# THE CANCER LETTER

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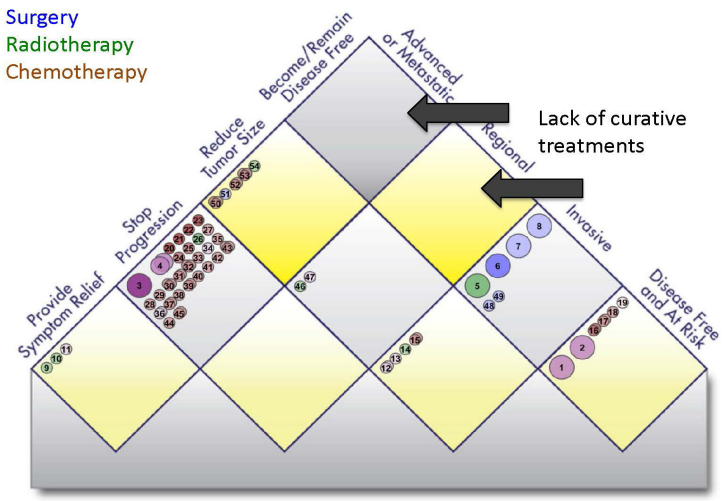


A matrix of therapies for non-small cell lung cancer generated by the PACE Continuous Innovation Indicators. *Source: Silvia Paddock/ Rose Li and Associates and Jacqueline Ferguson/Lilly Oncology*

## How Much is a Drug Worth? A Provocative Model Puts a Price on Benefit

*By Matthew Bin Han Ong*

Eli Lilly & Co. didn't ask Dan Goldstein, an oncologist at the Winship Cancer Institute at Emory University, to price their drugs, but he volunteered his services anyway.

Indeed, Lilly Oncology is unlikely in the extreme to concur with the price he proposed for necitumumab, a front-line treatment for locally advanced or metastatic squamous non-small cell lung cancer.

(Continued to page 2)

*Conversation with The Cancer Letter*

## Lilly's PACE Continuous Innovation Indicators Visualize Progress and Value in Research

Lilly Oncology has launched a novel value assessment tool that aggregates 40 years of oncology data to measure progress and identify unmet needs in cancer treatments.

The tool, called PACE Continuous Innovation Indicators, or PACE CII, is an effort to visualize progress in cancer treatments with the flexibility to accommodate different cancer subtypes.

(Continued to page 5)

*In Brief*

## Helzlsouer Named NCI DCCPS Chief Medical Officer

**KATHY HELZLSOUER** was named chief medical officer and an associate director in **NCI's Division of Cancer Control and Population Sciences**.

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# A Provocative Model Puts A Price on Clinical Benefit

(Continued from page 1)

Necitumumab, which at this writing is awaiting FDA approval, would be used in combination with a doublet treatment of gemcitabine and cisplatin. This Biologics License Application is all the more important because the treatment of squamous NSCLC hasn't changed in over 15 years.

In a paper recently published in JAMA Oncology, Goldstein argued that the drug could be worth as little as $563 per month. For perspective, the average launch price for cancer agents is $12,000 a month.

Realistic or not, Goldstein's paper, "Establishing a Value-Based Cost," is the first to prospectively model drug prices based on clinical benefit.

At a glance, Goldstein's model might appear similar to other value assessment tools that have been proposed by researchers and cancer organizations:

• The American Society of Clinical Oncology's value framework, published in June this year, quantifies clinical benefit, side effects and cost as components of value (The Cancer Letter, June 26).

• Peter Bach's DrugAbacus, an online tool that allows users to assess the value of 54 cancer drugs that have received U.S. approval since 2001 (The Cancer Letter, June 19).

• The National Comprehensive Cancer Network's Evidence Blocks, a visual representation of five key value measures that reflects the evolving standard of care for a given disease state (The Cancer Letter, Oct. 16).

These approaches use existing data on the components of value—efficacy, safety, quality of evidence, and affordability—to educate providers and patients. ASCO's framework, DrugAbacus and NCCN Evidence Blocks incorporate cost analyses, but none suggest prices for drugs before they are approved.

Goldstein does just that. His model differs by solving the cost equation ahead of a drug's launch using trial results.

However, Lilly Oncology officials aren't persuaded. Goldstein's preemptive cost estimates for necitumumab are deflated, they said to The Cancer Letter. "Had Dr. Goldstein chosen more real-world standard of care, that wouldn't have been the conclusion of the study," said Jax Ferguson, senior director of global oncology corporate affairs at Lilly Oncology.

Lilly Oncology earlier this year published its own value tool, called PACE Continuous Innovation Indicators. While the model doesn't deal with cost, it aggregates oncology data in an effort to understand the evolution of value by visualizing progress in 12 disease types over 40 years.

A conversation with Lilly Oncology officials can be found on page 1.

Goldstein's study is a part of a larger movement to understand the value of drugs, pricing experts say.

"Goldstein and his team's work is important, because it illustrates the value of prospective economic analyses for prospectively estimating value-based pricing," said Rena Conti, an assistant professor of health policy and economics in the Department of Pediatrics and Public Health Sciences at the University of Chicago.

Some elements of value aren't included in Goldstein's estimates, said Conti, who published an article on new pricing policies on Health Affairs Blog earlier this year.

"Goldstein and his team's work is one tool for helping payers' set coverage and patient cost-sharing requirements," Conti said to The Cancer Letter.

Value-based pricing is becoming a central feature in setting coverage decisions.

"On a large scale, the Centers for Medicare and Medicaid Services has decided to move to value-based payments, which will necessarily incorporate costs," said Peter Bach, a pulmonologist, health systems researcher, and director of the Center for Health Policy and Outcomes at Memorial Sloan Kettering Cancer Center.

"We're going to target particular conditions like oncology. We have to understand the landscape of costs in terms of how they're linked to particular diseases."

But what is value? And should drugs be priced strictly according to value?

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The cost equation is complicated: drug prices aside, researchers making value calculations have to take into account the benefits, harms and toxicities of any particular drug.

"Drug prices are also a constraint that researchers deal with, as they do with the challenges of biology," Bach said at the 2015 ASCO annual meeting in May. "Why not close this loop? If [the other variables] are equal except for cost, why not just say 'no' to a higher priced agent?"

**How to Price Necitumumab**

Enter Goldstein, armed with the idea to use necitumumab—a highly anticipated lung cancer drug—as a case study.

"What I was interested in was trying to see if we could develop a price for a drug before the drug comes to the market," Goldstein said to The Cancer Letter. "So we heard about necitumumab and that it was a drug that was likely to get approved by the FDA, so then we used the data from the clinical trial to essentially develop a value-based price for the drug."

But should we be solving for price anyway?

"I think we do need to do exactly what Dan Goldstein just presented," Bach said, discussing Goldstein's presentation at the ASCO 2015 annual meeting. "He actually goes ahead and solves for price."

Necitumumab, a first-line therapy for metastatic squamous non-small cell lung cancer, is worth no more than $1,300 per cycle, according to Goldstein's study. Based on the value it provides, necitumumab could fetch as little as $563 per cycle.

"What we're trying to do is trying to link the benefit to the price," Goldstein said. "For example, a drug like necitumumab, because there's a low level of efficacy, it should have a relatively low price."

This means that, at a conservative estimate of $50,000 per quality-adjusted life year, necitumumab should cost $500 a month, Bach said. At $200,000 per QALY, it's $2,700 a month.

"This sounds crazy, a drug approved maybe this year, for only $2,700 a month?" Bach said. "But let me remind you that that is close to Gleevec's launch price in 2001—in today's dollars—and Gleevec is many times more effective. But the truth is it sounds crazy today."

Based on the contemporary average launch price for cancer drugs, necitumumab would cost $900,000 per QALY, Bach said.

Necitumumab, when used in combination with gemcitabine and cisplatin, is the first regimen in the first-line setting to show significant improvement in overall survival over chemotherapy alone for patients with advanced squamous NSCLC.

No first-line therapies exist for this indication—necitumumab promises to fill an unmet need in a disease with a five-year survival rate of less than 5 percent.

The drug received overwhelmingly positive comments from the FDA Oncologic Drugs Advisory Committee July 9 (The Cancer Letter, July 10).

No formal vote was taken by the committee—in what appears to be the new FDA approach to getting advice on oncology treatments—but The Cancer Letter's analysis of the public comments made by ODAC members suggests that, had a vote been tallied, necitumumab would have received an overwhelming 11:1 vote in favor of approval.

FDA is expected to announce its decision later this year.

**Goldstein: Lilly Drug Does Not Deserve High Prices**

How does all this translate into value?

Necitumumab provides a "minimal" incremental benefit for patients who have metastatic squamous NSCLC, said Goldstein.

"They're going to die anyway, but it basically just extends life by about six weeks," Goldstein said to The Cancer Letter.

Goldstein has authored multiple studies on the cost effectiveness of different cancer treatments—many new agents are not very cost effective, he concluded.

"Value is benefit divided by cost, and cost is an essential component when discussing value," Goldstein said. "For instance, a drug that is developed for an unmet need is more beneficial than a drug that is developed for a need that has already been met. If the two drugs are priced the same, the drug for the unmet need is therefore more valuable."

Necitumumab's efficacy was tested in a phase III trial, called SQUIRE, that randomized 1,093 patients to receive necitumumab plus gemcitabine and cisplatin (n=545) or gemcitabine and cisplatin (n=548).

Necitumumab is a second-generation, recombinant human monoclonal immunoglobin G1 EGFR antibody that binds to the extracellular domain of the human epidermal growth factor receptor and blocks interaction between EGFR and its ligands.

The trial demonstrated that adding necitumumab to chemotherapy in the first-line setting increased median overall survival by 1.6 months and progression-free survival by 0.2 months.

Two drugs were recently approved for the squamous NSCLC indication, but not in the front-line

and not in combination with chemotherapy.

The new second-line drugs are:

• Ramucirumab, approved in December 2014 in combination with docetaxel, for treatment of metastatic NSCLC (both squamous and non-squamous) with disease progression on or after platinum-based chemotherapy, and

• Nivolumab, approved in March 2015 for patients with squamous NSCLC with progression on or after platinum-based chemotherapy.

For necitumumab, Goldstein and his team of investigators developed a Markov model using data from multiple sources, including the SQUIRE trial, to evaluate the costs and patient life expectancies associated with each regimen.

In the analysis, patients were modeled to receive gemcitabine and cisplatin for six cycles or gemcitabine, cisplatin and necitumumab for six cycles, followed by maintenance necitumumab.

The cost inputs included drug costs, based on the Medicare average sale prices, and costs for drug administration and management of adverse events, based on Medicare reimbursement rates.

"With value-based pricing, if it were a drug that's essentially a game-changer drug—something that really cures the disease or really changes the course of the disease—drugs like that would still carry a high price," Goldstein said.

"Drugs that come to mind that would warrant a high price are drugs such as imatinib or the new drugs to treat hepatitis C. These drugs truly change the course of a disease. They're truly game changing, and they warrant high prices.

"And that's the good thing, in my mind, because value-based pricing will continue to incentivize the development of truly game-changing innovations."

Goldstein establishes a threshold for what is cost effective with a system called the Incremental Cost Effective Ratio, or ICER—that is, the number of dollars it costs to gain one year of life or one year of quality-adjusted life by a specific treatment.

"So the quality of quality-adjusted life here is taking into account of the fact that patients with advanced cancer, their quality of life is not as good as patients who don't have cancer," Goldstein said. "There is no absolutely accepted value in the United States, but it is somewhere between $50,000 to $150,000 to gain one quality-adjusted life year.

"And so we use that as essentially the end result, and work backwards to find out how much necitumumab would have to cost in order for it to be cost effective by those thresholds."

**Eli Lilly: Goldstein Model Not "Real-World"**

Goldstein's study is methodologically sound, Lilly Oncology's Ferguson said.

"However, the comparator that he chose in his clinical trial—he didn't actually take into account the real range of treatment options available and reflect real-world choices," Ferguson said to The Cancer Letter. "So unfortunately he chose gemcitabine and cisplatin and generic comparators, which resulted in the deflated annual costs and per cycle costs of necitumumab."

Using a different set of comparators would not have made a difference, Goldstein said.

"Our sensitivity analyses make the study extremely robust—such criticism does not hold water, and it's an excuse to avoid the real issue—that prices should be related to the benefit that a drug provides," Goldstein said.

"If we had used—as the comparator arm—other regimens aside from gemcitabine and cisplatin, such as carboplatin and paclitaxel, it would have had essentially zero impact on the model since the cost of carboplatin and paclitaxel is very similar to gemcitabine and cisplatin, and this wouldn't have impacted the model results significantly.

"Our study was very robust in that it had multivariate sensitivity analyses, and it took account of any variation in the cost of the comparator arm, so this potential difference would not have affected the results of this study at all."

Goldstein said he hopes his findings will help payers, the pharmaceutical industry and the U.S. government address the issue of high cancer drug prices.

"Currently, FDA has no mandate to assess cost of value. However, it would appear that that some governmental intervention may be required," Goldstein said. "Some people have argued that we should just bring down prices in kind of a simplistic way.

"However, I feel that we shouldn't just simply bring down prices but more that the price should be linked to the benefit that the drug provides, and that's a value-based price.

"I hope that industry will take notice of this study and recognize the importance of it—and if and when necitumumab gets approved, it will be priced appropriately by the manufacturer.

"I'm also hoping that governmental institutions will take note in recognizing the importance of developing some type of independent institution to aid in the development of drug prices prior to them reaching the marketplace."

**Bach: Answers that Lead to Questions**

Researchers studying value-based pricing have—in this era—somehow decided on a hierarchy of comparative decision-making factors in oncology, MSKCC's Bach said in his critique of Goldstein's presentation at the 2015 ASCO annual meeting.

"That begins with efficacy, and then toxicity, and then costs," Bach said. "I don't know how we ended up there."

There is no rationale for abiding by that hierarchy when, like Goldstein, researchers can calculate prices to solve the cost equation, Bach said.

"Does efficacy always drown out cost? Would we really pay an infinite amount for a microscopic benefit?"

What are the next steps?

Before value-based pricing can be used a comprehensive tool for understanding costs, there are many questions that need to be answered, Bach said.

For instance, researchers have to methodically quantify numerous confounding variables, and decide on which measurements are most reliable.

"Do we use the average life expectancy or do we start looking for this tail?" Bach said. "Do we look for the cures? Do we look for the lottery winners? Is a drug worth a lot more because there's a small group that might benefit a lot?

"Do we discount for toxicities? Or do we just use QALY? What about cost replacement? If a drug prevents or adds a hospital day, does that go into the price?

"Should we pay more for rare conditions? Should we pay more for unmet needs in populations or diseases that have no treatment? What about first-in-class? Does new science get a reward?

"What about the cost of R&D? If it costs a lot to develop a drug, should a company be able to recoup that to some extent, because it's hard to find populations?

"Are we paying for the past or the future? Are we paying so that people keep rushing into the void and filling needs that we need for our patients? Are we going to pay extra for that? Or are we going to just say, 'whatever we have today, let's price it out.'

"For measuring benefits, should we use life years or QALYs?" Bach said. "Dan Goldstein showed both of them. I'm actually not sure which way to go. Do we use the mean benefit? The median underestimates in general.

"I mean these as open questions, not as cynical statements. They are answerable, but we're not there now."

*Conversation with The Cancer Letter*

## PACE CII Visualizes Progress And Value in Cancer Research

(Continued from page 1)

PACE CII, launched earlier this year, contains data on 12 solid tumors: namely cancers of the breast, colon, rectum, liver, pancreas, and prostate, as well as melanoma, non-small cell lung cancer, gastric cancer, renal cancer, testicular cancer and endometrial cancer.

Users can make comparisons across tumor types, disease stages and treatments to identify where unmet needs still exist.

"The actual goal of this tool is to foster this better understanding of innovation and progress for the entire cancer community," said Jax Ferguson, senior director of global oncology corporate affairs at Lilly Oncology. "What we're really hoping for is that folks who use it—these diverse stakeholders—are going to use the tool to make their own conclusion about value and progress."

PACE CII does not include any economic inputs in the database, said Ferguson, who runs the PACE (Patient Access to Cancer care Excellence) organization.

"It is purely a scientific assessment of value, which we believe is important," Ferguson said to The Cancer Letter. "What we want to do is help people understand the scientific value of these treatments, and very importantly, want to make sure that this becomes a dataset that people reference in their discussion on economic value."

Lilly Oncology designed PACE CII to create an objective record of progress in cancer research and present a more nuanced view on the evolution of value over 40 years, said Silvia Paddock, lead CII researcher, and senior associate at Rose Li and Associates, a consulting company in Bethesda, Md.

"I think what we need to teach our audience is to get away from a static assessment of value—a moment in time, one single outcome—to better understanding how value of treatments evolve over time," Paddock said to The Cancer Letter. "If someone wants to use our data to incorporate that into a more sophisticated value

model that takes into account a dynamic view, I think we would be very happy to make our tool available for that."

Ferguson and Paddock spoke with Matthew Ong, a reporter with The Cancer Letter.

**Matthew Ong:** *What was the genesis of this idea? Why was the tool created, and why is it important?*

**Jax Ferguson**: The PACE organization—Patient Access to Cancer care Excellence—is an initiative we started at Lilly Oncology about five years ago when we saw a very dynamic policy environment in the United States and abroad.

Unfortunately, what we felt was happening was that patients were getting lost in the center of policy decision-making.

So we, along with what we call our PACE Global Council, which is kind of our external board of directors, made up of a multitude of influential stakeholders across the world in oncology, sat down and said, 'What are some of these guiding principles that we need to be active on, and which we stayed true over those five years?'

Briefly, what we decided we needed to focus on from a policy perspective was developing policy that was actually going to support speeding innovation, making sure that we were enhancing patient access to those treatments.

We wanted to make sure that we were doing everything we could to elevate the patient voice in the policy arena, and then where it relates to the CII, taking an active role in what we would call myth-busting some of the more common misconceptions in the cancer community.

And one of the greatest myths that we were dealing with and still do on a day-to-day basis in oncology, is that the progress we see against cancer is a result of mostly breakthrough treatments. That's just not true.

So that's really the genesis of the idea of the CII, along with some quantitative and qualitative research studies that we have performed with the general public and the cancer community to really try and guide us on: What exactly do people believe about the progress we're making against cancer, and where is the truth?

We've seen significant advances in cancer treatment over the last 40 years. There are still major unmet medical needs, but the majority of the progress that we've seen has come from smaller innovations. So we want to correct that perception in the marketplace, but we knew we needed to deal with data.

When you think about the CII as the first-ever evidence-based tool that makes it possible for anybody who makes decisions about cancer research and policy to visualize progress against cancer, we're really hoping and what we've seen so far, to date, that health policy experts, patient advocates, health economists, are typically the audience who have initially gravitated to the tool, and are coming to us with really intriguing research questions that we're helping them think through the analysis of those via the database.

**MO:** *Silvia, how long have you been working on the PACE CII?*

**Silvia Paddock:** We've been supporting PACE for three years now, and started to work on the Continuous Innovation Indicators more than two years ago.

We're consultants, we work for the government a lot, obviously, being physically close to the NIH, but also nonprofits and other organizations. I really appreciate working on the initiative and we did a road show visiting scientists, advocacy groups, and professional organizations. We've been focused on this project for more than two years now.

**MO:** *Would you call the CII a record keeping system for progress in cancer research?*

**SP:** Accurate record keeping is an important part of the CII. Of course we already have PubMed and other systems, so of course our system goes far beyond that. In PubMed, one study report can contain multiple treatment arms, for example, and multiple results.

Our system breaks them down into individual observations that then later we store in relational database, but then we can pull out these individual observations rather than having to look at the full study or full PubMed report. In addition to these accurate records that we do, and have published on methodology about blind duplicates, and all that.

Of course, what our system then does is to allow us to visualize this for those who don't have the time to sit for hours, days, or months and study the history of cancer to create visuals that, in a much shorter amount of time, get people that accurate information about where are we, what are the unmet needs, and also, importantly, how did we get to where we are right now. So that's really the strength and the goal to make it much faster for people to understand that process.

**MO:** *Was the PACE CII created with Lilly Oncology's drug pipeline in mind?*

**JF:** I think based on what we've been able to build with Silvia's help, there's going to be natural benefits for Lilly Oncology, but that wasn't the original intent of the design.

Neither the PACE organization nor the CII is a promotional engine or commercial engine for Lilly

Oncology. In fact, we're actually quite separate from that.

The actual goal of this tool is to foster this better understanding of innovation and progress for the entire cancer community and what we're really hoping for is that folks who use it—these diverse stakeholders—are going to use the tool to make their own conclusion about value and progress, and some of which might come from our biggest critics. And we're okay with that.

We launched the tool in January of this year in Washington, D.C., alongside the National Patient Advocate Foundation, Friends of Cancer Research and the Pancreatic Cancer Action Network.

When we did that, we said, 'There are probably thousands of stories that people are going to tell with this database, and you want to see all of them. We're not going to ask to control them or approve them or anything.'

The release of the tool is to better educate our entire cancer community on what we can do to speed innovation and to appropriately recognize continuous innovation.

**MO:** *I see that the PACE CII identifies metastatic squamous non-small cell lung cancer as sort of a blank spot where treatment is concerned. Would Lilly Oncology's necitumumab be addressing that unmet need?*

**JF:** Necitumumab has been submitted for FDA approval. It recently had an Oncologic Drugs Advisory Committee meeting that was quite encouraging. Lilly Oncology is committed to being a leader in lung cancer—necitumumab is kind of our next milestone, pending FDA approval, to meet an unmet need specifically in the squamous non-small cell lung cancer population.

I think the connection that we're hoping people make with the CII is if you look into the history of progress around squamous non-small cell lung cancer treatment, what should we expect from new treatments that come to market, with regards to their ability to extend survival, to achieve a range of quality of life outputs etc. for patients?

**MO:** Using necitumumab as an example, what can the CII tell us about the value of that drug? I don't see an explicit cost angle.

**JF:** The CII itself will not answer people's questions about the value associated with necitumumab in increasing overall survival from a cost perspective.

But it should inform people to understand that this is a devastating disease, and one in which we haven't actually seen medical progress over the past 20 years. If approved, we believe necitumumab could represent a meaningful advance for this patient population.

We do have another investigational compound that is in a phase III trial for non-small cell lung cancer, and that is our CDK 4 and 6 inhibitor abemaciclib. It's being studied as a monotherapy in patients with KRAS mutation-positive non-small cell lung cancer that failed a prior platinum-based chemotherapy.

The CII does not include any economic inputs in the database. It is purely a scientific assessment of value, which we believe is important—you've seen the advent of all these various value screening tools, whether it's ASCO, NCCN, ESMO, there's a proliferation of them, and they're all taking an individual approach to defining the economic value of new treatments. That is not what the CII tool does.

What we want to do is help people understand the scientific value of these treatments, and very importantly, want to make sure that this becomes a dataset that people reference in their discussion on economic value.

The data that we've included in this tool is specifically for 12 types of cancer, it certainly does not today span the entire cancer disease spectrum, but we do hope to update the tool with new cancers and new data in the coming years.

**MO:** *What do you think of the recent study by Dan Goldstein on the value-based price of necitumumab? Is it possible to look at Goldstein's work and the CII, and learn something about value from both, or am I putting apples and oranges next to each other here?*

**JF:** It is a little bit of apples and oranges—this is a hybrid fruit, that's really what this is.

When people are developing these economic or cost effectiveness assessments, they're usually looking at price of effectiveness value judgments. And therefore, it's apples to oranges with the CII.

But where they overlap, is that the CII should be able to inform these assessments in the context of what we've been able to see: progress against cancer. That's where there is overlap.

Dr. Goldstein's study was sound methodologically, however, the comparator that he chose in his clinical trial—he didn't actually take into account the real range of treatment options available and reflect real-world choices.

So unfortunately he chose gemcitabine and cisplatin and generic comparators, which resulted in the deflated annual costs and per cycle costs of necitumumab.

Had he chosen more real-world standard of care, that wouldn't have been the conclusion of the study.

**MO:** *How does CII allow us to better understand how the value of new treatments evolves over time?*

**SP:** So I think what we need to teach our audience is to get away from a static assessment of value—a moment in time, one single outcome—to better understanding how value of treatments evolve over time. And we can learn a lot from the history from our tool.

So if you have various established treatments, if we look at the very beginning, the initial trials did not show improved overall survival, there were recurrence rates and so on.

In the history, we've seen the exact same things that we're seeing now. It's just that we forget about them, and then a little later, someone writes up milestones and highlights and you think that, 'Oh yeah, that was all easy, why can't we keep doing that?'

So to teach people about that dynamic view about how long does it take until we understand the value, how long does the value increase after the initial approval, how often does it decrease, and get a realistic picture of that.

Then, if someone wants to use our data to incorporate that into a more sophisticated value model that takes into account a dynamic view, I think we would be very happy to make our tool available for that.

**MO:** *Is there a business model for the CII? Also, how can people access the CII, and what is your target audience?*

**JF:** People who want to use the tool—we're giving away access for free. There's not a financial incentive for Lilly to have users of this tool.

We do ask anybody who wants access to all layers of data in this tool to sign a very simple data sharing agreement with us, that again, has no financial responsibility or commitment, but that just states that they will use our tool with integrity, that they obviously won't manipulate and can't manipulate the data within it, etc.

For anybody who wants to see how the tool works, that's publicly available right now through the PACE website.

**SP:** We emphasized that we asked, 'What is the audience for this?' After the Newseum launch this January, we were very surprised that we were contacted by a testicular cancer advocacy group and we included testicular cancer pretty much as the model cancer for which we have a cure even when patients present with advanced or metastatic cancer.

We found that during our effort, it took so many different baby steps on the way and combination therapies and trying things out that we thought it was very interesting cancer to model on, and then these testicular cancer advocates contacted us and just said, 'We need to get this message out. We have a cure, people need to get treatment.'

We cannot even foresee all the different uses, and we've even been surprised—so I think that we need to emphasize. We strongly believe that having accurate data and this ability to visualize will benefit people even beyond what we can currently think of.

**JF:** The two most important things about the CII are that people are adopting it to more deeply understand the progress we're making against cancer.

We know that the financial sustainability of cancer care is an incredibly serious and complex issue, and there are all these efforts that are going on to help us understand how we should better value new treatments in cancer.

We feel that these more static assessments of value do patients a disservice in the long run, because they could in fact end up reducing access to new treatments. We haven't had time to demonstrate that value that they would actually bring to different patient populations in the future.

And that's what we worry about, and that's where we feel like the CII can educate and inform both our supporters and our critics about how we as a community should be evaluating the progress we're making against cancer in the past, but importantly, for the future.

*Capitol Hill*

## Budget Deal Eases Sequestration, Includes Medicare Site Neutrality

*By Conor Hale*

Congress passed a two-year budget deal that would raise government spending as well as the debt ceiling.

The bill includes an $80 billion total budget increase, divided evenly between non-military and military programs, and raises the previous caps set by sequestration. The bill also suspends the debt limit until March 2017.

To pay for the increases, the government would raise money from changes to Social Security disability insurance and Medicare—as well as by auctioning off sections of public broadcast spectrum and selling barrels of oil from the government's petroleum reserve, both occurring over the next 10 years.

The House of Representatives passed the bill with a vote of 266 to 167 Wednesday, with 79 Republican representatives breaking with the majority of their conference to join 187 Democrats in moving the measure to the Senate.

The Senate then passed the bill at the end of a marathon session late Thursday evening, with the final 64 to 35 vote coming after 3 a.m. Friday, following speeches against the bill from presidential candidate Sen. Rand Paul (R-Ky.).

Paul—as well as two fellow senators running for president, Ted Cruz (R-Texas) and Marco Rubio (R-Fla.)—ultimately voted against the bill, as did 32 other Republicans. Sen. Lindsay Graham (R-S.C.) was the only Republican presidential candidate to vote in favor of the bill.

The president is expected to sign the bill as soon as it reaches his desk.

"This agreement will strengthen the middle class by investing in education, job training, and basic research," President Barack Obama said in a statement. "It will keep us safe by investing in our national security. It protects our seniors by avoiding harmful cuts to Medicare and Social Security. It is paid for in a responsible, balanced way—in part with a measure to ensure that partnerships like hedge funds pay what they owe in taxes just like everybody else. It locks in two years of funding and should help break the cycle of shutdowns and manufactured crises that have harmed our economy."

The budget deal— one of the last bills overseen by outgoing Speaker of the House John Boehner (R-Ohio), and crafted with Obama and other Capitol Hill leaders—will push the main debates over funding the federal government and raising the debt ceiling until after the 2016 presidential election. Rep. Paul Ryan (R-Wis.), elected to succeed Boehner as speaker of the House on Thursday, also supported the bill.

Congress still has to pass a definitive appropriations bill by Dec. 11.

The bill would stop a potential cut to Social Security disability insurance by transferring money within the program, and by making other changes.

The bill also includes a site-neutral payment structure for Medicare. Starting in 2017, Medicare will pay identical rates for critical cancer care services, such as the administration of chemotherapy, whether provided in physician-directed community cancer clinics or hospital outpatient departments.

The Community Oncology Alliance applauded Congress for including the change that would directly affect hospital outpatient departments and physician offices.

"We wholeheartedly endorse the inclusion of the Medicare payment site-neutrality provision in the budget deal. This is a much-needed first step to lowering the costs of cancer care for both seniors and Medicare," said Ted Okon, executive director of COA. "Cancer patients are hit with higher bills when a hospital acquires a community cancer clinic, even though they are being treated in the same facility and by the same physicians and nurses. This is unconscionable."

In the days before the passage of the bill, the American Society of Clinical Oncology called for comprehensive physician payment reform to support the full scope of services required by patients with cancer. ASCO published a policy statement on site-neutral payments in oncology in the Journal of Clinical Oncology.

"The current systems for reimbursement of outpatient cancer care under Medicare are outdated," said ASCO President Julie Vose in the Oct. 26 statement. "Alternative payment models that shift the emphasis away from face-to-face office visits and administration of intravenous anticancer drug regimens and toward providing patients with high-quality, high-value oncology care are needed in order to provide the full scope of oncology services to all Medicare beneficiaries, regardless of where they are treated."

**Budget Stability, for a Change**

"This bill will allow for certainty in the budget process for the next two years—something that has been greatly lacking in this recent era of government 'shutdown showdowns,'" said Rep. Hal Rogers (R-Ky.), chairman of the House Appropriations Committee.

Rep. Nita Lowey (D-N.Y.), ranking member of the appropriations committee, said: "Since the beginning of this year's budget and appropriations process, Democrats have called for relief from damaging austerity-level budget cuts so that Congress can enact spending laws that invest in this nation's future.

"Republicans finally engaged in constructive talks, and negotiators have yielded a bipartisan package that increases funding equally for defense and non-defense investments. The agreement also protects the full faith and credit of the United States, extends the solvency of Social Security Disability Insurance, and prevents a significant increase in seniors' Medicare Part B premiums and deductibles."

In a statement, Research!America CEO Mary Woolley said, "The two-year budget deal is a significant step towards restoring necessary funds for medical research and other discretionary programs that have borne the brunt of sequestration and flat budgets over the last decade.

"Federal health agencies, including the National Institutes of Health, will be in a stronger position

to combat current and emerging health threats with sustained and increased investments," said Woolley. "We commend congressional champions for medical progress who worked diligently to lift the budget caps, and call for swift approval of this budget agreement."

## A Third of Hospitals Will Drop Out of 340B if HRSA Enacts New Guidance, Survey Finds

*By Matthew Bin Han Ong*

Hospitals serving large populations of low-income patients stand to lose up to seven figures a year in drug discounts if proposed regulatory changes to the 340B program are enacted, the program's supporters say.

The Health Resources and Services Administration issued a sweeping guidance that would provide stricter definitions for which patients and entities should be covered (The Cancer Letter, Sept. 11).

The draft guidance, called the 340B Program Omnibus Guidance, was issued Aug. 28. Its public comment period for the long-awaited "mega-guidance" ended Oct. 27 (The Cancer Letter, Oct. 16).

HRSA's new guidelines for the 340B Drug Discount Program would have a devastating impact on hospitals' ability to provide uncompensated care to needy patients, said 340B Health, a Washington, D.C. association.

In a recent survey of its members, the group found that—if the guidance is finalized—about a third of hospitals would be forced to drop out of the discount program. Half of the hospitals surveyed said the proposed rules were "highly problematic" to their patient care mission.

"As we prepared our comments, we were struck by how many hospitals contacted us to raise serious concerns about the proposal," Ted Slafsky, president and CEO of 340B Health, said Oct. 28. "The bottom line: The number of hospitals that would be hurt by the proposed mega-guidance is staggering. We hope HRSA hears our concerns and significantly modifies the final guidance."

Critics say this may not be such a bad thing. According to the Government Accountability Office, about 40 percent of U.S. hospitals—more than 11,000 institutions—receive 340B discounts. In recent years, many key players in oncology have been questioning the 340B program's expansion and the eligibility criteria it uses to enroll institutions.

340B Health represents over 1,100 safety-net hospitals that participate in the 340B program. To get 340B discounts, institutions must demonstrate that Medicaid or Medicare covers about 30 percent of their patients. These entities are called "disproportionate share hospitals." Rural critical access hospitals are also in the program because they serve remote populations.

In a letter to HRSA, 340B Health outlines three concerns:

• Prescriptions given to patients upon discharge from a hospital would be ineligible for discounts.

• Cancer drugs written outside of the hospital would be ineligible for 340B.

• 340B discounts would be blocked for outpatients later admitted to the hospital.

The group's public comments are available here.

According to 340B Health, Nash Hospital, a DSH institution located in Rocky Mount, N.C., would lose nearly $200,000 in discounts for a single drug.

"The hospital's stroke center uses 340B to purchase Activase, a covered outpatient drug that Nash administers to patients while they are outpatients in the emergency department," 340B Health said in a statement. "Approximately 67 percent of stroke patients who receive Activase at Nash Hospital are subsequently admitted within three days of receiving it.

"Nash Hospital estimates that losing 340B for Activase will substantially increase the hospital's cost for the drug from $70,236 per year to $262,855. That $193,000 loss would impact Nash Hospital's ability to fund services for uninsured and underinsured patients."

340B Health statements on four other hospitals can be found on their website.

**Testoni: HRSA Draws Arbitrary Lines**

HRSA's mega-guidance would fundamentally change the 340B program and hurt patients who need the discounts, said Maureen Testoni, 340B Health senior vice president and general counsel.

"One of our key concerns has been that—the way the guidance is drafted, 340B would no longer be available for patients that are treated on the premises of the hospitals," Testoni said during a press call Oct. 28. "HRSA draws lines among the patients in a hospital, where some are committed to use 340B, and some are not. We don't think that this is appropriate."

HRSA does not require DSH hospitals to track and report their 340B revenues. Critics say this data void makes it difficult for researchers to quantify patient benefit, which in turn raises questions as to whether the program is meeting the stated intent of the program (The Cancer Letter, Oct. 16).

"The program generates profits for qualified hospitals and clinics on the backs of paying patients and their insurers, most notably those insured by fee for service Medicare," said Rena Conti, an assistant professor of health policy and economics in the Department of Pediatrics and Public Health Sciences at the University of Chicago.

"These providers don't have to share the discounts with patients and their insurers," Conti said to The Cancer Letter. "If 340B hospitals and clinics cannot show how vulnerable patients or all patients are benefiting from 340B profits, they should give the money back to the people who can use it—patients and taxpayers."

These data exist, Testoni said.

"A lot of data has been reported by hospitals on their Medicare costs in forms that they submit to the IRS," Testoni said to The Cancer Letter. "What's really important to know about the 340B is that, even though the largest amount of spending is going to hospitals that qualify for 340B by meeting the disproportionate share requirement, these hospitals are already treating a lot of Medicaid and low-income Medicare patients.

"Our research shows that, in addition to that, they are responsible for 60 percent of the uncompensated care provided by hospitals in this country. The hospitals that we are talking about only make up about a third of the total number of hospitals in the U.S. These hospitals also treat twice as many Medicaid and Medicare patients as the non-340B hospitals.

"It seems to us that there is a lot of information out there if people are interested in using it and looking at it to show that 340B hospitals really are providing a lot of uncompensated care, which they would obviously not be able to do to the level that they are not doing it if they didn't have access to 340B discounts."

*The full text of Testoni's Oct. 28 remarks follows:*

One of our key concerns has been—the way the guidance is drafted, 340B would no longer be available for patients that are treated on the premises of the hospitals.

HRSA draws lines among the patients in a hospital, where some are committed to use 340B, and some are not. We don't think that this is appropriate.

We believe that the statute requires that 340B be available for patients of the hospitals, and so we think that this arbitrary line drawing by HRSA is not appropriate.

Some of the areas where this line has been drawn would impact hospital outpatients that receive infusion at the hospital. If the order for the infusion is written outside of the hospital—this is actually a common occurrence, especially in rural areas, for example, a resident of a rural area may travel a few hours to a large urban center to have their cancer diagnosed and their treatment plan developed, and then come home to have their chemotherapy infused at their local 340B hospital.

Under HRSA proposal, the infusion drugs for that individual would not qualify for 340B, even though the hospital is responsible for infusing that drug, they're responsible for all their various services that a company infusing that drug performs.

Infusion of chemotherapy is a highly specialized service requiring highly skilled people to perform. Many hospitals have said that, if this provision goes through, they would have to significantly reduce their ability to provide infusion, which is going to obviously hurt people in rural areas if they have travel long distances to get their infusion drugs. And it will also hurt people in urban areas if hospitals are not able to provide as much uncompensated care in this area.

Another big issue for our members has to do with HRSA no longer permitting 340B use for discharge prescriptions, which are written for individuals as they are being discharged from an inpatient stay.

These are prescriptions that are very important for helping to avoid the individual be readmitted to the hospitals. 340B plays a very key role in allowing hospitals to have special programs to promote these discharge prescriptions for their patients. Removing 340B for discharge prescriptions that are so critical for health care just does not make sense.

Another key issue for us relates to not allowing 340B for outpatient drugs if the patient is later admitted to the hospital.

There are some insurer rules, like Medicare, for example, that have put into place billing requirements that are intended to reduce payments to hospitals, and will require that any outpatient services that are provided to an individual who's ultimately admitted, that those services, for payment purposes are included in patient payment that the hospital receives.

What HRSA is doing is they are basically using those rules as a way to draw a line between what drugs count for 340B and what drugs do not. This is something that really impacts emergency room departments and stroke patients, for example.

Instead of requiring manufacturers to give a discount to the hospitals that provide these services, the hospital would be required to pay for this at a non-discounted rate, which is a difference of thousands of dollars per administration.

*In Brief*

# Helzlsouer Named Chief Medical Officer of NCI DCCPS

(Continued from page 1)

Helzlsouer will direct the Epidemiology and Genomics Research Program, which includes the Office of the Associate Director, Clinical and Translational Epidemiology Branch, Environmental Epidemiology Branch, Genomic Epidemiology Branch, Methods and Technologies Branch, and Risk Factor Assessment Branch.

DCCPS Director Robert Croyle said, "Dr. Helzlsouer is a highly accomplished epidemiologist and clinician with a broad vision of cancer epidemiology, prevention, and control. She brings a valuable blend of medical, scientific, and leadership skills, which will be a strong asset for NCI and DCCPS."

Prior to joining NCI, she was a professor in the Department of Epidemiology at the Johns Hopkins Bloomberg School of Public Health and, since 2004, directed The Prevention & Research Center which she established at Mercy Medical Center in Baltimore. Her research interests are focused in cancer etiology and prevention, cancer survivorship, and clinical and translational research.

She also is an associate editor of the Journal of the National Cancer Institute and a member of NCI's PDQ Screening and Prevention Editorial Board. Helzlsouer is a recipient of the Martin D. Abeloff Award for Excellence in Public Health and Cancer Control for her service on the Maryland State Council on Cancer Control.

**INOVA** named **Thomas Graves** as vice president for cancer services and **Jeanny Aragon-Ching** as clinical program director of genitourinary cancers at **the Dwight and Martha Schar Cancer Institute**.

Aragon-Ching, is a genitourinary medical oncologist with particular expertise in prostate, bladder, and kidney cancers. At the cancer institute, she will lead the multidisciplinary clinical care program and research for patients with GU malignancies.

Prior to joining ISCI, Aragon-Ching served as an associate professor of medicine at the George Washington University School of Medicine and Health Sciences, where she also served as a principal investigator of trials on drug treatment and biomarkers in GU cancer.

Graves also joined ISCI as associate director for administration. Graves has previously held administrative positions in cancer institutes such as MD Anderson Cancer Center and the University of Texas San Antonio Cancer Center. He comes to Inova most recently from Geisinger Health System, where he served as vice president of cancer services.

**FRIENDS OF CANCER RESEARCH** honored **Marlene Malek**, and **Reps. Diana DeGette** and **Fred Upton** for their leadership in cancer advocacy at the 19th Annual Cancer Leadership Awards Reception, Oct. 22 in Washington, D.C.

Malek, president of Friends of Cancer Research, received The Ellen V. Sigal Advocacy Leadership Award for "her contributions both to Friends, as well as more broadly by bringing together the right people to discuss and then take action against cancer," according to FOCR.

The 2015 Cancer Leadership Award was given to Reps. DeGette (D-Colo.) and Upton (R-Mich.) for "their work on the 21st Century Cures Act, which would increase patient-focused drug development and save FDA resources in regards to supplemental drug review, amongst other items."

Reps. DeGette and Upton have shown a continued commitment to improving health for all Americans and have taken the lead on many initiatives to do so, FOCR said in a statement.

"I am so proud of the wonderful work we have accomplished over the past 19-plus years, from the breakthrough therapy designation, Lung-MAP, and 21st Century Cures," said Ellen Sigal, founder of Friends of Cancer Research. "We never would have been able to achieve some of these successes without the help and support of our friends, Reps. DeGette and Upton, and are forever grateful for their time commitment and dedication to the cause."

**MD ANDERSON CANCER CENTER** expanded the cancer targets of its Moon Shots Program.

The program will now include focuses on B-cell lymphoma, glioblastoma, cancers caused by human papillomavirus, high-risk multiple myeloma, colorectal and pancreatic cancers.

These join the original moon shots launched in 2013 to address breast and ovarian cancer, chronic lymphocytic leukemia, lung cancer, melanoma, myelodysplastic syndrome/acute myeloid leukemia and prostate cancer.

The six new moon shots began as pilot projects, chosen by internal and external reviewers during summer of 2014 from among 14 proposals.

The pilots received initial funding for researchers to develop their ideas a year ago. Both pilots and inaugural moon shots were subjected to rigorous peer-review this summer by the program's external Scientific Advisory Board, comprising 11 experts from other cancer centers and biopharma. The board's feedback helped mold priorities and funding for fiscal year 2016.

**CURESEARCH FOR CHILDREN'S CANCER** awarded $260,000 in grants, co-funded by Gateway for Cancer Research.

The CureSearch Community Impact Award in clinical trials was awarded to 13 recipients focusing on pilot or early phase clinical trial programs for pediatric cancers. The award recipients are:

**Pietro Bonacossa**, of Variety Children's Hospital/ Miami Children's Hospital; **Kathleen Dorris**, of The Children's Hospital Association in Aurora, Colo.; **Jennifer Elster**, of University of Louisville Research Foundation Inc.; **Adam Green,** of the Regents of the University of Colorado; **Leo Mascarenhas**, of Children's Hospital, Los Angeles; **Gary Mason**, of Children's Hospital of Pittsburgh of UPMC; **William Petersen**, of The Rector and Visitors of the University of Virginia; **Bassem Razzouk**, of St. Vincent Hospital and Health Care Center Inc. in Indianapolis; **David Walterhouse**, Ann & Robert H. Lurie Children's Hospital of Chicago; **Zhihong Wang**, of Wayne State University; **Brenda Weigel**, of the Regents of the University of Minnesota - Twin Cities; **Cynthia Wetmore**, of Children's Healthcare of Atlanta Inc.; and **Sarah Whittle**, of Baylor College of Medicine.

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*Drugs and Targets*

# Imlygic Approved as First U.S. Oncolytic Viral Cancer Therapy

**FDA approved Imlygic (talimogene laherparepvec) as the first oncolytic viral therapy in the U.S.**

Imlygic, developed by Amgen, is indicated for the local treatment of unresectable cutaneous, subcutaneous and nodal lesions in patients with melanoma recurrent after initial surgery. Imlygic has not been shown to improve overall survival or have an effect on visceral metastases.

Imlygic is a genetically modified herpes simplex virus type 1 designed to replicate within tumors and produce granulocyte-macrophage colony-stimulating factor, an immunostimulatory protein. Imlygic causes cell lysis rupturing tumors and releasing tumor-derived antigens, which along with GM-CSF, may promote an anti-tumor immune response. However, the exact mechanism of action is unknown according to Amgen.

"Imlygic is the first clinical and regulatory validation of an oncolytic virus as a therapy, which Amgen is proud to bring to patients with a serious form of skin cancer. Not all melanoma patients currently benefit from available therapies, and Imlygic represents an important new option that can provide meaningful durable responses for patients with this aggressive and complex disease," said Sean Harper, executive vice president of research and development at Amgen.

"Immunotherapy is an exciting area for cancer research, and we are currently studying Imlygic in combination with other immunotherapies in advanced melanoma and other solid tumors."

The approval of Imlygic is based on data from Study 005/05, or OPTiM. OPTiM was a phase III, multicenter, open-label, randomized clinical trial comparing Imlygic to GM-CSF in patients with advanced melanoma (Stage IIIB, IIIC, or IV) that was not surgically resectable.

The primary endpoint of the study was durable response rate, defined as the percent of patients with complete response or partial response maintained continuously for a minimum of six months.

OPTiM enrolled 436 patients. In the study, 16.3 percent of patients treated with Imlygic achieved a durable response compared to 2.1 percent of patients treated with GM-CSF ($p < 0.0001$). Of the patients who experienced a durable response, 29.1 percent had a durable CR and 70.8 percent had a durable PR. In the study, the median time to response was 4.1 (range: 1.2

to 16.7) months in the IMLYGIC arm.

The most common adverse drug reactions in IMLYGIC treated patients were fatigue, chills, pyrexia, nausea, influenza-like illness and injection site pain. Most adverse reactions reported were mild or moderate in severity and generally resolved within 72 hours. The most common grade 3 or higher adverse reaction was cellulitis.

Imlygic recently received a positive opinion from the Committee for Medicinal Products for Human Use of the European Medicines Agency, for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease.

Amgen anticipates the average cost of Imlygic therapy to be approximately $65,000. Given that Imlygic represents a novel and first-in-class oncolytic viral therapy, the company expects variability of Imlygic dosing from patient to patient, and intends to work with the healthcare community to implement a program that helps limit the average cost of Imlygic therapy to $65,000 for eligible participating institutions.

**Imbruvica was awarded the prestigious Prix Galien 2015 Award for Best Pharmaceutical Agent.**

Imbruvica won this distinction out of 24 category nominees, all of which were deemed innovative in the field of medicine and were approved by the FDA within the past five years. Imbruvica is jointly developed and commercialized by Pharmacyclics LLC, an AbbVie Company, and Janssen Biotech Inc.

"We are honored that Imbruvica, a first-in-class, oral therapy has been recognized by the Prix Galien USA Committee for the role it continues to play in treating patients with certain blood cancers," said Erik von Borcke, president of Pharmacyclics. "Our goal is to continue developing clinically meaningful, scientifically sound therapies that offer healthcare professionals and their patients the opportunity at the best possible outcome, allowing them to resume as normal a life as possible."

Imbruvica (ibrutinib) is currently approved for the treatment of patients with chronic lymphocytic leukemia who have received at least one prior therapy, all CLL patients who have del 17p and patients with Waldenstrom's macroglobulinemia.

Imbruvica is also approved for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy. Accelerated approval was granted for the MCL indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Imbruvica is a first-in-class, oral, once-daily therapy that inhibits Bruton's tyrosine kinase. Imbruvica was one of the first medicines to receive FDA approval via the new Breakthrough Therapy Designation pathway, and is currently the only product to have received three Breakthrough Therapy Designations.

Imbruvica is being studied alone and in combination with other treatments in several blood cancers. More than 6,100 patients have been treated in clinical trials of Imbruvica conducted in 35 countries by more than 800 investigators. Currently, 13 phase III trials have been initiated with Imbruvica and 67 trials are registered on www.clinicaltrials.gov.

**FDA granted Priority Review to MCNA, developed by Telesta,** for the treatment of high-risk, non-muscle invasive bladder cancer patients who are refractory or relapsing from BCG front-line treatment.

The FDA has assigned a review date of Feb. 27, 2016. Telesta retains full and sole ownership of MCNA rights in the US and Japan and will be responsible for the commercial launch of MCNA in the United States while Ipsen will initiate discussions with regulatory authorities to identify the regulatory path and potential requirements for the product in Europe and other key licensed territories.

Under the financial terms of the agreement, Telesta is eligible to receive up to $137 million in upfront and milestone payments comprising a $10 million upfront payment and additional payments contingent upon achievement of regulatory and sales milestones. In addition, Telesta is eligible to receive meaningful tiered double-digit royalties on net sales of MCNA in the licensed territories.

MCNA is derived from the cell wall fractionation of a non-pathogenic bacteria. Its activity is believed to be through a dual mechanism of immune stimulation and direct anti-cancer effects. The efficacy, duration of response and safety data from MCNA's phase III trial was recently published in The Journal of Urology. If approved, MCNA will represent the first new therapeutic for U.S. patients in this indication since 1989.