Precision Oncology Decision Support: From Monotherapy to Combinations

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Professor, Divisions of Cancer Medicine and Surgery
## Disclosures

<table>
<thead>
<tr>
<th>Nature of Relevant Financial Relationship</th>
<th>Commercial Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Funding</td>
<td>Novartis; AstraZeneca; Taiho Pharmaceutical; Genentech; Calithera Biosciences; Debiopharm Group; Bayer; Aileron Therapeutics; PUMA Biotechnology; CytomX Therapeutics; Zymeworks; Curis; Pfizer; eFFECTOR Therapeutics; Abbvie; Guardant Health; Daiichi Sankyo, GlaxoSmithKline</td>
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<td>Honoraria</td>
<td>Sumitomo Dainippon Pharma; Dialectica</td>
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<td>Consultancy/Advisory</td>
<td>Genentech; Inflection Biosciences; Pieris Pharmaceuticals; Darwin Health; Samsung Bioepis; Aduro, Spectrum; OrigiMed; Debiopharm Group; Xencor; Jackson Laboratory, Mersana</td>
</tr>
<tr>
<td>Employee</td>
<td>MD Anderson Cancer Center</td>
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Personalized Cancer Therapy

Molecular Profiling

1. Prognostic Markers
   - Markers predictive of drug sensitivity/resistance
   - Markers predictive of adverse events

2. Treatment with tailored therapies

Personalizedcancertherapy.org
Genomically-Informed Targeted Therapy

• Identifying genomic alterations that are
  • Drivers of tumor growth and progression
  • Targetable directly or indirectly with approved
    or investigational agents

• Mutations
  • Somatic and germline
  • SNVs and indels
• Copy number changes
  • Amplifications/deletions
• Fusions
Targeting Actionable Genes

A genomic alteration can be considered “actionable” if it:

• predicts therapy response (sensitivity or resistance)
• affects the function of a cancer-related gene, and can be targeted directly or indirectly with approved or investigational therapies.
• is a specific eligibility criteria for enrollment onto genotype-selected trials,
• has demonstrated the ability to establish diagnosis or influence prognosis
• is a germline alteration that predicts drug metabolism and/or adverse effects
• is a germline alteration that predicts future risk of cancer or other diseases (usually considered more “actionable” if prevention or screening with early treatment is feasible)
Increasing Number of Genomically Informed Trials

Umbrella trial
- 1 type of cancer
- Different genetic mutations (○○○)

Test drug 1
Test drug 2
Test drug 3

Basket trial
- Multiple types of cancer
- 1 common genetic mutation (○)

Test drug

West, JAMA Oncology, 2017
Basket Trials

Increasing number of Genotype-matched Trials

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Trials submitted</th>
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</thead>
<tbody>
<tr>
<td>2012</td>
<td>17</td>
</tr>
<tr>
<td>2013</td>
<td>19</td>
</tr>
<tr>
<td>2014</td>
<td>12</td>
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<tr>
<td>2015</td>
<td>27</td>
</tr>
<tr>
<td>2016</td>
<td>35</td>
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</table>
Need for Medical Decision-Support

Doc, you must know everything!
Getting to the Right Patient, with the Right Drug at the Right Time

*Precision Oncology Decision Support System (PODSS)*

of the Khalifa Institute for Personalized Cancer Therapy
Confirm sequencing/variant calling quality; Identify mutations, copy number changes, fusions

Determine functional consequences of alterations: Clinical data (prognosis and response)
Preclinical data/functional genomics
Computational functional predictions
Prediction of driver vs passenger

Functional Alteration in Driver Gene?

Relevant targeting drugs (direct and indirect)

Assess evidence for using each drug in the context of altered gene/disease/molecular subtype

Level I evidence
Select optimal approved therapy: genomically-matched or other approved therapy

Level II or III evidence
Retrieve clinical trials using genotype-relevant drugs

Prioritize mutations/targets Identify optimal treatment
**Precision Oncology Decision Support**

**Selected publications**
Meric-Bernstam F, J Natl Cancer Inst. 2015
Meric-Bernstam F et al, J Clin Oncol. 2015
Chen K et al, Clin Chem. 2015
Kurnitt, Cancer Research, 2017

Zhou W et al., Nat Methods. 2015
Johnson A et al., Drug DiscovToday.2015
Johnson A et al, JCO PO, 2017
Kurnitt, Clin Can Research 201
Bailey MH, Cancer Cell, 2018

**Funding**
CPRIT RP150535
U01 CA180964, CTSA UL1TR000371
Creating Drug Gene Associations

1. **Search drug databases/catalogues for drugs that directly target the gene**
   - Selleckchem
   - MedKoo
   - NCIDD
   - DGIdb

2. **Use literature retrieval tools to search PubMed and clinical trial descriptions for drugs that directly or indirectly target the gene**
   - AIMED
   - RetriLite TI
     - Drug A
     - Drug B
     - Drug C
     - Retrieves PubMed abstracts and clinical trial descriptions mentioning gene and any clinical drug
     - Gene
     - Retrieves PubMed abstracts using gene and defined therapeutic implications (TI) terms

3. **Annotation of all drugs in MD Anderson clinical trials and oncology development notifications**
   - Clinical Trial
   - Drug Newsletter
     - Drug A
     - Drug B
     - Search for targeted/relevant genes
       - PubMed
       - Company websites

4. **PODSS Drug Database**
   - Auto-retrieval
     - NCI definition
     - SEER remarks
     - aliases
   - Annotator records
     - Direct/Indirect target genes
     - IC50
     - References
     - Category
     - Development Phase
     - FDA indications
PODS Level of Evidence Scale

Level of Evidence
For drug effectiveness in tumors harboring a specific biomarker

1A Drug is FDA-approved for a specific biomarker in a specific tumor type or a histology-agnostic indication.

1B* Evidence demonstrating that a biomarker predicts tumor response to the drug or that the drug is clinically effective in a biomarker-selected cohort. Evidence could be:
  - An adequately-powered, prospective study with biomarker selection/stratification
  - A meta-analysis/overview
  - A consensus recommendation for standard of care (as recommended by NCCN guidelines or other consortia)

2A* Large-scale retrospective study demonstrating that a biomarker is associated with tumor response to the drug. Evidence could be:
  - A prospective trial where biomarker study is the secondary objective
  - An adequately-powered retrospective cohort study
  - An adequately-powered case-control study

2B Clinical data that a biomarker predicts tumor response to the drug in a different tumor type**.

3A Unusual responder(s), either single patient case studies or small case series, showing a biomarker is associated with response to the drug and is supported by scientific rationale.

3B Preclinical data demonstrating that a biomarker predicts response of cells or tumors to drug treatment.

* Within a specific tumor type or compelling evidence across multiple tumor types with minimal tumor-type heterogeneity.
** Does not fulfill criteria of level 1B or 2A.

Modified on 8/23/2017
Annotation of Variants of Known Functional Significance

Oncogene

Functional Significance

- Activating: Yes
- Inactivating: No

Likely Benign: No

Tumor Suppressor

Functional Significance

- Activating: No
- Inactivating: No

Inactivating and Neomorphic*: Yes

-------------------------------Actionable Variant Calls-------------------------------

• Yes: Literature based
• Yes: Inferred
• Yes: Functional Genomics
Annotation of Variants of Unknown Functional Significance

Functional Significance

- Confers drug sensitivity or resistance

Does research show:
- Other variants of the codon are actionable
- Hot-spot area
- Functionally significant domain w/ other actionable alterations
- Splice-site mutations in tumor suppressors

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Actionable Variant Calls

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Resources

- UniProt
- dbSNP
- Ensembl
- ClinVar
- Published Literature
- High-quality abstracts
Functional genomics to assess VUSs

Gordon Mills
Han Liang Gaddy Getz
Ken Scott
Yiling Lu
Lynda Chin
Wai Ting Cheung
Jane Li
Shuangxing Yu
Turgut Dogruluk

Data sets
MDACC
TCGA
ICGC
Patients

Interactive algorithms to identify
POTENTIAL DRIVER ABERRATIONS

High throughput generation of
mutant ORFs
500 per month

Lentiviral vector carrying wild type
or mutated ORF
shRNA for knockdown

Introduce into “addicted” sensor cell line
(Ba/F3, MCF10A, tumor lines)

Cell viability assay

Select potential drivers

Establish “driver addicted” stable cell lines

Sensitivity to “informer” targeted therapeutic library

RPPA to define signaling network

Integrate functional proteomics and drug screen
DRUGS AND MECHANISMS
In vivo context dependent screen
Personalized cancer therapy is a treatment strategy centered on the ability to predict which patients are more likely to respond to specific cancer therapies. This approach is founded upon the idea that tumor biomarkers are associated with patient prognosis and tumor response to therapy. In addition, patient genetic factors can be associated with drug metabolism, drug response, and drug toxicity. Personalized tumor molecular profiles, tumor disease site, and other patient characteristics are then potentially used for determining optimum individualized therapy options.

Tumor biomarkers can be DNA, RNA, protein, and metabolomic profiles that predict therapy response. However, the most recent approach is the sequencing of tumor DNA, which can reveal genomic alterations that have implications for cancer treatment. This Personalized Cancer Therapy website was specifically developed as a tool for physicians and patients to assess potential therapy options based on specific tumor biomarkers.

Kurnit et al, Cancer Research, 2017

- Launched April 2014
- All content publicly accessible with free registration.
- First 33 genes with dozens of individual aberrations annotated.
- Therapeutic implications
- Relevant trials
- New genes and respective gene-level variants added continuously.
Web-based Annotation Request Form

Currently:
• Only directly accessible for MD Anderson employees but with capability of providing annotations for patients treated outside of MD Anderson

• However, a data feed has been established for a collaboration we have with a commercial company

Enhancements planned:
• Accessibility beyond MD Anderson employees
## Patient Reports

Emailed and Deposited into EHR

### Clear Functional Significance Call
- **STAGA1**: PTEN, T319R*6
- **STAGA1**: RB1, V1936*9
- **STAGA1**: PIK3R1, E666*

### Clear Alteration-Level Actionability Calls
- **STAGA1**: PTEN, T319R*6
- **STAGA1**: RB1, V1936*9
- **STAGA1**: PIK3R1, E666*

### Test Results

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>cBIO</th>
<th>COSMIC</th>
<th>CMS500</th>
<th>T200</th>
<th>Germline in T200 dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN</td>
<td>T319R*6</td>
<td>0 / 1205 (0%)</td>
<td>13 / 30036 (&lt;1%)</td>
<td>1 / 10673 (&lt;1%)</td>
<td>0 / 2141 (0%)</td>
<td></td>
</tr>
<tr>
<td>RB1</td>
<td>V1936*9</td>
<td>0 / 11513 (0%)</td>
<td>0 / 10673 (0%)</td>
<td>0 / 2141 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIK3R1</td>
<td>E666*</td>
<td>0 / 11308 (0%)</td>
<td>0 / 10673 (0%)</td>
<td>0 / 2141 (0%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Aggregated Frequencies

**Frequency in all tumor types**

- **PTEN**: T319R*6
- **RB1**: V1936*9
- **PIK3R1**: E666*
The PODS trial has identified the following clinical trials that may be relevant to your patient’s alterations. Please note the following: although this list has been filtered by its relevance to your patient’s gene and disease type, further consultation regarding enrollment eligibility and availability of clinical trial slots should be discussed with respective PI and/or clinical trial coordinator.

**Biomarker-Selected Trials**

<table>
<thead>
<tr>
<th>Selected Biomarker(s)*</th>
<th>Drugs**</th>
<th>Title</th>
<th>NCTID</th>
<th>MDACC Protocol ID</th>
<th>Phase</th>
<th>PI</th>
<th>Dept</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN_Mutation, PIK3R1 Any Alteration</td>
<td>MSC236331BA</td>
<td>A Phase I, First-in-Human, Dose Escalation Trial of MSC236331BA, a Dual p70S6K/Akt Inhibitor, in Subjects With Advanced Malignancies</td>
<td>NCT01971515</td>
<td>2013-0525</td>
<td>Phase 1</td>
<td>Tamirindos, Apostolos</td>
<td>Investigational Cancer Therapeutics</td>
</tr>
<tr>
<td>PTEN Any Alteration, PIK3R1 Any Alteration</td>
<td>Brevacizumab, Valproic Acid, Temsirolimus</td>
<td>A Phase I Trial of Brevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications</td>
<td>NCT01552434</td>
<td>2012-0061</td>
<td>Phase 1</td>
<td>Pha-Paul, Sarina A.</td>
<td>Investigational Cancer Therapeutics</td>
</tr>
<tr>
<td>PTEN Any Alteration, PIK3R1 Any Alteration</td>
<td>AZD5363</td>
<td>A Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Ascending Doses of AZD5363 Under Adaptable Dosing Schedules in Patients With Advanced Solid Malignancies.</td>
<td>NCT01226316</td>
<td>2014-0160</td>
<td>Phase 1</td>
<td>Meric-Bernstam, Funda</td>
<td>Investigational Cancer Therapeutics</td>
</tr>
<tr>
<td>PTEN_Mutation</td>
<td>ARQ-751</td>
<td>Subjects With Advanced Solid Tumors With AKT1, 2, 3 Genetic</td>
<td>NCT02761694</td>
<td>2016-0212</td>
<td>Phase 1</td>
<td>Paat, Shubham</td>
<td>Investigational Cancer Therapeutics</td>
</tr>
</tbody>
</table>

*All genotypes being selected for may not be listed in this column. Only those relevant to the patient’s genomic profile are listed. **All drugs used within the trial are listed; however, drugs curated by IPCT to be relevant to the patient’s genomic profile are underlined.

**Biomarker-Relevant Trials**

<table>
<thead>
<tr>
<th>Relevant Biomarker(s)*</th>
<th>Drugs**</th>
<th>Title</th>
<th>NCTID</th>
<th>MDACC Protocol ID</th>
<th>Phase</th>
<th>PI</th>
<th>Dept</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN Any Alteration, PIK3R1 Any Alteration</td>
<td>Ceritinib, Everolimus</td>
<td>A Phase I/II Dose Escalation and Biomarker Study of Ceritinib (LDK378) in Combination With Everolimus in Patients With Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression</td>
<td>NCT02321501</td>
<td>2014-0890</td>
<td>Phase 1</td>
<td>Blume-Peytavi, George R</td>
<td>Thoracic and Head and Neck Med</td>
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<tr>
<td>PTEN Any Alteration, PIK3R1 Any Alteration</td>
<td>CUDC-907</td>
<td>Phase I, Open-Label, Multi-center Study to Assess the Safety, Tolerability and Pharmacokinetics of Orally Administered CUDC-907, an HDAC and PI3K Inhibitor, in Subjects With Advanced/Relapsed Solid Tumors</td>
<td>NCT02397240</td>
<td>2015-0033</td>
<td>Phase 1</td>
<td>Pha-Paul, Sarina A.</td>
<td>Investigational Cancer Therapeutics</td>
</tr>
</tbody>
</table>

**Trials retrieved only if targets a potentially actionable or actionable alteration**
Annotation of Actionability

Review of 1,669 requests for annotation of 4,084 alterations (2,254 unique) across 49 tumor types for 1,197 patients

Johnson et al JCO PO 2017
Accrual of Genomically-Matched Trials

- Patients annotated in 2015 (535)
  - Actionable variant classification
    - YES: Literature Based
      - Total # patients with variant call: 214 (40.0%)
      - # patients with variant call enrolled on a trial: 49 (22.9%)
    - YES: Inferred
      - Total # patients with variant call: 54 (10.1%)
      - # patients with variant call enrolled on a trial: 26 (48.1%)
    - Potentially
      - Total # patients with variant call: 65 (12.1%)
      - # patients with variant call enrolled on a trial: 17 (26.2%)
    - Unknown
      - Total # patients with variant call: 136 (25.4%)
      - # patients with variant call enrolled on a trial: 16 (11.8%)
    - No (Non-actionable)
      - Total # patients with variant call: 66 (12.3%)
      - # patients with variant call enrolled on a trial: 2 (3%)

* \( p=0.00004 \)

- Actionable / Potentially actionable alterations
- Unknown alterations
- Non-actionable alterations

Johnson et al, JCO Precision Oncology, 2017
1. Triggered by new mutation coming in to MOCLIP database (select genes).

2. MOCLIP communicates with PODSS to see if the new mutation meets the criteria for actionability (Literature based, Inferred or Potential).

3. Criteria met - pull the selected and relevant trials.

4. Highlight the trial if it matches tumor type of the patient (please note: tumor type is not always available).

5. Send the trials to sequence requesting clinician/PA/NP

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Patient Alert (PI requested)

1. PI/Trial Coordinator contacts PODS team (emailPCT@mdanderson.org) to set up a new alert.

2. Choose Gene(s) / Alteration based or Protocol based alert.

3. Choose Daily or Weekly alert.

How it works:

1. Alert is triggered by new mutation in a selected gene or set of genes coming in to MOCLIP database.

2. MOCLIP talks to PODSS to bring functional significance and actionability calls (if available) for the mutations detected.

3. MOCLIP then compiles the list of patients and send them to requesting clinician.
Single Driver – Single Drug Success: TRK Fusions

Efficacy of larotrectinib in TRK-fusion cancers

Drillon
NEJM 2018

TRK fusions found in diverse cancers

Who do we test for fusions?
How do we test?

Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually
HER2-Targeted Therapy Across Histologies

Pertuzumab/trastuzumab
Hainsworth, JCO, 2018

ZW25
Breeram, EORTC/AACR/NCI, 2018

DS8201a
Iwata et al ASCO 2018
Limitations of Single Agent Therapy

- The minority of patients have tumors with a single actionable alteration
- Targeting with single agent rarely leads to objective responses
- Objective responses to targeted therapy are rarely durable

- Variety of resistance mechanisms:
  - Loss of target (eg HER2)
  - Adaptive responses
  - Acquired mutations downstream or alternate drivers
Strategies for Combination Therapy

• Targeting with single agent rarely leads to objective responses
  • One potential reason may be that we are unable to hit the target hard enough due to toxicity

• Targeting coalterations that may confer intrinsic resistance

• Targeting adaptive responses

• Targeting acquired mutations

• Rationale combinations:
  • SOC agents such as chemotherapy
  • Other molecular targets
Vertical Inhibition of BRAF in Melanoma

Long et al *NEJM* 2014

Vemurafenib, 2011 FDA approval
Dabrafenib, 2013 FDA approval
Trametinib, 2013 FDA approval
Dabrafenib+trametinib, 2014 FDA approval
Vemurafanib+cobimetinib, 2015 FDA approval
Encorafenib+binimetinib, 2018 FDA approval

For BRAF V600E or K-Mutant Melanoma
Targeting Coalterations in Combination Therapy: The I-PREDICT Study

- I-PREDICT Study: Investigation of Profile-related Evidence Determining Individualized Cancer Therapy

- 149 pts consented, 83 pts (56%) treated and evaluable

- Targeting of larger fraction of identified alterations yielded higher “matching score”, with improved disease control rates, PFS, and OS

Sicklick, Nat Med, 2019
Targeting Adaptive Responses

Refractory Melanoma

81% Response Rate

Flaherty et al. NEJM '10

Refractory Colorectal

5% Response Rate

Kopetz et al. JCO '15

Targeting BRAF+MEK+EGFR

Corcoran Cancer Discovery 2012

Van Culsem, JCO, 2019
Targeting Acquired Resistance: EGFR+MET for acquired MET Amplifications

Acquired genomic changes in EGFR and C-Met in EGFR TKI-resistant lung cancer

Sequist LV, et al. 2019 AACR Annual Meeting
Combinations with Standard of Care Therapy: Akt1 as a Therapeutic Target

Randomized Phase 2 trial (LOTUS) ipatasertib
Ipatasertib +paclitaxel vs ipatertib

Advanced/metastatic previously untreated TNBC

In PIK3CA/AKT1/PTEN-altered pts
PFS of 9·0 months vs 4·9 months (HR 0·44; p=0·041)

Kim et al, Lancet Onc, 2017

Similar results obtained in the AZD5363 TNBC PAKT trial (Schmidt et al, ASCO, 2018)
Targeted + Targeted: Targeting EGFR and VEGFR2

**RELAY Primary Endpoint: PFS (Investigator-Assessed)**

1 yr PFS rates: 71.9% vs. 50.7%

<table>
<thead>
<tr>
<th>RAM+ERL n=224</th>
<th>PBO+ERL n=225</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>122</td>
</tr>
<tr>
<td>Median, mo</td>
<td><strong>19.4</strong></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(15.4–21.6)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td><strong>0.591</strong> (0.461, 0.760)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Consistent PFS benefit by independent, blinded central review (HR 0.671, 95% CI 0.518 – 0.869; p=0.0022)
Planning Novel Combination Therapies

Preclinical Modeling

• Models have differing strengths
  • Cell line derived xenografts
  • GEMMS
  • Patient-derived xenografts/organoids

• When possible testing in models with relevant treatment history
• Testing multiple models in vivo
• Tumor stasis or preferably regression
• Enhanced growth inhibition compared to either agent alone

Clinical considerations

• Consideration of overlapping toxicity
  • If there will be a dose reduction compared to either RP2D, is combination efficacy really better than either agent alone?
Need for Systems Analysis
Upcoming NCI Precision Oncology Initiatives

• Three precision oncology trials in development:
  • ComboMATCH - focus on drug combinations vs single agent focus of MATCH
  • iMATCH - focus on providing prospective immunologic profiling to feed IO study arms defined by histology or biomarkers
  • AML/MDS master trial - focus on matching AML molecular subtypes to targeted therapies in different age/fitness groups

• ComboMATCH is currently soliciting concepts
  • Combinations with safety data (or rationale for small run-in)
  • Safety data can be Combinations with strong scientific rationale and preferably strong preclinical data for safety trials

• PDXNet consortium as additional avenue for preclinical data generation
Acknowledgments

Sheikh Zayed Bin Sultan Al Nahyan Building for Personalized Cancer Care
Built with major support from the Khalifa Bin Zayed Al Nahyan Foundation

Institute of Personalized Cancer Therapy

MD Anderson Department of Investigational Cancer Therapeutics
THANK YOU!

Questions/comments/collaborations/concepts:

fmeric@mdanderson.org