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IN BRIEF

DRUGS & TARGETS

FLATIRON COMPILES RICH DATA ON THE UPTAKE OF PD-1 INHIBITOR DRUGS; A CASE STUDY IN REAL-WORLD EVIDENCE?

By Matthew Bin Han Ong

Utilization data compiled by Flatiron Health and made available to The Cancer Letter make it possible to visualize the dramatic uptake of immunotherapy drugs in the academic and community settings.

The data illustrate nothing less than the real-time anatomy of the creation of a new standard of care in oncology. Charts, bars and tables published here first show these drugs emerge in the treatment of non-small cell lung cancer in early 2015 and rapidly build momentum.

Today, two years after these drugs started to trickle in, one in four NSCLC patients gets a PD-1 checkpoint inhibitor in the first-line setting. More than half get these drugs in the second-line setting, according to an analysis of electronic health data by Flatiron, an oncology bioinformatics company headquartered in New York.

The study, based on a cohort of about 35,000 patients, tracks the rapid uptake of checkpoint inhibitors over two years. The numbers are staggering: the use of PD-1 therapies increased more than sevenfold from May 2015 through April 2017.

It's likely that this rate of uptake of a cancer drug is unprecedented, but, then again, such comparisons of utilization data would be problematic. That's because cancer researchers have never had access to this level of granularity, and never has it been provided with such immediacy.

By April, at least 37 percent of NSCLC patients, overall, in Flatiron's data are receiving PD-1 and PD-L1 drugs. These agents are:

- Bristol-Myers Squibb's Opdivo (nivolumab), which was approved in October 2015 as second-line therapy for patients with metastatic squamous NSCLC, or after platinum-based chemotherapy, and, based on data from another clinical trial, was later approved for non-squamous NSCLC as well, and
- Merck's Keytruda (pembrolizumab), which received accelerated approval in October 2016 as first-line therapy for patients with metastatic NSCLC whose tumors express PD-L1, as determined by a biomarker test. On May 10, Keytruda, in combination with pemetrexed (Alimta) and carboplatin (pem/carbo), a commonly used chemotherapy regimen, was approved by FDA under accelerated approval regulations for the first-line treatment of metastatic nonsquamous NSCLC, irrespective of PD-L1 expression. Continued approval for this indication will be contingent upon verification and description of clinical benefit in the confirmatory trials as first line therapy in adenocarcinoma histology of NSCLC.

Flatiron's findings mark a fundamental shift in how cancer researchers understand and interpret clinical data: in real-time, without the need for lengthy retrospective studies, and without exhaustive manual curation and aggregation of data from health records.

"I found these figures to be both exciting and terrifying," Cary Gross, professor of medicine and of epidemiology at Yale School of Medicine, said to The Cancer Letter. "Because, on the one hand, it's great that doctors are closely attentive to scientific progress and are rapidly responding to new evidence—providing their patients with prompt access to exciting new therapeutic options.

"But it's also terrifying, because, at the time of FDA approval, in many cases, we only have a very scant amount of data concerning whether a drug will be effective in the real world," said Gross, author of a study about disparities in access to PD-1 and PD-L1 agents. He will be presenting the initial results of the study, which is based on Flatiron's data, at the 2017 annual meeting of the American Society of Clinical Oncology in Chicago. "Now that we know standard of cancer care can change so rapidly, the pressure is really on clinical community and policymakers to ensure that we are rapidly and rigorously assessing the impact of these new agents outside the trial setting."

A conversation with Gross appears on page 11.

Real-world evidence, Flatiron illustrates, can now be collected instantaneously. With advances in data science, researchers can track the uptake of drugs in each therapeutic setting and see which agents are being used off-label. Down the road, this information can be used in longitudinal studies focused on effectiveness, toxicity, and other patient outcomes.

"This is truly a revolution," Maria Koehler, vice president of oncology strategy, innovations, and collaborations at Pfizer Oncology, said to The Cancer Letter. "Because it's something that, for sure, was not possible even a few years ago, when we did not have not only electronic health records, of which usage picked up very fast, but we did not have the technology to understand how to use the rich data available in the electronic health records."

The push to expand the role of real-world evidence in drug development has the potential to provide justification for FDA approval.

Of course, effectiveness in the real world is not the same as efficacy in a clinical trial. "I think this data should be looked at," said Shakun Malik, head of thoracic oncology therapeutics at the NCI Cancer Therapy Evaluation Program. "For instance, you may or may not see certain toxicities in a clinical trial, because you have this best-case scenario of a patient whose performance status is zero, liver, kidneys, and bone marrow etc. functions are within normal limit.

"I'm glad that FDA is looking at the data. That should give us more information on how well real-world patients can tolerate these therapies without developing intolerable toxicities."

On June 1, CTEP and Flatiron announced a collaboration to explore how real-world evidence derived from de-identified patient data captured at the point of care can be used for clinical trial design and prospective research studies. The initiative will first focus on real-world evidence derived from Flatiron's melanoma and non-small cell lung cancer datasets.

The goal will be to improve study planning, inform sample size calculations, ease study implementation, improve understanding of current trends in standards of care, and address specific study planning questions.

Flatiron's NSCLC data come at a time when informatics companies are racing to collaborate with FDA—and establish bragging rights—to fulfill a mandate in the 21st Century Cures Act: combining real-world evidence and regulatory science. The bill requires the agency to establish, within two years from December 13, 2017, a draft framework for implementation of the program.

"The FDA currently is working to implement the 21st Century Cures Act, including provisions around utilizing RWE [real world evidence], specifically establishing a program to evaluate the potential of RWE to support the approval of a new indication or to help support or satisfy post-approval requirements and issue guidance on this topic," agency officials said to The Cancer Letter. "To accomplish this will require an understanding of what questions to ask, including how such data can be generated and appropriately used in product evaluation, what the challenges are to appropriate generation and use of these data, and how to address such challenge.

"The FDA will publish draft guidance on how RWE can contribute to the assessment of safety and effectiveness in regulatory submissions, for example, in the approval of new supplemental indications and for the fulfillment of post-marketing commitments and requirements."

Califf: The Cures definition of RWE is "an annoyance"

The real-world evidence provision in the Cures Act caused significant consternation in 2016. Public health advocacy groups opposed the incorporation of real-world evidence into FDA's regulatory toolkit, calling it an erosion of FDA's standards and patient-safety protections.

That erosion will not happen, then FDA Commissioner Robert Califf pledged.

"The language [in the bill] just didn't quite come out right," Califf said to The Cancer Letter. "It's just an annoyance, because it misleads people as to what we're really trying to get accomplished."

In the Cures Act, real-world evidence is defined as "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials."

Congress made two mistakes in the wide-ranging health care reform bill, Califf said: the inclusion of an limited definition of real-world evidence—which the agency clarified in a blog post—and the omission of language that would have ensured funding for the Oncology Center of Excellence (The Cancer Letter, May 12).

"It's kind of amazing, a bill that complicated, those are the only two things that were problematic," Califf said. "By the time we realized what was going on, it was too late. They wrote 'essentially anything but randomized trials,' when they should've said, 'real-world evidence includes randomization in the real world.'

"We're not trying to replace randomized trials, we're trying to make randomized trials more efficient by using digital data that's already there, and then supplementing randomized trials. There are other parts of the same paragraph that sort of make it okay, but it would be good to clarify in the bill."

FDA is building a network of informatics partners to better understand the opportunities and challenges associated with the use of real-world data from electronic health records, said Sean Khozin, a senior medical officer at the FDA Office of Hematology and Oncology Products and co-founder and project lead for Information Exchange and Data Transformation, also known as INFORMED.

"The Oncology Center of Excellence is working on a host of regulatory science research initiatives focused on enhancing our understanding of the patient's experience using real-world data," Khozin said to The Cancer Letter. "In doing so, we are actively engaged with academia, professional organizations such as ASCO (and their CancerLinQ initiative), other federal agencies such as the NCI and the VA, and innovators in the private sector to develop new approaches to capturing therapeutic-related outcomes and the longitudinal experience of patients with their disease.

"Through efforts such as the INFORMED initiative, the OCE is exploring the utility of real-world data beyond conventional electronic health records, investigating sources such as patient-generated data from sensors and crowd-sourced platforms."

Khozin will be presenting the initial findings from FDA's collaboration with Flatiron at the ASCO annual meeting June 3.

Of FDA's research partners in this effort, Flatiron appears to be among the first to produce concrete data that will help the agency understand how real-world evidence can be generated, and how it can be used to develop a regulatory framework for evaluating the safety and effectiveness of drugs.

"By examining Flatiron's datasets, in addition to other ongoing efforts, we have identified critical concepts related to assurance of data quality in electronic health records and have initiated discussions with the FDA's Office of Scientific Investigations on developing a framework for incorporating real world data into regulatory decision making for oncology products," Khozin said. "We shared our experience alongside our OSI colleagues at the recent AACR annual meeting as part of a session on real-world evidence."

A new way of tracking uptake and outcomes

Amy Abernethy, chief medical officer, chief scientific officer, and senior vice president of oncology at Flatiron, said the uptake of PD-1 therapies in NSCLC is exponential in part because the disease has such poor outcomes.

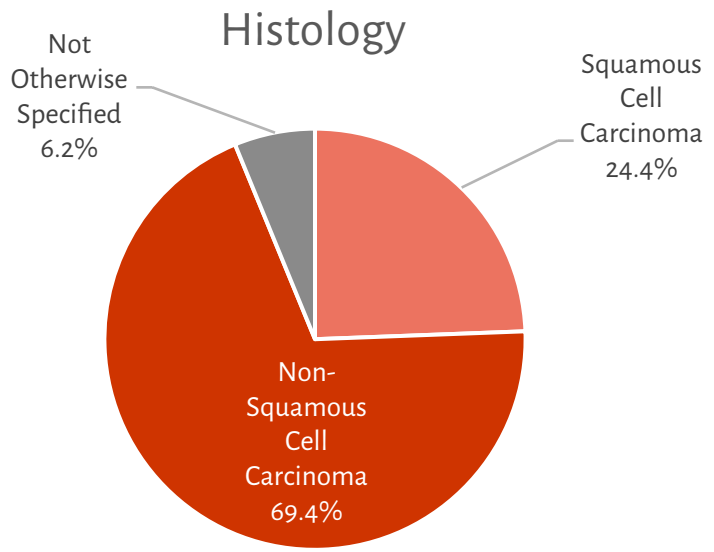
"I think part of the reason it looks this dramatic is because treatment options for lung cancer have been dismal for so long, the idea of having something that might work conceptually spreads like wildfire," Abernethy said to The Cancer Letter. "That's number one. You see unprecedented uptake of treatments in settings of unmet medical need, like this."

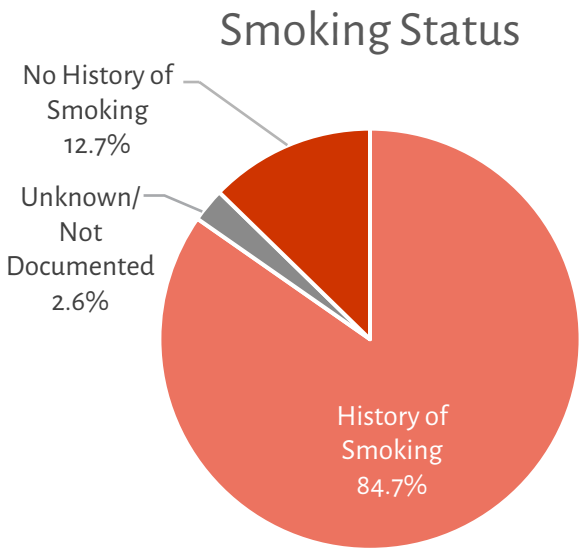
To consolidate data from nearly 35,000 patients, Flatiron relies on its electronic health record system—OncoEMR, for instance—and other software solutions that the company provides to community and academic medical centers. According to Flatiron, the data are de-identified and patient privacy is protected.

"At Flatiron, we have a system we call 'technology-enabled abstraction' that enables the extraction of the critical data needed to answer these questions," Abernethy said. "In order for real-world evidence on oncology to be useful, we have to deal with the complexity of getting to all of these important data points, which currently live, mostly, in unstructured documents in the electronic health record.

"In order to do meaningful work within the context of real-world evidence, you need many, many patients from lots of different settings, which means that you've got to be able to combine datasets, and basically pool a lot of information. And you've got to be able to do it in a way that's consistent."

COHORT DEMOGRAPHICS AS OF APRIL 30, 2017 – Source: Flatiron Health
Patients in Cohort: 34,239 (Community: 30,864 | Academic: 3,375)





This level of uptake in the NSCLC population is consistent with clinical observations over the past few years, said NCI's Malik.

"I'm not surprised. It is a standard of care," Malik said. "Why are more patients getting it? These PD-L1 inhibitor drugs are approved by the FDA based on data showing clinical benefit, including improved survival in some settings. More data is emerging that you don't need to have a PD-L1 expression of more than 50 percent when used in combination with chemotherapies. Anyone can receive this irrespective of their expression, either in combination as first line or in second line if they have not yet received in first line."

It's not publicly known how patient outcomes are affected by this shift in the standard of care, as observed in this dataset.

"It's something I can't disclose to you yet. I will be able to very soon," Abernethy said. "With our FDA collaboration, the first population of data for patients, basically, was a year follow up, because you need to follow them for some period of time. We delivered the first data set in March of 2016 and the one-year follow up happened last month. Right now, we're actually putting together the data set for the FDA that's got the survival information."

Currently, the five-year survival rates for immunotherapy vs. non-immunotherapy treatment has not been pooled together based on the data available from multiple trials compared to historical control, Malik said.

"Three or four years ago, the survival for lung cancer was about 14 percent. Now, it is hitting up to 17 and 18 percent," Malik said. "But I wouldn't chalk all of that up to the immunotherapies, because we had a number of other drugs that have come into the space. For example, we now have ALK inhibitor drugs that have improved outcomes in patients with ALK mutations and EGFR inhibitor drugs that have improved outcomes.

"But what will be the impact of immunotherapies is still evolving as newer combinations are being tested in ongoing clinical trials."

The Flatiron data also provides evidence of substantial off-label use of immunotherapy agents. For instance, PD-1 agents were administered in the first-line setting as early as May 2015—and going up to about 13 percent of all therapies by September 2016—before Keytruda's approval for first-line treatment of NSCLC in October 2016.

"The term off-label often comes with a connotation of 'bad medicine.' But what the data show us is that off-label prescribing reflects oncologists' decision-making when practicing in the gray zones of medicine," Abernethy said. "For example, 'What do you do when you treat the patient with platinum doublets in the 3-B setting?' In this case, maybe off-label PD-1 inhibitor is the best treatment for first-line metastatic care.

"Some of what you see here also is oncologists starting to practice first line management before the approval happened but based on what they knew from the evolving literature."

Tracking off-label use with real-world evidence would give FDA the ability to study potential new indications for drugs, said Jeff Allen, president and CEO of Friends of Cancer Research.

"It's important to define what the different potential uses for real-world evi-

dence are," Allen said to The Cancer Letter. "I think most frequently, at least in recent history, it's been used more for active safety monitoring. And that's important, but that's probably a different level of evidence than will be required to determine the use of, or identify different biomarkers like the mutational frequency in the case of PD-1s, or looking at dose modifications, or potential new subsets of patients.

"I think what we've seen, and where oncology is an interesting case study, is with the frequency of off-label use, many products are being used for indications that aren't necessarily in the drug label," Allen said. "So, it is worth considering how to identify those additional currently off-labeled uses that are supported by high quality evidence and demonstrate a positive health outcomes that could be shifted into the label to ensure that physicians have access to that as a tool.

"The FDA is the agency that we trust to make these decisions based on pre-market evidence. They could have a greater role in adjudicating between high quality post-market evidence versus exploratory aggregated data. I think that as more data sources become available, real-world evidence may become a little bit more difficult for the individual physician to sort out, even in terms of things that have been published. Readily determining the quality of the evidence that's supporting some of the conclusions that are made in some of these real-world studies may be a challenge. The FDA could play a role over time in identifying uses supported by substantial evidence, particularly for older drugs where applications for some supplemental use weren't pursued."

Rigorous, new research methods will need to be developed, Yale's Gross said.

"We've been genuflecting at the altar of the randomized trial for many years," Gross said. "But if we are going to make the leap into incorporating real-world data into the decision-making process, we really need to figure out how to analyze real-world observational datasets in a rigorous way.

"But my concern is that if we're not using state-of-the-art techniques to analyze it—and if we're not making the data available to the scientific community at large so they can reanalyze it using different techniques—we're going to be drawing improper or inappropriate conclusions."

The immunotherapy surge will start to settle as oncologists develop a better understanding of which patient groups should or should not receive these drugs, Abernethy said.

"I think our understanding of PD-1, specifically PD-L1 biomarker testing and other biomarkers that are starting to be understood better, is going to refine that," she said. "My expectation is probably that immuno-oncology agents will hit their heyday. Then, we will slowly start to refine. I anticipate what you'll start to see is PD-1 inhibitors being more thoughtfully placed in the toolbox, then pulled out of the toolbox when needed.

"I also think that this is just the beginning of the story. We're likely going to see oncology agents combined with other treatments. We're going to start to see immuno-oncology agents combined with other immuno-oncology agents. We're going to start to have a better understanding of when to combine, for example, immuno-oncology agents and surgery or radiation.

"We're just now starting to get a sampling of that. The real-world evidence piece that starts to play into this is going to accelerate our ability to figure out all those permutations."

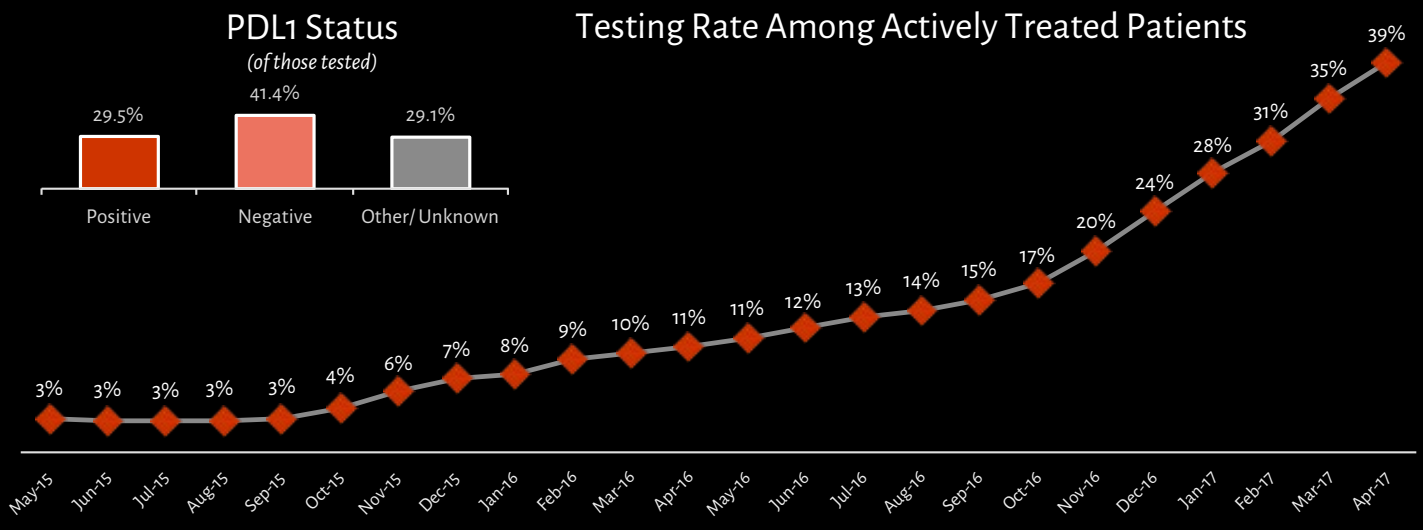
FDA will be working with the National Academies of Sciences, Engineering, and Medicine on a workshop series to examine the impact of the evolving use of real-world evidence on medical product development.

"As part of the FDA's continued focus on utilizing emerging regulatory science tools, the workshops will be on the generation and utilization of RWE to evaluate efficacy, effectiveness, tolerability, and safety for both review of new indications and post-approval studies," agency officials said.

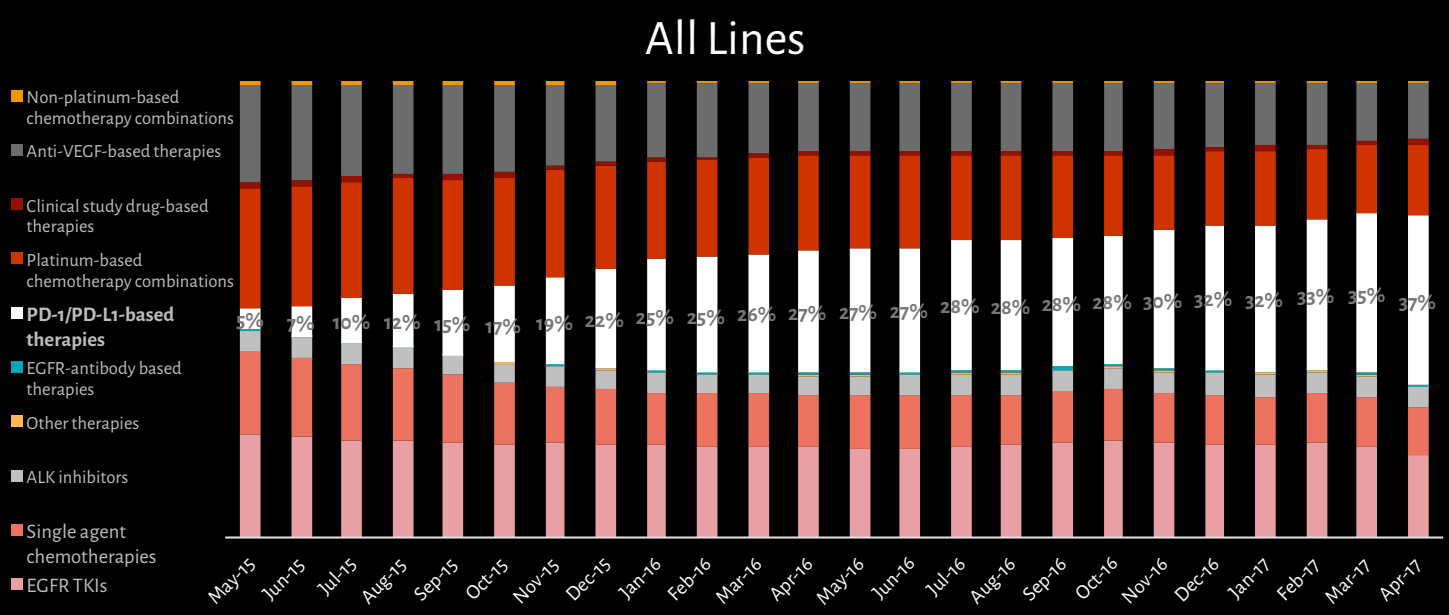
Officials said the agency is engaged with other stakeholders to explore issues presented by real-world evidence. Examples include:

- Duke University Margolis Center for Health Policy expert workshop: Incorporating Evidence from Clinical Experience in Regulatory Decision-Making: A Pragmatic Approach to Randomization in the Clinical Setting
- Duke-Margolis public meeting: Enhancing the Application of Real-World Evidence in Regulatory Decision-Making
- Clinical Trials Transformation Initiative Project: Registry Trials
- Clinical Trials Transformation Initiative Project: Mobile Clinical Trials
- FDA-Catalyst Project: Implementation of a Randomized Controlled Trial to Improve Treatment with Oral Anticoagulants in Patients with Atrial Fibrillation (IMPACT-AFib)
- FDA-Catalyst Project: Collection of Patient-Provided Information through a Mobile Device Application for Use in Comparative Effectiveness and Drug Safety Research
- Fitness-for-Use of Electronic Health Records as Source Data for Clinical Research

PDL1 BIOMARKER TEST OVERVIEW AS OF APRIL 30, 2017



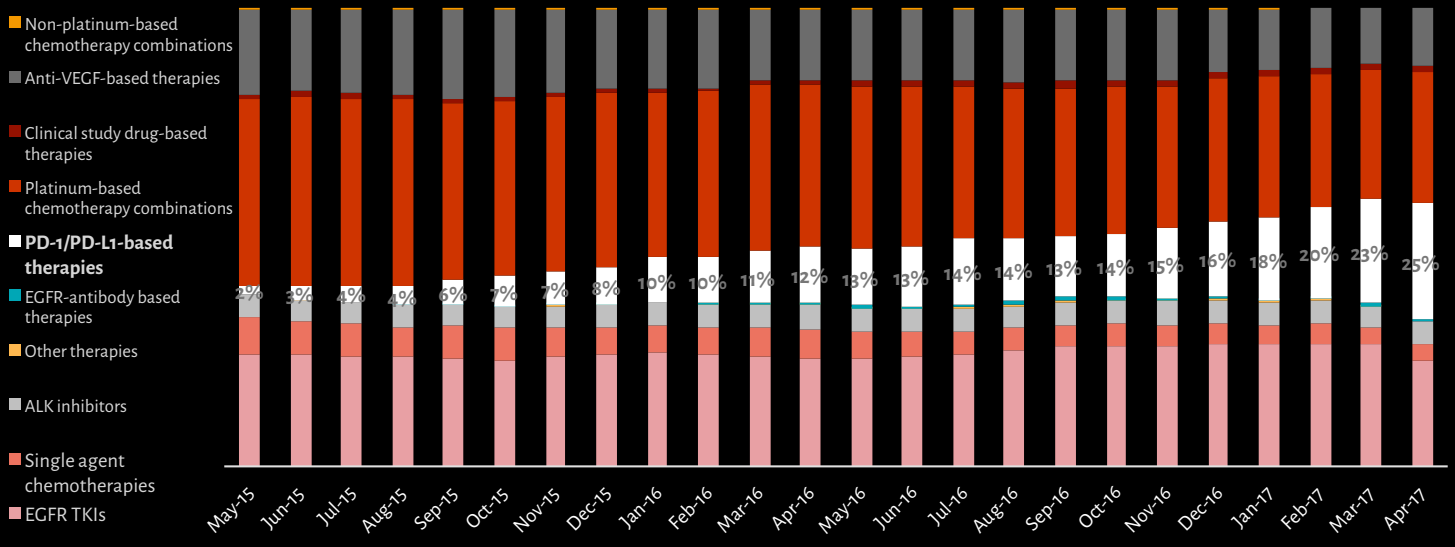
PATIENT SHARE BY THERAPY CLASS--PD1/PDL1



Source: Flatiron Health

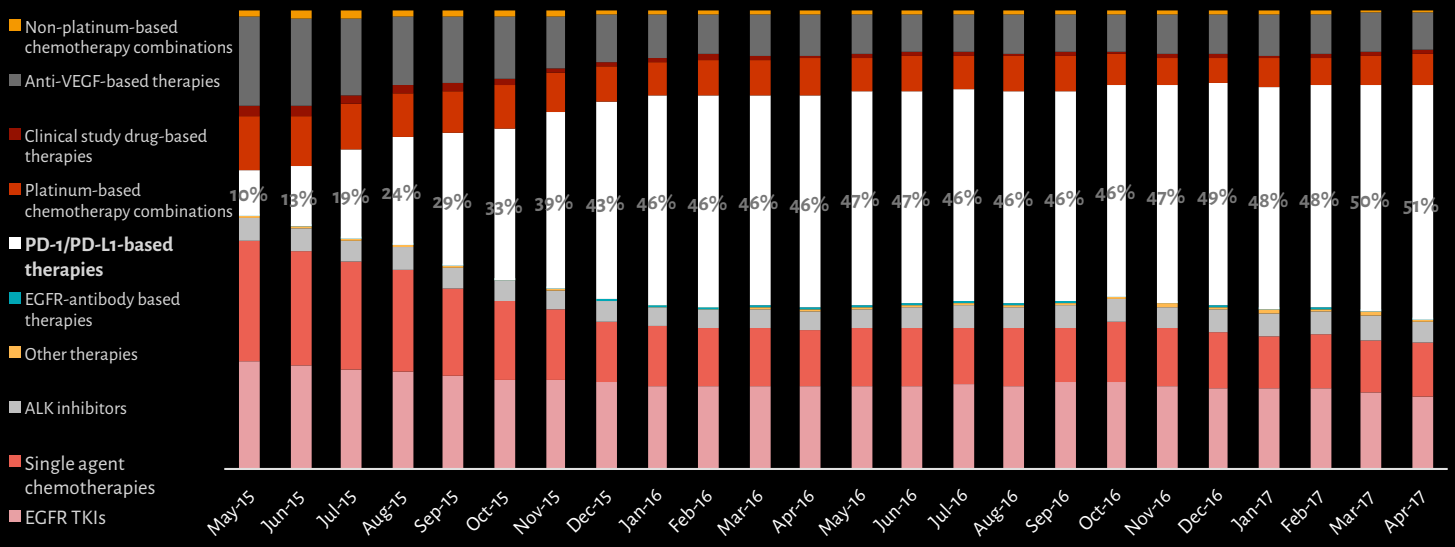
PATIENT SHARE BY THERAPY CLASS--PD1/PDL1

1st Line



PATIENT SHARE BY THERAPY CLASS--PD1/PDL1

2nd or 3rd Line+



Source: Flatiron Health

Q & A

Gross spoke with Matthew Ong, a reporter with The Cancer Letter.

CONVERSATION WITH THE CANCER LETTER

Cary Gross: We need to learn to analyze real-world evidence rigorously

Cary Gross
Professor of medicine and of epidemiology, Yale School of Medicine

> If we are going to make the leap into incorporating real-world data into the decision-making process, we really need to figure out how to analyze real-world observational datasets in a rigorous way.

Cary Gross, professor of medicine and of epidemiology at Yale School of Medicine, has been working with a dataset of 35,000 non-small cell lung cancer patients, looking for signs of disparities in access to PD-1 checkpoint inhibitors.

Working with data gathered by Flatiron Health, Gross has also been pondering the role real-world evidence can legitimately play in the development and approval of cancer drugs.

The Flatiron dataset tracks the rapid uptake of immunotherapy agents over two years—illustrating, in real-time, more than a sevenfold increase from May 2015 through April 2017.

"Now that we know standard of cancer care can change so rapidly, the pressure is really on clinical community and policymakers to ensure that we are rapidly and rigorously assessing the impact of these new agents outside the trial setting," Gross said to The Cancer Letter. He will be presenting the initial results of the study at the 2017 annual meeting of the American Society of Clinical Oncology in Chicago.

"My concern is that if we're not using state-of-the-art techniques to analyze it—and if we're not making the data available to the scientific community at large so they can reanalyze it using different techniques, we're going to be drawing improper or inappropriate conclusions.

How is Flatiron's data on PD-1 important for changing the way we understand and interpret drug uptake and patient outcomes?

Cary Gross: For a long time, we were told that it takes 17 years for randomized trial data to have an impact on clinical practice. It was dogma—"docs don't respond to evidence."

What got me excited about these data also is that it showed that within months of FDA approval of these new immunotherapy agents, there was a dramatic change in clinical practice. It's really striking because this stands in stark contrast to our prior understanding of how clinicians respond to new evidence.

But I found these figures in the accompanying article to be both exciting and terrifying. Because on the one hand it's great that doctors are closely attentive to scientific progress and are rapidly responding to new evidence—providing their patients with prompt access to exciting new therapeutic options.

But it's also terrifying, because, at the time of FDA approval, in many cases, we only have a very scant amount of data concerning whether a drug will be effective in the real world. Now that we know standard of cancer care can change so rapidly, the pressure is really on clinical community and policymakers to ensure that we are rapidly and rigorously assessing the impact of these new agents outside the trial setting.

Which part of this data really translates into how FDA thinks about creating a new regulatory framework for including real-world evidence in review of oncology products?

CG: As "Big Data" are being compiled, packaged, and analyzed, its critical to understand that the "real-world evidence" movement is still a work in progress. The FDA is charged with figuring out how to incorporate RWE [real-world evidence] into the evaluation process, and that's a good thing. RWE can dramatically improve our ability to generate meaningful evidence—as long as it's done thoughtfully and rigorously. For instance, these observational real-world data can completely transform the way we monitor drug safety.

Unlike earlier days in which we were limited by small samples, lengthy lag times (to do things like perform chart reviews), or relied on a passive reporting events by various stakeholders, we now have timely, comprehensive data that can help to identify safety issues promptly. Based on the data we are seeing from the adoption of these immunotherapy agents, the revolutionary aspect is that we're going to be able to glean information about potential risks within months after something comes onto the market.

But the key is, you have to do it right. That is, if there is an early signal of a safety issue, what are we going to do about it? How transparent will our data be? Will safety data be available to patients and providers? How or when will efficacy or safety data be updated? There are many important questions, and our approach to addressing them has the potential to substantively impact patient outcomes.

A second issue is the development of research methods. If you think about the history of the "pivotal trial," the majority of FDA regulatory policies are built around the altar of the randomized clinical trial. We've been genuflecting at the altar of the randomized trial for many years.

But if we are going to make the leap into incorporating real-world data into the decision-making process, we really need to figure out how to analyze real-world observational datasets in a rigorous way.

But my concern is that if we're not using state-of-the-art techniques to analyze it—and if we're not making the data available to the scientific

community at large so they can reanalyze it using different techniques, we're going to be drawing improper or inappropriate conclusions.

These data also show off-label use. Can this type of tracking be useful for assessing effectiveness? For instance, looking for positive outcomes of specific therapies, and then using that data for approving new indications?

CG: Yes, these data are absolutely for helping to understand the patterns and outcomes of off-label use. But to build on what you're saying, these real-world data can actually help to identify pertinent research questions and inform study designs. Here's the story. Say you were to find, after a drug is approved for second-line therapy of a metastatic disease, that its rapidly being adopted by clinicians for use in a first-line setting. That would be a strong indicator that we'd better find out if it works in that setting, as the docs are already off and using it.

So the point is, if we are able to track how are drugs being used in the real world, that can tell the policymakers that, here, these are the clinical scenarios that we need to be studying, and these clinical questions need to arise not from the pharmaceutical company's interests in getting FDA additional approvals. They need to arise from clinical questions that are being asked by patients and by providers.

Let's turn the tables. What do you think is missing from FDA's approval toolkit? Do you consider it sufficient for assessing real-world situations?

CG: That's a good question. I'm very concerned about the rush to approve drugs quickly, based on surrogate endpoints and short-term follow up without adequate subsequent studies. So I think one of the main things that's missing is a concrete plan to ensure appropriate long-term assessment of outcome. I think one can make an argument for a disease such as cancer—which is life-threatening—that we really need to get new drugs onto the market quickly, so that people can have access to them.

But that argument only resonates if we're going to continue to study the drugs after they're being used in the real world to see if they truly are effective. This is the concept underlying what is known as a "lifecycle approach."

But I'm worried that the "lifecycle" has a bit of a flat tire, so to speak. That is, the quality of evidence that is being generated after FDA approval is not always adequate.

In some instances, even the studies that are explicitly required or requested by the FDA are not conducted and reported. In other instances, drugs that approved based on surrogate endpoints don't undergo follow-up studies that assess hard clinical endpoints.

As a result, the FDA approval process is at risk of remaining focused on a single point in time with a dichotomous thumbs-up or thumbs-down. But what we really need is having an iterative, longitudinal approach to assessing the benefits and risks of this new therapy and incorporating new evidence into our approving and continuing the approval of drugs.

And one other idea—which is already being piloted—is integrating payers so they're collaborating with the FDA, and providing input into the approval process or the study design process for new agents. This "dual review" process is already being used by the FDA and CMS for some devices. So why not build upon this idea? With many of these drugs costing exorbitant amounts of money, it seems silly to have the FDA have one standard of approval and then for the payers to then have a different standard. Why not collaborate up front before the large pivotal trials are begun?

And you think the aggregation of real world evidence would sort of be that supplementary no-man's land that can be used to breach these gaps, say, between efficacy and effectiveness?

CG: Well, we need both study designs. I think, when feasible, well-controlled, well-designed randomized trials are the state-of-the-art, we can and should push for more of those, both before and after a drug is approved.

However, randomized trials aren't always feasible. Sometimes they're prohibitively expensive, if the effect size is small. Sometimes people won't agree to be randomized. So the point is, we're not always going to be able to do randomized trials.

But more importantly, RCTs often exclude many patients who are older, or have functional impairment or comorbidity. They are seeking to tell us whether a drug can work. We need the observational studies—using real world data—to tell us whether it does work. So it's important to not consider the observational studies as second-rate, so to speak.

This is hardly a novel or new one at this point, but one of my major concerns is that drugs that seem to be helpful based on RCTs conducted in relatively young, healthy patients could potentially end doing more harm than good.

We go out and use them on older patients with multi-morbidities.

How would you want the role of real-world evidence to evolve over the next few years?

CG: I would like to see a few things. I would like to see continued evolution of the cancer data ecosystem. We need to make sure we're not only collecting and cleaning clinical data. We need to make sure that the data are widely accessible to the scientific community.

Just like there is a movement towards ensuring that patient-level clinical trial data are shared, we need to ensure that these large proprietary databases that are being constructed are being used to help patients.

These real-world data represent a treasure-trove of information. We need to ensure they can be analyzed by all members of the scientific community—because after all—who really owns the data?

I'd posit that at the end of the day, the data belong to the thousands or even millions of patients who are included in the databases. We owe it to them to ensure that we are wringing as much knowledge out of those data as possible. And that's not possible if the data are kept away from the light.

Secondly, I would like to see the data being used to identify research priorities. Like I was saying, looking at patterns of care. So we can understand where are there signals of potential harm or where are the major off-label uses happening? Use real-world data to identify places that could guide research question for the future.

And third, I'd love to see us constantly evaluating new drugs in all different scenarios. So basically, in the long run it would be wonderful if the adult cancer community were a little bit closer to the pediatric cancer community. And what I mean by that is there's some amazing data regarding the enrollment of kids with cancer in clinical trials, and the data suggests as many as 70 percent of kids with cancer are enrolled in a research study at some point during their care.

For adults with cancer, it's more like 5 percent. Now there are certainly reasons for that discrepancy. There are fewer kids with cancer, they're concentrated at major centers. But that being said, it also speaks to this philosophy of "...we should always be testing something, always be learning something."

And I would love to see us, in this era of Big Data, develop new approaches to make research easier, less expensive, and more relevant. Bridge the lab and the clinic more seamlessly. Let's follow the lead of the pediatric cancer doctors who have made such terrific progress, because they're always, always trying to learn something, embarking on a constant quest, rather than a series of one-off studies.

Could you describe the study that you are presenting at ASCO, and how that is related?

CG: Sure. Led by our National Clinician Scholars Program investigator Dr. Jeremy O'Connor, we studied disparities in access to the anti-PD-1 agents to see if there was an equitable access to the new drugs. While we found that there were no racial disparities among patients being treated for lung or renal cancers, we did find some gender-based disparities in access. And that's what we're going to present.

If you think about it, that's another value of this type of Big Data, of data that are rapidly available and collected across a multitude of settings. Think about it this way: if there's a new effective treatment for cancer, wouldn't it be great to be able to assess really quickly whether there are equity gaps? This allows you to potentially address those much sooner. It's all about constantly looking for ways to understand and improve the system.

> “RCTs often exclude many patients who are older, or have functional impairment or comorbidity. They are seeking to tell us whether a drug can work. We need the observational studies—using real world data—to tell us whether it does work. So it's important to not consider the observational studies as second-rate, so to speak.”

Q & A

Lichter, chair of the consortium, spoke with Paul Goldberg, editor and publisher of The Cancer Letter.

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CONVERSATION WITH THE CANCER LETTER

A nascent group of academics plans to conduct randomized trials to determine value of care

> We can add to the value of cancer therapy, not by passing a new law or needing importation of drugs from overseas, or changing the entire way the drug distribution system works in this country.

Allen S. Lichter
Chairman, Value in Cancer Care Consortium

A group of cancer researchers is trying to conducting randomized trials aimed at maximizing the value of oncology treatment regimens.

The group, called the Value in Cancer Care Consortium, is headed by Allen Lichter, former CEO of the American Society of Clinical Oncology.

The new consortium plans to ask research questions that fall into three categories:

- Can a lower dose or a different administration schedule produce similar results as the dose on the FDA label?
- Can a less expensive drug be used insetead of a more expensive drug?
- Should patients be on drugs continuously as long as they're experiencing a response?

"We have the resources to organize our board and the scientific committee to begin to engage sites and to sign sites up as study participants, to begin to write the first protocols and to get them IRB-approved, and to build a small staff," Lichter said. "And so that we are fully prepared now to move forward with the organization. What we do not have in hand right now are the funds to actually do the studies. And we need to begin to share with the world that we are duly constituted and ready to do this type of work."

I understand you're focusing your attention on drug pricing. What will you be doing?

Allen Lichter: Well, that's actually not accurate.

I like to be corrected.

AL: I mean, drug pricing is an important issue. But the focus of this effort is not on drug pricing. The focus is on asking whether we can add value to cancer care by optimizing the dose and scheduling of current drugs, or at times substituting a less expensive drug for a more expensive drug, but getting the same outcome for our patients. So we're really focusing on value. The price issue is a real issue, but that is something that others are tackling.

Who is involved?

AL: The group was started with collaborations between Mark Ratain from the University of Chicago, Len Saltz from Memorial Sloan Kettering, and Larry Baker from the University of Michigan. I attended a meeting recently at ASCO, where this group presented the concept of an organization like this, and presented some of the early results from a pilot study about dosing the prostate cancer drug abiraterone. And I was attracted to their work. They asked me if I would chair the board of directors of this organization, knowing that I had some time on my hands in my retirement, and I said that I would.

I guess I'm backing into it, but what's the name of the organization?

AL: It's the Value in Cancer Care Consortium, and we call it Vi3C.

Oh, cool. What kind of questions will you be asking?

AL: I would say they fall into three main areas at the moment. One, again, is looking at the dose and scheduling of current cancer drugs. It is unlikely for most drugs that the first time through the FDA approval process, the dose and scheduling has been perfectly optimized.

Abiraterone is an interesting example of that, where the drug is better absorbed with food and yet the FDA trials and the label say the drug should be taken on an empty stomach.

So, it becomes fairly natural to begin to explore whether for certain cancer drugs, under the appropriate circumstances, where we could test whether a different way of administering, a different dose or a different schedule would optimize value, that is maintain the outcome while reducing the amount of drug the patient is required to take.

The second group of studies is the study of substitution: whether a less expensive drug can do the same job as a more expensive drug.

I think an interesting example of studies like that come from the field of ophthalmology, where in both macular degeneration and edema secondary to retinal vein occlusion, a dose of bevacizumab at $50 produces the same results as a dose of more expensive drugs in the range of $2,000.

And the ophthalmologists have carefully done these studies and shown convincingly that this less expensive agent can be substituted. And we think there are situations in oncology that deserve attention along those lines.

And finally, there are situations where we must ask questions about the duration of therapy.

For many drugs, we understand about starting them. We don't know that much about when to stop them.

Should patients be on drugs continuously as long as they're experienc-

ing a response? In some of the newer targeted therapies or immunotherapies, is the result achieved after a few months of therapy, and the therapy can be stopped or at least interrupted? So those are examples of the types of studies we will be paying attention to.

How will you select agents that you would test?

AL: I think the approach that we have taken is to form a scientific advisory committee. We were delighted when Ian Tannock [of Princess Margaret Cancer Centre] and Gabe Hortobagyi [of MD Anderson Cancer Center] said that they would co-chair this group.

They are meeting for the first time at ASCO to begin organizing, and we've asked them to take a look at the landscape to suggest a series of studies that they feel are both scientifically important and relate to this question of value.

We on the board will work with the scientific advisory committee to rank order these studies, and we'll start from the top and start to work our way through them. So, it's not clear yet, since the committee hasn't met, what they're going to recommend to us, but we're very anxious to hear their thoughts.

Are we talking about pilot studies, or are we talking about definitive studies? Are these going to be superiority trials or non-inferiority trials? Or are you trying to ask questions to intrigue prescribing physicians and maybe not even answer them definitively?

AL: Yes, well, that is one of the key questions. Obviously, there's a whole field in literature and science to non-inferiority studies, depending on how close you want your definition of non-inferiority to be.

The size of the trials can get impressively large. We probably do not have the resources to do studies of thousands of patients, and are going to be asking some important questions about how equivalent these two arms need to be, how tight must the error bar be around them if clinicians were going to say the two therapies are clinically identical enough to be substituted.

And the answers to those questions are not known right now. We have to begin to explore that.

And we think, Paul, that they're context-related as well. That is, the clinically relevant answer for one drug in one set of circumstances may be quite different than the clinically relevant answer for another set of drugs and another circumstance.

So, this is new space that we're going to be exploring as we design the statistical sections of these studies.

Is price going to be an end point?

AL: No. Although, obviously, if the duration of therapy is reduced, the total cost of the therapy begins to come down.

If a less expensive drug is substituted, the price begins to come down, or if a drug that is being given at a dose of 100 can be used at a dose of 50, the cost comes down. But that is really an offshoot, if you will, of what we're trying to do, in terms of showing that we can add to the value of cancer therapy, not by passing a new law or needing importation of drugs from overseas, or changing the entire way the drug distribution system works in this country.

We can have an immediate effect on the value of cancer care by just using drugs more wisely.

Well, there's this paper that you referred to in JAMA, the Avastin paper. I see that this was funded by [National Eye Institute]. Has NCI expressed interest in such studies?

AL: We have not spoken to the NCI. We will be talking to them.

And it would be wonderful if the NCI wanted to participate in this. I don't know whether they will or not. But I think the National Eye Institute has set a wonderful example of saying that some of these questions about drug equivalence and sparing patients and the healthcare system unnecessary costs are scientifically meaningful questions.

How will you get the results disseminated?

You know, the standard way of doing this, of course, is to present your findings both at meetings and in journals, the ASCO meeting being one of the prime examples of where we hope the results of our studies can be put forward.

We won't be able to go into physician offices and detail them about these studies. But we hope that much like the ophthalmologists have experienced, that as these results become more widely known, tactics patterns will change. They certainly have in ophthalmology.
And we hope that if our studies show that there's a higher value way of using the therapy, that clinicians will use it.

What about funding? Do you have any funding and who would be giving you money? Is it the foundations or is it the pharma companies? Would pharma companies give you money to check and test the value of their drugs and of their competitors' drugs?

AL: Well we were hoping The Cancer Letter would underwrite most of this ...

We will. We will be happy to direct at least $1,000 worth... No, actually, strike that. We can't, because then we won't be able to cover you.

AL: All right, let's start over.

No, let's keep it.

AL: So, we were pleased to have the opportunity to apply for a grant from the Arnold Foundation in Texas to provide funds to set up the infrastructure for the Vi3C organization and we were pleased to have that grant funded.

So, we have the resources to organize our board and the scientific committee to begin to engage sites and to sign sites up as study participants, to begin to write the first protocols and to get them IRB-approved, and to build a small staff.

And so that we are fully prepared now to move forward with the organization. What we do not have in hand right now are the funds to actually do the studies. And we need to begin to share with the world that we are duly constituted and ready to do this type of work.

If you look at this abiraterone study of 72 patients that was presented at the ASCO GU meeting earlier this year, equivalent results were seen with a 75 percent reduction in dose just by taking the drug with food versus fasting.

This is a drug that costs several thousand dollars a month and is well over a billion dollars in sales worldwide and potentially increasing over time. So, the potential increase in value is enormous for the investment of a relatively small amount of money in doing the study. So we hope that we can attract interested organizations to help us with the resources to get the studies actually done.

So, you're probably thinking insurers, right? And foundations.

AL: Well, you know, we would hope that, and have been in contact with the foundations of some of the major health insurance companies, and they've expressed some interest. But most major corporations in this country self-fund their health care costs.

We hope that individual organizations or business associations who are interested in health might be interested in this. And, of course, as evidenced by the Arnold Foundation, we hope that other foundations might be interested in this. If a prostate cancer foundation wanted us to do a more definitive study of a prostate cancer drug, or if a lung cancer organization was going to help us with a lung cancer study, we think these types of things would be wonderful.

What would the costs be of studies?

AL: You know, we haven't finalized that yet, but one could estimate that per case, the fully loaded cost of a study could be in the $10,000-$15,000 per patient range, to help support the infrastructure of the group, all the data collection and statistical analysis, the regulatory reporting and to reimburse the sites for their cost.

So, the ophthalmology study that was recently published was 350 patients, and we've been, at least in a very back of the envelope way, thinking about studies that going to be somewhere in the 300-400 patient range.

So, you're talking about, on the low end, a $3 million cost to do the study and maybe at the high end $6 million.

That's not a lot of money, as major clinical research goes, and the potential benefit from that modest investment could be 100 times what was put into it.

Yeah, system-wide but per funder it could be... actually it could still be worth it, if you're a GM.

AL: Yeah, I think that just on the front end, if you had an expensive drug and were doing a trial where half the patients received a much smaller dose, interestingly enough, they're savings during the cost of the trial, because the patients are not consuming and having to pay for as much drug.

Oh my, so that would actually be the reason for somebody to fund it.

AL: I think there are a lot of reasons for them to fund it.

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> We have been, along with everybody else, concerned about the ever-increasing cost of care and the financial toxicity that we find our patients facing. This is something that can produce results in a fairly rapid fashion.

But this is not a study where the control arm is X and the experimental arm is something that costs five times X. This is actually in many respects just the opposite.

I also point out that there's a tremendous importance for doing these studies for the practicing community itself. As we get into more and more the value based purchasing and payment systems, when we get into risk sharing and such, it is imperative upon practices to learn how to reduce costs in a fairly continuous fashion.

And studies like this that can show how you can treat patients at lower costs with the same or potentially even better results become not only beneficial for the patients, but beneficial for practices as they negotiate these new payment models.

This is something that just is starting to be recognized right now. This is connected to the issue of real world evidence? Do you even need to run prospective trials? Could you perhaps glean this information from datasets that are already in existence?

AL: We don't think so. Most physicians will use drugs very much along the lines of the labeled dose of the drug. Dose reductions and modifications are done depending on clinical symptoms.

But it is unlikely that, spontaneously, a large group of physicians would begin to start therapy for patients at a very different dose than the labeled dose. Somebody's gonna have to show the evidence. As a physician, I'd want to know that if I said to my patient, "We're gonna treat you with half the dose, but I have data to show that it's just as effective," I would need that.

If I were a patient, I'd want to know that I can safely take this lower dose and not sacrifice any of the benefits. So, I don't think this will come simply spontaneously from analyzing real world data.

So, nobody is collecting that; therefore you need to go forward prospectively.

AL: Well, CancerLinQ is an example of a database that is, in fact, collecting drug utilization, drug dose and outcome data and could make observations along these lines. But as I say, I don't think a natural experiment is occurring right now. We have to prime the pump with these types of studies.

Well, sounds like people should be flagging you down at ASCO and asking you how they can help.

AL: We would love to talk to people who are interested in seeing this work move forward. We think it's very important.

As I say, Paul, we have been, along with everybody else, concerned about the ever-increasing cost of care and the financial toxicity that we find our patients facing. And doing something about it has been difficult. There have been lots of policy discussions, but relatively little concrete action.

And this is something that can produce results in a fairly rapid fashion, and in a meaningful fashion, without having to do anything but the clinical science that oncologists have been engaged in for decades. And we're excited about the possibility.

Well, thank you very much.

MD Anderson posts four months of positive operating margins as deficit shrinks to $43.9 million

By Paul Goldberg

MD Anderson Cancer Center reported positive operating margins after posting losses over the first four months of the fiscal year.

Between September and December, the institution's losses totaled $169.4 million, but between January and April, operating revenues added up to $125.5 million.

This reduces the year-to-date deficit to $43.9 million.

"Thanks to everyone's hard work and commitment to our patients, we've had four straight months of positive operating margins," Steve Hahn, deputy president and chief operating officer, said to The Cancer Letter. "We are making great progress and feel as though we've turned the tide back toward financial sustainability. With continued momentum, we're cautiously optimistic that we'll achieve a positive margin for this fiscal year ending Aug. 31, 2017."

MD Anderson's monthly financials dipped into the red in March 2016, when the institution switched to the Epic system. Clinical productivity is often reduced during such switchovers as doctors take longer to enter data, but productivity usually recovers as they become more familiar with the system.

The trend was broken in January, when the operating margin jumped to $92.1 million.

This included a $63.4 million settlement from Medicare, which allowed the cancer center to claim a portion of its expenses for implementing the Epic system (The Cancer Letter, March 3).

MD Anderson officials said the second half of the fiscal year at the institution is traditionally stronger, and cautious optimism exists that a positive operating income for the fiscal year will be achieved.

The results of austerity measures—including staff cuts—were expected to kick in in May (The Cancer Letter, Jan. 6)

MD Anderson is in the process of recruiting a new president, following resignation of Ronald DePinho, who stepped down on March 8, acknowledging his shortcomings as an administrator (The Cancer Letter, March 9)

	Actual September 2016		Actuals October 2016		Actual November 2016		Actual December 2016		Actual January 2017		Actual February 2017		Actual March 2017		Actual April 2017	
Revenue																
Hospital Gross Patient Revenue	$ 527,053,725		$ 547,141,855		$ 553,162,416		$ 546,740,639		$ 592,978,574		$ 559,701,686		$ 616,230,799		$ 558,451,691	
Professional Fee Gross Patient Revenue	103,957,679		107,838,878		105,339,452		118,409,303		117,028,229		113,551,042		127,867,365		118,667,734	
Total Gross Patient Revenue	631,011,405		654,980,732		658,501,868		665,149,942		710,006,803		673,252,727		744,098,164		677,119,425	
Deductions from Gross Patient Revenue	343,906,711	54.5%	384,418,941	58.7%	371,839,317	56.5%	393,608,817	59.2%	318,551,507	44.9%	351,838,441	52.3%	400,122,225	53.8%	359,191,611	53.0%
Total Net Patient Revenue	287,104,694		270,561,791		286,662,552		271,541,125		391,455,296		321,414,286		343,975,940		317,927,813	
Other Operating Revenue	35,790,604		37,341,656		42,930,870		36,133,733		58,290,074		45,098,464		35,709,943		46,802,804	
Total Operating Revenue	**322,895,298**		**307,903,447**		**329,593,422**		**307,674,858**		**449,745,370**		**366,512,750**		**379,685,883**		**364,730,617**	
Operating Expense																
Personnel Expenses	210,045,936	65.1%	207,714,858	67.5%	209,302,995	63.5%	212,622,998	69.1%	211,643,280	47.1%	197,030,762	53.8%	207,742,417	54.7%	205,241,457	56.3%
Other Operating Expense	154,316,447		161,083,445		129,324,468		153,061,456		146,011,114		149,484,984		159,093,629		158,898,552	
Total Operating Expense	**364,362,383**		**368,798,302**		**338,627,463**		**365,684,454**		**357,654,394**		**346,515,746**		**366,836,046**		**364,140,009**	
Total Operating Income(Loss)	**(41,467,084)**		**(60,894,855)**		**(9,034,041)**		**(58,009,596)**		**92,090,976**		**19,997,004**		**12,849,837**		**590,608**	
Non-Operating Operating Revenue(Expense)																
State Appropriations	16,753,839		17,406,957		17,056,518		16,743,918		16,738,771		16,792,482		16,790,017		16,780,433	
Restricted and Designated Gift	4,590,378		8,120,731		9,611,699		25,856,727		15,941,995		12,480,479		5,050,357		4,748,971	
Investment Income	9,188,375		11,791,475		17,342,692		9,961,843		19,723,043		17,085,441		9,668,240		11,490,392	
Adjusted Income / (Loss)	**(10,934,493)**		**(23,575,693)**		**34,976,868**		**(5,447,108)**		**144,494,784**		**66,355,406**		**44,358,451**		**33,610,404**	
Change in Investment Value	362,736		12,919,239		(38,906,609)		(11,847,236)		7,002,222		46,860,902		40,870,753		15,945,367	
Net Income / (Loss)	**$ (10,571,757)**		**$ (10,656,454)**		**$ (3,929,741)**		**$ (17,294,344)**		**$ 151,497,006**		**$ 113,216,307**		**$ 85,229,204**		**$ 49,555,772**	

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MD Anderson settles trademark litigation with Pelotonia, Soon-Shiong

By Paul Goldberg

MD Anderson Cancer Center has settled two separate trademark suits protecting the Houston-based cancer center's Moonshot program.

> Dr. Soon-Shiong and his companies will use a different mark to avoid confusion and will abandon their applications to trademark Moonshot. As a result, MD Anderson is withdrawing its oppositions to such trademark applications.

One of the actions settled was filed against Pelotonia, a non-profit that coordinates a bike ride that raises money for The Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard Solove Research Institute. MD Anderson claimed in a lawsuit that Pelotonia's taglines "One Goal" and "One Goal: End Cancer" infringe the Houston cancer center's trademark "One goal. Stop cancer" (The Cancer Letter, April 14).

The second suit was filed against Patrick Soon-Shiong, a pharmaceuticals billionaire. Until recently, his companies used the MoonShots2020 trademark. Though the details of the settlements weren't discussed, they appear to be different. Pelotonia's website continues to use the "One Goal" trademark, which is printed on t-shirts and jerseys. Soon-Shiong's website no longer refers to moonshots.

Asked to comment on the Soon-Shiong litigation, MD Anderson officials issued a statement:

"The University of Texas MD Anderson Cancer Center has resolved its differences with Patrick Soon-Shiong, M.D., and his companies regarding the Moonshot and related trademarks. Dr. Soon-Shiong and his companies do not admit any fault or liability, and acknowledge MD Anderson has prior use and ownership of the Moonshot term in the fields of healthcare and charitable fundraising.

"Dr. Soon-Shiong and his companies will use a different mark to avoid confusion and will abandon their applications to trademark Moonshot. As a result, MD Anderson is withdrawing its oppositions to such trademark applications."

To announce resolution of their dispute, MD Anderson and Pelotonia said in a joint statement that they are "pleased to announce we reached an amicable agreement over the use of the 'One Goal,' 'One Goal End Cancer,' and 'One Goal Stop Cancer' trademarks. At our request, the court dismissed the lawsuit earlier this month. We look forward to continuing to work toward our shared goal of supporting cancer research."

IN BRIEF

CancerLinQ partners with FDA to study real-world use of newly approved cancer treatments

CancerLinQ LLC, an initiative of the American Society of Clinical Oncology, announced a long-term partnership with FDA that will rely on cancer patient information and big data analytics to examine the real-world use of emerging and newly approved cancer therapies.

Real-world data from will be used to grow the knowledge base about patterns of care across all cancer types and therapies, accelerate development of novel insights that might otherwise be challenging to obtain through standard research initiatives and data collection means.

Under the partnership, FDA and CancerLinQ will use CancerLinQ Discovery, a research and analytics platform that allows users to analyze real-world, aggregated, de-identified patient care data from oncology practices that participate in the CancerLinQ data-sharing program. The CancerLinQ network currently includes a growing number of patient records from nearly 90 oncology practices and institutions, making it among the largest and most robust sources of real-world evidence in oncology.

"This collaboration addresses one of oncology's central challenges – to quickly learn about the real-world impact of cancer therapies once a drug is approved," said Clifford Hudis, CEO of ASCO and chairman of the CancerLinQ board of governors. "Until now, our learning about new treatments was hindered by the limited number of physicians and patients involved in traditional research and slowed significantly when formal clinical trials ended. CancerLinQ Discovery addresses this gap and fulfills the need, picking up where trials leave off and opening up a new world of insights to guide the use of new therapies and improve the lives of everyday patients with cancer."

"This is an important collaboration in our regulatory science research portfolio that can contribute to the development of an empirically-derived framework for incorporation of real-world evidence into regulatory decision making," said Sean Khozin, director of the FDA's INFORMED initiative.

The initial FDA and CancerLinQ project, which focuses on treatments for advanced melanoma, aims to characterize the real world experience of these patients, inform the clinical use of currently approved therapies, and potentially inform future FDA regulatory review of targeted drugs and immunotherapies.

CancerLinQ and FDA investigators will explore a variety of issues related to the use of newly approved therapies, including the optimal sequence of treatments, the impact that other health problems have on treatment tolerability and cancer outcomes, and the experience with immunotherapy combinations versus single agents.

Previously, CancerLinQ announced partnerships with the American Academy of Physician Assistants, American Society of Radiation Oncology, Cancer Informatics for Cancer Centers, College of American Pathologists, Hematology/Oncology Pharmacy Association, National Comprehensive Cancer Network, Oncology Nursing Society, and Society of Gynecologic Oncology and AstraZeneca, which is the founding enterprise partner of CancerLinQ Discovery.

NCCN and CancerLinQ collaborating to provide evidence-based, decision-making resources to physicians

The National Comprehensive Cancer Network and ASCO's CancerLinQ LLC announced a collaboration to provide a link to the NCCN website for easy access to the NCCN Drugs & Biologics Compendium within CancerLinQ.

This resource will support CancerLinQ physicians and provides evidence-based guidance regarding the appropriate use of drugs and biologics in patients with cancer. With this collaboration, CancerLinQ subscribers will now have access to a link that will bring them directly to the NCCN Compendium, where they can subscribe, for a fee.

NCCN is able to make available its resources to the growing CancerLinQ network, which includes thousands of oncologists treating millions of patients from a variety of practice types and institutions across the United States. This collaboration represents one of the ways in which NCCN is empowering physicians to access NCCN resources through everyday health information technology workflow.

The NCCN Compendium contains recommendations for the appropriate use of drugs and biologics to support decision-making for patients with cancer. The recommendations are derived directly from relevant NCCN Clinical Practice Guidelines in Oncology, along with their clinical context, route of administration, recommended use, and NCCN category of evidence.

In addition to NCCN Guidelines-specific indication and use, NCCN adds relevant information, such as pharmacologic class, relevant classification codes, and FDA indication, to the searchable database. All information is reviewed by members of the relevant NCCN Guidelines panel before publication.

First analysis of AACR Project GENIE data is published in Cancer Discovery

The first analysis of nearly 19,000 de-identified genomic records from the American Association for Cancer Research international data-sharing initiative known as AACR Project Genomics Evidence Neoplasia Information Exchange was published in Cancer Discovery, an AACR journal.

AACR Project GENIE is a multi-phase, multi-year, international data-sharing project that was launched by the AACR in partnership with eight global academic leaders in clinical cancer genomics in November 2015.

In January 2017, the AACR Project GENIE consortium made public nearly 19,000 de-identified genomic records collected from patients who were treated at the eight international institutions participating in the first phase of the project.

The report includes examples of how the AACR Project GENIE genomic data can be used to facilitate clinical research, including:

- Analysis showing more than 30 percent of the samples had mutations that are clinically actionable, meaning that they are suggestive of a specific treatment that is either already approved by the FDA or is being tested in clinical trials.
- Analysis showing that the rate at which patients with samples in the AACR Project GENIE registry would match with arms of the NCI-MATCH trial reflected the actual accrual rates for the trial.
- Details of two studies underway linking certain genetic characteristics of metastatic breast cancer with clinical and pathological features of the tumors, as well as with patient outcomes.

"We are particularly excited by the clinical actionability analysis," said Charles Sawyers, chair of the Human Oncology and Pathogenesis Program at Memorial Sloan Kettering Cancer Center. "Prior studies looking at how often tumor genome sequencing identifies a clinically actionable mutation have yielded variable results, leading some to question its clinical utility. The huge number of samples in our study and the high rate of clinical actionability give us confidence that tumor genome sequencing can have an important role in clinical care."

The eight institutions who participated in AACR Project GENIE phase 1 are: Dana-Farber Cancer Institute; Gustave Roussy Cancer Campus; The Netherlands Cancer Institute; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; Memorial Sloan Kettering Cancer Center; Princess Margaret Cancer Centre; MD Anderson Cancer Center; and Vanderbilt-Ingram Cancer Center.

National Breast Cancer Coalition partners with DNA.Land to crowdsource large-scale breast cancer genomics database

The National Breast Cancer Coalition announced a new collaborative research project with DNA.Land, the nonprofit crowdsourcing website created by scientists at the New York Genome Center.

The project asks women and men who have participated in genealogy tests to answer questions about breast cancer, including their family history. These genomic data, along with answers from the breast cancer questionnaire will be used to develop a large-scale database that researchers can use to identify genetic variants that impact risk and recurrence of the disease that may help develop approaches to prevention, new treatments and therapies for the disease.

"NBCC has a history of supporting innovative approaches to ending breast cancer. Through collaboration with DNA.Land researchers, we will be able to leverage existing data and support sharing of this data to advance breast cancer research," said NBCC President Fran Visco. "We plan to tap into the millions of people who already have had their DNA sequenced through commercial companies to participate in this potentially life-saving study."

The new database will serve as an important tool for breast cancer researchers and has the potential to help develop approaches to prevention, new treatments and therapies for the disease. NBCC and DNA.Land scientists need participation from as many participants as possible who have, or have

had breast cancer or have a first degree relative with a history of breast cancer.

"An emerging lesson from a decade of studies is that large sample sizes are needed to obtain robust findings on complex traits," said Yaniv Erlich, core member and co-creator of DNA.Land at the NYGC and assistant professor of computer science at Columbia University. "If you have a genetic genealogy test from any of the direct-to-consumer companies like 23andMe, MyHeritage, AncestryDNA or Family Tree DNA, you can help with the study. It does not matter if you are a male or female. Just come to nbcc.dna.land and help us end breast cancer."

Fred & Pamela Buffett Cancer Center is dedicated in Omaha

The University of Nebraska Medical Center and its clinical partner, Nebraska Medicine, dedicated the Fred & Pamela Buffett Cancer Center. Former Vice President Joe Biden was the keynote speaker at the May 23 ribbon cutting and dedication.

The $323 million facility, which is the largest project on the medical center's Omaha campus, will open June 5. The facility was named in recognition of a gift from Pamela Buffett, through her foundation, the Rebecca Susan Buffett Foundation. Pamela's husband, Fred "Fritz" Buffett, died of kidney cancer in 1997.

The cancer center includes:

- The Suzanne and Walter Scott Cancer Research Tower, a 10-story, 98-laboratory research tower;
- The C.L. Werner Cancer Hospital, an eight-story, 108-bed inpatient treatment center; and
- A multidisciplinary outpatient center which includes clinics, radiation oncology, surgery, radiology, a 24/7 treatment center, lab and collaborative treatment/diagnostics.

"The Buffett Cancer Center brings together a powerhouse team of more than 200 oncologists and basic scientists to find better ways to diagnose, treat and prevent cancer," said Nebraska Medicine CEO Dan DeBehnke.

The cancer center is the most fully integrated cancer center in the world, said Ken Cowan, director of the Fred & Pamela Buffett Cancer Center. The 615,000-square-foot center puts clinical providers in close proximity with their research colleagues with the goal of more efficiently translating research to patient care.

The teams are specifically focused on breast cancer and other women's cancers, leukemia and lymphoma, lung cancer, pancreatic and gastrointestinal cancers, prostate cancer, head and neck cancer, and cancers diagnosed in childhood. Commissioned artwork at the center includes:

- The Chihuly Sanctuary (given by Suzanne and Walter Scott)--created by Dale Chihuly;
- The 82-foot-tall 'Search' tower – created by Jun Kaneko of Omaha; and
- Leslie's Healing Garden, an outdoor, all-season garden created with support from Marshall and Mona Faith. Patient amenities include the use of high-technology tablets so inpatients can see who their caregivers are, ask questions, see their labs and what tests are coming. The Fred & Pamela Buffett Cancer Center also received $90 million from the state of Nebraska, the city of Omaha and Douglas County.

University of Pittsburgh Cancer Institute becomes UPMC Hillman Cancer Center

Officials from UPMC and the University of Pittsburgh Cancer Institute announced that all 50-plus cancer center locations within the global network will be renamed UPMC Hillman Cancer Center.

Through the Hillman Foundation and the Henry L. Hillman Foundation, the late Henry and Elsie Hillman made contributions throughout the region, especially in science and medicine. Their vision of making Pittsburgh a world leader in cancer care became a reality in 2002 with a $10 million grant to establish the Hillman Cancer Center.

Markus Müschen named to The Norman and Sadie Lee Foundation Professorship in Pediatrics at COH

City of Hope's Markus Müschen, the founding chair of the Department of Systems Biology, received The Norman and Sadie Lee Foundation Professorship in Pediatrics.

Müschen is the first City of Hope physician-scientist to serve as the Lee professor in pediatrics. Müschen joined City of Hope in December 2016 to develop new approaches in treating pediatric leukemia for City of Hope, which has a strong track record in pioneering novel therapies for adult leukemia patients.

His goal is to wipe out acute lymphoblastic leukemia, the most common form of cancer in children, by tapping into the strengths of computational biology for the discovery of better drugs for children with ALL.

After medical training in Germany and France, Müschen completed his M.D. thesis in biochemistry (summa cum laude) in the laboratory of Helmut Sies and joined the laboratories of Ralf Küppers and Klaus Rajewsky in Cologne and Janet Rowley in Chicago for postdoctoral training.

In 2006, he was recruited to the United States to start his independent laboratory at the University of Southern California and Children's Hospital Los Angeles. In 2010, Müschen joined the faculty of the University of California, San Francisco and was promoted to full professor and program leader of the Hematological Malignancies Program at the UCSF Comprehensive Cancer Center.

He joined City of Hope as the inaugural chair of the Department of Systems Biology. Given his main research interest in diagnosis and prevention of childhood ALL relapse, Müschen was also appointed City of Hope's associate director of pediatric oncology.

His laboratory at City of Hope has also developed a multidiscipinary research program to study oncogenic signaling and clonal evolution in ALL, as well as a comprehensive research program that will predict relapse of ALL.

DRUGS & TARGETS

Zykadia gets first-line ALK-positive metastatic NSCLC indication

FDA approved the expanded use of Zykadia (ceritinib) to include the first-line treatment of patients with metastatic non-small cell lung cancer whose tumors are anaplastic lymphoma kinase-positive, as detected by an FDA-approved test.

The drug is sponsored by Novartis. Zykadia first received accelerated approval in 2014 for patients with ALK-positive metastatic NSCLC who progressed on or are intolerant to crizotinib. In January, FDA granted Zykadia Breakthrough Therapy designation for the first-line treatment of patients with ALK-positive metastatic NSCLC with metastases to the brain, and Priority Review for first-line ALK-positive metastatic NSCLC.

The first-line approval of Zykadia is based on results from an open-label, randomized, multicenter, global, phase III trial, ASCEND-4. ASCEND-4 is a phase III randomized, open-label, multicenter, global clinical trial to evaluate the safety and efficacy of Zykadia compared to standard chemotherapy, including maintenance, in adult patients with Stage IIIB or IV ALK-positive advanced NSCLC who received no prior therapy for their advanced disease.

The study demonstrated that patients treated with first-line Zykadia had a median progression-free survival of 16.6 months (95% confidence interval: 12.6, 27.2), compared to 8.1 months (95% CI: 5.8, 11.1) for patients treated with standard first-line pemetrexed-platinum chemotherapy with pemetrexed maintenance. Overall intracranial response rate in patients with measurable brain metastases was 57% (95% CI: 37, 76; n = 28) for patients treated with Zykadia, versus 22% (95% CI: 9, 42; n = 27) for patients treated with chemotherapy. The whole body overall response rate was 73% (95% CI: 66, 79; n = 187) in patients treated with Zykadia.

Patients received Zykadia orally at 750 mg/daily or standard pemetrexed-based platinum doublet chemotherapy (pemetrexed 500 mg/m2 plus cisplatin 75 mg/m2 or carboplatin AUC 5-6) for four cycles followed by pemetrexed maintenance. Of 376 patients,

189 (59 with brain metastases) were randomized to Zykadia and 187 (62 with brain metastases) to chemotherapy.

Approximately 70% of patients with measurable brain metastases at baseline did not have prior radiation therapy, the current standard of treatment for baseline brain metastases. Among patients randomized to the chemotherapy arm, 43% received Zykadia as their next treatment after platinum-based chemotherapy1. Patients treated with first-line Zykadia had a median PFS of 16.6 months (95% CI: 12.6, 27.2), compared to 8.1 months (95% CI: 5.8, 11.1) for patients treated with standard first-line pemetrexed-platinum chemotherapy with pemetrexed maintenance.

A 45% risk reduction in PFS was obtained in the Zykadia arm compared to the chemotherapy arm (hazard ratio [HR] = 0.55 [95% CI: 0.42, 0.73; one-sided p value< 0.0001]). Patients without brain metastases at screening receiving Zykadia experienced a median PFS of 26.3 months (95% CI: 15.4, 27.7), compared with 8.3 months (95% CI: 6.0, 13.7) among patients treated with chemotherapy (HR = 0.48 [95% CI: 0.33, 0.69]).

Among patients with brain metastases at screening, the median PFS was 10.7 months (95% CI: 8.1, 16.4) in the Zykadia group versus 6.7 months (95% CI: 4.1, 10.6) in the chemotherapy group (HR = 0.70 [95% CI: 0.44, 1.12]). The most common adverse reactions in ASCEND-4 (incidence ≥25% all grades) were diarrhea (85%), nausea (69%), vomiting (67%), fatigue (45%), abdominal pain (40%), decreased appetite (34%) and cough (25%).

Approximately 3-7% of all patients with NSCLC have an ALK gene rearrangement. An FDA-approved test at the time of diagnosis may help to determine the presence of this mutation and, thus, the most appropriate treatment option.

Advaxis and BMS announce collaboration focused on metastatic cervical cancer

Advaxis, Inc. and Bristol-Myers Squibb announced a clinical development collaboration to evaluate ADXS-DUAL, an investigational immunotherapy targeting HPV-associated cancers, and Bristol-Myers Squibb's PD-1 immune checkpoint inhibitor, Opdivo (nivolumab), as a potential combination treatment option for women with metastatic cervical cancer.

The study will evaluate the combination regimen in women with persistent, recurrent or metastatic (squamous or non-squamous cell) carcinoma of the cervix who have failed at least one prior line of systemic chemotherapy. Advaxis developed ADXS-DUAL by building on the learnings from the clinical development of axalimogene filolisbac and has incorporated additional HPV target antigens into its Listeria monocytogenes (Lm) bacterial vector.

"The additional HPV antigens have the potential to provide coverage against numerous HPV types in cervical cancer and other HPV-associated cancers," said Daniel O'Connor, president and CEO of Advaxis.

Johns Hopkins and Eisai extend drug collaboration

The Johns Hopkins University and Eisai Inc. have extended their drug discovery collaboration through a licensing agreement.

"Our initial goal of working with Eisai to identify compounds acting at specific targets and advance the chemistry towards potential clinical candidates has been a success," said Barbara Slusher, professor at Johns Hopkins and the director of Johns Hopkins Drug Discovery.

The Johns Hopkins Drug Discovery Program consists of a multidisciplinary team of scientists with industrial experience and core expertise in drug discovery research, including medicinal chemistry, screening assay development, drug metabolism and pharmacokinetics and animal pharmacology/toxicology. Eisai has licensed the intellectual property for further research, development and commercialization at its AiM Institute.

Under the agreement, Johns Hopkins will receive an upfront payment of $500,000 for license consideration, as well as future milestones and royalties upon successful commercialization of a product based on these compounds. In recognition of the ongoing success of the collaboration, a further $500,000 will be provided by Eisai to support future Johns Hopkins Drug Discovery research.

In 2011, Johns Hopkins and Eisai formalized the initial joint drug discovery collaboration. Under that agreement, Johns Hopkins Drug Discovery, led by Slusher, provided Eisai with novel therapeutic targets. For the targets of interest, screening assays were developed and validated by the Johns Hopkins Drug Discovery team, and then transferred to Eisai, which utilized the Johns Hopkins assay to conduct high-throughput screening of its proprietary compound library collection to identify compounds that interact with the targets.

Utilizing hybrid industry-academic drug discovery teams, the newly identified screening compounds were then subject to extensive structure-activity relationship studies and characterization in preclinical models to identify lead compounds for potential clinical development.