Rare Cancer Drug Development

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Examples of Approvals for Rare Cancers in 2023

New Molecular Entities

- **Pirtobrutinib (Jaypirca):** adult patients with relapsed/refractory mantle cell lymphoma
- **Retifanlimab-dlwr (Zynyz):** adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma
- **Nirogacestat (Ogsiveo):** adult patients with progressing desmoid tumors

Other Approvals

- **Bosutinib (Bosulif):** pediatric patients with chronic phase Philadelphia chromosome-positive chronic myelogenous leukemia
- **Encorafenib (Braftovi) & Binimetinib (Mektovi):** adult patients with non-small cell lung cancer with a BRAF V600E mutation
- **Dabrafenib (Taflinar) & Trametinib (Mekinist):** Pediatric patients with low-grade glioma with a BRAFV600E mutation
- **Eflornithine (Iwilfin):** adult and pediatric patients with high-risk neuroblastoma as maintenance treatment

Examples of Flexibility in Oncology Approvals

- **Alpelisib (Vijoice)**
  - Adult and pediatric patients with severe manifestations of PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy
  - Volumetric-based response criteria
  - One adequate and well controlled trial plus confirmatory evidence
  - Primary source of evidence of evidence: real-world data from EPIK-P1, a single-arm clinical study in patients 2 years of age and older with PROS who received treatment through an expanded access program for compassionate use
- **Eflornithine (Iwilifin)**
  - To reduce the risk of relapse in adult and pediatric patients with high-risk neuroblastoma who demonstrated at least a partial response to prior multiagent, multimodality therapy, including anti-GD2 immunotherapy
  - One adequate and well controlled study plus confirmatory evidence
  - The single adequate and well-controlled trial was an externally controlled trial comparing outcomes from Study 3b to Study ANBL0032 (clinical trial-derived external control arm)
- **Dabrafenib (Taflinar) and Trametinib (Mekinist)**
  - Adult and pediatric patients with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options
  - Tissue agnostic indication relying on data from 131 adult patients and 36 pediatric patients with a variety of cancer types

Oncology Companion Diagnostics Voluntary Pilot Program

- As described in FDA's in vitro companion diagnostic (CDx) guidance[1], there are specific circumstances where FDA may decide to approve a drug without clearing, approving, or authorizing a corresponding CDx test at the same time.
  - In these cases, tests offered as laboratory-developed tests (LDTs)[2] with unknown performance are being used for patient treatment decisions.
- Historically, FDA has generally exercised enforcement discretion with respect to most LDTs[3]
- FDA is piloting a new approach to provide greater transparency regarding minimum performance characteristics that certain tests for certain oncology drugs should meet (guidance issued in 2023)[4]

[1] https://www.fda.gov/media/81309/download

[2] For the purposes of FDA's guidance "Oncology Drug Products Use with Certain In Vitro Diagnostic Tests: Pilot Program", the term laboratory developed test (LDT) means an in vitro diagnostic device that is intended for clinical use and designed, manufactured and used within a single laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA) (42 U.S.C. 263a) that meets the requirements to perform tests of high complexity, as described in 42 CFR 493.17(c)(4) and 493.25, and is a location that has its own CLIA certificate as described in 42 CFR 493.43(a).

[3] Meaning that, except in certain circumstances, FDA generally does not exercise its authority to enforce the regulatory requirements for these devices, although it maintains that authority.

[4] https://www.fda.gov/media/169616/download

Pilot Program Process

FDA will request performance information for the tests used to enroll patients into the clinical trials that support drug approval

FDA will post to its website the minimum performance characteristics recommended for similar tests that may be used to select patients for treatment with the approved drug

Laboratories may use this information to guide their development of LDTs to identify specific biomarkers used for selecting cancer treatment

This transparency aims to help facilitate better and more consistent performance of these tests, resulting in better drug selection and improved care for patients with cancer

FDA Oncology International Collaboration

- Began in 2004 with European Medicines Agency (EMA)
- Now, monthly “hexalateral” meetings
  - FDA
  - EMA
  - Health Canada (HC)
  - Japan’s Pharmaceuticals and Medical Devices Agency (PMDA)
  - Australia’s Therapeutic Goods Administration (TGA)
  - Swissmedic (SM)
- Monthly “Pediatric Cluster” discussions began in 2007
  - FDA, EMA, PMDA, HC, TGA

OCE Project Orbis

- Collaborative review program launched in May 2019
- Launched in May 2019
- FDA review includes independent multi-disciplinary assessment including full review of datasets
- Current participating countries (Project Orbis Partners): TGA, HC, Brazil, Canada, Israel, Singapore, Switzerland, United Kingdom
- **Each country retains independent decision-making for each application**
  - Earlier submission of applications to Orbis countries, often within 1-2 months of FDA submission
  - Includes mechanisms for collaborative review with other regulatory authorities
- 81 FDA-approved Project Orbis applications (approx. 1/3 are US new molecular entities)
- Median number of countries per application: 3

Relevant FDA Guidances

- 2019 Draft Guidance for Industry: *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products
- 2023 Draft Guidance for Industry: *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation* - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-one-adequate-and-well-controlled-clinical
- 2023 Draft Guidance for Industry: *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products
- 2023 Draft Guidance for Industry: *Tissue Agnostic Drug Development in Oncology* - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/tissue-agnostic-drug-development-oncology


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