Session 5: Incorporation of Overall Survival into the Benefit-Risk Assessment

MODERATOR:

Nicole Gormley, MD
U.S. Food & Drug Administration

OVERVIEW OF RECOMMENDATIONS SESSION CHAIR:

George Demetri, MD, FAACR
Dana-Farber Cancer Institute

ADDITIONAL PANELISTS:

- **Pallavi Mishra-Kalyani, PhD,** FDA
- **Nicholas Richardson, DO, MPH,** FDA
- **Cong Chen, PhD, FASA,** Merck
- **David Mitchell,** Patient Advocate
- **Grzegorz Nowakowski, MD,** Mayo Clinic
- **Craig Tendler, MD,** Janssen of Johnson & Johnson

2305014M

FDA-AACR-ASA Workshop

OVERALL SURVIVAL IN ONCOLOGY CLINICAL TRIALS

July 18, 2023 | 8 a.m.-5 p.m. | Bethesda, Maryland

Session 5: Incorporation of Overall Survival into the Benefit-Risk Assessment

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Dana-Farber Cancer Institute and Ludwig Center at Harvard Medical School, Boston MA

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#AACRSciencePolicy

FDA U.S. FOOD & DRUG ADMINISTRATION

AACR American Association for Cancer Research

ASA AMERICAN STATISTICAL ASSOCIATION Promoting the Practice and Profession of Statistics

George Demetri, MD, FAACR

I have the following relevant financial relationships to disclose:

Employee of: Dana-Farber Cancer Institute

Consultant for: Bayer, Jazz Pharmaceuticals, PharmaMar, Daiichi-Sankyo, EMD-Serono/Merck KGaA, Mirati, WCG/Arsenal Capital, Rain Therapeutics, Aadi Biosciences, G1 Therapeutics, Caris Life Sciences, Erasca Pharmaceuticals, RELAY Therapeutics, Bessor Pharmaceuticals, CellCarta, Ikena Oncology, Kojin Therapeutics, Acrivon Therapeutics, Blueprint Medicines, Boundless Bio, Point Biopharma, Tessellate Bio, IDRX (co-founder)

Speaker's Bureau for: no entity whatsoever

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Stockholder in: G1 Therapeutics, Caris Life Sciences, Erasca Pharmaceuticals, RELAY Therapeutics, IDRX, Bessor Pharmaceuticals, CellCarta, Ikena Oncology, Kojin Therapeutics, Acrivon Therapeutics, Blueprint Medicines, Tessellate Bio, Boundless Bio

Honoraria from: none

- and -

My additional financial relationship disclosures are: none

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Session Objectives

- To discuss “best practices” for incorporation of early (or limited) OS results into the overall benefit-risk assessment.
- To identify “best practices” for incorporation of other safety information into the benefit-risk assessment, such as deaths, adverse events, and drug tolerability.
- To discuss potential regulatory implications of OS analyses for potential harm based on early or limited OS results, including (*but not limited to) accelerated approval for randomized trials without sufficient OS information and post-marketing requirements to obtain additional OS information.

OS in Benefit-Risk Assessment

1. **What amount of uncertainty or immaturity in OS data should prompt requests for post-marketing data to obtain additional OS information?**

- It is a complex decision that depends on several factors including (but not limited to):
  - magnitude of uncertainty
  - feasibility of obtaining additional information in a timely fashion
  - severity of the condition being treated
  - availability of alternative treatments
  - potential risks and benefits associated with the approved therapy
- Disease setting and treatment intent plays a major role – frontline versus R/R; Curative vs. Palliative therapy

OS in Benefit-Risk Assessment

2. The FDA has used endpoints such as PFS or ORR to support both accelerated and regular approval, depending on the disease context, magnitude of effect, and presumed relationship with OS. If trial data suggest

(a) potentially divergent results, and/or

(b) there are immature OS data, and/or

(c) there is significant uncertainty regarding the OS results,

what supportive analyses might be done to increase confidence in the overall benefit-risk assessment?

- Consistency of results across other relevant endpoints in the same class of drugs may be key
- Further investigation of mean response duration, durable response rate, or any other alternative endpoints potentially helps put regulatory decision-making as well as clinical development decision-making on a more solid footing.

OS in Benefit-Risk Assessment

3. Should more OS data be required from the same trial? (If so, when and under what criteria?)

- Additional data from other ongoing trials or RWD can also be helpful.
- In general, it is helpful to collect more OS data from the same trial.
- However, in case the trial is for Accelerated Approval with limited sample size, OS data from the post-marketing commitment study may be even more informative.

OS in Benefit-Risk Assessment

4. Should the Accelerated Approval (AA) pathway be used in instances where there is significant uncertainty regarding the OS data?

- AA is for serious conditions that fulfill a major unmet medical need. While detrimental OS effect is always a showstopper, barring major safety/tolerability concerns, it may still be used if the uncertainty is solely due to small number of OS events.
- The disease setting and what constitutes clinical benefit plays a major role in whether uncertainty in the OS data should be considered in deciding on the regulatory approval pathway.
- In situations, such as curative therapy, there is a clear need for new products to demonstrate a favorable impact on OS and if the initial data yield significant uncertainty, use of accelerated approval is reasonable followed by confirmation of benefit with longer follow-up to adequately assess OS.

OS in Benefit-Risk Assessment

5. **Patients with oncologic diseases often receive post-trial therapy that can impact the interpretation of long-term outcomes such as OS.**
How should other long-term efficacy data (e.g. time-to next treatment, PFS2, etc.) be incorporated into the overall benefit-risk assessments?

- Side effects can impact a patient's ability to receive effective subsequent therapy. It is a concern when there is substantial imbalance in these long-term efficacy effects. However, there may be many confounding factors that make it difficult to interpret the data. Proper causal analyses may need to be conducted to assess veracity.

- There is a need to adequately capture data on receipt of subsequent therapy and the reason for initiation (post-PD versus in the absence of PD). This would allow for an accurate summary of subsequent therapies which allows further characterization of the OS data.

OS in Benefit-Risk Assessment

6. **OS is a composite endpoint comprising both safety and efficacy.**

In addition to the standard assessments of adverse events, serious adverse events, deaths, drug discontinuations, etc., are there toxicity metrics, additional statistics, or other information that should be included in risk assessments?

- In case dose reduction/interruption/discontinuation of standard-of-care in combination therapy is not evenly assessed and thoroughly analyzed, there may be subtle harm. Reduction of exposure to standard-of-care therapy options may be considered a violation of the "first do no harm" principle.

OS in Benefit-Risk Assessment

7. Are there considerations for when OS should be prioritized or de-prioritized in the benefit-risk assessment? For example, how should very early or immature OS results be weighed in the benefit-risk assessment?

- If the disease being treated is life-threatening or has a significant impact on patient survival, OS is generally given high priority. In such cases, demonstrating a clear and meaningful improvement in OS becomes a crucial factor in determining the benefit-risk profile of a therapy.
- If there are established treatments with proven OS benefits, the priority of OS as an endpoint may be higher too. Comparisons against standard of care or active comparators may require demonstrating a superior OS outcome to establish the added benefit of a new therapy.
- OS may be deprioritized when it is already approved in later line settings and a substantial number of patients crossover (the OS benefit should be evident early on and not detrimental later), in which case the treatment effect after proper adjustment of the crossover effect needs to be clinically meaningful.

OS in Benefit-Risk Assessment

8. Considering the global conduct of clinical trials, how should information about the local therapeutic landscape and availability of subsequent therapy options be considered?

- There are often many similar drugs in similar classes under active development. It may be inevitable that patients in the control arm in the current study of some such drug class might receive a similar treatment after progression.
- A proper analysis that adjusts the crossover effect under varying assumptions about the treatment effect of the subsequent therapy (e.g., 50% effective) may again be conducted to assist with the regulatory decision-making.
- In the spirit of Project FrontRunner, availability of subsequent therapies should not be a deterrent to drug development in earlier disease settings.

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Session 5 Questions

1. What amount of uncertainty or immaturity in OS data should prompt requests for post-marketing data to obtain additional OS information?
2. If trial data suggest: (a) potentially divergent results, and/or (b) there are immature OS data, and/or (c) there is significant uncertainty regarding the OS results, what supportive analyses might be done to increase confidence in the overall benefit-risk assessment?
3. Should more OS data be required from the same trial?
   (If so, when and under what criteria?)
4. Should the AA pathway be used in instances where there is significant uncertainty regarding the OS data?
5. How should other long-term efficacy data (e.g. time-to next treatment, PFS2, etc.) be incorporated into the overall benefit-risk assessments?
6. In addition to the standard assessments of adverse events, serious adverse events, deaths, drug discontinuations, etc., are there toxicity metrics, additional statistics, or other information that should be included in risk assessments?
7. Are there considerations for when OS should be prioritized or de-prioritized in the benefit-risk assessment? For example, how should very early or immature OS results be weighed in the benefit-risk assessment?
8. Considering the global conduct of clinical trials, how should information about the local therapeutic landscape and availability of subsequent therapy options be considered?