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CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation

Investigational drug shows significant improvement in cancer survival rate

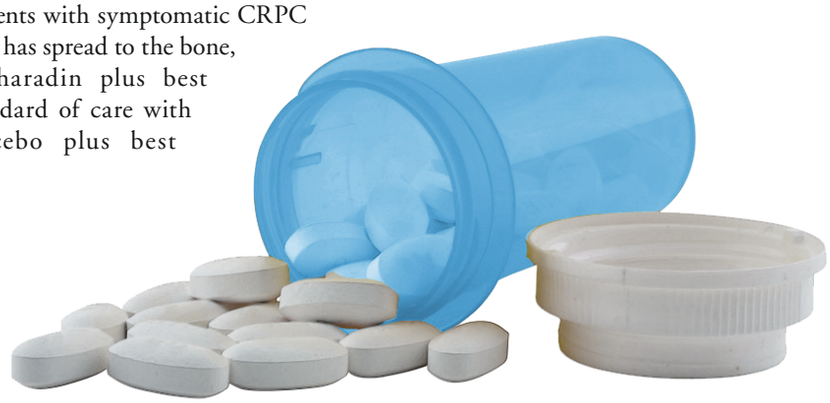
The Phase III study of Alpharadin® (radium-233 chloride) has produced positive data on the investigational drug, Bayer Healthcare Pharmaceuticals have announced. The ALSYMPCA trial of the alpha-pharmaceutical met its primary end point, as well as all of the main secondary end points.

The data indicated that overall survival in patients with castration-resistant prostate cancer (CRPC) and bone metastases was significantly improved by 44% ($p=0.00185$; HR=0.695). These results suggest that Alpharadin could represent a new standard of care in the treatment of these patients.

Prostate cancer is the sixth leading cause of death from cancer in men, with 258,000 men dying from the disease globally in 2008. It is the most common cancer among men in developed countries. A majority of men with CRPC, also known as hormone-refractory prostate cancer, have radiological evidence of bone metastases. These cancer cells affect bone strength, causing pain or bone fracture as well as other complications. Bone metastases are the primary case of disability and death in CRPC patients.

The ALSYMPCA trial, a Phase III, double-blind, randomized, placebo-controlled international study, was initiated in June 2008 by Algeta ASA (Oslo, Norway). The primary end point of the study is overall survival, with secondary end points including time to occurrence of skeletal-related events, safety and impact on quality of life.

The trial involved 922 patients who were docetaxel-ineligible or intolerable, or who had failed docetaxel therapy previously. The data collated compares, in patients with symptomatic CRPC that has spread to the bone, Alpharadin plus best standard of care with placebo plus best standard of care. Patients were administered Alpharadin or placebo intravenously up to six times, with an interval of 4 weeks between doses.



Patients who were treated with Alpharadin had a median overall survival of 14 months, compared with 11.2 months in the placebo group. There was also shown to be a 49% improvement in time to prostate-specific antigen progression, and total alkaline phosphotase normalization in 33% of patients. Median time to first skeletal-related events showed, at 13.6 months, a 64% improvement in comparison with patients treated with a placebo.

Alpharadin overall safety and tolerability was consistent with results form previous studies. Bone pain, nausea, diarrhea, constipation and vomiting were among the most common non-hematologic adverse effects of the treatments, occurring in at least 15% of patients in the study. Anemia was one of the most common hematologic adverse events.

Speaking exclusively to *Clinical Investigation*, Editorial Board member Cora Sternberg, chief of the Department of Medical Oncology at San Camillo Forlanini Hospital, Rome, Italy, highlighted the significance of the study findings. "The results of this trial are overwhelmingly positive for patients with castration-resistant cancer and metastases, with a 30% increase in overall survival and a 40% decrease in the time to a skeletal-related event. The therapy had little toxicity and will certainly offer new hope for patients with this disease."

These data were presented during the Presidential Session at the 2011 European Multidisciplinary Cancer Congress in Stockholm, Sweden. Bayer plan to file Aspharadin with regulatory authorities in the USA and Europe in 2012.

Source: Phase III data on alpharadin show significant increase in overall survival: www.bayer.com/en/news-detail.aspx?newsid=15028

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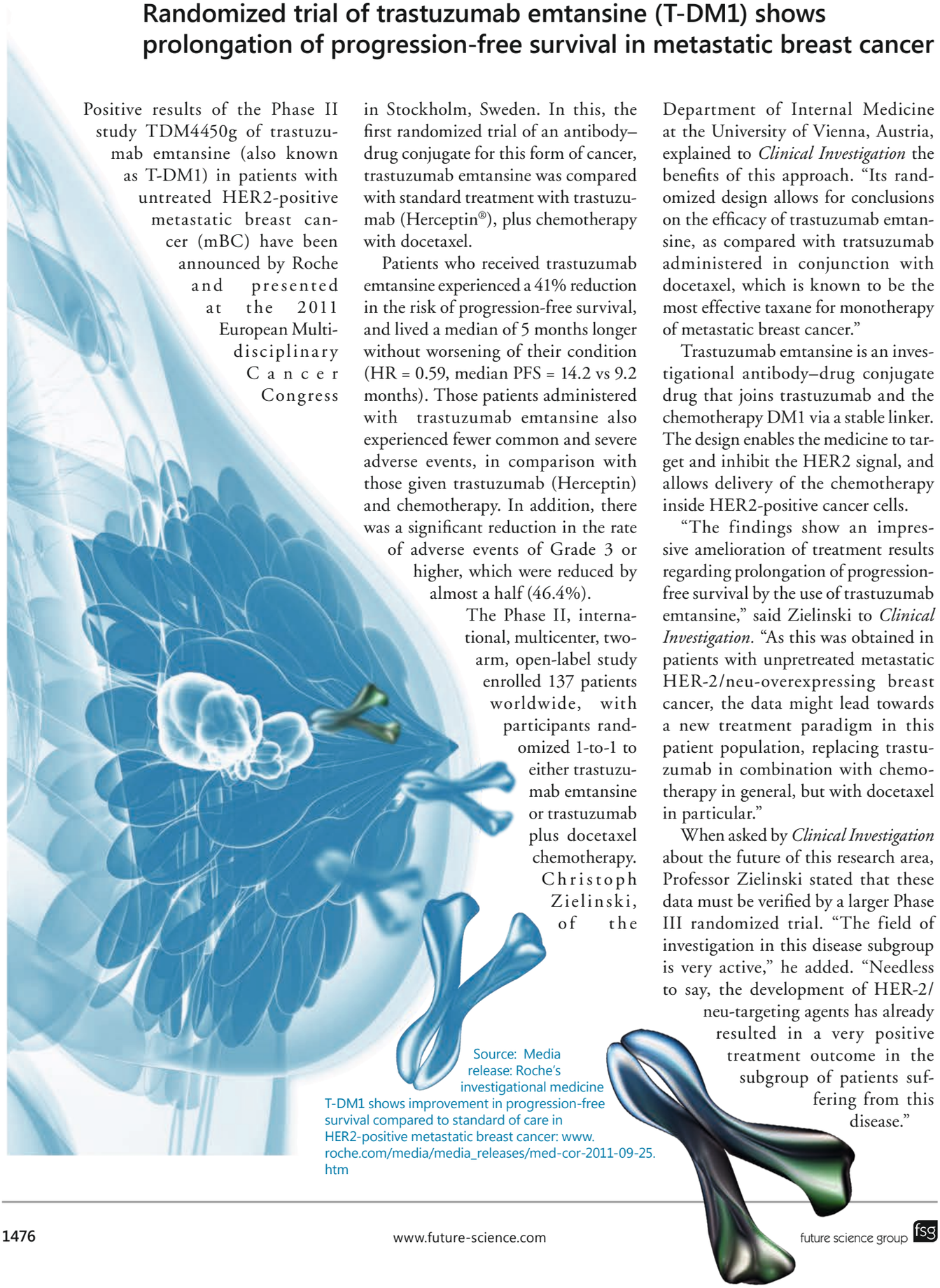
Randomized trial of trastuzumab emtansine (T-DM1) shows prolongation of progression-free survival in metastatic breast cancer



Positive results of the Phase II study TDM4450g of trastuzumab emtansine (also known as T-DM1) in patients with untreated HER2-positive metastatic breast cancer (mBC) have been announced by Roche and presented at the 2011 European Multidisciplinary Cancer Congress in Stockholm, Sweden. In this, the first randomized trial of an antibody–drug conjugate for this form of cancer, trastuzumab emtansine was compared with standard treatment with trastuzumab (Herceptin®), plus chemotherapy with docetaxel.

Patients who received trastuzumab emtansine experienced a 41% reduction in the risk of progression-free survival, and lived a median of 5 months longer without worsening of their condition (HR = 0.59, median PFS = 14.2 vs 9.2 months). Those patients administered with trastuzumab emtansine also experienced fewer common and severe adverse events, in comparison with those given trastuzumab (Herceptin) and chemotherapy. In addition, there was a significant reduction in the rate of adverse events of Grade 3 or higher, which were reduced by almost a half (46.4%).

The Phase II, international, multicenter, two-arm, open-label study enrolled 137 patients worldwide, with participants randomized 1-to-1 to either trastuzumab emtansine or trastuzumab plus docetaxel chemotherapy. Christoph Zielinski, of the Department of Internal Medicine at the University of Vienna, Austria, explained to *Clinical Investigation* the benefits of this approach. "Its randomized design allows for conclusions on the efficacy of trastuzumab emtansine, as compared with tratsuzumab administered in conjunction with docetaxel, which is known to be the most effective taxane for monotherapy of metastatic breast cancer."

Trastuzumab emtansine is an investigational antibody–drug conjugate drug that joins trastuzumab and the chemotherapy DM1 via a stable linker. The design enables the medicine to target and inhibit the HER2 signal, and allows delivery of the chemotherapy inside HER2-positive cancer cells.

"The findings show an impressive amelioration of treatment results regarding prolongation of progression-free survival by the use of trastuzumab emtansine," said Zielinski to *Clinical Investigation*. "As this was obtained in patients with unpretreated metastatic HER-2/neu-overexpressing breast cancer, the data might lead towards a new treatment paradigm in this patient population, replacing trastuzumab in combination with chemotherapy in general, but with docetaxel in particular."

When asked by *Clinical Investigation* about the future of this research area, Professor Zielinski stated that these data must be verified by a larger Phase III randomized trial. "The field of investigation in this disease subgroup is very active," he added. "Needless to say, the development of HER-2/neu-targeting agents has already resulted in a very positive treatment outcome in the subgroup of patients suffering from this disease."

Source: Media release: Roche's investigational medicine T-DM1 shows improvement in progression-free survival compared to standard of care in HER2-positive metastatic breast cancer: www.roche.com/media/media_releases/med-cor-2011-09-25.htm

Cancer survival could be improved by faster, smaller clinical trials

Research presented at the 2011 European Multidisciplinary Cancer Congress suggests that long-term cancer survival could be improved by running smaller and faster trials. Marie-Cécile Le Deley, Associate Professor of Clinical Epidemiology and Biostatistics at the Institut Gustave-Roussy, Villejuif, France, said that the advent of personalized medicine and targeted treatments means that conventional large-scale trials may not always be the best means of developing new cancer treatments.

Le Deley cited her work undertaken with colleagues from the Mayo Clinic in Rochester, MN, USA, where a series of two-treatment superiority trials were simulated over 15 years with different parameters of design. Parameters simulated included number of trials over the time period and experimental treatment criteria, these were used to estimate the expected improvement in survival rate for each strategy.

It is suggested that increased knowledge of tumor biology means that the most common cancers are increasingly recognized as being made up of subsets with particular abnormalities. "Specific therapies can be used to target these individual abnormalities, but the need to run a single large trial over many years, investing many resources, can hinder the ability to test many promising agents," said Le Deley.

The research at the Mayo Clinic produced data to suggest that conducting more trials, with smaller sample sizes and relaxed evidential criteria produced important gains in survival. Le Deley stated that, despite reducing the certainty of findings with such an approach, "the fact that we will conduct many more trials will allow such errors to be quickly remedied".

Le Deley went on to add that the most positive element of her proposed strategy is the ability to test a greater number of treatments. "Our approach of viewing a succession of clinical trials as a whole, as opposed to looking at them trial by trial, may help us to move forward. Our work has shown that the current risk-averse trial design strategy is not always appropriate as patient populations become more and more specific, and hence smaller". Le Deley added, "We hope that regulators will take this into account and re-examine their procedures in the interests of getting new, effective treatments to selected groups of patients as quickly as possible".

Source: Smaller and faster clinical drug trials could improve gains in cancer survival: www.sciencenewsline.com/medicine/2011092522430012.html

FDA approval granted for first biologic treatment for pediatric ulcerative colitis

The US FDA has approved Remicade® (infliximab) for the treatment of moderate-to-severe ulcerative colitis (UC) in children who have not responded to conventional therapy, as announced recently by Janssen Biotech, Inc. This is the seventh approval of infliximab for the treatment of inflammatory bowel disease (IBD). UC is a chronic IBD of the colon, and it is estimated that 150,000 children under 17 years of age suffer with the symptoms of IBD in the USA.

Evidence from studies of infliximab in adults with UC plus data from a Phase III trial in pediatric patients supported this approval. Results from the pediatric study showed that treatment with infliximab 5 mg/kg induced clinical response in 73% of patients at week 8.

Designed to determine the efficacy of a three-dose regimen of infliximab 5 mg/kg at weeks 0, 2, and 6 in inducing clinical response in pediatric patients, as well as to evaluate safety, the Phase III randomized, multicenter, open-label trial involved a total of 60 patients. All participants had failed to respond to or tolerate conventional treatments, had a median Mayo score of 8.0 and median Pediatric Ulcerative Colitis Activity Index score of 55. The primary end point was a decrease from baseline of the Mayo score of 30% or more, and a decrease in rectal bleeding subscore of at least 1.

Previously, there have been no approved therapy options for pediatric UC sufferers who have had an inadequate response to conventional therapy, said the lead study investigator, Jeffrey Hyams of the Connecticut Children's Medical Center and University of Connecticut School of Medicine. The approval of this treatment, therefore, represents an important step in providing care to affected children.

Safety data from the pediatric UC trial were consistent with current infliximab labeling. No new safety concerns emerged in evaluating infliximab in the treatment of a pediatric UC population.

Source: Remicade® receives FDA approval as first biologic treatment for pediatric ulcerative colitis: www.jnj.com/connect/news/all/remicade-receives-fda-approval-as-first-biologic-treatment-for-pediatric-ulcerative-colitis

Efforts increased to improve minority enrollment in clinical trials

At the American Association for Cancer Research (AACR) annual "Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved" meeting in Washington, DC, USA, Eli Lilly and Company (NYSE: LLY) have announced findings from an observational study that has resulted in new methods to improve diversity in clinical trials.

Only 17% of clinical trial participants are from minority groups, even though racial and ethnic minorities are more likely to develop and die from cancer than the rest of the US population. The Lilly study assessed the impact of ethnicity on second-line treatment of non-small-cell lung cancer (NSCLC).

With only 19% minority participants at the start, the company took steps to increase the underserved minority representation. Methods employed to increase accessibility included:

- Selection of new trial sites in areas likely to include patient populations with a minority presence of over 50%;
- Providing information on patient assistance programs to patients, helping them to secure treatment;
- On-site visits to trial sites to identify and address existing barriers;
- Translation of all patient materials into Spanish.

Post-trial, Lilly has began work on patient tools, such as a Latino Toolkit to provide trial sites with information in recruiting and supporting Hispanic patients in future studies.

There are numerous reasons for the lack of minority participation in clinical trials; for example, language and cultural barriers and patient mistrust. Coleman Obasaju, Senior Medical Director at Lilly Oncology emphasized the importance of efforts to overcome these obstacles, "Since lung cancer outcomes differ for different racial groups, it is imperative that these populations are represented in clinical trials."

Source: Lilly steps up efforts to improve diversity in clinical trials: http://newsroom.lilly.com/releasedetail.cfm?ReleaseID=606649

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