Traditional sensitivity analyses in oncology clinical trials – what questions are they answering?

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Overview

- Framework of Oncology trial analysis with PFS as primary end point
- Sensitivity analyses (Before ICH E9)
- An example
- Interpretation in light of new addendum

Sensitivity analyses (Before ICH E9)
(Example with Progression free survival)

Hypothetical setup of an Oncology trial with PFS in solid tumor

- Double blind, randomized clinical trial, Treatment A vs Placebo
- Primary end point
  - Progression free survival: (Progression or Death before progression) (investigator's assessment).
  - Stratified log-rank test / hazard ratio (stratification factors during randomization).
  - Treated set.
  - Estimate median PFS from Kaplan Meier.
- Sensitivity analysis
  - Relaxing/altering different censoring rules handling intercurrent events.
  - Per protocol set.
  - un-stratified log-rank test/ Cox regression.

Intercurrent events

- Intercurrent events
  - Discontinuation of treatment due to
    - New anti cancer therapy
    - adverse events
    - Clinical progression but not as per RECIST
    - Subject's decision
    - other.
  - Prohibited concomitant medication
  - Missing visits
  - Lost to follow up

Rules to address main intercurrent events

- Different Censoring rules to address different intercurrent events
  - New anti cancer therapy:
    – Censored at last adequate assessments before the start new drug (Hypothetical estimand).
  - More than one Missing assessments : Censored at last adequate assessments before two or missing assessments (Hypothetical estimand).

  - At last adequate assessment before Loss to follow-up/ withdrawal of consent, early withdrawal.

Different sensitivity analyses (Before ICH E9)

Everything in one bucket

1. un-stratified log-rank test/ Cox regression; Different stratification factors other than planned for primary analysis.
2. Analysis based on per protocol set. (excluding non-measurable disease, prohibited concomitant medication etc.).
3. By not censoring patients at start of anti-neoplastic therapies.
4. Impute as event at the last assessment before the start of anti-neoplastic therapies.
5. Nonobjective progression as a PFS event: Patient discontinued due to non-objective progression like symptomatic progression are considered as event.
6. Taking all events after two or missing assessment with event time as the actual time of assessment.
7. Backdating of events, occurring after two or more missing assessment/ new antineoplastic therapy, by taking the event date as time of last adequate assessment.

Are they addressing the same Estimand/ question?

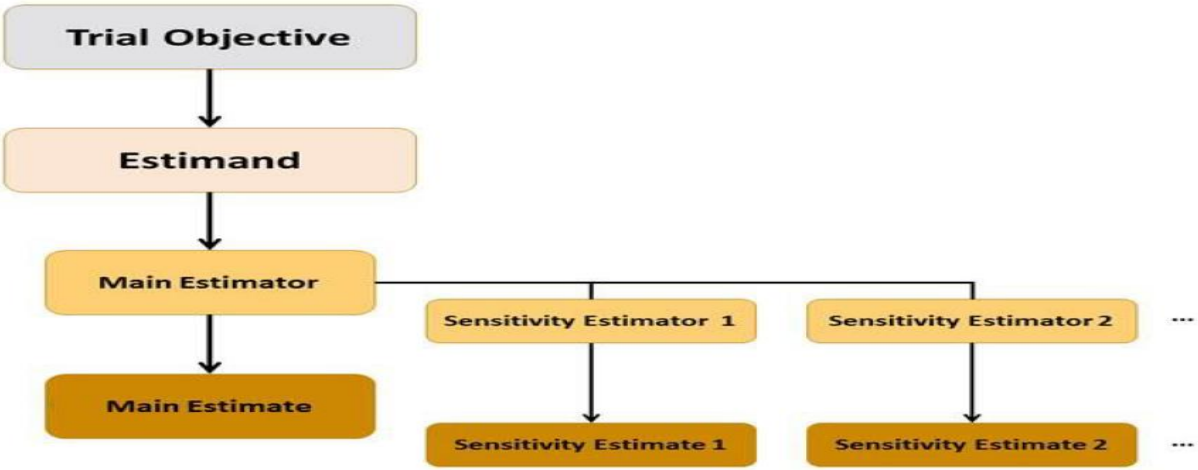
An Example :Different censoring rules with same end point

- Efficacy comparison of CDK4/6 inhibitors in treatment naïve patients with HR+/HER2- advanced breast cancer:

study	Treatment ARMs	Median PFS (Trt vs Placebo) (in months)	Censoring rule for new antineoplastic
Paloma-2	Palbociclib/letrozole vs placebo/letrozole	24.8 vs 14.5	New anticancer treatment prior to progression or death.
Monaleesa-2	Ribociclib/letrozole vs placebo/letrozole	25.3 vs 16	New anticancer treatment prior to progression or death
Monarch-3	Abemaciclib/AI vs placebo/AI	28.18 vs 14.76	Primary analysis ***was not censored*** for anticancer therapy

- *Shah et. al., CDK4/6 Inhibitors: Game Changers in the Management of Hormone Receptor–Positive Advanced Breast Cancer?, Oncology (Williston Park). 2018 May 15; 32(5): 216–222.*
- Hortobagyi et. al., *Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer, The New England Journal of Medicine, Nov 3, 2016, 375;18 supplementary document.*
- Finn et. al., Palbociclib and Letrozole in Advanced Breast Cancer, *The New England Journal of Medicine, No 17, 2016, 375;20 supplementary document* .
- Goetz et. al., MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer, Journal of clinical oncology, Nov 10, 2017, Vol 35: 32, supplementary.
- Johnston1 et. al., MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer, Breast cancer,17 Jan, 2019.

Censoring and supplementary analysis Estimand framework (ICH E9(R1))



- **Sensitivity Analysis**
  - **Assess key assumptions of the main estimator.**
- **Supplementary Analysis**
  - **Addition to main and sensitivity analysis to provide additional insights and targeting different estimand.**

Interpretation in light of new addendum

Sensitivity analyses??

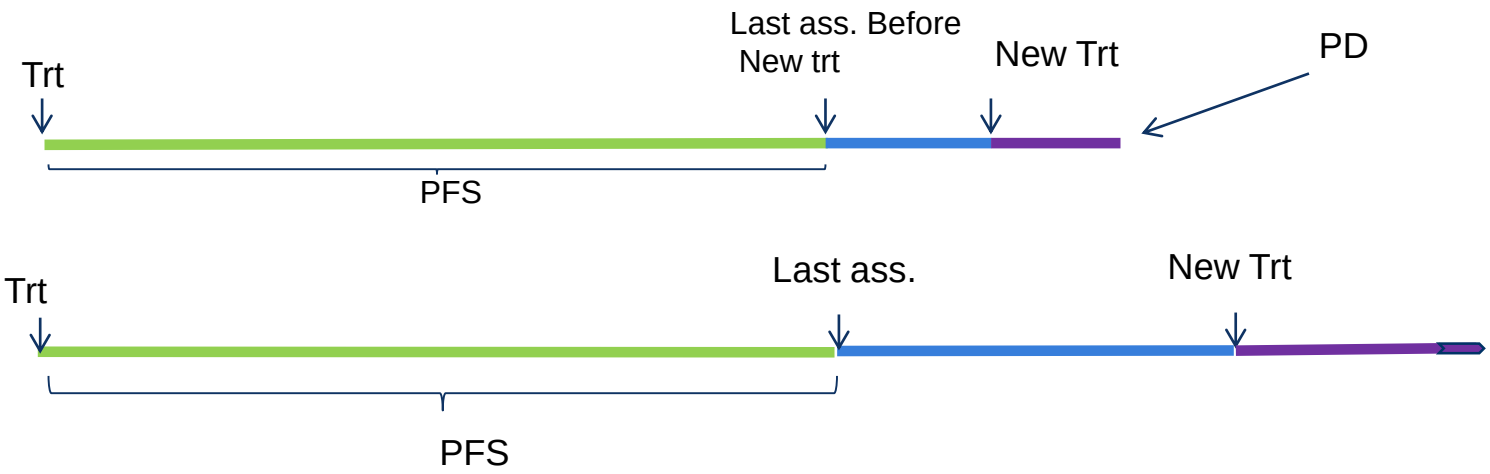
1. Un-stratified log-rank test/ Cox regression

   – Main analysis is adjusted for the affect of prognostic factors like (e.g. axillary lymph node status, histologic subtype, tumor grade etc. in Breast cancer) assuming underlying hazard function vary across strata.

   – Relaxing the above assumption but addressing the same estimand.
   – Same estimand but with different model assumption in a sense true sensitivity analysis.

2. Analysis based on per protocol set????
   – It is not clear which estimand it is addressing or whether it is adding any value.
   – Modified version of “Principal Stratification”?

Censoring at new anticancer therapy



- Primary analysis
  - Assuming that no new subsequent anti-neoplastic therapy will be started before progression.
  - Excluding the effect of new anti-neoplastic therapy started before an event (progression) by censoring at last adequate assessment.
  - **Hypothetical estimand** as we are assuming that the both censored patients would have similar longer PFS.

Reference: Treatment effect quantification for time-to-event endpoints–Estimands, analysis strategies, and beyond- Rufibach, Pharmaceutical Statistics. 2018;1–21.

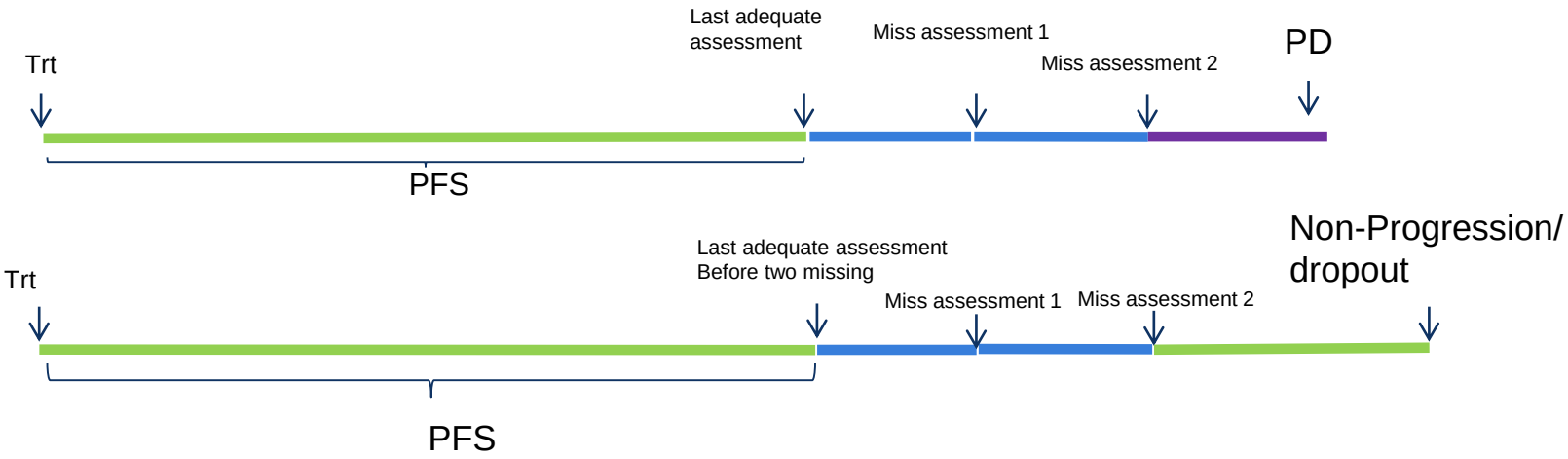
Sensitivity analyses??

3. Not censoring patients at start of anti-neoplastic therapies.
   - **Treatment policy estimand (supplementary analysis).**
   - Compare treatments regardless of the effect of a new anti-neoplastic therapy.
   - Combined effect of study treatment and subsequent therapy.

4. Impute as event at the last assessment before the start of anti-neoplastic therapies.
   - **Composite estimand (supplementary analysis).**
   - **Event = min (Death, Progression, anti-neoplastic therapies before progression).**
   - Administration of new anti-neoplastic therapy is treated as part of event.

5. Nonobjective progression as a PFS event
   - **Composite estimand (supplementary analysis).**
   - **Event = min (Death, Progression, nonobjective progression).**

Two or more missing assesments



- Two different situations but censored at the same time.
- Hypothetical estimand for primary analysis.

Sensitivity analyses??

6. Taking all events after two or missing assessment with event time as the actual time of assessment.
   - **Treatment policy estimand (supplementary analysis)**
   - Regardless of timing of event

7. Backdating of events- Taking all events after two or missing assessment but event time is last assessment before missing

   - **Composite estimand (supplementary analysis)**
   - Making time of missing assessment as part of the event definition.

Sensitivity/ supplementary analysis for PFS by IRC

- Progression free survival (Independent reviewer's assessment)
  - Supportive to PFS by investigator
  - Same rule of censoring
  - Hypothetical estimand
  - Informative censoring due to "progression by investigator" but not confirmed by IRC.

  - Estimate of PFS median (by IRC) may get exaggerated (Stone et. al., 2019)
    - 22.4 months vs 16.4 months (abemaciclib) (MAONRCH-2)
    - 30.5 months vs 24.8 months (Palbociclib) (PALOMA-2)

Sensitivity analysis for PFS by IRC

- One particular sensitivity analysis to handle informative censoring.
- Olaparib, Niraparib, FDA review.
- Composite endpoint. FDA was looking for different estimand.

Sensitivity Analysis 2: Approximately 12% of patients randomized across both cohorts were censored in the primary IRC-PFS analyses due to disease progression determined by investigator but not confirmed by central review and no further follow-up disease assessment. This might lead to informative censoring. This sensitivity analysis considered those patients as PFS events at the next scheduled assessment time.

Summary

- Except analysis with different model assumptions (stratified/ un-stratified analysis) most of the frequently used “sensitivity analyses” are actually supplementary analysis which answering different questions. Some **still may be important to establish robustness of treatment affect for specific trial. But do we need all these analyses every time?**

- If “Treatment policy estimand” is the question of interest then does hypothetical estimand adding any value? Also how to interpret all the outcomes together.

- The rational behind those censoring rules for primary analysis and supplementary (as per new addendum) analyses were not well documented or clear and varied for same end-point, for similar class of compound and same indication.

Summary

- Introduction of ICH E9 provides a better framework/platform for handling these **intercurrent events/structuring sensitivity/secondary analyses.**
  - Hopefully may result in fewer, but better justified, analyses.

- Current practice is to alter different censoring rules while assuming random censoring; We rarely check the validity of the assumption of censoring distribution or possibility of treating some cases as missing rather than censoring it. Need more assessment in this area as lot of methods are already well developed.

- Implementation of ICH E9 framework, hopefully, will harmonize these strategies across trials by indication, population and there will be well documentation with clear clarifications/justifications behind all these analysis and primary estimands of interest.

- Estimand censoring sub-team is working for this goal.

References

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- *Treatment effect quantification for time-to-event endpoints–Estimands, analysis strategies, and beyond- Rufibach, Pharmaceutical Statistics. 2018;1–21.*
- *FDA Statistical review evaluation for Necitumumab (Application Number: 125, 547Orig1s000.*
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