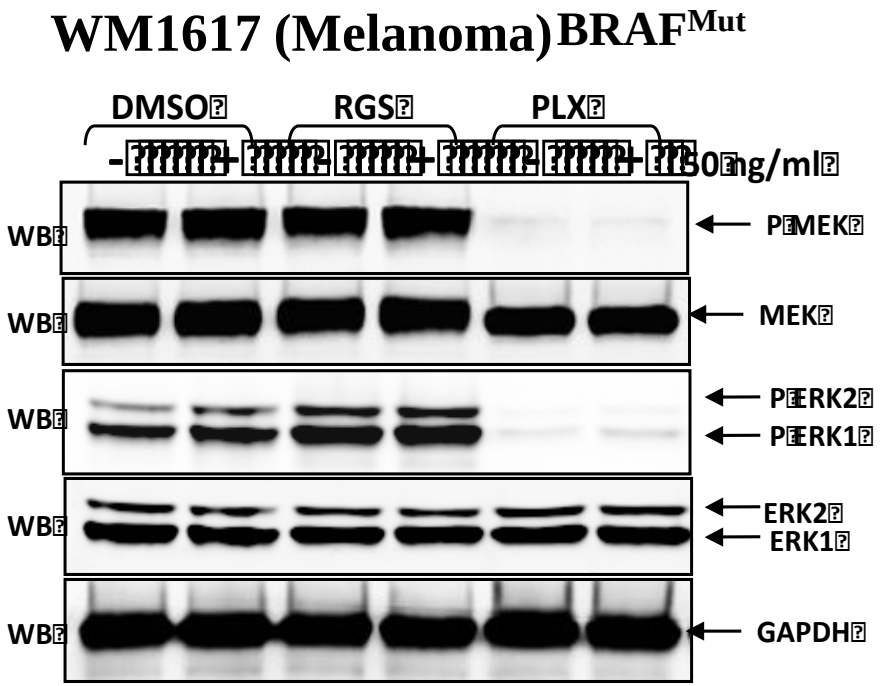
* Adapted from Papaemmanuil et al., 2013 Blood
** Athuluri-Divakar SK, Cell 2016;165:643

1. Athuluri-Divakar SK, Cell 2016;165:643; 2. Ritt et al: Molecular Cell 64, 87; 2016; 3. Jost et al: Molecular Cell 68, 210; 2017; 4. Chi Yan, E.Premkumar Reddy, and Ann Richmond, AACR 2019, VUMC

Rigosertib Inhibits MAPK/ERK and AKT Pathway

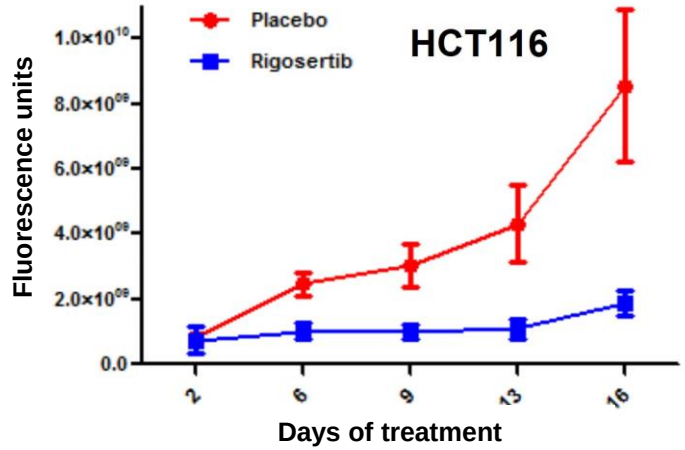


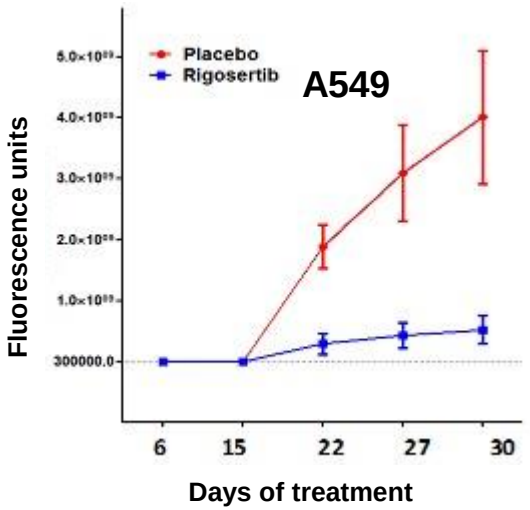


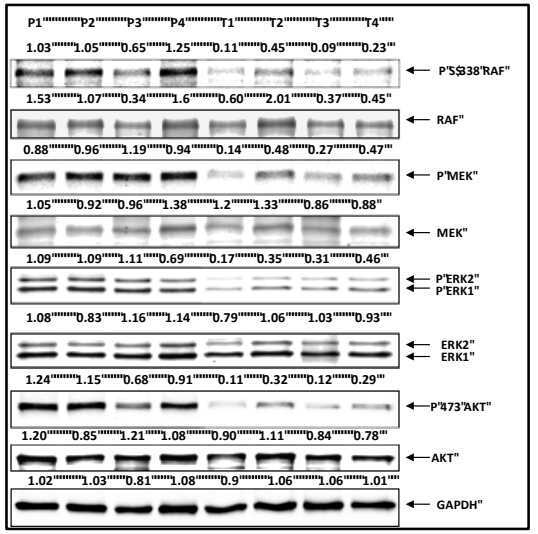


Athuluri-Divakar et al. *Cell*, 2016

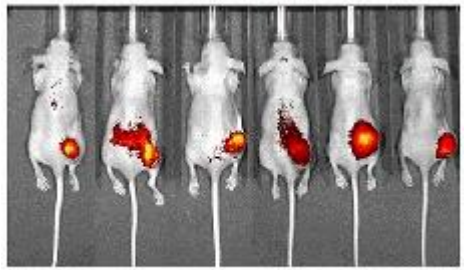
Inhibition of Tumor Growth by Rigosertib in Mouse Xenograft Assays



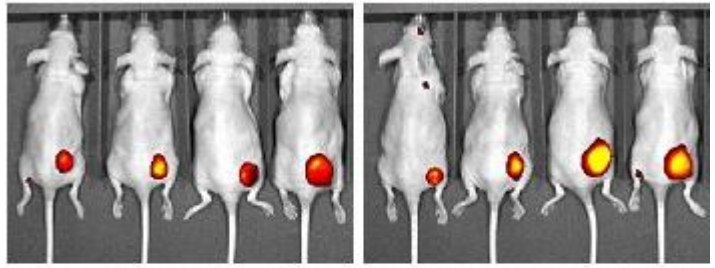




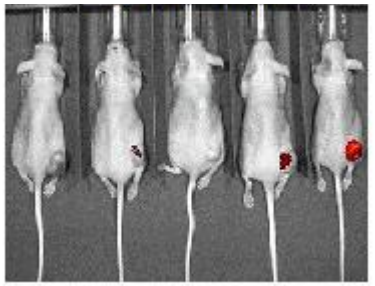
Control - untreated



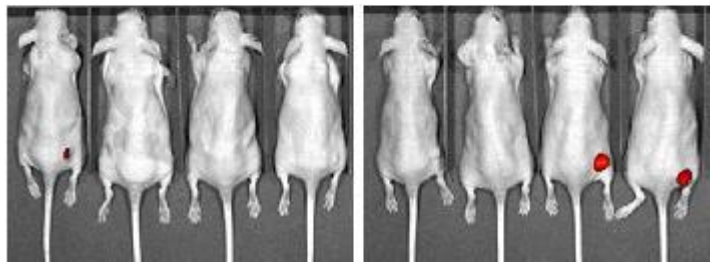
Placebo - treated

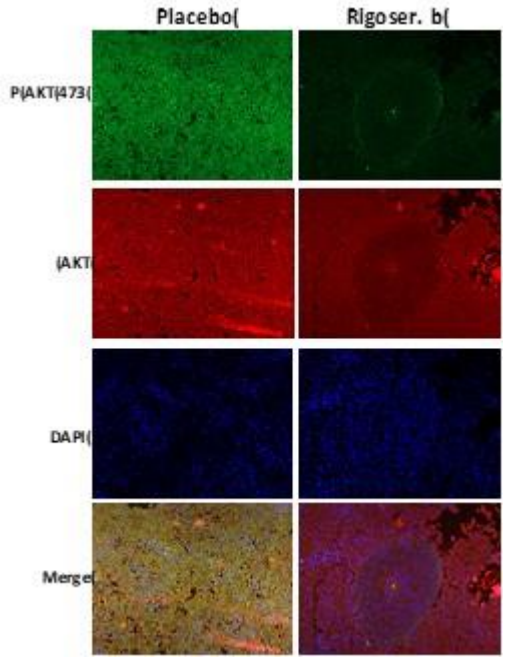


Rigosertib treated



Rigosertib treated





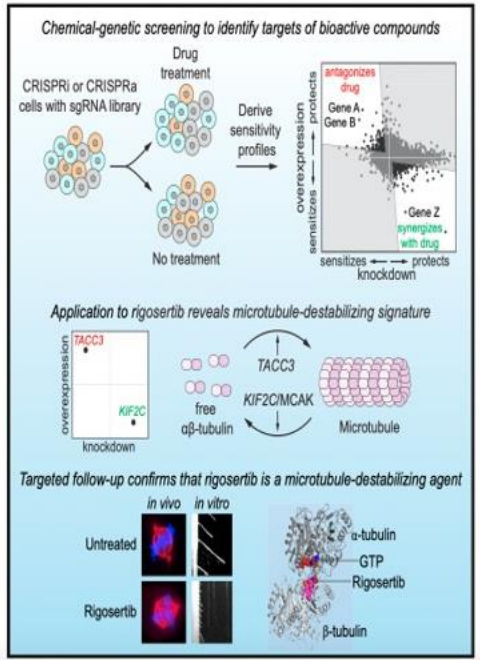
Athuluri-Divakar et al. *Cell,* 2016

Alternative Mechanisms of Action of Rigosertib

Molecular Cell

Combined CRISPRi/a-Based Chemical Genetic Screens Reveal that Rigosertib Is a Microtubule-Destabilizing Agent

Graphical Abstract



Authors

Marco Jost, Yuwen Chen, Luke A. Gilbert, ..., Michel O. Steinmetz, Marvin E. Tanenbaum, Jonathan S. Weissman

Correspondence

m.tanenbaum@hubrecht.eu (M.E.T.), jonathan.weissman@ucsf.edu (J.S.W.)

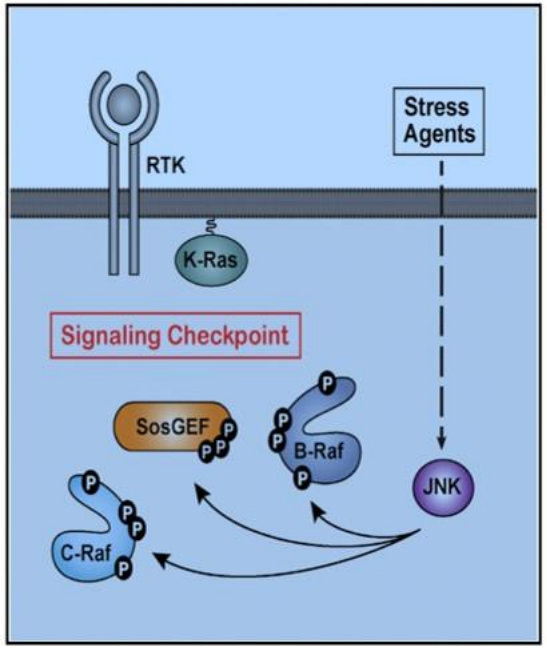
In Brief

Jost et al. present a two-tiered strategy to identify molecular targets of bioactive compounds using CRISPRi/a-mediated chemical-genetic screens. Application to rigosertib, an anti-cancer drug with an unclear mechanism of action, points to rigosertib being a microtubule-destabilizing agent. Targeted cell biological, biochemical, and structural approaches confirm this mechanism of action.

Molecular Cell

Inhibition of Ras/Raf/MEK/ERK Pathway Signaling by a Stress-Induced Phospho-Regulatory Circuit

Graphical Abstract



Authors

Daniel A. Ritt, María T. Abreu-Blanco, Lakshman Bindu, ..., Andrew G. Stephen, Matthew Holderfield, Deborah K. Morrison

Correspondence

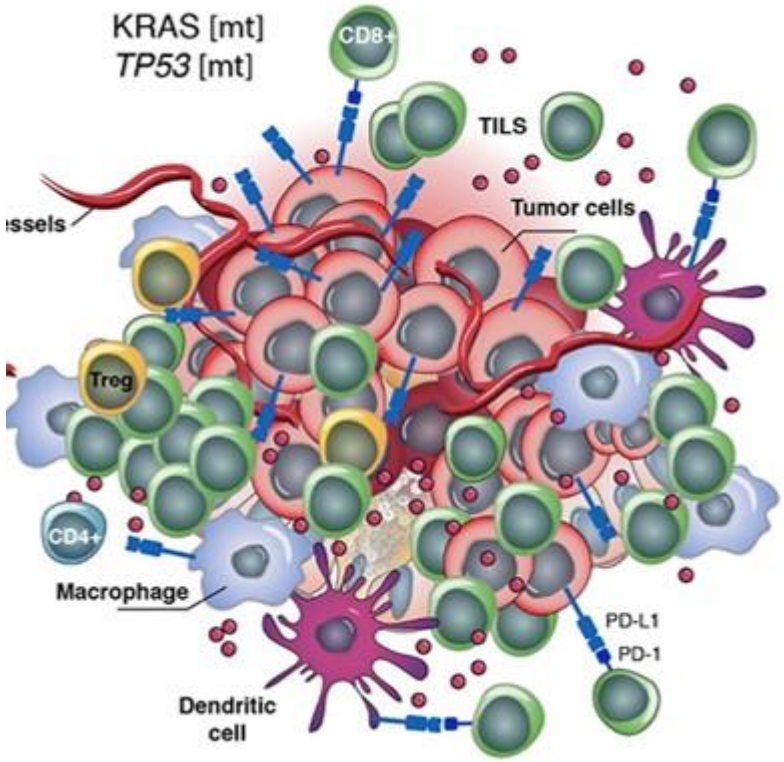
morrisod@mail.nih.gov

In Brief

The Ras pathway is an important cellular signal transduction pathway frequently activated in human cancer. Ritt et al. identify a route for the phospho-inhibition of key Ras pathway components, Sos1 and the Rafs, that is mediated by JNK cascade activation and may function as a stress-induced signaling checkpoint.

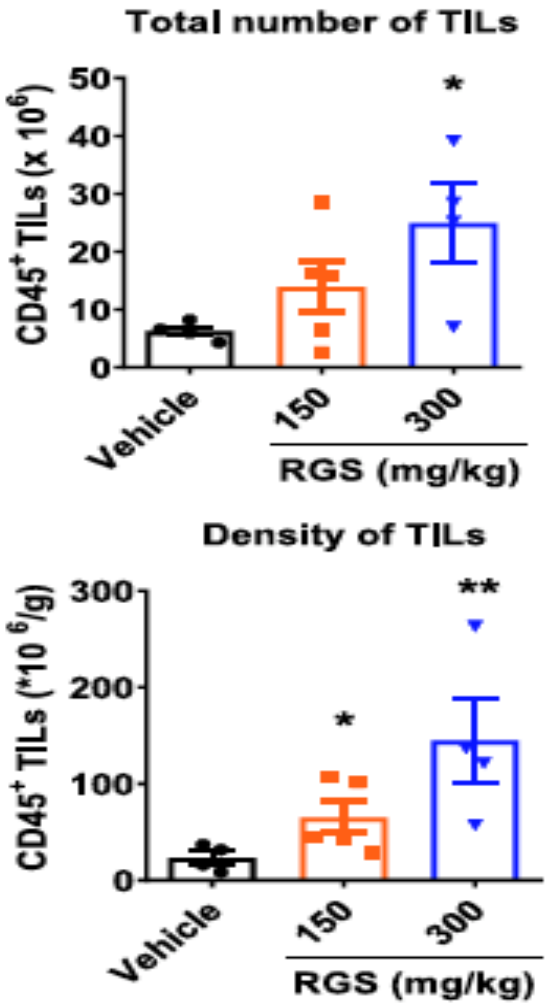
Immunotherapy in *KRAS*-Mutated NSCLC

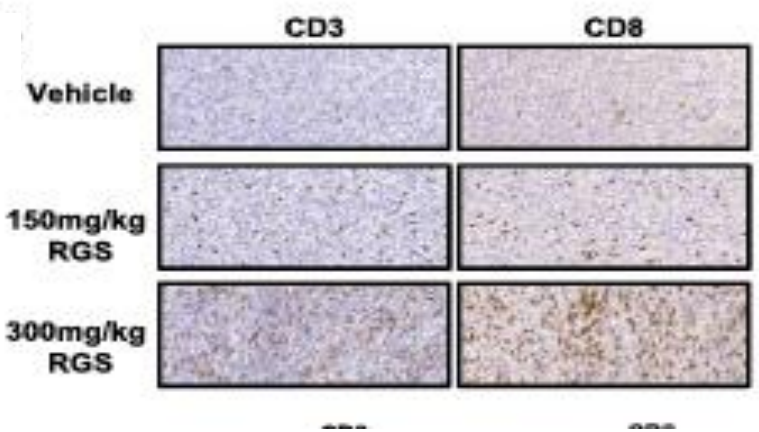
- Immune checkpoint inhibitors (ICIs) have become standard of care in metastatic NSCLC
- *KRAS* mutations are associated with ICI benefit in NSCLC
- *KRAS*-mutant NSCLC exhibits increased TMB, potentially leading to increased ICI sensitivity
- Concurrent mutations with *KRAS* affect immunogenicity – co-occurring *TP53* mutations associated with immune-rich microenvironment

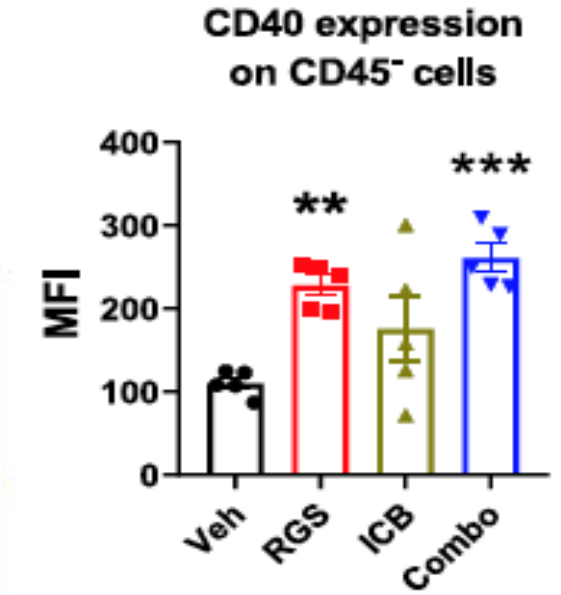


Friedlaender et al., Cancer Treat Rev 2020

Rigosertib Increases the TILs Infiltration and CD40 Expression



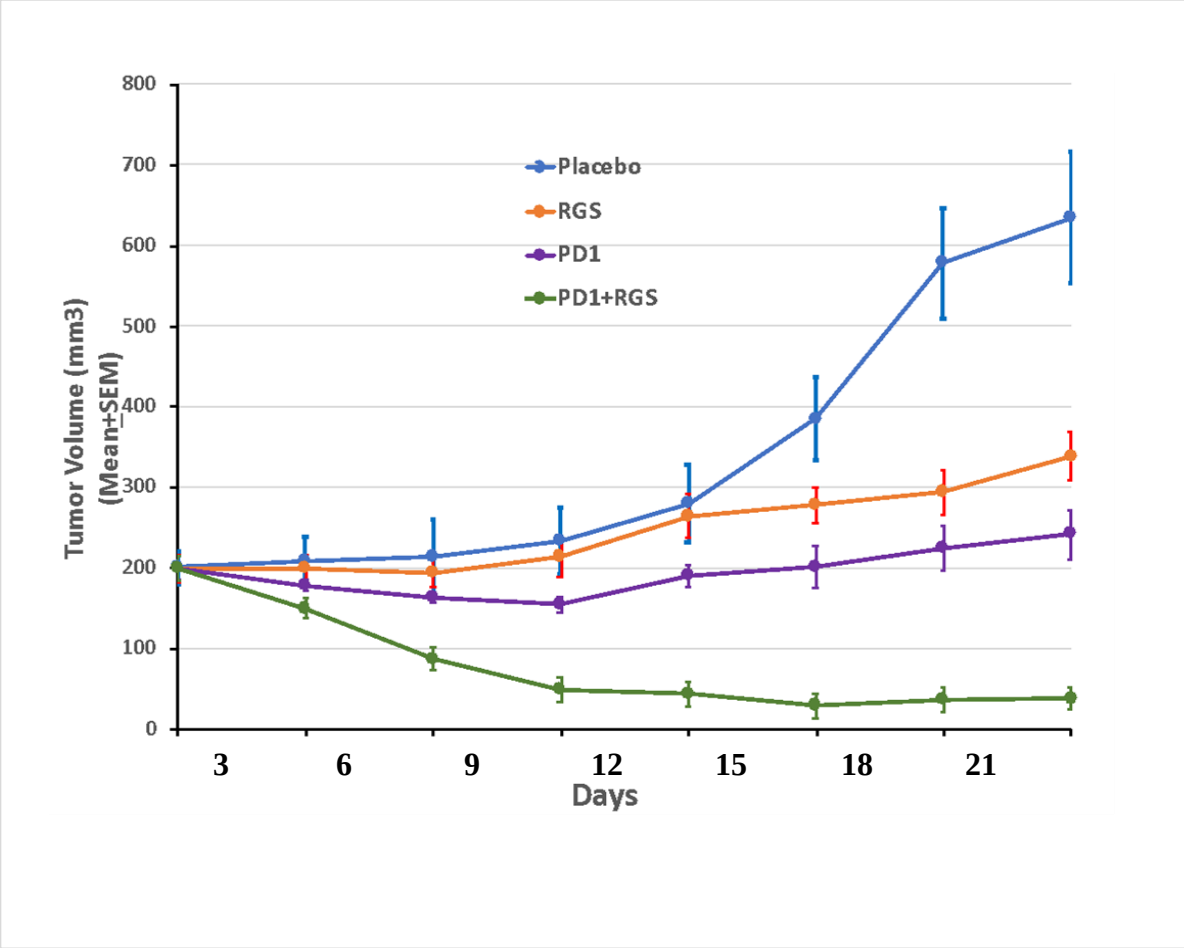




Yan et al. Molecular Cancer, 2021

Rigosertib and PD-1 Inhibitor Act Synergistically

- **Using MC38 models (immunocompetent CRC), rigosertib inhibits tumor growth as both monotherapy and synergistically with an anti-PD1 checkpoint inhibitor (HX-008)**



Data by Hanx Biopharmaceuticals

Study Design

Patient Selection

Main Inclusion criteria

- Stage IV Lung Adenocarcinoma with KRAS mutation
- POD or intolerant of checkpoint inhibitor monotherapy or in combo with platinum doublet chemotherapy
- ECOG 0-2

Main Exclusion Criteria

- EGFR sensitizing mutation or ALK translocation
- Active autoimmune disease or steroids > 10mg
- Untreated CNS metastases

Correlative Studies

- Genomic Studies
- Immunophenotyping

Dose Escalation Phase (n=8-18)

Oral Rigosertib days 1-21 of 28-day cycle
IV Nivolumab 240mg days 1 & 15

Accelerated Titration Design
Escalating single patient cohorts
Dose 1: RGS 280mg BID
Dose 2: RGS 560mg AM, 280mg PM
Dose 3: RGS 560mg BID

Primary Objective: Safety/Tolerability

3+3 design if
Gr 2 Toxicity

Dose Expansion Phase (n=12)

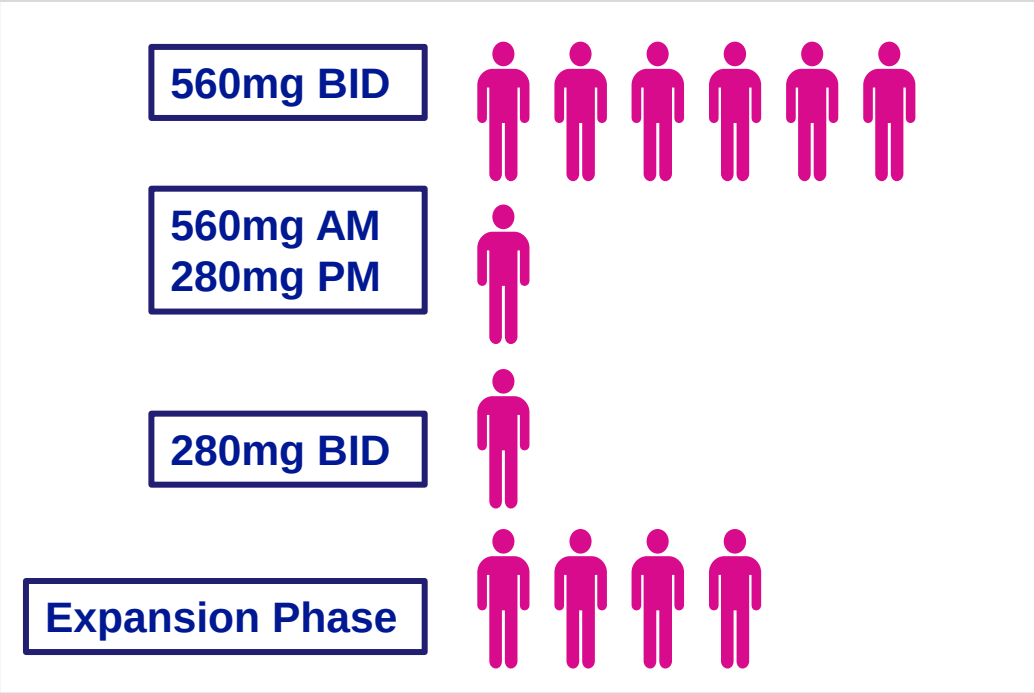
Rigosertib at Highest Dose + Nivolumab

Secondary Objectives:
Determine ORR per Recist 1.1, PFS, OS

Radiographic Scans every 8 weeks +/- 2 weeks

Patients

- Trial opened at Mount Sinai in June 2020
- 12 patients currently enrolled
- 92% of patients have non-G12C mutations
- Cohort is heavily treated - all patients progressed on prior PD1/L1 inhibitors



Baseline Characteristics	Entire Cohort N=12
Age in years – median (range)	60 (53 – 80)
Type of KRAS mutation – n (%)	
G12V	6 (50%)
G12D	4 (33%)
G12C	1 (8%)
I46T	1 (8%)
Smoking history – n (%)	
Current/Former	8 (67%)
Never	4 (33%)
ECOG performance status – n (%)	
0	8 (67%)
1	4 (33%)
Prior Lines of Systemic Therapy – n (%)	
1	3 (25%)
2	6 (50%)
≥ 3	3 (25%)
Type of prior systemic therapy – n (%)	
PD-1/PD-L1 inhibitor monotherapy	1 (8%)
Platinum chemo + PD-1 therapy	11 (92%)

Safety/Tolerability with Rigosertib+Nivolumab

TRAEs Were Mostly Mild – Only 1 DLT Thus Far

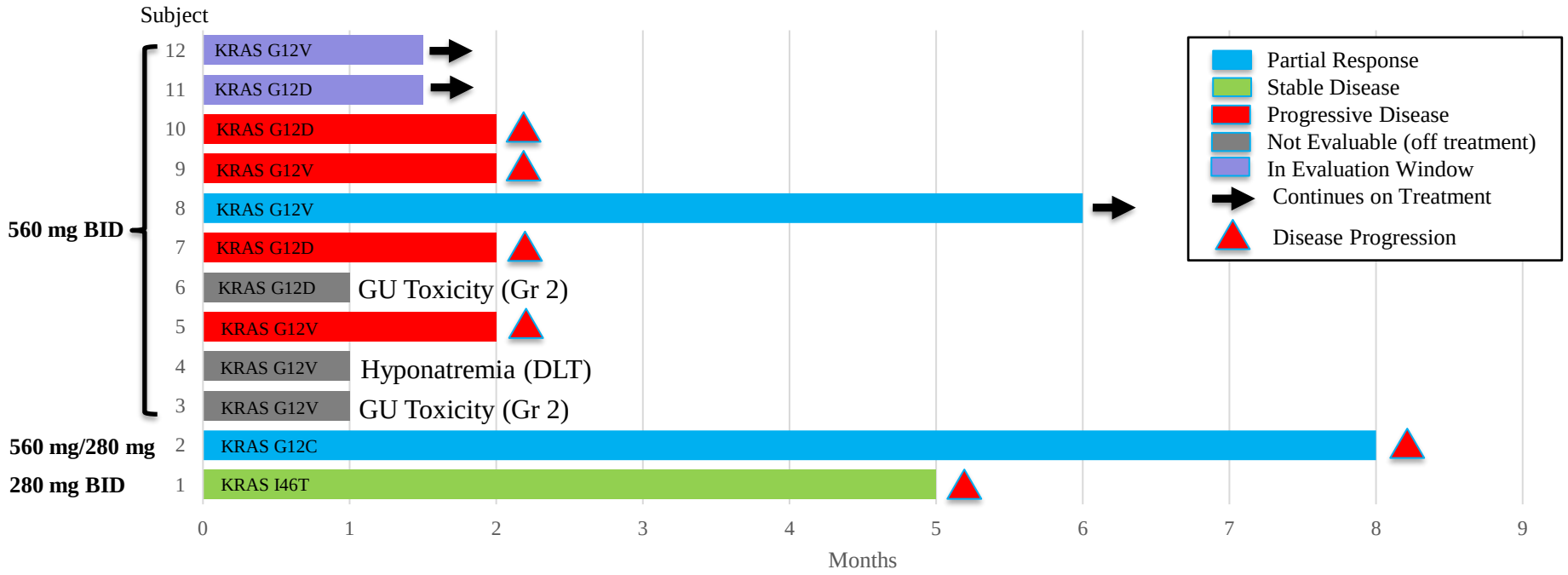
Treatment-Related Adverse Events (TRAEs) – n (%)	Entire Cohort: N=12	
	Grade 1-2	Grade 3
Dysuria	7 (58)	
Hematuria	7 (58)	
Urinary Frequency	2 (17)	
Abdominal Pain	4 (33)	
Fatigue	6 (50)	
Anemia	10 (83)	
Lymphopenia	3 (25)	1 (8)
Thrombocytopenia	2 (17)	
Hyponatremia*	3 (25)	1 (8)*
Hyperglycemia	11 (92)	
AST elevation	3 (25)	
ALT elevation	3 (25)	
ALK elevation	2 (17)	
Nausea/Vomitting	4 (33)	
Constipation	4 (33)	
Diarrhea	2 (17)	
Anorexia	2 (17)	
Pruritis	1 (8)	
Infusion-related Reaction	1 (8)	
*Dose Limiting Toxicity		

- Urinary toxicities well documented with Rigosertib were most common TRAE
- Most toxicities were manageable
- No synergistic toxicities noted for either study drug
- One DLT at 560mg BID for grade 3 hyponatremia – previously documented with Rigosertib

Response to Rigosertib+Nivolumab

3 of 7 (43%) Evaluable Patients had Disease Control (2 PR + 1 SD)

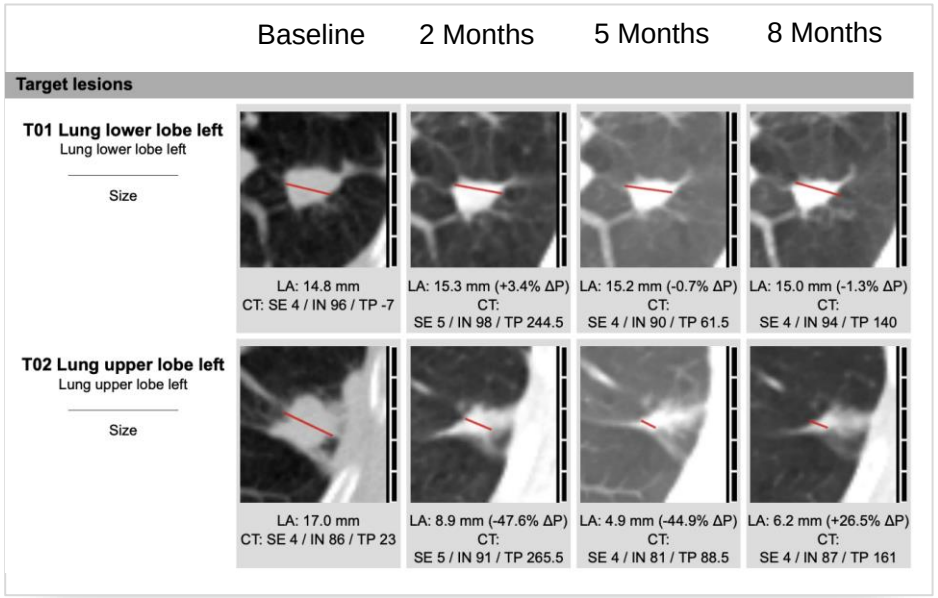
Best Overall Response in Evaluable Patients– n (%)	**N=7**
Complete Response	0 (0)
Partial Response	2 (29)
Stable Disease	1 (14)
Progressive Disease	4 (57)
Not Evaluable Patients – n (%)	**N=5**
Discontinued Study Drug due to Toxicity	3 (60)
Currently on Study Drug in Evaluation Window	2 (40)

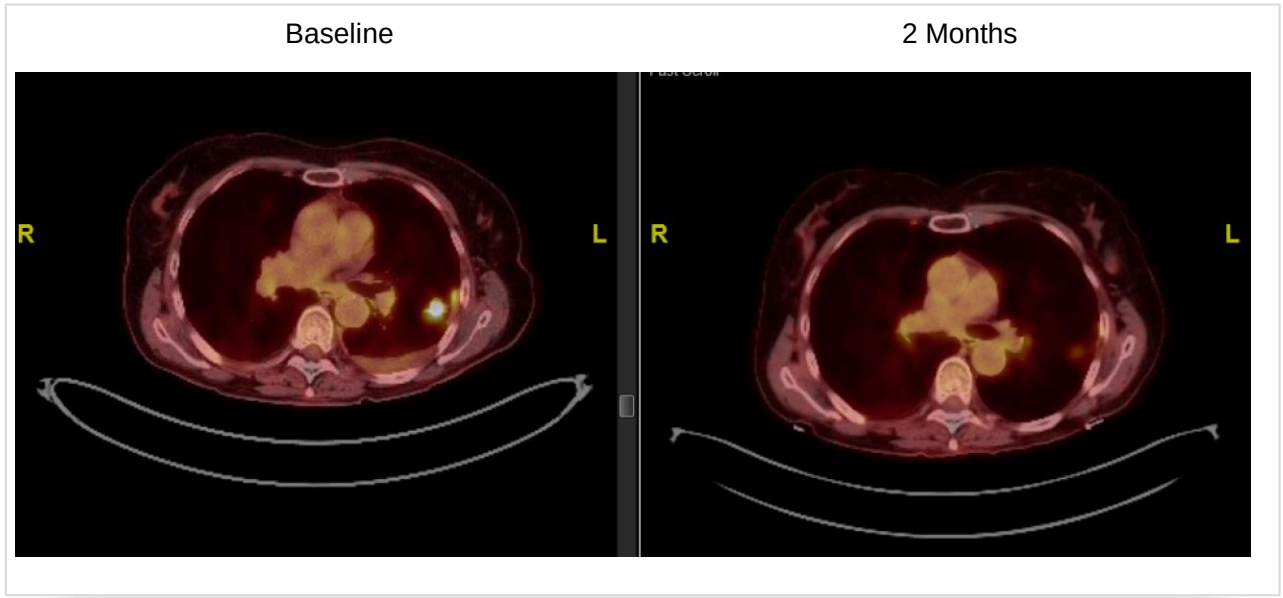


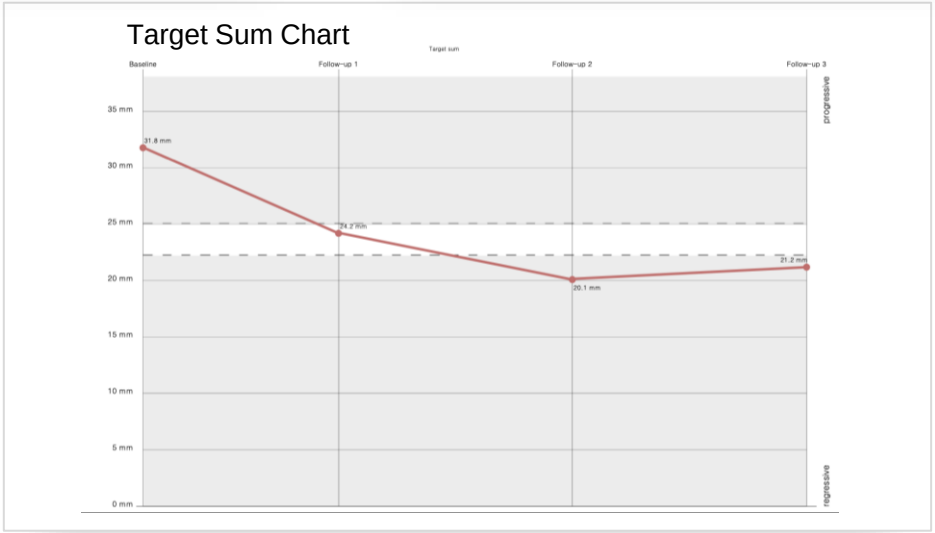
Patient #2: Partial Response at RGS 560mg AM / 280mg PM

Demographics		Clinical Characteristics	
		Histologic Type	Mucinous Adeno
Sex	F	Molecular Profile	KRAS G12C, STK11, SMARCA4
Race	White	PD-L1 Expression	99%
Smoking	current	Sites of Disease	Lung, Bone
ECOG PS	0	Prior Lines of Treatment	1st: neoadj trial with IO+chemo: 2 cycles 2nd: Carbo/Pem/Pembro (3 months)

Patient #2: Partial Response at RGS 560mg AM / 280mg PM



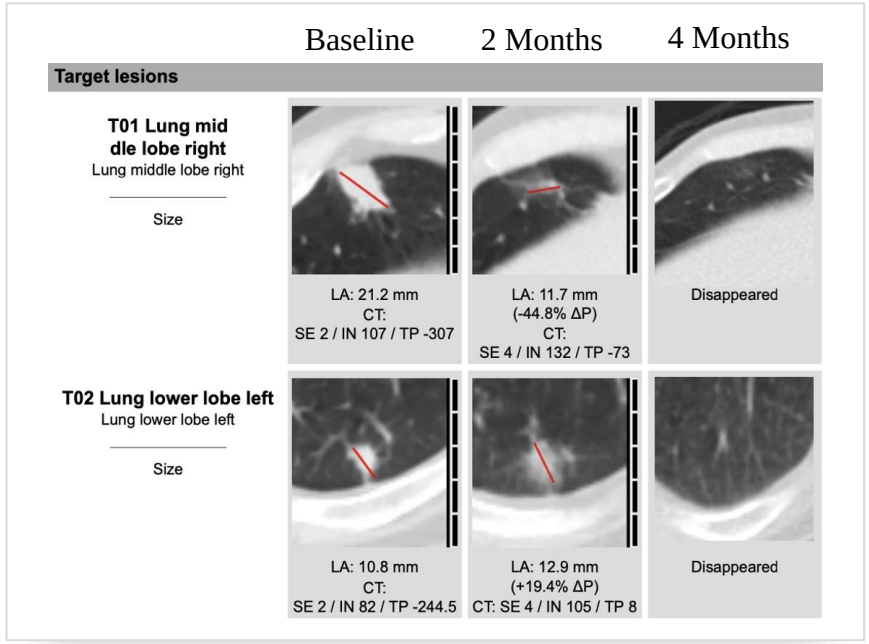


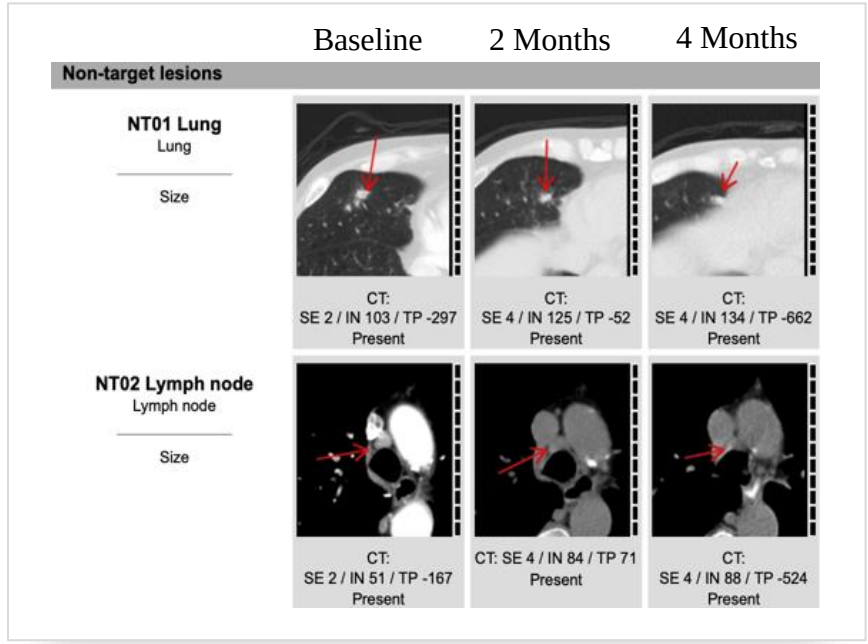


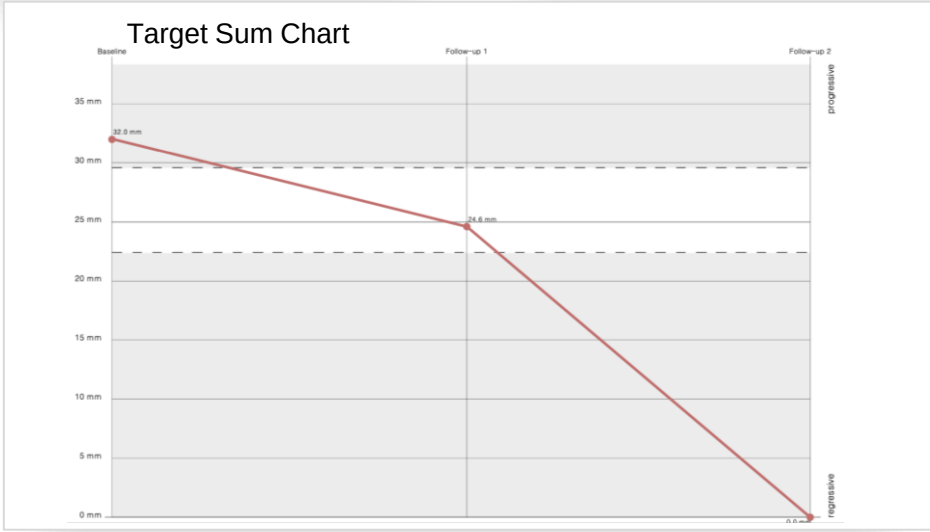
Patient #8: Partial Response at RGS 560mg BID

Demographics		Clinical Characteristics	
		Histologic Type	Lung Adeno
Sex	M	Molecular Profile	KRAS G12V, TP53
Race	White	PD-L1 Expression	5%
Smoking	former	Sites of Disease	Lung, Brain
ECOG PS	0	Prior Lines of Treatment	1st: Carbo/Pem/Pembro (5 months)

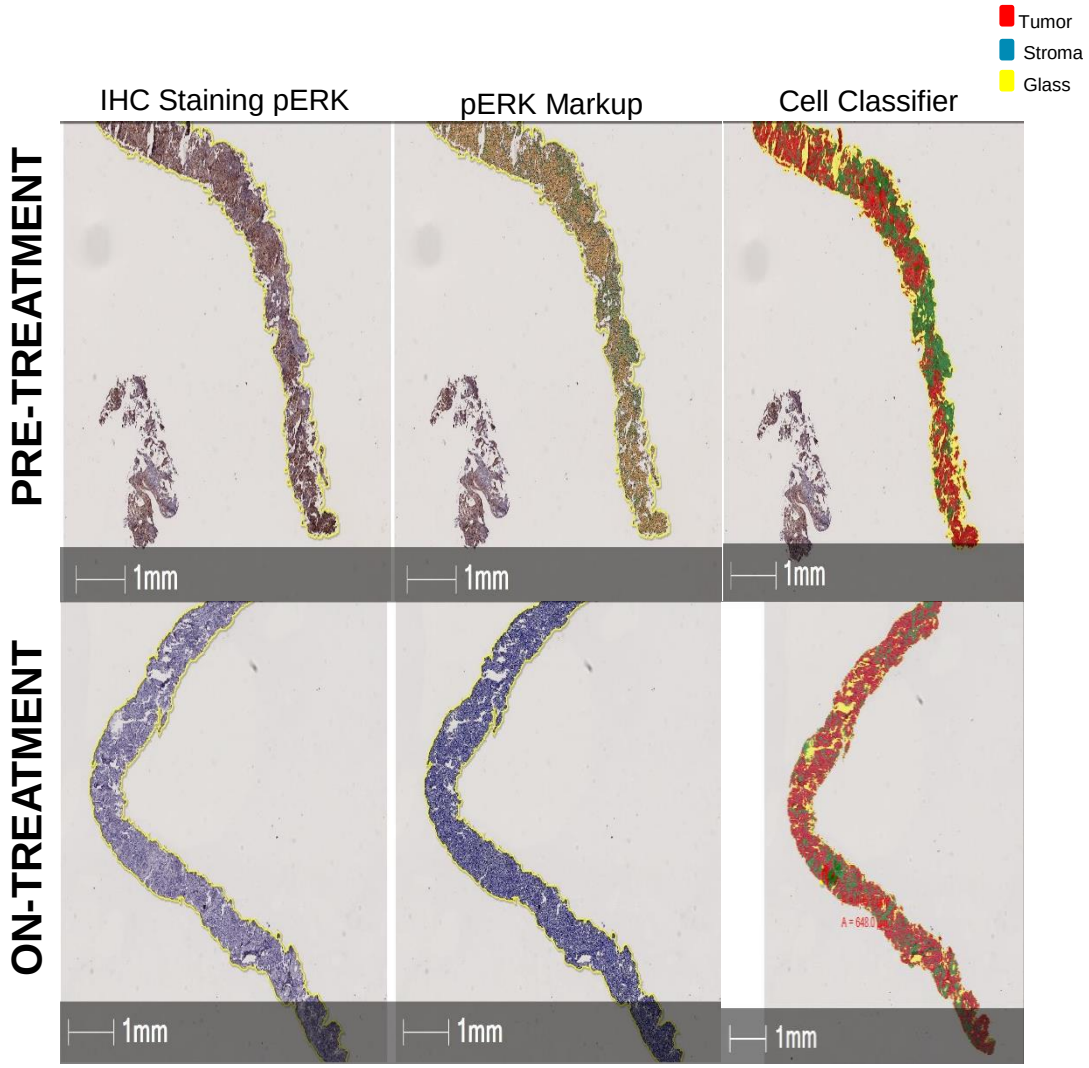
Patient #8: Partial Response at RGS 560mg BID



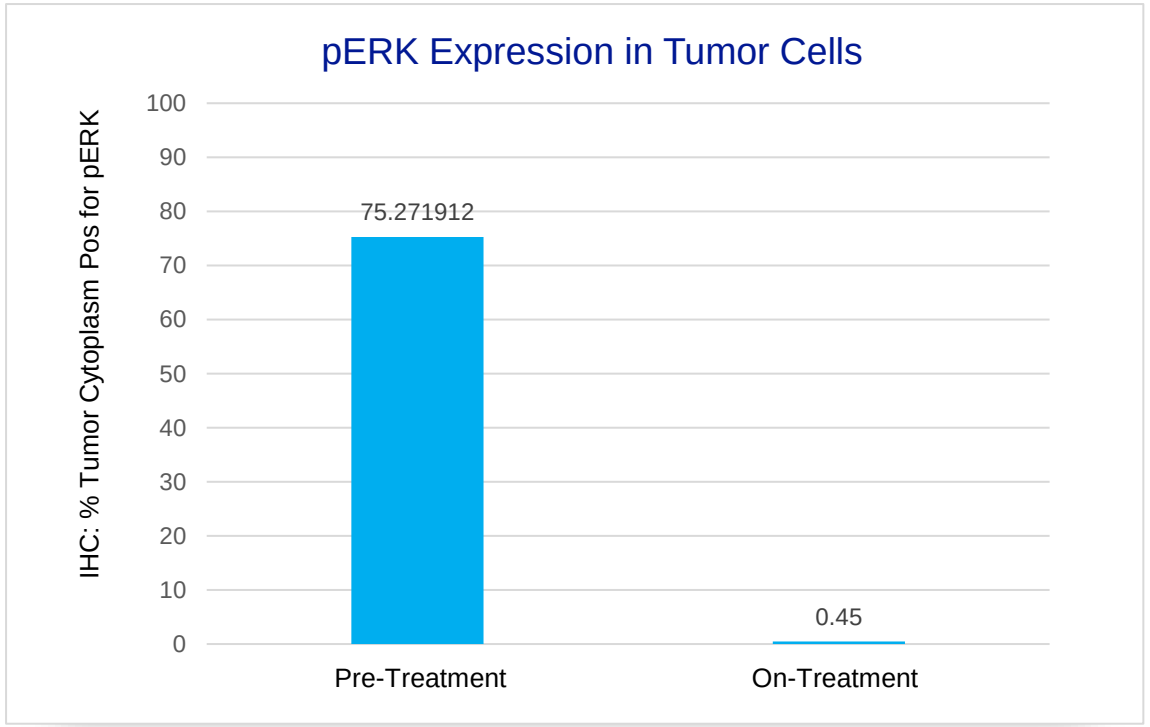




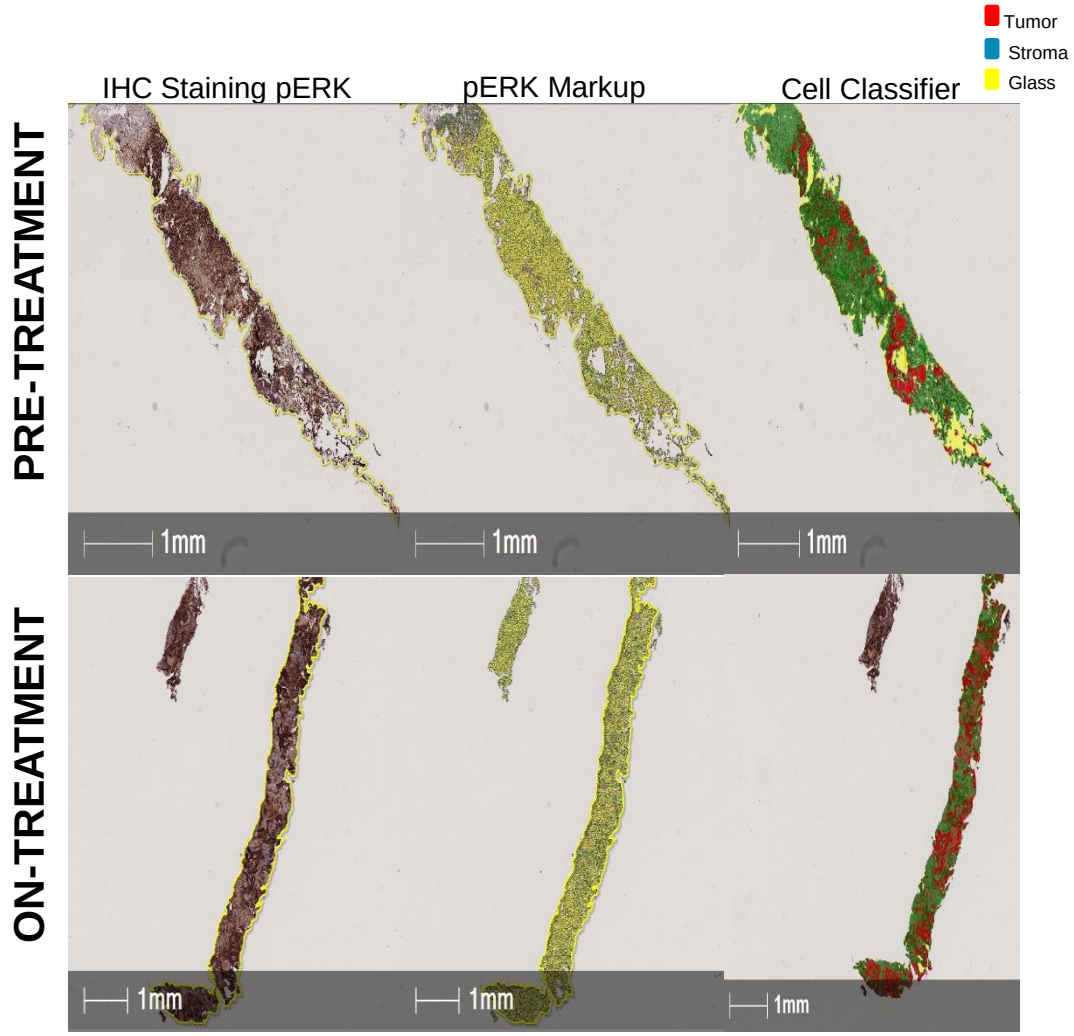
Patient #1: Stable Disease at RGS 280mg BID – pERK Staining



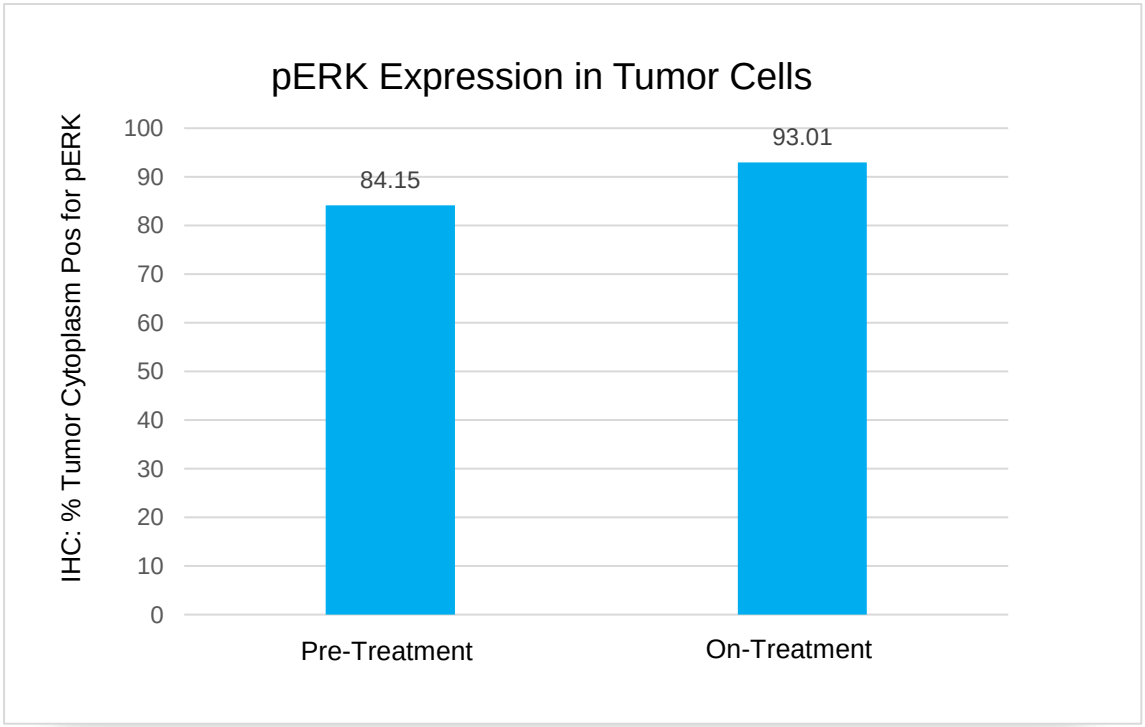
- Significant loss of pERK IHC Staining on Rigosertib/Nivolumab
- Correlates with Clinically Stable Disease



Patient #10: Disease Progression at RGS 560mg BID – pERK Staining



- No loss of pERK IHC Staining on Rigosertib/ Nivolumab
- Correlates with Clinical Disease Progression



Conclusions and Future Directions

- Rigosertib, a novel NME that down modulates mutated KRAS pathway (mutation agnostic), in combination with Nivolumab is well tolerated, with low incidence of grade 3 or higher toxicities
  - Only one DLT observed thus far (hyponatremia)

- 3 out of 7 (43%) evaluable patients on trial demonstrated clinical benefit
  - 2 PRs + 1 SD
  - Responses across different KRAS mutations (G12C, G12V, I46T)

- Future Directions
  - 9 more patients to be enrolled in 560mg BID Expansion Cohort
  - Molecular and Immune studies on pre-/on-treatment biopsies to further describe the pharmacodynamics and impact on immune microenvironment
  - Additional dose escalation cohorts to determine the MTD/RPTD are being considered

SUMMARY: THE ONCONOVA PERSPECTIVE

- Rigosertib may augment the response to checkpoint inhibitors
- Responses across multiple KRAS variants potentially differentiate rigosertib from RAS pathway modulators targeting particular KRAS mutations
- Rigosertib has the potential to address an unmet need in patients with limited treatment options
- Findings may be applicable across multiple indications

NEXT STEPS: THE ONCONOVA PERSPECTIVE

- Support the continued accrual to the Phase 1/2a trial's expansion cohort
- Potential investigator-initiated melanoma study evaluating rigosertib plus a PD-1 checkpoint inhibitor is under review for finalization
- Continue leveraging investigator-sponsored studies to advance rigosertib's clinical development in high-medical need KRAS mutated indications

ONCONOVA HIGHLIGHTS

- **ON 123300 (narazaciclib) is a multi-kinase inhibitor that targets CDK 4/6**
  - CDK 4/6 commercial agents are multibillion-dollar franchises
  - Potential to overcome resistance to approved CDK 4/6 inhibitors in HR+ HER 2- metastatic breast cancer, and in additional tumor types
  - Phase 1 dose-escalation and expansion studies underway in the United States and China.
- **Rigosertib is in multiple investigator-sponsored combination studies**
  - Identification of RAS-driven tumor indications in development
    - KRAS+ NSCLC
    - Advanced squamous cell carcinoma associated with recessive dystrophic epidermolysis bullosa
- **Ongoing commitment to business development**
  - In-license compounds to expand the product pipeline
- **Well-capitalized**
  - Cash and equivalents as of 6/30/21 ≈ $43.7 million
  - > 18 months of cash runway

KRAS+: KRAS mutated; NSCLC: Non-small cell lung cancer