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CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in clinical investigation

Phase III study shows promising results for personalized medicine in advanced melanoma

Roche has announced that the BRIM3 study, a clinical trial investigating the effect of a personalized therapy with RG7204 for skin cancer, has met its coprimary end points. The investigational drug showed a significant survival benefit in people with previously untreated BRAF V600E mutation-positive metastatic melanoma, an aggressive form of skin cancer, when compared to treatment with dacarbazine which is the current chemotherapy standard of care. Participants treated with RG7204 displayed greater overall and progression-free survival in comparison to those receiving dacarbazine. Full data will be presented later this year. On the importance of these provisional results to metastatic melanoma patients, James Larkin of The Royal Marsden Hospital and leader of the BRIM3 study in the UK, comments to *Clinical Investigation* "(these results are) very important, this is the first time a personalized or targeted treatment for melanoma has been shown to have an impact on survival".

RG7204 is an oral, small-molecule drug being developed by Roche and Plexxikon, designed to selectively inhibit a mutated form of the BRAF protein, known to drive cancer and found in approximately half of all cases of metastatic melanoma. Metastatic melanoma is the most aggressive form of skin cancer and, until recently, there have been no major advances in this area, limiting treatment options.

The BRAF protein is critical in pathways involved in normal cell growth; however, mutations in the gene responsible for manufacture of the BRAF protein cause these pathways to be overactive, which can lead to uncontrolled cell growth and cancer. The BRAF V600E mutation is found in approximately 50% of melanomas. A diagnostic test is being developed alongside RG7204, the BRAF V600E Mutation Test, in order to identify patients whose tumors carry the mutated *BRAF V600E* gene.

"(These results are) extremely important, melanoma is characterized by mutations which drive the disease, some of which we don't know how to target yet. (This study shows) it could be

The editorial team welcomes suggestions for timely, relevant items for inclusion in the news. If you have newsworthy information, please contact:
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very important (to treatment options) to know which mutation a patient has" Larkin says of the weight of these preliminary results in terms of the use of biomarkers and personalized therapy in skin cancer.

BRIM3, a randomized, controlled, multicenter, Phase III study evaluated RG7204 compared to the current standard chemotherapy treatment, dacarbazine, in patients with previously untreated, BRAF V600E mutation-positive metastatic melanoma. The mutation status of the 675 enrolled patients was determined by the diagnostic test being developed alongside RG7204. Participants received either a 960 mg oral dose of RG7204 twice-daily or 1000 mg/m^2 of dacarbazine, administered intravenously every 3 weeks. Patients continued with treatment until disease progression or unacceptable toxicity.

> "...this is the first time a personalized or targeted treatment for melanoma has been shown to have an impact on survival..."

This study introduces the concept of personalized therapy into clinical practice in melanoma; commenting on this, Larkin says "I think our approach in future trials will be to test patients for mutations and tailor the treatment options accordingly, with a view to this becoming part of routine clinical practice". "In terms of the next stages of future research, work needs to be done into why some patients are initially resistant to treatment as well as why some patients initially respond well but then acquire resistance," concludes Larkin.

Source: Roche personalized investigational medicine shows survival benefit in advanced skin cancer www.roche.com/media/media_releases/med-cor-2011-01-19.htm.

Aging population needs to be accounted for when designing clinical trial, new study suggests

A recent study by the Robert Wood Johnson Foundation (RWJF) Clinical Scholars® at the University of Michigan (MI, USA) demonstrates that older individuals, who make up a disproportionate share of healthcare utilization and cost in the US as well as worldwide, are excluded in more than half of clinical trials.

Lead researcher Donna Zulman comments "These findings are concerning because it means that doctors cannot be confident that clinical trial results apply to their older patients," she continues, "Healthcare providers and patients need better evidence about treatment strategies that improve the health and quality of life of seniors."

As of 2009 in the US, individuals over the age of 65 represented 12.5% of the American population and this number is expected to approximately double in 20 years. Although only representing 12.5% of the population, this group accounts for 34% of personal healthcare expenditures, the majority of which can be attributed to the treatment of chronic diseases.

The study published in the *Journal of General Internal Medicine* aimed to examine the inclusion of complex, older adults in randomized controlled trials and the analysis of the results from those individuals. The researchers undertook a PubMed search identifying Phase III or IV randomized controlled trials in 2007 published in the *Journal of the American Medical Association* , the *New England Journal of Medicine*, the *Lancet*, *Circulation* and the *British Medical Journal*. For each study the age eligibility criteria, average age of study population, primary and secondary outcomes and patient exclusion criteria were reviewed as well as the frequency, characteristics and methodology of age-specific subgroup analyses were reviewed.

A total of 109 trials were reviewed, of these, 22 (20.2%) excluded patients based on age alone. Study coauthor Jeremy B Sussman argues "It is rarely appropriate to exclude people from clinical trials based on their age alone," he continues, "This is especially true in trials investigating conditions that are common in older adults."

Additionally, almost half (45.6%) of the remaining trials (those that did not exclude based on age alone) used exclusion criteria that could reasonably disproportionately affect the number of older adults accepted, such as physical frailty or impaired cognition. Of the trials that performed age-specific subgroup analyses, less than half of these examined potential confounding variables, such as comorbidities, which could give rise to false results when assessing treatment effect and age.

It was also found that only approximately one in four trials (26.6%) examined outcomes considered highly relevant to older adults, such as health status or quality of life.

"These practices leave healthcare providers in the dark when determining which treatment will best serve the needs of their patients," says Zulman.

To improve trial evidence in relation to its relevance to older patient populations, the authors suggest eliminating upper age limits for inclusion, reduction in the use of eligibility criteria disproportionately affecting older patients as well as encouraging the strict use of recommended statsitical methods for evaluating treatment effects by age.

"There's a critical need to ensure that research findings are relevant for our most complex and vulnerable older patients," concludes Zulman. "Our findings suggest a need for policy change by government agencies, such as the US FDA and the NIH to increase the representation of typical older adults in clinical trials."

Sources: Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. *J. Gen. Intern. Med.* DOI: 10.1007/s11606-010-1629-x (2011) (Epub ahead of print); As US population ages, need grows for research to improve health and healthcare for seniors: www.medicalnewstoday.com/articles/215608.php

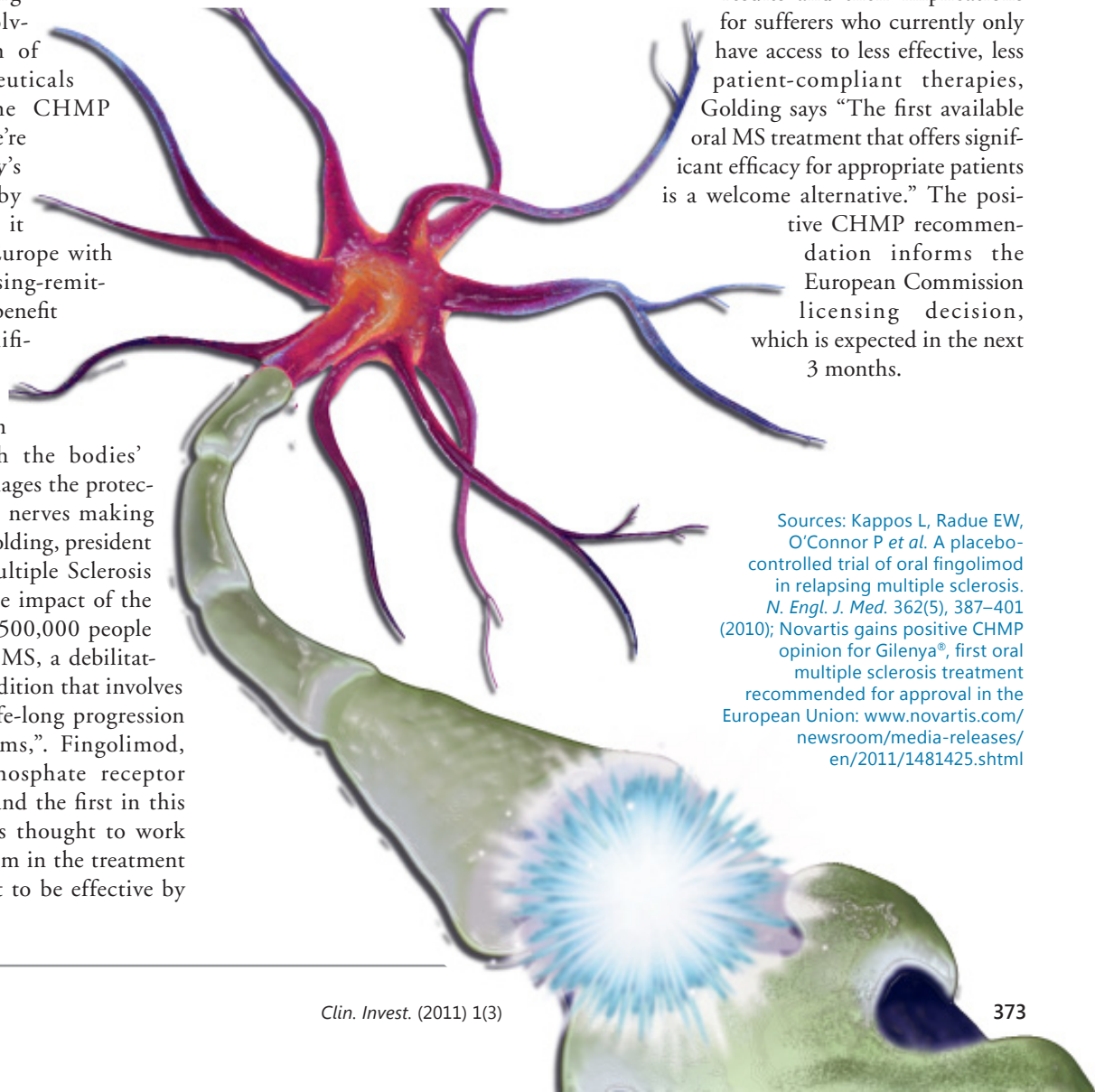
First oral multiple sclerosis treatment gets positive CHMP opinion for approval in the EU

A once-daily 0.5 mg dose of fingolimod (Gilenya®) has received positive feedback from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) as a treatment for multiple sclerosis (MS). This positive opinion comes on the back of a two-year, placebo-controlled study which demonstrated that fingolimod, developed by Novartis, showed efficacy in reducing relapses and significantly reduced the risk of disability progression. The CHMP has recommended fingolimod be approved in the EU for those whose relapsing-remitting MS is still highly active despite treatment with IFN-β, or in sufferers whose relapsing-remitting MS is rapidly evolving. David Epstein of Novartis Pharmaceuticals commented on the CHMP positive opinion "We're pleased with today's recommendation by the CHMP because it means patients in Europe with highly active relapsing-remitting MS could soon benefit from Gilenya's significant efficacy in a once-daily capsule".

MS is a debilitation condition in which the bodies' immune system damages the protective covering on the nerves making up the CNS. John Golding, president of the European Multiple Sclerosis Platform explains the impact of the disease "More than 500,000 people in the EU live with MS, a debilitating neurological condition that involves an unpredictable, life-long progression of complex symptoms,". Fingolimod, a sphingosine 1-phosphate receptor (S1PR) modulator, and the first in this new class of drug is thought to work via a novel mechanism in the treatment of MS. It is thought to be effective by limiting the immune system's attack on the CNS by retaining the white blood cells which could potentially attack the protective covering around the nerve fibers in lymph nodes, thus preventing them reaching the CNS. If fingolimod treatment is stopped, this white blood cell retention is reversible. In a 2-year, double-blind, randomized, placebo-controlled trial, fingolimod reduced relapses by more than 50% at 1 year, thus meeting the primary end point of the trial and demonstrating superior efficacy to intramuscular IFN-β1a, a commonly prescribed treatment for MS. The treatment also significantly reduced the risk of disease progression – a secondary end point. Fingolimod also demonstrated statistically significant reductions in MRI-measured brain lesion activity.

The trial involved 1033 participants (those who completed the study) with relapsing-remitting multiple sclerosis with a score at the lower end (0–5.5) on the Expanded Disability Status Scale and who had one or more relapses annually in the past year or two. Patients received either the 0.5 mg once-daily dose of fingolimod or placebo. Adverse effects related to the treatment included bradycardia, macular edema, elevated liver-enzyme levels and hypertension.

Commenting on the trial results and their implications for sufferers who currently only have access to less effective, less patient-compliant therapies, Golding says "The first available oral MS treatment that offers significant efficacy for appropriate patients is a welcome alternative." The positive CHMP recommendation informs the European Commission licensing decision, which is expected in the next 3 months.



Sources: Kappos L, Radue EW, O'Connor P *et al.* A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N. Engl. J. Med.* 362(5), 387–401 (2010); Novartis gains positive CHMP opinion for Gilenya®, first oral multiple sclerosis treatment recommended for approval in the European Union: www.novartis.com/newsroom/media-releases/en/2011/1481425.shtml

Expanded use of Alzheimer's drugs is recommended in NICE final appraisal

The National Institute for Health and Clinical Excellence (NICE) has announced its final appraisal, following a draft guidance last October, that recommended the use of three acetycholinesterase inhibitors (AChEIs) be extended to patients with mild Alzheimer's disease, as opposed to recent medical practice where practitioners in the UK were forced to request that patients with mild forms of the disease come back when their condition had deteriorated.

The new guidance means that the AChEI treatments – donepezil (Aricept®, Pfizer and Eisai), rivastigmine (Exelon®, Novartis) and galantamine (Reminyl®, Shire) – can be accessed early on in disease progression and help keep sufferers independent for as long as a possible. It also offers people with Alzheimer's disease the chance of an improved quality of life at all stages of their condition.

These draft recommendations are in contrast to recommendations made in the NICE 2006 guidance, suggesting that acetycholinesterase inhibitors be restricted to patients with moderate disease, on the basis of additional information from clinical trials.

Sir Andrew Dillon, chief executive of the NICE comments that, since the 2006 recommendations "clinical trials have continued to show the positive effects of these drugs and, in the case of [Ebixa], have reduced the uncertainty about its clinical effectiveness."

There are approximately 820,000 people living with dementia in the UK, Alzheimer's disease being the most common form of dementia, affecting 62% of dementia patients. Alzheimer's disease is an irreversible, progressive brain disorder that deteriorates memory function as well as reasoning and thinking skills, eventually leaving many patients unable to carry out basic tasks and represents a huge physical and mental burden for sufferers and family as well as a fiscal, social and practical burden for the state.

According to recent calculations, giving patients the drugs in the early stages of the disease saves US$800 of the $112,077 total treatment cost following diagnosis. Dillon comments that information about the costs of living with and treating Alzheimer's disease had a role in the new recommendations.

The final recommendations is welcome news to the UK Alzheimer's disease society and for people with early Alzheimer's disease and their families, the final guidance on the drugs is expected in March.

Sources: Final NICE appraisal recommends improved access to treatment and care of people with early Alzheimer's disease: www.eisai.co.jp/enews/enews201104pdf.pdf; NICE recommends expanded use of Alzheimer's drugs: www.firstwordplus.com/Fws.do?articleid=EE83EF36E9C349F6866883891797B844