Lungscape: a living lung laboratory

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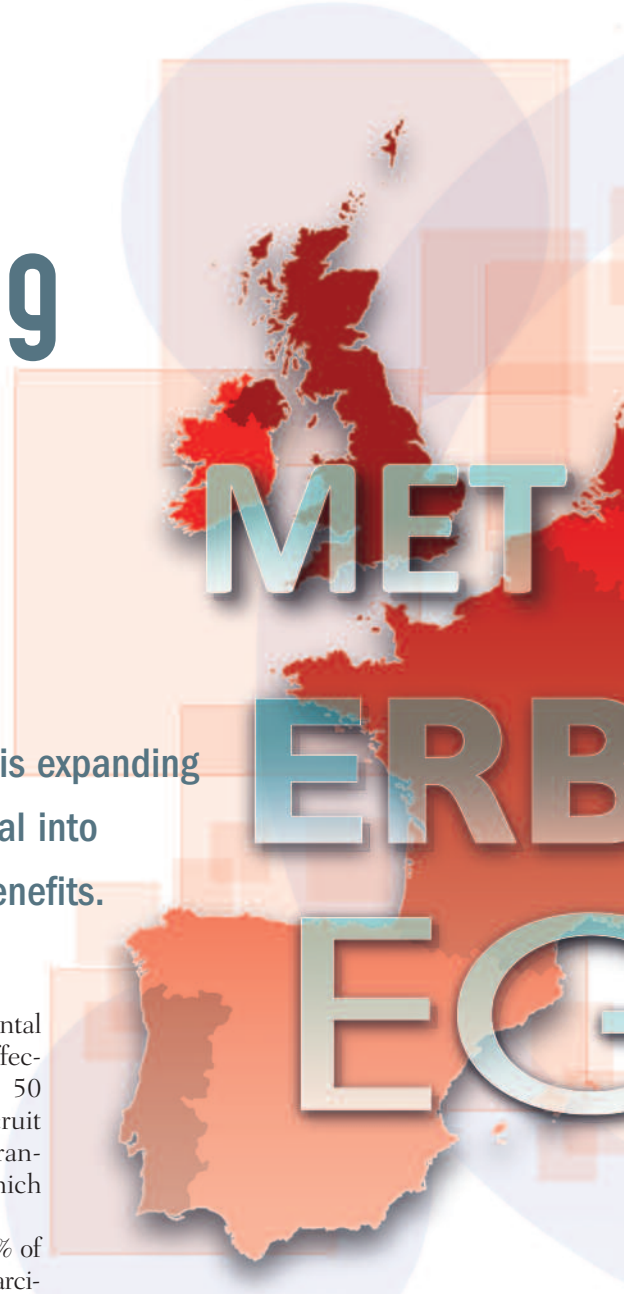

The potential for personalising lung cancer therapies is expanding rapidly. The challenge now is how to turn that potential into reality as fast as possible so patients can reap the benefits.

A network of cancer centres is planning to transform the way that the findings of molecular research into non-small-cell lung cancer (NSCLC) are brought into clinical use. The 16 centres are pooling clinical data on 2400 lung cancer patients and sharing information on the genetic structure of tumour samples obtained during surgery.

The Lungscape project, part of the European Thoracic Oncology Platform, aims to harmonise standards and improve the quality of genetic testing in cancer centres, and increase understanding about which patients may benefit from the latest targeted therapies. Of the 16 centres, 14 are based in nine European countries, with one each in China and the USA.

Lungscape will eventually help oncologists select patients who stand to benefit from innovative or experimental treatments. The aim is to produce effective trials on subsets of maybe 50 patients, instead of having to recruit hundreds of patients into large randomised controlled trials from which most derive no benefit.

NSCLC accounts for about 85% of lung cancers and includes adenocarcinomas and squamous cell carcinomas. Survival rates are low unless the disease is caught early – which it isn't in the majority of cases. Patients are currently graded according to tumour size (T), the number of nodes affected (N) and the degree of metastasis (M). However, research is increasingly suggesting that this TNM categorisation is insufficient, and the focus now is on defining numerous small subgroups of lung cancer patients based on the increasing number of genetic alterations reported to be driving the disease. EGFR mutations are present in the tumour cells of about 15% of lung cancer patients with adenocarcinoma, and they may benefit from EGFR inhibitors. Trials have shown positive responses from treatment with Xalkori (crizotinib) for the 24% of NSCLC patients whose tumours show a gene fusion between EML4 and ALK. Up to 90% of these tumours showed a response in clinical trials, and in some

MAP: JASON COOK

cases there has still been no disease progression after 15 months.

In addition to these, genetic research is identifying many new mutations that need to be investigated in customised clinical trials that can be rapidly set up with small numbers of well-targeted patients. It is this that Rolf Stahel, president of the ETOP Foundation Council, hopes that Lungscape will help to deliver.

Lungscape centres keep control of the biopsy specimens taken from patients, which remain locally stored and analysed. Each patient's biological information, together with their clinical data, will be anonymised and shared in what they are calling the Lungscape iBiobank – a virtual biobank. During September 2012, Lungscape hit its target of enrolling 2400 patients.

ETOP's Rolf Stahel, who is a professor and medical oncologist at the University Hospital, Zurich, says Lungscape will describe the molecular landscape of non-small-cell lung cancer in Europe by testing the tissue samples with molecular markers and defining their characteristics. "We will get there by coordinating the work of 16 different sites, which will also allow us to establish a network for clinical trials where alterations that have been identified can be put into early-phase trials. We will know what proportion of patients will benefit and we will have established high-quality molecular testing. In addition, we will be able to determine whether certain molecular changes are associated with different prognostic outcomes independent of the anatomical staging."

As a first step, they will focus on patients found to have the ALK fusion gene and carry out a retrospective analysis to see whether the course of their disease and general outcome differed from those without the fusion.

Solange Peters, medical oncologist at the Lausanne Cancer Centre in

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Switzerland, is responsible for the content of and access to the virtual biobank. "These are all surgical patients who have undergone radical surgery for NSCLC stages I–III and we have all the basic demographics, tumour pathologic characteristics and patient clinical follow-up annotated for these patients. We will be able to identify in this subset of patients several parameters: outcome in terms of recurrence of the disease, outcomes in terms of general prognosis as well as the contribution related to other parameters. In about half of them we will also have data about recurrence."

It is unlikely that the patients will benefit directly from this first phase of Lungscape – aggregating and analysing anonymised data – although they may benefit from improved genetic testing by their own teams.

Peters says, "We have a philosophy of wanting to leave the tissue in every centre as, on the one hand people do not like to send their tissue material out, and on the other hand we want to empower all the centres with the capability to do all the testing in-house, with full quality assurance. We want all the tests to be done in-house and no tissue to travel. That is what makes it a virtual biobank."

More than two years have passed since Stahel and colleagues developed the ibiobank idea at a translational research meeting in Lugano in May 2010. Data collection began in April 2011, but it then took a further 18 months to complete the registration of all 16 centres and recruit the 2400 patients.

Difficult terrain

Money

There have been three main hurdles, the first being money. So far Lungscape has been supported entirely by the industry, with an unrestricted grant from Roche and financial sponsorship from Pfizer, which makes Xalkori, to test the samples for prevalence of ALK gene fusion, as well as support from Abbott Molecular. Xalkori has been approved for use by the US drug regulators, the FDA, for patients with advanced non-small-cell cancer who are ALK positive. In Europe, it has been recommended for conditional approval, with a final decision from the EMA pending. Stahel says they are now preparing an application for grant money from the EU. "We first needed to show what we can do, and we are proving that now, so I am quite optimistic that in the future we will be able to get other financial resources."

Local laws

The second task was to ensure that centres complied with their national legislation, had ethical approval and met all the logistical hurdles. ETOP is run from the coordinating centre in Bern, Switzerland, that coordinates the International Breast Cancer Study Group (IBCSG), and some key staff play the same role for both groups. Anita Hiltbrunner, director of the coordinating centre, explained how this had helped ETOP and Lungscape.

"We have a regulatory office who are very experienced from the IBCSG trials with all the needs and regulations in all the countries. We act as the point of contact for everything. We work very closely together by e-mail or teleconferences and we have regular meetings. Communication with all the centres and investigators is the key. It is something you have to be on top of every day."

The average time for a centre to be approved was about six months, but some took more than a year to reach agreement with their local or national ethics committees. The main issue was informed consent from patients. Although patients themselves do not need to undergo tests, the tumour material removed during their operation may in future undergo genetic tests that have not even been heard of today. Some of these tests may be carried out after a patient has died. While a surgeon in Zurich was able to get patients to sign a single form consenting to future research on this material, centres in other countries had to be more specific.

The UK turned out to be the most difficult country to convince; centres have to get both local and national approval. While two UK centres (the Royal Infirmary in Aberdeen and the Lung Cancer Group in Manchester) have joined the network, one other centre could not reach agreement. The Shanghai Chest Clinic in China is one of only two centres outside Europe to have been included; their national regulations make it clear that there can be no exceptions ever to the rule about tumour material not travelling.

Quality

The third hurdle was the quality of testing. Rosita Kammler, who coordinates translational research at IBCSG/ETOP, says that centres have to achieve the same high standards for immunohistochemistry and for the ALK-FISH (fluorescence *in situ* hybridisation) test, so that results are comparable.

"There are several steps involved to ensure that the end result is comparable from one site to the next. The first part is an internal validation. A pathologist constructed tissue microarrays (TMAs) from specific identified samples. These were sent to each centre with the TMA map to work up the staining. The next step is a blinded external quality assurance round. They receive blinded samples and send in results that are then reviewed."

Following the review, some centres were asked to undergo further practice and testing before approval. As new tests are developed they need to keep up to speed and Stahel says that they may get pathologists from each centre together to carry out training with a super specialist and then do another external evaluation. "One of the clear things in our minds was to raise quality standards and to empower all the participants to be very strong in this field."

The future shape of research

Lungscape has started to raise its profile, making presentations at the European Lung Cancer Conference in Geneva in April 2012 and oral and poster presentations at the ESMO meeting in Vienna in September/October 2012. Stahel says that the project is generating a real sense of excitement amongst the multidisciplinary teams that now lead the way in lung cancer diagnosis and treatment.

Genetic testing is becoming increasingly important to determine best treatment for non-small-cell lung cancer. The French National Cancer Institute (INCa) and French Government have been funding molecular testing for all lung cancer patients since 2011 and find that genetic testing can save money. Jean Charles Soria, professor of oncology at South Paris University, told the 3rd European Lung Cancer Congress, in April 2012, that the French government had invested €1.7 million in testing for the EGFR mutation and saved €65 million in treatment costs by identifying 15,000 patients who would not benefit from gefitinib (Iressa).

Other centres will join clinical trials that spin off from Lungscape. "The way to go to the future is a network of networks," says Stahel. "As well as our big European network, you would have sub-networks. In Switzerland, for example, Zurich and Basel are part of Lungscape, but the clinical trial could also include Lausanne, Geneva and Bern. It is networking of networks that will allow future research."

Peters says, "We have a kind of regrettable tradition for unselective patient trials which end up being not beneficial for the patient or are negative. Building this network is a way to develop procedures to build new trials designed for subsets of non-small-cell lung cancer patients and not a whole crowd. That way, new trials emerge from the knowledge, and not only the other way around."

ETOP is already planning phase 2 of Lungscape when it will switch from retrospective analysis to generating prospective trials of about 1000 patients who will be followed from the point of diagnosis. Although the central biobank will remain anonymised, each centre will use the genetic testing to determine treatment.

That is when it becomes really exciting, as Lungscape will follow long-term outcomes of patients who have received personalised treatment. Stahel said, "Two years from now we will have a lot of biomarker data with clinical correlations and we will have begun a prospective Lungscape. Five years from now we will have demonstrated which of the biomarkers adds to the diagnosis in addition to the anatomical staging." ■

CENTRES IN THE LUNGSCAPE NETWORK

There are currently 16 centres in the Lungscape network. The majority are in Europe, but the network also includes one specialist centre in the US and one in China, to widen the research base and to allow data to be compared inside and outside Europe.

University Hospital Leuven, Belgium
University Hospital Aarhus, Denmark
St James Hospital Dublin, Ireland
Ospedale Clinicizzato Chieti, Italy
Netherlands Cancer Institute Amsterdam, the Netherlands
Free University Medical Centre Amsterdam, the Netherlands
University Medical Centre Maastricht, the Netherlands
Medical University Gdansk, Poland
Vall d'Hebron University Hospital Barcelona, Spain
University Hospital Valencia, Spain
University Hospital Basel, Switzerland
University Hospital Zürich, Switzerland
Royal Infirmary Aberdeen, UK
Lung Cancer Group Manchester, UK
Shanghai Lung Cancer Centre, China
Roswell Park Cancer Institute, Buffalo, USA

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