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Rare Cancers, More Common Than You Think:

Addressing the Challenges, Opportunities and Methodologies in Studying Small Populations

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Ontada®, a McKesson business dedicated to oncology, generates real-world data (RWD) and real-world evidence (RWE) and provides clinical education and provider technology to inform and improve cancer care.

Agenda

- Background & Introduction
- Challenges and opportunities associated with studying rare cancers
- Considerations for analyzing real-world data of rare cancer patients to generate robust real-world evidence and make reliable inferences

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Background and Introduction

Nicholas Robert, MD

Paradigm shift:

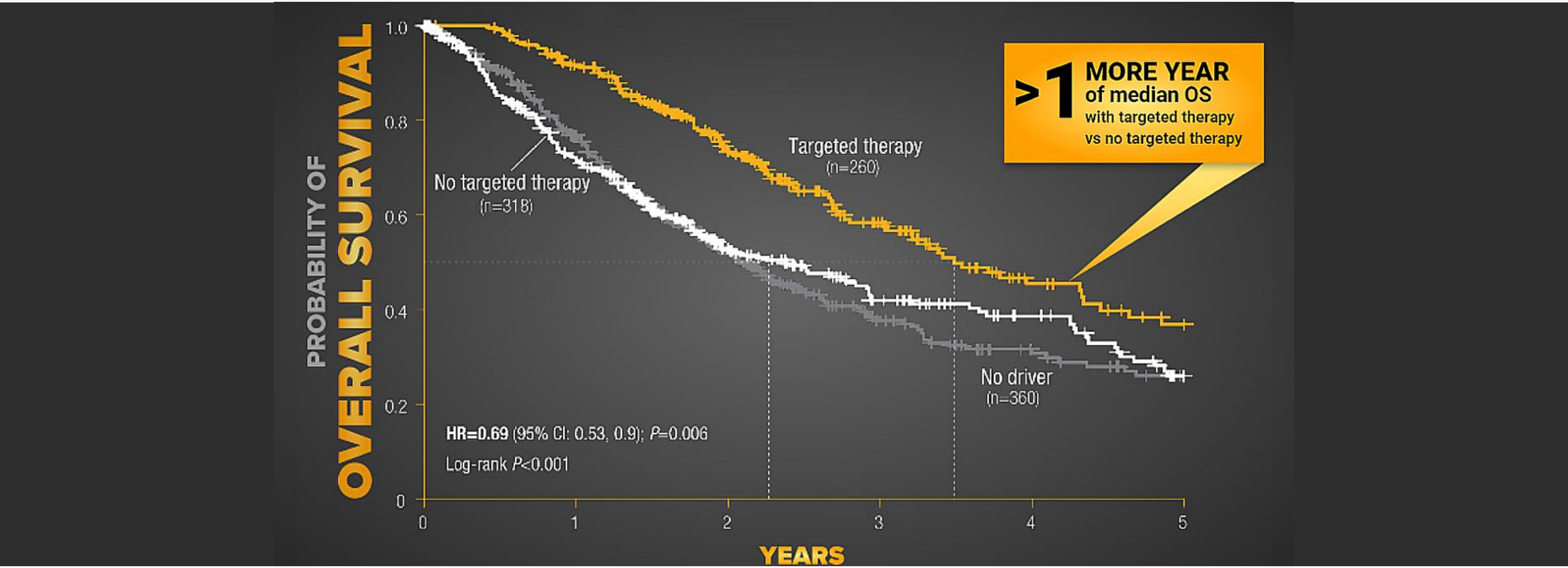
No longer can we view cancer as a singular disease entity; has transformed into a complex tapestry of rare biomarker-defined subtypes

Driven by advancements in genomic profiling and molecular diagnostics, allowing us to identify distinct genetic mutations, gene fusions, and altered protein expressions, within individual tumors that drive tumor growth

Advent of actionable biomarkers has shifted our thinking of therapeutic areas

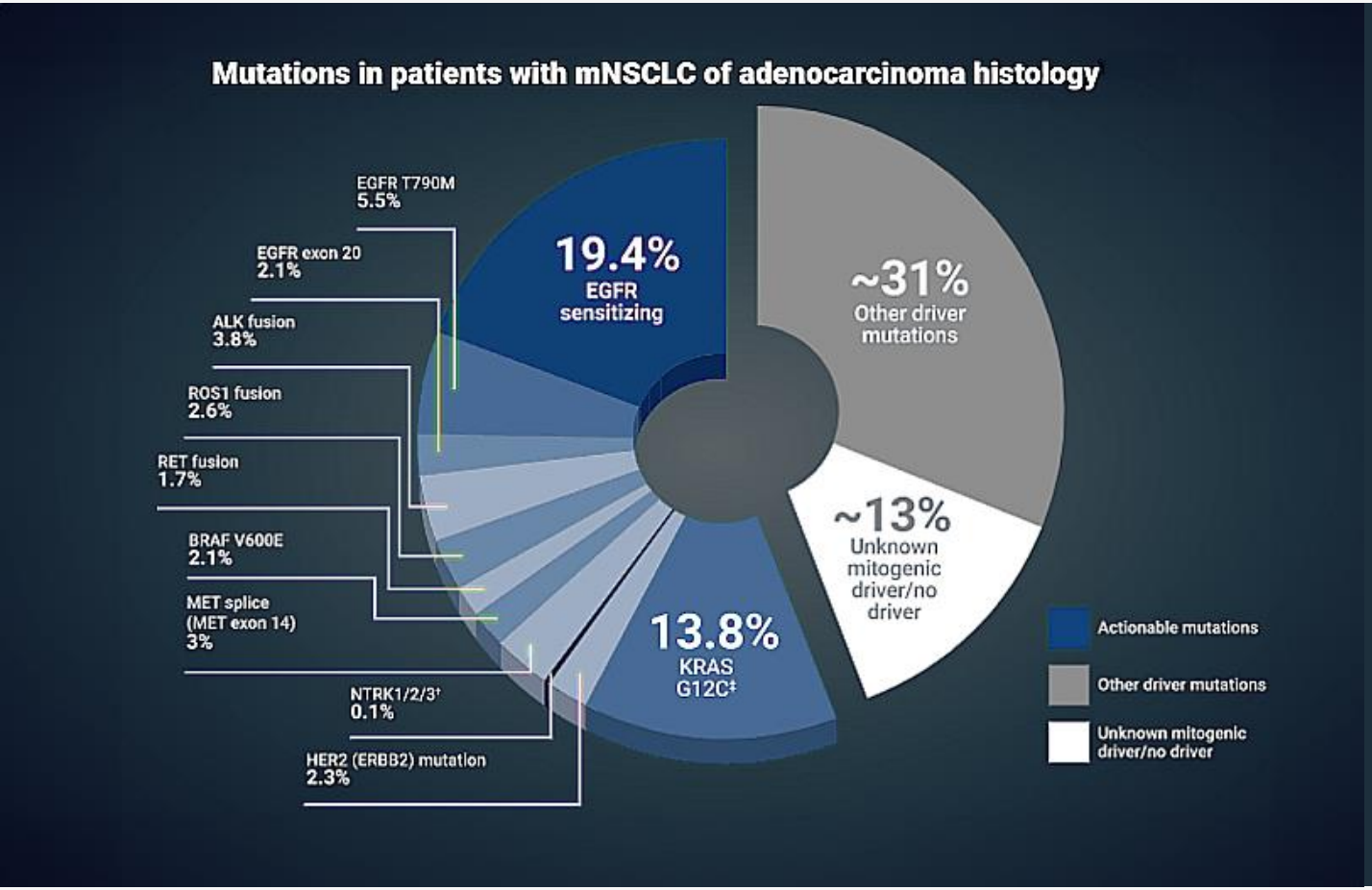
Lung cancer is a prime example: lung cancer is no longer SCLC and NSCLC but instead is becoming a group of biomarker-defined cancers with smaller and smaller subpopulations that require different treatments

Targeted therapy significantly improved overall survival



Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA. 2014;311(19):1998-2006.

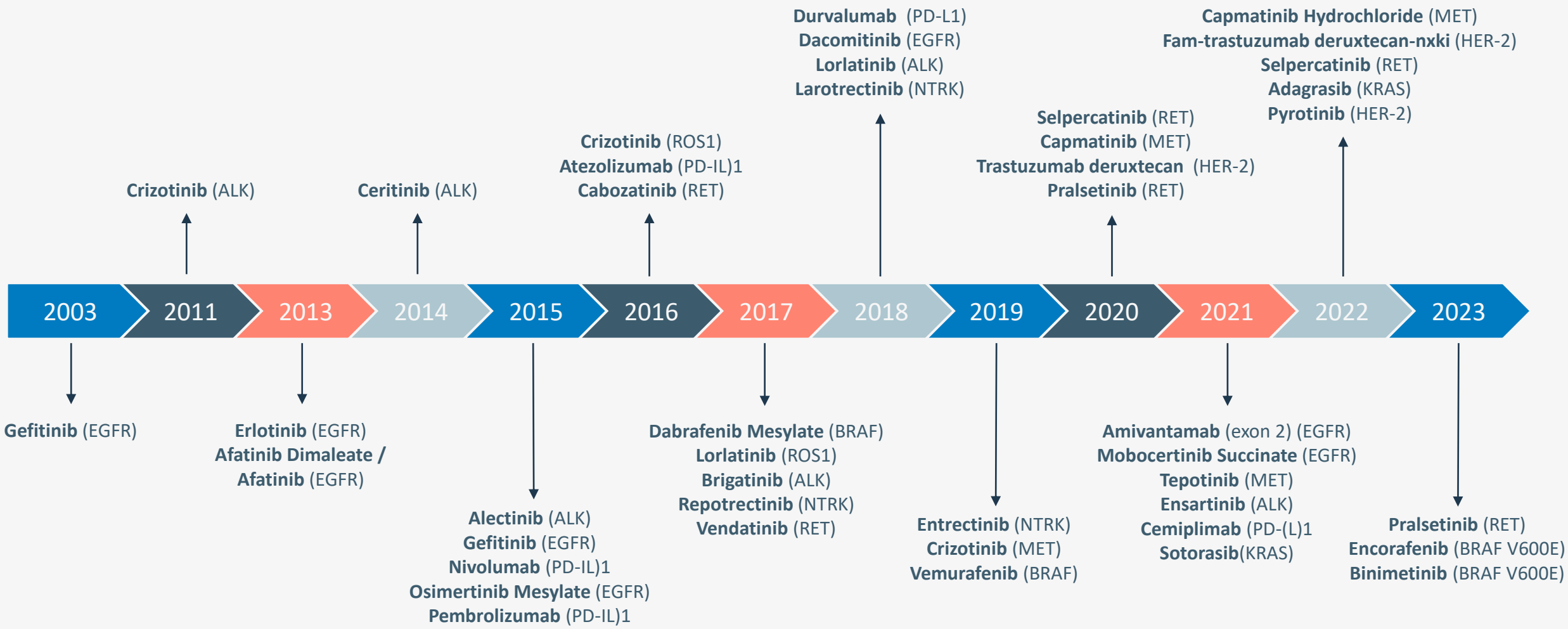
Treatment starts with knowing the driver of disease



Jordan EJ, Kim HR, Arcila ME, et al, Prospective comprehensive molecular characterization of lung adenocarcinomas for efficient patient matching to approved and emerging therapies. *Cancer Discov.* 2017;7(6):596-609. Gatalica Z, Xiu J, Swensen J, Vranic S. Molecular characterization of cancers with NTRK gene fusions. *Mod Pathol.* 2019;32(1):147-153. Nassar AH, Adib E, Kwiatkowski DJ. Distribution of $KRAS^{G12C}$ somatic mutations across race, sex, and cancer type [correspondence]. *N Engl J Med.* 2021;384(2):185-187.

Timeline of biomarker-targeted therapies

Since 2003, more than 40 targeted therapies have been developed based on biomarkers



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Challenges and Opportunities Associated with Studying Rare Cancers

Amy K. O'Sullivan, PhD

Implications of Precision Medicine in Oncology Across the Lifecycle

The shift to biomarker-defined subtypes of cancers has important implications for drug development, patient care, and real-world research

It has meant that large patient populations defined by tumor type are now much smaller, further categorized by specific biomarker within the tumor

Areas of challenges and opportunities:

- Drug development and clinical trials
- Cancer screening and early diagnosis
- Disease classification for treatment selection and prognosis
- Treatment outcomes

In addition to the clinical implications, there are significant implications for real-world research as well

Implications of Precision Medicine in Oncology Across the Lifecycle

	Clinical development	Cancer screening & early diagnosis	Treatment selection	Treatment outcomes
Opportunities	• Supports identification of specific genetic biomarkers associated with a disease • Enables **development of targeted therapies** designed for individuals with specific biomarkers • Clinical trials can **improve patient selection** for better treatment response and can enable early detection of treatment resistance	• Allows for identification of specific biomarkers for early-stage cancers, leading to **early detection** • Enables **targeted screening strategies**, can assess individual's genetic predisposition to developing certain types of cancer • Identify individuals who may benefit from **targeted prevention strategies** • Led to **development of liquid biopsies**, a non-invasive, repeatable method for cancer screening and monitoring	• Allows physicians to select therapies that are **more likely to be effective** for a particular patient--> better outcomes • Enables **identification of specific subgroups** who are more likely to respond to a particular treatment (avoids unnecessary treatments, potentially improves outcomes) • Allows for **identification of combination therapies** that target multiple pathways or targets simultaneously; potentially improves outcomes	• Precision medicine is shown to **improve overall patient outcomes** relative to standard of care
Challenges	• **Requires finding patients** with specific biomarkers, making patient recruitment and enrollment challenging and time consuming • Small patient populations can make **inferences difficult** • **Ethical considerations** such as privacy, data sharing, and informed consent	• Access to comprehensive genomic testing **may be limited** in certain geographic areas or subpopulations, leading to equity issues • Genomic testing is **costly** and not always reimbursed, limiting broad accessibility	• Not all cancers have actionable targets or biomarkers that can guide treatment decisions; research efforts are needed to find new targets • Targeted treatment selection only possible **if the patient is tested**; physician needs to wait for test results to determine best treatment option	• Tumors can be **genetically heterogeneous**; targeting a single mutation may not be sufficient to eradicate all tumor cells. • Despite initial responses to targeted therapies, many cancers develop **resistance** over time.

Implications of Precision Medicine in Oncology to Real-World Research

Real-World Research of precision medicine is also associated with opportunities and challenges due to smaller subpopulations

Challenges associated with small patient populations

- **Limited generalizability**
- **Limited statistical power**
- **Potential for bias and confounding**
- **Ethical and privacy concerns**

Increased Interest in Real-World Research on Rare Cancers

Leveraging Real-World Data to Investigate the Natural History of Rare Cancers Treated in the US Community Oncology Setting to Provide Clinical Context to Inform Future Research | FDA

Despite the challenges associated with studying rare cancers, it is recognized that understanding the natural history, clinical course and treatment outcomes associated with rare cancers is important, as they now represent up to **20% of all cancers** (American Cancer Society)

As one example, recently the FDA awarded a study to investigate the natural history of rare cancers treated in the US Community Oncology Setting

For 10 rare cancers, the study will evaluate patient and clinical characteristics, treatment patterns, long-term clinical outcomes, and survival following diagnosis

Findings from the study will facilitate a better understanding of oncology patient care in the community setting for rare cancers and may inform trial design to better study possible treatments for rare cancers

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Statistical Considerations for Studies of Rare Cancers

Zhaohui Su, PhD

Design the Study with Appropriate Statistical Power

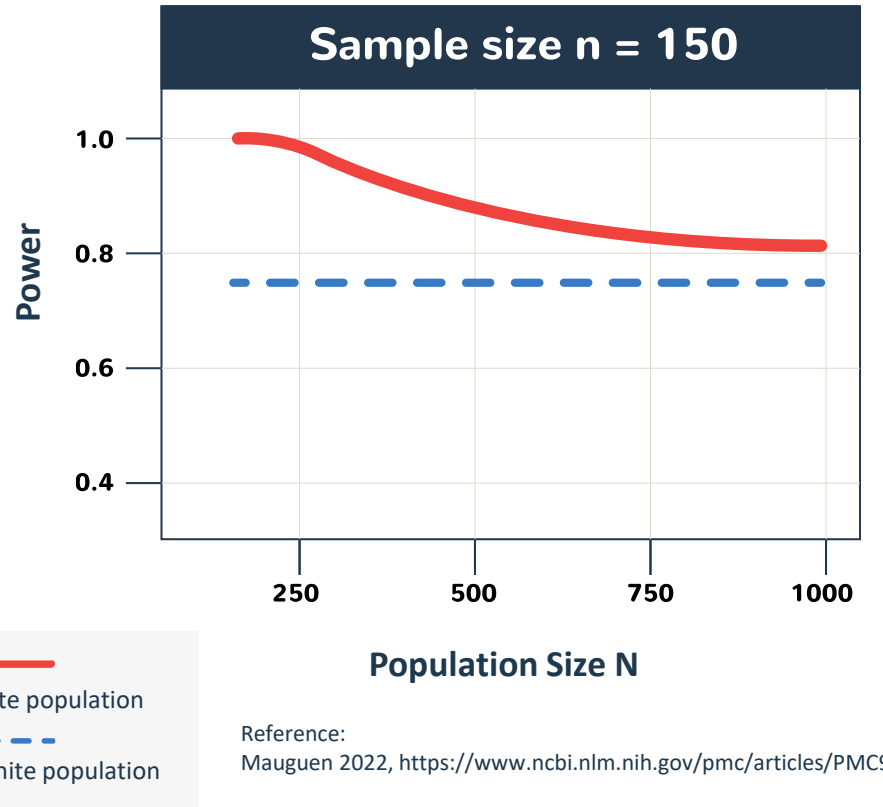
Why is this important?

- If under-powered, may not detect significant associations or a true effect
- If over-powered, may increase the cost and duration of the study
- The right study size depends on research objectives, the type of analyses, and quality of the data

How?

- **Precision analyses:** half of the width of the 95% confidence interval
- **Power analyses:** how much statistical power (eg, 80% or 90%) considering the rarity of the disease

Observed Proportion	Precision									
	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1	0.11
0.1	865	385	217	139	97	71	55	43	35	29
0.2	1537	683	385	246	171	126	97	76	62	51
0.3	2017	897	505	323	225	165	127	100	81	67
0.4	2305	1025	577	369	257	189	145	114	93	77
0.5	2401	1068	601	385	267	196	151	119	97	80
0.6	2305	1025	577	369	257	189	145	114	93	77
0.7	2017	897	505	323	225	165	127	100	81	67
0.8	1537	683	385	246	171	126	97	76	62	51
0.9	865	385	217	139	97	71	55	43	35	29



Reference:
Mauguen 2022, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9232871/

Four Ways to Maximize Statistical Power

1 Identify a large data source(s)

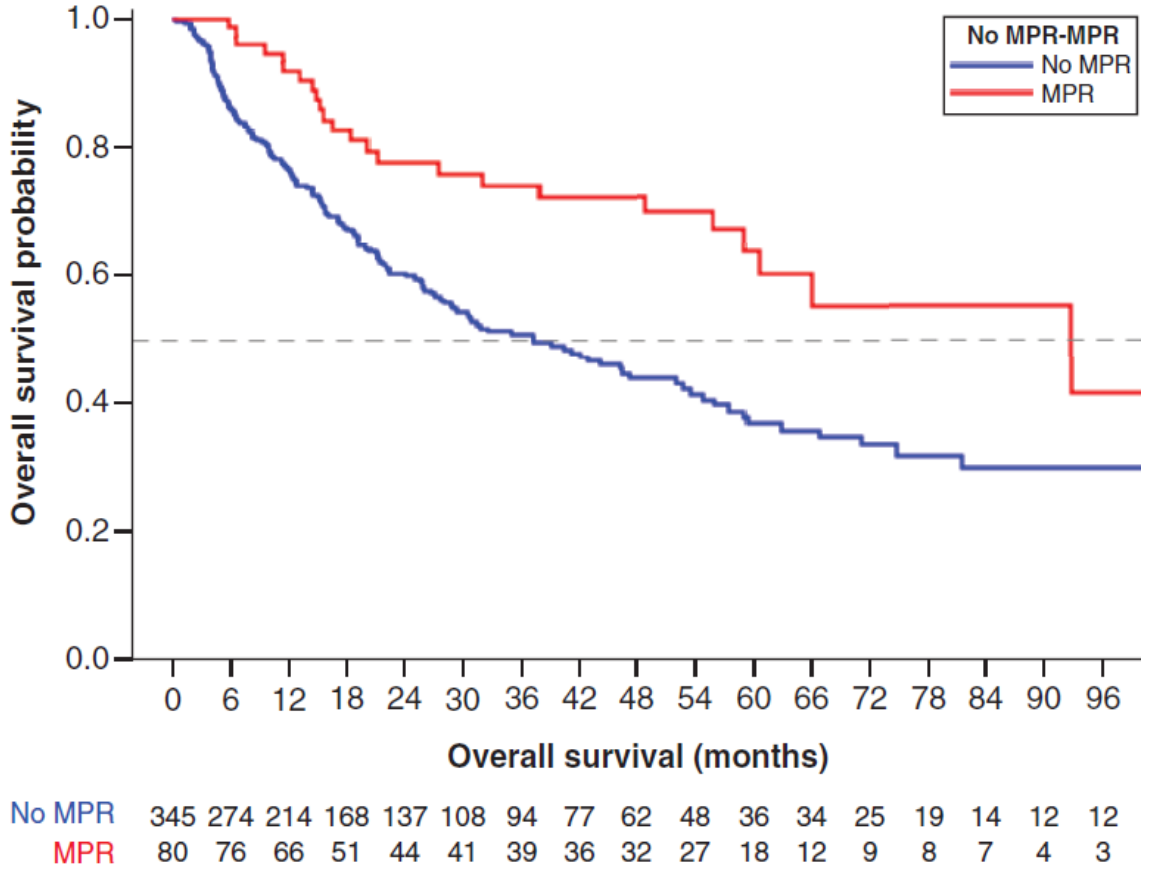
2 Extend the duration of follow-up

3 Select an appropriate surrogate endpoint

The Nadler 2023 study provides real-world evidence to support that major pathologic response (MPR) may be useful early surrogates for longer-term survival end points

4 Choose a study design and statistical methods that maximize power

Within-subject design, exact tests, meta-analysis



Reference: Nadler 2023, https://pubmed.ncbi.nlm.nih.gov/37665271/

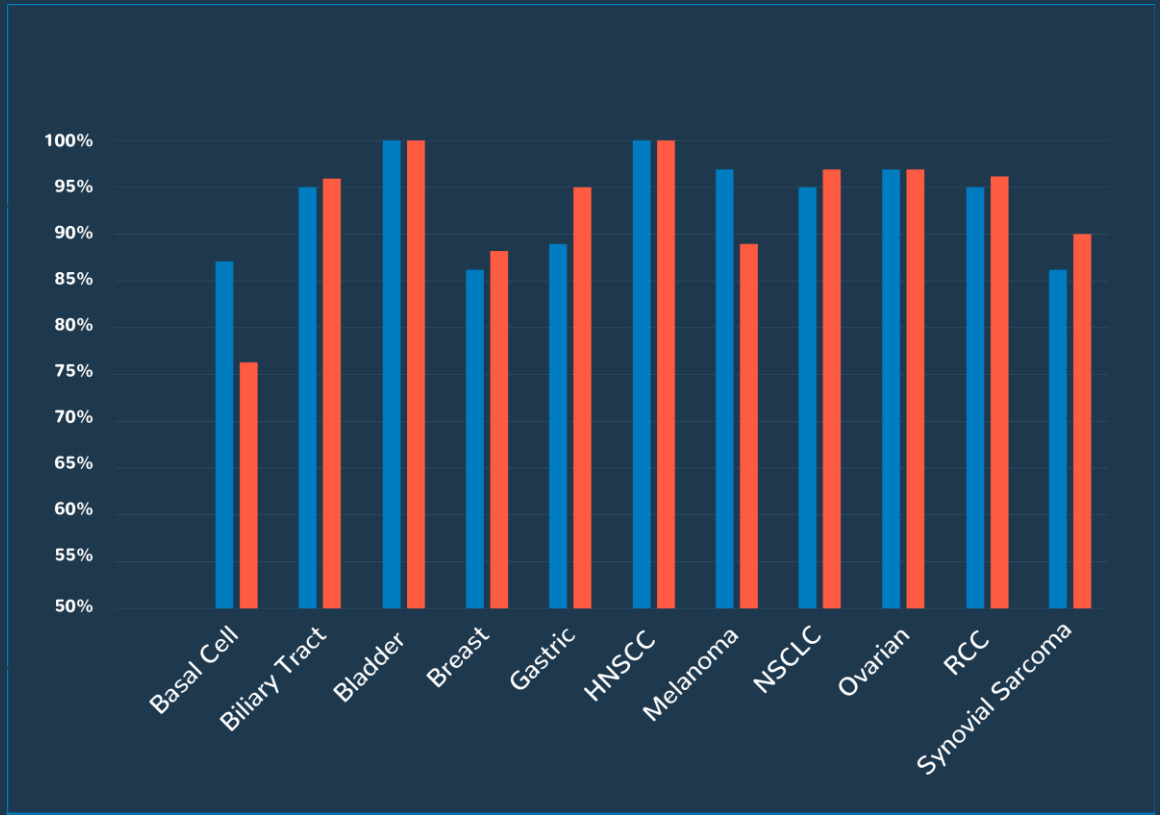
Enhance Data Completeness in the Context of Fit for Purpose

Why is this important?

- Sample sizes may be limited
- Missing data affects the study power
- Missing (data) not at random may lead to biased results
- Other reasons (covariates, matching, etc)

How?

- Ensure data are fit for the purpose
- Identify the appropriate data sources
  - Electronic health records (EHR), claims, commercial data linked to the primary data source
- Machine learning (ML), natural language processing (NLP) and chart abstraction



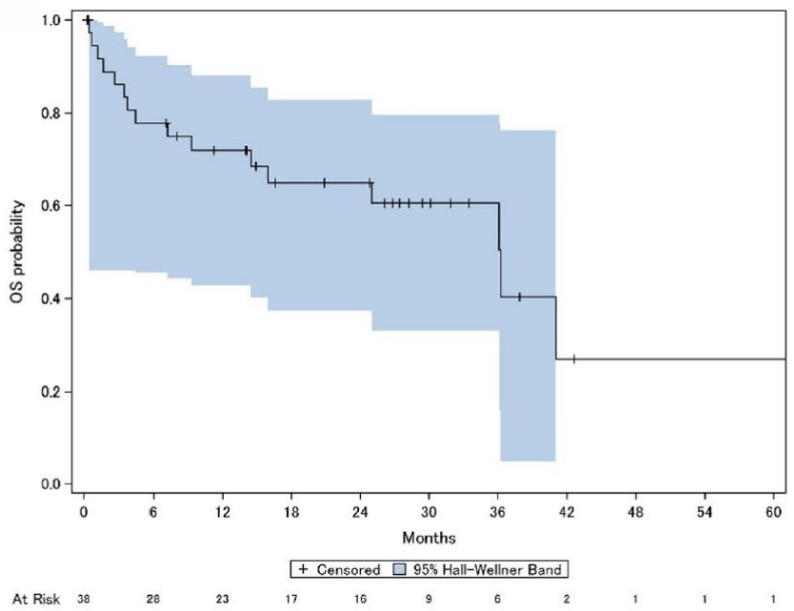
This table shows the results further broken down into the start and stop dates per type of cancer. Breast cancer had the lowest proportion of known starts dates while basal cell carcinoma had the lowest proportion of known stop dates

Reference: Ontada ISPOR Poster, https://www.ispor.org/docs/default-source/intl2023/ispor23reinwaldposter-pdf.pdf?sfvrsn=74aaaa03_0

A CASE STUDY:

Real-World Outcomes Among Crizotinib-Treated Patients with ROS1-Positive Advanced Non-Small-Cell Lung Cancer: **A Community Oncology-Based Observational Study**

Objective:
Assess real-world clinical outcomes among patients with ROS1-positive advanced NSCLC treated with crizotinib in the US community oncology setting.



Reference: Waterhouse 2021, https://pubmed.ncbi.nlm.nih.gov/34964940/

Methods:
- A retrospective cohort study (2013-2019) using iKnowMed EHR data.
- Outcomes include time to treatment discontinuation (TTD), time to next treatment (TTNT), and overall survival (OS).
- Kaplan-Meier analyses and Cox proportional hazards model were conducted.

Results:
- The study included 38 ROS1-positive patients treated with crizotinib.
- The median age was 68 years and 66% were female. Over 50% were current/former smokers, and 18% had an ECOG performance status of 2.
- Overall, 21 (55.3%) patients remained on crizotinib, 10 (26.3%) had evidence of subsequent treatment, and 16 (42.1%) died.
- The median TTD, TTNT, and OS were 25.2 months, 25.0 months, and 36.2 months, respectively. ECOG performance status of 2 was associated with a 4.9-fold higher risk of death compared to ECOG performance status of 0 or 1.

Conclusion:
This ROS1-positive NSCLC real-world population was older, had a higher proportion of smokers, and had poorer ECOG performance status than those investigated in clinical trials. Our findings support the clinical benefit of crizotinib in this patient population with ROS1-positive advanced NSCLC.

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Conclusions

Conclusions

Rapid advancements in genomic and molecular profiling of tumors has also led to an increase in actionable biomarkers that can be used to guide therapeutic decisions in oncology

This has had a number of implications across the lifecycle for oncology treatments; it has meant increased opportunities for clinical development, cancer screening and diagnosis, treatment selection, and patient outcomes

Precision medicine has meant huge changes for treating oncologists as well as patients

Along with great opportunities has come challenges in all areas above as well as with the study of real-world data for these patients

Despite challenges, there is increased interest in this area as there is recognition that specific cancer types will continue to become more rare as the field of genomics continues to grow

Therefore, the ability to understand natural history, treatment patterns, and long-term patient outcomes is essential

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Questions

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