Summary and Closing Remarks

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FDA-AACR Dosing Workshop

Please join us again on October 2-3

FDA-AACR Workshop on Quantitative Methods in Dosage Optimization of Oncology Products

At the FDA White Oak Campus

Registration Coming Soon

OVERALL SURVIVAL IN ONCOLOGY CLINICAL TRIALS: WORKSHOP SUMMARY

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Workshop Sessions and Objectives

Session 1: Trial Design Considerations for Optimal Assessment of Overall Survival

- Discuss best practices in the clinical trial design to allow for adequate assessment of OS including randomization schemes, crossover, duration of OS follow-up, etc.

Session 2: Overall Survival as a Pre-Specified Endpoint

- Discuss pre-specified statistical OS analyses to assess the potential for harm

Session 3: Post-hoc Analyses of Overall Survival

- Discuss analysis methods to assess for harm when no pre-specified analyses for OS were planned.

Session 4: Subgroup Considerations

- Discuss the role of subgroups in relation to the primary ITT analyses and the interpretation of subgroup results

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

- Discuss best practices for incorporation of early or limited OS results into the benefit-risk assessment and discuss potential regulatory implications of OS analyses evaluating the potential for harm

Session 1 Key Points (Trial Design)

- Intercurrent events (e.g. crossover or subsequent therapy) or known subgroups can affect interpretation of OS and should be considered and planned for at the time of trial design if possible

- Regardless of exploratory evaluation or formal testing for OS, studies should be designed to adequately assess OS to inform evaluation of patient safety and product benefit-risk
  - Planning for appropriate length of follow-up is important

Session 2 Key Points (Pre-specified)

- Trials can include thresholds for harm and may be used to inform decision-making, based on variety of considerations such as disease setting, feasibility for obtaining long-term OS data, rate of mortality, physician/patient input, known toxicities, and other available data

- Multiple pre-specified sensitivity/supplementary analyses can help interpret results to account for intercurrent events or deviations from assumptions (such as proportional hazards)
  - Whether or not the traditional treatment effect summary measures (e.g., hazard ratio; median survival time) are adequate requires further justification when the proportional hazards assumption is not met

Session 3 Key Points (Post-hoc)

- OS should always be evaluated, but post-hoc assessments are considered descriptive and may be complicated by post-hoc intercurrent event handling and limited OS information

- Simulation and supplementary analyses to investigate the robustness of results under diverse assumptions is useful
  - Interpretation of post-hoc OS results will consider the totality of evidence (e.g., if multiple studies show potential detriment)

Session 4 Key Points (Subgroups)

- Must interpret with caution if subgroups were not formally powered and tested; in general, post-hoc subgroup analysis are exploratory
  - Known subgroups should be planned for and may require longer follow-up

- Post-hoc OS subgroup analysis should be conducted to remove concern of potential harm
  - Safety signals, such as high rate of death or hazard ratio crossing 1, observed in post-hoc analyses of biologically plausible subgroups should raise concern, particularly when combined with other evidence, and may necessitate halting the trial or restricting the indication

Session 5 Key Points (Benefit-Risk Assessment)

- Patients should be followed long-term regardless of intercurrent events to inform the benefit-risk assessment

- A product may be granted Accelerated Approval if OS is uncertain due to immature data but has favorable benefit-risk based on earlier endpoints (see also OCE Project FrontRunner)
  - Incorporating additional data from other ongoing trials, including of drugs in the same class and RWD could help supplement immature OS data, but long-term data from the same trial is most informative, including use and reason for subsequent therapy

Workshop Results & Impacts

We hope that this workshop can positively impact clinical trials in oncology…

- Shared best practices of trial design, analyses, and interpretation of overall survival in oncology clinical trials with the clinical trial community
- Explored approaches to address the uncertainty of OS analyses based on early or limited data and incorporate this information into the benefit-risk assessment
- Increased collaboration between oncologists and statisticians and across sectors
- Future clinical trial designs can incorporate more early planning and pre-specified approaches for measuring and analyzing OS to better support evaluation of safety and efficacy for a product
- Regulatory submissions can include a variety of supplementary analyses to better characterize uncertainty and potential for harm for benefit-risk assessments

Next Steps

- Panel working groups will re-group to summarize workshop discussion, including valuable input from the audience
  - ➢ Thank you all for your contributions today!

- Will develop a perspective article containing recommendations
  - – To be submitted to an AACR journal

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FDA-AACR-ASA Workshop

OVERALL SURVIVAL IN ONCOLOGY CLINICAL TRIALS

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

Thank you for attending!

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