A challenge from oncologists: **smaller, targeted clinical trials**

By Chris Tachibana

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Cancer researchers are calling for an overhaul of the way we develop and test cancer drugs.
- It's clear that we urgently need a new paradigm for drug development, including targeted patient selection for clinical trials, shorter duration of clinical trials and improvement of the cost effectiveness of bringing a new drug to the market, said Dr. Fabrice André, Breast Cancer Unit, Institut Gustave Roussy, France, in a press release for the November 2010 Cancer Biology for Clinicians Symposium in Nice, France. The symposium was organized by the European Society for Medical Oncology (ESMO), a nonprofit organization founded in 1975 to promote scientific advances in cancer care and cures.
André is an author of a 2011 Nature Reviews Clinical Oncology article acknowledging that personalized medicine is having an impact on cancer diagnosis and treatment, and arguing that this requires a reform of clinical trials.
Two factors contribute to the increased personalization of oncology. One is genomic analysis showing that tumors have extensive genetic variety, sometimes within a single tumor from one individual. The other factor is the rise in therapies that target molecular features of tumor cells. Two examples are gefitinib and erlotinib, which inhibit a tyrosine kinase that is often overexpressed in lung or breast tumor cells.
The increasing molecular detail with which we can characterize patients and predict their response to treatment leads to increasing subdivisions of cancer. As subdivisions become more narrow, the different categories begin to resemble rare, orphan diseases. For example, breast cancer is no longer considered a single disease, but is classified as positive or negative for a panel of biomarkers such as the human epidermal growth factor receptor (HER2) that is the target of the anticancer drug herceptin. The combination of biomarker results predicts a tumor's response to a variety of therapies, with HER2+ cells predicted to be susceptible to herceptin treatment. From this point-of-view, oncologists like André see the need to reform clinical trials.

- If we want to facilitate the implementation of this kind of personalized medicine, then we urgently need to develop new strategies for cancer drug development, says Dr. Fabrice André, Breast Cancer Unit, Institut Gustave Roussy, France

A call for biology-driven trials

André believes that since molecular biology has driven this wave of personalized cancer analysis and treatment, we should now move to biology-driven clinical trials. Drug testing currently uses randomized trials, in which subjects are chosen and grouped in ways that deliberately ignore their particular genetic characteristics or the molecular features of their cancer. However, for drugs that target only certain types of tumor cells—ones that overexpress a particular protein for instance, the trial may include very few patients with the particular subtype of cancer against

which the drug is effective. In a trial including all breast cancer patients, for example, only a subset will have HER2+ tumors. The tested drug may appear to be ineffective, even though in the real world, it would be administered only to patients with cancer cells expected to respond to it.
Biology-driven trials select subjects specifically because they carry the molecular target of the tested drug. Since randomized trials are currently considered the most rigorous and powerful method to test the effectiveness of a new drug, biology-driven trials represent an entirely new approach, with challenges to overcome.
- The idea of biology-driven trials is welcome, overall. Nevertheless, a lot of people point out the limits, such as deciding which prerequisites are needed before a biomarker is selected for a biology-driven trial, figuring out how to optimally organize molecular screening, and learning how to handle trials that only include a few number of patients in academic centers, says Dr. Fabrice André.
He continues that biotechnology companies and the pharmaceutical industry have a responsibility in this new model, including collaborating with academic centers that run smaller clinical trials, to select patients for trials in a "molecular triage" process.

Using the right assays on the right tissues
Another challenge is that biology-driven trials require robust bioassays to screen trial subjects and monitor them throughout the trial.
Professor Jean-Charles Soria from the Institut Gustave Roussy, Paris, was a co-chair of the 2010 ESMO Symposium on Cancer Biology for Clinicians. He is a co-author with Dr. Fabrice André on the Nature Reviews Clinical Oncology paper and a 2011 Journal of Clinical Oncology comment on biology-driven phase II trials.
- Personalized medicine is a great focus of tomorrow, but optimizing drug development requires many commitments that are not currently being fully performed and embraced by stakeholders, including the pharmaceutical industry or clinicians. The first big issue is the material we are analyzing to optimize and speed up drug development.

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Soria says that by using samples that are not precisely relevant to the trial, for example tissue from biobanks.
- We are spending money getting molecular profiles of a caterpillar when we are treating a butterfly. The pharmaceutical industry in the end believes that any tissue is good enough, but any tissue is not good enough. Biobanks are not relevant if the therapy is being performed in a metastatic setting. There is a temporal evolution of biomarkers that no one is taking into account. Biomarker analysis needs to be done just before experimental therapy starts. The pharmaceutical and academic worlds are making a major mistake. They must perform new biopies at the time of metastatic disease, states Professor Jean-Charles Soria.
These new models for screening patients and conducting clinical trials offer many opportunities for biotechnology and pharmaceutical industries. Soria also notes that drug development is being driven by biomarker development. He emphasizes that drugs and biomarkers must be developed in parallel, with independent sets of validations for drugs and biomarkers. As Dr. André pointed out in press notes for the 2010 ESMO Symposium;
- As our understanding of cancer biology develops further, these kinds of personalized treatments are expected to become available for many more cancer types. If we want to facilitate the implementation of this kind of personalized medicine, then we urgently need to develop new strategies for cancer drug development.