Trends-in-Medicine

Quick Takes

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Trends-in-Medicine
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Check out the new *Trends-in-Medicine* blog on our website (www.trends-in-medicine.com). The first blog has some advice for traveling to Europe post the volcanic eruption in Iceland.

…Highlights from this week's news affecting drugs and devices in development…

SHORT TAKES

- **ALKERMES/LILLY/AMYLIN's Bydureon (extended-release exenatide or "Byetta LAR") –** A month after the FDA asked for more data before approving Bydureon, the companies filed it with European regulators to control glucose levels in Type 2 diabetics.
- **BLUECROSS BLUESHIELD OF DELAWARE** is under fire from several lawmakers after it put out new criteria requiring that imaging scans, such as CT and MRI, be pre-approved by a third-party company, MedSolutions, which will determine whether or not the test is "appropriate" for a patient.
- **CADENCE PHARMACEUTICALS' Ofirmev (intravenous acetaminophen)** will be resubmitted to the FDA within 30 days, after the company meets with the Agency and the drug's third-party manufacturer to resolve the manufacturing issues that caused the FDA to reject the application in February 2010. The FDA did not request additional clinical information about the pain reliever.
- **ELAN** may separate its main business from Elan Drug Technologies, a drug delivery service. This would be the second such attempt at separation.
- **GILEAD's GS-9450 –** A Phase II clinical trial of this caspase inhibitor for hepatitis C (HCV) treatment was halted after some of the 300 patients in the trial suffered liver damage not due to their underlying liver disease. The company plans to further review the data before deciding whether to proceed with any further development of GS-9450.
- **MERCK's telcagepant (MK-0974)** and **JOHNSON & JOHNSON's Topamax (topiramate) –** In an article in ***The Lancet***, researchers reported that telcagepant may be effective in treating migraines once they occur and that Topamax may prevent migraines. However, Phase III trial results showed liver enzyme elevations with telcagepant, and Merck will conduct another safety study prior to submitting a New Drug Application (NDA) to the FDA.

- **NOVARTIS/HUMAN GENOME SCIENCES' Joulferon/ Zalbin (albinterferon alfa-2b) –** Novartis withdrew its European application for Joulferon in hepatitis C out of concern that European regulators would request additional information. The FDA is currently reviewing the drug in the U.S.
- **NOVARTIS's Zortress (everolimus)** received FDA approval for preventing organ rejection in kidney transplant patients.

NEWS IN BRIEF

BIOGEN IDEC/ROCHE's ocrelizumab – meets RA outcome despite FDA halting trial

In the Phase III SCRIPT trial comparing ocrelizumab with placebo in patients with seropositive rheumatoid arthritis (RA), patients receiving the drug showed improvement in the signs and symptoms of RA after 24 and 48 weeks. This means that ocrelizumab met the primary study endpoint. However, in March 2010, the FDA halted the trial, preventing additional patients from being dosed because of a significantly higher number of serious infections occurring in patients receiving ocrelizumab. The Data Safety Monitoring Board (DSMB) found that safety risks outweighed the benefit, and some of the infections were fatal and some opportunistic. No cases of progressive multifocal leukoencephalopathy (PML) were observed in ocrelizumab patients. Dr. David Hagerty, vice president/chief medical officer of Biogen Idec, said, "We are committed to developing new treatment options for RA and will use our learning from this study to guide current and future development efforts." The ocrelizumab data will be further evaluated before a final decision on the future of ocrelizumab as an RA treatment.

BRISTOL-MYERS SQUIBB/SANOFI-AVENTIS's Plavix (clopidogrel) – non-compliance means poor outcome

A retrospective analysis of 7,402 patients after coronary artery stent placement published online in ***Circulation: Cardiovascular Quality and Outcomes*** showed that those who waited a day or more after discharge to fill their clopidogrel prescriptions were much more likely to have a poorer outcome. Among the patients, 16.3% waited at least a day before having the prescription filled, and 14.2% of these patients died or had an MI during the 664-day follow-up vs. 7.9% of those who filled their prescriptions promptly. A greater number of deaths and MIs occurred in the first 30 days post-stenting among those who waited to fill their prescriptions (28.5%) vs. those who did not wait (12.2%).

California Medical Association (CMA) – withdraws from doctor rating system

CMA withdrew from a BlueShield of California doctor rating system, saying that the way data are collected could result in inaccuracies and be misleading to consumers. The insurer's Blue Ribbon Recognition Program, set to begin June 1, 2010, will publish a blue ribbon symbol next to profiles of physicians if they have scored above average on 8 measures, such as preventive screening and diabetes care. CMA said the data are only gathered for physicians contracting with the insurer and don't account for patient refusal of tests or treatments or for patients who choose to see an out-of-network physician for a certain test, thus giving the rated doctor a falsely low score.

GLAXOSMITHKLINE's Avandia (rosiglitazone) – FDA considering halting TIDE trial, pulling drug

The FDA said it will schedule an advisory committee meeting in July 2010, during which experts will discuss halting the ongoing TIDE trial comparing Avandia with Takeda's Actos (pioglitazone) in Type 2 diabetics because of the substantially increased risk of heart attack and heart failure. In late March 2010, FDA Commissioner Dr. Margaret Hamburg said in a letter to Senate Finance Committee ranking member Sen. Chuck Grassley (R-IA), the move is "based on expert input and our own analysis." There is widespread speculation that advisory committee members also will discuss whether there is enough evidence to pull Avandia from the market.

The FDA approved the TIDE trial protocol in 2007. TIDE compares the two thiazolidinediones vs. placebo in 16,000 patients with Type 2 diabetes and also includes a Vitamin D arm, primarily to assess its effects on mortality and cancer. After approving the trial, a 2008 analysis of other clinical trials by two FDA reviewers revealed that Avandia was associated with 500 more heart attacks and 300 more cases of heart failure vs. Actos. In recent years, scientists and key opinion leaders often have been quoted as saying that a head-to-head trial like TIDE is unethical because, although Actos is not completely devoid of increased cardiovascular risk, evidence to date indicates that Avandia substantially raises those risks.

Meanwhile, GSK released a statement saying that the board overseeing TIDE "has not expressed any concerns regarding the safety of participants in the study and has recommended that the study continue without modification."

HUMAN GENOME SCIENCES/GLAXOSMITHKLINE's Benlysta (belimumab) – suffers a setback

Benlysta, a treatment for systemic lupus, was no better than standard treatment when taken for more than a year, according to study data released by the company. Last year, two 52-week trials comparing Benlysta to placebo in lupus showed it was significantly more effective in relieving symptoms. The longer-term results show that Benlysta loses its advantage when taken up to 18 months. ***Forbes.com*** reported that both U.S. and European filings for marketing approval will still go forward in 2Q10 and will be based on the 52-week data.

IMMUNOMEDICS' CD-74-RNase – preclinical results shows efficacy

In a report in the journal, ***Blood***, cell culture and animal study results indicated that this antibody fusion protein CD-74-ribonuclease (RNase) immunotoxin killed CD-74+ human lymphoma and myeloma cells, and the effects appear to be dose-dependent. A company statement said this is the first recombinant immunotoxin comprising a humanized antibody against CD-74 plus an engineered RNase. CD-74 is present on blood cells involved in the immune response as well as on lymphomas, myelomas, and some solid tumors.

JAZZ PHARMACEUTICALS' Xyrem (sodium oxybate) – improves sleep in fibromyalgia

Results of two Phase III trials show that Xyrem significantly improved fatigue and sleep disorder symptoms in patients with fibromyalgia. Pain scores and fibromyalgia symptom scores also were improved vs. placebo. After 14 weeks of a nightly dose of Xyrem, patients had a reduction in pain score of 29-32 points vs. a reduction of 18 points for placebo. Jenkins Sleep Scale score was reduced by 6.1-6.2 points vs. 2.9 points for placebo, and fatigue scores were reduced by 28-30 points vs. 17 points for placebo.

NABI BIOPHARMACEUTICALS' NicVax (nicotine conjugate vaccine) – aids smoking cessation

Early Phase III clinical trial results showed that NicVax, a vaccine that causes the immune system to generate nicotine antibodies that prevent nicotine from entering the brain and having the desired effect, was successful in helping some smokers quit. ***Among patients who responded*** to NicVax, 16% stopped smoking vs. 6% of those receiving placebo. The vaccine also caused smokers who responded but did not quit to reduce the number of cigarettes smoked per day by 50%. One 1,000-patient Phase III trial began in November 2009, and a second Phase III trial with the same number of patients started in March 2010. The endpoint is the number of patients who quit smoking and remain non-smokers for 12 months. The company expects to have full trial results in 3Q11.

Orion survey – men value QOL over prostate cancer management

Interim results of a survey of 100 physicians and 110 patients with prostate cancer indicated that a majority of men are more concerned about quality of life issues than they are about cancer management strategies. The survey reported:

- 72% of men prioritized quality of life over effective disease management and did not want treatment to impact their lives.
- 69% of patients said they want a balanced management approach that fits with their daily routine.
- Physicians said 68% of patients frequently talk about quality of life issues during office visits.

PFIZER's Sutent (sunitinib) – liver cancer trial stopped

A clinical trial of Sutent in hepatocellular carcinoma was stopped because it showed a survival ***deficit*** vs. Bayer/Onyx's Nexavar (sorafenib). In March 2010, Pfizer announced that Sutent failed to increase survival in a trial in advanced metastatic breast cancer. Sutent is approved for use in kidney and gastrointestinal cancers, and the company is continuing to investigate its efficacy in prostate cancer, non-small cell lung cancer (NSCLC), and in kidney cancer patients who have previously received surgical treatment.

STERIS's System 1 Processor – distribution halted

The FDA obtained a consent decree against Steris to stop the company from distributing the unapproved System 1 Processor (SS1) which sterilizes heat-sensitive instruments and devices. The decree was filed April 19, 2010, in the U.S. District Court, Northern District of Ohio, and is subject to court approval. In May 2008, the FDA sent a warning letter to Steris stating that uncleared, significant changes made to the SS1 caused it to be adulterated and misbranded. As a result of the consent decree, Steris has developed a transition plan and rebate program for customers to ease transitioning to available, approved alternatives. Handily enough, on April 5, 2010, the FDA cleared the Steris System 1E (SS1E), an alternative to the SS1.

FDA NEWS

➢ FDA initiative to reduce infusion pump errors

The ***Trends-in-Medicine*** report on the Health Information and Management Systems Society (HIMSS) meeting in March 2010 suggested that the FDA was about to clamp down on "smart" infusion pumps, and the FDA is doing exactly that. Dr. Jeffrey Shuren, director of the FDA's Center for Devices and Radiological Health (CDRH), announced on April 23, 2010, that the Agency is taking steps to address safety problems with all external infusion pumps, not just one manufacturer, including all smart pumps.

Infusion pumps have had persistent safety problems. In the past five years, the FDA received more than 56,000 reports of adverse events associated with them, including serious injuries and >500 deaths. Infusion pumps have been one of the most frequently recalled devices; from 2005 to 2009, 87 infusion pump recalls were conducted, and many of these were Class 1 recalls (the most serious). Infusion pump failures have occurred with multiple manufacturers and different pump types, and the FDA charged that many of the problems are related to deficiencies in device design and engineering.

Dr. Shuren said, "There have been problems with every kind of infusion pump on the market…Some of the problems we've seen may be the result of user error, but many are the result of engineering design errors…It is time for a more comprehensive approach than we've taken to date…Until [now] we have

responded largely on a case-by-case basis. This is a major shift in the FDA approach to medical device safety."

The most common problems with the pumps have been:

- Software defects, including failures of built-in safety alarms.
- User interface issues, such as ambiguous on-screen instructions that lead to dosing errors.
- Mechanical or electrical failures, including components that break under routine use, premature battery failures, and sparks or pump fires. Dr. Shuren said that in some cases infusion pumps have actually exploded in a patient's room.

Dr. Shuren said that instead of responding one-by-one and manufacturer-by-manufacturer, the FDA is taking three major actions as part of a multipronged initiative, and he said this initiative is "a marked departure" from how CDRH handled these devices in the past. The three actions are:

1. **Establishing additional premarket requirements** for new or modified infusion pumps. The FDA issued draft guidance and is seeking public comment before making the new rules official and permanent.
   - The new requirements will include **additional risk assessments** and design and engineering information.
   - Manufacturers will have to **test their devices in a "real world" environment**, with the kind of people expected to use the devices.
   - The FDA is offering manufacturers the ***option*** **of submitting their infusion pump software codes** to experts at the FDA for static analysis (a diagnostic technique that can help detect software problems earlier) prior to premarket review.
   - The FDA is urging manufacturers to "**consider the unique challenges of the home environment**, including lay users and household hazards like pets and children."
   - The FDA is warning that it may, in certain circumstances, **withhold premarket clearance until the manufacturer's facility has been inspected**. Dr. Shuren said this is the first time the FDA has employed this tool across all products in a class, "What we would be looking at are the manufacturing processes, what we call quality systems, the checks and balances the manufacturer has initiated to verify and validate the new technology. That is critically important with software. We will also look at how well they have the right processes for handling complaints and adverse events." Before this, Class III devices were subject to manufacturing inspections before marketing, but not Class I or II devices. Dr. Shuren explained, "If [a device is] Class II and a 510(k) submission, the law says that you actually are not held up from getting cleared to be on the market waiting for an FDA inspection. But there is an exception to that law…and it gives FDA the right to go in where there is substantial likelihood that non-compliance with systems requirements could result in serious injury to patients. In that circumstance, we can go in and inspect, and that product can't be marketing…We are now for the first time enforcing that for a whole class of devices."
   - The FDA will reach out to foreign regulators to develop a **global response**.
2. **Holding a public workshop** on May 25-26, 2010, on infusion pump design.
3. **Increasing user awareness by launching a new web page** devoted to infusion pump safety, including basic information about infusion pumps and steps that patients and healthcare professionals can take to prevent and report safety problems.

Are there other devices that may face this same stricter approval process and oversight? That seems likely. Dr. Shuren didn't identify any other device targets, but he did point out that there have been a large number of adverse event reports with implantable cardiac defibrillators (ICDs).

➢ FDA launches transparency website for devices and radiation-emitting products

The FDA's CDRH launched a website providing regulatory process and decision information as well as summaries of data that provided the rationale for Agency actions concerning medical devices and radiation-emitting products. The website is part of an ongoing transparency effort. CDRH's Dr. Shuren said, "The…website gives the public a window into our work…It provides a closer and clearer look at what we do and why we do it."

The new FDA website is to provide consumers and healthcare providers with better information regarding regulatory decisions about medical devices and radiation-emitting products. It will house premarket submissions and summaries of FDA reviews of related data, postmarket surveillance data, compliance and enforcement actions, and educational resources. It will also have a search feature and a feedback feature for public suggestions and comments.

➢ FDA monitoring home use devices

The FDA's CDRH recently posted new information for consumers on home use devices. A home use device is defined as a "medical device intended for users in a non-clinical or transitory environment, is managed partly or wholly by the user, requires adequate labeling for the user, and may require training for the user by a licensed healthcare provider in order to be used safely and effectively."

CDRH estimates that more than 7 million Americans receive home healthcare annually, with complex medical devices used more and more frequently and – according to the FDA – "many times under unsuitable conditions" which have safety implications.

What's interesting about this posting is that CDRH points out that it doesn't have sufficient regulatory authority over these products: "[CDRH's] regulatory authority alone is not enough to ensure that devices are safe and effective when used in the home. CDRH has been receiving an increasing number of adverse event reports about medical devices that are used in the home...CDRH wants to decrease the number of problems that occur in the home environment, but the issues are complex."

CDRH's solution is for the "relevant stakeholders" to collaborate: manufacturers and distributors, accrediting bodies, healthcare professionals, and human factors experts.

➢ FDA drafts new guidance on Advisory Committee disclosure and waivers

The FDA released draft guidance that would "expand transparency and disclosure" when the Agency grants a conflict of interest waiver to allow someone to participate in an FDA advisory committee meeting. The guidance, if implemented, would include posting online of the company name or institution associated with a member's financial interest along with the type of conflict of interest (including financial amount) when a waiver is granted. Acting associate commissioner for special medical programs Jill Hartzler Warner, J.D., said, "It would provide more transparency, so the public can better understand [the process]. It will also bring disclosure practice more in line with the standard practice in the academic community…FDA can obtain input and maintain integrity in the process." The guidance will be implemented after allowing 60 days for public comment.

Scientific advisory committees give expert advice on scientific, technical, and policy matters to help the FDA make policy decisions and actions on specific product approvals and clearances. Hartzler Warner said that the FDA has 49 advisory committees with more than 600 member positions and more than 200 vacancies. Asked if the guidance, if implemented, might result in even more vacancies, she said, "We have challenges in filling our vacancies, and that is certainly an important consideration for us. This number has been fairly high over a number of years. [And as part of a new initiative called FDA Track], one (initiative) is to reduce the vacancies to 10%."

There is a cap on the number of waivers that the FDA can grant to experts. For 2010, it is set at 13%. Hartzler Warner said that the FDA "currently grants waivers for <5%...FDA staff searches for individuals without conflicts of interest. However, many top authorities may have potential conflicts, and the FDA must at times ask for advice from those experts …There should be a balance between expertise and the need to maintain the integrity of the decision-making process."

FDA Commissioner Dr. Hamburg, in a letter to senior agency officials about the guidance, spelled out three principles "to minimize concerns when needed experts may have a conflict of interest":

- **Consideration of the nature of the conflict of interest**, recognizing that not all conflicts are created equal. For example, an academic researcher whose institution receives grants from an affected company but who does not personally participate in the studies has a more tangential relationship to the conflict than the researcher who conducts studies for the company directly.
- **Consideration of the type of advice to be provided** by the advisory committee. A waiver may be more appropriate for a meeting about a policy issue affecting a class of entities or products than for a meeting focusing on approval of a specific product.
- **Justification of waiver recommendations** with a description of the search for equally expert advisors without conflicts and an explanation of why the individual's participation is needed to afford the advisory committee essential expertise.

Asked if the letter means that Dr. Hamburg is seeking more flexibility so that more waivers could be granted, Hartzler Warner made several points:

- "We don't see this as a lessening of the stringency. We have two goals: (1) to get the best advisers for the committees…and (2) to minimize the chance that any decision the Agency makes based on those decisions…could be questioned for integrity purposes."
- "We need to strike the right balance…We are continually looking at this balance, but keep in mind that our conflict of interest review process is very much guided by federal law. The law has a cap on the number of waivers that we may grant, and it sets up specific criteria for us to administer."
- "We are not setting new policy on when waivers should be granted. We continue to make sure that when we grant a waiver, it is necessary for a committee to have expertise."
- "In terms of vacancies, we do screen candidates for vacancies, but it is a different screening than for a meeting. We have two types of screening. One is to see if an individual has conflicts that wouldn't be appropriate. Then, when we look at a particular meeting, we look at conflicts specific to that meeting."
- "There may be some specific meetings where a waiver would be granted, or he would be asked not to attend that meeting. We are open to taking members who may have some potential conflicts because we realize that the expertise is necessary."

- "The intent is to provide a series of principles which are consistent with existing policy. Dr. Hamburg wants to stress the Center director's judgment…when it comes to granting a waiver."
- "One [factor] is to look at the type of financial conflict. Typically, we have a lot of academic researchers on our committees. Academic statisticians often receive grants from industry and from NIH. We need to look at these… If an institution receives a grant from a company but the individual isn't involved in any way, we consider that a remote sort of interest."

AMERICAN ASSOCIATION OF CANCER RESEARCH (AACR)

Washington, D.C.
April 18-21, 2010

Due to scheduling conflicts, ***Trends-in-Medicine*** coverage of AACR this year is limited to reporting some of the highlights.

HIGHLIGHTS

➢ **GENENTECH's Herceptin (trastuzumab) – Radio-labeling Herceptin** with a copper isotope may become a non-invasive way to monitor the drug's effect on tumors and might eventually replace some biopsies that are typically performed for this reason. Researchers studied radiolabeled Herceptin in animal models and found two chelates, Oxo and PCTA, that give clearer results than the widely used DOTA. PET imaging was successfully used to detect the drug's action on tumors. The same platform can be used to test the action of other anti-tumor agents as well.

In another presentation, researchers said that treatment with Herceptin may **destroy cancer stem cells**, offering successful therapy to women with breast cancer that does not have HER2 overexpression. They used a mathematical model and predicted that 1 year of Herceptin treatment could kill breast cancer stem cells in patients with HER2 overexpression. In women with normal HER2 levels, it would take 3-4 years of treatment to destroy the breast cancer stem cells. Clinical trials to test this hypothesis are underway.

➢ **GLAXOSMITHKLINE's Tykerb (lapatinib)** may **help resistant breast cancer**. Preclinical cell culture studies indicated that breast cancer resistant to Herceptin may respond to Tykerb. Researchers conducted experiments with HER2+ breast cancer cell lines and found that Tykerb has activity in cell lines that have both acquired and *de novo* resistance to Herceptin. They tested 17 cell lines and found that 10 remained sensitive to Tykerb, including three that were resistant to Herceptin. Clinical trials to determine whether Tykerb can overcome resistance to Herceptin and extend survival are likely to use the two agents in combination.

➢ **IMMUNOMEDICS' clivatuzumab** is useful in a blood test to **detect pancreatic cancer and treatment response**. Researchers reported results of a clinical trial using clivatuzumab, a humanized antibody labeled with yttrium-90 (Y-90), in a blood assay to detect the PAM4-protein, which is a marker for early pancreatic cancer. It was previously reported that the immunoassay has a sensitivity of 62% for detecting Stage 1 pancreatic cancer, an 86% sensitivity for detecting Stage 2, and a 91% sensitivity for detecting Stage 3 or 4 disease. Newly reported trial results show that the same assay detected changes in the PAM4-protein level in patients treated with Y-90 clivatuzumab in Phase I and II clinical trials for efficacy. In these trials, including 17 evaluable patients, the assay correctly identified all 4 patients who partially responded to Y-90 clivatuzumab treatment, 4 of 9 patients classified as having stable disease as partial responders, and did not identify the 2 patients with progressive disease as non-responders.

In a related study, researchers reported that adding a conjugate targeted to pancreatic cancer to Y-90 clivatuzumab produced better response in an animal model, with mice receiving the highest dose achieving a tumor-free state in four weeks.

➢ **IMMUNOMEDICS' IMMU-114 (anti-HLA-DR)** was **50 times more potent than epratuzumab**, an anti-CD-22 antibody, in cell culture studies against B-cell lymphomas and leukemias. Another Immunomedics' antibody, the CD-20-targeting veltuzumab, also was more potent against these cancer cells than epratuzumab. Importantly, the researchers noted that epratuzumab exhibited very robust activity against a mantle cell lymphoma cell line that is resistant to rituximab (Roche/Genentech's Rituxan).

➢ **LILLY's Evista (raloxifene)** came **close to tamoxifen in preventing breast cancer**, with fewer adverse events. Long-term results of the STAR trial indicate that Evista is very similar to tamoxifen in terms of reducing the risk of invasive and non-invasive breast cancer and is associated with fewer side effects than tamoxifen. STAR was sponsored by the National Cancer Institute (NCI) and included 19,747 post-menopausal women at increased breast cancer risk. After five years of treatment and another 21 months of follow-up, Evista reduced the risk of both invasive and non-invasive breast cancer by 38% vs. a 50% reduction seen with tamoxifen. This equates to Evista being 78% as effective as tamoxifen.

Women taking Evista developed 45% fewer uterine cancers, had 28% fewer instances of deep vein thromboses, and were 20% less likely to develop cataracts during the trial. The rate of bone fractures and the development of cardiovascular events including stroke, myocardial infarction (MI), and transient ischemic attacks (TIAs) were similar between the two treatment groups. Researchers reported no differences in breast cancer prevention efficacy with either drug based on age, race, family history, or other known cancer risk factors.

➢ **PFIZER's oncology pipeline.** Pfizer presented **new data from its oncology pipeline** and stressed that the company is investing more than ever in research and development, as well as collaborations with other companies and institutions. Dr. Garry Nicholson, president and general manager of Pfizer's Oncology business unit, was optimistic, "There is more energy and momentum coming out of 2010 than in prior years. I can see a convergence between biology, therapeutics, and diagnostics that didn't exist a few years ago. [You're seeing] the integration of research and clinical development…[and] you're seeing the convergence of scientists and clinicians as collaborators."

Dr. Nicholson gave as an example Sutent (sunitinib), "Researchers in Boston and Tokyo discovered that this molecule had activity in certain patients. So, we've accelerated the learning curve through collaboration. What we're looking at is somewhat different from what we expected years ago. We talked about a cure for cancer and making a difference in the lives of patients. What we're looking for now is cancer control. We are considering molecules that can be administered for years at a time with minimal side effects which lead to almost normal lives. I believe that we'll demonstrate a number of breakthroughs. Pfizer has decided that this is one of the areas in which it must invest to win."

Dr. Mace Rothenberg, senior vice president of clinical development and medical affairs at Pfizer Oncology, said that the industry is entering a new age of research and development, "Two groups of drugs are being presented for the first time [at AACR] – two compounds that target the PI3K pathway. One is oral, and one is intravenous…We have a large and robust pipeline, and our approach has been to use our insights into the biology of disease to identify which ones of these are most likely to make a difference, and we set a high bar."

Dr. Rothenberg said Pfizer is looking at finding new ways to use animal models to predict which therapies will work, "[We are looking at] identifying more robust ways of evaluating these new drugs, using orthotopically planted tumors, for example…and through the use of genetically engineered mouse models. We think there are ways which will help us improve our ability to predict which drugs will work in the clinic."

Dr. Neil Gibson, chief scientific officer at Pfizer Oncology, said that Pfizer has been investing heavily in translational research and in a number of academic collaborations, particularly with institutions which have a collection of different tumor samples and which have been genetically profiling the samples, "It actually gives us a powerful dataset to be able to look retrospectively at information that is important...An example would be our collaboration with BC Cancer Agency in Canada (an agency of the Provincial Health Services Authority). It has 4,500 breast cancer samples, well annotated, well characterized, all linked to clinical outcomes. To have access to that kind of information is extremely important as we think about how to develop the next mechanism…in breast cancer."

Pfizer also is working on a colorectal cancer sample database, and the company has been investing heavily in stem cells, in an ongoing collaboration with the University of California at San Diego. Dr. Gibson said, "The oncology research unit has been investing a lot of money in this space."

PI3K/mTOR inhibitors. Pfizer Oncology presented new data on two novel dual PI3K/mTOR (phosphatidylinositol 3-kinase/mammalian target of rapamycin) inhibitors:

- **PF-04691502** – oral.
- **PKI-587**, also known as PF-05212384 – IV.

The PI3K pathway and the key kinases in it, including mTOR, are believed to play a central role in regulating cellular signaling that may influence cancer cell growth and survival. Genetic abnormalities in the pathway have been closely tied to cancer development and growth. Trials are ongoing to look at the safety and tolerability of these two agents in cancer patients with solid tumors.

Dr. James Christensen, director of translational pharmacology, Pfizer Global R&D, said, "There are multiple PI3K family class members. mTOR is a downstream signaling mediator. Each one of these individual isoforms has a role and a particular role in cancer, and mTOR is a key target in terms of regulating cell growth, cell survival, and metabolism. We have two molecules targeting this pathway – an orally administered agent and PF-05212384, an IV-administered agent. Both share a similar target profile. Each inhibits mTOR…in TORC1 and TORC2…Inhibiting this pathway in multiple doses both upstream and downstream may be important."

As for why Pfizer is developing two agents, Dr. Christensen said, "We believe that oral and IV may have different places… in cancer…Pulsatile administration of this class of molecule… is something we'd like to further explore. Secondly, it is possible that the IV administration paradigm may be [used] with some types of chemotherapy…The oral agent may be of use in certain types of settings where we are trying to treat for a longer period of time…or it might be interesting to combine with agents administered over a daily schedule, for example."

As for patient selection strategy, Dr. Christensen said, "This class of agents tends to work, for example, in breast cancer against tumors with PIC3A mutations and ER+ breast cancers. To suggest that these do differentiate, at least in the non-clinical models, may be something we can exploit in the development strategy."

First-in-class investigational agents. Two first-in-class agents Pfizer has in development that were highlighted are:

- **Crizotinib** (PF-02341066), an oral anaplastic lymphoma kinase (ALK) inhibitor that also inhibits c-MET. ALK is

a new therapeutic target in cancer. The fusion gene EML4-ALK is thought to be a key driver of lung tumorigenesis and is estimated to be present in ~40,000 patients worldwide with newly diagnosed NSCLC every year.

Dr. Christensen said, "This is a very selective molecule. We studied the agent in a non-clinical setting…and it exquisitely picked out a subset of cell lines. There were particular lines that had altered ALK…In terms of overall context, these defects aren't all that frequent – probably between 3% and 7% of all lung cancers – but the patients are rarely smokers, are almost always adenocarcinomas, and are usually very young patients. We had a paradigm to identify patients, and we noted very early on that the patients were starting to show objective responses…and in some cases, pretty dramatic responses, where there was no tumor left in some post-scans. Today, of those 50 (patients), ~64%-65% have exhibited confirmed RECIST responses, and 95% demonstrated clinical benefit on this particular agent. None of the clinical response data will be presented at this meeting, but will be updated at ASCO. It has entered a Phase III randomized, open-label study."

- **PF-04605412**, a fully human anti-α5β1 IgG1 antibody engineered to possess antibody-dependent cellular cytotoxicity (ADCC) activity in pre-clinical models. Pfizer researchers said that the adhesion molecule called integran α5β1 plays an important role in cancer progression by promoting cancer cell migration, proliferation, survival, and metastasis. In lung cancer patients, a five-year survival rate was inversely correlated with the degree of tumor α5 progression and similar associations have been found in melanoma and ovarian cancer. ADCC also may play a big role in anti-cancer therapy.

  Dr. Christensen said that this agent has a dual method of action, "The target may be important on the vasculature as well as the tumor. The presence of the antigen in a high level will be important…when tumor cells express this antigen, the ADCC activity is believed to add some extra bang for the buck…There are certain polymorphisms that track with a greater degree of efficacy…This is the first disclosure of this molecule characterizing the functions. The take-home message is that there has been a body of data where ADCC and non-ADCC-inducing antibodies are compared, and this helped build confidence [among researchers] that this is something relevant to move forward with. This is in Phase I clinical trials."

Other Pfizer agents in development with data at AACR. Pfizer Oncology also had abstracts at AACR on **other investigational and approved compounds**, including:

- **Sutent –** correlation of circulating biomarkers with clinical outcomes in advanced NSCLC.
- **Figitumumab**, an IGF-1R inhibitor – molecular predictors of sensitivity in pre-clinical models of lung and colon cancers.
- **Axitinib** – pharmacogenomic analysis of a Phase III trial of gemcitabine ± axitinib in advanced pancreatic cancer as well as an open-label Phase I study of the pharmacokinetics in healthy Chinese volunteers.

Resistance. Pfizer had three posters at AACR outlining mechanisms of resistance to its agents. Dr. Christensen said, "The reason we are studying this is to understand intrinsic and acquired resistance. If we can understand that…we can figure out which patients to select and or how to broaden the patient population. We are studying [Crizotinib], looking at gastric cancer and gastric cancer cell lines. We've characterized a number of clones and find some have genetic abnormalities… Novel BRAF fusion protein is one thing we're interested in. You can combine BRAF and an inhibitor and be effective, where neither works by itself. There are some other genetic abnormalities…some of which are presented at this meeting… Over a long time, the resistance mechanism that arises is associated with the ability of tumor cells to expand in the absence of vasculature. We are trying to understand the underlying basis of that resistance. We don't fully understand, but we did notice that there are some pathways that are regulated."

Dr. Christensen said that his group looked at more than 150 tumor cell lines in order to characterize their responses to the agent, "We noticed some cell lines are very sensitive, and there is some resistance. We set out to understand the underlying pathways. The bottom line is that you might be able to use those in the patient selection strategy. There were some cell lines that were resistant. It shows that you can combine the two classes of agents in a specific subset and get very robust activity where you don't see anything with the agents by themselves."

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