Table 1 The first five squamous cell lung cancer treatment arms chosen for the master protocol launch

Company/location	Compound	Target
MedImmune/Gaithersburg, Maryland	MEDI4736	mAb targeting programmed cell death 1 ligand
AstraZeneca/London	Azd4547	Fibroblast growth factor receptor tyrosine kinase inhibitor
Amgen/Thousand Oaks, California	Rilotumumab	A mAb directed against hepatocyte growth factor
Genentech/S. San Francisco	Pictilisib	Phosphoinositide-3 kinase inhibitor
Pfizer/New York	Palbociclib (pd-0332991)	A cyclin-dependent kinase (CDK)-4 and CDK6 inhibitor

mAb, monoclonal antibody.

of action of a particular compound. Within each arm, patients would be randomized to an experimental drug or standard of care.

Each arm will operate independently and be powered to demonstrate overall survival as the primary endpoint. Interim progression-free survival would be used to determine whether an experimental drug progresses from phase 2 to 3.

The core innovation in the master protocol is that multiple agents will be tested in several study arms in a single, ongoing, clinical trial. Another change is that testing patient DNA with next-generation sequencing can provide more diagnostic information than can be achieved with one test. This is a bold move away from testing each drug with its own companion diagnostic.

Box 1 First two drugs celebrate I-SPY2 graduation

While the Friends of Cancer Research prepare to launch the Lung Cancer Master Protocol, sponsors of the landmark phase 2 I-SPY2 trial are celebrating the graduation of its first two candidates, AbbVie's veliparib and Puma Biotechnology's neratinib. Veliparib and neratinib were the first two drugs to enter into the trial, suggesting it can deliver on its promise of efficiently identifying which patients respond to which drugs. Across the Atlantic, in December, the European Union's Innovative Medicines Initiative unveiled a €53 (\$72.7)-million adaptive trial to test Alzheimer's disease drug candidates.

"These trials are the wave of the future," says Hope Rugo, a trial investigator and oncologist at the University of California San Francisco School of Medicine.

The I-SPY2 trial, which launched in 2010, tests multiple drugs, from multiple companies, in newly diagnosed breast cancer patients before they undergo surgery (*Nat. Biotechnol.* **28**, 383–384, 2010). Investigators use up to ten biomarker signatures to stratify patients. They also feed early efficacy data into an adaptive randomization algorithm that enrolls patients into different treatment arms depending on how previous patients fare; the algorithm enrolls more patients into treatment arms when positive signals emerge, and fewer when negative signals emerge.

AbbVie's veliparib, a poly(ADP-ribose) polymerase inhibitor, graduated in triple-negative (HER2 negative, hormone receptor negative) patients, a particularly nonresponsive population. An estimated 62% of patients receiving veliparib had a pathologic complete response—no detectable tumor at the time of surgery—compared with 26% of patients receiving the standard of care, Rugo reported at the San Antonio Breast Cancer Symposium in December 2013. The most common adverse events were hematologic.

Puma's neratinib, a multi-tyrosine-kinase inhibitor, graduated in HER2 positive, hormone receptor–negative patients. Investigators will present pathologic complete response and adverse event data at a medical conference later this year.

QuantumLeap Healthcare Collaborative, who are coordinating the I-SPY2 trial, are talking with AbbVie and Puma about launching I-SPY3, an adaptive collaborative follow-on to I-SPY2. "I-SPY3 will hope to be a nimble way to move these agents relatively quickly into a phase 3," says Rugo, "but at the same time these agents might go in to company-sponsored trials." I-SPY2 is still testing five more monotherapy or combinations treatments, and more arms can be added. No drugs have dropped out of the trial so far.

In Europe, the biomarker-driven Alzheimer's disease trial is expected to enroll about 1,500 patients. The project is a proof-of-concept trial that shares many of the I-SPY2 features. It is part of the EU's Framework Programme 7 and applications are due April 8.

Asher Mullard *Ottawa, Ontario, Canada*

IN brief

It's official: biologics are pharma's darlings

Biologics have replaced small molecules as the dominant focus of big pharma's pipeline, and a new analysis from the Tufts Center for the Study of Drug Development (Boston) has quantified the phenomenon. In 2012, about 40% of all biotech products in clinical development were being developed by big pharma, up from 15.2% in 2000, according to Ron Evens, an adjunct professor at the University of the Pacific in Stockton, California, who conducted the study with Boston-based Tufts. And in an even more startling metric, biotech products accounted for only 7% of revenue generated by the top ten treatments worldwide in 2001, but made up 71% of that revenue in 2012. Over a similar period, biotech product sales more than quadrupled, financing of biotech research increased tenfold, and the amount invested in pharma-biotech research alliances increased sixfold. In fact, all parameters in the Tufts report point in the same direction: pharma has dramatically shifted its R&D strategy from an almost singular focus on small-molecule drugs in the early 1990s to a dominant focus on biotech products today. Driving the transformation are biotech products' novel mechanisms of action and ability to command high prices, combined with the declining patent lives of small-molecule drugs, the report said. Biotechnology Industry Organization spokesperson Tracy Cooley says her organization agrees that the growth of biotech has been driven in part by those factors, though the shift "can be largely attributed to a natural evolution of the industry."

Emily Waltz

IN their words

"This is among the worst applications of biotechnology. They will increase the use of toxic pesticides in industrial agriculture while providing absolutely no benefit to consumers."

Andrew Kimbrell,

executive director of the Center for Food Safety, heavily criticizes the USDA's recommendation to deregulate Dow AgroSciences Enlist corn and soybean, which combines resistance to three herbicides, among them glyphosate and 2,4,D. (*Reuters*, 3 January 2014)

"We lock up our refrigerator. We lock up our freezer. We lock up the pantry." Mark Greenberg of Denver, a consultant to a hedge fund, whose son has Prader-Willi, a rare condition that results in uncontrollable hunger. Zafgen of Cambridge, Massachusetts, announced some positive phase 2a results in this indication with its anti-obesity drug beloranib, a METAP2 inhibitor. (*New York Times*, 14 January 2014)