Innovations In Oncology

A medical and commercial trend report for marketers of anti-cancer modalities

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Overview: The Conventional Is in Remission

As cancer therapies become more precise and personalized, one of humanity's oldest and most dreaded scourges may finally be brought to heel. However, bringing new medical agents to market presents a whole new host of problems that must be overcome first. **Frank Celia** reports

Treating cancer with immunotherapy is not a new concept. It has existed since the 1990s with the introduction of rituximab, trastuzumab and several other agents launched since then. What has changed only in the past year or two, and what is setting the oncology world on fire with enthusiasm, is that where once immunotherapy was primarily thought to be limited to fluid-based cancers like leukemia, melanoma and lymphoma, stunning new research now indicates similar agents can induce the body to attack and destroy the so-called solid-tumor cancers, the ones that kill with devastating speed and frequency and account for 80% of cancer mortality.

So far response rates have only been around 20%. Yet those patients who do respond often demonstrate off-the-charts survival outcomes, many apparently cancer-free indefinitely. Because these drugs work on multiple tumor types among patients with differing genomic profiles, researchers are confident that by cross mixing and combining different agents among various diseases and sub-populations, response rates can be pushed much, much higher.

"Basically a subset of patients responds or achieves stable disease that goes on for years and years," noted Dr. Drew Pardoll, MD, professor of oncology at Johns Hopkins University, during a symposium sponsored by Bernstein Research. "I'm still reluctant to use the term 'cure,' but what I say to the patient is that, 'We all have to die of something, but I think there is a real possibility you are not going to die of your cancer.' That is really transformative."

Drugs in or near the market right now are either CTLA-4 or PD-1/PD-L1 inhibitors. Both classes can induce serious—sometimes life-threatening—inflammatory side effects. Although CTLA-4 drugs appear to be slightly more toxic, they will probably remain in use as a secondary or adjunctive capacity, researchers say.

Analysts see huge potential in the PD-1/PD-L1 market, possibly topping $33 billion by 2022. The two big rivals here are Merck's Keytruda and Bristol–Myers Squibb's Opdivo. Opdivo is favored to gain the lion's share of the market, with Keytruda close behind, then followed by two Roche and AstraZeneca agents nearing approval. Keytruda is projected to make $900 million this year and Opdivo $500 million, but the latter drug should eventually pull ahead as it adds indications.

Of the many tumors being targeted, experts see the real battle occurring in non-small cell lung cancer, a

"What I say to patients is that,'I think there is a real possibility you are not going to die of your cancer.'"

—Dr. Drew Pardoll, MD, *Professor, Johns Hopkins University*

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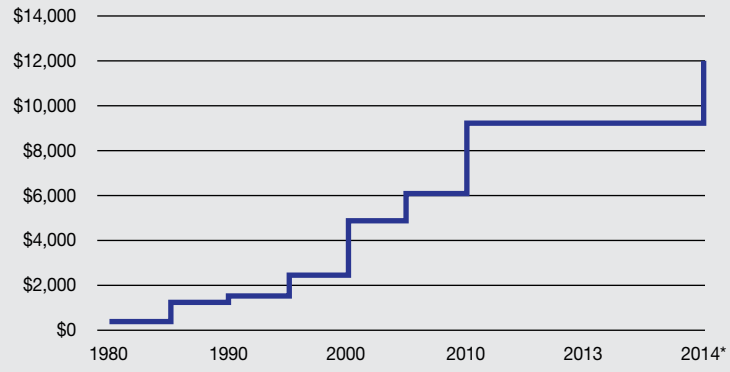
The number of cancer therapeutics approved by the FDA in 2014

—CDER reports

The Rising Price of Cancer Drugs

The median monthly price of treatment, 1980–2014



Source: Adapted from Memorial Sloan Kettering Cancer Center, as cited by Bernstein Research; *2014 based on Bernstein analysis and is meant to capture PD1/CDk pricing

Top 5 Therapeutic Classes by US Sales, 2014

Rank	Company	2014 Total (Billions)	2013 Total (Billions)
1	Oncology	$32.6	$27.9
2	Antidiabetes	$32.2	$24.7
3	Mental health	$23.1	$23.8
4	Autoimmune	$22.2	$17.9
5	Respiratory	$22.0	$20.4

Source: IMS Health, National Sales Perspectives

Overview: The Conventional Is in Remission

common disease type whose treatment could be worth $21 billion over the next several years. Whichever of these four agents prevails in NSCLC will probably dominate, analysts predict.

The most daunting challenge facing the approved drugs—not to mention hundreds of pipeline agents targeting other inhibitory pathways, plus upcoming disparate but equally promising modalities, like vaccines—is monetary. Even before new immunotherapies arrived, oncology was undergoing breathtaking growth. Between 2003 and 2013, global spending on cancer doubled. Expenditures on oncology medicines grew by 10% in 2014, reaching $100 billion, up from $75 billion just five years earlier.

More sobering, growth has thus far been driven by targeted therapies, drugs like Novartis's Gleevec. The industry has not yet begun to feel the full impact of immunotherapy, where a CTLA-4 combined with Opdivo retails for $270,000 annually—price tags that promise to redefine the word "unsustainable."

On their own, anti-PD1 therapies Keytruda and Opdivo sell for around $150,000 a year. Another recent example includes Pfizer's Ibrance (palbociclib), approved in February 2015 and priced at about $120,000 a year.

Assuming colossal pricing obstacles can be overcome, the next most significant challenge, from a commercialization standpoint, is reckoning with companion diagnostics (CDx). Identifying and evaluating biomarkers lie far outside the core competencies of most pharmaceutical companies.

From January 2004 to March 2015, only one-third of the oncology therapeutics approved had a biomarker or CDx on label for any indication, according to IMS Institute for Healcare Informatics. While this share has remained constant over the past 11 years, diagnostic-drug pairings may become more common as medicine goes personal. And marketing a drug and diagnostic in tandem requires a whole new business model.

"Even understanding where the test can be sent to be read is a big challenge for the physicians themselves," says Paul Cariola, a senior principal in IMS Health's oncology division. "Deciding on what lab test to use could be a significant differentiator. This is an area not just ripe for improvement in terms of patient care; it will now be part of a product's brand."

Another seismic shift involves quality of life (QoL). In the past, when therapies were primarily cytotoxic, survival outweighed all other factors. With other options limited, chemotherapy's devastating side effects were considered acceptable. Now patients might choose between a targeted oral oncolytic and an infusion treatment that offer similar survival outcomes yet very divergent QoLs. This new patient-centric paradigm—perhaps not completely appreciated by oncologists themselves—needs to be reflected in sales and marketing messages. ■

Case Study: FDA Explodes the Regulatory Process

When Congress passed laws in 2012 designed to streamline the FDA's approval process, many pharmaceutical manufacturers scoffed. But, in oncology at least, they seem to be working.

FDA oncology chief Richard Pazdur

In March the latest in a series of rapid oncology green lights saw the agency grant Opdivo an add-on indication for lung cancer, based on Phase-II data, mere days after receiving the application.

The FDA's oncology chief, Richard Pazdur, has vowed to continue the speedy pace, especially for drugs with approval histories: "Supplemental applications in the past have been treated as if they were new," he said in a recent interview with BioCentury. "And that doesn't make sense to me."

Two other pending FDA regulatory matters could have far-ranging impacts on the future of biomarkers. First, the FDA is in the process of changing its regulatory stance toward the laboratory developed tests (LDT) industry. Second, this summer the agency will hold public hearings on the possibility of loosening rules on off-label promotion. Even when not predictive enough to rate inclusion on labels, biomarkers can still play vital roles in treatment decisions, critics of the rules have argued.

"[CDx] is an area not just ripe for improvement in patient care; it will now be part of a product's brand."

—Paul Cariola, *senior principal, IMS Health*

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The number of cancer therapeutics approved over the last decade that had a biomarker or CDx on label for any indication vs. 47 that did not

—IMS Institue for Healthcare Informatics

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Data Streams: An Evidence Base Grows in Oncology

Traditionally, the launch of any first-in-class modality would rely on a burst of one-on-one sales calls and med ed to make a splash. Now, terabytes of data are being leveraged to keep a cancer treatment on track throughout its life cycle

When it comes to leveraging real-world evidence to augment the information about a treatment's clinical and economic outcomes, it's still early days. But the industry's data-driven agenda has matured beyond the single product to whole therapeutic areas, oncology being one.

"Pharma is at the beginning of a dialogue with the world on evidence, outcomes and patient well-being," Merck's former chief medical information and innovation officer, Sachin Jain, MD, wrote on mmm-online.com last year. "It's up to the leadership in pharma to overcome the risks and operationalize this conversation to enhance data-driven approaches, improve population health and critical care and support patient engagement."

Real-world evidence (RWE) is not so much about amassing Big Data, like IBM's Watson supercomputer ingesting copious amounts of information to personalize cancer care. It's more about performing targeted analyses on an expanding data set, including such sources as claims, retail and specialty pharmacy, healthcare registries and electronic medical records.

RWE enables a better understanding of a given market, allowing pharma to leverage it in the post-marketing phase to negotiate for better formulary positioning, tweak launch strategy, facilitate requirements for post-launch approvals or inform the development of future treatment.

Collaborations are the main catalyst driving this movement. Real-time research platform PatientsLikeMe's recent tie-ups with drugmakers AstraZeneca and Genentech, for example, aim to help improve outcomes in oncology.

They follow a number of manufacturer team-ups with PBMs and/or their data shops, like Pfizer and clinical data outfit Humedica, now owned by Optum; or AstraZeneca with HealthCore, which is part of Wellpoint.

Both Wellpoint and Optum are among the big payers starting to look for this type of data proactively, and the Academy of Managed Care Pharmacy (AMCP) now requires manufacturers to submit RWE with their formulary submissions.

One question is whether insurers are equipped to fully implement data and analytics. According to a 2015 study of 145 managed care organizations, 45% of MCOs indicated pharma companies aren't sharing data with them.

Another question going forward is whether industry can use results of these types of studies in its communications. The 21st Century Cures bill, now making its way through Congress, would allow the sharing of comparative-effectiveness research.

The patient conversations in social media provide another important lens for tracking real-world data related to brand performance. And EMRs and HCPs represent the next wave.

But challenges remain in pulling EMR data, including synthesizing it across siloed providers and EMR vendors, and accessing data in structured and unstructured sources.

This problem is particularly difficult in oncology, where the market is stratified into cancer subgroups via datapoints like biomarkers and histology, which are in hard-to-reach unstructured documents such as clinical notes and pathology reports.

Specifically in cancer, IMS Institute for Healthcare Informatics is working to demonstrate effectiveness in genetic populations by linking biomarker data to treatment information.

Better outcomes through cancer genomics is also at the heart of Flatiron Health, which bills itself as the largest real-world evidence platform for oncology. Google has invested $130 million in Flatiron, a start-up founded by two ex-Googlers which is building a cloud system to analyze cancer data—basically collecting information from hospital systems about cancer patients, treatments and outcomes.

Real-time analytics on top of this data has the potential to inform commercial decision making. It's an ideal time for industry to step up its data-driven oncology game. ■

"Pharma is at the beginning of a dialogue with the world on evidence, outcomes and patient well-being."

—Sachin Jain, *MD, MBA, chief medical officer of CareMore Health System*

45% of MCOs said pharma companies don't share data

—Digital and Data Trends in the Payer Marketplace report, 2015, Precision Advisors

Clinician Marketing: Forging New Alliances

The rise of biomarker-based pharmaceuticals, multiple indications and an upheaval in oncology's business model pose significant challenges to communicating with clinicians. New frameworks will need to be built from the ground up

In addition to the traditional informational challenges associated with launching any new set of revolutionary drugs, sales and marketing executives tasked with commercializing oncology's incoming wave of novel therapeutics will likely be forced to create and foster lines of communication that haven't existed in the history of the pharmaceutical business.

Perhaps the most significant factor affecting commercialization will be the explosive rise of biomarkers and their attendant companion diagnostics. According to a recent Tufts University report, 73% of all pipeline oncology drugs rely on biomarkers.

Even among non-cancer drugs billing themselves as "personalized," that same figure is only 43%, the report found. It's possible that within five years every cancer patient will undergo a biopsy as a standard of care. And that is to say nothing of genomic screening and prevention efforts among healthy patients.

This means that laboratories and in-vitro diagnostic manufacturers are poised to become industry stakeholders at a level never before seen in oncology or in any other field. Hence an entirely new trail needs to be blazed, one where "the relationship between two widely differing industries that operate in different environments with different end users of their products is perhaps the most vital aspect in ensuring the success of any drug-companion diagnostic," according to a white paper by Peter Thorton, a senior analyst at FirstWord Dossier.

Put another way, makers of new cancer drugs will be among the first ever to establish a logistical framework for mass promotion of personalized medicine.

Meanwhile, communicating the basic science presents its own challenges. For starters, noise is expected to be extreme. A recent analysis of pipeline agents for five popular mechanisms of action found at least 100 different Phase-II and Phase-III trials targeting 11 key tumors. Merck's promising anti-PD-1 agent Keytruda alone is zeroing in on 30 different tumor types. Moreover, the imminent arrival of double- and perhaps triple-combination drugs threatens to heighten perplexity, with companies perhaps collaborating on a combo therapy with two proprietary molecules while simultaneously those very same molecules compete against each other in different indications.

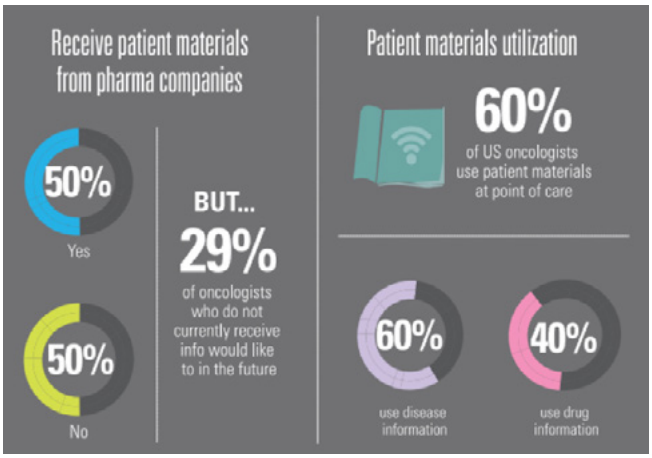
Additionally, financial push-back, already under way and near certain to worsen, means access to pathway and guideline creating organizations, such as the National Comprehensive Cancer Network, will be as important as targeting oncologists themselves—maybe more so.

Lastly, as oncology aggregates into larger group practices and hospital infusion centers play a bigger treatment role, mid-level practitioners, office staff and non-clinical employees will have an increasingly greater influence. Learning to communicate with the likes of pharmacy technicians, infusion nurses, reimbursement experts and social workers will gain importance.

Marketing ought to be part of the process early. "With proliferating options, creating a story for oncologists is more important than ever," says Kate Booth, VP of strategy at medical-communications agency LehmanMillet. "This speaks to the need to build those messages and RTBs [real time bids] from preclinical to in-clinic to in-vivo trials and ultimately to the market." ■

The Oncologist Will See You Now

Resources used, and those clinicians are open to receiving from pharma



Source: Concentric Health Experience

Makers of new cancer drugs will be among the first ever to establish a logistical framework for mass promotion of personalized medicine.

81% of oncologists say pharma must provide resources and services, alongside treatments, to stay relevant

—Manhattan Research, ePharma Physician 2014

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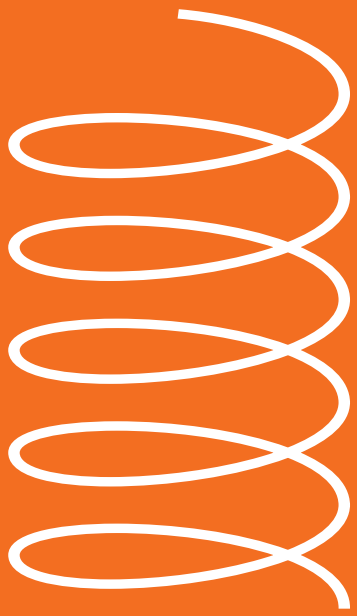

IV line
Genome
Disease progression
School of fish
Resilience

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The Patient Lens: Adding Context to Care

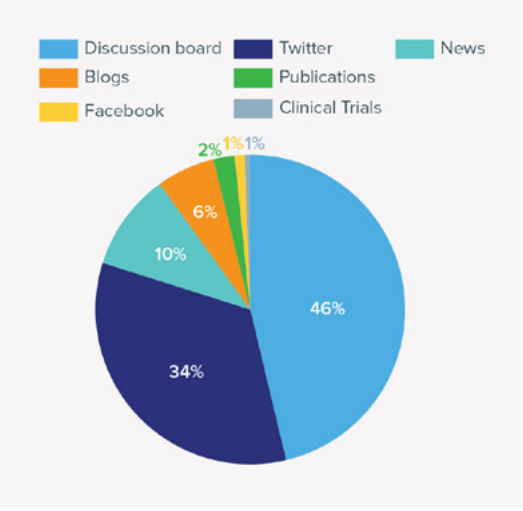
Researchers hope to transform the most aggressive cancers into chronic diseases rather than death sentences. To the extent they succeed, patient concerns, both collective and individual, will move to the forefront. Unfortunately, oncology's infrastructure is not fully prepared for this shift

Several factors have combined to make cancer a more patient-centric disease.

First and foremost, extended survival times mean quality of life (QoL) has gained significance. Second, as therapies grow more costly, patients want to know what they are getting in return for increased out-of-pocket outlays. Third, the rise of oral agents means therapy adherence has greater influence on outcomes. Finally, in an age where even the elderly are online, patients know more about clinical breakthroughs at a faster pace than ever before.

Where Patients Go

Discussion boards are the leading channels for brand conversations in prostate cancer (n=25,733)



Source: IMS Institute for Healthcare Informatics

Well aware that clinical trials are neglecting subjective patient feedback (it is often tacked on as an afterthought and/or not powered to be statistically significant), the FDA has taken steps to encourage pharma companies to give greater weight to patient-reported outcomes (PROs), patient comments not filtered through or interpreted by clinicians. In 2009 the agency published guidelines, "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims," in hopes of giving the term *clinical benefit* additional QoL emphasis. "In some diseases, waiting for overall survival data to mature can delay getting safe and effective drugs to patients," FDA Associate Director for Labeling Virginia Kwitkowski told the *ASCO Post* last year.

And patient voices are starting to be taken seriously by the medical establishment. Dave deBronkart, best known as "e-Patient Dave," had something of a moment when the chief residents at the Mayo Clinic invited him to be their visiting professor in internal medicine, a rotation he completed this past March.

DeBronkart also snared a fellowship at a think tank in Boston to study and develop patient engagement and spoke at the European Society for Medical Oncology (ESMO) last year.

"At ESMO, people were talking about patients getting involved much earlier in the clinical trial process, even in defining the goal of drug development," deBronkart said.

For industry, the new patient centricity can have myriad consequences. For one thing, in many markets outside the US, where pricing is tied to outcomes, QoL factors may impact profits. Moreover, among oral medications, a lack of patient adherence will negatively impact outcomes, thus ultimately the brand itself. For example, in chronic myelogenous leukemia, where oral agents have largely supplanted chemotherapy, clinicians face an uphill adherence battle, despite the lifesaving nature of the medications.

Hence the growing opportunities for companies that provide patients with discount cards to reduce co-pays. This simple service grants such companies insight into behavior, demographics and data analytics. In addition to cards improving adherence, according to some accounts by as much as 20%, company surveys and demographic information offer a window into patient conduct. For instance, data analytics can identify patients at risk for non-adherence before therapy even begins.

"Essentially what we offer are like patient-reported outcome programs," says Paul LeVine, VP of analytic services for North Carolina–based TrialCard. "The next step up is data profiling for determining risk factors."

No discussion of patients in oncology would be complete without touching on access to treatment. Overall oncology treatment costs have increased 39%

"At ESMO, people were talking about patients getting involved much earlier in the clinical trial process."

—Dave deBronkart, aka "e-Patient Dave"

#GetNaked

The Melanoma Research Foundation's campaign, which ranked one of the top four topics on Twitter since its launch in 2014

—Treato

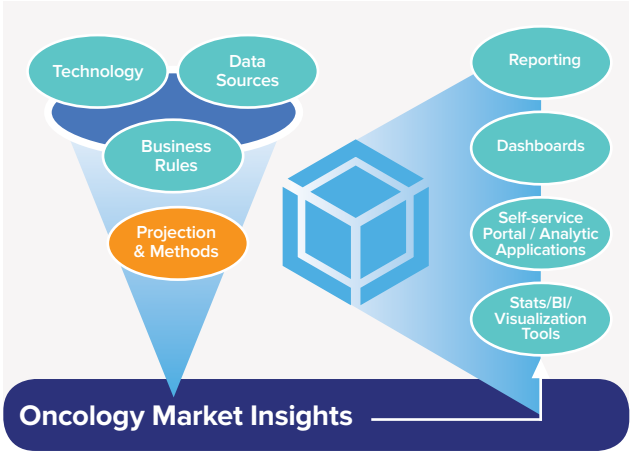
A new Real-World Evidence tool to improve the effectiveness of oncology communications

Announcing the launch of the Oncology Market Insights (OMI) Platform to deliver more precise and actionable commercial analytics to help strategic decision-making and optimize and measure sales execution and performance.

- Fully integrated technology solution that provides efficient access to clinically robust market, product and competitive data in the U.S.

OMI joins a suite of IMS Health's oncology offerings, including its anonymous real-world data oncology assets from EMR, claims, hospitals, diaries and mortality databases

- Covering 13+ countries, 3 continents and 25+ primary cancers
- Providing access to cancer-specific registries



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over the past 10 years, according to a report by the IMS Institute for Healthcare Informatics.

Between 2012 and 2013, intravenous oncology therapy costs shot up an astonishing 71%. Most oncologists now calculate patient co-pays and out-of-pocket expenses before discussing treatment options, an activity far less prevalent 10 years ago.

Financial concerns are a frequent discussion topic on social-media sites, where cancer patients increasingly gather, according to the IMS report. Online discussion boards and Twitter are the most popular venues, news websites and blogs less so and Facebook and clinical trial sites are least popular.

"They [cancer sufferers] aren't going to WebMD; they're going to melanoma.org," said Ezra Ernst, chief commercial officer for Treato, the Israeli digital health firm that crunches patients' online discussions about diseases and drugs into usable insights, at *MM&M*'s SkillSets Live event in May.

Despite manifold challenges, monitoring social media and engaging with patient advocacy groups are good ways to track brand performance and correct misinformation before it gains traction, experts say. ■

Overall oncology treatment costs have increased 39% over the past 10 years.

—IMS Institute for Healthcare Informatics

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GET

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The Value Question: Are Costs Justified?

Some hail recent advances in cancer therapy as the crowning achievement of biomedical progress. Others see a boondoggle of wasteful spending. Which side commands the moral high ground? Let's crunch some numbers

A recent National Bureau of Economic Research working paper offers a dismal cost-benefit analysis of recent cancer therapies. The authors calculated "price per life year" for cancer patients by taking the price per treatment episode, in 2013 dollars, and dividing it by the survival benefit conferred by the therapy.

From 1996 to 2013 the cost per life year of cancer therapy rose more than threefold, the paper found. And the inflation-adjusted price of cancer drugs and therapies grew fourfold.

"Put another way," the paper explains, "in 1995 patients and their insurers paid $54,100 for a year of life. A decade later, 2005, they paid $139,100 for the same benefit. By 2013 they paid $207,000.

"There was no significant relationship between cost and the percentage improvement in end point," the authors conclude, adding "our results suggest that the price of cancer drugs is independent of novelty … current pricing models are not rational but simply reflect what the market will bear."

The authors are not alone in their views. Although many see recent cancer breakthroughs as the dawn of a new era in medicine, an equally vocal faction argue that the relatively small efficacy gains made thus far are not equivalent to rising costs.

Usually payers, budget cutters and policy maker types advance such arguments, often along with calls for clinical pathways, competitive pricing, prior-authorization criteria and other forms of financial push-back. In the short term, market analysts believe oncology drug prices, especially for physician-administered modalities such as the new CTLA-4 and PD-1/PD-L1 drugs, are on more solid footing than other therapeutic categories undergoing similar pressure.

However, this year physicians and consumer advocacy groups joined the fight against rising costs, which could translate to political influence at higher levels. Calls for Congress to return Medicare and Medicaid's ability to negotiate directly with drug manufactures, rescinded in 2003, have emerged as a common rallying cry.

In response, industry advocates say efforts to highlight therapy's benefits should be redoubled. Numbers can be crunched differently. For example, a study by the IMS Institute for Healthcare Informatics found overall response rates in 2014 exceeded those in 2004 by 42%, while in that time period, price per month of therapy rose only 39%.

Also, scholars' calculations almost always use a drug's list price without factoring in the common practice of negotiated discounts, according to a blog post by Robert Zirkelbach, senior vice president of Communications at PhRMA.

"High generic utilization rates, competition among brand-name medicines and aggressive tactics by insurers to negotiate prices all help to control how much the US healthcare system spends on medicines," he wrote.

Generics are usually priced higher in Europe than in the US, he added. Hence, although Americans pay more for new drugs, they pay far less later on. ■

PBMs Gain Heft, Seek to Influence Pricing

In May CVS Health said it will buy nursing-home pharmacy company Omnicare in a deal valued at around $12.7 billion. Adding Omnicare to its PBM business gives CVS a big presence in Medicare Part D drugs, which are self-administered. Having a presence in long-term care could help CVS clamp down on oncology med spending, given that cancer is generally an older person's disease.

Soon after that, CVS's chief rival, Express Scripts, announced a plan to develop a new system that will tie what it will pay for a drug based on how well the oncology therapy performs in a patient with a certain type of cancer.

The moves show how PBMs are seeking to use their clout, which they've already mustered to negotiate large discounts on pricey new hepatitis-C therapies (and, they hope, to forthcoming lipid lowerers in the PCSK9 drug class), to cut costs in cancer, as well.

This year physicians and consumers joined the fight against rising costs, which could translate to political influence.

$62B

The amount Medicare spent on "Part D" oncology drugs vs. $20B on"Part B" drugs. It's the biggest payer for both types of drugs in the US

—GAO, CBO (2010), as cited by Bernstein Research