PHARE: shining a light for academic research in Europe

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Clinical research activity may be plummeting in the rest of Europe, but in France they're determined to substantially increase the numbers of hospitals and patients involved in clinical trials – starting with a strategic trial on Herceptin.

Reaping the rewards of the new era of molecular biology is proving harder than many had anticipated. Just as the trickle of so-called targeted drugs is turning into a steady flow, each one more expensive than the last, bureaucratic restrictions on clinical trials compounded by a lack of public funding for research are closing down opportunities to discover how to use these new drugs to greatest effect.

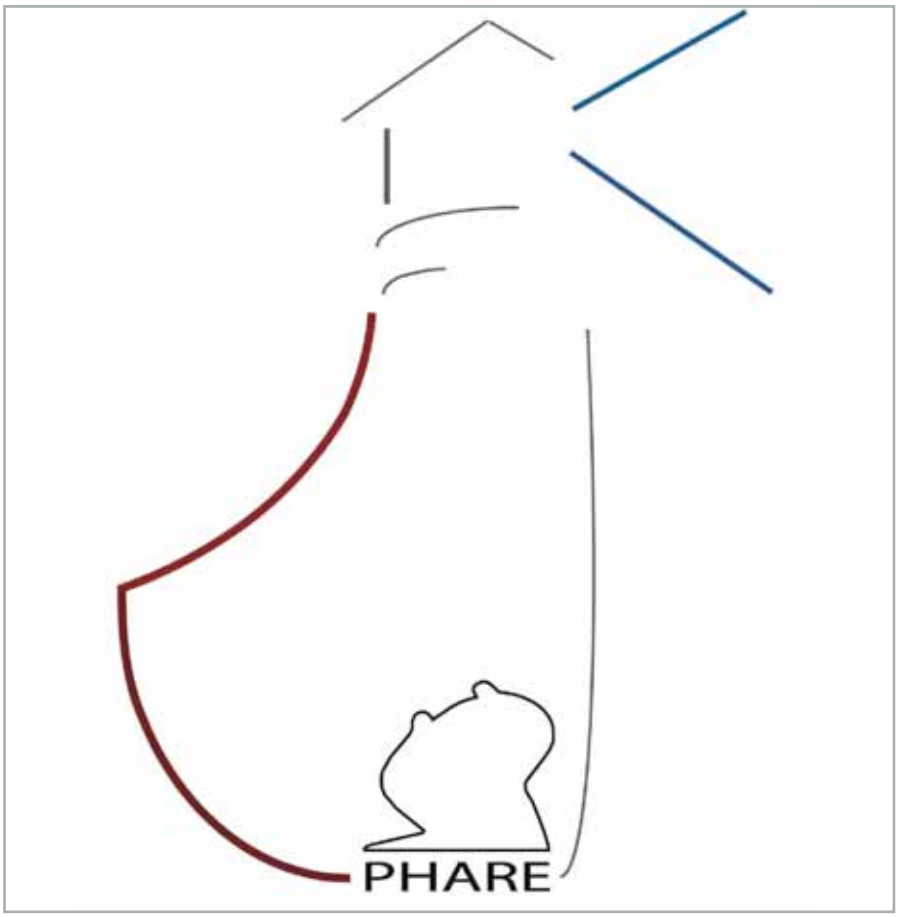
Not in France, however. Here the newly established National Institute for Cancer, INCa, is set to launch its first ever clinical trial. It will seek to clarify the optimal duration of adjuvant Herceptin (trastuzumab) treatment. And in admirable contrast to the clinical trials directive, it is specifically designed to encourage as many French cancer treatment centres as possible to join in. Now, trial coordinator Xavier Pivot, from the Besançon University Hospital, is inviting European researchers to join the project by setting up similar trials in their own countries.

The PHARE trial – Protocol of Herceptin Adjuvant with Reduced Exposure – is based on the French Temporary Treatment Protocol for Herceptin (www.enqueteinca.fr/medias/pttdefeng2710.pdf), which was drawn up under the auspices of INCa to enable eligible patients to receive adjuvant Herceptin pending approval by the European Medicines Agency (EMEA). It is a non-inferiority trial, with the main objective of establishing whether treatment for 6 months gives results that are no worse than treatment for 12 months. There are two secondary objectives, says Pivot. One is to compare Herceptin given sequentially to chemotherapy (as in the HERA trial, *New Engl J Med* 353:1659–1672), with Herceptin given concomitantly with a taxane-based chemotherapy (as in the BCIRG trial, www.bcirg.org). The second is to see whether the optimal duration of treatment varies according to whether the tumour is oestrogen-receptor positive or negative (ER+ or ER-).

Non-inferiority trials require a large number of patients and events in order to give statistically significant results, and PHARE is looking to recruit 7000 patients over the next two years. Given that only 1%–2% of French cancer patients are currently enrolled in clinical trials, this is a very ambitious target. But for the oncologists at INCa, this is the whole point. Much though they would like to know the answer to the PHARE questions, they are equally interested in simply extending the number of centres involved in clinical trials – any clinical trials – because they believe, on the basis of strong evidence, that centres involved in trials provide better quality treatment.

One of the targets INCa has set itself is to raise the proportion of patients in clinical trials to 10%. In order to help smaller hospitals and even private practices to participate in these trials, it has put together a team of 'flying data managers' who can be dispatched to give support as and when necessary. In addition to undertaking its own trials, like PHARE, INCa will also give support to trials organised by other bodies – whether they be French or international organisations such as the European Organisation for Research and Treatment of Cancer (EORTC) or the Breast International Group. Twenty-eight clinical studies groups have now been set up under the auspices of INCa – for lung, breast, colorectal, radiation therapy, etc – each with 10–12 experts who will select the trials INCa will support and propose new trials where they are needed.

The key to making this work is to keep things simple. The PHARE trial



was designed with an 'ultra-simple' protocol, which requires the same amount of work as normal treatment. It uses an 'ultra-simple' Case Report Form, and an 'ultra-simple' randomisation. All the documents will be downloadable from INCa's website. Sources within INCa stress that it is still possible to achieve this degree of simplicity at the level of the treating physician, even under the terms of the European clinical trials directive. This is because the additional bureaucracy and expense involved in complying with the directive fall directly on INCa, as the sponsor, and INCa has the resources, staff and experience to cope.

Keeping things simple doesn't just help when it comes to widening the group of French treatment centres involved in clinical trials. It also makes it easy for research groups in other countries to run similar trials with a view to conducting meta-analyses that could further clarify the best way to use adjuvant Herceptin. Pivot is very keen to see this happen, because he believes the results of the PHARE trial will simply open the way to further questions that need answering: "My belief is that we have a subset of patients who require maybe 6 months, probably a subset who require less and probably a subset who require more."

Working out which patients do best with which protocols will be a complex business, and the more groups who join the search, the better. "It is a French project, but my belief is that this project should not remain a purely French one, it should take on a European dimension, and other countries can participate in such a study or undertake similar studies, because it is a very simple one.

"If we have 5000 patients enrolled in France and 4000 in UK and 5000 in Germany and 4000 in Italy, we can be absolutely sure of the results. And in terms of subset analysis, if we want to identify a difference between the concomitant versus sequential administration or between ER- and ER+ tumours, we will probably need this type of meta-analysis, so a European dimension to such an approach would be very effective."

Whether or not research groups in other countries choose to take up this invitation, there is no doubt that finding how to use cancer drugs more effectively will be key to ensuring that Europe's patients can benefit from the very expensive new drugs that are coming on the market. And as Pivot points out, pharmaceutical companies are hardly going to volunteer to do studies like PHARE that may result in halving the period for which their drug is used.

"There is an urgent need," he says, "for more strategic, academic trials like PHARE", and he hopes that similar trials will soon be up and running for other targeted drugs, such as Avastin (bevacizumab).

France does not have an outstanding track-record on leading clinical trials, and those in Europe who have been plugging away at this for decades may be forgiven the odd wry comment about the fervour of the converted. That said, amidst the despondency created by the European directive and often chaotic way decisions are made over new drugs – who gets them and how they are used – the new "can do" approach of French oncologists in INCa will surely be welcomed as a ray of hope on the European scene.