Phase 1/2 Trial of Rigosertib & Nivolumab in KRAS-Mutated NSCLC in 2nd+ Line

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Disclosures

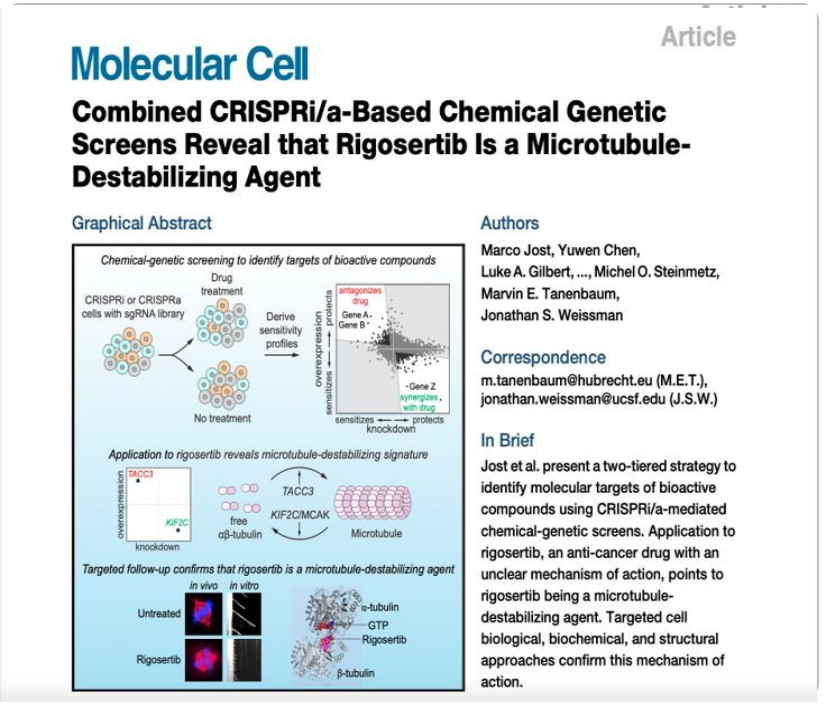
RRV has served on advisory boards for Bristol-Myers Squibb, Astrazeneca, Merck, Novocure, on unbranded speaker’s bureau of Astrazeneca, received consulting honorarium from Beigene, and research grants from Bristol-Myers Squibb, Onconova, Astrazeneca and EMD Serono.

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]


Article

Molecular Cell

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

Graphical Abstract

Authors

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In Brief

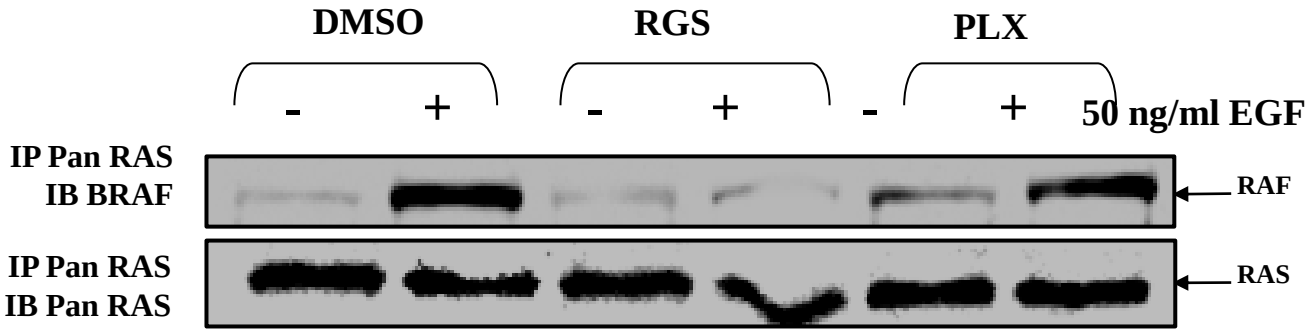
Jost et al. present a two-tiered strategy to identify molecular targets of bioactive compounds using CRISPRi/a-mediated chemical-genetic screens. Application to rigosertib, an anti-cancer drug with an unclear mechanism of action, points to rigosertib being a microtubule-destabilizing agent. Targeted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

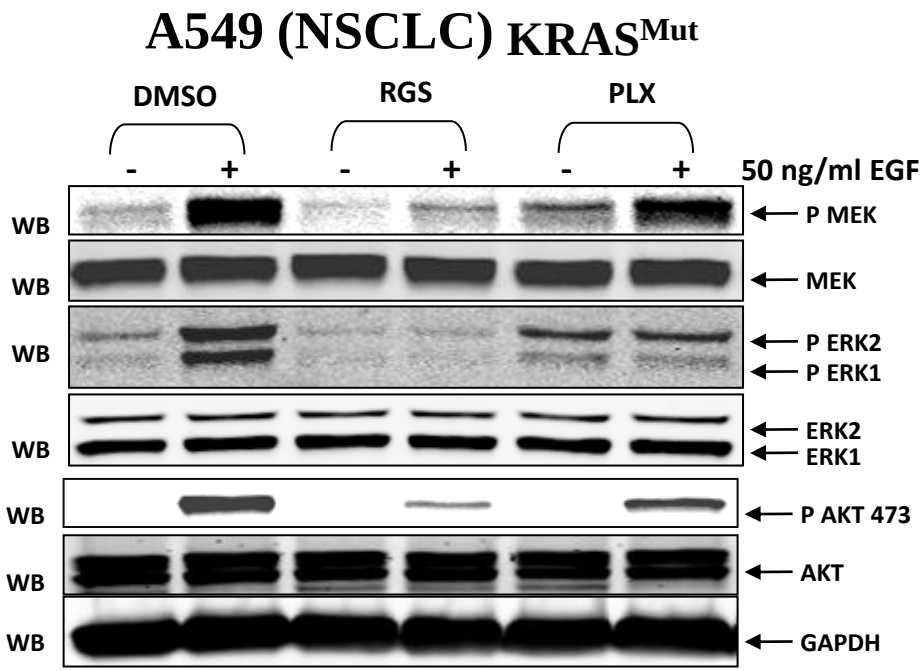
Clinical Studies

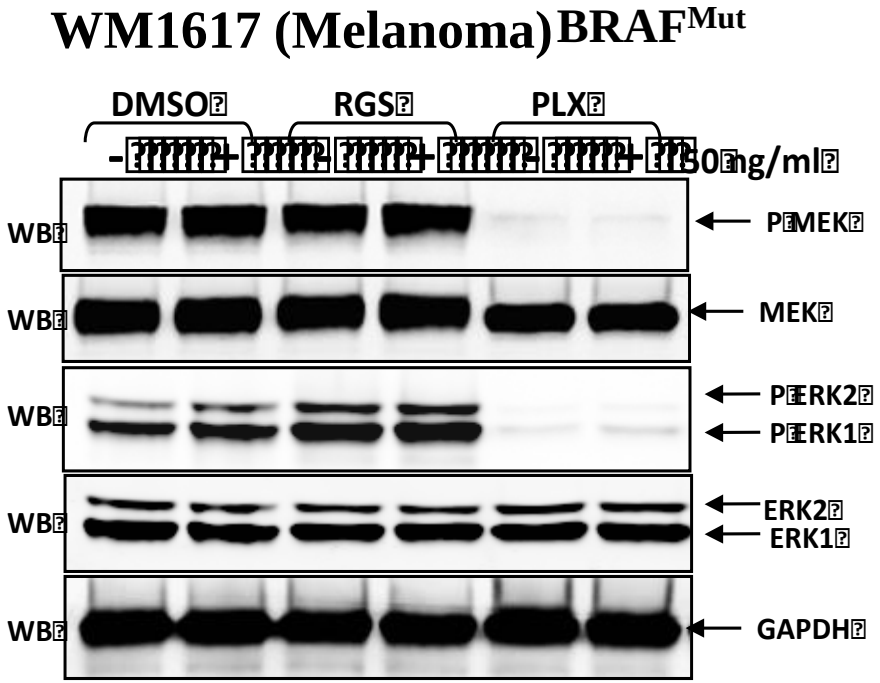
- Over 1,300 patients have been treated with established safety profile

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

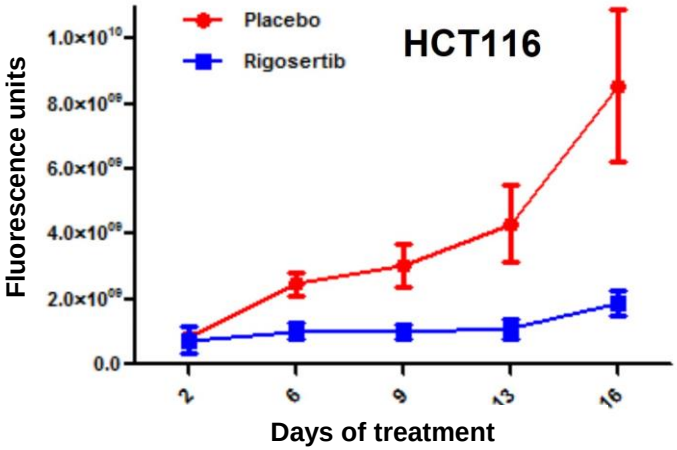


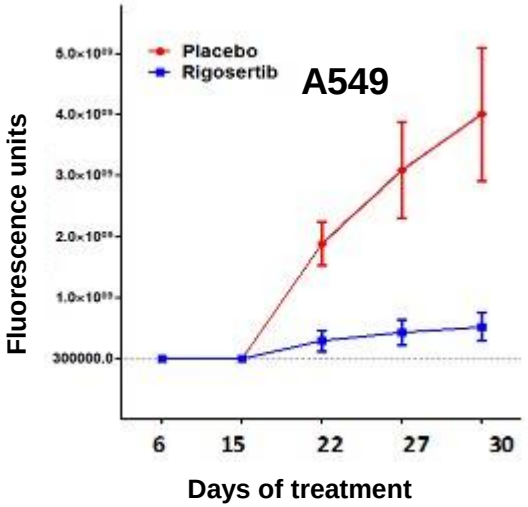


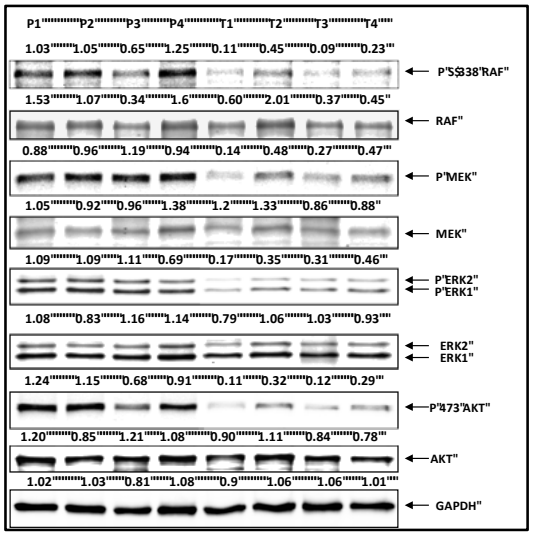


Athuluri-Divakar et al. *Cell*, 2016

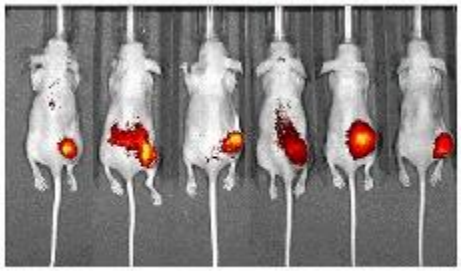
Inhibition of Tumor Growth by Rigosertib in Mouse Xenograft Assays



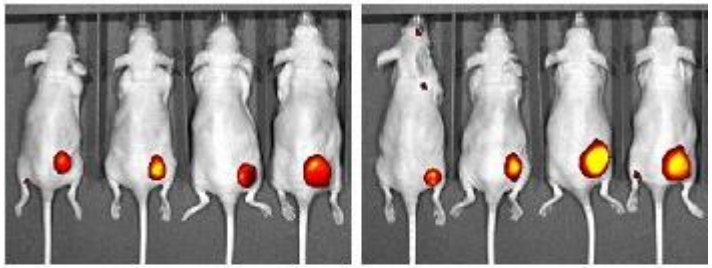




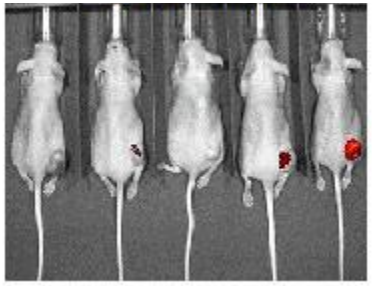
Control - untreated



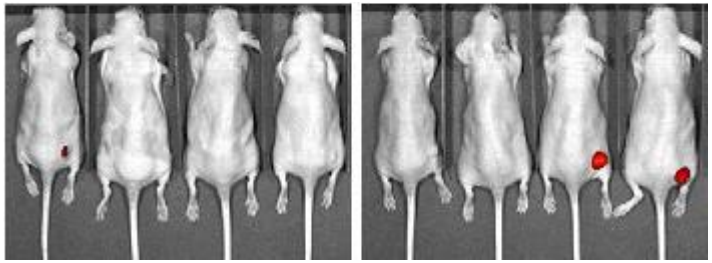
Placebo - treated

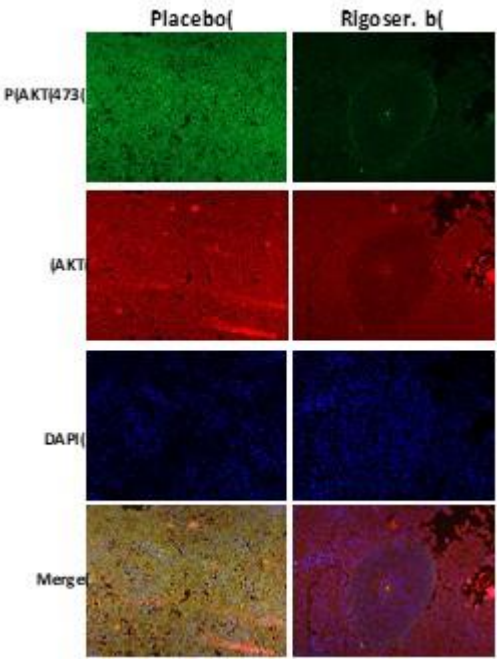


Rigosertib treated



Rigosertib treated

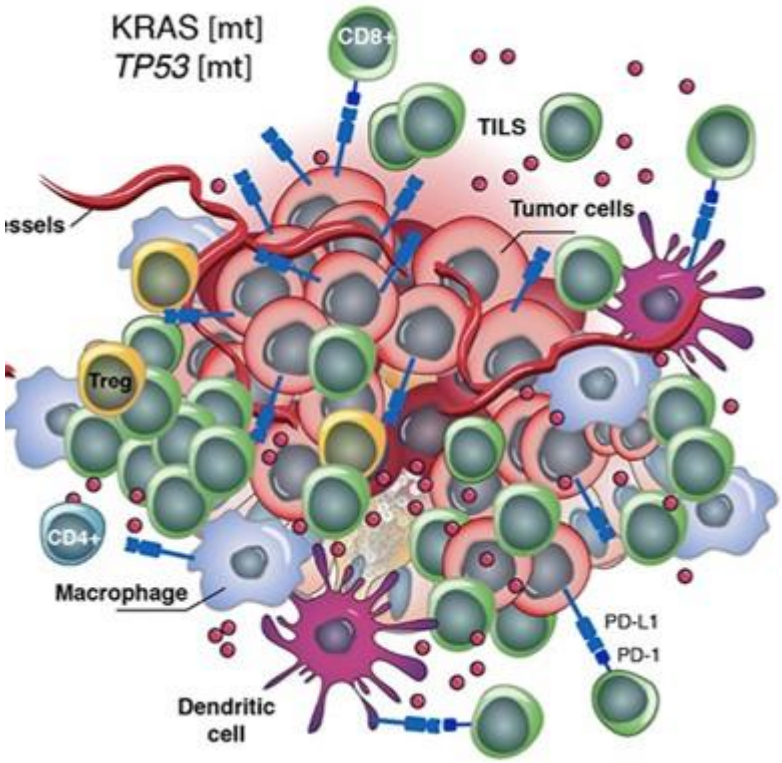




Athuluri-Divakar et al. *Cell*, 2016

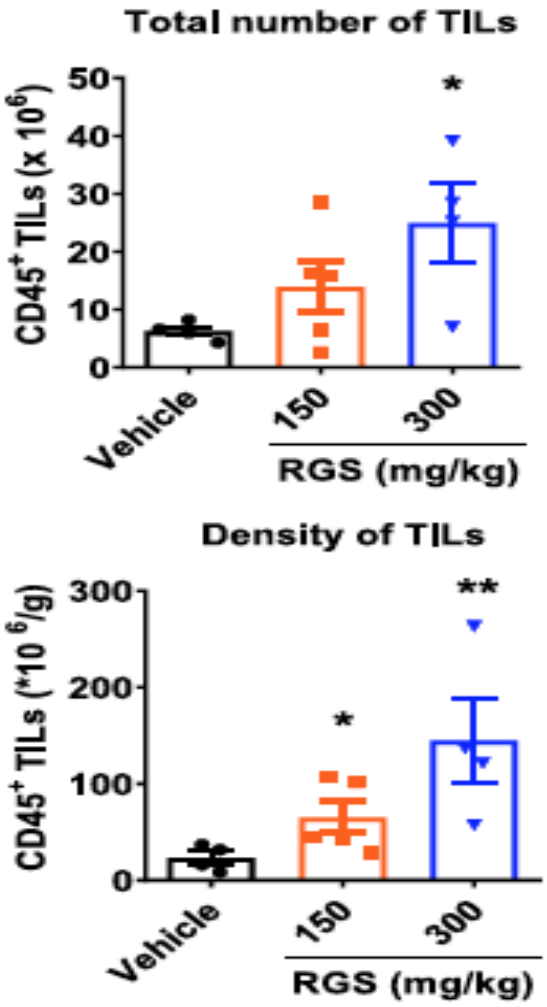
Immunotherapy in *KRAS*-Mutated NSCLC

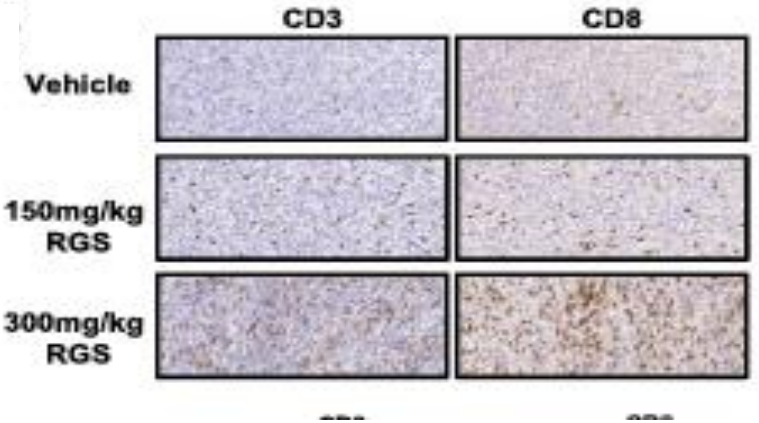
- Immune checkpoint inhibitors (ICIs) have become standard of care in metastatic NSCLC
- *KRAS* mutations are associated with ICI benefit in NSCLC
- *KRAS*-mutant NSCLC exhibits increased TMB, potentially leading to increased ICI sensitivity
- Concurrent mutations with *KRAS* affect immunogenicity –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

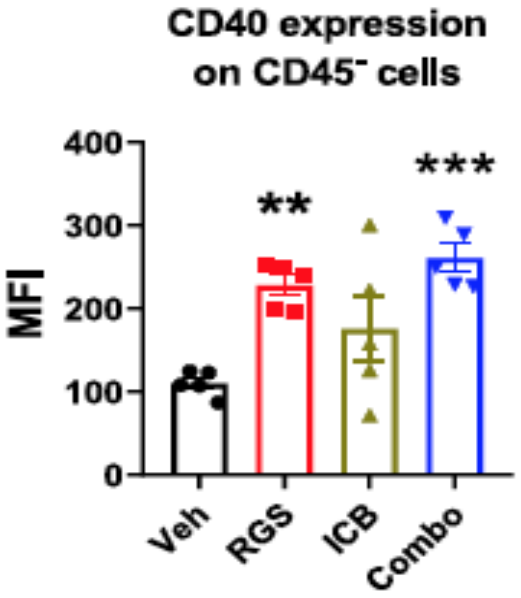


Friedlaender et al., Cancer Treat Rev 2020

Rigosertib Increases the TILs Infiltration and CD40 Expression



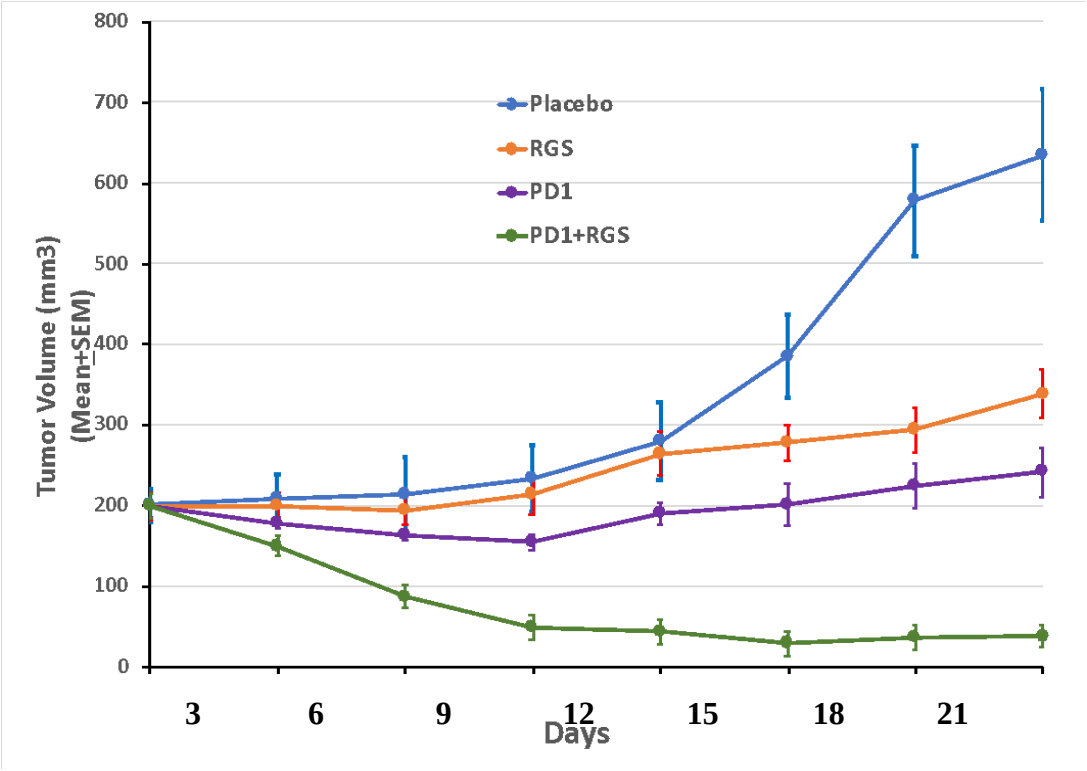




Yan et al. Molecular Cancer, 2021

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)

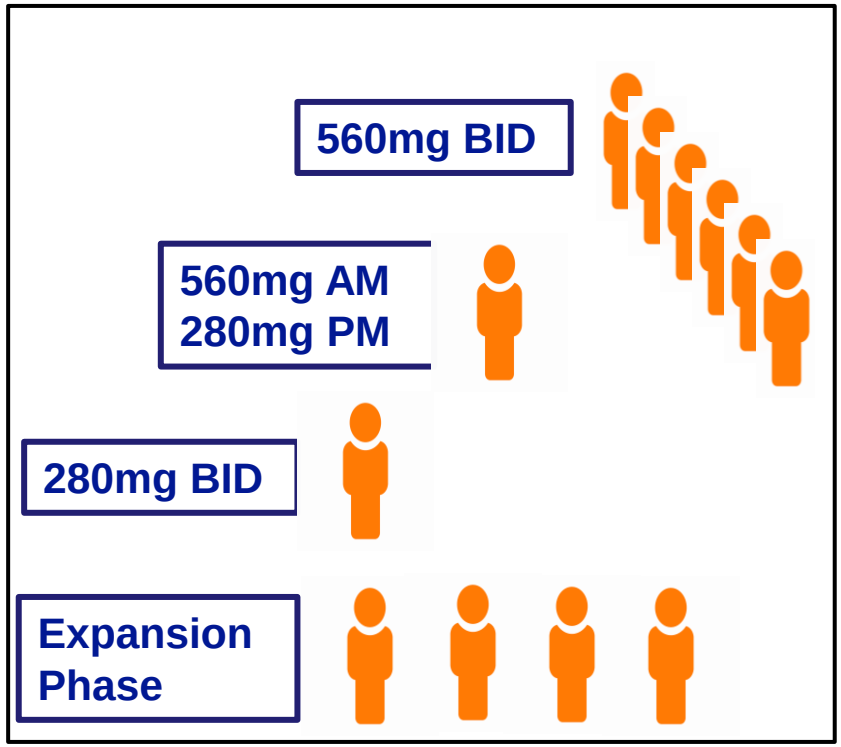
Rigosertib at Highest Dose + Nivolumab

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 G12D G12C I46T	 6 (50%) 4 (33%) 1 (8%) 1 (8%)
Smoking history – n (%) Current/Former Never	 8 (67%) 4 (33%)
ECOG performance status – n (%) 0 1	 8 (67%) 4 (33%)
Prior Lines of Systemic Therapy – n (%) 1 2 ≥ 3	 3 (25%) 6 (50%) 3 (25%)
Type of prior systemic therapy – n (%) PD-1/PD-L1 inhibitor monotherapy Platinum chemo + PD-1 therapy	 1 (8%) 11 (92%)

Safety/Tolerability with Rigosertib+Nivolumab

TRAEs Were Mostly Mild – Only 1 DLT Thus Far

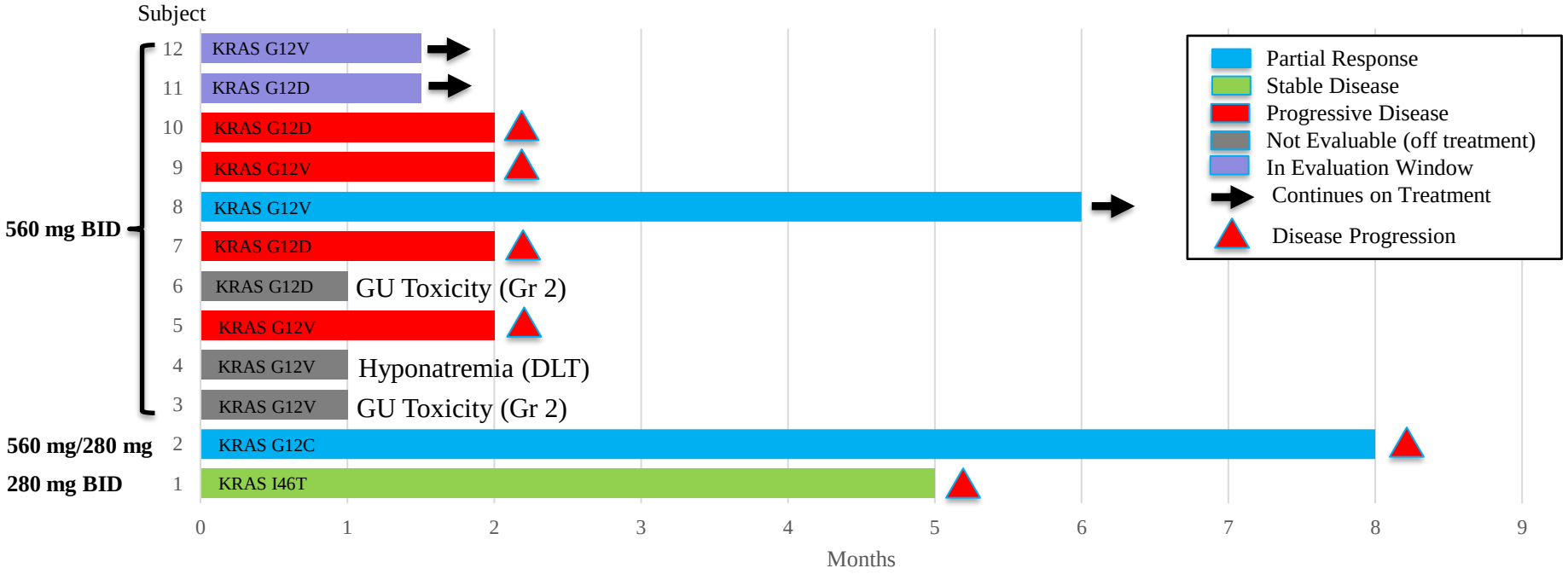
Treatment-Related Adverse Events (TRAEs) – n (%)	Entire Cohort: N=12	
	Grade 1-2	Grade 3
Dysuria	7 (58)	
Hematuria	7 (58)	
Urinary Frequency	2 (17)	
Abdominal Pain	4 (33)	
Fatigue	6 (50)	
Anemia	10 (83)	
Lymphopenia	3 (25)	1 (8)
Thrombocytopenia	2 (17)	
Hyponatremia*	3 (25)	1 (8)*
Hyperglycemia	11 (92)	
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)

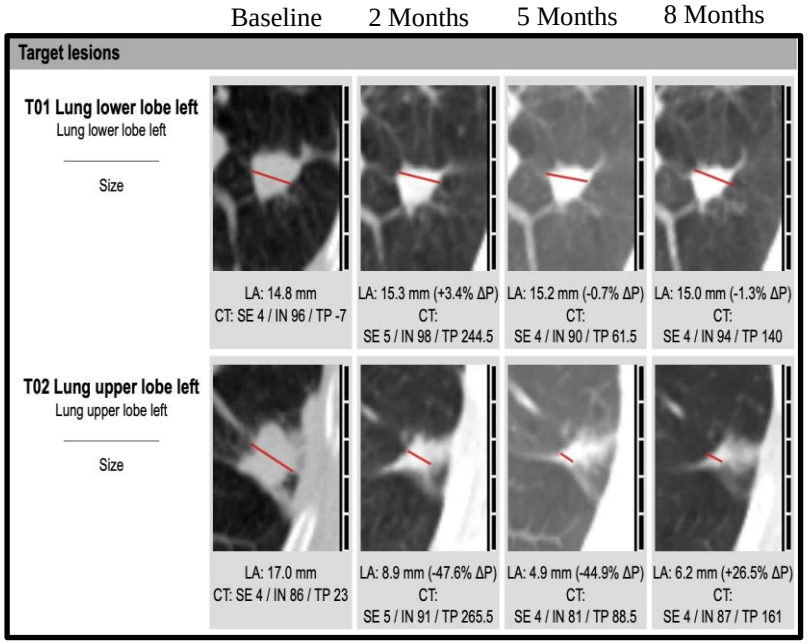
Best Overall Response in Evaluable Patients– n (%)	**N=7**
Complete Response	0 (0)
Partial Response	2 (29)
Stable Disease	1 (14)
Progressive Disease	4 (57)
Not Evaluable Patients – n (%)	**N=5**
Discontinued Study Drug due to Toxicity	3 (60)
Currently on Study Drug in Evaluation Window	2 (40)

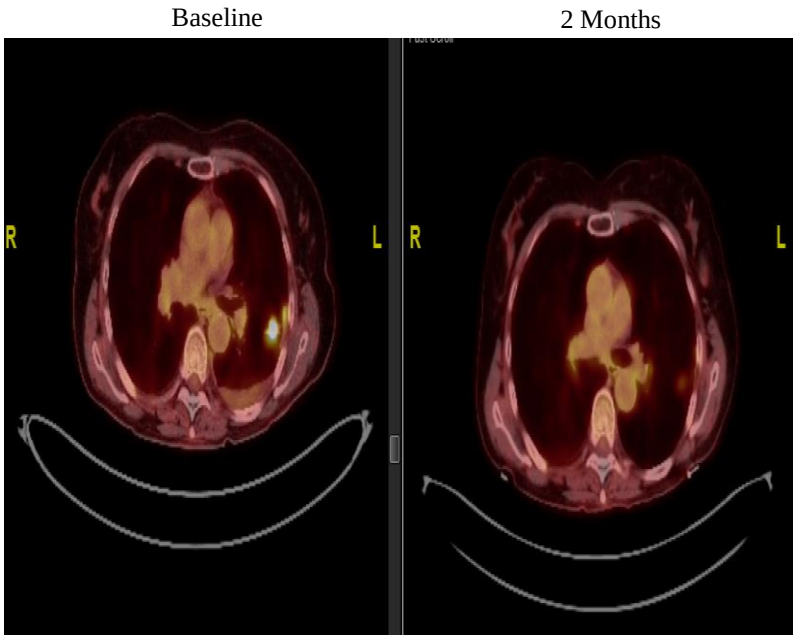


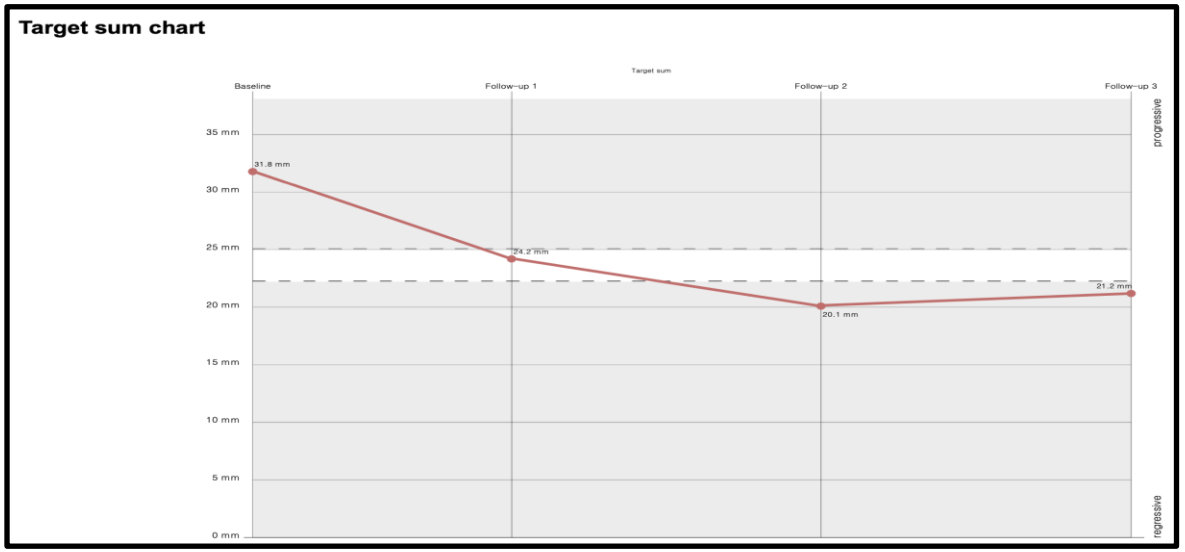
Patient #2: Partial Response at RGS 560mg AM / 280mg PM

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



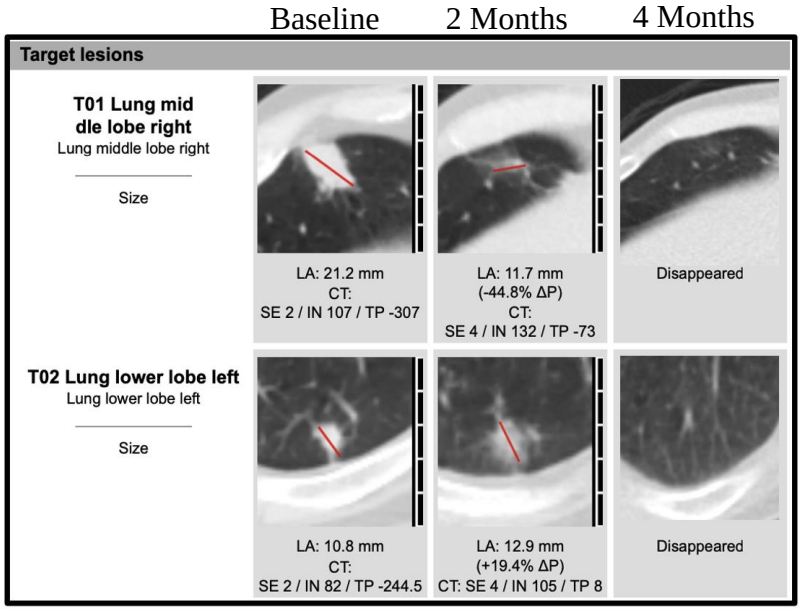


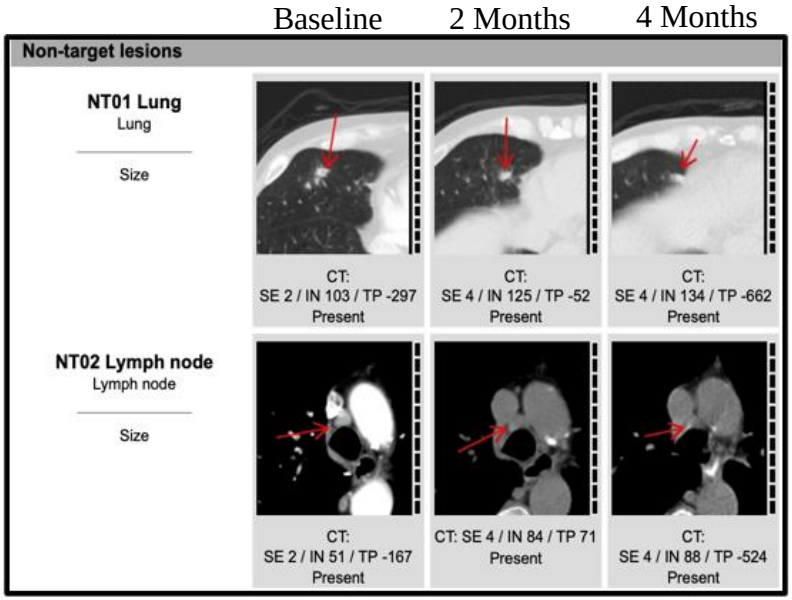


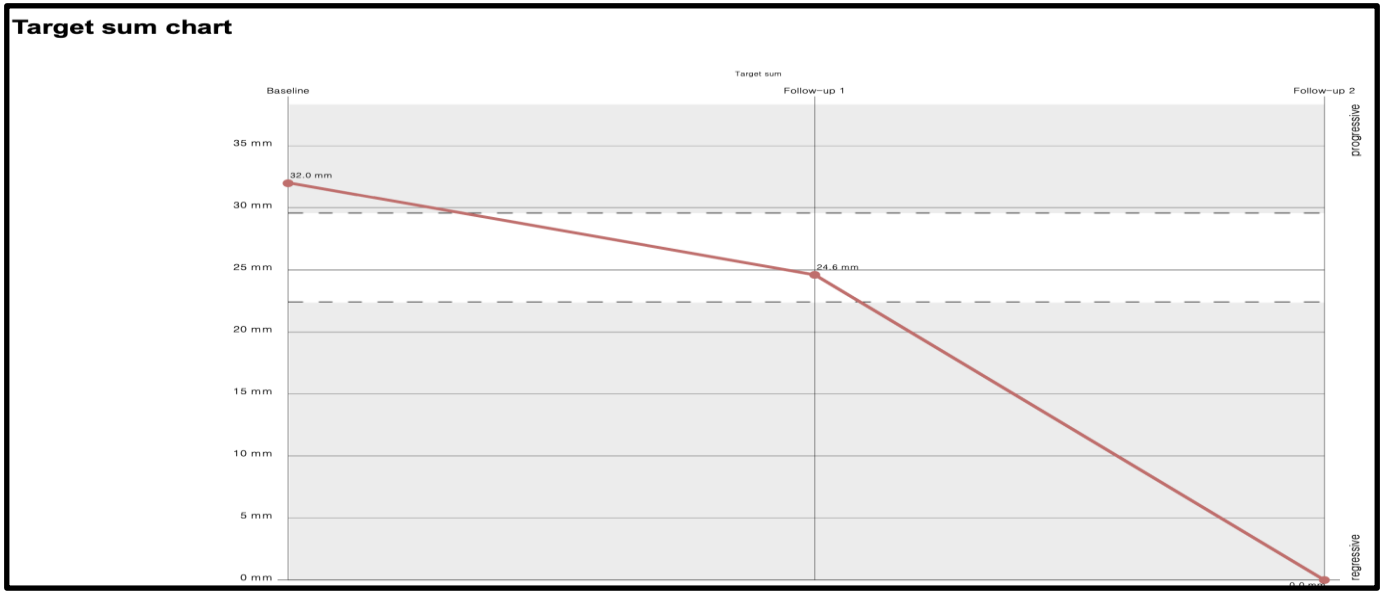
Patient #8: Partial Response at RGS 560mg BID

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)

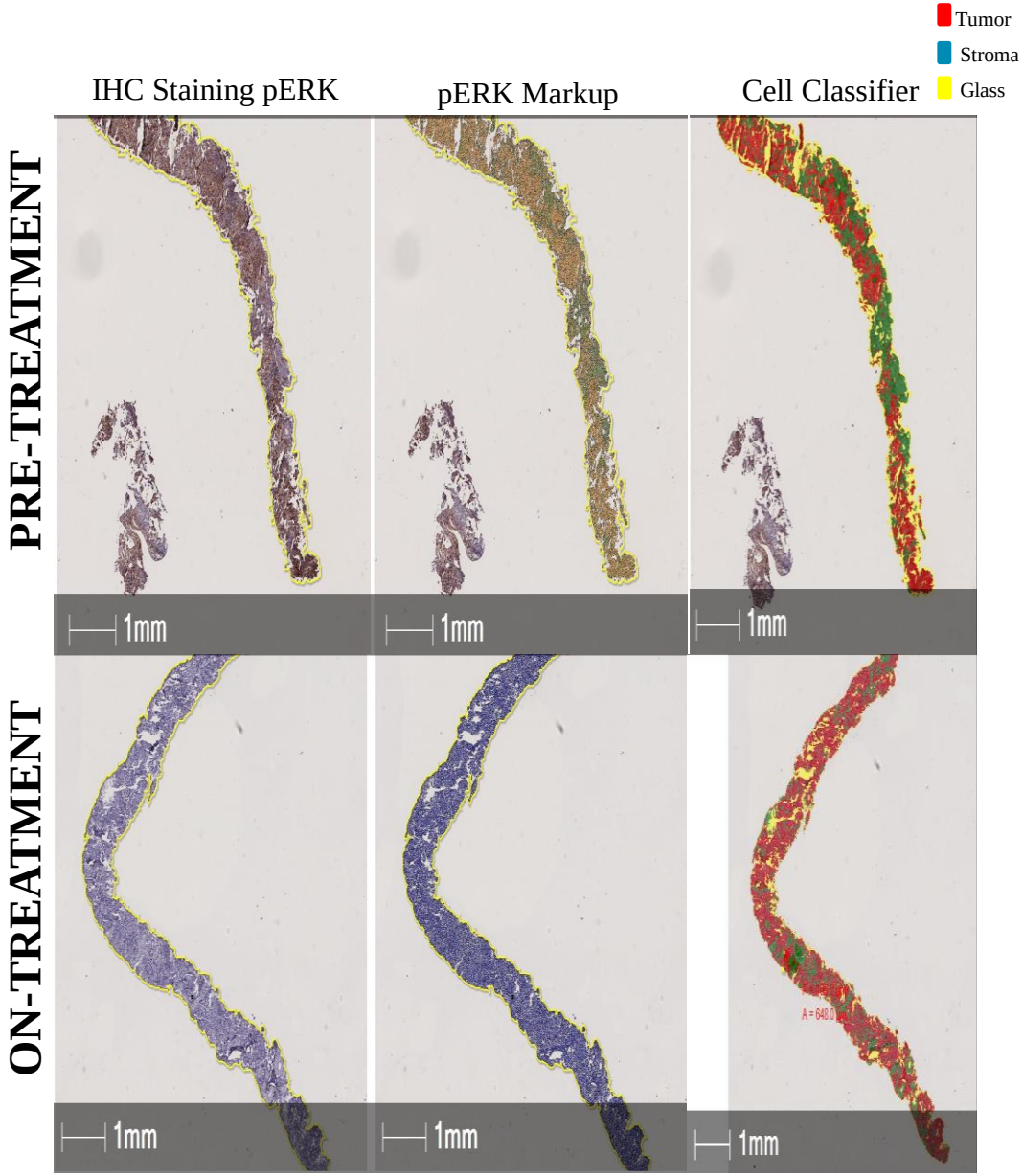
Patient #8: Partial Response at RGS 560mg BID



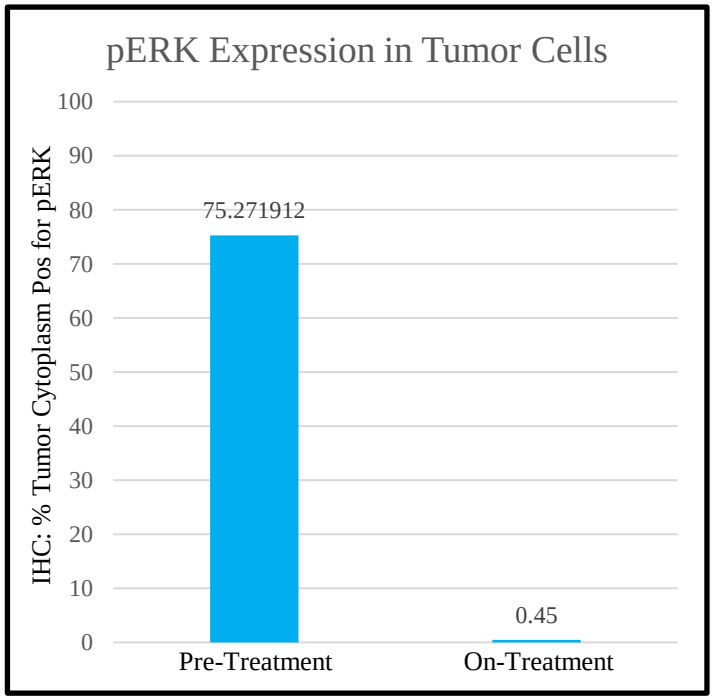




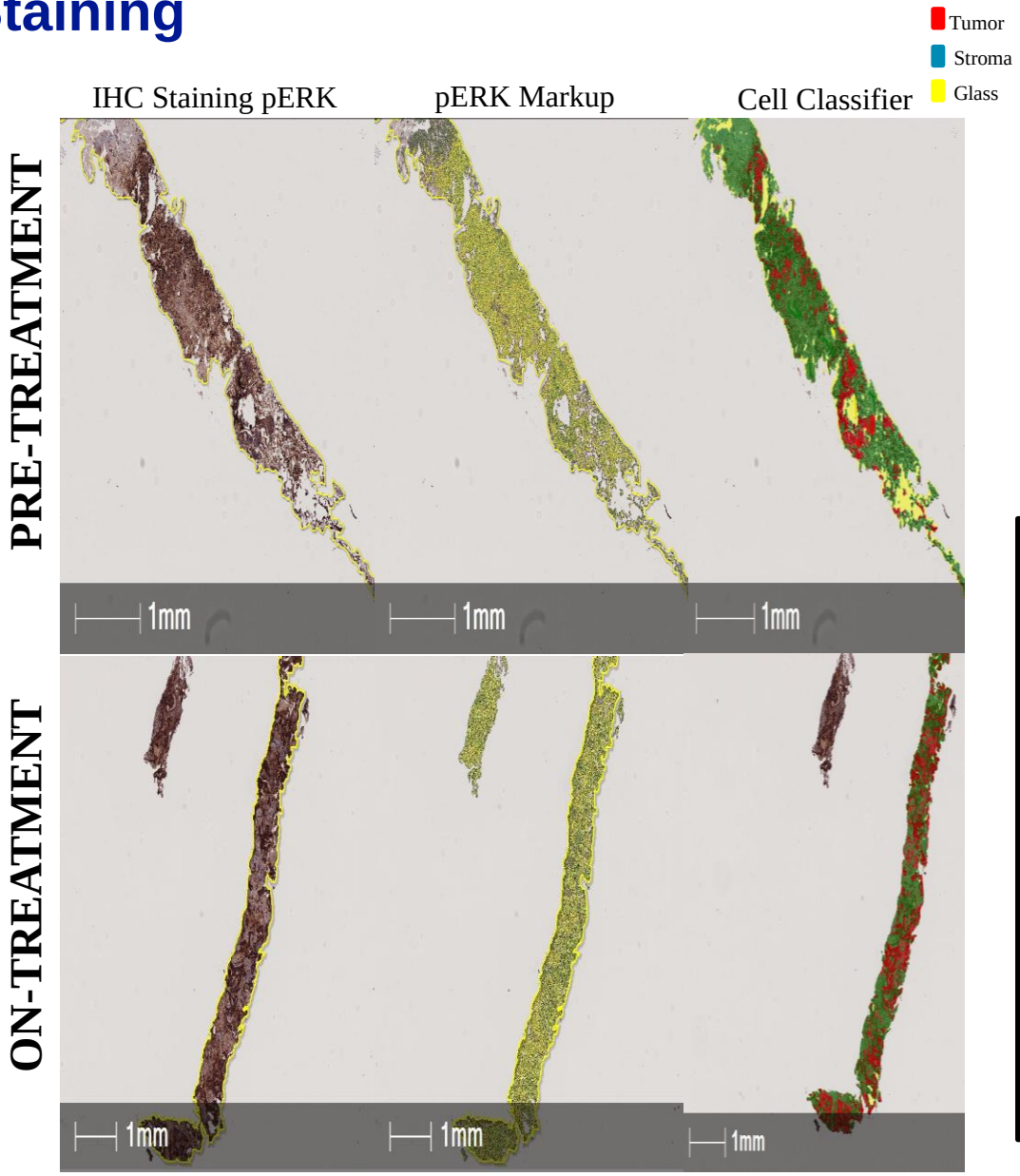
Patient #1: Stable Disease at RGS 280mg BID – pERK Staining



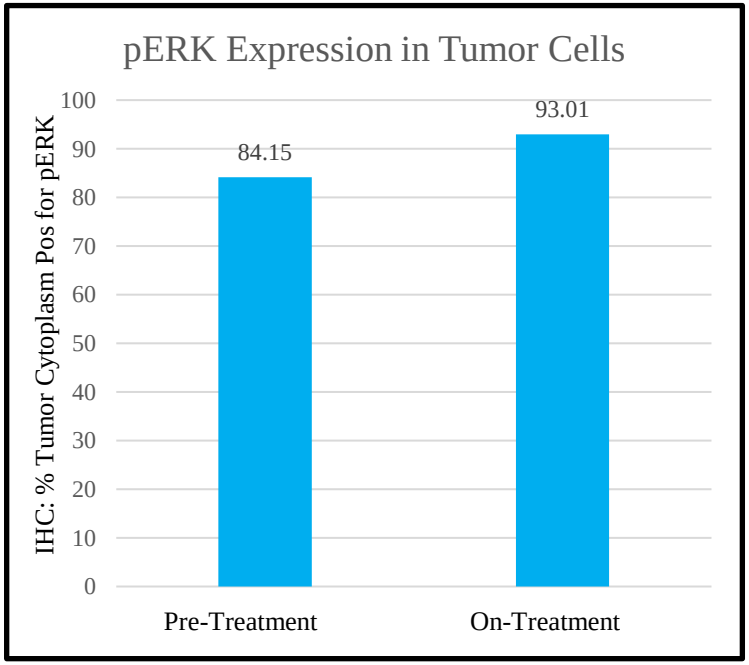
- Significant loss of pERK IHC Staining on Rigosertib/Nivolumab
- Correlates with Clinically Stable Disease



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