

# **Good news and bad news? An example of a challenging DMC situation**

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# The DMC function

- Ensure safety of trial participants
- Protect integrity of trial results
  - As the sole party with access to comparative results
- This avoids introduction of bias in trial conduct that could result from knowledge of accruing results by trial participants
- Enables trial personnel to perform their functions in the most objective manner
- **Not** the DMC function: proactively initiate changes to trial or program design, trial conduct, analysis plan, etc., based on their knowledge of accruing results
  - e.g., to “steer” the trial in a favorable direction
  - exception: acute safety risks to patients

# Communication

- Communications from the DMC to the sponsor team, Steering Committee, etc. are limited, *minimal* to meet the need, and avoid conveying comparative information or setting off speculation
- For major recommendations, initial communication with sponsor organization is generally confidential with designated management representative(s) not involved in trial operations
- *Question*: could there be a *hazy* situation, where the DMC notices some study aspect that is not ideal, and in the interest of a trial's ability to provide useful information, more communication than usual might be warranted?

# Our story

Trial involving an oncology therapy

- 2 arms, investigational product as add-on to standard of care
- Primary endpoint: Progression-free survival (PFS)
  - **Central** radiology assessment
- Trial was powered to detect a hazard ratio (HR) of 0.67
- Requires 287 primary events (death or disease progression)
- Group sequential scheme:
  - O'Brien-Fleming alpha spending function for efficacy
  - Beta spending function for poor effect  $\{\gamma(-0.5)\}$

# PFS: central vs local?

- There are precedents for using either **investigator** assessments, or **central** assessments, in main analyses
- Not without controversy, or at least understanding tradeoffs / limitations of each
  - e.g., subjectivity, informative censoring, etc.
- Extensively discussed in the literature, e.g.:
- *. . . failure to conduct timely IRC assessments has introduced significant bias. At the time of an investigator-determined diagnosis of progression, the investigator usually discontinues obtaining radiologic scans. The IRC has frequently disagreed with the investigator's judgment . . . Because IRC evaluations . . . rarely have been done in real time, such discordance has not been identified in time to ensure that the investigator continues obtaining radiologic scans until an IRC validated progression. This leads to informative censoring that can significantly bias the evaluation of PFS.*
  - Fleming, Rothmann, Lu (JCO, 2009)

# Preparation for interim analysis

- Planned interim analysis with about 60% of the maximum information (events)
- Based on blinded data review prior to the analysis, the team felt that there was potential for a meaningful degree of bias using the centrally-reviewed progression results due to **informative censoring**
- The DMC was alerted to this possibility in advance; the interim report thus included results for both central and investigator assessments, and additional sensitivity analyses

# ☺ **The good news . . . .**

At the 60% analysis, the PFS result using **investigator** assessment

- HR = 0.69, p = 0.003
- Reaches the O-F boundary for positive **efficacy** !

## ... and the bad news ☹️

The PFS result using **central** assessment

- HR = 0.90
- Reaches the threshold for **futility**



# The DMC dilemma

- The treatment might be effective, and important to the medical community
- But no matter what the reality, the inconsistency, if maintained, might lead to ambiguity and limit the interpretation of the trial results
- Is it possible that this can yet be “fixed” to some extent?
  
- The DMC chose to share with the sponsor and Steering Committee chair that the boundaries had been crossed
  - Not to trial personnel, but confidentially to designated sponsor management personnel

# Resulting actions

This set in motion a chain of events

- Further discussion led to a decision to establish a blinded **Adjudication Committee** to thoroughly re-review all discrepant PFS cases to make the most accurate assessments
- An analysis using the adjudicated PFS outcomes, on the same database, was subsequently presented to the DMC
- The treatment effect was slightly milder than the local assessment (HR = 0.74)
  - Would not have reached the O-F boundary, if applied similarly

# More . . .

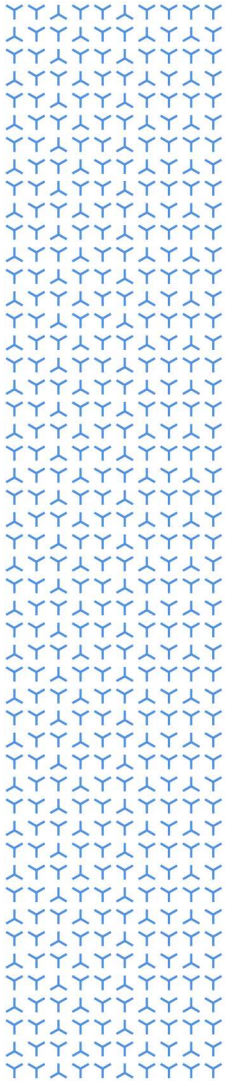
- Subsequent protocol amendments implemented the following changes:
  - The primary analysis of PFS was changed to use the *adjudicated* assessments, rather than the original *central* judgments
  - Event accrual was slower than expected and the original event target could not be reached in a sensible timeframe, so a calendar date was set for study termination
    - spending the remaining  $\alpha$  at this revised final analysis
- Final results: all 3 approaches (*investigator, central, adjudicated*) yielded effect estimates consistent with, but slightly milder than, the corresponding estimates at the interim analysis

# Reflections

- The primary endpoint change was advantageous for the investigational arm
- *Parties involved in the decision were aware of the weakness of the original endpoint in the interim data*
  - Though they believed this was well explained by informative censoring
- The decision to end the trial earlier than planned also potentially advantageous
- In general, *very problematic* if knowledge of comparative interim results contributes to these types of actions
  - After all, they're *unplanned adaptations*
  - Changes should be made objectively on purely scientific grounds, unaffected by results
  - But clearly the interim results *did*, at some level, lead to the endpoint change

# More . . .

- Might the DMC have simply emphasized to the sponsor that there was a difference between the local and central assessments that could raise difficulties in interpreting the final results?
  - Would such a communication have been compelling enough to the sponsor to initiate establishment of the adjudication committee?
  - Does it matter? - *Would the problem already exist regardless?*
- Early documentation of the rationale underlying the belief that the adjudicated assessment was most accurate would seem to be a good thing
- **Regardless of whether final results are favorable or unfavorable, is it in *anyone's interest* if they are difficult to interpret?**



***Thank you !***