Challenges and open questions in hematology
Estimand aspects in the RATIFY trial

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**RATIFY study in AML (Acute Myeloid Leukemia)**

- **Population:** newly diagnosed AML with a FLT-3 mutation
- **Design:** Phase 3, randomized, double-blinded, placebo-controlled
- **Endpoints**
  - **Primary:** Overall survival (OS)
  - **Key secondary:** Event-free survival (EFS)

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**Screening**

3277 pts

1:1 Randomization

N=717 pts

FLT3 mutation

**Induction**

+ Midostaurin

**Consolidation**

+ Midostaurin

12 mo. maintenance with Midostaurin

**Induction**

+ Placebo

**Consolidation**

+ Placebo

12 mo. maintenance with Placebo

**optional SCT**

**Failure**

CR

Survival, Relapse

**EFS:** time from randomization until failure to achieve remission, relapse, death due to any reason

**SCT:** Stem Cell Transplantation
“OS was significantly longer in the midostaurin group than in the placebo group, as was EFS. [...] In both the primary analysis and an analysis in which data for patients who underwent transplantation were censored, the benefit of midostaurin was consistent across all FLT3 subtypes”.

Which question are we asking?

- **Objective**: To determine if the addition of midostaurin to induction, consolidation, and maintenance therapy improves OS in mutant AML patients*

- **Primary analysis** (“not censored at transplant”) follows patients for survival regardless of receiving SCT or maintenance
  - Treatment effect of interest integrates outcome of SCT

- **Sensitivity analysis** “censoring for transplant”
  - “What would be the outcome if no SCT was given?”

- These analyses refer to completely different clinical questions

*Objective extracted from the study protocol
Stem Cell Transplantation (SCT)

- Eligible patients who achieved a CR after induction or consolidation chemotherapy and with a suitable marrow donor can proceed to SCT.
- SCT is potentially curative in ~50% of patients, but is associated with significant complications and with a 15-20% rate of transplant-related mortality.
- The use of SCT has significantly increased during the course of the study.
- If SCT is a key element of an AML therapy strategy, it seems reasonable to integrate the outcome of a transplant in the treatment effect of interest:
  - 57% of patients received a SCT, including 25% in first complete remission.
  - Study positive on OS and EFS regardless of SCT.
  - Treatment effect on OS and EFS maintained when censored at SCT.
Maintenance phase

- Maintenance was introduced for patients not eligible to SCT considering (1) that continuous inhibition of the FLT3 target might be necessary to optimize outcome, and (2) the favorable safety profile of midostaurin.

- A second randomization (maintenance vs. no maintenance) was considered not feasible given the relative rarity of FLT3 mutant AML.

- 29% patients started maintenance. OS and EFS analyses were conducted integrating the entire treatment plan including maintenance.

- Regulatory authorities were interested to characterize the contribution of the maintenance, but trial was not designed to address this question.
Which question are we asking?
Contrasting initial protocol objective with approved drug labels

- **Protocol objective**: To determine if the addition of midostaurin to induction, consolidation, and maintenance therapy improves OS in mutant AML

- **SmPC indication**: 
  - In combination with induction and consolidation, and for patients in complete response followed by single agent maintenance therapy

- **USPI indication**: 
  - In combination with standard induction and consolidation

*Wordings from Rydapt SmPC and USPI simplified for the purpose of this presentation*
How would we define the estimand today?

- **Clinical trial objective**
  - To determine if the addition of midostaurin to induction, consolidation, and maintenance therapy *with the option to receive SCT in CR* improves OS in mutant AML patients?

- **Treatment strategy**
  - **Experimental**: DNR-AraC + midostaurin induction, AraC + midostaurin consolidation *in pts with a CR, midostaurin maintenance, option to receive SCT in CR*
  - **Control**: DNR-AraC induction, AraC consolidation *in pts with a CR, option to receive SCT in CR*

- **Population**: newly diagnosed AML with a FLT-3 mutation *eligible for intensive chemotherapy*

- **Variable**: overall survival

- **Intercurrent events**: *none for OS (treatment policy for SCT, treatment discontinuation, new therapies)*

- **Summary measure**: hazard ratio
Conclusions and discussion

- The management of AML patients involves a treatment strategy including a sequence of multiple decision points and treatment modalities.

- For RATIFY, despite a detailed description of objectives and treatment in the protocol, there was insufficient alignment of the underlying question of interest.
  - The impact of SCT, a component of the treatment strategy with a potential major impact on benefit and risk, was not clearly outlined in the trial objective.
  - Despite its explicit inclusion in the study objective, the maintenance phase was not included consistently in approved labels (accepted by EMA, not accepted by FDA).

- The estimand framework may provide tools to more efficiently align on the key clinical questions of interest addressed by the trial.
References

Thank you