Session 2: Overall Survival as a Pre-specified Endpoint

MODERATOR:

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U.S. Food & Drug Administration

INTRO:

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OVERVIEW OF RECOMMENDATIONS SESSION CHAIR:

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ADDITIONAL PANELISTS:

- **R. Angelo de Claro, MD,** FDA
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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

Assessment of OS Data for Safety

as pre-specified endpoint for trials in indolent/early-stage cancers

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FDA U.S. FOOD & DRUG ADMINISTRATION

AACR American Association for Cancer Research

ASA AMERICAN STATISTICAL ASSOCIATION Promoting the Practice and Profession of Statistics

Minghua Shan

I have the following relevant financial relationships to disclose:

Employee of: Bayer

Consultant for: N/A

Speaker's Bureau for: N/A

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Honoraria from: N/A

- and -

My additional financial relationship disclosures are: None

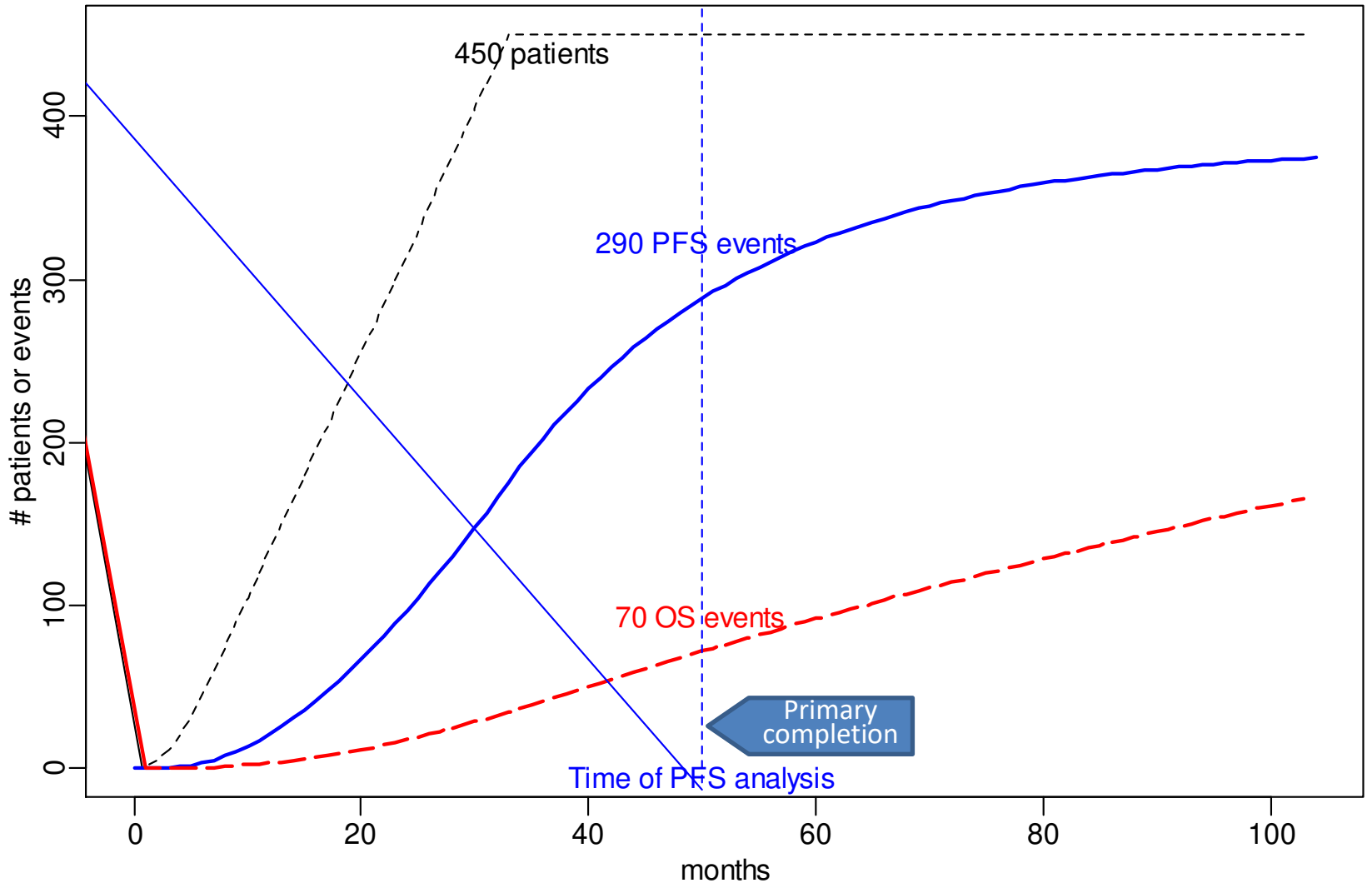
Efficacy Endpoints

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 and OS Event Projections

for a typical study In CLL or iNHL



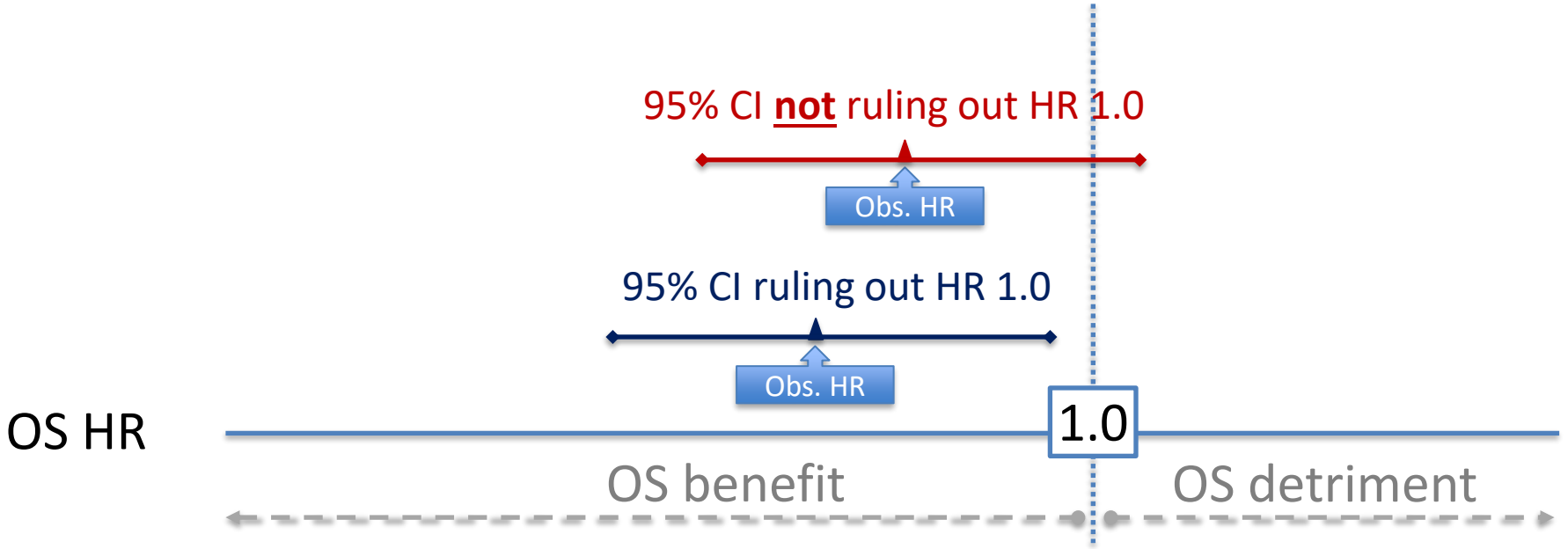
- PFS median: ~15 months
- OS median: ~10 years
- Study size: 450 patients
- PFS events: 290
- Study duration (to PFS analysis): ~4 years
- OS events at PFS analysis: ~70

Overall Survival Is Ultimate Safety Endpoint

- 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

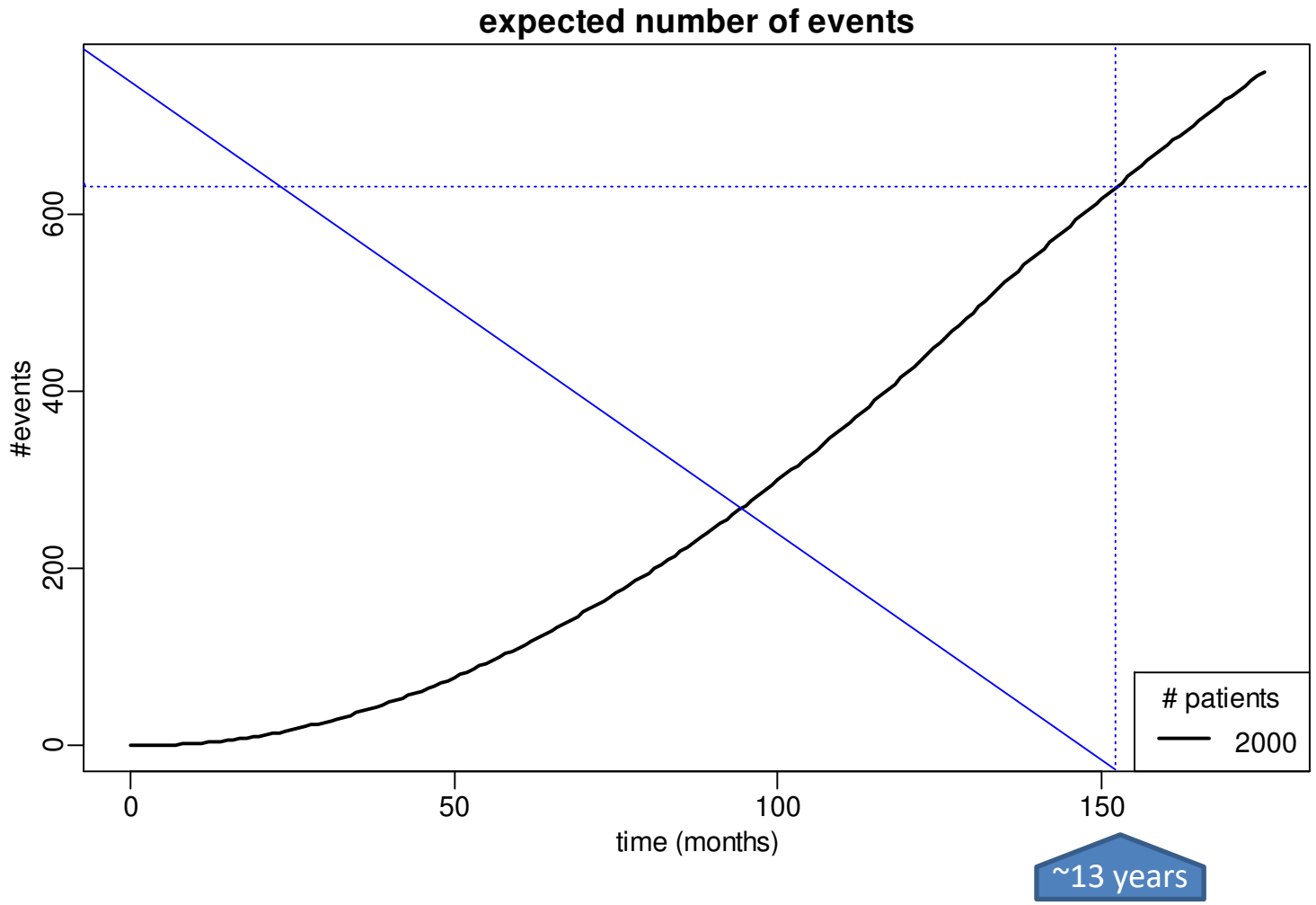


Ruling Out ANY OS Detriment for Safety

- 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**



Requiring Observed OS HR ≤ 1

- 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

Probability of observing an OS HR > 1

trueHR	20 events	40 events	60 events	80 events	100 events
0.800	0.309	0.240	0.194	0.159	0.132
0.850	0.358	0.304	0.265	0.234	0.208
0.900	0.407	0.369	**0.342**	0.319	0.299
0.950	0.454	0.436	0.421	0.409	0.399
1.0	0.5	0.5	0.5	0.5	0.5

Probability of observing an OS HR ≤ 1

trueHR	20 events	40 events	60 events	80 events	100 events
1.00	0.5	0.5	0.5	0.5	0.5
1.05	0.457	0.439	0.425	0.414	0.404
1.10	0.416	0.382	**0.356**	0.335	0.317
1.15	0.377	0.329	0.294	0.266	0.242
1.20	0.342	0.282	0.240	0.207	0.181

(Assuming 1:1 randomization)

Potential Approach 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-α**) 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-β**) to not (falsely) flag as OS concern
- Based on {HR_0, HR_1, α, β}, 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 (1) – ruling out substantial detriment

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

HR_0 (substantial OS detriment)	HR_1 ("marginal" OS benefit) 0.8	0.85	0.9	0.95
1.05	99/0.917	164/0.945	307/0.972	727/0.999
1.1	72/0.938	110/0.967	181/0.995	339/1.022
1.15	56/0.96	80/0.989	122/1.018	200/1.045
1.2	45/0.981	62/1.011	**88/1.039**	134/1.068
1.25	37/1.001	49/1.031	68/1.061	97/1.09
1.3	31/1.02	41/1.053	54/1.082	74/1.111

* Assuming 1:1 randomization

Scenarios and Sample Sizes (2)
– ruling out substantial detriment

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

HR_0 (substantial OS detriment)	HR_1 ("marginal" OS benefit) 0.8	0.85	0.9	0.95
1.05	154/0.917	254/0.945	477/0.972	1132/0.999
1.1	112/0.938	171/0.967	282/0.995	528/1.022
1.15	87/0.96	125/0.989	189/1.017	311/1.045
1.2	69/0.98	96/1.011	137/1.039	208/1.068
1.25	57/1	77/1.032	106/1.061	151/1.09
1.3	49/1.022	63/1.052	84/1.082	116/1.112

* Assuming 1:1 randomization

Scenarios and Sample Sizes (3)
– ruling out substantial detriment

$\alpha = 0.15, \beta = 0.15$ (# events / HR boundary*)

HR_0 (substantial OS detriment)	HR_1 ("marginal" OS benefit) 0.8	0.85	0.9	0.95
1.05	233/0.917	385/0.945	724/0.972	1716/0.999
1.1	170/0.938	259/0.967	427/0.995	800/1.022
1.15	131/0.959	189/0.989	287/1.018	471/1.045
1.2	105/0.98	145/1.01	208/1.039	315/1.068
1.25	87/1.001	116/1.031	160/1.061	229/1.09
1.3	73/1.02	96/1.052	128/1.082	175/1.111

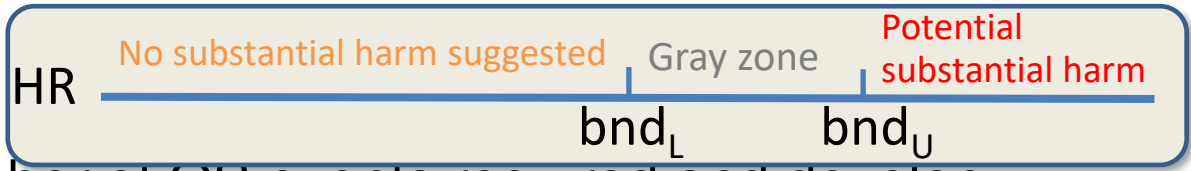
* Assuming 1:1 randomization

Potential Approach 2

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**, HR_0 (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 <u>not</u> 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**, HR_1 (e.g., OS HR of 0.8? 0.85? 0.9?)
  - if true, we would like relatively **high probability** (**π**) to <u>not</u> 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 {HR_0, HR_1, 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



Probability of Outcome		OS Safety Analysis Outcome		
		OS Concern Suggested	Gray zone	OS Concern <u>not</u> suggested
True OS Effect	Substantial detriment (HR_0)	η	$1-\eta-\alpha$	α
	Marginal benefit (HR_1)	β	$1-\pi-\beta$	π

Scenarios and Sample Sizes*

– ruling out substantial detriment but allowing gray zone

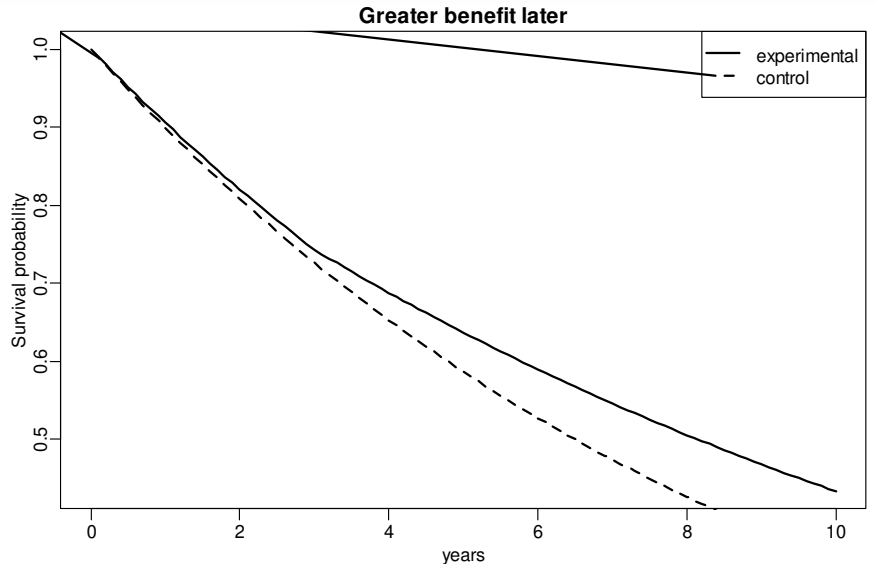
		α=0.25, β=0.25, π=0.65, η=0.65			α=0.2, β=0.2, π=0.7, η=0.7			α=0.15, β=0.15, π=0.75, η=0.75		
HR_0	HR_1	# events	bnd_L	bnd_U	# events	bnd_L	bnd_U	# events	bnd_L	bnd_U
1.10	0.85	68	0.934	1.002	113	0.939	0.997	177	0.941	0.994
1.10	0.90	112	0.968	1.023	186	0.972	1.019	291	0.974	1.016
1.15	0.85	50	0.950	1.031	82	0.955	1.024	129	0.958	1.021
1.15	0.90	75	0.984	1.052	125	0.989	1.047	195	0.991	1.044
1.15	0.95	124	1.019	1.073	205	1.022	1.069	321	1.024	1.067
1.20	0.85	38	0.964	1.059	63	0.971	1.051	99	0.974	1.048
1.20	0.90	55	1.000	1.082	91	1.006	1.075	142	1.008	1.072
1.20	0.95	**83**	**1.035**	**1.103**	137	1.039	1.097	215	1.042	1.095
1.25	0.85	31	0.981	1.088	51	0.988	1.079	79	0.990	1.074
1.25	0.90	42	1.015	1.110	70	1.022	1.103	109	1.025	1.098
1.25	0.95	60	1.050	1.132	100	1.056	1.126	156	1.059	1.122

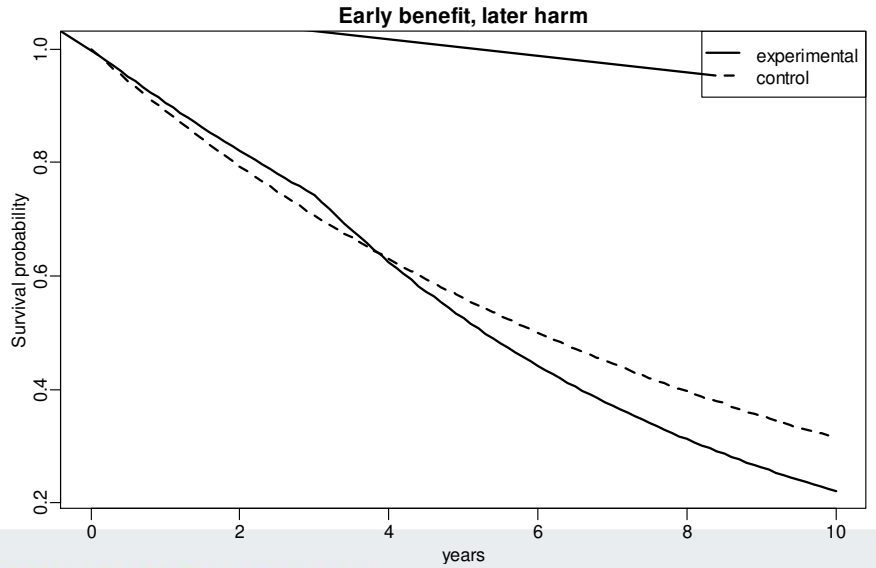
* Assuming 1:1 randomization

Probability of Outcome		OS Safety Analysis Outcome		
		OS Concern Suggested	Gray zone	OS Concern not suggested
True OS Effect	Substantial detriment (HR_0)	η	$1-\eta-\alpha$	α
	Marginal benefit (HR_1)	β	$1-\pi-\beta$	π

Non-Proportional Hazards

- 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?





Subsequent Anti-Cancer Therapies

- 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 to Experimental Study Treatment

- 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

Key Considerations

- 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

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Ruben Mesa, MD

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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

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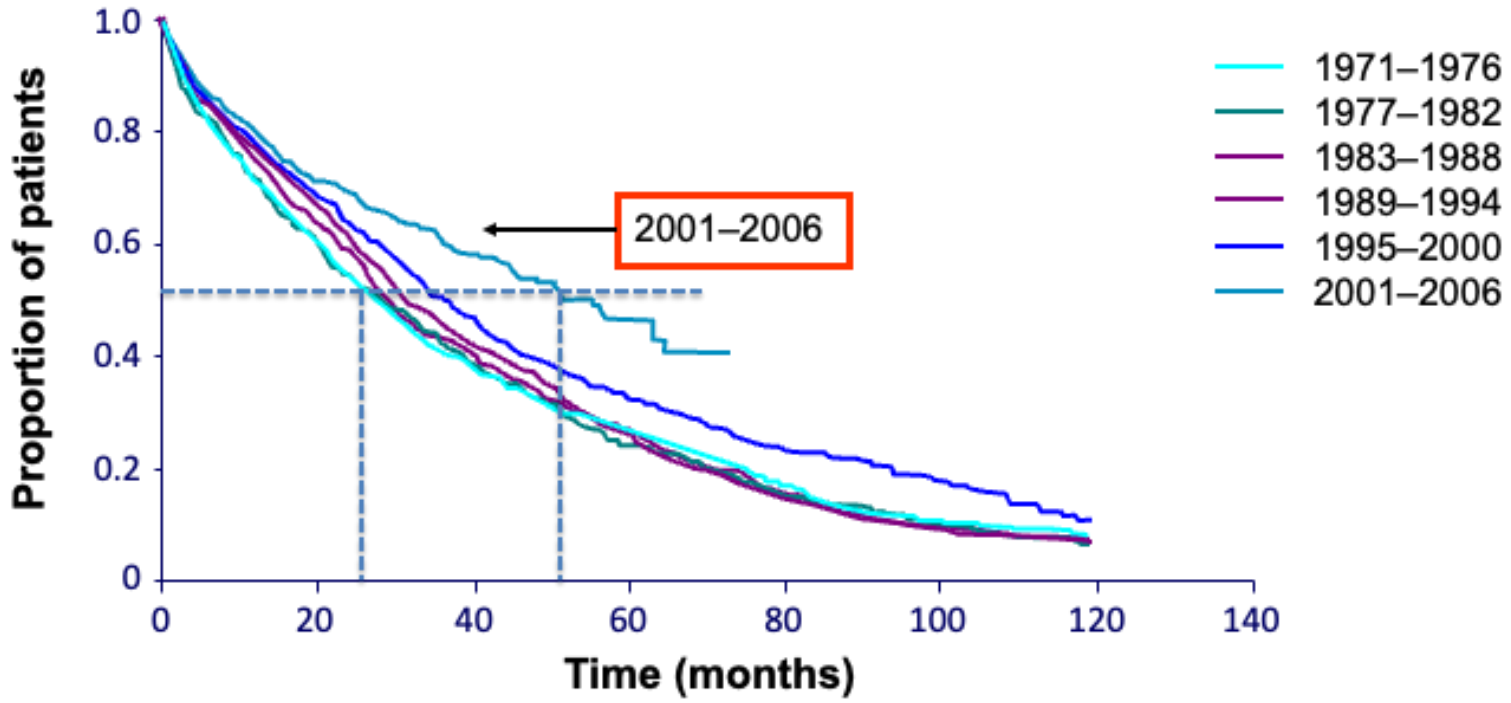
Objectives

- 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

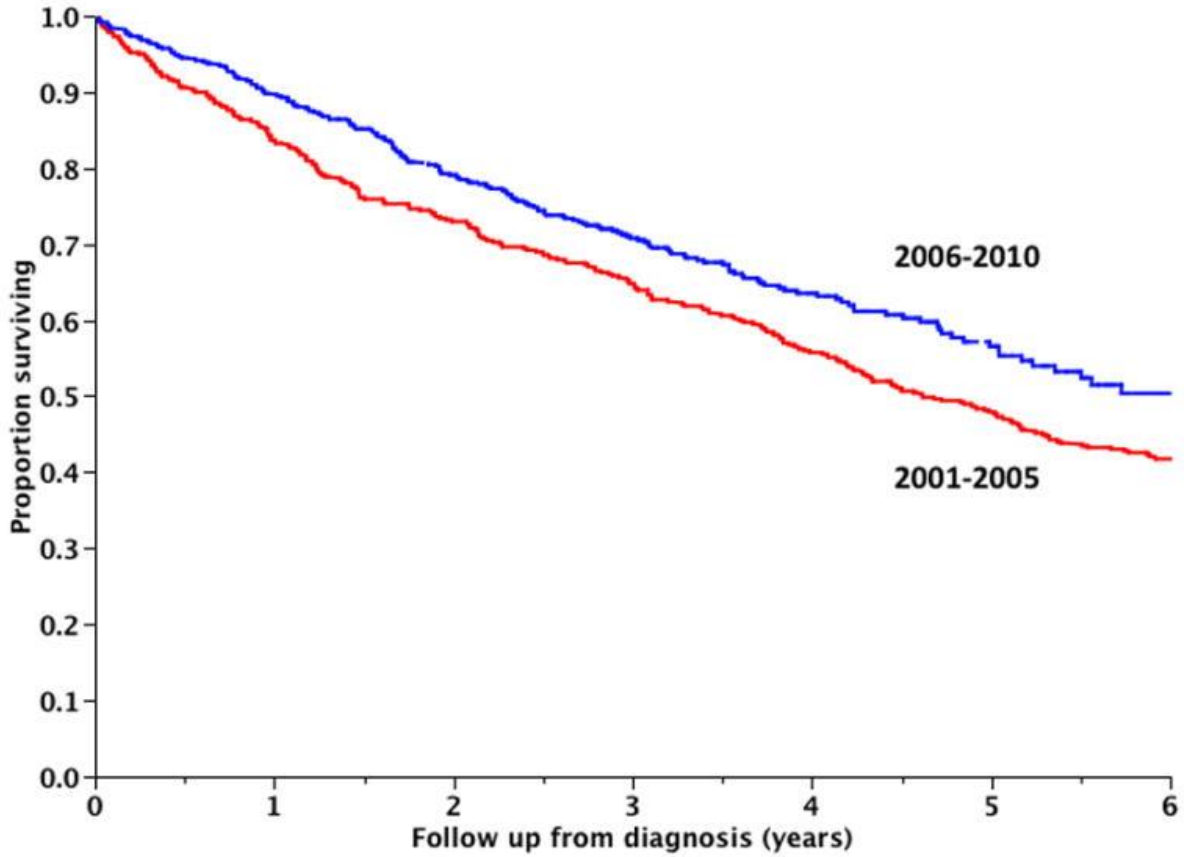
- Overall survival in 6-year intervals from time of diagnosis



Kumar SK et al., Blood. 2008;111:2516-20.

Further improving survival in myeloma

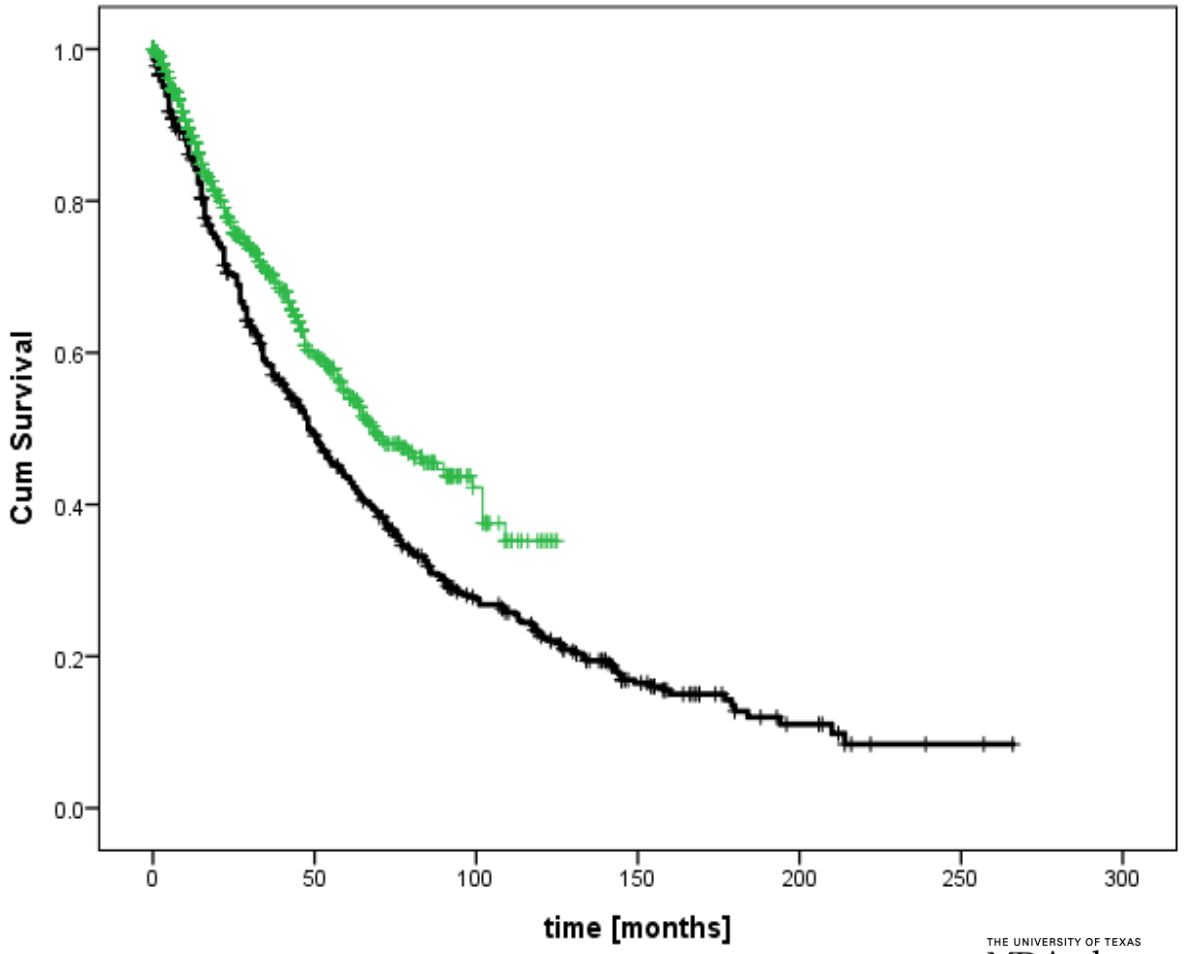
Figure 1A



Binder et al., Leukemia. 2022 Mar;36(3):801-808

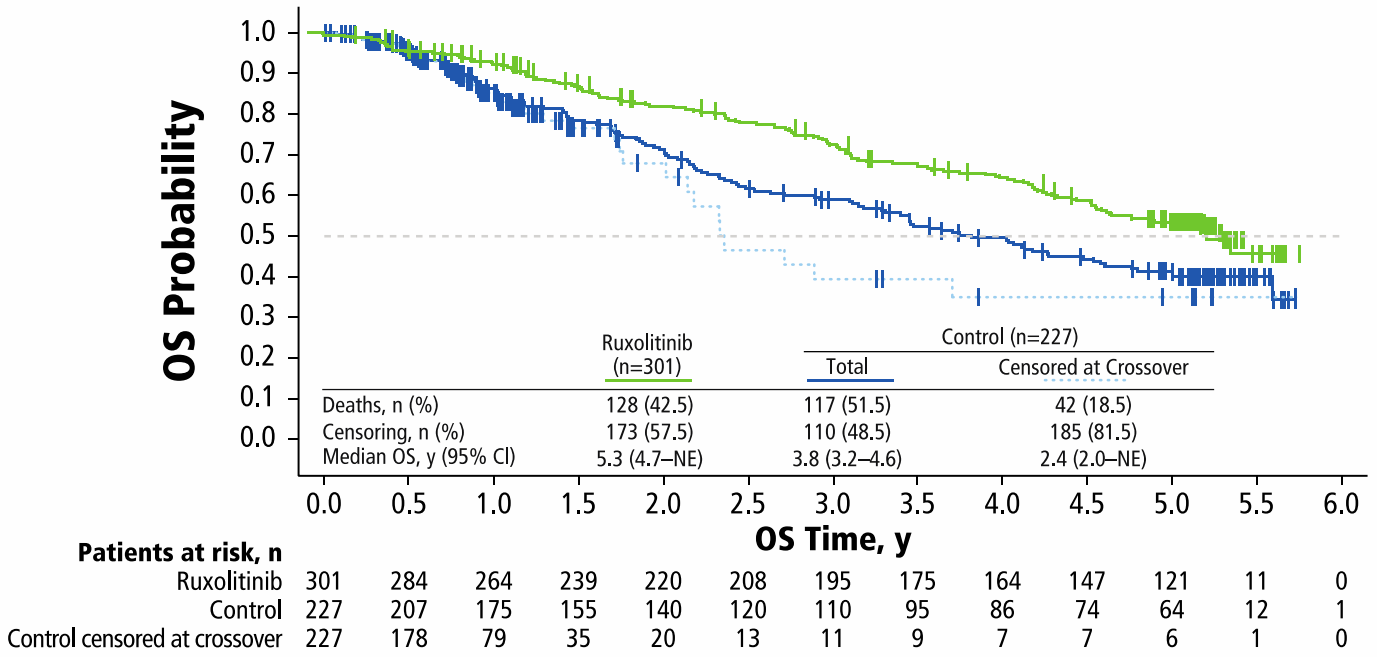
Results: Overall Survival and Overview

- 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

Prospective OS

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

Prospective OS

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

Prospective OS

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

Prospective OS

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.

Prospective OS

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

Session 2: Overall Survival as a Pre-specified Endpoint

MODERATOR:

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U.S. Food & Drug Administration

INTRO:

Michael Shan, PhD
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OVERVIEW OF RECOMMENDATIONS SESSION CHAIR:

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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,**
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- **Laura J. Esserman, MD, MBA, FAACR,** UCSF
- **Qi Xia, PhD,** AbbVie

Session 2 Discussion Questions

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?