Corporate Presentation
June 2022

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.

About Onconova Therapeutics

- Clinical-stage biopharmaceutical company focused on developing novel products for patients with cancer
- Proprietary targeted anti-cancer agents
  - Narazaciclib - multi-kinase inhibitor targeting CDK 4/6 and other kinases important for cell proliferation and motility
  - Rigosertib – targets RAS and PLK-1 pathways and is an immune modulator
- Public company (NASDAQ: ONTX)

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Company Highlights

Narazaciclib is a multi-kinase inhibitor that targets CDK 4/6

- Phase 1 dose-escalation and expansion studies underway in the United States and China
- CDK 4/6 commercial agents are multibillion-dollar franchises
- Studies planned in additional tumor types beyond HR+ HER 2- mBC
- Potential to overcome resistance to approved CDK 4/6 inhibitors

Rigosertib is in multiple investigator-sponsored studies

- CPI resistant KRAS+ NSCLC
- CPI refractory melanoma
- RDEB complicated by SCC (PLK-1 driven)

Strong Intellectual Property Position

- Narazaciclib – composition of matter 2031 and methods of treatment 2042
- Rigosertib – formulation 2037 and methods of treatment 2042
- Dates are projected and may be eligible for extension

Well-capitalized

- Cash and equivalents as of 03/31/22 ≈ $50.8 million

mBC: Metastatic breast cancer; CPI: Checkpoint inhibitor; NSCLC: Non-small cell lung cancer; RDEB: Recessive dystrophic epidermolysis bullosa; SCC: Squamous cell carcinoma

Clinical-stage Pipeline

Program	Indication	Preclinical	Phase 1	Phase 2	Phase 3
Corporate Programs					
Narazaciclib (Daily)	Solid Tumors				
Narazaciclib (3 wks. on 1 wk. off)	Solid Tumors				
Investigator-initiated Programs					
Oral Rigosertib + Nivolumab	CPI Resistant KRAS-mutated NSCLC				
Oral/IV Rigosertib	RDEB-associated Metastatic SCC				
Oral Rigosertib + Pembrolizumab	CPI Resistant Melanoma				

NSCLC: Non-small cell lung cancer; RDEB: Recessive dystrophic epidermolysis bullosa; SCC: Squamous cell carcinoma; CPI: Checkpoint inhibitors

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Experienced Leadership Team

Steven Fruchtman, M.D.
President & Chief Executive Officer

ORTHO BIOTECH · ALLOS THERAPEUTICS · NOVARTIS · SPECTRUM PHARMACEUTICALS · Syndax

Mark Guerin
Chief Operating Officer & Chief Financial Officer

Cardiokine · Barrier Therapeutics

Mark Gelder, M.D.
Chief Medical Officer

elevar therapeutics · BAYER · PIERIAN BIOSCIENCES · Pfizer

Adar Makovski Silverstein, Ph.D.
Head of Corporate Development

REGENERON · AMGEN

Matthew Parris
Vice President, Clinical Operations

Aegerion Pharmaceuticals · inovio · Eleison PHARMACEUTICALS LLC

Stephen Cosenza, Ph.D.
Lead Scientist

Icahn School of Medicine at Mount Sinai

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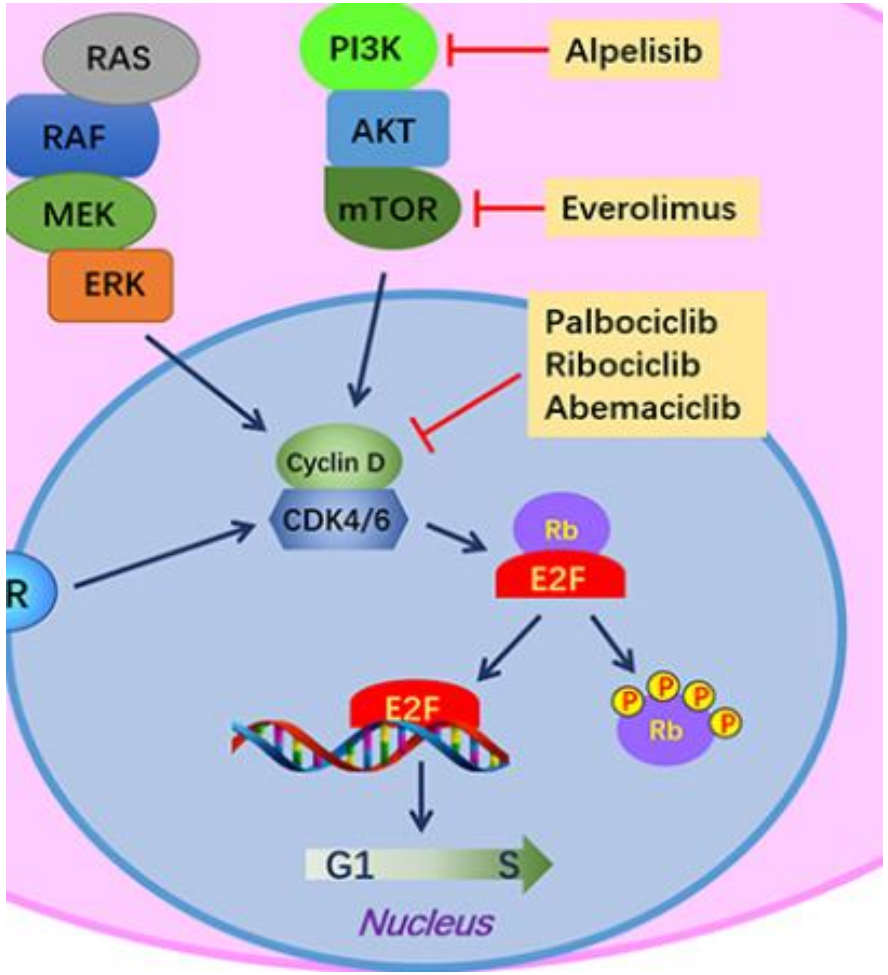
Narazaciclib:

Research & Development

CDK 4/6 in Cancer Therapeutics

- Overexpression of CDK 4/6 causes cell-cycle deregulation in certain cancers
- Role of Rb pathway in tumor initiation and progression is well-established
- Inhibition of Rb prevents CDK-mediated G1-S phase transition, suppressing DNA synthesis and inhibiting cancer cell growth
- Multiple therapeutic opportunities
- Approved CDK 4/6 inhibitors including Ibrance®(palbociclib), Kisquali® (ribociclib) and Verzenio®(abemaciclib) represent treatment advances for HR+ HER 2- metastatic breast cancer



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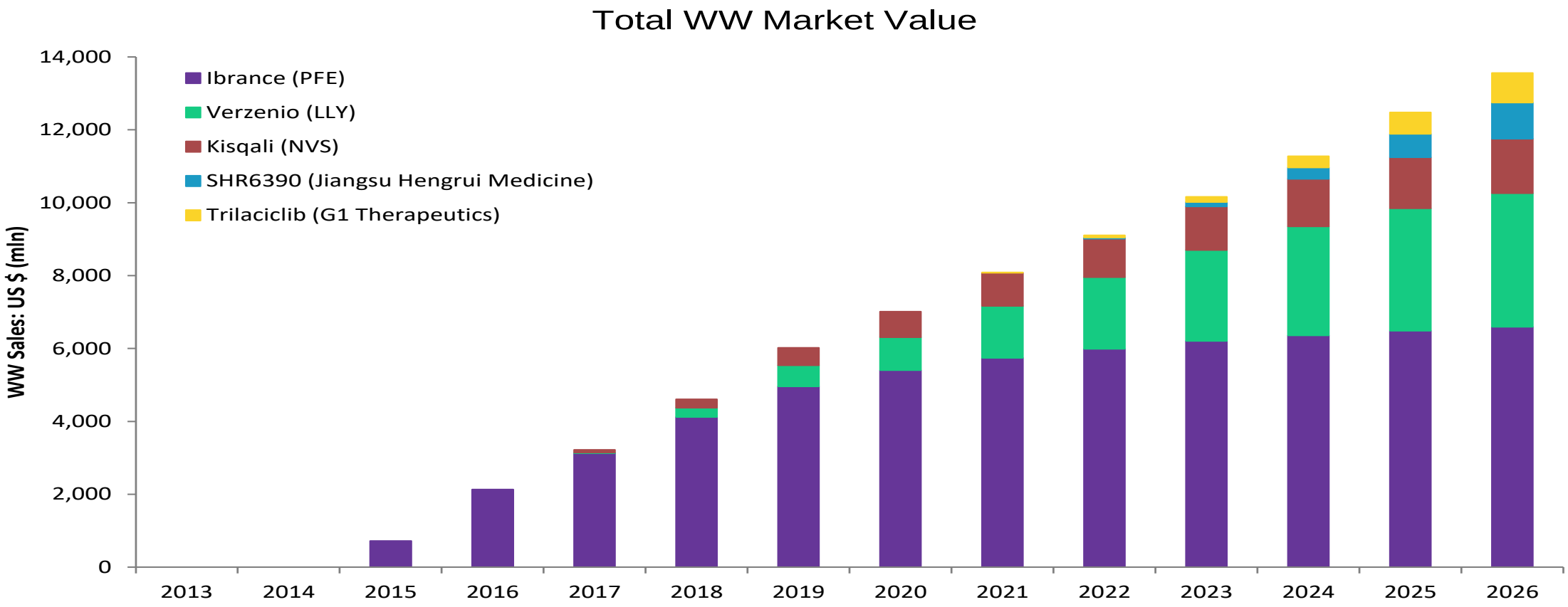
CDK 4/6 Marketed Products Sales

Total worldwide sales of CDK 4/6 inhibitors exceeded $6 billion in 2020



Source: Evaluate Ltd

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Narazaciclib Differentiation

- Active in numerous tumor types with acceptable and differentiated safety profile based on preclinical results
  - Narazaciclib may cause less myelosuppression and less neutropenia based on preclinical models
- A potent inhibitor of CSF1R
  - CSF1 promotes the infiltration of immunosuppressive Tumor-Associated Macrophages (TAMs) which support tumor progression
  - Blockade of CSF1R or inhibition of its kinase activity: the net effect is promotion of antitumor immunologic effects
- Inhibits ARK 5/NUAK1
  - ARK 5 /NUAK1 overexpression is found in multiple tumors and is associated with poor prognosis in metastatic breast cancer, multiple myeloma, and hepatocellular carcinoma
- Demonstrated BBB penetration in non-human primates
- Potential to be used where other CDK4/6 inhibitors have failed

Data on file; BBB: Blood Brain Barrier

In Vitro Multi-Kinase Activity - IC_{50} Values* (nM)

	Narazaciclib	**Palbociclib**	**Ribociclib**	**Abemaciclib**
Sponsor	Onconova	Pfizer	Novartis	Lilly
CDK Family				
CDK4/cyclin D1	2	2	3	0.8
CDK6/cyclin D1	0.6	0.8	6.0	0.6
CDK1/cyclin A	2190	>10,000	>10,000	270
CDK2/cyclin E	69	2300	>10,000	130
CDK9/T1	48	630	390	7
Other Kinases				
CSF1R	0.7	>10,000	>10,000	>10,000
ARK 5/NUAK 1	5	1,400	1,540	773
FLT3	6.0	496	753	72

*IC_{50} is a quantitative measure indicating the concentration needed to inhibit the listed kinase by 50%

Reaction Biology 2021

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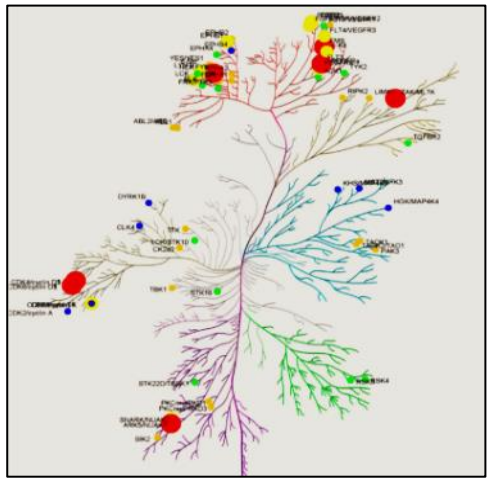
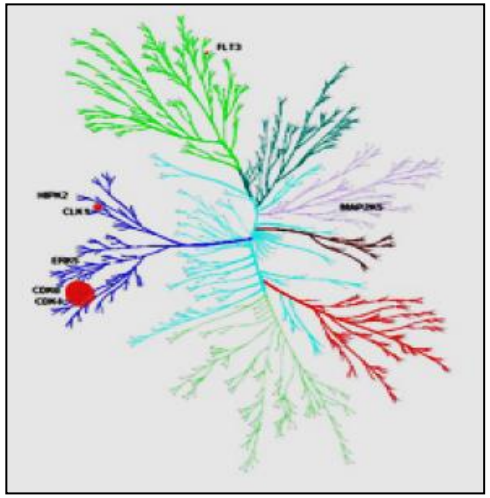
Kinome Tree for CDK 4/6 Inhibitors

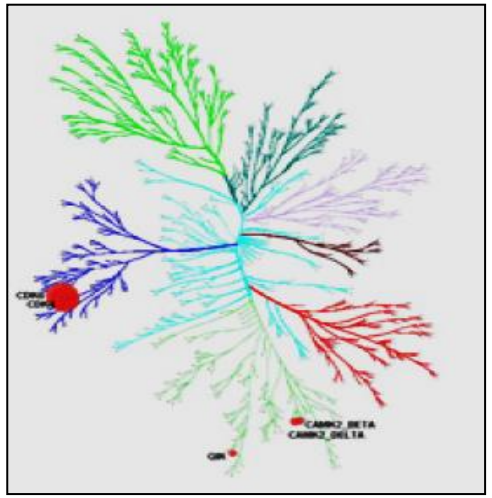
Narazaciclib



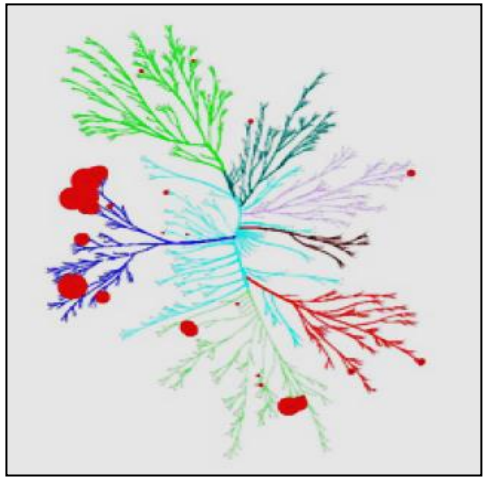
Palbociclib



Ribociclib



Abemaciclib



Reddy, 2014; Chen et al., 2016

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Clinical Profiles

	Palbociclib	**Ribociclib**	**Abemaciclib**
Sponsor	Pfizer	Novartis	Lilly
Warnings and Precautions*	Neutropenia, Interstitial Lung Disease (ILD), Embryo Fetal Toxicity (EFT)	Neutropenia; ILD; QT Interval Prolongation; Hepatobiliary Toxicity; Severe Cutaneous Adverse Reactions	Diarrhea; ILD; Neutropenia; Hepatotoxicity; Venous thromboembolism; EFT
Dose Limiting Toxicity	Neutropenia	Neutropenia	Diarrhea
Clinical Dosing	125 mg PO QD 3 wks on one wk off	600 mg PO QD 3 wks on 1 wk off	150-200 mg PO BID continuous

*Most recent package inserts

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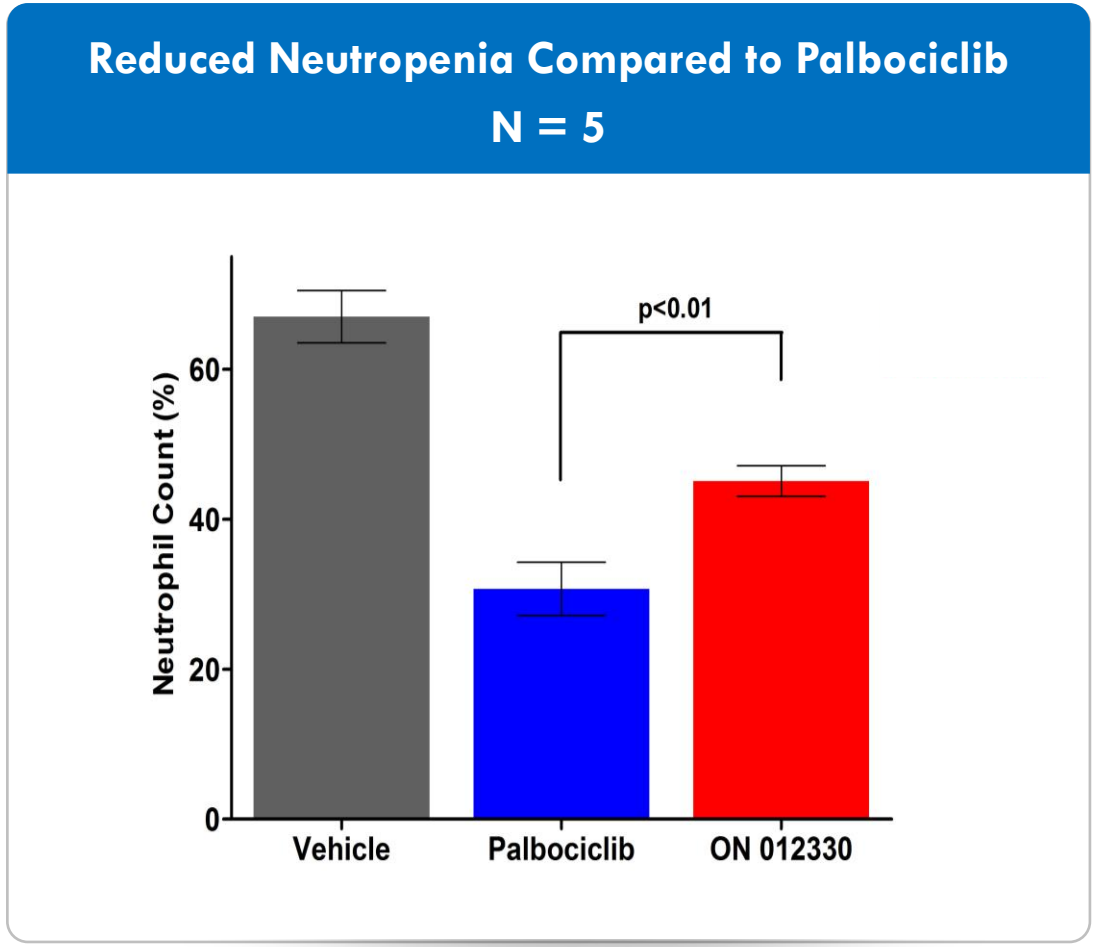
Narazaciclib Reduced Neutropenia: Preclinical Results



Note: MDA MB 435 Xenograft. *(Patel et. al, 2017 AACR Annual Meeting)*

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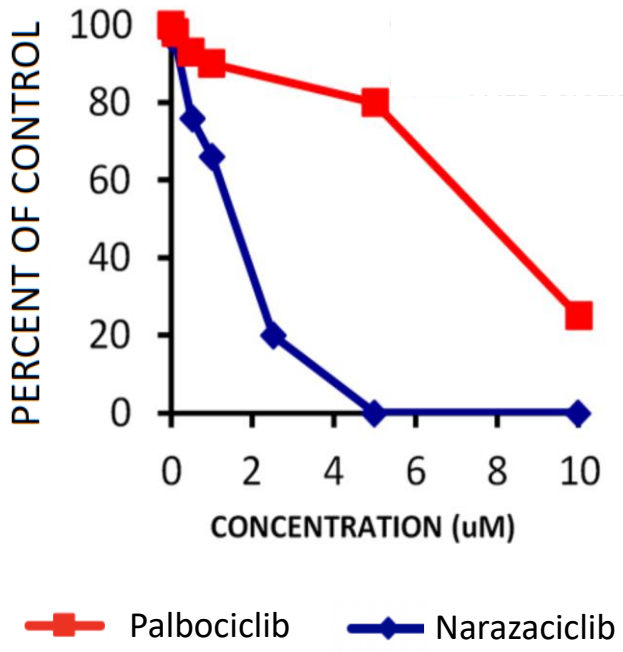
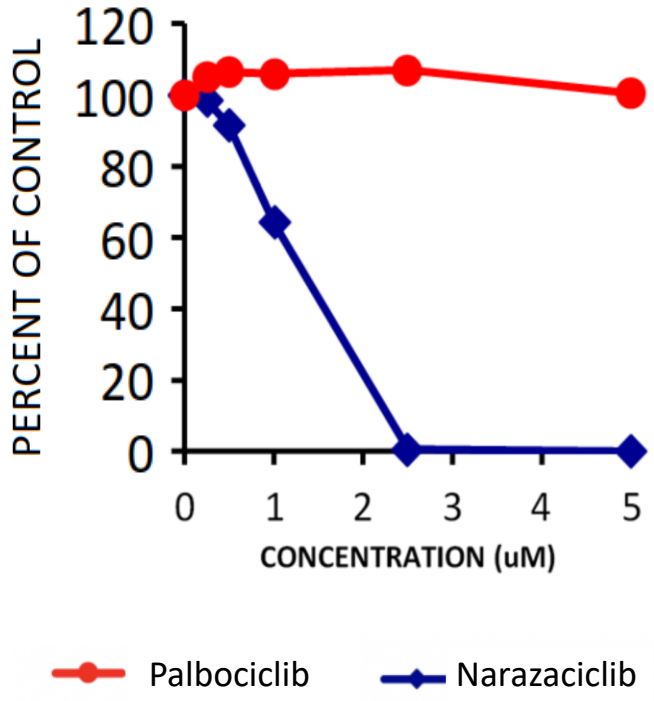
Narazaciclib Inhibits Growth of Cancer Cell Lines Resistant to Palbociclib

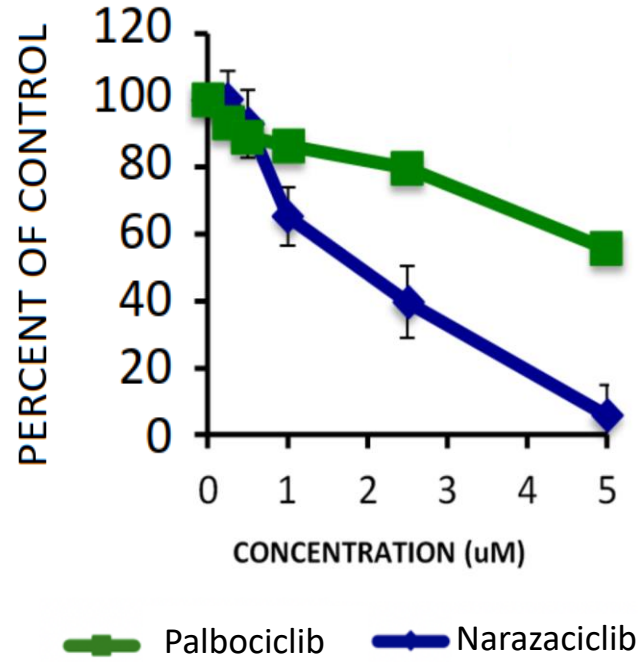
Breast Cancer Cells



Ovarian Cancer Cells



Prostate Cancer Cells



Data on file

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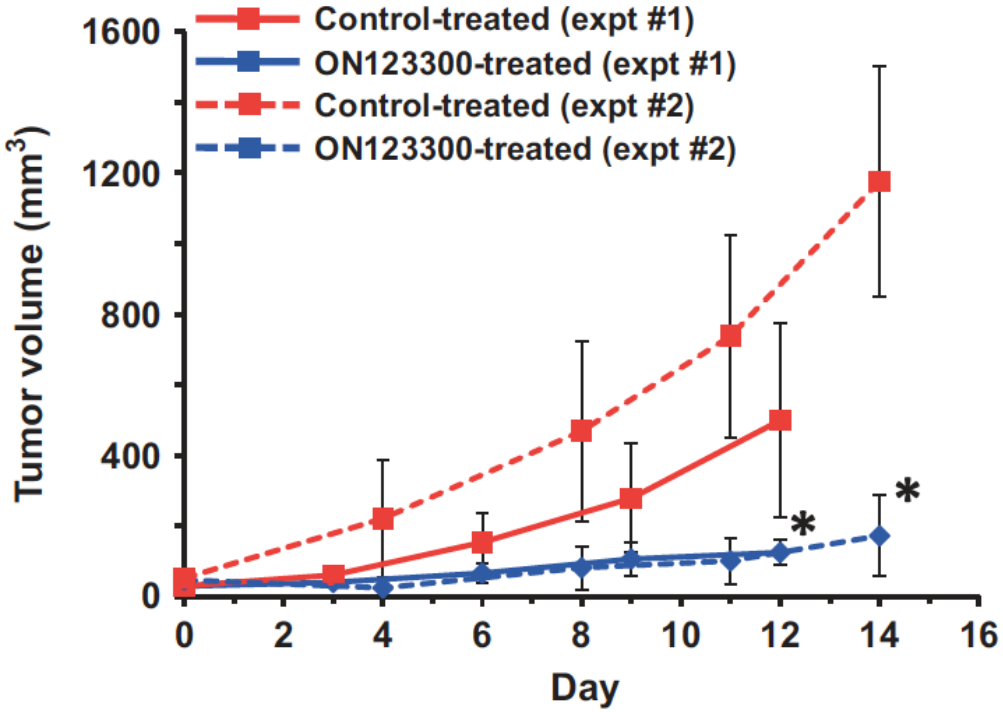
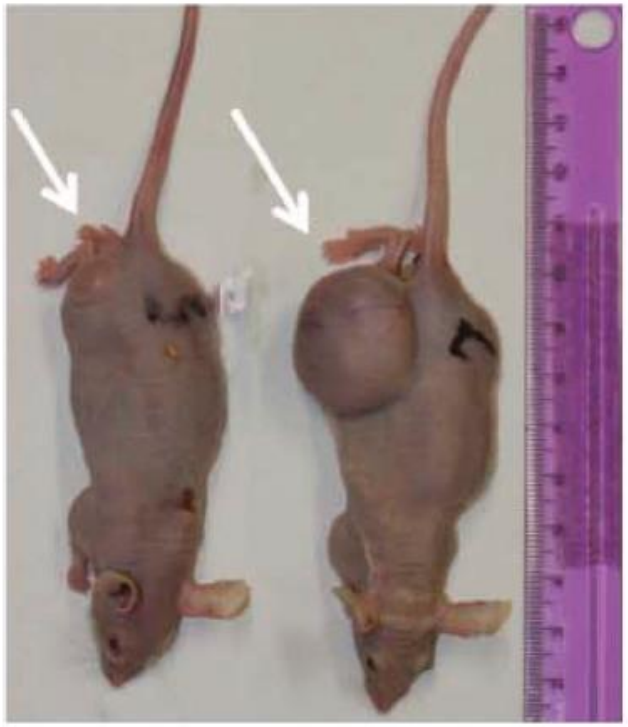
Narazaciclib Activity in Preclinical Mantle Cell Lymphoma Mouse Xenograft Model





Divakar et al., 2016

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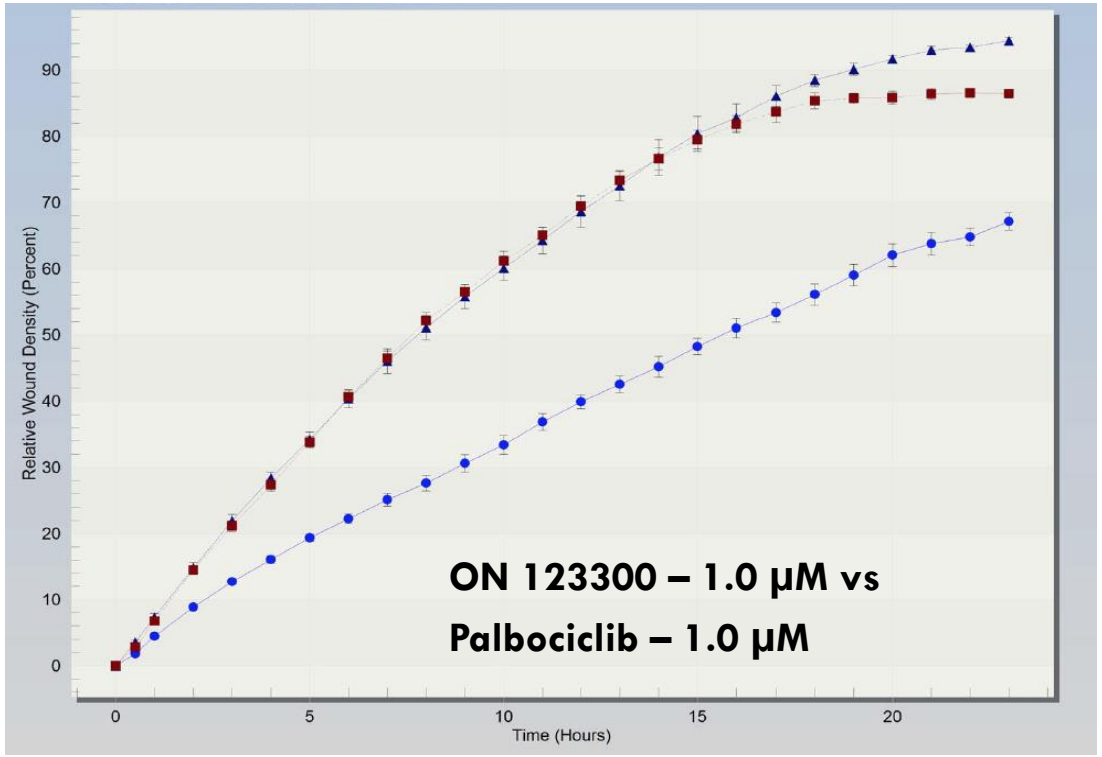
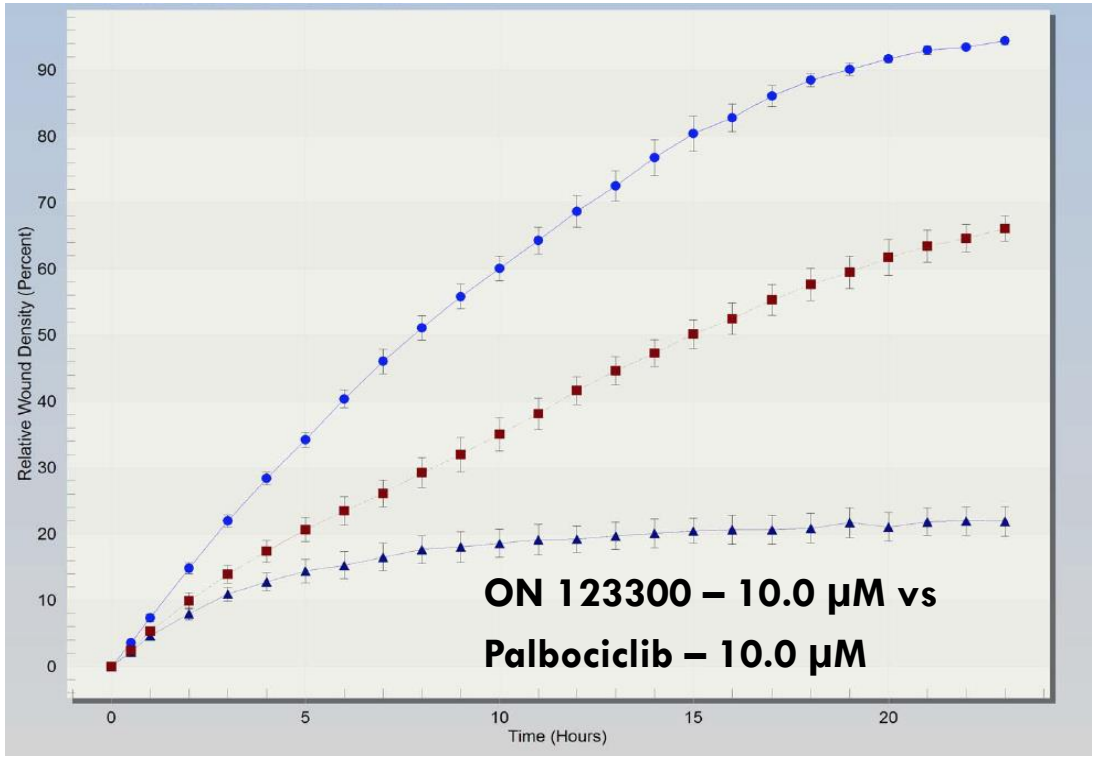
Narazaciclib Potential to Inhibit Cancer Cell Motility

Narazaciclib inhibits wound healing, a proxy for cancer cell migration, more than palbociblib

Two different breast cancer cell lines: Hs578t and MDA-MB-231 (TNBC)

MDA-MB-231 24 Hour Migration Assay





Reddy lab cell motility data, MSSM

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Narazaciclib Indications To Explore

Potential target diseases for investigational Phase 1/2 studies (including but not limited to):

01

HR+ HER 2- postmenopausal metastatic breast cancer resistant to CDK 4/6 inhibitors

02

Mantle cell lymphoma resistant to BTK inhibitors (e.g., Ibrutinib)

03

Multiple myeloma in ≥ second-line settings

And additional indications…

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Rigosertib : Research & Development

Rigosertib Mechanisms of Action

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

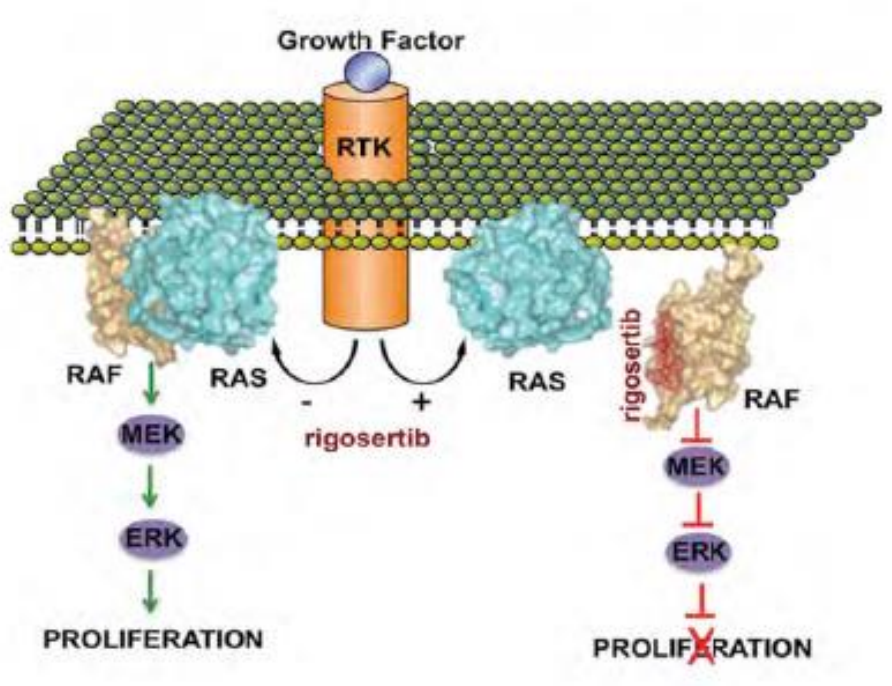
Proposed Mechanisms of Action

- Disruption of RAS effectors[1]
- Inhibition of Ras/Raf/MEK/ERK pathway signaling by a stress-induced phospho-regulatory circuit[2]
- Immunomodulatory activity enhancing checkpoint inhibitor activity[3]
- PLK1 Inhibitor[4]
- Microtubule-destabilizing agent[5]

Clinical Studies

- Over 1,300 patients have been treated with established safety profile
- Investigator initiated study program at minimal expense

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. Chi Yan, E.Premkumar Reddy, and Ann Richmond, AACR 2019, VUMC;
4. Atanasova ,et al. (2019). Clin Cancer Res 25, 3384- 3391; 5. Jost et al: Molecular Cell 68, 210; 2017

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Rigosertib May Overcome Resistance to Checkpoint Inhibitors in KRAS+ NSCLC and Other Cancers

- **A significant proportion of patients do not respond to checkpoint inhibitors[1]**
  - Checkpoint inhibitors are the current standard of care for stage IV NSCLC and many other cancers[1]
- **Resistance to checkpoint inhibition may be due to immunosuppressive TMEs[2]**
  - Immunosuppressive TMEs prevent tumor immune cell infiltration[2]
- **Rigosertib targets KRAS signaling and has the potential to augment the response to checkpoint inhibition[3,4]**
  - Immunosuppressive TMEs may be promoted by oncogenic KRAS signaling[5,6]
- **Rigosertib promotes CD40 expression by melanoma cells, induces immunogenic cell death, and enhances response to checkpoint inhibitors[7]**
  - Rigosertib converts the immune environment of melanoma tumors from “cold” to “hot”[7]

NSCLC: Non-small cell lung cancer; TME: Tumor microenvironment; 1. Boyero et al. 2020; 2. Hack et al. 2020; 3. Divakar et al. 2016; 4. Ritt et al. 2016; 5. Liao et al., 2019; 6. Gao et al. 2020; 7. Yan et al., 2021

Rigosertib Effect in NSCLC PDX Model

Clinical Summary:

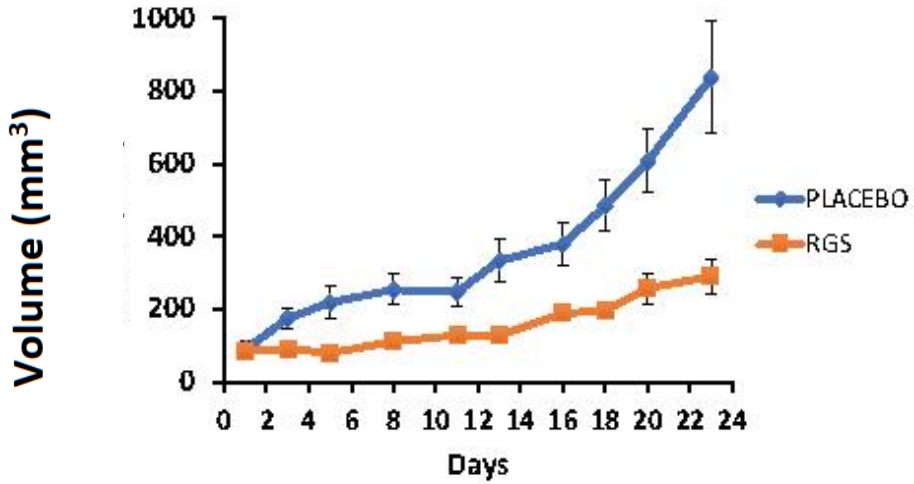
Metastatic lung adenocarcinoma

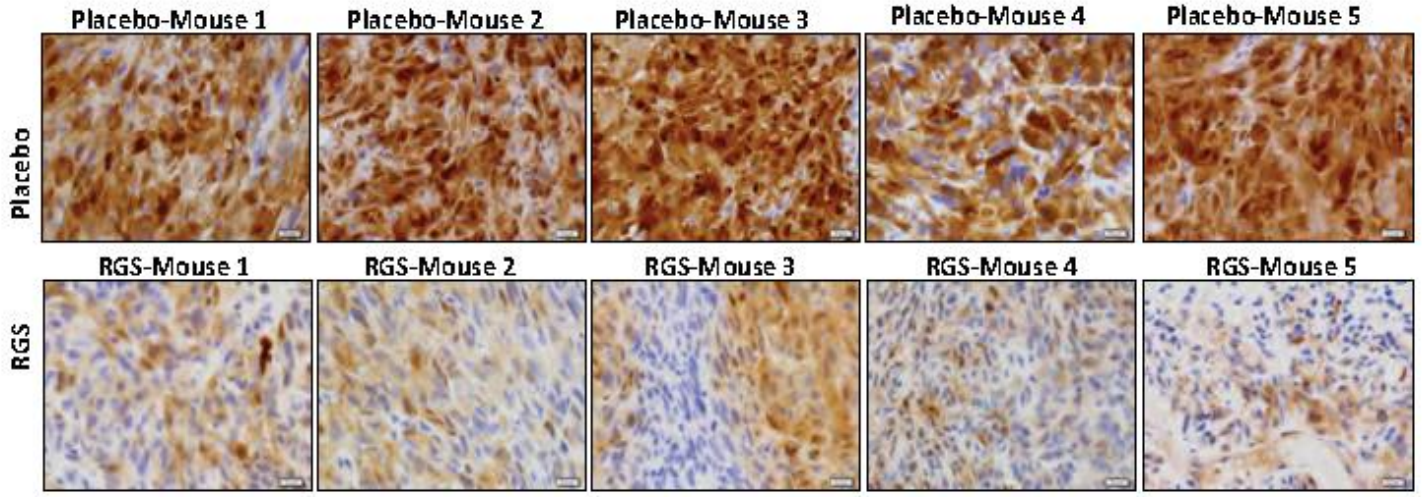
53 y/o female

mNSCLC KRAS^{G12D}

ALK+

89.1% PD-L1+ (surface)





pERK Staining

Data on file. NSCLC: Non-small cell lung cancer

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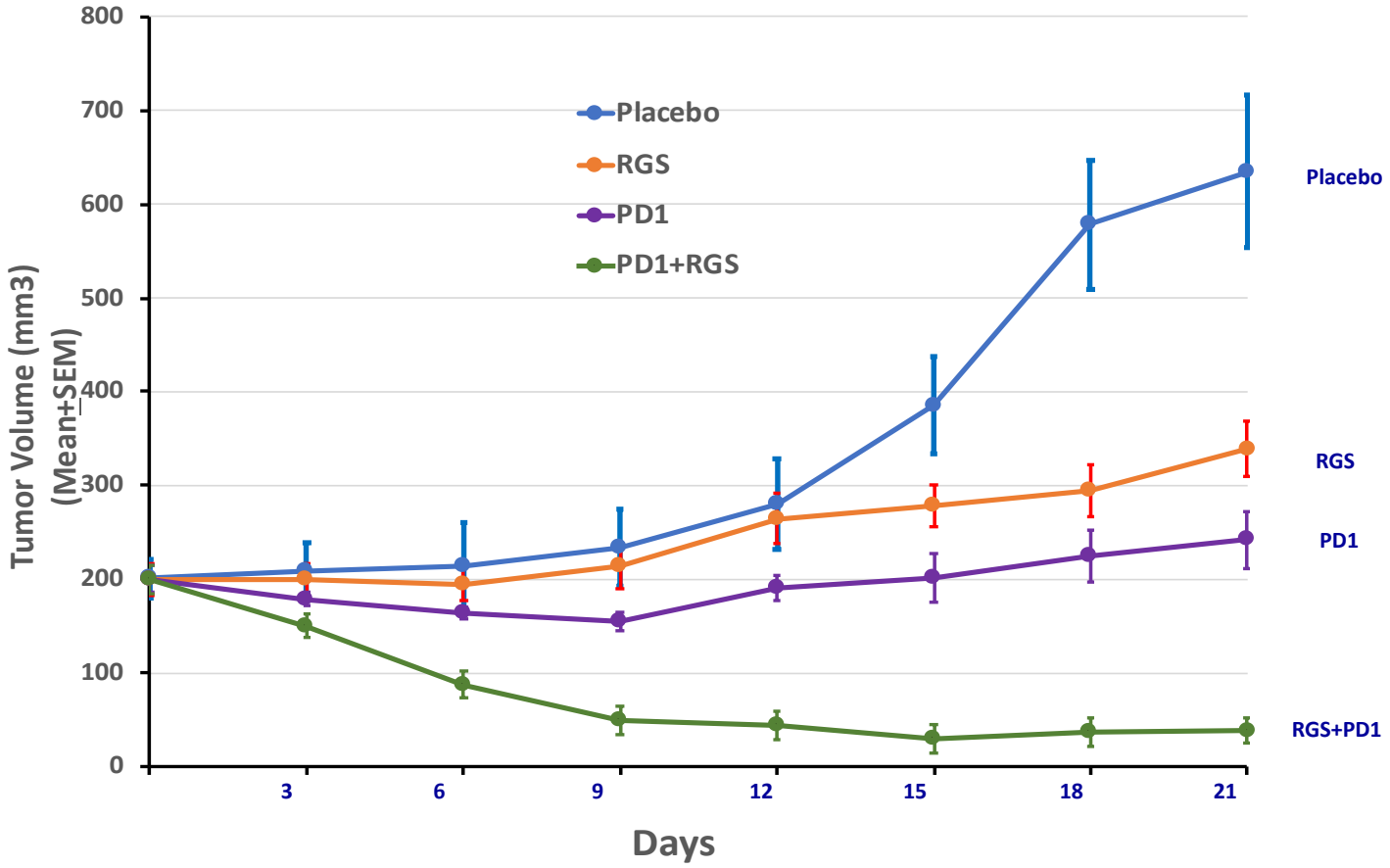
Rigosertib + HX-008 (PD-1) Act Synergistically

MC38 (colorectal cancer) Tumor Model



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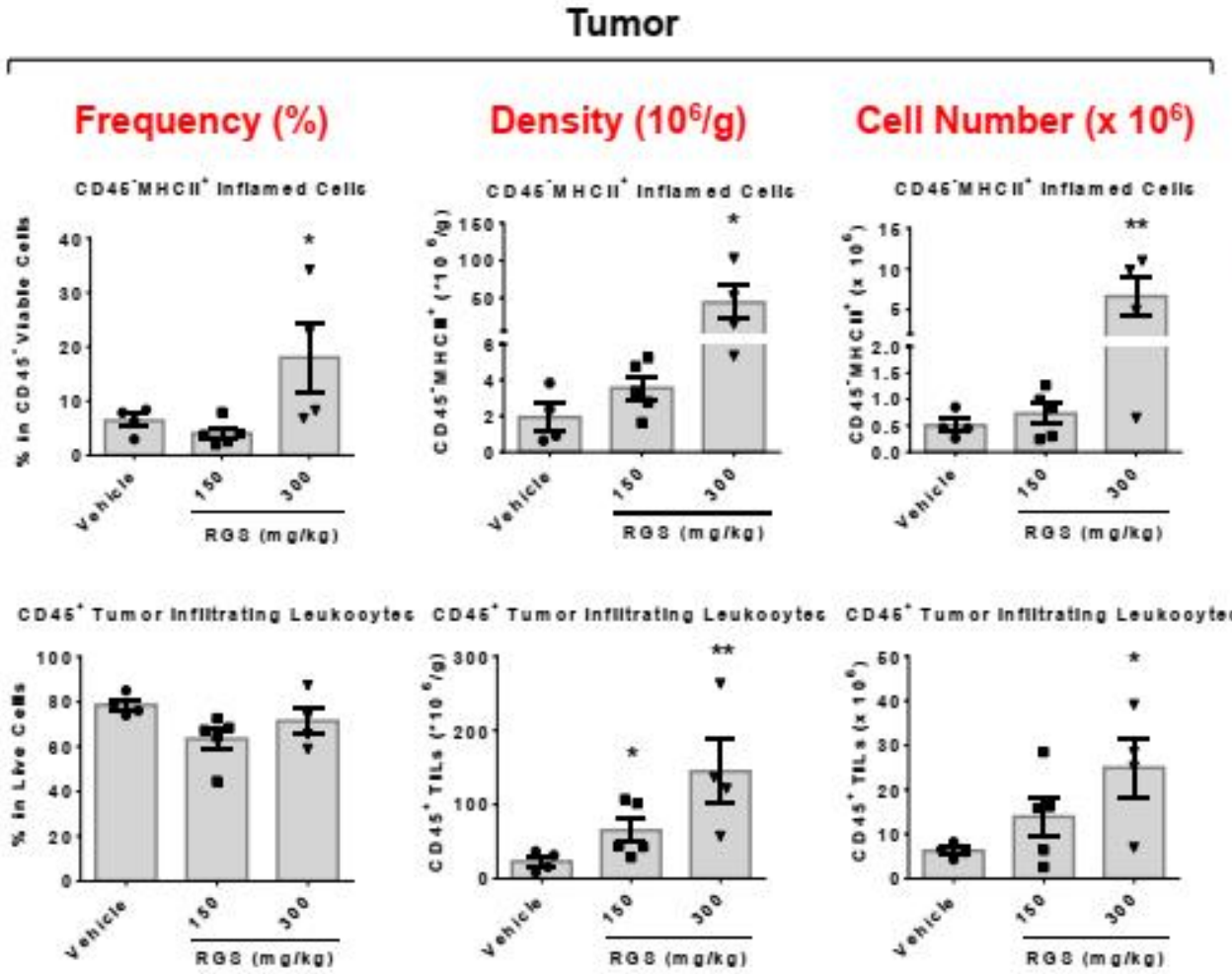
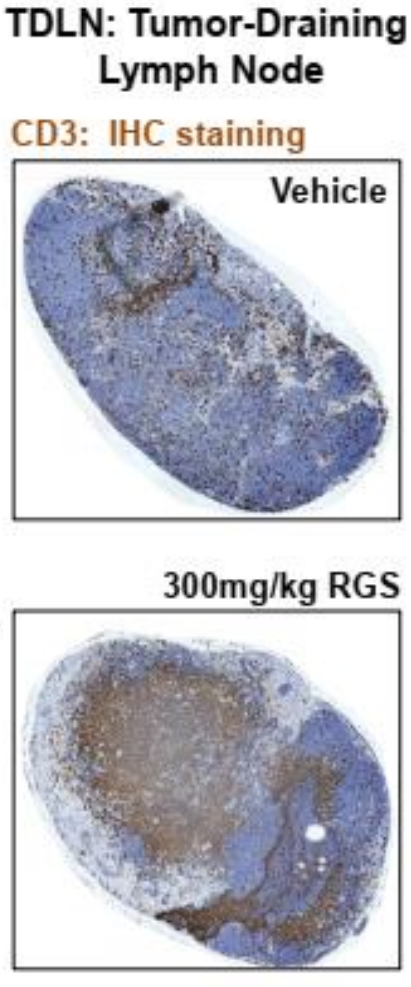
Turns the “Cold” Tumor/Lymph Node to “Hot”





Chi Yan, E.Premkumar Reddy, and Ann Richmond, AACR 2019, VUMC

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Phase 1/2a Trial: Rigosertib + Nivolumab in Advanced KRAS+ NSCLC

- Rigosertib plus nivolumab in stage IV lung adenocarcinoma with KRAS mutation who progressed on first-line treatment
- Preliminary data presented September 22, 2021 at 3rd annual RAS-targeted drug development summit

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

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

Correlative Studies
- Genomic Studies
- Immunophenotyping

Radiographic Scans every 8 weeks +/- 2 weeks

Veluswamy, 3rd Annual RAS Targeted Drug Development Summit, 2021. NSCLC: Non-small cell lung cancer

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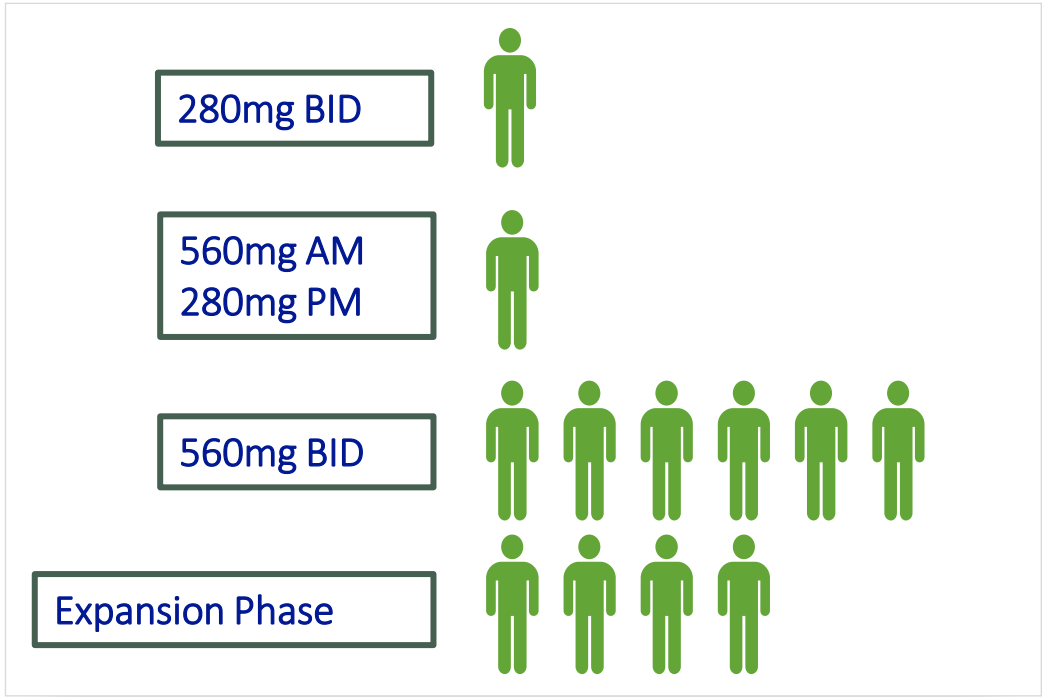
Phase 1/2a Trial: Patients

- Trial opened in June 2020
- 12 patients enrolled as of September 2021
- 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%)

Veluswamy, 3rd Annual RAS Targeted Drug Development Summit, 2021.

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Phase 1/2a Trial: Safety/Tolerability with Rigosertib + Nivolumab

Treatment related adverse events were mostly mild – only 1 DLT as of September 2021

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

Veluswamy, 3rd Annual RAS Targeted Drug Development Summit, 2021. TRAE: Treatment related adverse event; DLT: Dose limiting toxicity

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Phase 1/2a Trial: 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)

Veluswamy, 3rd Annual RAS Targeted Drug Development Summit, 2021. PR: Partial response; SD: Stable disease; Data as of September 2021

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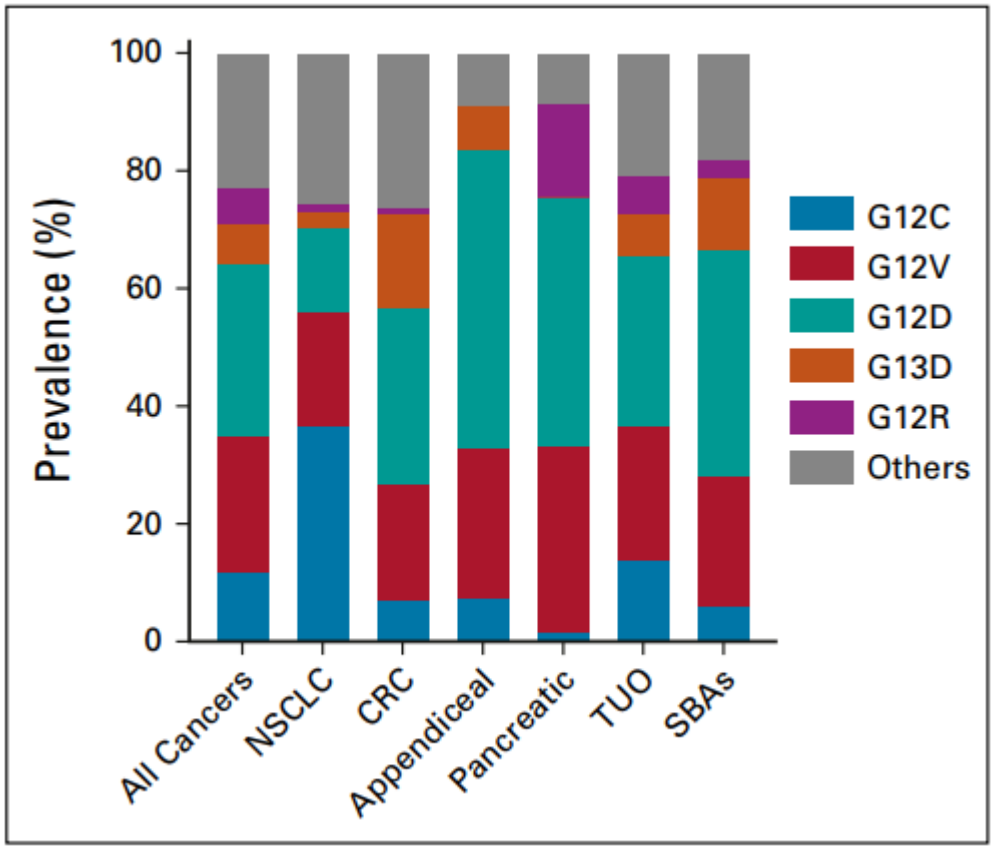
KRAS Variants by Tumor Subtype



Prevalence of KRAS variants by tumor subtype. Most common KRAS mutation variants observed in all KRAS-mutated tumors (n = 13,758) and subtypes. CRC, colorectal cancer; NSCLC, non-small cell lung cancer; SBA, small bowel adenocarcinoma; TUO, tumor of unknown origin.

SalemM, et al., JCO Precision Oncology, March 2022

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Phase 1/2a Trial Next Steps

- **3 out of 7 (43%) evaluable patients on trial demonstrated disease control**
  - 2 PRs + 1 SD
- **PRs across different KRAS mutations (G12C, G12V)**
  - Potentially differentiates rigosertib from RAS pathway modulators targeting particular KRAS mutations
- **Combination of rigosertib and nivolumab has been well tolerated**
  - No synergistic toxicities noted for either study drug
- **Next Steps**
  - 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/RP2D are being considered

Veluswamy, 3rd Annual RAS Targeted Drug Development Summit, 2021.. PR: Partial response; SD: Stable disease; MTD: Maximum tolerated dose; RP2D: Recommended Phase 2 dose; Data as of September 2021

Rigosertib's Promising Activity in RDEB-associated SCC

Single patient data show that rigosertib monotherapy led to a sustained complete response

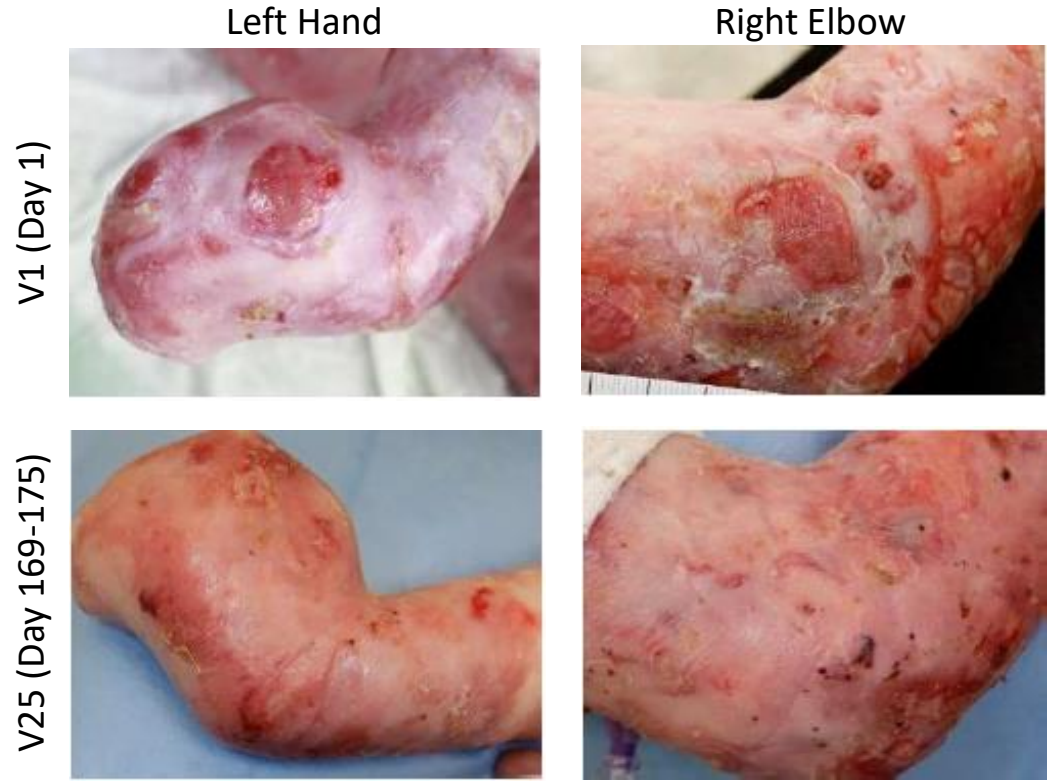
RDEB-associated SCC: An ultra-rare condition

- Absence of type VII collagen protein leads to extreme skin fragility and chronic wound formation
- Patients develop SCCs that arise in areas of chronic skin inflammation
- Cumulative risk of death: 78.7% by age 55
- Current therapies: Limited response of short duration

Rigosertib monotherapy in a 24-year old RDEB patient

- Multiple, unresectable SCCs unresponsive to prior treatments including cemiplimab
- Sustained clinical and histological remission of all target lesions following treatment with IV rigosertib

Lesions Display Clinical and Histological Remission Following Treatment with Rigosertib



RDEB: Recessive dystrophic epidermolysis bullosa; SCC: Squamous cell carcinoma; Source: Laimer et al. Austrian Society of Dermatology and Venerology Annual Conference 2021

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Upcoming Milestones

Recent and Upcoming Milestones

RIGOSERTIB

3Q21

Preliminary Phase 1/2a data of oral rigosertib + nivolumab in KRAS-mutated non-small cell lung cancer

RIGOSERTIB

Mid-22

Investigator-initiated study of rigosertib in combination with a PD-1 inhibitor in melanoma patients

NARAZACICLIB

2H22

Establish recommended Phase 2 dose

RIGOSERTIB

2022

Additional Phase 1/2a data of oral rigosertib + nivolumab in KRAS-mutated non-small cell lung cancer

NARAZACICLIB

2H22

Initiate Phase 2 basket trial

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Thank You!
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