U.S. FOOD & DRUG ADMINISTRATION

Oncology Center of Excellence: Envisioning Product Development for 2025

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Why OCE?

FDA Oncology Regulatory Review Pilots

Assessment Aid

Facilitates FDA assessment of NDA/BLA

- Review Template (3 parts): Data, Applicant Position, FDA Assessment
- Objectives: Focuses FDA Review on Critical Assessment and Increases Efficiency and Consistency by Decreasing Time on Administrative Tasks

Real-Time Oncology Review

Application Criteria: (1) Likely to Demonstrate Substantial Improvements; (2) Straightforward Study Designs; (3) Endpoints Easily Interpreted

- Submissions with Greater Complexity May Be Excluded
- Allows FDA Review of Data Prior to Complete Application Submission

PROJECT POINT/COUNTERPOINT

Oncologic Drugs Advisory Committee (ODAC) Meeting Briefing Material

- Combines the Company's Position and FDA Position into One Document
- Increases Transparency of Differences in Viewpoints
- Focuses on Salient Data to Facilitate Committee's Understanding of the Critical Issues for Discussion

PROJECT ORBIS

Project Orbis: Collaborative Review

- Identify any regulatory divergence across review teams
- Drug labels exchanged to learn about differences
- RTOR and Assessment Aid may be used

ONCOLOGY CENTER OF EXCELLENCE
PROJECT RENEWAL
Evaluate. Collaborate. Educate.

FDA

Initial FDA approval is only the beginning of a drug's story…

Issues:

- Scientific evidence accumulates over the course of a drug's lifecycle
- Longstanding cancer drugs can have product labels that become out of date
- Labeling updates are resource intensive for both sponsors and FDA
- Awareness of FDA labeling could be improved

Develop Repeatable Processes
to evaluate scientific evidence and determine whether labeling updates are needed

Use Published Data
to research off-label uses and develop a method to update existing labels

Engage with Oncology Community
to increase transparency of FDA processes and encourage collaboration

Foster Educational Experiences
for Oncology Fellows to learn about FDA's mission and regulatory process

PROJECT COMMUNITY

Engagement & Outreach

- Expose FDA oncologists to concerns of cancer survivors, patients, advocates and families
- Expose US public to the diverse OCE staff
- Increase cancer drug development knowledge

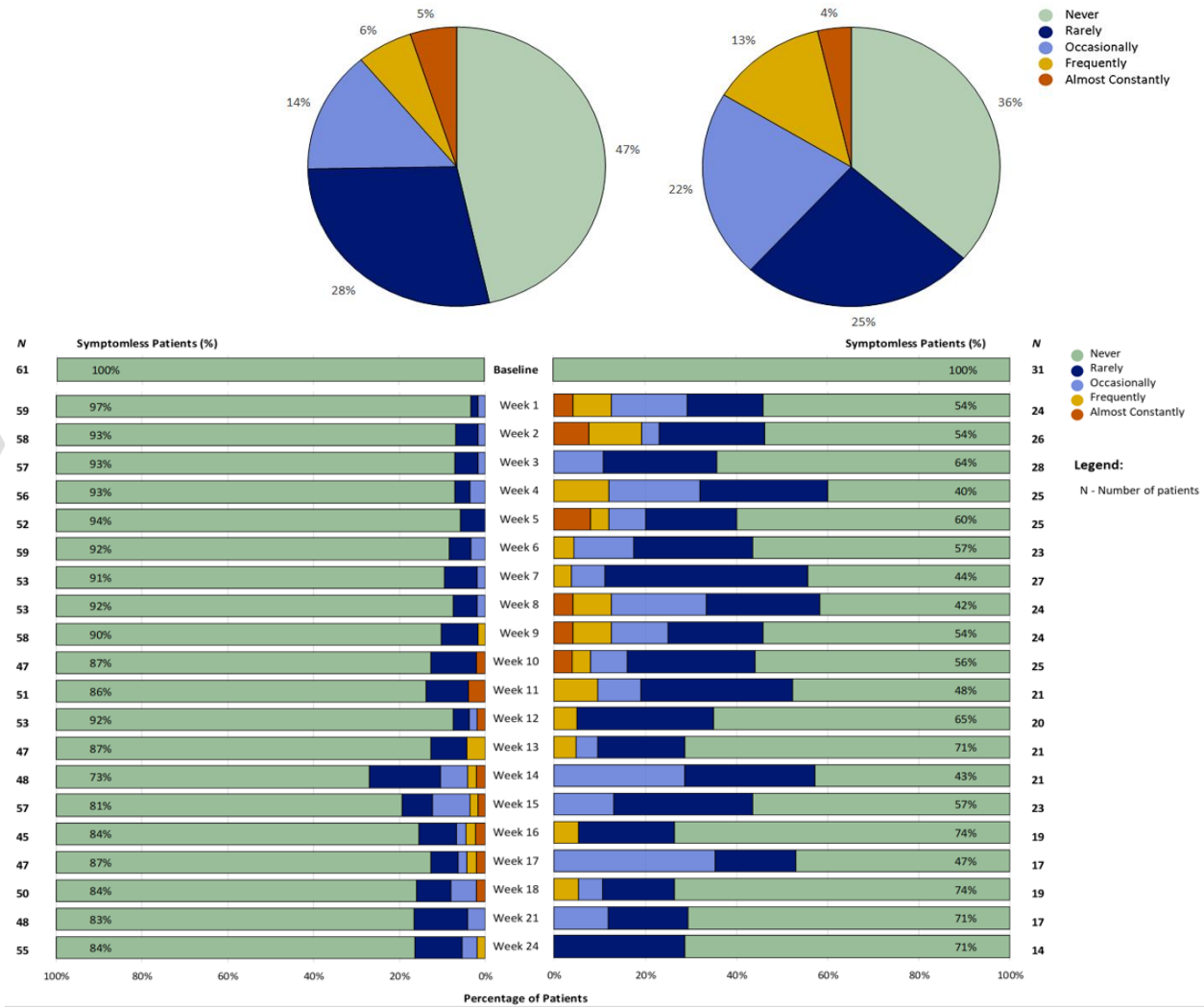
Project Patient Voice

Project Patient Voice: a pilot website describing patient reported, longitudinal, symptomatic adverse event data collected in registrational cancer trials for approved drugs

FDA

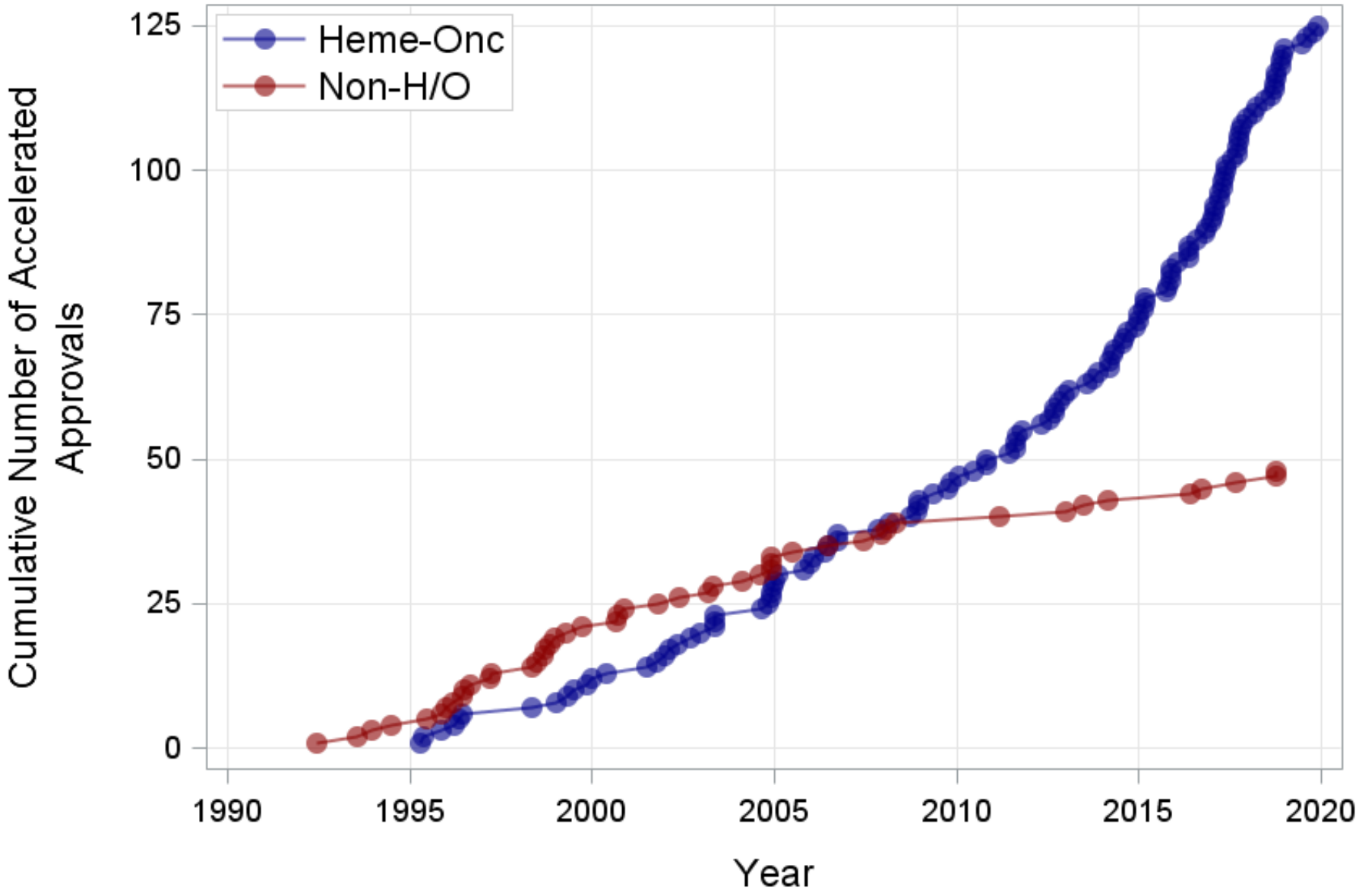
Challenge:

- Patient-reported outcome (PRO) data are frequently submitted to marketing applications
- Heterogeneity exists in **analysis** and **presentation** of data
- Labels have **limited space** to communicate patient experience data



FDA Expedited Pathways

	Fast Track	Breakthrough Therapy	Priority Review	Accelerated Approval
Program	Designation	Designation	Designation	Approval Pathway
Qualifying Criteria (all require condition to be serious)	• Nonclinical or clinical data demonstrate potential to address unmet need	• Preliminary clinical evidence demonstrates substantial improvement over available therapies	• If approved would result in significant improvement in safety or efficacy	• Demonstrates effect on endpoint reasonably likely to predict clinical benefit over available therapies
When to Submit	IND or after	Ideally no later than EOP2	With (s)BLA, (s)NDA	Discuss during development
Features	• Expedite development and review • Rolling review	• Intensive development guidance • Organizational commitment • Rolling review	• 6 month vs. 10 month review clock for regulatory action after filing	• Approval based on effect on endpoint that is reasonably likely to predict clinical benefit



Accelerated approvals for applications received from Jan 1, 2010 to Jun 30, 2019 (**10 year period**):

- 88 accelerated approvals
  - **79 (90%)** approved by OHOP
  - **75 (85%)** for oncology or malignant heme indications

Envisioning Drugs 2025

Strength of Efficacy Endpoint Results

- **What** is being Measured**? (Endpoint Selection)**
  - Direct Benefit (Feels/Functions/Survives) considered more meaningful

- **How** accurately is it being measured**? (Measurement Characteristics)**
  - Accuracy of the measure
  - Susceptibility to Bias
  - Accuracy of the Timing of the Event

- **How Much** effect on the endpoint is observed? **(Magnitude of Effect)**

No Free Lunch:
Strengths and Limitations of Endpoints

	Clinical Outcome	Low Risk of Bias	Feasibility
Overall Survival			
Tumor Endpoints			
Clinical Outcome-PRO			
Clinical Outcome-Reduction in Healthcare Utilization (e.g. Steroid Use, morbid procedure)			

Paradigm Shift?

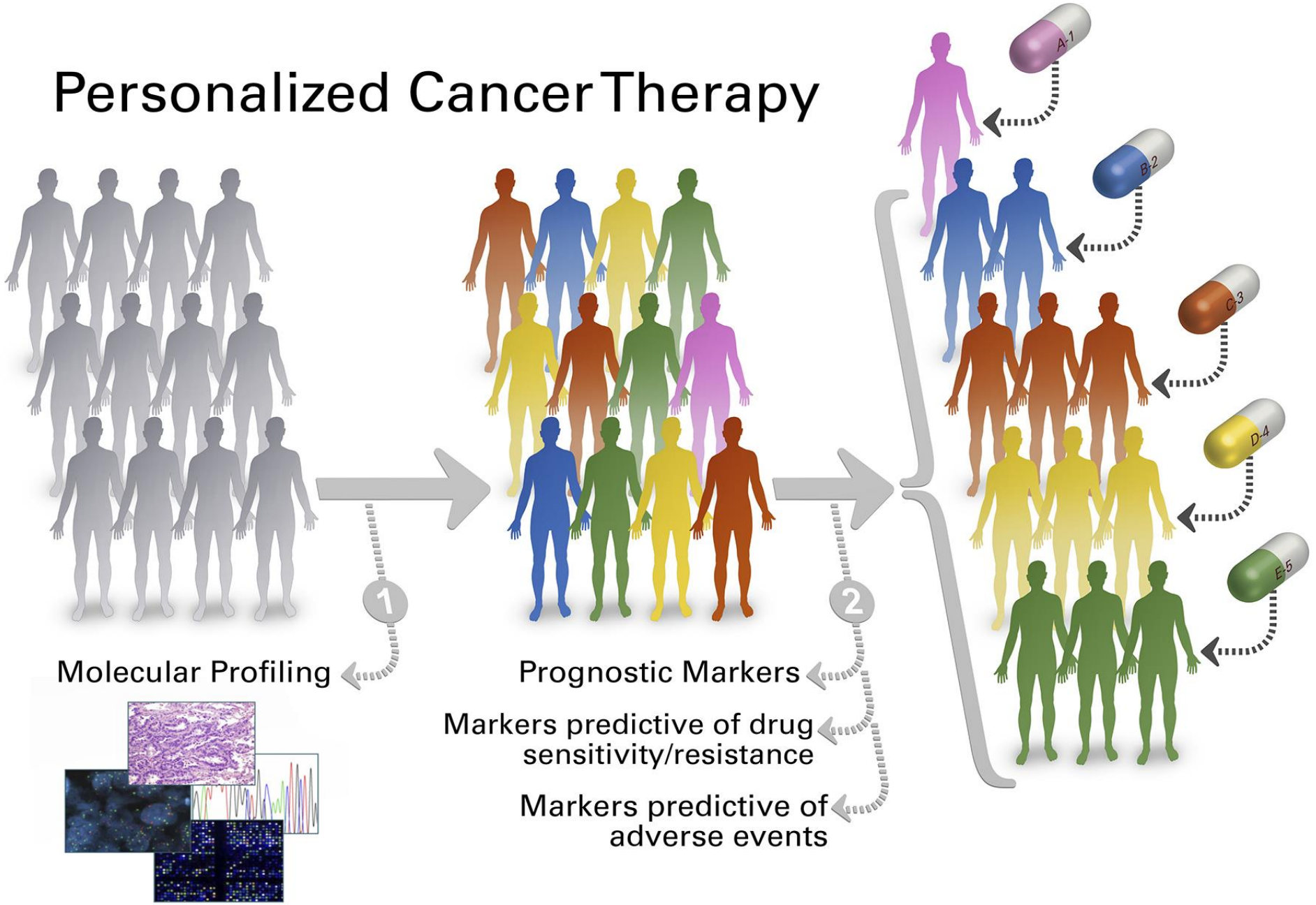
Location,
Location,
Location

Biomarker,
Biomarker,
Biomarker*

Prerequisite: detailed **biologic understanding** + clinical data showing **large magnitude and consistency of effect** in patients with **rare & refractory cancers**, **limited therapeutic options**, **unmet need**

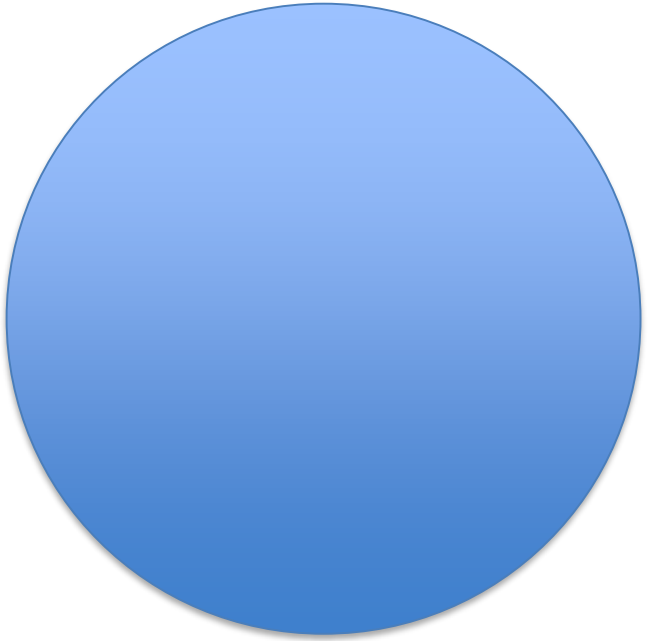
* At least- some of the time

Personalized Cancer Therapy

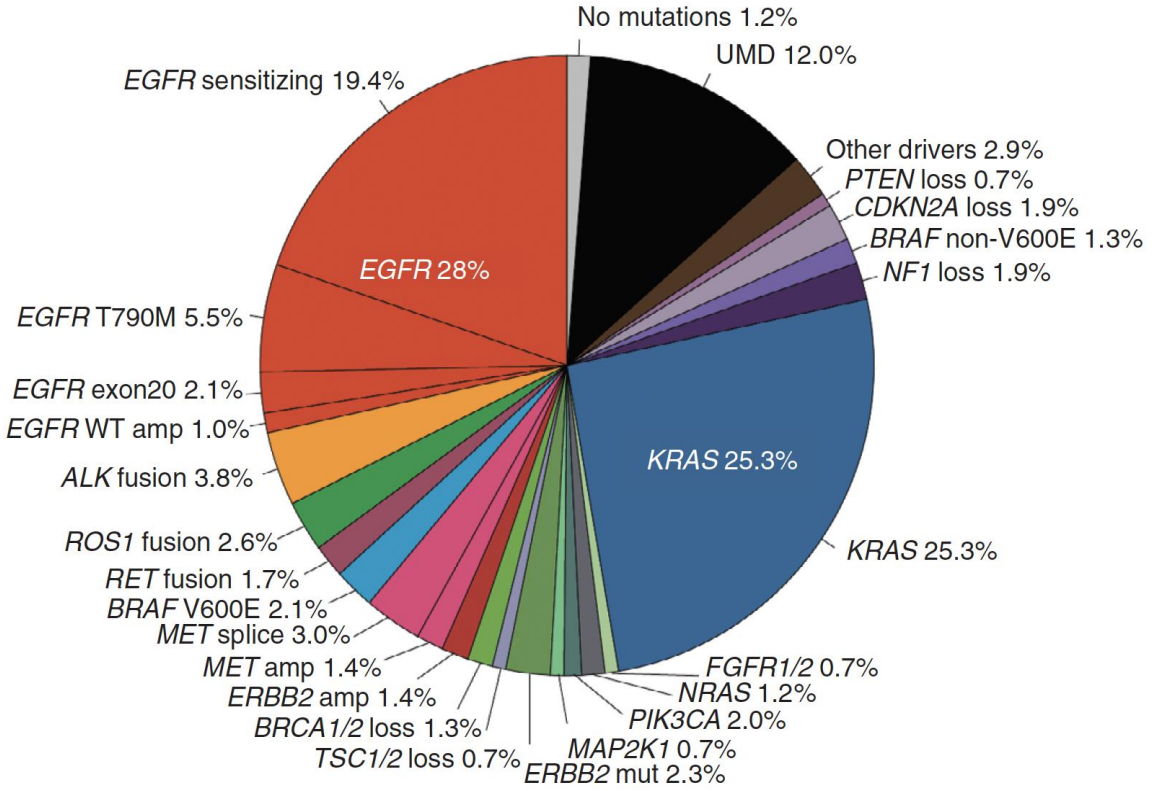


Oncogenic drivers in lung adenocarcinoma

Pie Chart 20 years ago



Pie Chart Today



Jordan et al., Cancer Discov 7: 596-609, 2017

Pembrolizumab (supplement)	Larotrectinib (new molecular entity)
Pooled data from **149** pts with MSI-H or dMMR **advanced refractory** solid cancers across 5 trials	Pooled data from **55** pediatric and adult patients with **advanced refractory** solid tumors with NTRK gene fusions across 3 trials
PCR or IHC (local labs)	NGS/FISH (local labs)
ORR: 40% (95% CI 32, 48)	ORR: 75% (95% CI: 61, 85)
DoR > 6 months: 78%	DoR > 6 months: 73%
Responses in 12 of 15 tumor types	Responses in 8 of 12 tumor types (across multiple fusion partners)
Postmarketing study: patients with CRC, non-CRC, including prostate, thyroid, SCLC, ovarian, & children. Characterize response and duration for at least 12 months	Postmarketing study: Further characterize response/ durability: CRC, NSCLC, CNS, melanoma, breast, GIST, cholangio, biliary)

Pembrolizumab & Larotrectinib Accelerated Approvals

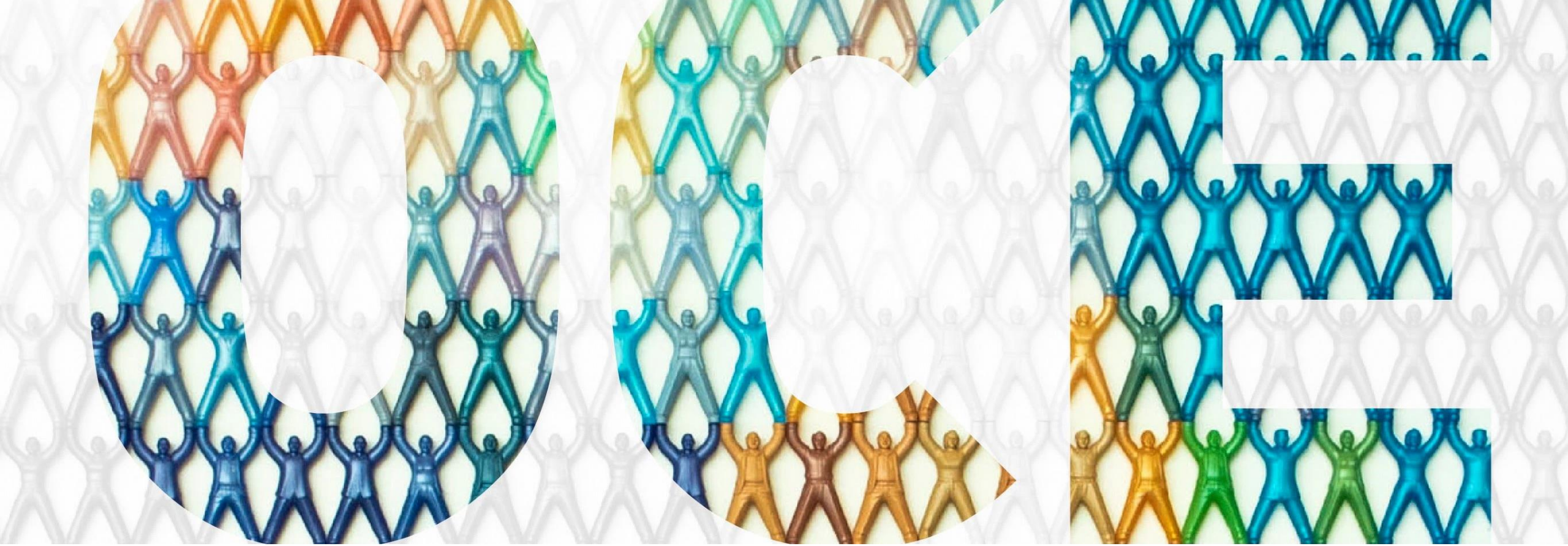
Tissue agnostic approvals:

pembrolizumab and larotrectinib

- Facilitated access to effective therapies for patients with unmet need and limited therapeutic options
- Most efficient approach to generate reliable evidence
  - Randomized trials likely infeasible and lacking equipoise
- Granted without every tumor type studied
  - Including children
  - Post-marketing data forthcoming
- Granted without companion in vitro diagnostic devices
  - Post-marketing commitments

Challenges

- Industry Cooperation
  - Platform trials
  - Common controls
- Changing role of regulatory agencies



Thank You

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