

News & Views in ...

CLINICAL INVESTIGATION

Highlighting the latest news in clinical investigation

Non-small-cell lung cancer in the elderly: updated expert opinion published

A follow-up to an expert opinion paper discussing the management of non-small-cell lung cancer (NSCLC) in the elderly, authored by the EORTC Cancer in the Elderly Task Force and Lung Cancer Group along with the International Society for Geriatric Oncology in 2010, has recently been published in the *Annals of Oncology*.

It is estimated that approximately half of all patients diagnosed with NSCLC are aged 70 years or over, yet the under-representation of these individuals in clinical trials has led to a lack of available clinical data that could otherwise be used to make evidence-based clinical recommendations.

“Treatment decisions for elderly patients with NSCLC should not be based on their chronological age alone; there are many other factors that need to be considered. For instance, what is the patient’s life expectancy

and preferences? What are the expected benefits and risks of the treatment?” commented Mary O’Brien of the Royal Marsden Hospital (London, UK).

With regards to this elderly NSCLC patient population, the updated expert opinion incorporates recommendations for screening, surgery, adjuvant chemotherapy and radiotherapy, treatment of locally advanced and metastatic disease, as well as new data on screening procedures, patient preferences and geriatric assessment.

The authors suggest there is evidence of the feasibility of age-specific clinical trials, which provide reliable data that can be used to help guide treatment decisions. They suggest that more efforts should be made to carry out such trials in all stages of NSCLC and that steps should be taken to ensure enrolled patients are truly representative of the general elderly population.

“People do not all age the same, so we also need to consider their biological or functional age when deciding on treatment. Multidimensional, multidisciplinary, comprehensive geriatric assessment can lead to better treatment for elderly patients with NSCLC,” explained Ulrich Wedding, Treasurer of the EORTC Cancer in the Elderly Task Force.

– Written by Emily Brown

Source: EORTC and SIOG update expert opinion on management of elderly patients with NSCLC: <http://www.eortc.org/news/eortc-and-siog-update-expert-opinion-management-elderly-patients-nsclc>

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Ramucirumab receives US FDA approval for use in advanced stomach cancer

The US FDA has recently approved the monoclonal antibody therapy ramucirumab for use in second-line treatment of advanced stomach cancer that has progressed following standard chemotherapy. This move marks the first approval of a single-agent drug for advanced stomach cancer, an aggressive and difficult-to-treat malignancy.

“For years we have looked for new and really effective drugs for stomach cancer,” commented Charles Fuchs of the Dana-Farber Cancer Institute (MA, USA). “We have relied on standard chemotherapies for a long time, and we’ve needed targeted agents based on the fundamental biology of stomach cancer.”

Ramucirumab is an antiangiogenesis agent that targets VEGF receptor-2 and can promote tumor shrinkage by preventing the formation of new blood vessels, and therefore depriving tumor cells of oxygen and nutrients. Reported in 2013, the results of the Dana-Farber-led REGARD trial indicated that patients with

advanced or metastatic gastric cancer who received ramucirumab had a significantly improved rate of survival when compared with placebo. The therapy increased the median overall survival of patients by 37% and progression-free survival by 62%.

“The benefit is modest, but it’s clearly better than what we were previously doing,” Fuchs explained. As in other diseases such as colon cancer, he added, new drugs provide incremental benefits, “but when you chip away and develop drugs in sequence, ultimately you do have meaningful clinical improvements.”

A further randomized trial termed RAINBOW has indicated that ramucirumab displays greater efficacy when combined with chemotherapy, in this case paclitaxel. This FDA approval does not include the use of the treatment in combination therapy, but the drug’s manufacturer Lilly Oncology (IN, USA) are planning to submit these data in the hopes of expanding the approval.

– Written by Emily Brown

Source: Dana-Farber Cancer Institute press release: <http://www.dana-farber.org/Newsroom/News-Releases/fda-approves-first-targeted-drug-for-advanced-stomach-cancer.aspx>

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First large-scale dengue vaccine efficacy study achieves primary clinical end point

Dengue hemorrhagic fever, a mosquito-borne tropical disease caused by the dengue virus, is a threat to nearly half of the world’s population and affects approximately 500,000 individuals each year. Often misdiagnosed due to a large spectrum of clinical symptoms, it is a leading cause of hospitalization that places a significant burden on health systems and has become a public health priority in a number of countries in Asia and Latin America, where epidemics occur.

Now, Sanofi Pasteur (Lyon, France), who has been working on the development of a dengue vaccine for over 20 years, announced that the first of two Phase III efficacy studies with its dengue vaccine candidate achieved its primary clinical end point. Demonstrating a significant reduction of 56% of dengue disease cases, initial safety data are consistent with the good safety profile that was observed in previous studies. In a press release, the company state that full analysis of the data will be undertaken in the coming weeks and reviewed by external experts before being disclosed at an international scientific congress.

“This achievement is the result of more than 20 years of work in the field of dengue, collaborating with investigators, volunteers, authorities, scientific experts and international organizations” commented Olivier Charmeil, President and CEO of Sanofi Pasteur. “Developing a dengue vaccine for the benefit of children and their parents is at the heart of our mission. Our goal is to make dengue the next vaccine-preventable disease and to support the WHO’s ambition to reduce dengue mortality by 50% and morbidity by 25% by 2020.”

Principal investigator Rosario Capeding added, “This is the first time ever a dengue vaccine successfully completed a Phase III efficacy study. These significant clinical results, associated with the good safety profile of the vaccine, bring real hope to more than 100 million people affected each year by dengue, a disease without any specific treatment today.”

The results of the large-scale efficacy study, which includes more than 20,000 volunteers from Brazil, Columbia, Honduras, Mexico and Puerto Rico, will be further completed in the third quarter of 2014.

– Written by James Potticary

Source: Sanofi Pasteur press release: *The world's first, large-scale dengue vaccine efficacy study successfully achieved its primary clinical endpoint*: www.sanofipasteur.com/en/articles/theworld-s-first-large-scale-dengue-vaccine-efficacy-study-successfully-achieved-its-primary-clinical-endpoint.aspx

Newly developed thyroid cancer model highlights potential therapy combination

Details of a new mouse model that accurately demonstrates the progression of papillary thyroid cancer to anaplastic thyroid cancer (ATC) have recently been described in *Proceedings of the National Academy of Sciences*. The work, carried out by investigators at Massachusetts Institute of Technology's Koch Institute for Integrative Cancer Research (MA, USA), also demonstrates that combination treatment with MEK and BRAF inhibitors demonstrates enhanced antitumor activity in the model.

There has been little progress in developing effective therapies for ATC as incidence is low, and prognosis of individuals with the disease is very poor and therefore carrying out clinical trials is difficult. "There have been very few successful clinical trials in ATC in part because it is hard to get patients recruited, and, when these patients present with ATC, the disease may be so aggressive that they are too sick to participate in the trial," explained lead author David McFadden (Koch Institute for Integrative Cancer Research).

It has been observed that mutations affecting p53 are the most prevalent genetic aberrations in human ATC, while a subset of these cases will also harbor BRAF mutations. Hypothesizing that a mouse model with these mutations in the thyroid might allow for observation of the development of ATC, McFadden and colleagues engineered a mouse in which BRAF and p53 could be conditionally mutated specifically in the thyroid gland.

Investigation of disease progression in this model determined that BRAF mutation alone was sufficient for the initiation of tumorigenesis, yet loss of p53 was required for the disease to progress from a papillary state to ATC. From this it was concluded that BRAF mutation and loss of p53 cooperate *in vivo* to

– Written by Emily Brown

Source: Koch Institute for Integrative Cancer Research press release: <http://ki.mit.edu/news/2014/jacks-laboratory-develops-novel-mouse-model-aggressive-thyroid-cancer>

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promote disease progression to ATC. However, it was noted that there was a significant time period of some months between initiation of the mutations in these mice and development of ATC. The team plan to further this work by investigating whether there are any further genetic or epigenetic changes that are required to facilitate this disease progression.

Furthermore, based on models of BRAF resistance and the results of recent clinical trials, the team predicted that combining a MEK inhibitor with BRAF inhibitors in the treatment of BRAF inhibitor-resistant ATC may improve treatment response. The combination was demonstrated to be effective in both this preclinical model and in a human ATC cell line with mutations of BRAF and p53.

"Despite our efforts to maximize ATC treatment approaches by integrating surgery, radiation, and chemotherapy, we have made little to no headway with these standard therapeutic tools. A more sophisticated targeted approach will likely be required to improve ATC treatment options and offer some hope for improving survival," commented Lori Wirth of Massachusetts General Hospital (MA, USA). "The greatest promise for this new ATC mouse model is, perhaps, its utility in studying new treatment approaches for this rare and devastating disease. McFadden and colleagues' data are readily applicable to ATCs in humans that harbor mutant BRAF V600E, and will hopefully be translated directly to clinical trial development soon," Wirth adds.

As a result of this work, the model will now be used to investigate drivers of eventual acquired resistance to MEK-BRAF combination treatment and also to investigate whether the combination could be used in combination with standard chemotherapy.

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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