

FDA-AACR-ASA Workshop

OVERALL SURVIVAL IN ONCOLOGY CLINICAL TRIALS

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



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

Mikkael A. Sekeres, MD, MS

Sylvester Cancer Center, University of Miami

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Disclosure Information

Overall Survival in Oncology Clinical Trials
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Mikkael Sekeres

I have the following relevant financial relationships to disclose:

Employee of:

Consultant for: BMS, Novartis, AstraZeneca, Kurome

Grant/Research support from: BMS

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



MODERATOR:

Ken Anderson, MD, FAACR

Dana-Farber Cancer Institute

OVERVIEW OF RECOMMENDATIONS

SESSION CHAIR:

Mikael Sekeres, MD

Sylvester Comprehensive Cancer Center
University of Miami

ADDITIONAL PANELISTS:

- **Lola Fashoyin-Aje, MD, MPH, FDA**
- **Alexei Ionan, PhD, FDA**
- **Margret Merino, MD, FDA**
- **Tatiana Prowell, MD, FDA**
- **Roy S. Herbst, MD, PhD, Yale Cancer Center**
- **Pabak Mukhopadhyay, PhD, AstraZeneca**
- **Anas Younes, MD, AstraZeneca**
- **Godwin Yung, PhD, Genentech/Roche**

Trial Design Considerations

1. Recent trials have used 2:1 randomization against a control arm known to confer a survival benefit. However, some of these trials have read out with observed OS detriments. Under what conditions could other randomization schemes (e.g., 2:1) be considered?

- 2:1 randomization may be preferable if there is prior evidence of a favorable benefit-risk profile (e.g., strong signal of preliminary activity in earlier trials or in other disease settings). Rationale: minimize risk to patients, minimize loss of power due to unequal randomization.
- But -- unequal randomization may also expose patients to unequal toxicities.
- But -- unequal randomization may result in similar or less power than 1:1. This depends on the hazard ratio, event-patient ratio, and survival duration
- 2:1 randomization may increase the likelihood of enrollment (patient interest) with less chance of randomization to control arm.
- Potential impact of unequal randomization: impact on number of events, delayed trial readout, increased number of patients, larger safety database.

Trial Design Considerations



2a. Crossover, an intercurrent event, allows patients access to promising agents if they have progressed on the control arm, but may have an impact on the interpretation of endpoints measured later in the trial, such as OS, time-to-next treatment (TTNT), etc. When could crossover be permitted in trials? Should there be a limit on the number of patients allowed to crossover, and in what circumstances is crossover most detrimental to interpretation of study results?

- Crossover may complicate assessment of OS!
- Consideration of crossover is context-dependent – is the drug first to market, or are other, similar drugs available?
- In some cases, OS assessment is still interpretable with a crossover design– therapies received after cross-over may not alter OS, and study drug may not be effective.
- Interpretation of crossover differs with cancers that are aggressive v. indolent

Trial Design Considerations

2b. Crossover, an intercurrent event, allows patients access to promising agents if they have progressed on the control arm, but may have an impact on the interpretation of endpoints measured later in the trial, such as OS, time-to-next treatment (TTNT), etc. When could crossover be permitted in trials? Should there be a limit on the number of patients allowed to crossover, and in what circumstances is crossover most detrimental to interpretation of study results?

- Crossover interpretation differs with primary trial endpoint: EFS, PFS, OS
- Crossover interpretation of results should be pre-specified *a priori* and being clear and aligned about the scientific questions to be answered is requisite. ITT analyses are required.
- Crossover should support collection of information for subsequent therapies: when it is started, how long it is given, and its efficacy.
- Crossover design may be based on the assumption that the trial drug is superior (patients and investigators).

Trial Design Considerations

3. Aside from crossover, what other intercurrent events (e.g., subsequent therapy, COVID-19 infection or death) may have an impact on the assessment of OS, specifically as being attributable to the investigational product?

- Death due to e.g., Covid may be “too true and unrelated,” or it may be a consequence of an investigational agent AE such as immunosuppression
- New treatment (protocol-specified or non-protocol specified) - including supplements/complementary therapies - before reaching the endpoint may affect interpretation
- Missing data, e.g., missed appointments, can affect interpretation of risks and benefits.
- Special populations, e.g., older populations with comorbidities and competing causes of death can affect trial eligibility, generalizability, and drug-specific risk/benefit interpretation.
- Impact of next line therapy on OS should be a routine analysis. This is challenging when the experimental treatment has already been approved in the subsequent line.

Trial Design Considerations

4. What factors should determine the appropriate length of follow-up for OS information?

- 1) Proportion of patients who have died;
- 2) Amount of information necessary to answer trial questions;
- 3) Precision of a given efficacy measure (e.g., hazard ratio, survival probability, etc.);
- 4) Expected survival (based on known data) in control arm based on tumor type/stage/de novo v. R/R: indolent v. aggressive disease;
- 5) The tail of the curve is a low confidence area; the neck of the curve is too early to assess survival

Trial Design Considerations

5. Overall survival is often a secondary endpoint in trials. Independent data monitoring committees will often monitor OS formally or informally as the trial progresses. Should IDMCs have strict criteria to assess OS throughout the trial? Are there any specific statistical considerations in this setting? Should there be a separate consideration for assessing futility vs. harm?

- When OS is a primary (or dual primary) endpoint, which is alpha controlled, the IDMC usually will have strict criteria to evaluate. As a key secondary endpoint, IDMC don't always assess OS after the primary endpoint has been met. Futility should be in scope when OS is primary/dual primary endpoint. Even if a formal futility analysis is not in place, IDMC should look at OS to assess risk.
- IDMCs should have access to OS throughout the trial and have pre-established guidance in place to react to results, so they don't stop a trial prematurely based on a small number of events, but also don't allow trials to continue with worrisome safety signals.
- IDMCs should exercise caution in interpreting OS differences early in a RCT based on small numbers of events as confidence intervals are wide and likely overlapping.

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Dana-Farber Cancer Institute

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Session 1 Questions

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2. When could crossover be permitted in trials? Should there be a limit on the number of patients allowed to crossover, and in what circumstances is crossover most detrimental to interpretation of study results?
3. Aside from crossover, what other intercurrent events (e.g., subsequent therapy, COVID-19 infection or death) may have an impact on the assessment of OS, specifically as being attributable to the investigational product?
4. What factors should determine the appropriate length of follow-up for OS information?
5. Should IDMCs have strict criteria to assess OS throughout the trial? Are there any specific statistical considerations in this setting? Should there be a separate consideration for assessing futility vs. harm?

Session 2: Overall Survival as a Pre-specified Endpoint

MODERATOR:

Lisa Rodriguez, PhD

U.S. Food & Drug Administration

INTRO:

Michael Shan, PhD

Bayer

OVERVIEW OF RECOMMENDATIONS

SESSION CHAIR:

Ruben Mesa, MD

Atrium Health

ADDITIONAL PANELISTS:

- **R. Angelo de Claro, MD, FDA**
- **Xin Gao, PhD, FDA**
- **Jaleh Fallah, MD, FDA**
- **Jian Zhao, PhD, FDA**
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- **Laura J. Esserman, MD, MBA, FAACR, UCSF**
- **Qi Xia, PhD, AbbVie**