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How the Changing Landscape of Oncology Drug Development and Approval Will Affect Advanced Practitioners

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Learning Objectives

1. Understand FDA regulatory principles with respect to trial design, endpoints, randomization, and accelerated approval programs
2. Differentiate among various endpoints used in clinical trial design and understand their strengths and weaknesses
3. Discuss emerging initiatives in the quest to expedite the drug development process

Disclosures

I have no conflicts of interest to disclose.

FDA Mission

- FDA is responsible for:
  - Assurance of the **safety, efficacy**, and **security** of:
    - **Drug and biological** products
    - Medical **devices**
    - **Food** supply
    - **Radiation products**
  - **Accounts for 25 cents of every dollar spent by Americans…**
- FDA **does not** take into account cost or payment issues
- FDA **does not** regulate "practice of medicine"

Key FDA Centers

Center for Drug Evaluation and Research (CDER)

- Drugs and antibodies
- Six offices across therapeutic areas, including the Office of Hematology and Oncology Products

Center for Biologics Evaluation and Research (CBER)

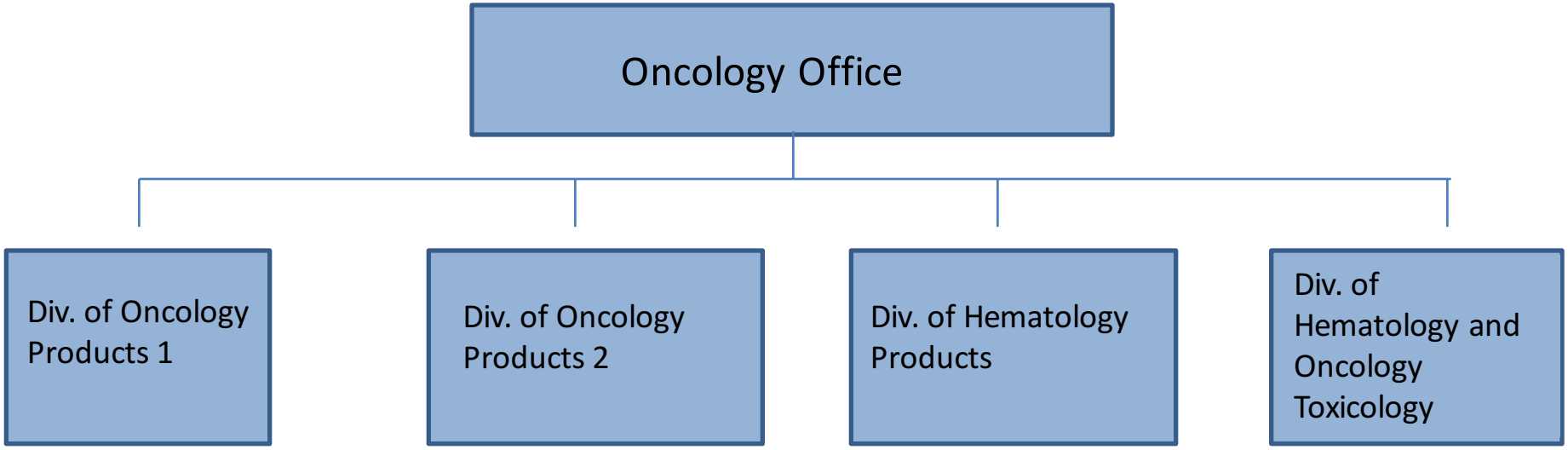
- Cellular and gene therapies, vaccines

Center for Devices and Radiologic Health (CDRH)

- Devices, in vitro diagnostics, diagnostic and therapeutic radiologics

Office of Hematology and Oncology

Disease-specific structure akin to current academic models



- Breast cancer
- Gynecologic cancer
- GU malignancies

- Thoracic, head and neck
- Gastrointestinal
- Melanoma-sarcoma
- Pediatric-neuroendocrine-Rare tumors

- Benign heme
- Lymphomas
- Leukemias
- Transplant

- Toxicologists supporting each clinical division

FDA Oncology Center of Excellence

Overall Aims

- Evaluate products for prevention, screening, diagnosis, and treatment of cancer
- Support development of companion diagnostic tests and use of combinations of drugs, biologics, and devices
- Develop and promote use of methods created through the science of precision medicine
- Facilitate incorporation of the patient view in regulatory decision making

How Is Oncology Different From Other Therapeutic Areas?

- Severe and life-threatening diseases
- Large public interest, need to expedite drugs
- Different risk tolerance for side effects
- Active advocacy groups
- Active area of biomedical research
- 50% of breakthrough therapies
- Biomarker-defined populations

Traditional ("Regular") Approval

- **Traditional approval** requires
  - Substantial evidence of safety and efficacy
  - Well-controlled clinical trials (usually two or more)
  - Based on **prolongation of life, a better life, or an established surrogate for either of the above**

- No **comparative efficacy** for traditional approval
  - As safe and effective as existing therapies, allowing for non-inferiority designs

Accelerated Approval

- *Can be based on a **"surrogate endpoint…reasonably likely…to predict clinical benefit"***

- "Provide meaningful therapeutic **benefit…over existing therapies**"

- **Post-marketing clinical trials may be required**
  - Should usually be underway at the time of accelerated approval
  - Applicant should carry out studies with due diligence

What Is Clinical Benefit?

Strength of Efficacy Endpoint Results

- **What** is being measured?

  (Endpoint Selection)

- **How** accurately is it being measured?

  (Measurement Characteristics)

- **How much** effect on the endpoint is observed?

  (Magnitude of Effect)

How Is the Endpoint Measured?

- How much **interpretation** is required?
  - More interpretation = more risk for bias/variability
- How accurate is the **timing** of the event?

Direct Measures of Efficacy

Overall Survival: Gold Standard

- Strengths
  - Direct measure of benefit
  - Least prone to bias, no interpretation of the event (death yes or no)
  - Event timing (date of death) typically known to the day
  - Includes information regarding safety
    - Deaths due to drug toxicity are part of the endpoint
- Limitations
  - Last event in a disease's natural history = longer and larger trial
  - Requires randomized controlled trial
    - Comparison with historical control limited (differing populations, differing standards of care, etc.)
  - May be confounded by crossover (depending on magnitude of effect) and subsequent therapies if given unequally between arms

* Meaningful clinical benefit of a survival advantage is still based on toxicity of drug and **magnitude** of OS result

Surrogate Endpoints

Radiographic Evidence of Anti-Tumor Effect

- **Response rate (RR)**
  - Shrinking a tumor
  - ***Critically important: tumor location, number of CRs, duration of response***

- **Time to progression (TTP), progression-free survival (PFS)**
  - Time from randomization to growth of tumor past predefined threshold
  - PFS counts death as a progression event and is preferred

- **Radiographic endpoints: Strengths**
  - Earlier events than survival = smaller, shorter trial
  - Radiographs can be captured and stored to verify the event
  - Not confounded by crossover or subsequent therapies (event occurs prior to crossover)

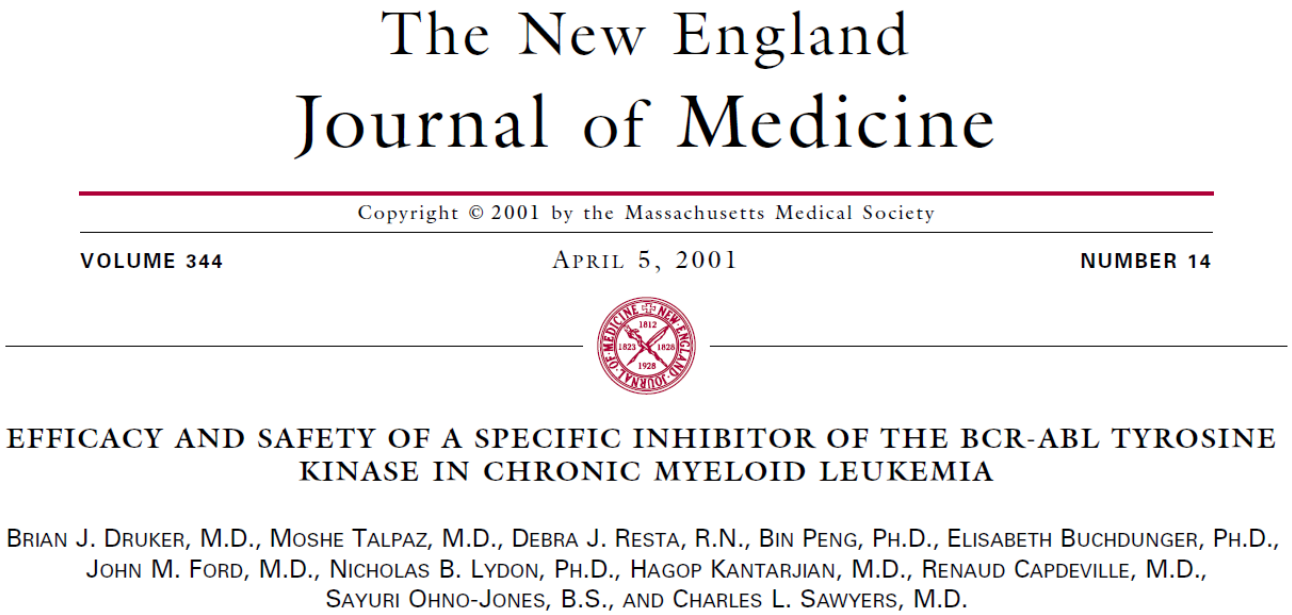
- **Radiographic endpoints: Limitations**
  - Uncertainty regarding clinical benefit: Will a given change in an asymptomatic radiographic finding predict true clinical benefit?
  - Missing, incomplete, infrequent, or uneven assessments
  - Difficult to measure disease (ill-defined lesions), bone metastases, peritoneal carcinomatosis

FDA Historical Perspective
Oncology Efficacy Endpoints

- **1970s**: A setting of limited available therapies
  - **Tumor shrinkage (response rate)** was accepted as a primary efficacy endpoint for regular approval
- **1980s**: A change in this interpretation occurred:
  - 10% to 20% of patients with asymptomatic radiographic tumor shrinkage may not translate into an improvement in overall outcome (particularly given the toxicity of the agents being evaluated)
- Ideally, measurement should reflect **direct clinical benefit**
  - **How one "feels, functions, or survives"**
  - **A move away from ORR for traditional approval and a focus on overall survival**

FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.

And then this started to happen…



The New England
Journal of Medicine

VOLUME 344 APRIL 5, 2001 NUMBER 14

EFFICACY AND SAFETY OF A SPECIFIC INHIBITOR OF THE BCR-ABL TYROSINE KINASE IN CHRONIC MYELOID LEUKEMIA

BRIAN J. DRUKER, M.D., MOSHE TALPAZ, M.D., DEBRA J. RESTA, R.N., BIN PENG, PH.D., ELISABETH BUCHDUNGER, PH.D., JOHN M. FORD, M.D., NICHOLAS B. LYDON, PH.D., HAGOP KANTARJIAN, M.D., RENAUD CAPDEVILLE, M.D., SAYURI OHNO-JONES, B.S., AND CHARLES L. SAWYERS, M.D.

Complete hematologic response in 53 of 54 patients with IFN-refractory chronic phase CML…

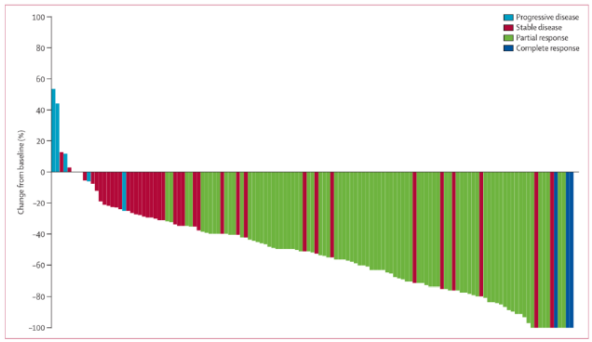
"Our results…demonstrate the potential for the development of anticancer drugs based on the specific molecular abnormality present in human cancer."

Druker BJ, et al. *N Engl J Med* 2001;344(14):1031-7.

Unprecedented Response Rates

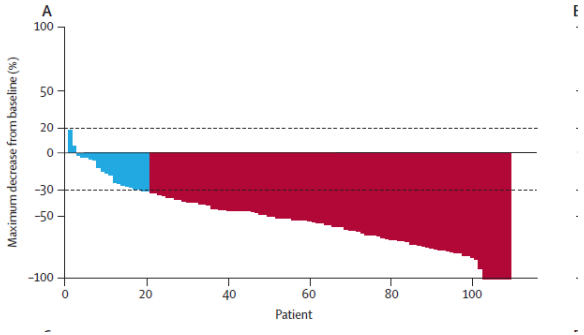
- Enriched populations
- Strong basic science

ALK+ NSCLC: ORR 61%



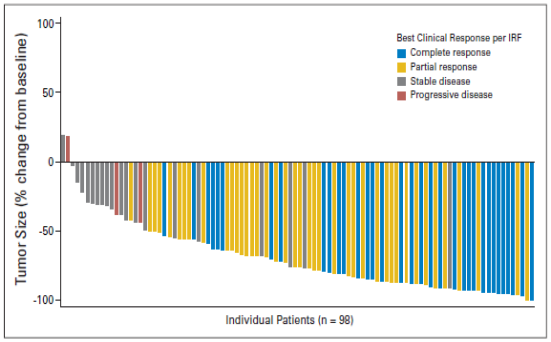
Crizotinib: Phase 1
Camidge DR, et al. *Lancet Oncol* 2012;13:1011-9.

EGFR-Mut+ NSCLC: ORR 61%



Afatinib: LUX-LUNG-2
Yang JC, et al. *Lancet Oncol* 2012;13:539-48.

CD30+ Hodgkin: ORR 75%



Brentuximab Vedotin: Phase 2
Younes A. et al. *J Clin Oncol* 201;30:2183-9.

Looking Closer at ORR

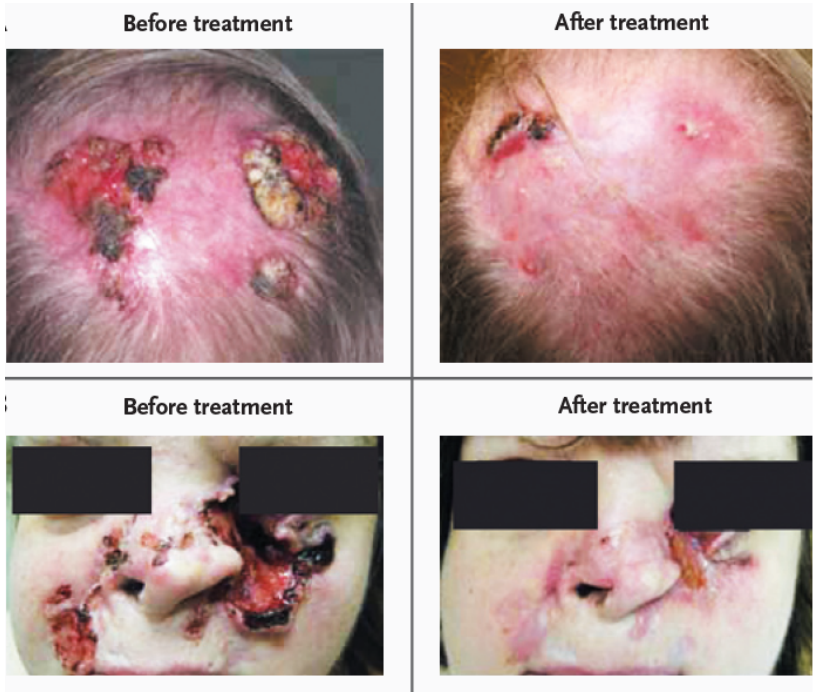
There are multiple variables in "response rate"

- Location of tumor
- Number of complete responses
- Duration of responses
- What was initial tumor burden?
- How many patients' tumors reduced, but < 30%?
  - Not currently captured in RECIST ORR
  - These patients may derive benefit if activity/stability of long duration depending on toxicity of the treatment
  - Value of the waterfall plot

Where Are the Tumors That Are Responding?

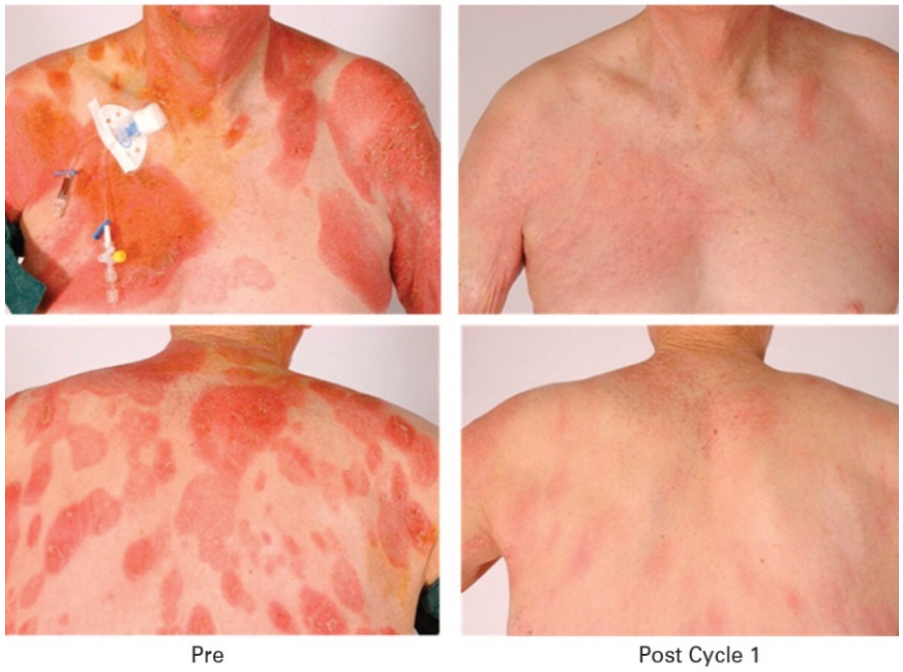
When "response rate" may be considered direct clinical benefit…

- Near complete responses of disfiguring or fungating skin lesions are a different context
- **Traditional approval** granted based on ***clinical*** response rate (and duration), the cosmetic improvement, and the high likelihood of tumor-related symptomatic relief



Vismodegib Response

Von Hoff DD, et al. *N Engl J Med* 2009;361:1164-72.



Depsipeptide Response

Piekarz RL, et al. *J Clin Oncol* 2009;27:5410-17.

Clinical Equipoise

When there is general uncertainty in the expert medical community on whether a treatment is effective

- Important for ethical conduct of randomized trials AND can affect feasibility
- What is ORR improvement over existing therapies where equipoise is lost?

Best Response	Arm A N=151	Arm B N=156	Arm C N=152
CR	0	0	0
PR	0	2 (1%)	13 (9%)
P value	0.0002 for Arm A vs. Arm C		
95%CI	0-2.4%	0.2-4.6%	4.6-14.2%

Arm A: 5-FU/LV, Arm B: oxaliplatin, Arm C: 5-FU/LV + oxaliplatin

FDA Review: Oxaliplatin in Colorectal Cancer

- **9% ORR, all partial responses with added toxicity over the chemo backbone…**

Efficacy Parameter	Study A N=136	Study B N=119
ORR (CR+PR)[b] [% (95% CI)]	50% (42%, 59%)	61% (52%, 70%)
Number of Responders	68	71
Duration of Response[c] [Median (range) weeks]	41.9 (6.1+, 42.1+)	48.1 (4.1+, 76.6+)

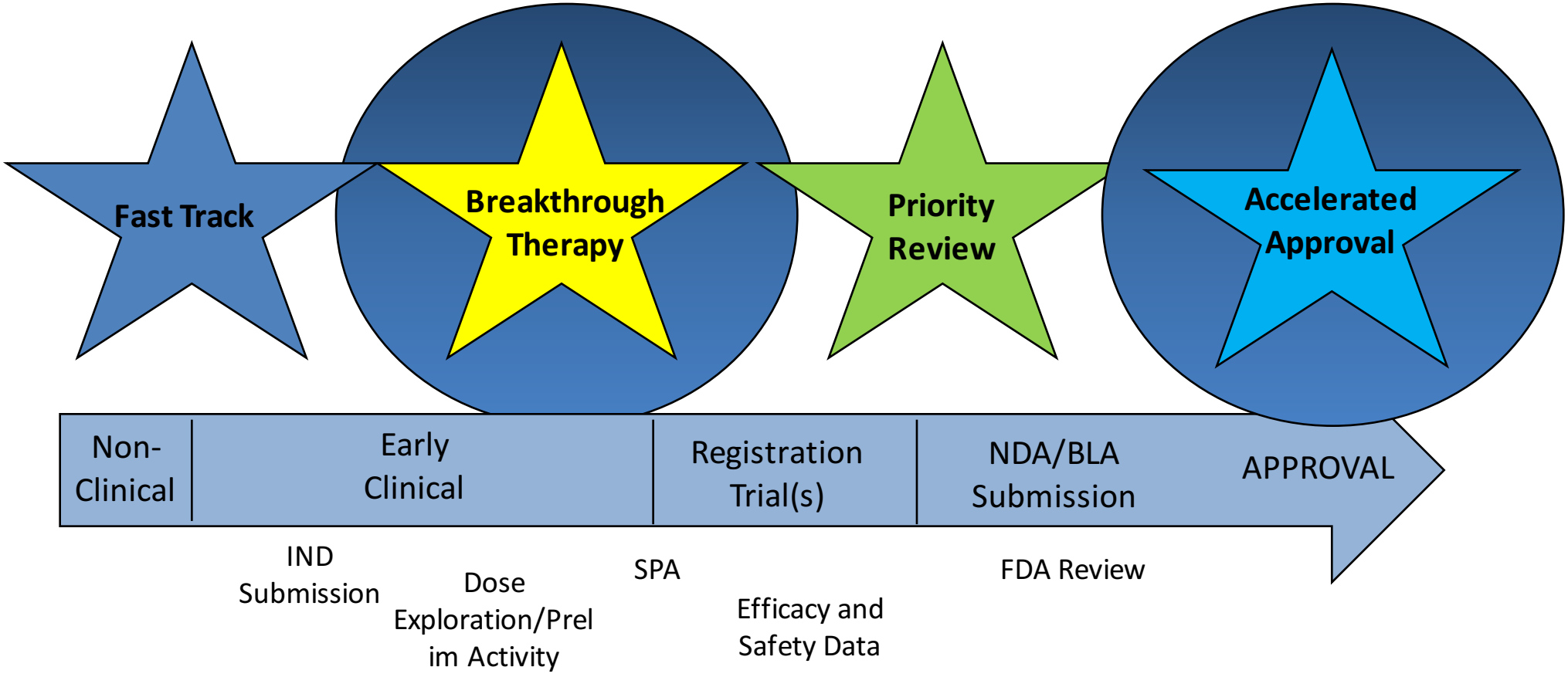
FDA Review: Crizotinib for Non–Small Cell Lung Cancer

- **50%–61% ORR, median duration of over 10 months with deep responses and favorable toxicity when compared with chemotherapy doublet…**

Barriers to Randomized Controlled Trials

- Feasibility in low frequency populations
- Crossover impacts OS difference assessment
- Ethical issues when intervention is highly active or comparator is toxic/has minimal efficacy
  - Equipoise lost?

FDA Expedited Programs



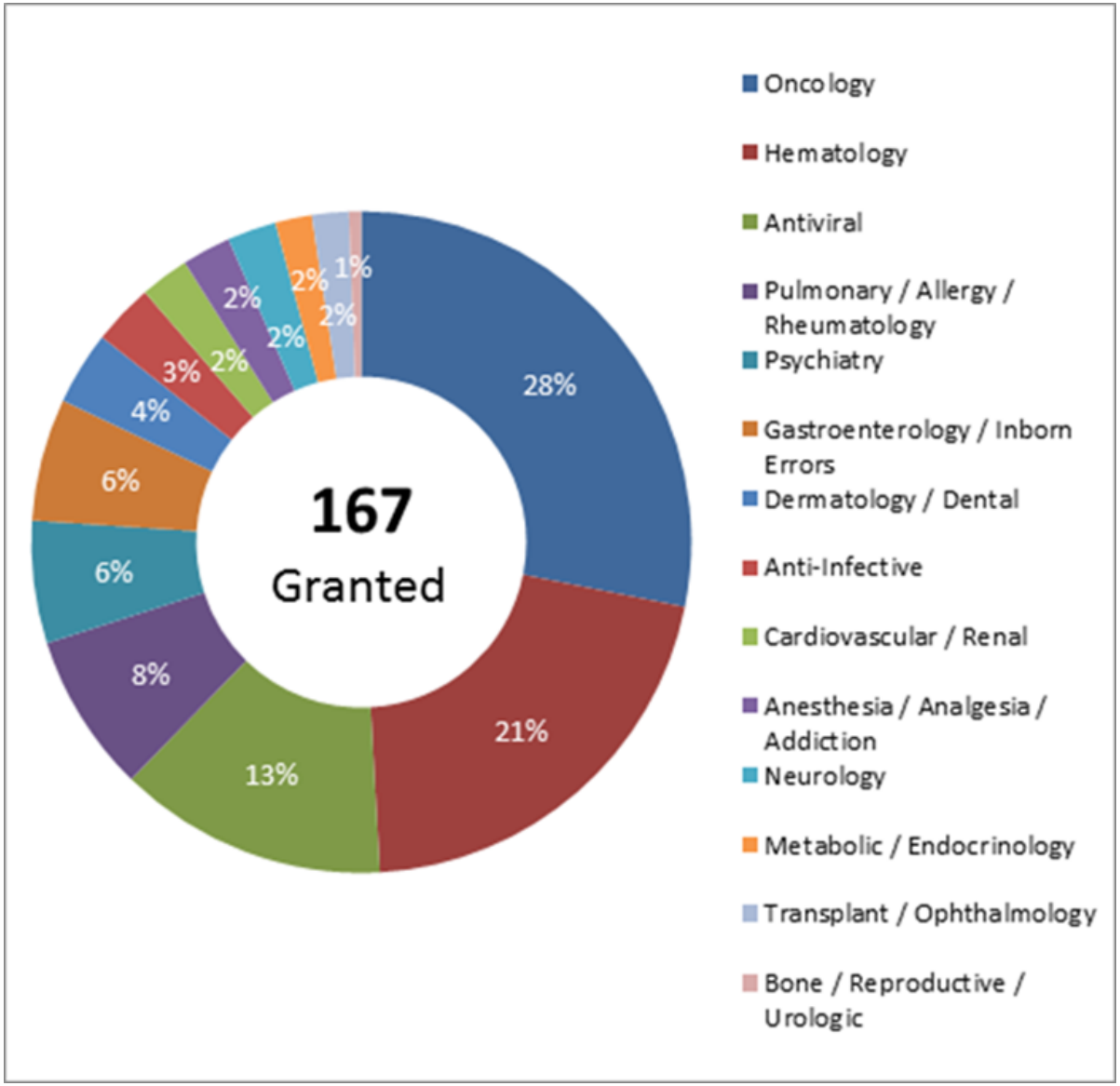
★ If considering accelerated approval, post-marketing clinical trials should be underway at the time of approval.

Breakthrough Therapy Designation

- Signed into law in 2012
- For serious life-threatening disease, a drug, based on preliminary clinical evidence, has substantial improvement over available therapy
- About 50% of breakthrough therapy requests across drug center have been in oncology
  - About one-third have been granted

US Food and Drug Administration. www.fda.gov.

Breakthrough Therapy Designation



Moonshot Initiatives

- **Seamless design—expansion cohort**
- **Large simple trials**
- **Reevaluating eligibility criteria**
- Patient-reported adverse events
- Real-world data
- Site-agnostic indications

Discrete Phases to Seamless Transition

- **Oncology drug development historically involved three discrete phases**:
  - *Phase 1*: MTD, DLTs, preliminary efficacy
  - *Phase 2*: Efficacy assessment for "go/no-go"
  - *Phase 3*: RCTs designed to provide adequate efficacy/safety data to support drug approval

- **These distinct phases have become more seamless:**
  - Early biomarker discovery/companion diagnostic development → earlier identification of efficacy and larger treatment effect sizes
  - Desire for greater efficiency in drug development
  - Demand for access to promising investigational agents

MTD = maximum tolerated dose; DLT = dose-limiting toxicity; RCT = randomized controlled trial.

OHOP Experience

- **Almost 40 commercial INDs for large FIH trials (100 to > 1,200 patients)**
  - Up to 14 expansion cohorts with 10–180 patients/cohorts
  - *More than one-third are anti-PD-1/PD-L1 agents*
- **Nature of expansion cohorts in these trials**
  - Dose/schedule refinement
  - Variety of tumor types
  - Variety of molecularly defined subsets
  - Variety of drug combinations
- ***Stated* objectives, endpoints, eligibility criteria, and informed consent language are more consistent with usual phase 1**
- ***However*, sample size, nature of data collected, and actual goals more consistent with usual phase 3**

OHOP = Office of Hematology and Oncology Products; IND = investigational new drug; FIH = first in human.

Prowell TM, et al. *N Engl J Med* 2016;374:2001-3.

Large Simple Trials

Randomized trials conducted in context of routine cancer care in post-marketing setting (phase 4)

- Ask/answer limited number of clinically relevant questions
- Utilize **focused** data collection from EHRs
- Are (ideally) not burdensome to busy clinicians or patients
- Benefit from a large sample size (i.e., high level of power) to reliably estimate the risk-benefit of a drug
- Assess clinical benefit endpoints, not surrogates

Why Modernize Eligibility Criteria?

- **Many potential participants excluded:**
  - *CNS involvement*
  - *Marginal performance status*
  - *Organ dysfunction or limited marrow reserve*
  - *HIV positivity*
  - *Extremes of age*
  - *Prior malignancy*
- **Result is slow accrual to trials in patients who may not characterize those who will receive the drug in post-marketing setting**

Pros and Cons of Broadening Eligibility Criteria

- Arguments in favor
  - Makes results more generalizable
  - Expedites accrual
  - Potential for "niche" indication/labeling claim (e.g., "only TKI shown to improve OS in patients with x tumor & brain mets")
- Arguments against
  - Potential to confound interpretation of efficacy/safety and introduce risk into development (minimized if eligibility criteria are thoughtfully selected and effect size is more than modest)

TKI = tyrosine kinase inhibitor.

US Food and Drug Administration. www.fda.gov

Challenges for PRO Unique to Oncology

- Asymptomatic/minimally symptomatic populations
- Open-label trials
- Single-arm trials
- Missing data

- Most pivotal trials have included large HrQOL instruments
  - FACT, QLQ-C30, EQ-5D
  - Static questions, cannot adapt to differing trial contexts
  - Infrequently assessed leading to missing data

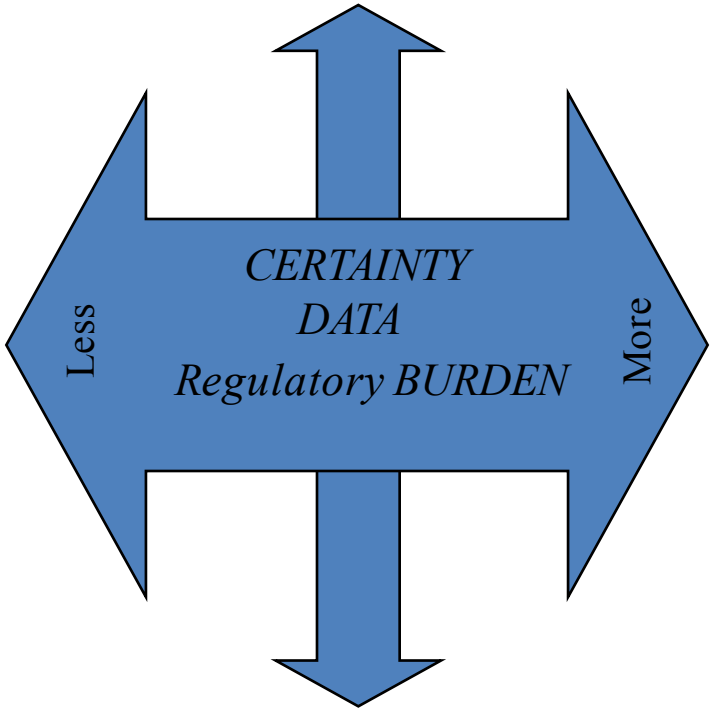
Striking a Balance

Flexible, Efficient, Interactive

"Toxic deaths!

Delayed safety findings!

FDA asleep at the wheel"



"Too cautious!

Stifling innovation!

Reduce regulatory burden!"

Consistent, Thorough, Independent

How Will Dynamics Affect Advanced Practitioners?

Thanks

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