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
• Boris Freidlin, PhD, NCI
• George Demetri, MD, FAACR, Dana-Farber Cancer Institute
• Laura J. Esserman, MD, MBA, FAACR, UCSF
• Qi Xia, PhD, AbbVie
Assessment of OS Data for Safety
as pre-specified endpoint for trials in indolent/early-stage cancers

Minghua (Michael) Shan, PhD
Bayer U.S. LLC, Pharmaceuticals
Whippany, NJ
Minghua Shan

I have the following relevant financial relationships to disclose:

- Employee of: Bayer
- Consultant for: N/A
- Speaker’s Bureau for: N/A
- Grant/Research support from: N/A
- Stockholder in: Avid Bioservices, Bayer, Beigene, Celldex, Intellia, Moderna, Seagen
- Honoraria from: N/A

- and -

My additional financial relationship disclosures are: None
Efficacy Endpoints for Studies in Chronic Diseases such as CLL and iNHL

- Imaging endpoints, such as progression-free survival (PFS), are typically used as primary endpoint for drug approvals
  - Substantial increase in PFS may be considered clinical benefit
- Overall Survival (OS) is often a secondary/descriptive/exploratory endpoint with low (or unknown) statistical power
- OS median is typically much longer than PFS
  - Relatively few OS events occur at time of trial primary completion (e.g., PFS analysis)
  - High uncertainty regarding OS benefit or detriment
  - Challenging to interpret such OS results
PFS median: ~15 months
OS median: ~10 years
Study size: 450 patients
PFS events: 290
Study duration (to PFS analysis): ~4 years
OS events at PFS analysis: ~70
PFS prolongation with shortened survival is not clinical benefit overall

However, given limited OS data, it is challenging to assess any OS effect:

- OS benefit,
- OS harm, or
- No OS effect at all
OS Efficacy Study

- To rule out, with high confidence, that true OS HR ≥ 1.0
  - For example, 95% confidence interval (CI) for OS HR excludes 1.0
Ideally, we would like to rule out any OS harm.

However, it would require ruling out that the true underlying OS HR > 1.0.

An OS efficacy study is only designed to rule out HR ≥ 1.0.

Therefore, ruling out HR > 1.0 for safety would essentially require a sample size and study duration of an OS efficacy trial.
Hypothetical OS Efficacy Study in CLL or iNHL

- Control OS median: 10 years
- Targeting HR of 0.8 with 80% power
- Randomize 2000 patients
- Time to final OS analysis: ~13 year
If the true underlying OS HR is 1, the likelihood of observing OS HR > 1 is about 50% regardless of the number of OS events.

This requirement could potentially, by chance,

- reject many treatments with PFS benefit and no OS detriment (or even with some OS benefit)
- accept many treatments with OS detriment

<table>
<thead>
<tr>
<th>trueHR</th>
<th>20 events</th>
<th>40 events</th>
<th>60 events</th>
<th>80 events</th>
<th>100 events</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.800</td>
<td>0.309</td>
<td>0.240</td>
<td>0.194</td>
<td>0.159</td>
<td>0.132</td>
</tr>
<tr>
<td>0.850</td>
<td>0.358</td>
<td>0.304</td>
<td>0.265</td>
<td>0.234</td>
<td>0.208</td>
</tr>
<tr>
<td>0.900</td>
<td>0.407</td>
<td>0.369</td>
<td><strong>0.342</strong></td>
<td>0.319</td>
<td>0.299</td>
</tr>
<tr>
<td>0.950</td>
<td>0.454</td>
<td>0.436</td>
<td>0.421</td>
<td>0.409</td>
<td>0.399</td>
</tr>
<tr>
<td>1.0</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probability of observing an OS HR &gt; 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>trueHR</td>
</tr>
<tr>
<td>1.00</td>
</tr>
<tr>
<td>1.05</td>
</tr>
<tr>
<td>1.10</td>
</tr>
<tr>
<td>1.15</td>
</tr>
<tr>
<td>1.20</td>
</tr>
</tbody>
</table>

(Assuming 1:1 randomization)

Probability of observing an OS HR ≤ 1
Ruling Out Substantial OS Detriment

“Rule out” substantial OS detriment and limit rejection of treatments with “marginal” OS (but significant and meaningful PFS) benefit

- Pre-specify what constitutes substantial OS detriment, \( HR_0 \) (e.g., OS HR of 1.1? 1.15? 1.2? 1.25?)
  - if true, we would like relatively high probability \((1-\alpha)\) to flag as potential OS safety concern

- Pre-specify “marginal” OS benefit, \( HR_1 \) (e.g., OS HR of 0.8? 0.85? 0.9?)
  - if true, we would like relatively high probability \((1-\beta)\) to not (falsely) flag as OS concern

- Based on \( \{HR_0, HR_1, \alpha, \beta\} \), determine number of OS events required and develop guideline (“decision boundary”) for evaluating and interpreting OS data

- Note: equivalent to requiring CI exclude \( HR_0 \) (at appropriate confidence level)
### Scenarios and Sample Sizes

- **α = 0.25, β = 0.25**  
  (# events / HR boundary*)

<table>
<thead>
<tr>
<th>HR₀ (substantial OS detriment)</th>
<th>HR¹ (“marginal” OS benefit)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>1.05</td>
<td>99/0.917</td>
</tr>
<tr>
<td>1.1</td>
<td>72/0.938</td>
</tr>
<tr>
<td>1.15</td>
<td>56/0.96</td>
</tr>
<tr>
<td>1.2</td>
<td>45/0.981</td>
</tr>
<tr>
<td>1.25</td>
<td>37/1.001</td>
</tr>
<tr>
<td>1.3</td>
<td>31/1.02</td>
</tr>
</tbody>
</table>

* Assuming 1:1 randomization
### Scenarios and Sample Sizes

- **Ruling out substantial detriment**

**Assuming 1:1 randomization**

\[ \alpha = 0.2, \ \beta = 0.2 \] (# events / HR boundary*)

<table>
<thead>
<tr>
<th>HR(_0) (substantial OS detriment)</th>
<th>HR(_1) (“marginal” OS benefit)</th>
<th>0.8</th>
<th>0.85</th>
<th>0.9</th>
<th>0.95</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.05</td>
<td></td>
<td>154/0.917</td>
<td>254/0.945</td>
<td>477/0.972</td>
<td>1132/0.999</td>
</tr>
<tr>
<td>1.1</td>
<td></td>
<td>112/0.938</td>
<td>171/0.967</td>
<td>282/0.995</td>
<td>528/1.022</td>
</tr>
<tr>
<td>1.15</td>
<td></td>
<td>87/0.96</td>
<td>125/0.989</td>
<td>189/1.017</td>
<td>311/1.045</td>
</tr>
<tr>
<td>1.2</td>
<td></td>
<td>69/0.98</td>
<td>96/1.011</td>
<td>137/1.039</td>
<td>208/1.068</td>
</tr>
<tr>
<td>1.25</td>
<td></td>
<td>57/1</td>
<td>77/1.032</td>
<td>106/1.061</td>
<td>151/1.09</td>
</tr>
<tr>
<td>1.3</td>
<td></td>
<td>49/1.022</td>
<td>63/1.052</td>
<td>84/1.082</td>
<td>116/1.112</td>
</tr>
</tbody>
</table>

* Assuming 1:1 randomization
### Scenarios and Sample Sizes

- **ruling out substantial detriment**

Assuming 1:1 randomization, \( \alpha = 0.15, \beta = 0.15 \) (# events / HR boundary*)

<table>
<thead>
<tr>
<th>HR(_0) (substantial OS detriment)</th>
<th>HR(_1) (“marginal” OS benefit)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>1.05</td>
<td>233/0.917</td>
</tr>
<tr>
<td>1.1</td>
<td>170/0.938</td>
</tr>
<tr>
<td>1.15</td>
<td>131/0.959</td>
</tr>
<tr>
<td>1.2</td>
<td>105/0.98</td>
</tr>
<tr>
<td>1.25</td>
<td>87/1.001</td>
</tr>
<tr>
<td>1.3</td>
<td>73/1.02</td>
</tr>
</tbody>
</table>

* Assuming 1:1 randomization
Ruling Out Substantial OS Detriment but allowing a gray zone

“Rule out” substantial OS detriment and limit rejection of treatments with “marginal” OS (but significant and meaningful PFS) benefit - allow an indeterminant/gray zone (i.e., 3 outcomes) to reduce required sample size

- Pre-specify what constitutes substantial OS detriment, HR₀ (e.g., OS HR of 1.15? 1.2? 1.25?)
  - if true, we would like relatively high probability (η) to flag as potential OS safety concern
  - if true, we would like relatively low probability (α) to not flag as potential OS safety concern
  - we allow a gray zone (probability = 1 – η – α) to reduce sample size required

- Pre-specify “marginal” OS benefit, HR₁ (e.g., OS HR of 0.8? 0.85? 0.9?)
  - if true, we would like relatively high probability (π) to not flag as potential OS concern
  - if true, we would like relatively low probability (β) to flag as potential OS concern
  - we allow a gray zone (probability = 1 – π – β)

- If result in gray zone, further data may be necessary

- Based on {HR₀, HR₁, α, β, η, π}, determine number of OS events required and develop guidelines (two “decision boundaries” for “no substantial harm” and “potential substantial harm”) for evaluating OS for Safety

<table>
<thead>
<tr>
<th>Probability of Outcome</th>
<th>OS Safety Analysis Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>True OS Effect</td>
<td>OS Concern Suggested</td>
</tr>
<tr>
<td>Substantial detriment (HR₀)</td>
<td>η</td>
</tr>
<tr>
<td>Marginal benefit (HR₁)</td>
<td>1 – η – α</td>
</tr>
<tr>
<td></td>
<td>α</td>
</tr>
<tr>
<td>Gray zone</td>
<td>1 – π – β</td>
</tr>
<tr>
<td>Potential substantial harm</td>
<td>π</td>
</tr>
</tbody>
</table>

No substantial harm suggested
Gray zone
Potential substantial harm
### Scenarios and Sample Sizes* - ruling out substantial detriment but allowing gray zone

<table>
<thead>
<tr>
<th>HR_0</th>
<th>HR_1</th>
<th>α=0.25, β=0.25, π=0.65, η=0.65</th>
<th>α=0.2, β=0.2, π=0.7, η=0.7</th>
<th>α=0.15, β=0.15, π=0.75, η=0.75</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.10</td>
<td>0.85</td>
<td>68</td>
<td>113</td>
<td>177</td>
</tr>
<tr>
<td>1.10</td>
<td>0.90</td>
<td>112</td>
<td>186</td>
<td>291</td>
</tr>
<tr>
<td>1.15</td>
<td>0.85</td>
<td>50</td>
<td>82</td>
<td>129</td>
</tr>
<tr>
<td>1.15</td>
<td>0.90</td>
<td>75</td>
<td>125</td>
<td>195</td>
</tr>
<tr>
<td>1.15</td>
<td>0.95</td>
<td>124</td>
<td>205</td>
<td>321</td>
</tr>
<tr>
<td>1.20</td>
<td>0.85</td>
<td>38</td>
<td>63</td>
<td>99</td>
</tr>
<tr>
<td>1.20</td>
<td>0.90</td>
<td>55</td>
<td>91</td>
<td>142</td>
</tr>
<tr>
<td>1.20</td>
<td>0.95</td>
<td><strong>83</strong></td>
<td><strong>137</strong></td>
<td><strong>215</strong></td>
</tr>
<tr>
<td>1.25</td>
<td>0.85</td>
<td>31</td>
<td>51</td>
<td>79</td>
</tr>
<tr>
<td>1.25</td>
<td>0.90</td>
<td>42</td>
<td>70</td>
<td>109</td>
</tr>
<tr>
<td>1.25</td>
<td>0.95</td>
<td>60</td>
<td>100</td>
<td>156</td>
</tr>
</tbody>
</table>

* Assuming 1:1 randomization

* Assuming 1:1 randomization

<table>
<thead>
<tr>
<th>Probability of Outcome</th>
<th>OS Safety Analysis Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>True OS Effect</td>
<td>Substantial detriment (HR_0)</td>
</tr>
<tr>
<td>OS Concern Suggested</td>
<td>1–π–α</td>
</tr>
<tr>
<td>Gray zone</td>
<td>1–π–β</td>
</tr>
<tr>
<td>OS Concern not suggested</td>
<td>α</td>
</tr>
</tbody>
</table>

* Assuming 1:1 randomization

**FDA-AACR-ASA WORKSHOP: OVERALL SURVIVAL IN ONCOLOGY CLINICAL TRIALS**
Potential underlying causes include:

- Differences between predictive/prognostic subgroups
  - uncovering these subgroups would be best solution
- Varying treatment effect over time relative to control
  - early OS data may not represent overall OS effect

When non-PH is anticipated, what should we do in collecting and analyzing OS data?

- scenario at top: even though treatment effect (i.e., HR) changes, no OS concern is warranted as there is always benefit. However, immature OS data (i.e., early data) could more likely result in false suggestion of OS harm
- scenario at bottom: early benefit and later harm (or vice versa). What are the most appropriate ways to collect and analyze OS data?
In cancer trials, patients should, and do, receive potentially life-prolonging post study anti-cancer treatments when they exist.

These therapies may affect overall survival and confound OS results.

However, such therapies (and their benefit) could be related to study treatment:

- Experimental treatment could affect patients’ ability to receive and tolerate subsequent life-prolonging treatments.
- That is, getting more or less benefit from subsequent therapies could be an indirect result of study treatment.

Typical approach is to include all OS information even after subsequent therapy starts (i.e., ITT principle or treatment policy approach).
Crossover can also confound OS results
- It could dilute OS result and lead to underestimation of OS benefit, or
- It could obscure OS detriment

Analyzing OS data in presence of crossover is challenging
- Most analytical methods require unverifiable assumptions

What should be done to address crossover when designing a trial?
- Avoid crossover in study design whenever feasible and ethical?

Exception: Testing a treatment in earlier line when it is already part of standard of care in later line
- Crossing over to test treatment in later line should be treated as any other subsequent anti-cancer therapy
OS data can be limited at time of trial’s primary completion (e.g., PFS analysis) in indolent or early-stage disease settings.

Even though ideal, it may not be practical to rule out ANY OS detriment (i.e., HR>1).

Requiring observed HR≤1 could reject many treatments with no survival detriment and even some with marginal survival benefit and accept many with OS detriment.

It may be feasible to rule out substantial OS detriment:
- Need to define what constitutes substantial detriment - but how to define it at study planning?
- May need to relax alpha and beta
- May need to accept a gray decision zone (i.e., 3-outcome design)
- May need to wait for more OS data after trial primary completion

Other issues to consider:
- Potential non-proportional hazards
- Subsequent therapies
- Crossover
Session 2: Overall Survival as a Pre-specified Endpoint

Ruben Mesa, MD
Atrium Health
Wake Forest Baptist Comprehensive Cancer Center
Ruben Mesa, MD

I have the following relevant financial relationships to disclose:

- Employee of: N/A
- Consultant for: Novartis, BMS, Incyte, CTI, Pharmessentia, Blueprint, Genentech, Telios, Abbvie
- Speaker’s Bureau for: N/A
- Grant/Research support from: Incyte, CTI, BMS, GSK, Abbvie

My additional financial relationship disclosures are:
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
• Boris Freidlin, PhD, NCI
• George Demetri, MD, FAACR, Dana-Farber Cancer Institute
• Laura J. Esserman, MD, MBA, FAACR, UCSF
• Qi Xia, PhD, AbbVie
Objectives

- To discuss and identify issues which may impact pre-specified statistical analyses for OS regardless of Type I error control including, but not limited to handling of intercurrent events, pre-specification for observation of non-proportional hazards, crossover, and impact of subsequent therapy.
Improving survival in myeloma

- Overall survival in 6-year intervals from time of diagnosis

Further improving survival in myeloma

Binder et al., Leukemia. 2022 Mar;36(3):801-808
Results: Overall Survival and Overview

- **MF Survival ~ last Decade**
  - Median follow-up 30.4 months (range, 0.9-266), ↑ after y. 2010: 37.5 vs 25m (p < 0.001)
  - Died 659 (49%) patients, ↑ before y. 2010: 74% vs 32% (p < 0.001)
  - AML in 85 patients (10%) or 2 per 100 P-Y
  - RX 1105 (82%) patients, 358 ruxolitinib (27%); 78 SCT (6%)

Masarova et al., ASH 2020
A Pooled Overall Survival (OS) Analysis of 5-Year Data from the COMFORT-I and COMFORT-II Trials of Ruxolitinib for the Treatment of Myelofibrosis (MF)

Vannucchi et al., Haematologica. 2015
Considerations for when OS should be the primary efficacy endpoint

- Important factors to consider:
  - Expected length of survival of disease in question
  - Trial visibility
  - Validated trial-level surrogates for OS
  - Reliable intermediate endpoints

- Strong validation that OS is always the goal for cancer, but PFS perhaps for Accelerated Approval with OS for full approval?

- Concern around how to rule out harm if OS is not feasible; OS for indolent disease is to rule out shortening of survival due to toxicity or interference with receiving effective standard/salvage therapies

- Indefinite/prolonged administration(maintenance) requires special consideration
Disease-specific considerations for evaluating harm

- Expected Survival (years vs month)
- Adjuvant
- Curative intent
- Anticipated recruitment (e.g. time, patient numbers)
- Known biomarkers or subgroups of interest/concern
- Toxicities and severity of impact on patient populations
Prospective OS

How do we rule out harm?
What are appropriate thresholds?

- Longer follow-up for accelerated approval?
- Prespecify long-term OS follow-up (what amount is feasible?)
- Plan to obtain sufficient OS data to specify what “harm” to rule out and reduce uncertainty
- For harm assessment use relaxed evidentiary thresholds (relative to thresholds used for efficacy)
- Thresholds should be guidelines, not hard boundaries
- Clearly define stopping rules for futility and harm
- Toxicity profile
- Rate of mortality
- Consider methods to assess probability of harm (e.g., Dr. Shan’s intro presentation)
Prospective OS

Considerations that can guide determination of thresholds

- Harm specific considerations (i.e., temporary or non-temporary toxicity)
- Physicians/patients input
- Control arm expected benefit
- Feasibility for obtaining long-term OS data
- Other available data
- Disease setting (adjuvant/curative – more stringent in assuring no harm)
- Rate of mortality during treatment with the study drug vs after coming off the trial and receiving other treatments
Prospective OS

Pre-specified sensitivity analyses in the SAP to address potential non-proportional hazards

- Relying on overall average HR
  - OS data needs to be sufficiently mature as “average HR” depends on follow-up

- First step is to examine OS in biologically plausible subgroups. Subgroup effect: for example, in check-point inhibitor trials there are numerous examples where marginally positive treatment effect in the overall population shows NPH, with harm shown in low CPS score subgroup

- FDA strongly recommends prespecifying the analyses in the SAP if the sponsor anticipates non-proportional hazard in the trial and submit the SAP to FDA for review at the study design stage. Include planned long-term OS follow-up with prespecified final and interim analysis times.

- In addition to log-rank analyses, evaluate landmark OS rates at clinically relevant timepoints
Prospective OS

Methods to include in the SAP that assess non-proportional hazards or other deviations from statistical assumptions

- **Primary Evaluation of OS** is likely to remain as traditional hazard ratio from a Cox proportional hazards model, but supplementary analyses may be performed

- **Pre-Specified Analysis** should be in the SAP to ensure robust and unbiased interpretation of the results

- **Specify Robust Summary Measures** that can capture OS safety signals like differences in landmark OS rates and KM curves

- **Analysis Examples:**
  - Precise exponential, RMST, max-combo test etc., and various methods to test the assumption such as graphical approach

- **Other Commonly Used Methods:**
  - Visually examining the Kaplan-Meier curves, incorporating a time-dependent treatment variable in the Cox model, employing the reverse Kaplan-Meier method, and conducting the Wilcoxon test to identify early separation between the curves, among others. Weighted log-rank test or other appropriate methods may be pre-specified as the primary analysis method (as opposed the conventional log-rank test) with justification
Under the estimand framework, what considerations should inform how intercurrent events (such as crossover) are handled for the primary analysis of OS?

- Generally should follow intention-to-treat (ITT) principle -> “treatment policy” assumes intercurrent event as part of study treatment/regimen, but crossover confounds evaluation of OS

- Treatment policy approach may potentially underestimate the effect of the experimental treatment; considered conservative and is often recommended as the primary analysis to maintain rigor in clinical trials; however, patients may not be followed with same rigor after an intercurrent event

- Avoid crossover in study design if possible, especially if there is substantial uncertainty regarding OS benefit or harm

- Methods to deal crossover OS data typically have strong and unverifiable assumptions and their conclusions are not usually sufficiently convincing as the primary evaluation for OS

- Evaluating subsequent therapies, time-to-next therapy, and extent/pattern of crossover would be helpful to assess effects of intercurrent events.

- The control arm should receive the appropriate standard of care post-progression therapies
Prospective OS

Which analyses should be included in the SAP to address crossover if it is planned as a part of the trial?

- Any statistical methods that adjusts for crossover depend on unverifiable assumptions
- The most interpretable sensitivity analyses are simple and based on assuming the worst/best outcome for the crossover patients
- These analyses provide supplementary information (not pivotal information)
- Appropriateness depends on specific trial design and objectives

Which supplementary analyses methods are the most robust to address this issue?

- Rank preserving structural failure time (RPSFT) model
- Inverse probability of censoring weighting (IPCW)
- Two-stage method
What supplementary analyses for OS should be specified? What additional clinical questions of interest and estimands should be specified (e.g., to assess the impact of subsequent therapy)?

- In the case of treatment policy approach, where the clinical question may be “What is the hazard ratio regardless of the intercurrent event?”, then the analysis would ignore this intercurrent event and use all available data.
  - Subsequent therapies (representing the standard of care) and their effect are then included as part of the overall OS benefit or harm.

- The underlying assumptions and clinical questions of interest for each method should be clearly specified and justified in order to adequately specify what is being estimated (estimand).

- Multiple sensitivity analyses based on different methods, clinical questions, and/or assumptions should be provided to adequately inform the evaluation of OS.

- A variety of parameters can provide a reasonable range of possible estimates.
If OS is considered as a supplementary endpoint without a prospectively defined sample size to adequately power an assessment of OS, what degree of uncertainty is acceptable for the assessment of survival with regards to safety and/or efficacy?

- In good prognosis settings where relatively few OS events are expected relaxed evidentiary thresholds (e.g., confidence levels of 90% or 80%) may be appropriate.

What should be specified in the SAP regarding maturity of the OS data to adequately inform a benefit-risk assessment?

- Specify number of OS events to rule out substantial harm.
- An informed estimate of the number of events available at each planned analysis timepoint will quantify the projected information; more or less uncertainty may be acceptable depending on disease and known toxicity.
- If it is an aggressive and life-threatening disease where OS measurement is feasible, the study should be designed such that OS can be formally tested with appropriate Type I error control.
- If there is concern for OS detriment, longer follow up should be planned to rule out harm from delayed/persistent toxicities, with or without formal testing.
End of working group summary
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
• Boris Freidlin, PhD, NCI
• George Demetri, MD, FAACR, Dana-Farber Cancer Institute
• Laura J. Esserman, MD, MBA, FAACR, UCSF
• Qi Xia, PhD, AbbVie
1. What are the considerations for when OS should be the primary efficacy endpoint?

2. When OS is secondary or supportive endpoint, what analyses can be pre-specified in the Statistical Analysis Plan (SAP) to rule out harm?

3. How do we rule out harm? What are appropriate thresholds? Are there disease-specific considerations?

4. What are the considerations that can guide determination of thresholds?

5. What sensitivity analyses can be pre-specified in the SAP to address potential non-proportional hazards? What methods to specify to assess NPH or other deviations from assumptions?

6. Under the estimand framework, what considerations should inform how intercurrent events (such as crossover) are handled for the primary analysis of OS? What information should be collected that would be most helpful in assessing the effects of intercurrent events?

7. Which analyses should be included in the SAP to address crossover if it is planned as a part of the trial?

8. What supplementary analyses for OS should be specified? What additional clinical questions of interest and estimands should be specified (e.g., to assess the impact of subsequent therapy)?

9. If OS is considered as a supplementary endpoint without a prospectively defined sample size to adequately power an assessment of OS, what degree of uncertainty is acceptable for the assessment of survival with regards to safety and/or efficacy?