B**reakout group 3B – Assays for Monitoring Disease Response and Recurrence**
Leaders: Drs. Radich, Hunger and Owzar

Morning session

We will be focusing on three questions, using three illustrative case examples:

Questions

1. What is the definition of clinical utility of classifier assays?
2. What evidence is needed for an assay to be used as a marker of response/recurrence?
3. What are the relevant endpoints for a molecular marker?

Three case studies

1. **CML:** In CML the measurement of BCR-ABL mRNA has quickly become a surrogate of response, and even was the main outcome in the upfront registration trial of dasatinib? How did this happen? What worked, and in retrospect, what didn't? (Hughes, Kaeda et al. 2003; Hughes, Hochhaus et al. 2010; Branford, Kim et al. 2012)
2. **ALL:** In pediatric ALL, large studies using either flow cytometry or RQ-PCR for Ig/TCR gene rearrangements have shown that the level of minimal residual disease (MRD) present after induction and consolidation is highly associated with relapse and survival, and is the single strongest prognostic factor in multivariate analyses. Can MRD be used as a surrogate for clinical trial design and drug registration (accelerated approval)? What is the appropriate surrogate (level of MRD, timing of MRD)? Which assay is best, or does it matter? (Borowitz, Devidas et al. 2008; Conter, Bartram et al. 2010; Bruggemann, Raff et al. 2012)
3. **Myeloma:** Here MRD has been associated with outcome, but the association is weaker, and the path for MRD to be a surrogate of outcome is less clear. Is this because of the test, and/or does it reflect the overall inadequacy of the drugs in treating this disease? (Sarasquete, Garcia-Sanz et al. 2005; Martinez-Sanchez, Montejano et al. 2008; Hart, Jagasia et al. 2012)

Afternoon session

While the morning session will examine where we are and where we want go, the afternoon session will focus on how to get there and how to facilitate acquisition of key data and information.

How do we get the evidence we need to move forward? Given that these are relatively rare diseases, how do we best study molecular assays of response and relapse? Do we really need randomized controlled trials? How do we deal with issues of statistical power, especially when we use molecular markers to carve rare diseases into really rare diseases?

How can the NCI help? Can the NCI help with organizing and supporting cooperative trials that bridge intergroups, and include community centers? Can they help fund the development, standardization, and testing of promising assays? Can they help to facilitate interactions with the FDA, particularly given limited resources available for cooperative group and investigator-initiated clinical trials?

Please review the following articles relevant to the case studies noted above.

Borowitz, M. J., M. Devidas, et al. (2008). "Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study." *Blood **111**(12): 5477-5485.*

Branford, S., D.-w. Kim, et al. (2012). "Initial Molecular Response at 3 Months May Predict Both Response and Event-Free Survival at 24 Months in Imatinib-Resistant or -Intolerant Patients With Philadelphia Chromosome–Positive Chronic Myeloid Leukemia in Chronic Phase Treated With Nilotinib " *J Clin Oncol **30**(35): 4323-4329.*

Bruggemann, M., T. Raff, et al. (2012). "Has MRD monitoring superseded other prognostic factors in adult ALL?" Blood 120(23): 4470-4481.

Conter, V., C. R. Bartram, et al. (2010). "Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study." Blood 115(16): 3206-3214.

Hart, A. J., M. H. Jagasia, et al. (2012). "Minimal residual disease in myeloma: are we there yet?" Biol Blood Marrow Transplant 18(12): 1790-1799.

Hughes, T. P., A. Hochhaus, et al. (2010). "Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS)." Blood 116(19): 3758-3765.

Hughes, T. P., J. Kaeda, et al. (2003). "Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia." N Engl J Med 349(15): 1423-1432.

Martinez-Sanchez, P., L. Montejano, et al. (2008). "Evaluation of minimal residual disease in multiple myeloma patients by fluorescent-polymerase chain reaction: the prognostic impact of achieving molecular response." Br J Haematol 142(5): 766-774.

Sarasquete, M. E., R. Garcia-Sanz, et al. (2005). "Minimal residual disease monitoring in multiple myeloma: a comparison between allelic-specific oligonucleotide real-time quantitative polymerase chain reaction and flow cytometry." Haematologica 90(10): 1365-1372.