

# Plenary Speakers



**Razelle Kurzrock, M.D.**  
**Chair, Early Therapeutics**  
**Committee**

# **“Precisionalized” Cancer Therapies The Next Frontier**

**Razelle Kurzrock, MD**

**Chair, Early Therapeutics and Rare Cancers Committee (SWOG)**

Senior Deputy Director, Clinical Science

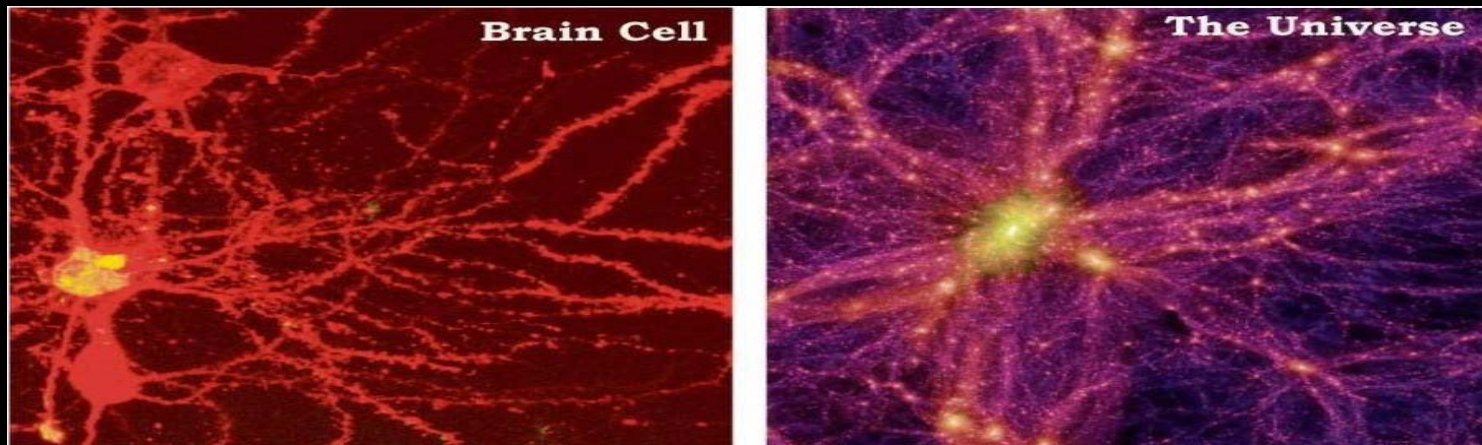
Director, Center for Personalized Cancer Therapy

Director, Clinical Trials Office

Director, Rare Tumor Clinic

Team Leader, Experimental Therapeutics

Chief, Division of Hematology/Oncology



## **Disclosures**

**CONSULTING OR ADVISORY ROLE (GAIDO, LOXO, X-BIOTECH, ACTUATE THERAPEUTICS, ROCHE, NEOMED, AND SOLUVENTIS).**

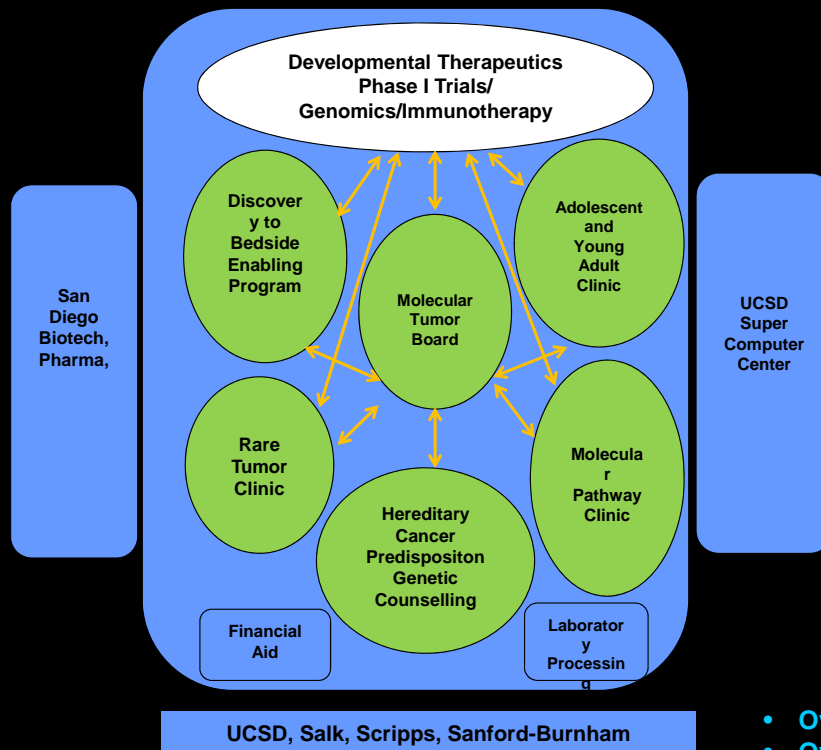
**SPEAKER'S FEE (ROCHE).**

**RESEARCH FUNDING (INCYTE, GENENTECH, MERCK SERONO, PFIZER, SEQUENOM, FOUNDATION MEDICINE, GUARDANT HEALTH, GRIFOLS, KONICA MINOLTA, AND OMNISEQ [ALL INSTITUTIONAL]).**

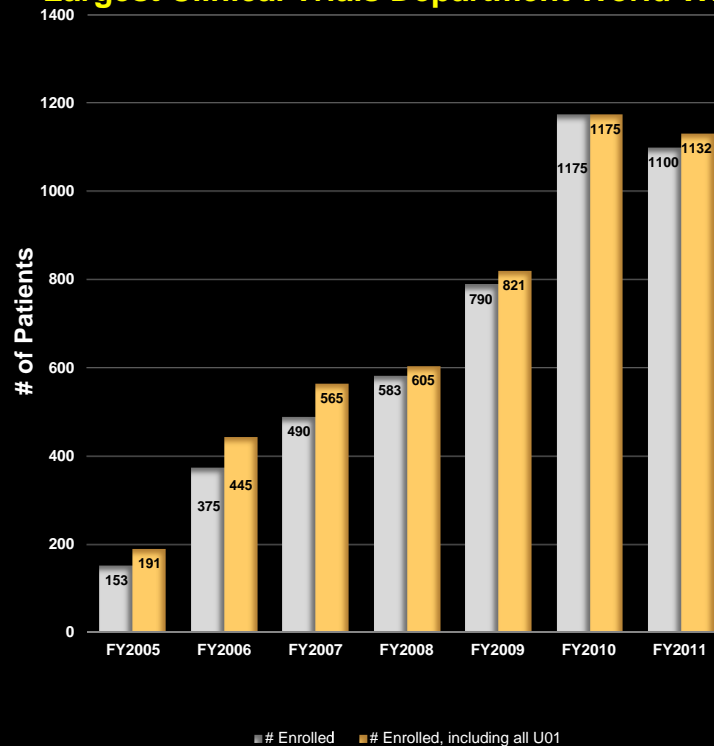
**EQUITY INTERESTS (IDBYDNA, CUREMATCH, INC.).**

# Precision Medicine in the Clinic: Experience

**Center for Personalized Cancer Therapy  
at UCSD Moores Cancer Center**  
Director: Razelle Kurzrock, MD



**Founder and Chair, MD Anderson (2004-2012)**  
**Largest Clinical Trials Department World Wide**



- Over 750 peer-reviewed publications on pubmed
- Oversight >500 early phase trials, including 7 drugs that have gone to FDA approval
- Clinical-grade genomic profiling >20,000 patients
- Leadership positions: SWOG, WIN, NCCN,

# Take-home points

## Right drug(s) to right patient at right time

- At the genomic level, every metastatic tumor is unique and complex→ malignant snowflakes
- In order to be precise, we must personalize treatment—precisionalized
- The pillars of precision medicine are genomics and immunotherapy and they are married to each other.
- Metastatic disease requires customized/individualized combination treatments, not single agents

# Molecular Tumor Board



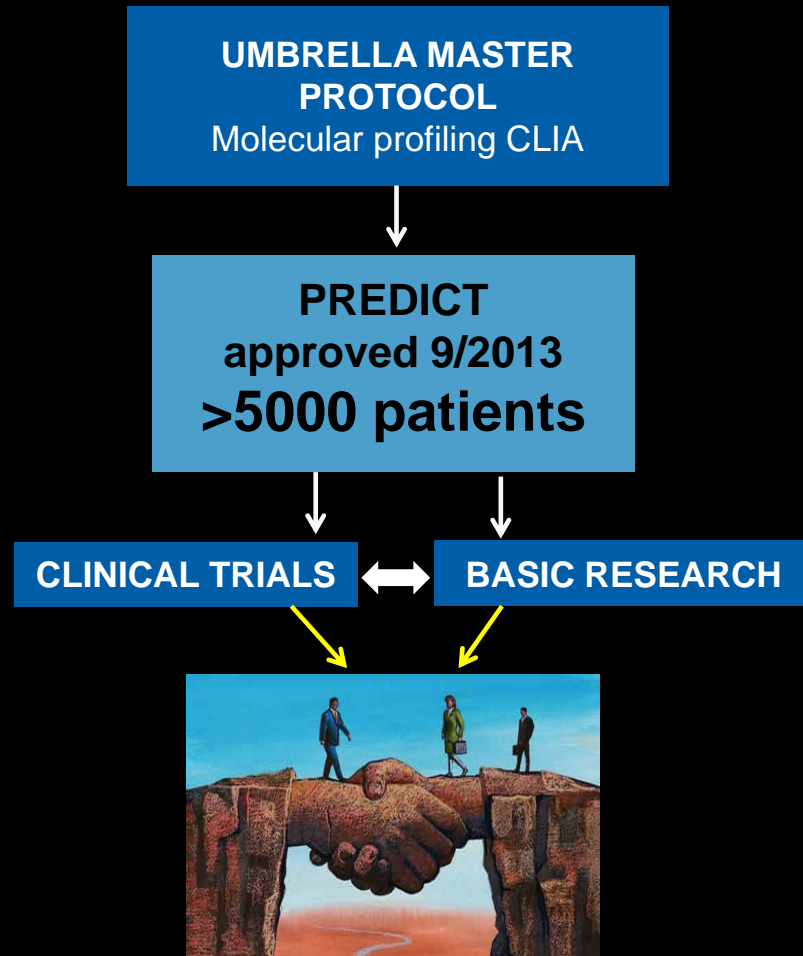
- Initiated December 12, 2012
- Weekly and *ad hoc* e-board
- Multidisciplinary discussion
- Molecular profiling (N ~ 16,000)
- Targeted, tailored treatments

## PUBLICATIONS

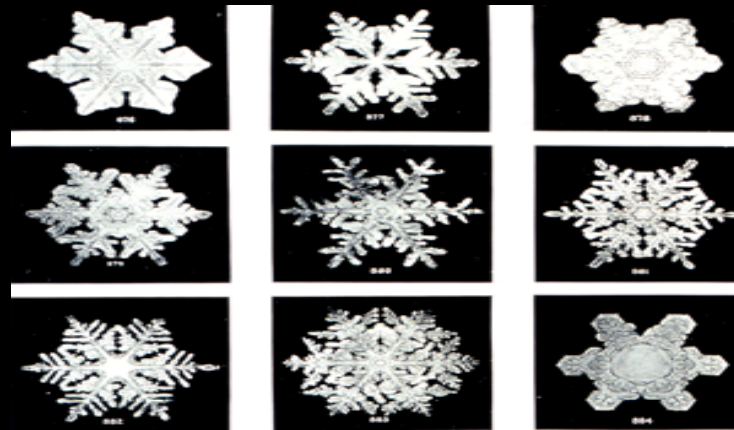
Schwaederle M....Kurzrock, Molecular Tumor Board: The UCSD Moores Cancer Center Experience. *Oncologist*. 2014 Jun;19(6):631-6.

Parker BA....Kurzrock, Breast Cancer Experience of the Molecular Tumor Board at the UCSD Moores Cancer Center. *Journal of Oncology Practice*, 2015.

Patel M, Kato S, Kurzrock R, Molecular Tumor Boards: Realizing Precision Oncology Therapy, *American Society for Clinical Pharmacology and Therapeutics*, 2017.



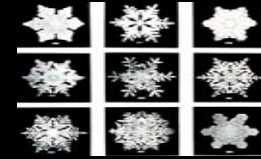
What if every patient  
with metastatic disease  
is different?







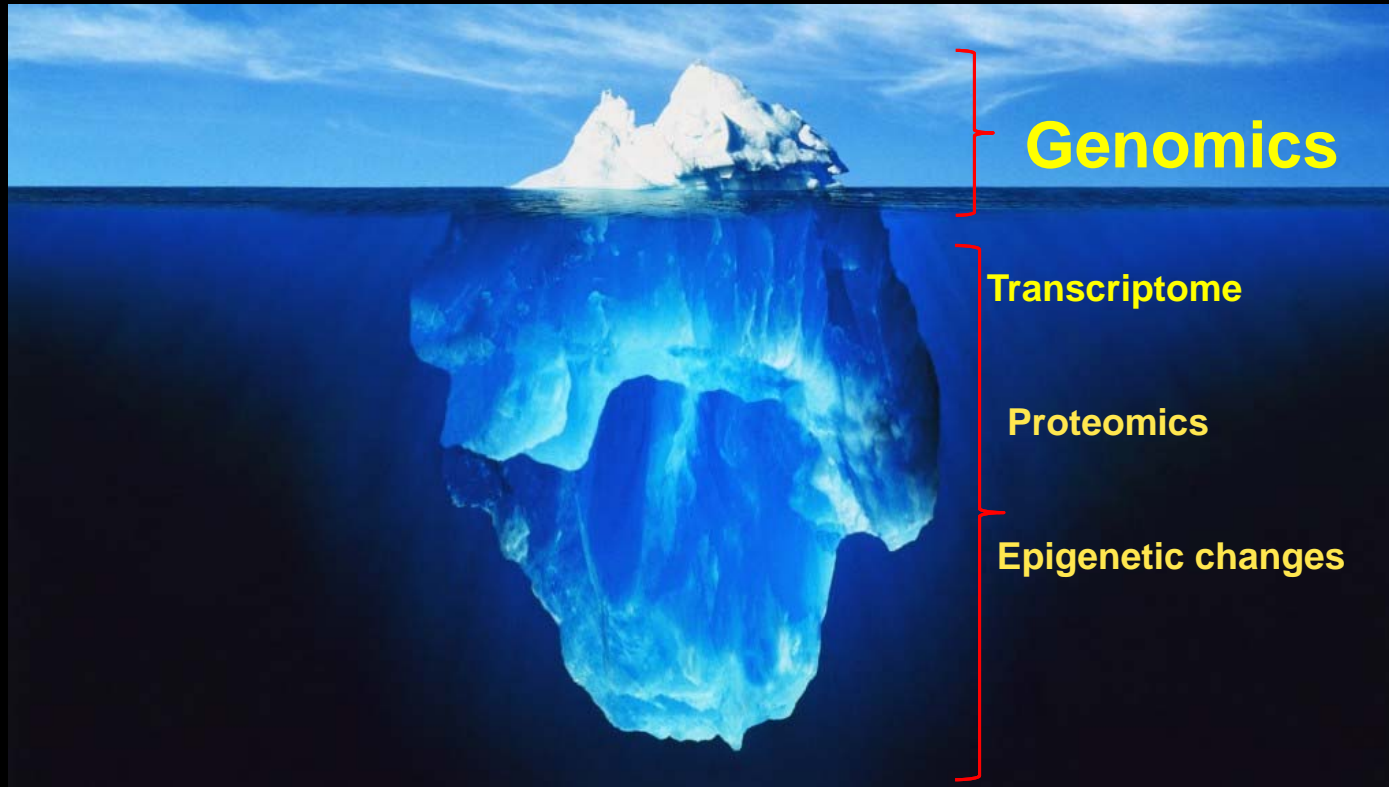
## Malignant Snowflakes Metastatic Breast Cancer



Pt number	Molecular Results (236 genes; NGS)—Breast Cancer
1	PIK3CA amplification, SOX2 amplification, TP53 G302fs*42, FLT3 L260*
2	AKT1 E17K, PIK3CA H1047R
4	EGFR amplification, CCND1 amplification, CDKN2A/B loss, FGFR1 amplification, MYC amplification, TP53 P151A
42	ERBB2 amplification, PIK3CA H1047L, AURKA amplification, TP53 R342P, CREBBP P858S, ZNF217 amplification
25	ERBB2 amplification, MYC amplification, CDK6 amplification, TP53 R213*
7	ESR1 Y537S
13	GATA3 *445fs*2+ , FGF3 amp, FGF4 amp, FGF19 amp
16	RET C634R, GATA3 P436fs*11+
18	AKT3 amplification, MYC amplification, MYCL1 amplification, TP53 R248Q

**Wheler....Kurzrock. Oncotarget. 2014: Wheler....Kurzrock. Cancer Research, 2014; Kurzrock Giles. Cell Cycle. 2015**

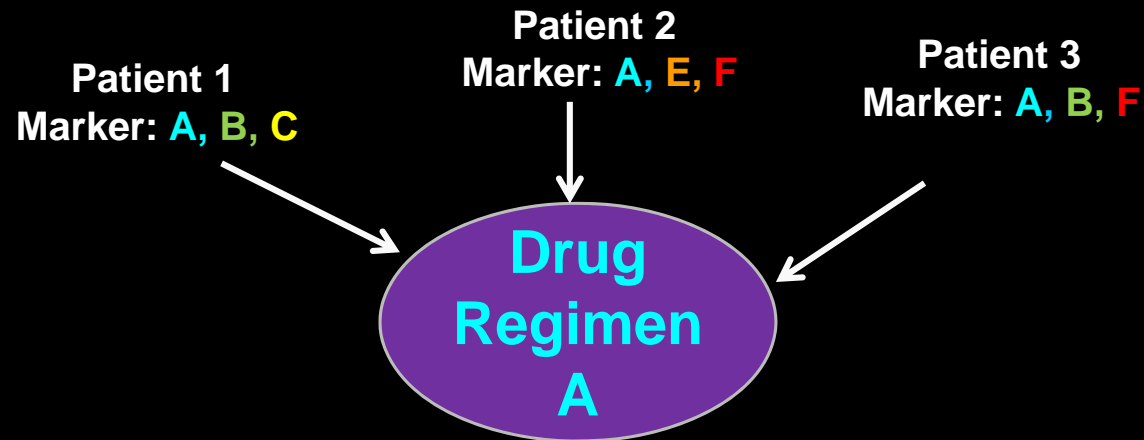
# Tip of the Iceberg



# Evolution of Clinical Trial Design

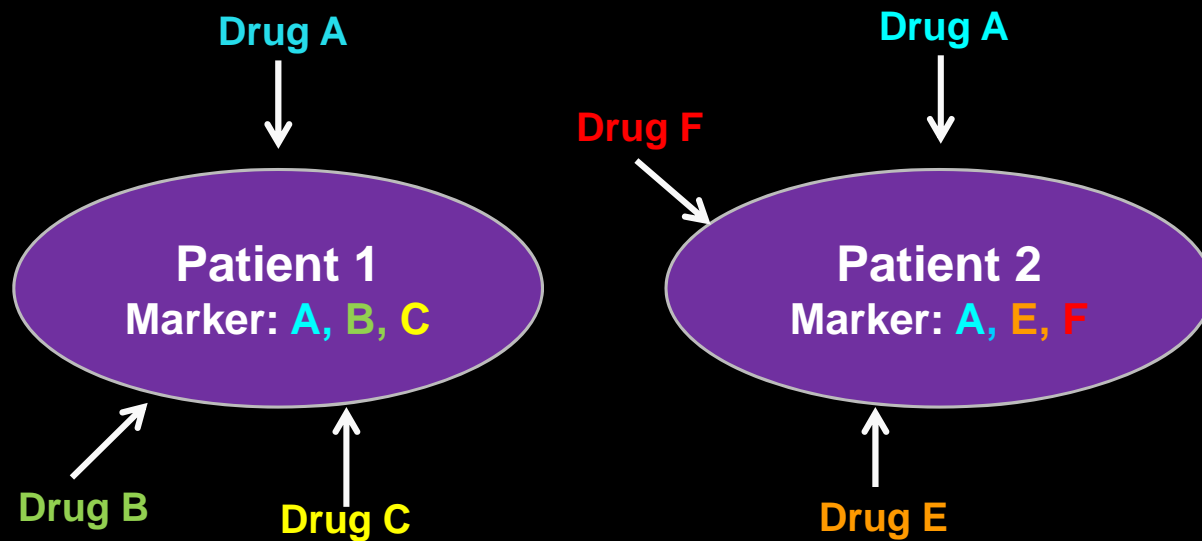


## Drug-Centric Trial (Traditional)



**Strategy:** Find common feature between patients (e.g. type of cancer or type of molecular aberration or immune marker) and place all on same drugs

## Patient-Centric Trial (N-of-One)



**Strategy:** Molecular and immune marker matching for each patient with customized therapy combination

# Are combinations of drugs safe?

## Patient R with breast cancer HER2+

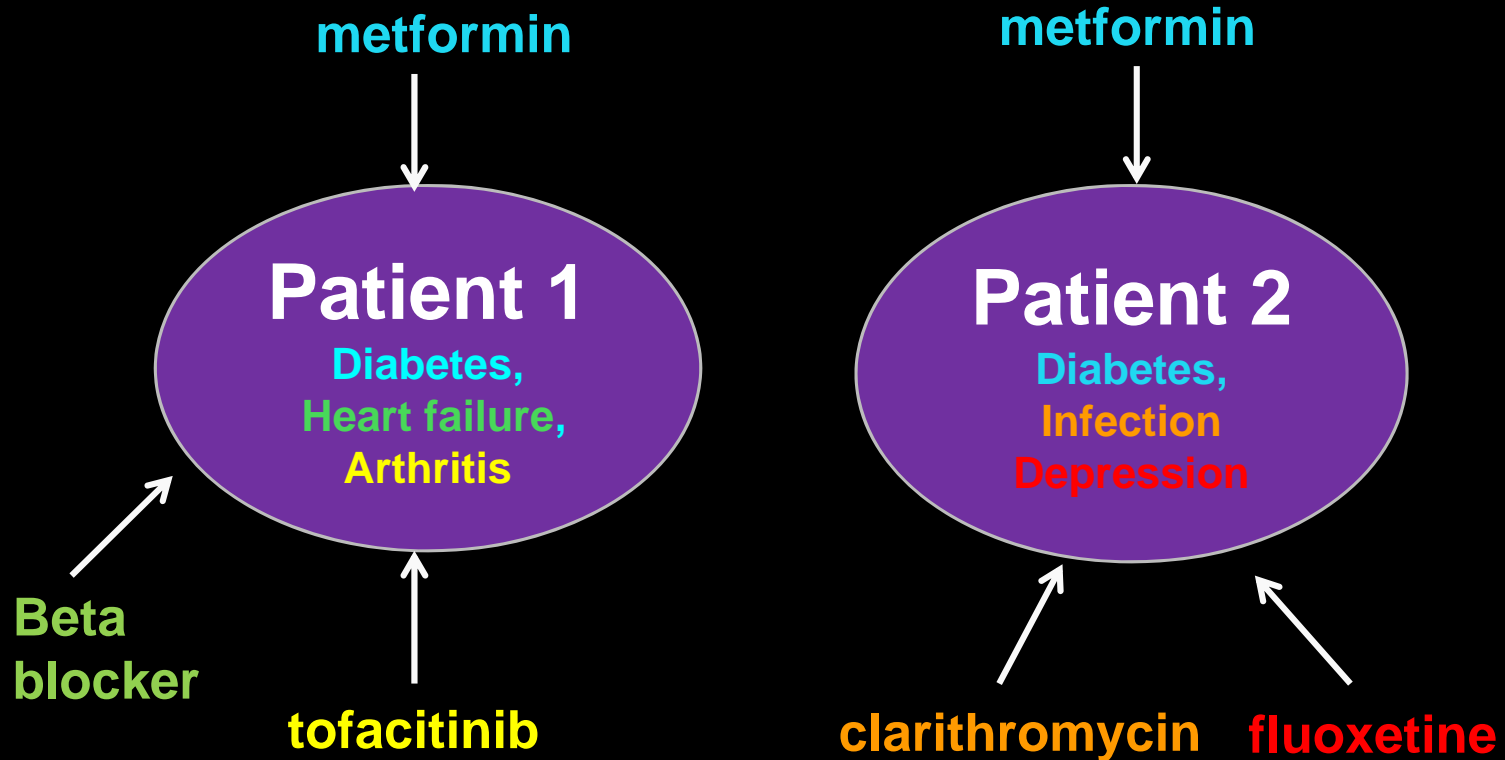
- Ado-trastuzumab emtansine (TDM1) → remission
- At relapse found to have a PIK3CA mutation
- Everolimus to be added → but “no phase I study demonstrating the safety of TDM1 and everolimus combination”

## Where is the safety data?

- TDM1 (ado-trastuzumab emtansine)
- Alprazolam
- Arformoterol tartrate
- ASA
- Levothyroxine
- Beclomethasone dipropionate
- Tiotropium bromide
- Bupropion
- Benzonatate
- Saliva substitutes topical
- Dextromethorphan and guaifenesin
- Ipratropium nasal
- Levalbuterol
- Spironolactone
- Fondaparinux

# Patient-Centric Therapy

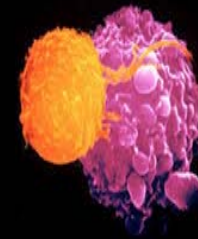
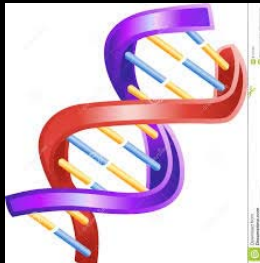
We already customize treatment (except in oncology)





# The Pillars of Precision/Personalized Medicine

Genomics      Immunotherapy



T-cell killing  
cancer cell

**The future  
is here.**

# MARRIAGE

## Genomics and Immunotherapy

### Mutanome-Directed Immunotherapy

The more mutated the tumor,  
the better the response to immunotherapy

- 4% response rate for low mutational burden
- 26% response rate for intermediate
- 45% response rate for high
- 67% response rate for very high mutational burden

Goodman.....Kurzrock. MCT, 2017

# **Super-Responders and Cutting Edge Technology**

# High-grade neuroendocrine cervical cancer

49-year-old woman from Saudi Arabia

## Past treatments at OSH in Saudi Arabia:

Myomectomy around 4/2015

Cisplatin/etoposide chemo x 3 cycles with progression\

Radiation treatment x 2 sessions with progression last session 11/15/2015

## First visit

Exam: Very large abdominal tumor

Impending bowel obstruction,

Partial ureteral obstruction

Urology consult → stent not indicated, suggest hospice

# Liquid Biopsy Program

Doing genomics on DNA from a small tube of blood or from urine

No tissue biopsy

**~5000 patient samples**



Schwaederle.....Kurzrock. Use of Liquid Biopsies in Clinical Oncology:  
Pilot Experience in 168 Patients. CCR, 2016

# High-grade neuroendocrine cervical cancer Genomic Profiling

## ctDNA Blood

PTEN R130Q  
FBXW7 R465H  
PIK3CA E545D  
PIK3CA R88Q  
NRAS Q61R  
CTNNB1 S33A  
VUS  
ARID1A P600P  
ARID1A P427L  
BRCA2 L3184V  
NOTCH1 G309D  
NOTCH1 N2389N  
STK11 W332\*  
APC Q767Q  
CDH1 A408A  
FGFR2 A260A  
ERBB2 I435F  
SMO T541T  
BRCA1 G1077R  
MET P325S



**Hypermutated  
ctDNA**

## High-grade neuroendocrine tumor of the cervix Ultra Rare

Immunotherapy: Nivolumab plus SBRT (radiation) plus somatostatin

Pre-Treatment

3 SE:3  
3  
EMERGENCY DEPT SCE

R  
1  
5  
2

20  
20  
1500



8 months after treatment

01:47:11 M:52 SE:4  
178.8 SE:4  
178.8  
J EMERGENCY DEPT SCE

09/14/  
02:0

L  
1  
9  
2

V:120  
mA200  
500msec  
75mm

09/14/

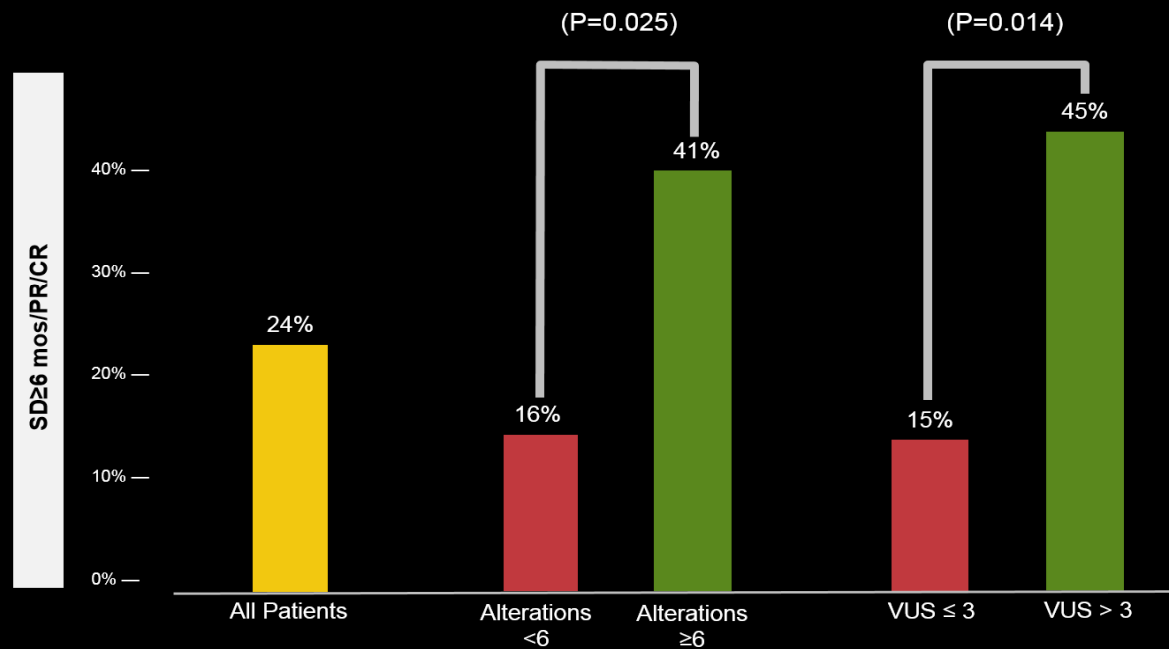


Sharabi.....Kurzrock. Oncologist, 2017

Complete remission at 1.5 years ongoing

# Using hypermutated cfDNA (blood) to predict immunotherapy response

## Mutation Burden (cfDNA) Predicts SD≥6 months/CR/PR



Guardant 360 cfDNA Assay

Khagi... Kurzrock, CCR 2017



# I-PREDICT

## Prospective

Investigation of Profile-Related  
Evidence Determining Individualized  
Cancer Therapy

### **Study Novelty**

- *Customized combinations*
- *Newly diagnosed patients with lethal malignancies*

**Activation Date:** February 13, 2015

**Consented:**  $N = 410$

**Treated:**  $N = 209$  (51%)

**Matched Therapy:**  $N = 175$  (43% of total; 84% of treated)

### **Treatment Decisions Guided by:**

FoundationOne (Heme), Foundation ACT (ct DNA), PD-1/PDL-1  
IHC, Tumor Mutational Burden, MSI

**Nature Medicine,  
In press**



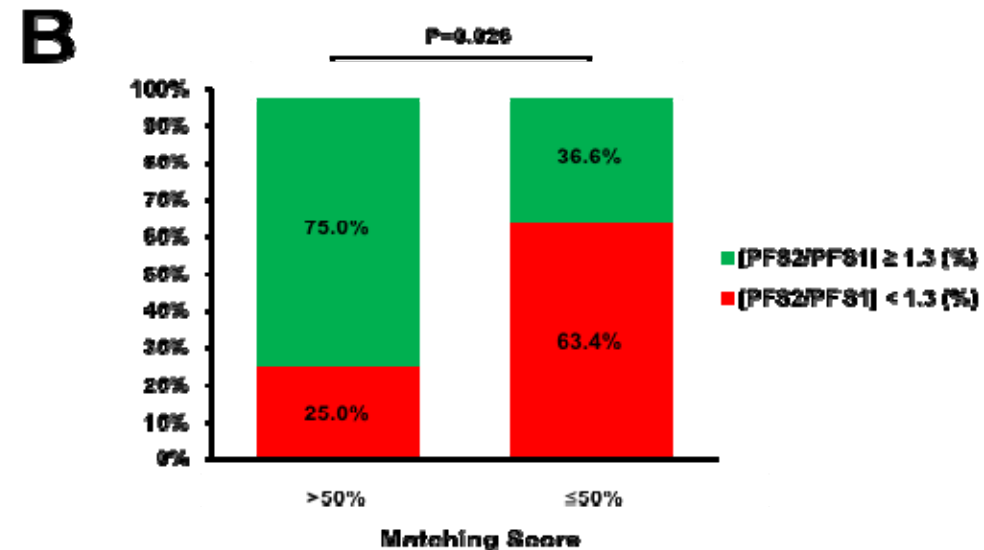
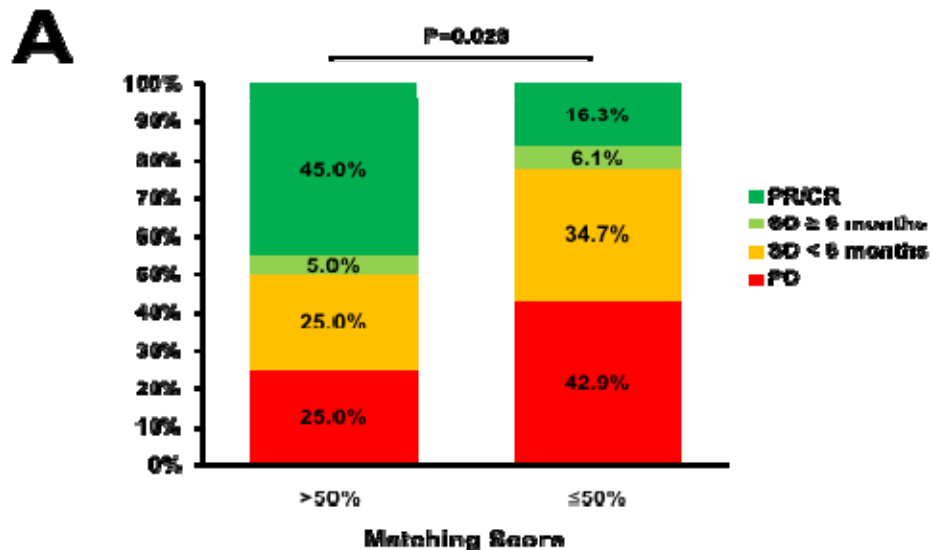
**PI:** Jason Sicklick, MD, FACS  
Associate Professor of Surgery  
Division of Surgical Oncology



**Co-PI:** Razelle Kurzrock, MD  
Director, Center for  
Personalized Cancer  
Therapy

**Avera PI:**  
Brian Leyland-Jones

**Higher degrees of matching correlated  
with higher response rate, progression-free and overall survival**



## 69 F with metastatic ampullary carcinoma

### Previous therapies:

Neoadjuvant FOLFIRINOX  
Whipple procedure

Adjuvant 5-FU

Presented with recurrent  
disease in lung.

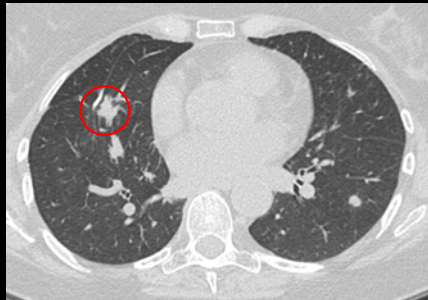
### Genomics:

- APC G1499\*
- APC S1400\*
- CDK6 amplification
- **ERBB2 amplification**  
→ Trastuzumab/Pertuzumab
- ERBB2 T733I
- TP53 C135G  
(Under MyPathway trial)

## 69 F with metastatic ampullary carcinoma



Trastuzumab/Pertuzumab  
(*ERBB2* amplification)  
Genentech Mypathway trial



Partial response  
35+ months



**61-year-old man with metastatic anaplastic thyroid carcinoma:  
Respiratory failure with intubation, on ventilator, intensive care unit**

**Molecular profiling**

**BRAF V600E → vemurafenib**

**Immune profiling**

Tumor-infiltrating lymphocyte: low

Tumor mutation burden: low

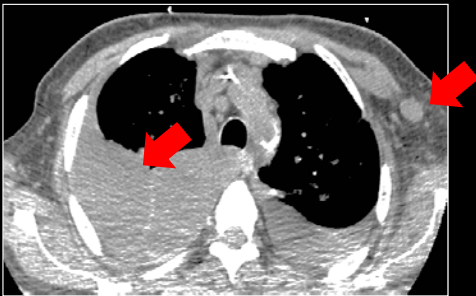
Microsatellite instability: stable

**PD-L1: high positive → nivolumab**

**61-year-old man with metastatic anaplastic thyroid carcinoma:  
Respiratory failure with intubation, on ventilator, ICU**

Vemurafenib plus nivolumab

Pre-treatment



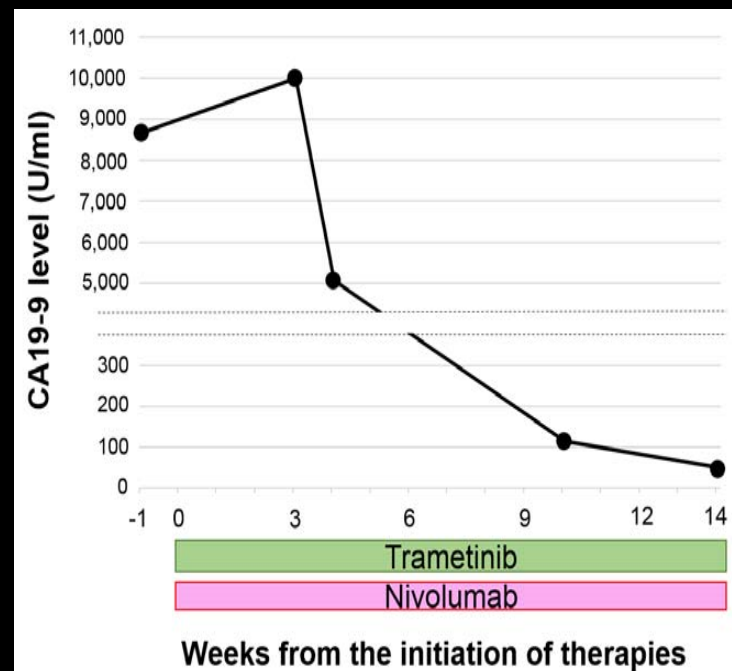
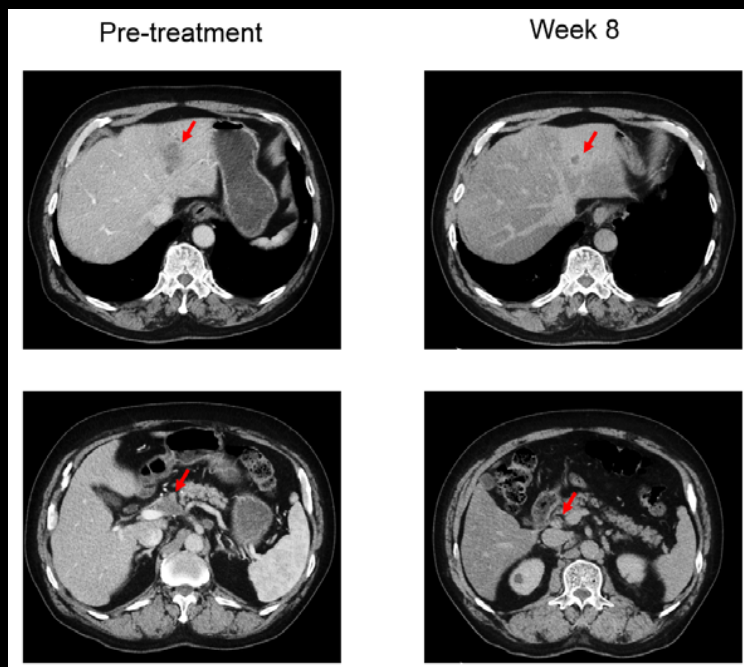
Post-treatment (5 months)



82 year-old man with carcinoma of unknown primary

**KRAS G12D** → Trametinib

**TMB = 16 mutations/mb** → Nivolumab



**Partial response for 15 months.**

*Kato ..... Kurzrock, Cancer Research 2017*

# Early Therapeutics and Rare Cancers (ETRC) Committee SWOG

## DART: Dual Anti-CTLA-4 & Anti-PD-1 Blockade in Rare Tumors

**Sandip Patel, MD**  
Assistant Professor  
Co-Lead Experimental Therapeutics  
UCSD Moores Cancer Center



**Young Chae, MD**  
Assistant Professor  
Vice Chair, SWOG Early Therapeutics  
and Rare Cancers Committee  
Co-Director Developmental Therapeutics  
Northwestern University

**Razelle Kurzrock, MD**  
Professor  
Chief, Division of Hematology,  
Medical Oncology  
Chair, SWOG Early Therapeutics  
and Rare Cancers Committee  
Director, Center for Personalized Cancer Therapy  
UCSD Moores Cancer Center



# DART

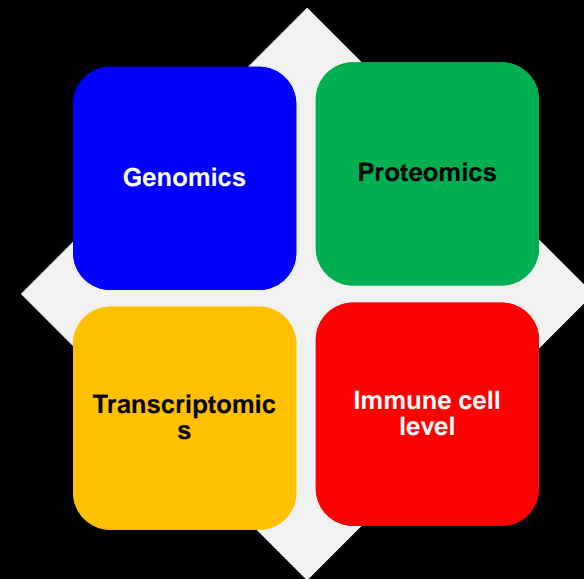
THE national immunotherapy trial for rare tumors  
~ 22% of cancer burden



# Rare Cancers in DART

## Rare cancers included in DART

- ✓ **Epithelial tumors of nasal cavity, sinuses, nasopharynx**
  - Squamous cell carcinoma with variants of nasal cavity, sinuses, and nasopharynx and trachea (excluding laryngeal, nasopharyngeal cancer [NPC], and squamous cell carcinoma of the head and neck [SCCHN])
  - Adenocarcinoma and variants of nasal cavity, sinuses, and nasopharynx. Some are related to dust inhalation and have p53, RAS, and p16 changes
- ✓ **Epithelial tumors of major salivary glands**
- ✓ **Salivary gland type tumors of head and neck, lip, esophagus, stomach, trachea and lung, breast and other location**
- ✓ **Undifferentiated carcinoma of gastrointestinal (GI) tract**
- ✓ **Adenocarcinoma with variants of small intestine**
- ✓ **Squamous cell carcinoma with variants of GI tract (stomach small intestine, colon, rectum, pancreas)**
- ✓ **Fibromixoma and low grade mucinous adenocarcinoma (pseudomixoma peritonei) of the appendix and ovary**
- ✓ **Pancreatic tumor including acinar cell carcinoma, mucinous or serous cystadenocarcinoma**
- ✓ **Intrahepatic Cholangiocarcinoma**
- ✓ **Cholangiocarcinoma and extrahepatic bile duct tumors**
- ✓ **Sarcomatoid carcinoma of lung)**
- ✓ **Bronchoalveolar carcinoma lung**
- ✓ **Non epithelia tumors of the ovary**
  - Germ cell tumor of ovary
  - Mullerian mixed tumor and adenosarcoma
- ✓ **Trophoblastic tumor of placenta**
  - Choriocarcinoma of placenta
- ✓ **Transitional cell carcinoma other than renal pelvis urethral or bladder**
- ✓ **Cell tumor of the testes and extra gonadal tumors**
  - Seminoma and testicular sex cord cancer
  - Non seminomatous tumor
  - Teratoma with malignant transformation
- ✓ **Epithelial tumors of penis - squamous adenocarcinoma cell carcinoma with variants of penis**
- ✓ **Squamous cell carcinoma variants of the genitourinary (GU) system**
- ✓ **Spindle cell type of kidney, pelvis and ureter**
- ✓ **Adenocarcinoma with variants of GU system (excluding prostate cancer)**
- ✓ **Odontogenic malignant tumors**
- ✓ **Endocrine carcinoma of pancreas and digestive tract**
- ✓ **Neuroendocrine carcinoma including carcinoid of the lung and other sides of other sites**
- ✓ **Pheochromocytoma, malignant**
- ✓ **Paraganglioma**
- ✓ **Carcinomas of pituitary gland, thyroid gland parathyroid gland adrenal cortex**
- ✓ **Dermoid tumors**
- ✓ **Peripheral nerve sheath tumors and NF1 related tumors**
- ✓ **Malignant giant cell tumors**
- ✓ **Chordoma**
- ✓ **Adrenal cortical tumors**
- ✓ **Tumor of unknown primary**
- ✓ **Other**



“TCGA” of Rare Tumors

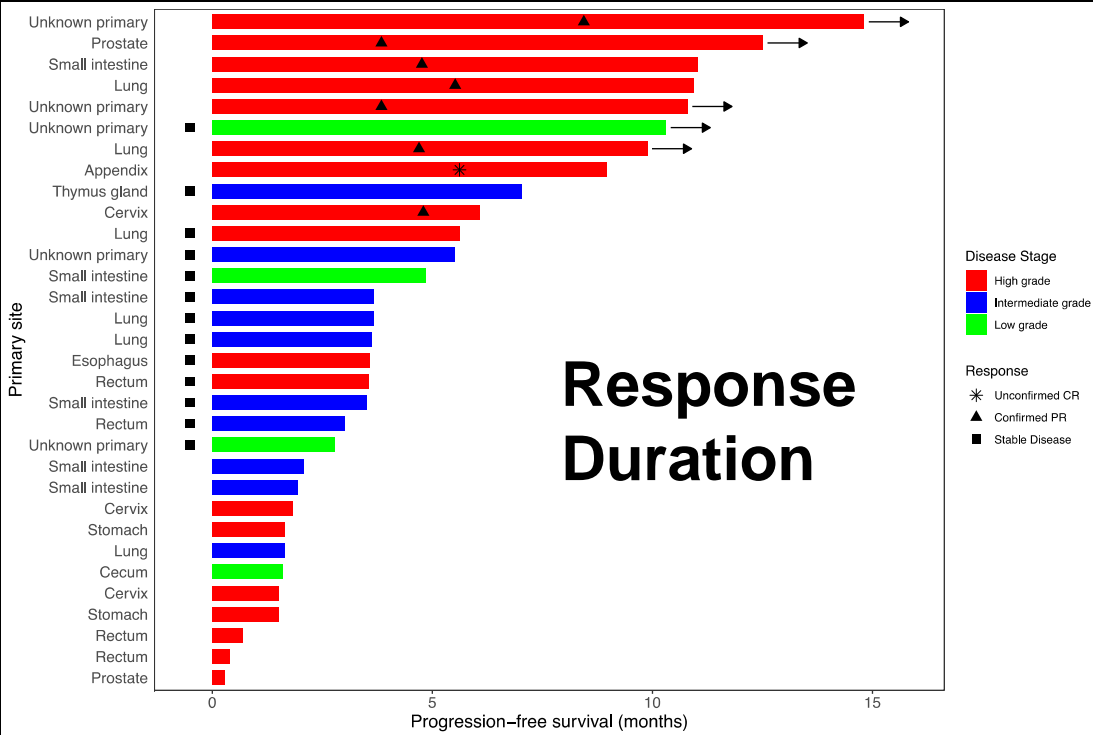
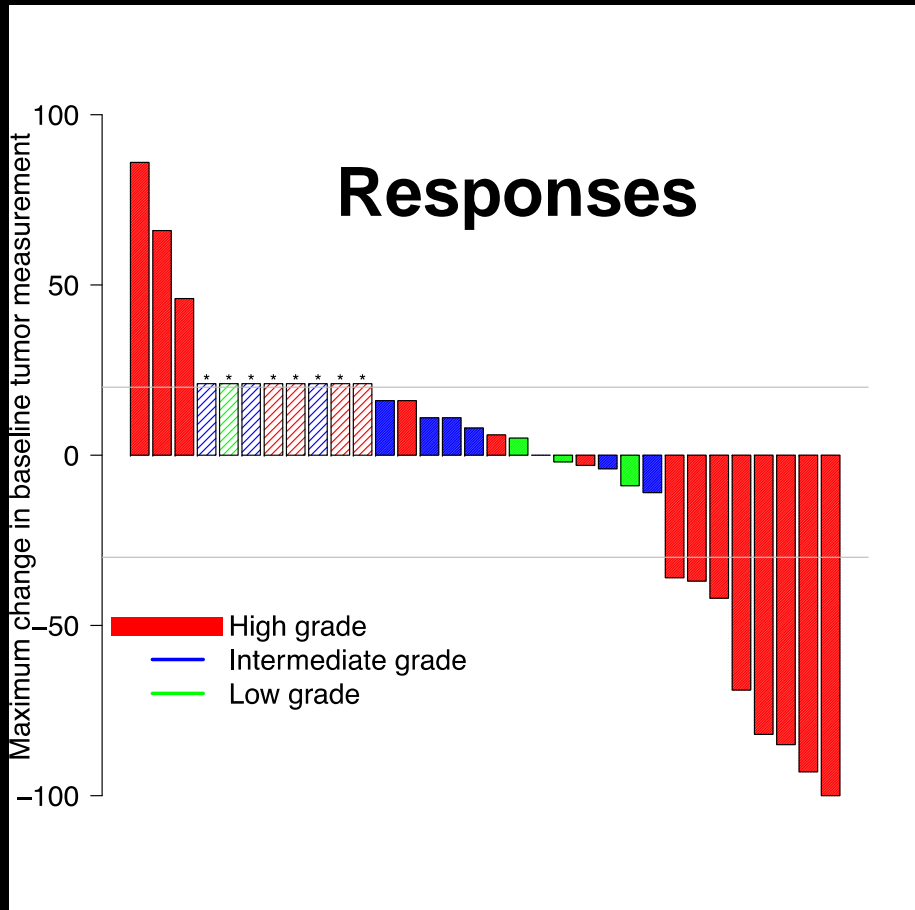
# DART by the numbers

- Date of activation = January 2017
- Number of patients accrued >550
- Number of sites >800
- Number of cohorts = 37 (up to 53 with new amendment)
- First cohort to complete stage II = neuroendocrine

# Response Rate and Duration by Tumor Grade of Neuroendocrine Neoplasms



PR/CR = 8 of 18 (44%) high grade  
vs 0 of 14 (0%) other) (p = 0.004)



# Other Innovative Precision Medicine Trials

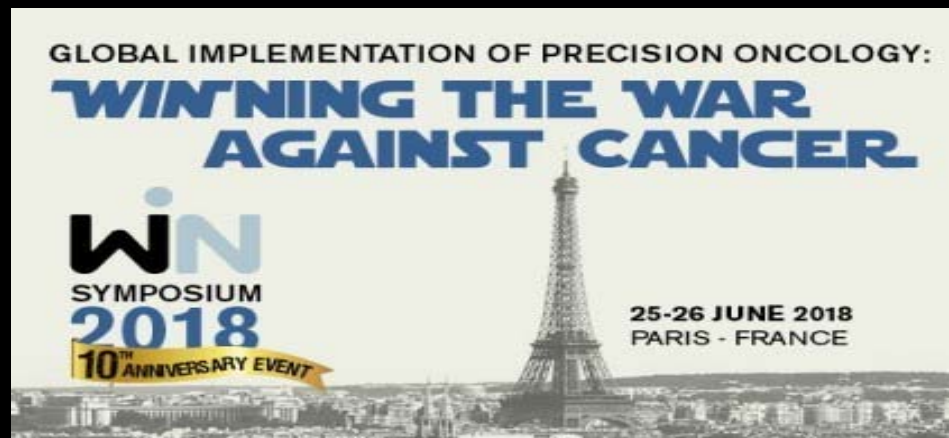
## Lung MAP

- SWOG, NCI, Friends of Cancer Research
- Umbrella trial
- >200 genes
- Assigned to sub studies

## Worldwide Innovative Network (WIN) for Personalized Cancer Medicine



Global delivery of precision medicine



# **WINTHER TRIAL NCT01856296**

An International WIN Consortium Precision Medicine Trial Using  
Genomic **and Transcriptomic** Analysis in Patients  
with Advanced Malignancies

**Nature Medicine,  
In press**

Jordi Rodon, Jean-Charles Soria, Raanan Berger, Wilson H. Miller, Vladimir Lazar, Eitan Rubin, Apostolia M. Tsimberidou, Pierre Saintigny, Aliza Ackerstein, Irene Brana, Yohann Loriot, Mohammad Afshar, Vincent Miller, Fanny Wunder, Catherine Bresson, Jean-François Martini, John Mendelsohn, Richard L. Schilsky, J. Jack Lee, Razelle Kurzrock

**First precision medicine  
trial that includes  
transcriptomics for  
solid tumors**

**303 patients enrolled  
107 patients treated (35%)**



Worldwide Innovative Networking  
in personalized cancer medicine

## What about the host?

Host and Toxicity/Response/Immunity/Microenvironments





THANK YOU  
for your time and interest

Questions??

[rkurzrock@ucsd.edu](mailto:rkurzrock@ucsd.edu)

[teoam2011@gmail.com](mailto:teoam2011@gmail.com)





20 minutes plus 10 minutes Q and A  
Slides corrected for 16:9

# Treatment

Nivolumab 240mg IV (fixed dose) q2 weeks

Ipilimumab 1 mg/kg IV q6 weeks

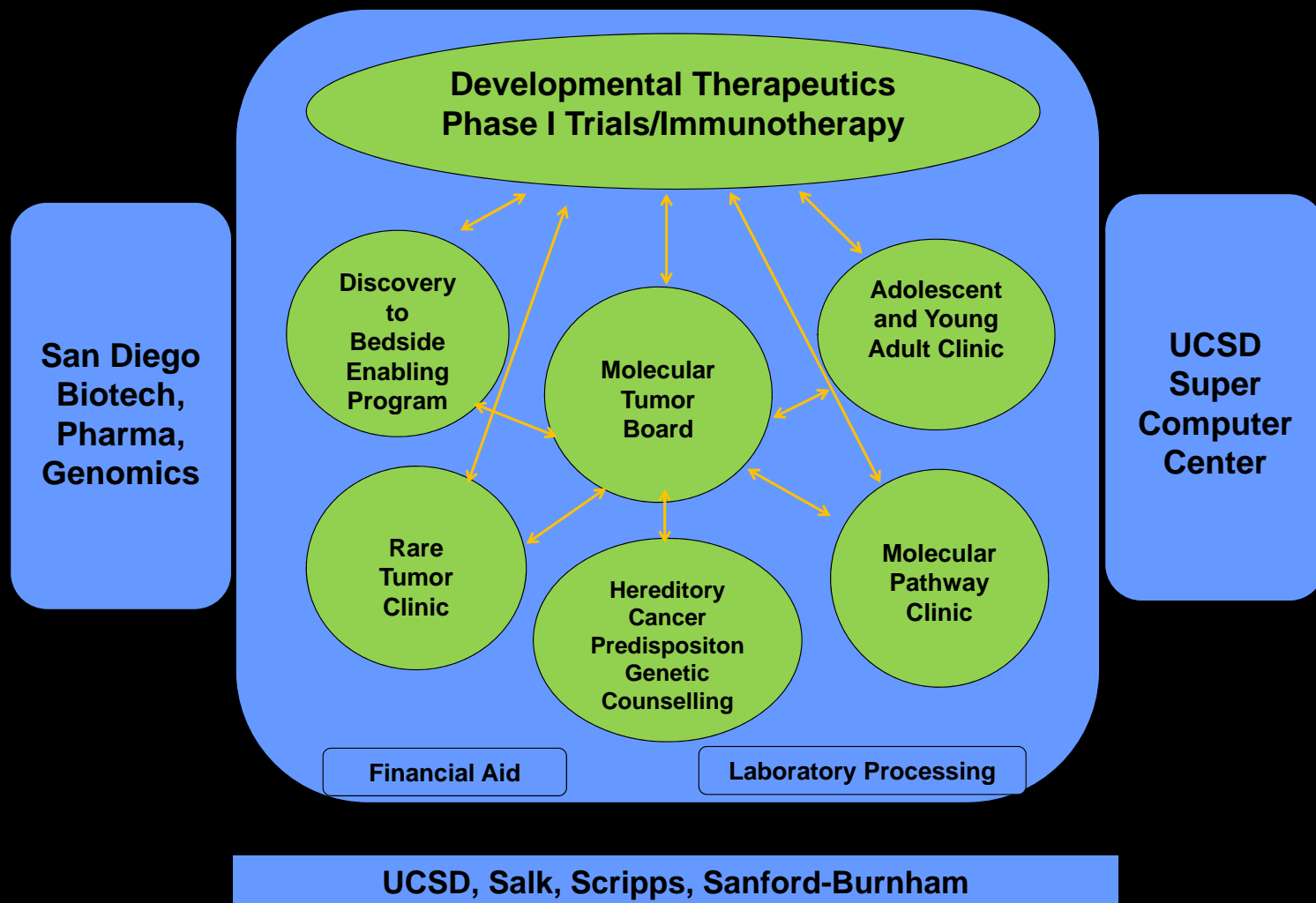
# Neuroendocrine Neoplasms



- Heterogenous group of rare tumors that can occur throughout the body
- Many are well-differentiated/low-grade tumors with more indolent biology
- Poorly-differentiated/high-grade (aggressive), usually in lung, GI tract, or unknown primary
- Usually classified based on primary site (i.e. pancreatic), proliferation (mitotic index, Ki-67)

Grade	Gastrointestinal NET (excluding pancreas)	Lung and Thymus
Low Grade (G1)	<2 mitoses/10 HPF AND/OR <3% Ki-67 index	<2 mitoses/10 HPF AND no necrosis
Intermediate Grade (G2)	2–20 mitoses/10 HPF AND/OR 3–20% Ki-67 index	2–10 mitoses/10 HPF AND/OR foci of necrosis
High Grade (G3)	>20 mitoses/10 HPF AND/OR >20% Ki-67 index	>10 mitoses/10 HPF

# Center for Personalized Cancer Therapy at Moores Cancer Center



Dr. Blanke re: keynote speaker invitation: I was so impressed by your comments in National Geographic's recent issue on the future of medicine, and I'd welcome a talk on the topic of personalized cancer therapies – where we've been and new directions ahead – for our full membership. Given the depth and breadth of your experience on this topic, you **could not only provide examples of innovative SWOG trials, but leading examples globally from the fields of translational science, genetic screening technologies, and clinical trial design.** It goes without saying, but you've been a champion of early therapeutics and novel trial designs at SWOG and beyond, and I would be so proud to have you share your expertise directly with our group.