REAL WORLD DATA –WAS IST DAS UND WAS SIND SIE WERT? SICHT DER INDUSTRIE

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Roche Austria

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RWD Definitions

FDA definition*:

- *"Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.*
- *"Examples of RWD include data derived from electronic health records (EHRs); medical claims and billing data; data from product and disease registries; patient-generated data, including from in-home-use settings; and data gathered from other sources that can inform on health status, such as mobile devices"*

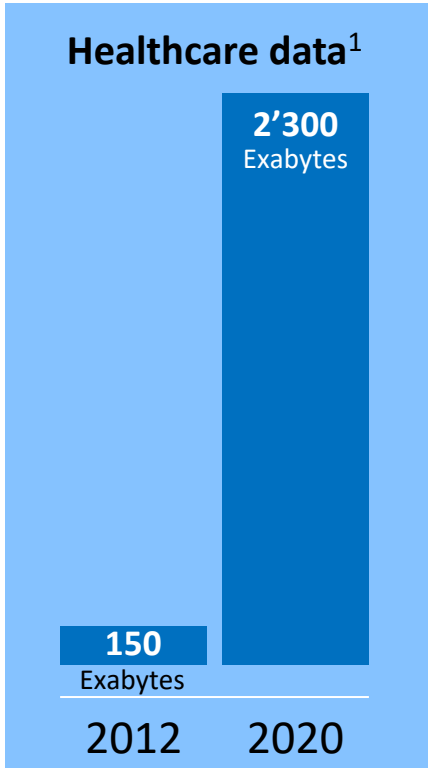
EMA definition**

- *"Routinely collected data relating to a patient's health status or the delivery of health care from a variety of sources other than traditional clinical trials"*
- *"We specifically exclude traditional clinical trials even if single arm but would incorporate data from pragmatic clinical trials if data were collected remotely through an electronic health record or other observational data source and solely under conditions of normal clinical care"*

*FDA RWE Framework December 2018

**EMA publication "Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe" April 2019 Publication in Clinical Pharmacology & Therapeutics

Size of health data



Health & fitness trackers tripled from 26m in 2014 to 87m in 2017

U.S. EHR adoption in oncology clinics has increased from ~10% to >95%[3]

Kaiser Permanente, …is believed to have between 26.5 and 44 petabytes of rich data from EHRs, including images and annotations[2]

1. International Data Corporation, US only; 2. Big data analytics in healthcare: promise and potential (Raghupathi and Raghupathi);
3. ONC/American Hospital Association (AHA), AHA Annual Survey Information Technology Supplement;

Many sources of RWD exist

They can be retrospectively leveraged or prospectively implemented to answer specific questions including regulatory questions

Disease and product registries[1,3]

Claims data[3,4]

Diagnostics / omics databases[2]

Digital health solutions[3]

Electronic/medical health record[1,3]

Non-investigational & cohort studies[1]

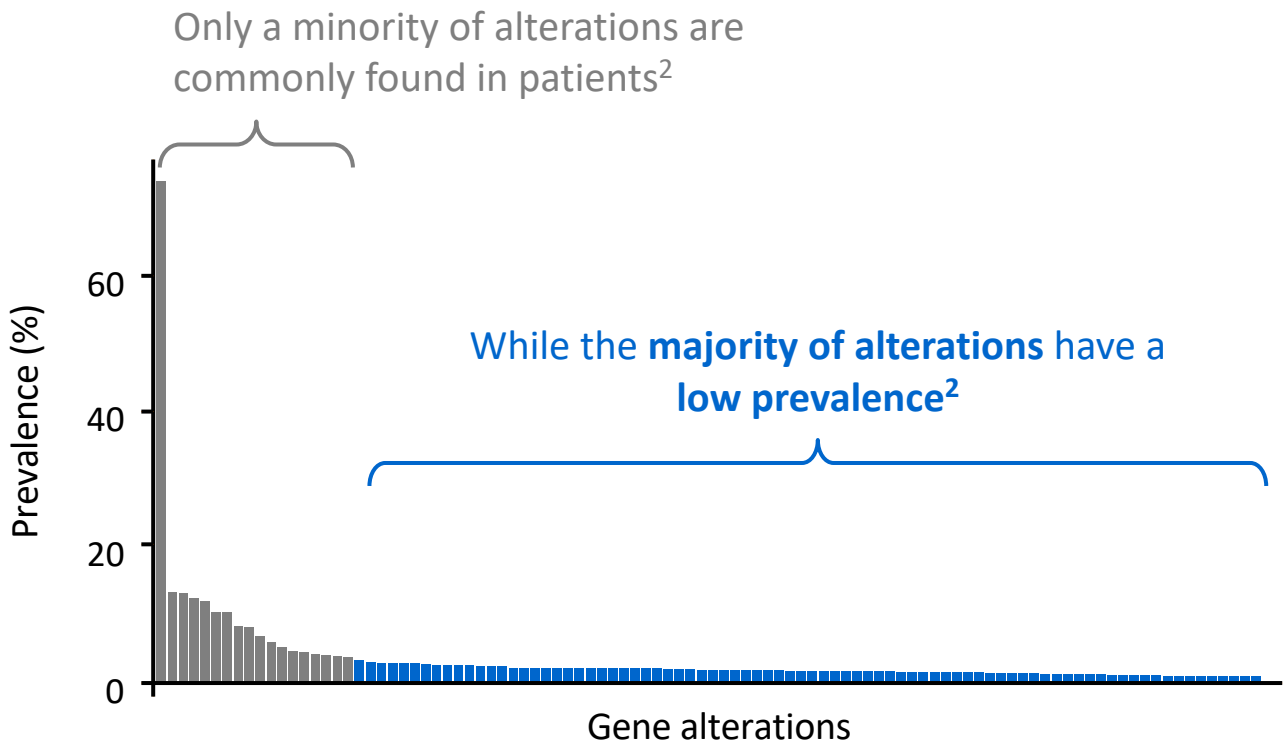
Health surveys, PROs[3,4]

Key RWD sources for regulatory and healthcare purposes

PRO: patient-reported outcomes; RWD: real-world data.

1. Khosla, S., et al. (2018) F1000Res 7:111 (Version 2); 2. Agarwala, V. (2018) Health Aff (Millwood) 37:765-772; 3. Khozin, S., et al. (2017) J Natl Canc Inst 109:djx187; 4. Duke-Margolis (2018) Characterizing RWD Quality and Relevancy for Regulatory Purposes.

RWD can complement modern clinical trials to demonstrate clinical benefit in rarer molecular subtypes[1]



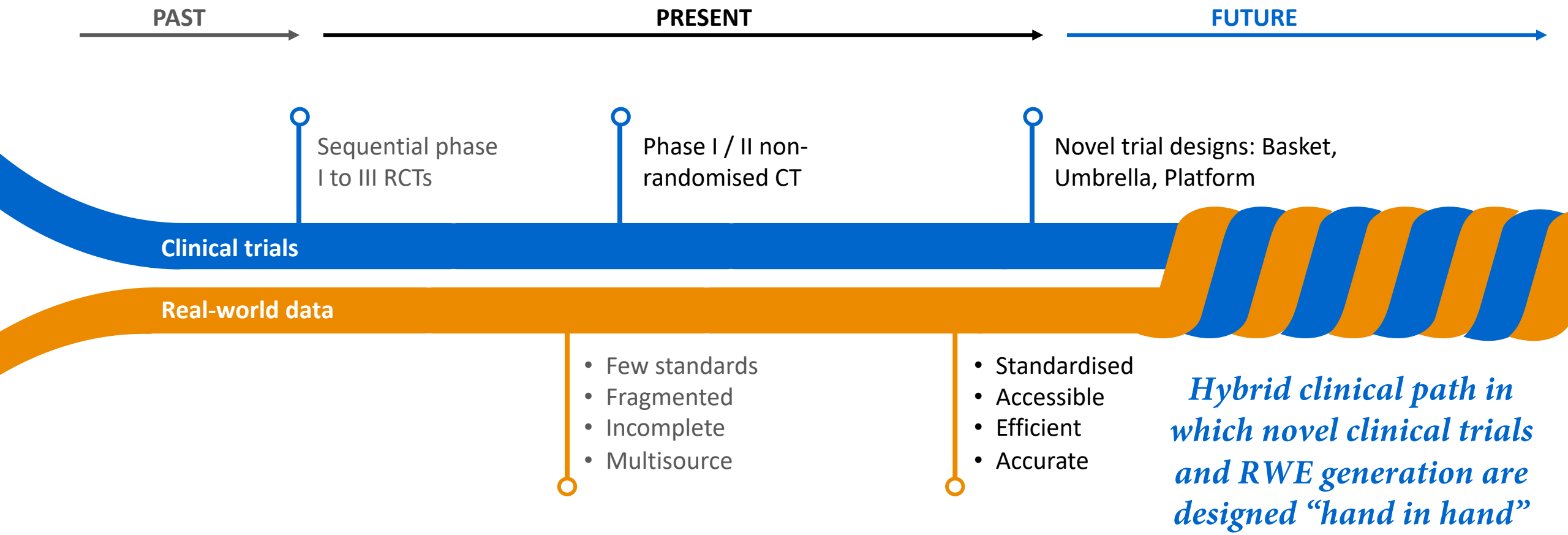
Precision oncology *– by its very nature –* ***deals with very small target populations***[3]

RWD *can address this challenges by* ***capturing the experience of the majority of cancer patients****, as compared to only the 5% who have the opportunity to participate in clinical trials*[1]

RWD: real-world data.

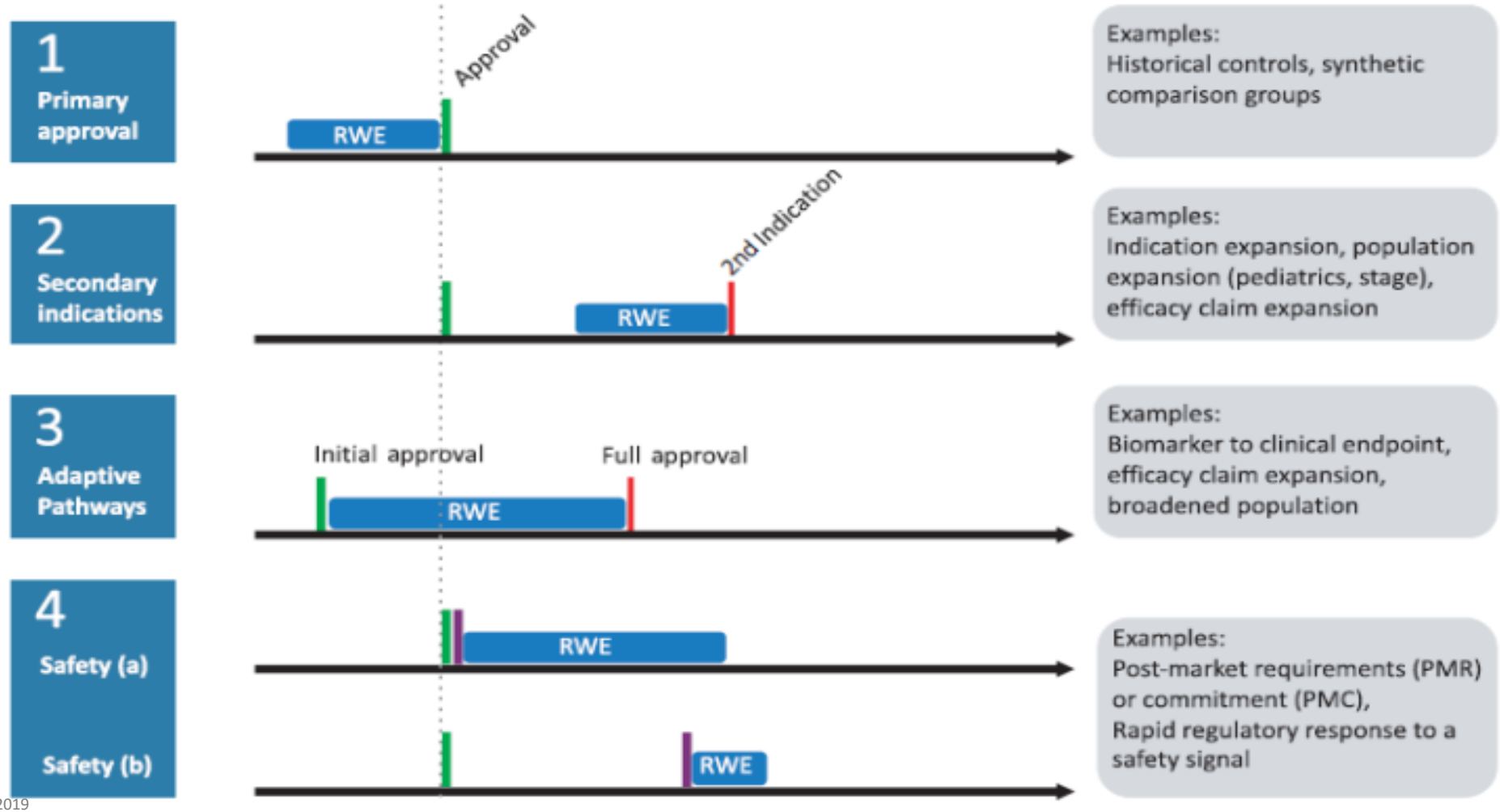
1. Booth, C.M., et al. (2019) *Nat Rev Clin Oncol* 16:312–25; 2. Data on File. FMI data base query;
3. Lewis, J.R.R., et al. (2017) *JCO Precision Oncology* doi:10.1200/PO.17.00157.

Co-evolution of clinical trials and RWD in precision medicine



CT: clinical trial; RCT: randomised controlled trial; RWD: real-world data; RWE: real-world evidence.

Real World Evidence in Regulatory Decision making



Franklin et al 2019

Opportunities and challenges for RWD use

Key considerations to harness the full potential of RWD

Collaborations

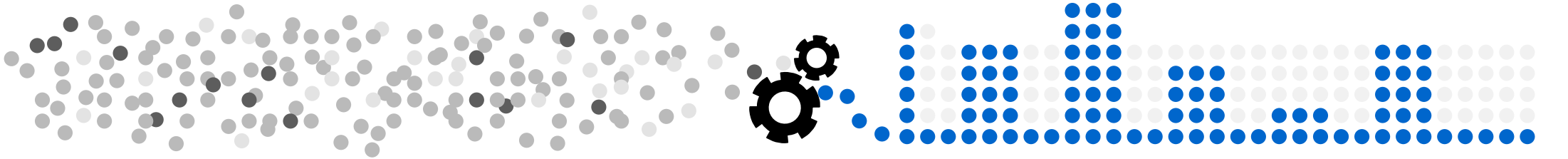
A single large initiative is more powerful than multiple initiatives with the same objective

> Set up a national / global initiative

Data protection

Data ownership, data sharing and data privacy

> Good governance structure is needed



RWD

RWE

Data considerations

RWD must be consistent, fit-for-purpose and of adequate quality to ensure generated evidence is valid[1]

> Strengthen data quality, standardisation and extraction

Methodological considerations

New statistical methodologies will become increasingly important and need to be validated

> Keep abreast of latest statistical analysis methods

RWD: real-world data; RWE: real-world evidence.

1. Duke-Margolis (2018) Characterizing RWD Quality and Relevancy for Regulatory Purposes; 2. Cave, A., et al. (2019) *Clin Pharmacol Ther* doi:10.1002/cpt.1426.

Quality needs for RWE

High quality
The provenance of each datapoint must be clear, traceable, and auditable. Data quality must be systematically measured with predetermined frameworks (e.g., interrater reliability) and against benchmarks (e.g., stage distribution in Surveillance, Epidemiology and End Results (SEER)).

Complete
Completeness requires predefined rules for abstraction of structured and unstructured data, data harmonization, and quality monitoring. Completeness needs to be benchmarked to appropriate gold standards (e.g., National Death Index for date of death).

Transparent
Transparent study designs and analysis plans are critical for robust RWE. In particular, the specific aims and cohort selection criteria need to be precisely defined. Study design considerations include retrospective vs. prospective data collection, the need for matching or propensity scores to facilitate comparisons, and endpoint validation.

Generalizable
RWE is often based on a broad range of patients, which can translate into better generalizability. Potential biases (e.g., geographic representation) must be identified and reported to allow for appropriate statistical adjustments and clinical interpretations.

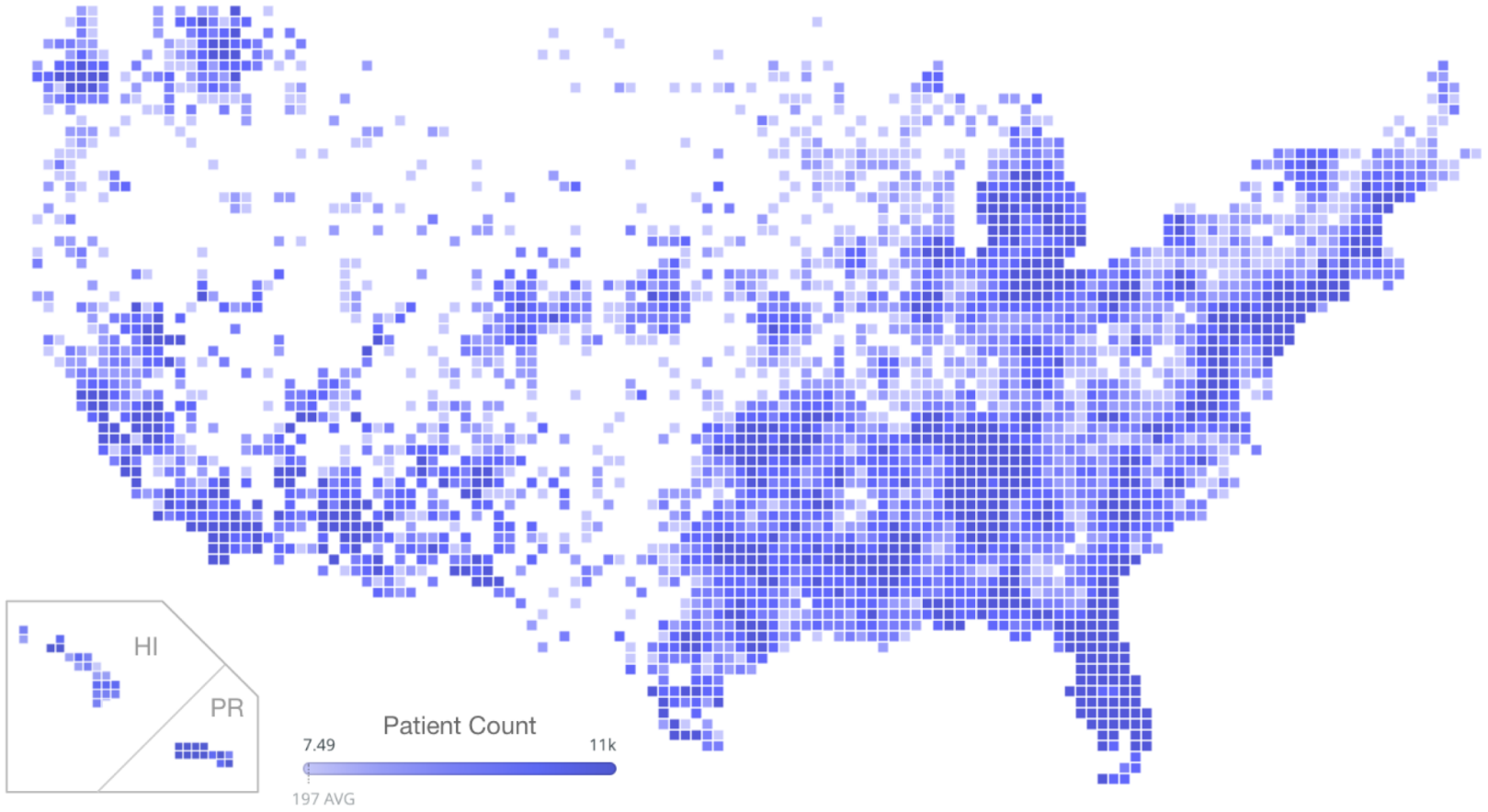
Timely
RWE reflects daily clinical decisions. Thus, reliable RWE needs to be recent and timely. Details about the timepoint that the data analysis represents must be reported (e.g., time period, last update, number of potential candidates, etc.).

Scalable
Data challenges become exponentially more complicated as the number of patients and variables increase. Therefore, scaling requires 1) a balance between high touch and automation; 2) a modular data model that can be used in multiple contexts and facilitates model evolution (e.g., frequency of intravenous regimens); and 3) unambiguous variable definitions, particularly for endpoints.

Miksad RA, Abernethy AP. Harnessing the Power of Real-World Evidence (RWE): A Checklist to Ensure Regulatory-Grade Data Quality. Clin Pharmacol Ther. 2018 Feb;103(2):202-205

Flatiron

Flatiron products are currently used across US-based oncology clinics*



2.2M
Active Patients

2,500
Clinicians

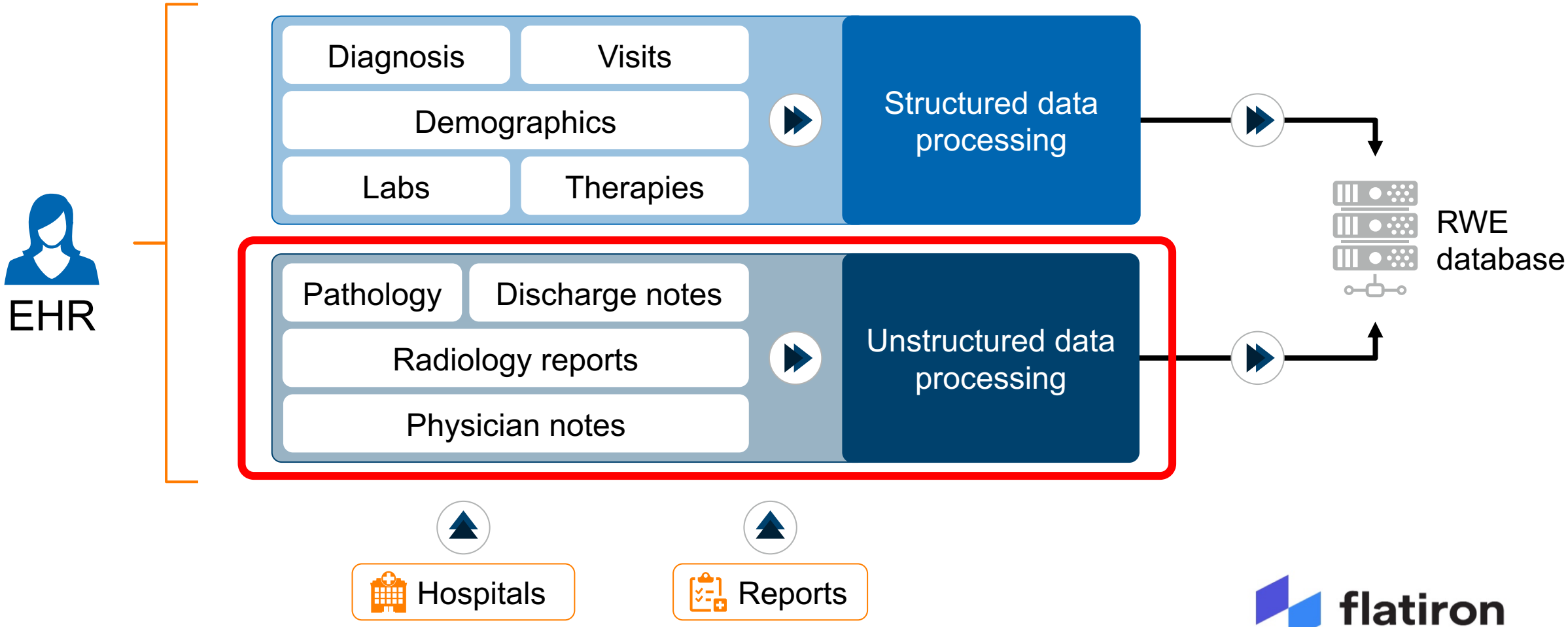
280
Cancer Clinics[1]

800
Sites of Care

* Majority are community-based clinics
1 Based on tax ID https://flatiron.com/

Flatiron: gold-standard database architecture

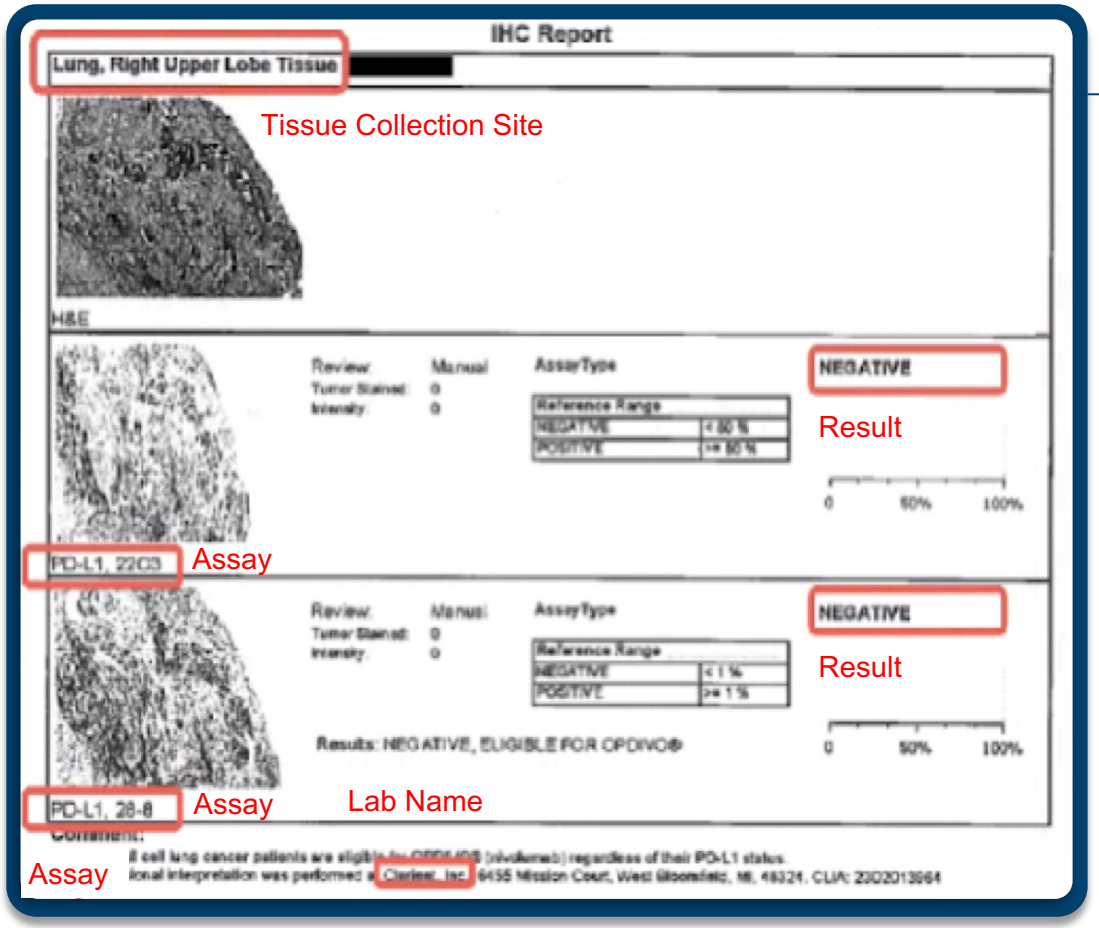
EHR with linkages to high value data sources



EHR: electronic health records; RWE: real-world evidence.
https://flatiron.com/

Key data elements in oncology are unstructured

Sample of PD-L1 Test



For every PD(L)-1 test a patient receives, Flatiron biomarker data model captures:

- Test Status
- Test Result
- Date biopsy collected
- Date results received by provider
- Lab name
- Sample Type Tissue Collection site
- Test Type (FISH)
- Assay/kit (e.g., Dako 22c3)
- Percent staining & staining intensity

Flatiron sample data. For illustrative purposes only.

A mixture of approaches exist to abstract data

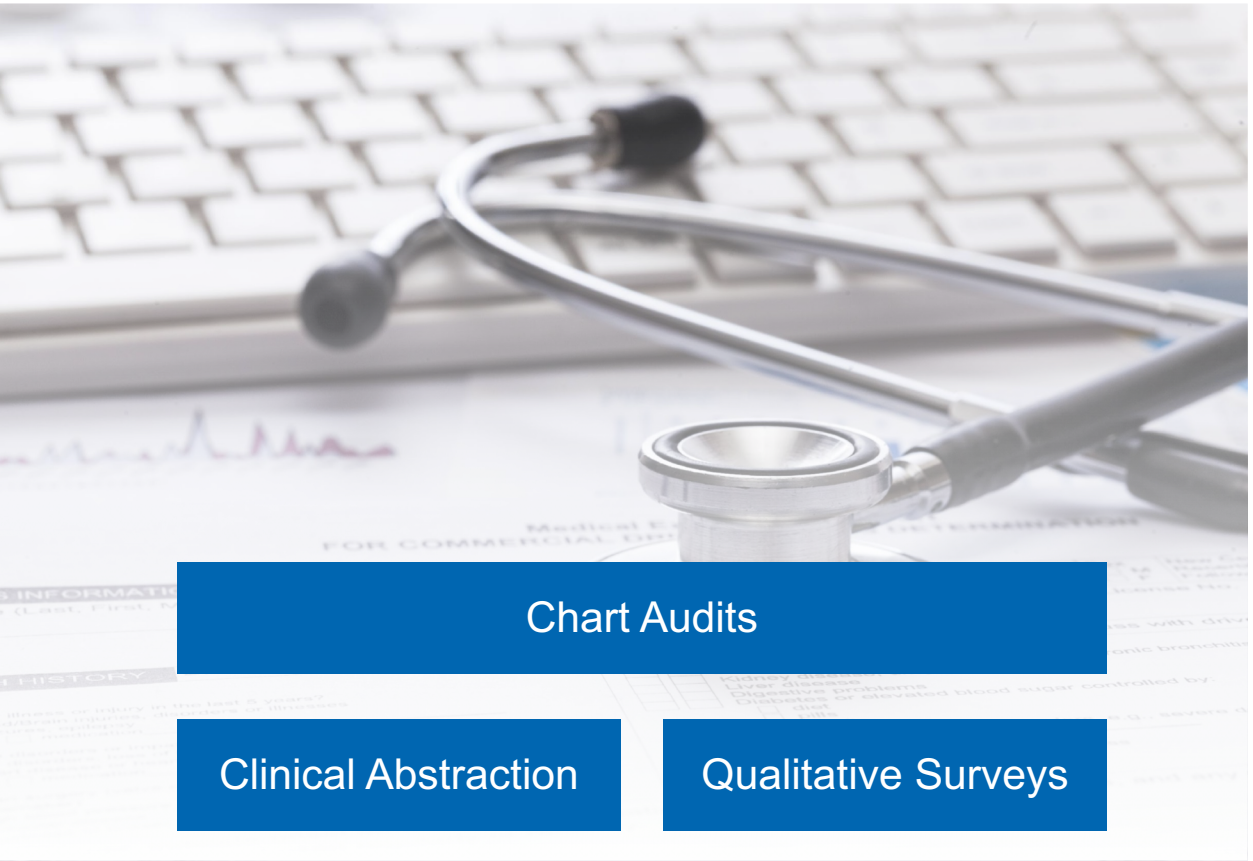


Chart Audits

Clinical Abstraction

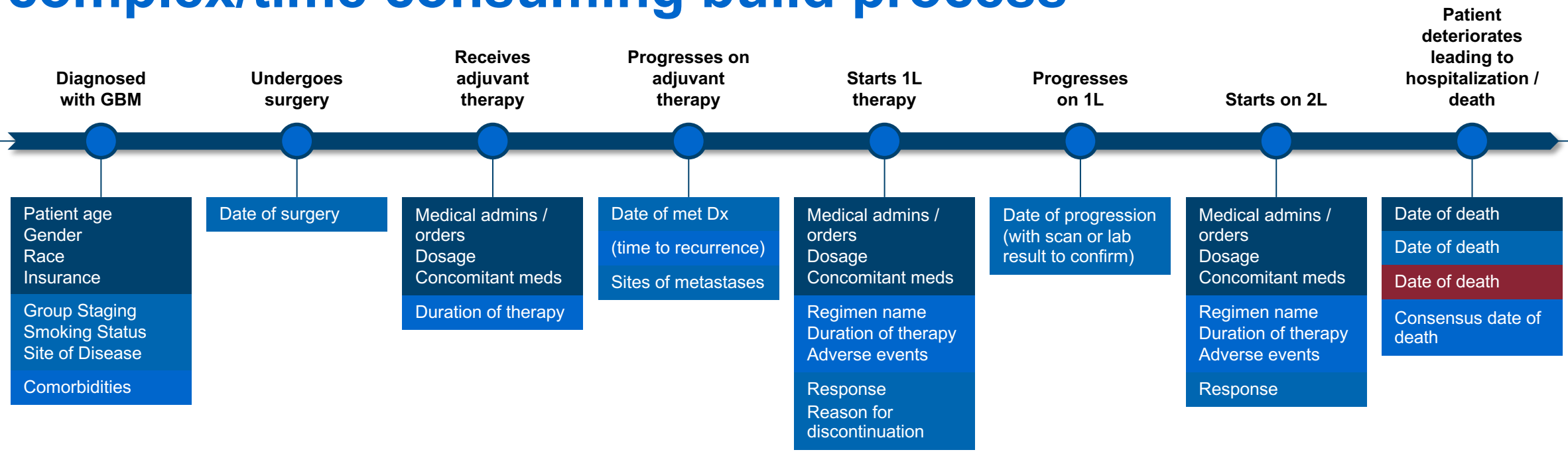
Qualitative Surveys

Machine Learning

Natural Language Processing

Artificial Intelligence

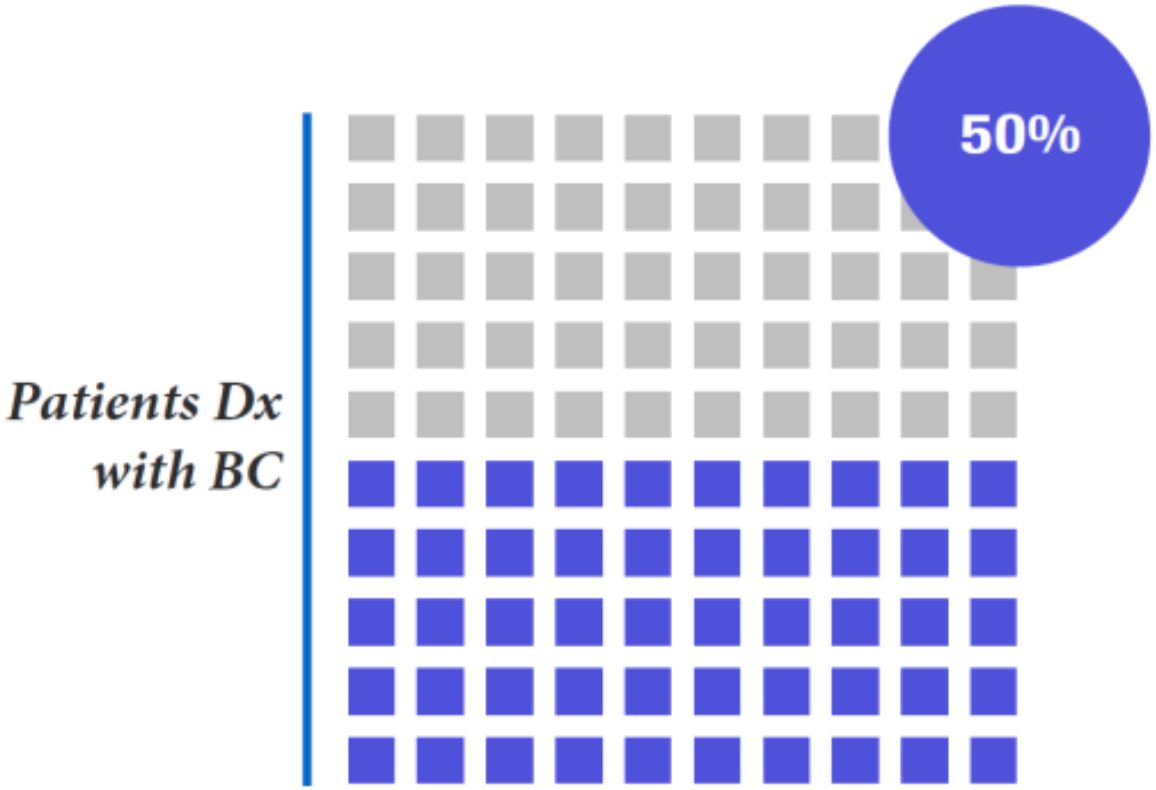
To get a comprehensive view of the patients multiple sources of data are needed with a complex/time consuming build process



* Relative timing not exact

Use cases

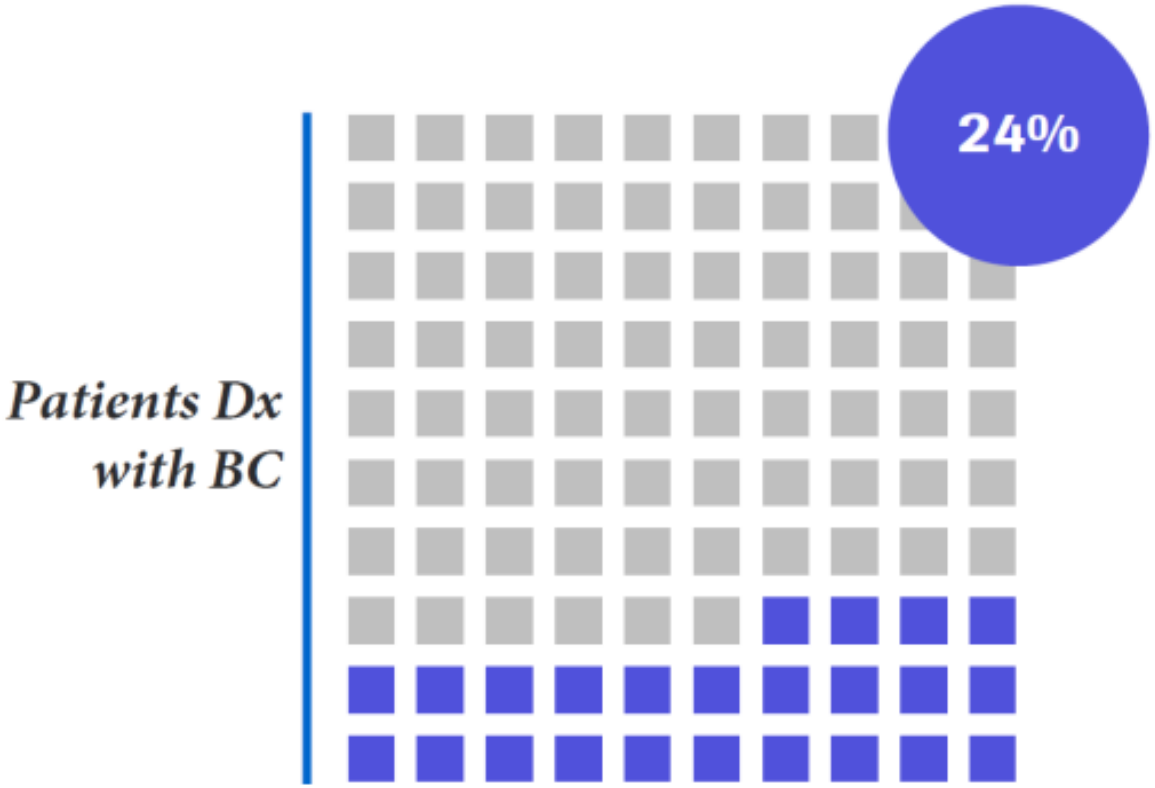
Use case: planning of a CT



- Metastatic disease
- Initiated therapy between 4/1/16 and 3/31/17
- HR + / HER2 -
- Have received drug X

Flatiron sample data. For illustrative purposes only.

Use case: planning of a CT



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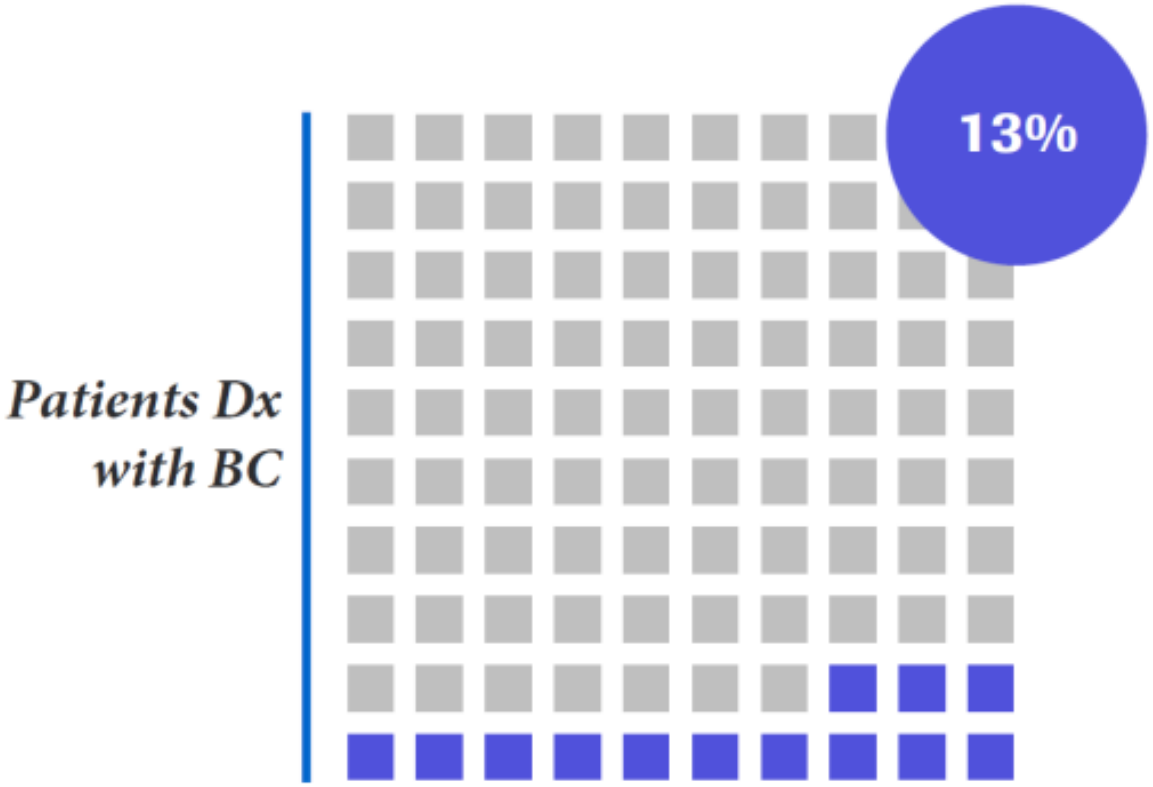

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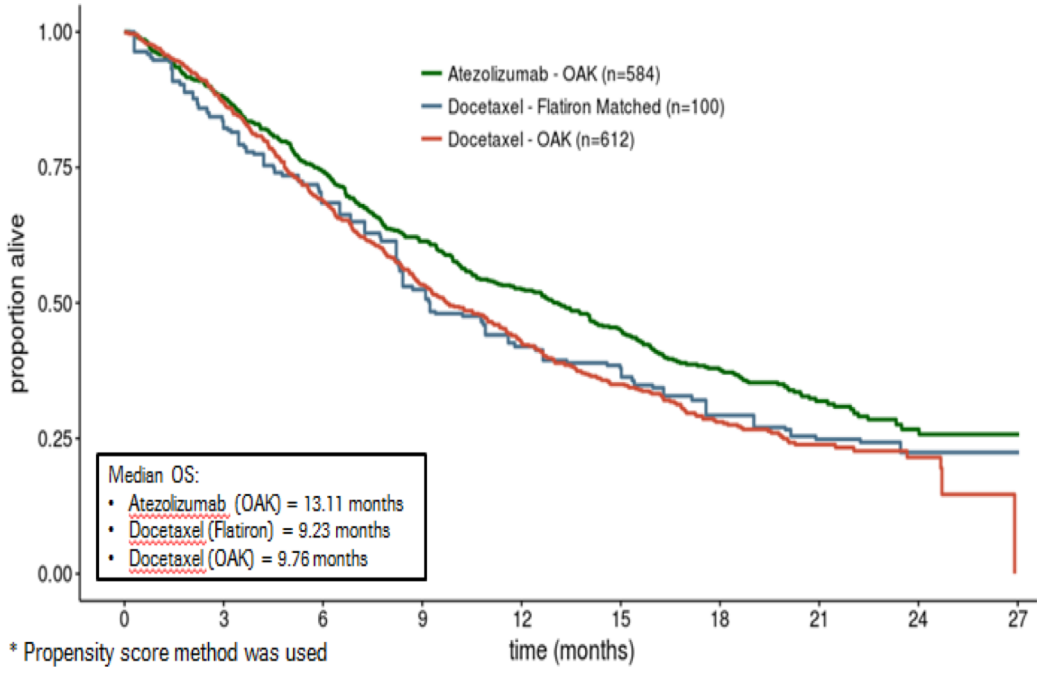
Flatiron sample data. For illustrative purposes only.

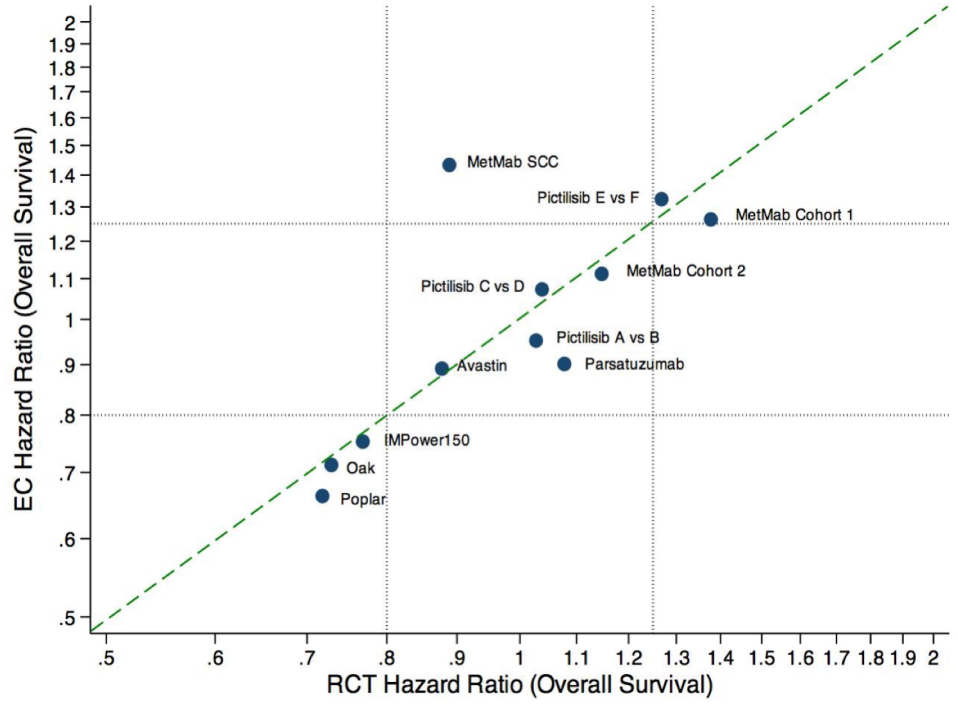
Providing confidence in RWE

Calibrating RWD to RCTs using Propensity Score Analysis

Retrospectively replicating docetaxel control arm in Atezolizumab OAK trial[1]



Replicating OS HR for nearly 11 comparisons among 8 recent NSCLC clinical trials[2]



RWE: real-world evidence; RWD: real-world data

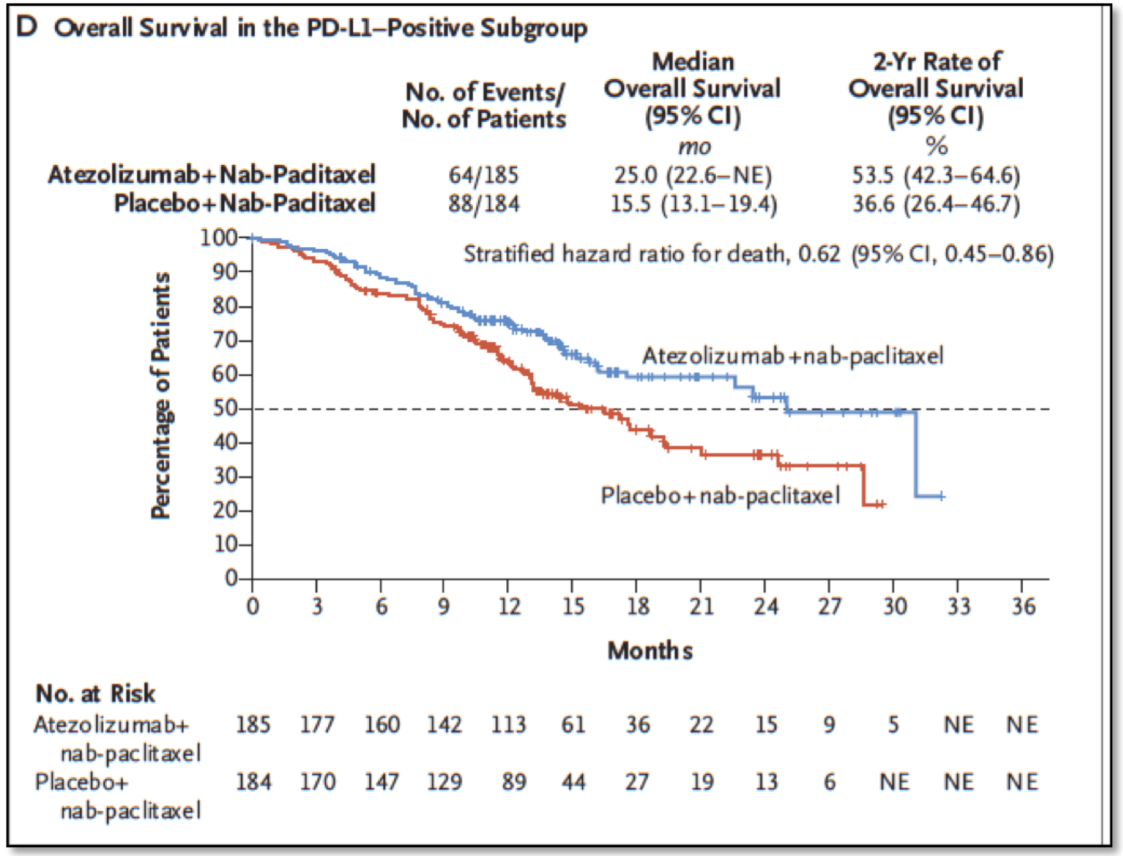
1 Capra, W. Real World Evidence in Oncology and its Implications. American Association for Cancer Research 2018.

2. Carrigan G, et al., Proof-of-Concept for using External Control Arm Derived from Electronic Health Records (EHR) to Replace Control Arms from Randomized Controlled Trials (RCT). Annual Meeting of the International Society for Pharmacoepidemiology 2018.

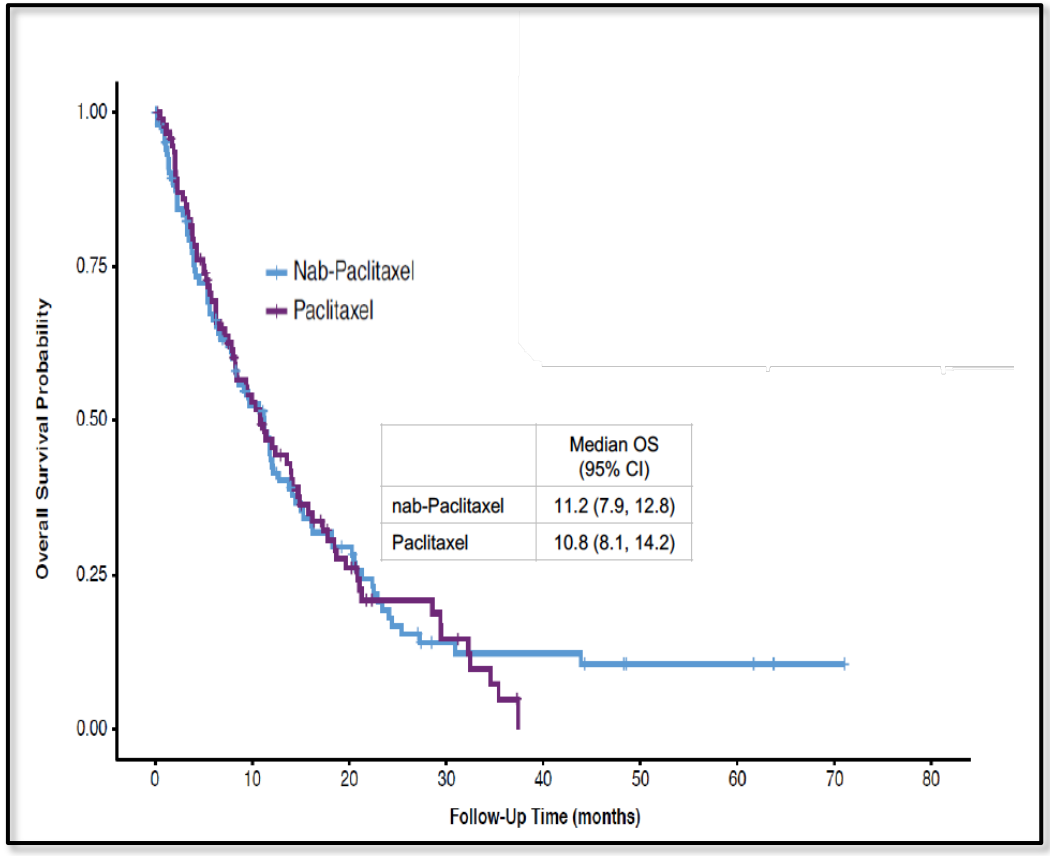
US RWE for EU submissions

RWE demonstrated comparable effectiveness between nab-paclitaxel (control arm in trial) and paclitaxel (standard of care in EU) in 1L TNBC

Clinical trial comparator arm: Nab-Paclitaxel



Real World Data: *Nab-Paclitaxel vs Paclitaxel*



RWE: real-world evidence

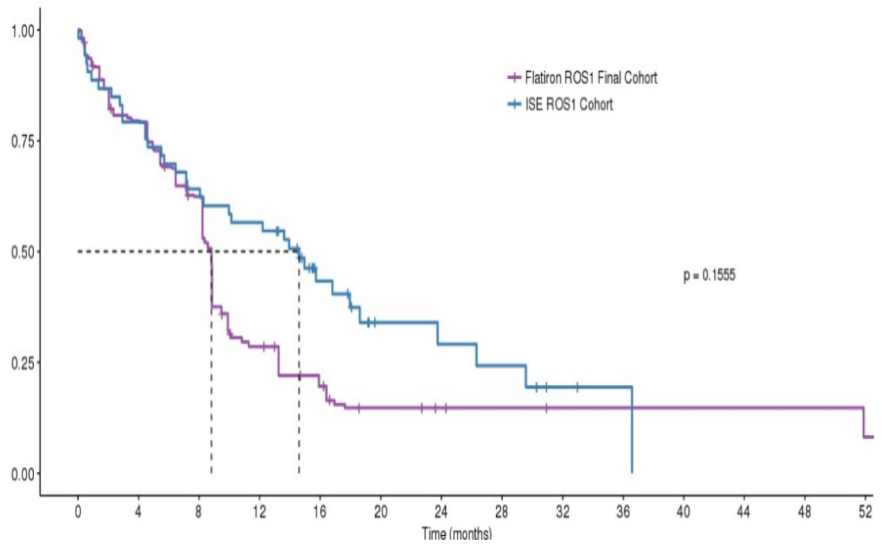
Schmid P. et al., N Engl J Med. 2018 Nov 29;379(22):2108-2121

Entrectinib ROS-1 NSCLC

Flatiron-based external control included in FDA/EMA filing

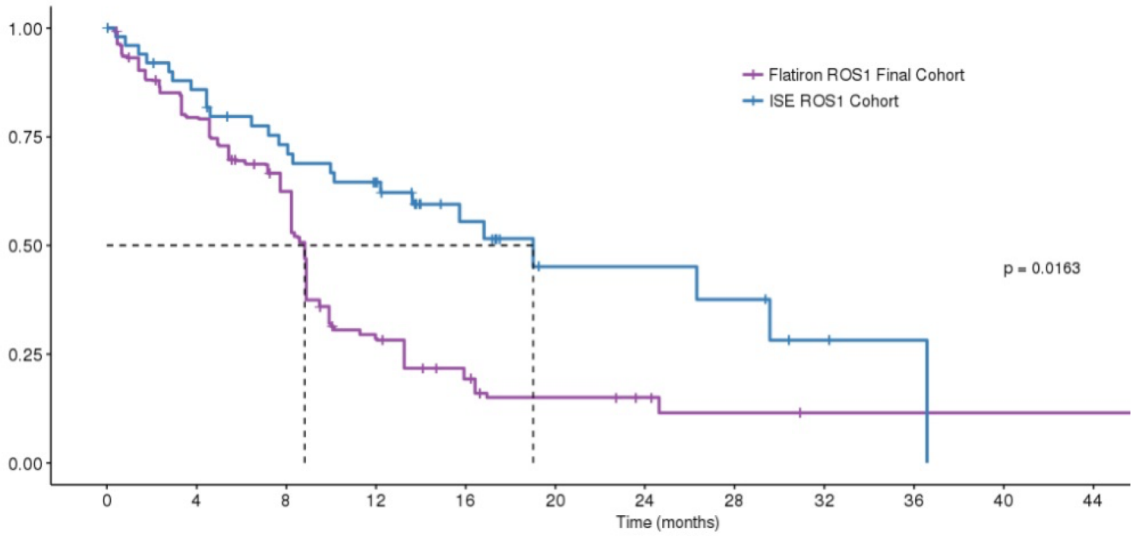
Time to treatment discontinuation:

Entrectinib (trial) vs Crizotinib (Flatiron External Control)



Progression-free survival:

Entrectinib (trial) vs Crizotinib (Flatiron External Control)



Among patients with ROS-1 advanced NSCLC, entrectinib was associated with longer time to treatment discontinuation (HR: 0.64 [95% CI: 0.4 - 1.015]) and longer progression-free survival (HR: 0.44 [95% CI: 0.26 - 0.742]) compared to crizotinib.

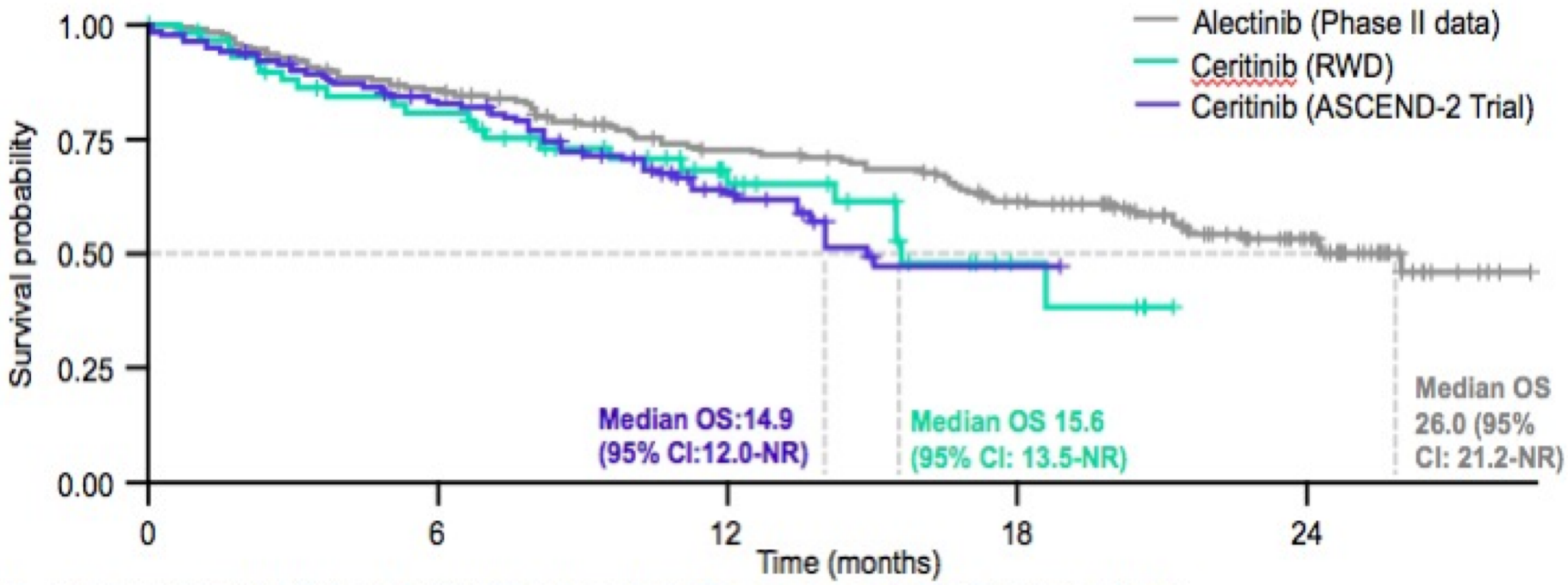
J Clin Oncol 37, 2019 (suppl; abstr 9070)

RW external control arm for single-arm ph II Alectinib studies

Alectinib is associated with significantly lower risk of death than ceritinib in ALK+ aNSCLC (post-crizotinib)

HR 0.65; 95% CI: 0.48–0.88, *p* = 0.006

Overall survival (OS) for RWD ceritinib, clinical trial ceritinib and alectinib populations (un-weighted)



Supported Alectinib ALK+ 2L NSCLC reimbursement (18 countries)

HR: hazard ratio; CI: confidence interval; NR: not reached; RWD: real-word data.

Davies J., et al. (2018) J Comp Eff Res. doi: 10.2217/cer-2018-0032 [Epub ahead of print].

Fulfilling post approval requirement for TDM1

Situation

Pharmacovigilance commitment: Evaluate cardiac safety outcomes in low LVEF patients treated with TDM1

Initial proposal of planned and on-going registries

Rare population

Solution

Propose use of secondary data (Flatiron EHR) to identify the relevant patients

Describe patients characteristics and cardiac outcomes

Provided **feasibility study** to PRAC to get buy-in

Key Insights

PRAC acknowledges the difficulties surrounding patient recruitment

PRAC is receptive to using EHR data to address PV

Secondary data now being used instead of initially proposed registries

Opportunities

Collaboration with PRAC

Obtaining an **insight into what is acceptable for future programs**

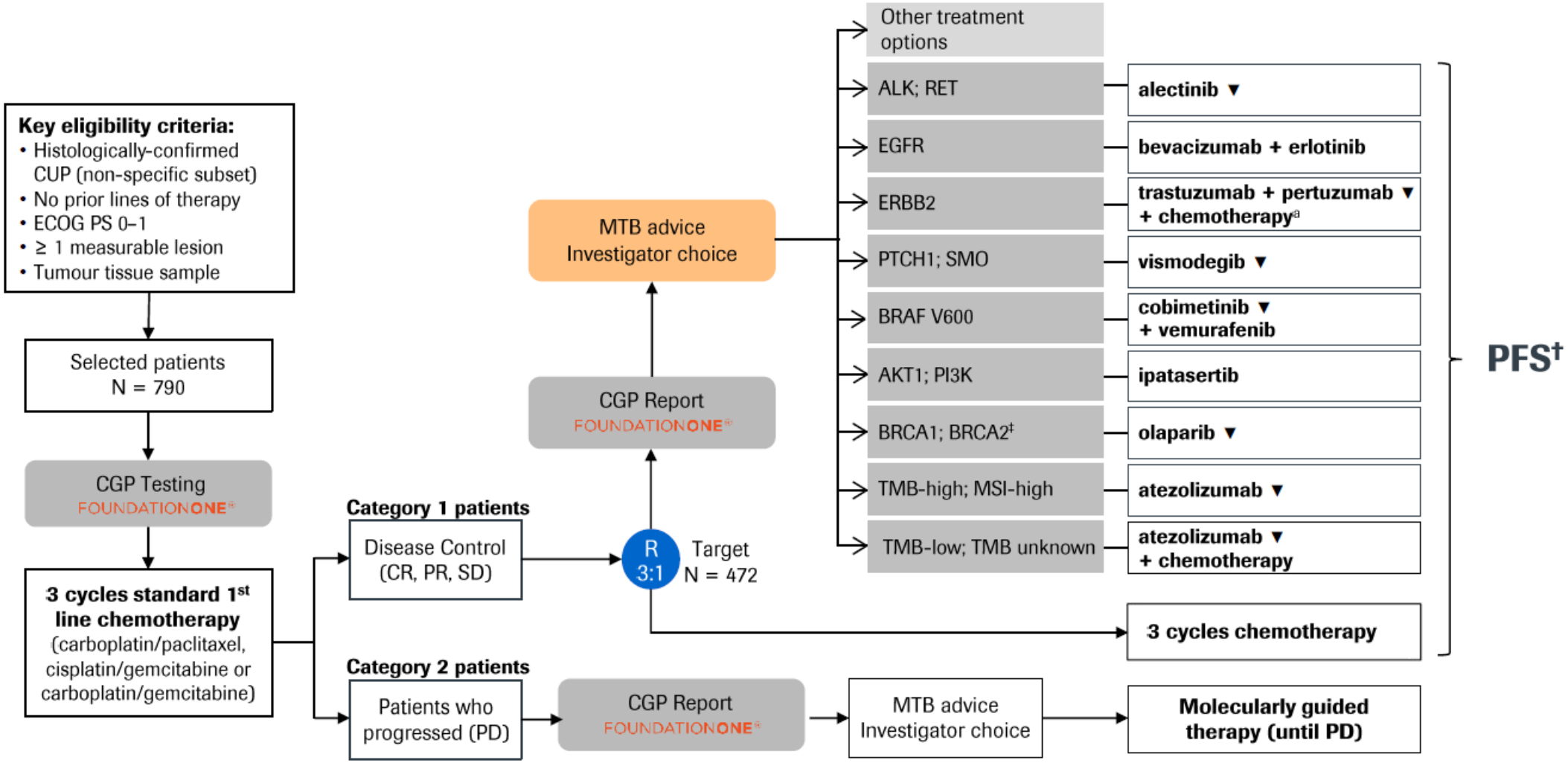
Timely inform HA, physicians and the patients

Cost savings

Roche, Data on file

Trial design - CUPISCO

with multiple investigational medicinal products



Cupisco trial design (NCT03498521). https://clinicaltrials.gov/ct2/show/NCT03498521

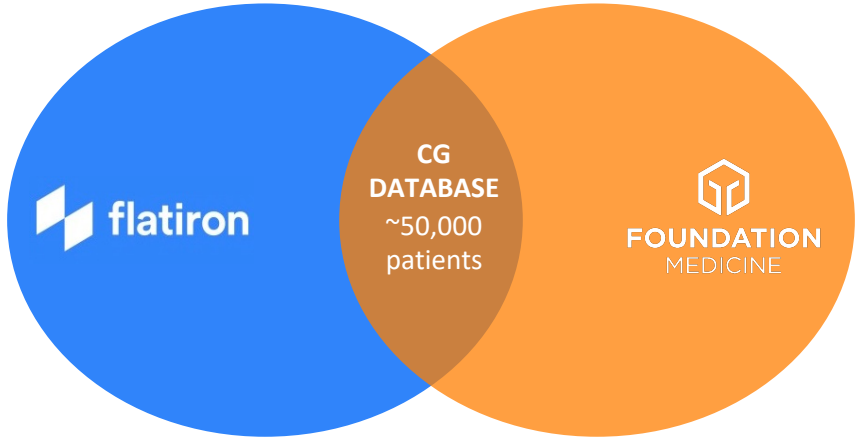
Flatiron and FMI join efforts to Combine Comprehensive Genomic data and Clinical Outcomes

flatiron

2.2M
Patients

280+
Cancer clinics

800
Unique sites of care



DATA MODEL

Enhanced clinical RWD	**Comprehensive genomic data**
Clinical outcomes	**Advanced genomic analysis**

FOUNDATION MEDICINE®

300k+
Genomic profiles

150+
Cancer subtypes

~400
Genes sequenced

2000+
Sample analysis per week

CG: clinico-genomic; FMI: Foundation Medicine, Inc.; RWD: real-world data. Flatiron 2018 from https://flatiron.com/ [Accessed June 2018]; Foundation Medicine 2018 from: https://www.foundationmedicine.com/insights-and-trials/foundation-insights#foundationcoretm; Frampton, G. M. et al. (2013) Nat Biotech 31(11): 1023-1031. [FMI information and total number of patients in CG database included is most recent as of Feb 2019.]

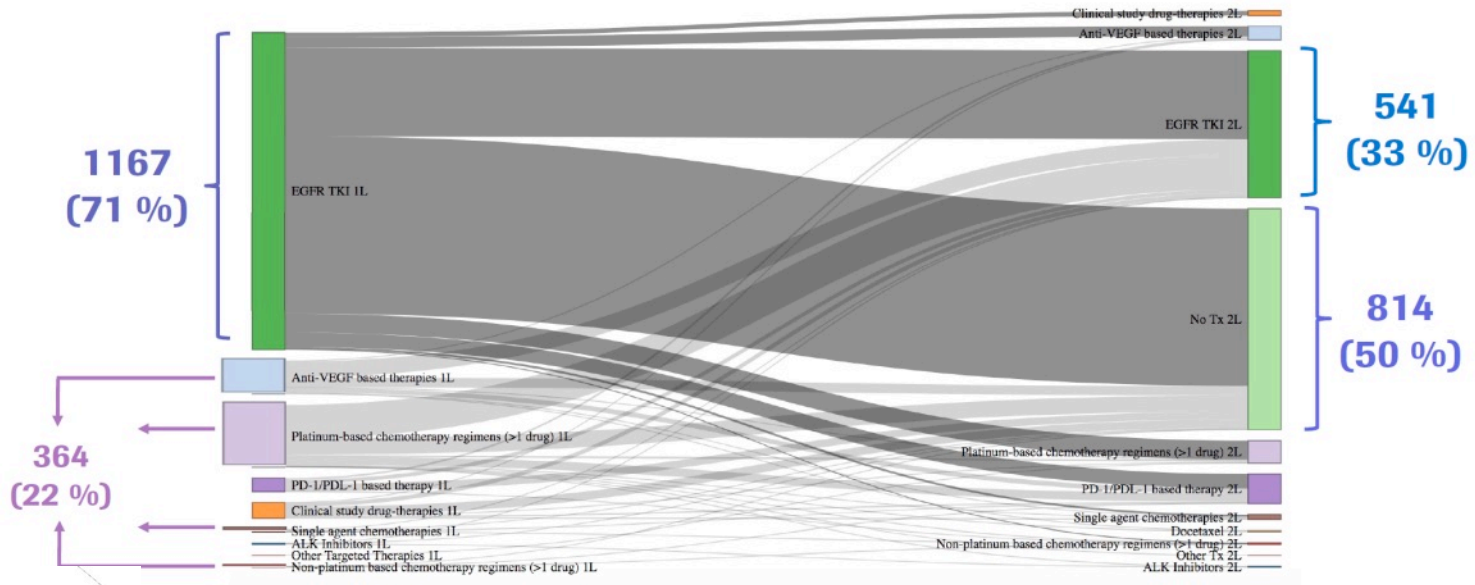
NSCLC patients

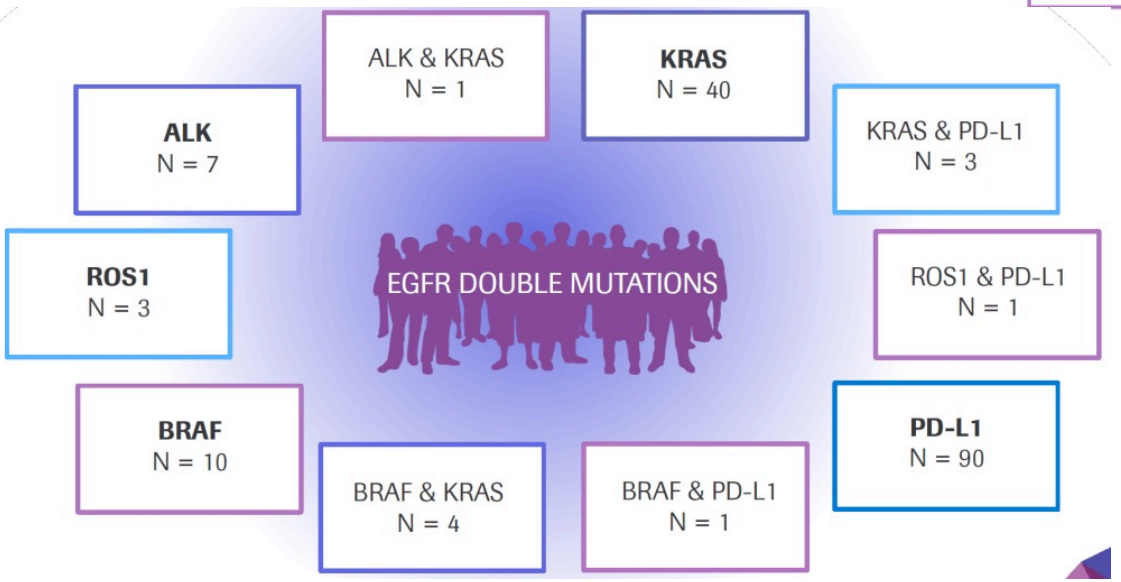
Flatiron aNSCLC data mart (N = 48,857)

1 January 2014 – 31 May 2018 (N = 31,532)

Non-squamous NSCLC histology (N = 23,519)

Positive EGFR test result date on or after their NSCLC diagnosis and prior 2L initiation (N = 1,645)





>20% der Patienten erhielten keinen EGFR TKI in der 1. Linie
50% der Patienten erhielten keine 2. Linien-Therapie
160 Patienten hatten zumindest eine weitere Mutation oder waren PD-L1 pos.

Roche, Data on file

Summary

- Control populations derived from RWD may be used to supplement evidence from clinical trials in settings where only limited data are available and randomization is not feasible.
- Working with the HA early during the filing process allowed us to agree on a novel endpoint to compare the trial arm vs the RWD
- Using a high quality dataset, allowed us to compare the trial and RWD populations in a manner that was meaningful to HAs
- Control populations derived from RWD can also be used to supplement evidence from clinical trials for reimbursement needs.
- Using a high quality dataset, allowed us to bring in comparative evidence from a recent standard of care, rather than historical treatments
- US data can be accepted in other countries, when local evidence is not available

KJGHSFRBLJ5TNALOXFRSNSHJYMSJXZSLYMHSKLYXMSTHSNKXGSXJSZSKDMDKHGDALDHSMXJDTZ
ZXNXZDNXJHDKXMNAH7NNSHASDASNBKJ6BKJG4JZFQ4KLSKJ8LKBKJ9LKHLKH4LKHLKH6POIOIUT
Z5KJHK77KJGKJG5LKVIELENHLKSH7LKHLKH5DANKLHLKH2KLHLKHKJJJGJHFTZ4LKLKJHKJGHJ7KJHK
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