FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2014 Conference on Clinical Cancer Research

Supported by:

ASCO® American Society of Clinical Oncology

Susan G. Komen for the Cure®

November 21, 2014 • Washington, DC

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2014 Conference on Clinical Cancer Research

Improving Evidence Developed from Population-Level Experience with Targeted Agents

Mark McClellan, MD, PhD
Brookings

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2014 Conference on Clinical Cancer Research

Improving Evidence Developed from Population-Level Experience with Targeted Agents

Speakers

- **Richard L. Schilsky, MD, ASCO**
- **Dane Dickson, MD, MolDX**
- **Jane Perlmutter, PhD, Gemini Group**
- **Vincent Miller, MD, Foundation Medicine, Inc.**
- **Dietmar Berger, MD PhD, Genentech**
- **Jeffrey Roche, MD, CMS**
- **Samuel Nussbaum, MD, WellPoint, Inc.**
- **Richard Pazdur, MD, FDA**

Contributors: Jennifer Malin, MD PhD, WellPoint Inc.; James Rollins, MD, CMS; Janet Woodcock, MD, FDA

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2014 Conference on Clinical Cancer Research

Improving Evidence Developed from Population-Level Experience with Targeted Agents

Richard L. Schilsky, MD
ASCO

Problem

- Patient with advanced cancer; no standard Rx options
- Genomic test performed on tumor
- Potentially actionable variant detected
- How to get the drug?
- How to learn from the treatment?

Potential Drug Sources

- Commercial drug used within indication
- Commercial drug used off label (reimbursement?)
- Clinical trial participation
- Expanded access program (company sponsor or individual patient IND)

Potential Drug Sources

- Commercial drug used within indication
- Commercial drug used off label
- Clinical trial participation
- Expanded access program (company sponsor or individual patient IND)

Proposed Solution: Targeted Agent and Profiling Utilization Registry (TAPUR)

- Create a registry of administered treatments and patient outcomes
- Facilitate patient access to marketed, targeted agents
- Participants: Patients, physicians, pharma, payers

What's Required?

Pharma provides drugs.

Patient agrees to data collection.

Physician submits required follow-up data.

CMS/commercial payers reimburse treatment costs.

ASCO hosts the outcomes registry and shares the data.

TAPUR Study Primary Objectives

- To describe the anti-tumor activity and toxicity of commercially available, targeted anti-cancer drugs used off label for treatment of patients with advanced solid tumors with a known genomic variant.

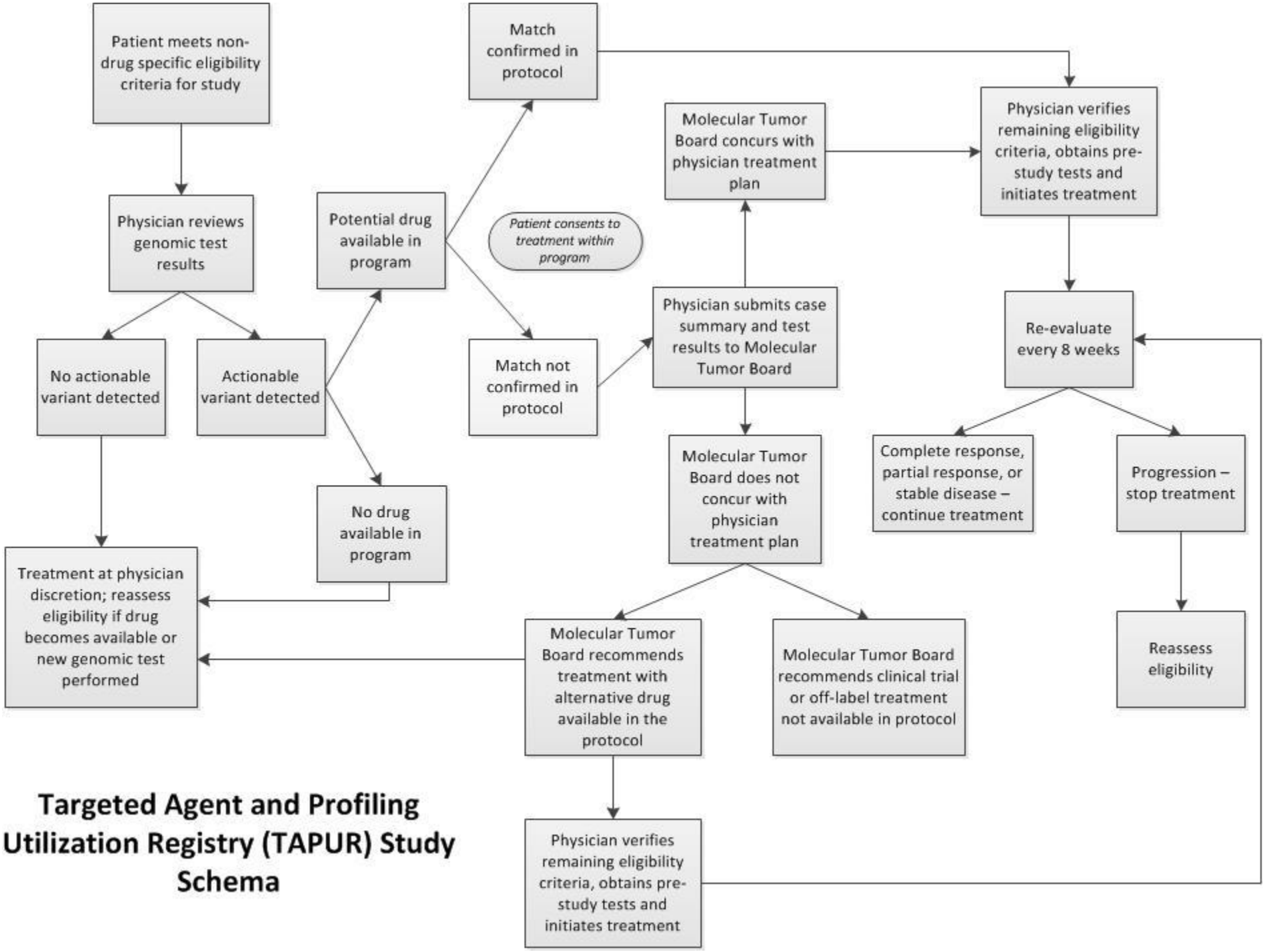
- To facilitate patient access to commercially available, targeted anti-cancer drugs of potential efficacy prescribed off label for treatment of patients with an advanced solid tumor with a known genomic variant.

TAPUR Study Secondary Objectives

- To record the treatment-related adverse events.
- To create a prospective registry of patient outcomes following off label treatment.
- To create a prospective registry of commercially available tumor genome profiling tests used by clinical oncologists in the usual care setting.
- To determine the concordance of the treatment plan proposed by the treating oncologist with that recommended by the molecular tumor board.

TAPUR Eligibility

- Patients with advanced solid tumors (and possibly myeloma) for whom no standard treatment options exist
- Adequate organ function; PS 0-2
- Results available from a genomic test (FISH, PCR, NGS) performed in a CLIA certified, CAP accredited lab that has obtained a McKesson Z code identifier. Labs located or offering services in NY must also have NY State accreditation


Patient meets non-drug specific eligibility criteria for study
Physician reviews genomic test results
No actionable variant detected
Actionable variant detected
Potential drug available in program
Match confirmed in protocol
Match not confirmed in protocol
Patient consents to treatment within program
No drug available in program
Treatment at physician discretion; reassess eligibility if drug becomes available or new genomic test performed
Physician submits case summary and test results to Molecular Tumor Board
Molecular Tumor Board concurs with physician treatment plan
Physician verifies remaining eligibility criteria, obtains pre-study tests and initiates treatment
Molecular Tumor Board does not concur with physician treatment plan
Molecular Tumor Board recommends treatment with alternative drug available in the protocol
Molecular Tumor Board recommends clinical trial or off-label treatment not available in protocol
Physician verifies remaining eligibility criteria, obtains pre-study tests and initiates treatment
Re-evaluate every 8 weeks
Complete response, partial response, or stable disease – continue treatment
Progression – stop treatment
Reassess eligibility
Targeted Agent and Profiling Utilization Registry (TAPUR) Study Schema

Why the Molecular Tumor Board?

- Protect patients from inappropriate treatment based on incorrect interpretation of molecular test results.
- Protect patients from inappropriate treatment based on misunderstanding of drug action.
- Compare physician selection and treatment choice to honest broker recommendation.
- Maintain compliance with FDA rules about promotion of off label use.

Possible Actions of MTB

- Concur with MD plan
- Recommend treatment with another drug in protocol targeting selected variant
- Recommend treatment with a drug in protocol targeting another variant
- Recommend treatment with a drug not in protocol
- Recommend a clinical trial

Study Endpoints and Analysis

- Primary endpoint: ORR per RECIST
- Other endpoints: PFS, OS, time on treatment, grade 3-5 AEs per CTCAE, SAEs
- Each tumor type-variant-drug is a “group”
- Enroll 8 patients/group. If no responses, stop
- If at least 1 response, enroll additional 16
- 4 or fewer responses/24, no interest; $\geq$ 5 responses; signal of activity
- 85% power and an alpha error rate of 7.8%

Data Collection

- Patient demographics to confirm eligibility
- Genomic test performed, tumor specimen used, and results obtained
- Treatment administered
- Patient most recent prior treatment and best response
- Efficacy (per RECIST): ORR, PFS, OS, time on treatment
- Safety (per CTCAE): SAEs, Gr 3-5 AEs

Who Benefits?

- **Patients** receive targeted agent matched to genomic profile
- **Physicians** receive interpretation of molecular test results, guidance in treatment recommendations and access to drugs
- **Pharma** receives data on drug use and outcomes to inform R&D plans and life cycle management
- **Payers** receive data on test and drug use and outcomes to inform future coverage decisions
- **Regulators** receive data on extent and outcomes of off label drug and test use and additional safety data

Issues for Discussion

- Will the data be reliable? How much data collection is necessary?

- How might it be used?

  - Hypothesis generation to inform new studies?
  - Label modification, e.g., for safety issues?
  - Label expansion, e.g., for new indications?
  - Compendia/guideline modifications?
  - Reimbursement policy, expand or reduce coverage?
  - Doctor-patient decision-making?

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2014 Conference on Clinical Cancer Research

Improving Evidence Developed from Population-Level Experience with Targeted Agents

Dane Dickson, MD
Palmetto GBA-MolDX

Molecular Evidence Development Consortium

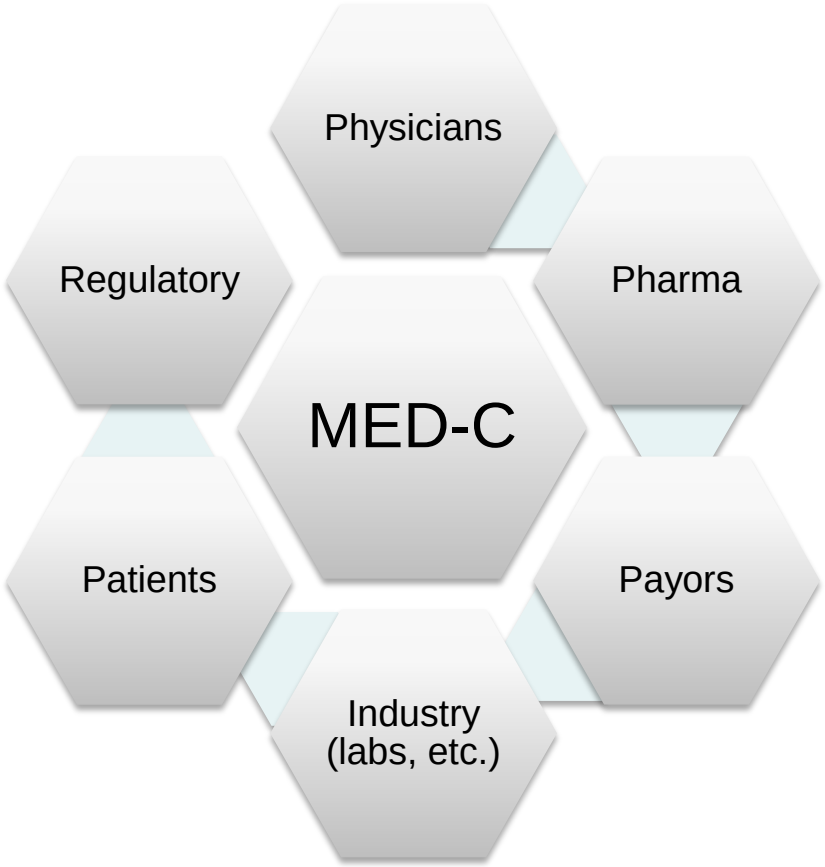
- MED-C
- Developed as a concept through Palmetto GBA and the MolDX program in connection with other stakeholders
- Although Palmetto is spearheading, it will be separate from all existing groups
- Although starting in Oncology – IT HAS BEEN DESIGNED to ADDRESS ALL AREAS of MEDICINE

Molecular Evidence Development Consortium (MED-C)

Goals

- Marked increase in number of patients enrolled in personalized medicine testing and treatment
- Capture research quality information (dx and tx)
- Streamline and unify diagnostics
- Greater number of patients screened and enrolled for clinical trials
- If not clinical trial, then high level data capture
- Marked decrease cost of molecular research with improved cost of overall care

MED-C Organization



- Shared Governance
- Shared Data
- Mutual Benefit

MED-C and Projects

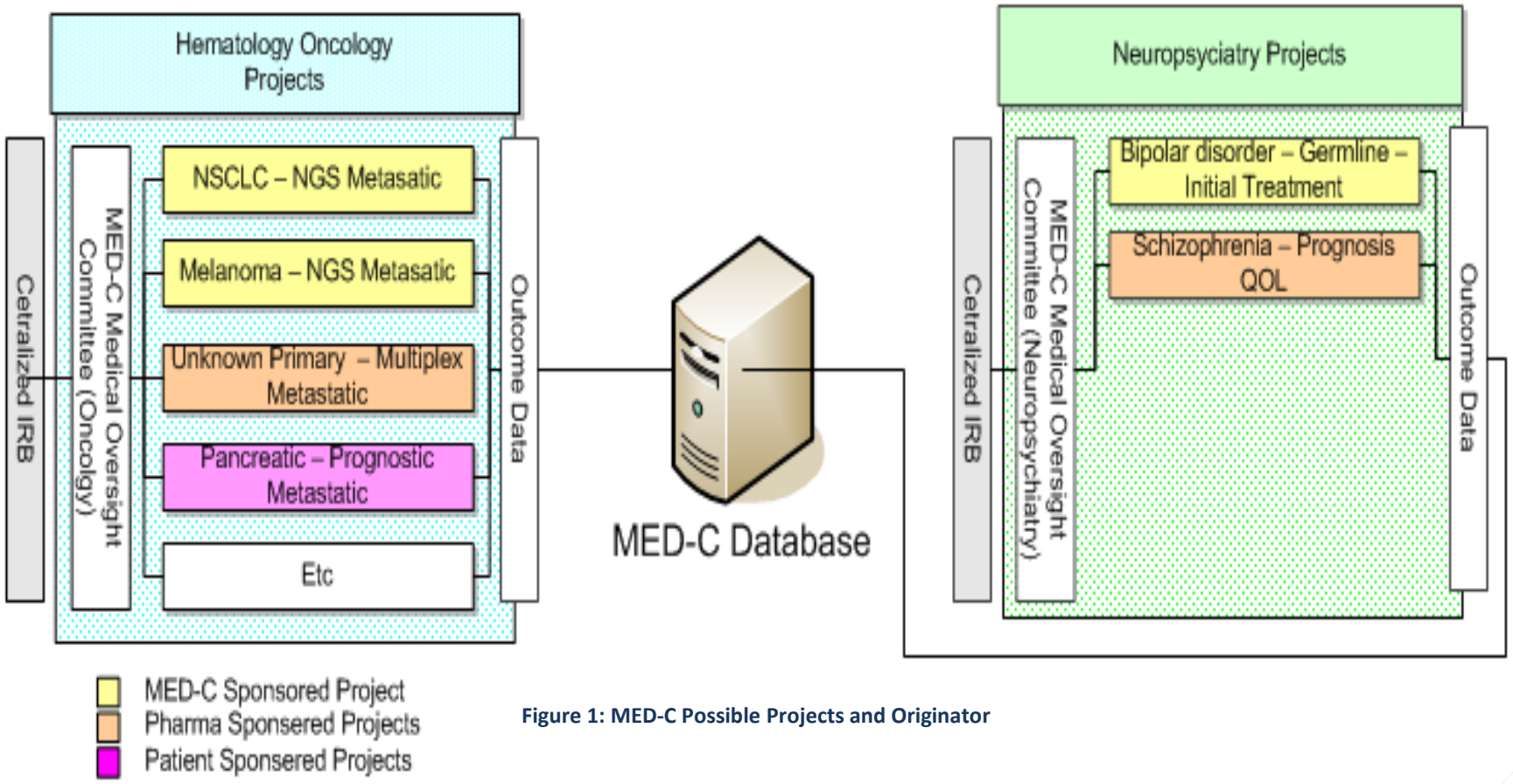
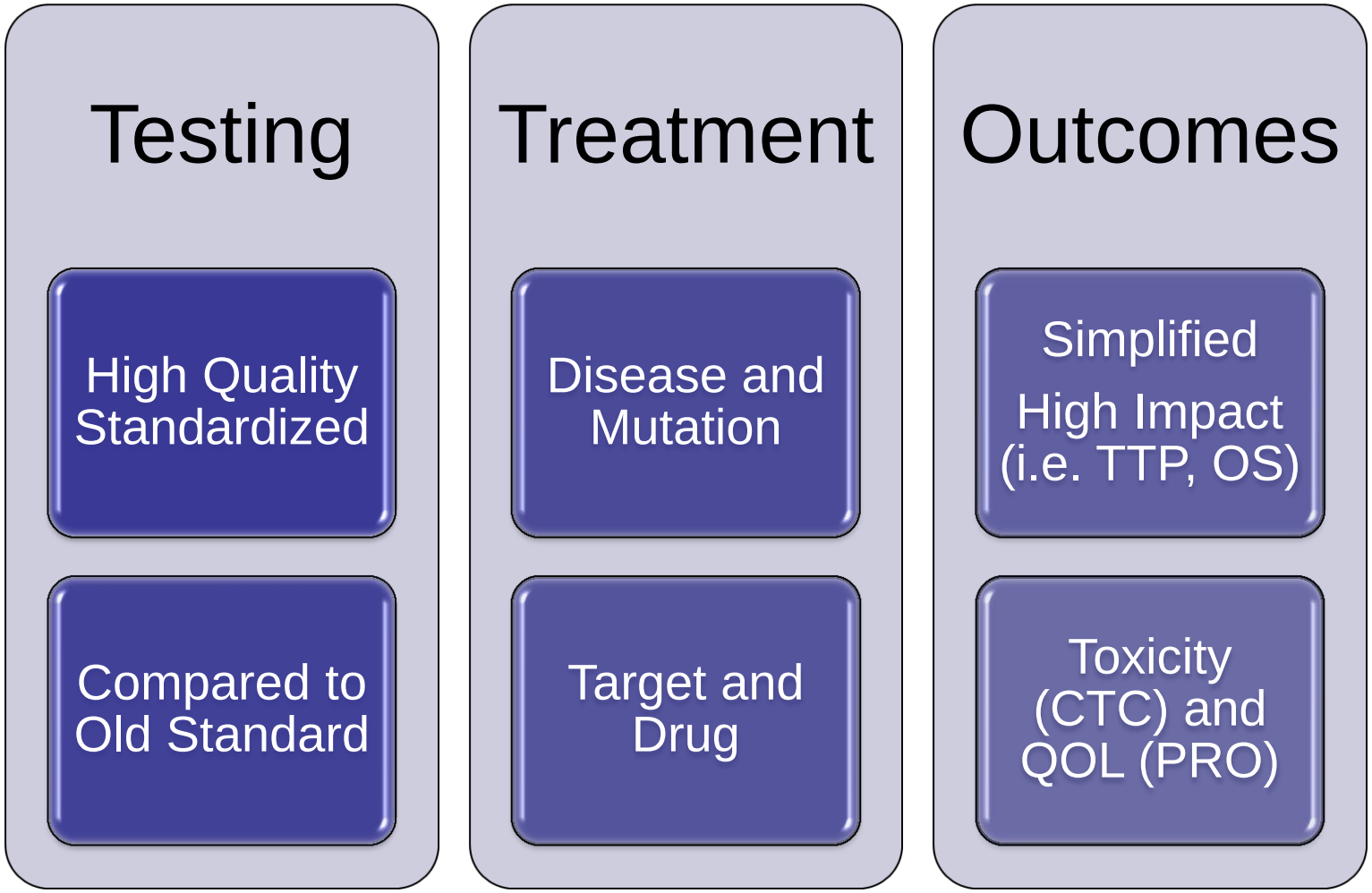
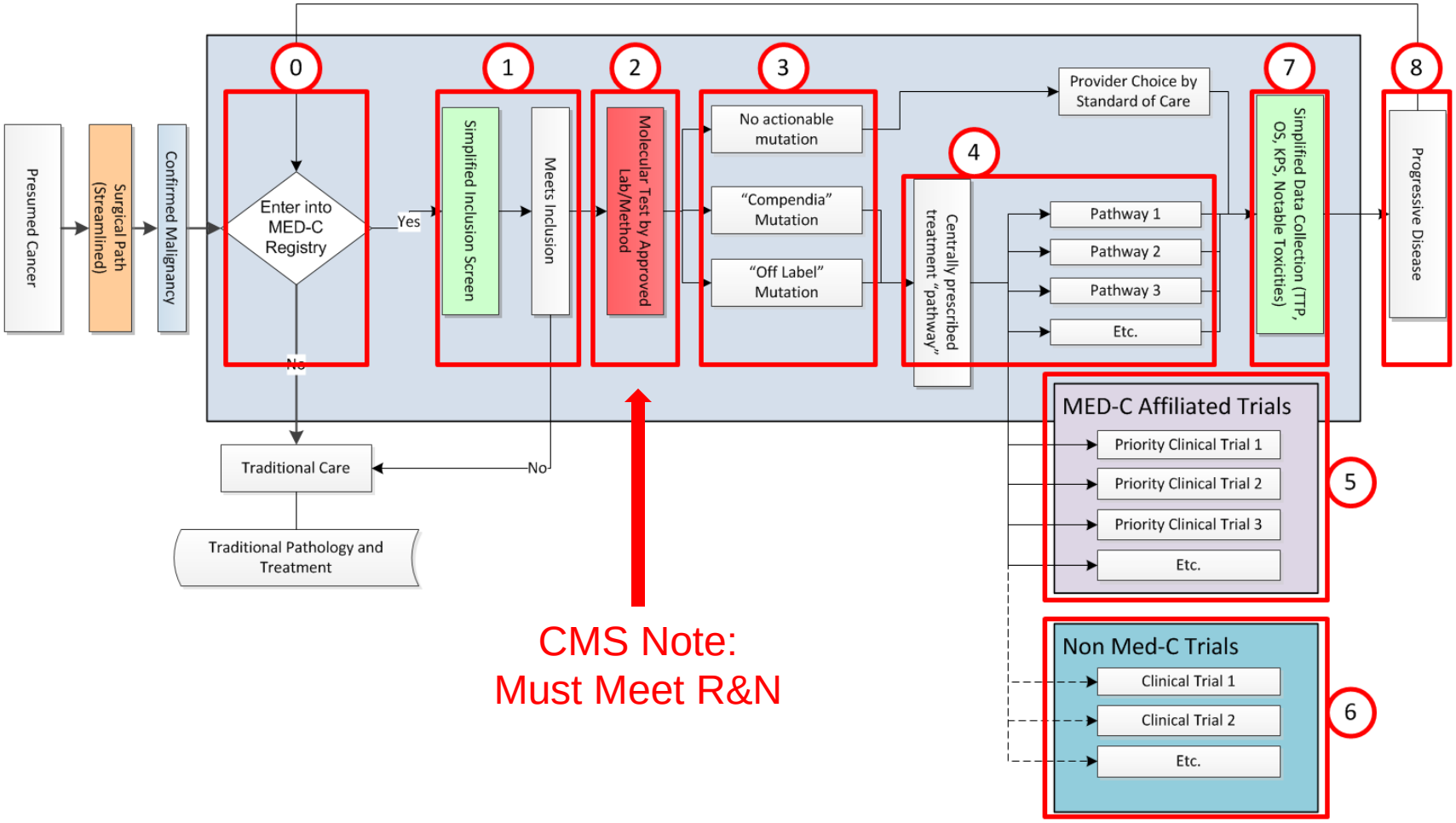


Figure 1: MED-C Possible Projects and Originator

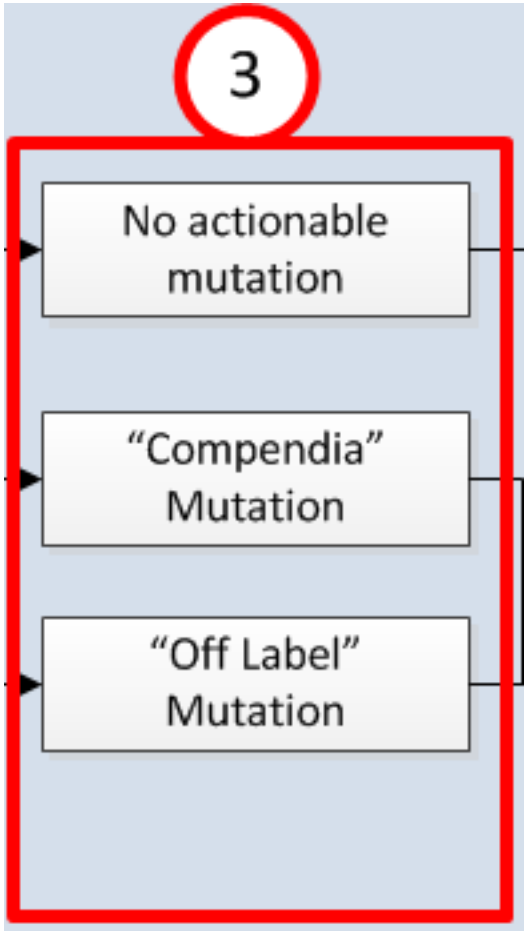
MED-C Project Design



NGS-NSCLC Project

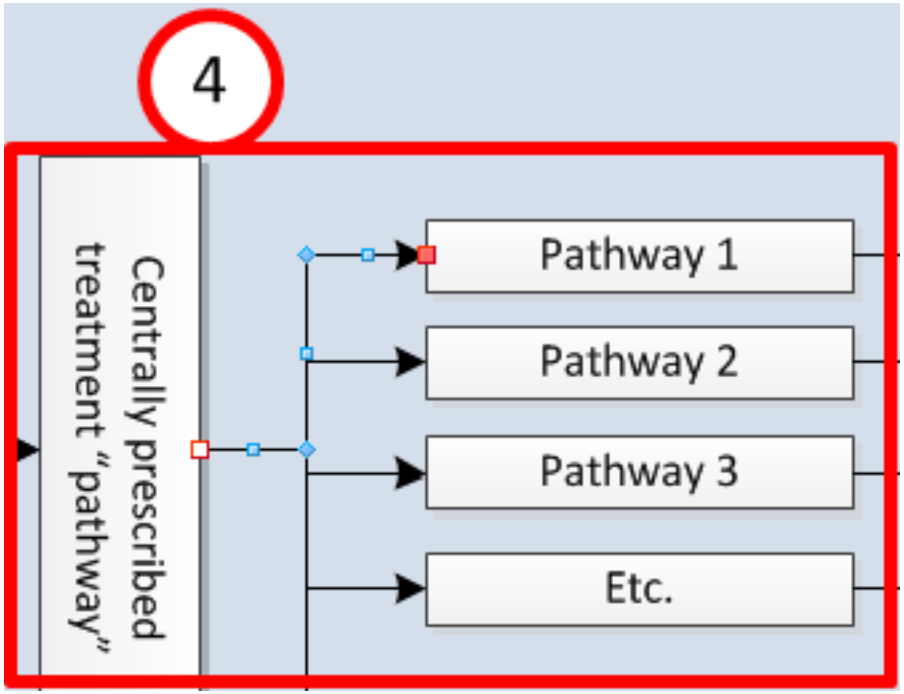


Mutation Analysis



- Defined mutation paradigms
- ADAPTIVE MODEL
  - Start with simple mutation models
  - As information is learned the complexity will increase
  - Off label mutations can be “transitional” (i.e.) early data or experimental but

MED-C Defined Pathways

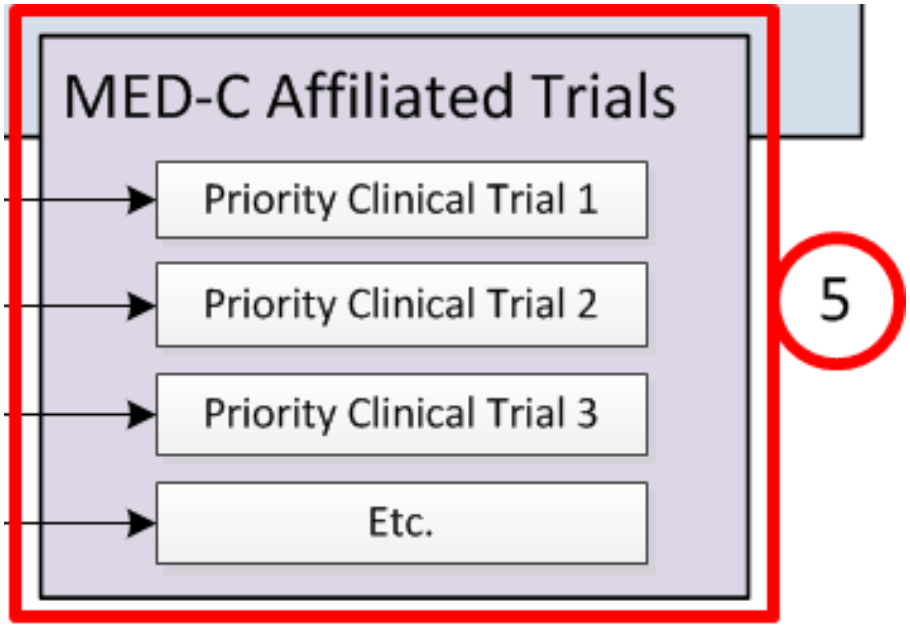


- Pathways
  - Centrally defined

    (i.e. patient with mutation X treated with standard first line therapy, but 2nd line treated with molecular based treatment)

    (Patient with mutation Y – preferentially entered into clinical trial or treated off trial with data capture)
  - ADAPTIVE PATHWAYS!!!!
  - ITERATIVE FINE TUNING!!!!
  - Facilitated access to drugs used on the Pathways

MED-C Affiliated Trials



- Goal is to enhance participation in existing and future trials (NCI, Lung-MAP, etc.)
- Trial >> MED-C Registry >>>>> No data

Implementation Timeline

- Q4 2014 – Formation of the MED-C Legal Entity
- Q1-3 2015 – Pilot Project of NGS in NSCLC
  - Q1 Building the Database/Interfaces with FDA/Pharma/Payor Input
  - Q1 Identifying a Oncology Medical Oversight Committee
  - Q2 Building the Target Mutation Definitions (Standard, Transitional, Experimental)
  - Q2 Building the Clinical Pathways for the Target Mutations
  - Q2 Finalizing the project details
  - Q3 Start enrolling patients in the project (likely without pharma support)
  - Q4+ Bring in Off-label FDA Approve therapies as part of the registry
- Q1 2016 –? Project 2

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2014 Conference on Clinical Cancer Research

Improving Evidence Developed from Population-Level Experience with Targeted Agents

Jane Perlmutter, PhD
Gemini Group

Patient Perspective

- Currently approved cancer treatments fail virtually all metastatic cancer patients, and many early stage cancer patients
- Patients do not have the luxury of patience
- Personalized, targeted therapies that will improve efficacy and reduce toxicity have been “on the horizon” for many years, but with only modest impact to patients
- Most patients would like their cancer experience to provide evidence that may help future patients, but may not be candidates for clinical trials

Bottom Line

Many Patients Are Likely be Enthusiastic About Participating in Population Level Registries to Gather Evidence about Targeted Therapies

But, don't over-hype

- What % of patients are likely to have treatable targets?
- What % of patients with targets are likely to benefit from currently available agents?
- How durable are the benefits likely to be?
- What are the likely toxicities?

Potential Patient Concerns

Number One: Costs

Other Possible Concerns

- Ensuring that learning is optimized/Sharing of tissue and data
- Privacy
- Receiving information from their tests:
  - Incidental germline findings
  - Tumor characteristics
- Potential requirement to participate in available clinical trial

Potential Ways to Cover Costs

- Coverage with Evidence Development (CED)
- Coverage by Test and Drug Developers
- Support from Federal Agency (e.g., PCORI, NCI) and/or Philanthropy
- Establishment of a Patient Assistance Payment Plan

	ASCO'S TAPUR	MED-C
Molecular Test	Outside of Registry	Medicare
Drugs	Drug Company Partners	Medicare
Standard Care	ACA	ACA

Reasons to Include Molecular Testing within Registry

- Ensure that all patients, regardless of financial status, have equal access to molecular testing
- Ensure inclusion of diverse patient populations within the registry
- Provide information about:
  - Probability of matches
  - Relatively frequent mutations for which there are no available drugs

FRIENDS of CANCER RESEARCH

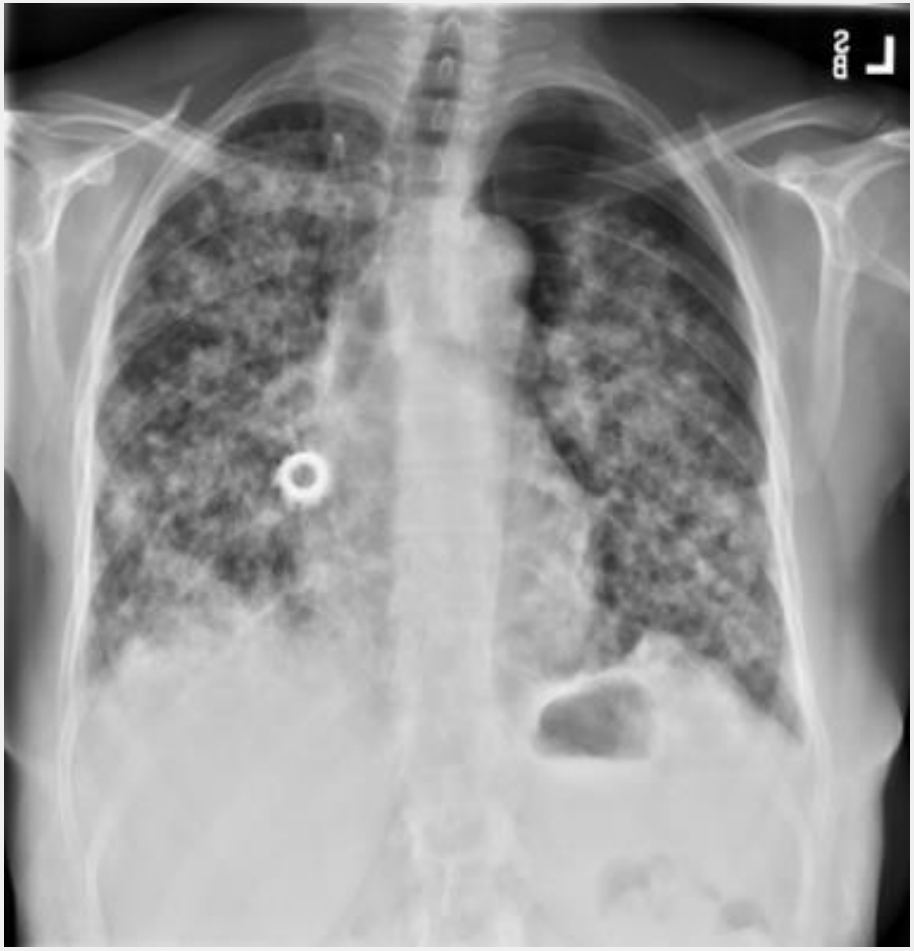
ENGELBERG CENTER for Health Care Reform at BROOKINGS

2014 Conference on Clinical Cancer Research

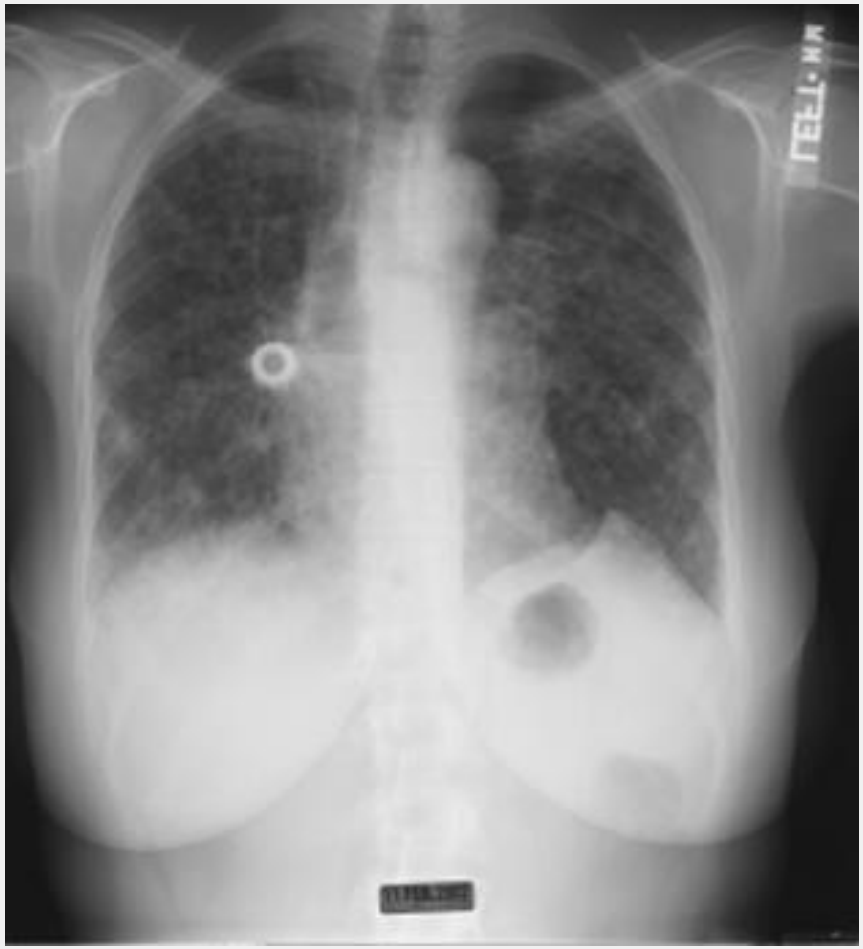
Improving Evidence Developed from Population-Level Experience with Targeted Agents

Vincent Miller, MD
Foundation Medicine, Inc.

Why Are 1 in 10 Like This?

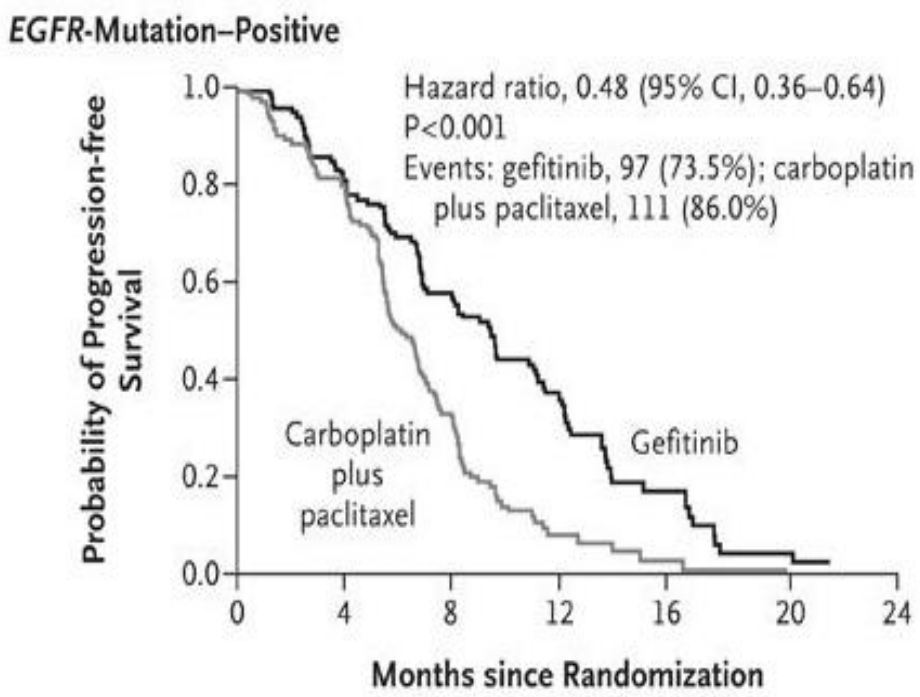


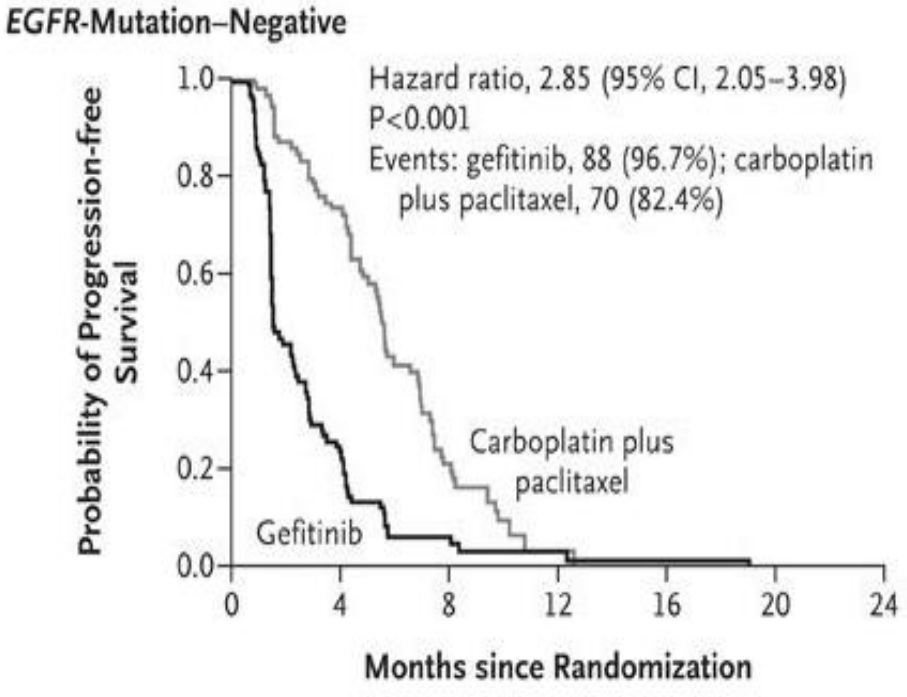
Day 1



Day 5

EGFR TKI vs Carboplatin-Paclitaxel





Mok T et al. N Engl J Med. 2009

Human Cancer Biology

Clinical Cancer Research

BRAF Fusions Define a Distinct Molecular Subset of Melanomas with Potential Sensitivity to MEK Inhibition

Katherine E. Hutchinson[1], Doron Lipson[6], Philip J. Stephens[6], Geoff Otto[6], Brian D. Lehmann[2], Pamela L. Lyle[3], Cindy L. Vnencak-Jones[3,5], Jeffrey S. Ross[6,7], Jennifer A. Pietenpol[2], Jeffrey A. Sosman[4], Igor Puzanov[4], Vincent A. Miller[6], and William Pao[1,3,4]

Abstract

Purpose: Recurrent "driver" mutations at specific loci in *BRAF*, *NRAS*, *KIT*, *GNAQ*, and *GNA11* define clinically relevant molecular subsets of melanoma, but more than 30% are "pan-negative" for these recurrent mutations. We sought to identify additional potential drivers in "pan-negative" melanoma.

Experimental Design: Using a targeted next-generation sequencing (NGS) assay (FoundationOne™) and targeted RNA sequencing, we identified a novel PAPSS1-BRAF fusion in a "pan-negative" melanoma. We then analyzed NGS data from 51 additional melanomas genotyped by FoundationOne™, as well as melanoma RNA, whole-genome and whole-exome sequencing data in The Cancer Genome Atlas (TCGA), to determine the potential frequency of BRAF fusions in melanoma. We characterized the signaling properties of confirmed molecular alterations by ectopic expression of engineered cDNAs in 293H cells.

Results: Activation of the mitogen-activated protein kinase (MAPK) pathway in cells by ectopic expression of PAPSS1-BRAF was abrogated by mitogen-activated protein kinase kinase (MEK) inhibition but not by BRAF inhibition. NGS data analysis of 51 additional melanomas revealed a second BRAF fusion (TRIM24-BRAF) in a "pan-negative" sample; MAPK signaling induced by TRIM24-BRAF was also MEK inhibitor sensitive. Through mining TCGA skin cutaneous melanoma dataset, we further identified two potential BRAF fusions in another 49 "pan-negative" cases.

Clinical Background

Previously healthy 45 yo woman who cycled 100 miles a week

Patient Presentation

- Previous diagnosis of metastatic melanoma to brain
- Failure of immunotherapy
- Specimen from resected intracranial lesion submitted to FMI for genomic profiling

Genomic Profiling

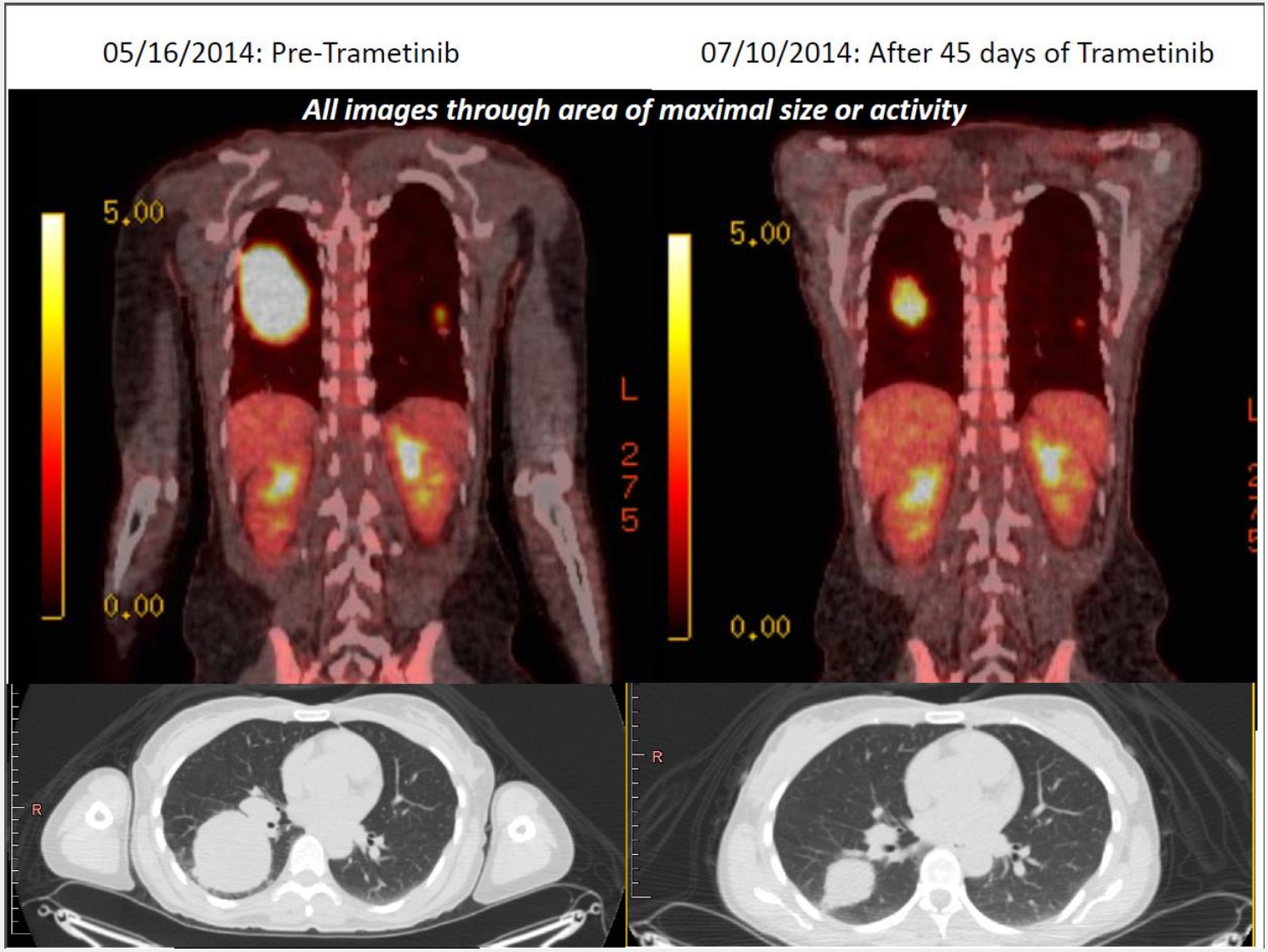
- FoundationOne indicated tumor harbors *BRAF* rearrangement c/w fusion
- Follow up RNA sequencing confirms presence of fusion

Therapy

- Patient receives trametinib
- Immediate symptomatic relief
- MRI suggests regression of brain metastases which had failed gamma knife multiple times
- PET/CT shows regression of thoracic disease

Response to BRAF Fusion Targeted Treatment

Fused PET/CT Imaging

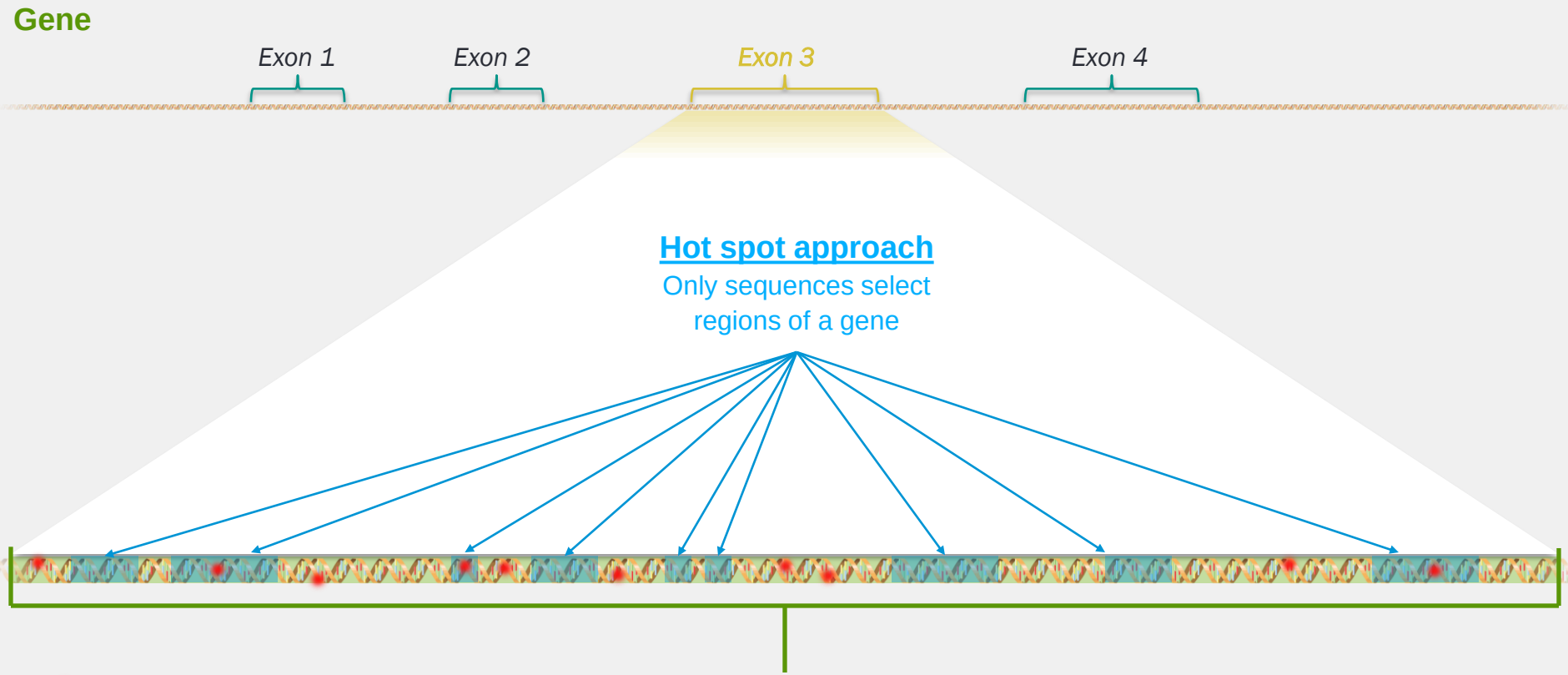


Takeaways

- Genomic profiling guided therapy effectively for this patient who had exhausted standard of care
- *BRAF* fusions may be targetable across multiple tumor types: melanoma, thyroid, lung and others.
- Phase II trial in melanoma to open imminently at Vanderbilt
  - Trametinib for *BRAF* fusion and non-V600E melanomas
  - Opening in Fall, 2014
- **Pace of progress-publication to "n of 1" to prospective Phase II trial in less than a year!**

FoundationOne vs. Hot-Spot Panels Approach

3X More Targeted Therapy Options For Patients



* As implemented by Foundation Medicine

FOUNDATION MEDICINE®

Perceived Challenges, Recommendations

- Start modest, build consensus
- Don’t let perfection obstruct excellence
- Engage facilitators/solution generators NOT problem identifiers/obstructionists
- Need consensus building leadership who pick battles carefully
- Relationship and opportunity for biopharma partners must be clearly enunciated in context of RWE

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2014 Conference on Clinical Cancer Research

Improving Evidence Developed from Population-Level Experience with Targeted Agents

Dietmar Berger, MD PhD
Genentech

Industry Perspective

- Molecular targeting and next generation diagnostics enable individualized therapy with improved benefit/risk
- Biomarker profiles (rather than histologic type) may define treatment benefits, even in small patient cohorts
- Innovative approaches to evidence generation and data analysis need to match the changing landscape in oncology
- Patient-level evidence generation and communication to prescribers and patients requires appropriate regulatory oversight

Importance of Population-Level Evidence

- Enhancing understanding of benefit and risk of targeted agents in an efficient manner, including small patient populations
- Improving access to targeted agents with specific molecular mechanism of action
- TAPUR and MED-C proposals are potential options to collect patient level data (in a standardized fashion)
- Population-level evidence may complement or replace standard models of evidence generation (depending on rigor and data quality)

Recommendations

- Robust diagnostic process to support identification of the appropriate patient population
  - Ability to perform confirmatory testing
- Standardized data collection resulting in quality data set
- Opportunity to include PROs
- Clear definition of decision criteria
  - Drug selection
  - Test selection
  - Data review – efficacy / safety / cohort decisions
  - Communication of results

Potential Applications of Population-Level Evidence

- Clinical decisions
- Coverage decisions
- Research and clinical development decisions
- Regulatory interactions
  - Adequate communication of evidence to patients and prescribers
  - Enable registrational pathway for small patient populations
  - Component of “totality of data”

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2014 Conference on Clinical Cancer Research

Improving Evidence Developed from Population-Level Experience with Targeted Agents

Jeffrey Roche, MD
CMS

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2014 Conference on Clinical Cancer Research

Improving Evidence Developed from Population-Level Experience with Targeted Agents

Sam Nussbaum, MD
WellPoint, Inc.

Our Shared Objectives

- Quality, safe, state-of-the-art, and affordable cancer care for patients (our members)
  - Evidence-based
  - Patient-centered
- Opportunity for our 37M members to advance knowledge of what works in health care
  - Encourage innovation to improve treatment options
  - Outcomes research subsidiary: HealthCore
  - Academic partnerships

Cancer Care Clinical Decisions: Current Environment

- 17 independent advisors for Medical Policy/Technology Assessment and Cancer Care Quality
  - 11 from leading academic cancer centers; 6 community based practice
- For drugs and biological therapies, NCCN 1 and 2A recommendations (unless advisors do not believe adequate level of evidence for 2A recommendations)
- Consult with oncologists from academic medical centers and preview policies with medical specialty societies (ASCO, ASTRO); full transparency
- Support off-label use when there is scientific evidence, Compendia: NCCN, American Hospital Formulary Service, Truven Health Analytics
- Review unique patient situations with treating oncologists

Health Plans' Role in Supporting Treatment Innovation

- Prior authorization requests for care that deviates from evidence raise concerns regarding quality and safety
- Under ACA, routine patient costs for services provided in connection with a clinical trial are covered by health plans; current contracts do not pay for investigational/experimental therapies or coverage with evidence development.
- Health plans support for and active participation in publicly funded research through PCORI
- Benefit and reimbursement policies across health plans/government payers for CED support
- Support evidence development including making data publicly available and safe-guard patient quality and safety
  - *Commitments to not treat patients "off protocol"*
  - *Data Safety Monitoring Board and clear stopping rules to address both safety and unsuccessful treatment (lessons from ABMT trials in breast cancer)*
  - *Health Plans provide data and analytic capabilities for members involved in study coupled with structured clinical and molecular data*

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2014 Conference on Clinical Cancer Research

Improving Evidence Developed from Population-Level Experience with Targeted Agents

Richard Pazdur, MD
FDA

FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2014 Conference on Clinical Cancer Research

Supported by:

ASCO® American Society of Clinical Oncology

Susan G. Komen for the Cure®

November 21, 2014 • Washington, DC