

Novel Preclinical Models to Assess the Value of New Drug Combinations

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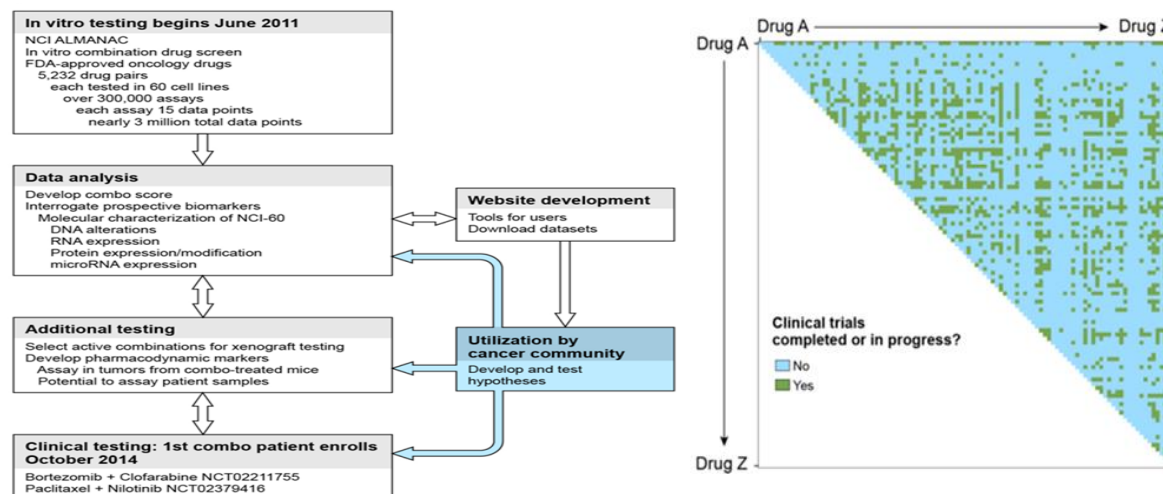


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The NCI Almanac: A Comprehensive Screening Resource for the Detection of Anticancer Drug Pairs with Enhanced Therapeutic Activity: *Cancer Res.* 77: 3564, 2017

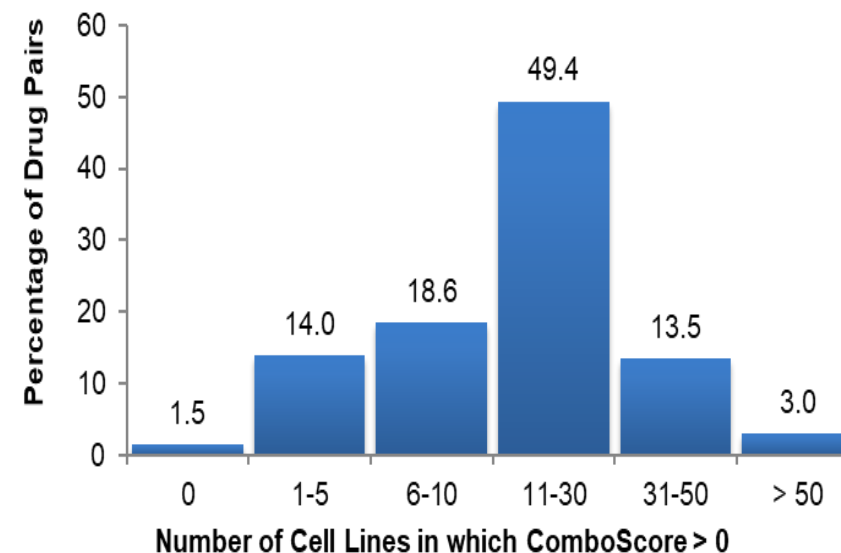
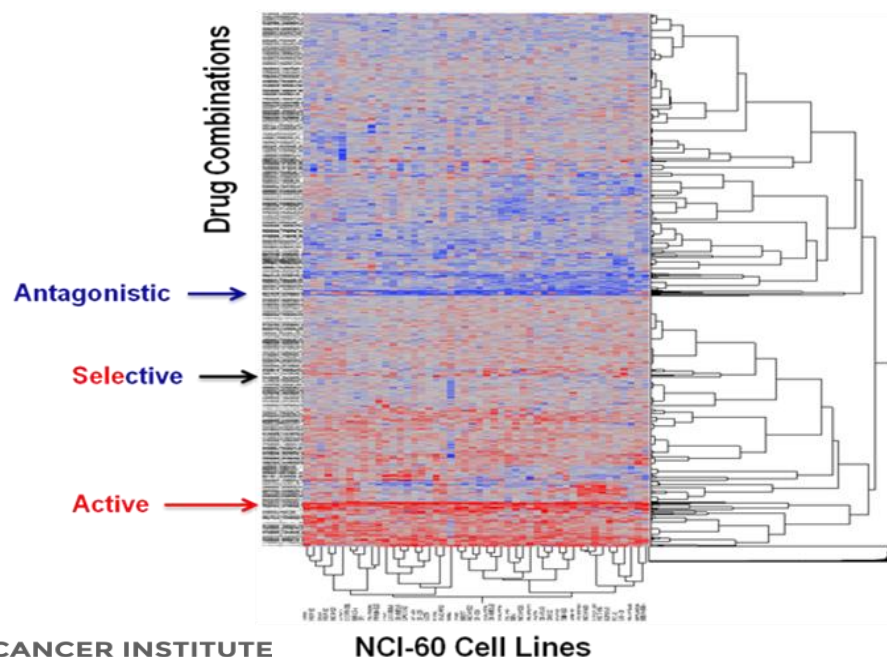
NCI Almanac Screening Strategy



-**Systematic** study of 5000 pair-wise combinations of all FDA-approved oncology drugs across NCI-60
 -Over 1200 **more than additive** combinations discovered

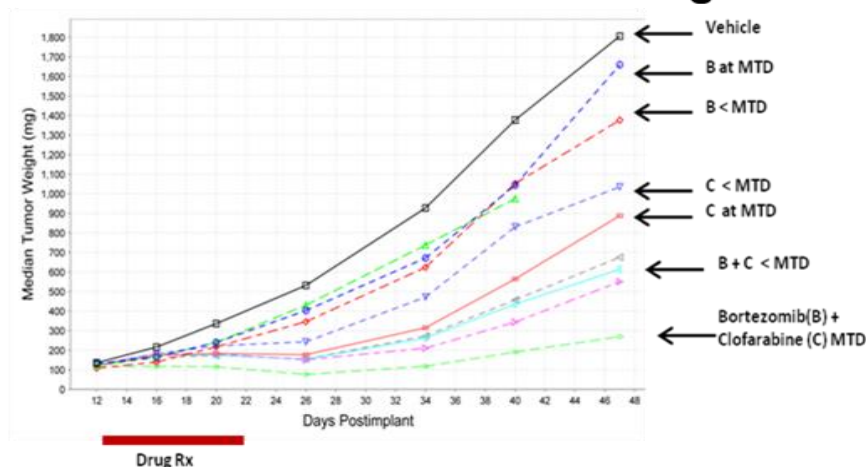
-In vivo validation conducted for promising combos never before studied in human trials to determine therapeutic index in Xgs from NCI 60 lines

-**NCI ALMANAC Website**: All combination data publicly available at: <https://dtp.cancer.gov/ncialmanac>

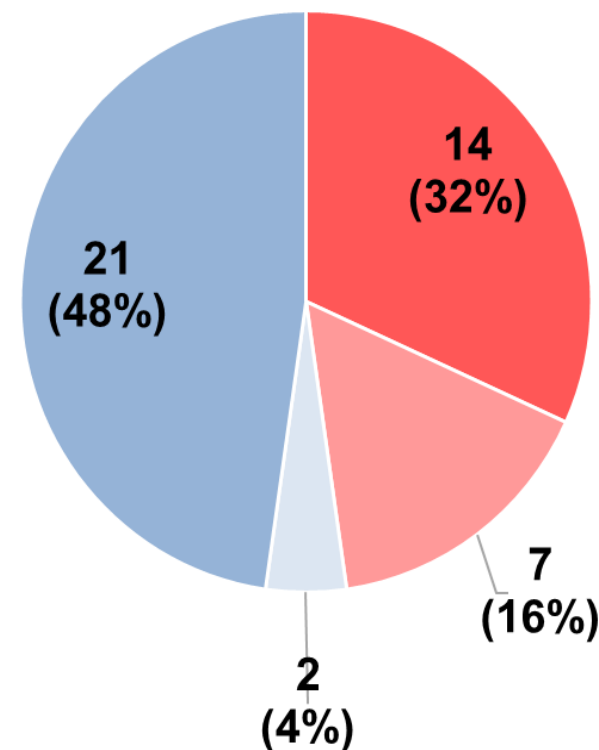
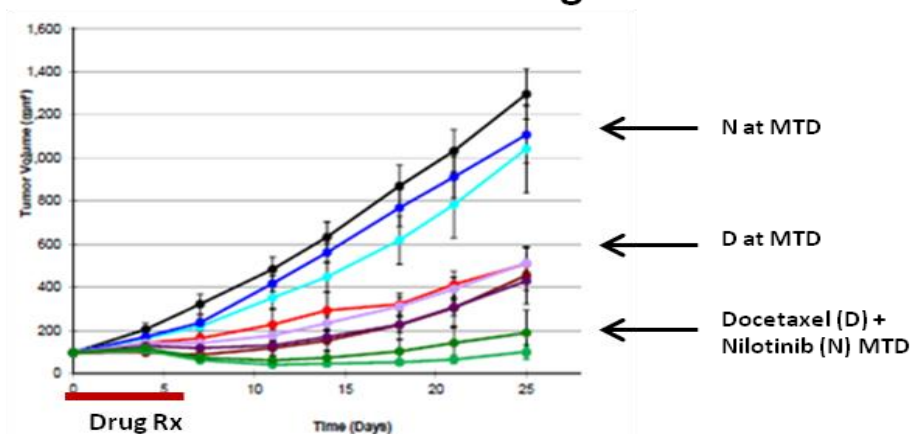


The NCI Almanac: A Comprehensive Screening Resource for the Detection of Anticancer Drug Pairs with Enhanced Therapeutic Activity: *Cancer Res.* 77: 3564, 2017 (2)

In Vivo: HT-29 Colon Ca Xenograft

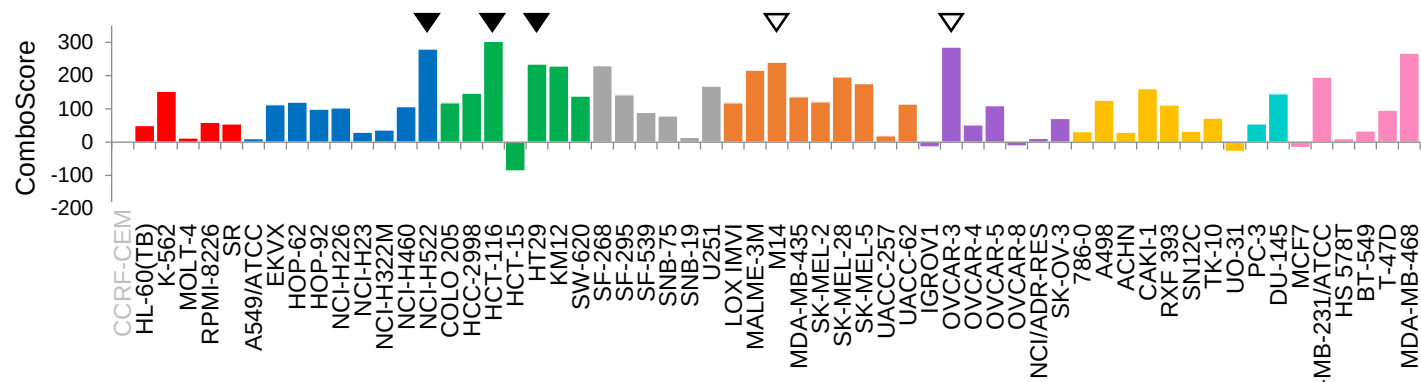


In Vivo: U251 Glioma Xenograft

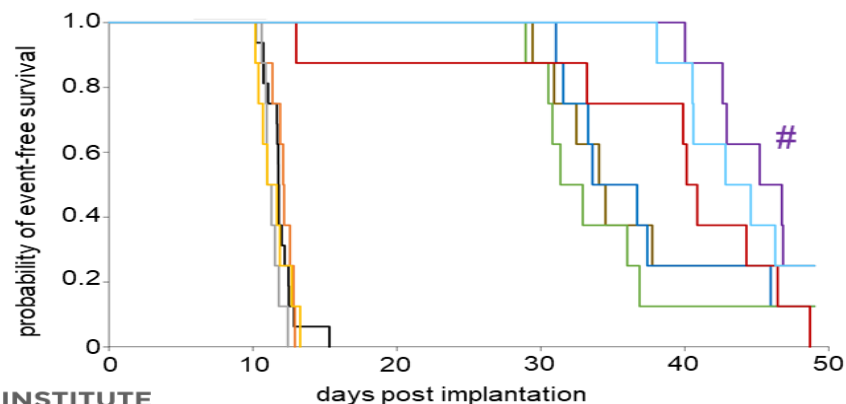
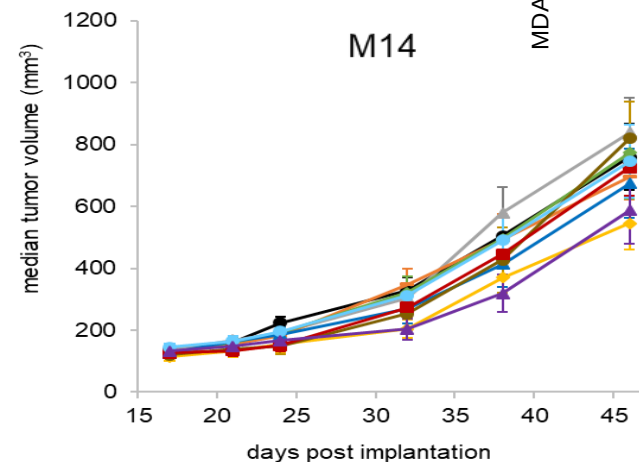
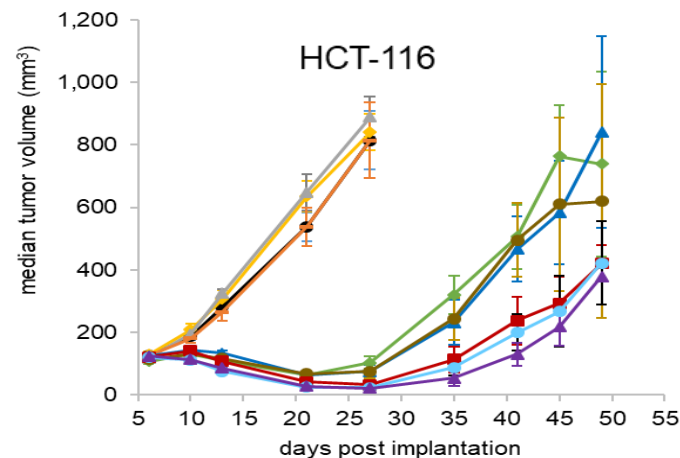


- combo has > single-agent activity (time-to doubling)
- combo has > single-agent activity (expert panel)
- highly efficacious single agent
- combo no better than single agents

In Vitro Activity and In Vivo Efficacy of Bortezomib and Clofarabine

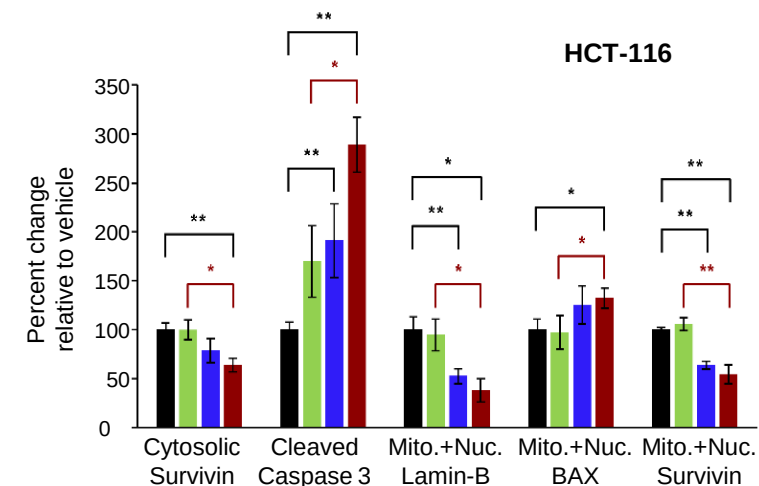
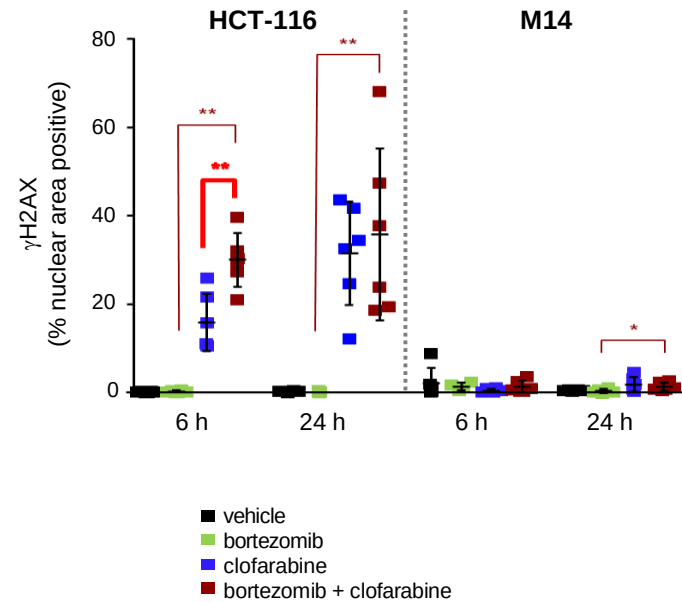
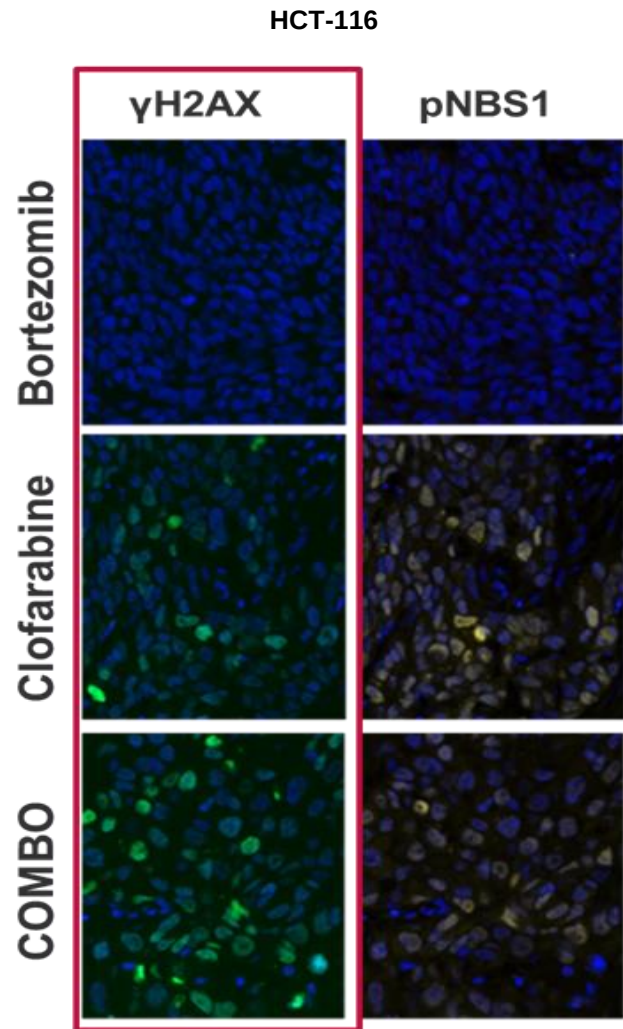


Solid diamonds indicate > additive *in vivo* activity

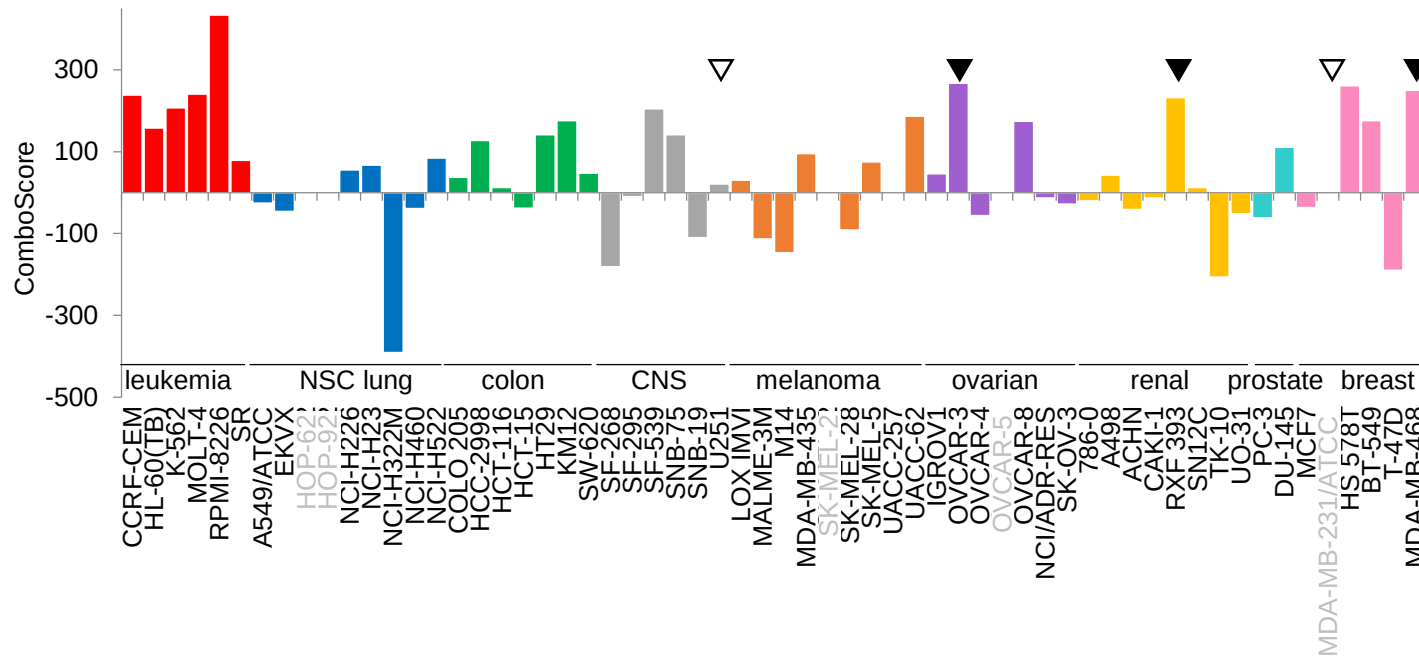


- vehicle
- ◆ bortezomib (0.35)
- ▲ bortezomib (0.75)
- bortezomib (1)
- ◆ clofarabine (60)
- ▲ clofarabine (100)
- ◆ clofarabine (60) + bortezomib (0.35)
- clofarabine (60) + bortezomib (0.75)
- ◆ clofarabine (100) + bortezomib (0.35)
- ▲ clofarabine (100) + bortezomib (0.75)

Bortezomib/Clofarabine Combination Produces DNA DSBs and Markers of Apoptosis in Responsive But Not Unresponsive Xenografts



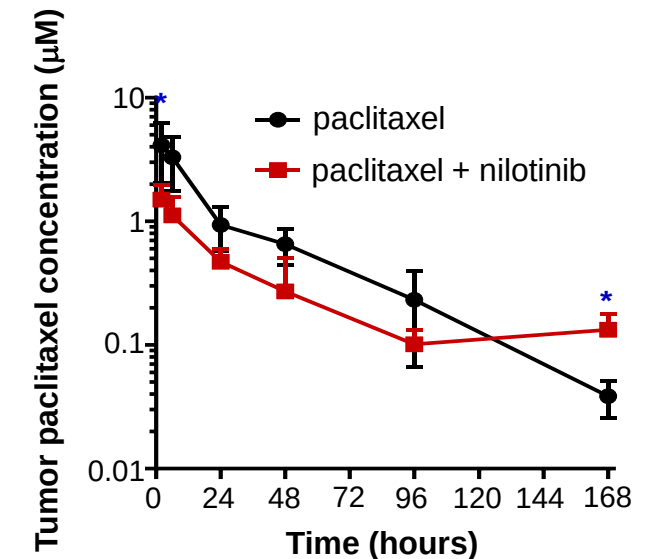
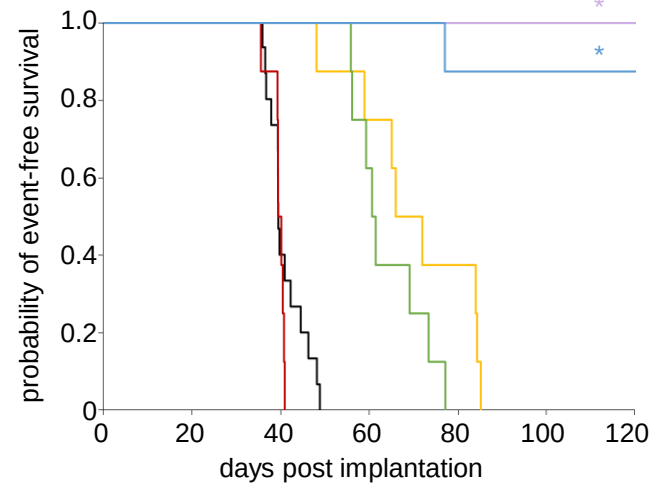
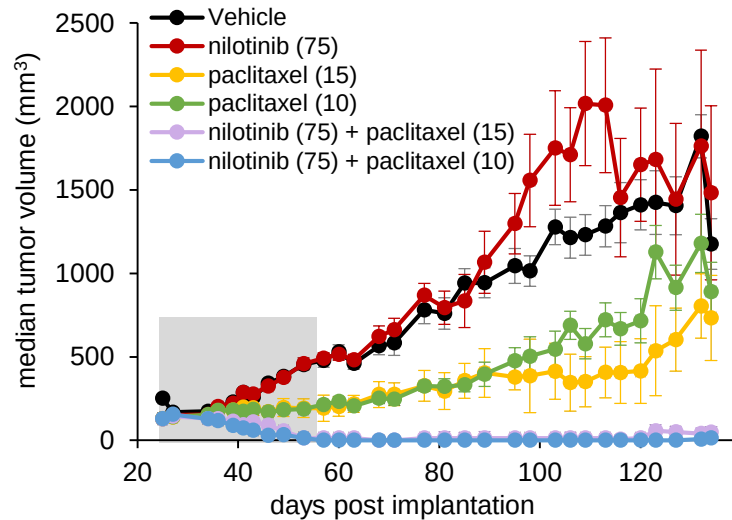
In Vitro Activity and In Vivo Efficacy of Nilotinib and Paclitaxel



Solid diamonds indicate > additive *in vivo* activity

-Synergy not due to enhanced apoptosis, decreased drug efflux
 -Clinical trial: 24 pts: 4 PRs, 12 SD; all 4 PRs (ovary, 2 endo, anal) progressed on prior paclitaxel, no gr 3 neuropathy (80 mg/m² D 1, 8, 15 paclitaxel), on study 7.3 mo median (2-41 mo)

MDA-MB-468



Exploratory Rare Tumor PDX Study: NCI's Patient Derived Models Repository

NCI Patient Derived Models Repository (PDMR)

PDX Model Development (solid tumor histologies)

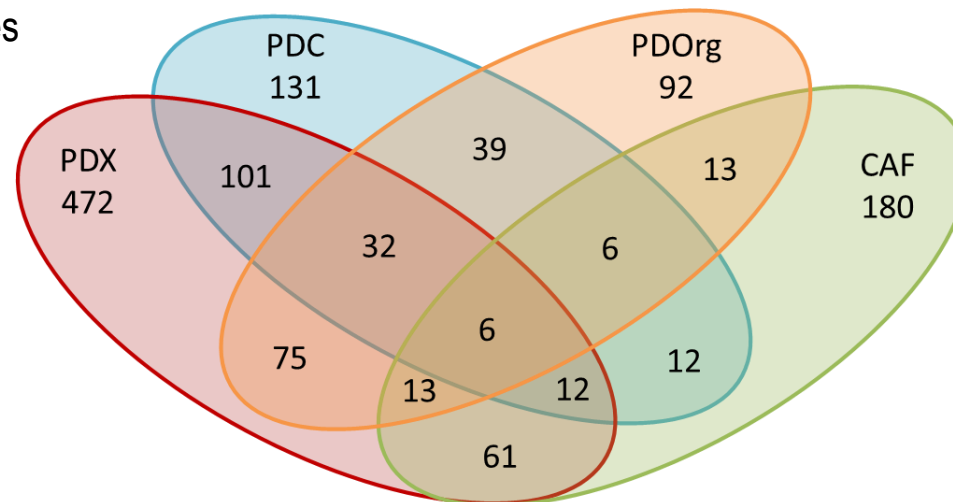
- ✓ **576** Histologically Confirmed PDX Models
 - **295** Models in Final QC (WES, RNASeq, STR, Regrowth from Freeze, etc.)
 - **281 Public PDX Models** (Median passage = P2)
- ✓ **525** PDX Models in P0, Pending Growth (Avg 47% take-rate)
- ✓ Focus on **Understudied/Rare Cancer Histologies**: MPNST, Ewing's Sarcoma, Osteosarcoma, Salivary Gland Cancer, etc.
- ✓ Molecular Data available through public website: <https://pdmr.cancer.gov/>
- ✓ Models available to academic and commercial researchers at minimal cost

In Vitro 2D & 3D Model Development, Public Models

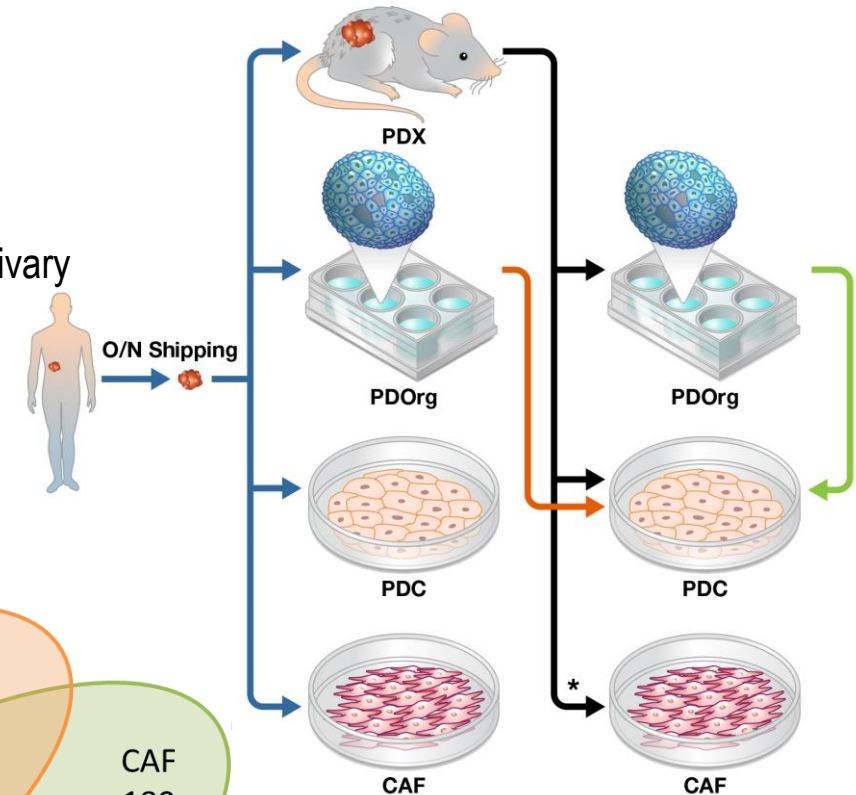
- ✓ **54 PDOrgs**: Patient/PDX-Derived Organoid Models
- ✓ **75 PDCs**: Patient/PDX-Derived Cancer Cell Cultures
- ✓ **177 CAFs**: Cancer-Associated Fibroblasts

Develop Matched PDX and 2D/3D Models

- ✓ Public and Final QC models
- ✓ 32 Models with matched PDX, PDOrg, and PDC
- ✓ Function as a Hub for PDXnet consortium



NCI PDMR Model Development Workflow



Exploratory Rare Tumors PDX Study

Perform a systematic in vivo screening study to identify novel therapeutic combinations in

39 PDX rare cancer models developed by NCI-PDMR

Selection of models based on:

- a) High need for effective therapeutics
- b) Lack of new therapies over the past 10-20 years
- c) Existing patient population in NCI clinics

56 Novel Investigational Therapeutic Combinations

selected for testing; only 2 in clinical trials

Total of **2,184 model x drug response assessments**

Adenocarcinoma - anal	1
Adenocarcinoma - small intest.	1
Alveolar soft part sarcoma	1
Carcinosarcoma of the uterus	3
Ewing sarcoma/Peripheral PNET	3
Gastrointestinal stromal tumor	2
Hurthle cell neoplasm (thyroid)	1
Liposarcoma	3
Malig. periph. nerve sheath tum.	3
Merkel cell tumor	3
Mesothelioma	2
Neuroendocrine cancer, NOS	3
Osteosarcoma	3
Penile squamous car.(epidermoid)	1
Rhabdomyosarcoma, NOS	2
Salivary gland cancer	3
Small cell lung cancer	1
Synovial sarcoma	3

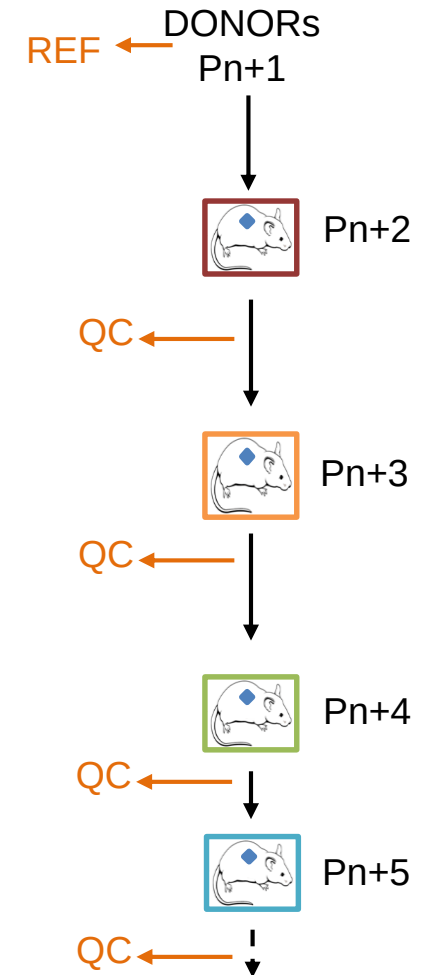
Exploratory Rare Tumors PDX Study: Methods

Phase 1: Test novel therapeutic combinations in n-of-4 treatment cohorts for exploratory studies. Monitor until tumor regrows

- 39 models x 56 combinations, sequential passaging required
- Each passage: One vehicle control arm and 7 combination arms; minimum of 8 passages to complete testing of combinations
- QC of material at every passage by Low Pass WGS, pathology review, and %human DNA by qRT-PCR. Body weight monitored throughout for toxicity

Phase 2: If a response is observed with the combination, repeat the study with single agent arms. Determine if response is driven by a single agent or the combination

Phase 3: For combinations that have additive/synergistic affects, perform a full efficacy study with planned sampling for biomarker exploration and PK

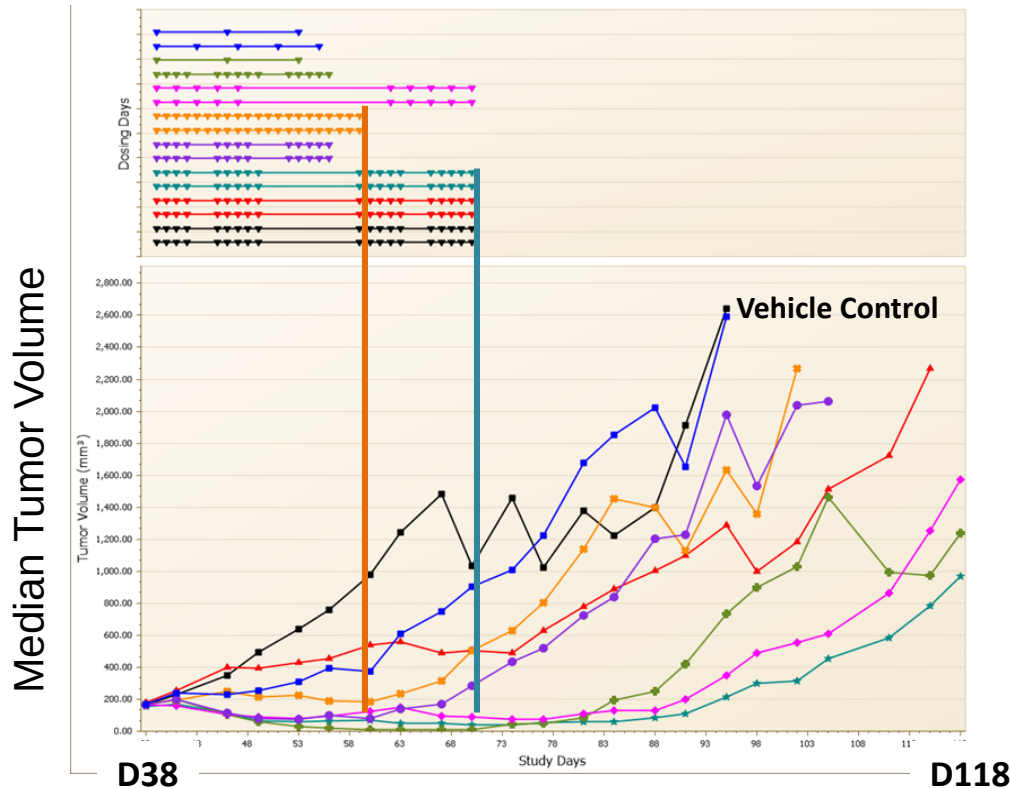


Exploratory Studies Underway

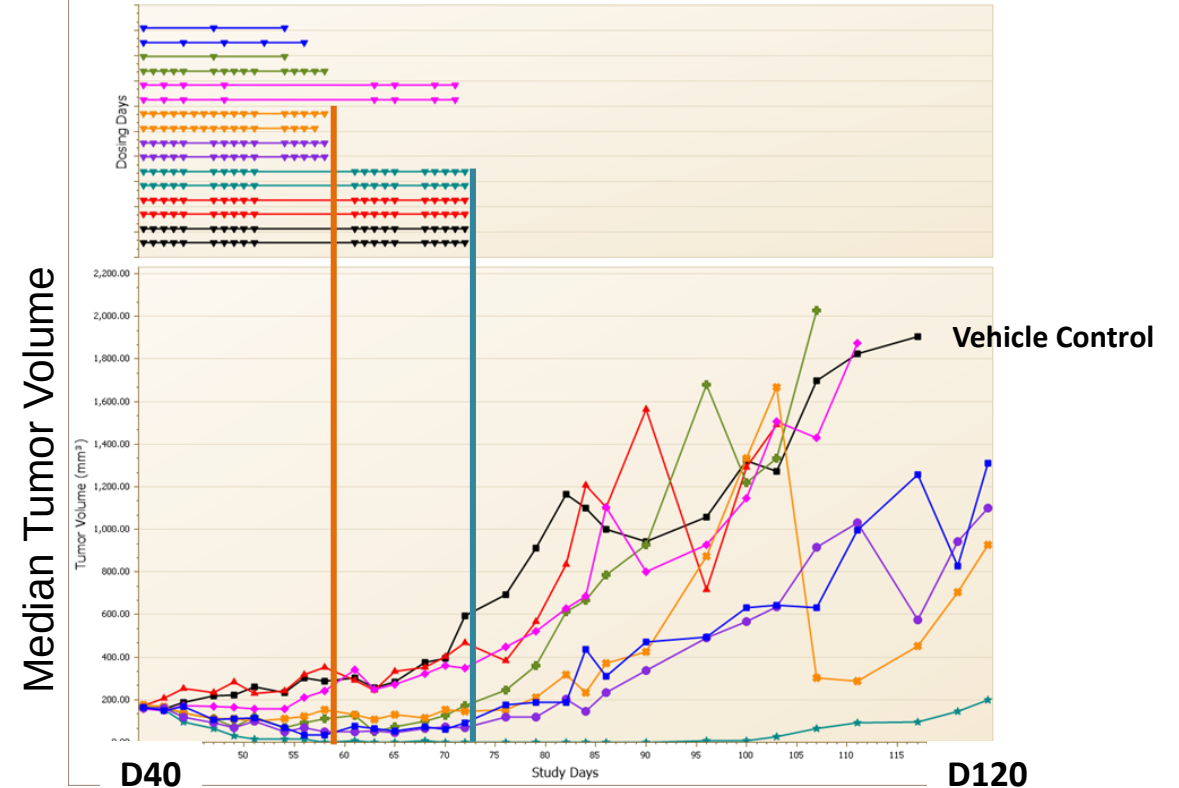
Phase 1: Test novel therapeutic combinations in n-of-4 treatment cohorts for exploratory studies

- Each passage of PDX: 1 vehicle control arm + 7 combination arms; minimum 8 passages needed
- Monitor models until tumors regrow to assess durable response

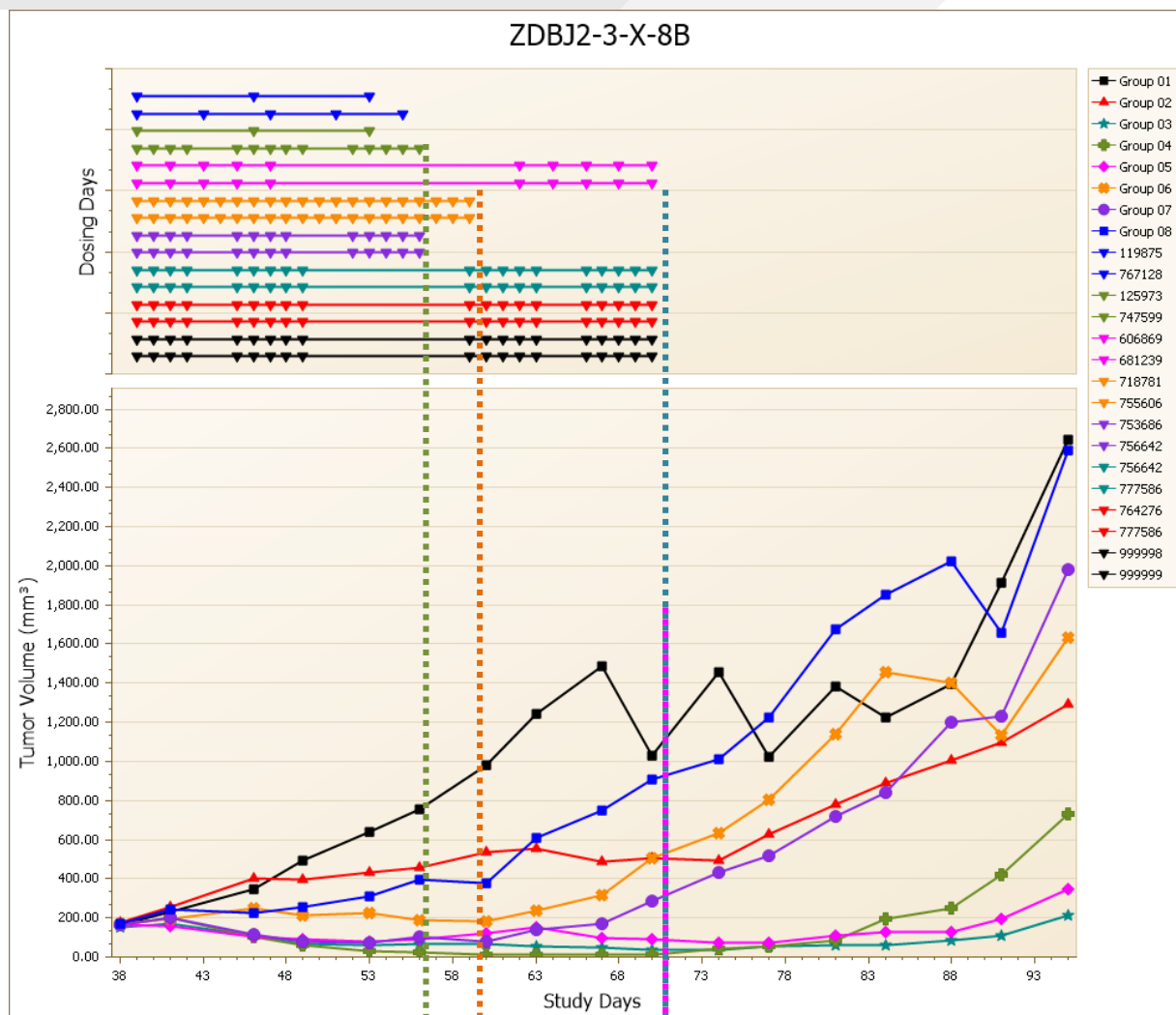
Ewing Sarcoma



Merkel Cell Carcinoma



Visual Best Response Binning Example



Bin 1	CR Achieved >1 timepoint (<60mm ³)
Bin 2	Tumor regressed ~30%, durable response (0.5-1c)
Bin 3	Tumor regressed ~30%, regrew at drug removal
Bin 4	Stable, durable response (0.5-1 cycle)
Bin 5	Stable, regrew at drug removal
Bin 6	Slowed, but progressive growth
Bin 7	Grew at Same Rate as Control

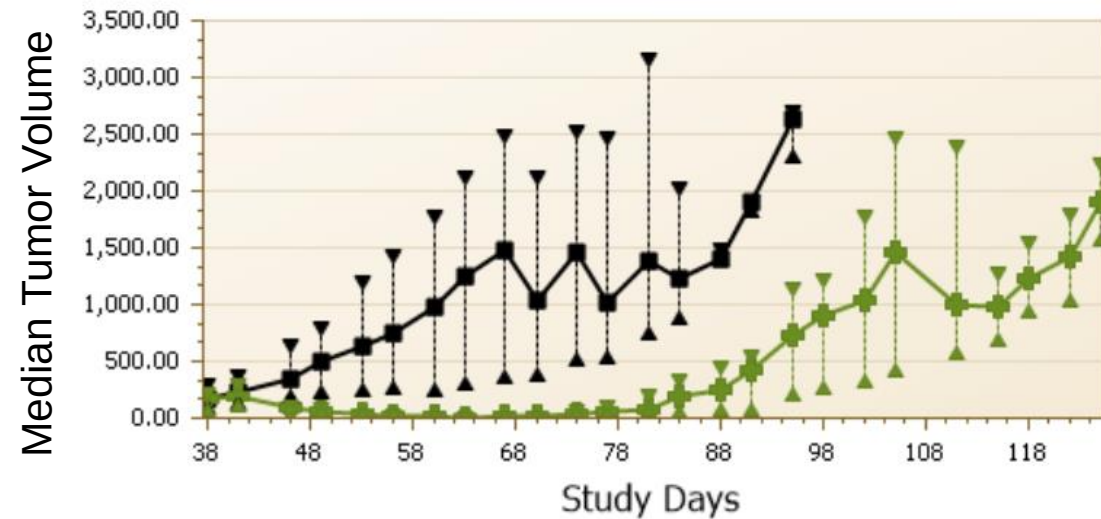
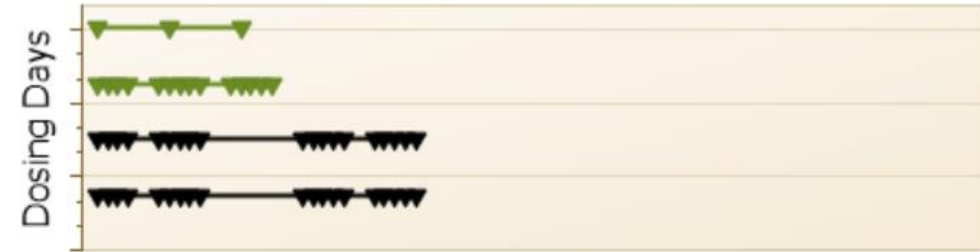
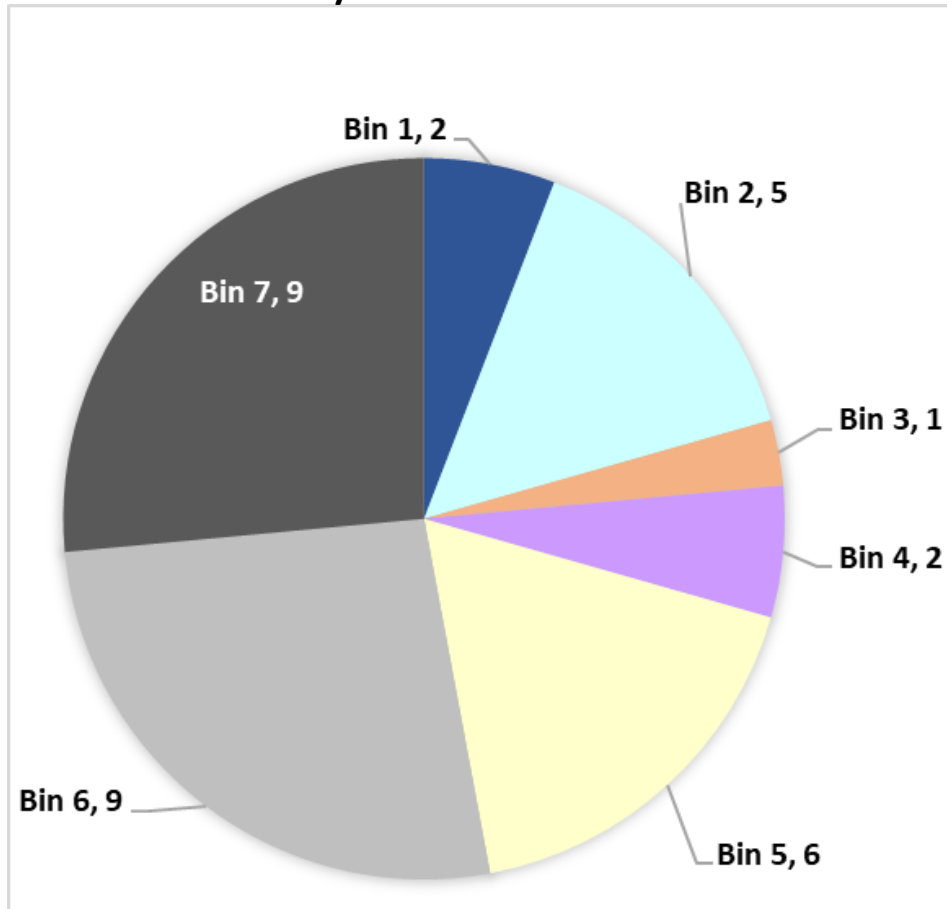
A	Bin 6
B	Bin 2
C	Bin 1
D	Bin 2
E	Bin 5
F	Bin 3
G	Bin 6

Also Use: RM-EFS: Relative Median to Event-free Survival (relative time to tumor quadrupling, right censored; adapted from Houghton et al., 2007)

Paclitaxel, Nilotinib (n=34)

Responses observed in 16/34 models

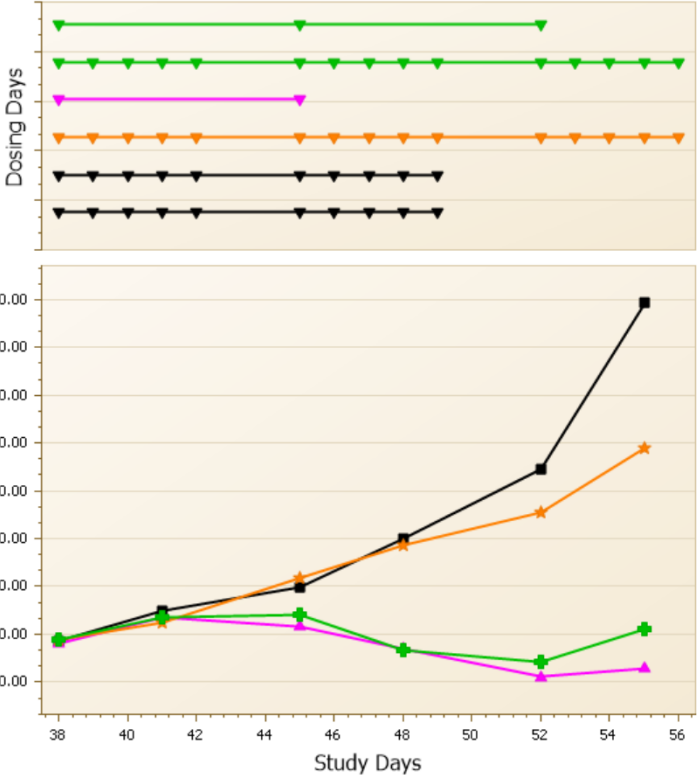
Bin/No. of Models



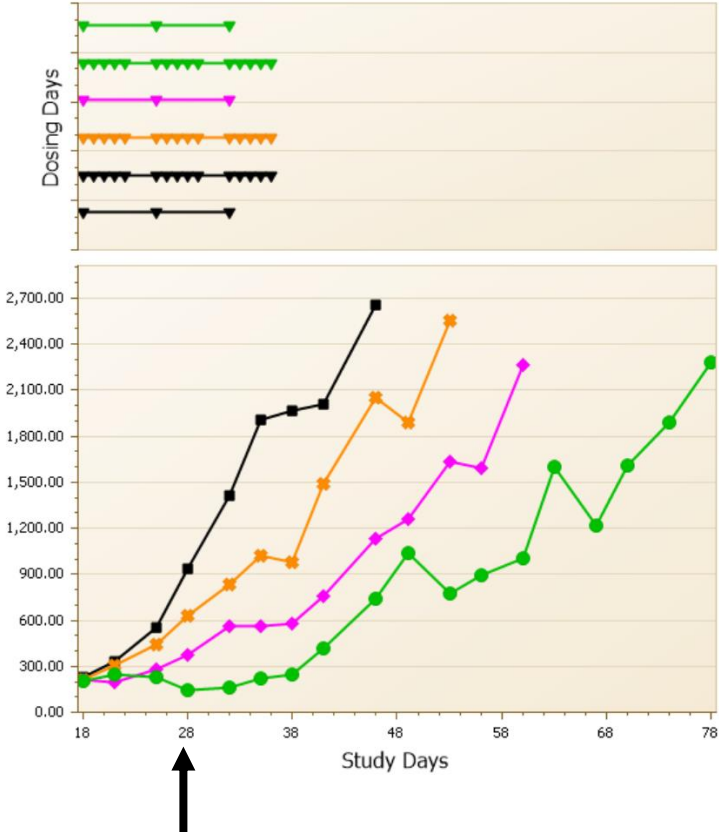
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Phase 2: Paclitaxel, Nilotinib Single Agent Comparisons Ongoing

GIST



Ewing Sarcoma



Control
Nilotinib
Paclitaxel
Nilotinib + Paclitaxel

First two studies completed, 10-15 additional studies planned

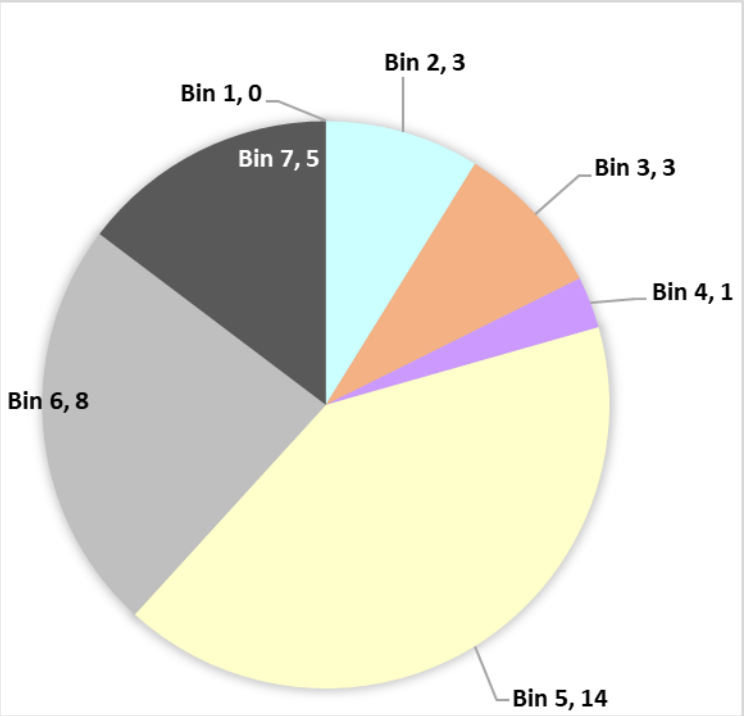
GIST: PR driven by Paclitaxel single agent

Ewing Sarcoma: regression only seen with combination (arrow)

Several Promising Combinations, Single Agent Studies Underway

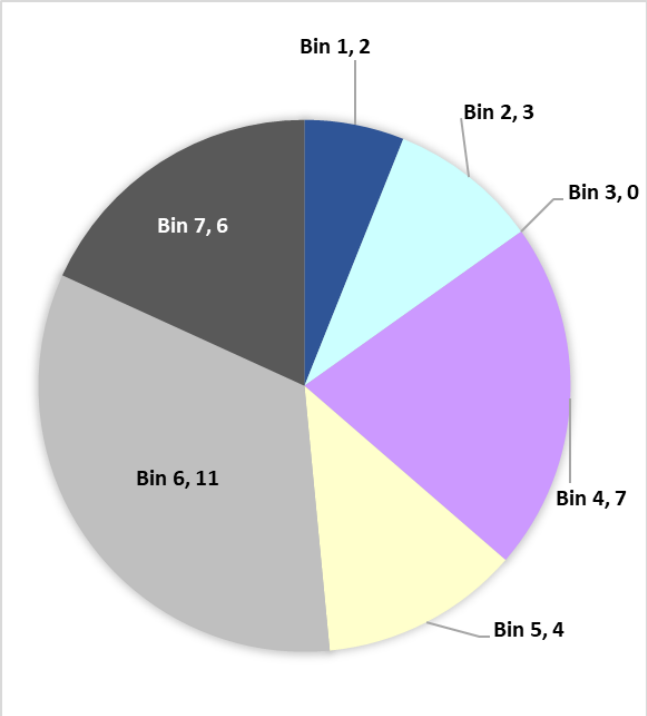
VEGFRi + EGFRi

21/34 models responding



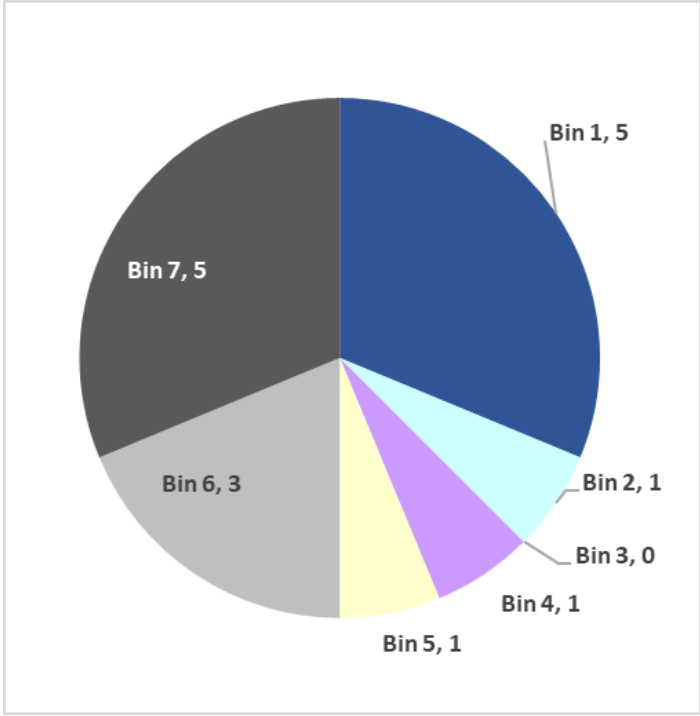
Nucleoside analog + HDACi

16/33 models responding



CDK4/6i + Alkylating agent

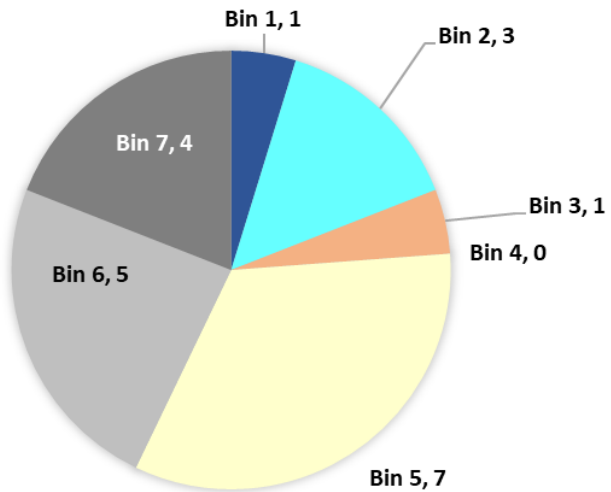
8/16 models responding



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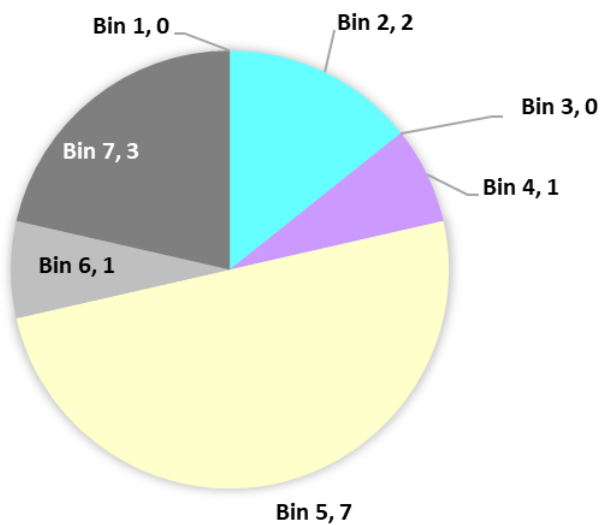
Merkle Cell Tumor Responses vs All Drugs

269878-174-B



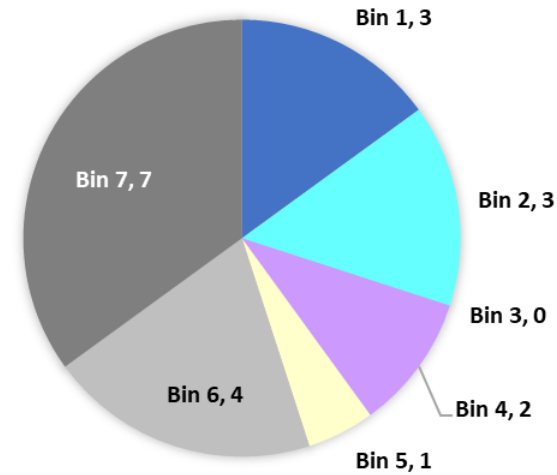
Drug combinations: n=21

138582-337-R



Drug combinations: n=14

787269-337-R

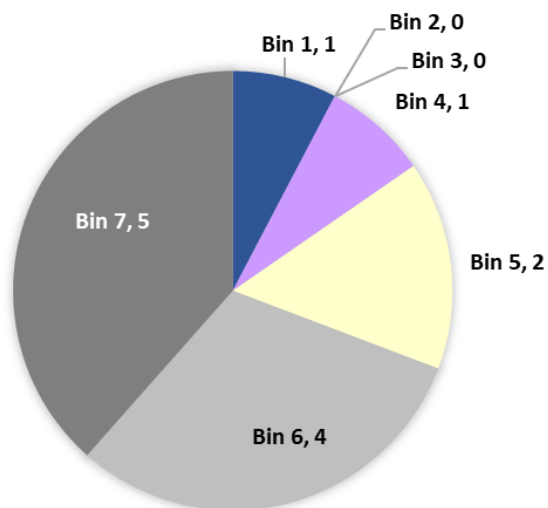


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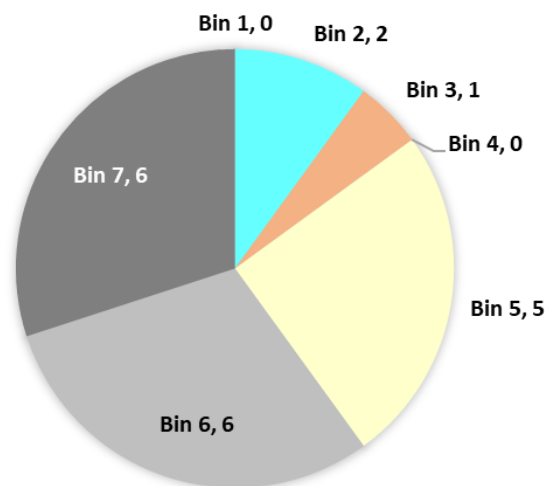
Synovial Sarcoma Responses vs All Drugs

761936-265-R



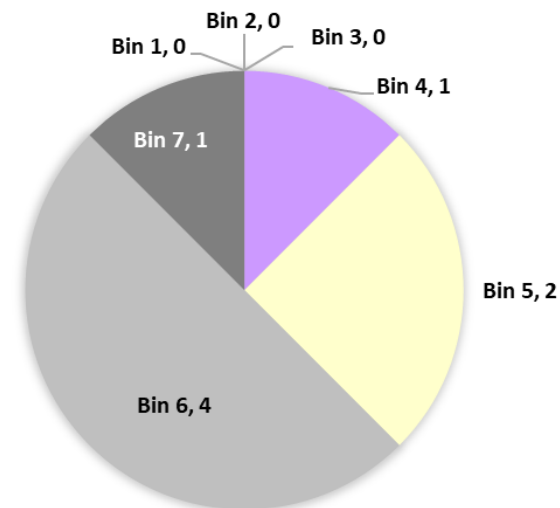
Drug combinations: n=13

119177-322-R1



Drug combinations: n=20

197587-005-T



Drug combinations: n=8

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Summary

- Systematic in vitro screening with in vivo follow-up of FDA approved anticancer drugs has produced multiple, novel, active therapeutic combinations, at least one of which is effective in the clinic
- In vivo combination investigational drug screening of rare tumor PDX models has demonstrated an unexpected number of active drug pairs that are now undergoing both therapeutic and mechanistic deconvolution which should form the basis of a public database that will support a wide range of novel clinical trials

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PDMR NCI Patient-Derived Models Repository
An NCI Precision Oncology InitiativeSM Resource

<https://pdmr.cancer.gov>