

## Innovative research advances personalised healthcare

*'Fitting of treatment to patients' is the foundation for Personalised Healthcare (PHC), which represents a major change in our approach to healthcare. We see PHC as a key enabler helping us to increase the success rate in drug development and bringing more clinically differentiated medicines to patients.*

*The targeted approach of PHC promises to provide patients with safer and more effective healthcare. Diagnostics and biomarkers help to identify those patients most likely to benefit or those who do not respond to a drug and may therefore avoid unnecessary exposure to possible side effects of therapy. That's why we are systematically incorporating PHC into our drug development efforts. By doing so, we have forged a pioneering role for Roche through early investment in molecular sciences and our combined expertise in Pharma and Diagnostics which we use throughout the value chain gives us a unique opportunity.*

*PHC is already happening. The following examples show many of the key aspects of PHC and how we are putting PHC into practice to bring more clinically differentiated medicines to patients.*

Jean-Jacques Garaud, Head of Pharma Research and early Development, Roche

Today's gold-standard in Personalised Healthcare is Roche's targeted breast cancer medication, Herceptin, and the Her2 companion tests to identify patients likely to benefit from Herceptin. Beyond this example, Roche continues to address the need for highly differentiated medicines through systematic implementation of PHC approaches in various disease areas as oncology, virology and immunology.

### Personalised treatment for melanoma cancer

Melanoma is treatable if caught early, but is very deadly when it becomes metastatic. The median progression-free survival for a patient with metastatic melanoma is less than 60 days, and the median overall survival for these patients is less than 12 months. Currently, there is no cure for the disease once it metastasizes.

Roche and Plexxikon are co-developing PLX4032 and other selective compounds for cancer treatment. PLX4032 is a novel, oral small molecule for the treatment of melanoma and other cancers harboring the so called V600E mutation of the *BRAF* kinase gene. This defect is present in approximately 60 percent of melanoma skin cancers, and occurs in about eight percent of all solid tumors, including melanoma,

colorectal, thyroid and other cancers. PLX4032 selectively targets and destroys tumor cells which contain this cancer-causing mutation. In contrast to many other available kinase inhibitors, this novel, anti-cancer compound is highly selective for its primary target, and is expected to be well tolerated since it does not have significant activity on other kinases.

A companion diagnostic test is being developed to enable the selection of patients who carry the *BRAF*<sup>V600E</sup> mutation for clinical trials, and ultimately, could be used to select patients most likely to benefit from PLX4032 treatment. Preliminary data from a phase I study presented at ASCO 2009 showed a consistent response for both tumor shrinkage and delay of tumor progression, which has been associated with an improved quality of life for most patients. These clinical data validate the hypothesis that a highly selective drug that targets the *BRAF*<sup>V600E</sup> mutation can specifically inhibit tumors harboring this mutation, while at the same time, delivering a treatment that is well tolerated by patients. Along with biomarkers and a companion diagnostic test, the selective drug PLX4032 represents the ideal personalized medicine for patients who are most likely benefit.

The biomarker and clinical data generated in biomarker studies validate the V600E mutation as an oncogenic, or cancer-driving, mutation in melanoma patients. Interest in the role of this mutation in other cancers prompted a collaborative study to retrospectively analyze data from approximately 600 colorectal cancer patients, led by Plexxikon, Roche and the Ludwig Institute for Cancer Research in Australia. This patient subset may also benefit from PLX4032 treatment.

### **Hepatitis C: Fitting treatment to the patient**

Hepatitis C virus (HCV) is a tough therapeutic target. Along with these efforts, it is important to optimize dosage and duration of the current standard of care, because different HCV-infected patients have different responses, depending on the genotype and viral load. In addition, different HCV-infected patients have different responses to current standard of care. In addition to determining a patients' viral load, genotyping tests/assays identify the genotype, allowing doctors to "fit" the treatment to the patient. Genotype 1 requires a longer duration of treatment (48 weeks). For genotype 2 or 3, which respond better, the duration is only 24 weeks.

This is important because interferons commonly used to treat HCV do not target the virus specifically, and they show side effects. This in itself demonstrates how PHC can help to optimize treatment and treatment outcome. But we are going on step further. New anti-viral compounds currently in development may have

less side effects, because they just target the virus and not the body's cellular machinery.

Research into new small molecule therapies is a huge medical need, as 75 percent of patients worldwide are infected with HCV genotype 1, the most difficult to treat with today's available therapies. Only about 50 percent of patients obtain a sustained virological response.

Another issue is drug resistance. Like other RNA viruses, HCV is not a single entity, but rather a population of genetically diverse entities called "variants." This viral population can rapidly replicate to high levels, adapting quickly to changes in the environment. Upon drug treatment, the virus can mutate, become resistant to the drug and continue to replicate – limiting the treatment's effectiveness.

While targeting the virus (and not the cellular machinery) potentially reduces side effects, it also raises concerns about the emergence of drug resistance. Researchers want to know whether an anti-viral selects for resistant viruses, and if so, how quickly and by what means. If resistance develops, it is possible to discontinue or modify the patient's treatment."

Roche's advanced pipeline targets two of the key enzymes for HCV – polymerase and protease. The goal is to discover new drugs that are going to be effective against potential resistant viruses that may be encountered by the time a new drug gets to market. It's an investment in PHC that will enable Roche to have the best and most effective therapies out there across the most patients.

### **Identifying Lung Cancer patients who will respond better to an established drug**

Tarceva is a small-molecule EGFR tyrosine kinase inhibitor (TKI) that is currently indicated as monotherapy in second-line and later Non Small Cell Lung Cancer (NSCLC) therapy (and first-line pancreatic cancer in combination with gemcitabine).

Studies in NSCLC have shown that some patients carry somatic mutations in the epidermal growth factor receptor (EGFR) gene. These mutations may correlate with responsiveness to the EGFR tyrosine kinase inhibitors, such as Tarceva.

The identification of EGFR mutations represents a novel way to predict treatment strategy for patients with lung cancer. It is known that as many as one in three Asian patients with lung cancer may have this new form of EGFR mutated lung cancer and it is estimated to also affect 10% of lung cancer patients in the Western

population.<sup>1</sup> Personalised treatment for patients with EGFR mutated NSCLC could lead to improved survival benefits with earlier treatment with Tarceva. Patients whose NSCLC does not have this mutation in the EGFR gene would benefit from Tarceva later in their treatment cycle, e.g. in the maintenance or 2nd line settings.

So far, there have been unprecedented results for EGFR mutated NSCLC patients treated with Tarceva with over 27 months overall survival (OS) compared to less than 12 months for traditional chemotherapies.<sup>2,3</sup> Patients with EGFR mutated NSCLC have been reported to live for 14 months without their disease getting worse (progression free survival - PFS) compared to 5.2 months with traditional chemotherapy.<sup>2,3</sup> However, all patients treated with Tarceva regardless of EGFR status have also been shown to benefit from treatment, with a 41% improvement in the time they lived without their disease getting worse and a 23% improvement in overall survival reported.<sup>4</sup>

#### **How to gain maximum benefit of therapy for patients with Rheumatoid Arthritis**

Rheumatoid arthritis (RA) is an autoimmune disease characterised by inflammation that leads to stiff, swollen and painful joints. This ultimately results in irreversible joint damage and disability. MabThera selectively targets B cells and represents a highly effective therapeutic approach for RA in addition to existing treatments such as disease-modifying anti-rheumatic drugs (DMARDs) and tumour necrosis factor (TNF) inhibitors.

In recent past, researchers have identified a group of rheumatoid arthritis patients in MabThera studies who are two to three times more likely to achieve a significant improvement in their disease. Identifying which patients that are most likely to benefit from treatment with MabThera will assist physicians in finding the best therapy choice for patients sooner.

In trials of MabThera, a pooled analysis showed patients who were seropositive to either of two characteristic RA autoantibodies, rheumatoid factor (RF) or anti-cyclic citrullinated peptide (aCCP), were two to three time more likely to achieve a significant improvement in their disease following treatment with MabThera, compared to patients who did not have these autoantibodies. Autoantibody production is one of the potential mechanisms that is thought to contribute to disease activity and joint damage which occurs in RA, with approximately 80% of the RA patient population being seropositive. The enhanced response observed in seropositive patients may be linked to one of MabThera's modes of action, as it targets the B cells which produce autoantibodies.

In the past, it has been difficult to predict which patients with RA will benefit most from a particular treatment. Therefore, the challenge faced by physicians is that many of these patients cycle through several types of treatment before achieving the optimum individual response. If physicians can predict which patients are likely to have the best treatment outcome with MabThera, then these patients can be offered this option early enough to gain maximum benefit in terms of symptom reduction and prevention of joint damage.

#### References

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