Researchers from the Karmanos Cancer Institute (MI, USA) have recently published a study suggesting that hormone therapy is linked to better survival after lung cancer diagnosis in women.

Typically, survival is better among women than men in people with lung cancer, and the current findings suggest that female hormones may be a factor in this difference. In the study the combination of estrogen plus progesterone and the use of long-term hormone therapy were associated with the most significant improvements in survival.

The authors reported that among the 485 women, the median survival time was 80 months for women receiving hormone therapy and 37.5 months for women not receiving hormone therapy. Combined estrogen and progesterone was associated with a slightly higher median survival time (87.0 months) than estrogen alone (83.0 months).

In the study the authors report that the use of hormone therapy for 11 years or more was associated with significantly improved survival, and remained significant among women who took either estrogen alone or estrogen plus progesterone, and among women who had never smoked or were smokers.

Discussing the study, one of the study’s authors Ann Schwartz (Karmanos Cancer Institute) commented, “What has emerged from this study and other published findings is a complex relationship between hormone use and lung cancer outcomes, with variation in results based on years of use.”

There are currently limited studies on the effect of hormone use on lung cancer survival, and the results have been inconsistent; therefore, additional research is warranted to evaluate the significance of long-term use of hormone therapy on outcomes in lung cancer, with better characterization of tumors in terms of expression of estrogen and progesterone receptors.

Schwartz added, “There is more to learn about survival differences between men and women; hormone use may contribute to those differences. The largest impact on lung cancer outcomes will come from successful early detection and treatment.”

— Written by Dominic Chamberlain
Illustrated by Clare Dolan

Source: International Association for the study of Lung Cancer; press release: www.iaslc.org/articles/hormone-therapy-linked-better-survival-after-lung-cancer-diagnosis-women
Non-small-cell lung cancer: clinical trial success influenced by biomarker- and receptor-targeted therapies

A recently published analysis of clinical trials evaluating therapies for advanced non-small-cell lung cancer (NSCLC) has demonstrated that the cumulative success rate for new agents for advanced NSCLC is lower than the industry-estimated rate. However, the study also found that biomarker- and receptor-targeted therapies were found to substantially increase clinical trial success.

The team running the study were from the University of Toronto (ON, Canada) and designed the analysis to evaluate the risk of clinical trial failure in advanced (stage IIIb–IV) NSCLC drug development over the past 14 years. The success rate was defined as the likelihood that a new drug would pass all phases of clinical trial testing and be approved. The researchers compared success rates with the rates estimated by the biopharmaceutical industry, as well as rates determined by risk analysis research in other disease indications.

The success rate for NSCLC drug development was determined as 11%, which is lower than the industry estimate of 16.5%. However, success rates were higher for certain drug indications; the cumulative success rate was 62% for biomarker targeted therapy, which was nearly six-times higher than the rate for trials without a biomarker-targeted indication (11%). The analysis also demonstrated that success rates became worse with each new phase of testing, indicating that earlier phase trials may provide little help in ensuring the success of later phase trials.

“...clinical trials involving the use of biomarker- and receptor-targeted therapies should be a priority for patients with advanced non-small-cell lung cancer who wish to enroll in a clinical trial.”

Discussing the study Jayson Parker (University of Toronto), one of the study’s authors, commented “The findings suggest that some treatment modalities and drug design strategies may help to decrease drug-development risk and promote the development of innovative drugs to treat advanced NSCLC.”

The cumulative success rates for small-molecule and biologic drugs for advanced NSCLC were lower than industry aggregate rates; the rate for small-molecule drugs was 17% (compared with the industry aggregate of 32%) and the rate for biologic drugs was 10% (compared with 13%). When the team analyzed the impact of the mechanism of action they observed that the cumulative success rate was 31% for receptor-targeted therapies (e.g., bevacizumab, crizotinib, erlotinib and gefitinib), which was nearly threefold better than nontargeted therapies (11%). The rate was lowest (6%) for immunotherapy.

Adam Falconi (University of Toronto), another of the study’s authors commented “Our analysis suggests that biomarker-targeted treatment indications and compounds that have a receptor-targeted mechanism of action offer the best chance of clinical success in this indication and should be the focus of future clinical trial development.”

These results suggest that clinical trials involving the use of biomarker- and receptor-targeted therapies should be a priority for patients with advanced NSCLC who wish to enroll in a clinical trial.

—Written by Dominic Chamberlain

Source: International Association for the study of Lung Cancer press release: www.iaslc.org/articles/clinical-trial-success-influenced-biomarker-and-receptor-targeted-therapies-nsclc

New assay for detecting ALK rearrangements in non-small-cell lung cancer may be superior to established techniques

Researchers have developed a novel method of detecting rearrangements of the ALK gene in non-small-cell lung cancers (NSCLCs), one they describe as more sensitive and easier to carry out than the tests currently utilized. Detection of such genetic changes is vital for identifying individuals with the disease who are most likely to benefit from treatment with ALK inhibitors. Further details of the study appear in the March issue of the Journal of Thoracic Oncology.

“Researchers have developed a novel method of detecting rearrangements of the ALK gene in non-small-cell lung cancers...”

FISH is currently the only method approved for use in the detection of ALK mutations clinically. However, it represents a complex and low-throughput assay that in actuality is difficult to use in diagnostic practice. Other routine methods that are able to detect rearrangements in this gene include immunohistochemistry and reverse transcription-PCR (RT-PCR). These methods are also noted for their pitfalls, such as weak and variable immunoreactivity in immunohistochemistry.
Researchers have identified a novel drug combination of two already-in-use drugs that may inhibit the growth of KRAS-mutated lung adenocarcinoma.

Lung adenocarcinomas account for approximately 40% of all lung cancers, of which 30% contain KRAS mutations; KRAS-mutated adenocarcinomas thus represent the single biggest subset of lung cancer patients. KRAS mutations contribute to the growth and proliferation of tumors, yet there has so far been little success in developing an effective agent that targets these mutations. This has led current research to investigate the possibility of inhibiting the effects of KRAS at points further downstream of its signaling pathways.

One such pathway involves the protein TBK1, which is active in the immune system. David Barbie of the Lowe Center for Thoracic Oncology at the Dana-Farber Cancer Institute (MA, USA) and the Broad Institute of Harvard and MIT (MA, USA) was investigating this protein and noticed that a drug known as CYT387 that is active against TBK1 was already being tested as a treatment for the bone marrow disorder, myelofibrosis.

Further studies, including animal studies, by Barbie and colleagues confirmed that CYT387 is a potent inhibitor of TBK1 and also has the ability to suppress cytokines, which can congregate in the tissue around tumors and help cancer cells survive and metastasize.

The research team then progressed to running tests on more aggressive forms of lung adenocarcinoma that, in addition to having mutations in KRAS, also had mutations in the gene p53. The investigators tested two drugs in tandem against these tumor samples: CYT387 and AZD6244, which inhibits MEK, another downstream protein of KRAS. Neither drug had a significant effect by itself but together, they formed a potent combination against the tumors, both in laboratory cell samples and in animals with the disease.

“KRAS mutations contribute to the growth and proliferation of tumors, yet there has so far been little success in developing an effective agent that targets these mutations.”

“Cytokines play a key role in tumor survival and spread in cells with KRAS mutations,” Barbie states, “so blocking cytokine signaling can deprive cancer cells of a critical survival strategy. Because the combination of a TBK1 and MEK inhibitor targets two pathways at once, it shuts off cytokine signaling very quickly.” The shutdown of cytokines contrasts with the effects of many other forms of targeted therapy, which impede cancer cells’ ability to proliferate.

Although there were no notable adverse side effects of the drug combination in animal models, the tumor cells become resistant to the therapy after approximately 8 weeks, highlighting the potential need for additional drug combinations to produce lasting remissions.

“The next step will be to take these results to the clinic, where the combination can be tested in lung cancer patients,” said co-author Kwok-Kin Wong (Dana-Farber Cancer Institute), “We’re in the process of developing a clinical trial. Because KRAS mutations are also common in colon and pancreatic cancer, we’re hopeful that trials will be organized for these patients as well.”
A recent study led by researchers from the Cancer Institute and Chinese Academy of Medical Sciences (Beijing, China) suggests that, within the Asian population, the frequency of EGFR mutations associated with other demographic and clinical characteristics is higher than previously reported, even in patients with a history of smoking, suggesting that mutation testing should be done on a broader basis among Asian patients with advanced adenocarcinoma of the lung.

Asian ethnicity, along with adenocarcinoma histology, female sex and a never-smoking status, have been considered the most important factors associated with EGFR mutations in non-small-cell lung cancer and response to EGFR inhibitors.

The PIONEER study, the first of its kind, is a prospective, multinational epidemiologic study to document the frequency of EGFR mutations in lung adenocarcinoma in the Asian population. In the study the researchers report that EGFR mutations were present in 51.4% of stage IIIB or IV adenocarcinomas of the lung among 1450 patients from seven regions of Asia. Previously, reports had suggested a frequency of approximately 30% among the Asian population (compared with 20% among the white population).

The frequency of EGFR mutations was highest among women (61.1%) and never smokers (60.7%), but EGFR mutations were also common among men (44%), occasional smokers (51.6%) and previous smokers (43.2%). With regard to Asian regions, the frequency was highest in Vietnam (64.2%) and lowest in India (22.2%).

Commenting on the study, Yuankai Shi (Cancer Institute and Chinese Academy of Medical Sciences), one of the paper’s lead authors, said “The frequency of EGFR mutations in demographic and clinical subgroups of Asian patients in PIONEER suggests that EGFR mutation testing should be considered for all patients with stage IIIB or IV adenocarcinoma of the lung in Asian populations.”

– Written by Dominic Chamberlain

Source: International Association for the Study of Lung Cancer, press release: www.iaslc.org/articles/high-frequency-egfr-mutations-found-asian-population

About the News
The News highlights some of the most important events and research. If you have newsworthy information, please contact: Dominic Chamberlain, Commissioning Editor, Lung Cancer Management
d.chamberlain@futuremedicine.com