that binds Ang-2) currently in phase 1 trials for ovarian cancer.

Roche is adopting a similarly robust attitude. "The majority of the relevant studies are in the early phases of development, so it is too early to comment on the outcome of this approach," says a company spokesperson, "and Roche will continue to investigate combining such therapies." They are currently running the phase 3 ATLAS trial using an anti-VEGF/anti-EGFR combo for the first-line treatment of patients with advanced NSCLC.

From the studies to date, one lesson is becoming apparent: combining pathway-targeted cancer therapeutics is not as side effect–free as might have been hoped. "All these targeted agents that are currently available affect major cellular pathways," says Amgen's Chang. "When you inhibit one, that might be tolerable; when you inhibit two or more, that may have effects that are not acceptable for clinical use."

As more targeted agents are approved, the choice of combinations will become much more complicated. Thus far, with only a handful of pathway-directed agents on the market, the approach has been largely empirical, guided by trial and error. This could soon change. "We're just not sure which drugs should be paired with which," says MD Anderson's Kim. "We need to figure this out, and find the best markers to indicate which patients should receive certain combinations."

Steps are already being taken in this direction. Just as Genentech's Herceptin (trastuzumab) shows efficacy only in HER2-positive breast cancers, so other targeted drugs work against a certain genetic background. The efficacy of Amgen's Vectibix in colorectal cancer, for example, is restricted to individuals without mutations in the *KRAS* signaling gene. If other targeted therapies show similar selectivity, then combinations of these therapies will have to take this fact into account.

On this basis, Paul Workman of the UK's Institute of Cancer Research in London says that it is unfair to judge the whole field of combination targeted therapy on the basis of the VEGF/EGFR inhibitor studies to date. "The full benefits of the approach will only come to fruition when we can really apply genetic stratification and pathway-activation profiling," he argues.

Perhaps the major challenge facing combination targeted therapies is to move away from a pragmatic empiricism to a more rational, scientifically based strategy. This requires integrating new insights into the pathway perturbations that drive various cancers with knowledge of how specific targeted agents act. "An understanding of the underlying fundamental biology should allow the right targeted therapeutics to be matched to generate a synergistic effect rather than the additivity that we've been used to," says Amgen's Chang. Capitalizing on combination therapies, in Workman's view, mandates a comprehensive systems biology perspective that will serve as its scientific foundation.

For all the false starts and dashed hopes, there is still an upbeat feeling about combination targeted therapies, both from the perspective of helping patients and commercial success. "If a drug combination works or improves efficacy compared with what a single agent would do, that in itself will increase market penetration or expand indications beyond the drugs' original use," says Chang. "But it is the scientific rationale that really drives interest in pursuing combination therapies."

The painful lessons that have been and continue to be learned in this pursuit should, however, eventually strengthen the field. "As we get more drugs, we'll have to ask the tougher questions, and that is what will force us to be more scientifically rigorous," says Kim.

Dan Jones *Brighton, UK*

Table 1 Selected efficacy trials of VEGF/EGFR combination therapies

Company	Trial description	Results
Amgen	Phase 3 (PACCE) trial of chemotherapy (folinic acid, 5-fluorouracil plus Eloxatin) and Avastin with or without Vectibix in 231 patients with advanced colorectal cancer.	Trial halted after preliminary review of data indicated increased toxicity and no increase in benefit for the treatment arm[a].
ImClone	Phase 3 (CAIRO) trial of Xeloda, Eloxatin and Avastin, with or without Erbitux in individuals with previously untreated metastatic colorectal cancer.	Median PFS 10.7 months versus 9.8 months in Erbitux arm; response rates 40.6% versus 43.9% and median overall survival 20.4 months versus 20.3 months. No significant difference in PFS or overall survival between patients with a *KRAS* mutation or those without.
OSI	Phase 3 (BeTa Lung)[b] trial of Tarceva and Avastin or Tarceva and placebo in 636 individuals with advanced NSCLC.	Did not meet primary endpoint of increasing overall survival. But median PFS on combination increased to 3.4 months versus 1.7 months for Tarceva alone and objective response rate rose to 12.6% versus 6.2% on Tarceva alone.

[a]Amgen is now studying Vectibix in combination with chemotherapy in colorectal cancer patient stratified according to *KRAS* status. [b]Results of a second study (ATLAS) in which OSI is evaluating Avastin and Tarceva for NSCLC patients whose disease has not progressed on Avastin or other chemotherapy are also expected in the first half of the year. PFS, progression-free survival.
Source: IDDB

IN brief

Stem cells caught in morality clause

The European Patent Office (EPO) will not be issuing patents for stem cells that have been obtained through the destruction of human embryos. The ruling announced last November invokes so-called 'morality clauses', invalidating the University of Wisconsin-Madison's key patent for a method of obtaining embryonic stem cell cultures from primates, including humans (the Wisconsin Alumni Research Foundation/Thomson patent will still be upheld in the US). Although the European ruling expressly rejects destruction of the human embryo, there is still some confusion. Aurora Plomer, professor of law and bioethics, University of Sheffield, says the ruling has "left open the question of whether specific moral exclusion extends to downstream derivative products, that is, products based on stem cell lines whose original derivation would have involved destruction of a human embryo." In Europe the situation remains quite fluid, with researchers bypassing the EPO by filing applications directly to their national patent office. But the stem cell ruling may have further implications, such as "increased costs for the industry, as investors revert to discrete selective national filings to secure patent protection on [human embryonic stem cell] inventions in favorable environments," says Plomer. This ruling comes as experts warn that the UK may lose its place as leader in the field, as Obama's administration has pledged to inject more money into federal funding of stem cell work. *–Nayanah Siva*

Land use stirs biofuels ruckus

The Biotech Industry Organization (BIO) has been asking the US Environmental Protection Agency (EPA) to publicly release its new methodology for calculating biofuels' life cycle greenhouse gas emissions, which will include emissions from indirect land use changes. The biotech industry needs "an actual measurement" of the effects biofuels have on the agricultural market, and how those effects are "translated into the actual land use around the world," says Paul Winters, BIO communications director. The calculations are required by the Energy Independence and Security Act (EISA) of 2007 and help determine which biofuels qualify for inclusion in the annual US quota for renewable fuel blended into gasoline, thus allowing the petroleum industry to purchase the biofuels to meet this quota. (For 2009, this quota is set at about 11 billion gallons.) Though some argue that indirect land use effects cannot be reliably measured, Tim Searchinger, visiting scholar at Princeton University in Princeton, New Jersey, counters that his analysis suggests even "the most heroic of assumptions" won't show that greenhouse gas emissions are reduced over "a reasonable period" by the use of biofuels in the gas supply. Regardless, BIO's biofuel members have a meaningful stake in the EPA's calculations. EPA has not set a date for the release of its Notice of Proposed Rule Making for EISA 2007. *–Susan Kim*