Sensitive detection of *BRAF* gene mutation is key to a cure

With medical advancements being made in the treatment of metastatic melanoma, **Bioron Diagnostics** has come up with a system that enables the robust sensitive detection of mutations at the *BRAF* gene associated with sensitivity of melanoma cells to inhibitors of the *BRAF* kinase. Such breakthroughs could help to significantly increase the survival rates of cancer patients by allowing the use of efficient target therapy.

Metastatic melanoma is often considered to be one of the most aggressive and treatment-resistant human cancers. The worldwide incidence of melanoma has increased over the past few decades, claiming 9,500 lives in 2013 in the US and more than 21,000 in Europe in the same year.

Aside from early surgical resection, no effective therapy has been found until recently. The alkylating chemotherapeutic agent dacarbazine, approved in the 1970s, has demonstrated response rates of about 15%. Over the past 30 years, no other drug or combination of drugs has had a significant impact on patient survival rates.

Blocking agents

The discovery in 2002 of activating mutations in the serine/threonine kinase gene *BRAF* in about 50% of melanomas led to efforts to develop agents to block this kinase. Some 80% of mutations result from the substitution of glutamic acid (E) for valine (V) in codon 600, giving rise to the *BRAF* V600E mutation. Other common *BRAF* mutations in melanoma are V600K (about 16%) and V600D/R (3%). These less-common variants are found at higher rates in melanomas in older patients.

> “The discovery and use of *BRAF* V600E inhibitors certainly represents a success story for translational oncology research.”

A decade later, vemurafenib, the very first orally administered and well-tolerated *BRAF* V600E inhibitor to be made available, started the new era of molecular treatments for advanced disease. The discovery and use of *BRAF* V600E inhibitors certainly represents a success story for translational oncology research.

Since vemurafenib is effective only for patients exhibiting mutations (V600E, V600K, V600D/R) of the *BRAF* gene, the need for a validated mutation assay is obvious.

Diagnostic tests

A real-time PCR-based assay for the detection of the mutation has been launched together with vemurafenib. Initially the system was used to select patients for clinical trials that involved this drug. This assay has subsequently been approved for use in conjunction with vemurafenib as a companion diagnostic test.

Sample of DNA showing a mutation.

Specifically designed to detect the V600E mutation using formalin-fixed paraffin-embedded tissue, it also has the capability to detect other V600 variants. However, in 38 patients who were confirmed to have a V600K mutation with direct sequencing, the assay detected mutation in only 25 patients, demonstrating a 66% rate of agreement.

Mutation detection system

A recent study by scientists from Bioron Diagnostics (Ludwigshafen, Germany) and Erlangen University demonstrates the possible reasons for disagreement in sequencing and popular real-time PCR-based assays for V600 mutations. The results were published in *Melanoma Research*.

On the basis of this study, Bioron designed a diagnostic system for a sensitive *BRAF* V600 mutations assay, which it recently launched on the market.

The *BRAF* V600 detection system is an open system that can be used with the majority of real-time PCR machines. There are strong reasons to believe that this system can provide results in complete agreement with the direct sequencing. Moreover, the sensitivity of the test can be superior to sequencing due to the possibility to detect 1% of mutations in the mixed population of cells. ■

References available upon request.

Further information
Bioron Diagnostics
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