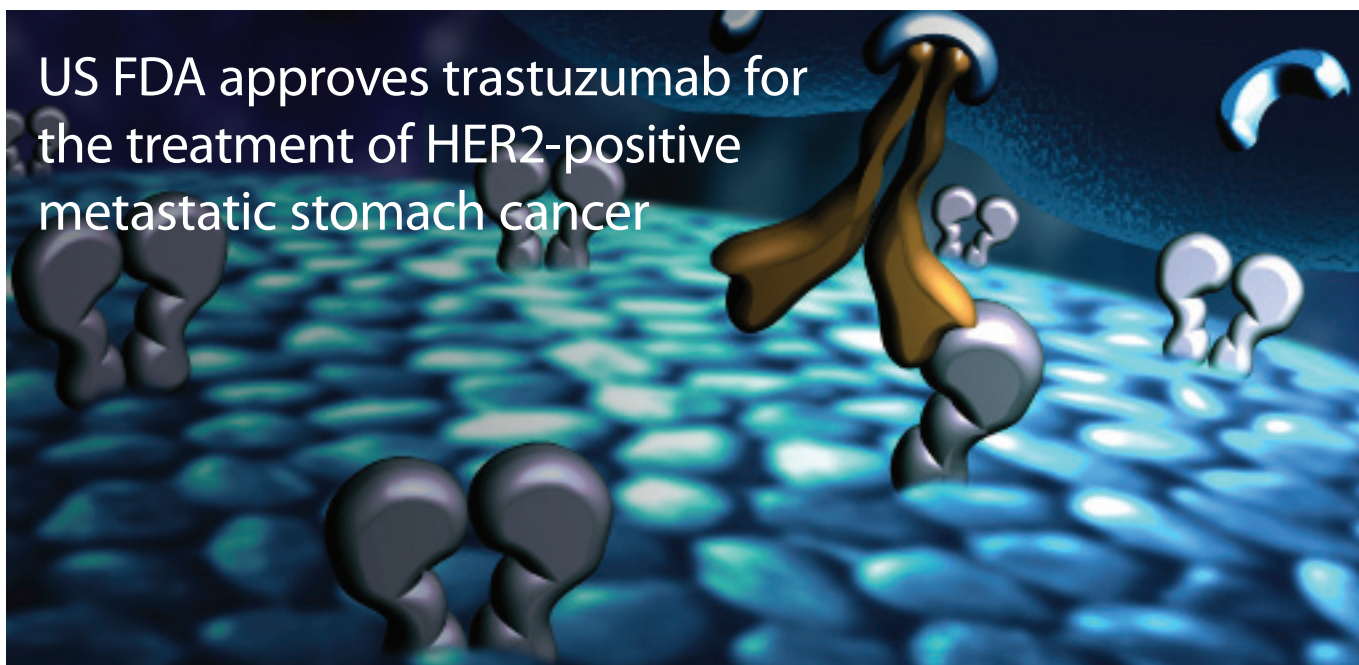


NEWS

Highlights from the latest news and research in clinical investigation



US FDA approves trastuzumab for the treatment of HER2-positive metastatic stomach cancer

Progress made towards cancer therapy and personalized medicines

Genentech recently announced that the US FDA has approved trastuzumab (Herceptin®) for the treatment of metastatic, HER2-positive stomach or gastroesophageal cancer in patients who have not previously received any treatment. The approval was specifically for the use of trastuzumab in combination with chemotherapy agents such as cisplatin.

Trastuzumab is an antibody that is believed to target receptors expressed on the surface of tumors, inhibiting the spread of cancer by blocking the receptors from receiving signals to trigger tumor growth. It differs from chemotherapy agents in that it affects tumor growth but not existing cancer cells, hence the use in conjunction with chemotherapy agents which act on tumor cells. Trastuzumab adds to a recent trend for targeted molecular therapy and personalised medicine in oncology.

The combined treatment of advanced stomach cancer with chemotherapy and trastuzumab was approved by the FDA following the results from an international Phase III study, known as ToGA (trastuzumab for gastric cancer), presented at the 2009 ASCO (American Society of Clinical Oncology) Annual Meeting. Trastuzumab received approval by the EMA early this year for the treatment of stomach cancer in combination with chemotherapy and FDA approval in the treatment of metastatic breast cancer over a decade ago.

Metastatic stomach cancer (stomach cancer that has spread), can be divided into subcategories based on the genetics of the tumor. This includes either human epidermal growth factor receptor 2 (HER2)-positive and HER2-negative. The tumor diagnosis affects the treatment given. Only those patients with HER2-positive stomach cancer are eligible for

“The success of the ToGA trial ... provides hope to patients but also reinforces the increasing importance of biomarkers in the development of new oncology therapeutics and treatment.”

combined treatment with trastuzumab and chemotherapy agents. Trastuzumab targets HER2 receptors, only expressed on the surface of HER2-positive tumors.

Stomach cancer is the cause of the second-highest number of cancer-related deaths worldwide, particularly as early diagnosis is difficult due to sufferers being asymptomatic until the later stages of the disease when surgical intervention is no longer an option and the tumor has spread.

The ToGA study involved the randomized treatment of 594 people with metastatic or advanced HER2-positive

...continued from page 1

stomach cancer, with trastuzumab and chemotherapy or with chemotherapy alone. The results showed that overall survival was greatly improved with the combined treatment of trastuzumab and chemotherapy rather than chemotherapy alone. In addition, the safety of trastuzumab in the treatment of stomach cancer was consistent with the safety profile for the treatment of breast cancer and no new adverse effects were observed in the combined treatment group.

“This development for the treatment of gastric tumors highlights the progress made towards cancer therapy and personalized medicines.”

This development for the treatment of gastric tumors highlights the progress made towards cancer therapy and personalized medicines. Hal Barron, executive vice president of product development and chief medical officer at Genentech summarizes the progress made by scientists in the study of the HER2 biomarker and its effect on tumor growth: “Since trastuzumab’s approval in HER2-positive advanced breast cancer more than a decade ago, we have continued to study how the HER2 pathway contributes to the growth and spread of other cancers, such as stomach cancer”.

Commenting on the approval, Yoon-Koo Kang from the Asan Medical Center at the University of Ulsan College of Medicine in Seoul said “The success of the ToGA trial and the approval of trastuzumab in gastric cancer not only provides hope to patients but also reinforces the increasing importance of biomarkers in the development of new oncology therapeutics and treatments”.

Dr Kang provides further discussion on the ToGA trial in the review article ‘Results and implications of the ToGA (Trastuzumab for Gastric Cancer) trial’ that features in this issue of *Clinical Investigation*.

Sources: www.gene.com/gene/news/press-releases/display.do?method=detail&id=13007; www.cancer.gov/ncicancerbulletin/110210/page7

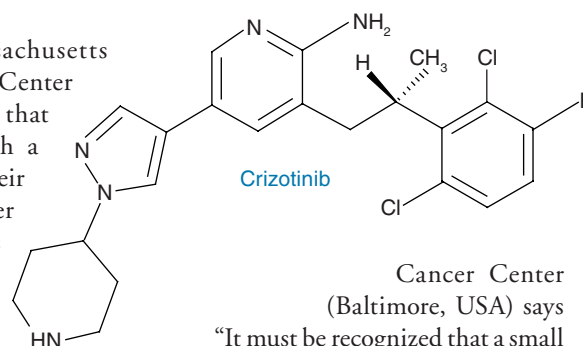
Promising early results for novel kinase inhibitor in NSCLC treatment

Researchers at the Massachusetts General Hospital Cancer Center (Boston, USA) have found that a minority of patients with a particular gene fusion in their non-small cell lung cancer (NSCLC) tumors responds remarkably well to a new chemotherapy agent, crizotinib, which acts to ‘switch off’ this gene. A total of 2–7% of NSCLC tumors display this specific mutation in the anaplastic lymphoma kinase (ALK) gene.

The mutation, a fusion gene *echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (EML4-ALK)* is expressed by the tumor to produce an enzyme with carcinogenic activity. Crizotinib, an experimental drug being developed by Pfizer, is believed to work by inhibiting the function of this enzyme. A study by Eunice Kwak of the Massachusetts General Hospital Cancer Center found that the inhibition resulted in shrinkage of the tumor or stabilization of the disease in most patients with tumors displaying the fusion gene [1]. This research was published alongside two other studies on crizotinib, one reporting the effect of crizotinib on a soft-tissue tumor displaying the same ALK fusion gene [2] and the other highlighting the potential problem of drug-resistant mutations in crizotinib therapy [3].

In an editorial accompanying the research papers, Bengt Hallberg and Ruth Palmer, both of Umeå University (Sweden) commented “Despite the lack of a control group in the 82-patient study, these results compare very favorably with the reported 10% response with second-line chemotherapy” [4].

The prevalence of NSCLC means that despite the fact that only 2–7% of NSCLCs have the fusion gene, those patients who can benefit from crizotinib treatment still represent a significant number of people. Martin Edelman, director of solid tumor oncology at the Greenebaum



Cancer Center (Baltimore, USA) says “It must be recognized that a small percentage of a very common disease represents a fairly large number of people”, emphasizing his point, Edelman raises imatinib, a treatment for chronic myelogenous leukemia, which affects a population of under 5000 per annum which is “considered the biggest success story for molecularly targeted anticancer therapy”.

Although the study is in its early stages, it emphasizes the advances in targeted molecular therapy as well as the progress being made in personalized medicine. According to NSCLC expert Mark Kris, of Memorial Sloan-Kettering Cancer Center (New York, USA), “This concept is extremely important not just to the care of those persons with lung cancer that have that particular mutation but for every patient with lung cancer and every cancer that is driven by a driver oncogene”.

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Sources: www.nejm.org; www.medpagetoday.com/HematologyOncology/LungCancer/23019

Consortium assembled to design human trials of mosaic HIV vaccine

“The mosaic vaccine comprises many synthetic, computer-generated sequences of proteins, which stimulate the immune system to respond to a wide variety of circulating HIV strains.”

An international team of scientists, all members of the Global HIV Vaccine Enterprise, has announced its formation to work on the design and implementation of a mosaic HIV vaccine for humans.

One of the major challenges of HIV vaccine design is the genetic diversity of the virus. The usual approach to HIV vaccine design is to stimulate the immune system to recognize specific amino acid sequences in the proteins synthesized by the virus by exposing it to small doses of the protein with the appropriate amino acid sequence. Following infection, these proteins will be recognized by the immune system of the immunized individual and destroyed. The downfall of this approach is the huge genetic diversity of HIV viruses and, therefore, range of proteins produced. This means that an immune system capable of recognising one specific protein produced by a particular HIV virus will not necessarily have an immune response to all proteins synthesized from all strains of HIV. The mosaic vaccine comprises many synthetic, computer-generated sequences of proteins, which stimulate the immune system to respond to a wide variety of circulating HIV strains. A pioneer in the development of mosaic vaccines, Bette Korber of the Los Alamos National Laboratory (New Mexico, USA) said “HIV’s diversity is vast, and the mosaic gene design represents a novel vaccine to directly tackle HIV diversity in human clinical trials. Based on computational models, mosaic vaccines were predicted to perform better than natural HIV vaccines; experimental studies in animals that directly compared mosaic to natural vaccines supported that prediction. We are excited to test this concept in humans.”

This vaccine type has had some success in animal trials, broadening the range of immune responses. The newly formed consortium, assembled by vaccine experts at Duke University Medical Center, has started designing safety trials with a view to test the mosaic vaccine in humans. The research will receive funding from the Bill & Melinda Gates Foundation and the National Institute of Allergy and Infectious Diseases (NIAID).

Barton Haynes, director of the Duke Human Vaccine Institute and the Center for HIV/AIDS Vaccine Immunology (CHAVI) who will head the consortium, announced that the group will use the NYVAC vaccinia vector, which was derived from the vaccine to protect against smallpox, and DNA that contains a new set of computer-designed HIV genes in the Phase I clinical trial. The consortium hopes to launch human trials by late 2012.

Sources: www.lanl.gov/news/releases/consortium_to_design_human_trials_of_mosaic_hiv_vaccine_nr.html



Once-daily HIV integrase inhibitor to enter Phase III clinical trials

An experimental once-daily integrase inhibitor, S/GSK1349572 (‘572) has entered Phase III clinical trials. ‘572 is being studied for the treatment of HIV infection and is the lead compound of Shionogi-ViiV Healthcare LLC.

‘572, is currently the only drug of its type to reach the late clinical trial stage. John Pottage, chief scientific and medical officer, points out the significance of this news: “Progression of one of our lead pipeline compounds into late-stage

“Progression of [‘572] into late-stage development ... is an important milestone for ... those living with HIV.”

development for use in treatment-naive and -experienced patients is an important milestone for ViiV Healthcare in its first year, and ultimately we hope for those living with HIV. We believe that this clearly demonstrates the benefit of our 100% focus on HIV and commitment to delivering new or improved treatment options”.

The late-stage clinical program can be subdivided into two trial designs, SPRING-2 and SAILING, both randomized, active-controlled, multicenter, parallel group, non-inferiority studies. SPRING-2 will compare the safety and efficacy of once-daily 50-mg doses of ‘572 with raltegravir (RAL) 400 mg twice-daily. The SAILING trial will assess the effect of a ‘572 50 mg once daily compared with RAL 400 mg twice-daily in addition to a background regime of HIV medication, over a 48-week period. Assessment of the activity and patient-tolerability of ‘572 compared with RAL will occur over a 96-week period.

Source: www.viivhealthcare.com/en/media-room/press-releases/2010-10-21.aspx and www.shionogi.co.jp/ir_en/news/detail/e_101021.pdf

The placebo effect: stronger than expected?

“How often study results are affected by what’s in the placebo is hard to say ... most of the time we have no idea what the placebo is.”

The structure of placebo-controlled clinical trials has been called into question in a recently published editorial by Beatrice Golomb of the University of California (CA, USA).

Placebo-controlled trials are designed based on the logic that to study the efficacy of a drug two groups of people, only one of which is receiving the treatment, must be compared in order to evaluate the effect of the drug. The issue is that the control group, those who are not being treated with the drug in question, must believe that they are receiving treatment. This approach accounts for any expectation-related response in the patients, which would be a potential source of differences between the two groups. If one group knew it was not receiving treatment, it would not expect to see any kind of effect, whereas the positive group would, which may manifest itself in a response that would then be attributed to the drug.

As such, the control group is given a placebo, an inert tablet that is believed to be active. However, Golomb points out a number of problems with this design

in her recent editorial. “There isn’t anything actually known to be physiologically inert” she says, immediately calling into question whether the effect of the drug can be ascertained by ‘subtracting’ the response from the positive group from the control.

“There are no regulations about what goes into placebos, and what is in them is often determined by the makers of the drug being studied, who have a vested interest in the outcome.”

Further to this, she states “There are no regulations about what goes into placebos, and what is in them is often determined by the makers of the drug being studied, who have a vested interest in the outcome”. A solution to this would be to present the placebo ingredients in the trial report, allowing those reading it to draw their own conclusions. However, as Golomb explained “There has been no expectation

that placebos’ composition be disclosed. At least then readers of the study might make up their own mind about whether the ingredients in the placebo might affect the interpretation of the study.”

In a letter to *Nature* 15 years ago, Golomb raised these issues, pointing out that the positive or negative effects of a placebo can be misleading in terms of the effect of the drug. Her recent editorial, which assesses the number of randomized trials published in four leading medical journals that disclosed placebo ingredients, highlights the problem. According to the results, placebo ingredients were disclosed in less than 10% of cases. Summarizing her research, Golomb concluded “How often study results are affected by what’s in the placebo is hard to say - because, as this study showed, most of the time we have no idea what the placebo is”.

Sources: Golomb BA, Erickson LC, Koperski S, Sack D, Enkin M, Howick J. What’s in placebos: who knows? Analysis of randomized, controlled trials. *Ann. Intern. Med.* 153(8), 532–535 (2010); www.medicalnewstoday.com/articles/205078.php

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