ONCONOVA THERAPEUTICS

International EB symposium in Osaka

May 8/9 2023

Steven Fruchtman, M.D
President and CEO
Onconova Therapeutics

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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Rigosertib:

Research & Development

Rigosertib Interferes with Multiple Signaling Pathways

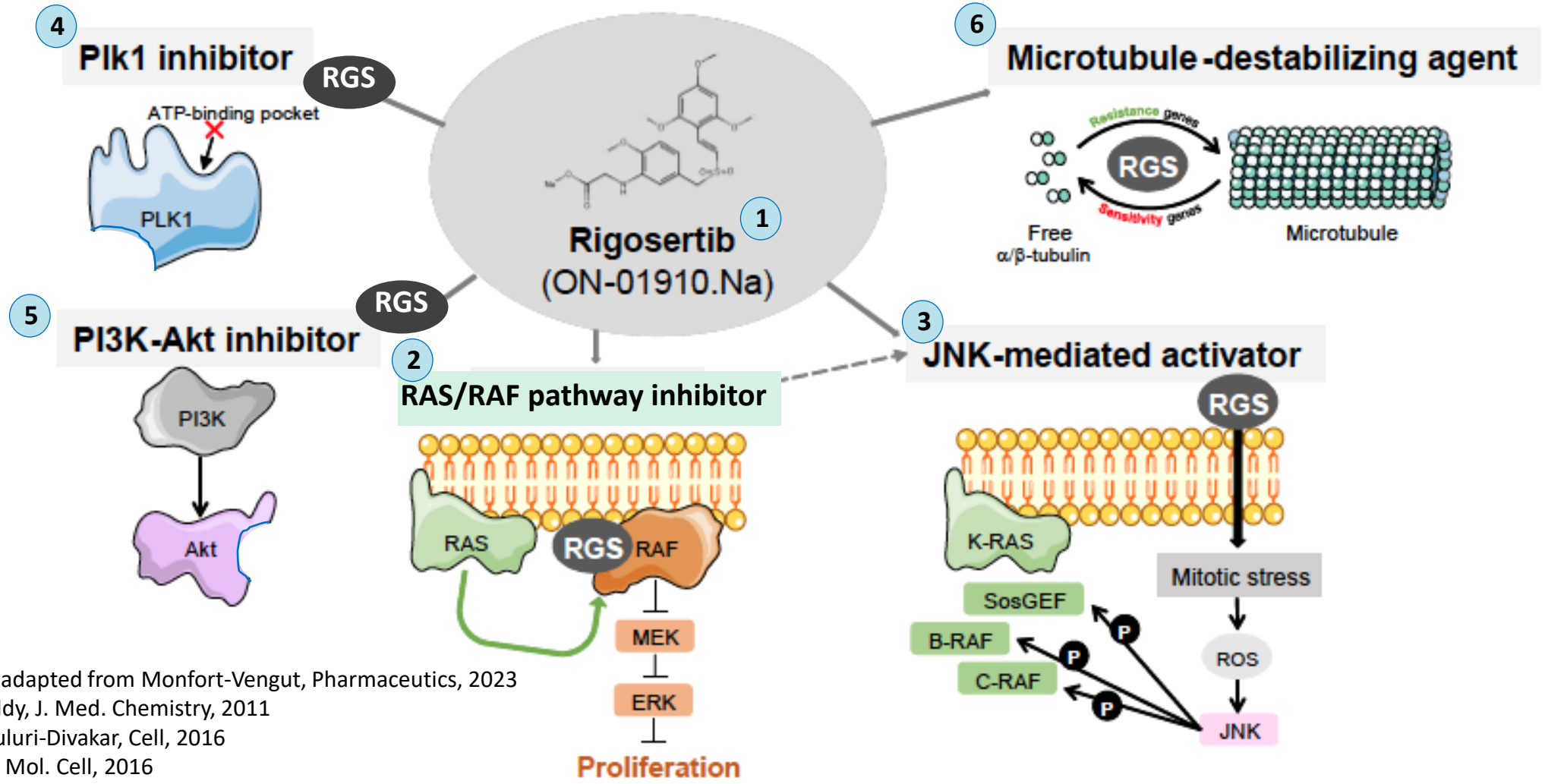

Figure adapted from Monfort-Vengut, Pharmaceutics, 2023

1: Reddy, J. Med. Chemistry, 2011
2: Athuluri-Divakar, Cell, 2016
3: Ritt, Mol. Cell, 2016
4: Atanasova, Clin. Cancer Res., 2019
5: Anderson, Mol. Cancer Ther., 2013
6: Jost, Mol. Cell, 2017

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Rigosertib Effect in NSCLC PDX Model

Clinical Summary:

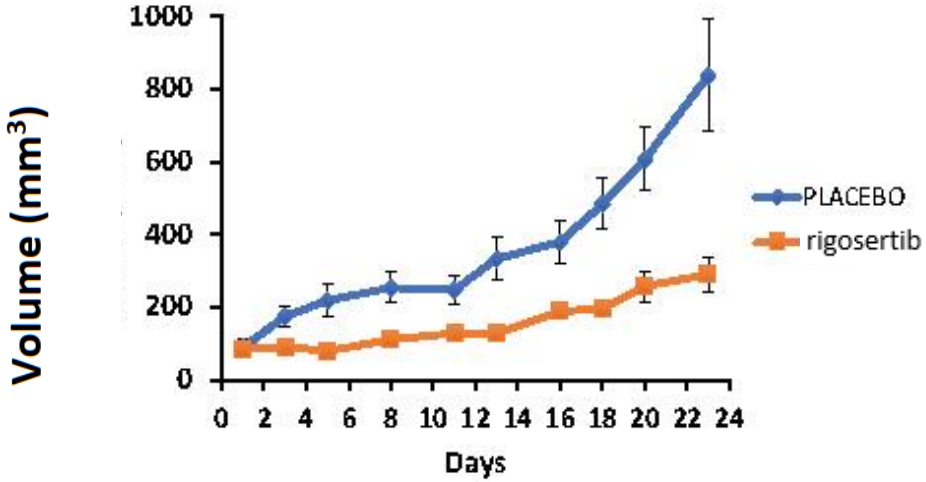
Metastatic lung adenocarcinoma

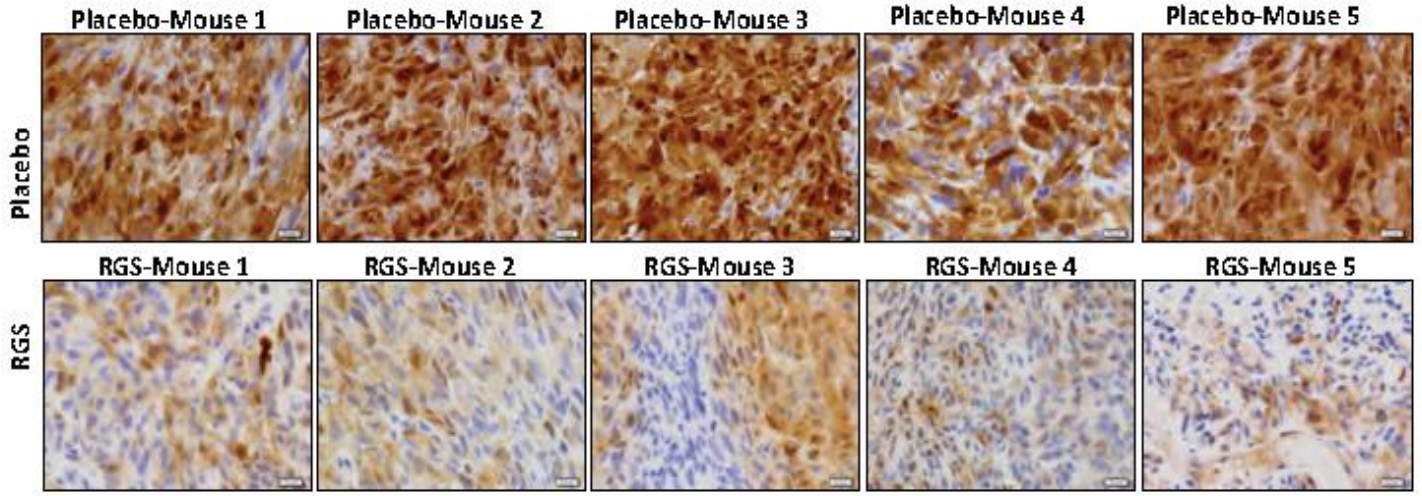
53 y/o female

mNSCLC KRAS^{G12D}

ALK+

89.1% PD-L1+ (surface)





pERK Staining

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

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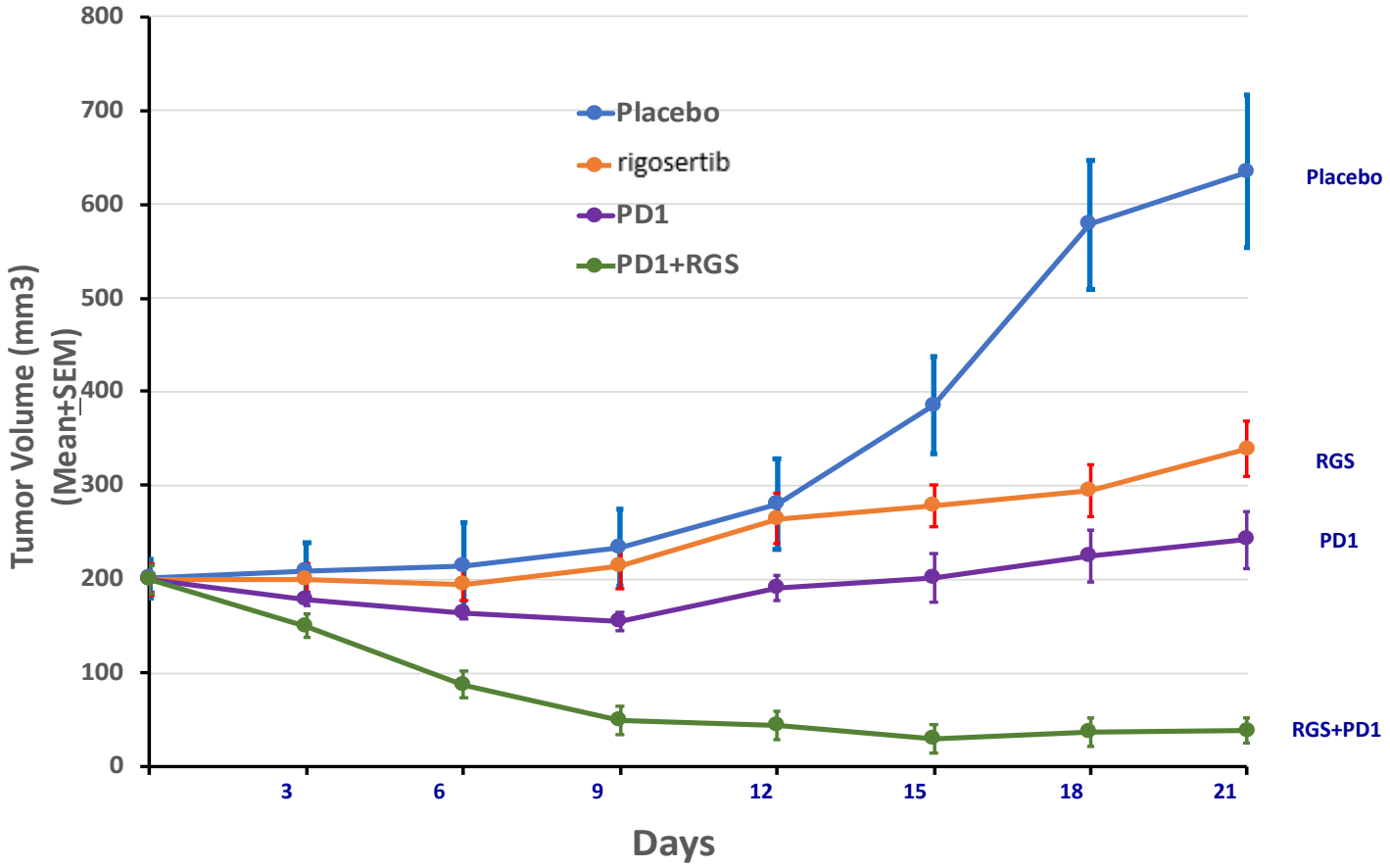
Rigosertib + HX-008 (PD-1) Act Synergistically

MC38 (colorectal cancer) Tumor Model



Data on file

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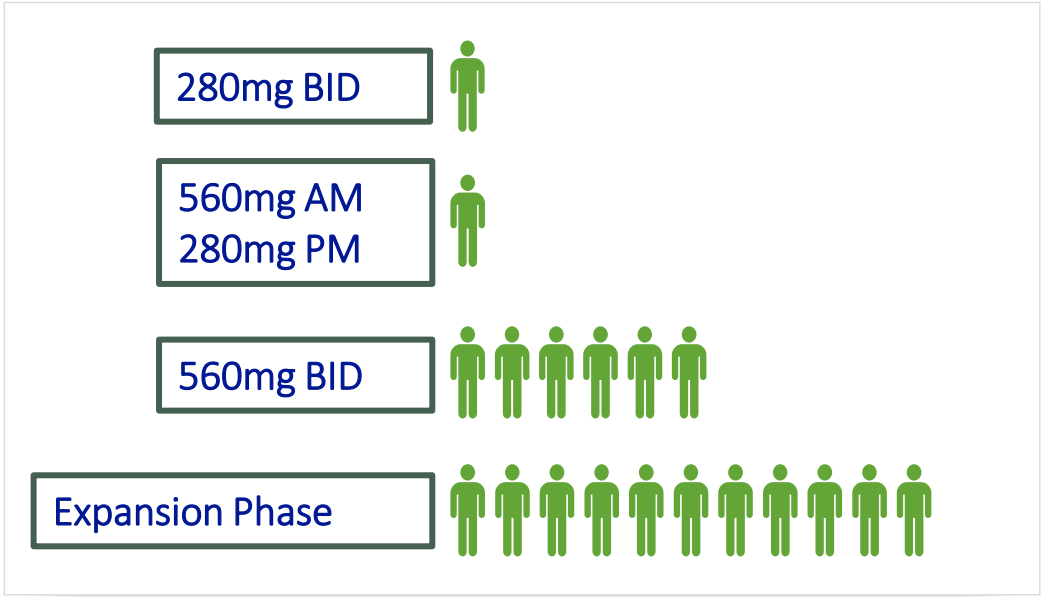
Phase 1/2a Trial: Patients

- Trial opened in June 2020
- 19 patients enrolled as of August 2022
- 95% of patients have non-G12C mutations
- Cohort is heavily 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%)

Adapted from Veluswamy et al. European Society for Medical Oncology Congress 2022.

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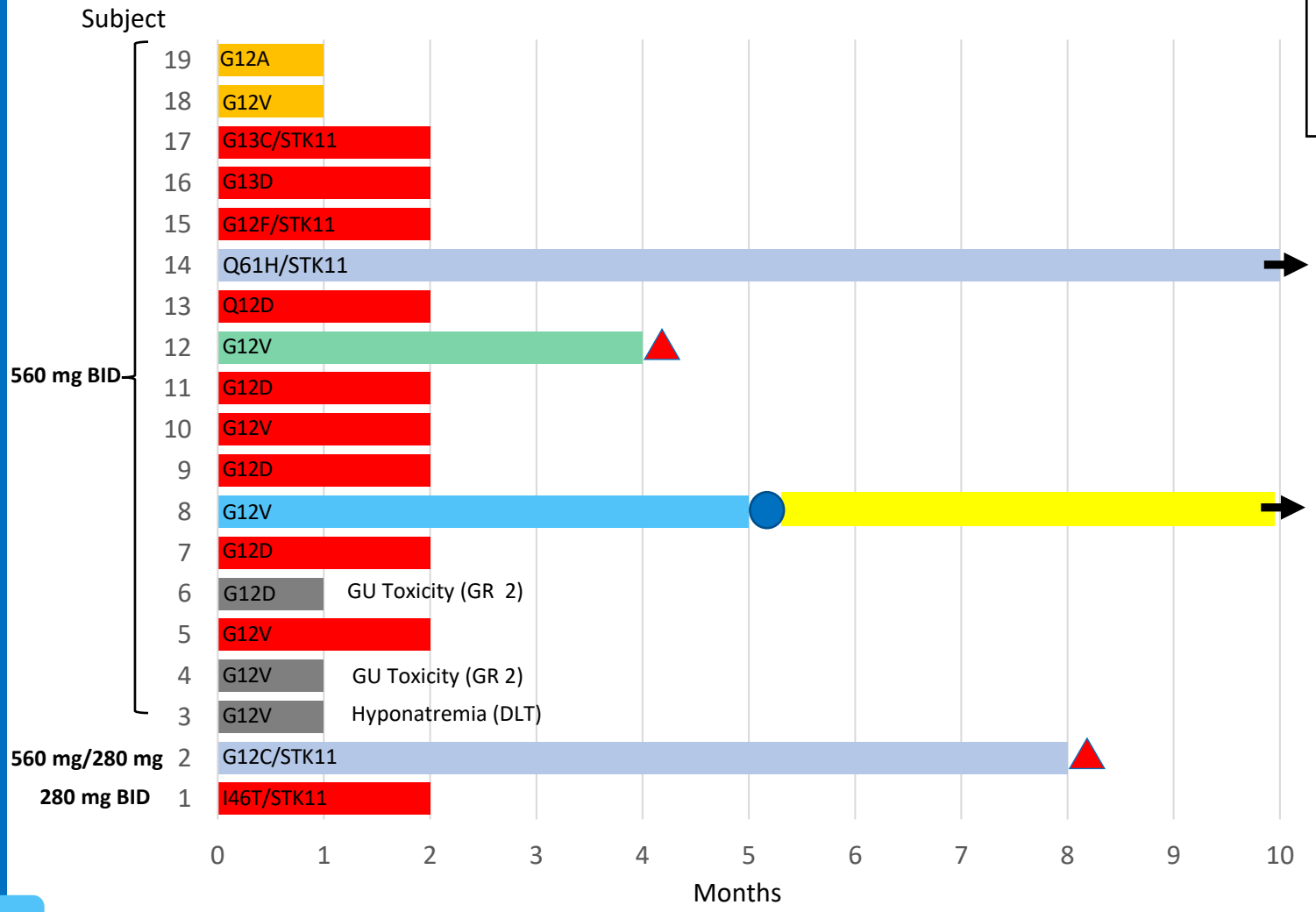
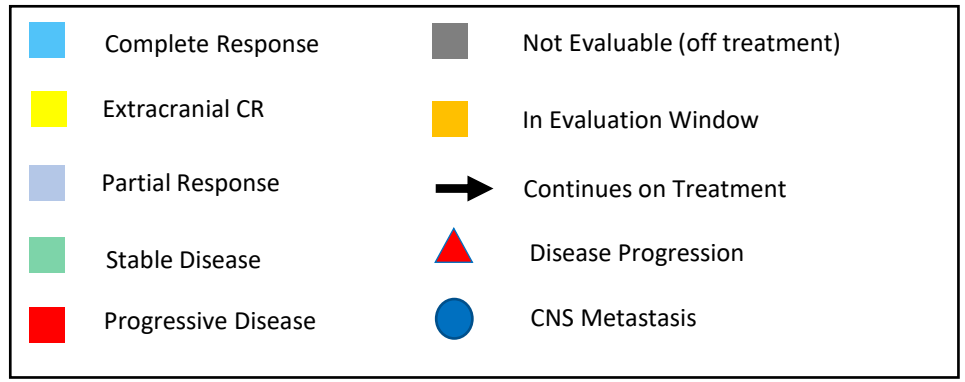
Efficacy Results

4 of 14 (29%) Evaluable Patients had Disease Control (1 CR + 2 PR + 1 SD)

4 of 13 (31%) above minimum clinically effective dose of rigosertib had Disease Control





Best Overall Response in Evaluable Patients (N=14)	
Complete Response (CR)	1 (7%)
Partial Response (PR)	2 (14%)
Stable Disease (SD)	1 (7%)
Mean Duration of Response = 6.75 months **Mean Duration of Extracranial Response = TBD**	

Adapted from Veluswamy et al. European Society for Medical Oncology Congress 2022. DLT: Dose limiting toxicity; CNS: Central nervous system

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Safety/Tolerability with Rigosertib + Nivolumab

Treatment related adverse events were mostly mild

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

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

Adapted from Veluswamy et al. European Society for Medical Oncology Congress 2022. TRAE: Treatment related adverse event; DLT: Dose limiting toxicity

Rigosertib in Patients with Recessive Dystrophic Epidermolysis Bullosa-associated SCC

Investigator initiated trials:

- **NCT03786237:** Prof. Johann Bauer, EB House Austria, University Hospital Salzburg
- **NCT04177498:** Dr. Neda Nikbakht, Thomas Jefferson University, PA

ClinicalTrials.gov

Rigosertib's Promising Single-agent Activity in RDEB-associated SCC

Complete remission of all cancerous skin lesions in 2 of 2 evaluable participants

RDEB-associated SCC: An ultra-rare condition

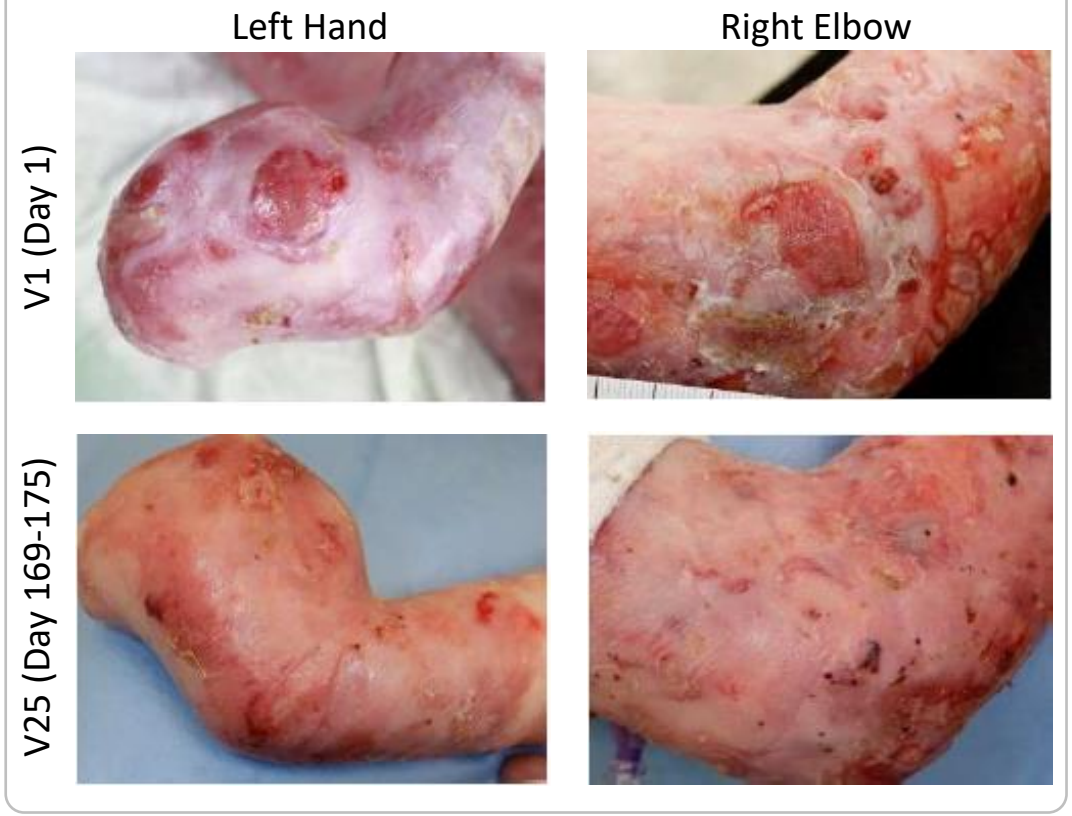
Absence of type VII collagen protein leads to extreme skin fragility and chronic wound formation

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

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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How was rigosertib matched with RDEB SCC?

Andrew South, PhD

Polo-like kinase-1 identified as a therapeutic target in RDEB cSCC

Open

Oncogene (2011) 1 12

www.nature.com/onc

ORIGINAL ARTICLE

Integrative mRNA profiling comparing cultured primary cells with clinical samples reveals PLK1 and C20orf20 as therapeutic targets in cutaneous squamous cell carcinoma

SA Watt[1,8], C Pourreyron[1,8], K Purdie[2], C Hogan[1], CL Cole[1], N Foster[3], N Pratt[3], J-C Bourdon[1], V Appleyard[1], K Murray[1], AM Thompson[1], X Mao[2], C Mein[4], L Bruckner-Tuderman[5], A Evans[6], JA McGrath[7], CM Proby[1], J Foerster[1], IM Leigh[1] and AP South[1]

Oncogene. 2011 30(46):4666-77. PMID: 21602893 PMCID: PMC3219832

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Rigosertib identified as lead PLK1 inhibitor in RDEB cSCC

Translational Cancer Mechanisms and Therapy

Clinical Cancer Research

Identification of Rigosertib for the Treatment of Recessive Dystrophic Epidermolysis Bullosa–Associated Squamous Cell Carcinoma

Velina S. Atanasova[1], Celine Pourreyron[2], Mehdi Farshchian[1], Michael Lawler[1], Christian A. Brown IV[1], Stephen A. Watt[2], Sheila Wright[2], Michael Warkala[1], Christina Guttmann-Gruber[3], Josefina Piñón Hofbauer[3], Ignacia Fuentes[4,5], Marco Prisco[1], Elham Rashidghamat[6], Cristina Has[7], Julio C. Salas-Alanis[8], Francis Palisson[4,9], Alain Hovnanian[10,11], John A. McGrath[6], Jemima E. Mellerio[6], Johann W. Bauer[3], and Andrew P. South[1]

Clin Cancer Res March 7 2019 DOI:10.1158/1078-0432.CCR-18-2661. PMID: 30846478

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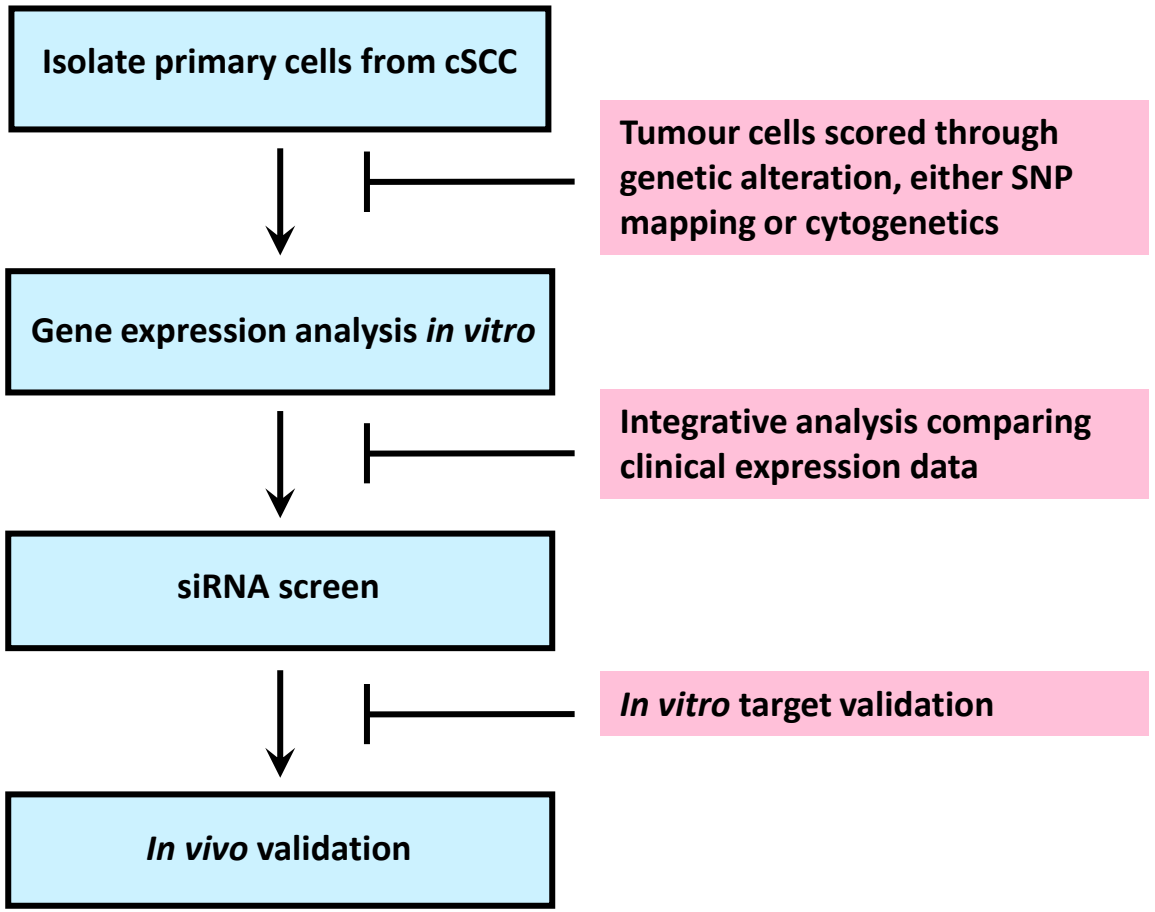
Polo-like kinase-1 identified as a therapeutic target in RDEB cSCC



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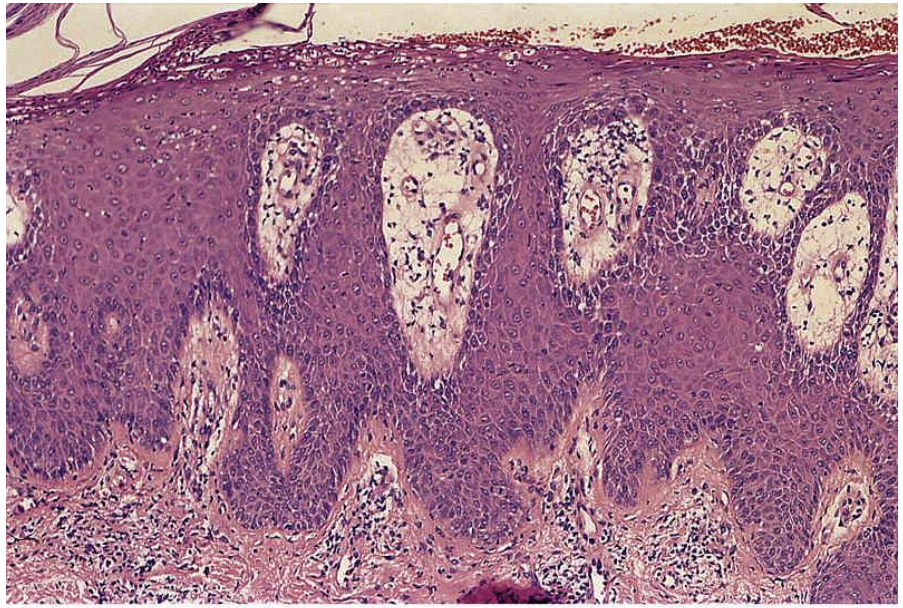
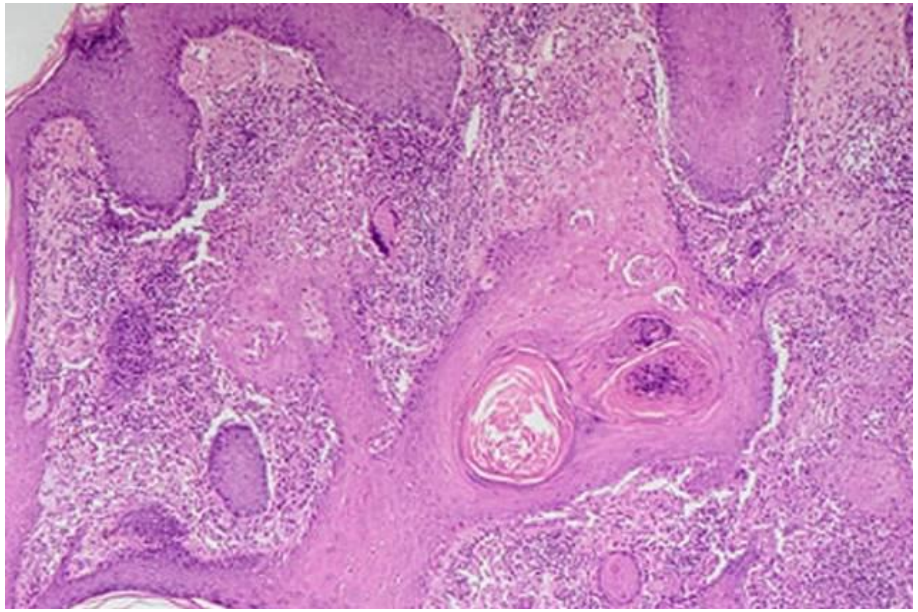


Psoriasis skin = benign



SCC = malignant

Oncogene. 2011 30(46):4666-77. PMID: 21602893 PMCID: PMC3219832

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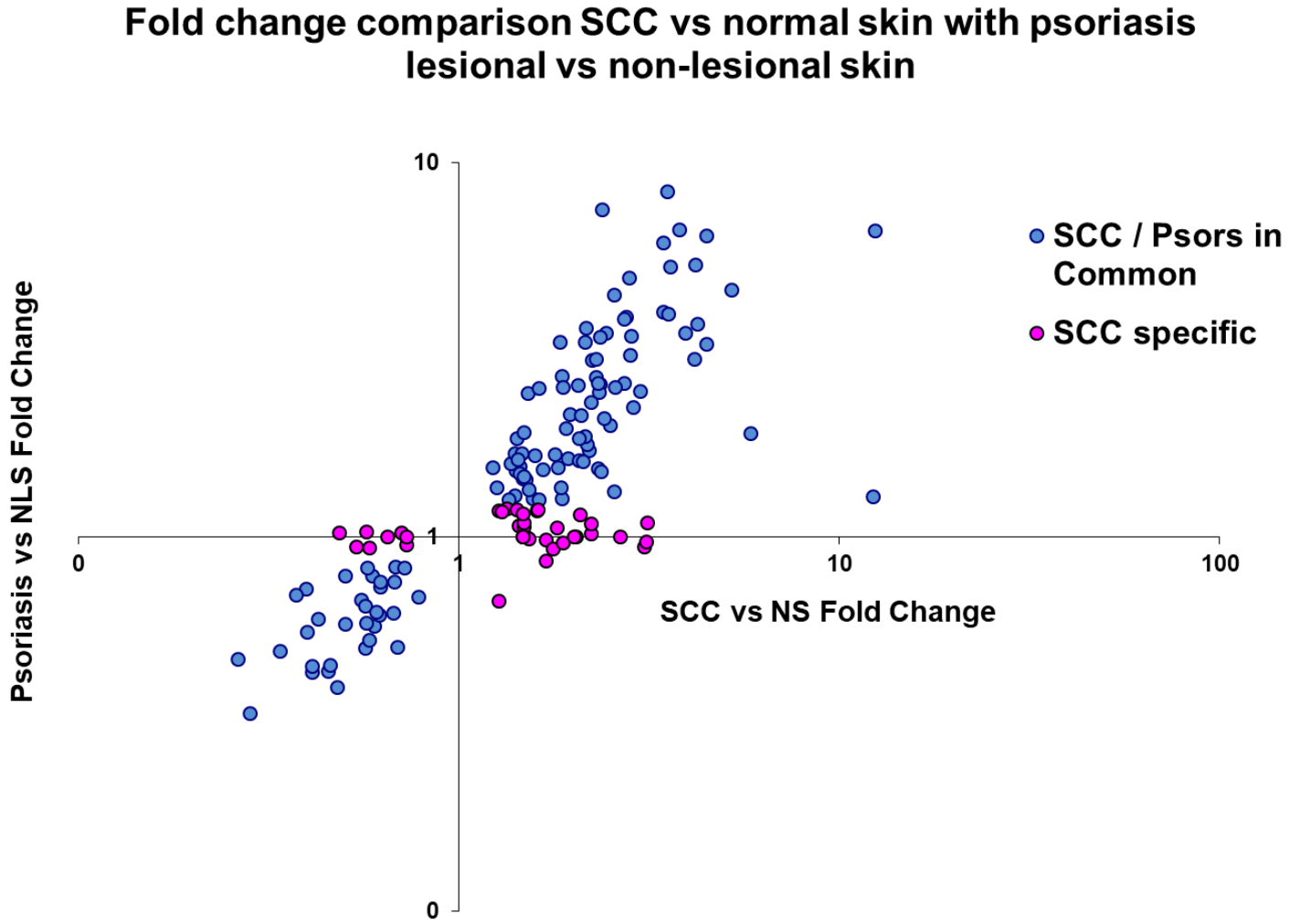

Oncogene. 2011 30(46):4666-77. PMID: 21602893 PMCID: PMC3219832

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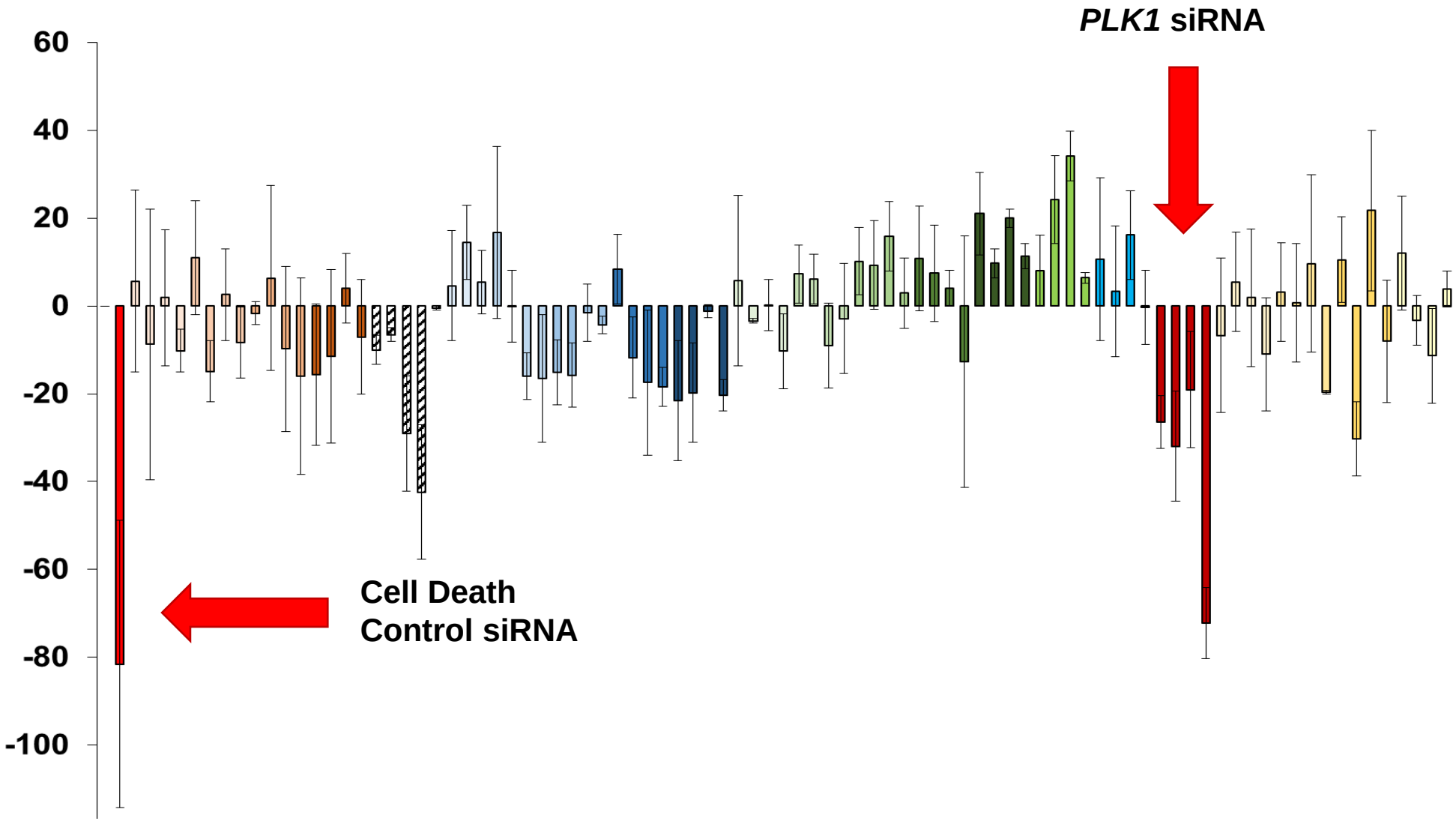

Oncogene. 2011 30(46):4666-77. PMID: 21602893 PMCID: PMC3219832

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Rigosertib identified as lead PLK1 inhibitor in RDEB cSCC

Inhibitor	Pharma	Supplier	PLK1 IC50	Clinical trial	Delivery	References
BI 2536	Boehringer Ingelheim, Ingelheim, Germany	Selleck Chemicals, Houston, TX	IC50 0.83nM	Phase II complete	IV	Steegmaier et al. Current Biology.2007 17(4):316-322
GW843682X	GlaxoSmithKline, Middlesex, UK	Tocris Biosciences, Bristol, UK	IC50 2.2nM			Lansing et al (2007) Mol.Cancer Ther. 6 450.
GSK461364	GlaxoSmithKline, Middlesex, UK	Selleck Chemicals, Houston, TX	IC50 2.2nM EC50 <100nm in cell lines	Phase I complete	IV	Sato Y et al. Bioorg Med Chem Lett. 2009 19(16):4673-8.
TKM-080301	Tekmira Pharmaceuticals Corporation			Phase I recruiting	IV	
NMS-1286937	Nerviano Medical Sciences, Milano, Italy	Active Biocehmical Co., Ltd. or Jihpharma		Phase I recruiting	Oral	Beria et al., Presented at EORTC-NCI-AACR 2008; Geneva, Switzerland.
BI 6727	Boehringer Ingelheim, Ingelheim, Germany	Shanghai Sun-shine Chemical Technology Co., Ltd.		Phase II recruiting	IV	Rudolph et al., Presented at EORTC-NCI-AACR Geneva, Switzerland, 2008.
CYC-800	Cyclacel Ltd, Dundee, UK		EC50 low nM range		Oral	AACR 2010 abstract
TAK-960	Millennium Pharmaceuticals, Inc.			Phase I recruiting	Oral	
ON-01910	Onconova Therapeutic, Newtown, PA	Selleck Chemicals, Houston, TX	IC50 9nM EC50 50-250nM	Phase II recruiting	IP	Gumireddy K et al. Cancer Cell. 2005 7(3):275-86.
HMN-214	Nippon Shinyaku Co. Ltd, Kyoto, Japan	Selleck Chemicals, Houston, TX	EC50 118nM		Oral	Tanaka H et al. Cancer Res. 2003 63:6942-7
5-(5,6-Dimoxy-1*H*-benzi-1-yl)-3-[[4-(methylsulfonyl)phenyl]methoxy]-2-T.		OTAVA Ltd, Toronto, Canada	IC50 6.9nM			
ZK-Thiazolidinone (TAL)	Bayer Schering Pharma AG	N/A	IC50 19nM Cell lines EC50 0.2-1.3uM			Santamaria et al (2007) Mol Biol Cell 18, 4024-4036
DAP-81	Rockefeller University, New York		IC50 0.9nM			Peters et al., Nat Chem Biol 2006;2:618–626.

Clin Cancer Res March 7 2019 DOI:10.1158/1078-0432.CCR-18-2661. PMID: 30846478

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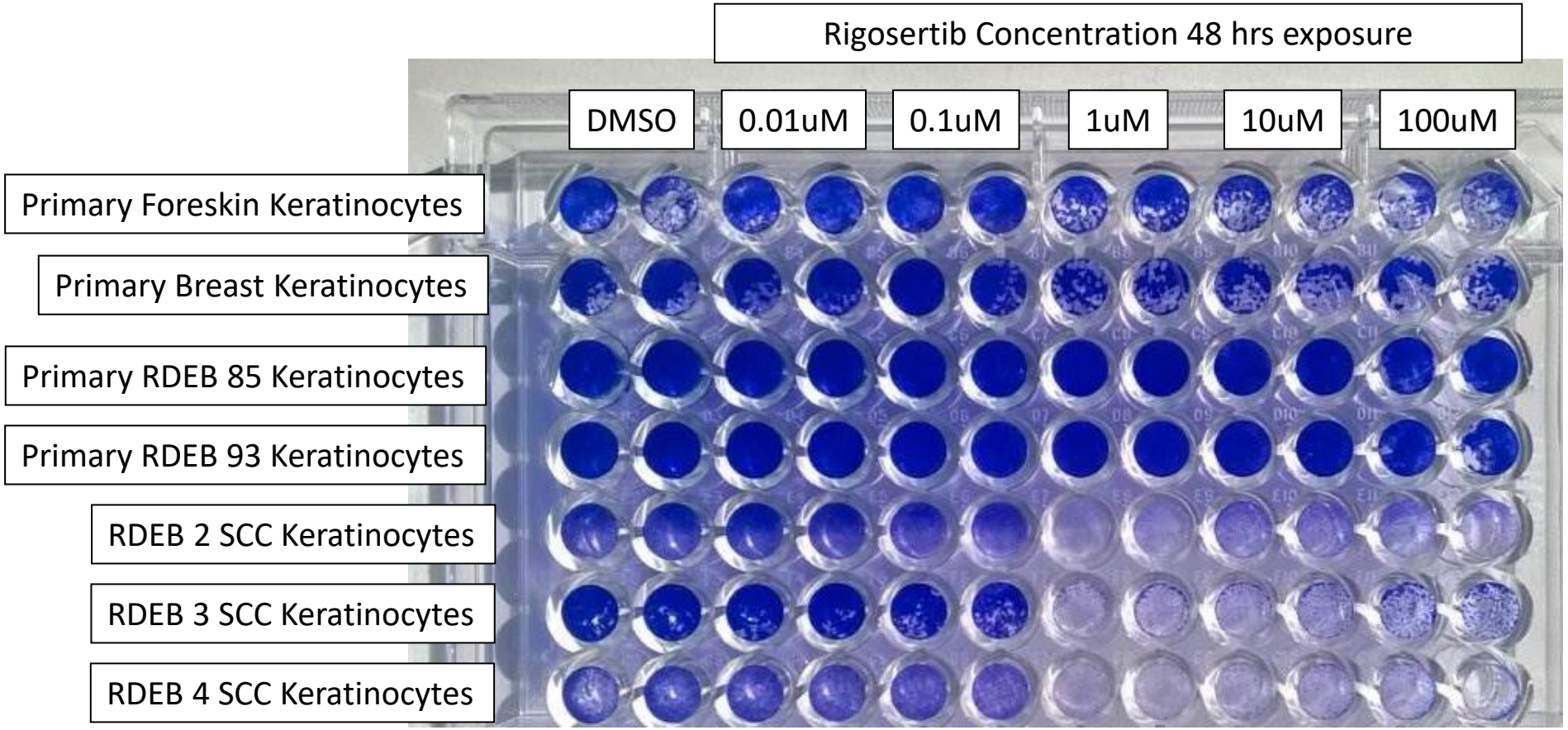

Clin Cancer Res March 7 2019 DOI:10.1158/1078-0432.CCR-18-2661. PMID: 30846478

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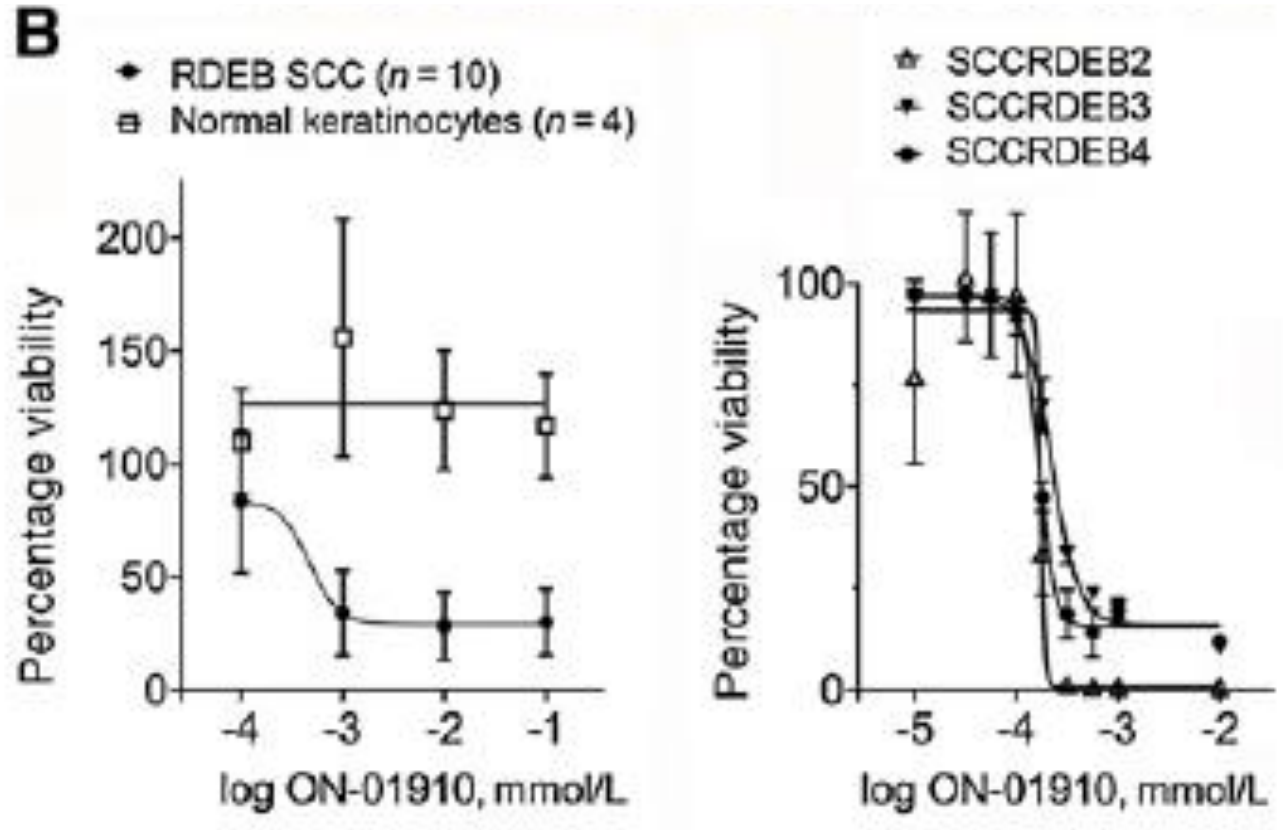

Clin Cancer Res March 7 2019 DOI:10.1158/1078-0432.CCR-18-2661. PMID: 30846478

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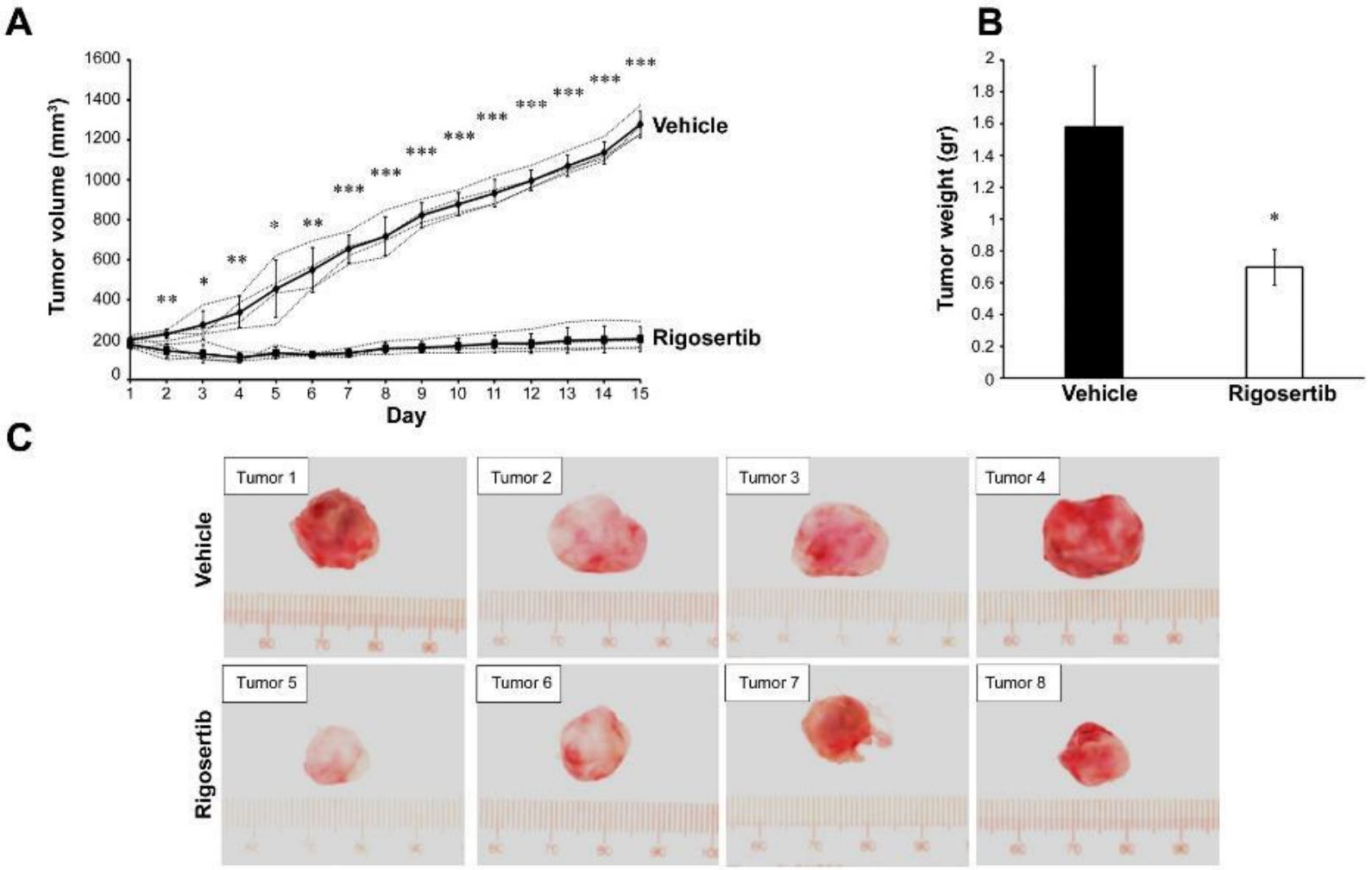

Clin Cancer Res March 7 2019 DOI:10.1158/1078-0432.CCR-18-2661. PMID: 30846478

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Rigosertib: IV or oral delivery

Published OnlineFirst February 3, 2014; DOI: 10.1158/1078-0432.CCR-13-2506

Clinical Cancer Research

Cancer Therapy: Clinical

Phase I Study of Oral Rigosertib (ON 01910.Na), a Dual Inhibitor of the PI3K and Plk1 Pathways, in Adult Patients with Advanced Solid Malignancies

Daniel W. Bowles[1], Jennifer R. Diamond[1], Elaine T. Lam[1], Colin D. Weekes[1], David P. Astling[1], Ryan T. Anderson[1], Stephen Leong[1], Lia Gore[1], Marileila Varella-Garcia[1], Brian W. Vogler[1], Stephen B. Keysar[1], Elizabeth Freas[1], Dara L. Aisner[2], Chen Ren[3], Aik-Chook Tan[1], Francois Wilhelm[3], Manoj Maniar[3], S. Gail Eckhardt[1], Wells A. Messersmith[1], and Antonio Jimeno[1]

Clin Cancer Res Feb 3 2014 DOI:10.1158/1078-0432.CCR-13-2506 MID:

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Rigosertib: low toxicity profile

Clin Cancer Res Feb 3 2014 DOI:10.1158/1078-0432.CCR-13-2506 MID:

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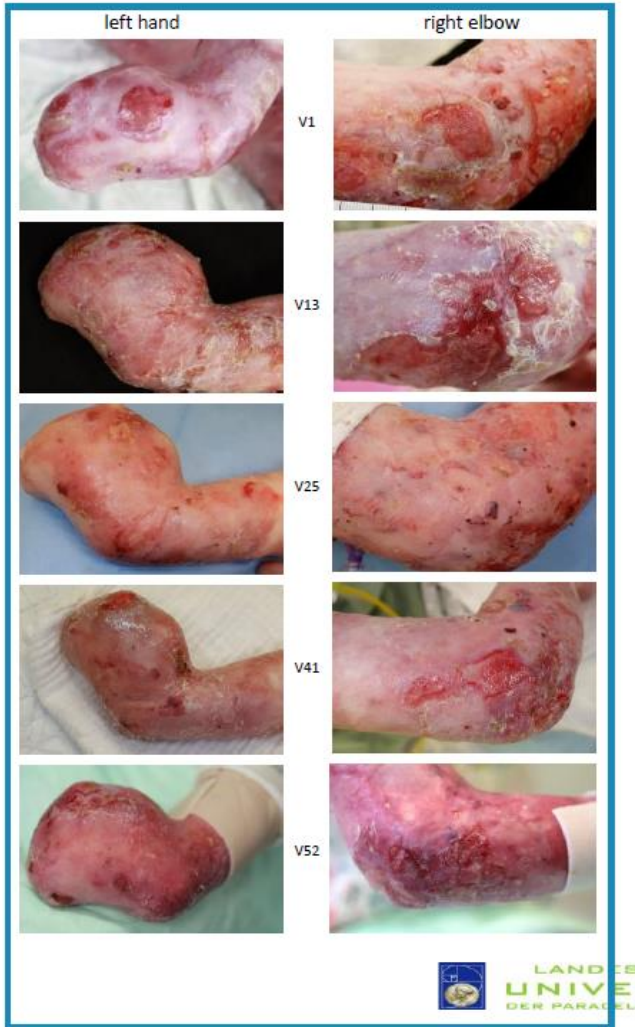
NCT03786237

Austrian Rigosertib Trial

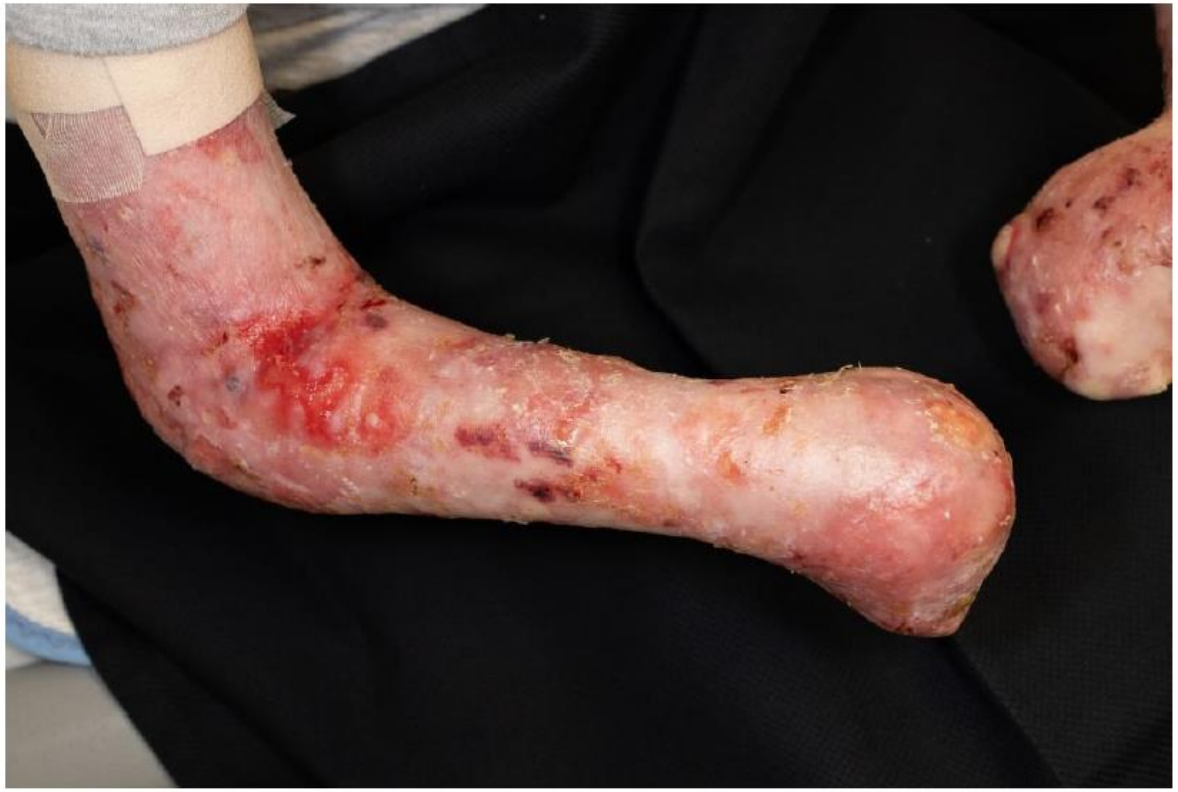
Johann Bauer, MD

Patient AT-01_01

April 21 -April 22



December 22



Presented at the annual meeting of the Austrian Society of Dermatology and Venerology, virtual 2021

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eb Haus
Austria

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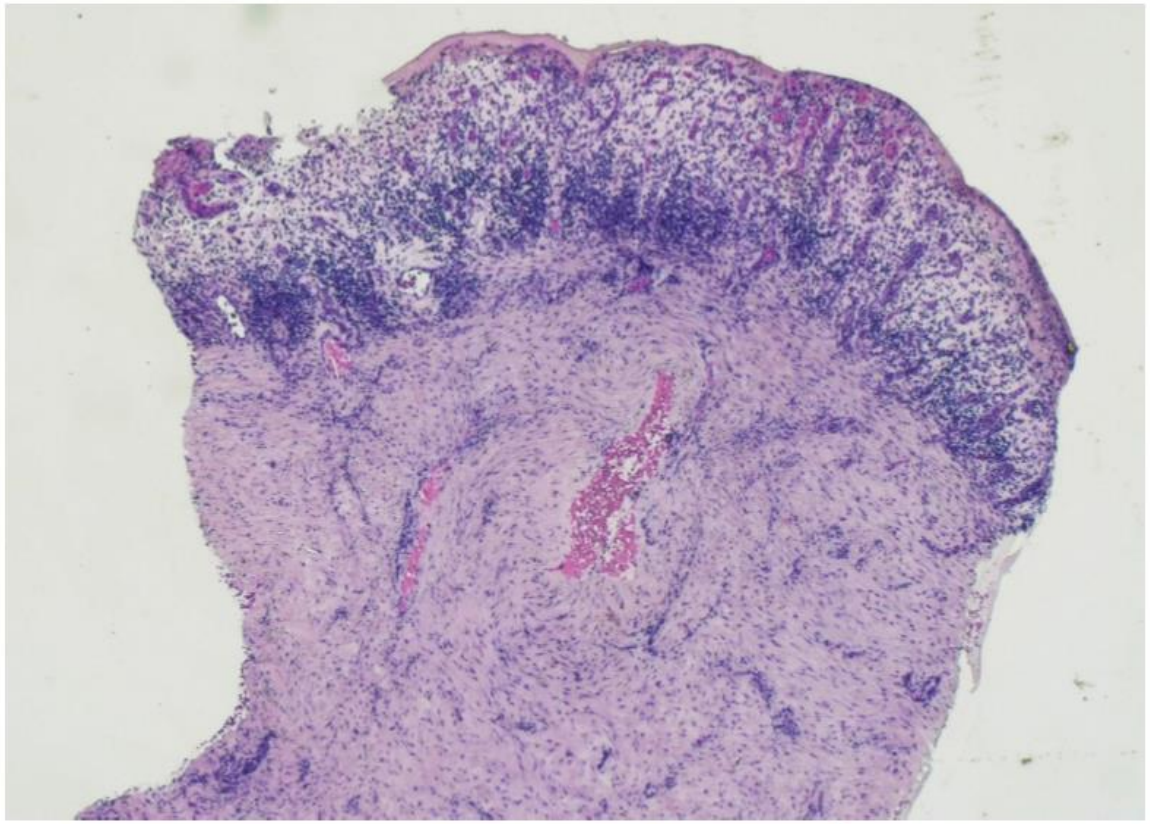
ri. elbow: August 2021, 8 cycles_V15; granulation tissue



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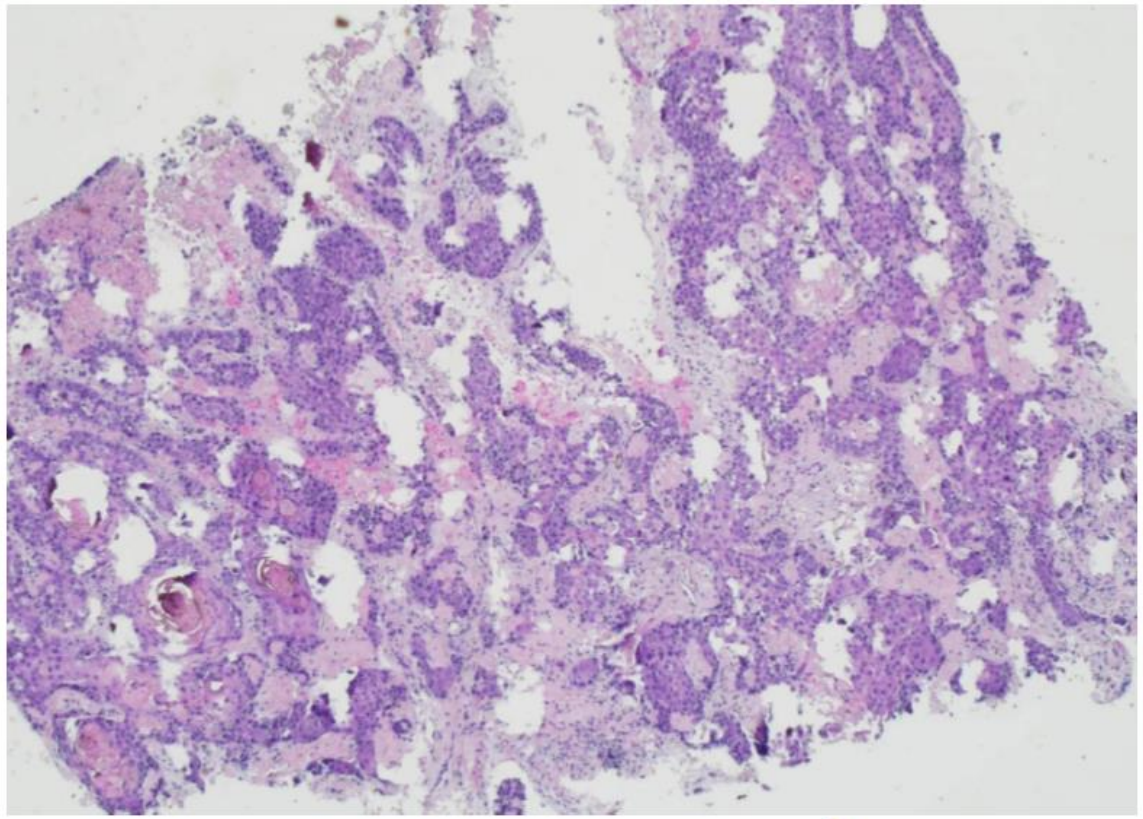
Recurrence 02/23: 8/10

ri. hand

No systemic metastases (04/23)



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Patient AT-01_02

TU initial (3/23)

TU follow up (4/23): 3 cycles

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NCT04177498

USA Rigosertib Trial

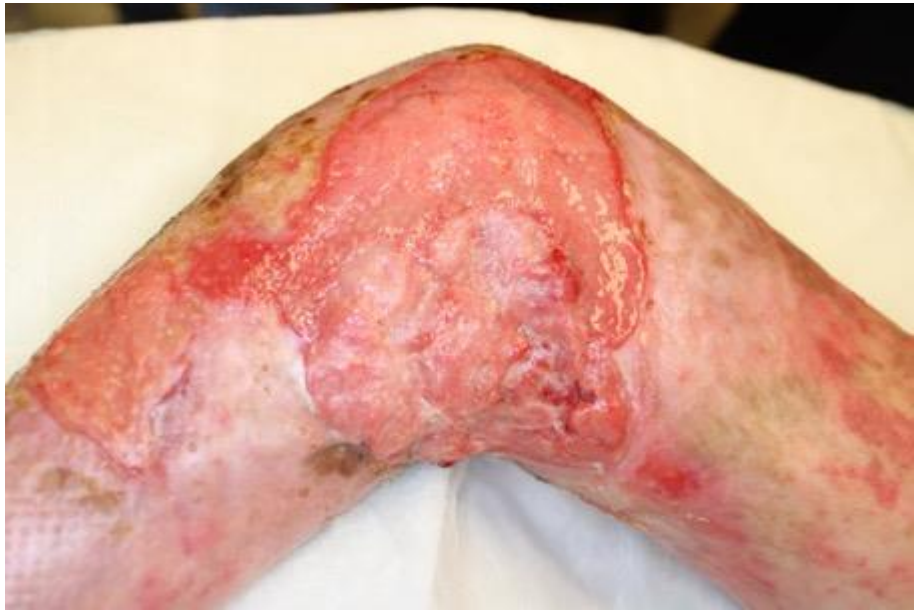
Neda Nikbakht, MD, PhD, FAAD

Lauren Banner, Linda Hosler, Alexa Cohen

NCT04177498:

“A Pilot, Open Study to Assess Efficacy and Safety of Rigosertib in Patients With Recessive Dystrophic Epidermolysis Bullosa Associated Locally Advanced/Metastatic Squamous Cell Carcinoma”

USA site: Thomas Jefferson University, Philadelphia, PA
Status: Active and Enrolling , oral arm is recruiting



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USA Trial: NCT04177498

Study Population: RDEB patients with advanced SCC who have failed prior standard of care.

Primary Objectives:

- **To estimate the anti-tumor activity of oral or IV rigosertib** by determining the overall response rate, defined as the proportion of patients who achieve either a complete response or a partial response by RECIST v1.1 criteria

- **To evaluate the safety and tolerability** of oral rigosertib administered daily three weeks on, one week off for 12 cycles or IV rigosertib administered as continuous 72h IV infusions once every two weeks for 8 cycles and then once every 4 weeks thereafter

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Jefferson Patient

HPI: A 32-year-old woman with RDEB and history of several cutaneous SCCs with nodal involvement who failed multiple treatment modalities presented to Jefferson in 2022.

Prior treatments:

- Excision: left hand, scalp SCC (2015)
- Mohs: right and left arm SCC (2015), left wrist SCC (2017)
- **Cetuximab** (2016)
- **Pembrolizumab** (11/2018-1/2019, 4 cycles)
- Excisions: right hip, thigh, arm, ankle, foot, left hand, wrist, thigh, knee (2020-2022)

Medical history:

- Esophageal Strictures
- Malnutrition
- Loss of teeth
- Anemia

Medications:

- Iron infusions, PRN
- Gabapentin, PRN
- Ibuprofen, PRN
- Acetaminophen with codeine, PRN
- Hydroxyzine, PRN

Banner, et al. poster 613, ISID 2023

Nodal Involvement at Enrollment:

- **Before Pembrolizumab: (**10, 2018) Left axillary lymph node core needle biopsy demonstrated squamous cell carcinoma
- **Pembrolizumab** (11/2018-1/2019, 4 cycles) discontinued due to autoimmune sequelae
- **After Pembrolizumab:** (4, 2019) Left axillary lymph node dissection suggested metastatic squamous cell carcinoma
- **At Enrollment:** (9, 2022) Multiple enlarged lymph nodes on imaging, none were eligible as target lesions per RECIST v1.1

Banner, et al. poster 613, ISID 2023

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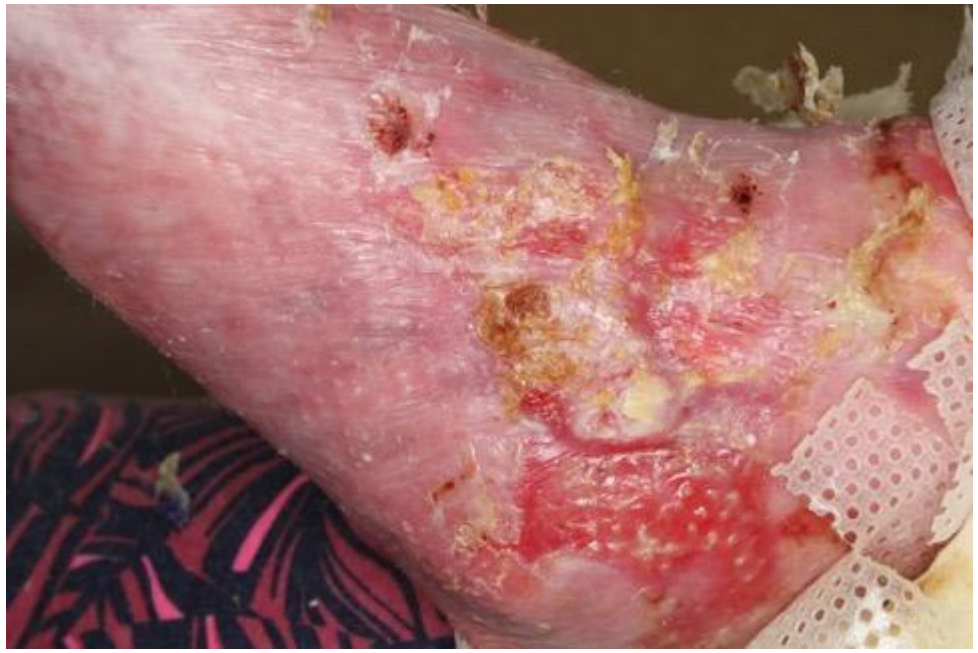
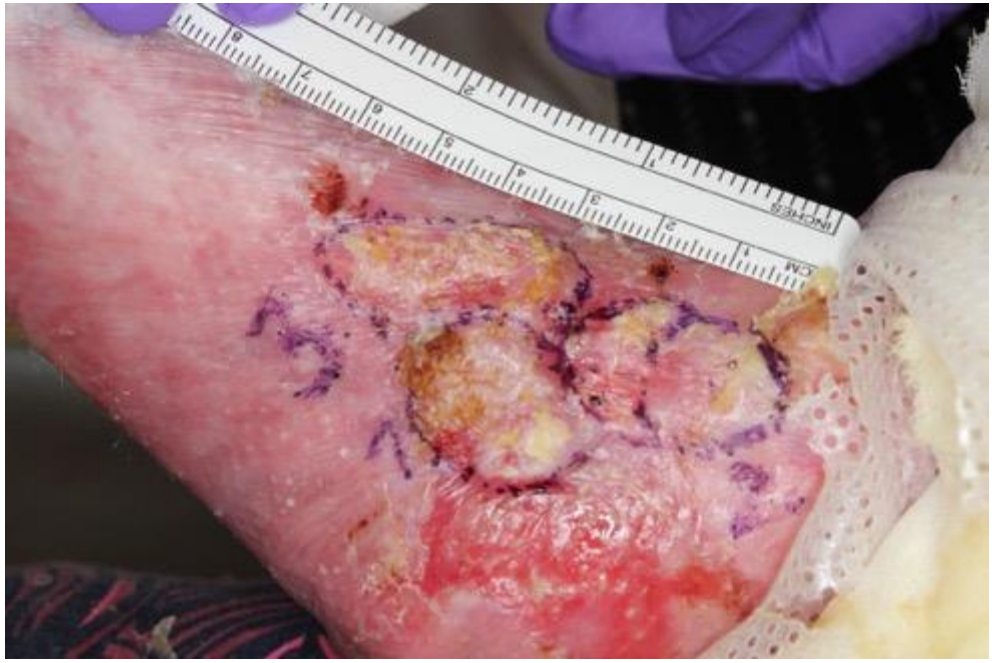
Skin Involvement at Enrollment:





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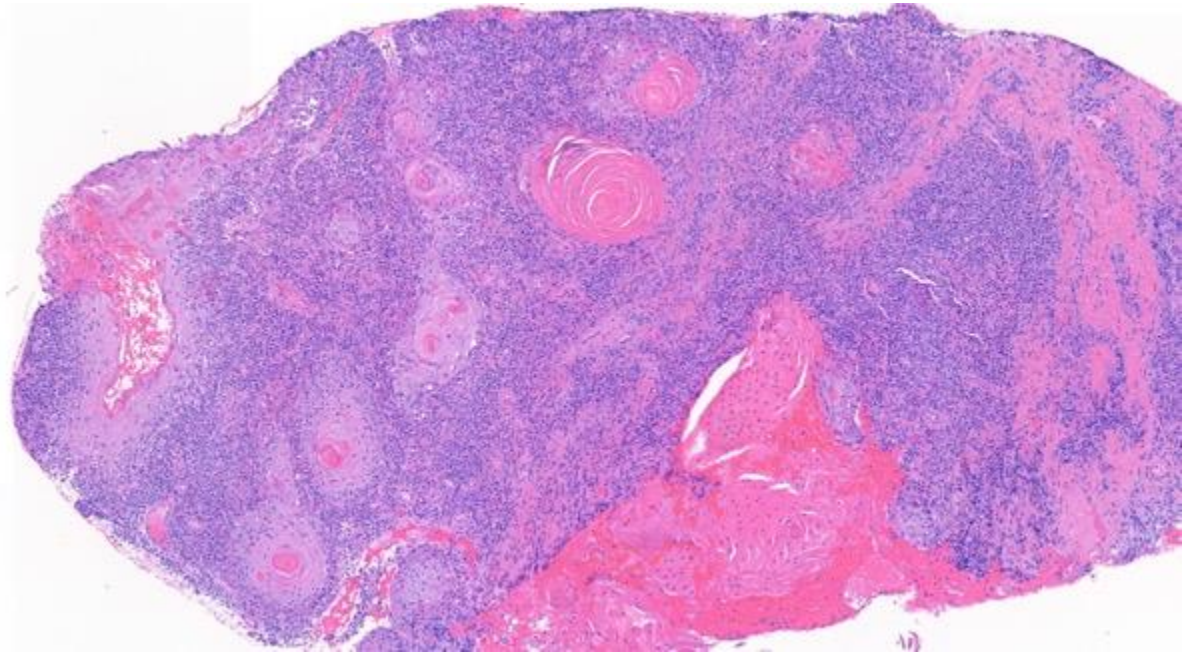
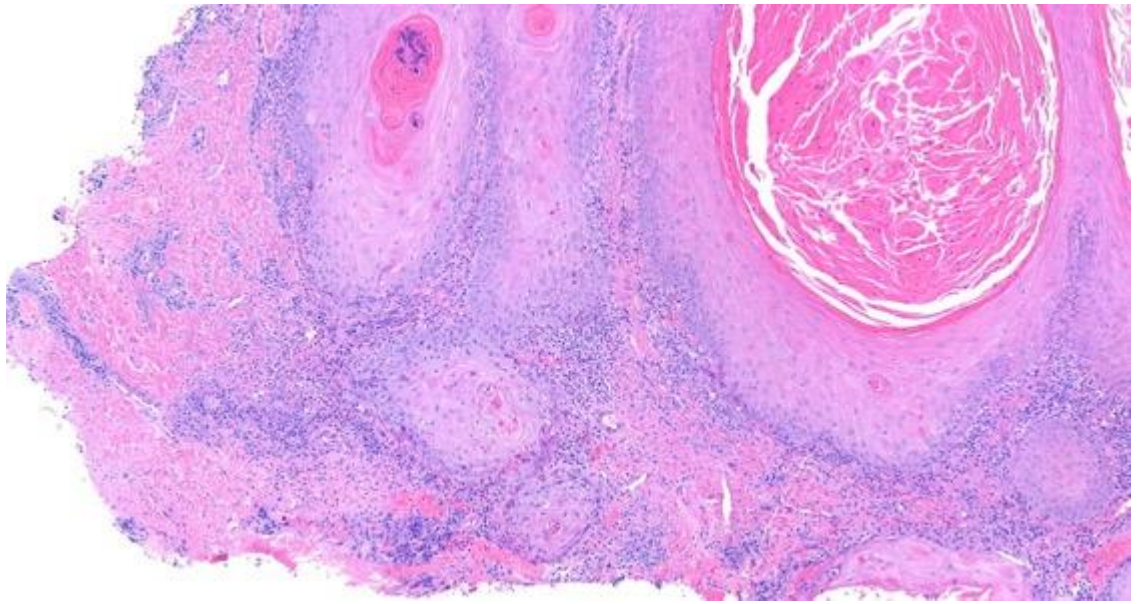
Skin Involvement at Enrollment:





Left elbow: Squamous Cell Carcinoma

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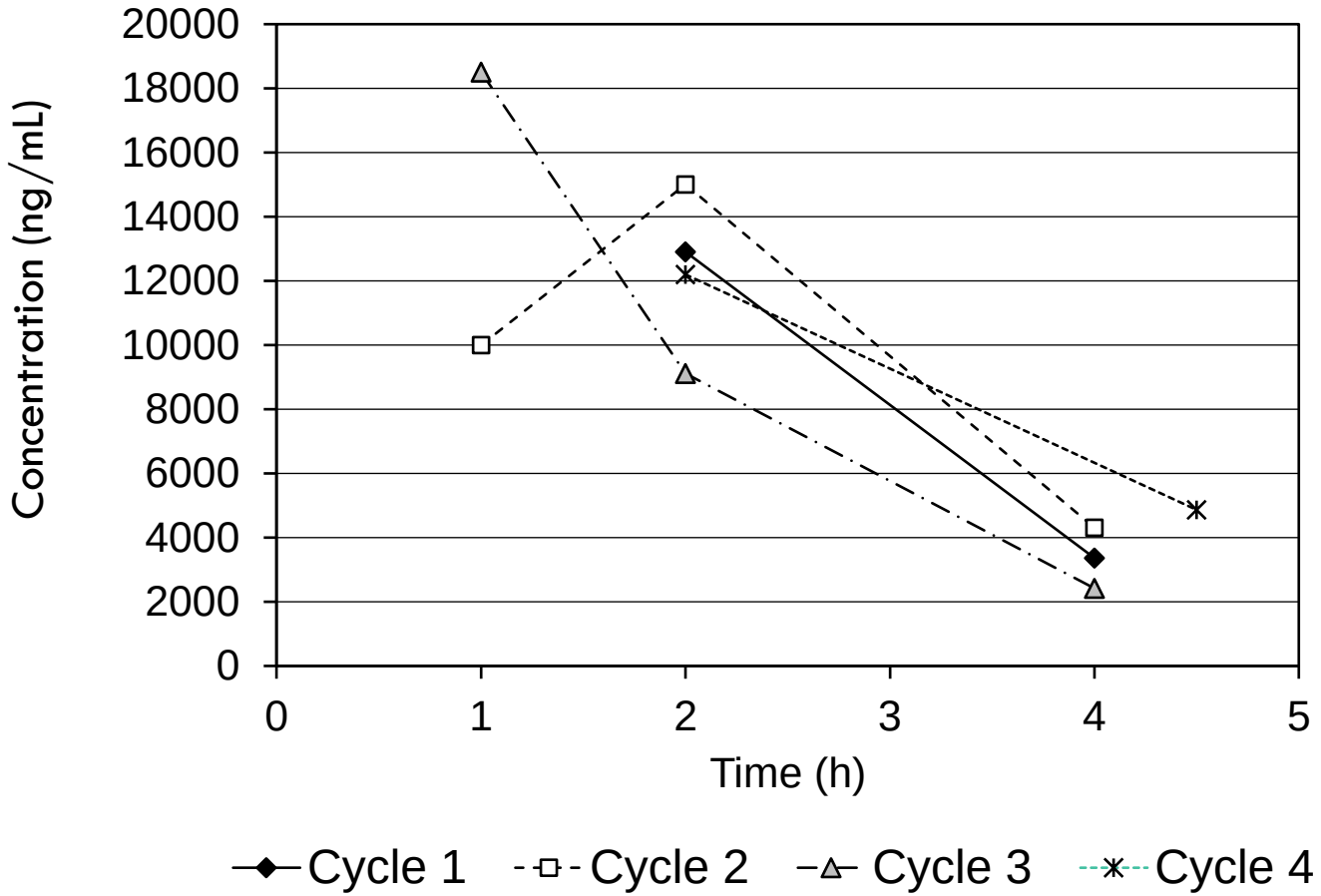
Oral Rigosertib produces levels in blood comparable to non-RDEB patients

Dosing: 560 mg BID, 3 weeks on, one week off



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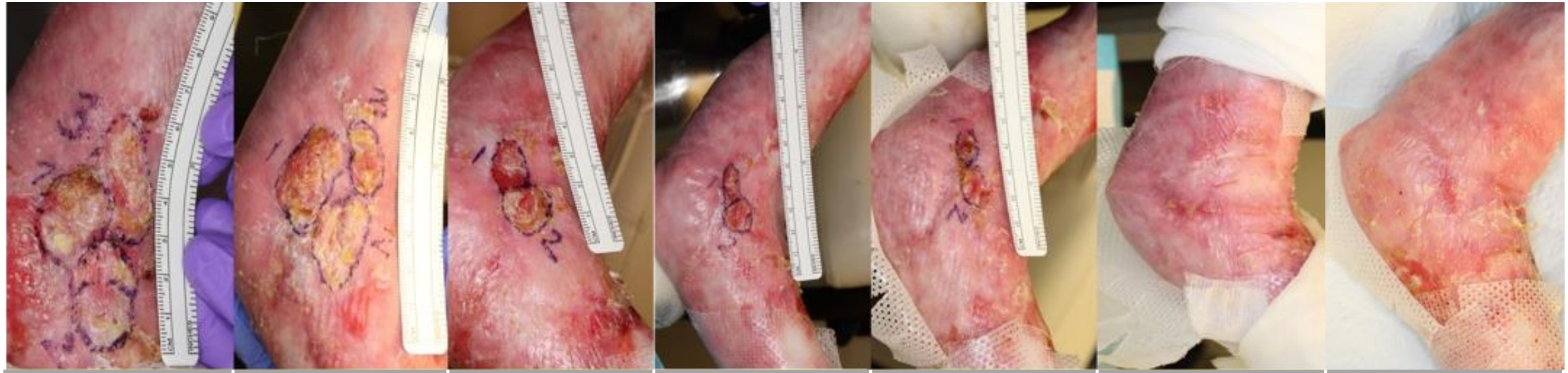
Patient achieved complete clinical remission with oral Rigosertib



Baseline	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycles 6-8
1045 mm^2	770 mm^2	453 mm^2	337.5 mm^2	248 mm^{2*}	0 mm^2	0 mm^2

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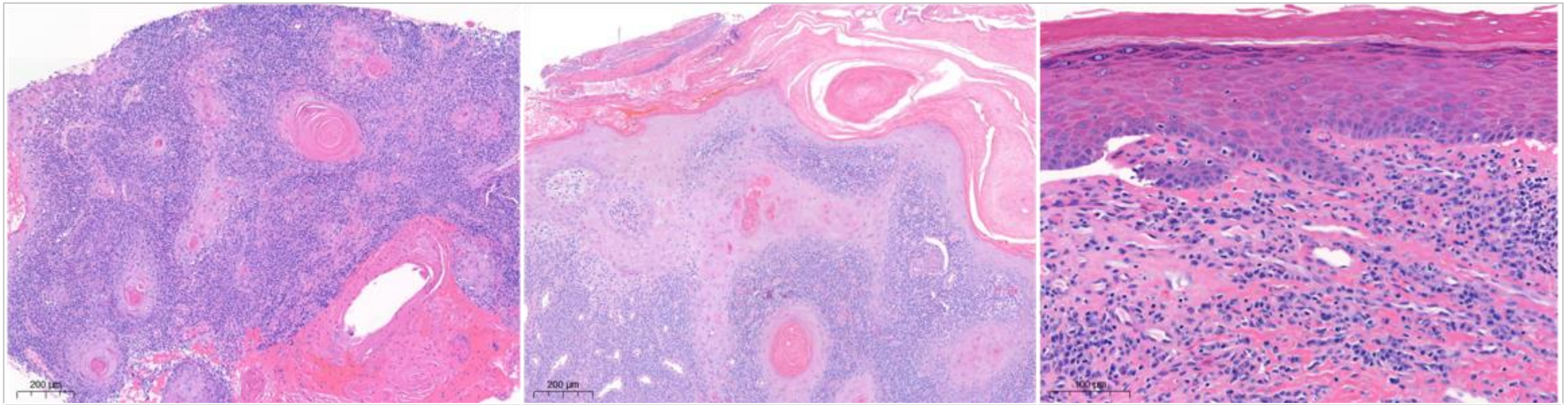
Patient achieved complete histological remission with oral Rigosertib



Baseline	Cycle 4	Cycle 6
SCC, invasive	SCC, resolving superficial	Scar

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Challenges: Urinary symptoms

- Patient experienced urinary urgency and frequency often
  - Trial of Oxybutynin (not helpful), Mirabegron (slightly more helpful)

- Patient experienced grade 3 hematuria leading to dose reduction
  - Sodium bicarbonate, Phenazopyridine, hydration

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Challenges:

- Difficulty with oral intake
  - Protocol was most recently amended to allow modification of oral intake for patients with esophageal strictures or G-tubes
  - Dissolving capsules in water before intake
  - Allowing administration of dissolved medication through G-tube
- Venous access issues
  - Prioritizing and balancing studies requiring IV access
- Medical insurance coverage
  - Patients traveling out of state (Michigan and New York)

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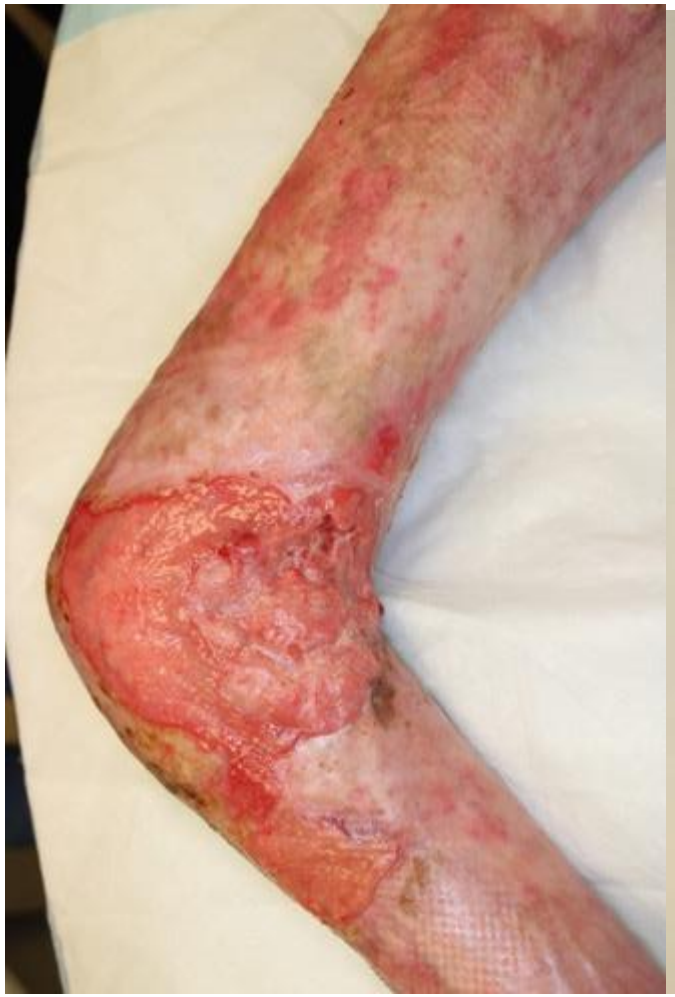
Second patient from New York was enrolled last week at Jefferson



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Steven Fruchtman, M.D
President and CEO
Onconova Therapeutics

Rigosertib's Current Status and Potential Next Steps

Including but not limited to:

- Continue enrollment for the Phase 1/2a trial of oral rigosertib + nivolumab in KRAS-mutated, CPI resistant, non-small cell lung cancer
- Identification of additional sites and patients for the RDEB-associated SCC trial
- Initiation of investigator-sponsored study of oral rigosertib + pembrolizumab in patients with CPI resistant melanoma
- Ongoing preclinical studies in various RASopathies
- Preclinical combinations studies with sotorasib and other combinations of interest


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Thank You!
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