1018P - Phase 1/2 Trial of Rigosertib and Nivolumab for KRAS Mutated Non-Small Cell Lung Cancer (NSCLC) Patients

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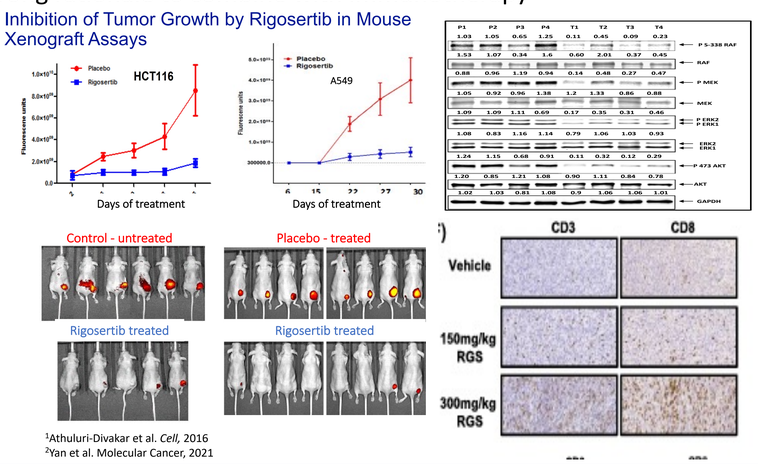
Introduction

Rigosertib is a panRAS signaling inhibitor that competitively binds to RAS binding domains of downstream effector proteins, resulting in disruption of multiple RAS-mediated pathways (MAPK, PI3K, RalGDS) and tumor suppression in preclinical models.[1] Rigosertib has also been shown to increase T cell infiltration of tumors (bottom right), providing strong rationale to combine with immunotherapy[2]

Inhibition of Tumor Growth by Rigosertib in Mouse Xenograft Assays



[1]Athuluri-Divakar et al. *Cell*, 2016
[2]Yan et al. Molecular Cancer, 2021

Study Design

Here we report safety and interim efficacy of the first clinical trial of rigosertib in combination with the immune checkpoint inhibitor (ICI) nivolumab, in advanced KRAS mutated NSCLC patients who progressed on first line ICI-containing treatment

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

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
3+3 design if Gr 2 Toxicity

Primary Objective: Safety/Tolerability

Dose Expansion Phase (n=12)

Rigosertib at Highest Dose + Nivolumab

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

Results: Patients

- 19 patients enrolled
- 95% of patients have non-G12C mutations
- Cohort is heavily pre-treated. All patients progressed on prior PD1/L1 inhibitors

Baseline Characteristics	Cohort N=19
Age in years – median (range)	65 (45 – 80)
Type of KRAS mutation – n (%)	
G12V	7 (37%)
G12D	5 (26%)
G12C	1 (5%)
G12F	1 (5%)
G12A	1 (5%)
G13 (D/C)	2 (11%)
Other (Q61H, I46T)	2 (11%)
STK11 Co-mutations	5 (26%)
PDL1 Expression –n (%)	
≥50%	4 (21%)
1-49%	7 (37%)
<1%	8 (42%)
Smoking history – n (%)	
Current/Former	15 (79%)
Never	4 (21%)
Prior Lines of Systemic Therapy – n (%)	
1	3 (20%)
2	9 (60%)
≥ 3	3 (20%)

Results: Safety/Tolerability

Treatment-Related Adverse Events (TRAEs) – n (%)	Entire Cohort: N=19	
	Grade 1-2	Grade 3
Dysuria	10 (53)	
Hematuria	12 (63)	
Urinary Frequency	5 (26)	
Abdominal Pain	6 (32)	
Fatigue	10 (53)	
Anemia	13 (68)	1 (5)
Lymphopenia	4 (21)	2 (11)
Thrombocytopenia	2 (11)	
Hyponatremia*	7 (37)	1 (5)*
Hyperglycemia	11 (58)	
AST elevation	4 (21)	1 (5)#
ALT elevation	3 (16)	1 (5)#
ALK elevation	6 (32)	
Nausea/Vomiting	5 (26)	1 (5)
Constipation	7 (37)	
Diarrhea	3 (16)	
Anorexia	6 (32)	1 (5)
Acute Kidney Injury	7 (37)^	
Infusion-related Reaction	1 (5)	

*Dose Limiting Toxicity; #Resolved with steroids; ^Resolved with IV fluids

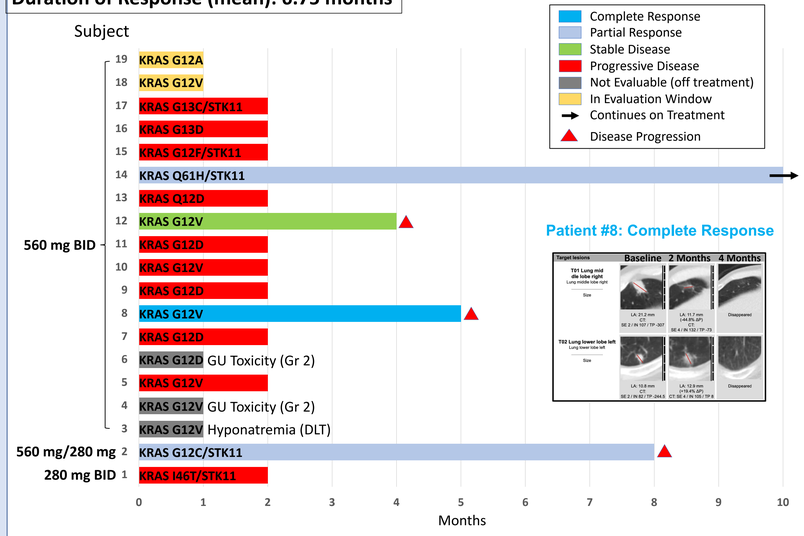
- TRAEs were mostly mild and manageable
- Urinary toxicities well documented with Rigosertib were most common TRAE
- No synergistic toxicities noted for either study drug
- One DLT at 560mg BID for grade 3 hyponatremia – previously documented with Rigosertib

Results: Efficacy

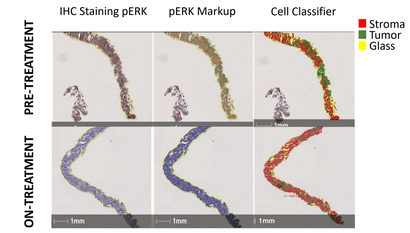
4 of 14 (29%) Evaluable Patients had Disease Control

Best Overall Response in Evaluable Patients– n (%)	N=14
Complete Response	1 (7)
Partial Response	2 (14)
Stable Disease	1 (7)
Progressive Disease	10 (71)

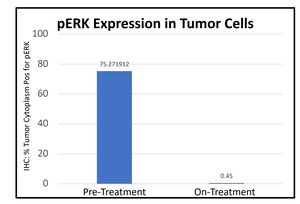
Duration of Response (mean): 6.75 months



RGS 280mg BID – pERK Staining



- Significant tumor loss of pERK IHC staining on Rigosertib/Nivolumab



Conclusions

- Combination of Rigosertib and Nivolumab is safe, well tolerated and has shown early efficacy for the treatment of KRAS mutated NSCLC patients with prior progression on ICI
- Based on this promising data, Rigosertib combined with Nivolumab should be further studied in a larger randomized phase 2 trial to provide an effective treatment for panKRAS mutated NSCLC patients

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