Five inspiring examples…

but also one oncologist
Clinical Perspective: Bringing the Community Care Setting Into the Learning Versus Confirming Paradigm

Michael Maitland, MD, PhD
Director of Therapeutics, Inova Center for Personalized Health
Professor of Internal Medicine, Virginia Commonwealth University
Assoc. Director for Cancer Therapeutics, Inova Schar Cancer Institute
A nearby health system...
CENTER FOR PERSONALIZED HEALTH (ICPH) - 2019

Inova Schar Cancer Institute Care Center

Inova/UVA Global Genomics and Bioinformatics Institute (wet & dry labs)

Biotech/Health IT Accelerator
Research in community medical practice
### Pt 1
- 30’s yo presented w/ prolonged menses, endometrial bx 09/14 with endometrioid adenocarcinoma T2N2M0= IIIC2
- Adj. cddp/doxo->RT/prog.
- 03/16 cbcda/pac
- 11/16 procedure

### Pt 2
- 30’s yo presented abnl screening cytology, then developed sx, d&c 01/14 with endometrioid adenocarcinoma T3bN1M0= IIIC1
- Adj. cbcda/pac-> RT
- 10/15 cbcda/lipo-dox
- 12/15 doce/gem
- 09/16 bevacizumab
Molecular pathology as destiny

Pt 1
- 08/17 nodal recurrence
  **MLH1** M587fs*6
  **TP53** R175H
  "Additional findings"

High tumor mutation burden
21 Muts/Mb

Pt 2
- 09/17 progressive disease on bevacizumab
  **PIK3CA** R88Q
  **CTNNB1** S37C
  **PTEN** N323fs
  **PTEN C.1026+1G>C**

MSI testing not performed
Overall mutation burden
intermediate
Professional Society (ASCO)-sponsored trial

ASCO’s Targeted Agent and Profiling Utilization Registry (TAPUR) Study is a clinical trial to understand the efficacy and safety of FDA-approved, targeted anticancer drugs for patients whose advanced cancer has a genomic variant targeted by a TAPUR study drug.

**OUR STUDY AIMS**

- Collect data on clinical outcomes to help learn about new uses of approved drugs.
- Learn from real-world prescribing practices.
- Educate oncologists about how to use genomically targeted drugs.
- Catalogue oncologists’ choice of genomically profiling tests.
- Learn about the use of registry data to generate hypotheses for additional clinical trials.

**WHO BENEFITS**

- **Participants:** Access to targeted study drugs matched to the genomic profiles of their cancers
- **Physicians:** Assistance interpreting genomic results and identifying potential treatment options
- **Cancer Community:** New uses of targeted anticancer drugs for patients who have exhausted standard options
- **Drug Manufacturers:** Insights on new uses of existing drugs
- **Regulatory Authorities:** Learn about side effects and treatment outcomes from use of approved drugs in other cancers

**HOW IT WORKS**

1. Treating physician reviews patient’s genomic profile and determines that patient is eligible for TAPUR study. Patient makes informed decision to participate.
2. Physician matches participant to an available study drug
   - OR - Physician refers case to study Molecular Tumor Board in cases of:
     - No protocol-defined matches and potential clinical benefit (review required)
     - Multiple drug matches (review optional)
     - Desire for guidance (review optional)
3. Physician and participant confirm choice of TAPUR study drug (consistent with Molecular Tumor Board report, if applicable)
4. A central TAPUR study pharmacy provides the approved study drug at no cost to the participant
5. Patient data on standard toxicity and efficacy outcomes are collected for analysis.

**ELIGIBILITY**

- Advanced cancer (including solid tumors, multiple myeloma, and B cell non-Hodgkin lymphoma) with a genomic variant that can be targeted with a study drug
- No longer benefiting from standard treatment, or no standard treatment available
- Healthy enough to participate
Pt 1
- 05/23/17
  Keytruda/pembrolizumab indication for advanced MSI-H/dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options
- 08/17 begins pembrolizumab

Pt 2
- No FDA-approved PI3Ki
- NRG GY008 A Phase II Evaluation of Copanlisib (BAY 80-6946), a Selective Inhibitor of PI3KCA, in Patients With Persistent or Recurrent Endometrial Carcinoma Harboring PIK3CA Hotspot Mutations
- 09/17 begins paclitaxel
Pt 1
• 10/17 CT imaging reveals decreased retroperitoneal adenopathy
• Had elevation of liver enzymes associated with fatigue now resolved
• Had changes in TSH, but no symptoms
• Works full time

Pt 2
• 10/17 vaginal bleeding controlled, pain persists
• Develops progressive, manageable peripheral neuropathy
• Pain/fatigue continue
• 11/17 NRG copanlisib study still on hold, team pursues single pt IND
Approval After Phase I: Ceritinib Runs the Three-Minute Mile

BRUCE A. CHABNER
Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA

Thirteen years ago, I wrote an editorial applauding discovery, development, and marketing approval of imatinib for chronic myelogenous leukemia (CML), a signal event in the history of targeted therapy, and the oncology equivalent of the four-minute mile [1]. It took 3 years from the start of trials and required the confirmatory evidence of two phase II studies to receive the U.S. Food and Drug Administration’s (FDA) stamp of conditional approval. A decade later, these pages called attention to the rapid 3-year development of crizotinib for ALK-translocated non-small cell lung cancer (NSCLC), again based explained by its greater potency and its particular ability to inhibit ALK with gatekeeper mutations that confer resistance to crizotinib. In this trial, mechanisms of resistance were characterized in a subset of 19 crizotinib-resistant tumors prior to ceritinib treatment, and responses to the new drug were observed in settings where gatekeeper mutations were present, where ALK was amplified, or where no obvious mechanism was identified. While activation of alternative pathways is suspected of contributing to resistance, particularly when tumors fail to show amplification or mutation
Learning versus confirming in clinical drug development

Lewis B. Sheiner, MD San Francisco, Calif.
THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS

BASIC RESEARCH

DRUG DISCOVERY

PRE-Clinical

CLINICAL TRIALS

FDA REVIEW

POST-APPROVAL RESEARCH & MONITORING

PHASE I

PHASE II

PHASE III

PHASE IV

POTENTIAL NEW MEDICINES

IND SUBMITTED

NUMBER OF VOLUNTEERS

TENS

HUNDREDS

THOUSANDS

1 FDA-APPROVED MEDICINE

NDA/BLA SUBMITTED

FDA APPROVAL
Clinical Regulatory Pathway: Now

**Phase 0:**
- PD evaluation; Biomarkers of target engagement

**Phase 1a:**
- Safe dose

**Phase 1b:**
- "Dose expansion": Looking for activity in specific population; may be biomarker-selected

**Phase 2:**
- Randomized: Accelerated approval

**Phase 3:**
- Post-marketing safety; Postmarketing commitments and requirements in context of accelerated approval

**Potential New Medicines**
- International Trials: may be conducted prior to IND submission
Our near future...

21 FDA-APPROVED MEDICINES

POTENTIAL NEW MEDICINES

PHASE I

PHASE II

PHASE III

PHASE IV

BASIC RESEARCH

DRUG DISCOVERY

PRE-Clinical

CLINICAL TRIALS

FDA REVIEW

POST-APPROVAL RESEARCH & MONITORING

NUMBER OF VOLUNTEERS

TENS

HUNDREDS

THOUSANDS
With 20 agents, 803 Trials, and 166,736 Patient Slots, Is Pharma Investing Too Heavily in PD-1 Drug Development?
Better data in the context of routine care?
Better quality of pilot study assessments?
More learning and innovative confirming...

21 FDA-APPROVED MEDICINES

1. Increased accessibility
2. Better generalizability
3. New era of life-cycle management
4. New era of regulatory management
5. Better capacity to enhance/extend value
What is an appropriate initial dose for my particular patient?
How soon will intended effect start?
How long will it last?
Will tolerance develop?
What happens if my patient misses some doses?
What are the chances that the initial dose will have to be altered?
What do I follow to see if it needs to be altered?
How do I alter it? Do I wait 1 week, 2 weeks, 3? Do I then suggest a big increment or a small one?
It’s all immunotherapy these days…

- **PEMBROLIZUMAB** - Case Example I: Characterization of Post-progression Outcomes as a Function of Time on Treatment – **David Turner, Ph.D.**

- **DURVALUMAB** - Case Example II: Durvalumab in NSCLC and mUC – **Yanan Zheng, Ph.D.**

- **IPILIMUMAB** - Case Example III: Tumor Growth Dynamic-Overall Survival Modeling with Ipilimumab in Melanoma – **Amit Roy, Ph.D.**

- **ATEZOLIZUMAB** - Case Example IV: Applications of Tumor Growth Inhibition-Overall Survival Models to Support Atezolizumab Combination Studies – **René Bruno, Ph.D.**

- **AVELUMAB** - Case Example V: Using Modeling Approach to Inform the Decision at Early Drug Development Stage – **Jenny Zheng, Ph.D.**