Assessing the Correlation Between Surrogate Endpoints and Clinical Benefit in Oncology Accelerated Approvals: A Comparative Analysis

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Introduction

In recent years, there has been a rise in the number of oncology therapeutics seeking approval through the accelerated approval pathway by the US Food and Drug Administration (FDA) to address unmet medical needs.[1]

- Accelerated approval guidelines allow manufacturers to use surrogate endpoints as substitutes for clinical endpoints as a quicker way to evaluate the efficacy of a proposed therapeutic.[2] However, these surrogate endpoints may not always accurately predict the desired clinical outcomes and thus validation of these endpoints is necessary.[3]
- Although surrogate endpoints can speed up the approval process for oncology clinical trials and make evaluation by the FDA more efficient, there are potential downsides to relying on them.
- Short-term data may be used to predict clinical outcomes, which means the actual long-term clinical benefit of a medication may not be accurately represented.[4]

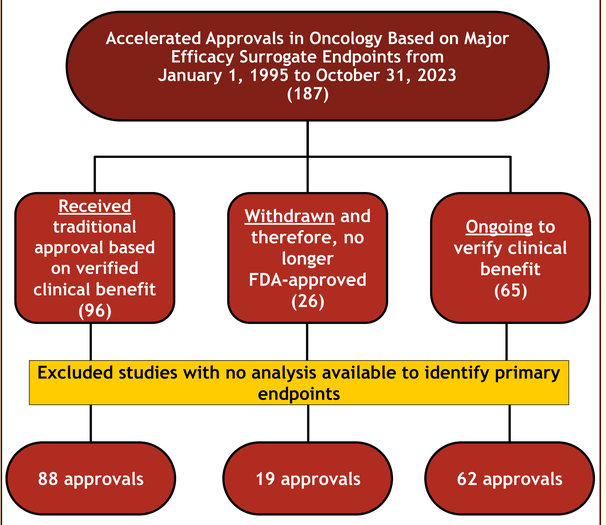
Objective

To **evaluate surrogate endpoints** utilized in accelerated approvals to **assess the validity in determining clinical benefit**, which can ultimately have implications on regulatory decision-making and thus, improve patient health outcomes in oncology.

Methods

A search within the **Food and Drug Administration (FDA) website** was conducted to collect information regarding **Oncology (Cancer) / Hematologic Malignancies Approvals**.

Target Population	Accelerated oncology trials that received traditional approval, were withdrawn, or are still ongoing
Timeline	January 1, 1995 to October 31, 2023
Surrogate Endpoints	Objective Response Rate (ORR), Progression Free Survival (PFS), Duration of Response (DOR), etc.



Results

Figure 1. Withdrawn Approvals - Surrogate Endpoints Utilized

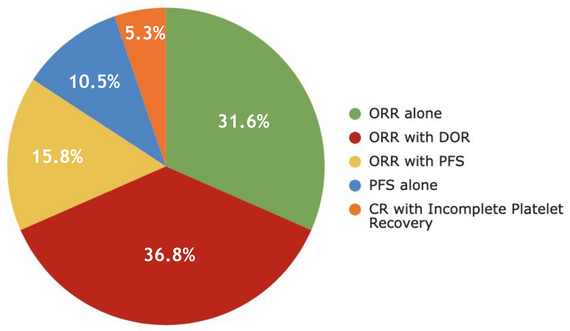


Figure 2. Ongoing Approvals - Surrogate Endpoints Utilized

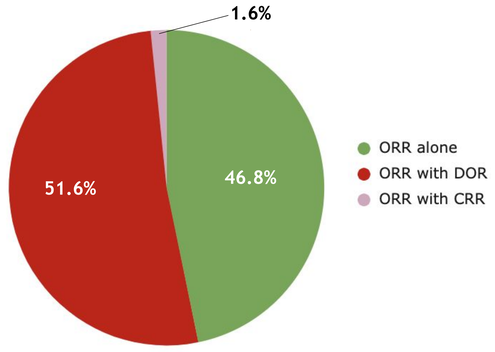


Figure 3. Verified Clinical Benefit - Surrogate Endpoints Utilized

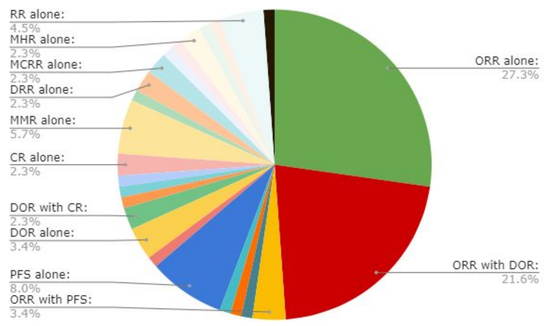


Figure 4. Frequency of Top Surrogate Endpoints Utilized

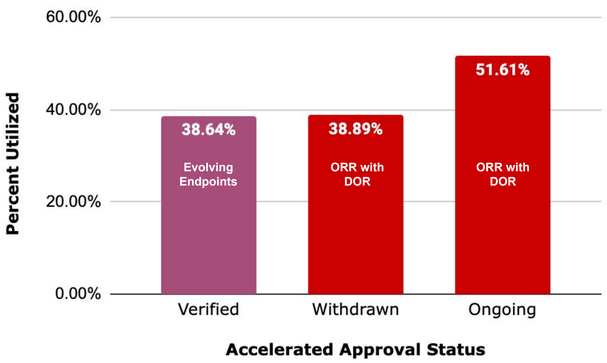
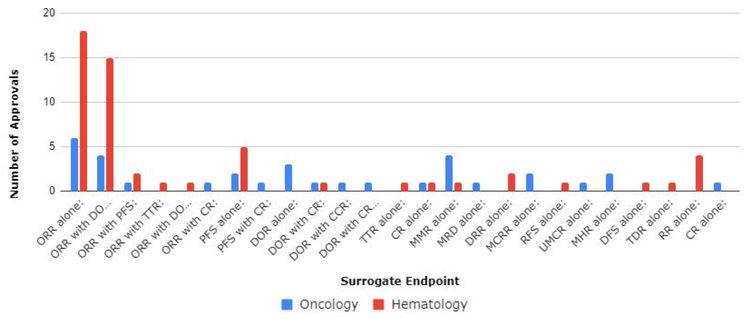


Figure 5. Verified Clinical Benefit - Surrogate Endpoints Utilized - Oncology vs. Hematology



Key Takeaways:

- **ORR with DOR emerges as the highest endpoint** used for withdrawn (38.89%) and ongoing approvals (51.61%), while **evolving endpoints**, which includes all other endpoints used apart from the traditional clinical endpoints, are **most prevalent in verified approvals** (38.64%).
- 88.89% of withdrawn approvals, 52.27% of verified approvals, and 100% of ongoing approvals utilized ORR either alone or with supporting endpoints for the basis of accelerated approval.
- The utilization of PFS as a surrogate endpoint is varied across approval status, with **approvals that have been subsequently withdrawn demonstrating a higher reliance on PFS** (27.78%) compared to verified approvals (12.5%) and ongoing approvals (0%).

Discussion & Conclusion

- ORR with DOR is notably the most frequently utilized endpoint among withdrawn and ongoing approvals.
  - However, ORR, either alone or with supporting endpoints, yields inconsistent results and may not always predict meaningful clinical benefit.
  - Therefore, there is a growing recognition of the need to shift towards evolving endpoints that hold promise in better predicting clinically meaningful outcomes.
- Evolving endpoints are surrogate endpoints which encompass a broader range of measures beyond traditional clinical endpoints seen in many of the ongoing and withdrawn approvals.
  - These evolving endpoints such as Minimal Residual Disease (MRD), Recurrence-Free Survival (RFS), and Disease-Free Survival (DFS) are frequently employed in verified approvals, signaling a shift away from traditional endpoints such as ORR, DOR, and PFS.
  - They offer promising alternatives to traditional endpoints by considering the complexities of cancer treatment and the need for more accurate measures of efficacy.

Conclusion

- The correlation between surrogate endpoints and clinical benefit proves to be multi-faceted & reliant on other factors.
- There are profound inconsistencies in the ability for surrogate endpoints to predict clinical outcomes.
- Recent utilization of newer endpoints such as MRD, RFS, and DFS seem to more successfully lead to verification of clinical benefit.
- Further explanation of these evolving surrogate endpoints should be further explored and evaluated instead of relying solely on traditional surrogate endpoints.

Limitations

- Validation of endpoints is limited to the primary outcome measures that are the basis for efficacy, and secondary endpoints such as Quality of Life (QoL) assessing patient tolerability and safety were not factored in.
- Limited data available online prior to 2006 caused challenges in identifying primary endpoints these older approvals.

References

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2. Johnson JR, Williams G, Pazdur R. End points and United States Food and Drug Administration approval of Oncology Drugs. Journal of Clinical Oncology. 2003;21(7):1404-1411. doi:10.1200/jco.2003.08.072
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