

May 2014

Innovation in cancer care and implications for health systems

Global oncology trend report



Introduction

Cancer remains a top priority for health systems around the world as incidence levels rise, fueled by growing and aging populations. While some incidence is preventable and early diagnosis and treatment can reduce or delay mortality significantly the reality is that countries struggle to bring together the right combination of measures including vaccines, diagnostics and therapeutics.

The economic consequences of cancer also make it a priority due to the impact of patient and caregiver productivity loss, and rising treatment costs. Recent increases in the numbers of new treatment options raise concerns about affordability for publicly and privately funded health systems alike.

In this report, we bring together the most comprehensive review of current trends in the oncology market, the state of innovation in therapeutics, measures of the value of treating cancer, and pricing trends. The report also assesses the opportunity for biosimilars to reshape the oncology drug market, especially in low and middle income countries, and the specific dynamics playing out in the U.S. where changes in site of care and patient sharing of costs associated with cancer treatment are having a significant impact on costs and behaviors.

The development of this report was guided by an external Advisory Board whose input on topics to cover and perspectives to develop was invaluable. The support of the entire global, multi-disciplinary IMS Health Global Oncology team, led by Kjell Johnson, was also critical to the report's creation. We gratefully acknowledge Kjell Johnson, Lee Blansett, Marla Kessler, Michael Kleinrock, Jennifer Lyle, Stefano di Biase, Hemanth Kumar, Bernadette Collins-Griffin, Radha Mawrie, Jane Quigley, Walter Colasante, Tracy Milanette, Xiaolong Jiao and many others for their substantial contributions to this piece.

This report was produced as a public service without industry or government funding.

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Executive Summary

The intensifying global focus on oncology reflects its increasing impact on patients and expanding share of healthcare expenditure. The vast, growing market of oncology drugs is dynamic, with characteristics differing greatly across markets. While developers continue to innovate cancer therapeutics, greater scrutiny is placed on the price/benefit ratio of those innovations. Establishing the value of cancer treatments is challenging even with the most robust clinical data, and not surprisingly, payers have different approaches in determining which treatments to reimburse, in what circumstances, and at what levels. Amidst these dynamics, broader reforms in healthcare systems – such as those currently underway in the U.S. – bring additional sources of disruption as the intended and unintended consequences of change unfold.

Market dynamics

The global market for oncology drugs, including supportive care, reached \$91 billion in 2013, as measured at ex-manufacturer prices and not reflecting off-invoice discounts and rebates. Although this is up from \$71 billion in 2008, it represents a compound annual growth rate of 5.4%. The modest rate reflects a lack of breakthrough therapies for very large patient populations, patent expiries, reductions in the use of supportive care medicines and stronger payer management. This rate of growth is significantly lower than seen during the 2003-2008 period when growth each year exceeded 15%, driven by a small number of breakthrough therapies. Differences in incidence rates, access to medicines and treatment protocols are substantial between countries, but cancer is still a leading area of healthcare spend. In pharmerging markets, oncology is expected to be the fourth highest spend therapy class by 2017. While the U.S. and top five European markets have declined in their share of the global market, they still dominate it with 65% of total sales. Targeted therapies have dramatically increased their share of the oncology market, now accounting for 46% of total sales, up from 11% a decade ago.

Innovation

Developers have brought innovation across cancer types and therapeutic approaches, including preventive vaccines. Pharmaceutical company investments remain high and cancer therapies account for more than 30% of all preclinical and phase I clinical developments, with 21 new molecular entities being launched and reaching patients in the last two years alone. These new medicines have increased the complexity of treating cancer, leading to more combination therapies and additional lines of therapy. Clusters of innovation based on similar underlying science but separate development paths have transformed patient care in areas such as advanced melanoma and sub-populations of cancers with higher prevalence. Commercial returns for some recently launched oncology drugs have been as high as earlier benchmarks such as bevacizumab or imatinib. Many new drugs, however, are for small patient populations and face strong competition, lowering their level of sales and therefore returns to manufacturers. Investment in near-term future innovation has shifted toward biologics, mostly concentrated in targeted treatments, though preclinical products are mostly small molecule. While much of the pipeline is focused on lung and breast cancer, tumor types with lower prevalence such as ovarian, leukemia, stomach, and liver cancers are also being actively pursued. Immunology therapy has become a strong focus of investment recently based on current success in clinical trials and a promising outlook.

Value of treating cancer and pricing trends

The high number of new targeted therapies launched and available for cancer patients has also escalated payer scrutiny of their value relative to their incremental benefits compared to existing treatments. The average cost per month of branded oncology drug treatment in the U.S. is now about \$10,000, up from an average of \$5,000 a decade ago. Judging the incremental value of these treatments for individual patients is fraught with challenges due to the high level of variability of patient response, the frequent changes to protocol needed for patient care, and underlying issues of equity and patient care. The American Society of Clinical Oncology recently issued recommended targets for meaningful clinical trial outcomes, a useful step to guide those investing in innovation as well as those paying for patient care.

Concentrated payer systems and those with strong health technology assessment bodies tend to pay less for medicines than in the U.S. Pricing discount mechanisms in major European markets drive national net prices down by approximately 20 to 40% compared to U.S. list prices.

Biosimilars

The introduction of regulatory pathways for biosimilars and increased production capacity around the world are bringing a new competitive dynamic to the greater than \$40 billion biologics portion of the oncology market. The potential role of biosimilars in developed markets will be limited, however, if the expected flow of patent-protected innovative products continues to displace older off-patent products subjected to biosimilar competition. Biosimilars already play a role in the supportive care segment of the oncology market in Europe which can be expected to expand to the U.S. in the near-term. In low and middle-income countries, “non-original biologics” – which are based on original molecules never introduced in a particular country – are expected to play a significant role and already capture 60% or more of certain recombinant and synthesized biologics therapy areas. Their role in antineoplastics can also be expected to be significant by 2020. On a global basis, biosimilars – including non-original biologics – are expected to generate \$6-12 billion in oncology sales by 2020, increasing competition but accounting for less than 5% of the total biologics market at that time.

U.S. specific oncology dynamics

The U.S. market accounts for 41% of total oncology drug sales but reforms are impacting cancer treatment site of care, reimbursed fees and patient out-of-pocket costs. While the number of medical oncologists has been rising steadily over the past decade, they are rapidly changing their practice profile. Over 40% of oncologists are now in practices with seven or more physicians, up from 29% in 2012, as smaller practices are aggregated and/or acquired by hospital systems. Oncologists themselves attribute this trend to financial pressures and the desire to alleviate risk.

At the same time, Accountable Care Organizations and healthcare organizations that are covered by the 340b Drug Discount Program have expanded their presence in oncology, moving more patient care from physician offices to hospital outpatient facilities. To reflect hospitals' higher costs and overheads, they receive higher reimbursement to administer drugs compared to physician offices. For typical therapies that are infused or injected by an oncologist, reimbursed costs for hospitals are at least double those for physician offices, sharply increasing costs to payers over the past two years. Patient out-of-pocket costs are then driven higher, depending on the patient's insurance plan and benefit design, which can trigger reduced levels of therapeutic persistence by the patient and higher overall cost of care.

The trends identified and described in this report will continue to evolve in rapid and unexpected ways. Relative to other parts of the healthcare system, oncology brings high levels of uncertainty – in terms of the nature and rate of innovative treatments, the willingness by payers to reimburse care at current levels, and the shifting composition of the cancer patient population from mature and developed markets to low- and middle-income countries. As the sales of cancer treatments rise to \$100 billion annually, more intensive scrutiny of this market can be expected and a deeper understanding of global oncology trends will be required by all stakeholders.

Market dynamics

The global oncology market reached \$91Bn in 2013, marked by a slowing rate of growth; most sales continue to be in the U.S. and Europe although oncology is a dominant spend area for pharmerging nations; the shift in spend to targeted products and away from biologics is occurring globally.

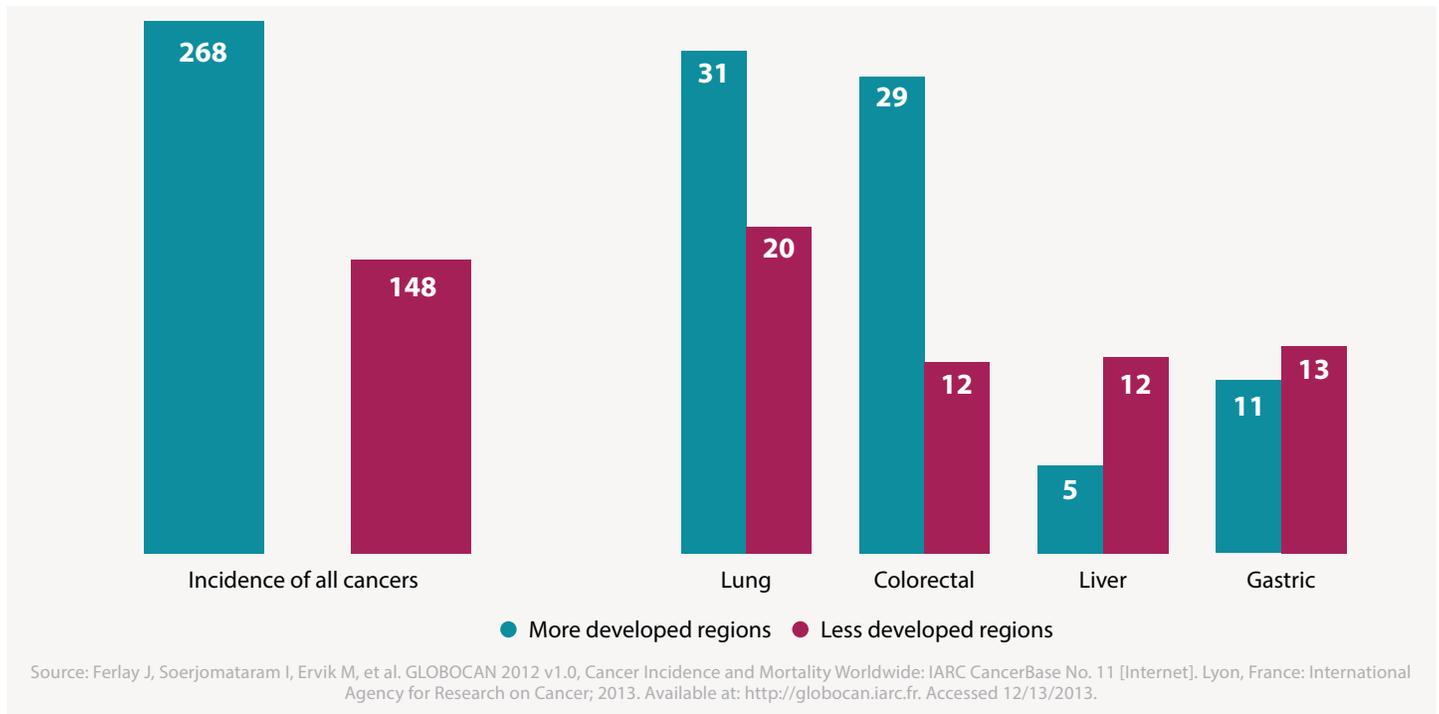
- While incidence of cancer varies by tumor and geography, survival appears to be improving.
- Growth has been more steady in recent years, expanding at a compound annual growth rate (CAGR) of 5.4% from 2008 to 2013 when it reached \$91Bn.
- Oncology spend is still dominated by the U.S. at \$37.2Bn in 2013 although pharmerging nations have made cancer their fourth largest healthcare spend area and are poised for more growth.
- The advent of targeted therapies signaled the first explosion of growth in the global oncology market in the early 2000s and continues to shift the market away from biologics and other agents.

Pharmerging:

China, Brazil, Russia, India, Mexico, Turkey, Venezuela, Poland, Argentina, Saudi Arabia, Indonesia, Colombia, Thailand, Ukraine, South Africa, Egypt, Romania, Algeria, Vietnam, Pakistan and Nigeria

Global cancer incidence rates vary by regions and cancer types

2012 incidence rates (age-standardized incidence rate/100,000)



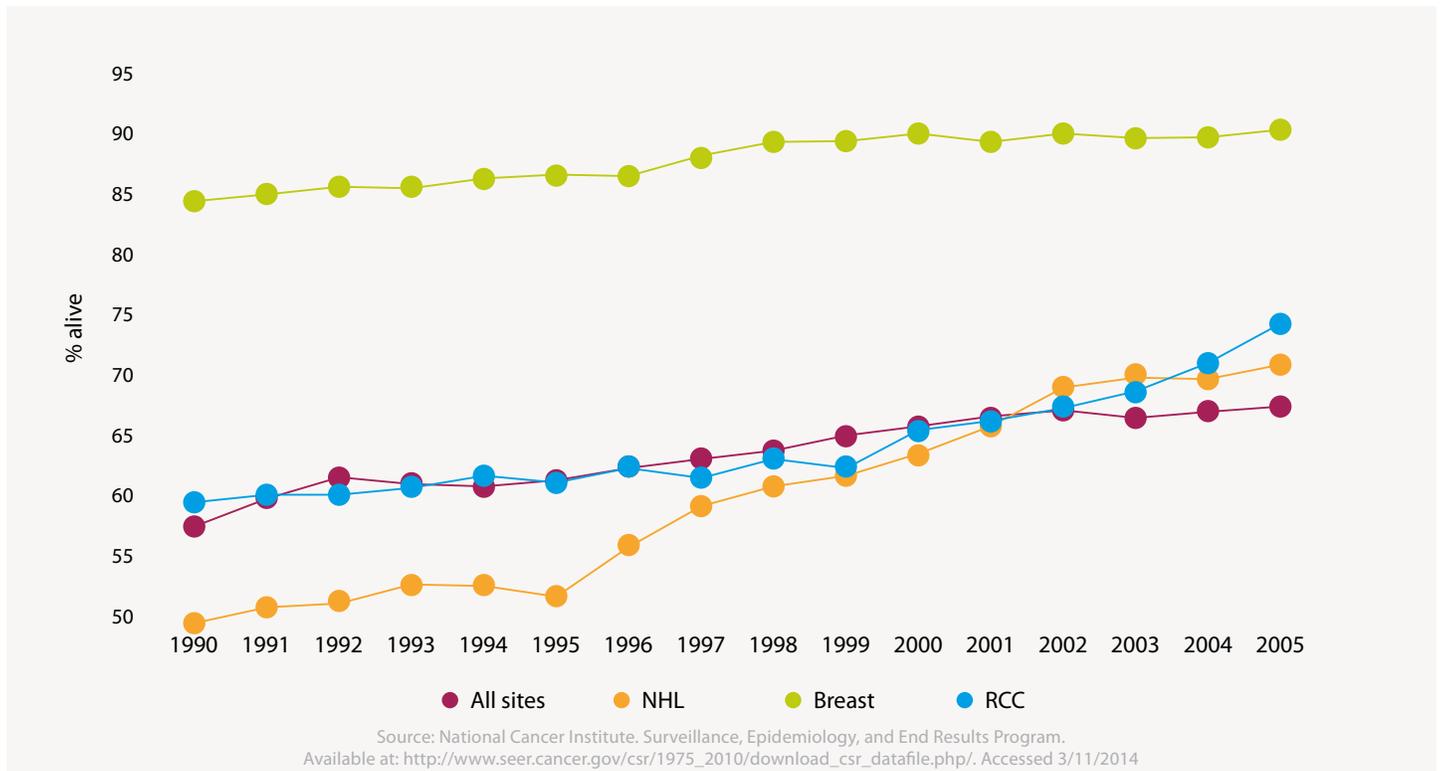
- The degree to which cancer incidence rates differ among countries can be quite substantial: differences arise from both disease trends and data availability.
- Overall, cancer incidence rates are lower in less developed regions; this may be the result of a number of factors.
- Populations in less-developed regions may have diminished access to health care services, and a higher probability of dying before being diagnosed with cancer.
- Public health organizations may be less likely to track and record case information for epidemiologic purposes, potentially resulting in lower perceived incidences.
- In terms of cancer type, lung and colorectal cancer incidence tends to be higher in more developed nations.
- Conversely, liver and gastric cancer incidence tends to be higher in less developed countries.
- A causal link between hepatitis C infection and liver cancer as well as higher likelihood of exposure to environmental toxins may offer some explanation of this phenomenon.
- In developed countries liver cancers will be on the rise due to life style. Obesity will take over as the main cause of hepatocellular carcinoma (HCC) in the U.S. (by 2030 forecasted) and in Europe shortly after.

Chart Notes:

More developed regions: all regions of Europe plus Northern America, Australia/New Zealand and Japan. Less developed regions: all regions of Africa, Asia (excluding Japan), Latin America and the Caribbean, Melanesia, Micronesia and Polynesia.

Cancer survival is improving steadily as detection and treatment improve

Five-year U.S. relative survival by year of diagnosis

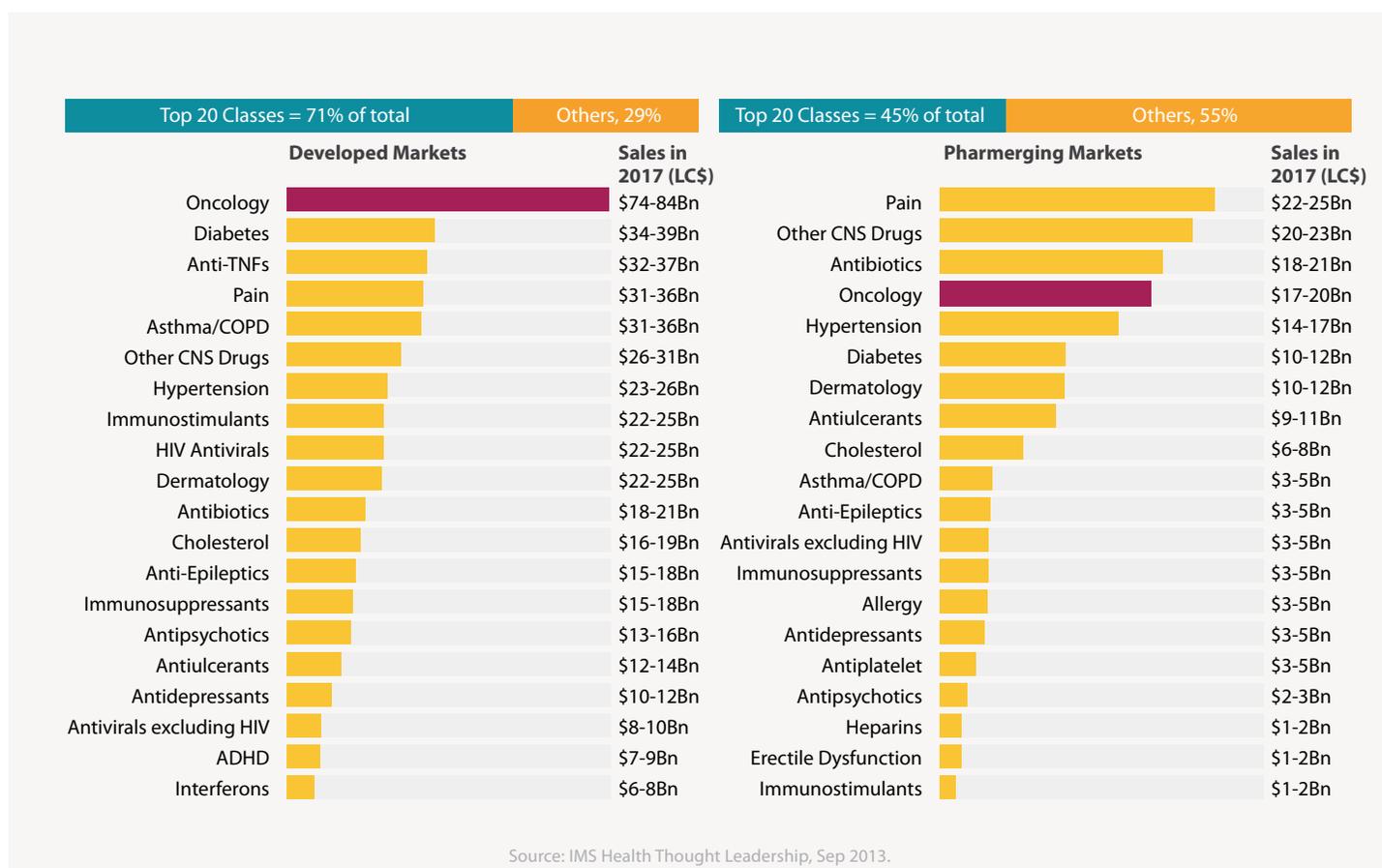


- Survival has improved significantly over the past two decades with published research suggesting that 23% of the improvement is due to behavioral changes, 35% is due to screening, 20% to advances in treatment, and the remaining 22% attributed to other factors.¹
- Non-Hodgkin’s lymphoma (NHL) provides an example of one group of cancers where improving survival is especially pronounced, due in part to the adoption of new targeted and cytotoxic therapies beginning in the 1990s.
- Improvements in survival vary substantially among cancers. Breast cancer, for example, has a historically high survival rate, and has seen only modest improvements despite new therapies being approved.

1. Cutler, David M. Are We Finally Winning the War on Cancer? Journal of Economic Perspectives. Volume 22, Number 4. 2008.

Oncology drives major medicines spend in developed and pharmerging markets

Spending by therapeutic area in 2017 (oncology does not include supportive care)



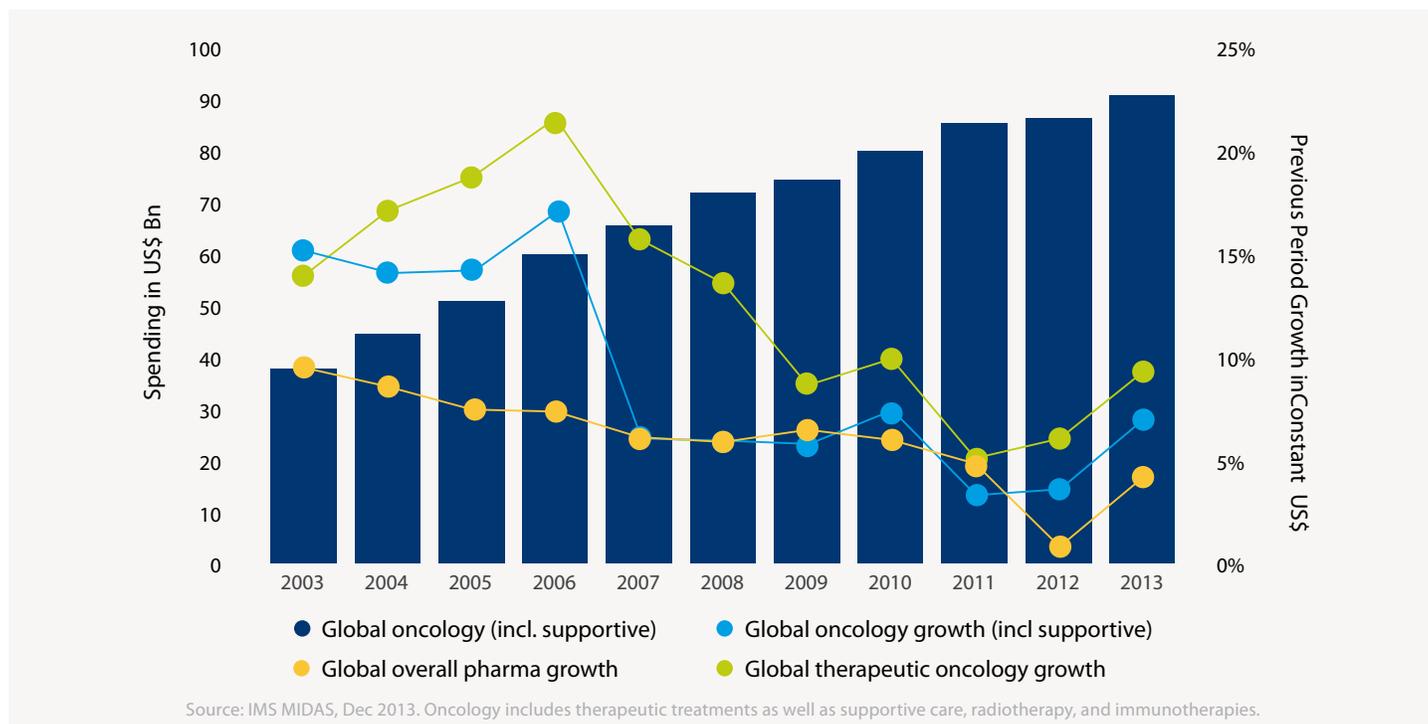
- Oncology is forecasted to be the number one therapeutic area for developed nations in terms of 2017 spending leading all other therapeutic areas, even those associated with primary care.
- Among pharmerging nations, oncology is anticipated to be the fourth-largest therapeutic area in terms of spending in 2017 and the largest specialty area, only falling behind certain primary care therapeutic areas.

Chart notes:

Pharmerging: China, Brazil, Russia, India, Mexico, Turkey, Venezuela, Poland, Argentina, Saudi Arabia, Indonesia, Colombia, Thailand, Ukraine, South Africa, Egypt, Romania, Algeria, Vietnam, Pakistan and Nigeria.

Global spending on oncology drugs has grown to \$91Bn in 2013, including supportive care

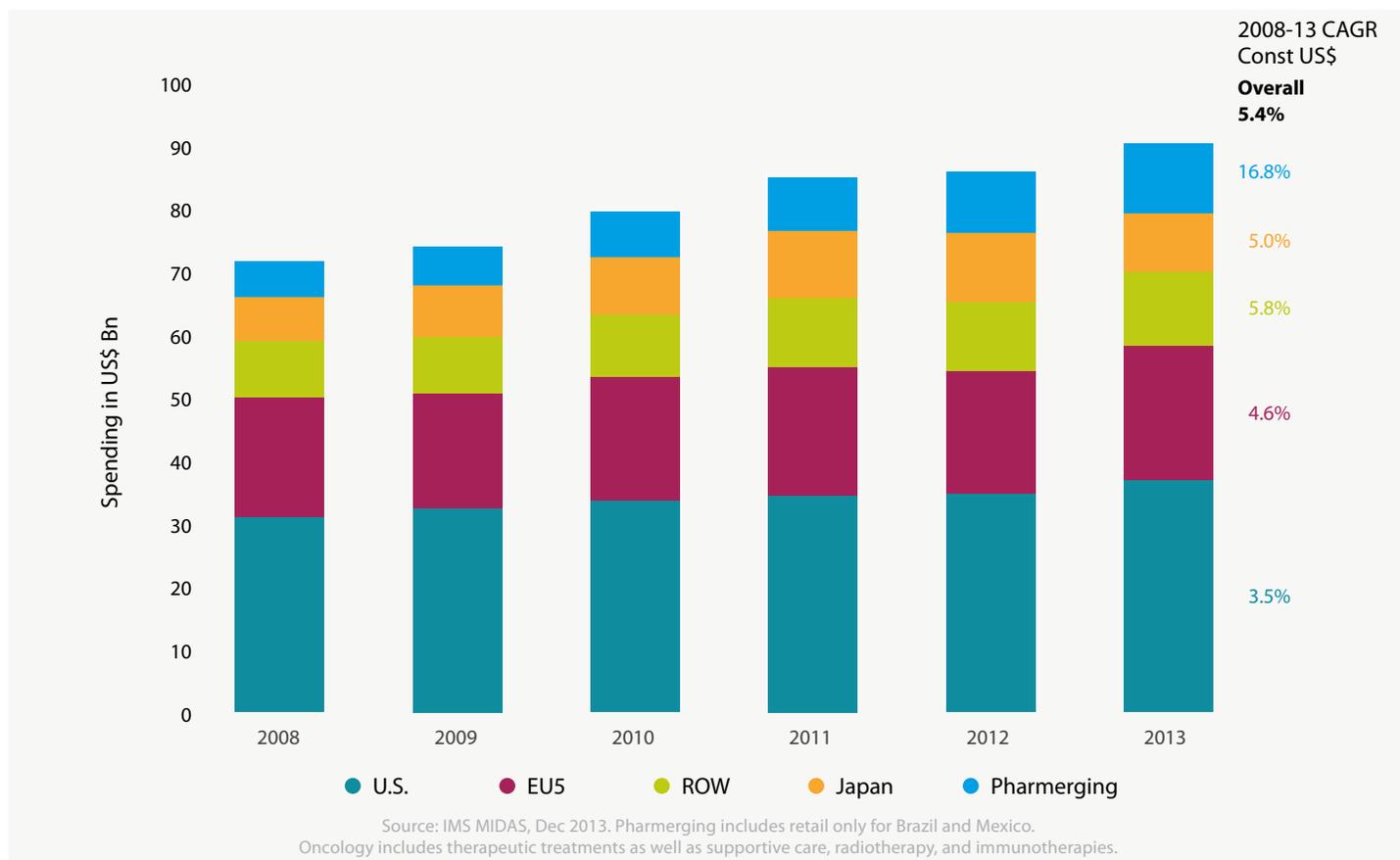
Global oncology market dynamics 2003-2013



- From 2003 to 2008, growth was consistently above 15% for therapeutic agents, reflecting the launch of bevacizumab (Avastin) and expansion of trastuzumab (Herceptin) into adjuvant breast cancer.
- Safety issues regarding the use of the erythropoietin stimulating agents (ESA) in 2007 resulted in a dramatic drop in their use, particularly in the U.S.
- Most launches between 2005 and 2009 addressed smaller patient populations and saw lower adoption rates than earlier products.
- 2012 featured a record number of FDA approvals, particularly in oncology.
- Meanwhile, the growth of Herceptin and rituximab (MabThera/Rituxan) sales slowed in 2013.
- Recent approvals for lymphomas, immunotherapy agents for melanoma, PD-1 modulators, and anti-PD-L1 therapies represent the next phase of targeted agents in oncology.

The global oncology drug market grew annually by 5.4% from 2008 to 2013

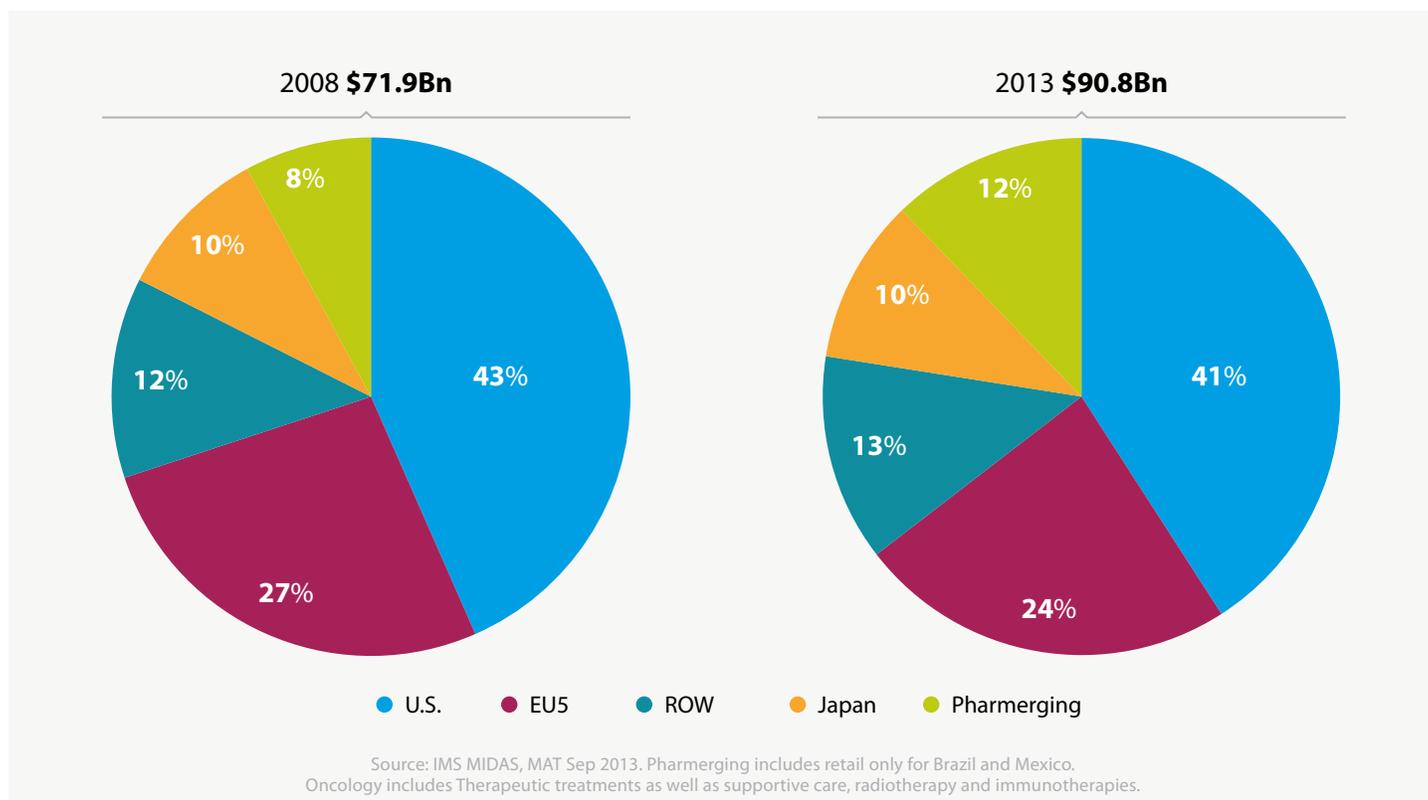
Global sales of oncology drugs 2008-2013



- Annual oncology sales have consistently increased globally.
- The U.S. has maintained the largest share of these sales since 2008, most recently tallied at \$37.2Bn in 2013.
- U.S. oncology growth was impacted by reduced use of ESA and slow sales uptake from launches as reflected in the 2008 to 2010 figures.
- Pharmerging nations have been demonstrated to be the fastest growing segment of the global of the global market, while European growth has been more stable.

Oncology spending is still dominated by the U.S. and EU5

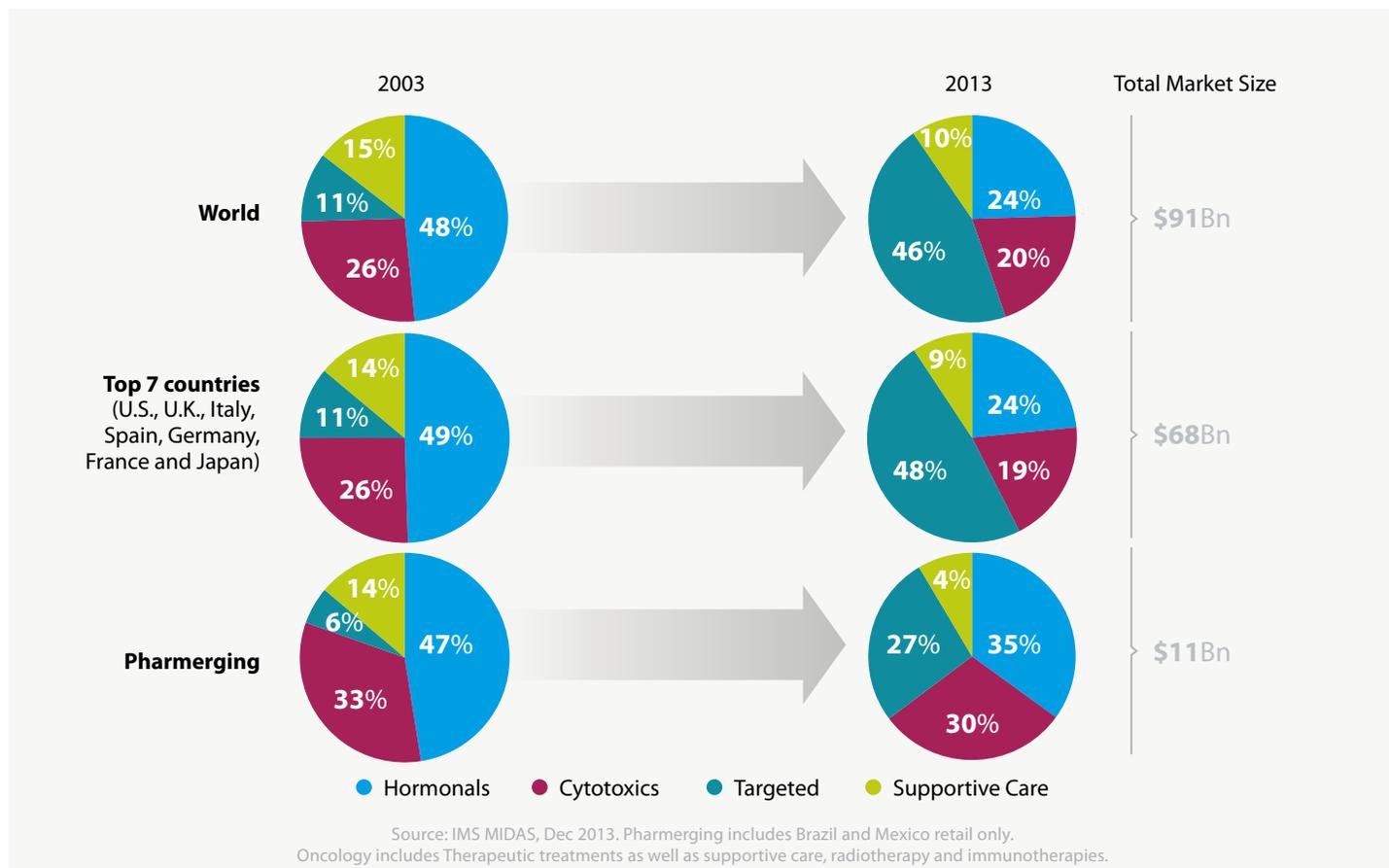
Proportion of oncology spending by global market share, 2008-2013



- U.S. share of total spending declined by 2% but remains the largest oncology market.
- The five largest European markets also reduced their share of the global spending by 3%.
- While the pharmerging share of total spending has grown by 12%, 75% of total sales are represented by the U.S., EU5, and Japan alone.
- The U.S. relevance in global oncology extends beyond its size but also because the access and pricing associated with the U.S. health care system have encouraged use of innovative treatments.

Targeted therapies have dramatically increased their share over the past 10 years, especially in mature markets

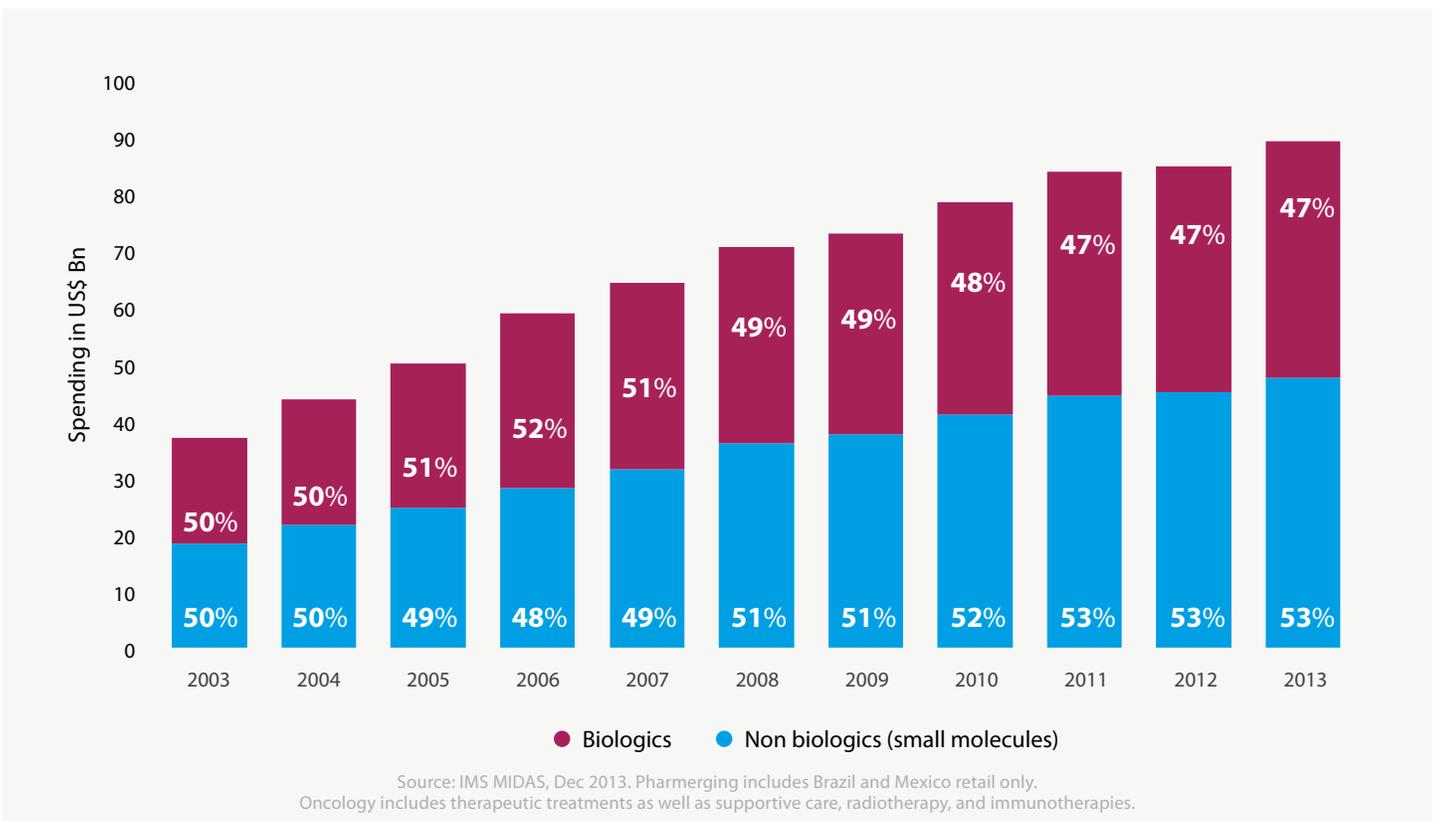
Transformation of oncology treatment modalities, 2003-2013



- Targeted therapies such as MabThera/Rituxan, Avastin, and Herceptin truly represent the present and future of the oncology market.
- As a result, the cytotoxic therapy share of spend is declining.
- Hormonal therapies are experiencing a relative decline in share similar to that of cytotoxic therapies, although to a less dramatic extent.
- The top seven countries in the global market are leading the charge toward targeted therapies, ahead of the world as a whole.
- Pharmerging countries are lagging behind that of the top seven countries in share of targeted agents.

Biologics share of the global oncology market has been declining

Oncology 2003-2013: biologics vs. non-biologics sales



- Oncology sales have more than doubled over the past 10 years.
- As the markets continue to grow, they are shifting to non-biologic products reflecting more targeted therapies and less supportive care use.
- To date biosimilars have not had a large impact in oncology.
- Biologics share of the global oncology market has been declining since 2008, driven by less supportive care use.
- Most oncology products launched since 2007 are small molecules and many are available in oral form.

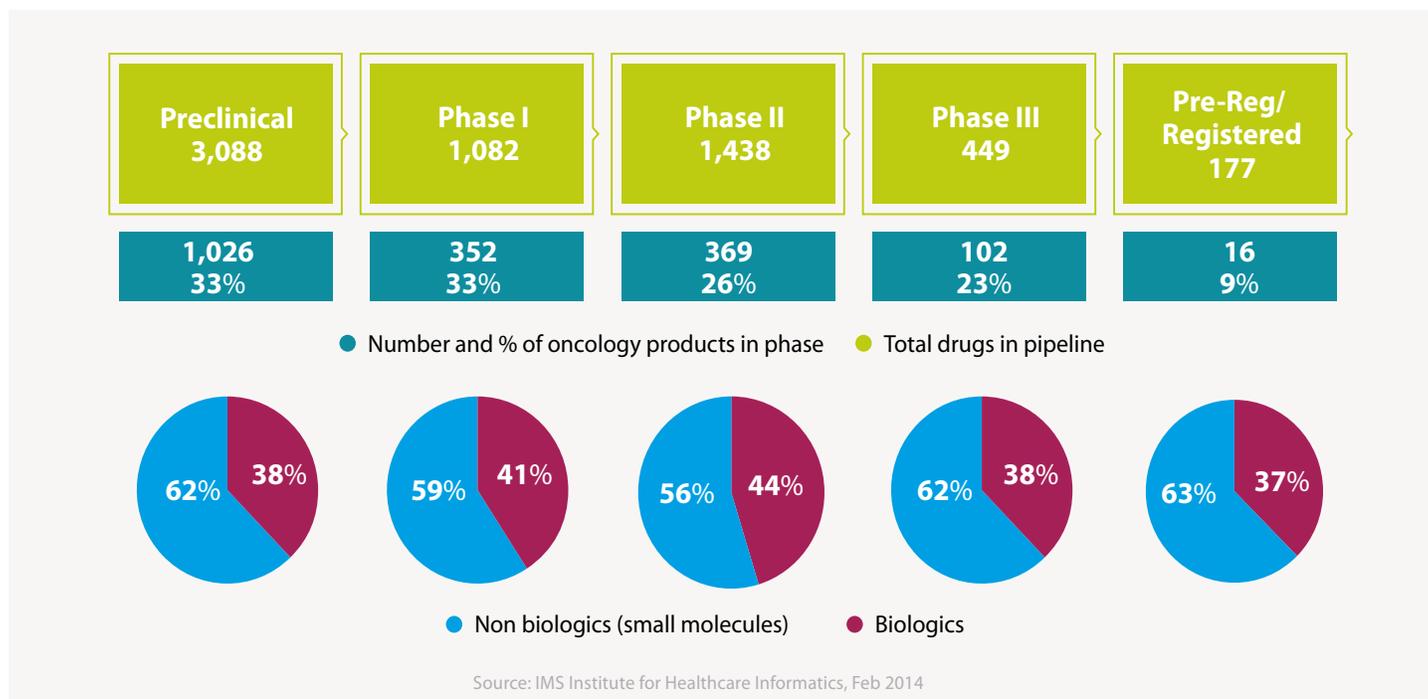
Innovation

Innovation in oncology continues to dominate the drug development pipeline, led by targeted therapies and clustering around cancer types as new molecular targets are identified; the high failure rate and increasing competition, however, make it notably risky and expensive to bring new cancer therapies to patients.

- Cancer remains the biggest portion of the overall drug development pipeline in earlier phases with four times the number of drugs in the pipeline than the next largest therapeutic class.
- After an innovation slowdown through 2008, the oncology pipeline has increased with more accelerated approvals (34% of Breakthrough Therapy Designations (BTDs) are for cancer) and a clear shift to non-biologics.
- The environment for oncology launches has changed with evolving diagnosis practices, more complex treatment paradigms, and increased competition; the result is that a number of oncology launches reaching blockbuster status while others have fallen flat quickly after launch.
- Nevertheless, advances in underlying science have led to innovation clusters around certain cancer types, as reflected in the recent developments in therapies for metastatic melanoma, prostate cancer, and lung cancer.

Oncology is the largest area of focus in R&D, with almost 2000 products in the pipeline

Number of active products in the pipeline to date = 6,234



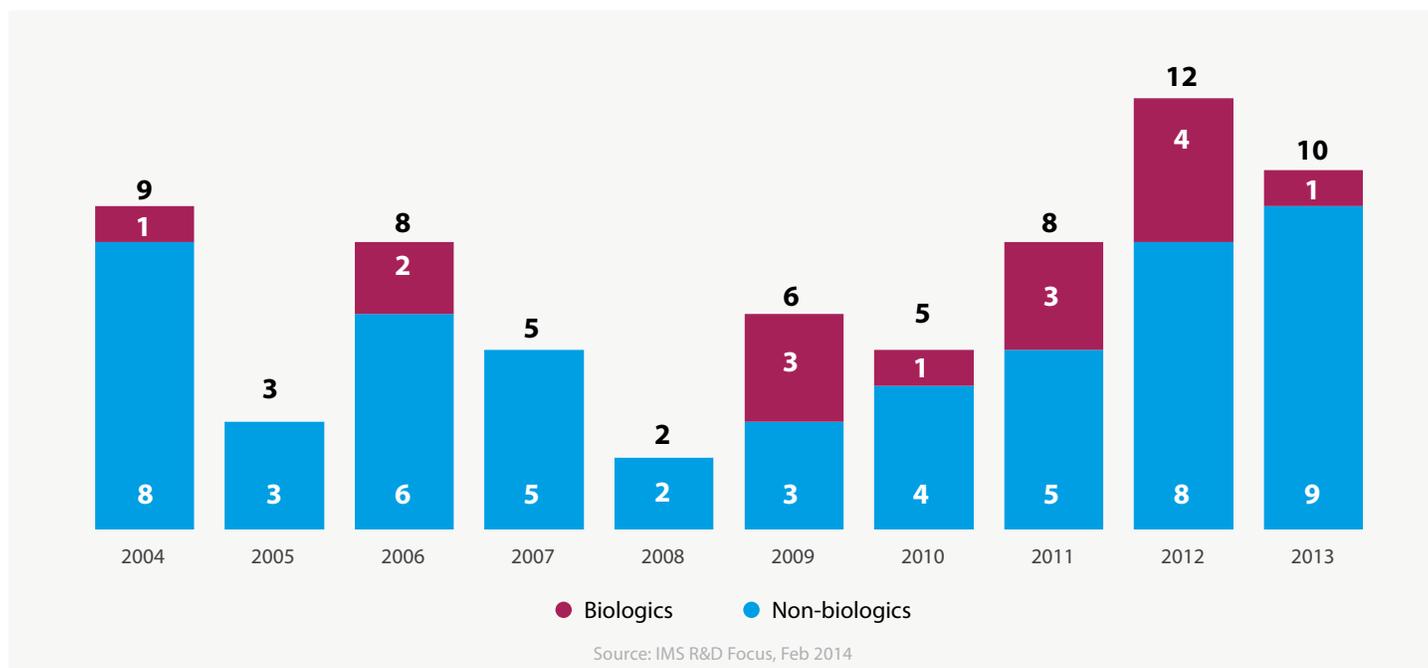
- Oncology represents the largest cluster of R&D activity, with over 30% of preclinical and phase I activity.
- Fewer cancer drugs are progressing to phase II and III which indicates both the high levels of early phase activity and the difficulties in generating successful results in the clinic.
- While only 9% of drugs pending with regulators were for cancer, over a quarter of NME launches in the past three years in the U.S. were cancer medicines, and cancer medicines are more likely to be fast-tracked by regulators and progress rapidly from phase III to approval.
- The first drug launched with an FDA breakthrough designation was a cancer drug (obinutuzumab; Gazyva), and many of the others pending with FDA with this designation are also cancer treatments.
- In 2013, 17 new drugs were launched to treat orphan diseases, rare conditions affecting less than 200,000 people and for which few therapies are effective. Eight of the new orphan drugs were for the treatment of cancer, and many were fast-tracked by the FDA.

Chart notes:

Chart notes: Chart counts the number of unique products in R&D for the most-advanced phase they are being researched for. Many cancer drugs are investigated for multiple indications and counting only unique products may understate late-stage cancer research.

The majority of new molecular entities approved in cancer over the last decade have been non-biologics

Oncology NMEs launched globally 2004-2013



- Most common malignancies among non-biologic therapies between 2011 and 2013 were blood cancers (7); skin cancers (5); and colorectal, lung, and prostate (all 2).
- The 2013 non-biologics group included a number of kinase inhibitors and a new immunotherapy for chronic lymphocytic leukemia (CLL).
- The years spanning 2004 to 2006 represented the last big period of major oncology approvals including transformative products like Avastin and its line extensions, cetuximab (Erbix), sunitinib (Sutent), sorafenib (Nexavar), and erlotinib (Tarceva).
- Some of the most interesting new mechanisms first approved in 2011-13 were antibody-drug conjugate (ADC; trastuzumab emtansine; Kadcyla in solid tumors), an immunomodulatory agent (pomalidomide; Pomalyst), and a CD20 B-cell antibody (Gazyva).
- Launches have progressed at differing rates globally, but the U.S. and global launch totals in 2012 and 2013 are two of the highest in a decade with 21 global oncology launches and 19 in the U.S., bringing new therapeutic options to millions.

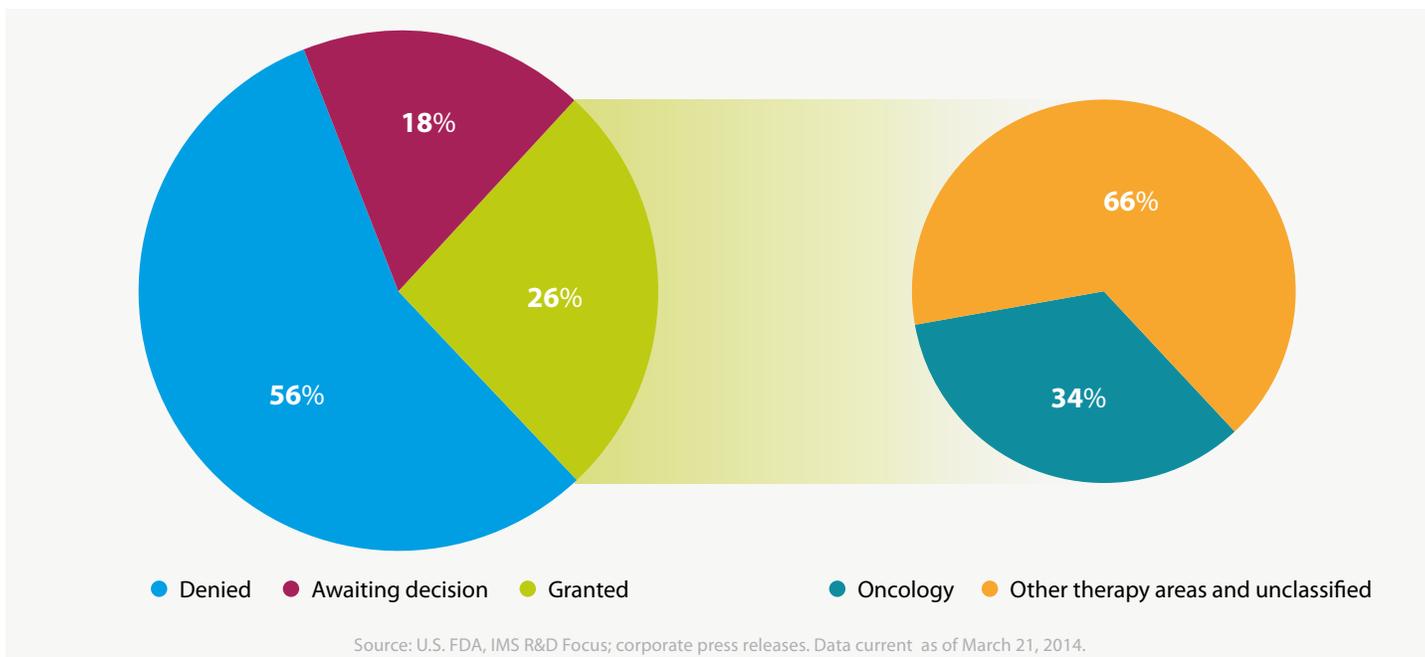
Chart notes:

New Molecular Entity (NME): A novel molecule or biologic entity or combination where at least one element is novel.

NME launches globally by year of launch, regardless of timing approval. Oncology NME launches include therapeutic oncology treatments, and include supportive care and diagnostics. Pipeline includes reformulations, drug delivery systems, and fixed dose combinations in addition to fully novel entities. Pipeline includes most advanced indications of the product, and does not include other indications.

Manufacturers seek accelerated approvals under regulatory provisions to reduce time-to-market

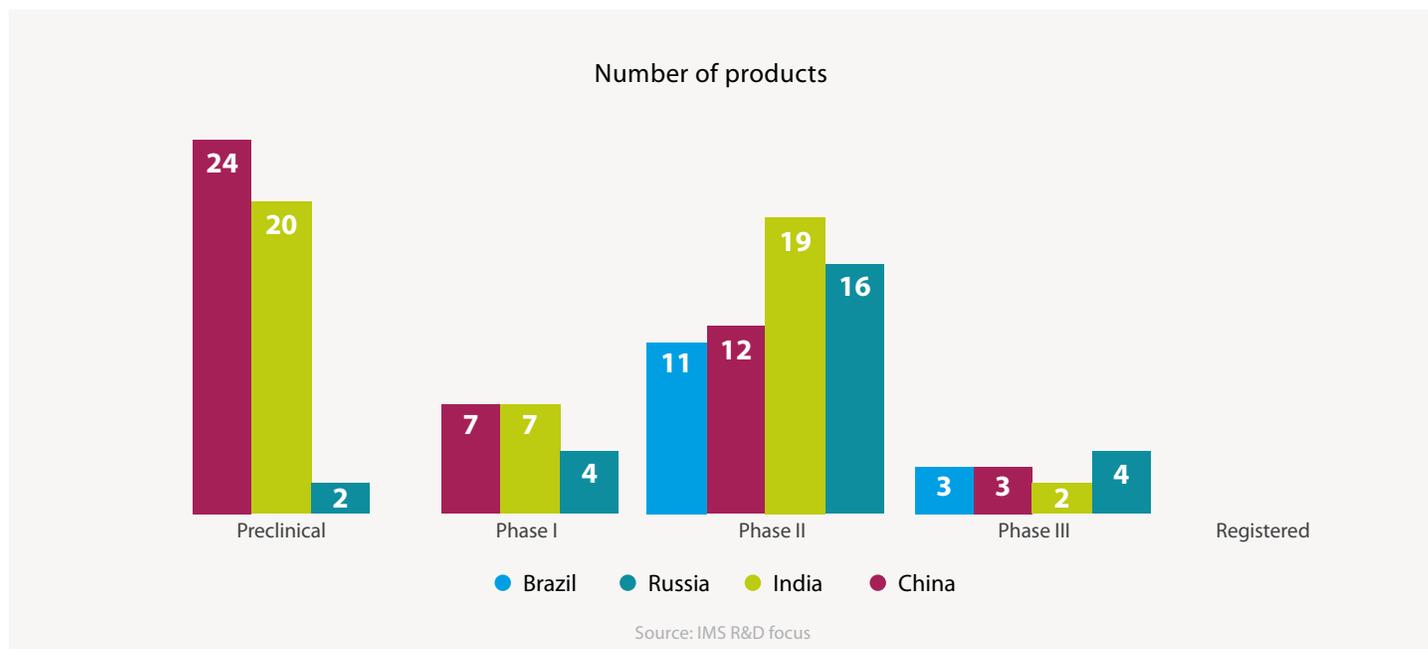
FDA breakthrough therapy designations 2012-2014



- The FDA’s BTM category is a fast-track process that allows investigational agents to receive FDA approval as early as 3 months ahead of schedule.
- The FDA recommends that submissions for breakthrough therapy designation be made no later than the end of phase II.
- Since the initiative’s inception in 2012, manufacturers have applied for 157 agents to receive the designation, 41 of which have been granted, 14 in oncology.
- Oncology products comprise 34% of BTMs.
- However, since the designations are not reported publicly by the Agency, the therapeutic area of all current BTM therapies has not been fully characterized; approximately a quarter of designated agents have not been reported by their manufacturers.
- In 2013, Roche’s Gazyva and Pharmacyclics’ ibrutinib (Imbruvica) received FDA approval between one and three months earlier than anticipated under the BTM initiative.
- In the U.K., the Medicines and Healthcare Products Regulatory Agency (MHRA) recently announced a two-step process for the Early Access to Medicines program that launched in April 2014.
- The first step is a Promising Innovative Medicines (PIM) designation based on early clinical data.
- The second step, Early Access to Medicine Scientific Opinion, will support the prescriber and patient to make a decision as to whether to use the medicine before its license is approved.
- Both of these programs in the U.S. and U.K. could play a significant role in accelerating oncology drug development and approval.

Oncology R&D spending in BRIC countries is lower than ROW

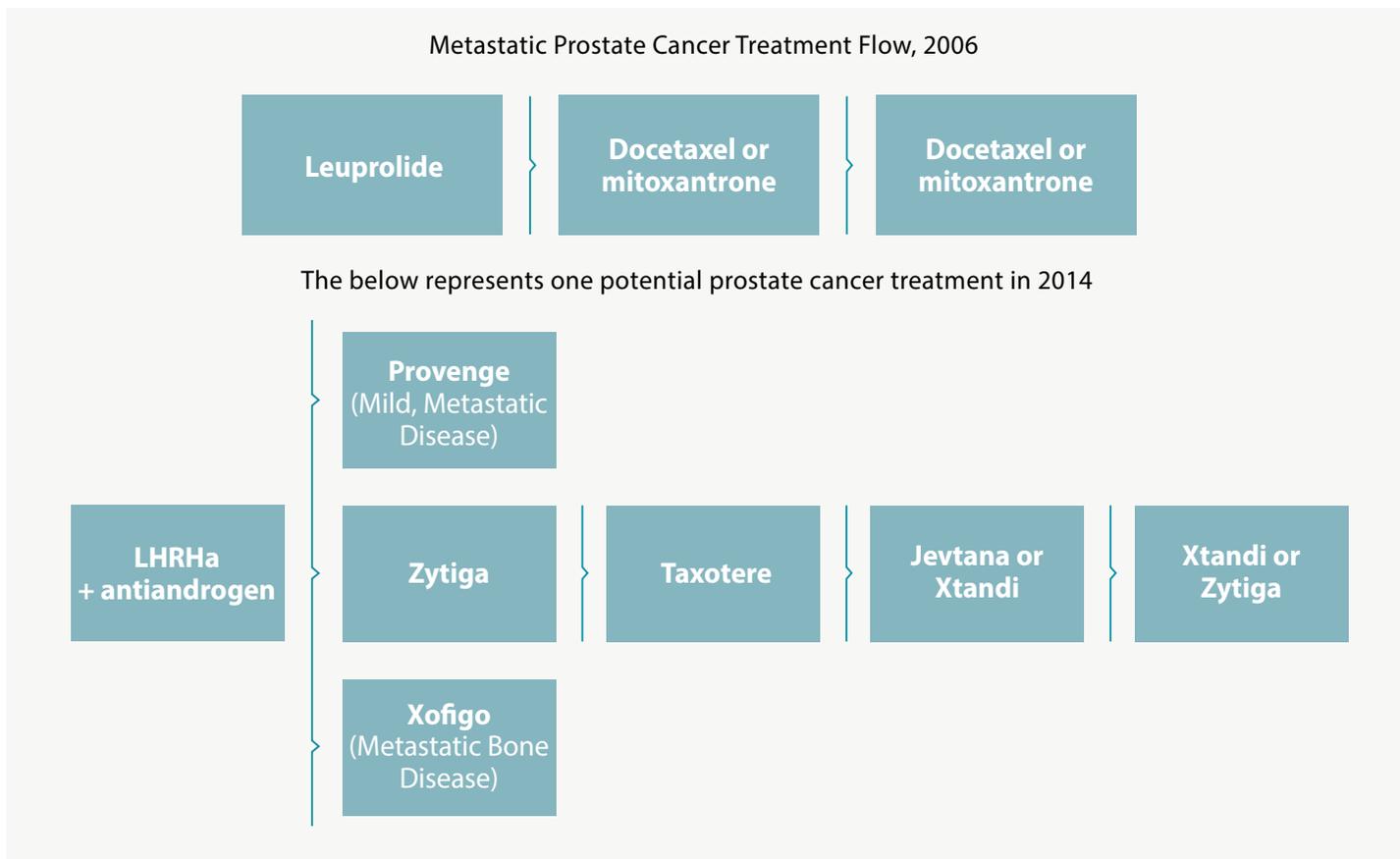
Oncology pipeline in Brazil, Russia, India, and China (BRIC)



- The products being researched in these countries are largely already available in more developed countries.
- Increasingly China, Brazil and Russia see early launches of cancer drugs relative to the global launch, whereas India often lags behind. New regulations passed in January 2013 in India are more stringent making approval for running clinical trials more difficult.
- Cytotoxics and targeted therapies make up the majority of the pipeline across all BRIC countries.
- Some very advanced pipeline drugs are at the same phase or only slightly behind in BRIC countries when compared to developed markets. Notable candidates include trebananib for ovarian cancer, which is in phase III in both Russia and the U.S.; obinutuzumab, in phase III in a dozen countries for CLL and NHL, including Russia and Brazil; lenvatinib, in phase III in China for HCC and in phase II in Russia for endometrial cancer and in the same phases in the U.S. for both indications.
- Early stage oncology drug testing is generally not conducted in BRIC countries.
- About a quarter of phase II oncology drugs progress to phase III in developing countries, consistent with global trends.

Prostate cancer illustrates how new product launches can change the treatment paradigm dramatically, creating complexity in applying new and future innovations

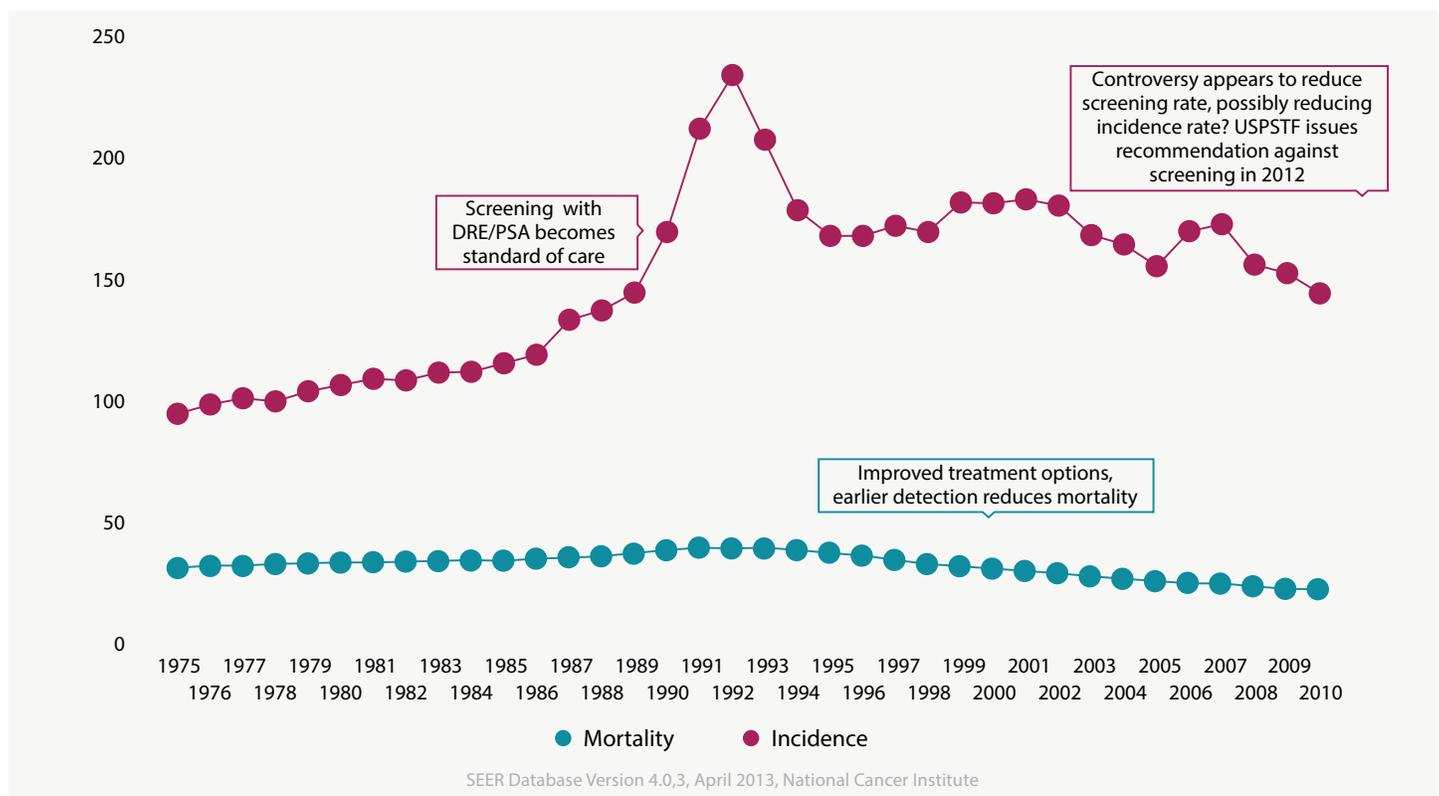
Metastatic prostate cancer treatment flow



- Prostate cancer illustrates how new product launches can change the treatment paradigm dramatically, creating complexity in applying new and future innovations.
- A wave of approvals in castration-resistant prostate cancer (CRPC) promises to completely change the treatment landscape with agents such as sipuleucel-T (Provenge), abiraterone (Zytiga), radium Ra 223 dichloride (Xofigo), and enzalutamide (Xtandi) increasing the number of treatment options.
- Competition within this indication is likely to play out through sequencing in addition to displacement. Understanding the range of potential scenarios, and their probabilities, is crucial.
- Finally, the introduction of orals with relatively low toxicity may lead to a shift in site of care as urologists will retain control of patients who are further advanced in disease progression.

Changes in screening utilization and technologies will shift the stage at which many cancers are diagnosed - sometimes unpredictably

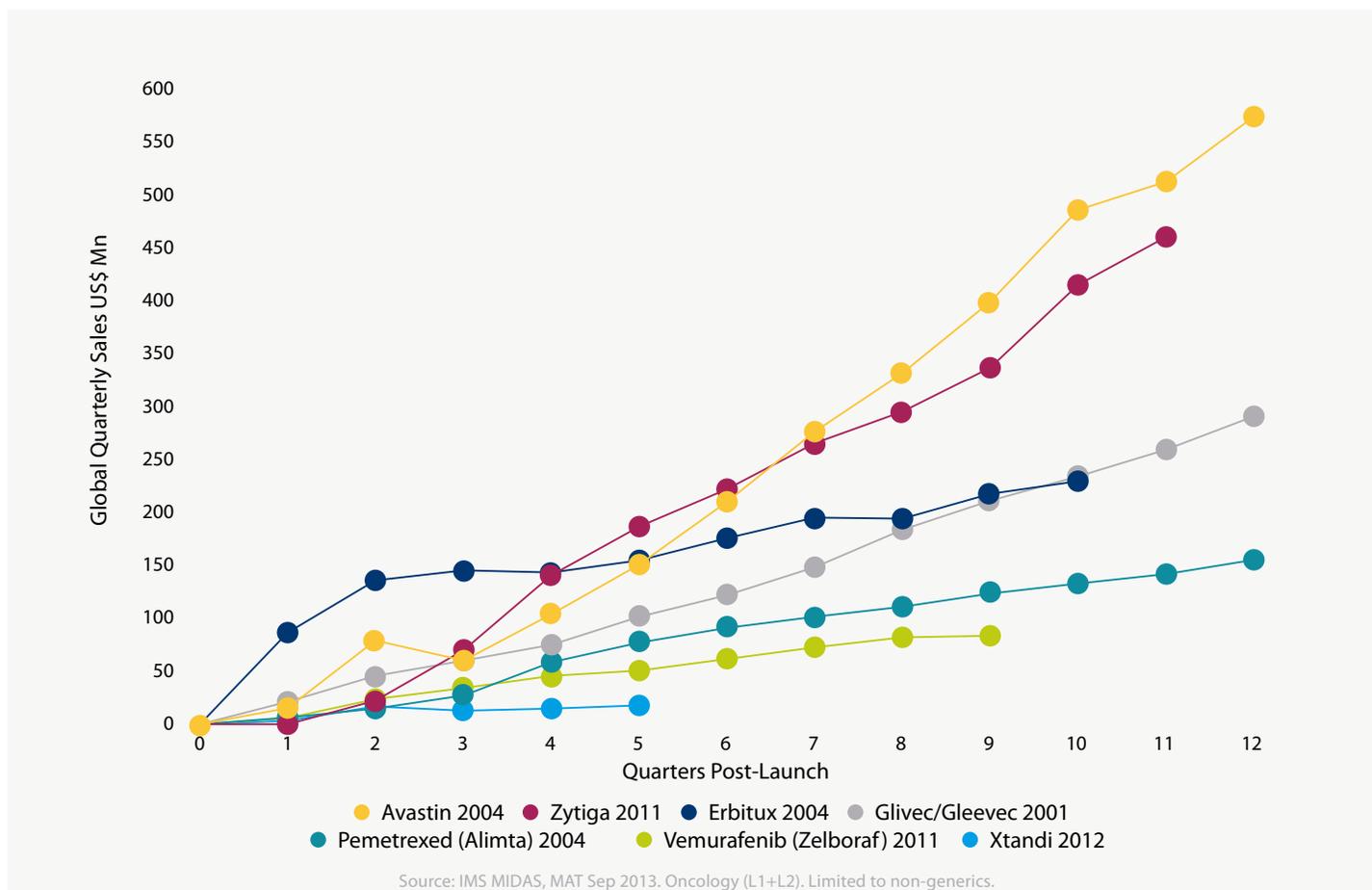
Prostate cancer U.S. incidence and mortality rates/100,000 men, 1975-2010



- Changes in clinical practices related to screening/detection may result in perceived changes in incidence rather than actual underlying epidemiologic trends. Prostate cancer in the U.S. provides one example of this.
- After a number of studies published in the 1990s validated the use of prostate-specific antigen (PSA) as a clinical marker for prostate cancer, a test to measure PSA levels was approved in 1994.
- The advent of the PSA test presumably resulted in a spike in the number of prostate cancers diagnosed and a rising incidence that subsequently declined as pre-existing early stage cases were diagnosed.
- The trend of increased prostate cancer incidence likely declined further after the U.S. Preventive Services Task Force (USPSTF) recommended against non-high-risk screening in 2012.
- The question remains as to whether this recent recommendation will ultimately result in prostate cancer being diagnosed at later stages as routine screening rates decline, leading to a rising incidence of later stage tumors.
- Ramifications of this potential phenomenon include increasing mortality and increased utilization of late-stage therapies indicated for metastatic disease.

Recent blockbuster launches have rivaled those of a decade ago

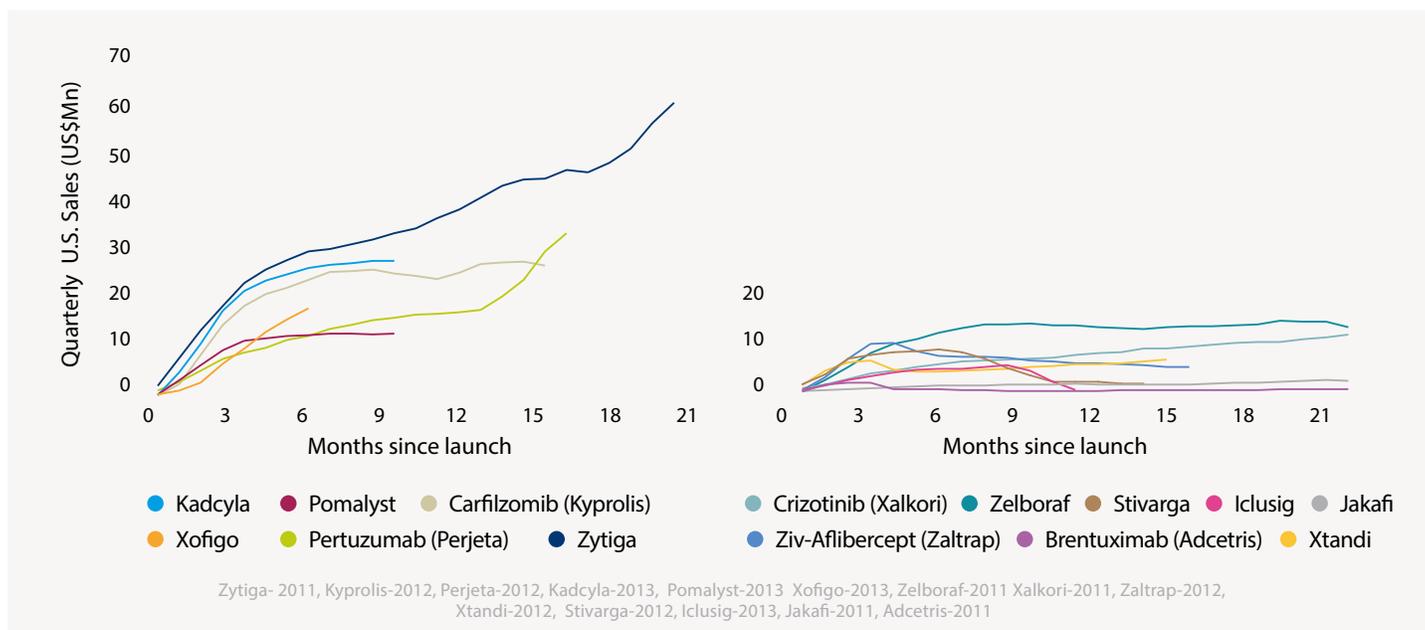
Global results of selected oncology launches



- The approval of blockbuster oncologics such as Avastin and imatinib (Glivec/Gleevec) were part of the explosion of therapies at the beginning of the new millennium.
- Additional indications of these original blockbusters led to increased uptake and an impressive trend in growth.
- Later agents approved between 2005 and 2009 failed to match this level of growth, due in part to limitations of indications and market saturation by the aforementioned earlier approvals.
- A group of oncologics that have been launched in the past three years are following the same trajectory as Avastin, Gleevec and Erbitux, suggesting a new group of blockbuster therapies.
- In the case of Xtandi, which treats metastatic CRPC representing a group of historically undertreated patients, improved growth would likely be seen with more aggressive and guideline-based treatment.

U.S. results of newly launched oncology drugs have been mixed

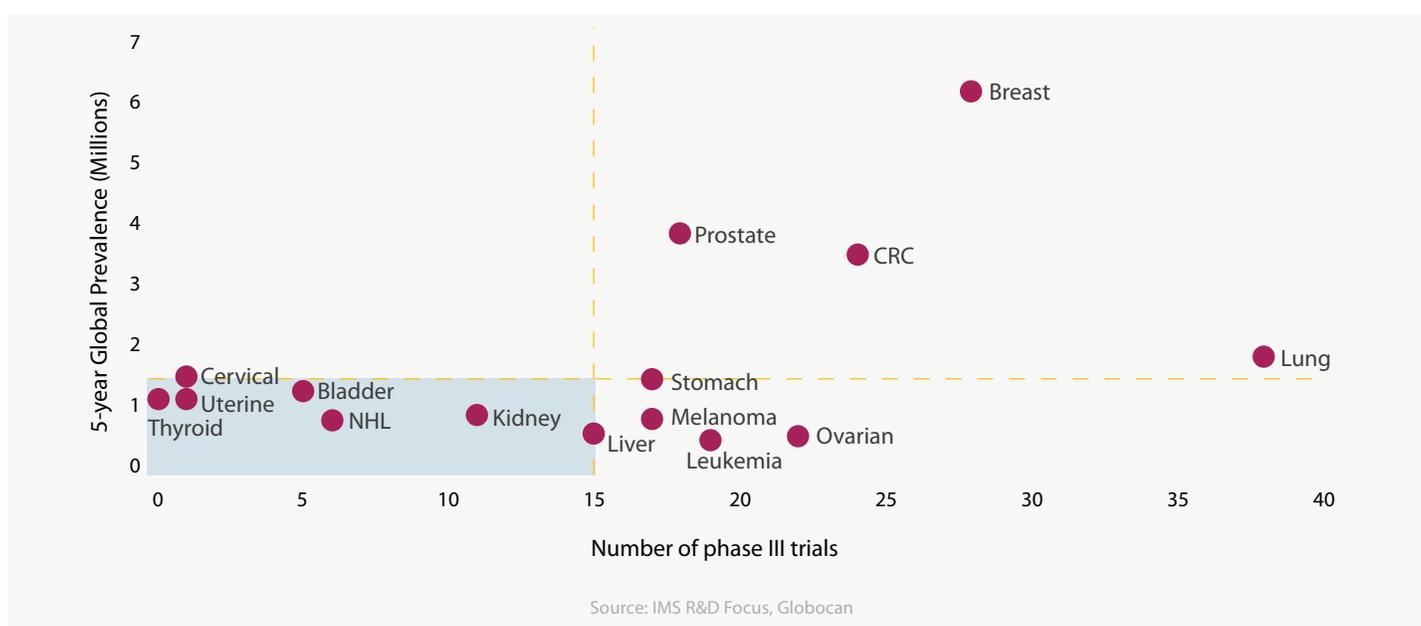
Selected U.S. oncology launches on a 3-month rolling average in first 24 months since launch US\$Mn



- Some of the most successful launches focused on diseases which previously had few treatment options, such as CRPC and melanoma.
- Initially approved for late stage castration-resistant prostate cancer (CRPC), the indication to early phase disease was expanded for Zytiga, resulting in a successful first 24 months.
- There was a 5FU shortage (component of the FOLFOX and FOLFIRI regimens for CRC) starting in the summer of 2011, which affected many of these newer treatments for solid tumors.
- Both Zaltrap and regorafenib (Stivarga) had strong starts in August and September of 2012, but a competitive market with established treatments for colorectal cancer has perhaps hampered their uptake.
- Ruxolitinib (Jakafi) for myelofibrosis—a disease that affects less than two in 100,000 people—was approved by the FDA and EMA (European Medicines Agency).
- Ponatinib (Iclusig) for chronic myeloid leukemia (CML) was suspended in October 2013 due to “the risk of life-threatening blood clots and severe narrowing of blood vessels”. This suspension was partially lifted on December 20, 2013.

R&D focus appears to be based on factors other than disease prevalence or potential treatment populations

Phase III trials by cancer type and 5-year disease prevalence



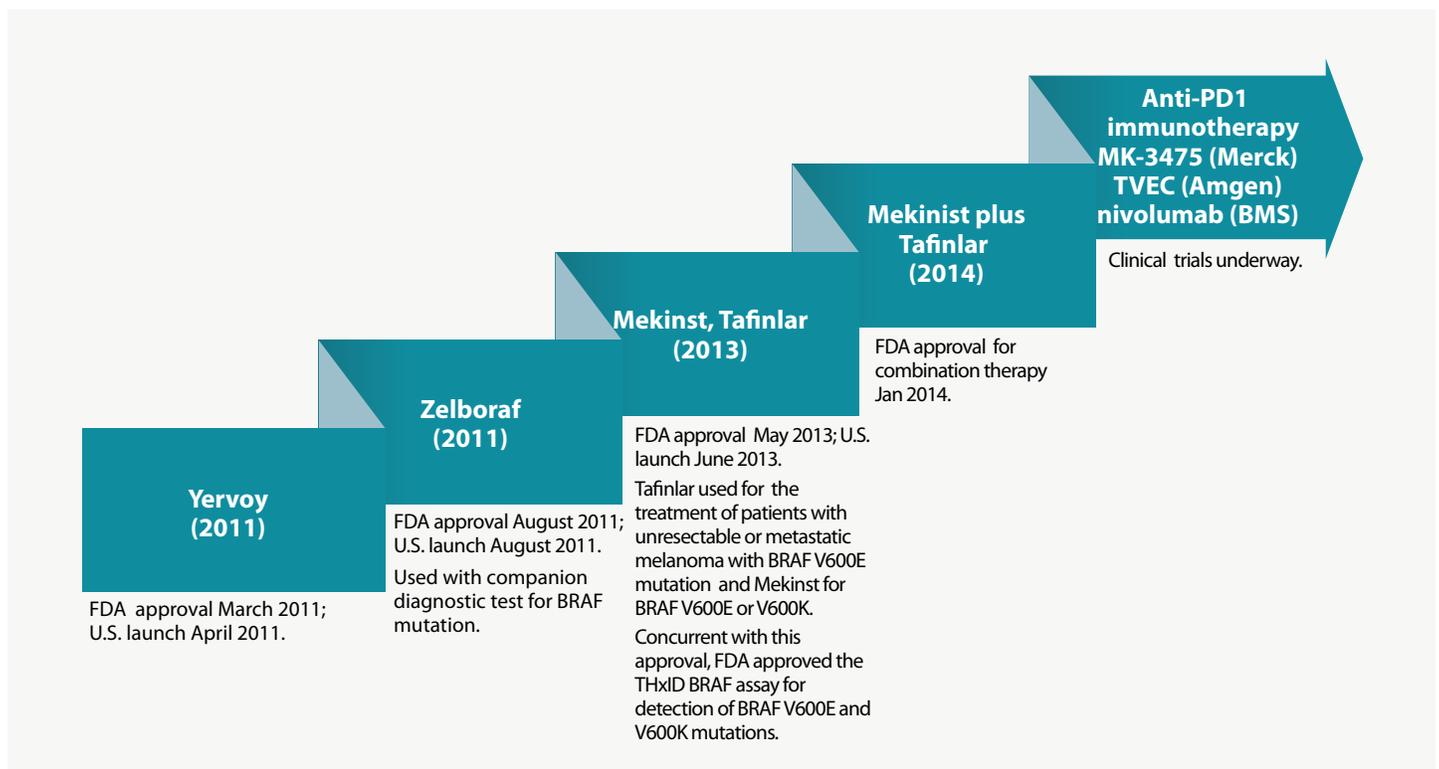
- While it is not surprising that higher prevalence tumors have more late-stage pipeline development, another key driver of innovation is unmet needs, which are not always tied to prevalence.
- Although prostate cancer has approximately twice the 5-year global prevalence, the number of trials investigating agents for the treatment of lung cancer is more than twice that for prostate cancer.
- This is presumably due to the fact that molecular targets in non-small cell lung cancer—particularly epidermal growth factor receptor (EGFR)—have been long-since identified and extensively studied.
- Similar phenomena likely play a role in the relatively high number of agents being investigated for colorectal, breast, and ovarian cancer, specifically those targeting KRAS, BRAF, and ALK mutations and human epidermal growth factor receptor 2 (HER-2).
- So in a pipeline overwhelmingly populated by targeted therapies, agents with well characterized molecular targets and accompanying biomarkers appear to be high potential investments.
- Conversely, six key tumor types (thyroid, uterine, cervical, bladder, NHL, and kidney) with lower prevalence and corresponding lower numbers of clinical trials evaluating investigational therapies, represent an opportunity for R&D efforts in the future.
- It is also important to note the impact of immune therapy and recent success in clinical trials. This is expected to enhance focus in lung cancer and melanoma, and has already impacted gastrointestinal cancers.

Chart notes:

Phase III numbers refers to counts of drugs in clinical trials

New drug launches manifest in waves of agents indicated for the same cancer type

Melanoma example



- Prior to the launch of Yervoy in 2011, advanced melanoma was treated with mixed immunotherapy and chemotherapy without an overall survival benefit.
- The approval of Yervoy signaled a wave of agents indicated for the disease, bringing the total now to four targeted therapies and a host of agents in development.
- Additional approvals such as that of Zelboraf, Tafinlar, and Mekinist all offer new therapies for patients with late stage disease who have had very limited treatment options in the past.
- Beyond melanoma, a wave of recent approvals for therapies in the treatment of prostate cancer serves as another prime example of this phenomenon.

Value of treating cancer and pricing trends

With increasing oncology spend and innovation has come more focus on the cost-benefit outlook for new products. Stakeholders must weigh their apparent value in terms of current medical needs and clinical outcomes as well as in light of cost; the influence of single-payer health care and associated discount mechanisms in nations other than the U.S. have driven down the list price and ultimately the net price paid.

- While ASCO has made an important step forward to align views of trial outcomes to help stakeholders “value” the clinical benefit of new products, the RCTs, targeted approaches, and treatment patterns for new products make them difficult to evaluate and complex (or even meaningless) to compare to each other even as positive OS and PFS results are seen.
- Recently approved oncology treatments have an average cost of ~\$10,000 per month up for ~\$5,000 a decade earlier, though, raising expectations for improved outcomes on the part of patients, physicians, and payers.
- Although prices vary greatly across markets, there is a trend to decrease list price for E.U. versus the U.S. at launch. And even then, the E.U. list price is likely not the final price paid considering the multitude of discount mechanisms in place in the E.U.
- Concentrated payer systems and health technology assessments have been key drivers of the pricing trends.

The American Society of Clinical Oncology recently published recommended targets for meaningful clinical trial outcomes

Cancer type ¹	Patient population	Current baseline median OS (months)	Primary End Point		Secondary End Point	
			Improvement over current OS that would be clinically meaningful (months)	Target HRs	Improvement in 1 year survival rate(%)	Improvement in PFS (months)
Pancreatic Cancer	FOLFIRNOX-eligible patents	10 to 11 ²	4 to 5	0.67 to 0.69	48 to 63	4 to 5
Pancreatic Cancer	Gemcitabine or gemcitabine/hab-pacitaxel-eligible patients	8 to 9 ^{3,4}	3 to 4	0.6 to 0.75	35 to 50	3 to 4
Lung Cancer	Nonsquamous cell carcinoma	13 ⁵	3.25 to 4	0.76 to 0.8	53 to 61	4
Lung Cancer	Squamous cell carcinoma	10 ⁶	2.5 to 3	0.77 to 0.8	44 to 53	3
Breast Cancer	Metastatic triple negative, previously untrated for metastatic disease	18 ^{7,8}	4.5 to 6	0.75 to 0.8	63 to 71	4
Colon Cancer	Disease progression with all prior therapies(or not a candidate for standard second or third-line options)	4 to 6 ⁹	3 to 5	0.67 to 0.67	25 to 36	3 to 5

Abbreviations: FOLFIRNOX, leucovorin, fluorouracil, irinotican and oxaliplatin; HR , hazard ratio; OS, overall survival; PFS, progression-free survival

Source: 1 Ellis LM, et al. *J Clin Oncol.* 2014; Mar 17: epub ahead of print 10.1200/JCO.2013.53.8009, 2. Conroy T, et al. *N Engl J Med* 2011;364:1817-1825. 3. Kindler HL, et al. *Lancet Oncol.* 2011;12:256-262. 4. Von Hoff DD, et al. *N Engl J Med.* 2013;369: 1691-1703. 5. Porter ME. *N Engl J Med.* 2010;363:2477-2481. 6. Rossi A, et al. *J Clin Oncol.* 2012;30:1692-1698. 7. O’Shaughnessy, et al. *Oncologist.* 2012;17:476-484. 8. Cortazar P, et al. *J Clin Oncol.* 2012;30:1705-1711. 9. Grothey A, et al. *Lancet.* 2013;381:303-312.

- The American Society of Clinical Oncology (ASCO) Cancer Research Committee convened four working groups in 2013 to help guide the development of definitive, randomized phase III trials.
- The working groups were composed of experts in carcinomas of the pancreas, breast, lung, and colon, and included clinical investigators, patient advocates, biostatisticians, FDA oncologists, and industry oncologists.
- Conclusions reached by the working groups were not intended to set standards for regulatory approval or insurance coverage but instead to encourage patients and investigators to demand more from clinical trials.
- Although OS was selected as the primary end point by all working groups, ASCO commented that this does not necessarily diminish the value of PFS and other surrogate end points as valid end points in certain clinical situations.
- The working groups also largely agreed that if a therapy is less toxic than prevailing treatments, a smaller improvement in efficacy is acceptable; alternatively, a highly toxic therapy should be accompanied by an expectation of substantially greater benefit to provide a clinically meaningful outcome to patients.
- These recommendations set the stage for future oncology drug development.

Metastatic melanoma - treatment cost and incremental benefit of recently approved agents

Product	Clinical Data				Treatment Costs	
	Incremental RR	Incremental PFS	Incremental OS	(Median) Duration of Tx	Monthly	Total
Zelboraf ¹ Vemurafenib	42.9% Investigator assessed best overall response rates	+3.7 months	+3.3 months	4.2 months	\$10,995	\$46,178

Zelboraf in patients with previously untreated metastatic or unresectable melanoma with the BRAFV600E mutation:

- OS was significantly improved compared with dacarbazine [HR 0.47 (95% CI 0.35, 0.62), p<0.0001]
- PFS was also significantly improved [HR 0.26 (95% CI 0.20, 0.33), p<0.0001]

Product	Clinical Data				Treatment Costs	
	Incremental RR	Incremental PFS	Incremental OS	(Median) Duration of Tx	Monthly	Total
Yervoy ² ipilimumab	9.4% Investigator assessed best overall response rates	NA	+4.0 months	4 doses (12 weeks)	\$42,557	\$117,648

Yervoy in patients with unresectable or metastatic melanoma who had received at least one prior systemic treatment for melanoma:

- OS was extended compared with the tumor vaccine [HR 0.66 (95% CI 0.51, 0.87), p=0.0026]

Product	Clinical Data				Treatment Costs	
	Incremental RR	Incremental PFS	Incremental OS	(Median) Duration of Tx	Monthly	Total
Mekinist ³ Trametinib	14%	+3.3 months	Not reported	4.3 months	\$9,256	\$39,804

Mekinist in patients with Unresectable or Metastatic melanoma determined to be BRAFV600E or V600K mutation-positive:

- Prolongation of investigator-assessed PFS was demonstrated compared with chemotherapy [HR 0.47 (95% CI 0.34, 0.65), p<0.0001]

Product	Clinical Data				Treatment Costs	
	Incremental RR	Incremental PFS	Incremental OS	(Median) Duration of Tx	Monthly	Total
Tafinlar ⁴ Dabrafenib	35%	+2.4 months	Not reported	4.9 months	\$8,086	\$49,327

Tafinlar in patients with, unresectable or metastatic melanoma determined to be BRAFV600E mutation-positive:

- Statistically significant prolongation of investigator-assessed PFS compared with dacarbazine [HR 0.33 (95% CI 0.20, 0.54), p<0.0001]

Product	Clinical Data				Treatment Costs	
	Line of Therapy	Incremental RR	Incremental PFS	Incremental OS	(Median) Duration of Tx	Monthly
Mekinist + Tafinlar ⁴ Trametinib + Dabrafenib	Investigator assessment: 22% IRRR Committee Assessment: 11%	Not reported	Not reported	10.9 months	\$17,343	\$189,041

Mekinist plus Tafinlar in patients with unresectable or metastatic melanoma that was determined to have a BRAF V600E or V600K mutation:

- Objective response rates and response durations were 76% (95% CI: 62, 87) and 10.5 months (95% CI: 7, 15), respectively, compared with 54% (95% CI: 40, 67) and 5.6 months (95% CI: 5, 7), respectively, in the single-agent Tafinlar arm

Sources: 1. Zelboraf Prescribing Information. Available at: http://www.gene.com/download/pdf/zelboraf_prescribing.pdf.

2. Yervoy Prescribing Information. Available at: http://packageinserts.bms.com/pi/pi_yervoy.pdf.

3. Mekinist Prescribing Information. Available at: <http://www.gsksource.com/gskprm/htdocs/documents/MEKINIST-PI-PIL.PDF>.

4. Tafinlar Prescribing Information. Available at: <https://www.gsksource.com/gskprm/htdocs/documents/TAFINLAR-PI-MG.PDF>.

Chart notes:

Manufacturers' Prescribing Information used for clinical data. Select clinical information highlighted. Treatment costs calculations based on ASP from CMS report accessed on 3/4/2014. The tables above are not intended to compare disparate patient populations and treatments. Rather, it outlines the type of patients treated at the time of approval and the cost of that treatment today."

Metastatic colorectal cancer (mCRC) - treatment cost and incremental benefit of recently approved agents

Product	Clinical Data				Treatment Costs	
Line of Therapy	Incremental RR	Incremental PFS	Incremental OS	Duration of Tx	Monthly	Total
Zaltrap ¹ ziv-aflibercept 2nd Line	8.70%	+2.2 months	+1.4 months	9 cycles (18 weeks)	\$4,939	\$20,471
Zaltrap in patients with mCRC whose disease progressed during or within 6 months of receiving oxaliplatin-based combination chemotherapy, with or without prior bevacizumab: <ul style="list-style-type: none"> • Median OS Zaltrap plus FOLFIRI (-fluorouracil plus irinotecan) was 13.5 months compared with 12.06 months for placebo plus FOLFIRI [HR 0.82 (95% CI 0.71, 0.94), p=0.0032] • Median PFS was 6.9 months compared to 4.67 months [HR 0.758 (95% CI (0.66,0.87), p<0.0001] 						
Product	Clinical Data				Treatment Costs	
Line of Therapy	Incremental RR	Incremental PFS	Incremental OS	Duration of Tx	Monthly	Total
Stivarga ² regorafenib 3rd Line	0.60%	+0.3 months	+1.4 months	7.3 weeks	\$11,192	\$30,925
Stivarga plus Best Supportive Care resulted in a statistically significant improvement in survival compared to placebo plus supportive care: <ul style="list-style-type: none"> • Median OS was 6.4 months compared to 5.0 months for placebo (HR 0.77 (95 % CI 0.64, 0.94), p=0.0102] • Median PFS was 2.0 months vs. 1.7 [HR 0.49 (95 % CI (0.42, 0.58), p<0.0001] 						

Sources: 1. Zaltrap Prescribing Information. Available at: <http://products.sanofi.us/zaltrap/zaltrap.html>.

2. Stivagra Prescribing Information. Available at: http://labeling.bayerhealthcare.com/html/products/pi/Stivarga_PI.pdf.

Chart notes:

Manufacturers’ Prescribing Information used for clinical data. Select clinical information highlighted. Treatment costs calculations based on ASP from CMS report accessed on 3/4/2014. The tables above are not intended to compare disparate patient populations and treatments. Rather, it outlines the type of patients treated at the time of approval and the cost of that treatment today.”

Metastatic Castration-resistant prostate cancer (mCRPC) - treatment cost and incremental benefit of recently approved agents

Product	Clinical Data				Treatment Costs	
Line of Therapy	Incremental RR	Incremental PFS	Incremental OS	Median Duration of Tx	Monthly	Total
Provenge ¹ Sipuleucel-T 1st Line	NA NA	NA NA	+4.1 months +4.5 months	3 doses (6 weeks)	\$71,436	\$98,694

Provenge in patients with metastatic disease in soft tissue and/or bone and evidence of disease progression:

- OS of 25.8 vs 21.7 months for patients who received the control treatment [HR 0.775 (95% CI 0.61, 0.98), p=0.032]

Provenge in patients with metastatic disease and no cancer related pain:

- OS of 25.9 vs 21.4 months for patients who received control treatment [HR 0.586 (95% CI 0.39, 0.88), p=0.010]

Product	Clinical Data				Treatment Costs	
Line of Therapy	Incremental RR	Incremental PFS	Incremental OS	Median Duration of Tx	Monthly	Total
Zytiga ² Abiraterone acetate pre-chemo post-chemo	NA NA	NA NA	+5.2 months +4.6 months	13.8 months 8 months	\$6,928	\$95,603 \$55,422

Zytiga in patients with mCRPC who had not received cytotoxic chemotherapy and metastases to the bone, soft tissue, or lymph nodes only:

- OS of 35.3 vs. 30.1 in the placebo group [HR 0.79 (95% CI: 0.66, 0.96)].

Zytiga in patients with mCRPC who had received prior docetaxel chemotherapy:

- OS of 15.8 months was demonstrated in Zytiga group vs. 11.2 in the placebo group [HR 0.74 (95% CI 0.64 - 0.86), p<0.0001]

Product	Clinical Data				Treatment Costs	
Line of Therapy	Incremental RR	Incremental PFS	Incremental OS	Median Duration of Tx	Monthly	Total
Xtandi ³ Enzalutamide post-chemo	NA	NA	+4.8 months	8.3 months	\$7,995	\$66,356

Xtandi in patients with mCRPC who had received prior docetaxel:

- OS of 18.4 vs. 13.6 months for patients receiving placebo [HR 0.63 (95% CI 0.53, 0.75), p<0.0001]

Product	Clinical Data				Treatment Costs	
Line of Therapy	Incremental RR	Incremental Median PFS	Incremental OS	Median Duration of Tx	Monthly	Total
Jevtana ⁴ Cabazitaxel 2nd Line	10%	NA	+2.4 months	6 cycles (18 weeks)	\$11,600	\$48,079

Jevtana in metastatic hormone-refractory prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen:

- OS of 15.1 vs. 12.7 months for patients treated with mitoxantrone [HR 0.70 (95% CI 0.59-0.83), p<0.0001]

Sources: Sources: 1. Provenge Prescribing Information. Available at: <http://www.provenge.com/pdf/prescribing-information.pdf>.

2. Zytiga Prescribing Information. Available at: http://www.zytiga.com/sites/default/files/pdf/full_product_information.pdf.

3. Xtandi Prescribing Information. Available at: <https://www.astellas.us/docs/us/12A005-ENZ-WPI.pdf>.

4. Jevtana Prescribing Information. Available at: <http://products.sanofi.us/jevtana/jevtana.html>.

Metastatic breast cancer (mBrC) - treatment cost and incremental benefit of recently approved agents

Product	Clinical Data				Treatment Costs	
Line of Therapy	Incremental RR	Incremental PFS	Incremental OS	Duration of Tx	Monthly	Total
Perjeta Pertuzumab 1st Line	10.9%	+6.1 months	Median OS Not Reached	18.1 months	\$5,838	\$109,691 Includes one time loading cost of \$8151

Perjeta in HER2-positive metastatic breast cancer

- PFS was 18.5 months or PERJETA plus trastuzumab and docetaxel vs. 12.4 months in placebo plus trastuzumab and docetaxel [HR 0.62 (95% CI 0.51, 0.75), p< 0.0001]

Product	Clinical Data				Treatment Costs	
Line of Therapy	Incremental RR	Incremental PFS	Incremental OS	Duration of Tx	Monthly	Total
Kadcyla Ado-Trastuzumab Emtansine	12.7%	+3.2 months	+5.8 months	7.6 months	\$10,439	\$59,503

Kadcyla in HER2-positive metastatic breast cancer with prior taxane and trastuzumab therapy. Patients who received these therapies only in the adjuvant setting must have experienced disease recurrence during or within six months:

- PFS of 9.6 months for patients receiving ado-trastuzumab emtansine vs 6.4 months for patients receiving lapatinib plus capecitabine. [HR 0.65 (95% CI 0.55, 0.77), p<0.0001]
- OS was 30.9 vs 25.1 months for patients who received lapatinib plus capecitabine [HR 0.68 (95% CI 0.55, 0.85), p=0.0006]

Sources: 1. Perjeta Prescribing Information. Available at: http://www.gene.com/download/pdf/perjeta_prescribing.pdf.

2. Kadcyla Prescribing Information. Available at : http://www.gene.com/download/pdf/kadcyla_prescribing.pdf.

Metastatic renal cell carcinoma (mRCC) - treatment cost and incremental benefit of recently approved agents

Product	Clinical Data				Treatment Costs	
Line of Therapy	Incremental RR	Incremental PFS	Incremental OS	Duration of Tx	Monthly	Total
Inlyta Axitinib 2nd Line	10%	+2.0 months	+0.9 months	6.4 months	\$9,853	\$66,014

Inlyta in patients with advanced renal cell carcinoma after the failure of one prior systemic regimen with the primary efficacy endpoint being PFS:

- A statistically significant Improvement in PFS was demonstrated compared with patients receiving sorafenib
- PFS was 6.7 months vs 4.7 months for patients receiving sorafenib [HR 0.67 (95% CI 0.54, 0.81), p<0.0001]

Sources: 1. Inlyta Prescribing Information. Available at: <http://labeling.pfizer.com/ShowLabeling.aspx?id=759>.

Non-small cell lung cancer (NSCLC) - treatment cost and incremental benefit of recently approved agents

Product	Clinical Data				Treatment Costs	
Line of Therapy	Incremental RR	Incremental PFS	Incremental OS	(Median) Duration of Tx	Monthly	Total
Tarceva ¹ Erlotinib 1st Line (EGFR mutant)	49%	+5.2 months	+3.4 months	9.6 months	\$6,295	\$60,431

TARCEVA as monotherapy for the first-line treatment of patients with metastatic NSCLC containing EGFR exon 19 deletions or exon 21 (L858R) substitution mutations compared to chemotherapy:

- PFS was 10.4 months vs. 5.2 months [HR 0.34 (95% CI 0.23, 0.49), p<0.001]

Product	Clinical Data				Treatment Costs	
Line of Therapy	Incremental RR	Incremental PFS	Incremental OS	(Median) Duration of Tx	Monthly	Total
Xalkori ² Crizotinib (ALK+)	45%	+4.7 months	No improvement	7.1 months	\$11,567	\$58,595

Xalkori compared to Chemotherapy in ALK-Positive Metastatic NSCLC:

- PFS was 7.7 months vs. 3.0 months [HR 0.49 (95%CI) (0.37, 0.64), p < 0.001]
- OS was 20.3 months vs. 22.8 months [HR 1.02 (95% CI) (0.68, 1.54), p = 0.54]

Product	Clinical Data				Treatment Costs	
Line of Therapy	Incremental RR	Incremental PFS	Incremental OS	(Median) Duration of Tx	Monthly	Total
Gilotrif ³ Afatinib (EGFR mutant)	31.3%	+4.2 months	No improvement	11 months	\$6,074	\$66,813

Gilotrif compared to Pemetrexed/Cisplatin in EGFR mutation- positive metastatic NSCLC:

- PFS was 11.1 months vs. 6.9 months [HR 0.58 (95% CI 0.43, 0.78), p < 0.001]
- OS was 28.1 vs. 28.2 [HR 0.91 (95% CI 0.66, 1.25), p = 0.55]

Sources: 1.Tarceva Prescribing Information. Available at: http://www.gene.com/download/pdf/tarceva_prescribing.pdf.

2.Xalkori Prescribing Information. Available at: <http://labeling.pfizer.com/showlabeling.aspx?id=676>.

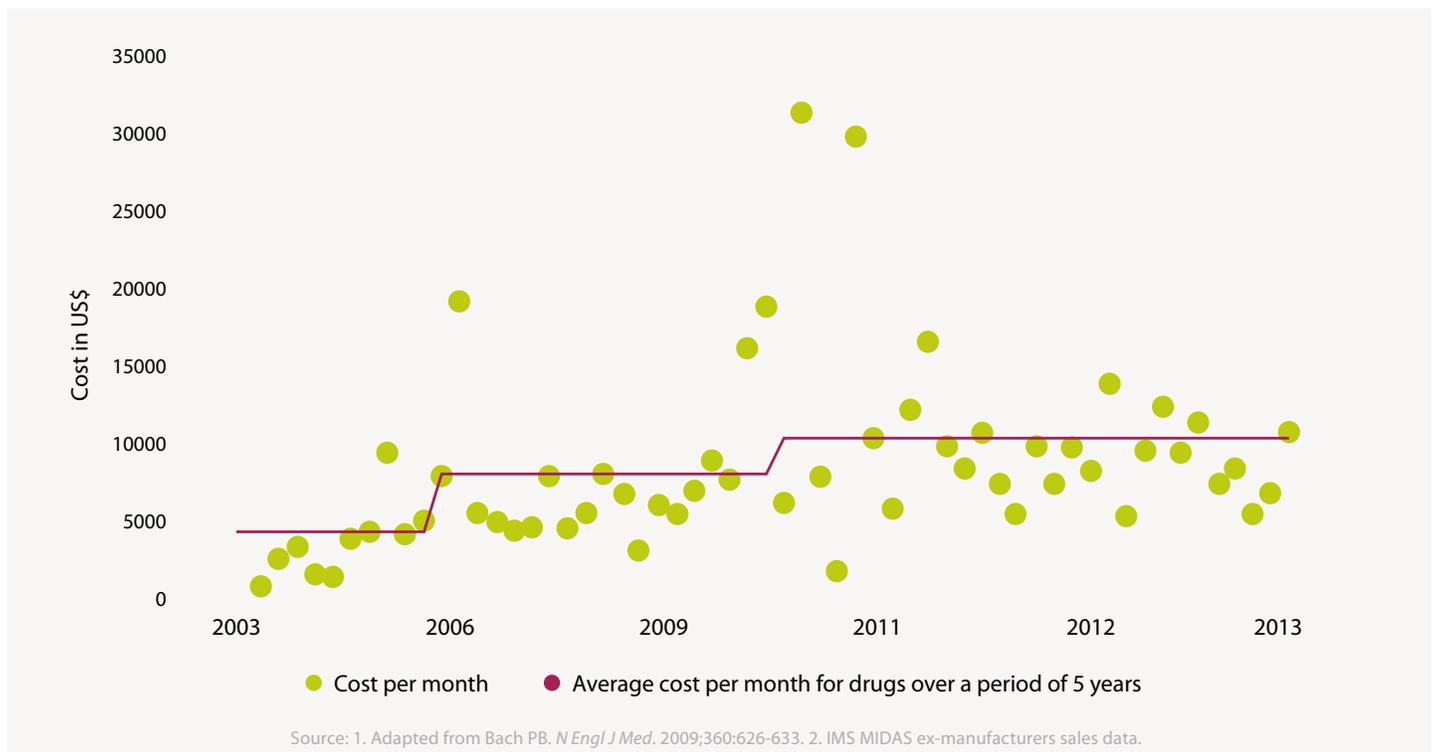
3.Gilotrif Prescribing Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/201292s000lbl.pdf.

Chart notes:

ORR=objective response rate.

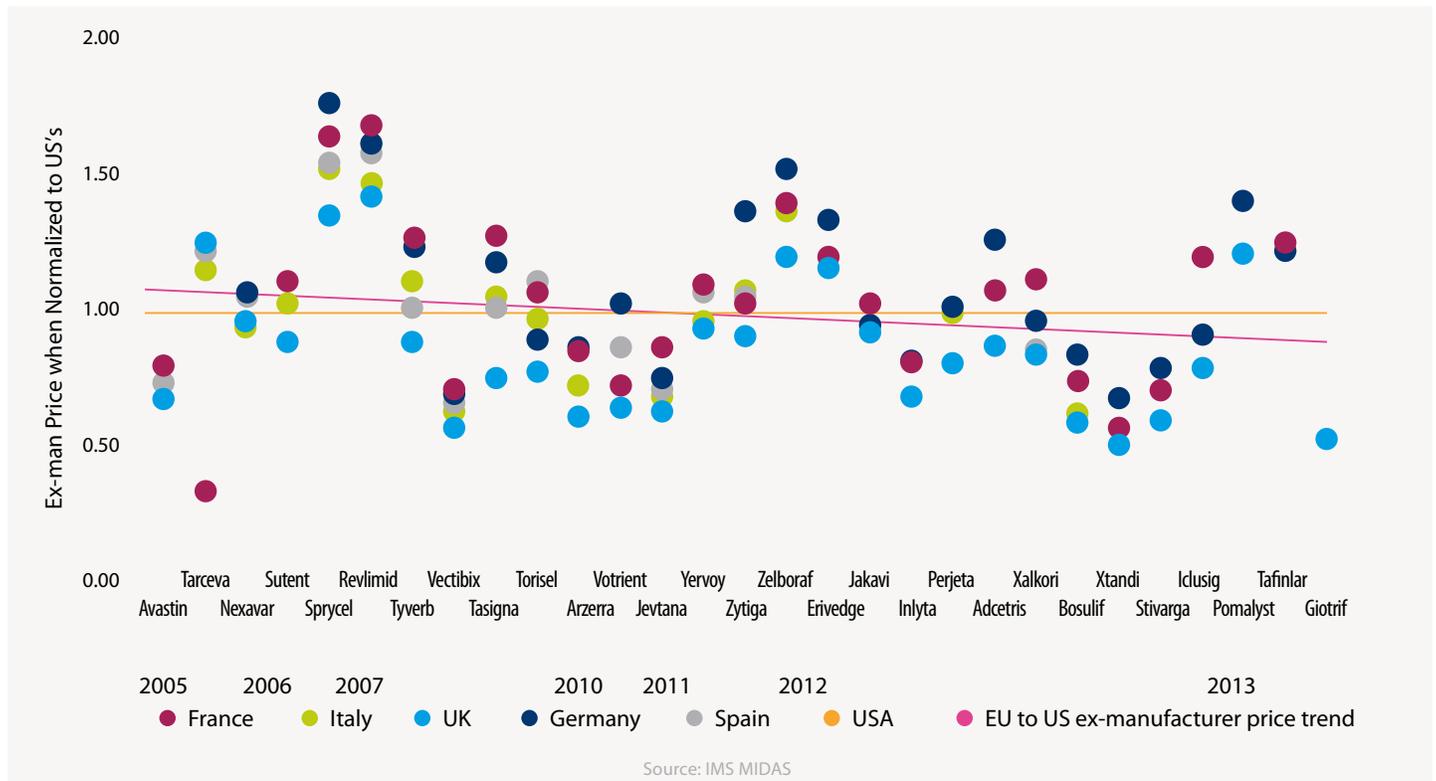
The average monthly cost of branded oncology drugs has doubled over the past decade

U.S. cost per month of branded oncology drugs (2003-2013)



- The average monthly cost of branded oncology drugs was ~\$5,000 in 2003 compared with ~\$10,000 in 2013.
- Certain individual branded oncology agents cost upwards of \$30,000 per month.
- These costs do not include discounts, or patient payment shares.

While EU5 relative to U.S. ex-manufacturer price is extremely variable, there is a trend towards lower pricing over time



- Ex-manufacturer oncology prices in the E.U. vary widely, compared to U.S. prices. More recently, there is an overall trend of a lower average ex-manufacturer price at launch in the E.U. compared to U.S. ex-manufacturer launch prices.
- Even in scenarios where the E.U. ex-manufacturer price appears higher, it is likely not the final price paid considering the multitude of discount mechanisms in place in the E.U.
- These discount mechanisms are enacted by payers at different levels in the E.U., allowing for a lower net price in these countries.

Varied discount mechanisms are in place in the EU5, allowing for a lower net price paid by payers

	 U.S.	 France	 Germany	 Italy	 Spain	 U.K.
National	—	✗ PV Agreements	✓ National rebate	✓/✗ Mandatory discounts, Payment by results, PV agreements	✗ Confidential discounts	✓/✗ Patient access schemes
Regional	—	—	—	✗ Discounts	✗ Discounts	—
Local	—	✗ Contracting	✗ Contracting	✗ Contracting	✗ Contracting	✗ Contracting
MSP (per course, indexed to US)	1	—	1.03	1.03	1.08	0.98
National Discounts	—	—	24% MSP	40% MSP	29% list price	31% list price
Net Price (indexed to US MSP)	1	—	0.79	0.62	0.77	0.63

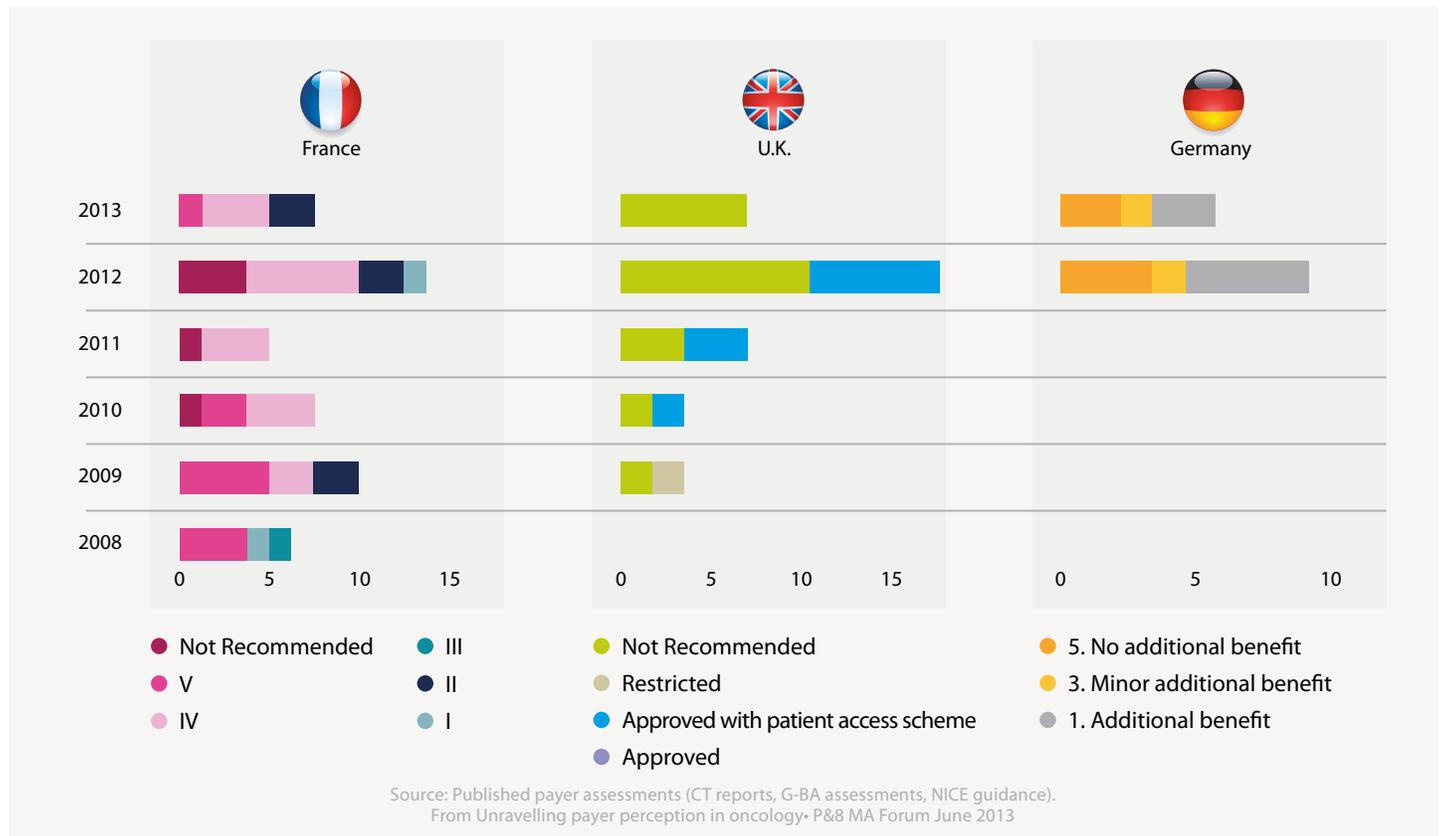
✓ Published and transparent ✗ Not publicly disclosed/confidential — No discount at this level

- Final prices are between 21% to 38% lower in European countries when compared to the U.S.
- In the U.S., there are very minimal, if any, discounts there are, however, rebates.
- In France the cost of oncologic drugs not included in the T2A lists (i.e. the Diagnosis Related Group system through which public hospitals get funded in France) is borne nationally and there may be price/volume agreements in place, but these are not publically disclosed and are confidential. Discounting agreements are possible at local level.
- In Germany, for intravenous (IV) drugs, additional discounts and rebates for office-based practices are available in some regions and offered by some payers. For open care units of hospitals the conditions are negotiated for every region.

Chart notes:

All countries in the E.U. feature discount mechanisms at the national level, with those in Italy being the most varied. Discount mechanisms are less prevalent at the regional level. At the local level, non-publically disclosed contracting arrangements are in place for all countries in the E.U.

Recent submissions have had less favorable Health Technology assessments in European countries



- Over time, European assessment bodies have increased scrutiny regarding the incremental value and cost of new treatments for cancer.
- In France, appraisals done by the Commission d’Evaluation des Médicaments are a comparative assessment of the new product with existing products or therapies and are assigned a Improvement of Medical Benefit (ASMR I and ASMR V) score. Unless the product is first in its class, the evaluation is done in comparison with products that are already listed. I is a major improvement and V is no improvement.
- In the United Kingdom, the National Institute for Health and Care Excellence (NICE) conducts appraisals for the NHS and develops guidelines based upon the Incremental Cost Effectiveness Ratio of a new therapy, guiding its access or restriction. Patient Access Schemes (PAS) can be negotiated to assist in the financing of new products.
- In Germany, the Institute for Quality and Efficiency in Healthcare (IQWiG) evaluates the effectiveness of drugs on behalf of the Federal Joint Committee, assigning from no additional (5) to considerable additional (1) benefit to each submission.

Biosimilars

Considering the importance biologics have played in the oncology market, stakeholders are paying much attention to biosimilars and non-original biologics, but although patent expiry is imminent for a number of agents, biosimilar competition will largely affect supportive care agents and pharmerging nations.

- The key players in the global biologics market include “bio-betters”, featuring an improved target or a more specific mechanism of action- and non-original biologics (NOBs) which are copies that have gone through a less stringent regulatory process.
- Although the U.S. is the largest biologics market, it is lagging behind the rest of the world in the emergence of biosimilars; a developed U.S. biosimilar market is a mixed story: although biosimilars will only account for 2% to 5% of the U.S. biologics market in 2020, it represents \$6Bn to \$12Bn in sales.
- Biosimilars and NOBs will inevitably play an increasing role in pharmerging markets, where the overall share of branded pharmaceuticals is already declining.
- Although oncology biosimilars have had a notable uptake for supportive care treatments, the pipeline of potential biologics targets could expand their role in therapeutics.

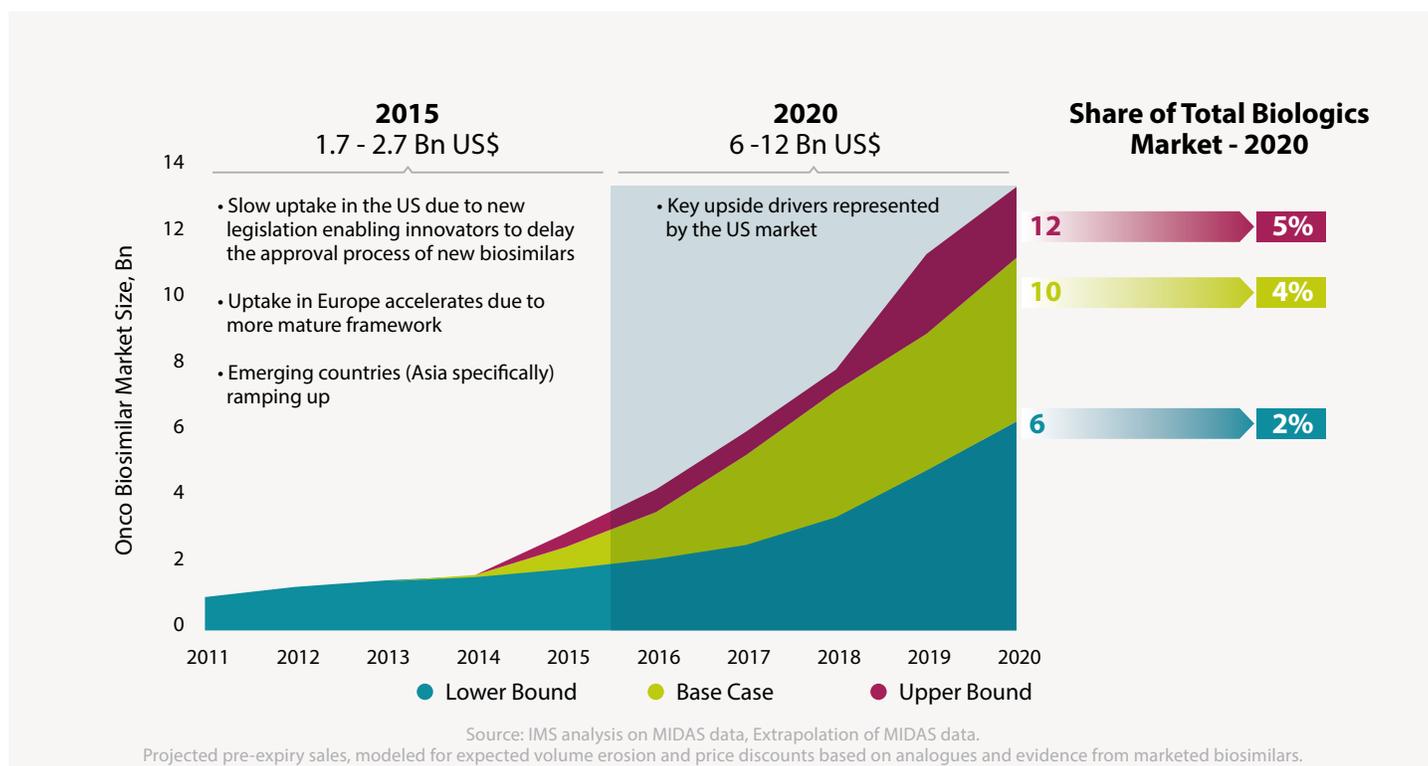
Biologics can be classified into a hierarchy based on date of approval and level of innovation

Biologics					
		Originals		Non Originals	
Type	True Innovator	Biobetters	Biosimilars	Non Original Biologics	
Description	Disruptive technologies, big advances in efficacy	Efficacy/safety improvements	Affordable high quality	Less stringent comparability	
Target	New drug against new target	Same target but differentiated (e.g. Better efficacy, safety, administration)	Clinically equivalence and comparability to originators	Drug aiming to copy innovator Focus on patient access, EMs	
Example	Herceptin	Perjeta	Herzuma	Reditux	

- Biologic molecules are complex macromolecules with some form of polymer structure. They can be purified from naturally derived substances, produced by recombinant DNA technology or chemically synthesized. Biosimilars are defined as copies of innovative brands that have been approved by a dedicated regulatory pathway while NOBs are copies that have not been approved through such a dedicated pathway and generally did not undertake stringent comparability and bioequivalence studies.
- Various challenges exist in developing specific biosimilars, including the difficulties of replicating such complex medicines, the layers of patents that protect biologics and their manufacturing techniques, and unfinished rules for gaining approval in certain geographies, the U.S. in particular.
- Biobetters are a group of agents featuring an improved target or more specific mechanism of action than the original innovative biologic therapy.
- Although the potential impact of biosimilars is well recognized, the influence of NOBs cannot be overlooked, particularly in emerging markets.
- As governments in emerging markets extend health coverage, they will push for lower prices and gravitate toward NOBs, challenging originators.
- Decisions about when, how, and at what price to launch a novel biologic product in emerging markets need to be thought through carefully because of the threat of the manufacture of NOBs from local manufacturers.

The oncology biosimilars market is predicted to be at \$12Bn in 2020, assuming a developed U.S. market

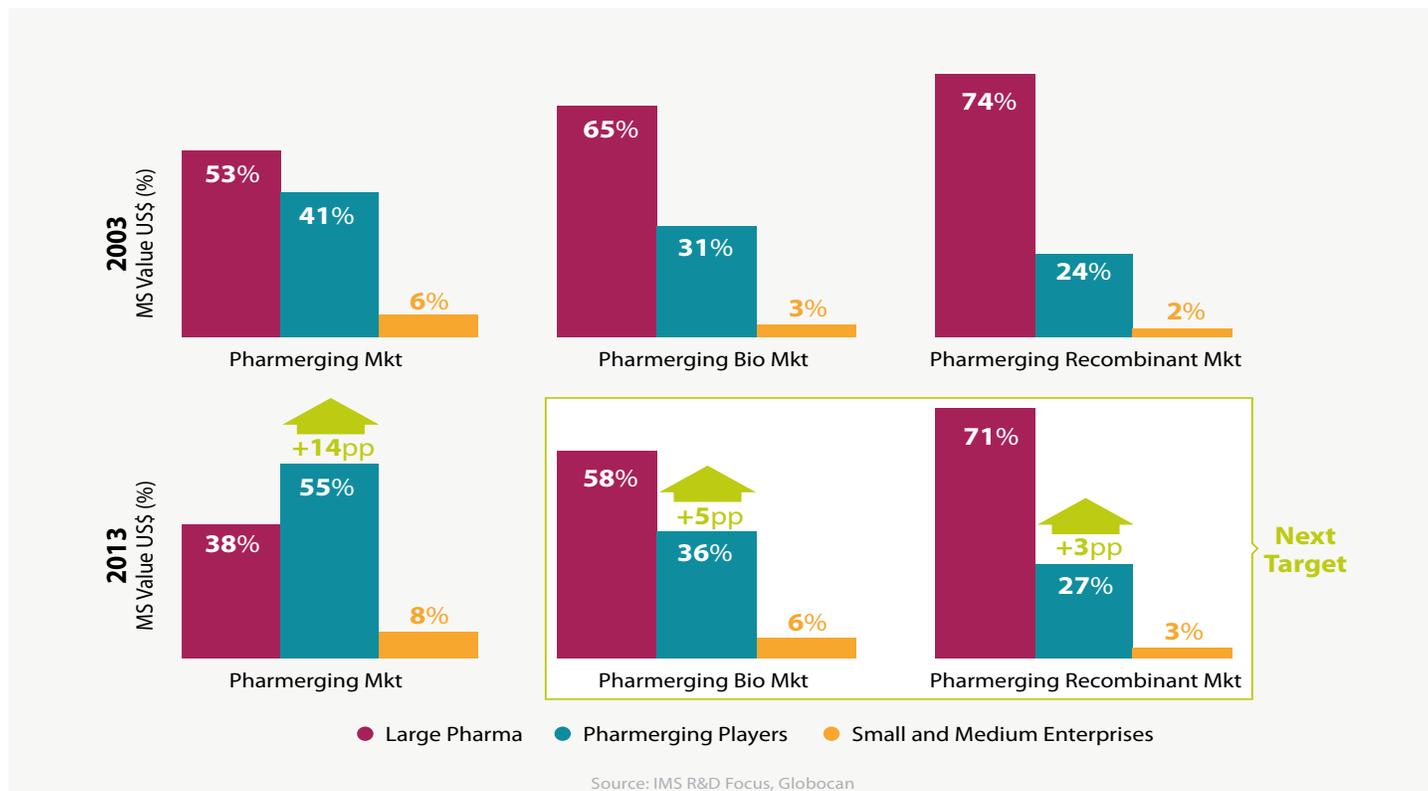
Oncologics and supportive care biosimilars market evolution, 2011-2020



- It is generally assumed that the U.S. will have a developed biosimilar market by 2020, although this will require resolution of the aforementioned challenges.
- In 2020, oncology biosimilars are estimated to reach between \$6Bn and \$12Bn in sales, or about 2% to 5% of the total global biologics market
- The U.S. is the largest biologic market by size, and is pivotal to the success of the overall biosimilar market.
- The regulatory process for biosimilars in other countries is better defined than in the U.S., The US situation is rapidly changing - the FDA has issued 4 draft guidances and current companies that produce biologics are likely to expand and produce biosimilars.
- The U.S. faces several challenges, since it is very difficult to prove that a biosimilar is the same product as the innovator and the means of proving this is ill defined; when a biosimilar is launched, the discount offered will likely be matched by the originator, which will have recouped its investment costs long ago.

Local manufacturers in pharmerging markets have taken overall drug market share from big pharma and this is expected to continue for biologics

Market share by company type



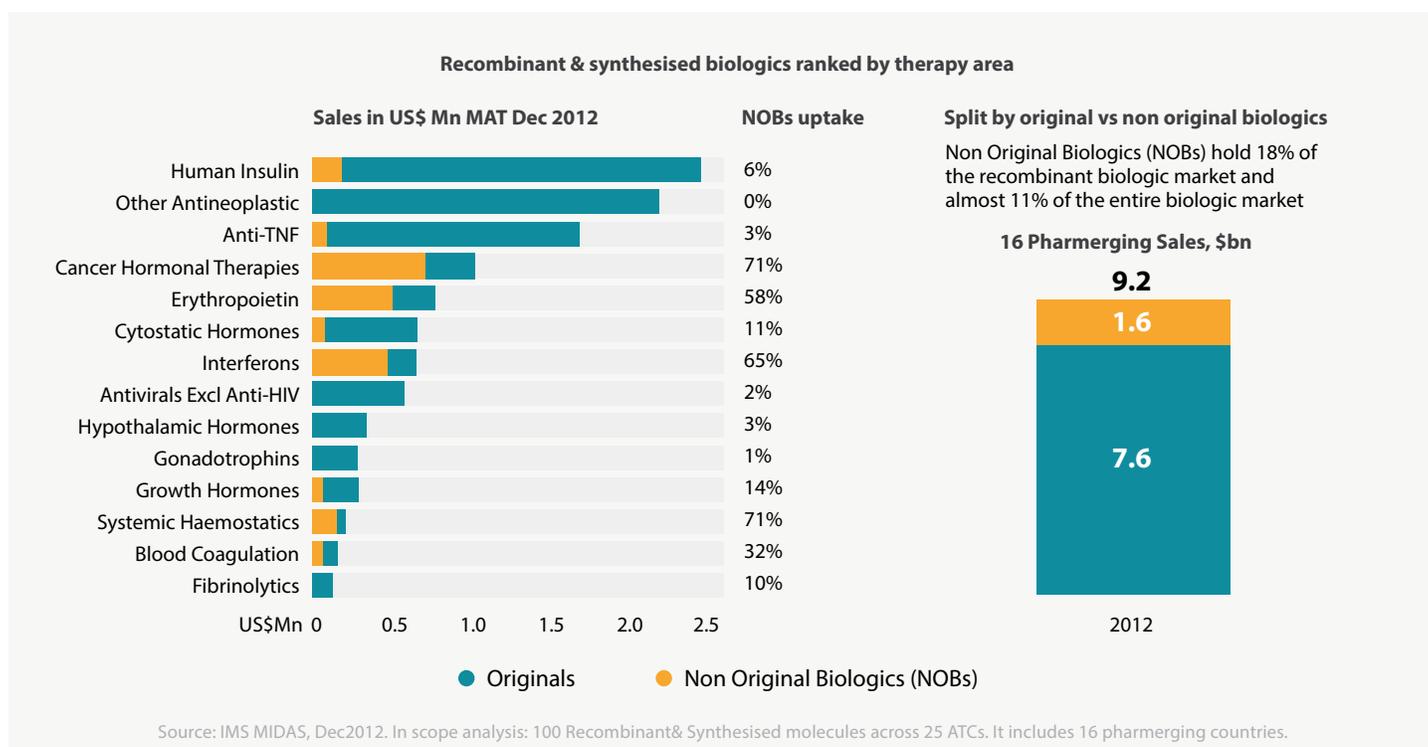
- In the overall pharmaceutical market, big pharma’s share in emerging markets has dropped from 53% in 2003 to 38% in 2013; a similar, albeit slower, shift has been taking place in the biologics market.
- A decade ago, local pharmerging players had 31% of the biologics market and 24% of the recombinant therapies market; today, those numbers have increased to 36% and 27%, respectively.
- Therefore, big pharma has lost 8 percentage points in biologics market share to players in pharmerging markets and small to medium-sized companies.
- If the market continues to grow at the same pace of 25% annually, big pharma can be expected to lose an additional seven to eight percentage points of market share by 2023, equating to several billion dollars captured by others.

Chart notes:

Recombinant and synthesized includes molecules that are synthetic or derived by recombinant DNA technology. In the analysis, monoclonal antibodies, insulins, growth hormones, haematopoietic growth factors, other proteins, polypeptides and peptides are included.

NOBs demonstrate significant uptake among chemotherapy support drugs but not among antineoplastics

Therapy areas in pharmerging markets



- While multi-national corporations (MNCs) have focused their efforts on mature markets, local players in emerging markets have been inserting themselves, little by little, into the NOB arena.
- By now, this parallel market development, sometimes backed by the local governments, is well under way, and the stage is set for great change.
- Over 10% of the value of pharmerging biologics markets already comprises NOBs; in contrast, only 0.4% of the developed market biologic market is currently from biosimilars.
- This share held by NOBs in pharmerging markets is even greater among the recombinant biologics (18%).

Biologic products with more than \$20Bn in global oncology spending will serve as targets for biosimilars in the next five years

Products losing patent protection by 2020

Product Name	Anticipated U.S. expiry date	Anticipated EU expiry date
Revlimid (lenalidomide)	2019	2017(France)/2022(rest of EU)
Avastin (bevacizumab)	2019	2019
Herceptin (trastuzumab)	2019	2014
Rituxan/Mabthera (rituximab)	2018	Expired
Prolia/Xgeva (denosumab)	2017	2017
Zytiga (abiraterone acetate)	2016	2021
Erbitux (cetuximab)	2016	2016
Neulasta (pegfilgrastim)	2016	2016
Xeloda (capecitabine)	Expired	Expired

*Patent expiry dates are estimates based on available information

- The top three compounds in oncology are biologics, and the top five represent a \$20Bn annual opportunity for biosimilar competition.
- Oncology agents facing patent expiry represent an approximate \$35Bn annual opportunity.

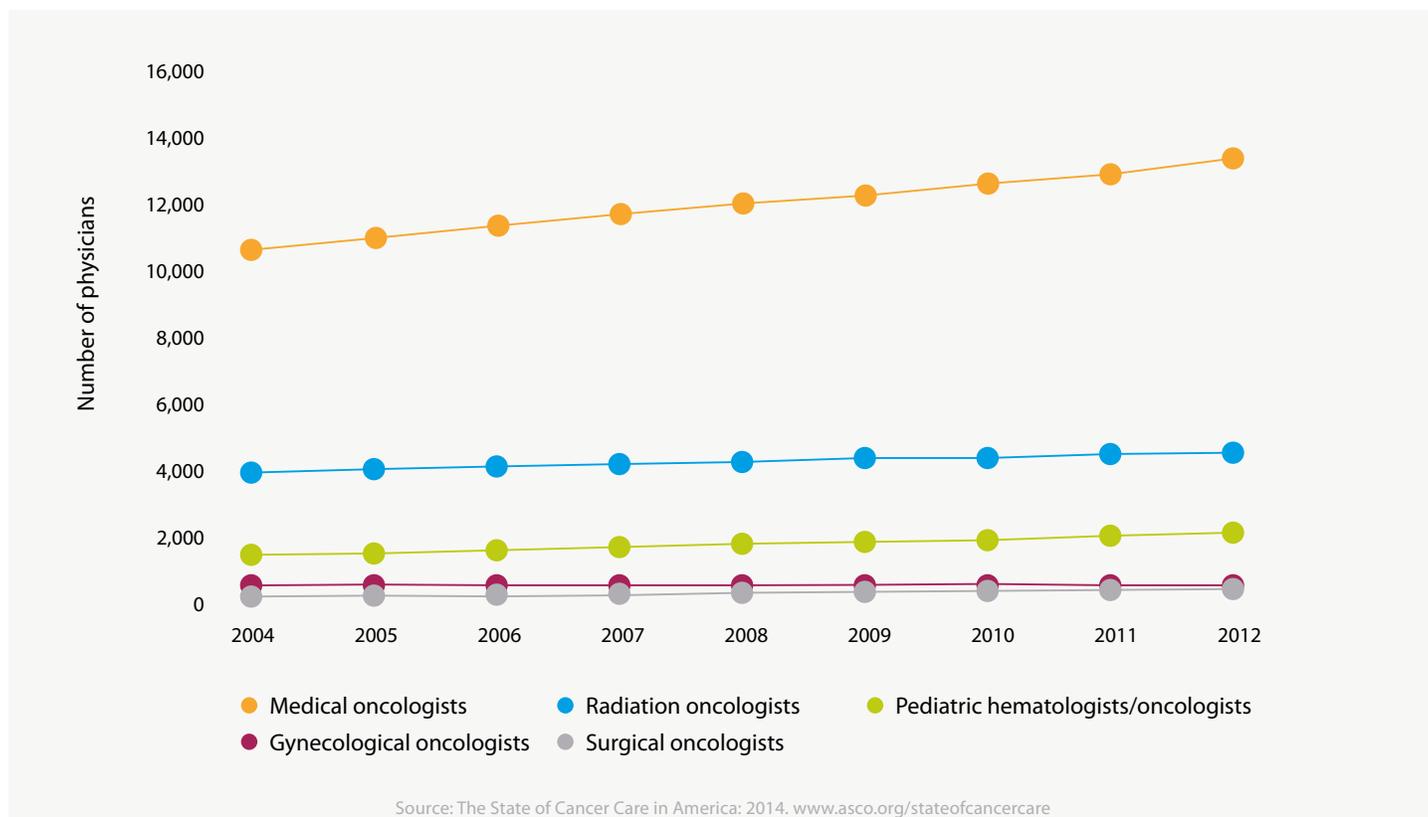
U.S. specific oncology dynamics

In the U.S., the delivery of cancer care is shifting. Physician practices are becoming larger and more cancer care is provided by Accountable Care Organizations and hospitals who enjoy increasingly favorable pricing under the ACA. Thus, some of the increases in cancer costs attributed to drug makers may actually be driven by the shift in setting of care. One unintended consequence is more cost is shifting to patients, potentially leading to reduced adherence.

- The U.S. has exhibited steady growth in the number of oncologists over the past decade although smaller physician practices have merged into larger ones or closed down completely, often driven by financial pressures felt by the oncologists.
- The change was driven in part by both the 2010 ACA, which encouraged the development of Accountable Care Organizations (ACOs) whose model required practice aggregation and hospital systems leveraging expanded 340B eligibility (340B Drug Pricing Program was created in 1992 to provide discounts to select “safety net” settings).
- Thus, more care is now provided in the hospital setting, whose reimbursement levels likely are passing more costs onto payers and subsequently passed patients via benefit design interventions and increased cost sharing.
- Increasing patient financial contribution is linked to declining therapeutic adherence, potentially resulting in drug discontinuation and higher overall total costs of care.

The number of oncologists in the U.S. continues to rise

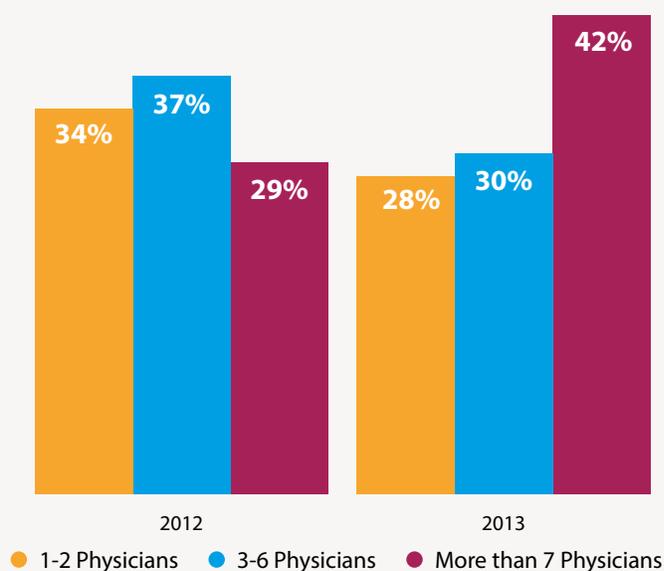
Growth in the number of oncologists in the U.S.



- In the U.S., the number of oncologists in nearly every subspecialty has increased over the past decade, with the overall number of oncologists increasing faster than the growth in U.S. population.

The operating model and viability of the average U.S. oncology practice is changing

Oncology Practice Measure	Result (2012, 2011 % change)
Referring drug infusions elsewhere	47 v. 48, no change
Merged / acquired (non hospital)	132 v. 111, 19% increase
Closed	241 v. 199, 21% increase
Acquired by hospital	392 v. 314, 24% increase
Struggling financially	442 v. 369, 20% increase

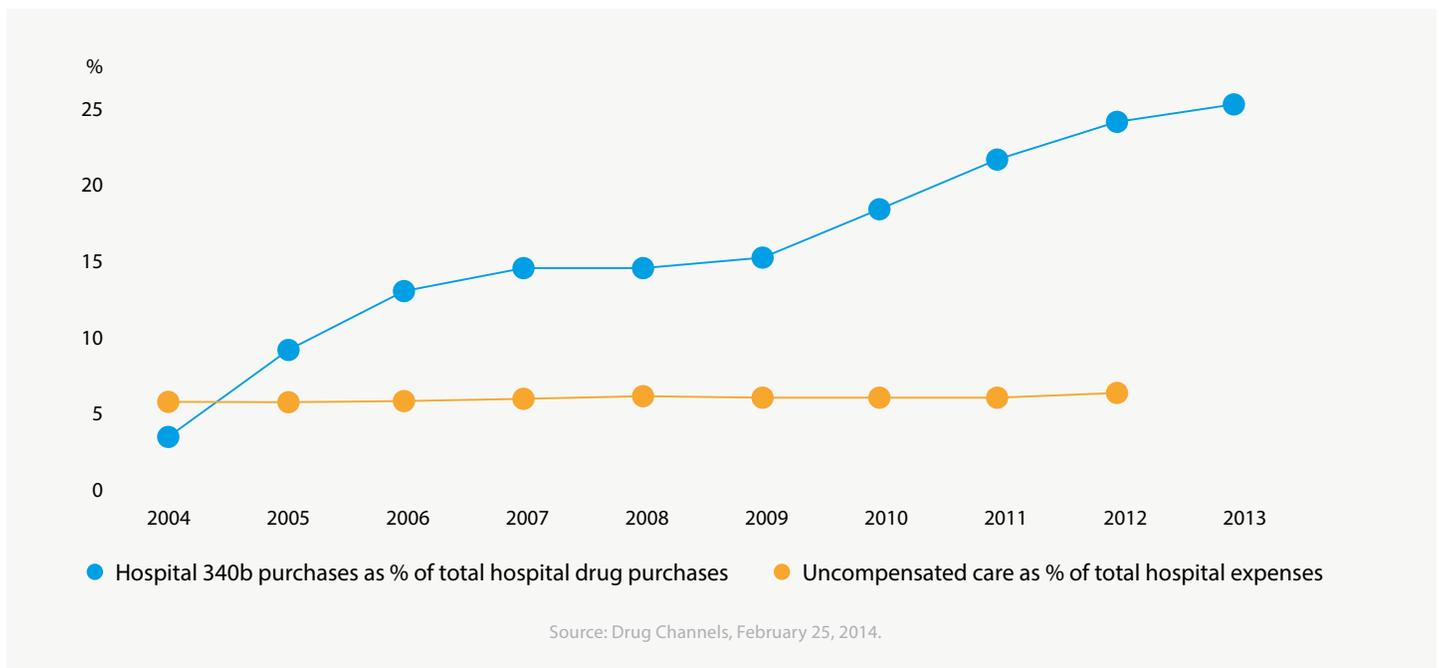


Source: Community Oncology Alliance (COA) Practice Impact Report, 2012, 2013
The State of Cancer Care in America: 2014. www.asco.org/stateofcancerca

- Practice dynamics are changing in the U.S., demonstrating a clear trend toward the aggregation of smaller practices and the acquisition of practices by hospital systems.
- Many of these changes are viewed as unfavorable by practicing oncologists, with a tendency for practices to report financial troubles and even close their doors permanently.
- As a result of such financial struggles, the dwindling number of independent practices are likely feeling increased pressure to aggregate with other practices and alleviate risk.
- Underscoring this overall trend toward larger and/or hospital system-owned practices, the proportion of oncology practices comprising seven or more physicians increased from 29% in 2012 to 42% in 2013.

The Affordable Care Act expanded 340B eligibility and encouraged formations of ACOs, prompting these dynamics

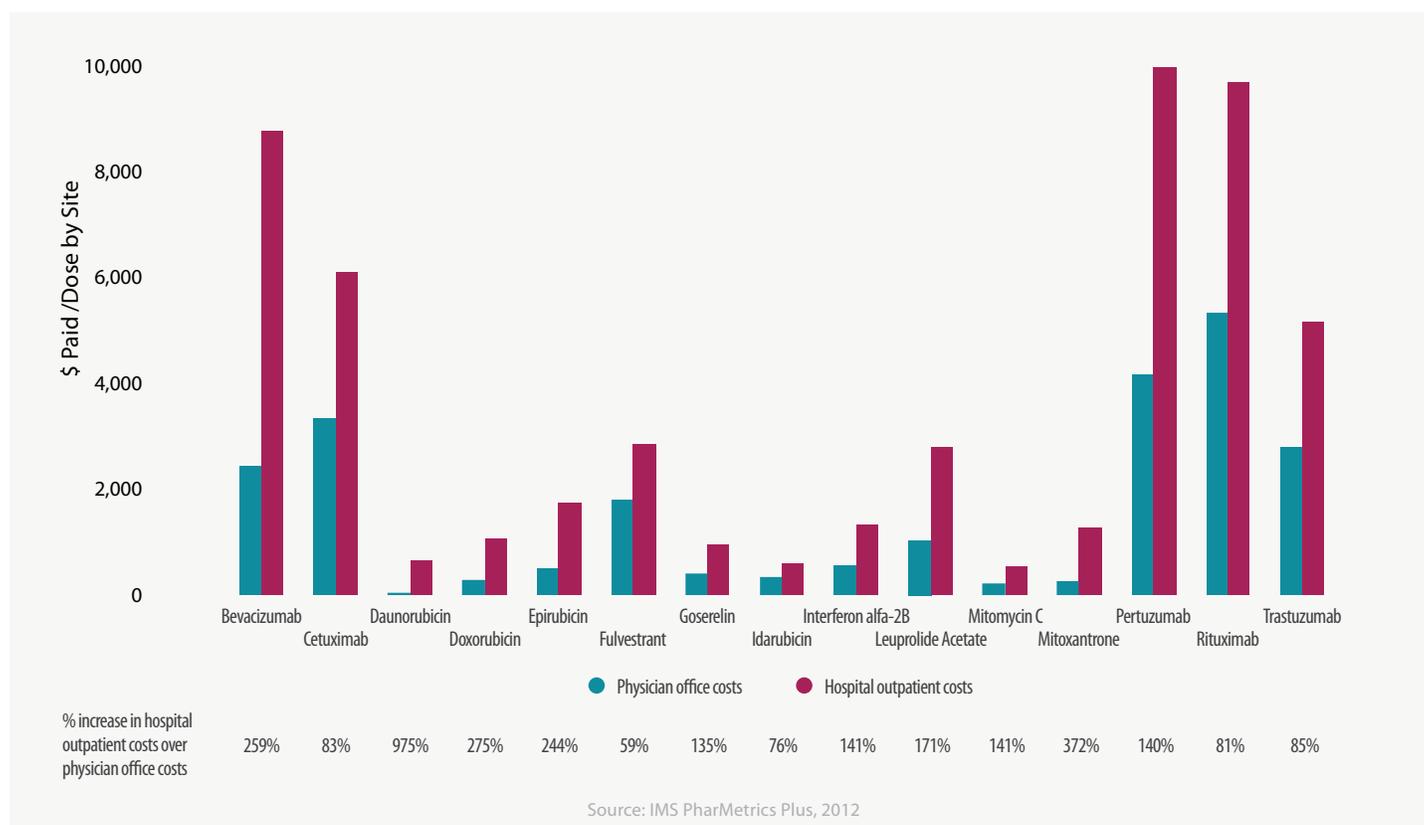
340B drug purchases vs. uncompensated care, 2004-2013



- These shifting practice dynamics are driven by a number of factors, some of which are a result of the ACA .
- One predominant change, expanded 340B pricing eligibility, available to hospital outpatient settings.
 - 340B pricing provides an approximate 51% discount to AWP, encouraging eligible hospitals to pull drug administration services into the more costly hospital outpatient setting.
 - The ACA has expanded 340B eligibility such that designated cancer research centers can now qualify for these discounts.
- While the proportion of uncompensated care has remained steady over the past several years—essentially a proxy for the proportion patients that enable a hospital to qualify for these discounts—the percentage of total hospital drug purchases using these discounts is up nearly 20% from six years ago.
- Hospitals can use 340B purchasing discounts for oncology practices that they have acquired while still charging facility-level prices to commercial payers.
- The ACA has also facilitated the formation of ACOs, further encouraging hospitals to purchase oncology practices to infuse cancer drugs in the hospital outpatient setting.
- Separately, low reimbursement for cancer treatments administered in the oncologist’s office, by both government and commercial payers, leads the oncologist to “refer” the patient to the hospital for drug administration.

Hospitals have higher drug administration costs than physician offices

Hospital outpatient costs compared to physician office costs



- Reimbursement levels for drug administration costs in hospital outpatient facilities are on average an incremental 189% of the level of physician office reimbursed costs for commercially insured patients under the age of 65 years. These higher reimbursement levels are in part associated with higher costs incurred by hospitals and overheads related to their delivery of care.
- Higher costs in hospital outpatient facilities are incurred despite the increasing proportion of hospital systems that benefit from discounted drug pricing via 340B eligibility.
- Competitive advantages achieved through 340B pricing, in conjunction with the decline of independent oncology practices, suggest a trend toward hospital outpatient drug administration at a substantially elevated cost to payers and increase patient out of pocket expenses.

As the cost of chemotherapy increases by site of care, so does patient contribution

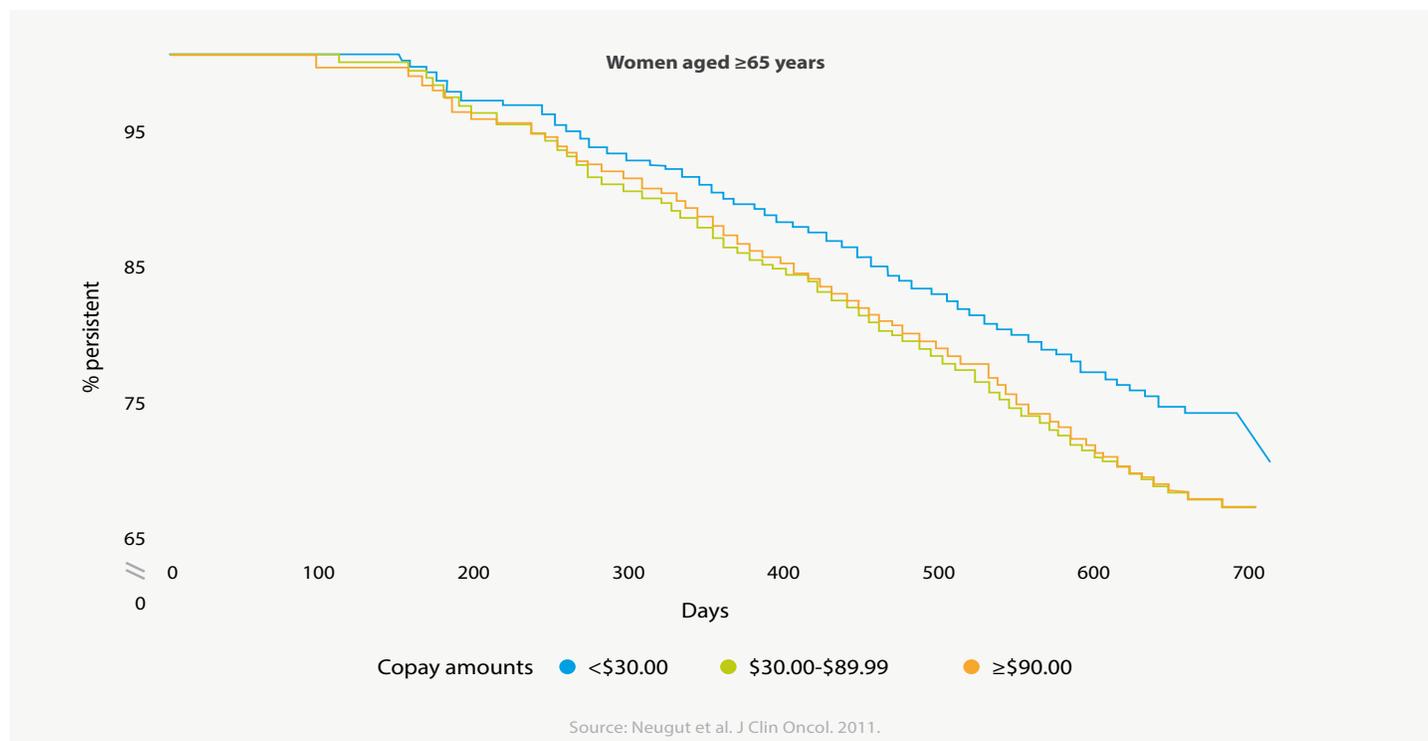
Therapy	\$ difference / dose paid by payor	\$ difference / dose paid by patient
	HOP v MD Office	HOP v MD Office
Alemtuzumab	6,251	-10
Bevacizumab	6,298	312
Cetuximab	2,764	374
Epirubicin	1,231	-2
Fulvestrant	1,054	-9
Leuprolide Acetate	1,756	121
Mitoxantrone	991	116
Pertuzumab	5,792	0
Rituximab	4,330	398
Trastuzumab	2,354	35

Source: IMS Pharmedics Plus, 2012

- Looking at a list of ten routinely prescribed chemotherapies, the covered cost per dose increased by 189% in the hospital outpatient setting when compared to the oncologist’s office.
- Dollars allowed represents the amount that the payers will cover or reimburse and include the portion paid by the patient and the reimbursement to the provider. Amounts paid by the patient are the difference between the allowed amount and the amount reimbursed to the administering provider.
- In many of these cases, these higher allowed costs in the hospital outpatient setting lead to increased patient costs, since patient costs are commonly a percent of the overall payment amount.
- Lower or no differences in patient cost in the hospital outpatient setting are likely explained by benefit design – some legacy benefits contain no patient costs for hospital infusions; such benefits are now being phased out. Also, if a patient reaches their OOP maximum for the year by the time they receive a particular therapy, the patient contribution would be \$0 regardless of the site of care at which the drug is administered. This phenomenon is most commonly observed for later-line therapies, such as those indicated for metastatic disease, since the patient will have already satisfied their maximum yearly OOP obligation during earlier treatments.
- For these commonly used oncology drugs, the average increased cost to the patient is \$134 per dose received in the hospital as an outpatient when compared to the oncologist’s office. Of note is that multiple therapies may be given per treatment cycle when both combination and chemotherapy support drugs are considered, leading to significant increases in member financial burden.

Increases in patient financial burden are associated with reductions in therapeutic persistence

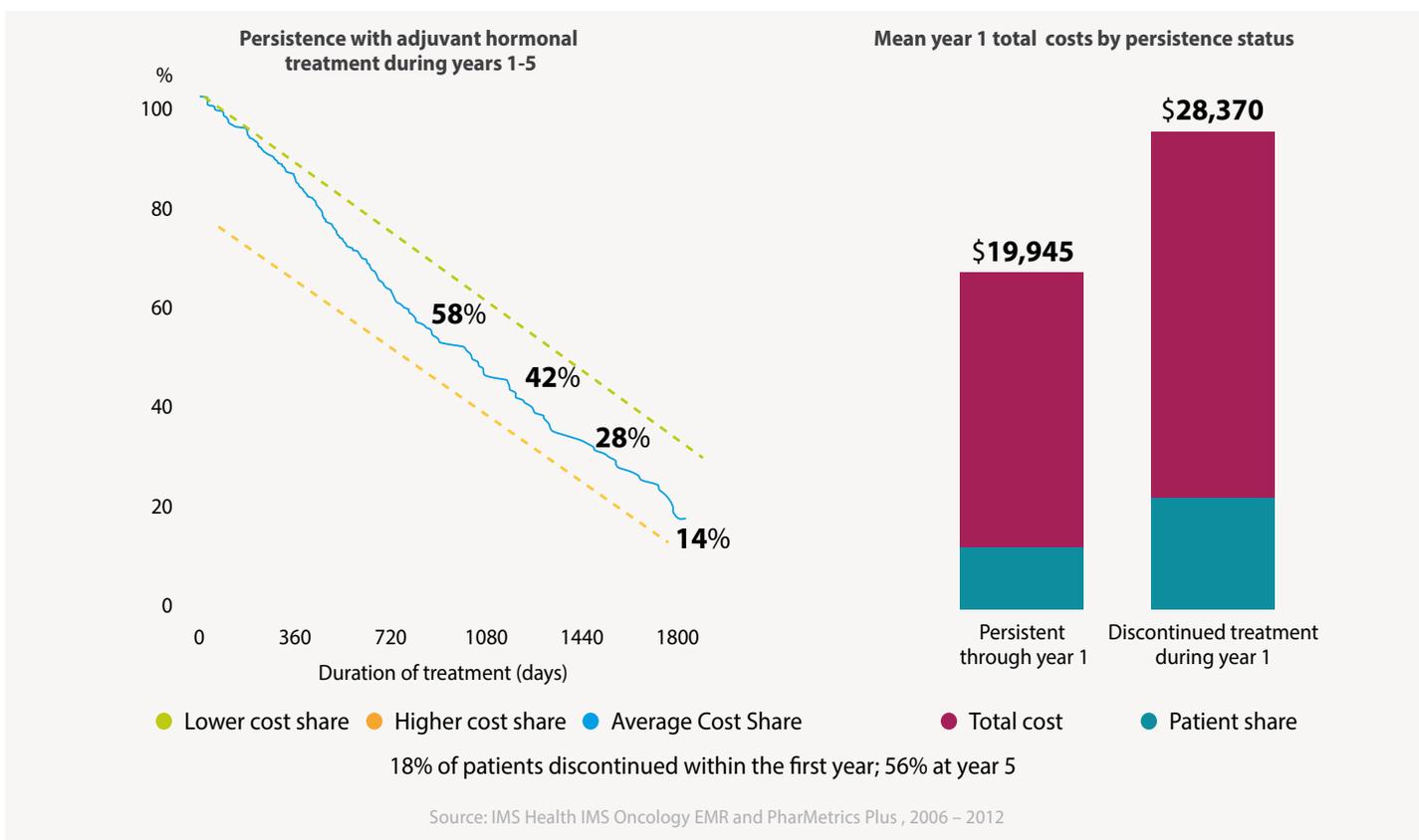
Adjuvant hormonal therapy persistence in breast cancer patients



- Looking specifically at adjuvant hormonal therapy for breast cancer demonstrates an inverse relationship between patient OOP cost and drug persistence.
 - As copay amounts increased, persistence fell with more than a \$30 copay. This suggests even small changes in patient contribution can lead to measurable changes in drug compliance.
- Even copays as modest as \$30 - \$90 appear to have an effect on therapy persistence, and the effect becomes more pronounced as copays increase.
- While copays are a function of the payer's benefit design, co-insurance is a function of both the benefit design (% of drug price that is charged to the patient) and the manufacturer's drug price, each of which can lead to unsustainable patient financial burden.

In certain scenarios, a reduction in therapeutic adherence can drive up the total cost of care

Early-stage ER+/PR+ breast cancer patients who discontinued adjuvant hormonal treatment



- Reduced therapeutic persistence is a key consideration because adherence can directly impact outcomes and, ultimately, the total cost of care.
- Again, focusing on adjuvant hormonal therapy in breast cancer, persistence levels declined over a 5 year time span and declined to an even greater extent among patients with a higher cost share.
- A \$9000 savings was associated with improved therapeutic persistence through the first year of therapy.
- Taking these findings into consideration, sites of care that increase patient contribution and cost sharing may actually lead to a significant increase in the total cost of care. Stakeholders are questioning the sustainability of rapid growth among hospital outpatient facility settings for oncology drug administration.

Notes on sources and definitions

The data and analyses presented in this report are from various IMS assets, including databases, analytics platforms, forecasting tools, and published literature. Among the internal services utilized were IMS MIDAS™, IMS LifeCycle™R&D Focus™, IMS LifeCycle™Patent Focus™, and PharMetrics Plus. External data cited in this report are from government agencies and reputable professional organizations in the field of oncology, such as the FDA, EMA, International Agency for Research on Cancer (IARC), World Health Organization (WHO), ASCO, and National Comprehensive Cancer Network (NCCN).

Oncology includes therapeutic treatments as well as supportive care, radiotherapy and immunotherapies. Supportive care includes anti-emetics, chemoprotectants, cancer pain, immunosupportive agents (e.g. hematopoietic growth factors), erythropoietins, and therapeutic cancer vaccines. Costs used for the Value of Cancer are based on Average Sales Price (ASP) where applicable.

IMS MIDAS™ is an analytics platform used to assess worldwide healthcare markets. It aggregates IMS's global audits and normalizes to international standards of product naming, company ownership, currency exchange rates, volume metrics and product segmentations, and estimates of price levels at different points in the supply chain. Segmentations include therapy classes, forms, dosages, and those related to brands, generics and patent protection. Results are commonly reported as Moving Average Total (MAT).

IMS LifeCycle™R&D Focus™ is a global database for evaluating the market for medicines, covering more than 31,000 drugs in R&D and over 8,900 drugs in active development worldwide. It includes information about the commercial, scientific and clinical features of the products, analyst predictions of future performance, and reference information on their regulatory stage globally.

PharMetrics Plus is a closed-source de-identified longitudinal patient database that captures a patient plan experience through his/her pharmacy, medical provider, and hospital. Patient membership eligibility is accounted for within the source which ensure complete longitudinal activity per patient PharMetrics Plus captures activities from a membership of approximately 60Mn lives per year. PharMetrics Plus integrates IMS legacy PharMetrics data with Health Intelligence Company's participating plan claims data. Health Intelligence Company is the operating entity of Blue Health Intelligence.

IMS Lifecycle™ Patent Focus™ is a global database for tracking patent protections for pharmaceutical products. It contains evaluated patent information on commercially significant pharmaceutical compounds at phase III and above, with a total of over 256,000 individual patent records worldwide.

IMS Oncology Analyzer™ is a global database that captures over 100,000 patient histories per year, in more than 30 major cancer types in 11 countries.

Definitions and conventions:

Spending is reported at ex-manufacturer prices and does not reflect off-invoice discounts and rebates.

Values are converted from local currencies to US\$ using variable exchange rates, except where noted.

Growth is calculated using US\$ at constant (Q2 2013) exchange rates.

Products are categorized as brands, generics or other using IMS's proprietary MIDAS™ market segmentation methodology.

Biologic medicines are defined as molecules of biologic origin, either purified natural biologic compounds, or those created through recombinant DNA technology. These complex macromolecules, including proteins, nucleic acids, must be clearly identified (e.g. not "Vegetable Extract"), must be an active ingredient in a product, and must have undergone (or be undergoing) a regulatory human clinical trial program under the auspices of a national / regional regulatory authority.

Developed markets are defined as the U.S., Japan, Top 5 Europe countries (Germany, France, Italy, Spain, UK), Canada and South Korea.

Pharmerging countries are defined as those with >\$1Bn absolute spending growth over 2013-17 and which have GDP per capita of less than \$25,000 at purchasing power parity (PPP). Tier 1: China; Tier 2: Brazil, India, Russia; Tier 3: Mexico, Turkey, Venezuela, Poland, Argentina, Saudi Arabia, Indonesia, Colombia, Thailand, Ukraine, South Africa, Egypt, Romania, Algeria, Vietnam, Pakistan and Nigeria.

Authors



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Kjel A. Johnson, PharmD, BCPS, FCCP, FAMCP is the Vice President of Global Oncology for IMS Health, where he oversees oncology data acquisition and analytics, as well as the development of novel oncology technology and informatics businesses across the globe.

Prior to IMS Health, he was Senior Vice President of Strategy and Business Development at Magellan Pharmacy Services / ICORE Healthcare, where he developed specialty management strategies and services for payors, assisting scores of health plans to develop and implement various pharmacy programs for all benefits across all sites of service. Kjel was a co-founder of ICORE in 2003, and continued with the company through its acquisition by Magellan Health Services in 2006. Prior to ICORE, Dr. Johnson was a Senior Manager at Deloitte Consulting specializing in pharmacy and medical management operations at national and regional payors. Prior to working at Deloitte Consulting, Dr. Johnson was a Vice President at UPMC HealthPlan, an integrated delivery system, and has also been a Regional Director for Coventry Healthcare.

Dr. Johnson has published over 100 articles, abstracts and book chapters focusing on the value of medicines and procedures. He is a Fellow of both the Academy of Managed Care Pharmacists and of the American College of Clinical Pharmacy, Board Certified in Pharmacotherapy and was the founder and publisher of Managed Care Oncology. He received both Undergraduate and Doctoral degrees from the University of Minnesota, and completed a post-doctoral fellowship at St. Paul Ramsey Medical Center.



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Lee is a Senior Principal in P&MA Consulting in the U.S. He currently serves as the IMS Consulting Group's representative to IMS Health's Global Oncology Initiatives.

Lee has twenty years of experience working with, consulting to, and studying providers and payers in the U.S. and EU. He has extensive experience with hospital and community oncology providers, with commercial and public reimbursement, and with managed care, including contracting and medical management.

Prior to IMS, he led research and analysis for DaVinci's publications Oncology Market Access-U.S., and Oncology Market Access-EU. He also partnered DaVinci Healthcare Partners, later part of KantarHealth

Lee has an M.B.A. in Entrepreneurial Studies at The Wharton School, University of Pennsylvania, and a B.Sc. in Finance at Santa Clara University, where he was a National Merit Scholar

**Radha Mawrie****Senior Manager, IMS Health**

Radha Mawrie, is a Senior Manager at IMS Health and works on new product development in the Global Oncology business.

Radha's prior experience is in Healthcare information services and includes launching evidence-based decision support tools to meet the needs of healthcare stakeholders including hospitals and physicians across multiple specialties. She has worked at Reed Elsevier and Wolters Kluwer Health and has led client-focused, data-driven market assessments of the global healthcare market to identify white space opportunities for product development.

Radha holds an MBA from the Indian Institute of Management, Bangalore.

**Stefano Di Biase****Consultant, European Thought Leadership, IMS Health**

Stefano Di Biase currently holds the position of consultant in the European Thought Leadership team, focusing on strategic issues within the pharmaceutical industry. Stefano's research experience spans across several therapy areas and emerging markets with particular emphasis on oncology and biosimilars. Stefano has delivered several presentations to clients and presented Biosimilars' perspectives at conferences across Europe.

Prior to IMS Health, Stefano has worked in various consulting firms and, more recently, for a major investment bank in London. Stefano holds a BA in Economics and further master degrees in International Management from Audencia Nantes School of Management and in International Business from Aston Business School.

About the Institute

The IMS Institute for Healthcare Informatics leverages collaborative relationships in the public and private sectors to strengthen the vital role of information in advancing healthcare globally. Its mission is to provide key policy setters and decision makers in the global health sector with unique and transformational insights into healthcare dynamics derived from granular analysis of information.

Fulfilling an essential need within healthcare, the Institute delivers objective, relevant insights and research that accelerate understanding and innovation critical to sound decision making and improved patient care.

With access to IMS's extensive global data assets and analytics, the Institute works in tandem with a broad set of healthcare stakeholders, including government agencies, academic institutions, the life sciences industry and payers, to drive a research agenda dedicated to addressing today's healthcare challenges.

By collaborating on research of common interest, it builds on a long-standing and extensive tradition of using IMS information and expertise to support the advancement of evidence-based healthcare around the world.

Research Agenda

The research agenda for the Institute centers on five areas considered vital to the advancement of healthcare globally:

Demonstrating the effective **use of information** by healthcare stakeholders globally to improve health outcomes, reduce costs and increase access to available treatments.

Optimizing the **performance of medical care** through better understanding of disease causes, treatment consequences and measures to improve quality and cost of healthcare delivered to patients.

Understanding the future **global role for biopharmaceuticals**, the dynamics that shape the market and implications for manufacturers, public and private payers, providers, patients, pharmacists and distributors.

Researching the role of **innovation in health system products, processes and delivery systems**, and the business and policy systems that drive innovation.

Informing and advancing the healthcare agendas in **developing nations** through information and analysis.

Guiding Principles

The Institute operates from a set of Guiding Principles:

The advancement of healthcare globally is a vital, continuous process.

Timely, high-quality and relevant information is critical to sound healthcare decision making.

Insights gained from information and analysis should be made widely available to healthcare stakeholders.

Effective use of information is often complex, requiring unique knowledge and expertise.

The ongoing innovation and reform in all aspects of healthcare require a dynamic approach to understanding the entire healthcare system.

Personal health information is confidential and patient privacy must be protected.

The private sector has a valuable role to play in collaborating with the public sector related to the use of healthcare data.

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