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

- Developmental Therapeutics
- Phase I Trials/Genomics/Immunotherapy
- San Diego Biotech, Pharma,
- UCSD Super Computer Center
- Molecular Tumor Board
- Molecular Pathway Clinic
- Hereditary Cancer Predisposition Genetic Counselling
- Financial Aid
- Laboratory Processing
- Rare Tumor Clinic
- Discover to Bedside Enabling Program
- Adolescent and Young Adult Clinic

UCSD, Salk, Scripps, Sanford-Burnham

 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**


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

UMBRELLA MASTER PROTOCOL
Molecular profiling CLIA

PREDICT
approved 9/2013
>5000 patients

CLINICAL TRIALS ↔ BASIC RESEARCH
What if every patient with metastatic disease is different?
Malignant Snowflakes
Metastatic Breast Cancer

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

Tip of the Iceberg

Genomics

Transcriptome

Proteomics

Epigenetic changes
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
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)

Patient 1

- Diabetes
- Heart failure
- Arthritis

- Beta blocker
- metformin
- tofacitinib

Patient 2

- Diabetes
- Infection
- Depression

- clarithromycin
- fluoxetine
- metformin
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
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 $\rightarrow$ 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

# 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

8 months after treatment

Complete remission at 1.5 years ongoing

Sharabi.....Kurzrock. Oncologist, 2017
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
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

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

Nature Medicine, In press
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 angiofibroma, 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, nasopharynx, 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)
- Fibromyxoma and low grade mucinous adenocarcinoma (pseudomesenchymal proliferation) of the appendix and ovary
- Pancreatic tumor including acinar cell carcinoma, mucinous or serous cystadenocarcinoma
- Intrahepatic Cholangiocarcinoma
- Cholangiocarcinoma and intrahepatic bile duct tumors
- Sarcomatoid carcinoma of lung
- Bronchoalveolar carcinoma lung
- Non epithelial tumors of the ovary
  - Germ cell tumor of ovary
  - Mullerian mixed tumor and adenocarcinoma
- 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 seminomatosus 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
- Endodocrine carcinoma of pancreas and digestive tract
- Neuroendocrine carcinoma including carcinoid of the lung and other sites of other sites
- Pheochromocytoma, malignant
- Paraganglioma
- Carcinomas of pituitary gland, thyroid gland parathyroid gland adrenal cortex
- Dermoid tumors
- Peripheral nerve sheath tumors and NPS 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

GLOBAL IMPLEMENTATION OF PRECISION ONCOLOGY:
WINNING THE WAR AGAINST CANCER

WIN SYMPOSIUM 2018
25-26 JUNE 2018
PARIS - FRANCE
WINOTHER TRIAL  NCT01856296
An International WIN Consortium Precision Medicine Trial Using Genomic and Transcriptomic Analysis in Patients with Advanced Malignancies

Nature Medicine, In press


First precision medicine trial that includes transcriptomics for solid tumors

Worldwide Innovative Networking in personalized cancer medicine

303 patients enrolled
107 patients treated (35%)
What about the host?

Host and Toxicity/Response/Immunity/Microenvironments
THANK YOU
for your time and interest

Questions??
rkurzrock@ucsd.edu
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)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Gastrointestinal NET (excluding pancreas)</th>
<th>Lung and Thymus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Grade (G1)</td>
<td>&lt;2 mitoses/10 HPF AND/OR &lt;3% Ki-67 index</td>
<td>&lt;2 mitoses/10 HPF AND no necrosis</td>
</tr>
<tr>
<td>Intermediate Grade (G2)</td>
<td>2–20 mitoses/10 HPF AND/OR 3–20% Ki-67 index</td>
<td>2–10 mitoses/10 HPF AND/OR foci of necrosis</td>
</tr>
<tr>
<td>High Grade (G3)</td>
<td>&gt;20 mitoses/10 HPF AND/OR &gt;20% Ki-67 index</td>
<td>&gt;10 mitoses/10 HPF</td>
</tr>
</tbody>
</table>
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.