Sheikh Khalifa bin Zayed Al Nahyan Institute for Personalized Cancer Therapy

John Mendelsohn  Gordon Mills  Funda Meric-Bernstam  Kenna Mills  Shaw

DELIVERING ON THE PROMISE OF PERSONALIZED MOLECULAR MEDICINE
POTENTIAL CONFLICT OF INTEREST DISCLOSURES

Financial Relationships

- **SAB/Consultant:** AstraZeneca, Catena Pharmaceuticals, Critical Outcome Technologies, ImmunoMET, Ionis, Medimmune, Nuevolution, Pfizer, Precision Medicine, Signalchem Lifesciences, Symphogen, Takeda/Millennium Pharmaceuticals, Tarveda,

- **Stock/ Options/Financial:** Catena Pharmaceuticals, ImmunoMet, SignalChem, Spindle Top Ventures, Tarveda

- **Licensed Technology** HRD assay to Myriad Genetics

- **Sponsored Research:** Abbvie, Adelson Medical Research Foundation, AstraZeneca, Breast Cancer Research Foundation, Critical Outcomes Technology, Horizon Diagnostics, Illumina, Ionis, Immunomet, Karus Therapeutics, Komen Research Foundation, Pfizer, Nanostring, Takeda/Millennium Pharmaceuticals, Tesaro

I will discuss off label use and/or investigational use of drugs
Targeting the Genetic Changes Specific to Each Patient’s Cancer
Small molecules and immune therapy

Capitalizing on the vulnerabilities (Achilles Heel) of cancer
Khalifa Institute for Personalized Therapy

MDACC patients without curable disease 20,000
5-9000 per year

Actionable mutations
Targetable
Predict patient outcomes
(Paraffin compliant)

Targetable aberration present

Standard of care
N of 1 trials
Clinical trial cohorts

No Targetable Aberration
Deep characterization
High throughput biological validation

Deep learning from each patient; Real time adaptive treatment
Efficacy of targeted therapy conditioned by mutation, comutation and tissue lineage BRAF in melanoma and bowel

* Clinical progression
+ Continuing response

Janku et Mol Can Ther
Can we achieve truly personalized therapy?

N of one problem

Precision Medicine?

Stratified Medicine

Homogenous patient groups

Ductal Breast Cancer

8 subclasses

A set of orphan diseases

Rare aberration populations

AKT mutant tumors

2-3% in any major lineage

0.7% in trial sets

Multiplex analysis of multiple aberrations allows “amortization” of costs across multiple trials
19000 (2000 in set) patients likely to enter trials
Hot Spot Mutation CMS46 (Ion Torrent)
Potentially actionable 39%
TP53 not counted (31%) KRAS counted (11%)

Most targetable aberrations are rare across cancers
All testing covered by philanthropy: Not sustainable
19000 (2000 in set) likely to enter trials

Hot Spot Mutation CMS46 (Ion Torrent)

Potentially actionable 39%

TP53 not counted (31%) KRAS counted (11%) Oct 2014

Endometrioid ovarian primary, 480mg BD 4d on/3d off Confirmed RECIST PR (maximum reduction 55%). Ongoing in study (more than 600 days on drug).

% Patients with Likely Somatic Mutations

AKT mutant tumors respond to AKT targeted drugs
HOW DO WE DETERMINE WHETHER RARE MUTATIONS INDICATE VULNERABILITY

AKT1 1.4%
2% in breast cancer

Want 50 patients on trial
50% positive will not be eligible
Test 5,000 patients at $3000 per patient
15 million dollars in testing
Multiplex across many aberrations
THERAPEUTIC INDEX IS LIMITING FACTOR
COULD WE IMPLEMENT MUTATION SPECIFIC DRUGS (1-2% frequency)
ie PIK3CA H1047R vs pan PIK3CA drug

Hotspot frequency might allow mutation specific drugs
Outcomes for first 2000 patients

- Underwent Genomic Testing
  - N = 2000

  - Potentially Actionable Mutations
    - Yes (789)
    - No (1211)

  - Genomically-matched trial after genomic testing?
    - Yes (83)
    - No (706)

  - Genomically-Selected Trial N = 54
  - Genomically-Relevant Trial N = 29

- 4% of patients tested were ultimately treated with “matched” agent
- 39% of patients had aberration in actionable gene
- 11% of pts with mutations in actionable genes went on genotype-matched trials
What did we learn  Goal 25% of patients to trials

• Increasing scope of testing increases rate of actionable events modestly (39-53%):
  • 90% of actionable aberrations are in limited set of genes
• Time to results critical in Phase I due to patient deterioration
  • Test when likely to need information and have therapeutic options
• Physician decision support is critical
  • Aberration level information
  • Not all alterations in actionable genes are actionable
  • Clinical trials alert to curated results and eligible clinical trials
• The utility of genomic testing is dependent on availability and efficacy of therapeutic agents
  • Increase number of molecular marker driven trials
  • Develop basket trials to deal with rare events AKT, TRK
• Move from single aberrations to pathways and networks
• Circulating DNA allows for proximal analysis of metastases
Value of Molecular Testing

• Directing patients to standard of care or off label use is important outcome

• Rapid approval of effective drugs

• Reputational event to recruit patients

• Recruit high quality information rich trials

• Consider testing a “loss-leader”
  • Added cost of multiplex testing modest

• Critical to convince payors of value
  • Philanthropy non sustainable
ENTRY INTO CLINICAL TRIALS UNDERESTIMATES UTILITY OF MOLECULAR TESTING

Types of Genotype Matched Treatment Received
- Standard of Care: 36%
- Clinical Trial: 58%
- Off Label Use: 6%

Gene Alterations for Which Patients Received Treatment
- BRAF: 30%
- PIK3CA: 32%
- NRAS: 10%
- PTEN: 2%
- SMO TP53: 2%
- CDKN2A: 2%
- KRAS: 2%
- FGFR3: 2%
- EGFR: 2%
- ERBB2: 6%
Doc, you must know everything!
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.
27 potentially actionable genes fully annotated

• Mutations
• Copy number changes
• Fusions
• Germline alterations if relevant

• Interactive: Physician determines level of information

• Therapeutic implications and the level of evidence for each therapy

• Clinical trials available by location
All patients with identified somatic variants

188 patients with mutation(s) only in non-actionable gene

196 patients with variant in actionable gene

68 known activating

~20% enrolled

4 inferred activating

~20% enrolled

7 inactivating

34 inferred inactivating

291 variant of unknown significance

~7% enrolled

1 benign

Decision Support in Real Time Improves ‘Matching’ to ‘Right’ Drug

Approximately 25% of patients with mutations in actionable genes were enrolled on clinical trials using matched therapies (~12% can be potentially enrolled - still awaiting progression)
‘Matching’ to ‘Right’ Drug Improves Patient Outcomes

UNEXPECTED HIGH RATE OF FAILURE OF TARGETED THERAPEUTICS

Even for patients with the biomarker only subpopulations of patients benefit from monotherapy: Usually short term

Resistance is almost universal
  Intrinsic (Genetic)
  Selected (Genetic)
  Adaptive (Homeostatic loops, cross talk and bypass)
  Heterogeneity

Rationale combinatorial therapy will be required to fulfill the promise of targeted therapy

Yossi Yarden Arthur Lander
Cells in 2D, 3D, in vivo, or patient tumors

Add drug

Early time points: target engagement
Medium time points: adaptive responses
Late time points: genomic resistance

Harvest cells for Omic analysis
DNA, RNA, protein metabolomics
PARP inhibitors induce **synthetic lethality** in homologous recombination-deficient (HRD) cancer cells.

Normal cells have **many** DNA Repair Pathways.

DNA damage occurs **constantly**.

DNA damage induces cell cycle checkpoints to allow DNA damage repair.

PARP inhibitors induce DNA damage.

HRD cells do not accurately repair damage.

Three PARP inhibitors have been approved for ovarian cancer and OLYMPIAD Phase III trial in breast cancer has met its goals. Despite high response rate, duration of response remains short.
HUMAN PROTEOMICS ATLAS: RPPA

Quantitative high throughput multiplexed inexpensive ELISA

300 validated antibodies

Dot blot: less sensitive to degradation

Requires high quality validated antibodies and robotics

No Spatial orientation: combined tumor and stromal signature

>10,000 TCGA and internal patient samples with extensive DNA, RNA, miRNA, and clinical data

Tcpaportal.org
Search Cancer Proteome Atlas

Cell lines with RNASeq and drug data

700 lines in house

http://tcpaportal.org/mclp/#

Broad Cancer Cell Line Encyclopedia

130,000 samples in total
Rank-Sum Analysis of AZD2281 and BMN673

5 representative cell lines were treated with 2 doses for 72 and 96 hours in 2D and 3D cultures. Lysates were collected and analyzed by RPPA for 191 antibodies. High levels are represented in Red. >50,000 data points

Data is ratio of treated to untreated
Samples are ordered based on adding all antibody scores
Only significant changes presented

Public

Private

Yiling Lu Xiaohua Chen
Rank-Sum Analysis of AZD2281 and BMN673

5 representative cell lines were treated with 2 doses for 72 and 96 hours in 2D and 3D cultures. Lysates were collected and analyzed by RPPA for 191 antibodies. High levels are represented in Red.

Yiling Lu Xiaohua Chen
BKM and Olaparib demonstrate marked responses

77% OvCa gBRCA
57% BrCa gBRCA
Non mutant BRCA1/2 2 PR
One biopsy: ATR mutant

Ursula Matulonis
Shannon Westin

PI3K Dream Team
http://pi3k.org
American Association for Cancer Research
Time on Treatment
Olaparib, BKM120 Pan PI3K
PI3K alpha, mTOR and AKT in progress
Up to 24 months response: 50% of endometrial cancers

Ovarian Cancer
Breast Cancer

PI3K Dream Team
http://pi3k.org

Ursula Matulonis
Shannon Westin
OCTOPUS – PARP/PI3K pathway combinations

> 70 patients accrued

RR ~ 30% for OC, 50% for EC
Rank-Sum Analysis of AZD2281 and BMN673

5 representative cell lines were treated with 2 doses for 72 and 96 hours in 2D and 3D cultures. Lysates were collected and analyzed by RPPA for 191 antibodies. High levels are represented in Red.
SERENDIPITY IS CRITICAL

KRAS mutation is a marker for BMN673 resistance: markedly improved HR DNA repair in RAS mutant lines

Chaoyang Sun
Acquired PARPi resistance is associated with RAS MAPK pathway activation, acquisition of RAS mutations and sensitization to combination therapy.
Synergistic effect of PARP and MEK/ERK inhibition is lineage independent and observed with KRAS/NRAS/BRAF mutations.

35/37 models

Dong Zhang
Yong Fang
Chaoyang Sun

MEKi active as monotherapy
PARP plus MEK inhibitors are synergistic in vivo

Dong Zhang
Yong Fang
Chaoyang Sun

KRAS
OVCAugged

KRAS HPDE
Pancreas
SOLAR study: selumetinib and olaparib in RAS activated tumors

Original observation 4/8/2015
CRC Approved, IRB 3/1/17
FDA no Objection
SIV May 30 2017
First in human August 2017

DOSE EXPANSION
N=60

Endometrial Tumors with RAS Pathway Activation
N=15

Ovarian Tumors with RAS Pathway Activation
N=15

Ovarian Tumors with Progression on Prior PARP Inhibitor Treatment
N=15

Solid Tumors with RAS Pathway Activation
N=15

Shannon Westin
Funda Meric-Bernstam
Immune system contributes to response to PARP plus MEK

Dong Zhang
Yong Fang
Chaoyang Sun

MDX in immune competent mouse

MDX in immunoincompetent mouse
Niraparib plus anti-PD1 is effective in MDX T22 model

- Vehicle for Niraparib
- Isotype Control
- Niraparib
- Anti-PD-1
- Vehicle for Niraparib+Isotype Control
- Niraparib+Anti-PD-1

Treatment stopped

CCCT Collaboration with Tesaro
**STING / Type I IFN and immune priming**

DNA fragments in response to PARPi induces immune activation

- Activation of STING by cGAMP in response to cytoplasmic dsDNA results in secretion of Type I IFNs (IFNα, IFNβ)

- IFNα/β promotes DC maturation and cross-presentation of tumour antigens to CD8+ T cells

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**DNA Fragments Induce a Sting Response as Protection from Virus and Bacteria**

Hartlova et al., Immunity 2015

Chen et al., Nat Immunol, 2016
Phase I Trial of Talazoparib + Avelumab in Advanced Cancers
Currently enrolling in ICT (PI: Tim Yap)

1. Dose escalation

   Eligibility:
   - Advanced or metastatic solid tumors including NSCLC, breast, ovarian, bladder, and prostate.
   - PARP refractory excluded
   - PD-1/PD-L1 treatment naive
   - ECOG 0 and 1
   - Prior platinum eligibility varies by tumor type

   Avelumab Dose Fixed
   800 mg Q2W

   D0: Ave + tala 1.0 mg
   D-1: Ave + tala 0.75 mg
   D-2: Ave + tala 0.50 mg

   • Tumor types permitted as per those defined for the dose expansion cohorts
   • Dose escalation as per mTPI
   • Each dose level will have 3-12 pts
   • No backfill
   • DLT Observation period=28 days
   • N=12-36 total

2. Dose expansion

   A1. NSCLC
   N=40

   A2. NSCLC
   PD-L1 TPS ≥ 50%
   N=40

   B1. TNBC
   N=20

   B2. HR+ BC
   DDR Defect + assay
   N=20

   C1. Ovarian
   Recurrent platinum-sensitive
   N=40

   C2. Ovarian
   Recurrent platinum-sensitive BRCA defect
   N=20

   D. Urothelial
   N=40

   E1. CRPC
   N=20

   E2. CRPC
   DDR Defect + assay
   N=20
AMTEC
Adaptive Multi-Drug Treatment of Evolving Cancers

AMTEC will be designed to reveal the complexity of each individual’s cancer and its evolution under therapeutic stress, implementing uniquely designed therapeutic strategies that evolve concomitantly benefiting the patient we are treating while identifying underlying mechanisms of resistance to guide new drug combinations.
AMTEC
Adaptive Multi-Drug
Treatment of
Evolving
Cancers

PARP inhibitors
as example

Patient

Rules Based Clinical Trial
Decision tree

Trials underway
Trials in development

Imaging
Biopsy Analysis must be 7-10 days and tissue sparing
DNA, RNA, Protein
Blood cf DNA CTCs
Exosomes: DNA RNA Biomarkers
Date integration Computational biology

PARP inhibitors as example

Blood Biomarkers
Is there a change in DNA or RNA in blood ie emerging resistance mutations
Rebiopsy if evidence of progression?

3-6 weeks

Imaging
Biopsy Blood Analysis must be 10-14 days and tissue sparing
Adaptive mechanisms and tumor evolution identified
Modify patient therapy based on evolution

Imaging
Blood Biomarkers
Is there a change in DNA or RNA in blood ie emerging resistance mutations
Rebiopsy if evidence of progression?

PARP resistance mechanisms
Reversion mutation etc

Change to different drug A

DNA damage checkpoint activated
ATR/CHK1/WEE1 inhibitor Sequencing may decrease toxicity

Activated PI3K pathway
PI3K pathway inhibitor

Altered vascularity
VEFR inhibitor

Increase in MAPK pathway activation
MEK or MAPK inhibitor

Increase in PDL1
Anti PD1/PDL1

Tumor infiltrating lymphocytes

PARP resistance mechanisms
Reversion mutation etc

Change to different drug A

Incomplete inhibition of PARP
No DNA damage
No DNA damage checkpoint

Change to different drug A or increase PARPi dose

Incomplete inhibition of PARP
HR competent
BRD4 inhibitor

Altered apoptotic sensitivity
BCL2/MCL1/BCLxl inhibitor

EMT induction
BRD4 EZH2 inhibitor?

HR competent
BRD4 inhibitor

Incomplete inhibition of PARP
EMT induction
BRD4 EZH2 inhibitor?
Rational Strategy for Combination Therapies

Blocking critical signaling nodes “rewires” signaling pathways

Rewired networks contribute to cellular resistance to targeted therapeutics

Induced signaling events represent “vulnerabilities” that can be exploited leading to synthetic lethality

Adaptive responses can be restricted to specific tumor subpopulations

AMTEC
Adaptive Multi-Drug Treatment of Evolving Cancers
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