Molecular MRD detection by NGS can predict survival and relapse in newly diagnosed AML – LBA from ASH 2017

Minimal Residual Disease (MRD) present in the bone marrow (BM) of Acute Myeloid Leukemia (AML) patients in morphological Complete Remission (CR) after induction therapy is a source of relapse in this group of patients. At present, it is not very clear on which basis and also to what extent persistent somatic mutation contribute to AML relapse, hence the rationale for this study.

Moreover, assessment of MRD after induction treatment for specific markers by either multi-parametric flow cytometry or quantitative polymerase chain reaction has been clearly shown to predict relapse and overall outcome in AML patients, although it has been limited to specific subgroups of AML. The use of Next Generation Sequencing (NGS) aids for the assessment of a broad range of disease-related gene mutations in a single assay.

Tim Grob, MD, from the Erasmus University Medical Center, Rotterdam, Netherlands, and colleagues presented data at the Late-Breaking Abstract session of the 59th American Society of Hematology (ASH) Annual Meeting, Atlanta, GA, on Tuesday 12th December 2017, from their large prospective study, which aims to identify the value of molecular MRD by NGS in newly diagnosed AML.

In total, 482 AML patients were treated with two cycles of standard induction chemotherapy followed by consolidation in HOVON-SAKK clinical trials. At diagnosis and morphological CR, NGS was performed on samples from patients in order to detect mutations. At diagnosis, it was observed that 89.2% of patients (430/482) had
somatic driver mutations. Thus, patients were further split into two cohorts including Training (n = 283) and Validation (n = 147) cohorts. The primary and secondary endpoint of the study were relapse and Overall Survival (OS) respectively.

**Key findings:**

- Persistent mutations were detected in the BM of 51.4% patients in morphological CR
  - Most common persistent mutations include *DNMT3A* (78.7%), *TET2* (54.2%) and *ASXL1* (51.6%)
  - Persisting mutations *DNMT3A*, *TET2* and *ASXL1* (DTA) did not associate with the incidence of relapse in the training cohort
- Patients with undetectable NGS MRD had a higher risk of relapse than patients with detectable NGS MRD in the Training and Validation cohorts; SHR = 1.85, *P* = 0.001 and SHR = 2.81, *P* < 0.001, respectively
- 5-year cumulative incidence of relapse in NGS MRD+ and NGS MRD- patients; 58% vs 33.9%, *P* < 0.001
- NGS MRD predicted for reduced OS in both the Training and Validation cohorts; HR = 1.64, *P* = 0.012 and HR = 3.08, *P* < 0.001, respectively
- NGS MRD is an independent prognostic factor for relapse (SHR = 1.89, *P* < 0.001) and OS (HR = 1.64, *P* = 0.003)

The speaker, **Tim Grob**, stated that in this unprecedentedly large prospective study, targeted NGS defined by non−DTA mutations present in CR was shown to be a “powerful and independent predictor for relapse and survival”. Furthermore, this technique is applicable to virtually all newly diagnosed adults with AML.

Finally, mutations associated with clonal hematopoiesis in CR, DTA mutations, have no impact on relapse.
References:

1. Jongen-Lavrencic M. et al. Prospective Molecular MRD Detection By NGS: A Powerful Independent Predictor for Relapse and Survival in Adults with Newly Diagnosed AML. Late Breaking Abstract #LBA-5: 59th ASH Annual Meeting and Exposition, Atlanta, GA.