IMS INSTITUTE
FOR
HEALTHCARE INFORMATICS

May 2014

Innovation in cancer care and implications for health systems

Global oncology trend report

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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.

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.

Market dynamics

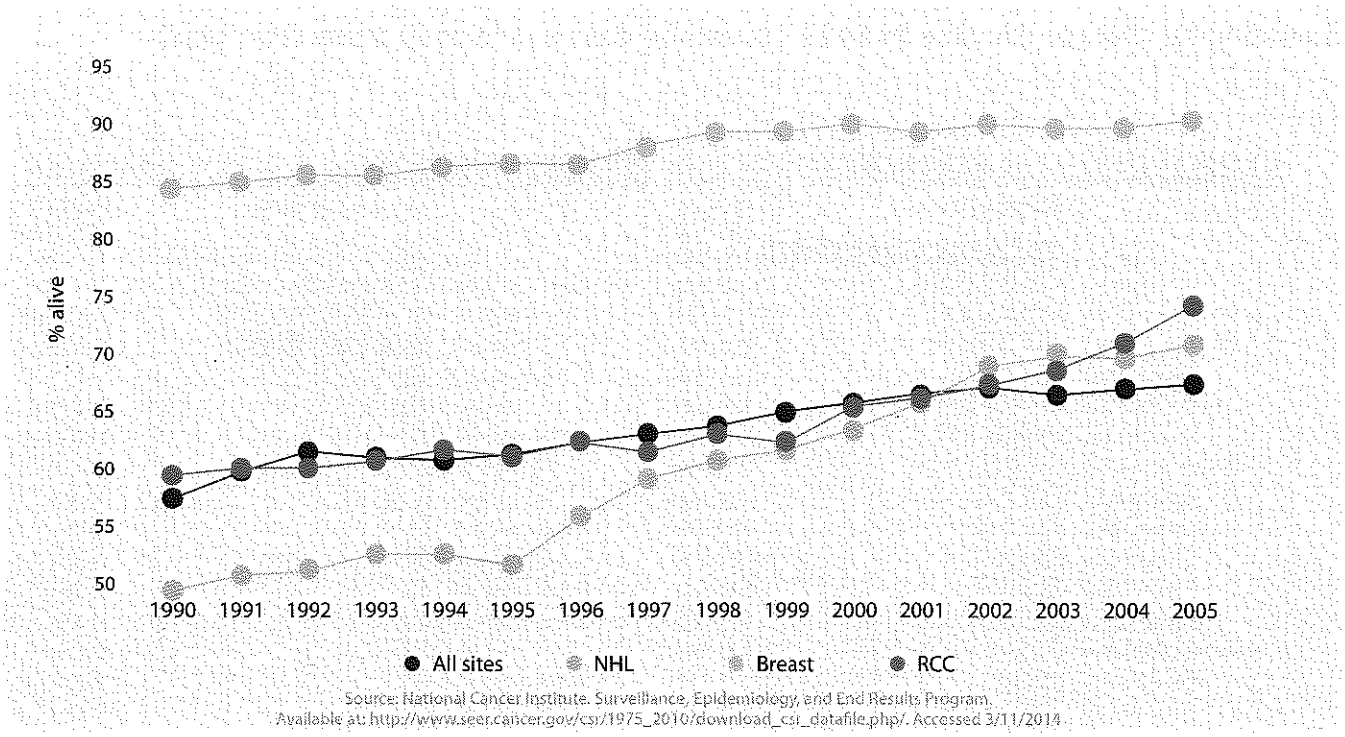
The global oncology market reached $91Bn in 2013, marked by a slowing rate of growth; most sales continue to be in the U.S. and Europe although oncology is a dominant spend area for pharmerging nations; the shift in spend to targeted products and away from biologics is occurring globally.

- 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

Cancer survival is improving steadily as detection and treatment improve

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



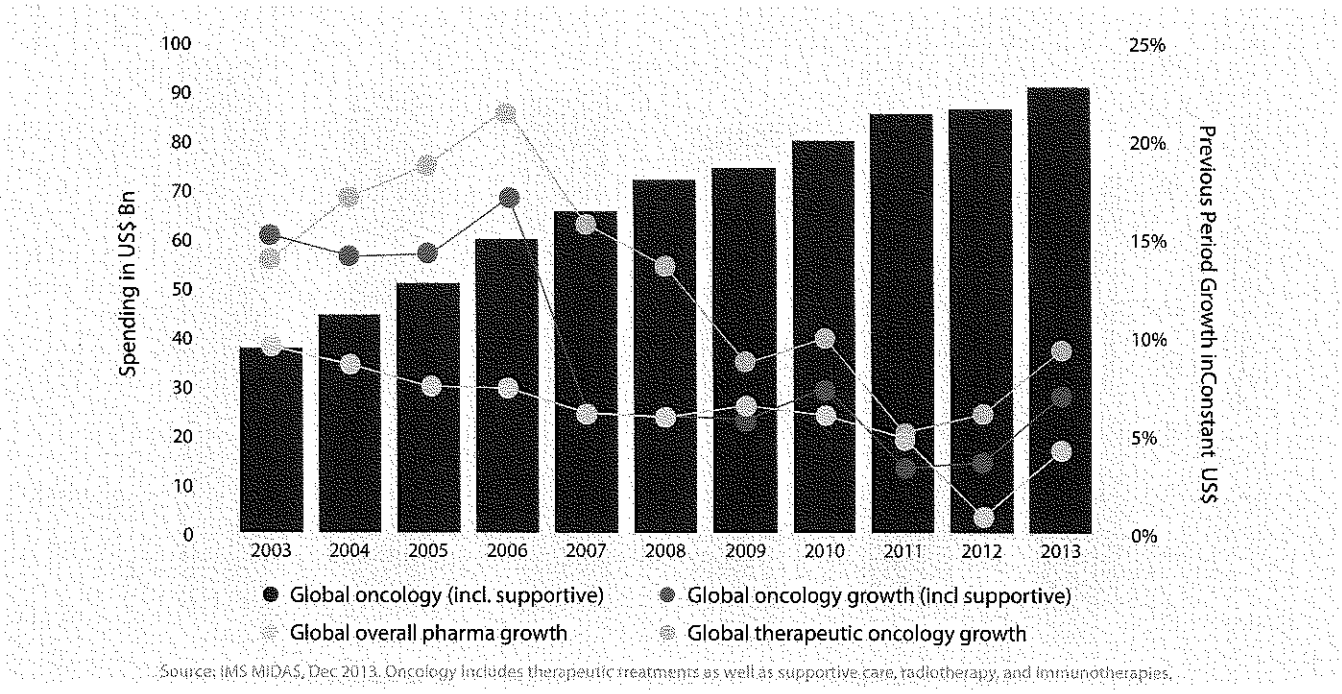
Source: National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Available at: http://www.seer.cancer.gov/csr/1975_2010/download_csr_datafile.php/. Accessed 3/11/2014

- 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.

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

Global oncology market dynamics 2003-2013

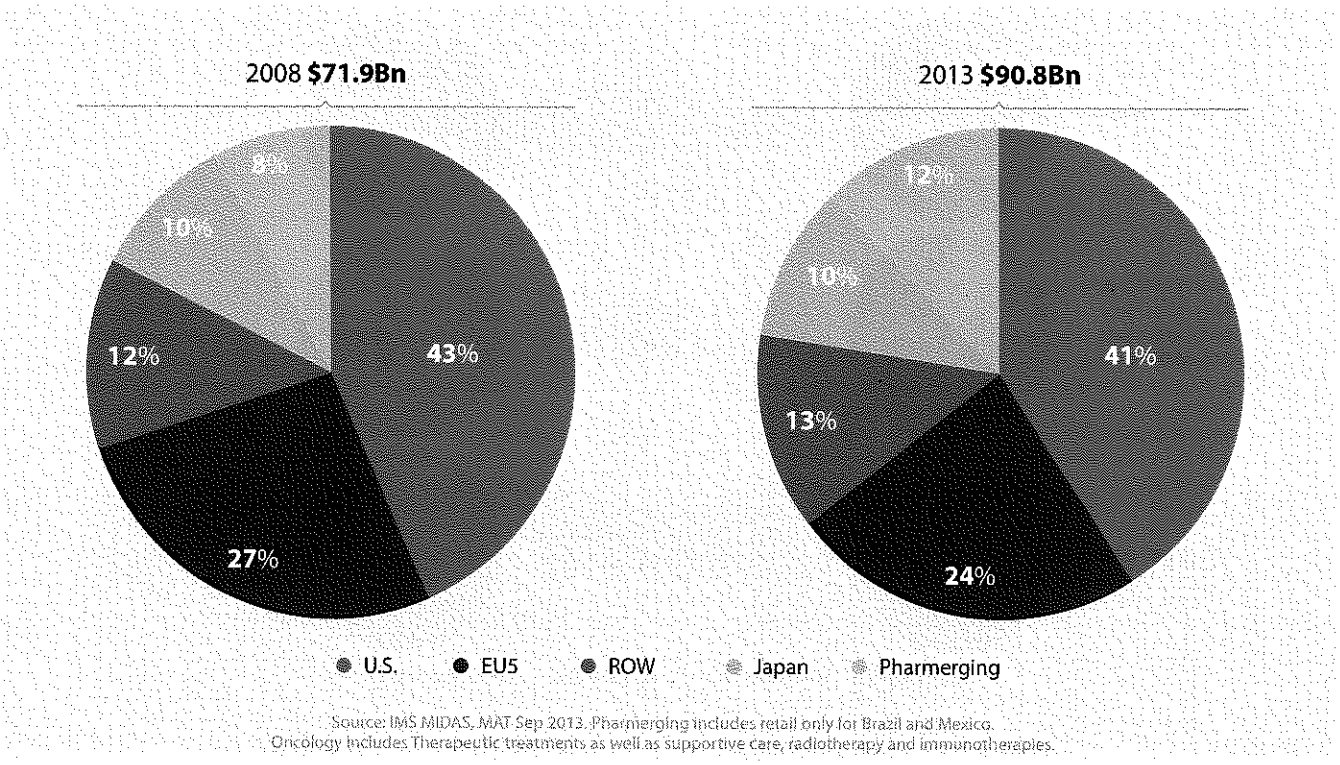


Source: IMS MIDAS, Dec 2013. Oncology includes therapeutic treatments as well as supportive care, radiotherapy, and immunotherapies.

- 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.

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

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

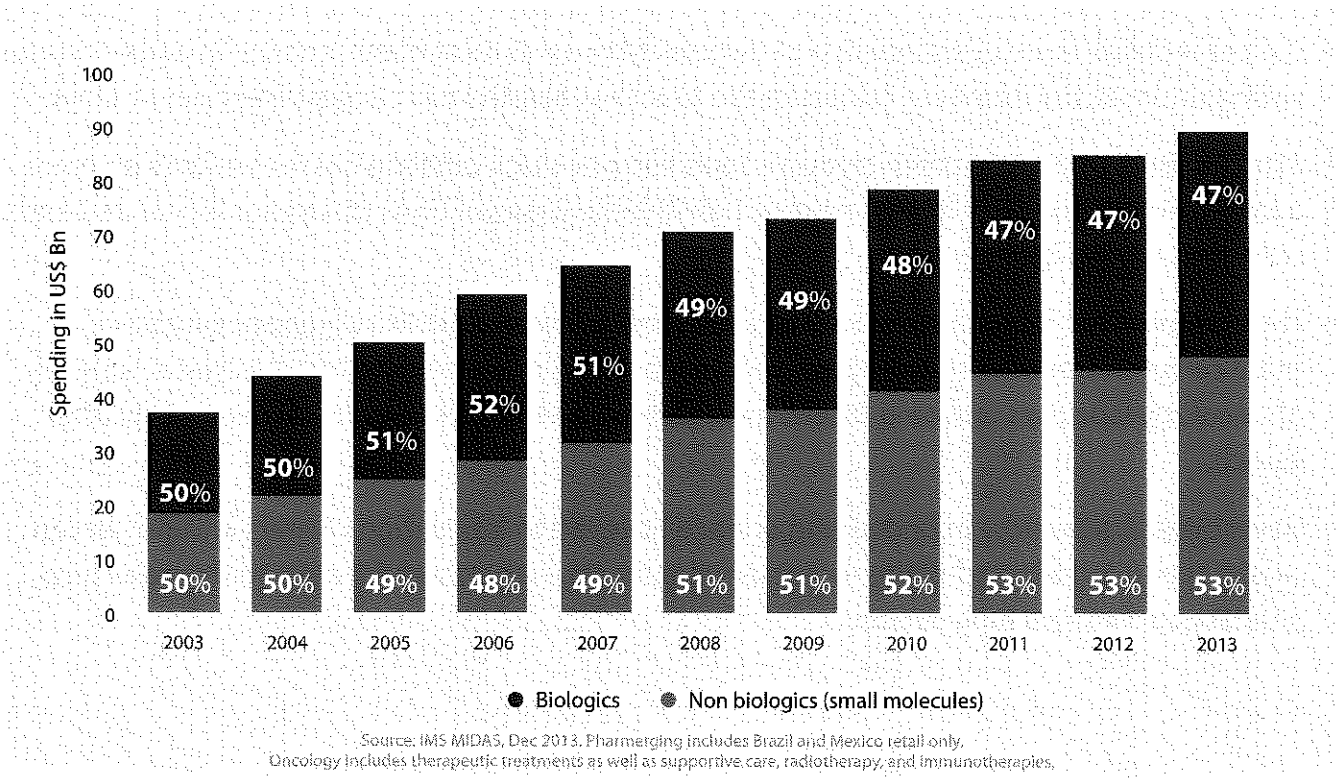


Source: IMS MIDAS, MAT Sep 2013. Pharmerging includes retail only for Brazil and Mexico.
Oncology includes Therapeutic treatments as well as supportive care, radiotherapy and immunotherapies.

- 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.

Biologics share of the global oncology market has been declining

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

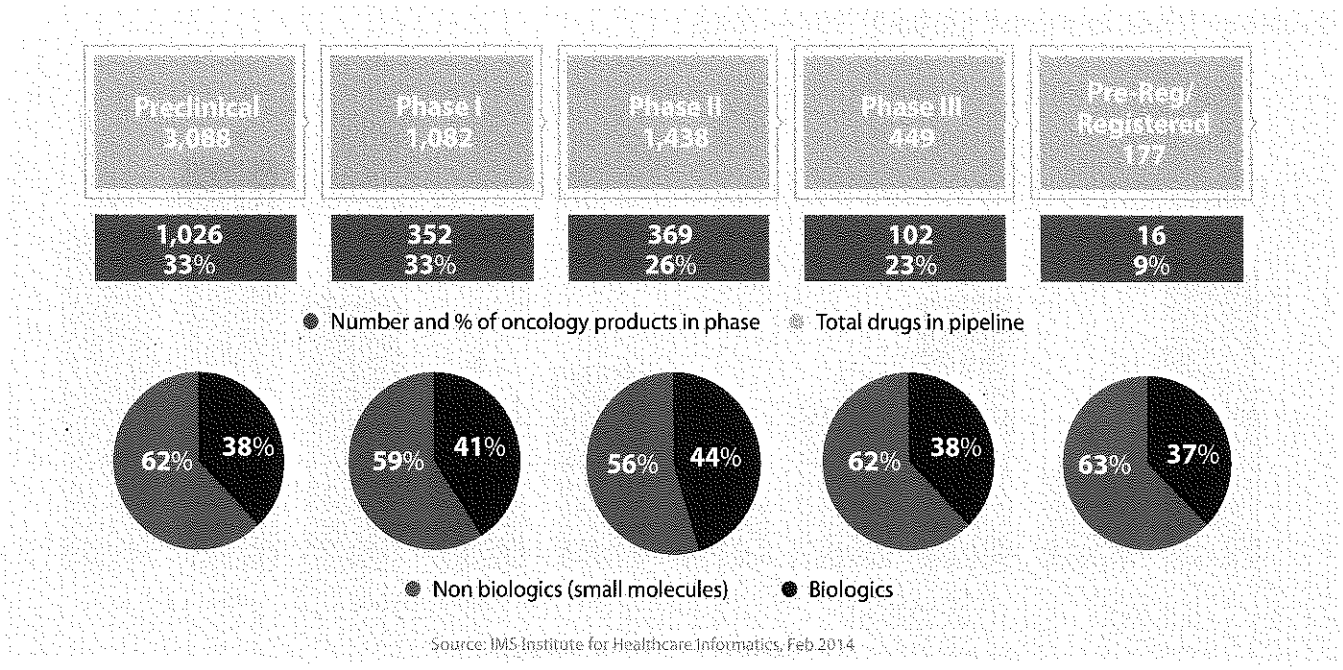


Source: IMS MIDAS, Dec 2013. Pharmerging includes Brazil and Mexico retail only.
Oncology includes therapeutic treatments as well as supportive care, radiotherapy, and immunotherapies.

- 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.

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



Source: IMS Institute for Healthcare Informatics, Feb 2014

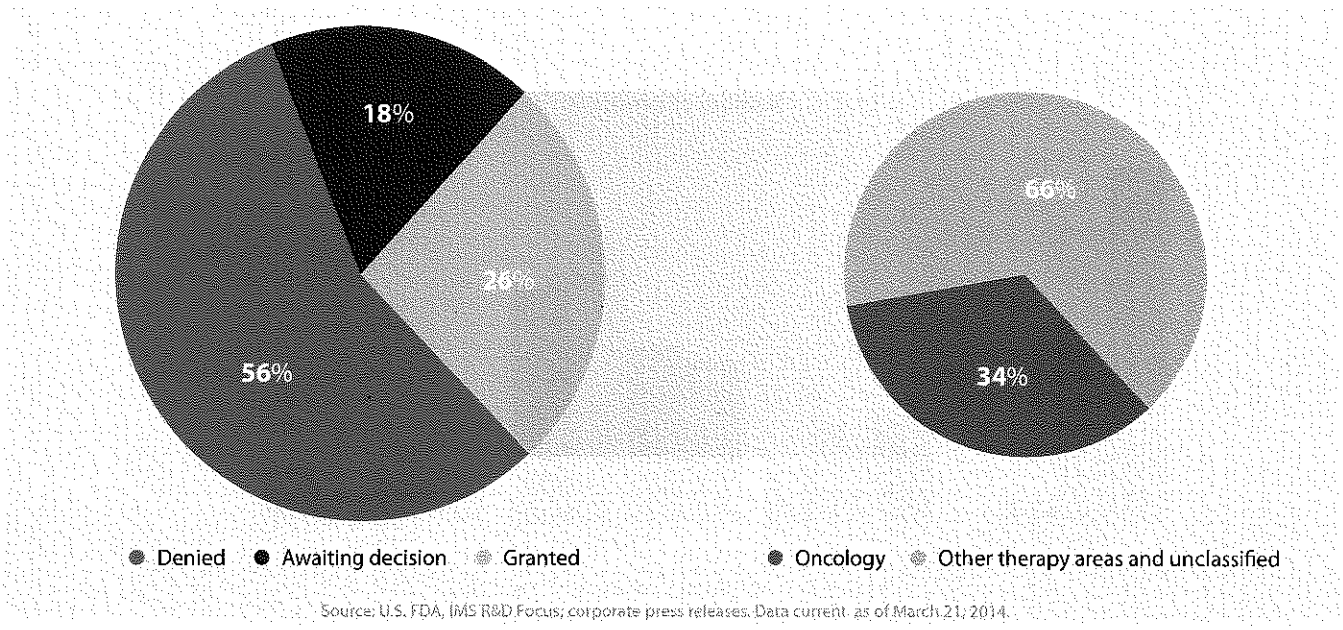
- Oncology represents the largest cluster of R&D activity, with over 30% of preclinical and phase I activity.
- Fewer cancer drugs are progressing to phase II and III which indicates both the high levels of early phase activity and the difficulties in generating successful results in the clinic.
- While 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.

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

FDA breakthrough therapy designations 2012-2014

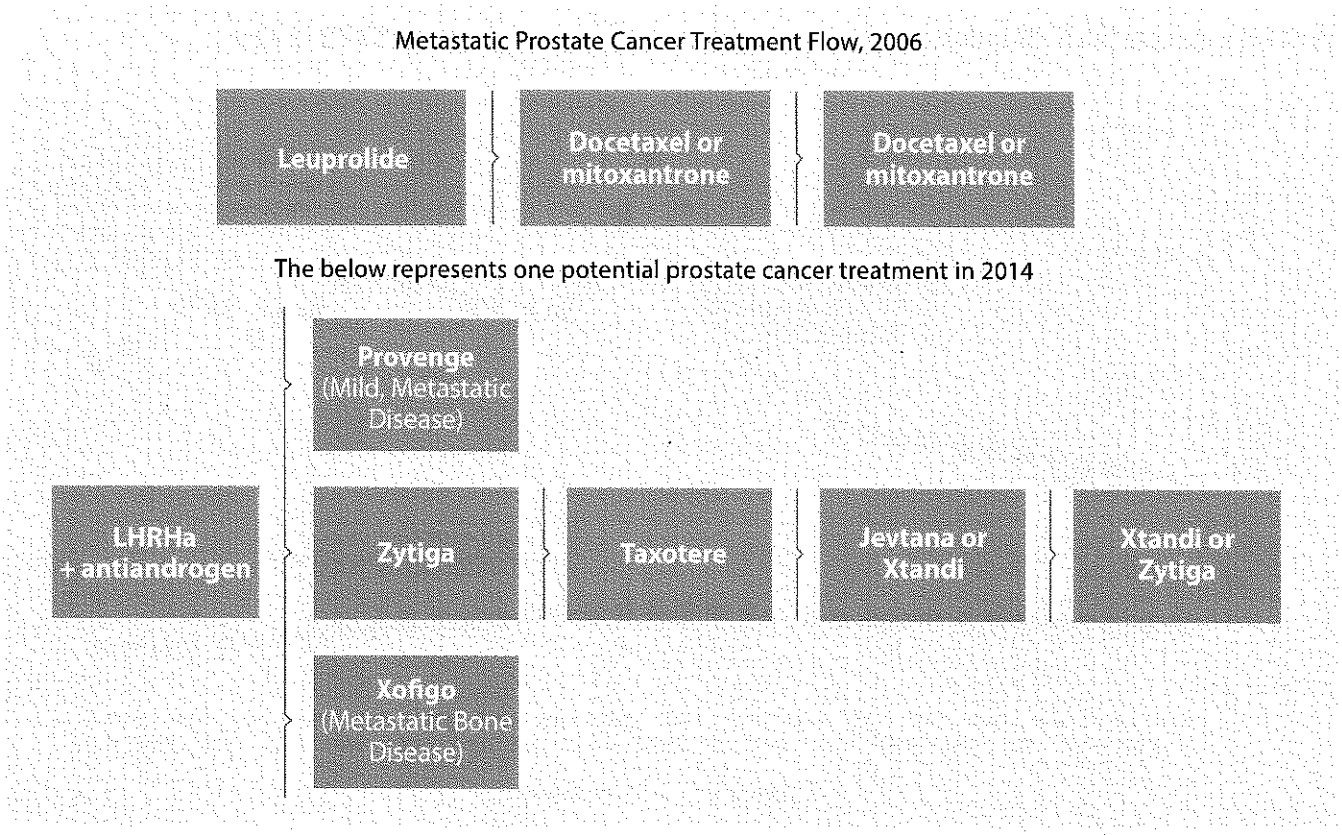


Source: U.S. FDA, IMS R&D Focus; corporate press releases. Data current as of March 21, 2014.

- The FDA's BTD 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 BTDs.
- However, since the designations are not reported publicly by the Agency, the therapeutic area of all current BTD 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 BTD 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.

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

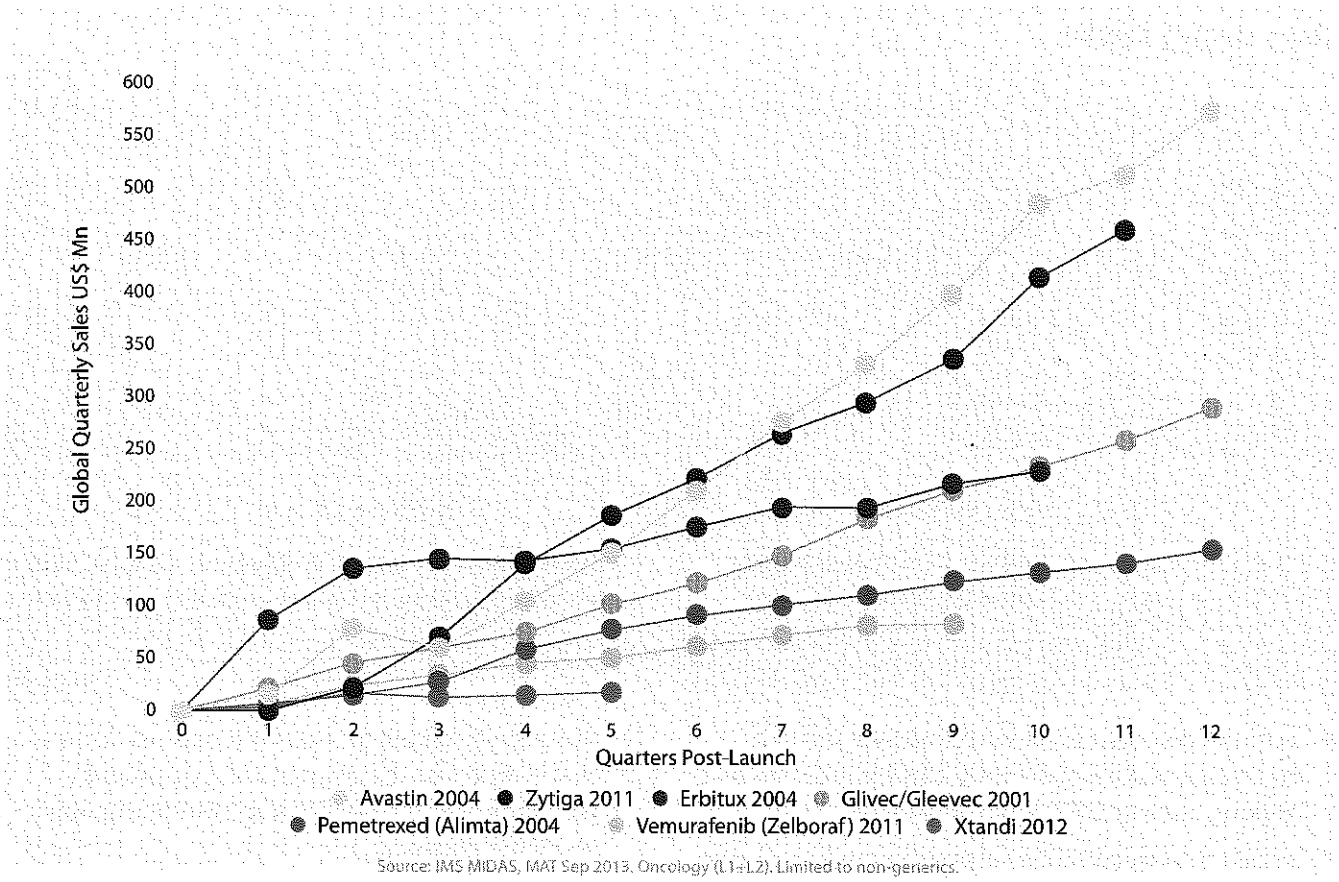
Metastatic prostate cancer treatment flow



- 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.

Recent blockbuster launches have rivaled those of a decade ago

Global results of selected oncology launches

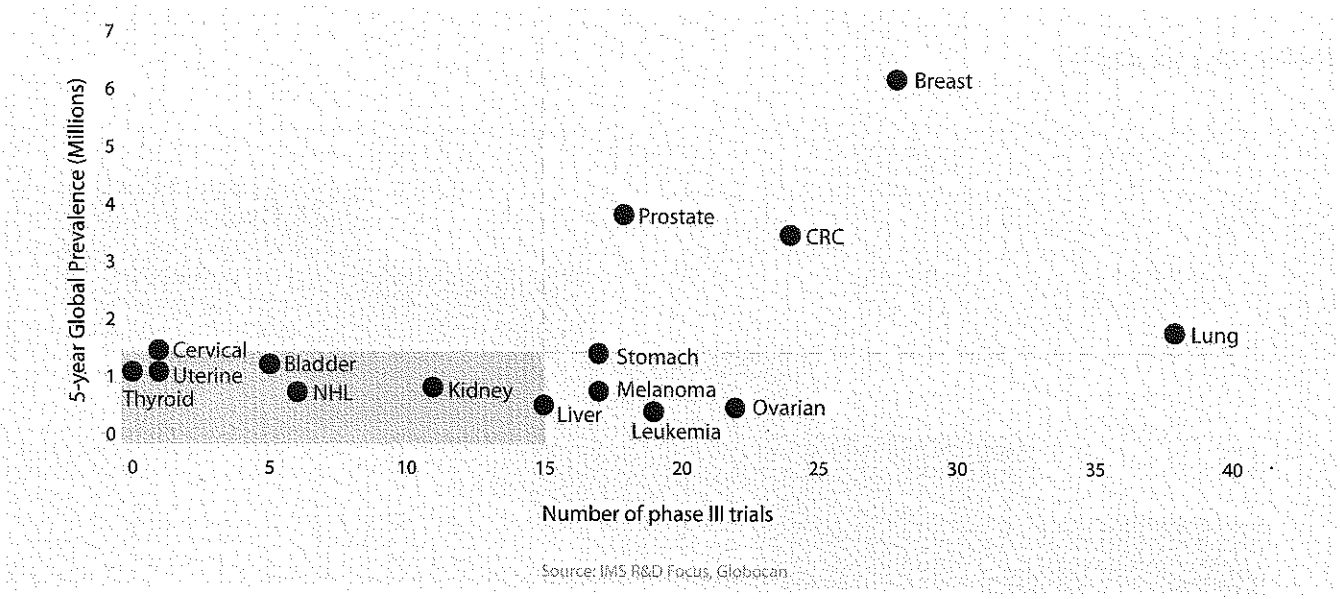


Source: IMS MIDAS, MAT Sep 2013. Oncology (L1+L2). Limited to non-generics.

- 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.

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



Source: IMS R&D Focus, Globocan

- 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

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.

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	Total
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 unresctable 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 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	NA	NA	+4.1 months	3 doses	$71,436	$98,694
1st Line	NA	NA	+4.5 months	*(6 weeks)*		

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]					$6,928	
Abiraterone acetate						$95,603
pre-chemo	NA	NA	+5.2 months	13.8 months		$55,422
post-chemo	NA	NA	+4.6 months	8 months		

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	NA	NA	+4.8 months	8.3 months	$7,995	$66,356
post-chemo						

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	10%	NA	+2.4 months	6 cycles	$11,600	$48,079
2nd Line				*(18 weeks)*		

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 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

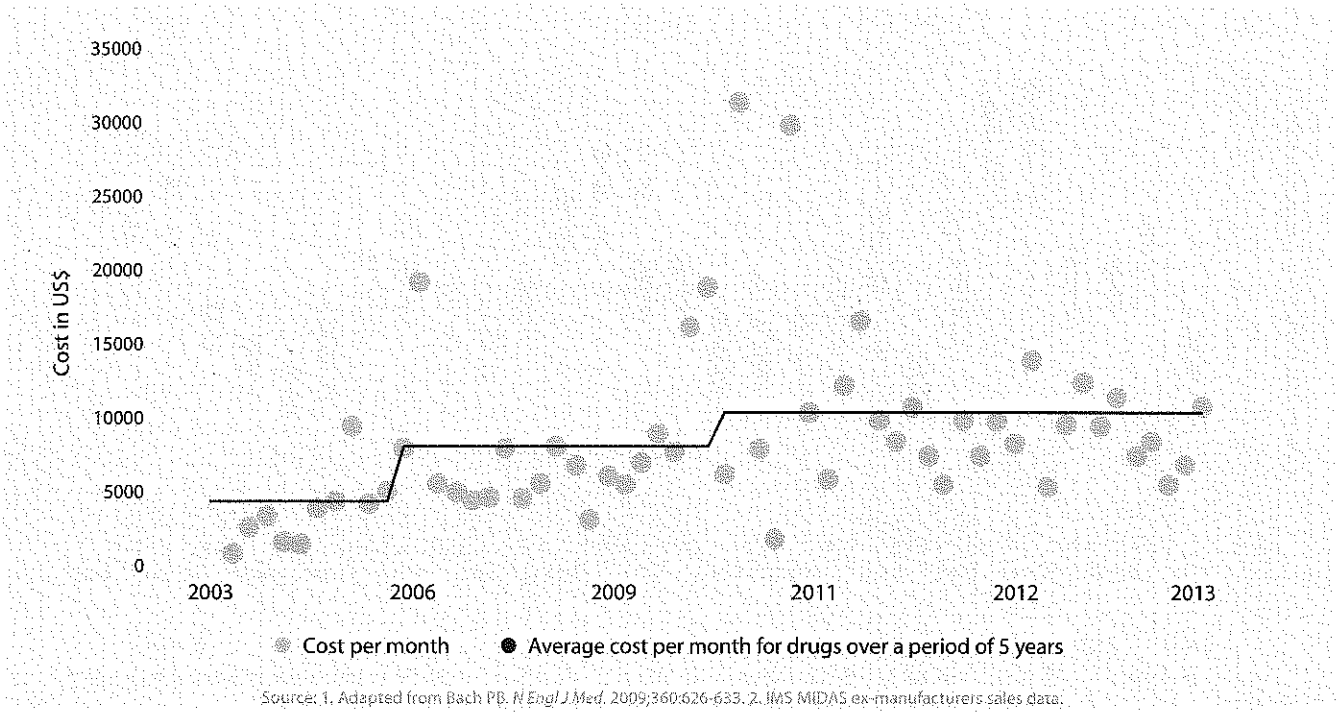
Inlyta in patients with advanced renal cell carcinoma after the failure of one prior systemic regimen with the primary efficacy endpoint being PFS:

- 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.

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)



Source: 1. Adapted from Bach PB. *N Engl J Med.* 2009;360:626-633. 2. IMS MIDAS ex-manufacturers sales data.

- 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.

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.

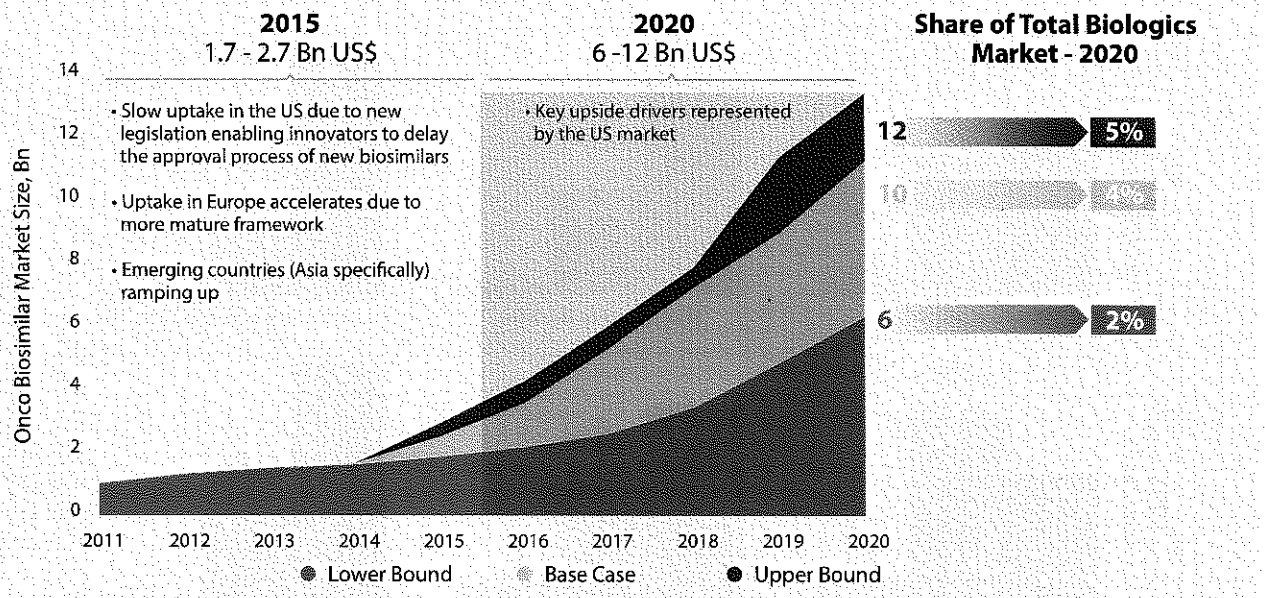
Biosimilars

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.

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

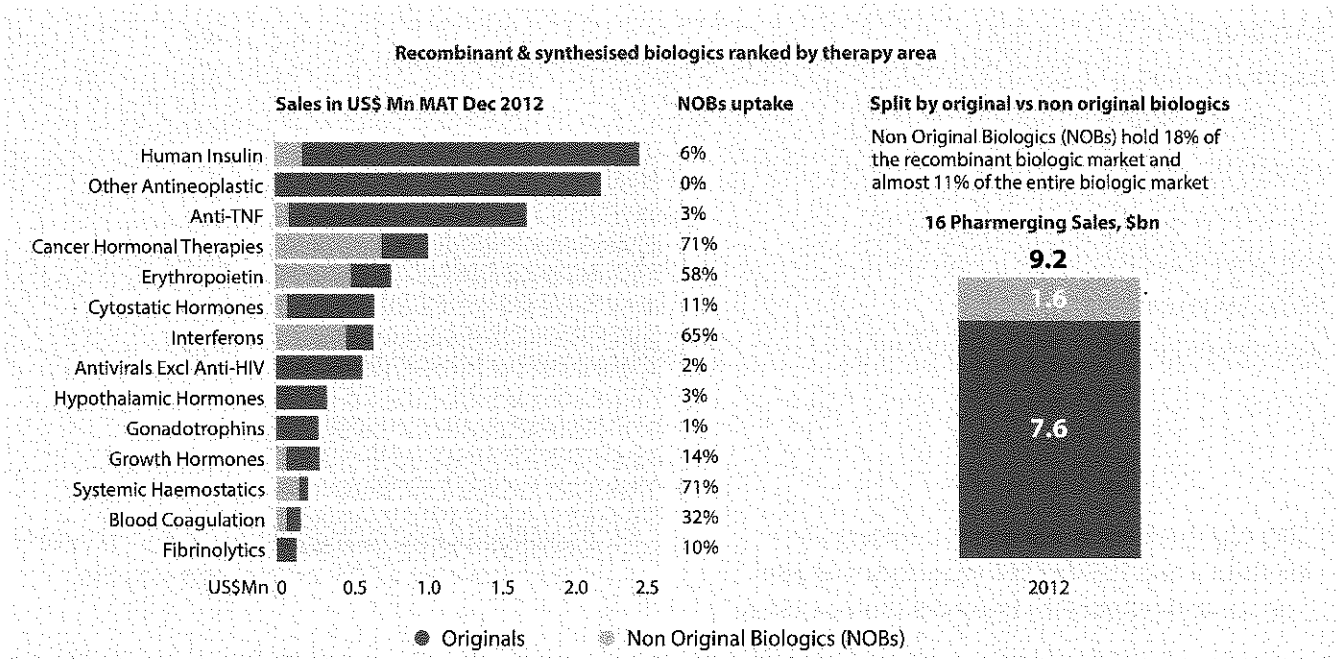


Source: IMS analysis on MIDAS data, Extrapolation of MIDAS data.
Projected pre-expiry sales, modeled for expected volume erosion and price discounts based on analogues and evidence from marketed biosimilars.

- 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 biosimlars 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.

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

Therapy areas in pharmerging markets



Source: IMS MIDAS, Dec2012. In scope analysis: 100 Recombinant& Synthesised molecules across 25 ATCs. It includes 16 pharmerging countries.

- 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%).

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).

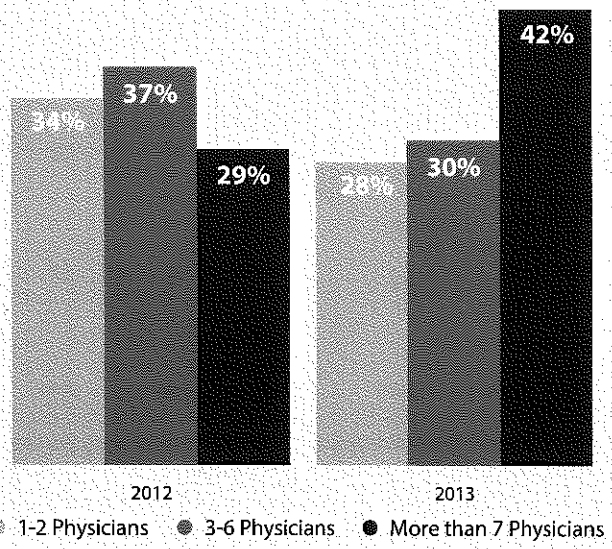
- Thus, more care is now provided in the hospital setting, whose reimbursement levels likely are passing more costs onto payers and subsequently passed patients via benefit design interventions and increased cost sharing.

- Increasing patient financial contribution is linked to declining therapeutic adherence, potentially resulting in drug discontinuation and higher overall total costs of care.

Source: National Association of Community Health Centers. http://nachc.com/client/documents/5.11%20340%20Manual%20Primer%20for%20Health%20Centers2.pdf. Accessed 4/21/2014.

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

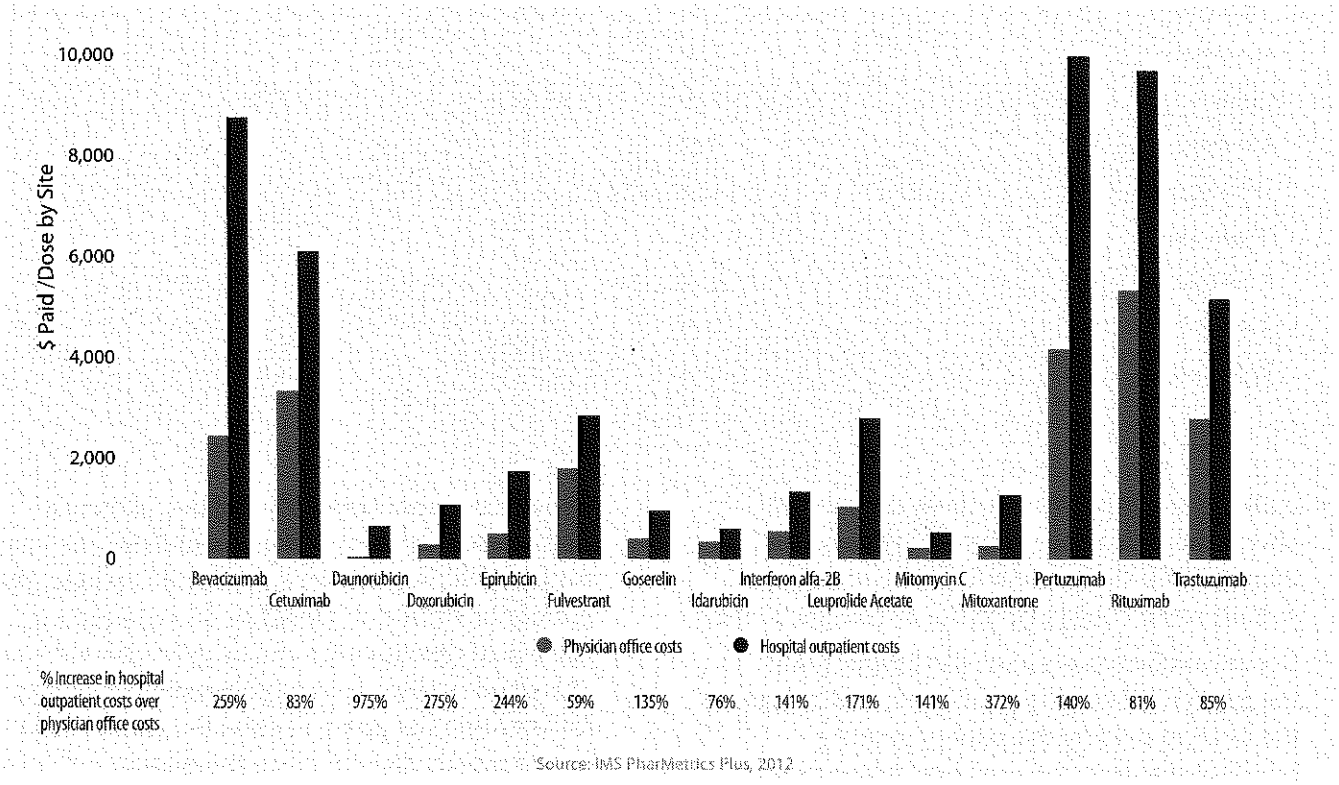


Source: Community Oncology Alliance (COA) Practice Impact Report, 2012, 2013
The State of Cancer Care in America: 2014. www.asco.org/stateofcancercare

- 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.

Hospitals have higher drug administration costs than physician offices

Hospital outpatient costs compared to physician office costs



Source: IMS PharMetrics Plus, 2012

- 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.

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

Adjuvant hormonal therapy persistence in breast cancer patients

Source: Neugut et al. J Clin Oncol. 2011.

- 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.

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 Comprehesive Cancer Network (NCCN).

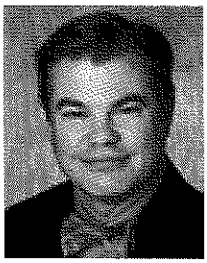
Oncology includes therapeutic treatments as well as supportive care, radiotherapy and immunotherapies. Supportive care includes anti-emetics, chemoprotectants, cancer pain, immunosupportive agents (e.g. hematopoetic growth factors), erythropoeitins, and therapeutic cancer vaccines. Costs used for the 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.

Authors



Kjel Johnson

Vice President of Global Oncology, IMS Health

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.

Lee Blansett

Senior Principal P&MA Consulting, IMS Health

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

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.

IMS INSTITUTE FOR HEALTHCARE INFORMATICS

IMS Institute for Healthcare Informatics,
One IMS Drive, Plymouth Meeting, PA 19462, USA
info@theimsinstitute.org www.theimsinstitute.org