Surrogate Endpoints Under Attack: Is It Still Worth Performing Surrogacy Validation? Lessons from NSCLC

The Use of Accelerated Approval in Oncology

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Attributes of Accelerated Approval

"The Secretary may approve an application for approval of a product for a serious or life-threatening disease or condition, including a fast track product, under section 355(c) of this title or section 351(a) of the Public Health Service Act [42 U.S.C. 262(a)] upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."[1]

Balancing Access & Uncertainty

[1] https://friendsofcancerresearch.org/wp-content/uploads/Optimizing_the_Use_of_Accelerated_Approval-2020.pdf

Accelerated Approval (AA) Examples for Oncology Products That Verified Benefit

Drug	Indication	Time from AA to Verification (Years)
Capecitabine	Metastatic Breast Cancer	3.4
Imatinib	CML, GIST	2.6, 6.7
Oxaliplatin	Colorectal Cancer	1.4
Bortezomib	Multiple Myeloma	1.9
Trametinib/Dabrafenib	BRAF Melanoma	1.9
Pembrolizumab	NSCLC	1.1
Nivolumab	Melanoma	4.3
Crizotinib	ALK+NSCLC	2.2
Enfortumab	Bladder Cancer	1.5
Olaparib	BRCA+ Ovarian Cancer	2.7
Pembro/Lenvatinib	Endometrial Cancer	1.8
Palbociclib	Breast Cancer	2.1

The use of Accelerated Approval in oncology has enabled patient access to new medicines to address unmet needs years sooner.

Beaver JA, Howie LJ, Pelosof L, et al. A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics: A Review. JAMA Oncol. 2018;4(6):849–856. doi:10.1001/jamaoncol.2017.5618. Accessed online 10/1/2020.

Regulatory Outcomes of Accelerated Approval Drugs

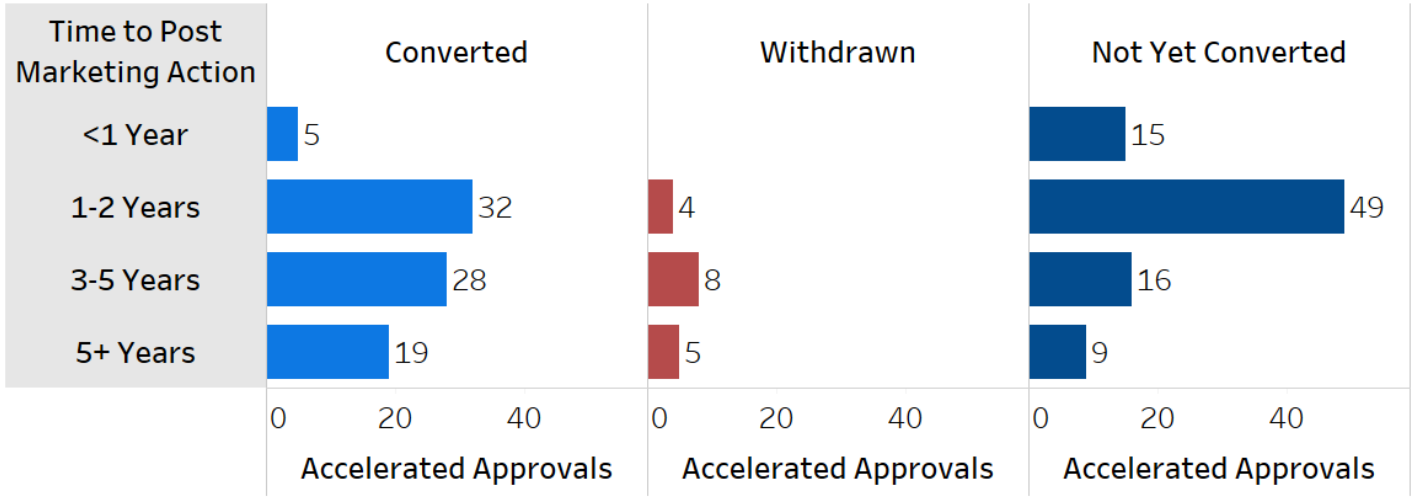
Accelerated Approval Indications	Total with Accelerated Approval	Total Converted to Full Approval	Total Withdrawn	Total Pending Action
All[1]	278	139 (50.0%)	28 (10.1%)	115 (42.8%)
All Approved Over 5-Years	66	34 (51.5%)	14 (21.2%)	18 (27.3%)
Oncology	190	84 (44.2%)	17 (9.0%)	89 (46.8%)
Oncology Products Over 5-Years[2]	33	19 (57.6%)	5 (15.2%)	9 (27.3%)

- In the past 10 years, ~80% of FDA's accelerated approvals were granted for oncology products.
- Approximately 10% of drugs have subsequently been shown to have unfavorable benefit-risk profile in follow-up studies

[1] Kaltenboeck A, Mehlman A, Pearson S. Strengthening the Accelerated Approval Pathway: An Analysis of Potential Policy Reforms and Their Impact on Uncertainty, Access, Innovation, and Costs. Apr 26, 2021. https://icer.org/wp-content/uploads/2021/04/Strengthening-the-Accelerated-Approval-Pathway-_-ICER-White-Paper-_-April-2021.pdf (accessed August 5, 2021).
[2] Friends of Cancer Research: https://friendsofcancerresearch.org/drug-development-dashboard (accessed February 9, 2022).

Median Years between Accelerated Approval and Follow-up Action

Accelerated Approval Indications	Converted	Withdrawn	Pending*
All (n=278)	3.2	6.9	1.8
Oncology (n=190)	3.1	3.8	1.8



- Generating confirmatory evidence for clinical endpoints can take additional time averaging 3-4 years
- Post-market confirmation studies are a critical component of the accelerated approval program, but can face trial participation and design challenges which may also necessitate development of long-term benefit data by other means or in similar indications

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Optimizing the Use of Accelerated Approval

FRIENDS OF CANCER RESEARCH ANNUAL MEETING 2020

Future Considerations

- Establish the use of comprehensive clinical development plans
- Timely initiation of confirmatory studies
- Implement a mechanism for post-market reporting/updates
- Streamline processes for dispute resolution of withdrawal

The Accelerated Approval (AA) Program has been an important regulatory mechanism for FDA to allow for earlier approval of drugs that treat serious and life-threatening illnesses than would occur through the traditional approval program. Created in 1992, the AA program was conceived as a direct response to patient therapy during the HIV/AIDS epidemic and recognition of the urgency of access to new therapy needs faced by patients living with serious illnesses. As opposed to traditional approval, which is based upon a direct measure of clinical benefit (Glossary) or a validated surrogate, AA is intended to allow earlier approval of a drug based on a demonstration of effect on a surrogate endpoint or an intermediate clinical endpoint—that is reasonably likely to predict a clinical benefit.[1-3] Under FDA regulations, sponsors should conduct post-marketing studies that verify and describe the expected clinical benefit of the drug with a clinical trial design as agreed upon with FDA at the time of approval. The AA program also establishes provisions for withdrawal of an AA drug where confirmatory trials fail to verify clinical benefit or safety concerns arise.

In 2012, the AA program (Subpart H – drugs and Subpart E – biologics) was codified in the Food and Drug Administration Safety and Innovation Act (FDASIA)[4]:

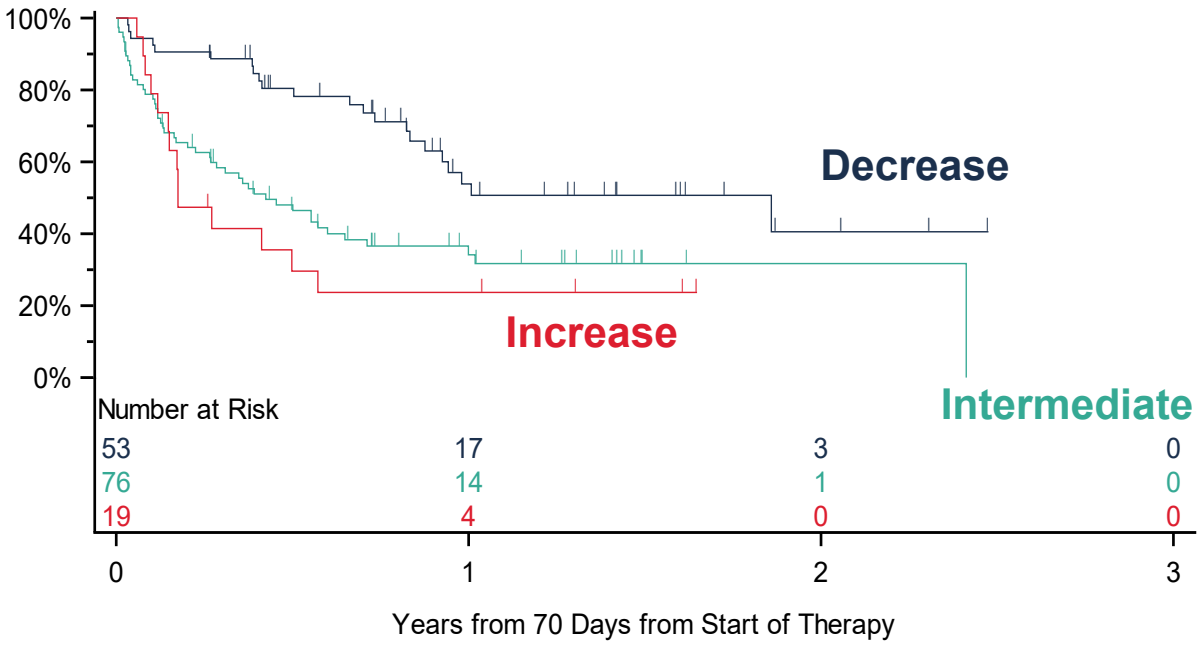
> *"The Secretary may approve an application for approval of a new drug or biologic for a serious or life-threatening disease or condition, including a fast track product, under section 355(c) of this title or section 351(a) of the Public Health Service Act [42 U.S.C. 262(a)] upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."*

FDASIA maintained the reliance of an AA on an intermediate endpoint (either surrogate or clinical endpoint that can be measured earlier) that is reasonably likely to predict an effect on clinical benefit but removed the initial requirement for an AA drug to "generally provide meaningful

https://friendsofcancerresearch.org/wp-content/uploads/Optimizing_the_Use_of_Accelerated_Approval-2020.pdf

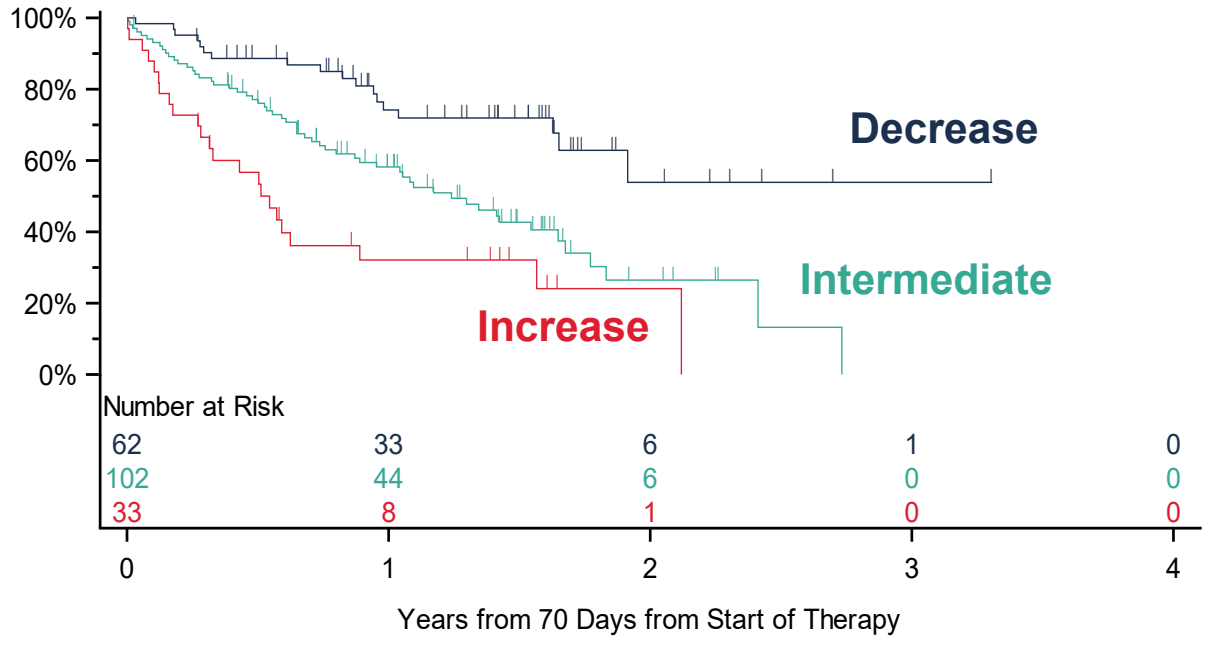
Robust Association Observed Between Strong Decreases in ctDNA and Patient Survival

Progression-Free Survival by Max VAF*



Log-rank Pairwise p-value	Decrease	Intermediate	Increase
Decrease	-		
Intermediate	**0.001**	-	
Increase	**<0.001**	0.426	-

Overall Survival by Max VAF



Log-rank Pairwise p-value	Decrease	Intermediate	Increase
Decrease	-		
Intermediate	**<0.001**	-	
Increase	**<0.001**	**0.014**	-

Survival Outcomes (3-Level)

Kaplan-Meier Curves

*Note: patients with progression within 70 days were excluded from the PFS plots.

Accelerated Approval Continues to be an Important Tool

- Accelerated Approval has enabled patients access to new medicines to treat serious illnesses with unmet medical need years sooner
- Oncology has been a therapeutic area to benefit from the pathway due to quantifiable and standardized disease measures
- This has been supported by rapidly evolving science leading to an improving understanding of disease biology and advanced drug design
- Most importantly the patient benefit is becoming clear – a recent study demonstrates a reduction in the 5-year mortality of NSCLC due to the availability of targeted therapies[1] many of which were approved through accelerated approval

[1] Howlader N, Forjaz G, Mooradian MJ, et al. The Effect of Advances in Lung-Cancer Treatment on Population Mortality. N Engl J Med. 2020;383(7):640-649. doi:10.1056/NEJMoa1916623