**Breaking New Ground in AML: Practical Applications of Emerging Treatment Options**
**Audience Q&A**

**Guillermo Garcia-Manero, MD**
Professor
Chief, Section of Myelodysplastic Syndromes
Deputy Chair, Translational Research
Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

**Jeffrey E. Lancet, MD**
Department Chair
Malignant Hematology
Moffitt Cancer Center
Tampa, Florida

**Elli Papaemmanuil, PhD**
Associate Director
Center of Hematological Malignancies
Computational Oncology Service
Department of Epidemiology and Biostatistics
Memorial Sloan Kettering Cancer Center
New York, New York

**Richard Stone, MD**
Professor of Medicine
Harvard Medical School
Chief of Staff
Director, Adult Acute Leukemia Program
Dana-Farber Cancer Institute
Boston, Massachusetts

***QUESTION #1***

**Dr. Jeffrey Lancet:** First question was, "Has CPX 351 shown efficacy in FLT3 mutation patients, and if so, should it be combined with FLT3 inhibitor?" There has been demonstration that the FLT3 mutated AMLs appear to be more sensitive to CPX than 7+3 in this group of secondary AML patients. FLT3 is not an overly commonly mutated event in secondary AML, but in our particular subset, there was evidence that FLT3 patients were more sensitive. For that reason, there are studies being planned right now that combine FLT3 inhibitors with CPX.

***QUESTION #2***

**Dr. Richard Stone:** One question is, "What do I believe is the potential role of the other FLT3 agents in development: crenolanib, quizartinib, and gilteritinib?" Clinical trials will answer the question. Really, the interesting issue is whether the biological behavior of the disease at diagnosis, the genomic landscape thereof, and the clonal diversity is different than it is at relapse. Dr. Levis from Johns Hopkins has talked about this a lot. He seems to think that midostaurin was a good drug to use upfront because of the clonal heterogeneity at diagnosis. Whereas when you relapse, it tends to be that the most fit clone grows out and maybe it is more indicative to FLT3. So, more of the specific FLT3 inhibitors might be useful. The trials that are being done now comparing gilteritinib to chemo in relapsed FLT3 mutated patients on the one hand, and the other trial comparing quizartinib to chemo, might be very interesting. It might turn out that we use midostaurin or a nonspecific drug upfront, and then these more

specific ones at relapse. Or, more interestingly, we maybe use midostaurin and one of the specific drugs early on plus chemo. There are obviously no trials yet, but that is interesting theoretical issue.

***QUESTION #3***

**Dr. Elli Papaemmanuil:** Considering the cost and limited utility, other than IDH in FLT3 mutations, should routine next-generations sequencing (NGS) be done if not part of a clinical trial? This is a highly multidimensional question that very much depends on which part of the globe you are in and what infrastructure it is that you have. Already I would say from the European Guidelines and what we heard today, TP53 status, RUNX1 status, ASXL1 status are all recognized consistently. They have been more or less validated to be informative in terms of appreciating those subsets of disease that, up until recently, would have been missed by standard subtyping algorithms. Therefore they would be advantageous in helping you understand what sort of disease you are dealing with. I have a very biased view that the more information you have, the more complete the picture. There are ways that we can address the cost in that not every regional clinic and center needs to have their own infrastructure, but there are centralized services both within the U.S. and Europe that can account for some of the cost, and deliver pretty quickly some of those results. I would welcome from the three of you to add comments on how, outside of the context of a clinical trial, you would use that information. I know for a fact that many of my collaborators will call me and say, "I have a patient who has RUNX1 mutation and has that mutation, should I transplant them or not? What is the risk profile of your data?" It seems to me that there is a need in the community to learn that information.

**Dr. Guillermo Garcia-Manero**: I totally agree with Elli, and I will actually add a little bit that makes it even maybe more expensive but more fundamental. From my own experience, this has transformed how we approach AML and MDS and I am sure other leukemias. I could not actually think about practicing without this type of information. The important issue is actually is that this data is not only important at baseline when you first see the patient. This data is fundamental for me as the disease evolves and the patient responds or does not respond to compounds, because we see the shifts on these mutational patterns that allow me to actually adapt therapy on a routine basis. The issue is not only how you do this the first time. You are going to be using this actually as the disease evolves because you will see that under pressure from an IDH inhibitor, a FLT3 mutation will pop up or vice versa. You are going to see tremendous shifts on this therapy. Then, the other aspect that you alluded to is something that I could actually not imagine, because I thought that this mutational data was going to help us with 7+3 type of prognostication, or maybe a biomarker of response to a hypomethylating agent. It turns out that, as of today, the most powerful information you get out of this type of profile is actually the prognosis of your patient when treated with a stem cell transplantation This is data that came actually first from Dr. Stone's group in Boston, but this is really transformative. We had these patients that were in remission, MRD, all this stuff, and why are they relapsing, and now you know they have a p53 mutation and, as Jeff was saying, the rate of

relapse is very, very high. Now, does it mean that you should transplant or not transplant that patient? We do not know. I actually think that those patients need to be transplanted on a clinical trial and that those patients probably need to be taken to transplant at the time of best response, not when you have a donor. We should really start thinking about maintenance therapy type of approaches with a hypomethylating agent, or whatever clinical trial you have, for those patients at very high risk of relapse, if you opt to transplant that patient. Actually if there is a situation where you really need to consider this type of assay is in the stem cell transplant context today. I do not know if Jeff or Rich wants to add on this. I think this is really a major issue for us right now.

**Dr. Richard Stone:** I agree with what you said.

**Dr. Jeffrey Lancet:** I completely agree.

**Dr. Elli Papaemmanuil:** To add to this, if you are doing and can aggregate molecular profiling data outside of a clinical trial, it will enable us to aggregate that information on as-is treated patients, a more representative cohort than the ones that we are getting from clinical trials. We will then be able to - through consortium collaborative analysis - perform correlated analysis to validate some of those of observations that are initially done in small patient populations.

***QUESTION #4***

**Dr. Jeffrey Lancet:** There was a question about thoughts about additional targets being looked at in AML, and yes there are other targets certainly that are being investigated. I am sure I am not going to be able to name all of them, but some of the important ones are CD-123, which is a myeloid leukemia antigen that is felt to be present on early progenitor leukemia cells in particular. There has been a lot of interest in developing monoclonal antibody therapy both as naked antibodies and as antibody drug conjugates against that particular antigen, both in the active phase of disease and in maintenance therapy. We have inhibitors to the MEK-MAP-kinase pathway which may be relevant in RAS mutated AML. We have inhibitors also looking at the Hedgehog pathway, so, smoothened inhibitors are being studied currently in combination with low-dose cytarabine. Dr. Cortes from MD Anderson presented data at ASH this year that indicated an overall survival advantage in a randomized phase 2 study combining the smoothened protein inhibitor, plus low-dose cytarabine. Those were three of the other interesting targets, and I would also point out that bispecific antibody studies are being done in AML (similar to what we have seen with glembatumumab) looking to target CD3 and CD33, so bispecific approaches in immunotherapy are beginning to be developed this disease as well.

***QUESTION #5***

**Dr. Richard Stone:** What is the best treatment for patients who relapsed after midostaurin or other new first-line treatments? Should they consider dual HMA treatment? Well, I think this

really segues to what Guillermo just said. If a patient relapses after midostaurin, they should be re-sequenced to see if they still have the FLT3 mutation or not: they may have lost it. If they still have it, they could respond to any of the newer generation FLT3 inhibitors, each of which has shown response in people who have had midostaurin or sorafenib before. Again, the goal would be to get them to a second remission if possible, and then do a stem cell transplant by whatever means. However, a newer agent should certainly be considered depending on the mutational profile at that time.

**Dr. Guillermo Garcia-Manero:** I agree with this and I think the message from that question is critical: repeat that sequencing. Do not trust your original FLT3 mutated profile, it probably changed under pressure with this drug.