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COMMENTARY

FDA regulatory considerations for oncology drug development

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Over the past 20 years, more than 150 oncology drugs have been approved by the US Food and Drug Administration (FDA) including 42 novel therapeutics in 2021–2023 (Table 1). In this highly competitive environment, a proper understanding of the addressable challenges is essential for successful drug development. A clinical development program may benefit from being granted Accelerated Approval (AA) status if the caveats and obligations are properly understood. For US aspirations, it is important to consider early efforts toward dose optimization and a sufficient representation of ethnic diversity in patient populations.[1,2]

A major challenge for oncology drug developers is the number of new drugs that reach approval every year. According to the annual report from the Oncology Center of Excellence (OCE), 66 new drugs or indications were approved in 2021, followed by 56 in 2022,[3,4] an average rate of more than one new approval per week. Recently, Demirci et al.[5] evaluated the clinical development time for 76 new anticancer drugs, using the earliest clinical trial start date to the date of submission of the marketing authorization application (MAA) in the United States. The study revealed how utilizing combinations of expedited regulatory approval programs is associated with shorter clinical development times, potentially benefiting the pharmaceutical industry by allowing earlier drug availability.

Clinical development for the early immuno-oncology drug ipilimumab spanned a total of 127.4 months. This length of time stands in stark contrast to the more recently approved pembrolizumab, which benefited from previous lessons learned and close interaction with the FDA, achieving approval in 46 months from First-Patient-In. Five PD-1/-L1 inhibitors, pembrolizumab, nivolumab, avelumab, atezolizumab, and durvalumab have since received breakthrough designations in various cancer types, and subsequent Accelerated Approval (AA).[6] Drug developers face ever-higher bars to show superior clinical efficacy against increasingly better comparators. Moreover, competition among comparators is not limited to the same class of drug but can extend beyond mechanisms of action.

With every new drug approval, the standard-of-care (SOC) changes accordingly. Drug developers must therefore seek to understand the unmet needs of today, as well as consider how upcoming approvals will impact the SOC in the future. The history of oncology clinical development has often shown a cyclical pattern, with the highest unmet needs moving from later lines of cancer treatment to earlier lines, before re-emerging in later lines with the appearance of resistance to newly approved drugs. To accelerate the impact of new therapies, the FDA initiative FRONTRUNNER encourages sponsors to prioritize the development and approval of new cancer drugs in an earlier clinical setting rather than the usual approach of starting development in later lines of therapy.[7] Despite this initiative, robust clinical development strategies may benefit from flexibility and a thorough real-time analysis of the competitive landscape, considering the priority indication, emerging targets, and how impending approvals from different drug classes may impact the SOC.

The FDA has created four mechanisms to expedite the development of new drugs: Fast Track, Breakthrough Therapy, AA, and Priority Review. For a deeper discussion, this paper will mainly focus on the AA program. The AA program is designed to enable earlier patient access to new therapies in areas of high unmet need, with relatively lower levels of evidence required. This can substantially

TABLE 1 FDA approvals in oncology.

	2021	2022	2023
NMEs/Original BLAs	16 (6 Regular, 12 AA) (9 RTOR, 6 AAid)	12 (5 Regular CDER, 5 AA CDER) (4 RTOR, 11 AAid)	14 (13 CDER, 1 CBER) (4 RTOR, 11 AAid) (RA 7, AA 6)
Supplements (new indication)	50 (43 Regular, 7 AA) (16 RTOR, 26 AAid)	44 (39 Regular, 5 AA) (11 RTOR, 36 AAid)	42 (42 CDER, 0 CBER) (2 RTOR, 26 AAid)
Supplements (new population)	8	5	9
505(b)(2)	6	29	15
Oncology-related devices (total, CDRH)		54	
In vitro diagnostic devices (PMAs)	16 (12 companion diagnostics)	18 (12 companion diagnostics)	62 (15 companion diagnostics)
Radiation oncology and diagnostic imaging, breast cancer sentinel lymph node, and orthopedic devices	-	33	41
Breakthrough designation	25 (22 CDER, 3 CBER)	17 (13 CDER, 4 CBER)	11 (10 CDER, 1 CBER)
Breakthrough device designation	13	14 (CDRH)	-
Fast track	58	7 (6 CDER, 1 CBER)	7 (7 CDER, 1 CBER)
Priority review	70 (68 CDER, 2 CBER)	39 (35 CDER, 4 CBER)	48 (47 CDER, 1 CBER)

Note: Refer to: Oncology Center of Excellence Annual Report 2021/2022/2023. FDA.

Abbreviations: AA, accelerated approval; AAid, assessment aid; BLA, biologics license application; NME, new molecular entity; PMA, premarket approval; RTOR, real-time oncology review.

offset the financial risk to drug developers, as AA can be granted at earlier developmental stages before confirmatory data is generated. The proportion of AA-designated programs was 29% in 2021 and 18% in 2022,[3,4] with 75% ($n=155$) granted in oncology.[8] Most have relied on data from single-arm trials using surrogate endpoints of objective response rate and duration of response. AA is always granted as a temporary measure with the understanding that drug developers must provide follow-up confirmatory evidence in a timely manner.

The FDA continues to encourage expedited regulatory approaches via the accelerated approval pathway. It is recommended that one or two randomized controlled trials should be conducted to support an AA program by confirming clinical benefits. The term "Dangling" refers to approvals where confirmatory trials did not verify clinical benefits, but for which marketing authorization continues. In certain cases where there are compelling reasons for a confirmatory trial failing to verify clinical benefit, approval can sometimes remain in place while another confirmatory trial is underway. When more conventional approaches such as single-arm trials are considered for AA, a confirmatory trial should be initiated with a defined timeline for the final report to the FDA.[9] Furthermore, in the field of oncology, drug developers must not only consider the planning of their pivotal trial but also pay careful attention to subsequent development plans with a precise timeline.

Maximum tolerated dose (MTD) is frequently used to determine the recommended phase 2 dose (RP2D) but was conceived during a time when most cancer drugs were cytotoxic chemotherapeutic agents, with the rationale being that the highest tolerable dose would achieve maximum benefit. The arrival of targeted agents has shown that the clinically optimal dose is not necessarily the highest possible dose, with efficacy plateaus and toxicities weighing into more complex risk–benefit decisions. The FDA's OCE launched Project Optimus in 2021 to provide clearer guidance on determining the optimal dose through clinical trials and modeling. Importantly, it emphasizes the need to collect sufficient safety data beyond dose-limiting toxicities at different dose levels for consideration in parallel with efficacy data.[1]

Project equity is an FDA initiative that aims to ensure that data submitted to the FDA for the approval of oncology medical products adequately reflects the patient demographics for which the products are intended. Draft guidance for this diversity plan was first issued in April 2022,[2] followed closely by ICH Guidance E17 stressing the importance of well-designed Multi-Region Clinical Trials (MRCTs) to factor in regional differences.[10]

Other initiatives include Project Orbis[11] and Real-Time Oncology Review (RTOR).[12] Project Orbis is an initiative by the FDA's Oncology Center of Excellence that facilitates a collaborative international review process for oncology drugs, aiming to accelerate approval times and synchronize regulatory decisions across multiple countries. RTOR allows for an expedited review process where drug manufacturers can submit parts of a drug application in advance to reduce review times by addressing FDA queries in real time.

Programs developed outside the United States often feature early clinical trials lacking US patient involvement while

simultaneously aiming for a US NDA or BLA, with the intention of accommodating US ethnic diversity in late-phase development. For this strategy, several factors should be considered for applications based on ethnic data alone[13]: (1) The data should be applicable to the US population and US medical practice; (2) the studies should be performed by clinical investigators of recognized competence; and (3) the data should be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means. The FDA recently approved toripalimab (Loqtorzi™) for advanced nasopharyngeal cancer based on clinical trial data derived solely from patients in China, Singapore, and Taiwan. The developer was requested to conduct a single-arm post-approval study with at least 100 patients in the United States and Canada with sufficient ethnic diversity. In this case, the FDA likely approved toripalimab due to the very high unmet need for nasopharyngeal cancer and the rarity of the disease in the United States. Global drug development programs benefit from such considerations in early phase trials and for programs originating outside the United States, a pivotal trial including US ethnic diversity is required for an NDA/BLA.

The goal of market authorization requires a robust clinical development plan with careful monitoring of the changing competitive landscape and close dialogue with regulatory agencies. Excellence in clinical trial strategy and management can help drug developers generate quality data more rapidly, a key factor for success in a highly competitive environment where numerous drugs are often under development for the same indication at the same time.

NOMENCLATURE OF TARGETS AND LIGANDS

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[14] and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019)[15].

AUTHOR CONTRIBUTIONS

Manuscript concept and design of structure: Moon H. Manuscript writing, Final approval of manuscript, Accountable for all aspects of the work: All authors.

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DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS STATEMENT

Not applicable.

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