

(HR = 0.54; P = .004). The hazard ratio (HR) corresponds to the magnitude of the difference in the two curves, while the P value corresponds to the significance of this difference. The authors concluded that greater reduction in normalized WT1 transcript levels following anthracycline and cytarabine-based chemotherapy predicts a reduced risk of subsequent relapse.

### e. Methodology tip – should biomarkers be measured before or after chemotherapy?

The Cilloni study (275) is distinguished from most other studies of oncology biomarkers in that it found post-chemotherapy measurements of a biomarker to have prognostic value. The Cilloni study directly addressed the possibility that pre-chemotherapy biomarker data might have prognostic value, and discovered they were not useful for this purpose. Penault-Llorca et al. (276) also studied the relative merits of measuring biomarkers before and after chemotherapy. In a study of breast cancer treated by chemotherapy, these authors found that HER2 negativity predicted better survival, and HER2 positivity predicted worse survival, in terms of the endpoint disease-free survival (DFS). These authors also conducted their analysis with an endpoint other than DFS, namely, the endpoint of overall survival. Surprisingly, HER2 expression was found to predict overall survival only when HER2 expression was measured after chemotherapy. Where HER2 expression was measured before chemotherapy, there was no difference in overall survival in the HER2-negative patients and in the HER2-positive patients. None of the patients had received trastuzumab (the antibody that targets HER2). As a general proposition, researchers interested in prognostic markers prefer to use biopsies from chemotherapy-naïve subjects in order to avoid the potentially confounding effects of the therapy on the biomarker. However, the above studies reveal that taking biopsies before as well as after chemotherapy might be the most productive approach.

### f. Example of use of minimal residual disease – the Grimwade study using PML-RAR-alpha fusion protein

Grimwade et al. (277) reveal the utility of collecting data on minimal residual disease (MRD) during anti-cancer therapy. MRD was measured by assays that detected expression of the mRNA encoding the fusion product, PML-RAR-alpha. Patients

<sup>275</sup> Cilloni D, Renneville A, Hermitte F et al. Real-time quantitative polymerase chain reaction detection of minimal residual disease by standardized WT1 assay to enhance risk stratification in acute myeloid leukemia: a European LeukemiaNet study. *J Clin Oncol.* 2009;27:5195–5201.

<sup>276</sup> Penault-Llorca F, Abrial C, Mouret-Reynier MA, et al. Achieving higher pathological complete response rates in HER-2-positive patients with induction chemotherapy without trastuzumab in operable breast cancer. *Oncologist.* 2007;12:390–396.

<sup>277</sup> Grimwade D, Jovanovic JV, Hills RK, et al. Prospective minimal residual disease monitoring to predict relapse of acute promyelocytic leukemia and to direct pre-emptive arsenic trioxide therapy. *J Clin Oncol.* 2009;27:3650–3658.