

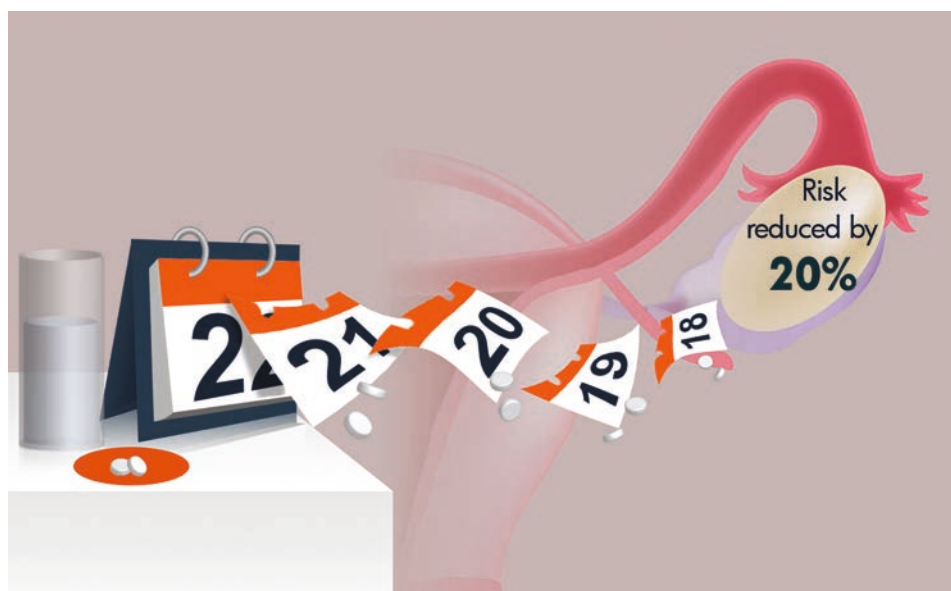
News & Views in ...

CLINICAL INVESTIGATION

Highlighting the latest news in clinical investigation

Clinical trial success influenced by biomarker- and receptor-targeted therapies

“...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.”



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 demonstrated that biomarker- and receptor-targeted therapies substantially increased the clinical trial success rate.

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 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 were lower with each new phase of testing, indicating that earlier phase trials may provide little help in ensuring the success of later phase trials.

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%)

**FUTURE
SCIENCE** part of

fsg

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 (such as 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), one 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-nscl

PCV significantly improves survival in low-grade glioma study

The Radiation Therapy Oncology Group (RTOG) has recently made public the data concerning long-term follow-up analysis of the RTOG 9802 study. This study investigated the addition of chemotherapy to the treatment of adults with low-grade glioma following completion of radiation therapy. Patients who received this additional systemic therapy were concluded to live significantly longer than those who received radiotherapy alone.

Estimates suggest that >23,000 individuals will be diagnosed with primary brain tumors in the USA in 2014. Of these individuals, it is estimated that 10–15% will be diagnosed with low-grade glioma. Low-grade gliomas are slow growing and are associated with better patient outcomes when compared with the more common glioblastoma.

RTOG 9802 enrolled 251 low-grade glioma patients between October 1998 and June 2002, all of whom underwent initial surgery followed by radiotherapy. All those enrolled were deemed to be at high risk due to either being >40 years of age or <40 years of age with incomplete surgical removal of their tumor. Patients were randomly assigned so that half ceased treatment after

radiotherapy and the other half received six cycles of three chemotherapy drugs. The chemotherapy regimen utilized was a combination termed PCV, which consists of procarbazine, lomustine and vincristine.

Overall survival was noted to significantly increase in those who received chemotherapy and radiotherapy, with a median overall survival of 13.3 years compared with 7.8 years in the radiotherapy-alone arm. Analysis continues of the molecular and genetic characteristics of tumors and how these might relate to patient outcomes. This analysis may indicate molecular characteristics that identify those likely to benefit from chemotherapy.

"The results of this study are practice-changing," commented co-lead investigator Jan Buckner of the Mayo Clinic (MN, USA). "Additionally, ongoing analysis of patient tumor samples should allow us to further identify the patients who will and will not benefit from chemotherapy, taking yet another step toward individualized therapy."

Yet to be published, the results will be presented in full at a scientific meeting this year and will also appear in a peer-reviewed publication in future.

– Written by Emily Brown

Source: National Cancer Institute press release: www.cancer.gov/newscenter/newsfromnci/2014/RTOG9802

Analysis confirms prognostic factors for long-term outcome in soft tissue sarcoma

A recently published analysis has confirmed the importance of known prognostic factors such as tumor grading for having a long-term outcome in advanced soft tissue sarcoma patients treated with an angiogenesis inhibitor. The study has also identified hemoglobin at baseline as a new prognostic factor in the disease.

Soft tissue sarcomas are a relatively rare tumor, with four people in every 100,000 developing the disease each year in Europe. Prognosis varies depending on the stage of this heterogeneous disease. Those with early-stage disease are associated with a favorable prognosis, while approximately half of all sarcoma patients will

develop metastases and have a median overall survival of approximately 12 months.

This analysis was carried out by the European Organisation for Research and Treatment of Cancer (EORTC) and led by Bernd Kasper of the Sarcoma Unit of the Interdisciplinary Tumor Center at the Mannheim University Medical Center (Germany). Using the data from two EORTC trials, the investigation characterized long-term advanced soft tissue sarcoma survivors and those who responded to treatment with the agent pazopanib.

"One approach to treat patients with advanced-stage soft tissue sarcoma is to target angiogenesis, and pazopanib is a recently approved orally available angiogenesis inhibitor. We analyzed pooled data from

two prospective EORTC trials, the Phase II trial in which 118 patients and the Phase III PALETTE trial in which 226 patients were treated with pazopanib, to characterize long-term survivors and responders," commented Kasper.

After a follow-up period of 2.3 years, 36% of patients had been progression-free for >6 months (termed long-term responders) and 34% survived 18 months or more (termed long-term survivors). Additionally, 3.5% of treated patients remained progression-free on pazopanib for >2 years. In terms of prognostic factors, good performance status, low or intermediate grade of the primary tumor and normal hemoglobin level at baseline were advantageous for long-term outcome.

– Written by Emily Brown

Source: European Organisation for Research and Treatment of Cancer press release: www.eortc.org/news/eortc-analysis-characterizes-long-term-responders-and-survivors-pazopanib-advanced-soft-tissue-

Could repurposing approved agents speed up therapy development in rare tumor types?

After screening a library of US FDA-approved cancer drugs, researchers at the University of Pittsburgh Cancer Institute (PA, USA) believe they may have identified several drug candidates that could potentially be utilized in the treatment of a rare cancer. Details of this study appear in the latest issue of *Cancer Research*.

"This is known as 'drug repurposing,' and it is an increasingly promising way to speed up the development of treatments for cancers that do not respond well to standard therapies," commented senior author of the study Anette Duensing (University of Pittsburgh Cancer Institute). "Drug repurposing builds upon previous research and development efforts, and detailed information about the drug formulation and safety is usually available, meaning that it can be ready for clinical trials much faster than a brand-new drug."

The study was orchestrated in an attempt to uncover further agents that might prove efficacious in the treatment of patients with rare gastrointestinal stromal tumors (GISTs). Figures from the American Cancer Institute indicate that there are approximately 5000 cases of GISTs each year in the USA, with 5-year survival of around 45% in those presenting

with advanced disease. Initiated by a single gene mutation, GISTs can be treated with the targeted therapy imatinib. However, approximately half of the GIST patients treated with imatinib will display resistance within the first 2 years of treatment.

Duensing and colleagues screened 89 previously approved drugs, studying how GIST samples responded at various drug concentrations *in vitro*. Of the agents tested, 37 demonstrated some anti-cancer activity at one or more concentration levels. The drugs with the most notable anti-GIST activity both originated from two major drug classes; inhibitor of transcription and topoisomerase II inhibitors. Consequently, two agents, one from each class, were selected for further investigations. These included the transcription inhibitor mithramycin A, which is in clinical trials to treat Ewing sarcoma, and the topoisomerase II inhibitor mitoxantrone, which is currently utilized in metastatic breast cancer and leukemia.

Further investigation indicated that both of these agents were highly effective against GISTs in laboratory test. "These are very encouraging results," concluded Duensing. "The next step will be moving our findings to clinical exploration to see if the results we found in the laboratory hold up in patients."

– Written by Emily Brown

Source: University of Pittsburgh School of Health Sciences press release: www.upmc.com/media/NewsReleases/2014/Pages/upci-scientists-detect-therapy-for-drug-resistant-cancer.aspx

Investigational targeted therapy meets primary end point in thyroid cancer trial

Eisai (Tokyo, Japan) has recently announced that the Phase III SELECT trial of the tyrosine kinase inhibitor lenvatinib in patients with radioiodine-refractory differentiated thyroid cancer has met its primary end point. When compared with placebo, lenvatinib demonstrated a significant improvement in progression-free survival in these individuals.

Lenvatinib is an investigational selective receptor tyrosine kinase inhibitor, which is noted for its novel binding mode. It is able to bind to receptors known to be involved in both tumor proliferation and angiogenesis, including VEGFR-2, VEGFR-1, RET, FGFR1, PDGFR- β and c-kit. The SELECT trial compared the progression-free survival of radioiodine-refractory differentiated thyroid

cancer patients treated with 24 mg of oral lenvatinib daily with that of individuals who received placebo treatment. Three-hundred and ninety two patients were enrolled in the trial in Europe, North and South America and Asia.

The preliminary data indicate that the most common adverse events related to treatment with lenvatinib included hypertension, diarrhea, decreased appetite, decreased weight and nausea.

Based on the significant improvement in progression-free survival seen in this study, Eisai are planning to submit marketing authorization applications for lenvatinib to health authorities in Japan, the United States and Europe. The company has also initiated trials of lenvatinib in hepatocellular carcinoma and endometrial cancer.

– Written by Emily Brown

Source: Eisai press release: www.eisai.com/news/enews201407pdf.pdf

Ovarian cancer risk may decrease by 20% with daily aspirin intake

Approximately 20,000 women are predicted to develop ovarian cancer in the USA in 2014 and 14,000 individuals will die from the disease. Ovarian cancer is a disease that can be treated easily and cured in the early stages but is often not caught until the cancer has progressed, as the presenting symptoms may be mistaken for more common conditions such as digestive and bladder problems. Later stages of ovarian cancer are much more difficult to treat and prognosis is poor. New research has revealed that women who take aspirin daily may decreased their risk of developing ovarian cancer by 20%

Chronic and persistent inflammation has been shown to put an individual at risk of cancer, and previous studies on the effects of aspirin and nonaspirin NSAIDS have suggested a potential benefit, but have mostly been inconclusive. Pooled data from 12 population-based case-control studies of ovarian cancer, which included 7776 case patients and 11,843 control subjects between 1992 and 2007, were analyzed by Britton Trabert, Nicolas Wentzensen (National Cancer Institute Division of Cancer Epidemiology and

Genetics, MD, USA) and colleagues in a recent study. They investigated the effect of these drugs on the risk of ovarian cancer.

The results demonstrated that women who took aspirin daily had a 20% decreased risk of developing ovarian cancer compared with those who took it less than once weekly. The results were less clear for the NSAIDS group, where a 10% decrease in risk was observed for those taking the medication at least once a week compared with less than once a week; however, the results were in the nonsignificant range. Side effects of daily consumption of aspirin are gastrointestinal bleeding and hemorrhagic stroke and daily use is not recommended without a doctor's approval.

Research has also suggested benefits of aspirin use in other cancers, such as colorectal cancer. Trabert commented, "However intriguing our results are, they should not influence current clinical practice. Additional studies are needed to explore the delicate balance of risk-benefit for this potential chemopreventive agent, as well as studies to identify the mechanism by which aspirin may reduce ovarian cancer risk."

– Written by Emily Hargrave

Source: Trabert B, Ness RB, Lo-Ciganic WH et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the Ovarian Cancer Association Consortium. *J. Natl Cancer Inst.* 106(2), djt431 (2014).

All stories also featured on: www.oncology-central.com