Friends Annual Meeting

Supported by:

American Association for Cancer Research
American Society of Clinical Oncology
Susan G. Komen

FRIENDS of CANCER RESEARCH

FRIENDS ANNUAL MEETING

PANEL TWO:
EXAMINING THE FEASIBILITY OF REAL WORLD EVIDENCE THROUGH PILOT STUDIES

Panelists

- **Gideon Blumenthal, MD;** US FDA
- **Amy Abernethy, MD, PhD;** Flatiron Health
- **Lisa LaVange, PhD;** FDA
- **Jane Perlmutter, PhD;** Gemini Group
- **Michael Taylor, PharmD, PhD;** Genentech

Friends Annual Meeting

Gideon Michael Blumenthal, MD
OHOP, US FDA

U.S. FOOD & DRUG ADMINISTRATION

Friends of Cancer Research
Annual meeting
November 16, 2016

What is RWD/RWE?

Real World Data (RWD)

Electronic Health Record (EHR) clinical data

Pragmatic trials

Administrative claims/billing

Patient registries

Surveys

Mobile health (smartphones, wearables, social media)

Real World Evidence (RWE)

"Data generated for purposes other than evidence-generation from a traditional clinical trial"

Why RWE/RWD?

- U.S. adult cancer clinical trials relatively homogenous, expensive, (s)low accrual, administrative burdens
- Questions regarding generalizability once the drug enters the clinic
- New technologies may enable the collection and curation of diverse pipelines of data to enhance learning lifecycle of a therapy

Potential uses for RWD/RWE in oncology

- Labeling expansion for efficacy (rare tumor types)
- Real world dosage and administration
- Post-marketing safety
- Assessment of REMS
- Use in patients excluded from pivotal trials (e.g. autoimmune disease with immune checkpoint inhibitors)
- Assessment of special populations (hepatic/renal impairment, brain mets, leptomeningeal mets, elderly)
- Patient-reported toxicity/efficacy/function
- Prognosis in rare genomic subtypes
- Biomarker prediction (e.g. ORR and DoR based on “liquid biopsy” results versus tissue)
- Drug utilization

Potential issues

- Missing data
- Data curation (structured vs unstructured)
- Cohort selection
- Informed Consent/ HIPAA
- Quality Assurance

Potential Use-Cases discussed in WG

- Observational post-marketing data in rare cancers
- Observational follow up of post-progression cross-over cohort in a randomized controlled trial
- Pragmatic randomized controlled trial exploring 2 different dosing strategies

The panel

- Presentations:
  - Michael Taylor (Genentech)
  - Amy Abernathy (Flatiron)
- Reaction: Lisa Lavange (FDA), Jane Perlmutter (patient advocate)
- Panel discussion/ Q&A

Friends Annual Meeting

Michael D. Taylor, PharmD, PhD
Genentech

RWE to Support Regulatory Decisions

Use cases and considerations

Michael D. Taylor, PharmD, PhD
Deputy Global Head of Oncology
Real World Data Science
Genentech, A Member of the Roche Group

RWE for Regulatory Decisions

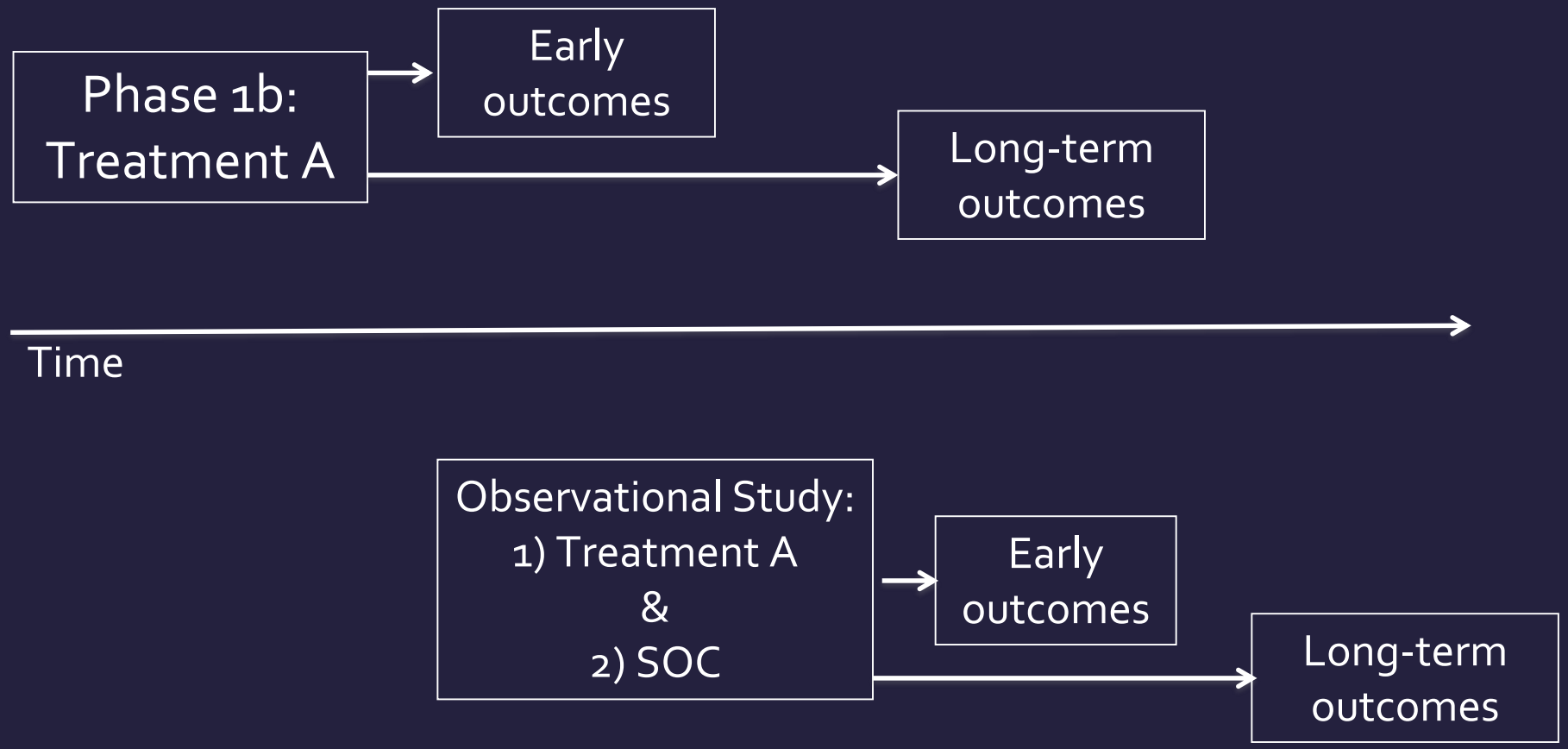
- What?
  - Safety & Effectiveness
  - PMC & Label expansion
- Why?
  - Opportunity to learn
  - Expedite clinical development for serious and life-threatening disease
  - RCT feasibility and appropriateness

RWE Use Cases

- Prospectively designed observational study
- Randomized Phase 2 plus observational study
- Pragmatic trial

Observational Study

Prospectively designed



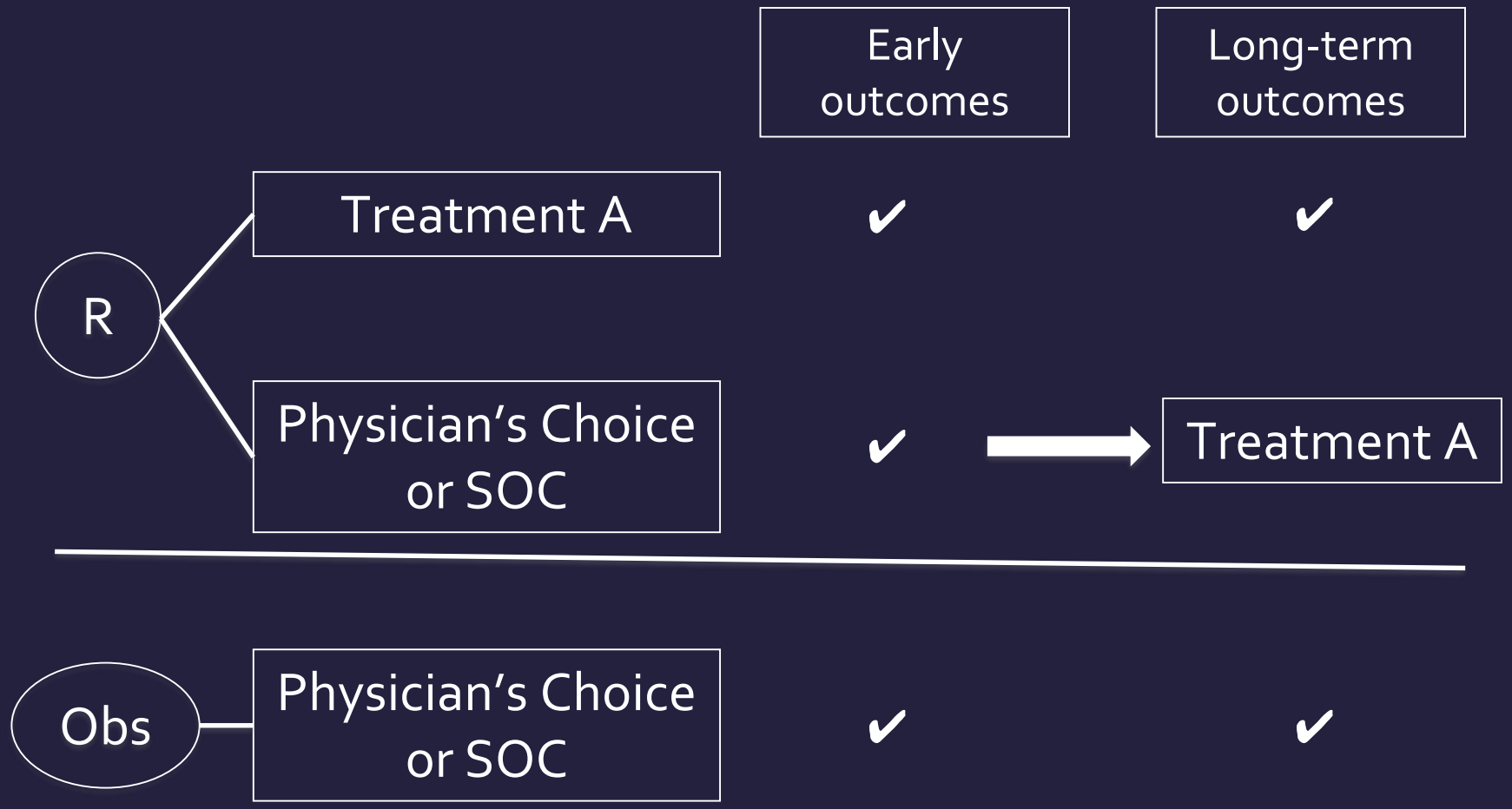
Observational Study

Prospectively designed

- Considerations
  - Study outcomes
  - Selection bias and confounding
  - Patient identification
  - Sample size

Randomized Phase 2 Study

Plus observational study



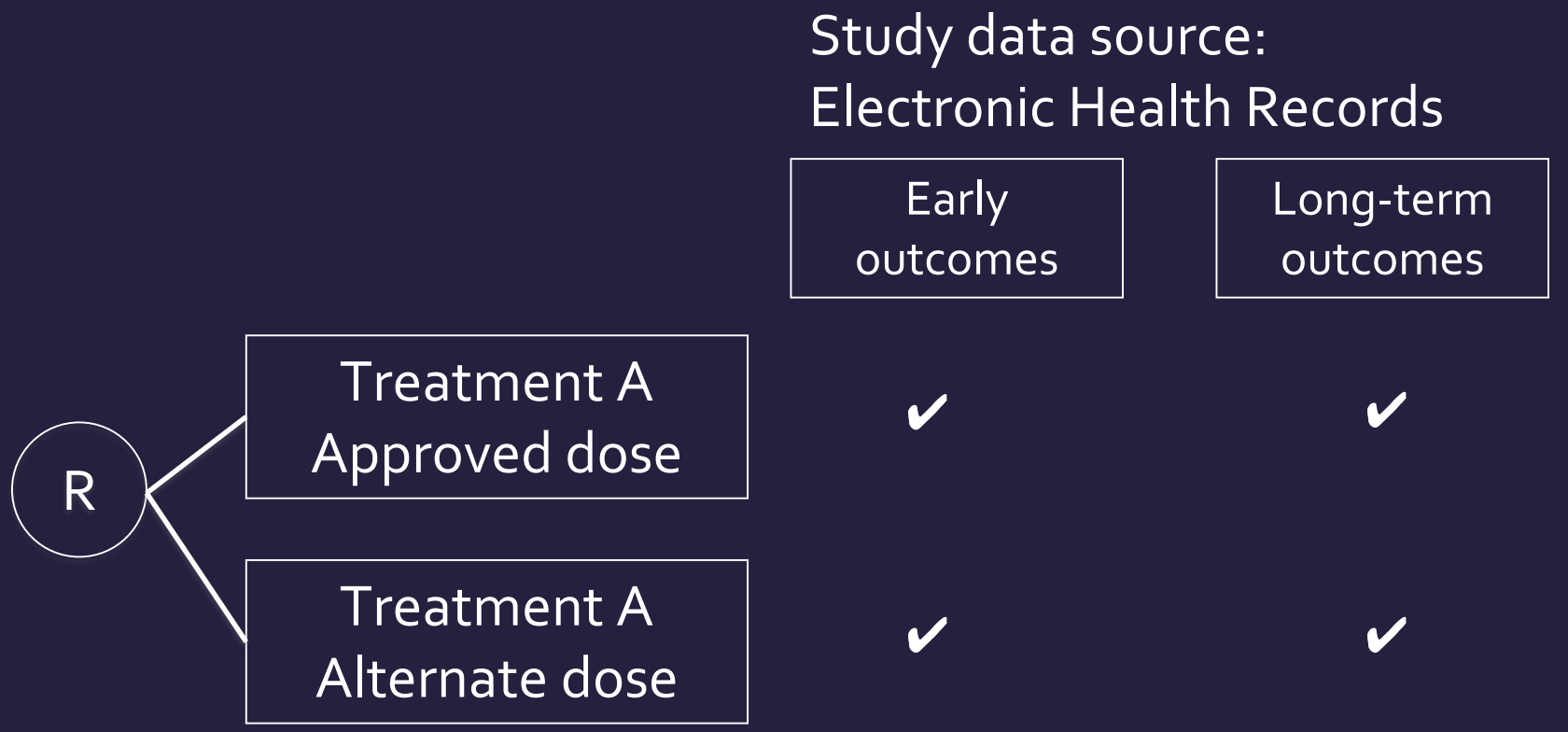
Randomized Phase 2 Study

Plus observational study

- Study Design & Methodological Issues
  - Trial setting vs observational setting
  - Sample size
- Potential for accelerated approval on randomized Ph2 and conversion with long term observational data

Pragmatic Trial

Explore new dose



Pragmatic trial

- Study Design & Methodological Issues
  - Randomization
  - Consent

Considerations

- Data Quality
- Operational & Logistical Issues
  - Patient level data submission
    - Auditing of source data
    - HIPPA
  - Data standardization across EMR systems
  - Linkage of EMR and claims
  - Consent

Final Thoughts

- Opportunity to learn through pilots and dialogue
  - Test ability of data to answer key questions
  - Test feasibility – can we identify and overcome operational/logistical challenges?
- Opportunity to help patients while learning

Friends Annual Meeting

Amy Abernethy, MD, PhD
Flatiron Health

FLATIRON

16 November 2016

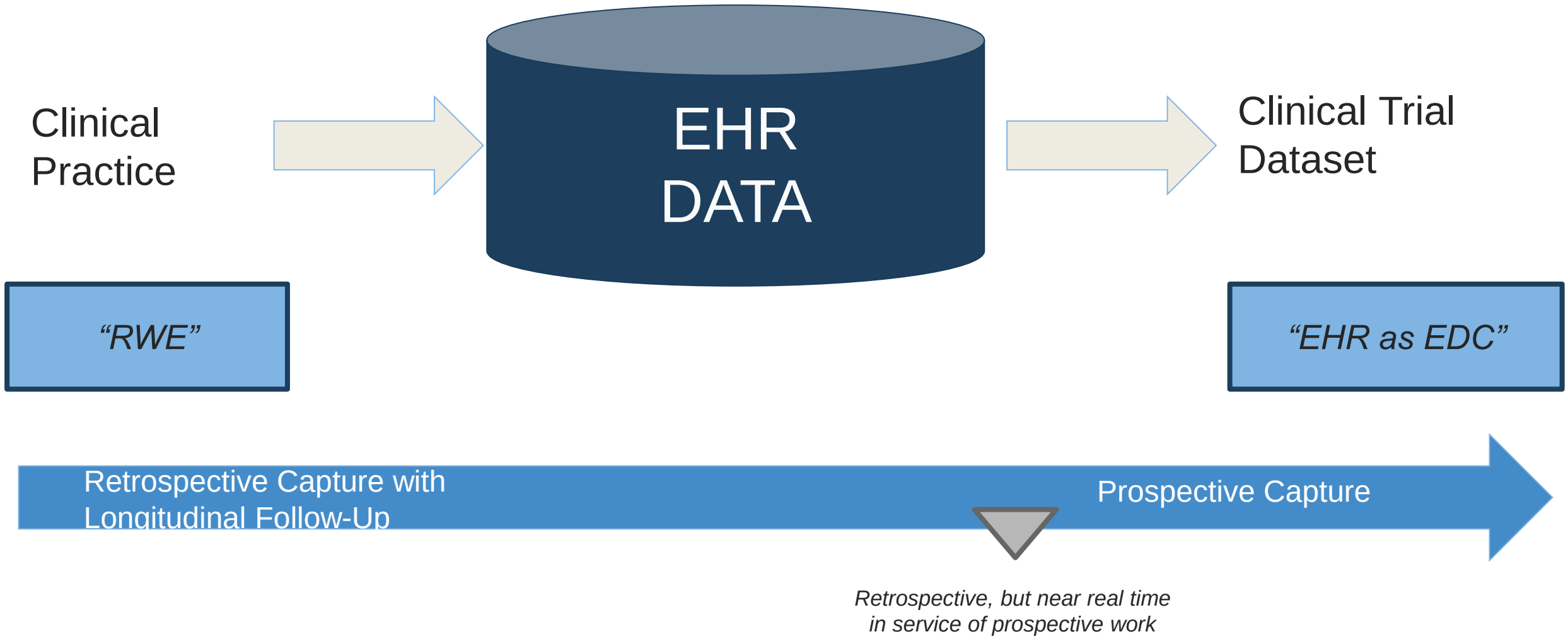
Applications of Oncology Real-World Evidence

Amy Abernethy, MD, PhD

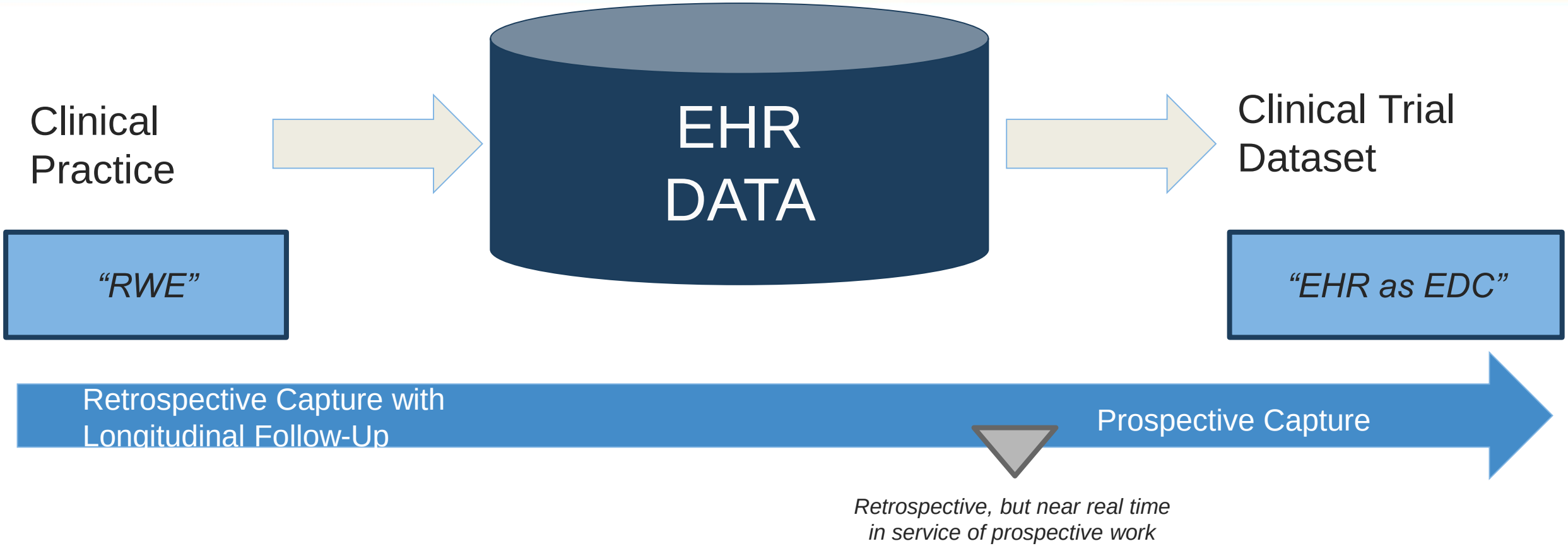
FRIENDS of CANCER RESEARCH

www.flatiron.com

Advances in clinical data capture are creating new opportunities for real-world evidence



Advances in clinical data capture are creating new opportunities for real-world evidence



Observational data on off label use

Real-world follow-up on clinical outcomes

Pragmatic trial

FLATIRON

Observational data to complement trials

Case 1: Use of observational data to examine effectiveness of approved agents used in the off-label setting

FLATIRON

RWE Potential Application:
Observational data for off-label use of approved agents

Context

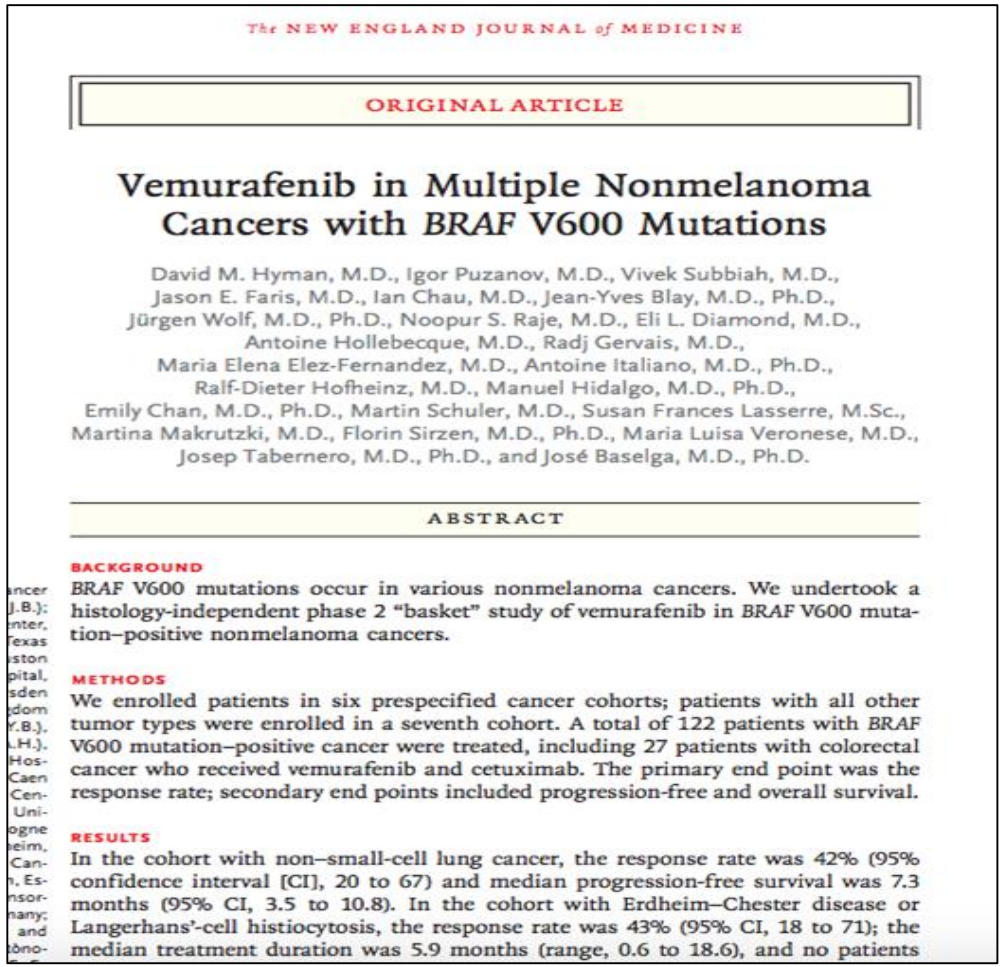
- BRAF V600 inhibitors are approved in melanoma
- Data from Phase II basket trial in non-melanoma cancers had a signal of response in non-small cell lung cancer (N=20)
- Among people with BRAF+ non-small cell lung cancer, is there differential improved response when a BRAF inhibitor is administered?
- Because of the difficulty of conducting clinical trials in small population, real-world evidence could potentially supplement the clinical trial data

RWE Application

- RWE database of >25,000 aNSCLC patients allows for identification and investigation of any patient cases with a BRAF V600 mutation, tested as part of routine clinical care
- Centralized, technology-enabled processing allows for further systematic assessment of outcomes by capturing “real-world” tumor endpoints, based on standardized methodology

FLATIRON

RWE Potential Application:
Observational data for off-label use of approved agents



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

David M. Hyman, M.D., Igor Puzanov, M.D., Vivek Subbiah, M.D., Jason E. Faris, M.D., Ian Chau, M.D., Jean-Yves Blay, M.D., Ph.D., Jürgen Wolf, M.D., Ph.D., Noopur S. Raje, M.D., Eli L. Diamond, M.D., Antoine Hollebecque, M.D., Radj Gervais, M.D., Maria Elena Elez-Fernandez, M.D., Antoine Italiano, M.D., Ph.D., Ralf-Dieter Hofheinz, M.D., Manuel Hidalgo, M.D., Ph.D., Emily Chan, M.D., Ph.D., Martin Schuler, M.D., Susan Frances Lasserre, M.Sc., Martina Makrutzki, M.D., Florin Sirzen, M.D., Ph.D., Maria Luisa Veronese, M.D., Josep Tabernero, M.D., Ph.D., and José Baselga, M.D., Ph.D.

ABSTRACT

BACKGROUND

BRAF V600 mutations occur in various nonmelanoma cancers. We undertook a histology-independent phase 2 "basket" study of vemurafenib in *BRAF* V600 mutation–positive nonmelanoma cancers.

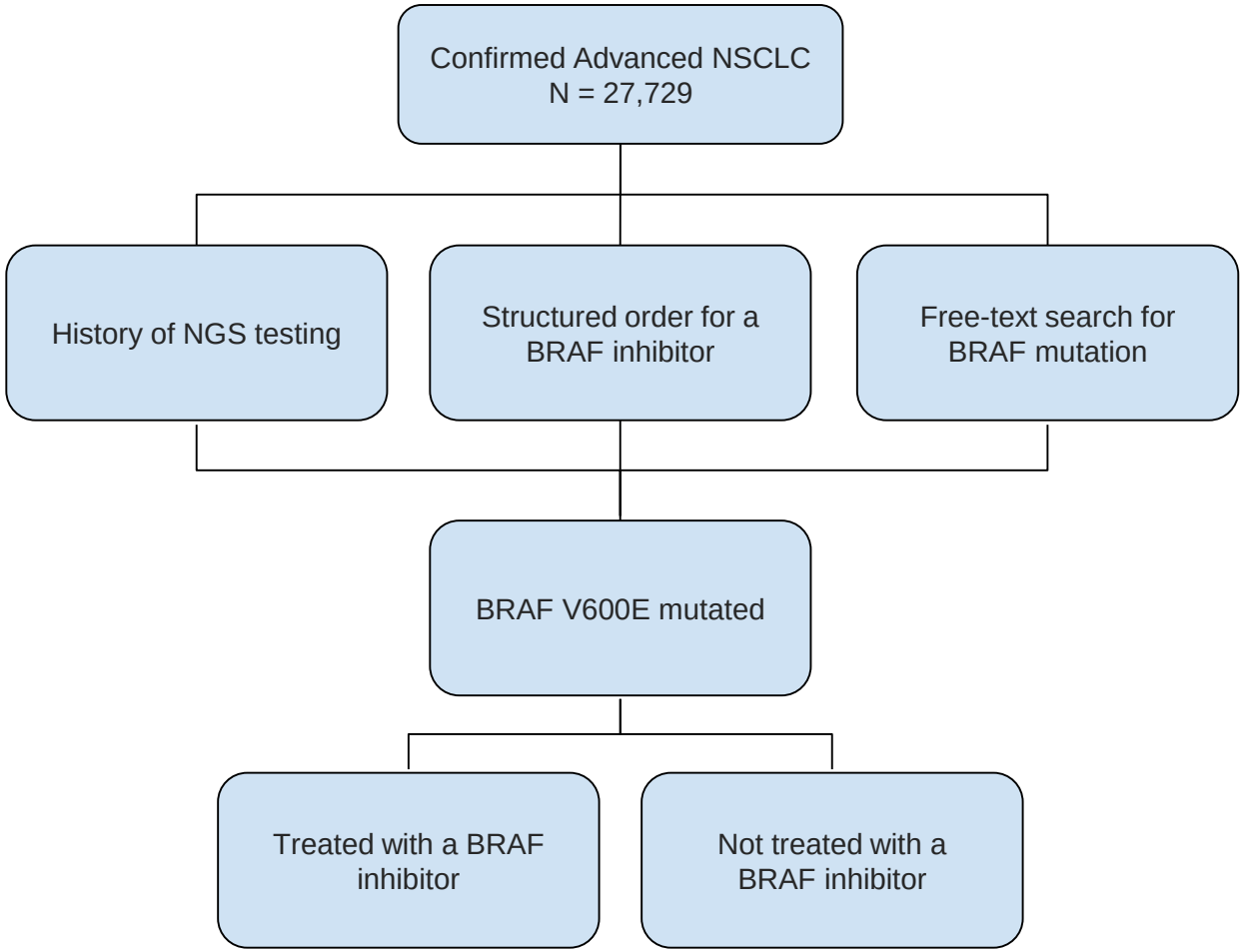
METHODS

We enrolled patients in six prespecified cancer cohorts; patients with all other tumor types were enrolled in a seventh cohort. A total of 122 patients with *BRAF* V600 mutation–positive cancer were treated, including 27 patients with colorectal cancer who received vemurafenib and cetuximab. The primary end point was the response rate; secondary end points included progression-free and overall survival.

RESULTS

In the cohort with non–small-cell lung cancer, the response rate was 42% (95% confidence interval [CI], 20 to 67) and median progression-free survival was 7.3 months (95% CI, 3.5 to 10.8). In the cohort with Erdheim–Chester disease or Langerhans'-cell histiocytosis, the response rate was 43% (95% CI, 18 to 71); the median treatment duration was 5.9 months (range, 0.6 to 18.6), and no patients

Potential selection diagram for BRAF+ patients in the aNSCLC RWE database, based on current cohort:



FLATIRON

Real-world follow up

Case 2: Tracking utilization, effectiveness and safety in the transition from clinical trials to real-world care after regulatory approval

FLATIRON

RWE Case Study: Tracking outcomes in the transition from clinical trials to real-world care

Context

- FDA/Flatiron collaborative project to understand safety and outcomes for immune checkpoint inhibitors in aNSCLC as these treatments are adopted post-approval

RWE Application

- Because patients continue to receive care, EHR platform and data processing supports longitudinal tracking
- Allows for “updating the story” with additional information on longer term outcomes - such as time on therapy, safety events and overall survival

Next Steps

- All cases in Flatiron national dataset through March 31, 2016
- Additional phases planned for further investigation based on preliminary findings

FLATIRON

PD-L1 Inhibitor Treatment Patterns

Evidence of lung cancer diagnosis (ICD code) and at least two visits at a community practice in the Flatiron network after 1/1/2011
N = 55,975

Clinical confirmation of non-small cell lung cancer (NSCLC) based on review of unstructured documents
N = 44,089

Clinical confirmation of advanced NSCLC (diagnosed stage IIIB - IV) or diagnosed early stage and developed advanced disease
N = 27,175

Diagnosis of advanced NSCLC on or after 1/1/2011
N = 23,319

Completeness of record: Less than a 90 day gap between advanced diagnosis date and structured first activity date
N = 20,430

Usage of a PD-1 inhibitor: Order or administration of nivolumab or pembrolizumab
N = 1,578

Final cohort
N = 1,578

FLATIRON

Comparison of PD-1 treated patients in Flatiron dataset to clinical trials

	Nivo (N = 292)*	Pembro (N = 495)**	Flatiron (N = 1578)
Age - yr			
Median	61	64	69.2
Range	37-84	28-93	32 - 85+
Age >= 75 yr - no. (%)	20 (7)	Not reported	430 (27%)
Male sex - no. (%)	151 (52)	261 (53)	885 (56)
Race/ethnicity - no. (%)			
White	267 (91)	406 (82)	1084 (69)
Asian	9 (3)	64 (13)	44 (3)
Black	7 (2)	20 (4)	89 (6)
Hispanic or Latino	Not reported	Not reported	46 (3)
Other	9 (3)	5 (1)	102 (6)
Unknown / Missing	0	0	213 (14)
Smoking status - no. (%)			
Current or former smoker	231 (79)	369 (75)	1396 (89)
Never smoked	58 (20)	126 (25)	169 (11)
Unknown	3 (1)	-	13 (1)
Histology - no. (%)			
Squamous	-	85 (17)	560 (36)
Nonsquamous	100%	401 (81)	967 (61)
Adenosquamous	-	7 (1)	-
Unknown	-	2 (0.4)	51 (3)
EGFR status - no. (%)			
Tested	Not reported	478 (97)	999 (63)
Mutated (% of tested)	44	74 (16)	79 (8)
ALK status - no. (%)			
Tested	Not reported	438 (88)	945 (60)
Translocated (% of tested)	13	9 (2)	16 (2)
KRAS status - no. (%)			
Tested	Not reported	295 (60)	368 (23)
Mutated (% of tested)	28	77 (26)	114 (31)

* Borghaei H, et al. *N Engl J Med*. 2015;doi:10.1056/NEJMoa1507643.

** Garon EB, et al. *N Engl J Med*. 2015;doi:10.1056/NEJMoa1501824.

FLATIRON

Pragmatic Trial

Case 3: Conducting a prospective pragmatic trial supported by electronic health record data

FLATIRON

RWE Case Study: Use of EHR data to support a pragmatic trial

Context

- Hypothetical example presented in white paper - Revised dosing schedule may be safer and equally efficacious compared to that which is approved in the label
- Salford Lung Study serves as a backdrop
  - COPD; new agent vs usual care; conducted in general practices using EHRs

RWE Application

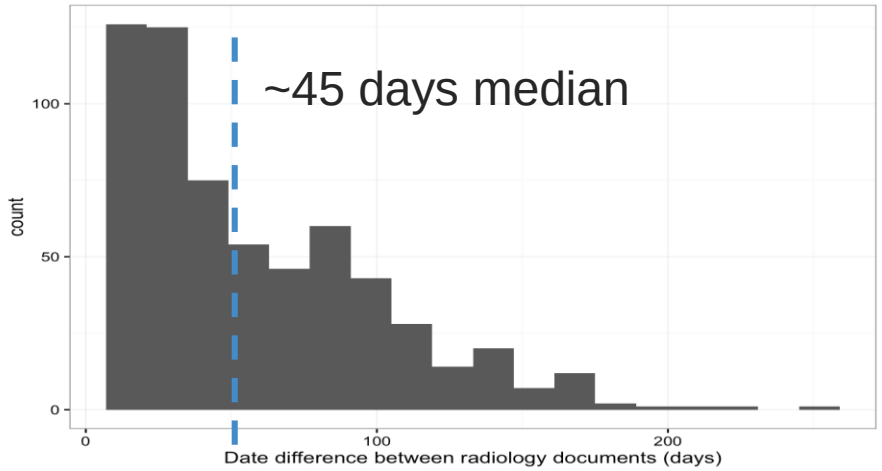
- Use an EHR-derived dataset to plan the study
  - Define standard of care; test eligibility criteria, seek pragmatism in design
- Use EHR data to populate the study dataset
- Use linked EHR data to populate study endpoints
  - Tumor response, mortality

FLATIRON

RWD in trial design and feasibility

Protocol design informed by common practice patterns

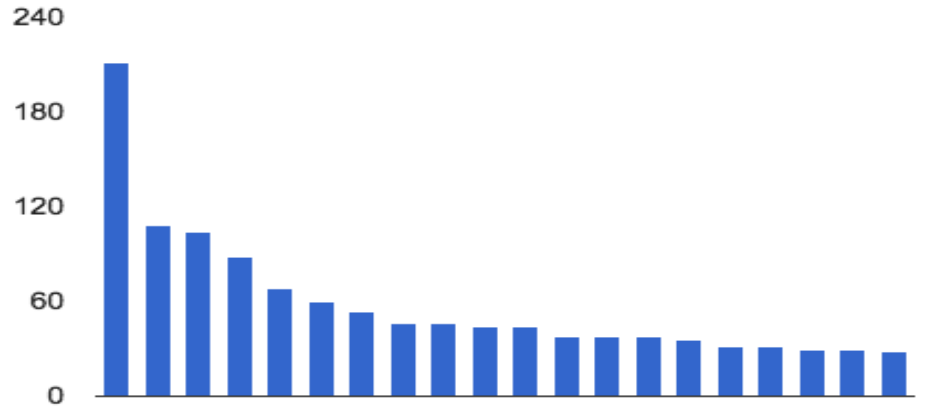
Time between scans
Days



- Ensured protocol design reflects routine clinical practice

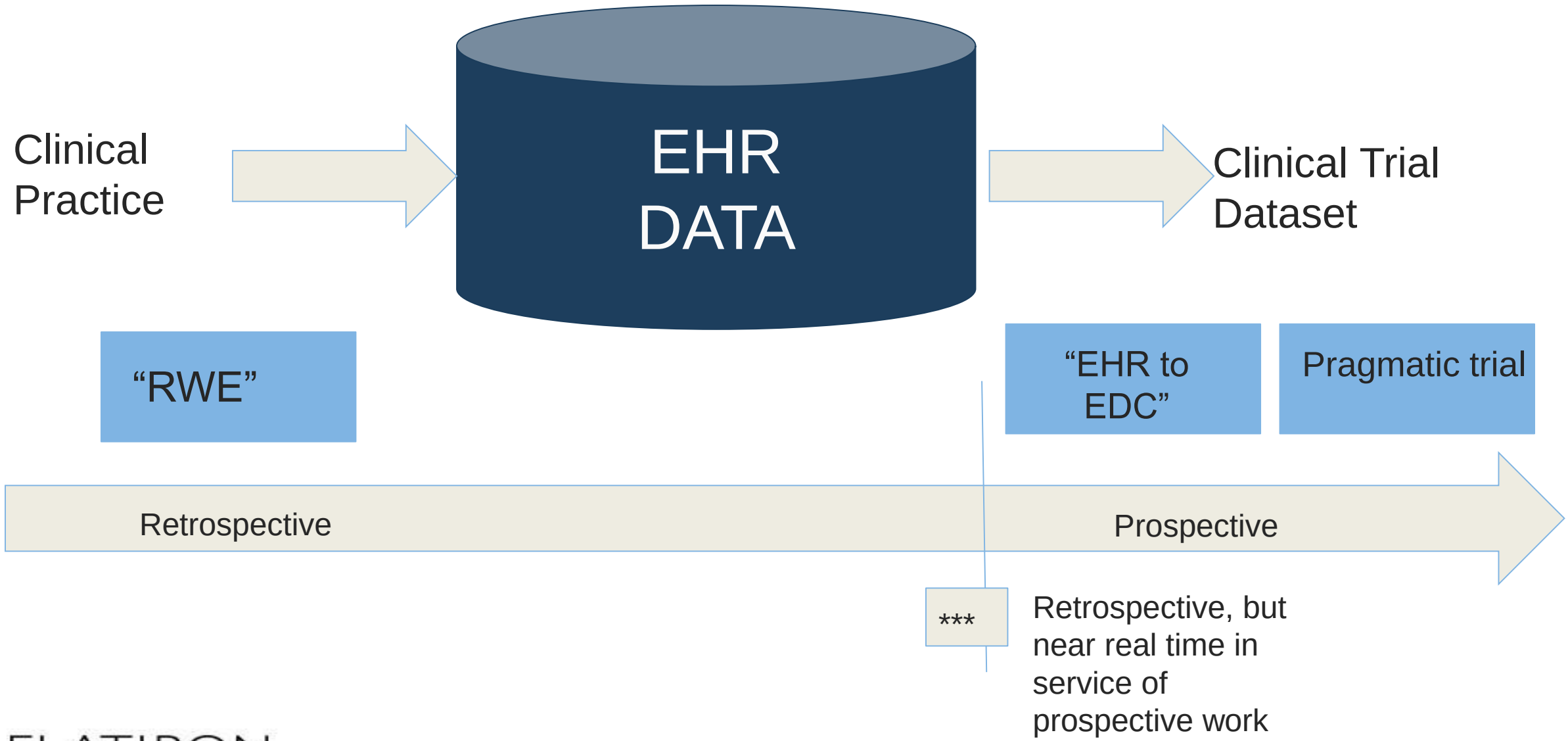
Sites selected based on rate of NGS testing in relevant patient populations

NGS results in target patient population
Patients per site



- Selected sites with the greatest potentially eligible patient volume

FLATIRON



FLATIRON

Conclusions

- Evolving portfolio of example studies where EHR-generated RWE can be used in service of regulatory and clinical decision-making
- Data quality must be characterized and optimized
- Approaches incorporate the longitudinal nature of clinical care
- Incorporate rigorous analysis plans and technology tools to support efficient understanding of information
- Rigorous assessment of outcomes is critical

FLATIRON

Panelists

- **Gideon Blumenthal, MD;** US FDA
- **Amy Abernethy, MD, PhD;** Flatiron Health
- **Lisa LaVange, PhD;** FDA
- **Jane Perlmutter, PhD;** Gemini Group
- **Michael Taylor, PharmD, PhD;** Genentech

Friends Annual Meeting

Supported by:

American Association for Cancer Research
American Society of Clinical Oncology
Susan G. Komen