NCI's Experimental Therapeutics Clinical Trials Network (ETCTN) & FNLCR's PD Biomarker Program

Jeff Moscow, M.D.

Acting Chief, Investigational Drug Branch

Program Director, PDXNet

CTEP/DCTD

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NExT program and clinical drug development

- NExT Special Emphasis Panel selects agents for **clinical** development assistance
  - These agents are assigned to the **Investigational Drug Branch (IDB),** CTEP for clinical development in the **Experimental Therapeutics Clinical Trials Network (ETCTN)**
- Pharmaceutical companies apply to NExT for NCI-sponsored development for several reasons**:**
  - CTEP has **access to novel agents from competitors**
  - Potential **therapeutic indications that do not compete** for limited corporate resources
  - CTEP has a **network of experienced early-phase clinical trialists**
  - NCI will **invest in correlative science** studies that expand knowledge of the agent
- NCI supports clinical development of Pharma agents because:
  - There is a **significant public interest** in finding indications for new oncology drugs beyond those that may be the most profitable
  - NCI can **advance the understanding of cancer biology and treatment** through carefully designed clinical trials and **through correlative biomarker studies**

NCI's Experimental Therapeutics Clinical Trials Network (ETCTN)

- The **ETCTN mission** is to design and perform the early-phase clinical studies of **agents that are approved through NExT**

- For NExT-selected agents, NCI
  - **Negotiates CRADAs** with Pharma applicant for clinical trial development
  - Assumes the **regulatory responsibility** for the trials (IND holder)
  - Sponsors clinical trials of NCI-IND agents through **cooperative grants** (UM1) to ETCTN clinical trial sites
  - Works with ETCTN investigators and pharma partners to formulate the **clinical and biomarker development plan** for the agent
  - NCI IDB physician staff **monitor ETCTN trials for safety**

- The **Investigational Drug Steering Committee** is the external advisory committee to IDB

NCI's Experimental Therapeutics Clinical Trials Network (ETCTN)

- ETCTN size and scope
  - 11 awards and **41** trial sites in US and Canada
  - **75** agents currently under CRADA
  - Currently **70** active phase 1 and early phase 2 studies
  - Expected to accrue **1000** patients to clinical trials in 2018
  - Extensive **centralized clinical trial support** for network functionality
    - Dedicated early therapeutics CIRB
    - Centralized Identity and Access Management (IAM), regulatory support services (RSS), document management services (CTSU),patient registration (OPEN), data collection (Theradex RAVE), adverse event reporting (CTEP-AERS)
- ETCTN clinical trial proposal review (LOIs)
  - **Protocol** Review Committee for study concept and design
  - **Biomarker** Review Committee for biomarker assay qualification

High impact NCI/IND agent clinical trials

- ***Agents that have achieved FDA approval based in part on early development in CTEP collaborative early phase programs***
  - **Azacytidine** – Myelodysplastic syndrome
  - **Bortezomib**- Mantle Cell Lymphoma
  - **Ipilumumab**- Melanoma
  - **Lenalidomide** and **bortezomib**- Multiple Myeloma
  - **Oxaliplatin**- Colorectal Cancer
  - **Romidepsin**- Peripheral T cell Lymphoma
  - **Sorafinib**- Thyroid Cancer
  - **Ziv-aflibercept**- Colorectal Cancer

- ***Primary FDA approval***
  - **Dinutuximab (ch14.18)-** Neuroblastoma

- ***Orphan Drug indications***
  - **Triapine**- Advanced uterine cervical cancer
  - **Selumetinib**- NF1

Validated biomarkers for the ETCTN

- ETCTN studies almost always **incorporate biopsies and correlative studies** to determine the relationship of tumor biology and target engagement with clinical response.

- However **numerous factors affect reliability and reproducibility** of these studies
  - Biopsy quality is variable
  - Pre-analytic variables are variable
  - Assays that are lab-developed tests have not been analytically validated and demonstrated to be fit-for-purpose

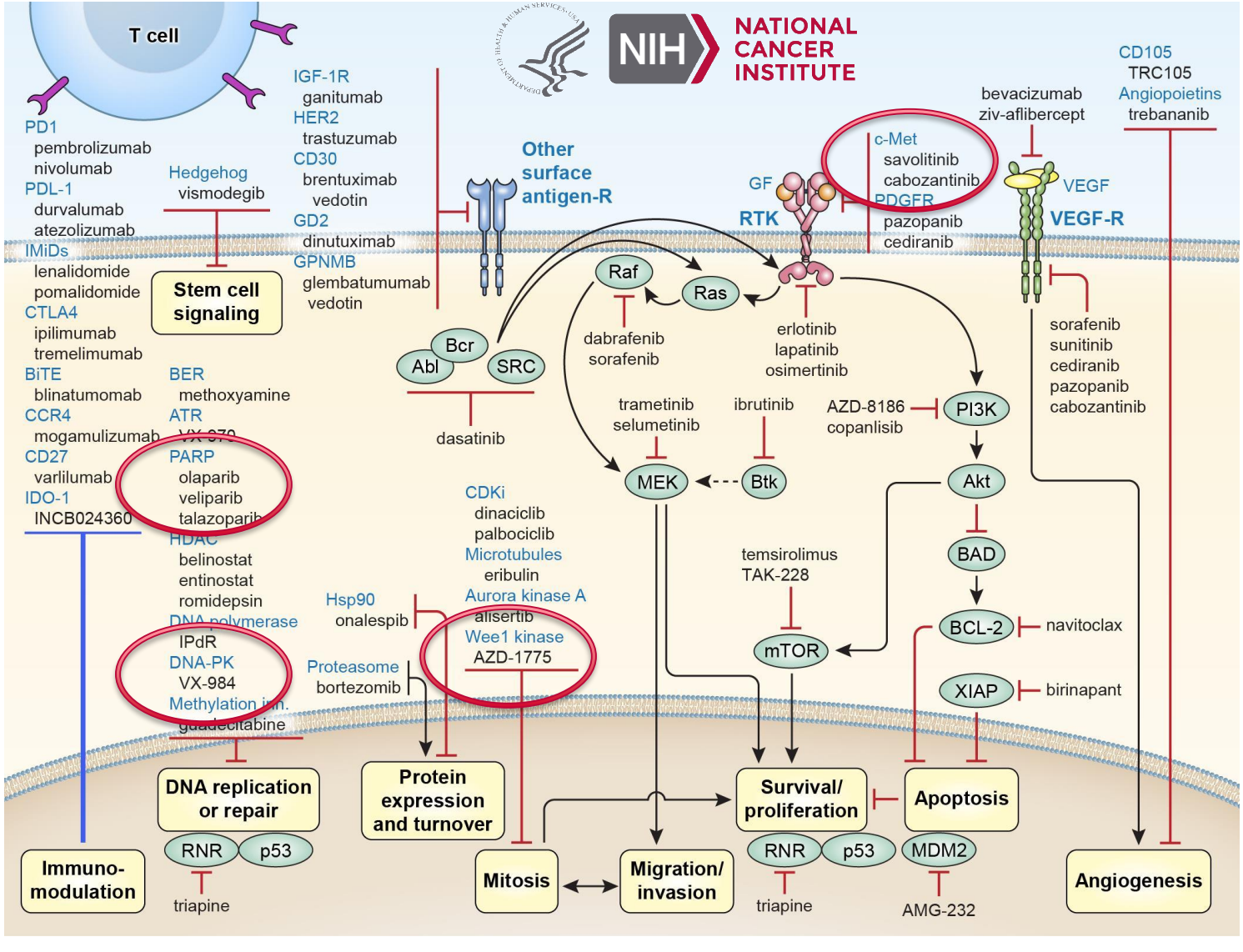
- FNLCR's PD Biomarker Program staff play a major role in clinical trial development in ETCTN by
  - Demonstrating the **need for rigor in biomarker assay development** through its own assay development activities – the scientific process starts long before the biopsy material enters the lab
  - Providing the **laboratory science expertise** for incorporating a new level of rigor in ETCTN biospecimen acquisition and analysis

FNLCR's PD Biomarker Program impact on ETCTN

- Provided the impetus to **involve of research pathologists and interventional radiologists** at the site level to improve biopsy quality
  - PD Biomarker evaluation of biopsy quality from ETCTN trials demonstrated the **need for a comprehensive quality effort**
  - Prompted and supported ETCTN to provide supplemental funding for interventional radiologists who are now developing SOP's for adoption at all ETCTN sites

- Provided the **expertise for scientific review of biomarker assays** that are incorporated into ETCTN studies
  - The Biomarker Review Committee now reviews integral and integrated assays for ETCTN studies, **utilizing the expertise of FNLCR's PD Biomarker Program staff**
  - PD program staff **provide consultation** to recipients of ETCTN UM1 Biomarker Assay Development supplements to support development of validated assays

- FNLCR's PD Biomarker Program **directly performs PD assays** on biopsy material obtained in ETCTN studies


T cell
NIH
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PD1
pembrolizumab
nivolumab
PDL-1
durvalumab
atezolizumab
IMiDs
lenalidomide
pomalidomide
CTLA4
ipilimumab
tremelimumab
BiTE
blinatumomab
CCR4
mogamulizumab
CD27
varlilumab
IDO-1
INCB024360
Hedgehog
vismodegib
Stem cell signaling
BER
methoxyamine
ATR
VX-970
PARP
olaparib
veliparib
talazoparib
HDAC
belinostat
entinostat
romidepsin
DNA polymerase
IPdR
DNA-PK
VX-984
Methylation inh.
guadecitabine
IGF-1R
ganitumab
HER2
trastuzumab
CD30
brentuximab
vedotin
GD2
dinutuximab
GPNMB
glembatumumab
vedotin
Other surface antigen-R
Bcr
Abl
SRC
dasatinib
Raf
Ras
dabrafenib
sorafenib
GF
RTK
erlotinib
lapatinib
osimertinib
c-Met
savolitinib
cabozantinib
PDGFR
pazopanib
cediranib
bevacizumab
ziv-aflibercept
VEGF
VEGF-R
sorafenib
sunitinib
cediranib
pazopanib
cabozantinib
CD105
TRC105
Angiopoietins
trebananib
trametinib
selumetinib
ibrutinib
MEK
Btk
AZD-8186
copanlisib
PI3K
Akt
BAD
BCL-2
navitoclax
XIAP
birinapant
CDKi
dinaciclib
palbociclib
Microtubules
eribulin
Aurora kinase A
alisertib
Wee1 kinase
AZD-1775
Hsp90
onalespib
Proteasome
bortezomib
temsirolimus
TAK-228
mTOR
DNA replication or repair
RNR
p53
triapine
Protein expression and turnover
Mitosis
Migration/ invasion
Survival/ proliferation
RNR
p53
triapine
Apoptosis
MDM2
AMG-232
Immuno-modulation
Angiogenesis

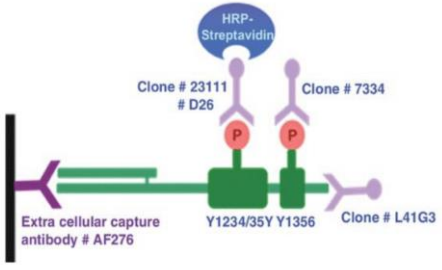
Novel agents accepted into the NExT pipeline from Pharma/Biotech in the past year

- M6620 (VX-970; ATRi)
- M3814 (DNA-PKi)
- Venetoclax (BCL2)
- TAK-243 (UAEi-ubiquitin-activating enzyme)
- GMI-1271 (E-selectin)
- **Radium-223**
- Hu5F9-G4 (anti-CD47 Ab)
- Rogaratinib (pan-FGFRi)

FNLCR PD Assays for Recent ETCTN Trials

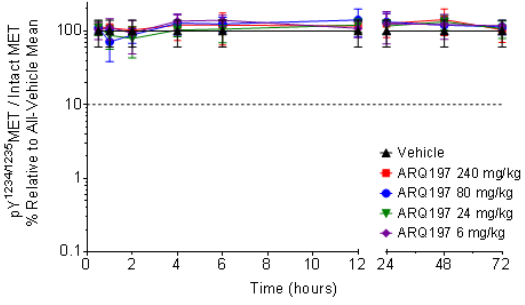
CTEP #	Tumor biopsies?	CTCs?	Title
8880	**yes** (baseline, C1D8)	no	Phase Ib Study of the Combination of Pazopanib, an Oral VEGFR Inhibitor, and ARQ 197 (Tivantinib), an Oral MET Inhibitor, in Patients with Refractory Advanced Solid Tumors
9350	**yes** (baseline, C1D3/C1D8)	**yes**	A Phase I Study of Single-agent MK-1775 (AZD1775), a Wee1 Inhibitor, in Patients with Advanced Refractory Solid Tumors
9284	no	**yes**	A Phase 2 Study of Cabozantinib (XL184), a Dual Inhibitor of MET and VEGFR, in Patients With Metastatic Refractory Soft Tissue Sarcoma
9483	**yes** (baseline, C1D4)	**yes**	A Phase I Trial of TRC102 (methoxyamine HCl) in Combination with Temozolomide in Patients with Relapsed Solid Tumors and Lymphomas
9510	**yes** (baseline, C1D8)	**yes**	Pilot Trial of BMN 673, an Oral PARP Inhibitor, in Patients With Advanced Solid Tumors and Deleterious BRCA Mutations
9762	no	**yes**	Phase I Trial of the Combination of Bortezomib and Clofarabine in Adults with Refractory Solid Tumors
9659	**yes** (baseline, C1D2, C1D28)	**yes**	Phase I Trial of the Combination of Nilotinib and Paclitaxel in Adults with Refractory Solid Tumors
9883	no	**yes**	Phase I Trial of 4'-thio-2'-deoxycytidine (TdCyd) in Patients With Advanced Solid Tumors
10002	**yes** (baseline, C1D2)	**yes**	A Phase I Study of Indenoisoquinoline LMP744 in Adults With Relapsed Solid Tumors and Lymphomas
10005	**yes** (baseline, C3D1)	**yes**	A Phase 2 Study of Anti-PD-L1 Antibody (Atezolizumab) in Alveolar Soft Part Sarcoma
10145	**yes** (baseline, C1D8, C2D15)	**yes**	Phase Ib Combination Study of Copanlisib and Nivolumab in Advanced Solid Tumors and Lymphomas
10114	no	**yes**	Phase I Trial of 5-aza-4'-thio-2'-deoxycytidine (Aza-TdC) in Patients With Advanced Solid Tumors

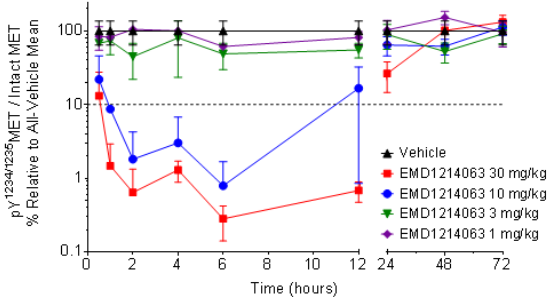
Pharmacodynamic Biomarkers - POM of MET-TKIs: Impact on CTEP portfolio development of MET inhibitors

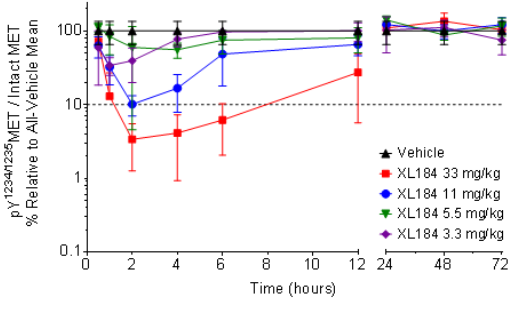


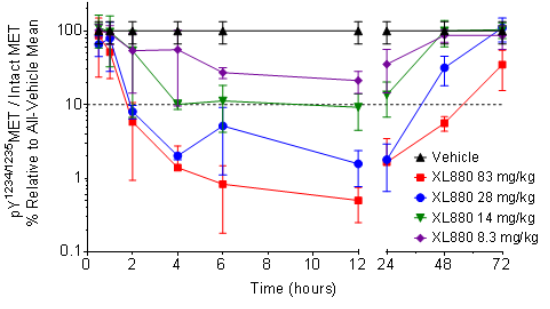
MET-TKI treatment of SNU5 X(

- EMD1214063 (NSC 758244, tepotinib)
- ARQ197 (NSC 758242, tivantinib)
- XL184 (NSC 761068, cabozantinib)
- XL880 (NSC 755775, GSK1363089, foretinib)







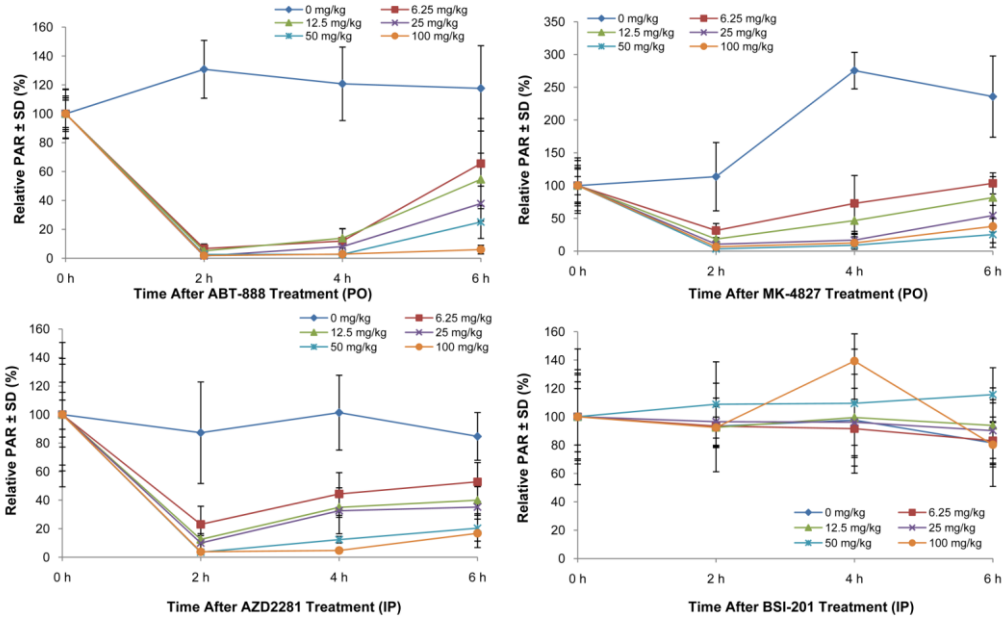


Apurva K. Srivastava et al. Clin Cancer Res 2016;22:3683-3694

Apurva K. Srivastava et al. Mol Cancer Ther 2018;17:698-709

Demonstration of lack of METi activity contributed to discontinuation of ETCTN development of ARQ197

Pharmacodynamic Biomarkers - POM of PARPi's: Impact on CTEP portfolio development of PARP inhibitors



Ji et al, AACR Annual Meeting 2011

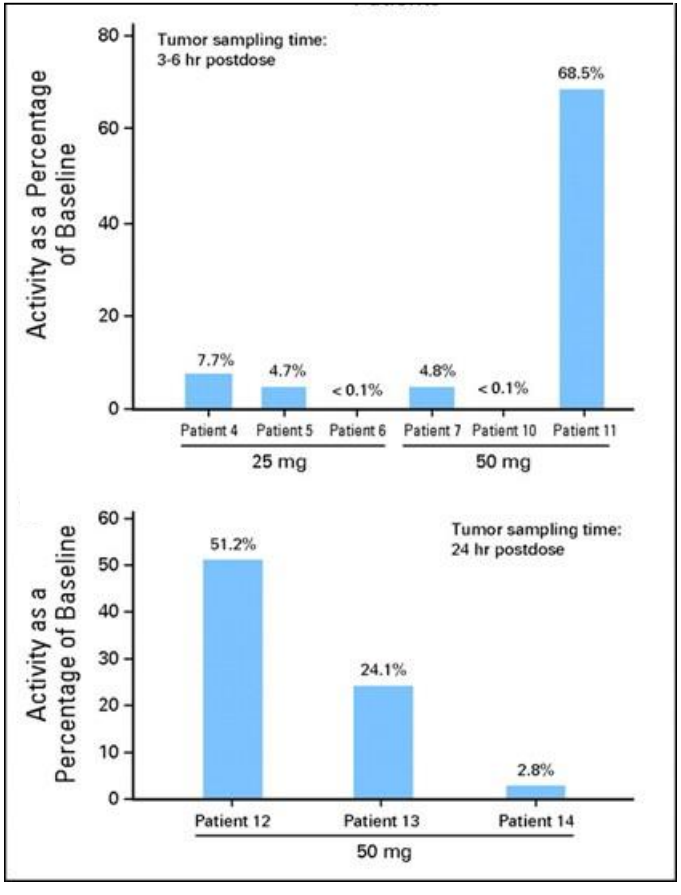
Demonstration that treatment with ABT-888, MK-4827, and AZD2281 decreased PAR levels in A375 xenografts, but treatment with BSI-201 did not, contributed to discontinuation of CTEP sponsorship of BSI-201

Scheduling of Veliparib (PARPi) for Constant Control of PARP 1/2

First-ever phase 0 trial in oncology justified by preclinical modeling

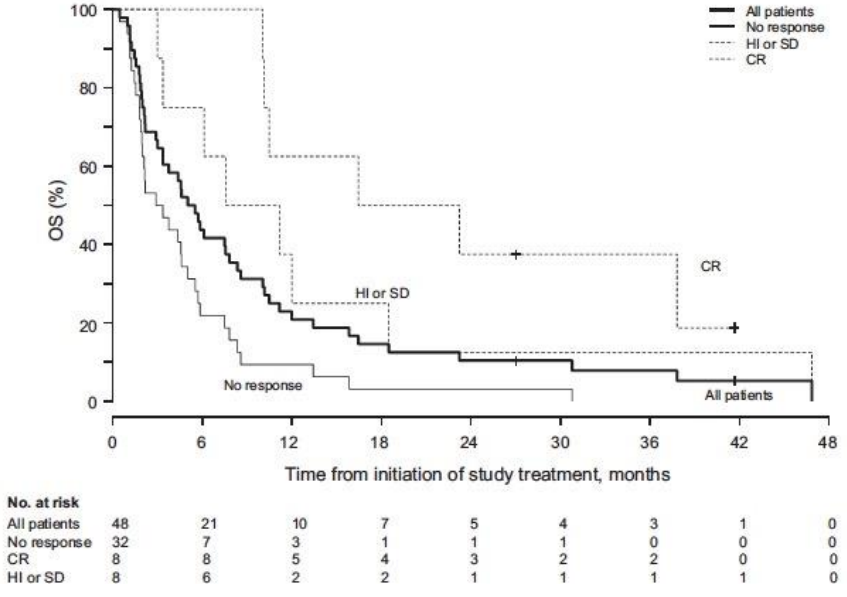
- PD biomarker as the Primary Objective of CTEP-sponsored trial at NIH Clinical Center
- POM and kinetics of molecular target control
- Exploratory IND filing

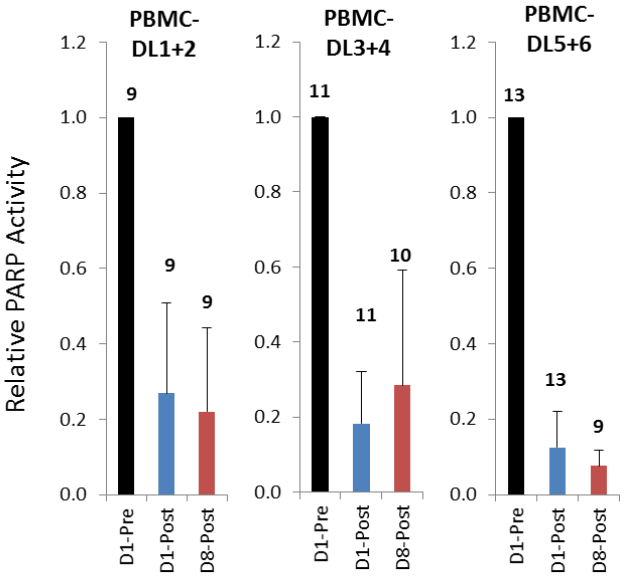
Time-Course of PD Biomarker Response (% of vehicle group) in model system			
Dose Level	2-hr	5-hr	24-hr
1.6	8%	57%	180%
3.2	3%	66%	60%
6.3	2%	53%	55%
12.5	1%	40%	44%
25	1%	20%	47%



Kummar et al. *JCO* 2009, 27, 2705-2711

Reproducible inhibition of PARP activity: Phase 1 study of veliparib and temozolomide in AML





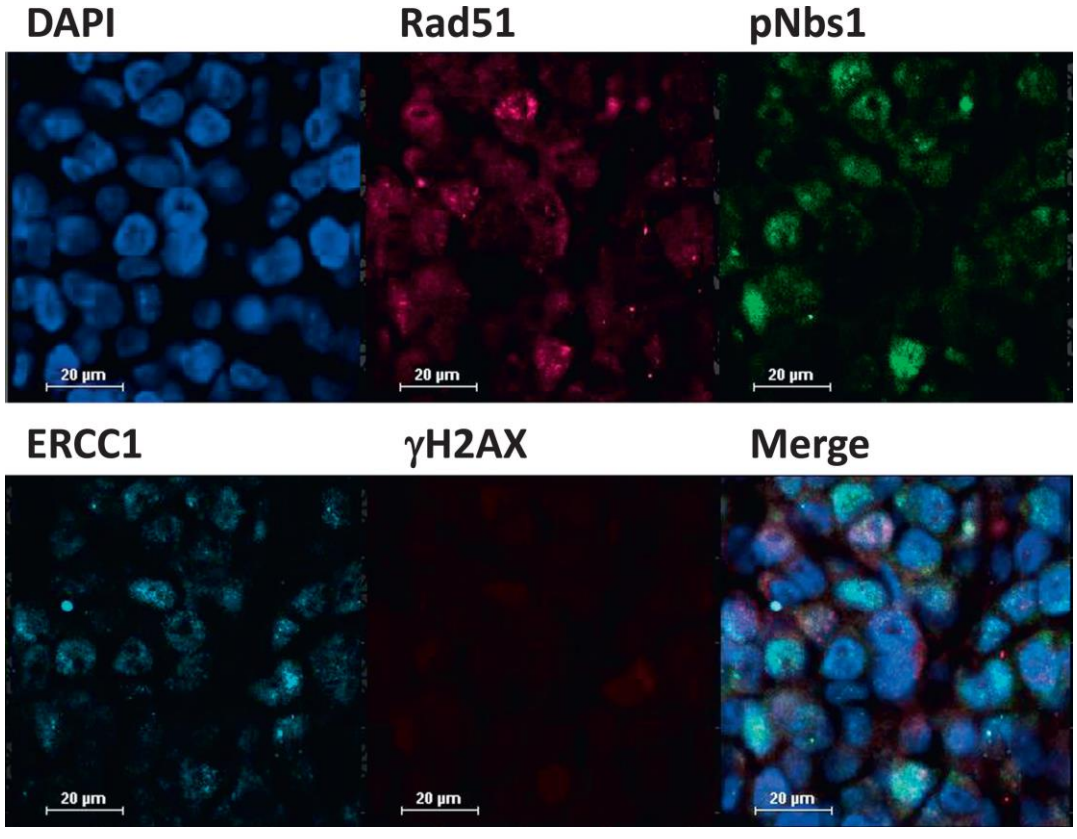
Clin Cancer Res 2017;23:697-706

"Veliparib at all dose levels suppressed PAR formation in peripheral blood cells with different percentages of circulating blasts… but no clear difference between responders and nonresponders"

ETCTN Early Phase Clinical Trial Development of DDR Modulators with PD Biomarkers

Pathway Target	Molecular Target	Agents	DDR PD Biomarker(s)
Single/Double Strand Break Induction	mulitple TOP1i	any chemoRx agents irinotecan, topotecan, indenoisoquinolines, AZD1775 (Wee1i)	pNBS1, γH2Ax, RAD51, ERCC1 γH2Ax w/cCasp3 (apoptosis)
Single Strand Break Response: BER	PARP1/2i	veliparib, olaparib, talazoparib	PAR polymer
	APE blockade w/TOP2 sensitivity	TRC102 (methoxyamine)	Late DNA damage (pNBS1, γH2Ax, RAD51)
Single Strand Break Response: TMB, MSI	PD1/L1 blockade	pembrolizumab nivolumab, durvalumab, atezolizumab	MLH1, MSH2, MSH6, PMS2
DDR Sensors	ATRi	M6620 (formerly VX-970)	pS1989 autophosphorylation
	DNA-PKi	M3814 M9831 (aka VX-984)	γH2Ax, pKAP1 (recent project plan)

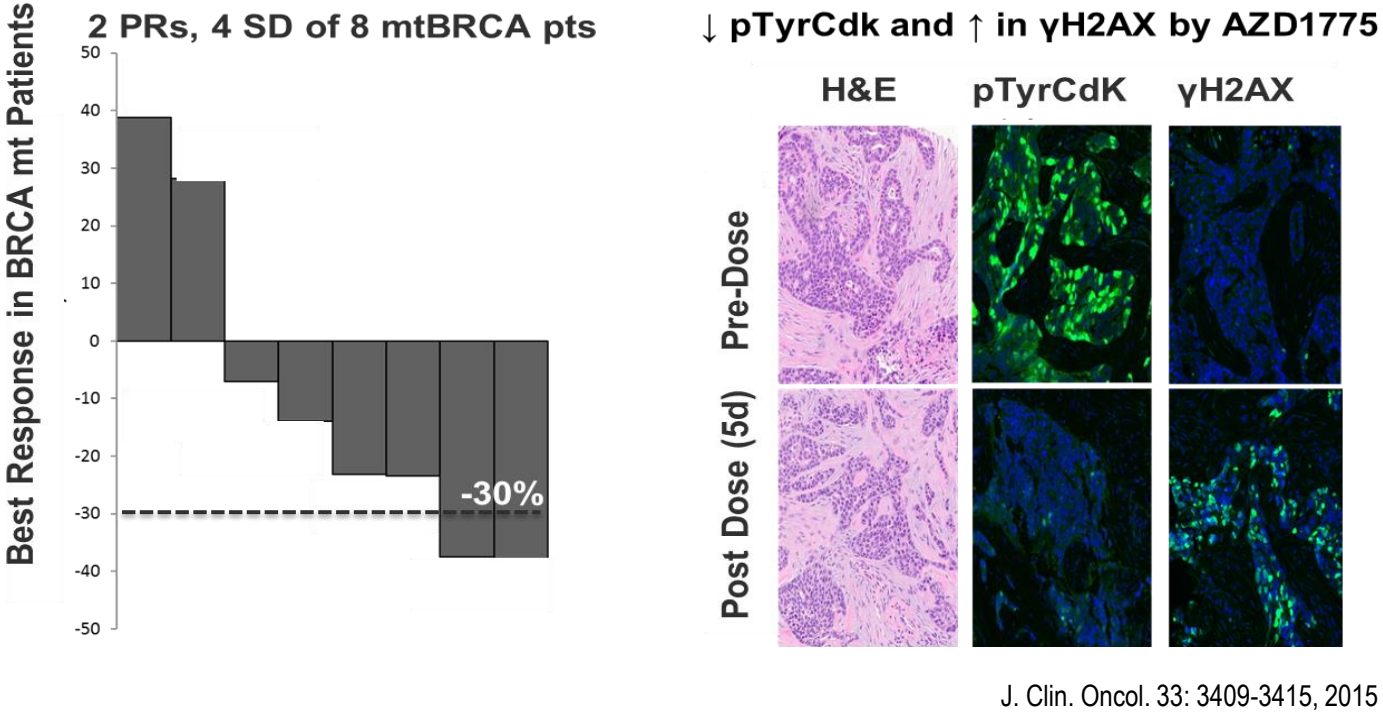
Multiplex Immunofluorecence DDR assays for ETCTN trials



Marrero et al (2016). Semin Oncol 43:453-463

DNA damage response of MX-1, a BRCA-deficient breast cancer model, to 7.5 mg/kg irinotecan; 40x

FNLCR PD Biomarker Assays in Development of the Wee1 Inhibitor AZD1775 by ETCTN



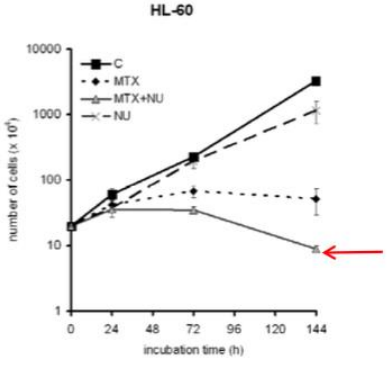
J. Clin. Oncol. 33: 3409-3415, 2015

Proof of Mechanism: Reduction in pTyrCdk and Concurrent Increase in γH2AX Signaling by AZD1775 in Paired Tumor Biopsies

FNLCR PD Biomarker Assays in M3814 drug development:

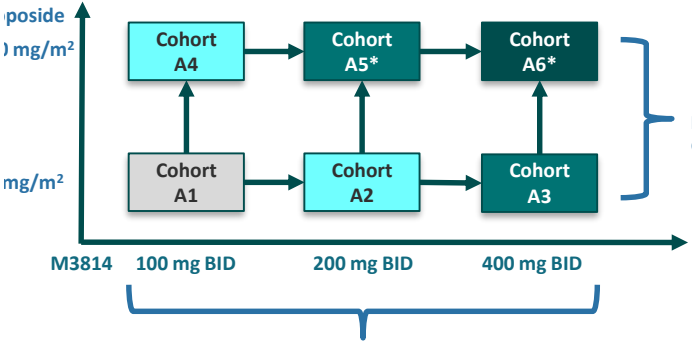
A phase I study of M3814 + mitoxantrone/etoposide/cytarabine (MEC) in refractory acute myeloid leukemia (AML)

A phase I/II study of M3814 + avelumab + hypofractionated radiation (SBRT) in Solid Tumors and Hepatobiliary Malignancies



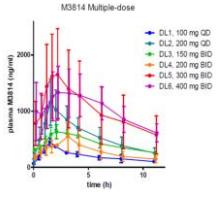
Treatment:

oral M3814 twice daily D2-D21 +
MEC (8 mg / 50-100 mg / 1g / m²) D1-5

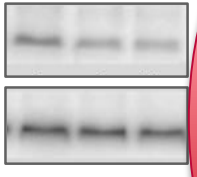


Phase I 3+3 design (*A5 / A6 open if left & below cohort clear)

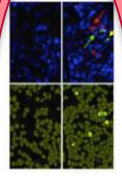
Correlatives:



pharmacokinetics (UPITT UM1)

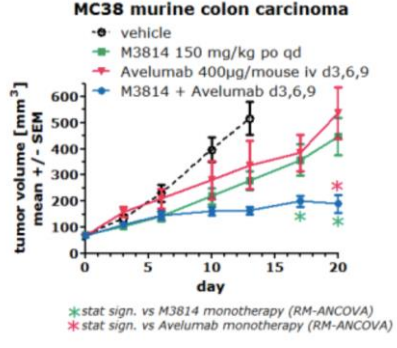


pDNA-PK assay (UCDavis UM1 supplement)

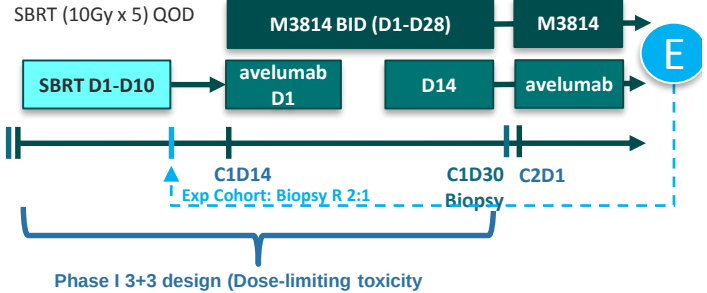


γH2AX/pKap1 (PADIS)

WES & RNA-seq (MoCha)

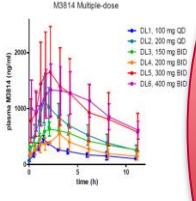


oral M3814 twice daily D1-D28 (dose escalation) +
IV avelumab 10mg/kg q2wk
SBRT (10Gy x 5) QOD



Phase I 3+3 design (Dose-limiting toxicity period)

Correlatives:



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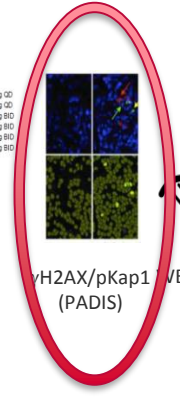

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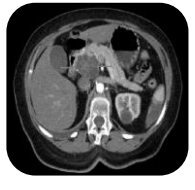

perfusion CT (Rutgers)

Future of FNLCR PD Program & ETCTN

- The ETCTN effort to provide supplemental funding to ETCTN investigators for biomarker assay development has had limited success
  - There is a big gulf between laboratory science discipline and the approach of basic scientists in clinical sample analysis

- **ETCTN will increasingly rely on the FNLCR PD Biomarker Program** for the development of PD assays to be used in clinical trials
  - Involve FNLCR PR Biomarker Program staff in the initial review of biomarker plans, for input into sampling strategy as well as in the technical assay development

- FNLCR PR Biomarker Program assays anticipated to be used in upcoming ETCTN studies include: EMT, MMR, DDR

Questions?

ETCTN accomplishments

- **Evaluate new molecular entity**
  - **Z-endoxifen** for ER-positive breast cancer
  - **MEDI570** for ICOS-positive peripheral T-cell lymphomas
  - PARP inhibitor **veliparib** for leukemia
  - **Fluorodeoxycytidine**, a novel DNA methyltransferase inhibitor

- **First in human, combinations and studies demonstrating activity**
  - **Eribulin/gemcitabine** in bladder cancer
  - **Cediranib/olaparib** in high grade serous ovarian cancer
  - **Osimertinib combinations** in EGFR-mut NSCLC (necitumumab/MTORC1 & MTORC2/navitoclax
  - **HDAC/proteasome** inhibitors in multiple myeloma

- **Immuno-oncology agents**

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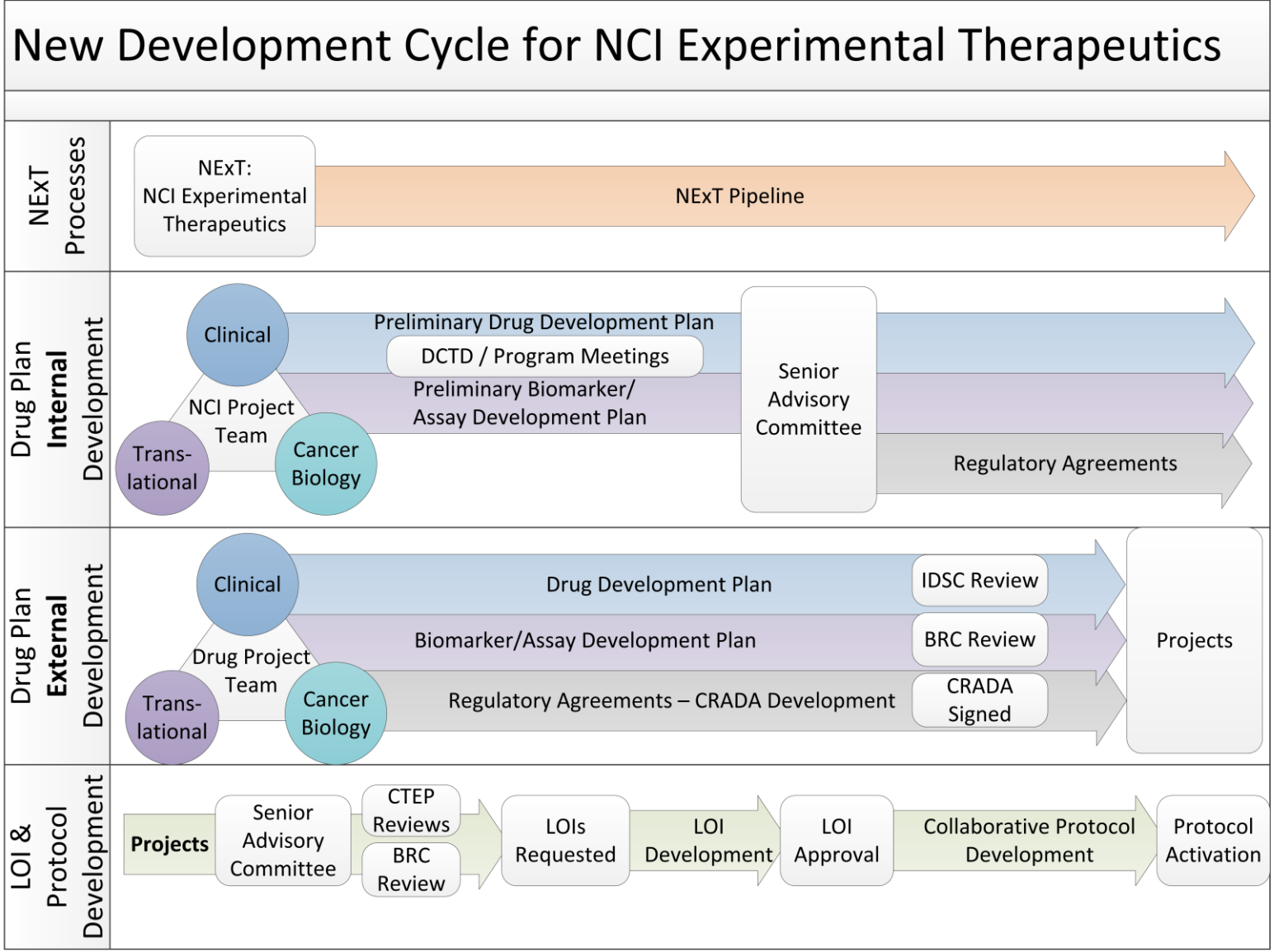
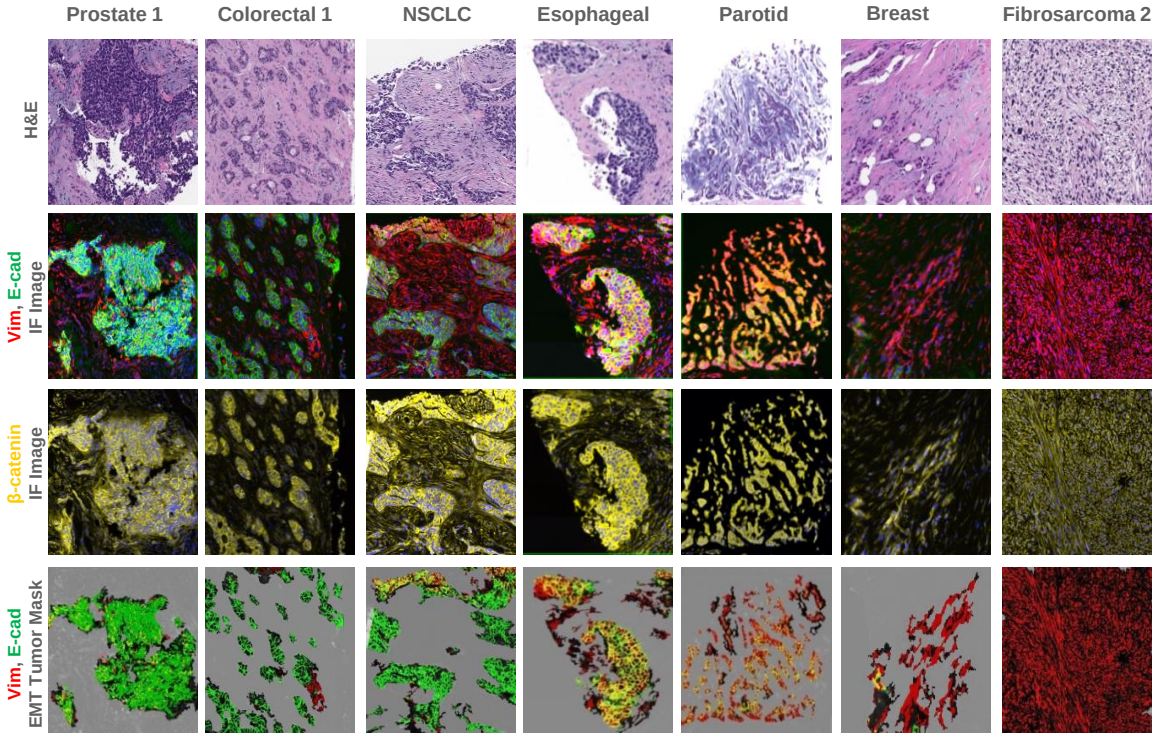
New Development Cycle for NCI Experimental Therapeutics

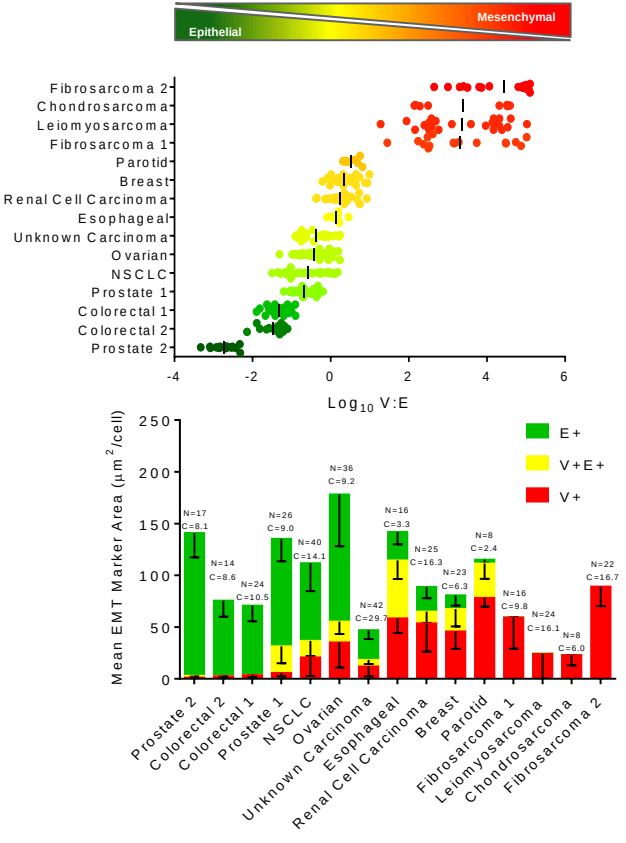


CRADA: Cooperative Research and Development Agreement **IDSC**: Investigational Drug Steering Committee **BRC**: Biomarker Review Committee

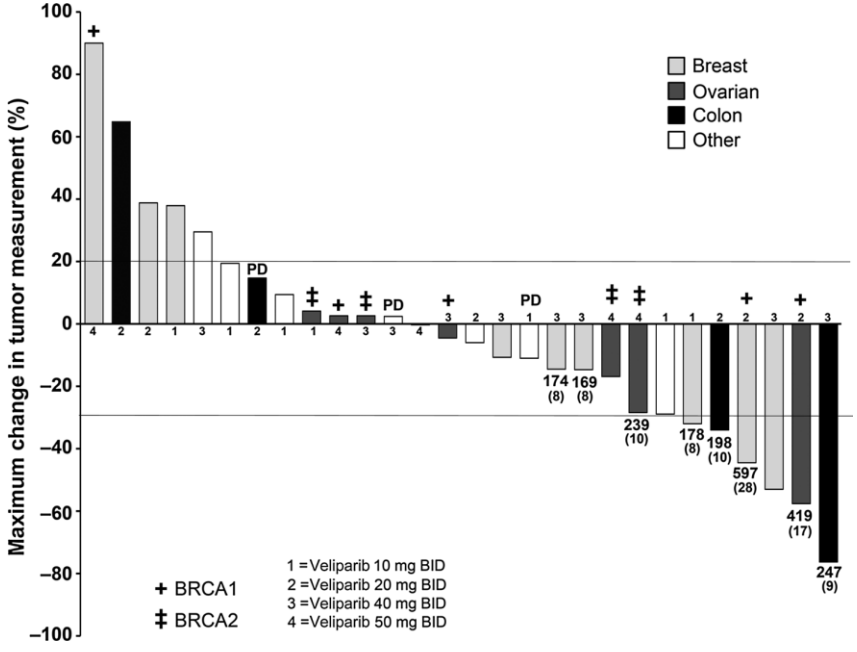
PD Biomarkers in Clinical Translation of Novel Drug Combinations: EMT assays for ETCTN trials

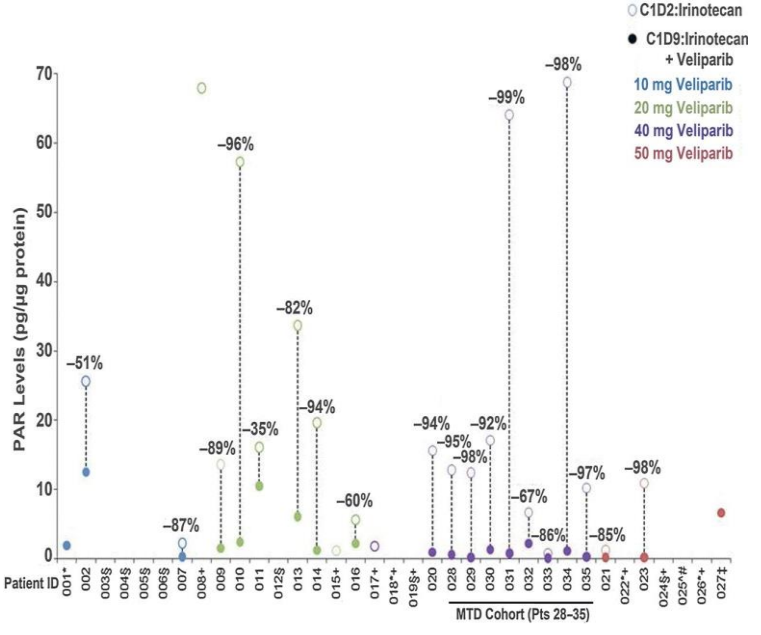


Kinders, Navas, 2018
unpublished



Reproducible inhibition of PARP activity: Phase 1 study of veliparib and irinotecan in solid tumors





LoRusso et al. Clin Cancer Res 2016;22:3227-3237
Figure 2: PARP inhibition in paired tumor biopsies

"There was no analogous positive association between the degree of PARP inhibition and best response"