ASTRAZENECA: ADVANCING THE SCIENCE AND MEDICINE OF TREATING CANCER

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AstraZeneca is hard at work pushing new boundaries in the understanding of cancer and personalized medicine to develop new therapeutic options that can make a difference in patients' lives.

The advances of the last 70 years have created a better understanding of tumour biology and cancer therapies, leading to targeted drugs and new technologies. Yet, cures and long-term survival rates are elusive. Cancer remains an area of increasing unmet medical need worldwide.

Redefining cancer

In the past, drug development often focused on cancers with large patient populations. There was little appreciation of the heterogeneity of molecular drivers of cancer growth. However, as scientific insights into these drivers have advanced, we have become better at identifying the right drug for the right patient, enabling us to have more informed conversations around the value of our medicines.

At AstraZeneca, our way forward in R&D is through improved characterization of individual tumour types and segments of disease and the right application of biologically targeted treatments. We have shifted our focus from purely target-based drug discovery – where the link from pre-clinical science to actual human disease is not always well understood – to an integrated, patient-based approach, informed by pathway biology and strategic investments in critical R&D capabilities.

Our work is being done in partnership with external collaborators in academia. We are also investing in understanding whether a target is present, mutated or amplified in a wide range of tumours before going into trials.

Over time, we have refined our areas of research to focus on a number of cancer types where there are considerable unmet needs and where we are confident we can deliver valued, effective medicines:

- Lung cancer, where we are exploring additional genetic drivers beyond the epidermal growth factor receptor;
- Breast cancer and prostate cancer, where we aim to overcome resistance to hormonal therapies, interaction with the PI3 kinase pathway and role of poly ADP ribose polymerase (PARP) inhibition;
- Haematological malignancies.

Simultaneously, we remain open to addressing other cancer types with high unmet medical needs.

Personalized approaches to care

We have achieved a number of scientific breakthroughs and built a solid portfolio of cancer drugs. IRESSA™ (gefitinib) was the first in a new class of anti-cancer drugs known as epidermal growth factor receptor (EGFR) inhibitors, providing the first truly targeted treatment for advanced lung cancer.

The development of IRESSA highlights the potential, the challenge and the cost of innovation in the field of personalized medicine. More than a decade ago, when IRESSA was in development, it was hoped it would be effective for all patients whose cancers had EGFR expressed on the cell surface, as this is the case in the vast majority of lung cancers.

We took IRESSA into clinical trials with patients selected solely on having advanced non-small cell lung cancer (NSCLC). However, after initial Phase III trials, data emerged suggesting an effective response was more likely to occur in patients whose tumours had a mutated form of EGFR. This mutation occurs in defined sub-sets of patient populations: approximately 10% of Caucasian and 30% of Asian patients.

Beyond obtaining regulatory approvals for IRESSA, we needed to make sure that the right patients would get it. For personalized medicines, health care systems need infrastructure that supports genetic testing of cancerous tissues to ensure the right patients are targeted and treatment is timely. The delivery of IRESSA to patients is dependent on having the right test available, along with the infrastructure to deliver test results in a timeframe acceptable to the patient and the treating physician.

Studies suggest IRESSA works better in Asian NSCLC patients who are non-smokers, and even more so in people with a specific type of tumour that can be detected using a diagnostic tool. The incidence of this specific tumour type is high in Asian NSCLC patients. We are now partnering with a biotech company in China and Hong Kong to train staff in more than 60 major hospitals to use a diagnostic tool that helps identify patients that can benefit most from treatment with IRESSA.

In 2002, Japan became the first country to approve IRESSA. Today it is one of the leading epidermal growth factor receptor-tyrosine kinase (EGFR-TK) inhibitors in the Asia-Pacific region, where it is used by physicians for pre-treated

advanced NSCLC.

IRESSA is currently approved in 81 countries, with indications varying across countries. In the EU, IRESSA has been made available as the first personalized medicine for adults with locally advanced or metastatic NSCLC with activating mutations. Outside the EU, indications are being sought or expanded from the pre-treated setting to include first-line patients whose tumours harbour activating mutations of the EGFR–TK inhibitor. In the US, we have no plans to pursue regulatory approval for IRESSA.

Learning from IRESSA, we have made Asia a core element of our R&D strategy. In 2007, with an initial investment of US$100 million, we opened the AstraZeneca Innovation Centre China (ICC) in Shanghai. ICC scientists aim to help develop therapies that target gastric, liver and lung cancers which are more prevalent and have higher mortality rates in Asian patients.

Partnering to deliver targeted medicines

As scientific partnerships and external alliances are a core priority for us, AstraZeneca aims to plays a key role is building strong networks of partners and collaborators across the spectrum of academia, governments, scientific organizations, patient groups, and other biopharmaceutical companies with the aim of speeding-up the delivery of high-quality, targeted medicines. For example in Asia, we are working closely with local companies and academics to develop more meaningful, innovative products and therapies to address the unmet medical needs of Asian populations. Our academic partners include:

- Fudan University, Peking University and Shanghai Chest Hospital in China;
- The National Cancer Centre, Keio University and the Shizuoka Cancer Centre in Japan;
- The National Cancer Centre and the National University Hospital in Singapore;
- Seoul National University and the Asan Medical Center in South Korea.

Around the world, we are partnering with other biopharmaceutical companies in pre-competitive collaborations to advance the science and technology of drug development.

Our approach to external partnerships allows us to access the best science that exists outside of our labs. Our R&D and business development people have become close collaborators, hunting in pairs for the next good idea. This new model of working together allows us to better leverage the scientific expertise and extensive deal-making experience within the company, customizing our approach to individual partnership opportunities. The result is a more science-driven approach to business development.

In December 2012, we announced a partnership in China with Hutchison MediPharma (HMP) to co-develop and commercialize an oncology compound (volitinib) that has now moved into Phase I studies. This is the first clinical-stage compound to be directly licensed from a China biotech company by a major multinational pharmaceutical company with plans to develop and commercialize it internationally. HMP will lead volitinib's development locally in China.

In February 2013, we expanded our research efforts in Russia through a collaboration with the N N Petrov Institute of Oncology. Cancer is the second leading cause of death in Russia, with mortality rates amongst the highest in the world with approximately 300,000 estimated deaths each year. The collaboration involves the first-in-patient enrolment for two pioneering new studies – IGNITE and ASSESS – that aim to advance knowledge in diagnostic testing in NSCLC across diverse geographical locations.

- IGNITE will enrol patients from Russia and the Asia-Pacific region (n=3,500), where testing rates are low, primarily investigating the mutation frequency in advanced NSCLC patients with adenocarcinoma (cancer of an epithelium that originates in glandular tissue) and non-adenocarcinoma.
- ASSESS will focus on patients from Europe and Japan (n=1,300), where testing is more established, primarily evaluating the reliability of EGFR mutation status obtained via tissue/cytology and plasma-based testing methods.

New boundaries

Oncology is a fast-paced, exciting and evolving therapeutic area. By embracing cutting-edge science and taking a dynamic approach to R&D, we are overcoming today's intellectual, technical and scientific challenges to deliver the cancer drugs of tomorrow.

We continue to build our robust pipeline of small and large molecule compounds to advance the treatment of cancer. We are striving to establish clinically relevant biomarkers to measure the progress of the disease or the effects of treatment. We are exploring avenues to better understand molecular pathways that can help us identify patients that are likely to respond to treatment. We also are investigating the potential of our compounds in combination with other novel or existing therapies.

By pushing new boundaries in redefining cancer, we hope to discover new medicines that will make a meaningful difference in patients' lives. •