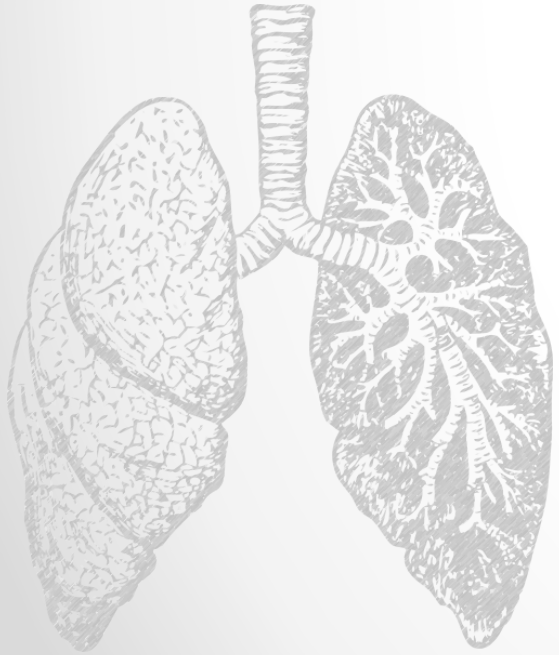
KRAS+ LUNG CANCER



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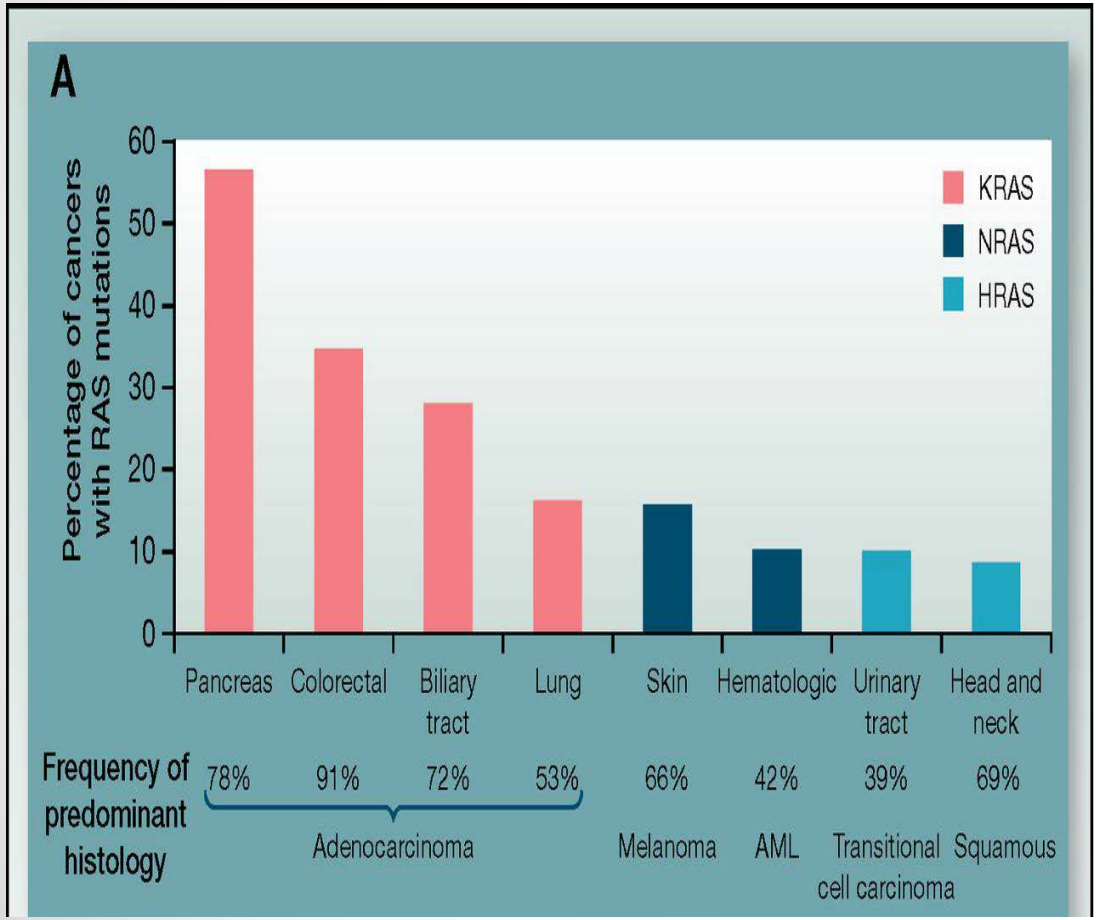
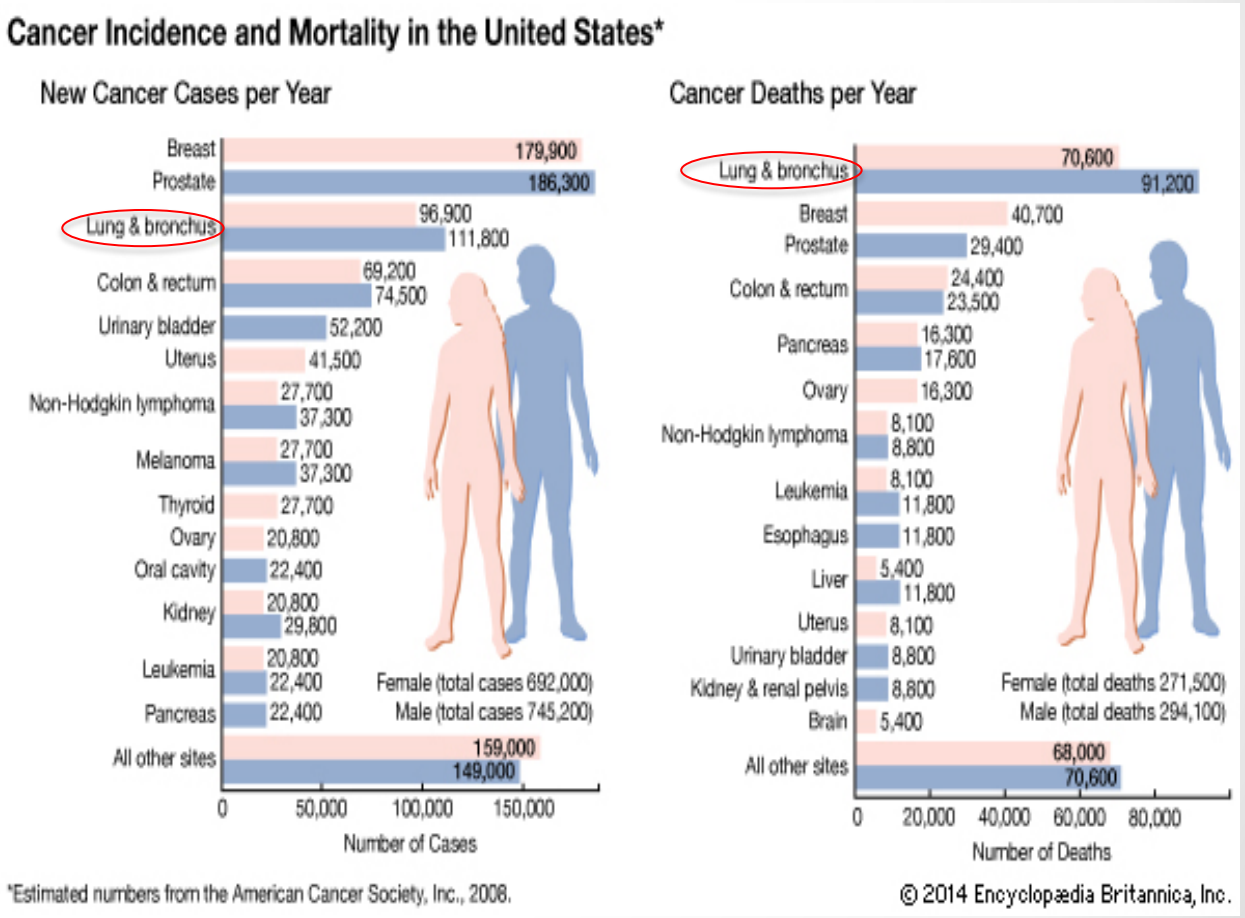
Key Opinion Leader Meeting
Thursday, February 7, 2019

Cancers With RAS Mutations

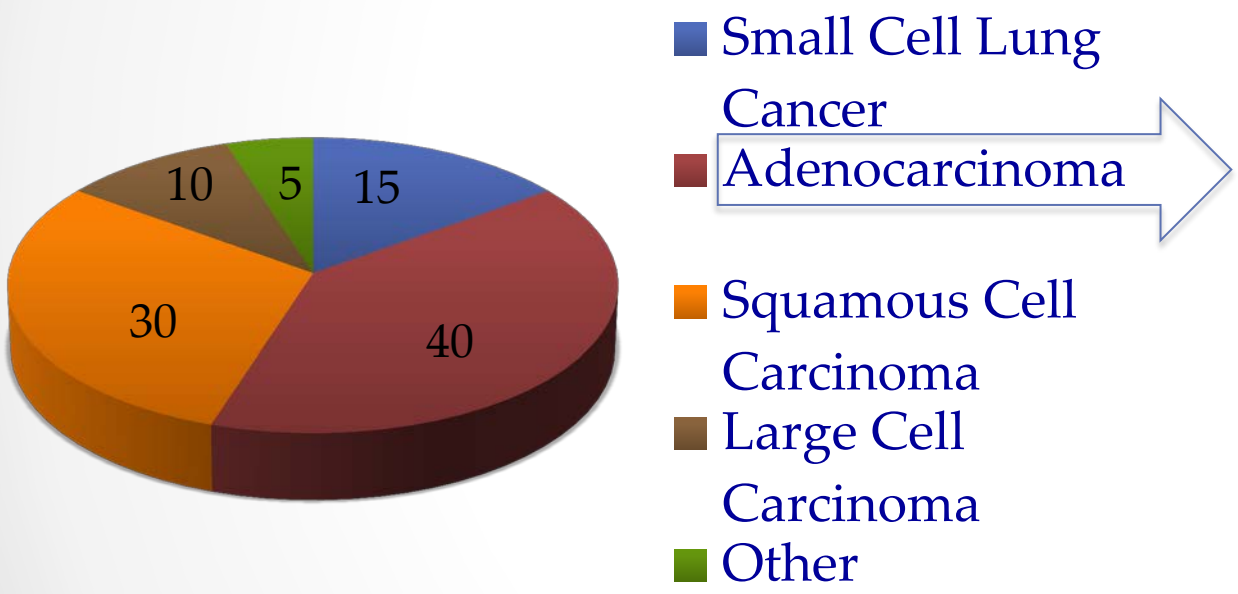




Neil Vasan et al. Clin Cancer Res 2014;20:3921-3930
American Cancer Society: Facts and Figures

Lung Cancer Classification

Histologic → **Molecular**

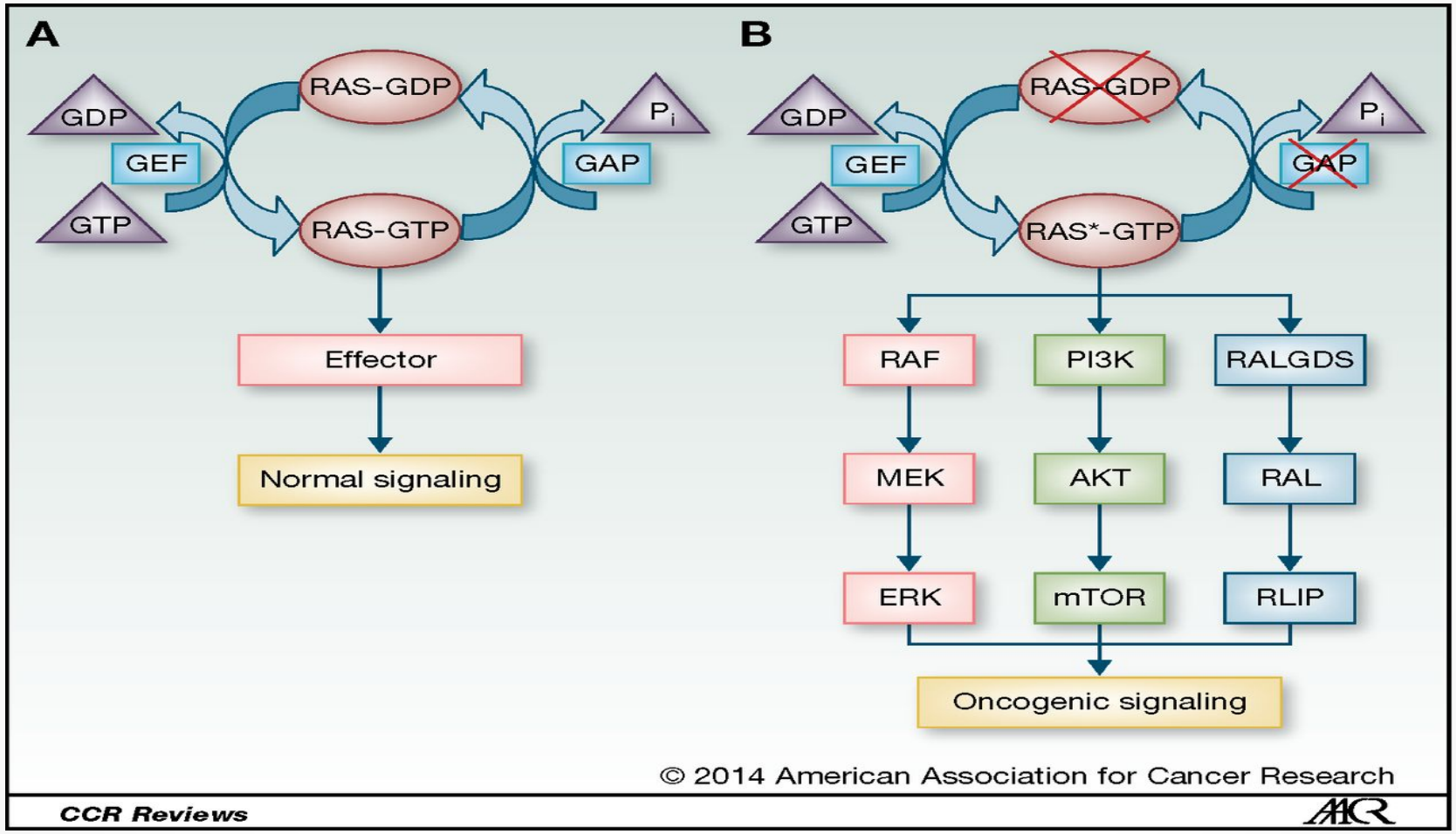


Hirsch et al., Lancet 2016

KRAS: 25% of Adenocarcinomas

- Most Common Molecular Driver

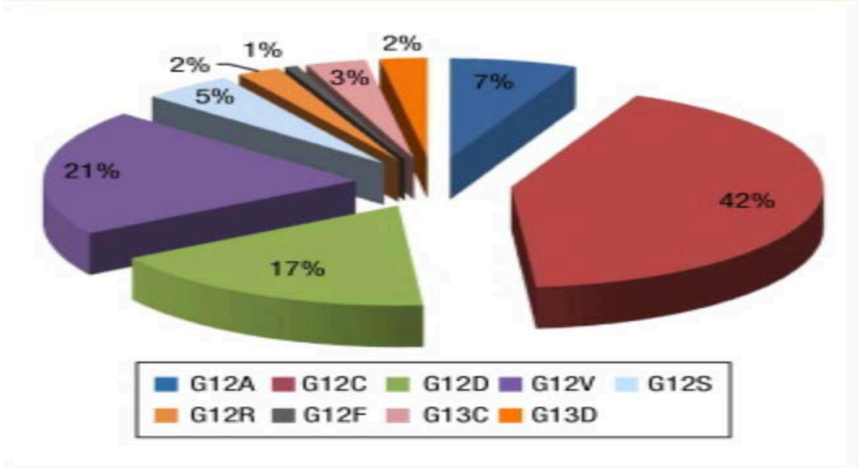
KRAS Signaling

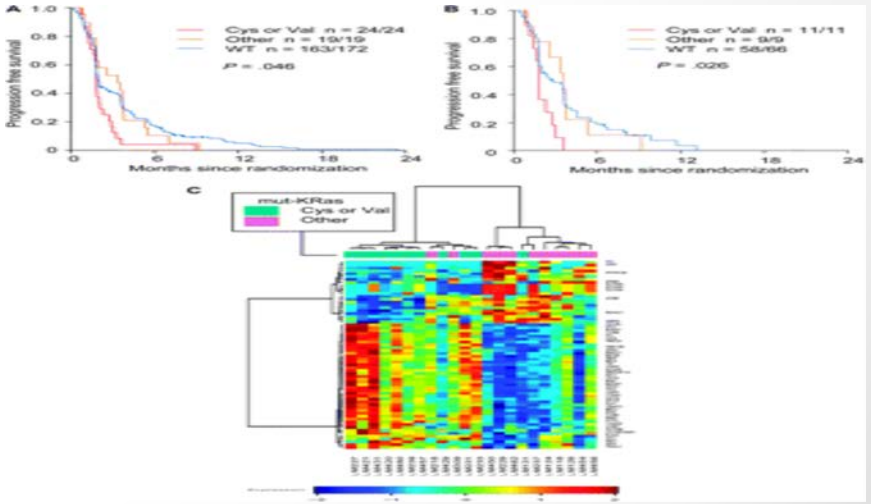


Neil Vasan et al. Clin Cancer Res 2014
Karachaliu N et al., Clin Lung Cancer 2013

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

Prognosis of KRAS+ NSCLC

Table 1 Prognostic Significance of KRAS

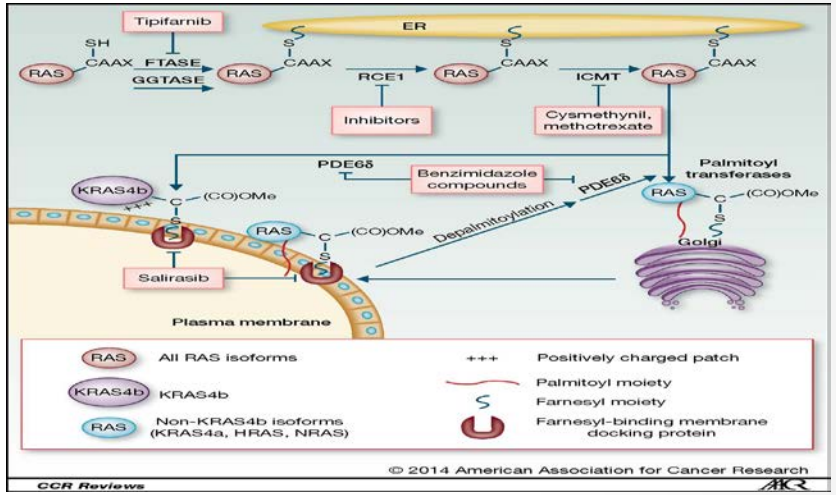
Study, Y	Study Population	KRAS Status	Results for Survival	*P* Value
Graziano et al,[14] 1999	I, II	Positive	OS, 39 mo	.33
		Negative	OS, 53 mo	
Keohavong et al,[15] 1996	I-IV	Positive	No difference between the 2 groups	.74
		Negative		
Lu et al,[16] 2004	I	Positive	No difference between the 2 groups	.998
		Negative		
Slebos et al,[17] 1990	I, II, IIIA	Positive	12/19 patients died within the follow-up period	.002
		Negative	22/50 patients died within the follow-up period	
Fukuyama et al,[18] 1997	I-IV	Positive	OS, 11 mo	.04
		Negative	OS, 30 mo	
Huang et al,[19] 1998	I, II, IIIA	Positive	The overall survival rate of patients with wild-type KRAS was better than that of patients whose tumors had mutations of KRAS	.033
		Negative		
Miyake et al,[20] 1999	I, II, IIIA	Positive	OS rate, 27.9%	.0001
		Negative	OS rate, 59.6%	
Nelson et al,[21] 1999	I, II, IIIA	Positive	There was a statistically significant association between KRAS mutation and decreased survival time	.009
		Negative		
Mascaux et al,[22] 2005	I-IV	Positive	HR 1.35 (95% CI, 1.16-1.56)	
		Negative		

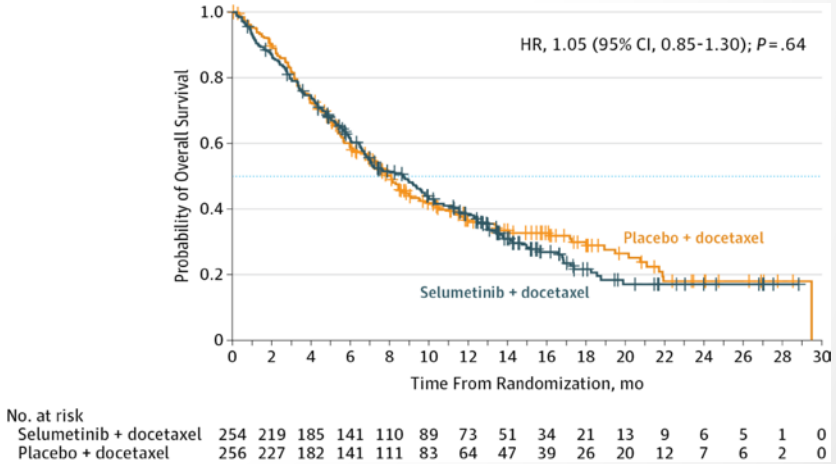
Abbreviations: HR = hazard raio; OS = overall survival.

Karachaliu N et al., Clin Lung Cancer 2013

Lack of Current Treatment Options for KRAS

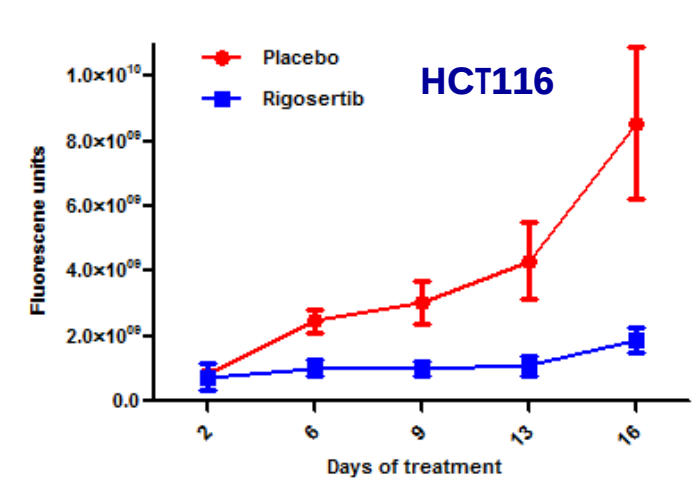
- KRAS+ NSCLC associated with decreased response to chemotherapy
- Lack of suitable drug-binding pocket to directly target KRAS
- Attempts to target RAS processing (i.e., farnesyl-transferase inhibitors) have failed
- Attempts to target downstream RAF or MEK kinases are disappointing

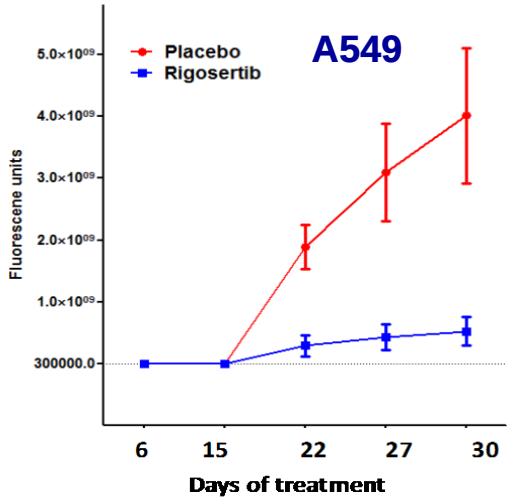


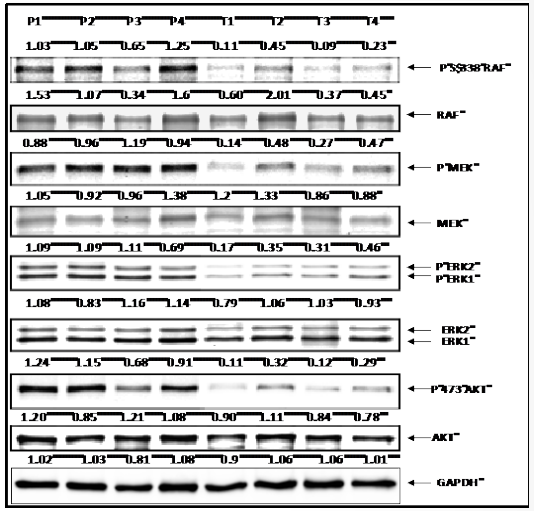


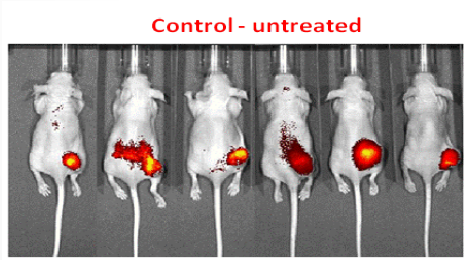
Neil Vasan et al. Clin Cancer Res 2014
Janne et al. JAMA 2017

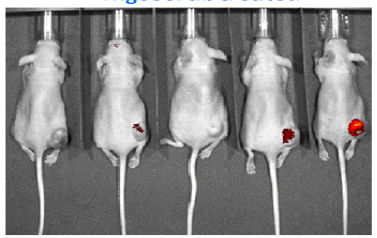
Inhibition of Tumor Growth by Rigosertib in Mouse Xenograft Assays

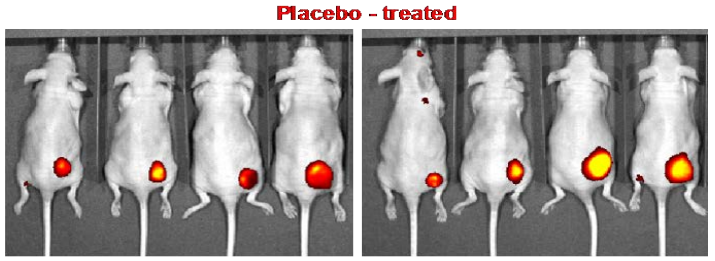


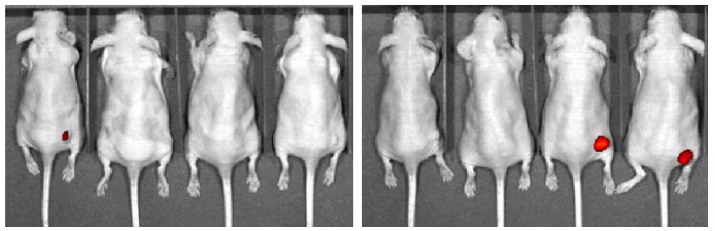


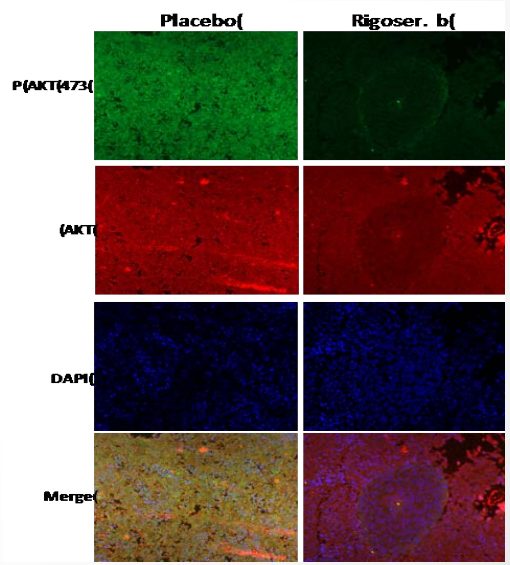




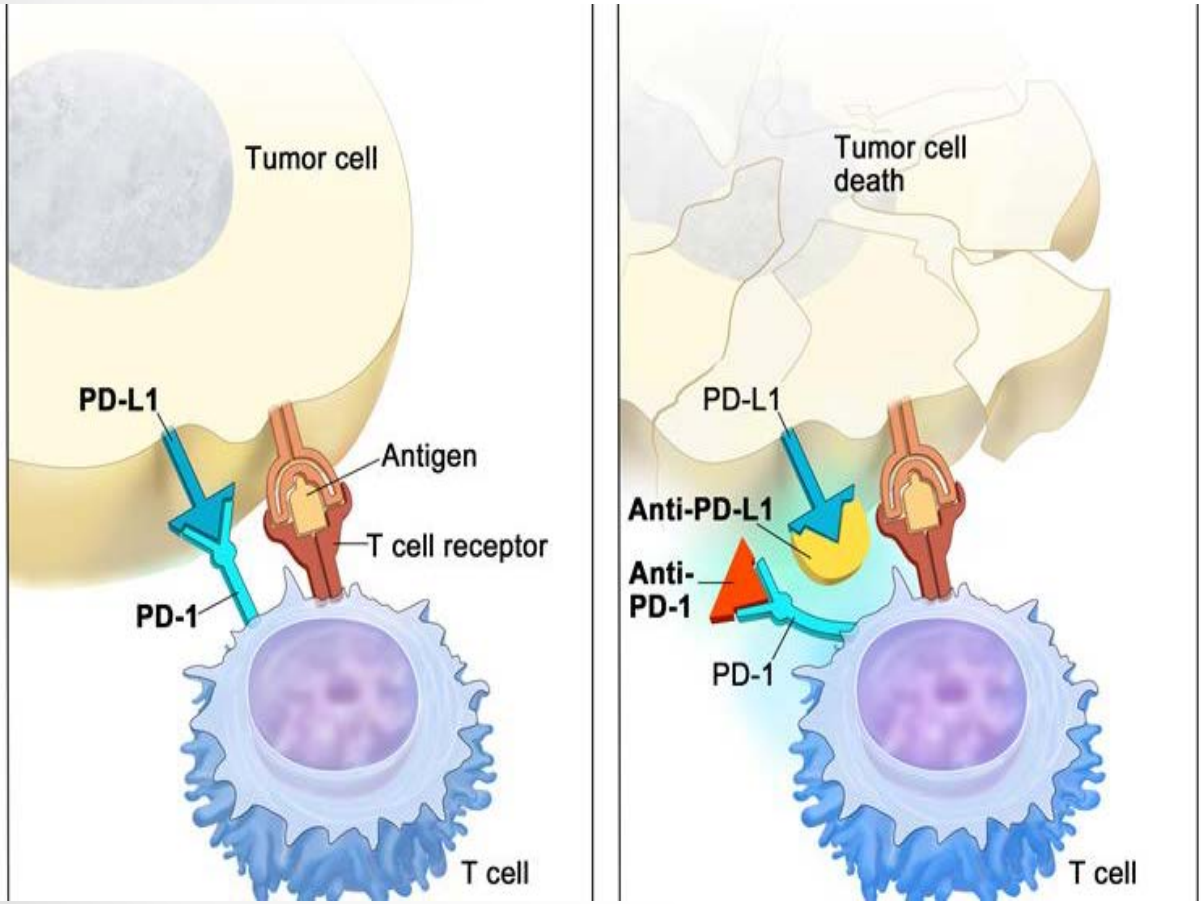








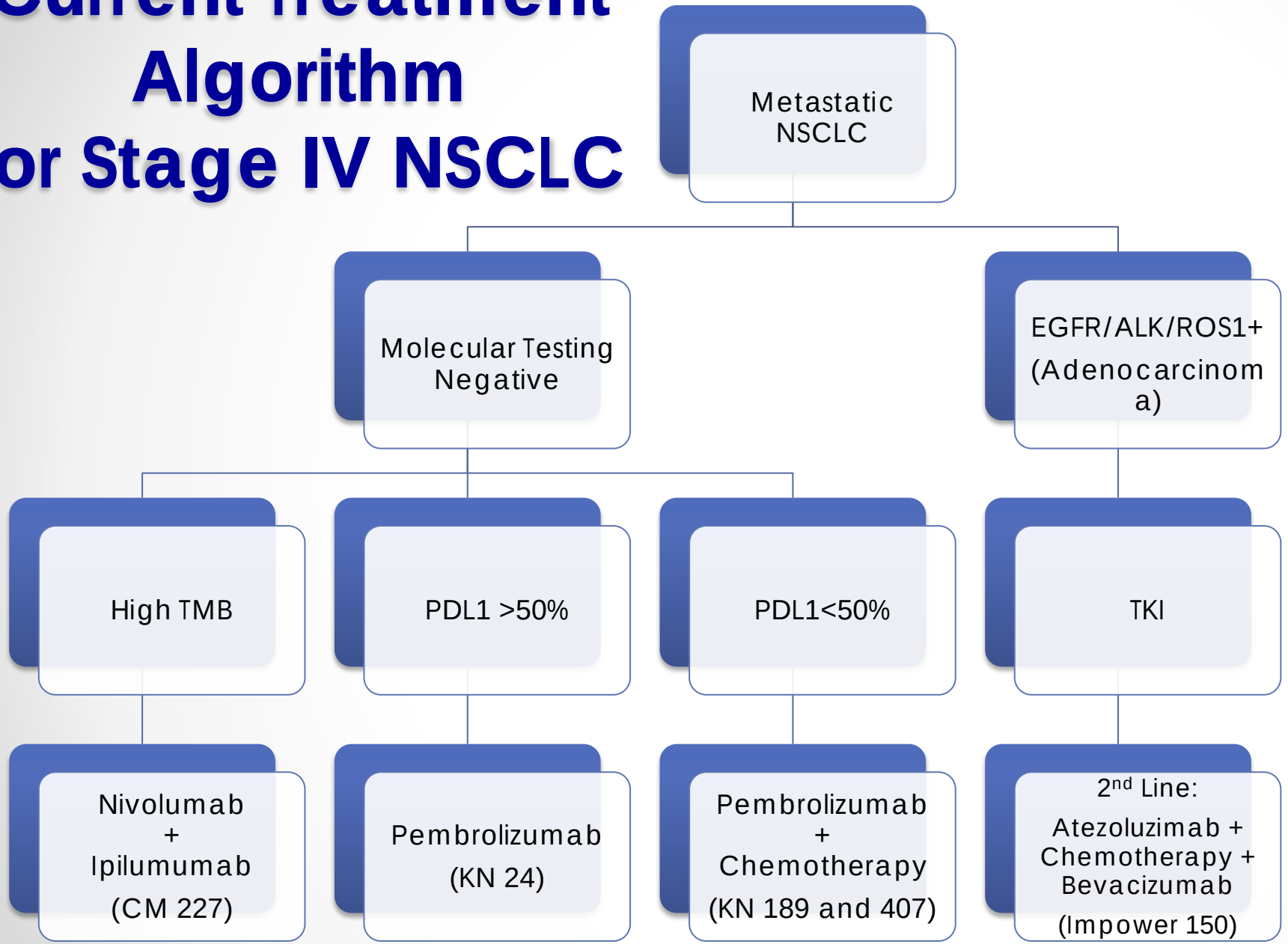
Immunotherapy for Lung Cancer



NCI

- Immune recognition and elimination of cancer is dependent on the immune system's ability to be stimulated or turned off by checkpoint interactions
- Immunogenic cancers upregulate PDL1 resulting in restrained T-effector function
- Monoclonal Abs blocking PD1 or PDL1 have now become the standard of care in treatment of NSCLC

Current Treatment Algorithm for Stage IV NSCLC

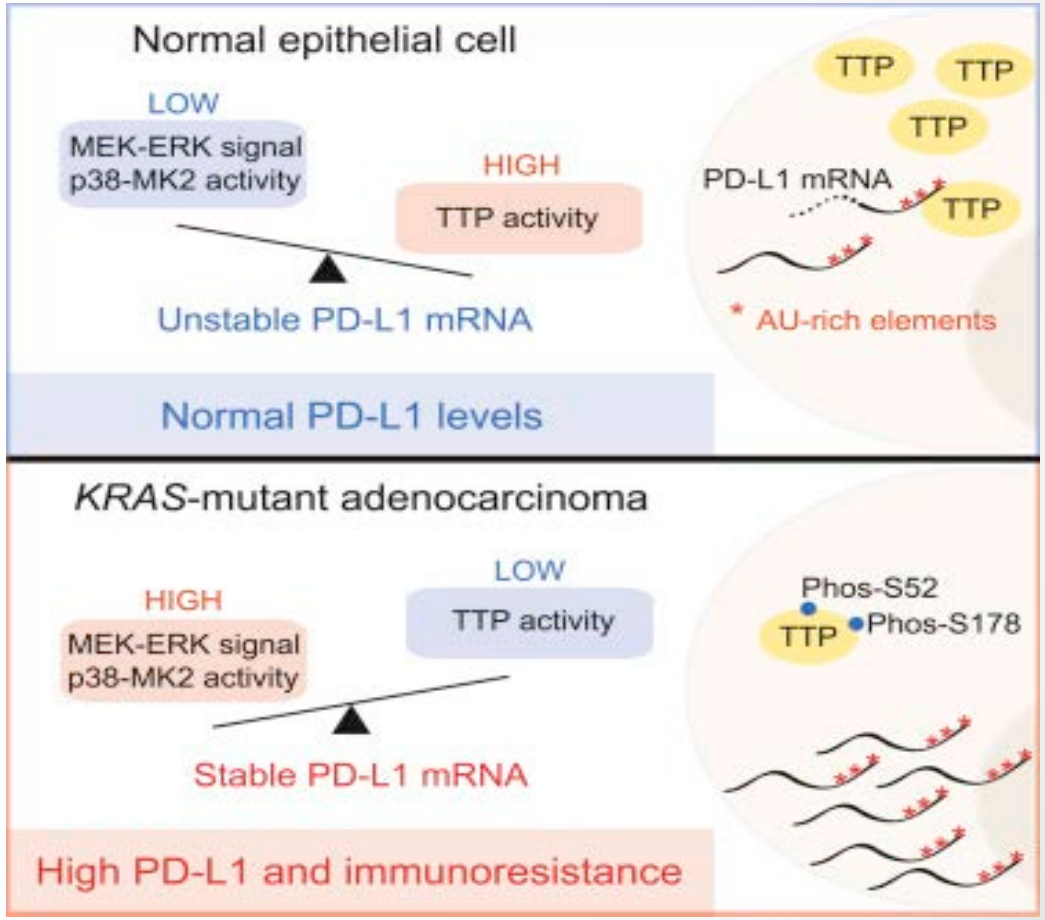


- Significant % of patients do not respond to immunotherapy

2nd Line ???

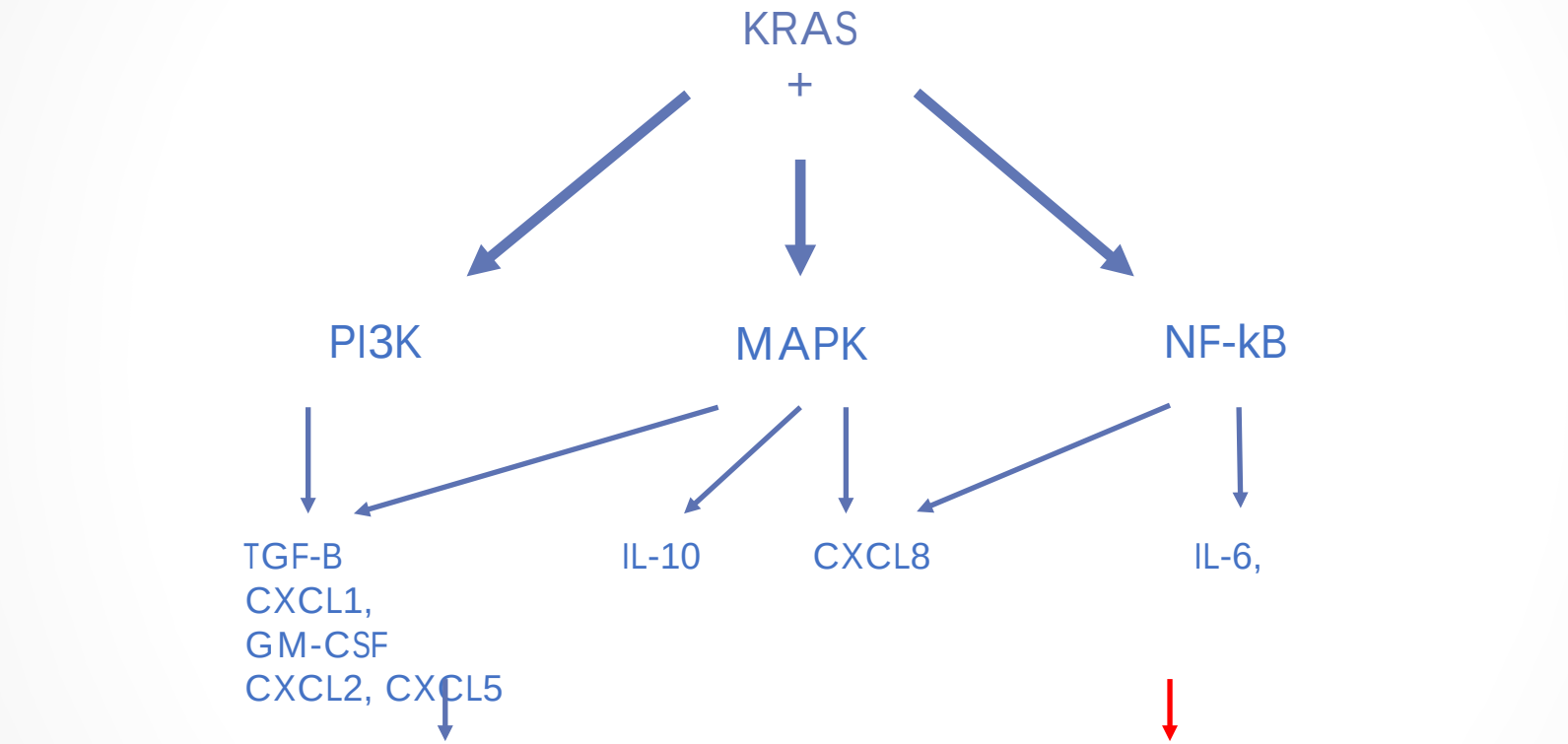
KRAS and Immunotherapy

- KRAS+ tumors may have higher TMB
  - o Smokers
  - o Overlap with other mutations (TP53)
- PDL1 may be upregulated by oncogenic RAS signaling
- KRAS a/w downregulation of HLA class I in Stage IV NSCLC



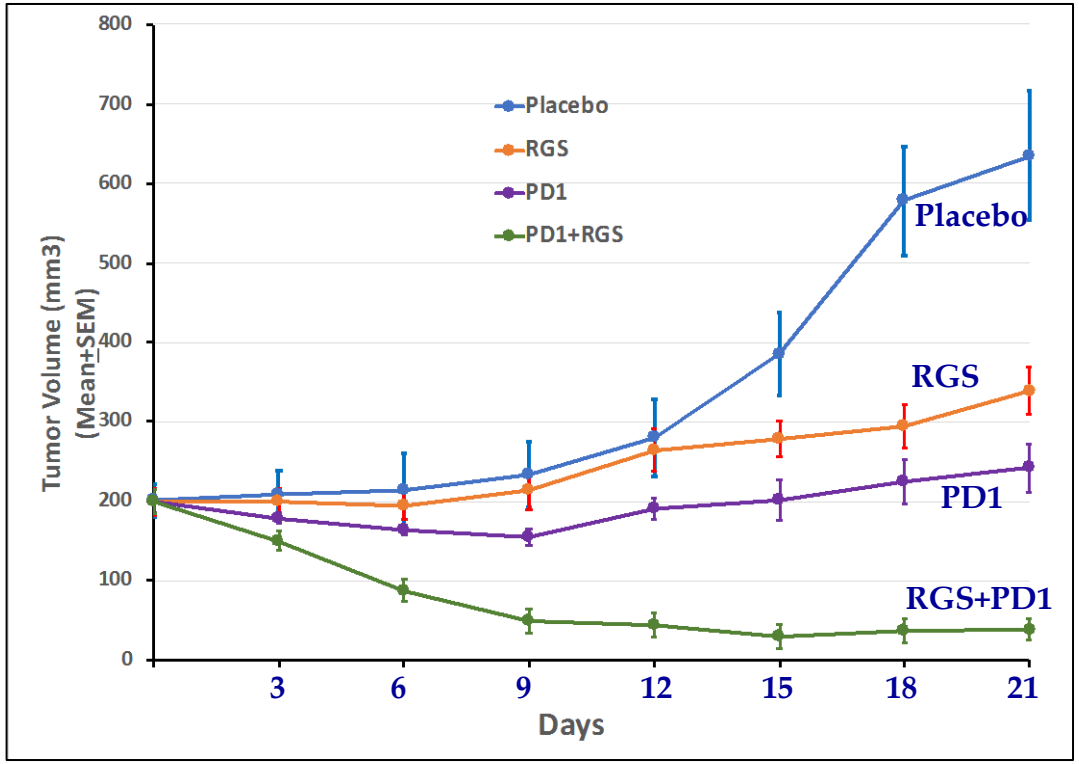
Coelho et al. Immunity 2017

Oncogenic KRAS Signaling Shapes the TME



Rigosertib & HX-008 (PD-1) Act Synergistically

MC30 (CRC) Tumor Model



DATA BY HANX BIOPHARMACEUTICALS

Phase 1 Clinical Trial

- Objective/Hypothesis: Rigosertib + PD-1 (or PD-L1) checkpoint inhibitor will demonstrate anti-tumor activity in KRAS+ NSCLC
  - Direct cytotoxicity by inhibiting oncogenic KRAS signaling
  - Synergistic immunomodulation of the TME

- Rationale for combination
  - Both Rigosertib and Immune Checkpoint Inhibitors have efficacy in NSCLC
  - Both Rigosertib and Immune Checkpoint Inhibitors have well established safety data that do not overlap

Study Design

- Phase 1 Dose-Escalation Trial followed by Dose-Expansion Phase
  - N=20-30 patients
- Inclusion: Metastatic KRAS+ NSCLC patients who have progressed on standard first line treatment
- Design: Accelerated Titration Design
- Outcomes
  - Primary: MTD and RPTD
  - Secondary: Efficacy
    - ORR, PFS and OS

Translational Research

- Genomic Analysis (WES/WTS)
  - Molecular Mechanisms of Response/Resistance (i.e., KRAS co-mutations)
  - Tumor Heterogenieity
- Immune Studies (MIBI, CyTOF)
  - Characterize the dynamic infiltration of effector lymphocytes and immunoregulatory cells
- Radiomics (Computer Tomography)
  - Extract quantitative image features from restaging CTs to identify immune infiltrates following treatment