Assessment of Supporting Evidence and Postmarketing Requirements for Therapeutic Indications with Real-Time Oncology Drug Review, 2018-2023

Maryam Mooghali, MD, MSc[1]; Ayman Mohammad, BA[2]; Joshua D. Wallach, PhD, MS[3]; Aaron P. Mitchell, MD, MPH[4];Joseph S. Ross, MD, MHS[1]; Reshma Ramachandran MD, MPP, MHS[1]

[1]Yale University School of Medicine, CT; [2]Emory University School of Public Health, GA; [3]Icahn School of Medicine at Mount Sinai, NY; [4]Memorial Sloan Kettering Cancer Center, NY

CRIT
COLLABORATION FOR REGULATORY RIGOR, INTEGRITY AND TRANSPARENCY

Yale University School of Medicine

Background

- U.S. FDA launched the **Real-time Oncology Review (RTOR)** program in February 2018 to facilitate **earlier submission of top-line results** to support an **earlier start** to the **FDA application review.**

- **RTOR eligibility criteria**
  - Clinical evidence from **adequate and well-controlled investigations** indicates that drug may demonstrate substantial improvement **on clinically relevant endpoint(s)** over available therapies.
  - Endpoints can be **easily interpreted** (e.g., overall survival, response rates).

Clinical Outcomes	Surrogate Endpoints
• Parameters that describe or reflect how an individual feels or functions, or how long the person lives.	• **Substitute** for a direct measure of how a patient feels, functions, or survives. • Do not measure the clinical benefit of primary interest by itself, but rather is **expected to predict** that clinical benefit.

Traditional Approval	Accelerated Approval
• **Standard approval pathway** • Mostly based on trials demonstrating clinical benefit. • While surrogate endpoints could occasionally be used, postmarketing studies are not always required.	• For drugs addressing **serious or life-threatening** diseases based on trials using **surrogate markers** that are **reasonably likely to predict clinical benefit**. • Subject to **postmarketing requirements** to prove the expected clinical benefits.

Objectives

For all approvals reviewed under RTOR:

1. To characterize the approval pathway and evidence supporting approval
2. For approvals based on surrogate markers as primary endpoints, to determine whether postmarketing studies were required to confirm clinical efficacy

Methods

Study Type:	Data source:	Timeframe:
Cross sectional	Drugs@FDA	2018-2023

Study Sample:
All original and supplemental RTOR approvals

Main Findings

✓ **One-fifth** of **new FDA oncology** indication approvals were reviewed under the **RTOR** program since its inception.

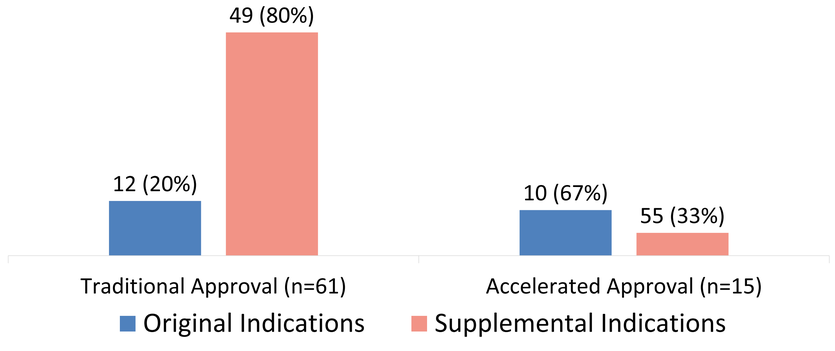
✓ These **approvals**, including those under traditional pathway, were **often supported** by pivotal trials using **surrogate endpoints**.

✓ **RTOR** indications with **traditional approval** based on **surrogate endpoints rarely** had **postmarketing requirements** to confirm their clinical benefit.

Results

FDA approved 363 new oncology indications between 2018 and 2023, of which 76 (**21**%) underwent **RTOR** based on 84 pivotal trials.

FDA Indication Approvals with Real-time Oncology Review (n=76)



Results

Table 1 – Characteristics of FDA Indication Approvals with Real-time Oncology Review

	Traditional approval N=61	Accelerated approval N=15	P-value
Primary endpoint of pivotal trial			
At least one clinical primary endpoint	34%	0%	<0.001
Only surrogate markers as primary endpoints	66%	100%	
Required postmarketing studies			
• No	97%	0%	<0.001
• Yes	3%	100%	

Table 2 - Characteristics of Pivotal Trials Supporting Approvals of Indications with Real-time Oncology Review

	Traditional approval N=68	Accelerated approval N=16	P-value
Study type			
• Interventional	100%	94%	0.21
• Observational	0%	6%	
Study design			
• Single arm with no comparator	15%	75%	<0.001
• Multiple arm	85%	25%	
Sample size, median (IQR)	612 (419-759)	108 (88-131)	<0.001
Study duration in months, median (IQR)	40.1 (32.1-51.2)	69.4 (53.5-83.5)	0.002
Primary efficacy endpoint			
• At least one clinical outcome	31%	0%	0.008
• Only surrogate marker	69%	100%	

Funding

This work was supported by a grant from Arnold Ventures.