CDDF Multi-stakeholder Workshop

Endpoints in Cancer Drug Development

Session 2: Endpoints in Expedited Approval Pathways

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Disclosures

- I have no financial disclosures
- I will not be discussing off-label and/or investigational use of named products in this presentation
- These slides represent current thinking in a rapidly evolving field of regulatory science

Requirements for NDA Approval

- Substantial evidence of efficacy with acceptable safety in adequate and well-controlled studies
- FDA examines the evidence in the context of the disease state, available therapy, study design, endpoints selected, and strength of the evidence
- Ability to generate product labeling that:
  - Defines an appropriate patient population
  - Provides adequate information to enable safe and effective use

Federal Food, Drug, and Cosmetic Act, Section 505

Approval Pathways

- **Regular Approval**
  - Approval is based on demonstration of clinical benefit or an effect on an **established surrogate**

- **Accelerated Approval**
  - Treatment of serious or life-threatening illness
  - Provides a meaningful therapeutic benefit to patients over existing treatments
  - Approval is based on an effect on a **surrogate endpoint reasonably likely to predict clinical benefit** or on a clinical endpoint other than mortality or irreversible morbidity
  - May require post-approval trials to verify anticipated clinical benefit

21 CFR 314.510
21 CFR 601.40
21 CFR 601.41

Overall Survival: The "Gold Standard"

- **Strengths:**
  - Direct measure of benefit
  - Least prone to bias, no interpretation of the event needed
  - 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 cross-over (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

Early Clinical Endpoints

- Necessary in the current context of drug development e.g. small molecularly defined subgroups
- In oncology, most accelerated approvals are based on trials with objective response rate (ORR) as the primary endpoint
- Example:
  - Since 2003, 8 out of 13 approved therapies for relapsed refractory multiple myeloma (MM) were initially approved using accelerated approval (7 using ORR)
  - Overall survival for patients with MM has improved dramatically over the same timespan, largely driven by therapeutic advancements (combination tx)
  - Four-year survival for newly diagnosed MM patients at Mayo clinic:
    - 50% for those diagnosed 2004-2007
    - 75% for those diagnosed 2013-2017

Nandakumar, et al ASCO 2019

Accelerated Approval Requirements

- Serious and life-threatening disease
- Substantial evidence of Efficacy and Safety
- Endpoint reasonable likely to predict clinical benefit
- Meaningful therapeutic benefit over available therapy
- May require confirmation of benefit

82 of 98 FDA AAs from 2010 through 2019 were for oncology indications

21 CFR Part 314, Subpart H;
21 CFR Part 601, Subpart E
Singh, et al. JAMA Oncology (2021)

Revisiting Accelerated Approvals

AAs may be reconsidered in settings where:

- Confirmatory trial has not verified benefit
- Clinical benefit has not been confirmed in other settings
- Treatment landscape has evolved over time

"The program allows the FDA to approve a drug or biologic product intended to treat a serious or life-threatening condition based on an outcome that can be measured earlier than survival that demonstrates a meaningful advantage over available therapies. **However, when confirmatory trials do not confirm clinical benefit, a reevaluation must be performed to determine if the approval should be withdrawn."**

- Richard Pazdur on March 11, 2021

https://www.fda.gov/news-events/fda-brief/fda-brief-fda-oncologic-drugs-advisory-committee-review-status-six-indications-granted-accelerated

Breakthrough Designation & Priority Review

- In addition to the accelerated approval pathway, there are other ways of expediting drug development
- Breakthrough therapy designation (BTD):
  - More frequent meetings, eligibility for PR, rolling review, intensive guidance on an efficient drug development program
  - Each year, over 40% of all BTDs are in oncology
- Priority Review (PR):
  - 6-month review timeline for supplemental drug applications
  - 8-month review timeline for NME marketing applications
- OCE Real Time Oncology Review (RTOR) pilot:
  - For 20 RTOR applications submitted between 2018-2020, median time from application submission to approval was 3.3 months (range of 0.4–5.9 months)

Singh, et al. JAMA Oncology (2021)
de Claro, et al. CCR (2021)

Conclusions

- Regulatory innovation has led to the approval of multiple practice changing therapeutics
- Smaller trials with molecularly defined populations and use of early clinical endpoints such as overall response rate are a reality of oncology drug development, however;
- Where clinical benefit is not confirmed, AAs may be reevaluated
- FDA OCE is committed to expediting drug development, which includes use of BTD and PR
- OCE has multiple pilot programs to streamline review and further shorten review times

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