CDDF Workshop Nov 2018

Minimal Residual Disease in Acute Myeloid Leukaemia and Chronic Lymphocytic Leukaemia

Reflection on Meeting outcome and next steps

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Disclaimer

I am an employee of F. Hoffmann La-Roche.

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Highlights of the Discussion – Technology

- *Divergent views from the regulators on whether only one technology for MRD assessment has to be pre-specified for a protocol.*
  - *FDA insisted on "pick one", whereas EMA encouraged to provide "all what you have".*
- *Plenum flagged that if such positions remain divergent this may represent a challenge for drug devleopjment on a global scale*
- *For now no «reconciliation of positions». FDA in final guidance does acknowledge the multiple technology approach and asks for rational and justification if not one single test is pre-specified (line 298, 299 of final guideline)*

Highlights of Discussion AML

- Value of industry and academia collaboration to generate meaningful data sets to demonstrate surrogacy via Meta analyses was flagged.
- It was acknowledged that absence of HTA agreement to have MRD outcome as a relevant outcome for patients limits the acceptance of MRD as an endpoint overall
- Suggestion to explore the good correlation of QoL data with MRD and OS in AML. Such a correlation could be used to strengthen the value of MRD in discussion with HTA bodies

Highlight of Discussion in CLL

- MRD testing in CLL is conceptually different than in AML
  - Clonal marker in CLL - cancer marker in AML (e.g. mutation, or mutations, that cause the disease - in neoplasm)
- Data emerging that there is no difference between MRD measurements in PB and BM
- Relevant threshold was discussed and capturing data at a single threshold can result in losing important information
- Encouragement to use MRD4, MDR5, MRD6 as in CML community
- Move from positive/negative to detectable and undetectable MRD

Meeting Outcomes and Insights

- *EMA confirmed that CLL as intermediate endpoint can be used for licensure in RCTs designed to show superiority in terms of PFS as described in CLL specific guidance from 2015. EMA confirmed that approval on an intermediate MRD endpoint was explicitly not tied to CMA in the guidance to allow flexibility (or avoid legal complexity around eligiblity for CMA).*
- *In November 2018 EMA only had three drugs (Mylotarg, Vyxeos, Rydapt) reviewed and eagerly awaited further phase 3 trials conducted after ELN recommendations*
  - *EMA emphasized that results are needed to answer open questions in regard to: mutations associated with relapse, timing for MRD, appropriate threshhold, validated tests, can results be extrapolated across risk groups within a subtype, can results be extrapolated across different treatments(transplant, nonintensive treatment, how to get statistical power in subtypes with low prevalence.*
- *It was flagged that even draft guidance on MRD in AML was not expected in the near future*
- *FDA guidance for CLL similar to EMA (in regard to threshold) and meaningful MRD results have been included in USPIs (e.g. Venetoclax)*
- *FDA draft guidance for MRD in AML asked for measurement of MRD at CR with recoverey of blood counts, BM preferred substrate, timepoint of measurement was debated and FDA clarified position in final guidance*

Take-Home Messages & Next Steps

- *Collaboration across industry to obtain appropriate data sets for Meta analyses to demonstrate surrogacy is key and was applauded by regulators at the workshop (FDA, EMA).*
- *Efforts to collaborate across industry and academic groups to contribute to a meta-analysis to establish surrogacy are ongoing*

- *Further workshop on surrogacy planned in 2020*
  - *Agenda currently being developed and may include*
    - *further discussions of MRD as surrogate endpoint*
    - *discussion of more established surrogate endpoint in oncology as PFS with a focus on access*

Update on FDA guideline since Nov 2018

- FDA published guidance for industry on January 2020 Regulatory Considerations for Use of Minimal Residual Disease in Development for Drug and Biological Products for Treatment. New definitions:
  - "**individual-level association**," which is the "strength of the association between the surrogate and the true clinical endpoint,"
  - "**trial-level association**," which is the "strength of the association between the effects of treatment on the surrogate and the true endpoint."

- Clarification: single-arm trial data may be used to demonstrate individual-level association and assess efficacy outcomes of interest in subgroups by MRD level for the purposes of hypothesis generation, "the meta-analysis to validate MRD at the trial level should include **only** randomized trials."
- Language on «detection threshold of the MRD assay should be at least 10-fold below the clinical decision making» was maintained – however in final guidance the qualifier «where technically feasible» was added

Changes in AML and CLL section of FDA guidance

- AML section remained stable
  - New reference to potential change in clonality
  - Openess to deviate from preferred time point of MRD assessment «CR with recovery of blood counts» if a rationale and data are provided to justify the plan
- CLL section remained stable
  - New reference to NGS as a reliable assay for MRD in CLL
  - Acknowledgement that timing of when to test for MRD has yet to be standardized
  - Request to pre-specify timing and method of MRD testing