Precision Oncology
Decision Support Core

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Genomically-Informed Targeted Therapy
Rapid Evolution of Genomic Testing

• Within each gene, hundreds of variants may be reported within different cancers.

• 29,459 genomic tests to date at MD Anderson
• 2888 patients with solid tumors underwent next generation sequencing on 50-134 gene panels in FY2017.
Doc, you must know everything!
Getting to the Right Patient, with the Right Drug at the Right Time

*Precision Oncology Decision Support (PODS) Core*
Precision Oncology Decision Support

Selected publications
Johnson A et al., Drug Discov Today.2015
Meric-Bernstam F, J Natl Cancer Inst. 2015
Meric-Bernstam F et al, J Clin Oncol. 2015
Johnson A et al, J Clin Oncol Pree Onc. 2017

Chen K et al, Clin Chem. 2015
Zhou W et al., Nat Methods. 2015
Boland GM et al. Oncotarget.2015
Johnson A et al, ASCO, 2016
Kurnot K et al, Cancer Research 2017
A Decision Support Framework for Genomically Informed Investigational Cancer Therapy


Implementation of Biomarker-Driven Cancer Therapy: Existing Tools and Remaining Gaps

Ann M. Bailey, Yong Mao, Jia Zeng, Vijaykumar Holla, Amber Johnson, Lauren Brusco, Ken Chen, John Mendelsohn, Mark J. Routbort, Gordon B. Mills, and Funda Meric-Bernstam

The right drugs at the right time for the right patient: the MD Anderson precision oncology decision support platform

Amber Johnson¹, Jia Zeng¹, Ann M. Bailey¹, Vijaykumar Holla¹, Beate Litzenburger¹, Humberto Lara-Guerra¹, Gordon B. Mills¹,², John Mendelsohn¹,³, Kenna R. Shaw¹, Funda Meric-Bernstam¹,4,5, 

Show more
What is an Actionable Genomic Alteration?

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)
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
Annotation of Variants of Known Functional Significance

Oncogene

- Functional Significance
  - Activating
    - Yes
  - Inactivating
    - No

Tumor Suppressor

- Functional Significance
  - Activating
    - No
  - Inactivating
    - No
  - Likely Benign
    - 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 with other actionable alterations
  - Splice-site mutations in tumor suppressors

--- Actionable Variant Calls ---

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

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

RPPA to define signaling network

Integrate functional proteomics and drug screen

DRUGS AND MECHANISMS
In vivo context dependent screen

Sensitivity to "informer" targeted therapeutic library

Gordon Mills
Han Liang Gaddy Getz
Ken Scott
Yiling Lu
Lynda Chin
Wai Ting Cheung
Jane Li
Shuangxing Yu
Turgut Dogruluk
PODS Submissions (N=1467)

- Informative Result: 712
- Non-informative Result: 287
- Dropped: 11
- In Progress: 31
- Technical Pending: 152
- More info needed: 199

AV call: PODS Submission of Unknown/Not Annotated (N=282)

- Yes: Literature based: 222
  - Yes: FG: 45
  - Potentially: 6
  - No: FG: 7
  - No: 7

79% new non-actionable alterations (222 results from 271 submissions; 16% new actionable alterations)
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
- 3,629 PODS annotation requests on 2,741 patients with over 50 tumor types for 158 clinicians

Enhancements planned:
- Accessibility beyond MD Anderson
  - Pilot: UT Southwestern
# Patient Reports

**Emailed and Deposited into EHR**

**Clear Alteration-Level Actionability Calls**

**Clear Functional Significance Call**

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## Aggregated Frequencies

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>cBio</th>
<th>COSMIC</th>
<th>CMS50</th>
<th>T200</th>
<th>Germline in T200 dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN</td>
<td>T319S*8</td>
<td>0 / 1205 (0%)</td>
<td>13 / 30036 (&lt;1%)</td>
<td>10673 (0%)</td>
<td>2411 (0%)</td>
<td></td>
</tr>
<tr>
<td>RB1</td>
<td>V1936*8</td>
<td>0 / 11513 (0%)</td>
<td>0 / 10673 (0%)</td>
<td>2411 (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>2411 (0%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Patient Reports

### 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>MSC2363318A</td>
<td>A Phase I, First-in-Human, Dose Escalation Trial of MSC2363318A, a Dual p70S6K/Akt Inhibitor, in Subjects With Advanced Malignancies</td>
<td>NCT01971515</td>
<td>Phase 1</td>
<td>Tsiatsios, Apostola</td>
<td>Investigational Cancer Therapeutics</td>
<td></td>
</tr>
<tr>
<td>PTEN Any Alteration, PIK3R1 Any Alteration</td>
<td>Bevacizumab, Valproic Acid, Temsirolimus</td>
<td>A Phase I Trial of Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications</td>
<td>NCT01552434</td>
<td>Phase 1</td>
<td>Pfa-Paul, Sarina A.</td>
<td>Investigational Cancer Therapeutics</td>
<td></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>Phase 1</td>
<td>Menic-Bernstam, Fanya</td>
<td>Investigational Cancer Therapeutics</td>
<td></td>
</tr>
<tr>
<td>PTEN_Mutation</td>
<td>ARQ-751</td>
<td>A Phase I Dose Escalation Study of ARQ 751 in Adult Subjects With Advanced Solid Tumors With AKTI, 2, 3 Genetic Alterations, Activating PI3K Mutations or PTEN-null</td>
<td>NCT02761694</td>
<td>Phase 1</td>
<td>Pant, Shubham</td>
<td>Investigational Cancer Therapeutics</td>
<td></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 (LDK176) in Combination With Everolimus in Patients With Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterised by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression</td>
<td>NCT02321350</td>
<td>Phase 1</td>
<td>Blumenstein Jr, George R</td>
<td>Thoracic and Head and Neck Med</td>
<td></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>NCT02607240</td>
<td>Phase 1</td>
<td>Pfa-Paul, Sarina A.</td>
<td>Investigational Cancer Therapeutics</td>
<td></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

Actionable Variant Calls

- Yes: 32.5%
- Potentially: 9.4%
- Unknown: 29.7%
- No: 28.4%

Actionable Variant Calls in Actionable Genes

- Yes: 40.7%
- Potentially: 11.9%
- Unknown: 36.1%
- No: 11.3%

Johnson and Khotskaya, *JCO Prec Onc*, 2017
Accrual of Genomically-Matched Trials

![Diagram showing the accrual of genomically-matched trials with different classifications.

Patients annotated in 2015 (535)

- **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 and Khotskaya, *JCO Prec Onc*, 2017
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.

Launched April 2014
All content publicly accessible with free registration.
First 32 genes with dozens of individual aberrations annotated.
Therapeutic implications
Relevant trials
New gene-level variants added continuously.

Kurnitt et al Cancer Research Nov 2017
Clinical Trial Email Alerts

Based on Variant Actionability

Gene selected Trials

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Relevant Pt Alteration</th>
<th>Protocol Title</th>
<th>Phase</th>
<th>Drugs</th>
<th>PI Name</th>
<th>Dept/Clin</th>
<th>NCT#</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG1591</td>
<td>ERBB2 Amplification</td>
<td>Molecular Analysis for Therapy Choice (MATCH)</td>
<td>2</td>
<td>Axitinib, Trastuzumab Emtansine, AZD4547, AZD5363, Binimetinib, Crizotinib, Dabrafenib, Dasatinib, Defactinib, GSK2636771, Nirbotsinib, Olametinib, Palbociclib, Sunitinib, Taselitinib, Temetinib, Vismodegib</td>
<td>Merc-Bevin, Punda</td>
<td>ICT</td>
<td>NCT02465960</td>
</tr>
<tr>
<td>2016-0024</td>
<td>ERBB2 Amplification</td>
<td>Phase 2 Randomized, Double-Blinded, Controlled Study of ONT-380 vs Placebo in Combination With Capicitabine and Trastuzumab in Patients With Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma</td>
<td>2</td>
<td>ARRY 380, Trastuzumab, Capecitabine</td>
<td>Moeller, Stacy</td>
<td>Breast Onc</td>
<td>NCT02614794</td>
</tr>
<tr>
<td>2015-0076</td>
<td>ERBB2 Amplification</td>
<td>A Multi-Center Study of the Bruton’s Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with MED4736, in Subjects with Relapsed or Refractory Solid Tumors</td>
<td>1,2</td>
<td>Duvralinab, Ibrutinib</td>
<td>Hong, David</td>
<td>ICT</td>
<td>NCT02493277</td>
</tr>
<tr>
<td>2014-0419</td>
<td>ERBB2 Amplification</td>
<td>MY Pathway: An Open-Label Phase IIa Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Venetanab, and Vismodegib in Patients who Have Advanced Solid Tumors with Mutations or Gene Expression Abnormalities Predictive of Response to One of Those Agents</td>
<td>2</td>
<td>Pertuzumab, Trastuzumab, Erlotinib, Venetanab, Vismodegib</td>
<td>Merc-Bevin, Punda</td>
<td>ICT</td>
<td>NCTD0091141</td>
</tr>
<tr>
<td>2013-0007</td>
<td>ERBB2 Amplification</td>
<td>A Phase II Trial of HKI-272 (Neratinib) for Patients With Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer and Brain Metastases</td>
<td>2</td>
<td>Neratinib, Capecitabine</td>
<td>Ibrahim, Nihad</td>
<td>Breast Onc</td>
<td>NCT01494662</td>
</tr>
</tbody>
</table>

On-demand link for screening

Alerts triggered only if actionable/potentially actionable alteration is selected trials
Recruiting Basket Trials

Mutations X  Fusion X  Amplification X

Histology-independent
or
Separate cohorts by histology

Industry-sponsored
Or
Investigator initiated
Or
NCI-Match or TAPUR

Increasing number of Genotype-matched Trials

![Graph showing increasing number of trials submitted over fiscal years 2012 to 2016.](chart)
Biomarker-Selected Trials in ICT

~ 100 targets; over 70 drugs, over 60 trials
Successes in Precision Oncology Basket Trials

**BRAF V600E NSCLC**
Vemurafenib


**RET fusion NSCLC**
Vandetinib+everolimus

- Cascone and Subbiah, *ASCO*, 2016

**BRAF V600 Anaplastic Thyroid Cancer**

- Dabranib/trametinib
- Sixteen patients with BRAF V600E-mutated anaplastic thyroid cancer were evaluable
- Overall response rate was 69%

Subbiah *JCO* in press
**HER2 as a Target**

**HER2 mutations**

SUMMIT trial: Neratinib for *HER2* mutant, HER2 nonamplified BC

Single agent ORR 8 weeks 33%; confirmed ORR 25% CBR 42%:

Combination ORR at 8 weeks 42%, confirmed ORR 25%, CBR 58%

Hyman, Piha Paul et al
SABCS 2016

**HER2 amplification**

HER2 amplified CRC; Hurvitz, ASCO GI 2017

HER2 amplified salivary ca; Kurzrock ASCO 2017
Conclusions

• Genomic sequencing is increasingly prevalent

• Its utility is dependent on:
  • likelihood of truly actionable alterations
  • Available therapies
  • Whether therapeutic intervention is feasible/appropriate

• Multianalyte analysis and combinatorial therapy is likely to enhance driver identification and responses
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Questions/comments/collaborations:

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