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IMPACT OF CYTOGENETICS ON OVERALL AND EVENT-FREE SURVIVAL IN MULTIPLE MYELOMA

Myeloma Today in conversation with Prof. Herve Avet-Loiseau

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Please give us a little background on the cytogenetics work of the IMWG, for which you serve as the principal investigator.

One of the projects of the International Myeloma Working Group (IMWG) is focused on the molecular classification of multiple myeloma. Until now, the prognostic impact of molecular changes in myeloma has been assessed from relatively small and/or incomplete studies, and there has been no large-scale analysis of molecular features linked to the International Staging System (ISS) of myeloma, which is a very useful staging system published by the IMWG in 2005. In the current project, the IMWG is looking at combining the ISS prognostic model, which is based on β2m and albumin levels, with cytogenetics, especially fluorescence in situ hybridization (FISH). We believe cytogenetics to be very important in myeloma and, in order to clarify the overall impact of chromosomal abnormalities, IMWG investigators undertook a collective analysis of 9,897 patients. At the 51st annual meeting of the American Society of Hematology (ASH), which was held in December 2009, we presented our analysis to date.

In brief, what were the IMWG findings presented at ASH?

Within the 9,897 myeloma patients in the study, 2,295 patients had presence of cytogenetic abnormalities (CA); 1,713 hypodiploidy; 1,673 hyperdiploidy; 2,309 cytogenetic deletion 13; 3,226 deletion 13 FISH; 1,573 FISH t(4;14); 1,486 FISH del 17p; 1, 683 FISH t(11;14); and 366 FISH t(14;16). Enrolled patients had complete clinical and treatment details available including baseline standard prognostic factors, ISS stage, as well as both progression-free survival (PFS) and overall survival (OS) information. Data was gathered from 14 studies in the U.S., Europe, Asia, and Latin America. Univariate and multivariate analyses were performed.

Each of the known adverse molecular features had a negative impact upon both PFS and OS. Among the deleterious FISH abnormalities, the t(4;14) abnormality was highly correlated with poorer outcomes. The t(4;14) abnormality combined with ISS stage also significantly enhanced predictive

capability (please see figure). The best outcomes were for ISS Stage I in the presence of t(11;14), with OS 89% at 4 years. Absence of any one adverse feature correlated with 80-81% OS at 4 years for Stage I. Presence of any one adverse feature had a more variable impact and correlated with 22%-40% OS at 4 years for Stage III.

FISH improves the prognostic value of the ISS and, in combination with ISS, provides the best predictive capability. Presence of any CA, t(4;14), 17p-, hypodiploidy, and cytogenetic 13q-contribute to poorer outcomes by ISS stage. The presence of hyperdiploidy and/or t(11;14) contribute to better outcomes. The IMWG analysis confirms the correlations between abnormal molecular findings and outcomes.

Since the ASH presentation in December, what updates are you able to share with us?

The project is moving forward rapidly. We are continuing to collect cytogenetics data on myeloma patients from centers around the world and, so far, the information has been very consistent with what we presented at ASH in December. Since ASH, we have received data from Italy and the United Kingdom, and those results are being analyzed and verified by our statisticians.

Once we have the results of the analyses that are still outstanding, I will begin work on the manuscript for publication. Our goal is to propose a new staging system for myeloma that will integrate the ISS with the newer findings on chromosomal abnormalities. Combining ISS with cytogenetics yields very valuable prognostic information, not only in the setting of clinical trials but also for doctors who see myeloma patients as part of their clinical practice. The information gleaned from cytogenetics allows us to present a more clear prognostic picture to the patient and to propose more specific treatment regimens that are more likely to successfully address the individual patient's disease. It is already clear to us that all myeloma patients would benefit from chromosomal analysis as part of their initial disease assessment. **MT**