News & Views in ..
CLINICAL INVESTIGATION

Amendment to UK Patent Act provides further exception to patent infringement

Broader version of the 'Bolar' exemption will help boost pharma R&D

The UK government has recently scheduled an amendment to the 1977 Patents Act, which would exempt activities involved in preparing or running clinical trials for innovative drugs from patent infringement actions.

The Legislative Reform (Patents) Order 2014, which introduces the amendments, has been published and laid before the UK's parliament for approval, following a consultation on the proposals by the UK Intellectual Property Office. The Order, which is expected to come into force on 1 October 2014, will amend section 60 of the Patents Act by broadening the so-called 'Bolar' exemption so as to cover the carrying out of necessary trials and health technology assessments for all drugs (novel as well as generic) and all applications for marketing approval (European as well as non-European).

The new legislative test to apply in deciding whether a study can benefit from the new Bolar exemption is whether it is carried out for the purposes of a 'medicinal product assessment' (for human or veterinary use). A medicinal product assessment is defined as meaning any testing, course of testing or other activity undertaken with a view to providing data for one of the following purposes: obtaining or varying an authorization to sell or supply, or offer to sell or supply, a medicinal product anywhere in the world; complying with any regulatory requirement imposed in relation to such authorization; or enabling any government or public authority to carry out an assessment of suitability of a medicinal product for human use for the purpose of determining whether to use it, or recommend its use, in the provision of healthcare.

The changes have been made specifically to permit two types of study in the UK (both of which were previously not permitted). The specific studies now permitted are: clinical trial studies required to obtain regulatory approval or market authorization for a new drug from a Competent Authority (e.g., the MHRA or the EMA). Often these require comparative work to be carried out using a currently available drug, which is patented. New combination therapies making use of a drug that is under patent protection also require testing to obtain market authorization; health technology assessments (carried out by organizations such as NICE), which are required for a new treatment to be recommended for use by the National Health Service. These can also require the use of a currently available patented drug for comparative studies.

The decision, if approved, will bring the UK in line with many other European jurisdictions and so should help to prevent clinical trials being moved to jurisdictions that have more favorable patent laws, which was thought to be a potential loss to the UK economy. Furthermore, it will mean that patient groups who would not be recruited for a trial abroad may now have access to treatments where no current effective medication exists.

Written by Alexandra Sklan

Source: The Legislative Reform (Patents) Order 2014: www.legislation.gov.uk/ukdsi/2014/9780111114537/contents

FUTURE SCIENCE part of fsg

Chemotherapy prior to other therapy modalities may increase patient tolerance in rectal cancer

A recent Phase II study has demonstrated that offering chemotherapy prior to radiation therapy and surgery in the treatment of rectal cancer increases patient tolerance and thus increases the number of patients able to receive a full regimen of treatment. The results of the trial, termed Complete Neoadjuvant Therapy in Rectal Cancer (CONTRE), will be presented on 31 May at the 2014 annual meeting of the American Society for Clinical Oncology in Chicago (IL, USA).

> "...we were able to get the numbers up of patients who were able to get all the chemotherapy indicated."

Previous studies have determined that only approximately 60% of individuals with rectal cancer comply with postoperative chemotherapy. The CONTRE trial found that reordering treatment regimens so that chemotherapy was administered prior to any other treatment allowed 33 of 39 patients to undergo a full course of standard treatment for rectal cancer.

"The thought was, what can we do to make it more tolerable and get the benefit that we wanted," commented Kimberly Perez of the Warren Alpert Medical School of Brown University (RI, USA), who will present the results at the ASCO meeting. "It's encouraging because we were able to get the numbers up of patients who were able to get all the chemotherapy indicated."

Upon enrollment, 32 of the patients had stage III rectal cancer and the remaining seven had stage II disease. The investigators state that the majority of these 39 patients responded in some manner to the indication chemotherapy; 13 had a complete pathological response, ten had disease that returned to stage I, seven were at stage II, and eight remained at stage III. No measure of overall survival is available for these patients as the trial occurred to recently to provide such.

The results generated by the CONTRE trial have prompted the development of a new national rectal cancer trial testing a protocol involving initial chemotherapy, followed by chemoradiation with biological anticancer agents and finally surgery.

Written by Emily Brown
Source: Brown University press release: http://news.brown.edu/pressreleases/2014/05/asco
This story is also featured on: www.oncology-central.com

Afatinib demonstrates significant overall survival benefit for specific lung cancer patients compared with chemotherapy

Boehringer Ingelheim (Germany) today announced new results of a combined overall survival *post-hoc* analysis of two Phase III trials (LUX-Lung 3 and 6). The analysis showed patients with non-small-cell lung cancer (NSCLC) with common EGF receptor (*EGFR*) mutations (exon 19 deletions [del 19] or exon 21 [L858R] substitutions, accounting for 90% of all known *EGFR* mutations) lived longer if treated with first-line afatinib compared with chemotherapy.

In the combined analysis from two of the largest trials in this patient population, afatinib prolonged survival of lung cancer patients whose tumors harbor common *EGFR* mutations compared with standard chemotherapy by a median of 3 months (27.3 vs 24.3 months), significantly reducing the risk of death by 19% (hazard ratio: 0.81; $p = 0.037$). The most pronounced reduction in risk of death, by 41% (hazard ratio: 0.59; $p < 0.001$), was noted for patients whose tumors have the common type of *EGFR* mutation – deletion in exon 19 of the *EGFR* gene. The conclusions of this analysis further substantiate earlier published results on delaying tumor growth (progression-free survival), better control of lung cancer symptoms and manageable adverse events associated with afatinib in comparison with chemotherapy.

> "...despite cross-over in the subsequent treatment, front-line use of a targeted treatment can prolong overall survival in patients..."

Commenting on the overall survival results of afatinib compared with chemotherapy, principal

investigator Professor James Chih-Hsin Yang, National Taiwan University Hospital in Taiwan, said: "The results of two afatinib trials independently show for the first time that despite cross-over in the subsequent treatment, front-line use of a targeted treatment can prolong overall survival in patients with del 19 *EGFR* mutation-positive lung cancer. The results add to the list of benefits already shown in these studies, which include improvements in tumor shrinkage, longer duration of disease control and life-restricting, disease-related symptoms such as cough, pain and shortness of breath."

Professor Klaus Dugi, Chief Medical Officer, Boehringer Ingelheim concluded, "The overall survival results of LUX-Lung 3 and 6, combined with our existing previously reported efficacy and quality of life data, contribute significantly to the robust body of evidence for the use of first-line afatinib in *EGFR* mutation-positive lung cancer."

Written by Theo Bond

Boehringer Ingelheim press release: www.boehringer-ingelheim.com/news/news_releases/press_releases/2014/15_may_2014_oncology.html

This story is also featured on: www.oncology-central.com

Experimental antibody therapy produces positive Phase I results in neuroblastoma

Researchers from St Jude Children's Research Hospital (TN, USA) have recently published the results of a Phase I safety study in which the use of a novel immunotherapy was investigated in the treatment of children with advanced neuroblastoma. The experimental, humanized anti-GD2 monoclonal antibody termed hu14.18K322A demonstrated promising efficacy, promoting tumor shrinkage and even disappearance in some patients. The findings were reported in the May 10th edition of the *Journal of Clinical Oncology*.

> "This new antibody is a modified version of a previously developed antibody, newly designed to help reduce treatment-limiting pain by way of a more tailored immune response."

A cancer of the sympathetic nervous system, neuroblastoma is a disease that can exceed a 90% cure rate in some patients. In individuals defined as high risk, a patient group that includes those in whom the disease has spread widely, the outlook is bleaker with less than half of these patients achieving long-term survival.

hu14.18K322A is an anti-GD2 monoclonal antibody, which represents one of several antibodies targeting GD2 that are in development for the treatment of neuroblastoma. This new antibody is a modified version of a previously developed antibody, newly designed to help reduce treatment-limiting pain by way of a more tailored immune response.

This Phase I study involved 38 St Jude patients, of median age 7.2 years, who were suffering from disease that was not responding to standard neuroblastoma therapies. Patients received one of nine varying doses of hu14.18K322A via an infusion once daily for 4 days, every 28 days. The study was designed with an aim of gaining further information about the safety and optimal dosages of the drug.

A total of 31 of the 38 patients enrolled in the trial were evaluated after two or more rounds of treatment with hu14.18K322A. Tumor shrinkage and delay in disease progression were observed in 15 of the children who received the therapy, and four of these patients are still alive two-and-a-half years later without additional treatment.

Pain was highlighted as the most common side effect of hu14.18K322A therapy, but reported pain was manageable with medication and lessened with each round of therapy. The study was able to conclude that the maximum tolerated dose of hu14.18K322A was 60 mg/m^2 per day for 4 days, the dose recommended for use in Phase II trials.

> "These initially positive results have prompted continuation and expansion of clinical trials involving hu14.18K322A at St Jude, for which patients newly diagnosed with neuroblastoma are now eligible."

"This was the first time this experimental antibody was tried in patients. We were encouraged with the response," commented first and corresponding author Fariba Navid of the St Jude Department of

Oncology. "The percentage of patients who benefited from treatment with hu14.18K322A was unusual for a Phase I study."

These initially positive results have prompted continuation and expansion of clinical trials involving hu14.18K322A at St Jude, for which patients newly diagnosed with neuroblastoma are now eligible. Trials are ongoing investigating the impact of weekly doses of the therapy and also testing it in combination with other therapies.

Written by Emily Brown

Sources: Navid F, Sondel PM, Barfield R et al. *Phase I trial of a novel anti-GD2 monoclonal antibody, hu14.18K322A, designed to decrease toxicity in children with refractory or recurrent neuroblastoma.* J. Clin. Oncol. *32(14), 1445–1452 (2014); St Jude Research Hospital press release: www.stjude.org/stjude/v/index.jsp?vgnextoid=caf4b9e7a7eb5410VgnVCM100000290115acRCRD&vgnextchannel=fa1113c016118010VgnVCM1000000e2015acRCRD*

This story is also featured on: www.oncology-central.com

RTOG 9003 demonstrates hyperfractionated radiation therapy improves local–regional control in head and neck cancer patients

A Phase III trial has recently reported that hyperfractionated radiation therapy (HFX) for patients with locally advanced head and neck cancer resulted in improved overall survival (OS) and local–regional control (LRC), with no increase in late toxicity.

The multi-institutional RTOG 9003 trial analyzed patients, who were 18 years old or more and had previously untreated, locally advanced stage III or IV (or stage II base of tongue) squamous cell cancers. These patients were randomized to receive standard fractionation (SFX), HFX (twice-daily), accelerated fractionation with a split (AFX-S) or accelerated fractionation–continuous (AFX-C). LRC was censored at 5 years.

> "...accelerated fractionation resulted in increased grade 3, 4 or 5 toxicity at 5 years when comparing 7-week treatments to 6-week ones."

The investigators compared all treatments with SFX, reporting that only HFX resulted in significant differences compared with SFX. HFX improved overall survival, and no differences were seen in prevalence of grade 3, 4 or 5 toxicity at 5 years, or use of feeding tube at 180 days or 1 year. They also noted that accelerated fractionation resulted in increased grade 3, 4 or 5 toxicity at 5 years when comparing 7-week treatments to 6-week ones. At 5 years post-treatment, it was reported that patients in the HFX arm had the highest OS rates (37.1%) compared with the AFX-C (33.7%), SFX (29.3%) and AFX-S (29.0%) arms.

Jonathan Beitler, lead author of the study (Winship Cancer Institute of Emory University, GA, USA), explained the importance of the study, "This study … demonstrates that patients who have head and neck cancers and who are being treated with radiation therapy alone have improved local–regional control and no increase in late toxicity when radiation therapy is delivered twice a day in two smaller doses." Noting that they saw a surprising decrease in the rate of new cancers, he also commented on the findings, "The large database and the long follow-up provided us with a window into information that had not previously been available about the long-term patterns of head and neck tumors and is particularly heartening. The results suggest that twice-daily radiation may improve cure and limit late side effects for patients."

The researchers believe that twice-daily radiation could be considered as a replacement for concurrent chemoradiotherapy for patients at low risk for distant metastases, and for those who cannot tolerate systemic therapy.

Written by Francesca Lake

Sources: Beitler JJ, Zhang Q, Fu KK et al. *Final results of local–regional control and late toxicity of RTOG 9003: a randomized trial of altered fractionation radiation for locally advanced head and neck cancer.* Int. J. Radiat. Oncol. Biol. Phys. *89(1), 13–20 (2014); ASTRO press release: www.astro.org/News-and-Media/News-Releases/2014/Hyperfractionated-radiation-therapy-improves-local-regional-control-without-increasing-late-toxicity-for-patients-with-locally-advanced-head-and-neck-cancer.aspx*

This story is also featured on: www.oncology-central.com

New studies initiated for medically ill patients and children at high risk of blood clots

It has recently been announced that the MARINER trial, in which rivaroxaban will be investigated for venous thromboembolism prevention in high-risk medically ill patients following hospital discharge, and the EINSTEIN JUNIOR trial, in which rivaroxaban will be tested for the treatment and secondary prevention of venous thromboembolism in children, are to be initiated.

Venous thromboembolism is a common disorder that regularly affects patients who have been hospitalized for the treatment of acute medical illnesses. Therefore, the MARINER trial will evaluate rivaroxaban 10 mg once-daily compared with placebo in approximately 8000 patients in more than 15 countries for up to 45 days following hospital discharge, whereas the EINSTEIN JUNIOR trial will assess rivaroxaban according to an age- and bodyweight-adjusted dosing schedule in 150 patients in 20 countries.

Joerg Moeller, member of the Bayer HealthCare Executive Committee and Head of Global Development, explained, "We have already completed an extensive clinical study programme with more than 10,000 patients to demonstrate the clinical benefits of rivaroxaban in the treatment and secondary prevention of deep vein thrombosis and pulmonary embolism, but we still see significant unmet needs in the area of venous thrombosis which we want to address through these additional studies."

Rivaroxaban is an oral anticoagulant that is currently approved in more than 125 countries.

Written by Natasha Leeson

Source: Bayer press release: http://press.healthcare.bayer.com/en/press/news/news-archive/index.php