Lines of Therapy in Oncology Real World Data: Navigating Complexity for Robust Evidence

ISPOR Europe

Glasgow, Scotland

10 November 2025

Disclosures

- Employment: The healthcare business of Merck KGaA, Darmstadt, Germany
- Stock and other ownership interests: Bayer AG

Introductions & Workshop Overview

- **Moderator:** Seyed Hamidreza Mahmoudpour, Merck Healthcare KGaA, Germany

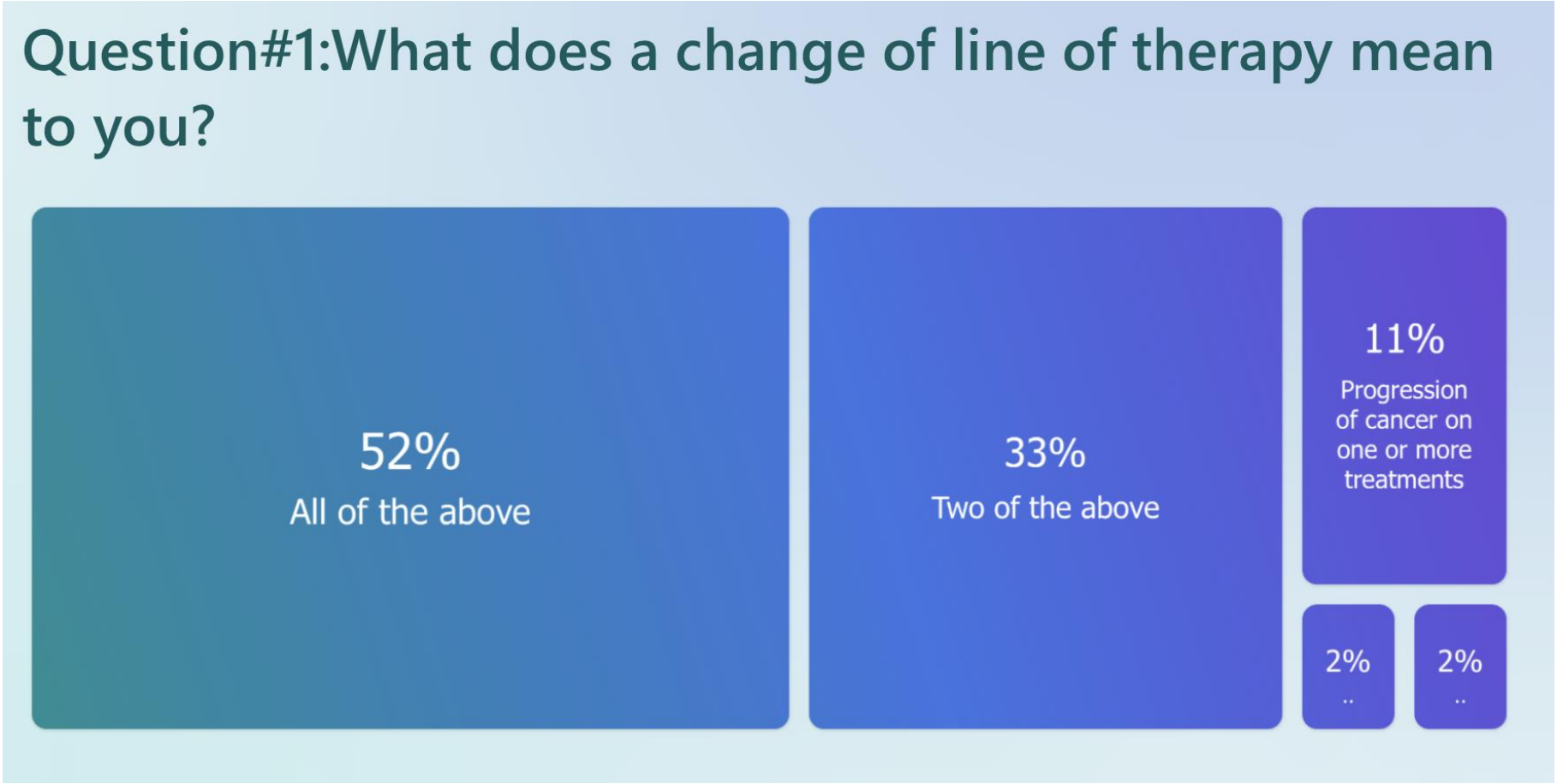
- **Speakers**:
  - Benjamin Bates, Rutgers University, United States
  - Arun Sujenthiran, Flatiron Health, UK
  - Denise Umuhire, European Medicines Agency, Netherlands
  - Karen Facey, RWE4Decisions, UK

Poll Question #1

What does a change of line of therapy mean to you?

a) Progression of cancer on one or more treatments
b) Change of treatment following an adverse effect
c) Treatment change from curative to palliative disease
d) Two of the above
e) All of the above

Among 166 responses....



RUTGERS HEALTH

Clinical Relevance and Ambiguity of Systemic Lines of Therapy in Oncology

Benjamin Bates, MD, MSc

Assistant Professor of Medicine & Epidemiology

Rutgers Center for Pharmacoepidemiology and Treatment Science (PETS)

Rutgers Center for Health Outcomes, Policy, and Economics (HOPE)

Rutgers University

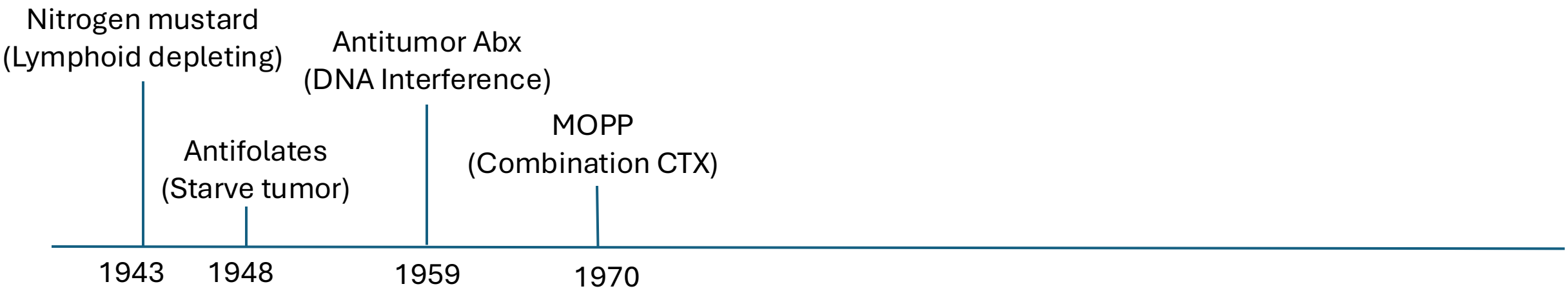
Disclosures

Statements and opinions are my own and do not necessarily reflect my employer or funding agencies

Research Funding Support

- Current funding NIH/NCI K08CA283268
- Prior funding NJ Commission on Cancer Research, Patterson Family Trust, Rutgers Cancer Institute

Selective History of Chemotherapy and Recommendations



RUTGERS

Davita et al Cancer Res (2008); Falzon et al Font Pharmacol (2018)

First successful use of multi-agent chemotherapy

Article | 1 December 1970

Combination Chemotherapy in the Treatment of Advanced Hodgkin's Disease

Authors: VINCENT T. DEVITA JR., M.D., F.A.C.P., ARTHUR A. SERPICK, M.D., F.A.C.P., and PAUL P. CARBONE, M.D. | AUTHOR, ARTICLE, & DISCLOSURE INFORMATION

Publication: Annals of Internal Medicine • Volume 73, Number 6 • https://doi.org/10.7326/0003-4819-73-6-881

MOPP: Mechlorethamine, Vincristine [Onvorin], Procarbazine, Prednisone)

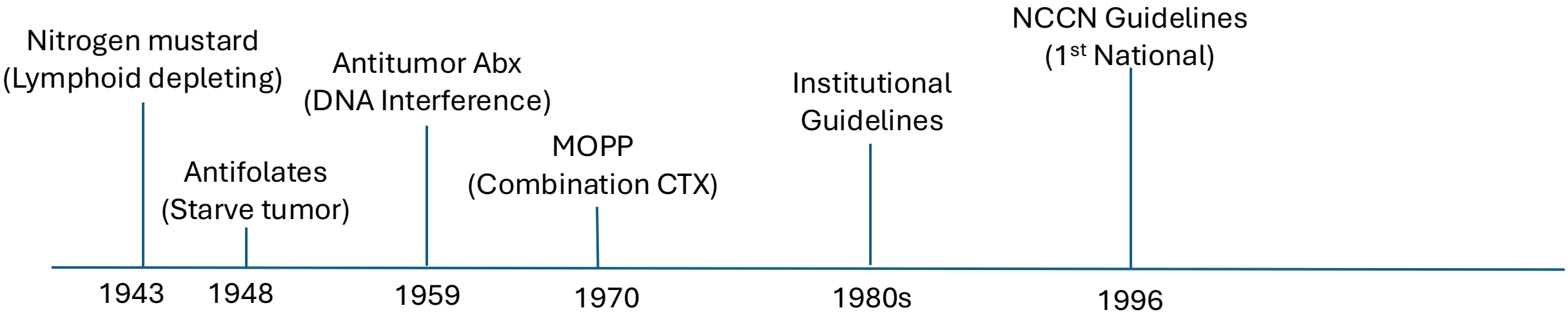
JAMA
THE JOURNAL of the American Medical Association
July 17, 1972 Vol 221, No 3

Combination Chemotherapy of Hodgkin's Disease in Private Practice

Lowell H. Greenberg, MD; Y. Stuart Wong, MD; Arthur P. Richardson, Jr., MD; and Malin R. Dollinger, MD

Devita et al Annal IM 1970;
Greenberg et al JAMA 1972

Selective History of Chemotherapy and Recommendations



RUTGERS

Davita et al Cancer Res (2008); Falzon et al Font Pharmacol (2018);
NCCN, 30 Years of NCCN Guidelines- https://www.nccn.org/home/about/nccn-history/30-years-of-nccn

NCCN Guidelines

8 Guidelines: Acute Leukemia, Breast, Lung, Ovarian, Pediatric, Prostate, Colon, and Rectal Cancers

88 Guidelines developed by 63 panels with input from 1,900 multidisciplinary members from 33 cancer centers in the US

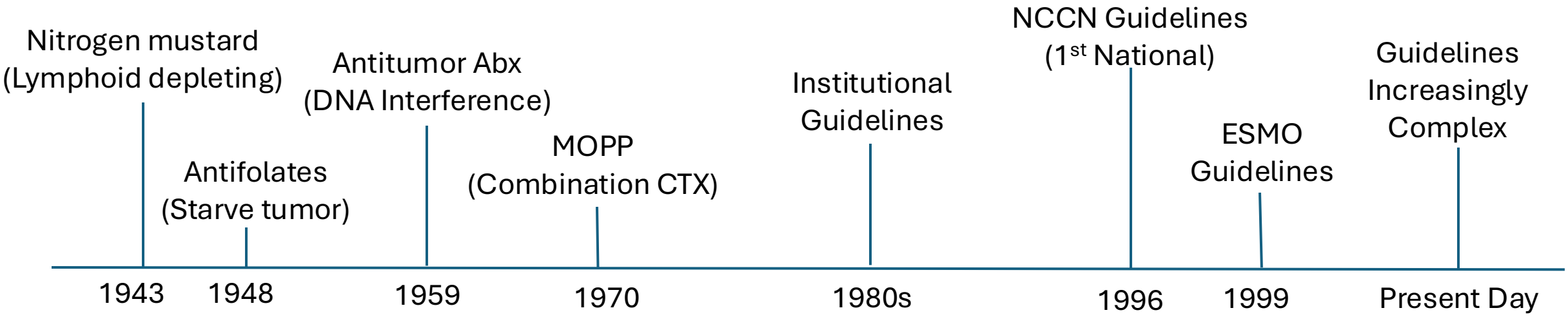
1995

2025

RUTGERS

NCCN, 30 Years of NCCN Guidelines- https://www.nccn.org/home/about/nccn-history/30-years-of-nccn

Selective History of Chemotherapy and Recommendations



Davita et al Cancer Res (2008); Falzon et al Font Pharmacol (2018);
NCCN, 30 Years of NCCN Guidelines- https://www.nccn.org/home/about/nccn-history/30-years-of-nccn;
Pavlidis Ann Onc 2011

RUTGERS

Increasing complexity and individualization of therapies

2010 (prior)- Metastatic NSCLC

clinical practice guidelines

Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

4 Pages

2023 (most recent) - Oncogene-Addicted Metastatic NSCLC **16 Pages**

Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up ☆

2023 (most recent) - Non-Oncogene-Addicted Metastatic NSCLC **16 Pages**

Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up ☆

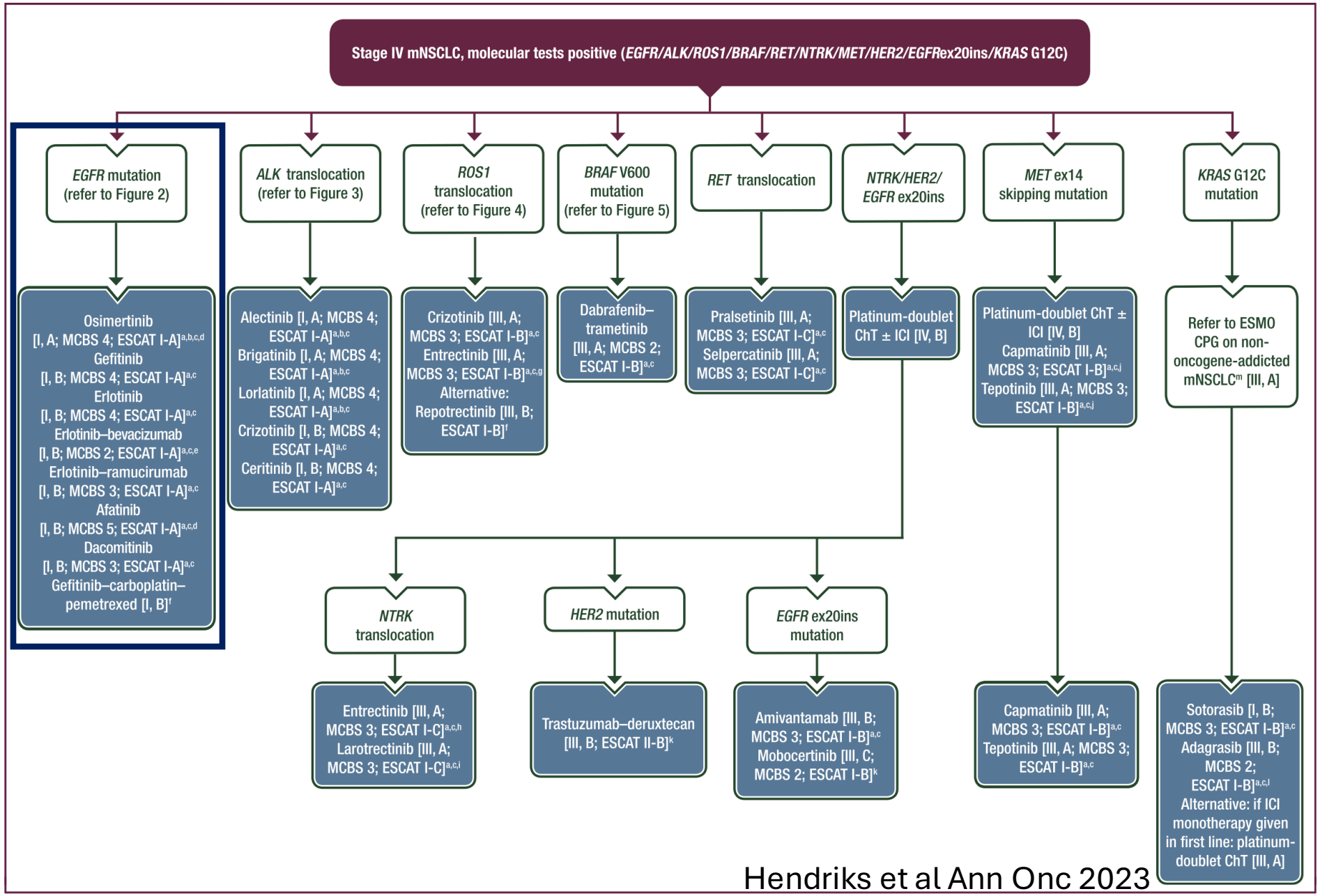
RUTGERS

D'Addario et al Ann Onc 2010; Hendriks et al Ann Onc 2023

Increasing complexity and individualization of therapies

2023- Oncogene-Addicted Metastatic NSCLC

Treatment recommendations for each oncogene



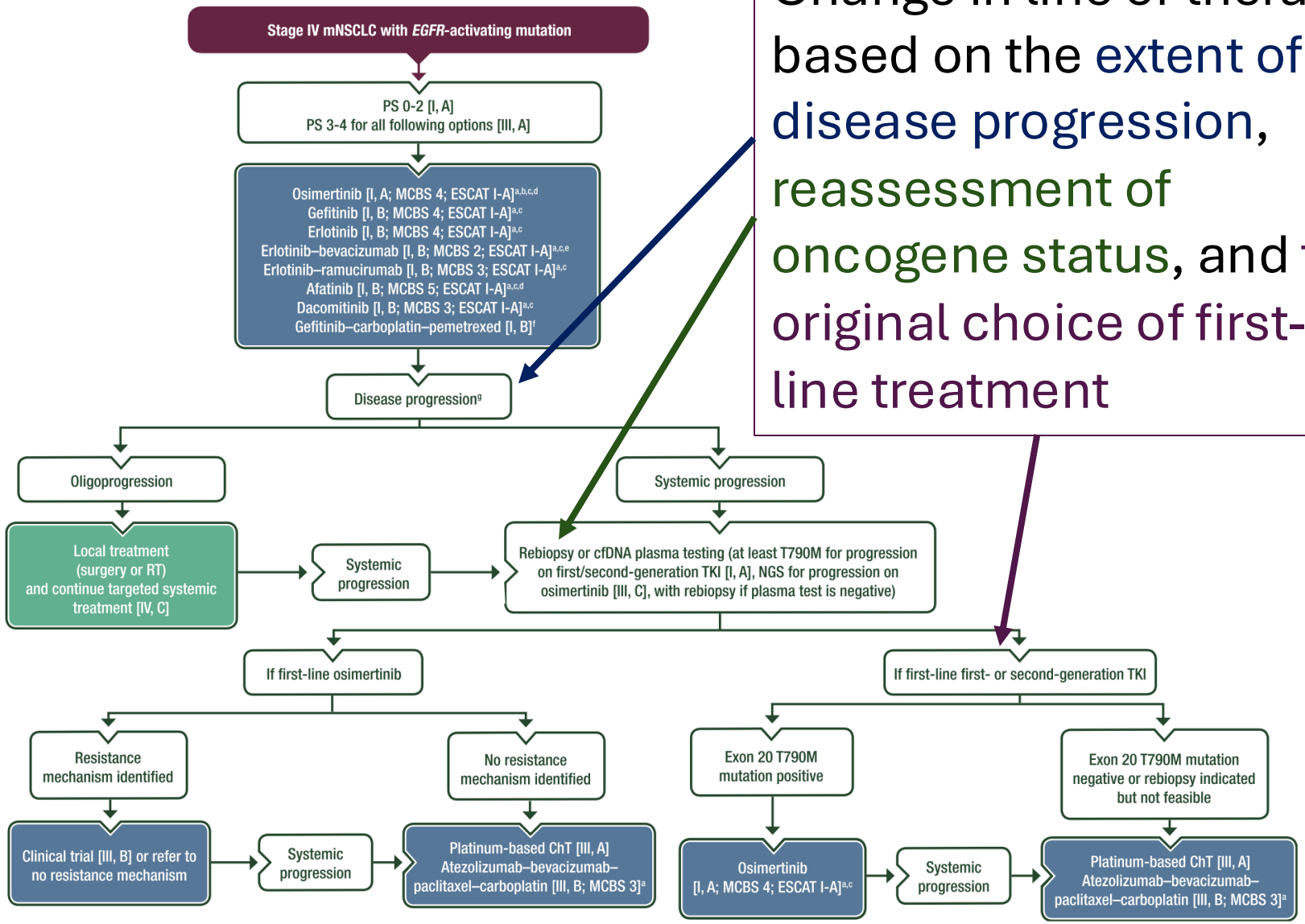
Hendriks et al Ann Onc 2023

RUTGERS

Increasing complexity and individualization of therapies

2023- Oncogene-Addicted Metastatic NSCLC

Treatment recommendations for EGFR activating oncogene



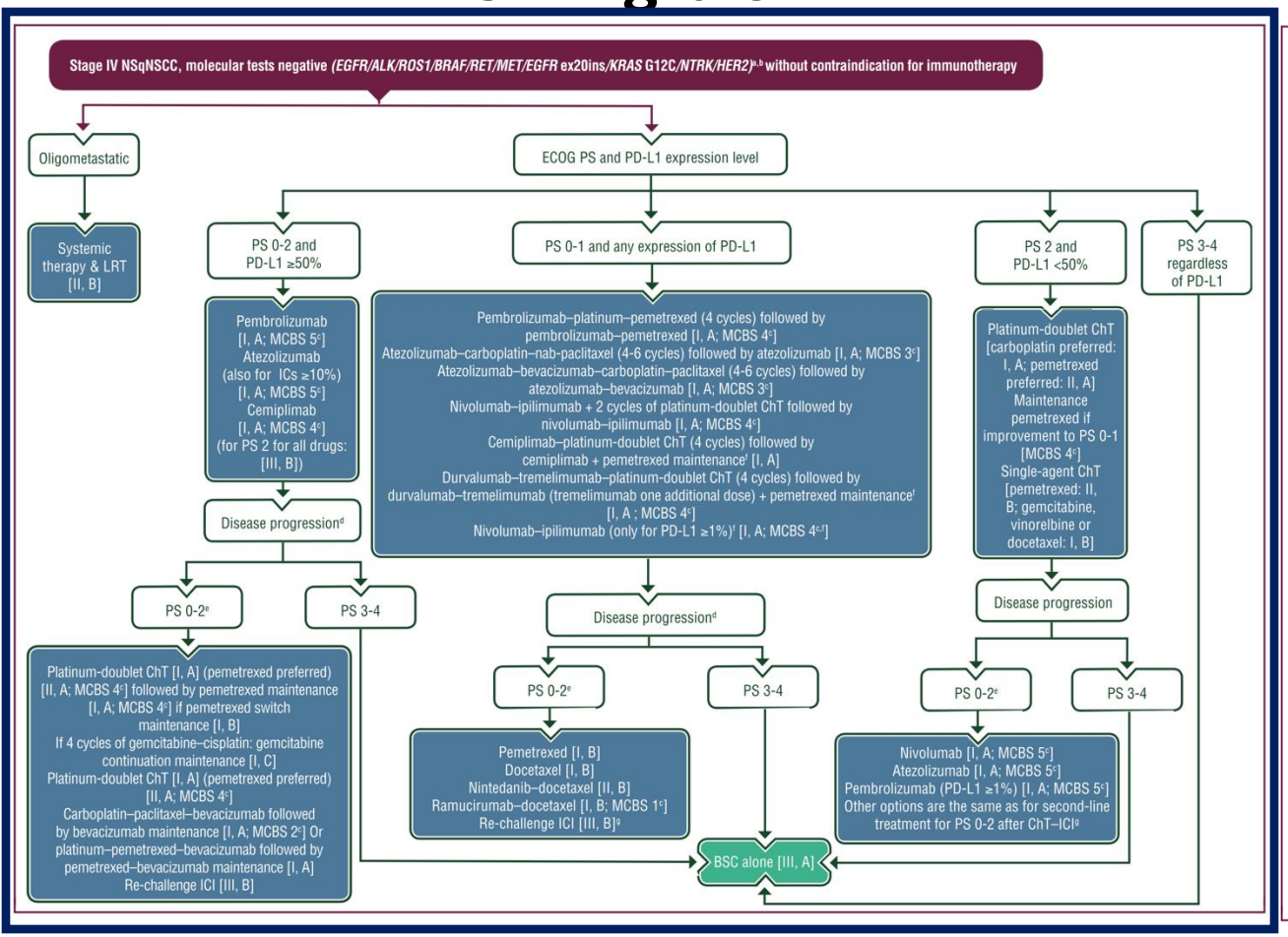
Change in line of therapy based on the extent of disease progression, reassessment of oncogene status, and the original choice of first-line treatment

Hendriks et al Ann Onc 2023

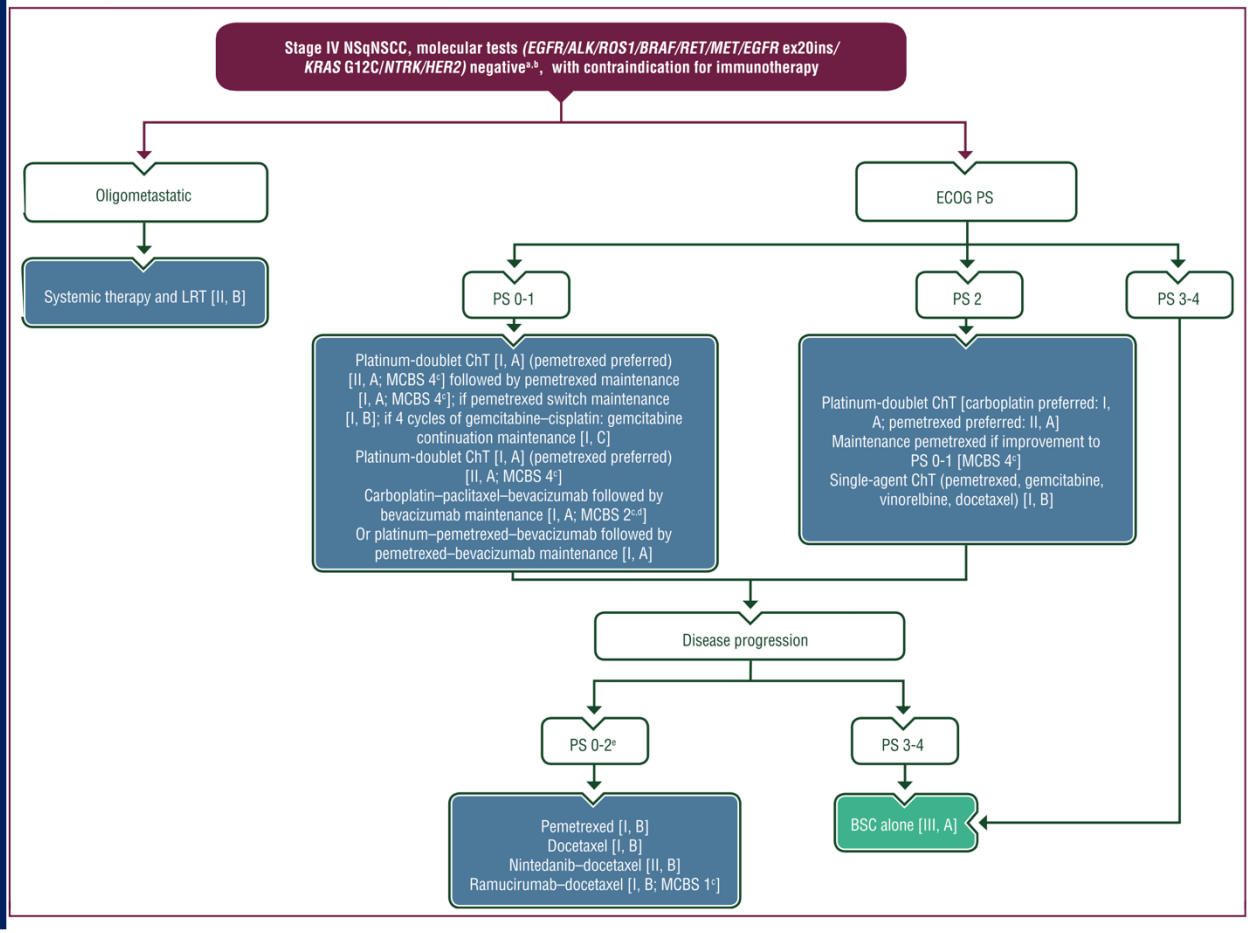
Increasing complexity and individualization of therapies

2023- Non-Oncogene-Addicted Metastatic NSCLC

ICI Eligible



ICI Ineligible

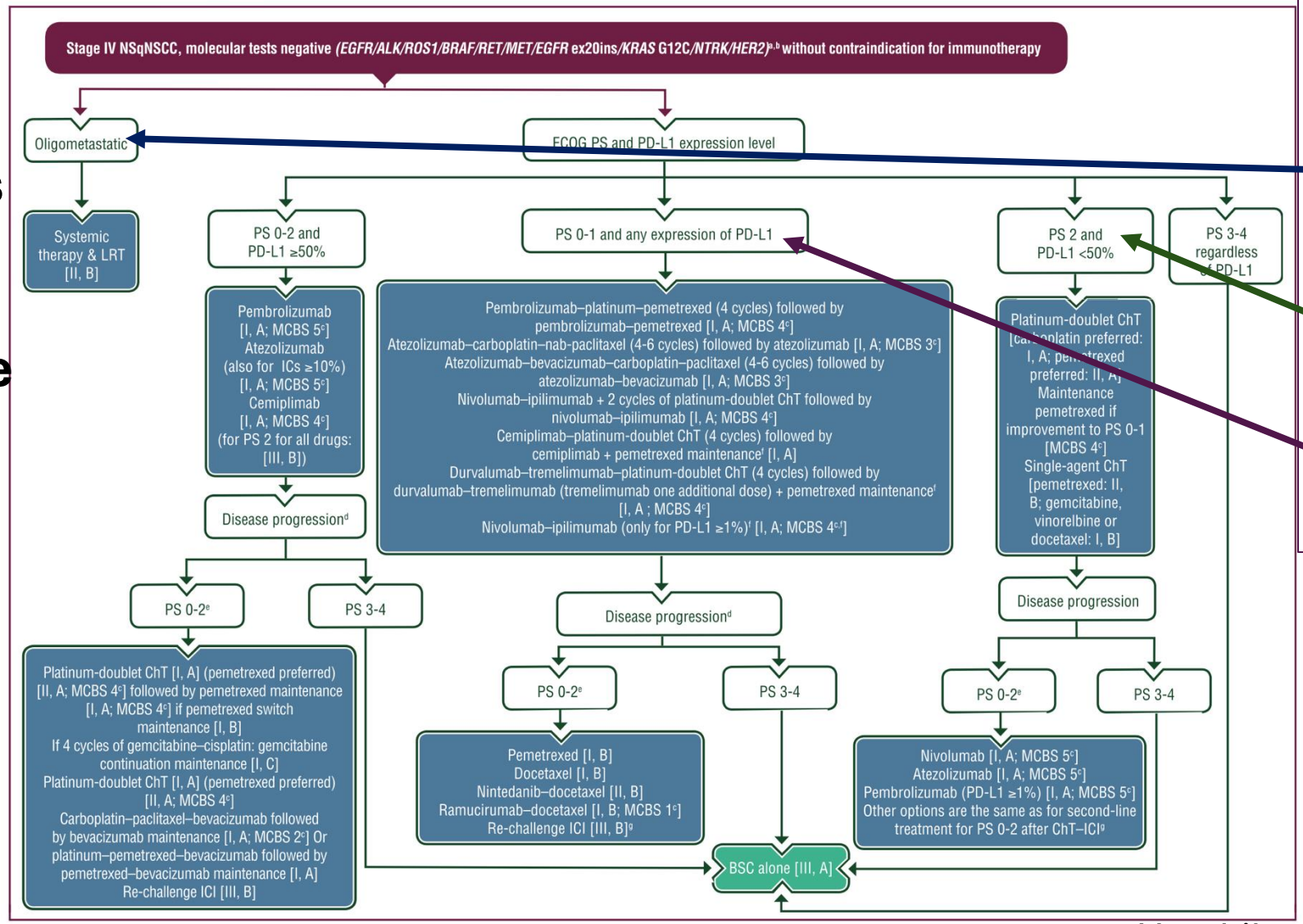


RUTGERS

Hendriks et al Ann Onc 2023

Increasing complexity and individualization of therapies

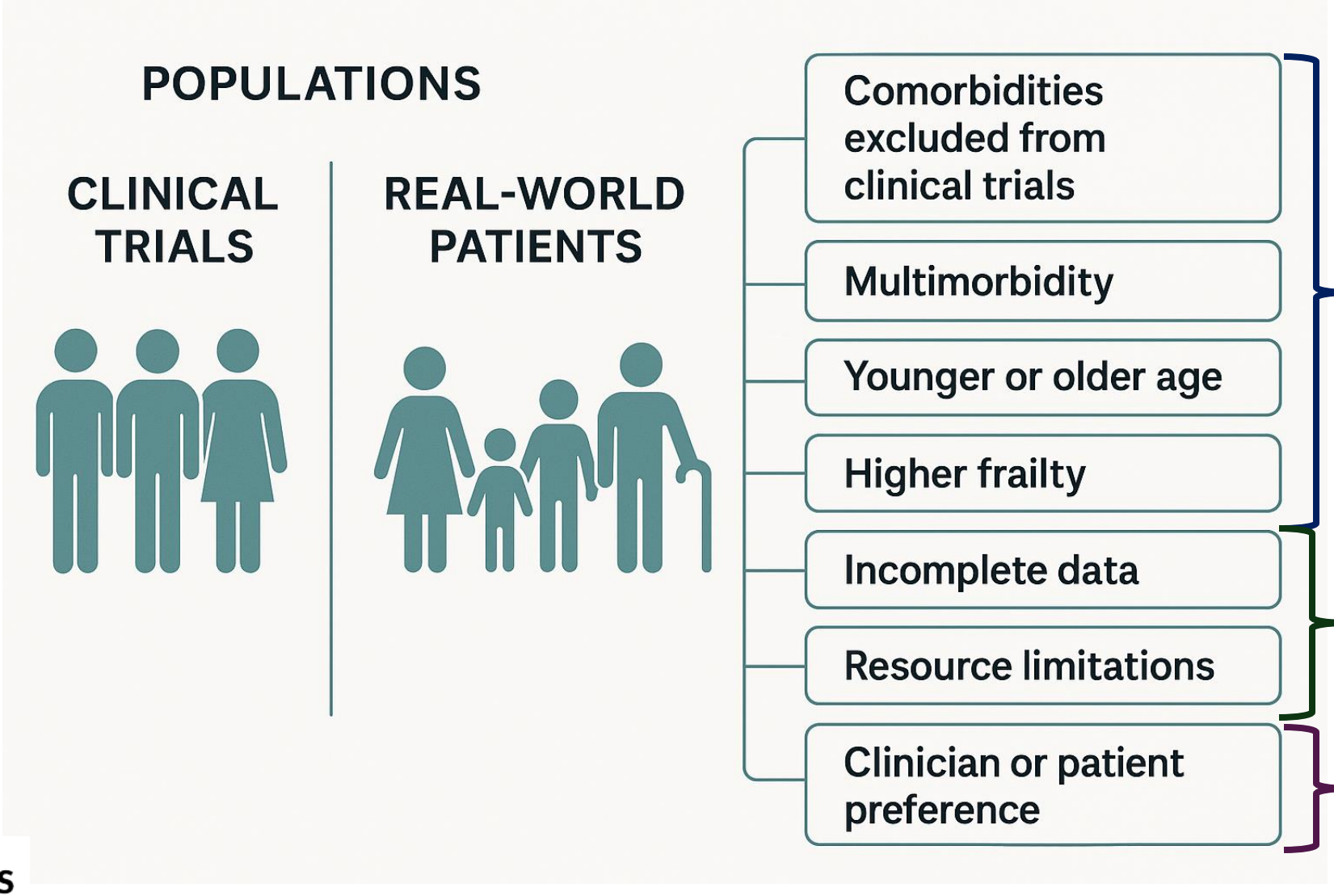
Treatment recommendations for ICI-eligible patients who are oncogene negative



Line of therapy choice based on the extent of disease progression, performance status, and %PDL1 expression

Hendriks et al Ann Onc 2023

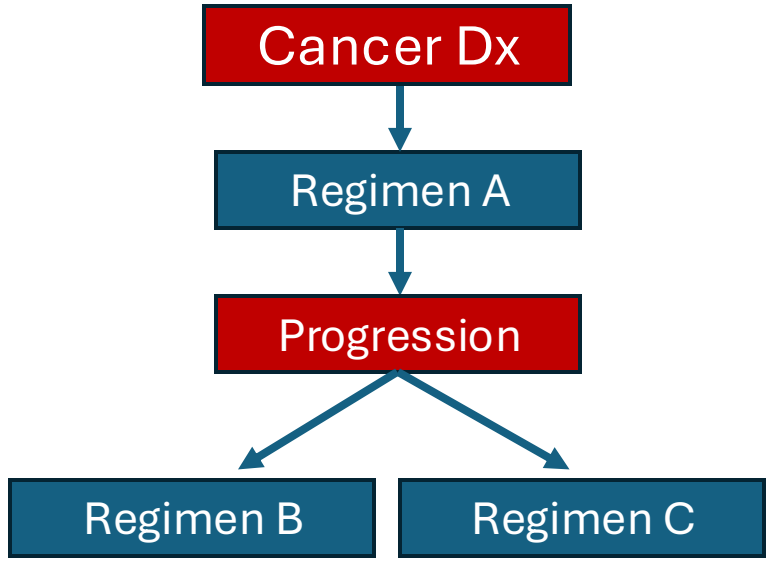
Clinical Practice Varies from Trials



RUTGERS

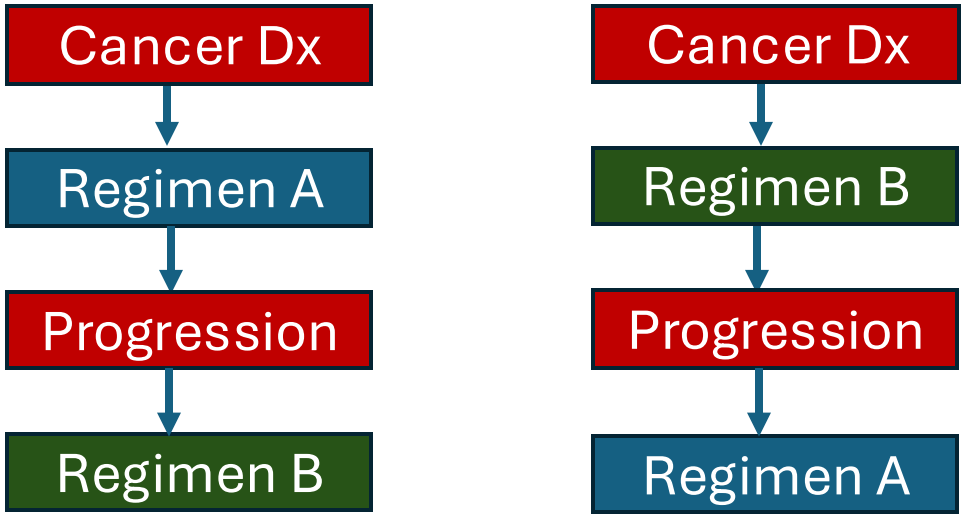
Variations in Care Enable Opportunities for Comparison

- After progression on treatment regimen A, should a patient receive treatment regimen B or C?
- Should the order of treatment regimens be A then B or B then A?
- Should drug B be initiated/continued and for how long following the completion of treatment regimen A?



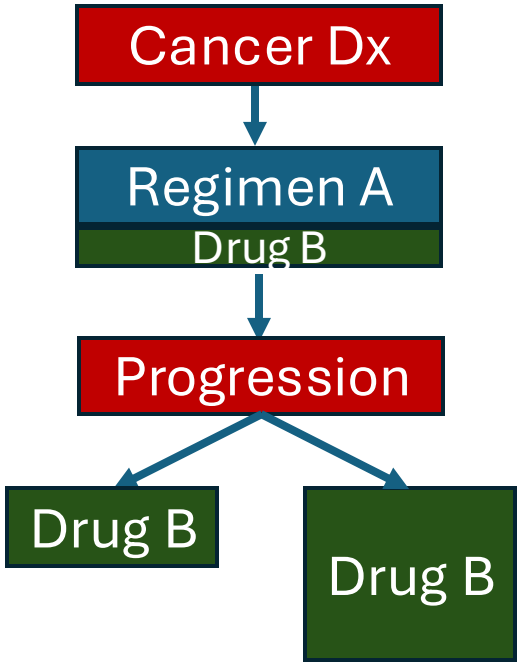
Variations in Care Enable Opportunities for Comparison

- After progression on treatment regimen A, should a patient receive treatment regimen B or C?
- Should the order of treatment regimens be A then B or B then A?
- Should drug B be initiated/continued and for how long following the completion of treatment regimen A?



Variations in Care Enable Opportunities for Comparison

- After progression on treatment regimen A, should a patient receive treatment regimen B or C?
- Should the order of treatment regimens be A then B or B then A?
- Should drug B be initiated/continued and for how long following the completion of treatment regimen A?



Lines of Therapy Concept is Imperfect and Not Standardized in the Clinical Setting

- **Areas of agreement**
  - Predicts Prognosis
  - No universal definition
  - Progression is a new LOT
  - Intraclass change = same LOT
- **Areas of uncertainty**
  - Localized/curative vs. metastatic/palliative
  - Treatment breaks
  - Addition/continuation of treatments
  - Change due to adverse effect

RUTGERS

Falchetto BMC Research Notes (2024); Falchetto BMC Cancer (2025)

Real World Data to Identify Line of Therapy- Varying Data Points and Populations

Electronic Health Records (EHR)

Claims Data

Cancer Registry

45 M- Initial Diagnosis **Caring-For-Your-Community Health System**

PCP

DM – A1c 6.5 – Metformin/GLP1
HTN – BP (130s/80s) – Lisinopril
Overweight– BMI 28
Screening Colonoscopy

Gastroenterology

- **Pathologist**
- Malignant CRC- Stage 2
- **Radiologist**

Central Cancer Registry

Cancer	CRC
Stage	2
Intent	Curative
Surgery	Yes
Chemotherapy	Yes
Immunotherapy	No
Hormonal therapy	No
Radiation therapy	No

Caring-For-Your-Cancer Health System

No mutations
Curative intent

Surg Onc — Partial Colectomy

Med Onc — CAPEOX
- Capecitabine
- Oxaliplatin

45 M- Initial Diagnosis **Caring-For-Your-Community Health System**

EHR RWD

PCP

DM – A1c 6.5 – Metformin/GLP1
HTN – BP (130s/80s) – Lisinopril
Overweight– BMI 28
Screening Colonoscopy

Gastroenterology

Pathologist

Malignant CRC- Stage 2

Radiologist

Community System EHR: Cancer treatments may not be present; details about non-cancer conditions, including health concerns leading to cancer

Central Cancer Registry

Cancer	CRC
Stage	2
Intent	Curative
Surgery	Yes
Chemotherapy	Yes
Immunotherapy	No
Hormonal therapy	No
Radiation therapy	No

Caring-For-Your-Cancer Health System

No mutations
Curative intent

Colectomy

CAPEOX
- Capecitabine
- Oxaliplatin

45 M- Initial Diagnosis

EHR RWD

Caring-For-Your-Community Health System

DM – A1c 6.5 – Metformin/GLP1
HTN – BP (130s/80s) – Lisinopril
Overweight– BMI 28
Screening Colonoscopy

Malignant CRC- Stage 2

Central Cancer Registry

Cancer	CRC
Stage	2
Intent	Curative
Surgery	Yes
Chemotherapy	Yes
Immunotherapy	No
Hormonal therapy	No
Radiation therapy	No

Caring-For-Your-Cancer Health System

No mutations
Curative intent

Surg Onc — Colectomy

Med Onc — CAPEOX
- Capecitabine
- Oxaliplatin

Cancer System EHR: Treatment present; nuanced details about non-cancer treatment less documented

45 M- Initial Diagnosis

Caring-For-Your-Community Health System

Claims RWD

PCP

DM – A1c 6.5 – Metformin/GLP1
HTN – BP (130s/80s) – Lisinopril
Overweight – BMI 28
Screening Colonoscopy

Gastroenterology

Pathologist

Malignant CRC - Stage 2

Radiologist

Care across the healthcare systems are present, though missing some aspects of clinical care (e.g, vitals, lab values, mutations, treatment intent)

Central Cancer Registry

Cancer	CRC
Stage	2
Intent	Curative
Surgery	Yes
Chemotherapy	Yes
Immunotherapy	No
Hormonal therapy	No
Radiation therapy	No

Caring-For-Your-Cancer Health System

No mutations
Curative intent

Surg Onc — Colectomy

Med Onc — CAPEOX
- Capecitabine
- Oxaliplatin

45 M- Initial Diagnosis

Caring-For-Your-Community Health System

Registry RWD

PCP

DM – A1c 6.5 – Metformin/GLP1
HTN – BP (130s/80s) – Lisinopril
Overweight– BMI 28
Screening Colonoscopy

Gastroenterology

Pathologist

Radiologist

Patient-level data that has <u>standardized</u> collection across the population for <u>incident cancer diagnosis</u>; less detailed healthcare data, further disease progression/treatment may not be documented

Central Cancer Registry

Cancer	CRC
Stage	2
Intent	Curative
Surgery	Yes
Chemotherapy	Yes
Immunotherapy	No
Hormonal therapy	No
Radiation therapy	No

Caring-For-Your-Cancer Health System

Surg Onc

Colectomy

Med Onc

CAPEOX
- Capecitabine
- Oxaliplatin

Summary & Interpretation of Example

- No RWD data source provides a comprehensive picture of the care for every patient diagnosed and treated for cancer
- Investigators utilizing RWD must make reasonable assumptions in the choice of RWD and be attentive in addressing and relaying potential misclassifications and biases

Identifying LOT for Metastatic Disease Using RWD- An ISPE Cancer SIG Initiative

- ISPE Cancer SIG initiative to review RWD literature on initiation of LOT for breast, lung, or CRC metastatic disease
- Among 273 original studies screened, 24 studies described algorithms to identify a new LOT among patients with metastatic disease
- Twenty-three (96%) studies required a *metastasis-free lookback period* followed by an incident metastatic disease diagnosis plus new systemic anti-cancer treatment
- Only three (12.5%) of these studies conducted validation studies

Standardization of LOT

- Proposing a new framework and standardized language
  - LOT N (CLoT + PLoT)
  - Clinical Progression of Disease (cPD) vs. PD

BJC British Journal of Cancer www.nature.com/bjc

PERSPECTIVE

Determining lines of therapy in patients with solid cancers: a proposed new systematic and comprehensive framework

Kamal S. Saini [1,2] and Chris Twelves [3]

RUTGERS

Saini KS, Twelves C. Br J Cancer (2021)

Standardization of LOT

- Proposing a new framework and standardized language

- ESMO Adaptation of Line of Systemic Therapy (EnLiST)

EnLiST – ESMO Adaptation of Line of Systemic Therapy

A project seeking to open a dialogue to facilitate the treatment of neoplasia and associated clinical research by proposing a systematic and comprehensive framework to determine Line of systemic Therapy uniformly across solid malignancies.

RUTGERS

Saini KS, Twelves C. Br J Cancer (2021); EnLiST- ESMO Adaptation of Lines of Therapy: https://www.esmo.org/guidelines/enlist-esmo-adaptation-of-line-of-systemic-therapy/enlist-esmo-adaptation-of-line-of-systemic-therapy

Integration of Real World Data Across Europe

- DARWIN EU
  - **D**ata **A**nalysis and **R**eal **W**orld **I**ntegration **N**etwork
  - Collaboration between the European Medicines Agency and the European Medicines Regulatory Network
  - Establishes a coordination center to provide RWE by utilizing RWD from health systems across the European Union
  - At least two initiatives utilize the concept of LOT

Initiatives to Standardize and Utilize RWD LOT Across Data

- DARWIN-EU
  - Overall survival in patients with advanced or **metastatic non-small cell lung cancer** treated with selected immunotherapies as first line of treatment (EUPAS1000000112)

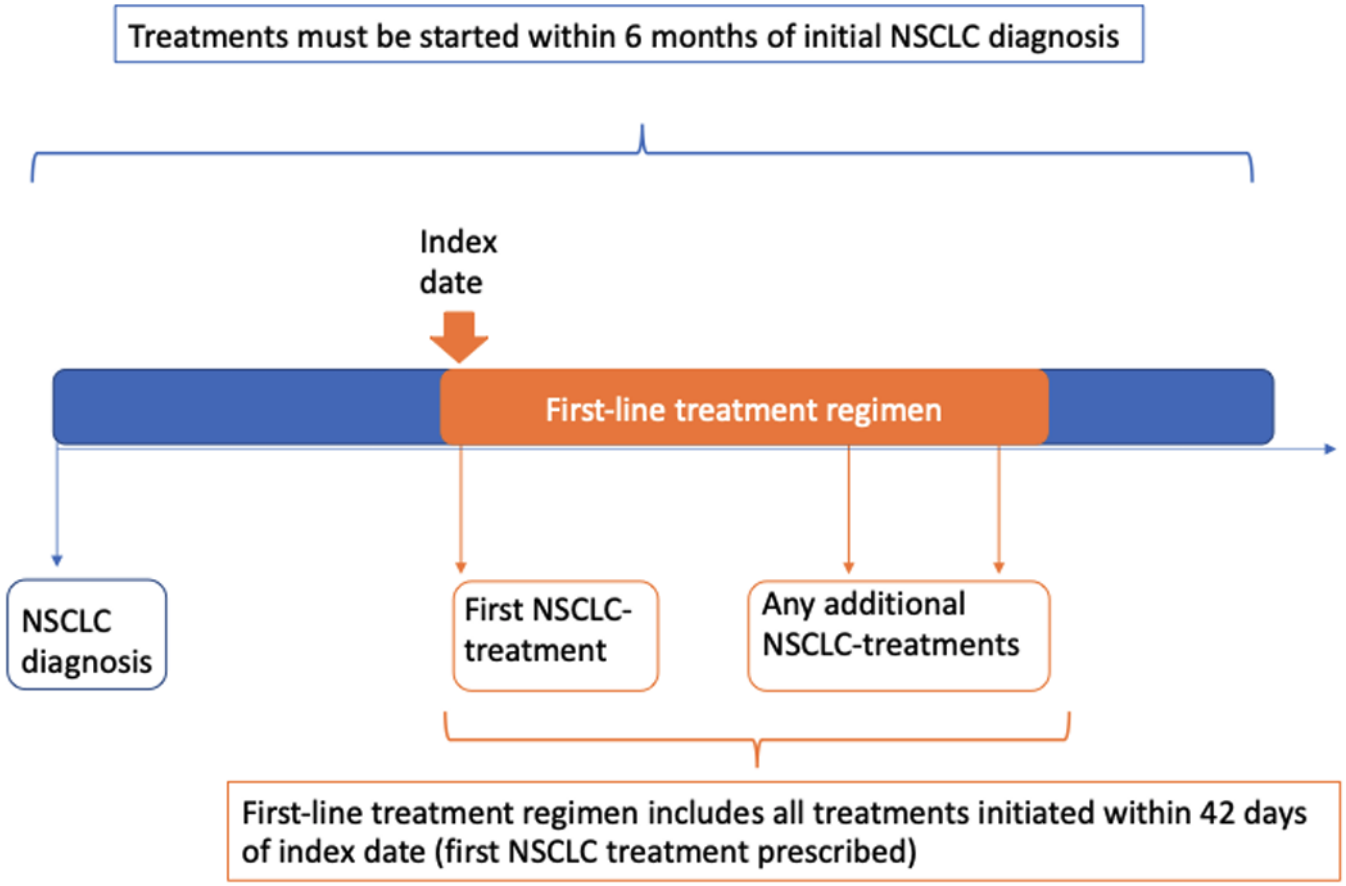


Figure 1. Timeline from NSCLC diagnosis, to index date, and first-line treatment definition.

Darwin EU: NSCLC- https://catalogues.ema.europa.eu/node/4013/administrative-details

Initiatives to Standardize and Utilize RWD LOT Across Data

- DARWIN-EU
  - **Multiple myeloma**: patient characterisation, treatments, and survival in the period 2012–2024 (EUPAS1000000757)

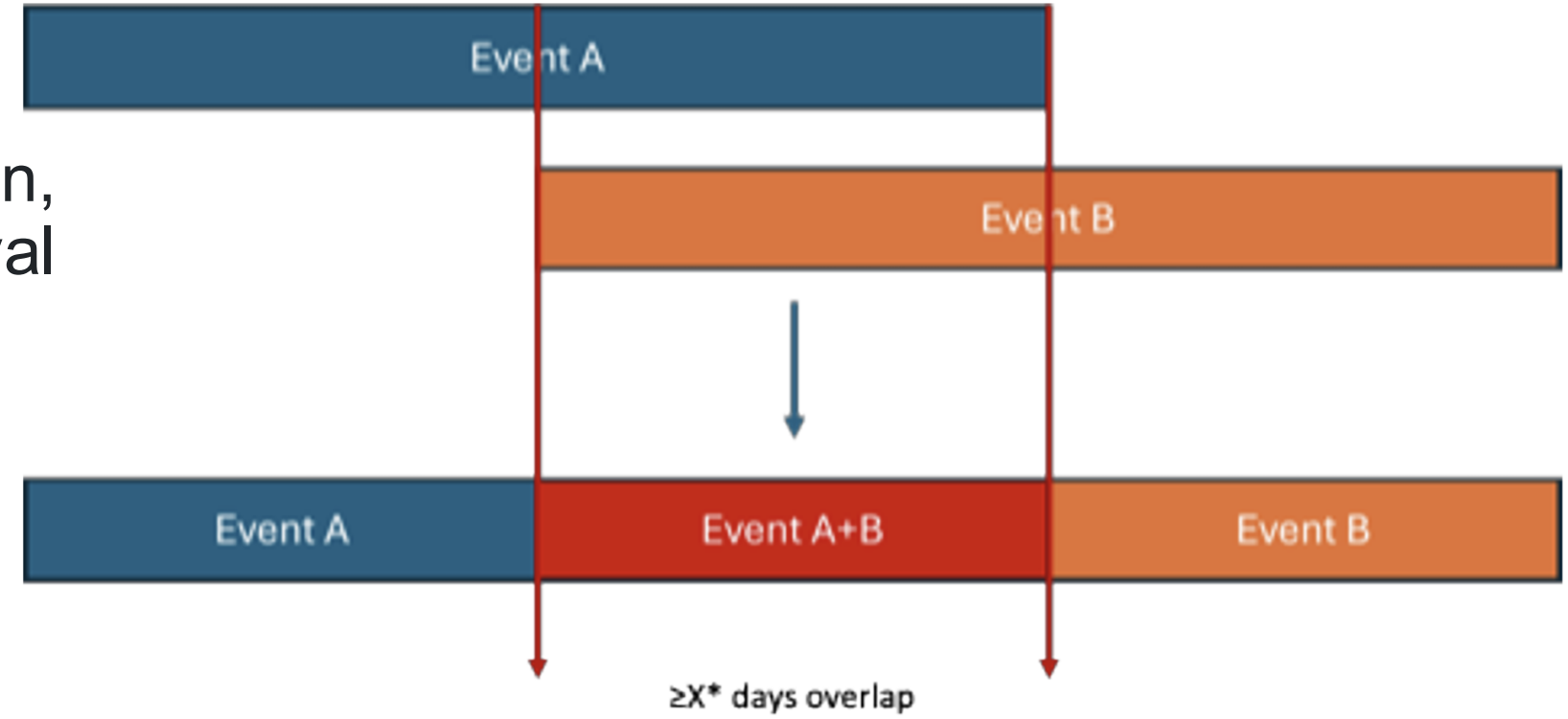


Figure 2. Graphical depiction of treatment combination definition.

*minimum number of days overlap to be decided after results of running the R package *DrugExposureDiagnostics*

Summary

- Use of systemic treatment and the concept of lines of therapy (LOT) in oncology have developed organically over time
  - Reflects advancements in cancer treatment and improving care to survivors
- The concept of LOT in the clinical setting is not yet standardized
- Identifying and differentiating between LOTs when using RWD is even more complex
- There are ongoing initiatives to use LOT in RWD to advance RWE

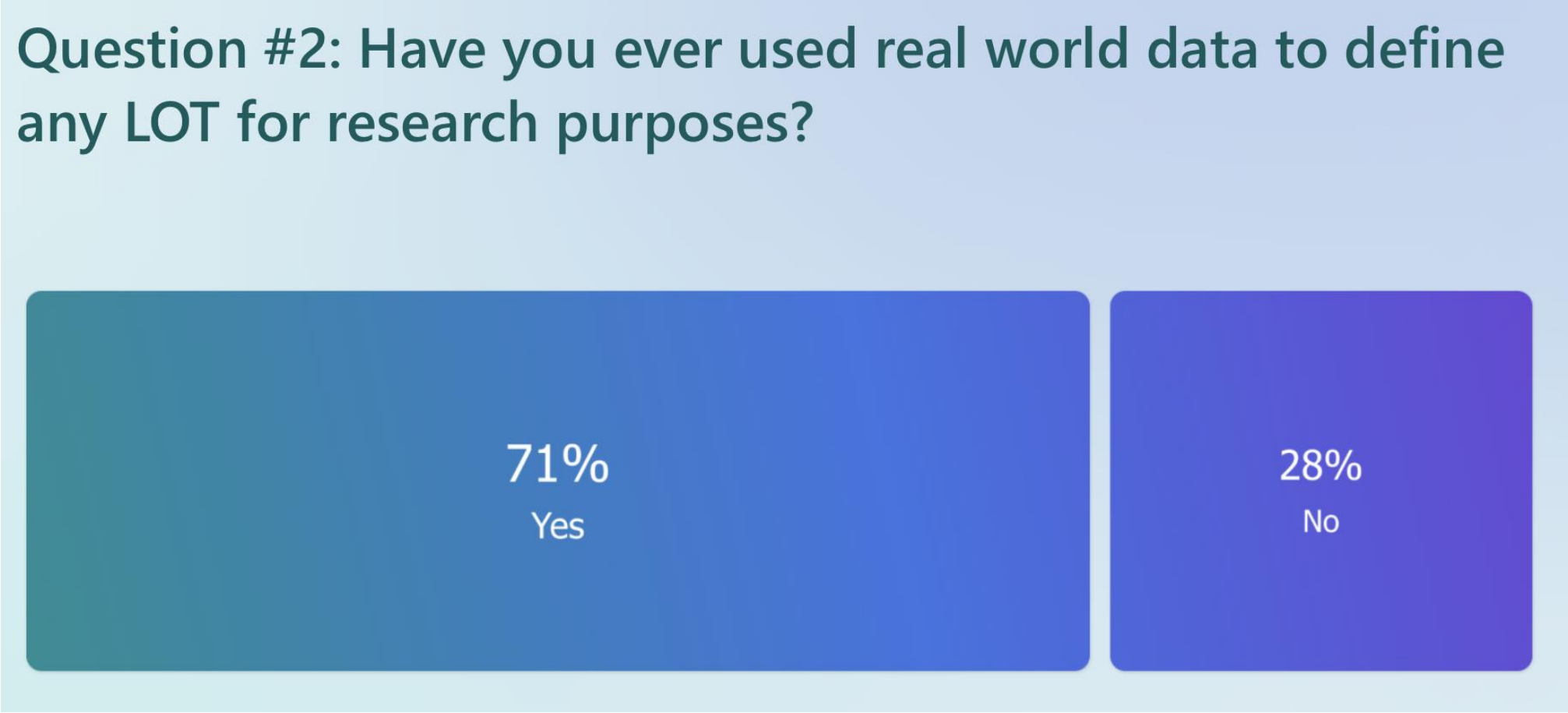
Poll Question #2

Have you ever used real world data to define any LOT for research purposes?

a) Yes

b) No

Among 101 responses...

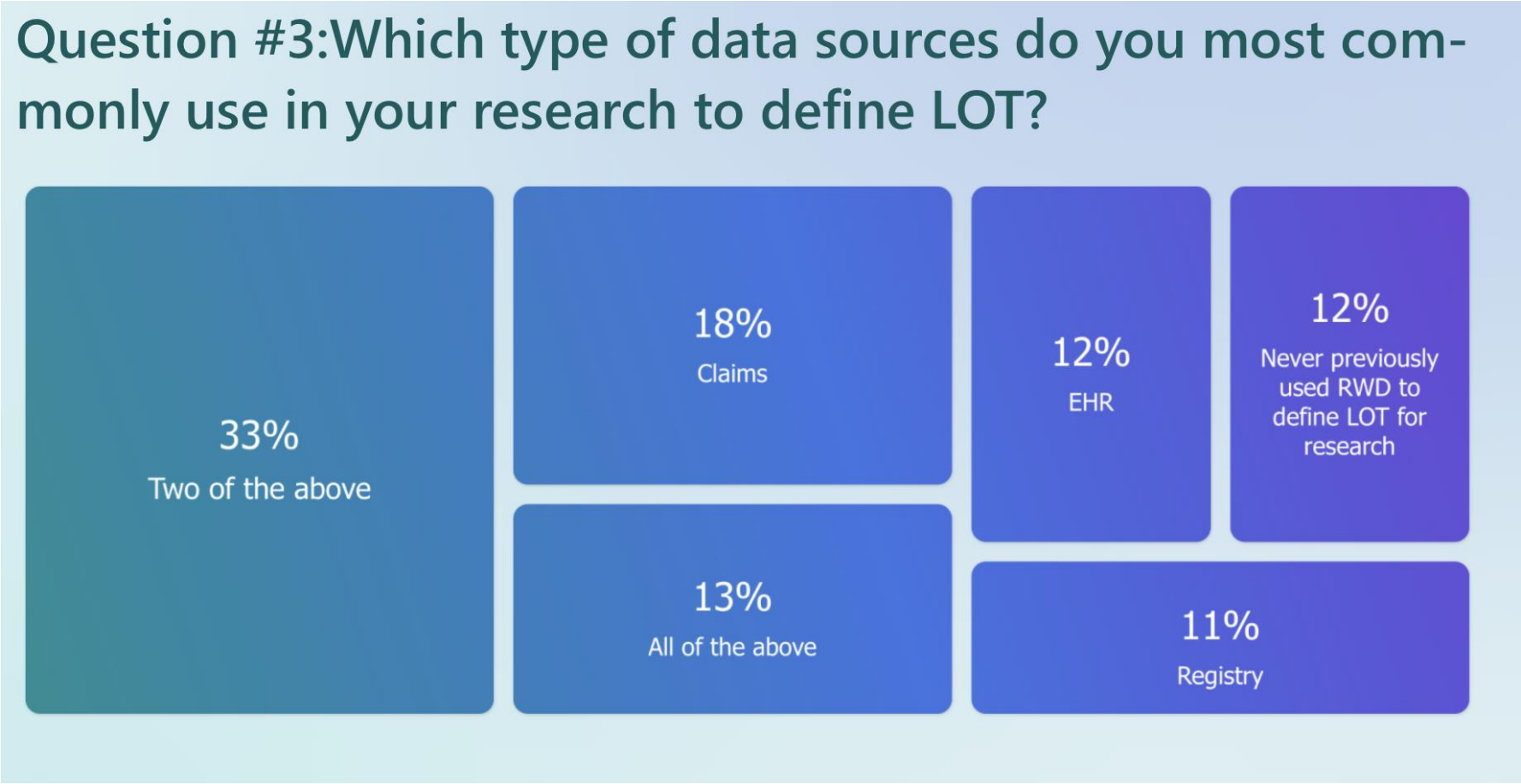


Poll Question #3

Which type of data sources do you most commonly use in your research to define LOT?

a) Claims
b) EHR
c) Registries
d) Two of the above
e) All of the above
f) Never previously used RWD to define LOT for research

Among 98 responses…



Lines of Therapy - Bridging the Gap between Clinical Practice & Real World Data

Arun Sujenthiran MD

Clinical Lead & Senior Medical Director
Flatiron Health International

Disclosures

- AS is employed by Flatiron Health and holds stock in Roche.
- Statements are my own and do not necessarily reflect my employer or support

Clinical Care & Lines of Therapy

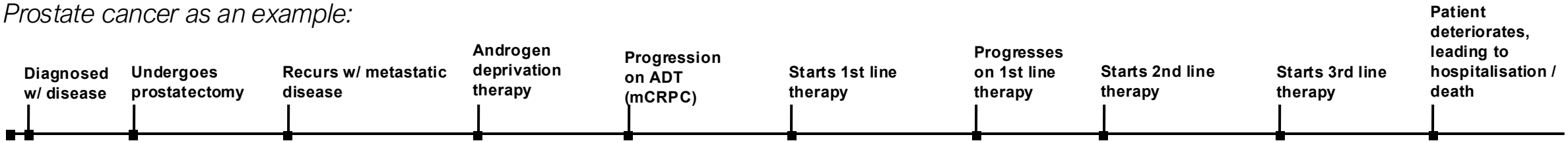
- **How do clinicians think about LOT?**

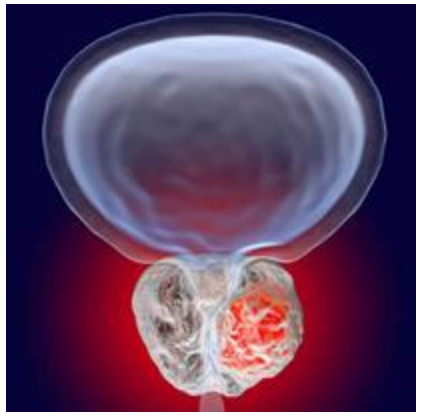
  “Sequence of treatment regimens a patient receives over time. Each "line" is essentially a different stage or round of treatment, typically started when the previous treatment stops working, and the cancer returns or progresses.”

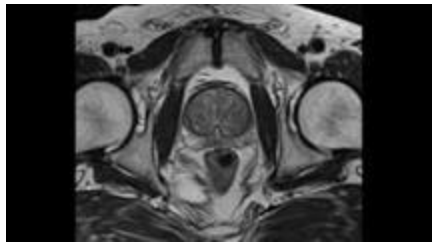
  - Referenced in Guidelines (National/Local/Oncology societies)
  - Oncology treatments are multi-modal & patient journeys are complex
  - **Patient-centred**

A cancer journey in a Health System

Prostate cancer as an example:

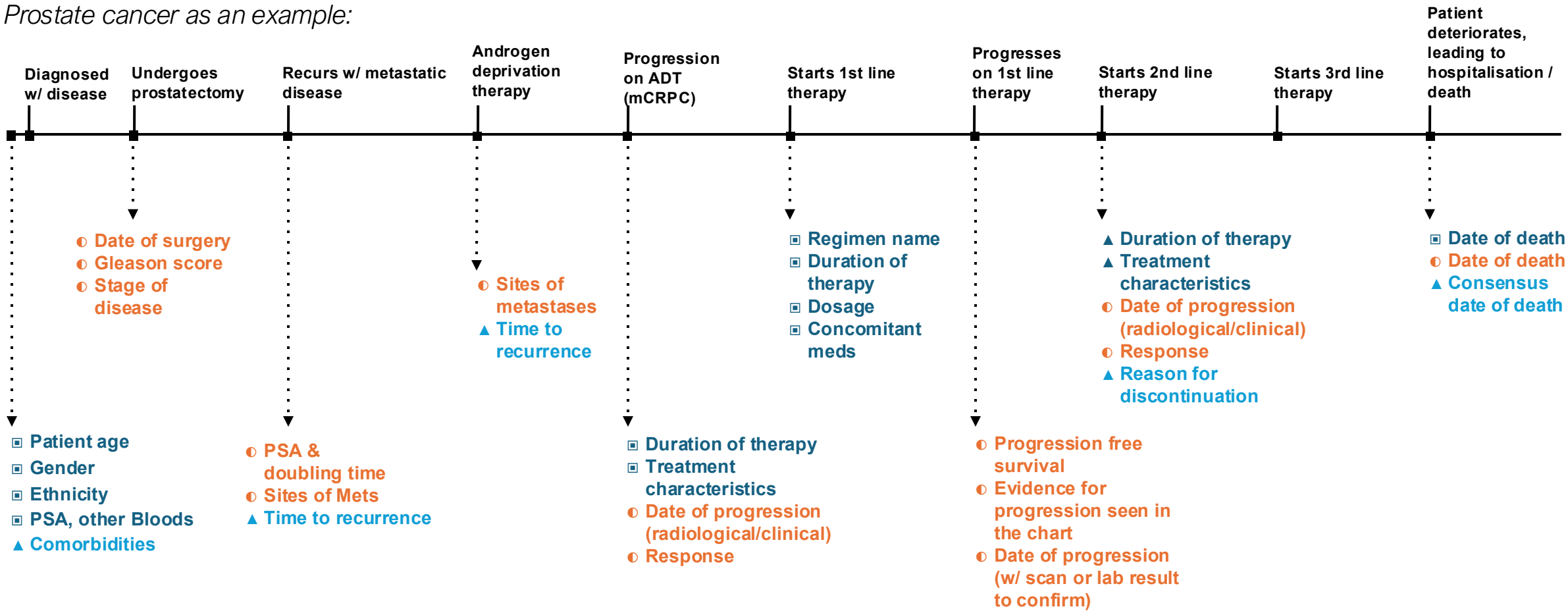






A cancer journey and Real World Data

Prostate cancer as an example:



flatiron

Legend: ▣ Structured EHR data ◐ Unstructured EHR data ▲Derived Data

Using RWD for LOT

RWD & LOT considerations

- **RWD sources** - Claims, EHR, Cancer Registries
- **Data Access** - Patient-level data vs Aggregate tables
- **Business LOT Rules & Logic**
- **Quality Assurance:** Underlying Data quality and LoT QA processes
- Use-cases

Questions from researchers & HTA/Regulatory bodies:

- How do treatments compare to current SOC in Line 1/2/3/etc?
- Can I match a study to IE criteria of an RCT for a particular line?
- Which Lines are there currently unmet needs and what are current outcomes?

How can we approach LOT rules within RWD?

Nine categories of rules are applied to group drug orders and administrations in order to create LOTs

1. Therapies eligible for inclusion in lines of therapy
2. Index date
3. Start of 1L therapy
4. Definition of a line of therapy
5. Maintenance
6. Gap in therapy
7. Changes permitted within a line of therapy
8. Changes not permitted within a line of therapy
9. Line of therapy end date

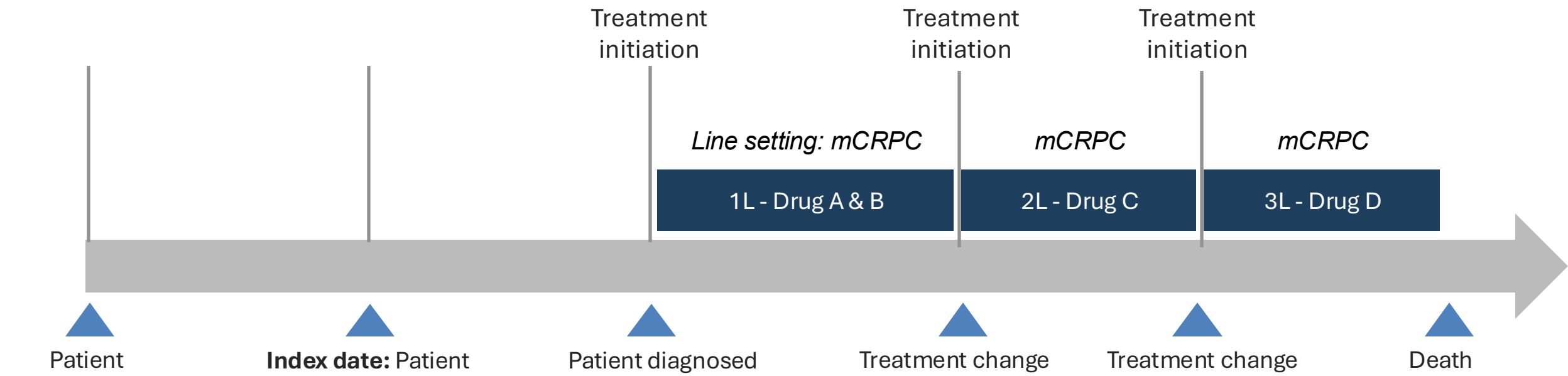
Key variables in LOT for Oncology

Line of Therapy (LOT) applies a set of disease-specific rules to summarize the sequence of anticancer therapies based on structured and abstracted treatment information (drug_name, start_date, end_date etc).

- **Line name** - the list of drugs/regimens given as part of a single line (e.g. FOLFOX + Bevacizumab)
- **Line number** - e.g. 1L, 2L
- **Line setting** - e.g. NEOADJUVANT, ADJUVANT, ADVANCED, LOCOREGIONAL, METASTATIC, mCRPC, nmCRPC, mHSPC
- **Start date & End date**
- **Is maintenance therapy** - Yes/No for whether therapy is given as maintenance for the main line treatment

LOT Example: metastatic Prostate Cancer

- Example of a LOT, with eligible therapies being captured as lines **beginning at CRPC date**
- The index date is the **first of either metastatic diagnosis date or CRPC date**



flatiron

Additional Complexities

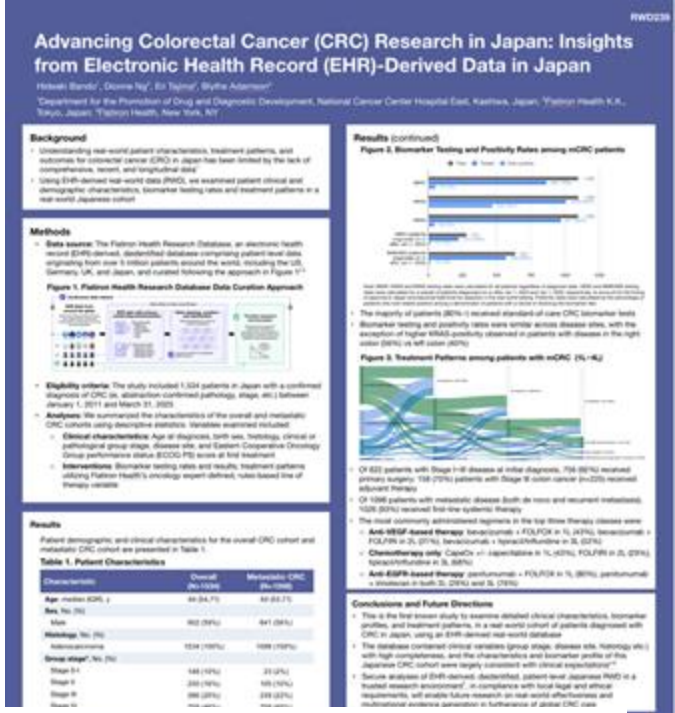
- **Source data**
  - LOT quality depends on **input** data - often messy, imperfect & across clinical systems
  - Structured data: how reliable are orders & admins? Can we leverage cancellation status? Drug names need to be harmonised upstream
  - Unstructured data: are end dates well documented?

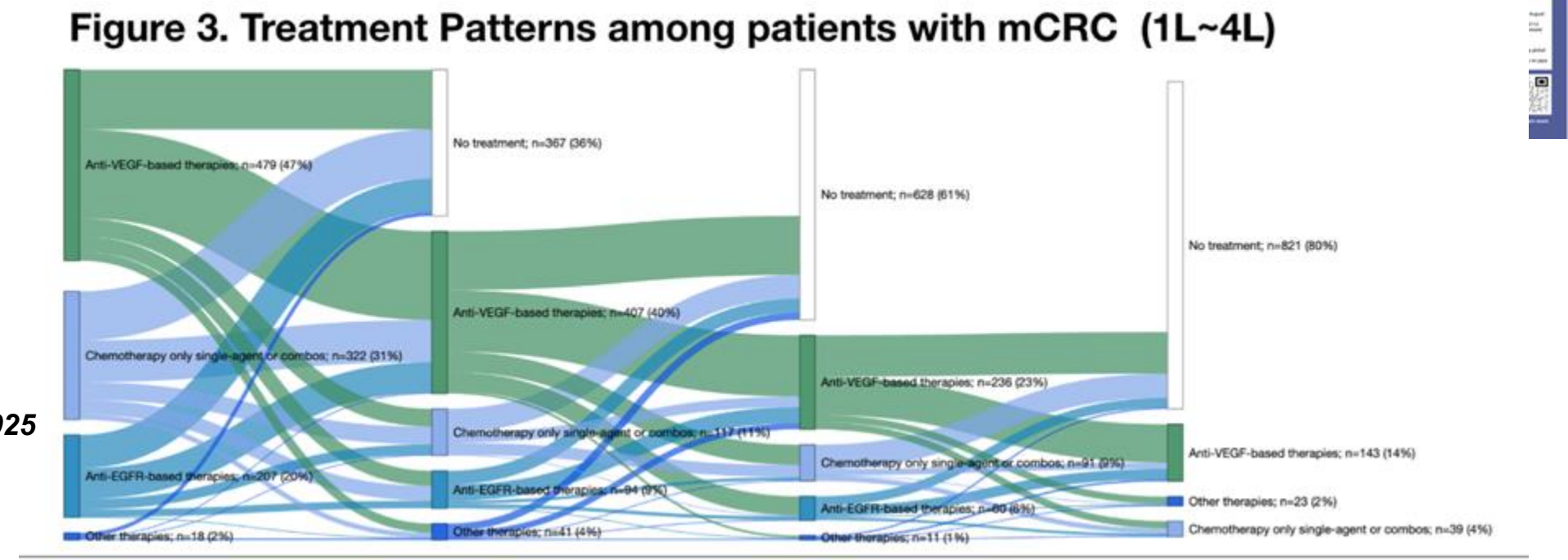
- **Quality Assurance**
  - Evaluation of LoT sequences that not in keeping with local clinical expectations
  - Patient-level data access important to validate
  - Disease-specific validation

- **Rapidly advancing medical landscape**
  - Newly approved anti-cancer therapies
  - Anti-cancer therapies shifting from metastatic to earlier stage disease
  - Multi-modal therapies

LOT across borders

- Accounting for in-country nuance, while maintaining a consistent set of business rules
  - Are there drugs only approved in certain countries? Are guidelines different?
  - Do we choose *different* input data source per country? In-country pre-processing & local clinical knowledge are Critical!





Presented at ISPOR RWE Summit 2025

flatiron

Takeaway Messages

- LOT is a key clinical consideration but is only one part of the patient journey and experience
- LOT is dynamic and a critical RWD variable enabling multiple use-cases.
- Implementing LOT globally is possible but complex, requiring cross-functional expertise & local health system knowledge.
- There are opportunities to standardise approaches and provide a framework for relevant stakeholders.

Regulatory Perspective

Denise Umuhire

European Medicines Agency

Health Technology Assessment Perspective

Karen Facey

RWE4Decisions

RWE4Decisions REAL WORLD EVIDENCE

Discussion

- **Moderator:** Seyed Hamidreza Mahmoudpour, Merck Healthcare KGaA, Germany

- **Panelists**:
  - Benjamin Bates, Rutgers University, United States
  - Arun Sujenthiran, Flatiron Health, UK
  - Denise Umuhire, European Medicines Agency, Netherlands
  - Karen Facey, RWE4Decisions, UK