Genomics and Cancer: Implications for Immune Therapy

Razelle Kurzrock, MD
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

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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
- Discover y to Bedside Enabling Program
- Molecular Tumor Board
- Adolescent and Young Adult Clinic
- UCSD Super Computer Center
- Rare Tumor Clinic
- Hereditary Cancer Predisposition Genetic Counselling
- Molecular Pathway Clinic
- Financial Aid
- Laboratory Processing

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 >10,000 patients
- Leadership positions: SWOG, WIN, NCCN,
Take-home points

• The pillars of precision medicine are genomics and immunotherapy and they are married to each other.

• Immunotherapy is best suited for genomically complex tumors

• At the genomic level, every metastatic tumor is unique and complex→ malignant snowflakes

• Metastatic disease requires customized/individualized combination treatments, not single agents

• The immune pharmacogenome determines responsiveness to immunotherapy
Right drug to right patient at right time
Molecular Tumor Board

• Initiated December 12, 2012
• Weekly and *ad hoc* e-board
• Multidisciplinary discussion
• Molecular profiling (N ~ 12,000)
• 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
~3400 patients

**CLINICAL TRIALS**

**BASIC RESEARCH**
I-PREDICT: UCSD and Avera

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:** $N = 298$

- **Treated:** $N = 131 \ (44\%)$
- **Matched Therapy:** $N = 109 \ (37\% \ of \ total; \ 83\% \ of \ treated)$

**Treatment Decisions Guided by:**

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

PIK3CA mutations were found in 10% of 1,000 patients with advanced cancers

• Endometrial cancers (29%)
• Breast cancers (24%)
• Colon cancers (17%)
• Ovarian cancers (14%)
• Lung cancer (13%)
• Head and neck squamous cell cancers (13%)
• Pancreatic cancers (13%)

Molecular aberrations do not segregate well by organ of origin
Fundamental Premise
Every metastatic tumor is complex and unique
<table>
<thead>
<tr>
<th>Pt number</th>
<th>Molecular Results (236 genes; NGS)—Breast Cancer</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>PIK3CA amplification, SOX2 amplification, TP53 G302fs<em>42, FLT3 L260</em></td>
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<tr>
<td>2</td>
<td>AKT1 (E17K)</td>
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<tr>
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<tr>
<td>42</td>
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<tr>
<td>25</td>
<td>ERBB2 amplification, MYC amplification, CDK6 amplification, TP53 R213*</td>
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<td>7</td>
<td>ESR1 Y537S</td>
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<tr>
<td>13</td>
<td>GATA3 <em>445fs</em>2+</td>
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<tr>
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<td>RET C634R, GATA3 P436fs*11+</td>
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<td>18</td>
<td>AKT3 amplification, MYC amplification, MYCL1 amplification, TP53 R248Q</td>
</tr>
<tr>
<td>54</td>
<td>NF1 R1276Q</td>
</tr>
</tbody>
</table>

Genomics and immunotherapy marriage
The Pillars of Precision/Personalized Medicine

Genomics  Immunotherapy

The future is here.

T-cell killing cancer cell
Bridging 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
Microsatellite instability

- Microsatellite instability high (MSI-High) is present in ~4% of cancers
- MSI-High is a hypermutation pattern that occurs at microsatellites
- Caused by defects in mismatch repair system
- Can be hereditary (germline) or somatic
- MSI-High without germline alteration usually due to epigentic silencing of MLH1
- Best characterized in colorectal, endometrial and gastric cancers
- Over 80% of MSI-High tumors have a high tumor mutational burden
- Chemotherapy refractory
- About 50% respond to immune checkpoint blockade
- Responses can be durable
MSI-High Incidence

~3% to 4% of cancers are MSI-High
~16% of MSI-High tumors have germline mutations (Lynch syndrome)
~0.3% of general population had germline mutations

MSI-high in various cancers
Endometrial ~ 25%
Stomach~22%
Colorectal: ~15%
Ovarian ~3%
Breast~2%
Lynch syndrome

AUTOSOMAL DOMINANT
Mismatch repair defect (MLH1, PMS2, MSH2, MSH6, EPCAM (turns off MSH2))

**Lynch syndrome 1**
- 1-7% of colorectal cancer;
- Hereditary nonpolyposis colon cancer
- Early age, proximal colon,
- Multiple primary colon cancers
- 85% penetrance

**Lynch syndrome 2**
- Above features but also extracolonic cancer, primarily endometrial
  **Cancers:** stomach, small intestine, liver, gallbladder, urinary tract, brain, skin, endometrial, ovary

**Muir-Torre syndrome**. Lynch syndrome with cancers listed above as well as benign skin growths (sebaceous adenomas, keratoacanthomas) and skin cancers (sebaceous carcinoma).
A new era is born
FDA Approves pembrolizumab (anti-PD1) for solid tumors based on MSI-H

May 23, 2017

- Tissue agnostic approval
- Approval based on genomic marker
- Approval based on retrospective data
Super-Responders and Optimized Immunotherapy
Metastastic Basal Cell Carcinoma
Ultra-rare tumor

55-year-old man, having failed multiple treatments

**Treatment history**
* Vismodegib (5/2014-10/2014), PD
* SBRT to right frontal lobe (11/2014)
* Paclitaxel/Cisplatin (11/2014-3/2015), PD
* Buparlisib/Sonidegib (4/28/2015-7/1/2015), PD
* Vismodegib + weekly taxol (7/2015-9/2015), intolerant
* Vandetanib (9/2015-9/2015), intolerant
Metastatic Basal Cell Carcinoma

Molecular profiling (liver biopsy)

Next Generation sequencing, 315 genes:

- PDL1 amplification,
- PDL2 amplification,
- JAK2 amplification,
- PTCH1 Q1366*, W197*,
- FLT1 E487K,
- PDGFRA E459K
  - PIK3R2 Q412*,
- CDKN2A p16INK4a P81L,
- TP53 P278S,
- CDKN1A R140Q,
- CTNNA1 R383H,
- LRP1B splice site 9121-1G>A, W2334*,
- MLL2 splice site 4132-1G>A,
- NOTCH1 W287*
  - SLIT2 K325*,
- SMARCA4 Q1166*,
- TERT promoter -139_-138CC>TT

High tumor mutational burden = 79/megabase

Goodman…..Kurzrock, TMB…MCT 2017
Goodman ….Kurzrock. PDL1. JAMA Oncology 2018
Super-Responder to Genomically Matched Immunotherapy

Pre-Nivolumab (anti-PD1)

Post: 2 months

Response ongoing at 24+ months
Cutting-edge technologies needed for complicated cancers
Liquid Biopsy Program

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

No tissue biopsy

~3500 patient samples

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
High-grade neuroendocrine cervical cancer
Genomic Profiling

<table>
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<tr>
<th>ctDNA Blood</th>
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<tr>
<td>PTEN R130Q</td>
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<tr>
<td>FBXW7 R465H</td>
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<tr>
<td>PIK3CA E545D</td>
</tr>
<tr>
<td>PIK3CA R88Q</td>
</tr>
<tr>
<td>NRAS Q61R</td>
</tr>
<tr>
<td>CTNNB1 S33A</td>
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<td>ARID1A P600P</td>
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<td>NOTCH1 G309D</td>
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<td>NOTCH1 N2389N</td>
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<tr>
<td>STK11 W332*</td>
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<td>CDH1 A408A</td>
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<tr>
<td>BRCA1 G1077R</td>
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<td>MET P325S</td>
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</table>

Hypermutated ctDNA
High-grade neuroendocrine tumor of the cervix
Ultra Rare

Immunotherapy: Nivolumab plus SBRT (radiation) plus somatostatin

Pre-Treatment

Near complete remission at 1.5 years ongoing

Sharabi.....Kurzrock. Oncologist, 2017
# High-grade neuroendocrine cervical cancer

Lynch syndrome

cDNA blood

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<thead>
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<tr>
<td>SMO T541T</td>
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<td>MET P325S</td>
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Tissue NGS

<table>
<thead>
<tr>
<th>FBXW7 R465H</th>
<th>MSH2 E48*</th>
<th>MSH2 Q324*</th>
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<td>ATRX D1940fs*15</td>
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<td>BLM N515fs*16</td>
<td>FGFR6V127M</td>
<td>JAK1 K860fs*16</td>
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<td>MLL2 P2302fs*20</td>
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<td>MLL3 K2797fs*26</td>
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<td>QKI A338T</td>
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<td>SETD2 F636fs*6</td>
<td>SMARCA4 Q214*</td>
<td>SMARCA4 T296fs*7</td>
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<tr>
<td>TET2 R1440fs*38</td>
<td>TET2 R550*</td>
<td>TET2 R1440fs*38</td>
</tr>
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</table>

Other markers

- High: tumor mutational burden
- 53 (>19 mutations per megabase = high)
- MSI-H
- PDL-1 low positive
The landscape analysis of targets of anti-PD-1/L1 combination trials. The size of the bubble correlates to the number of trials.

Numbers of trials using common combo strategies:

1. Anti-CTLA-4 agents: 251
2. Chemotherapies: 170
3. Radiotherapies: 64
4. Anti-VEGFA agents: 43
5. Chemoradiotherapy combos: 42

82 year-old man with carcinoma of unknown primary and mismatch repair gene defect

**KRAS** G12D → Trametinib  
**MLH1** R389W → Nivolumab

Partial response ongoing for 15+ months.

*Kato ...... Kurzrock, Cancer Research 2017*
49 F with metastatic colon cancer

- **Previous therapies:**
  - FOLFOX + bevacizumab
  - FOLFIRI + bevacizumab

Presented with progression in liver metastases and lymphadenopathy

- **Genomics:**
  - NRAS G12D
  - MAP2K1 (MEK1) G128D
  - PTEN A148fs*32
  - MRE11A R364*
  - MSS
  - TMB low

- **IHC:**
  - PD-L1 positive
49 F with metastatic colon cancer

- **Previous therapies:**
  - FOLFOX + bevacizumab
  - FOLFIRI + bevacizumab

Presented with progression in liver metastases and lymphadenopathy

- **Genomics:**
  - NRAS G12D $\rightarrow$ Trametinib
  - MAP2K1 (MEK1) G128D
  - PTEN A148fs*32
  - MRE11A R364*
  - MSS
  - TMB low

- **IHC:**
  - PD-L1 positive $\rightarrow$ Nivolumab
    (Under IPREDICT trial)
49 F with metastatic colon cancer

Pre-treatment

Trametinib (NRAS)
Nivolumab (PD-L1)

6 weeks post therapy
(Partial response per RECIST 1.1)
64 year old female with triple negative breast cancer

Treatment history:

- Neoadjuvant cyclophosphamide, doxorubicin and docetaxel
- Adjuvant capecitabine plus radiation
- Exemestane
- Letrozole plus palbociclib
- Capecitabine

Tissue NGS:
- ERBB2 D769H
- MTOR T1834_T1837 del
- PIK3CA E545K
- BRIP1 R798Q
- ATM R3008H
- BCRO S1717*
- CDH1 P260L
- CDKN1B splice site 476-1G>T
- MAP2K4 S184L
- SMAD4 E337K
- TP53 E285Q, R280K, E287*
- Microsatellite stable
- Tumor mutation burden high (76 muts/mb)
64 year old female with triple negative breast cancer

Consented on I-PREDICT protocol (NCT02534675)

Tissue NGS:
- **ERBB2** D769H
- **MTOR** T1834_T1837 del
- **PIK3CA** E545K
- **BRIP1** R798Q
- **ATM** R3008H
- **BCRO** S1717*
- **CDH1** P260L
- **CDKN1B** splice site 476-1G>T
- **MAP2K4** S184L
- **SMAD4** E337K
- **TP53** E285Q, R280K, E287*
- Microsatellite stable
- Tumor mutation burden high (76 muts/mb)

→ Nivolumab
64 year old female with triple negative breast cancer

Nivolumab x 2 months

Complete response per RECIST 1.1
Ongoing at 20+ months
Minimal toxicity
Remember the host?

Host and Toxicity/Response/Immunity/Microenvironments
Hereditary Cancers
High Incidence of Germline Mutations

- 1040 patients with advanced cancer
- 182 (17.5%) had germline alterations of clinical significance
- 101 of 182 patients (10% of the total 1040 patients; 55% of those with germline) would not have been detected by guideline-directed testing based on family history, age, and tumor type.

Diana Mandelker, MD, PhD; Liying Zhang, MD, PhD; Yelena Kemel, MS, ScM, et al. Mutation Detection in Patients With Advanced Cancer by Universal Sequencing of Cancer-Related Genes in Tumor and Normal DNA vs Guideline-Based Germline Testing
JAMA 2017
Pharmacogenomics

The study of how genes affect a person's response to drugs.
The Immune Pharmacogenome
MHC-I and MHC-II

CD8  TCR  CD4  TCR

MHC Class I  MHC Class II
HERE I AM. CHECK ME OUT
MHC1 ability to present predicts significantly better progression-free survival

~45% of high TMB tumors respond to immune checkpoint blockade

Bladder Cancer

Dwarfism

FGFR3 Mutation

BEYOND CANCER
Changing the lives of patients

Twin Boys
Normal Achondroplasia
THANK YOU
for your time and interest

Questions??

rkurzrock@ucsd.edu
teoam2011@gmail.com
~30 talk and 15 minutes Q and A; total = 45 minutes
Need emphasis on breast and ovarian cancers