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## MARKET WATCH

# Emerging companion diagnostics for cancer drugs

The use of molecular diagnostics for detecting variations such as mutations or amplifications of specific genes, in order to target therapies to patients who are most likely to benefit, is becoming increasingly common in anticancer drug development. For example, there are already several FDA-approved diagnostics for detecting amplification of the gene encoding human epidermal growth factor receptor 2 (HER2; also known as ERBB2) to guide the use of trastuzumab (Herceptin; Genentech/Roche), a monoclonal antibody (mAb) specific for HER2, in patients with breast cancer.

Another diagnostic that could potentially guide the use of drugs for patients with breast cancer is the BRACAnalysis test developed by Myriad Genetics. This test detects germline mutations in the tumour suppressor genes *BRCA1* or *BRCA2*, located on chromosome 17 and 13, respectively, that are associated with an increased risk of developing breast or ovarian cancer, and is currently used to aid decision-making about potential surgical interventions in high-risk patients. The application of the test to guide the use of drugs for cancers characterized by the presence of *BRCA1/2* mutations — such as ovarian cancer and triple-negative breast cancer (TNBC), which is defined by lack of expression of oestrogen and progesterone receptors and without overexpression of *HER2* — is emerging as a significant market opportunity.

Positive Phase II trial results in patients with metastatic TNBC were announced in 2009 for BSI-201 (developed by BiPar and Sanofi–Aventis) and olaparib (developed by Kudos and AstraZeneca), which both inhibit poly (ADP-ribose) polymerase 1 (PARP1) (*Nature Rev. Drug Discov.* 8, 437–438; 2009). A Phase III trial of BSI-201 in patients with metastatic TNBC began in late 2009, and a Phase III trial of olaparib in patients with metastatic TNBC is expected to commence in mid-2010. Myriad's BRACAnalysis test will be used to stratify patient populations for the olaparib Phase III trial. Should these trials prove

positive, Myriad's test could potentially be included in the drug labelling. At present, PARP inhibitors in development for ovarian cancer, including BSI-201 and olaparib, are in Phase II or earlier trials. As these drugs advance to late-stage trials, Myriad's BRACAnalysis test could be utilized in a similar manner.

Another emerging class of companion diagnostics detect mutations in the gene encoding *KRAS* to guide the use of anticancer mAbs that target the epidermal growth factor receptor (EGFR): cetuximab (Erbix; Eli Lilly/Bristol-Myers Squibb/Merck Serono) and panitumumab (Vectibix; Amgen). *KRAS* is a signalling molecule that is downstream from growth factor receptors, and retrospective analysis of clinical trials has shown that EGFR inhibitors are ineffective in patients with colorectal cancer who have *KRAS* mutations. This has recently led the FDA to approve revisions of the labels for cetuximab and panitumumab noting that the use of these mAbs is not recommended for such patients.

At present, the *KRAS* mutation test developed by Genzyme, which determines a patient's *KRAS* mutation status by analysing codons 12 and 13 of *KRAS*, is indicated for use as a companion diagnostic in treatment planning for colorectal cancer, non-small-cell lung cancer and other types of cancer. Qiagen anticipates that it will soon file for regulatory approval for its PyroMark Q24 *KRAS* assay kit for companion diagnostic use with EGFR-inhibiting drugs for the treatment of colorectal cancer. The PyroMark test amplifies the *KRAS* DNA sequence to detect mutations with increased sensitivity compared with sequencing methods. With market launch planned in 2011, Qiagen is well positioned to take advantage of the FDA's shift to support *KRAS* testing.

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