MOLECULAR DIAGNOSTICS UNIT

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OVERVIEW

The main objectives of the Molecular Diagnostics Unit (MDU) are directed towards offering quality molecular tests for patients with cancer in order to support the current clinical services and diagnostic laboratories in hospitals of the Spanish National Health System (NHS). In this regard, the Unit provides a wide range of highly sensitive molecular assays to determine changes in the sequence or expression levels of key genes involved in cancer, and to enable the detection of Minimal Residual Disease in patients showing clinical remission as well as to follow-up on their response to therapy. Likewise, MDU is also devoted to implementing recent up-to-date cancer diagnostics solutions, not only to support the NHS but also to assist the Clinical Research Units and Research Groups at the CNIO. In addition, MDU collaborates with international and national groups dedicated to standardising and improving molecular diagnostics tests in cancer, and participates in teaching as well as in educational programmes for clinical post-residents, undergraduate and graduate students.

"In this new era of precision medicine in cancer, Molecular Diagnostics is playing a fundamental role as demonstrated by the increasing variety of assays requested by haemato-oncologists throughout 2018."

CORE UNIT HIGHLIGHTS

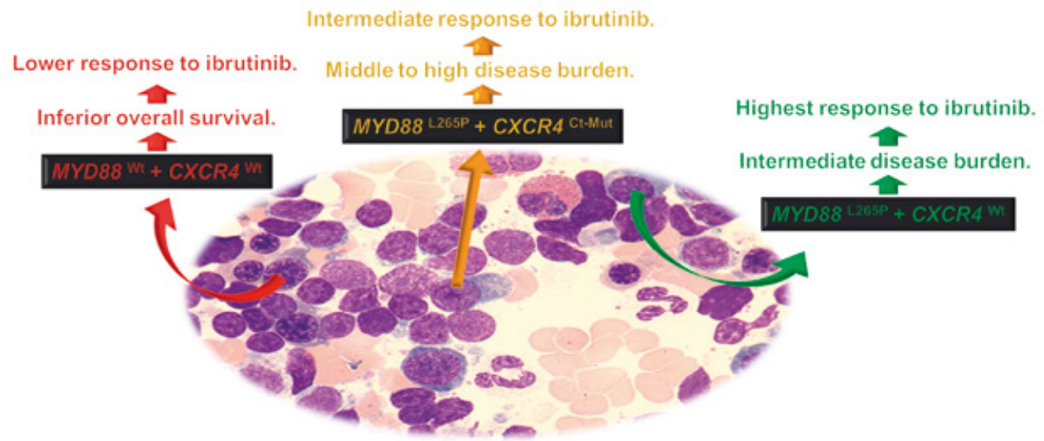

Figure Molecular testing of *MYD88* and *CXCR4* genes in plasmacytoid lymphocytes allows for different prognostic and/or therapeutic options for patients with Waldenström's Macroglobulinemia. (Wt: Wild Type; L265P: Leucine to Proline substitution at position 265; Ct-Mut: C-terminus nonsense/frameshift mutations).

During 2018, we have added and/or expanded 3 diagnostics tests.

First of all, the detection of the fusion gene *BCL1-IgH* by PCR was added to our list of services. Although the genetic translocation t(11;14)(q13; q32) is present in other lymphoproliferative diseases, it occurs mainly in mantle cell lymphomas (50-70%), which are more aggressive and have, in general, a worse prognosis than other low-grade B-cell lymphomas. This assay will be used not only to diagnose patients with a suspected mantle cell lymphoma, but also to monitor and evaluate recurrences of the disease.

We have also complemented the *MYD88* gene testing of patients with Lymphoplasmacytic Lymphoma/Waldenström's Macroglobulinemia (LPL/WM), by implementing a test that enables the detection, by Sanger sequencing, of nonsense and frameshift mutations in the *CXCR4* gene. The protein coded by this gene activates the AKT1/MAPK pathways in B-lineage cells and facilitates cell migration. Mutations in *CXCRA*, commonly found in association with *MYD88 L265P* mutation, are associated with primary resistance and initial lack of response to BTK, PI3K, and mTOR inhibitors. Thus, this assay will be used to aid in the prognosis and therapeutic management of LPL/WM patients (FIGURE).

Additionally, we directed our efforts towards improving the clinical utility of molecular testing based on the *BRAF* gene. In this regard, to complement the detection of the recurrent V600 mutation of BRAF in melanoma patients, we extended the analysis by bi-directional sequencing of exon 11 to enable the management of patients with lung cancer. Mutations in exon 11 are regularly found in lung tumours that are wild type for EGFR, KRAS, ALK, and other driver alterations. Moreover, these patients, with decreased sensitivity to gefitinib, responded to dasatinib with no additional treatment for several years.

Finally, during 2018, in the framework of our training policy, we hosted one medical resident and 2 undergraduate students. ■

AWARDS AND RECOGNITION

- Member of the Committee for Ethical Research *(CEI; Comité de Ética de la Investigación), Instituto de Salud Carlos III*, Madrid, Spain.