NCI's Patient-Derived Models Repository (PDMR)

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An NCI Precision Oncology Initiative℠ Resource

Frederick National Lab Advisory Committee

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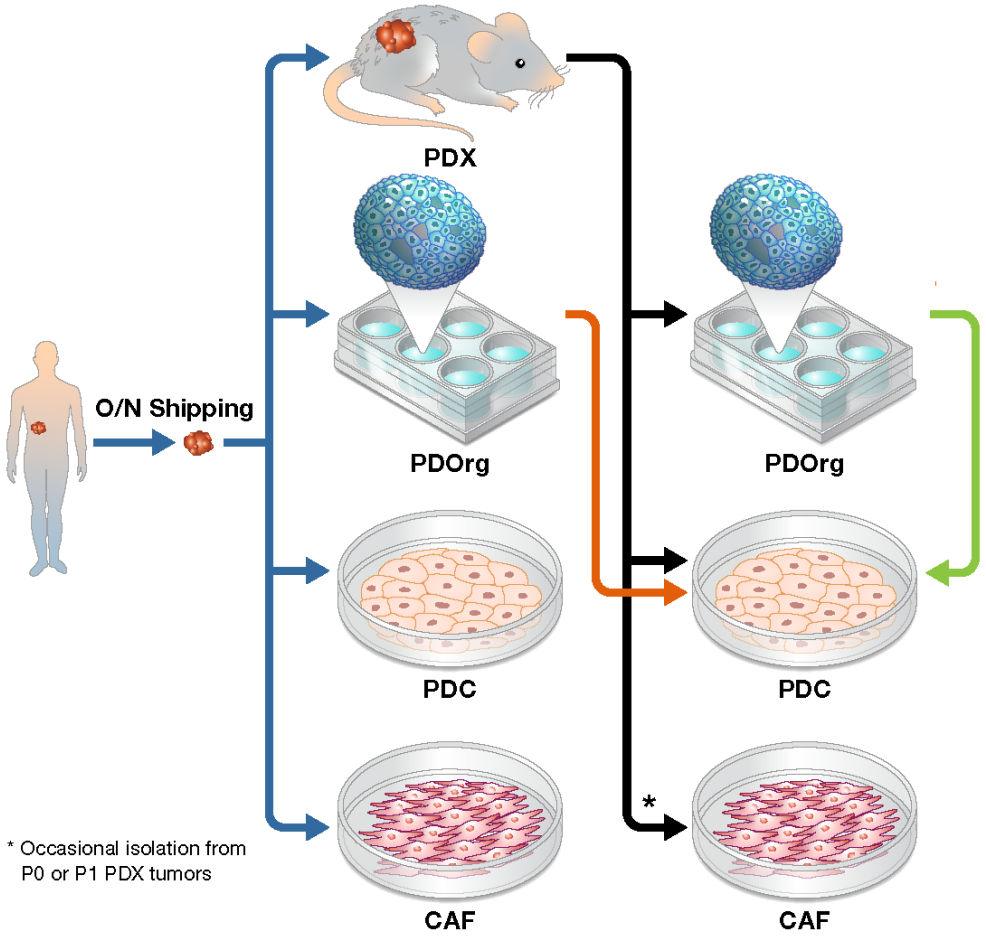
OUTLINE

- ✓NCI PDMR Models: Model Development and Distribution
- ✓Preclinical Studies: Nilotinib + Paclitaxel: Potential Mechanism of Action
- ✓PDXNet: Standardizing Reporting of Preclinical Tumor Volume Response

NCI's Patient-Derived Models Repository (PDMR)

- A national repository of Patient-Derived Models (PDMs) to serve as a resource for academic discovery efforts and public-private partnerships for drug discovery
- **Clinically-annotated** & **early-passage** models with comprehensive **molecular-characterization** and quality control metrics
- Complement existing PDM collections and focus on under-represented model types such as rare cancers and models representing racial and ethnic minorities
- Provide models to the research community at a modest cost compared to other distributors
- Provide all related metadata including: deidentified patient clinical history and outcomes, model histology, WES and RNASeq of models, and SOPs through a public website: https://pdmr.cancer.gov



NCI PDMR: Model Development and Distribution

NIH NATIONAL CANCER INSTITUTE

PDX Take-Rate from Fresh Tumor Tissue Implantations

✓ All tumor material collected and shipped priority overnight in CO2-independent media for next-day implantation into NSG host mice

Body Location	Total Specimens Received	Total Assessable Specimens	%Take-Rate of Assessable Specimens	Passageable Tumor	Discontinued†	*Not Yet Assessable: P0 tumors*
Breast	517	469	10%	48	421	48
Digestive/ Gastrointestinal	592	568	45%	254	314	24
Endocrine/ Neuroendocrine	252	224	9%	21	203	28
Genitourinary	549	507	16%	79	428	42
Germ Cell	22	17	18%	3	14	5
Gynecologic	650	553	30%	167	386	97
Head and Neck	288	254	53%	134	120	34
Hematologic/Blood	22	21	10%	2	19	1
Musculoskeletal	452	422	30%	126	296	30
Neurologic	6	6	17%	1	5	0
Respiratory/Thoracic	242	229	29%	67	162	13
Skin	117	100	59%	59	41	17
Unknown Primary	27	24	29%	7	17	3
Totals	**3736**	**3394**	**29%**	**968**	**2426**	**342**

PDX Take-Rate: Sarcomas

			%Take-Rate by Site			# Specimens by Site			%Take-Rate by Tx		#Specimens by Txt	
CTEP SDC Codes	Total Assessable Specimens	Overall %Take-Rate	Primary Lesion	Metastatic Lesion	Unknown Site	#Primary	#Met	#UNK	Txt Naive	Prior Txt	Txt Naive	Prior Txt
Alveolar rhabdomyosarcoma	**2**	**50%**	**0%**	**100%**	**--**	1	1	0	**0%**	**100%**	1	1
Alveolar soft part sarcoma	**8**	**25%**	**0%**	**50%**	**0%**	2	4	2	**--**	**25%**	0	8
Chondrosarcoma	**16**	**25%**	**0%**	**67%**	**22%**	4	3	9	**20%**	**33%**	10	6
Dermatofibrosarcoma	**5**	**0%**	**0%**	**--**	**0%**	2	0	3	**0%**	**0%**	4	1
Ewing sarcoma/ Peripheral PNET	**5**	**60%**	**100%**	**100%**	**0%**	2	1	2	**100%**	**50%**	1	4
Fibrosarcoma - not infantile	**28**	**39%**	**38%**	**50%**	**38%**	13	2	13	**50%**	**29%**	14	14
Gastrointestinal stromal tumor	**68**	**16%**	**19%**	**11%**	**0%**	48	19	1	**11%**	**20%**	27	41
Leiomyosarcoma - not uterine	**37**	**22%**	**22%**	**25%**	**20%**	9	8	20	**31%**	**17%**	13	24
Leiomyosarcoma - uterus	**14**	**57%**	**100%**	**56%**	**0%**	3	9	2	**33%**	**64%**	3	11
Liposarcoma	**130**	**15%**	**13%**	**38%**	**16%**	71	8	51	**19%**	**12%**	70	60
Malignant fibrous histiocytoma	**24**	**50%**	**50%**	**100%**	**43%**	16	1	7	**80%**	**42%**	5	19
Non-Rhabdo. soft tissue sarcoma incl undifferentiated pleomorphic	**96**	**36%**	**29%**	**60%**	**44%**	52	5	39	**52%**	**29%**	33	63
Osteosarcoma	**11**	**36%**	**38%**	**100%**	**0%**	8	1	2	**0%**	**50%**	3	8
Rhabdomyosarcoma	**6**	**50%**	**100%**	**0%**	**50%**	1	1	4	**100%**	**25%**	2	4
Soft tissue neoplasm	**21**	**29%**	**60%**	**0%**	**21%**	5	2	14	**25%**	**31%**	8	13
Synovial sarcoma	**14**	**43%**	**25%**	**0%**	**56%**	4	1	9	**57%**	**29%**	7	7

PDX Model Generation from Rapid Autopsy Tissue

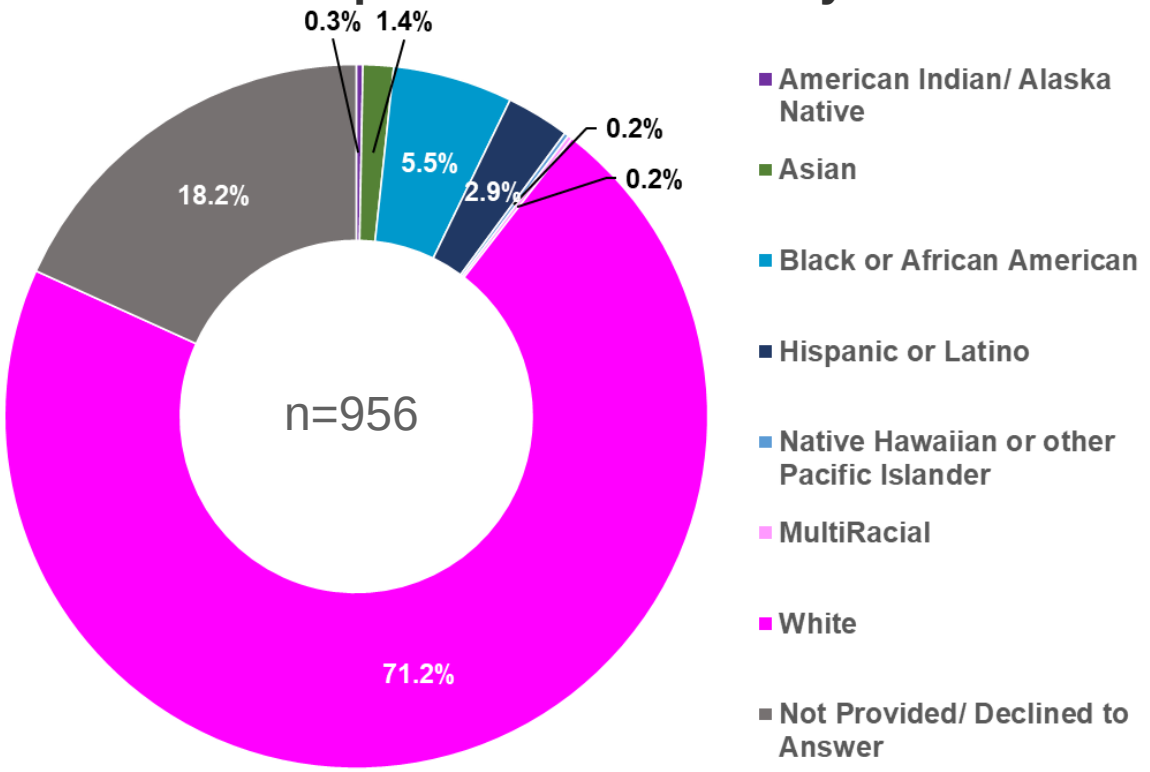
- ✓ 453 specimens from 82 unique patients (4-8 specimens/patient)
- ✓ Benefit: Multiple models from a single pateint from unique primary and metastatic lesions

Body Location	Total Specimens Received	Total Assessable Specimens	%Take-Rate of Assessable Specimens	Passageable Tumor*	Discontinued†	*Not Yet Assessable: P0 tumors*
Breast	5	5	0%	0	5	0
Digestive/ Gastrointestinal • Predominantly PAAD	324	308	**28%**	86	222	16
Endocrine/ Neuroendocrine	16	16	**13%**	2	14	0
Genitourinary	44	39	**5%**	2	37	5
Head and Neck	4	4	**25%**	1	3	0
Hematologic/Blood	2	2	0%	0	2	0
Musculoskeletal	21	21	0%	0	21	0
Neurologic	8	8	**13%**	1	7	0
Respiratory/Thoracic	21	21	**19%**	4	17	0
Skin	8	8	**75%**	6	2	0
Totals	**453**	**432**	**24%**	**102**	**330**	**21**

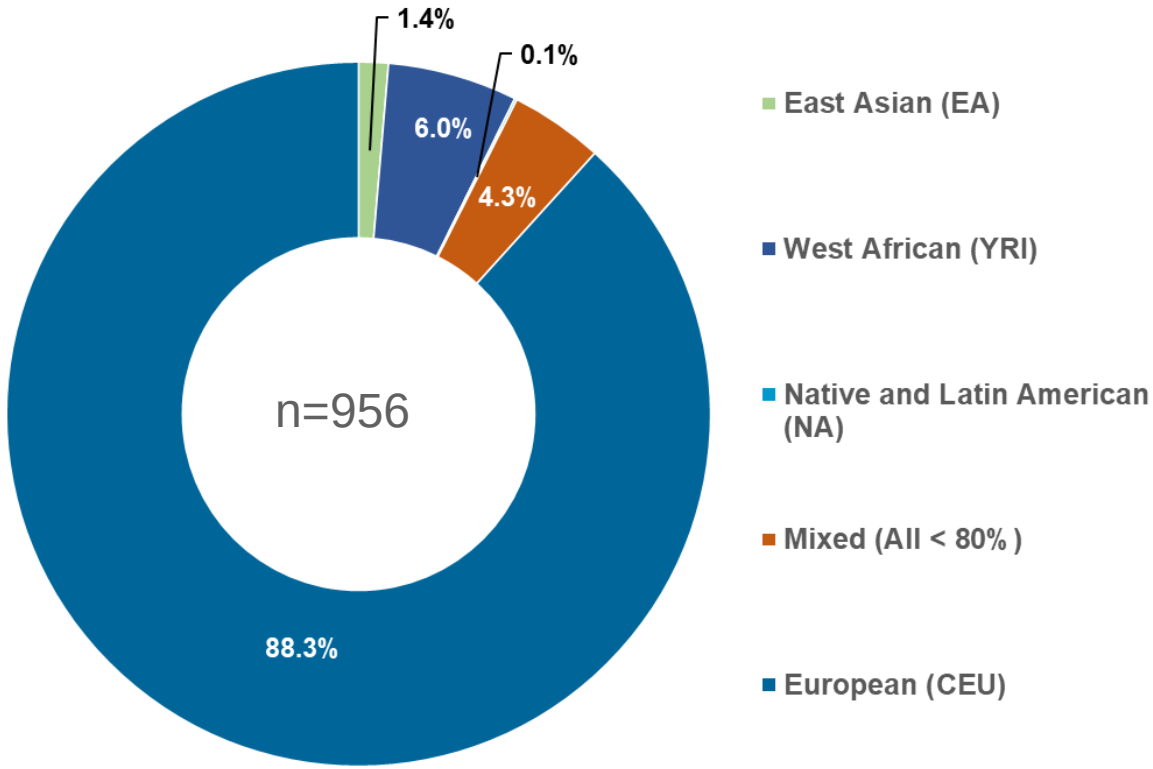
Self-Reported Race and Ethnicity and Genetic Ancestry for Successfully Generated NCI-PDMR Models

- ✓ 956 PDMR models have been sequenced to allow for additional genetic ancestry assessment
- ✓ 637 currently available to researchers

Patient Self-Reported Race/Ethnicity



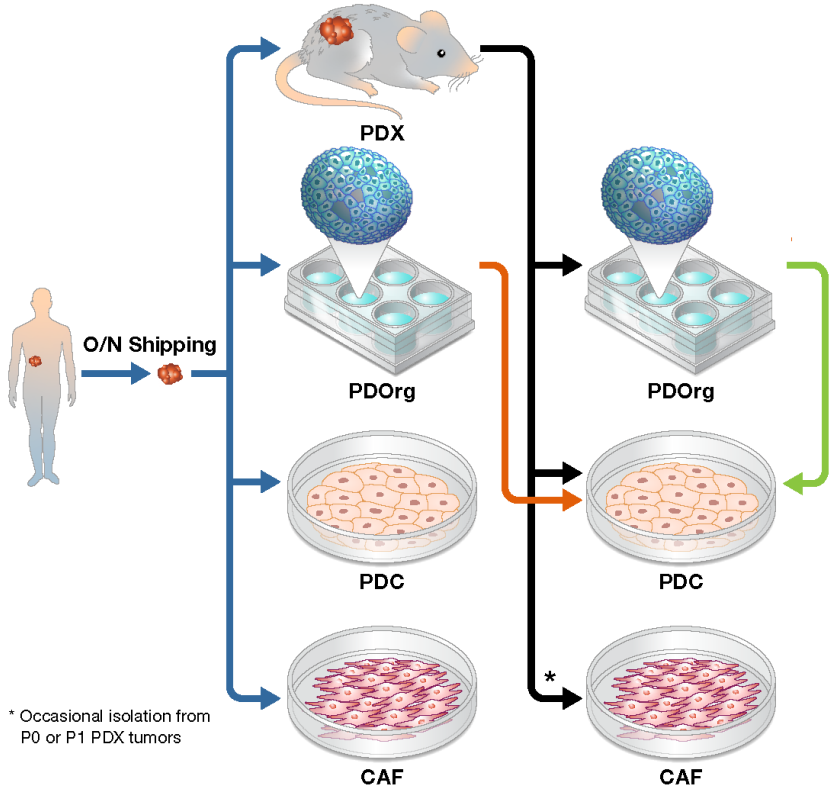
Inferred Genetic Ancestry (SNPWeights*)

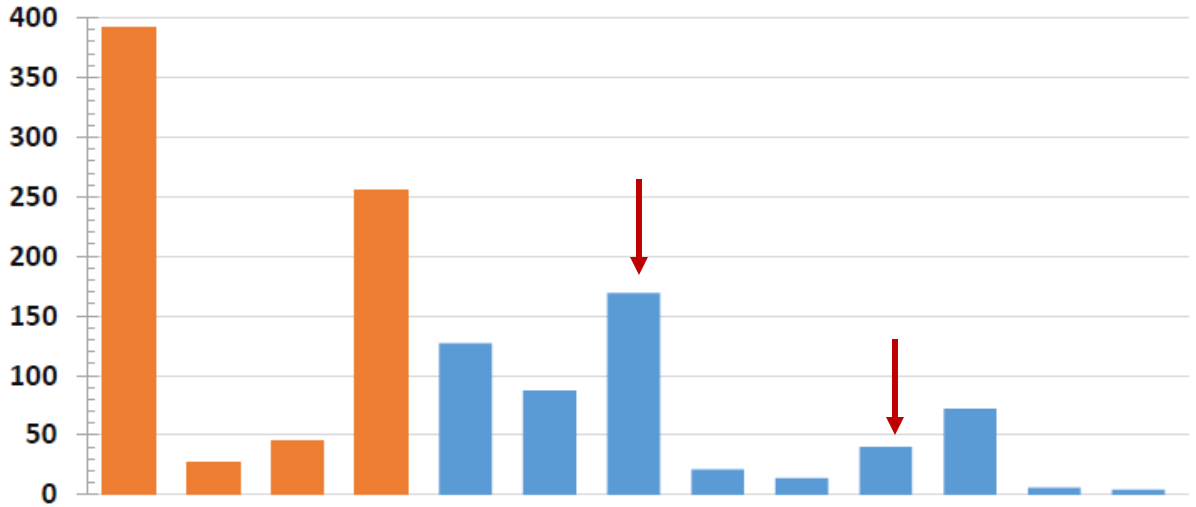


*NCI-PDMR is working with PDXNet and the UC Davis Minority PDTC on an updated genetic ancestry algorithm that provides a more robust call of Native and Latin American (NA) genetic ancestry

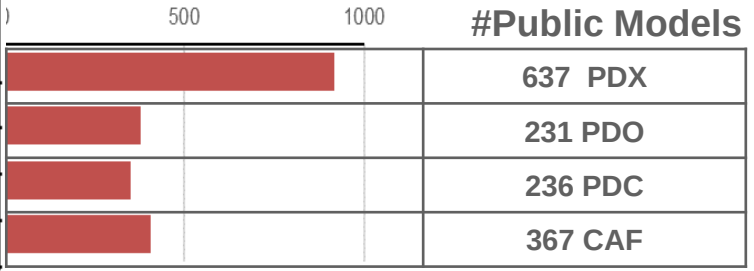
Multiple Model Types from Every Tumor Specimen

- ✓ Attempt to generate a PDX, PDOrg, PDC, and CAF from every tumor specimen received for translational research avenues
- ✓ 2098 Models Developed from 1265 Unique Patients





Total Individual	Total Intersect	392	27	45	256	127	87	169	21	14	40	72	6	4
922	PDX	■				■	■	■	■	■	■	■		
397	PDOrg		■			■		■	■		■		■	■
367	PDC			■			■	■		■	■		■	■
412	CAF				■				■	■	■	■		■

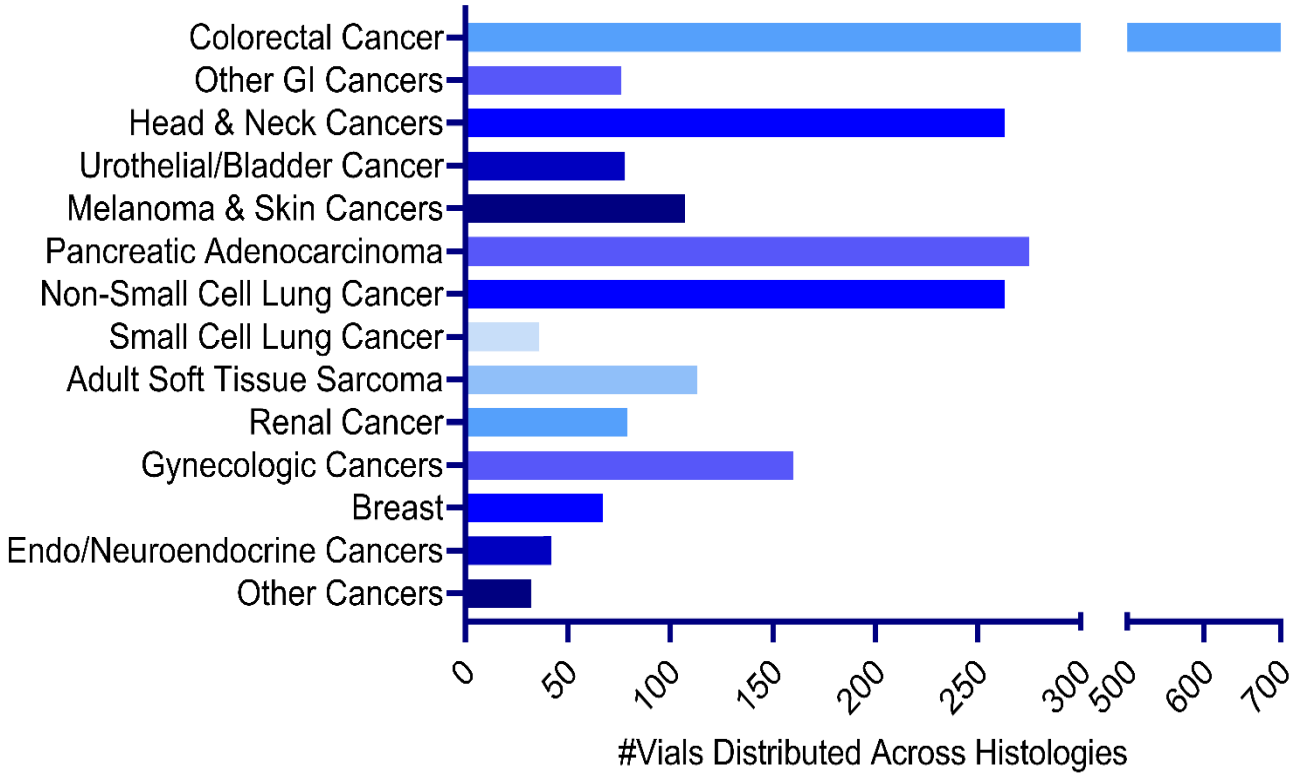


PDMR NCI Patient-Derived Models Repository
An NCI Precision Oncology Initiative℠ Resource

https://pdmr.cancer.gov

Distributed Vials of Material

Overview	
PDX fragment (cryopreserved)	927
DNA (solution)	20
RNA (solution)	43
Fragment for protein (flash-frozen)	623
CAF Cultures	48
PDC Cultures	476
PDOrg Cultures	401
Total	2538



Requesting Investigators/Sites

Academic/Non-for Profit

- Auburn Univ.
- Augusta Univ.
- Baylor College
- Boston Children's Hospital
- Brown Univ.
- Christiana Care Helen F. Graham Cancer Center
- Clemson Univ.
- Cleveland Clinic
- Columbia Univ.
- Dartmouth
- Emory Univ.
- Fred Hutchinson Cancer Research Center
- George Washington Univ.
- Georgetown Univ.
- Houston Methodist Research Institute
- Indiana Univ.
- Johns Hopkins Univ.
- Massachusetts General Hospital
- Mayo Clinic
- MD Anderson Cancer Center
- Morgridge Institute for Research
- Mount Sinai
- Northeastern Univ.
- Ohio State Univ.
- Oregon Health & Science Univ.
- Roswell Park Cancer Institute
- Saint Louis Univ.
- San Diego State Univ.
- SRI International
- Stanford Univ.
- Texas Tech Univ.
- Thomas Jefferson Univ.
- Univ. of Utah
- Univ. of Florida/Scripps Biomedical Research
- Univ. of Arizona
- Univ. of Buffalo
- Univ. of California, Davis
- Univ. of California, Irvine
- Univ. of California, Los Angeles
- Univ. of California, San Francisco
- Univ. of Connecticut
- Univ. of Georgia
- Univ. of Illinois
- Univ. of Maryland
- Univ. of Miami
- Univ. of Michigan
- Univ. of Nevada
- Univ. of Pennsylvania
- Univ. of Pittsburgh
- Univ. of Rochester
- Univ. of South Alabama
- Univ. of Southern California
- Univ. of Tennessee
- Univ. of Texas, Dallas
- Univ. of Texas, San Antonio
- Univ. of Vermont
- Univ. of Wisconsin, Madison
- Virginia Commonwealth Univ.
- Wake Forest Univ.
- Washington Univ.
- Wistar Institute
- Yale Univ.

Requesting Investigators/Sites (contd.)

Commercial

- Chimera Bioengineering
- Dicerna Pharmaceuticals, Inc
- GlaxoSmithKline LLC
- Ideaya Biosciences
- Kenjockety Biotechnology
- Life Technologies/Thermo Fisher Scientific
- Melior Discovery Inc.
- Merrimack
- Orphagen Pharmaceuticals
- Poseida Therapeutics

Government/ Intramural

- National Cancer Institute, NIH
  - Center for Cancer Research (CCR)
  - Division of Cancer Epidemiology and Genetics (DCEG)
  - Division of Cancer Treatment and Diagnosis (DCTD)
  - National Institute of Child Health and Human Development (NICHD)
  - Developmental Therapeutics Branch (DTB)
  - Thoracic and GI Malignancies Branch
  - Laboratory of Cancer Immunometabolism (LCIM)
  - Laboratory of Cell and Developmental Signaling (LCDS)
  - Laboratory of Cellular Oncology (LCO)
  - Laboratory of Metabolism
  - Pediatric Oncology Branch (POB)
  - Urologic Oncology Branch (UOB)
  - SOP)
- NCI-Frederick/Frederick National Laboratory for Cancer
- National Center for Advancing Translational Sciences (NCATS)
- Argonne National Laboratory (DOE)

Contributing Clinical Centers

Extramural Participating Sites

Augusta University — Georgia Cancer Center
Baptist Health System/Mid-South Minority/Underserved NCORP
Cancer Research Consortium of West Michigan, NCORP
Cancer Research for the Ozarks, NCORP
Cancer Research of Kansas Consortium, NCORP
Children's Cancer Therapy Development Institute, OR
Christiana Care Health Services NCORP
Columbia University Minority Underserved Site NCORP
Dana-Farber — Harvard Cancer Center, ETCTN LAO
Duke University — Duke Cancer Institute, ETCTN LAO
Fred Hutchinson Cancer Research Center/Univ. of Washington Cancer Consortium
Georgia Cares Minority/Underserved NCORP
H. Lee Moffitt Cancer Center & Research Institute
Heartland Cancer Research NCORP
Huntsman Cancer Institute, University of Utah
Indiana University, Simon Cancer Center
JHU Sidney Kimmel Comprehensive Cancer Center, ETCTN LAO
Mayo Clinic Cancer Center, ETCTN LAO
Medical University of South Carolina, Hollings Cancer Center
Michigan Cancer Research Consortium NCORP
Montefiore Minority/Underserved NCORP
Nevada Cancer Research Foundation, NCORP
Northwest, NCORP
Ohio State University, OH
Roswell Park Cancer Institute
Stroger Hospital Cook County Minority/Underserved NCORP
University Health Network — Princess Margaret Phase I Consortium, NCORP
University of Alabama at Birmingham Comprehensive Cancer Center, U54
University of California Davis Comprehensive Cancer Center
University of Colorado Cancer Center
University of Connecticut Health Center — Waterbury Hospital
University of Iowa, Holden Comprehensive Cancer Center
University of Texas MD Anderson Cancer Center, ETCTN LAO
University of Virginia Cancer Center
Vanderbilt-Ingram Cancer Center
Washington University School of Medicine, Siteman Cancer Center
Wisconsin, NCORP
Yale University Cancer Center, ETCTN LAO
Yale University Comprehensive Cancer Center

Rapid Autopsy/ Post-Mortem Participating Sites

City of Hope, Biomedical Research Project
Johns Hopkins Legacy Rapid Autopsy Program
University of Nebraska Medical Center
University of Michigan Comprehensive Cancer Center

NCI Clinics

Developmental Therapeutics Clinic (DTC, DCTD, NCI)
Immune Deficiency - Cellular Therapy Program (CCR, NCI)
Neuro-Oncology Branch (CCR, NCI)
Pediatric Oncology Branch (CCR, NCI)
Surgical Oncology Program (CCR, NCI)
Women's Malignancies Branch (CCR, NCI)
Suburban Hospital

Preclinical Studies: Nilotinib + Paclitaxel

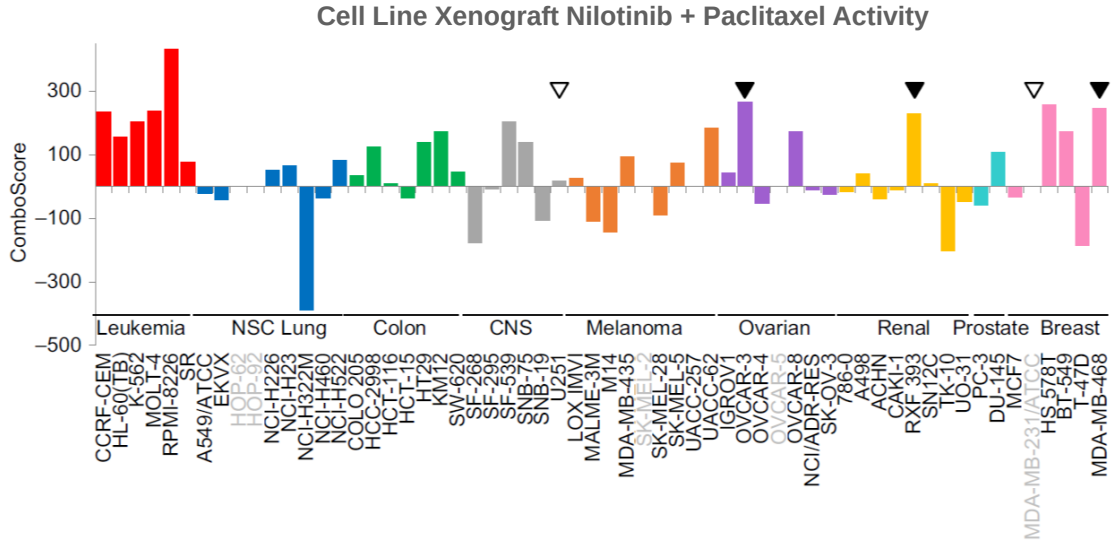
The nilotinib-paclitaxel combination was identified in the NCI-ALMANAC study as having greater-than-additive *in vitro* activity and greater-than-single-agent *in vivo* activity

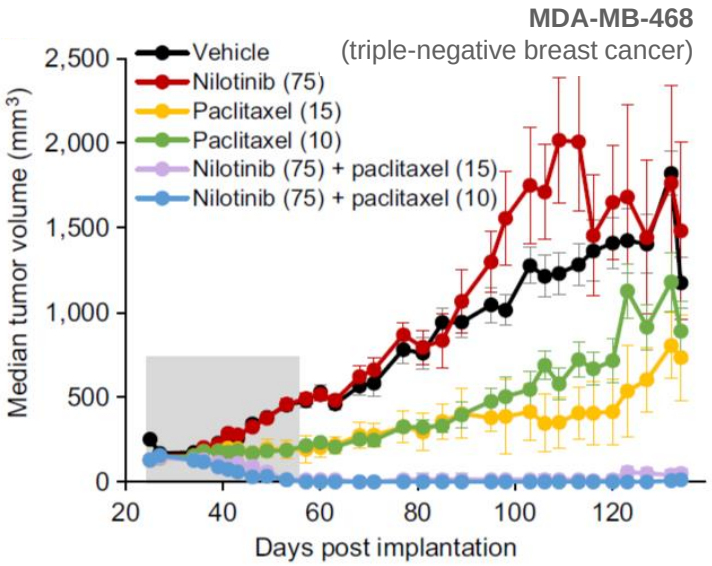
Therapeutics, Targets, and Chemical Biology

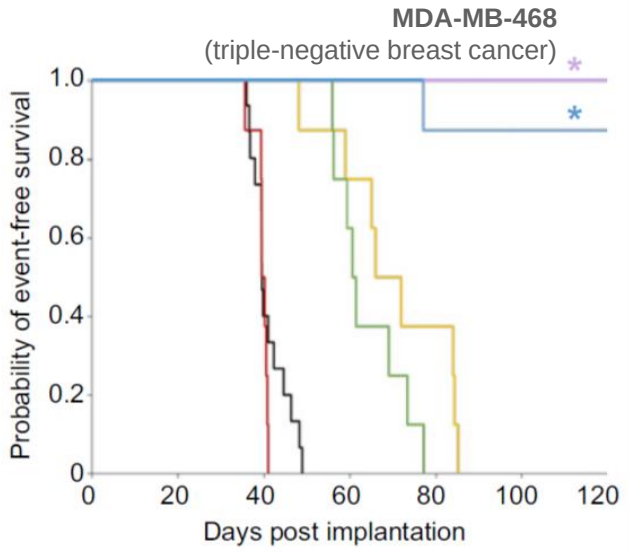
Cancer Research

The National Cancer Institute ALMANAC: A Comprehensive Screening Resource for the Detection of Anticancer Drug Pairs with Enhanced Therapeutic Activity

Susan L. Holbeck[1], Richard Camalier[1], James A. Crowell[1], Jeevan Prasaad Govindharajulu[2], Melinda Hollingshead[1], Lawrence W. Anderson[1], Eric Polley[1], Larry Rubinstein[1], Apurva Srivastava[2], Deborah Wilsker[2], Jerry M. Collins[1], and James H. Doroshow[1,3]





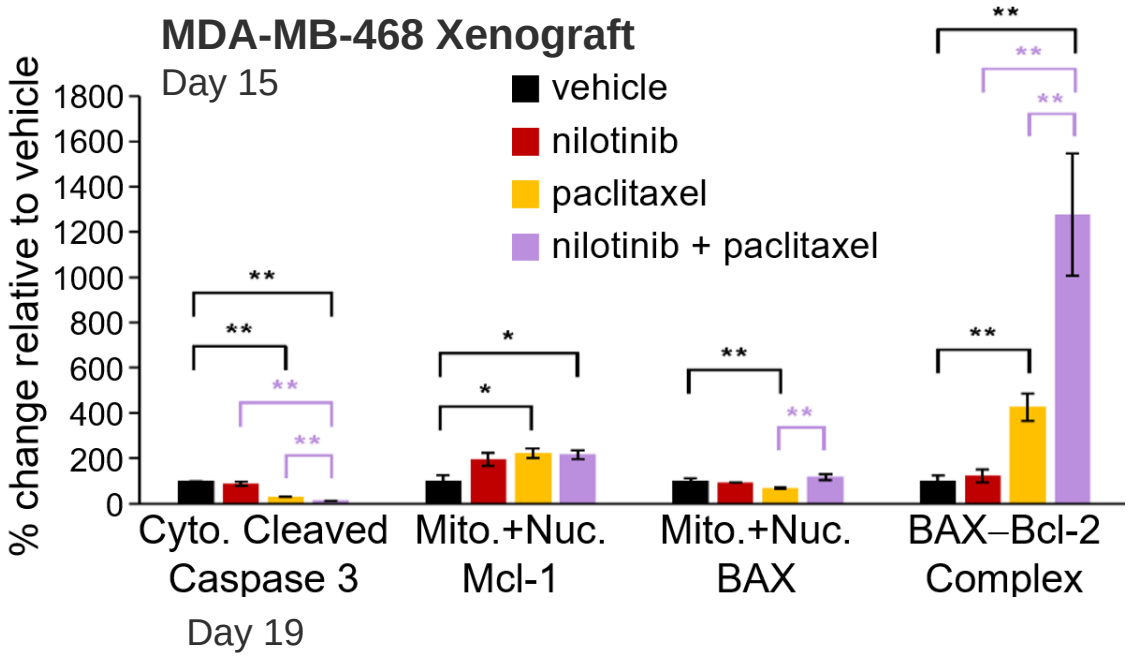


Nilotinib: tyrosine kinase inhibitor targeting BCR-ABL; other targets include KIT, DDR1 and 2, and PDGFRα. Structurally related to imatinib—designed to overcome acquired resistance to imatinib.

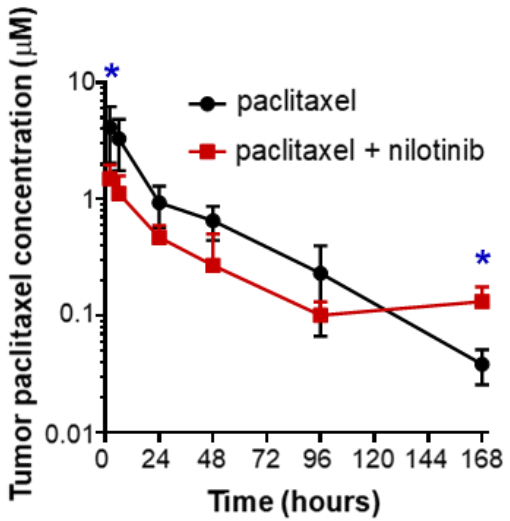
Paclitaxel: binds to β-tubulin and promotes mitotic arrest. Can also modulate proapoptotic signal transduction pathways (e.g., TLR4, JNK, MAPK, NF-κB, JAK/STAT).

Holbeck SL et al. *Cancer Res.* 2017

Nilotinib + Paclitaxel Treatment Lacks a PD Signature Consistent with Apoptosis Suggesting a Non-apoptotic Mechanism of Cell Death



Day 19

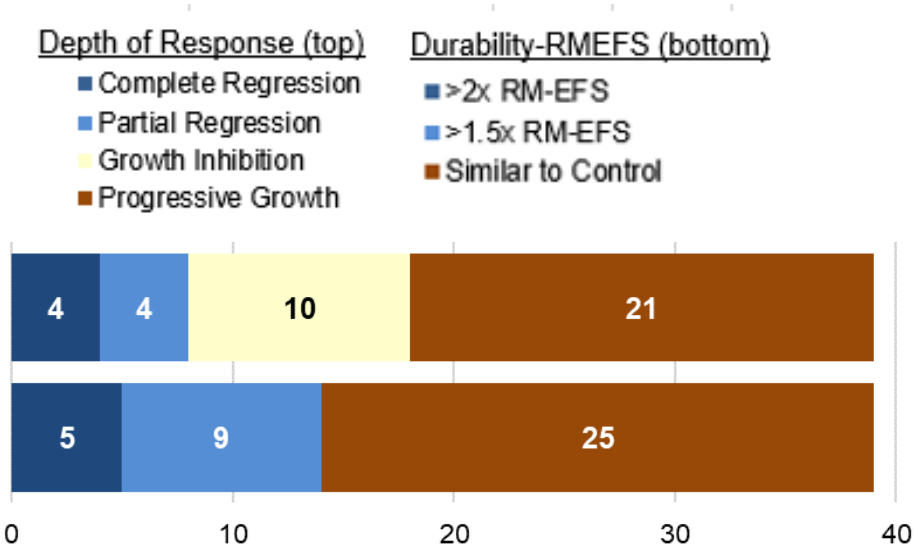


- **Overall**, apoptosis was minimal or largely absent
- Surviving cells after two cycles of treatment show EMT and markers of resistance to apoptosis
  - ✓ Cleaved caspase-3 not increased in either single-agent or combination groups vs. vehicle
  - ✓ Mitochondrial Mcl-1 levels, associated with anti-apoptotic activity, were higher in the combination and single-agent groups vs. vehicle
- No effect of nilotinib on paclitaxel uptake or efflux in vivo

Holbeck SL et al. *Cancer Res.* 2017

Nilotinib-Paclitaxel has Activity in a Variety of PDX Models

8/39 models had an PR or better
18/39 models had an SD or better



Qualitative Best Response

CR	CR Achieved >1 timepoint (<60mm^3)
PR	Tumor regressed ~30%, ***durable*** response (0.5-1c)
PR	Tumor regressed ~30%, regrew at drug removal
SD	Stable, ***durable*** response (0.5-1c)
SD	Stable, regrew at drug removal
PD	Slowed, but progressive growth
PD	Grew at Same Rate as Control

Model	Diagnosis	Qualit.	EFSx4	Regression	aAUC
269878-174-B	Merkel cell tumor	CR	1.65	PR 35d, CR 24	0.0862
144126-210-T	Neuroendocrine cancer, NOS	CR	1.74	PR, 28d; CR, 15d	0.0871
636974-082-R	Gastrointestinal stromal tumor	CR	>2.05	PR 38d, CR 38d	0.1203
761936-265-R	Synovial sarcoma	CR	2.00	PF, 68d; CR, 44d	0.1304
119177-322-R1	Synovial sarcoma	PR	1.67	PR 31d	0.1858
327498-153-R	Carcinosarcoma of the uterus	PD	1.53	none	0.1896
994434-217-R	Ewing sarcoma/Peripheral PNET	PR	1.85	PR 23d	0.1936
949853-013-R	Gastrointestinal stromal tumor	PR	1.51	PR 3d	0.2310
CN0446-F447	Adenocarcinoma - anal	SD	>2.1	none	0.2325
LG0978-F1565	Neuroendocrine cancer, NOS	SD	2.79	none	0.2933
287954-098-R	Ewing sarcoma/Peripheral PNET	SD	1.63	none	0.3187
698357-238-R	Osteosarcoma	PD	1.85	none	0.3555
138582-337-R	Merkel cell tumor	SD	1.29	none	0.3632
933738-175-T	Mesothelioma	SD	1.44	none	0.3698
544552-058-R	Neuroendocrine cancer, NOS	SD	1.49	none	0.3847
712881-215-R	Penile squamous car.(epidermoid)	SD	2.10	none	0.3975
197587-005-T	Synovial sarcoma	SD	1.62	none	0.4001
589616-265-R	Malig. periph. nerve sheath tum.	SD	1.41	none	0.4520
787269-337-R	Merkel cell tumor	PR	1.09	PR 21d	0.4857
193523-008-R	Carcinosarcoma of the uterus	SD	1.25	none	0.5116

19 models not shown, no activity

Nilotinib-Paclitaxel Activity Driven by Combination Effect

Arm of ComboMATCH Trial

		Qualitative Best Resp.			EFSx4			Regression			aAUC			
Model	**Diagnosis**	**N+P**	**P**	**N**	**N+P**	**P**	**N**	**N+P**	**P**	**N**	**N+P**	**P**	**N**	**Activity**
327498-153-R	Carcinosarcoma of the uterus	**CR**	**PD**	**PD**	2.26	1.30	1.04	PR 21d, CR 21d	none	none	0.0492	0.5883	0.9558	Combo
636974-082-R	Gastrointestinal Stromal	**CR**	**PD**	**PD**	1.89	1.02	1.11	PR 39d, CR 22d	none	none	0.1233	0.7547	0.7206	Combo
119177-322-R1	Synovial sarcoma	**CR**	**PR**	**PD**	2.03	1.49	1.02	PR 26d, CR 7d	PR 11d	none	0.1127	0.1717	0.7172	Combo
761936-265-R	Synovial sarcoma	**CR**	**PR**	**PD**	>1.64 (234d)	1.39	1.03	PR 87d, CR 65d	PR 19d	none	0.1092	0.2598	0.7651	Combo
CN0446-F447	Anal Adenocarcinoma	**SD**	**SD**	**PD**	>2.11 (126d)	1.69	1.07	none	none	none	0.2721	0.2625	0.8243	**Paclitaxel**
287954-098-R	Ewing sarcoma/Peripheral PNET	**SD**	**PD**	**PD**	1.77	1.56	1.19	none	none	none	0.2489	0.4711	0.6932	Combo
589616-265-R	MPNST	**SD**	**PD**	**PD**	1.55	1.43	1.06	none	none	none	0.2741	0.3992	0.8457	Combo
949853-013-R	Gastrointestinal stromal tumor	**SD**	**PD**	**SD**	1.58	1.09	1.55	none	none	none	0.2818	0.8478	0.2895	Nilotinib
544552-058-R	Neuroendocrine cancer, NOS	**SD**	**PD**	**PD**	1.81	1.15	1.02	none	none	none	0.2324	0.6185	0.9613	Combo
941425-263-T	Mesothelioma	**PD**	**PD**	**PD**	1.29	1.16	0.99	none	none	none	0.5631	0.6893	0.9146	NR
933738-175-T	Mesothelioma	**PD**	**PD**	**PD**	1.20	1.00	0.94	none	none	none	0.7420	0.9581	0.9212	NR
994434-217-R	Ewing sarcoma/Peripheral PNET	**PD**	**PD**	**PD**	1.59	1.23	1.02	none	none	none	0.3518	0.6236	0.8347	NR
698357-238-R	Osteosarcoma	**PD**	**PD**	**PD**	1.72	1.24	1.09	none	none	none	0.2051	0.3578	0.8375	NR
138582-337-R	Merkel cell tumor	**PD**	**PD**	**PD**	1.08	1.17	1.02	none	none	none	0.6673	0.5539	0.9839	NR
114551-080-T	Salivary gland cancer	**PD**	**PD**	**PD**	1.11	1.26	1.08	none	none	none	0.7926	0.6242	0.8496	NR

CR	CR Achieved >1 timepoint (<60mm^3)
PR	Tumor regressed ~30%, ***durable*** response (0.5-1c)
PR	Tumor regressed ~30%, regrew at drug removal
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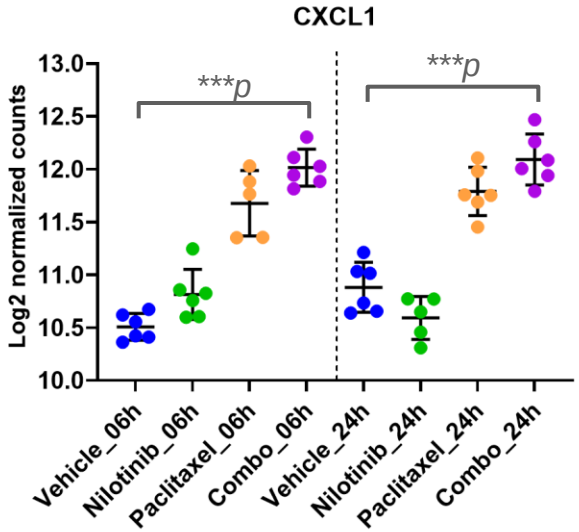
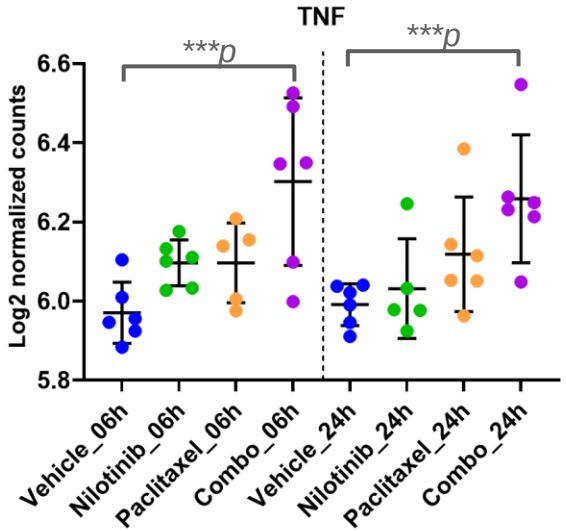
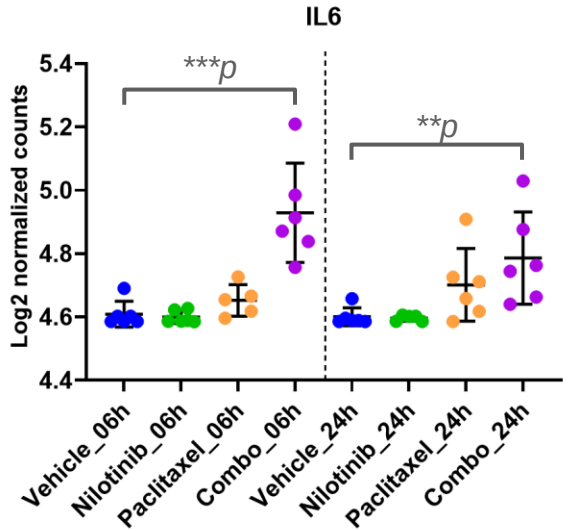
PD	Slowed, but progressive growth
PD	Grew at Same Rate as Control

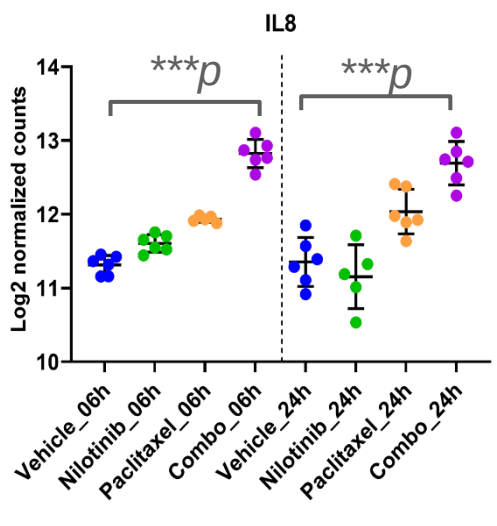
RNASeq Analysis Confirms Upregulation of Cytokines in PDXs and Xenografts

PDX 521955-158-R3, Pancreatic Adenocarcinoma

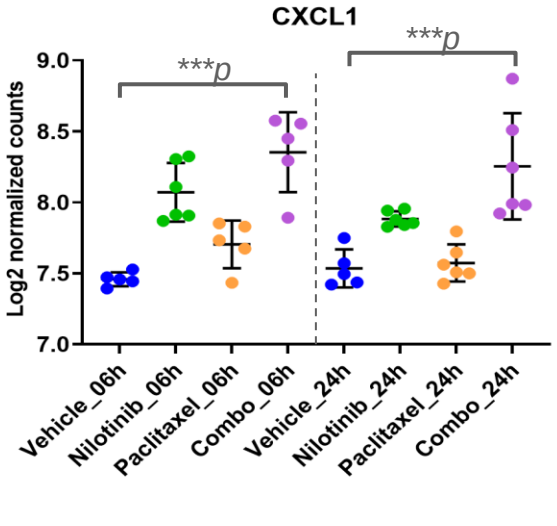


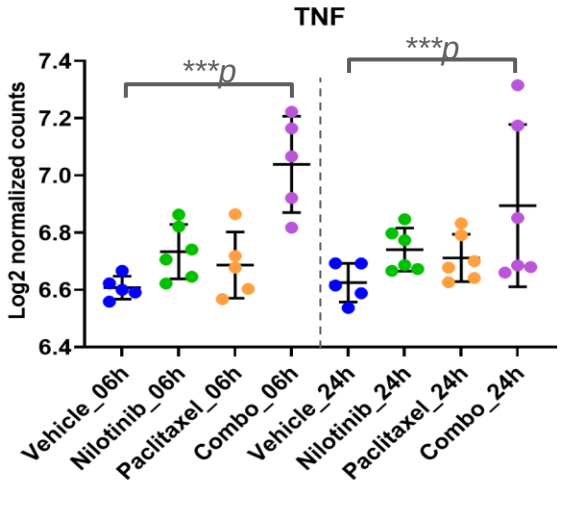


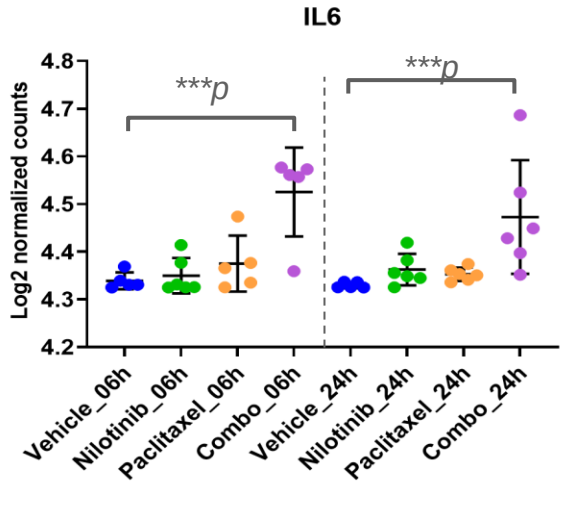


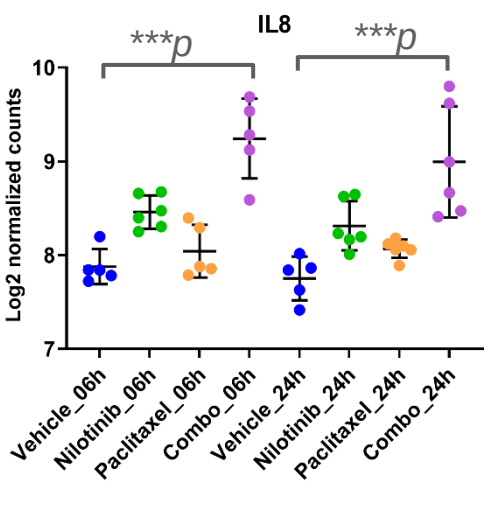


MDA-MB-468 Xenograft

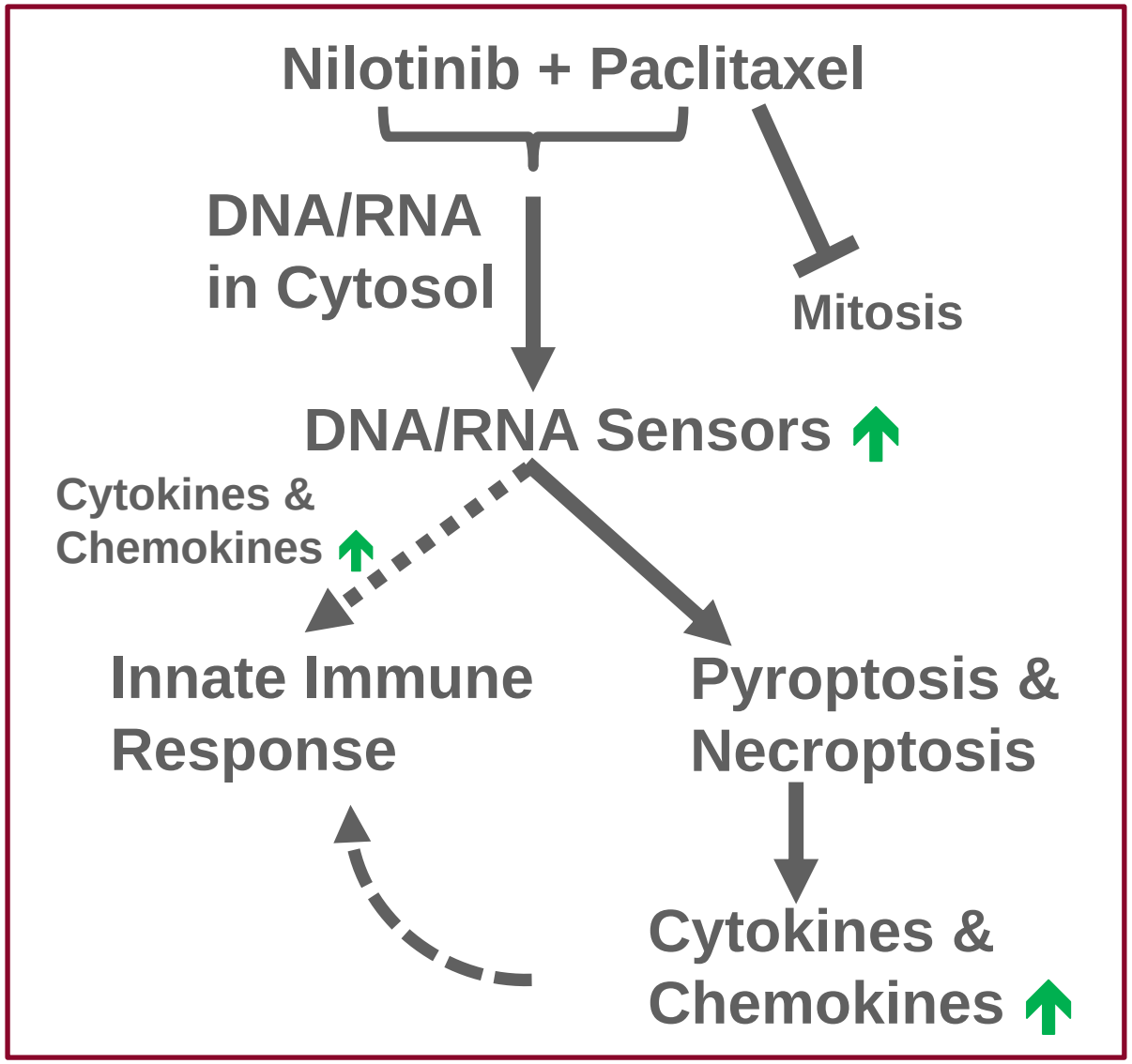








Proposed Hypothesis for Nilotinib + Paclitaxel Mechanism of Action



PDXNet: Standardizing Reporting of Preclinical Tumor Volume Response

NIH NATIONAL CANCER INSTITUTE

PDX (patient-derived xenografts) Development and Trial Centers Research Network (PDXNet): A Cancer Moonshot Program

PDXNet Data Commons and Coordination Center (PDCCC)

- The Jackson Laboratory
  - PI: Jeff Chuang, PhD
- Seven Bridges
  - PI: Brandi Davis-Dusenbery, PhD

Governance and Scientific Advisement

- Division of Cancer Treatment and Diagnosis, NCI
  - Jeff Moscow, MD
  - James Doroshow, MD
- Center to Reduce Cancer Health Disparities, NCI
  - Tiffany Wallace, PhD
- Frederick National Laboratory for Cancer; NCI Patient Derived Models Repository (https://pdmr.cancer.gov)
  - Yvonne A. Evrard, PhD

PDX Development and Trial Centers (PDTCs)

- Huntsman Cancer Institute - Baylor College of Medicine
  - PIs: Alana Welm, PhD, Bryan Welm, and Mike Lewis, PhD
- MD Anderson Cancer Center
  - PIs: Ramaswamy Govindan, MD, Shunqiang Li, PhD, and Li Ding, PhD
- Washington University in St. Louis
  - PIs: Jack Roth, MD, FACS and Funda Meric-Bernstam, MD
- The Wistar Institute - MD Anderson Cancer Center
  - PIs: Meenhard Herlyn, DVM, DSc and Mike Davies, MD, PhD
- Baylor College of Medicine (focus on investigations in racial and ethnic minorities)
  - PI: Nicholas Mitsiades, MD
- University of California, Davis (focus on investigations in racial and ethnic minorities)
  - PIs: Chong-Xian Pan, MD, PhD, Luis Carvajal-Carmona, PhD, and Moon Shao-Chuang Chen, MPH, PhD

Accelerating translational research using PDX datasets

https://www.pdxnetwork.org/ https://portal.pdxnetwork.org/

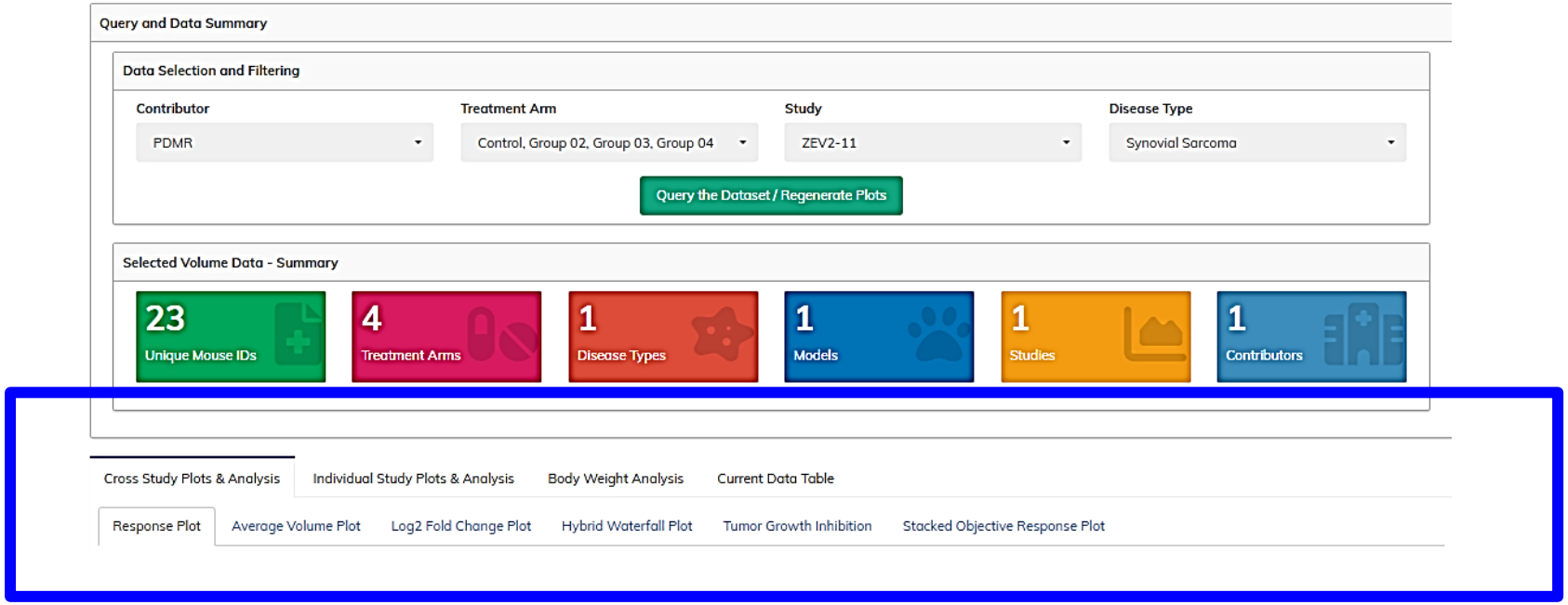
PDXNet Tumor Volume Assessment Project

- ✓ Effort spear-headed by Funda Meric-Bernstam (MDACC PDTC) and Jeff Moscow (IDB, DCTD, NCI).
- ✓ Participation from all PDXNet PDX Development and Trial Centers (PDTCs), the PDMR, and data coordinated through the PDX Data Commons and Coordinating Center (PDCCC).

"PDX Volumetric Analyzer^{TBD}" Tool for Community Use

In final development phase

Upload tumor volume data with provided template. An overview of data in the study is displayed and user can select multiple ways to view summaries of the study and anti-tumor activity.

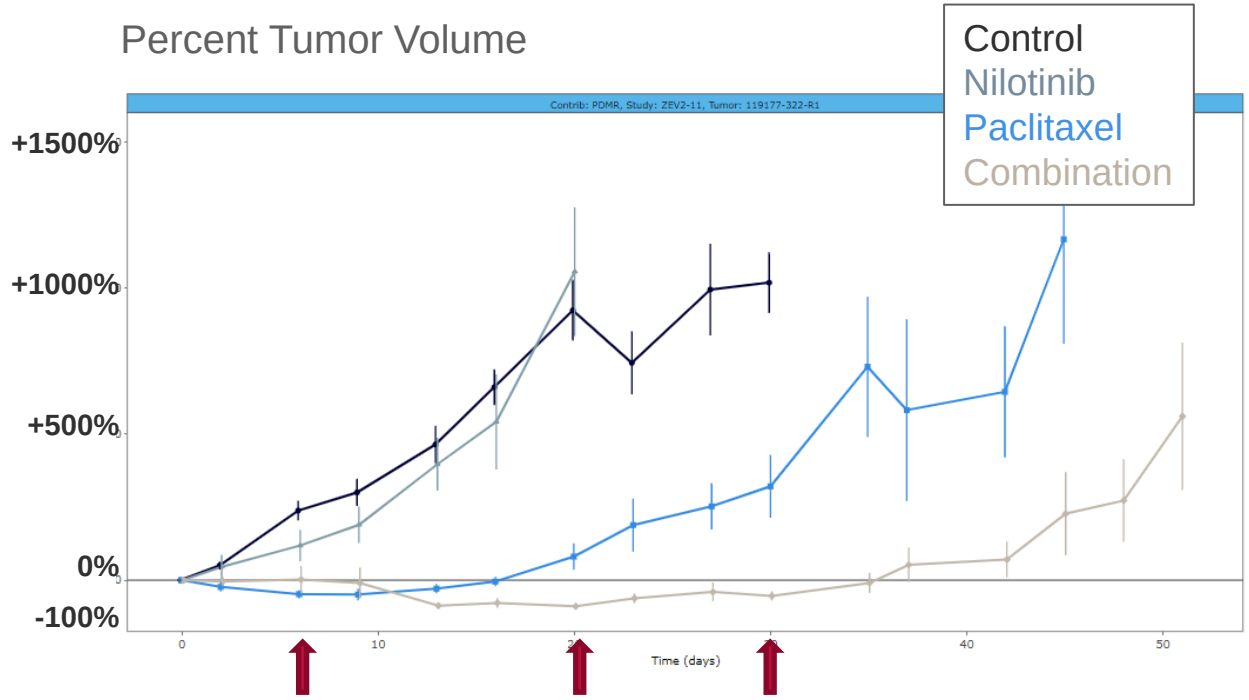


Manuscript In Final Preparation (Meric-Bernstam et al.)

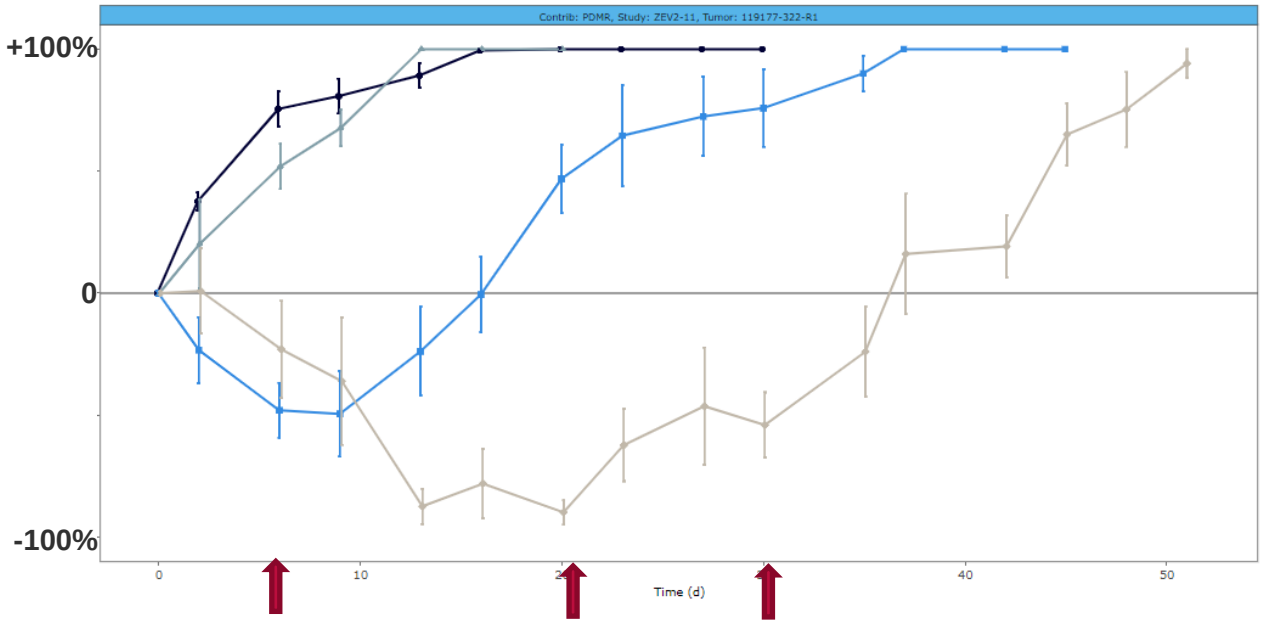
“PDX Volumetric Analyzer” Tool: Graphical Data Representations

NCI PDMR data for a Synovial Sarcoma PDX model with Nilotinib + Paclitaxel combination activity assessed with Analysis Tool

Percent Tumor Volume



Scaled Average Change (J. Moscow)



<u>Equally Weight Regression & Growth</u>

+Y Axis: %Tumor Volume Change with **defined endpoint (**e.g., quadrupling)

-Y Axis : %Tumor Volume Change (-100% = CR)

Fixed days for assessment on next slide

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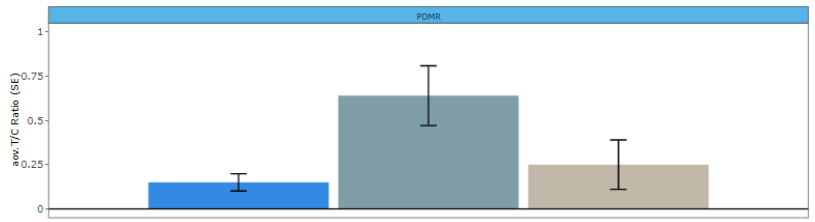
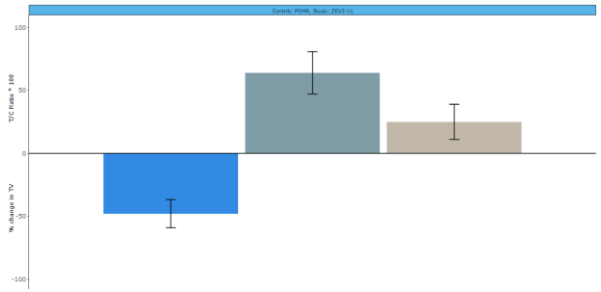
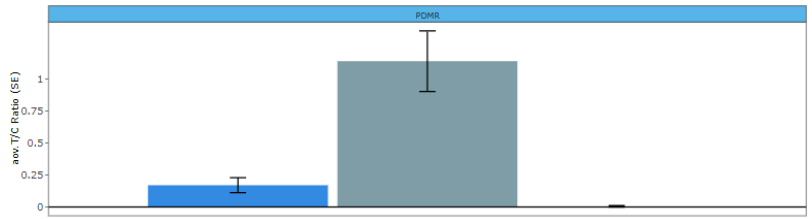
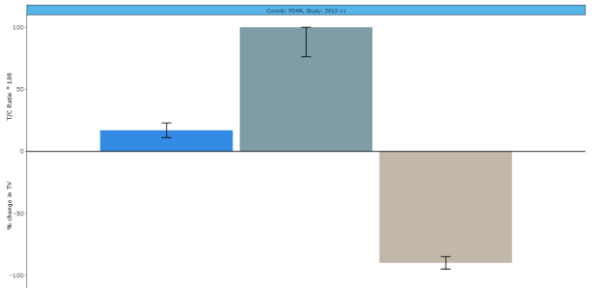
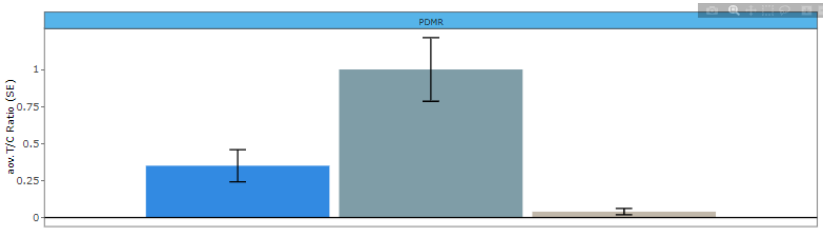
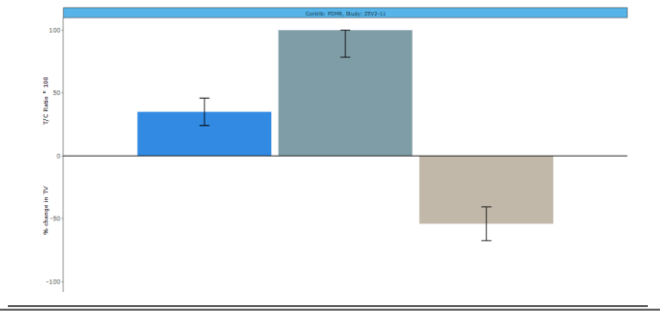
“PDX Volumetric Analyzer” Tool: Graphical Representations

Most metrics have multiple options for customization

Study Day	Tumor Growth Inhibition	Hybrid Waterfall Plot: T/C Above, %TV Change Below	Stacked Objective Response Plot
7			
21			
30			

Paclitaxel Nilotinib Combination

Paclitaxel Nilotinib Combination

Paclitaxel Nilotinib Combination

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“PDX Volumetric Analyzer” Tool: Drug Activity Representations

Most metrics have multiple options for customization

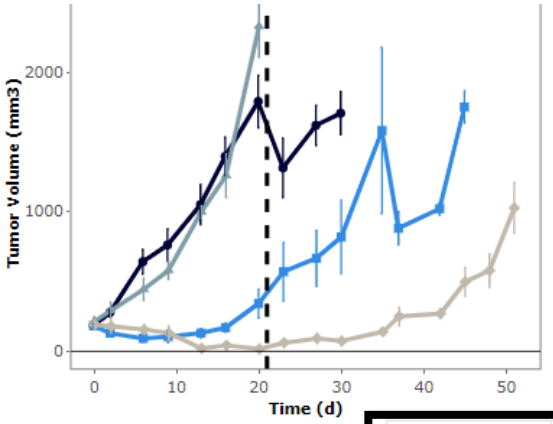
Objective Response

Objective Response (RECIST) | Waterfall Plot | Event Free Survival | ANOVA

RECIST Calc. Day

21

☐ Interpolate Data For Calculation



Control
Nilotinib
Paclitaxel
Combination

Tumor	Arms	Best.Response	Avg.Response	Response.Level
All	All	All	All	All
119177-322-R1	Control	444.05	906.37	PD
119177-322-R1	Group 02	25.89	80.77	PD
119177-322-R1	Group 03	635.71	1,056.66	PD
119177-322-R1	Group 04	-100.00	-89.80	CR

Showing 1 to 4 of 4 entries

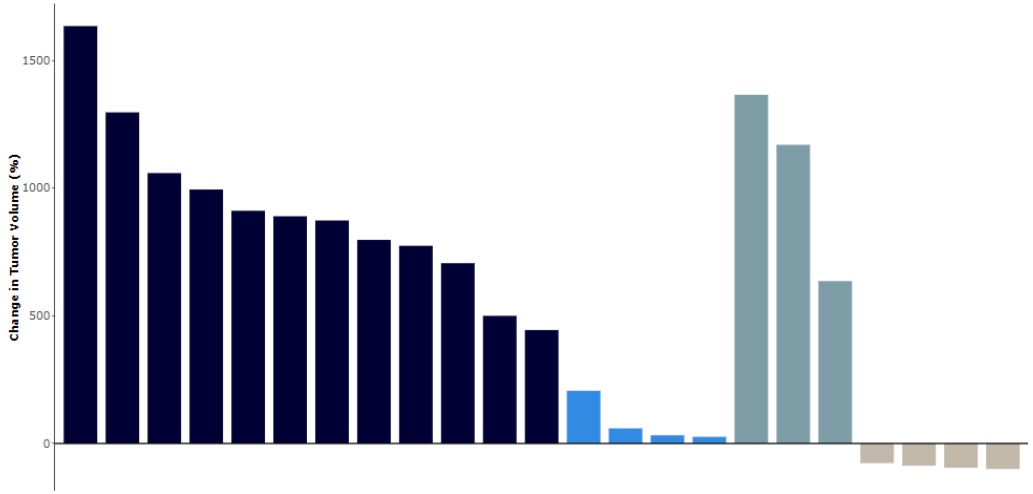
Waterfall Plot

Objective Response (RECIST) | Waterfall Plot | Event Free Survival

Waterfall Metric

dVt

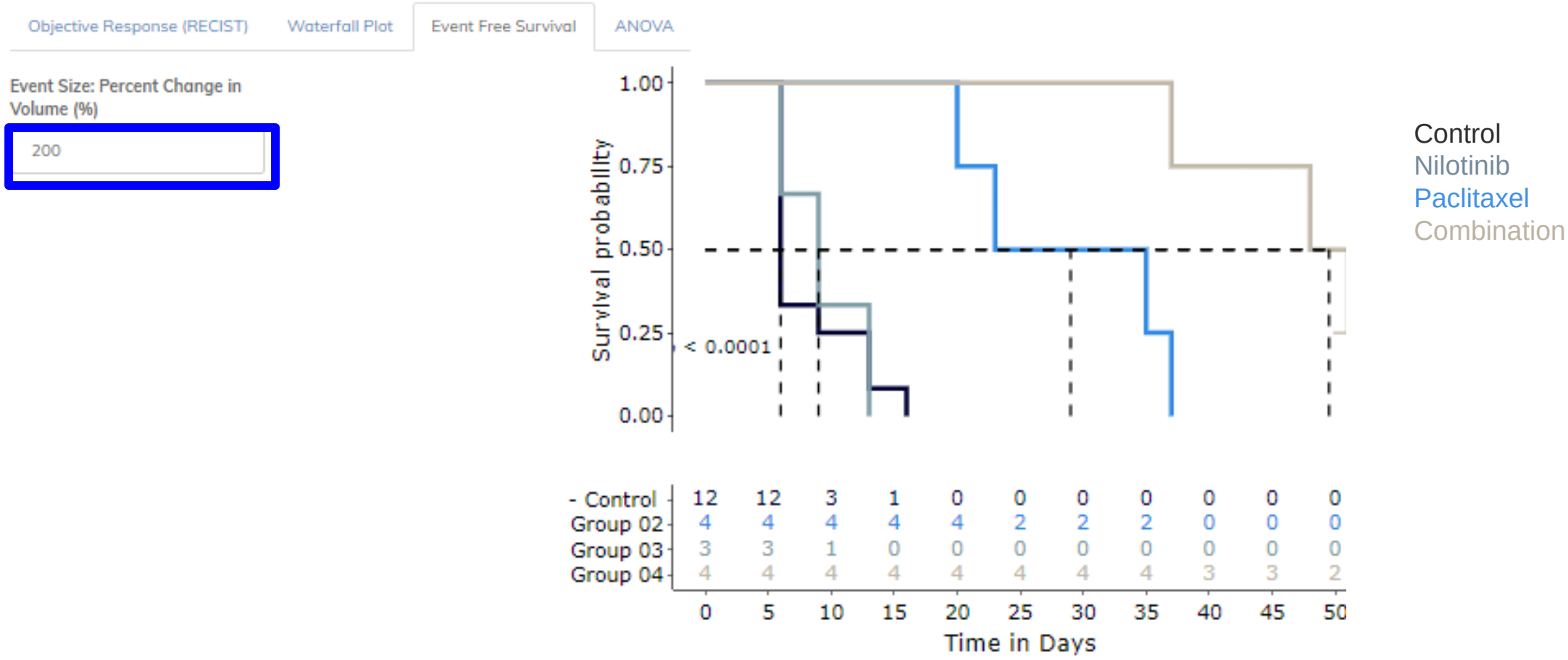
dVt
AUC.All.Measures
AUC.Filtered.Measures



Manuscript In Final Preparation (Meric-Bernstam et al.)

“PDX Volumetric Analyzer” Tool: Response Representation

Event Free Survival (durability)



Manuscript In Final Preparation (Meric-Bernstam et al.)

“PDX Volumetric Analyzer” Tool for Community Use: Recommendations

Over 15 Key Recommendations for Reporting Drug Activity in PDXs *(abstracted selection below)*

- ✓ PDX experiments should be performed using **clinically relevant** doses and schedules, if available.
- ✓ PDX experiments should include monitoring of body weight and overall health as toxicity readouts. Antitumor activity is only clinically relevant if it can be achieved **without substantial toxicity**.

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- ✓ Assessment of antitumor activity of drugs in PDXs should strive for **clinically meaningful anti-tumor activity**: tumor regression/response or prolonged growth inhibition/stable disease.
- ✓ Antitumor activity is best assessed using a combination of **2 or more metrics**. At least one metric should be used that determines whether there is tumor regression and another to compare growth inhibition achieved compared to controls. [**Depth and Durability metrics**]

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“PDX Volumetric Analyzer” Tool for Community Use: Recommendations

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- ✓ Combination treatment experiments should include **controls with each single agent** treatment arm. Combination treatments should enhance antitumor activity not only compared to untreated control or vehicle, but also compared to the individual single agents
- ✓ Demonstrating antitumor activity in multiple models is preferred with an expectation of demonstrating antitumor **activity in at least two clinically relevant models**

Manuscript In Final Preparation (Meric-Bernstam et al.)

PDXNet Acknowledgements

NCI Oversight

- James H. Doroshow, DCTD, NCI
- Jeff Moscow, IDB, DCTD, NCI
- Tiffany Wallace, CRCHD, NCI
- Kim Witherspoon, IDB, DCTD, NCI
- Melinda G. Hollingshead, BTB, DTP, DCTD, NCI

PDX Development and Trial Centers Research Network (PDXNet)

- Huntsman Cancer Institute - Baylor College of Medicine
- MD Anderson Cancer Center
- Washington University in St. Louis
- The Wistar Institute - MD Anderson Cancer Center
- Baylor College of Medicine
- University of California, Davis

- The Jackson Laboratory
- Seven Bridges

https://www.pdxnetwork.org/
https://portal.pdxnetwork.org/

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Dianne Newton, FNLCR

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Cindy R. Timme, FNLCR

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P. Mickey Williams

Biswajit Das

Shahanawaz "DJ" Jiwani

Chris Karlovich

Lily Chen

Cancer Imaging Program, DCTD, NCI & Small Animal Imaging Program, FNLCR

Paula Jacobs

Joseph Kalen

James Tatum

Biometric Research Program, DCTD, NCI

Lisa McShane

Pharmacodynamics, FNLCR

Apurva Srivastava

Sarah Miller

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