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Use of Accelerated Approval Pathway in Oncology

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Disclosures

- These slides represent current thinking in a rapidly evolving field of regulatory science

FDA's Role in Cancer Drug and Biologic Development

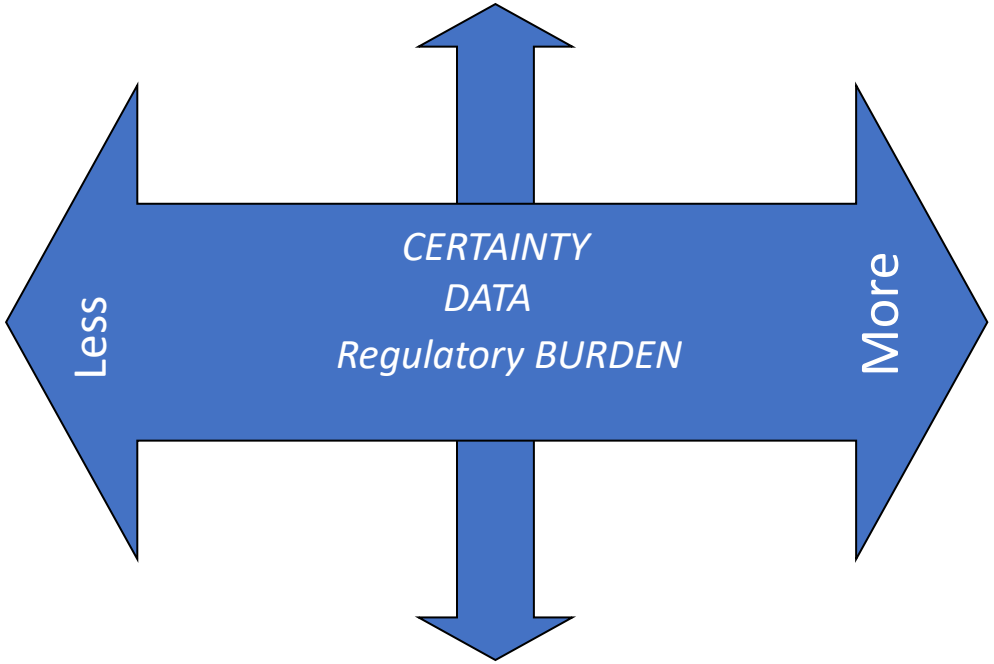
- FDA is responsible for:
  - Assurance of the Safety, Efficacy and Security of:
    - **Drug and Biological** products
    - Medical **Devices**
    - **Food** supply
    - **Cosmetics**
    - **Radiation products**
- Science and Collaboration

We **do NOT** regulate the cost of products

We **do NOT** regulate the practice of medicine

Striking the Balance

Flexible, Efficient, Interactive



Consistent, Thorough, Independent

"Toxic deaths!

Delayed safety findings!

FDA asleep at the Wheel"

"Too Cautious!

Stifling Innovation!

Reduce regulatory burden!"

Accelerated Approval (AA) pathway

- Originally developed in 1992 to address HIV and AIDS crisis
- Intended for serious and life-threatening diseases
- Expedites access to drugs using trials that use a surrogate endpoint reasonably likely to predict benefit, OR an intermediate clinical endpoint other than irreversible morbidity or mortality
- May require post-approval studies to verify clinical benefit
- Dr. Pazdur: “…this program is for the patients!”

Advantages of AA in Oncology

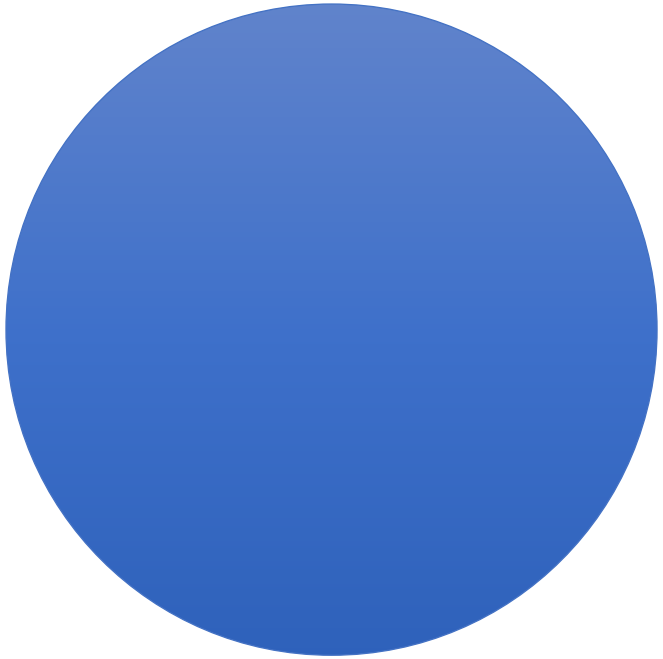
- AA provides patients earlier access to new and practice-changing drugs
- AA may require sponsors to conduct confirmatory trials to verify the drug's clinical benefit (typically required)
- AA is predominantly used in oncology, with cancer drugs accounting for about 85% of all AAs granted in the past decade (172 indications)
  - Clinical benefit has been verified in 50% of oncology AAs (86 indications)
  - Confirmatory trials ongoing in 38%, withdrawn indications 12%
- Median time to verification of clinical benefit and granting of traditional approval was 3.1 years (range, 0.5 to 17.6)
- Median time to withdrawal of an indication was 3.8 years (range, 1.3 to 12.5)

Fashoyin-Aje LA, Mehta GU, Beaver JA, Pazdur R. The On- and Off-Ramps of Oncology Accelerated Approval. N Engl J Med. 2022 Sep 21.

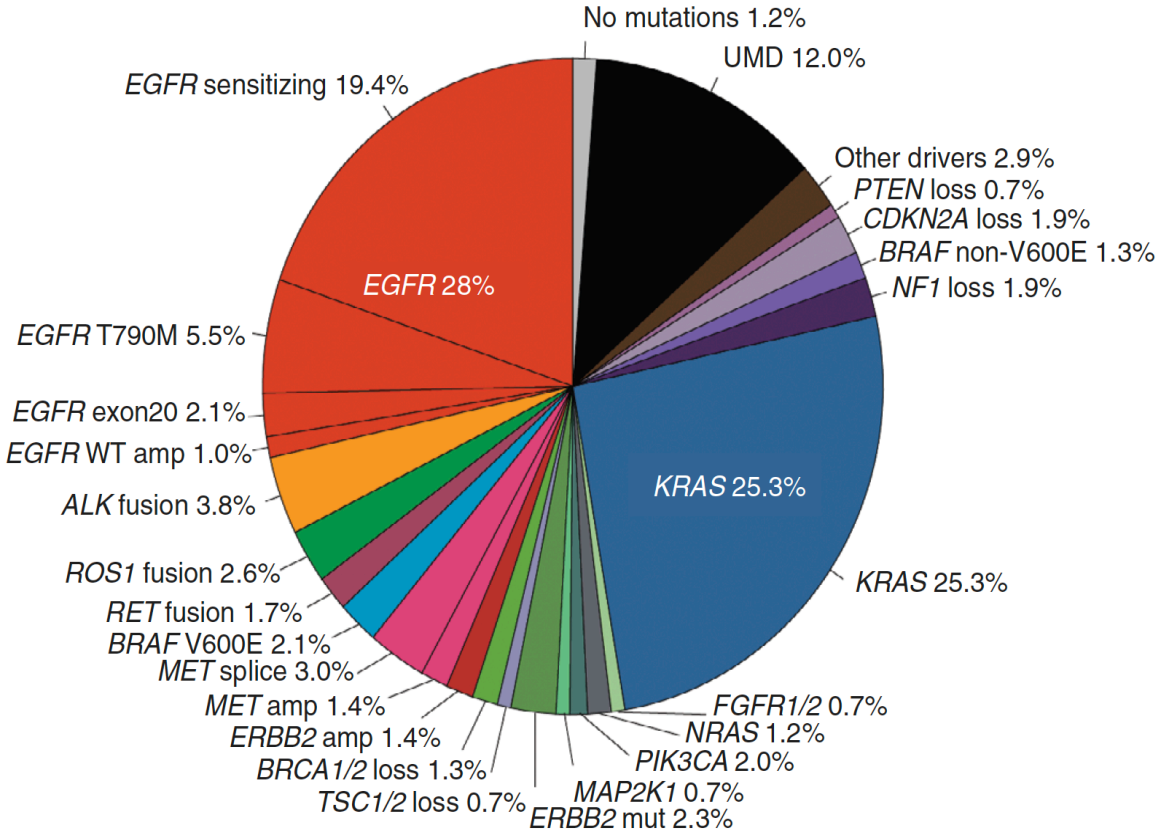
Response Rate is Becoming Increasingly Important

Formerly big populations are becoming very small subsets

Non-Small Cell Lung Cancer (NSCLC) 20 years ago



NSCLC Today



Jordan et al., Cancer Discov 7: 596-609, 2017

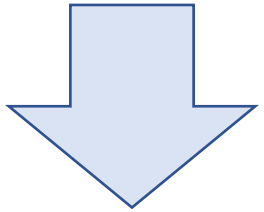
Precision Oncology – A Success Story

- Precision oncology (PO) has benefited from AA pathway → 42 AAs in precision oncology for solid tumors
  - 86% based on ORR
  - Median ORR 53%
  - No AAs in PO have been withdrawn
  - All PO AA indications granted before Nov 2018 have converted to traditional approval
- High ORRs, biomarker specific in early trials may make subsequent randomized trials difficult to conduct

Subbiah, V., Wirth, L.J., Kurzrock, R. *et al.* Accelerated approvals hit the target in precision oncology. *Nat Med* 28, 1976–1979 (2022).

Limitations of Single Arm Trials

- Rely on overall response rate
- Time-to-event endpoints (OS, PFS) uninterpretable
- Limited safety data
- Sponsors frequently delay initiation of confirmatory trials



- One randomized trial that could both support AA AND verify benefit.
  - AA could be granted on the basis of planned interim analysis of ORR
  - Traditional approval based on clinical benefit (OS) at the trial conclusion

Fashoyin-Aje LA, Mehta GU, Beaver JA, Pazdur R. The On- and Off-Ramps of Oncology Accelerated Approval. N Engl J Med. 2022 Sep 21.

Expanding Our Evidence Base in SATs

- Interpretation of PRO results supporting effectiveness (e.g. improvement in disease sx) can be challenging in SATs
- Safety data from single arm trials is usually limited
- Opportunity: to collect patient-reported tolerability in early phase trials
  - Collect 8-12 relevant treatment related symptoms using an item library
  - Overall side effect bother (e.g. FACT-GP5)
  - Physical/role function
  - Free text item where side effect profile is not well known
- Collection of PROs (tolerability) is feasible and informative in all trial designs, including SATs

Bhatnagar V, Kluetz PG. Encouraging Rigorous Patient-Generated Data All Along the Drug Development Continuum. J Natl Cancer Inst. 2022 Oct 6;114(10):1313-1314.

Conclusions

- Single-arm trials and AA are a reality of the oncology drug development paradigm
- Use of the AA pathway in oncology has led to therapies being available many years earlier – e.g. precision oncology
- There are ways to use the AA pathway that do not rely on SATs.
- FDA and sponsors should agree in advance on trial designs, criteria for attaining AA, and how to confirm clinical benefit
- OCE is driving change in the current drug development paradigm: Project Confirm, Project FrontRunner

Acknowledgements and Additional Resources

- Richard Pazdur
- Paul Kluetz
- OCE staff
- Project Confirm - https://www.fda.gov/about-fda/oncology-center-excellence/project-confirm
- Project FrontRunner - https://www.fda.gov/about-fda/oncology-center-excellence/project-frontrunner