Oncology: The Disease, the Dynamics and the Complexities

The Ipsos Oncology Center of Expertise

November 2018

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Introduction

According to the World Health Organization, 8.8 million people died from cancer in 2015 – accounting for nearly 1 in 6 of all global deaths[1]. To put this into context, it is approximately the entire population of Switzerland[2]. What's more, these figures are on the rise. One study suggests that the number of people with cancer is likely to surge by more than 75 percent across the world by 2030, with particularly sharp climbs in poorer countries.[3] Whether we experience the disease personally or know someone who has, each and every one of us will likely be impacted by cancer in some way during our lifetime.

The earliest documented case of cancer is over 3,000 years old and[4] yet, in some ways, it is still a mystery today. While we have learned a great deal about the causes and effective treatments, those who work in the oncology market are constantly faced with the challenges of this ever-changing disease.

Cancer is complex because it is one term that encompasses many different malignant diseases. There is no one cause of cancer, nor is there a single treatment protocol. The biology of cancer is also very complex, leading to an abundance of treatment approaches. Incidence and prevalence rates differ globally, and treatment of the disease is managed by numerous physician specialties. In addition to these challenges, the continually evolving nature of our understanding of the disease and treatment approaches makes it difficult to remain current. In this decade alone, over 80 new cancer drugs have been approved – and half of these were in the last 3 years[5]. These figures do not even include newly approved indications for existing agents.

In recent years, we have also seen the advent in cancer treatment of immunotherapy, a revolutionary treatment approach that uses the body's own immune system to fight disease. Meanwhile, a significant proportion of new agents have been approved alongside new companion diagnostics tests.

This paper provides an introduction to the complex market of oncology and highlights some of its distinct challenges. The aim is to inform and equip professionals who market, or conduct marketing research, for oncology products globally.

Complexity of the Disease Area

Cancer and its Causes

Simply put, cancer is the uncontrolled growth of poorly differentiated (non-functioning) cells. These cells' unchecked proliferation causes them to crowd out normal functioning cells, eventually leading to cell death.

The proximate cause of cancer (i.e. the event which is closest to, or immediately responsible for causing) is mutations of genes that keep normal cellular growth regulated. Mutations in key regulatory genes alter the behavior of cells and can potentially lead to the unregulated growth seen in cancer. Tumor suppressor genes, such as p53, regulate the cell cycle and thus function as a tumor suppressor involved in preventing cancer. When mutated, they lose this protective function.

Proto-oncogenes are genes that, when mutated, lead to unlimited cellular proliferation. It appears that a number of mutations are likely involved in cancer, and tumors rarely rely on one mutation alone; it is the accumulation of such mutations that lead to the occurrence of cancer.

The fact that cancer is caused by mutations has many implications for its treatment. In a subsequent section of this paper, the link between mutations and treatment will be further examined.

Mutations, however, do not occur in a vacuum. Many factors can be involved in the mutation of genes, including:

- **Lifestyle choices:** Smoking and alcohol are chemical teratogens (chemicals that cause mutations), while a diet high in fat and a sedentary lifestyle are thought to increase body fat, which stores teratogenic chemicals.

- **Environmental factors:** Radiation causes mutation directly by altering DNA; chemicals work to disrupt transcription and translation processes or act as endocrine disrupters that can stimulate cell growth.

- **Infectious agents:** Some viruses act by inserting their own DNA into the nucleus, which can lead to oncogenic mutations. Further, some bacterial infections may contribute to the proliferation of cancer cells.

Our bodies constantly fight off cancer. If damaged DNA is detected, our DNA repair mechanism typically restores the cell's genetic material. If this mechanism fails and poorly differentiated cells are detected, our immune system typically destroys the damaged cells before they can multiply and spread. However, increasing age has an impact on these processes: ➔

- Mutated DNA gets repaired before the cells have a chance to proliferate. These DNA repair mechanisms are less effective when older.

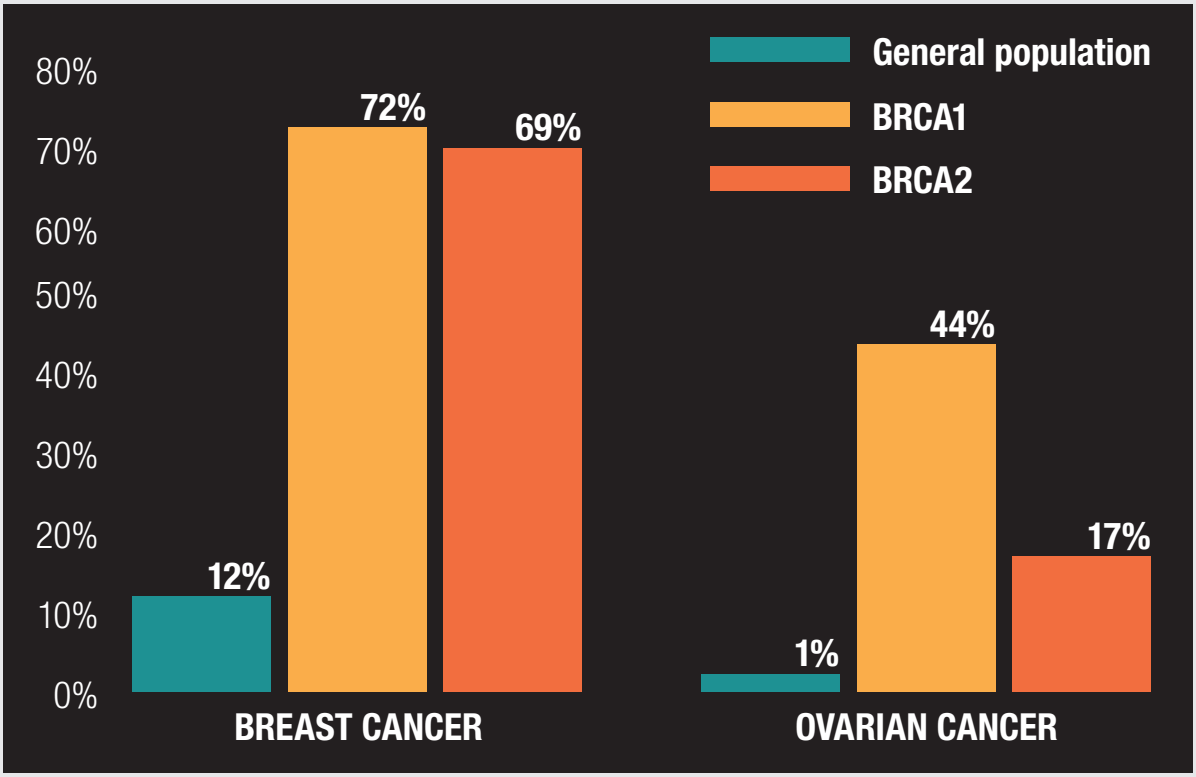
- It is thought that there is a delay in cancer development[6], meaning that someone who was exposed to cancer-causing agents as a young adult probably won't develop the disease until they are in their 60's or older. There is also likely to be a cumulative effect of lifetime exposure to certain chemicals.

- The development of cancer usually requires multiple mutations to accumulate in the same cell; the likelihood of this occurring increases with age.

Some people also inherit genes that predispose them to developing cancer; cancer is not inevitable, but it is much more likely to develop in people with so-called cancer genes than among the general population.

About 5-10% of cancers are thought to be hereditary[7]. Hereditary cancer tends to occur at an earlier age than the sporadic form of the same cancer, so screening is recommended. For example, mutations to tumor suppressor genes BRCA1 and BRCA2 predispose individuals who carry them to breast and ovarian cancers, in addition to a higher risk of other tumors as well.

Figure 1: Incidence of Cancer in General Female Population with BRCA Mutation vs. General Population



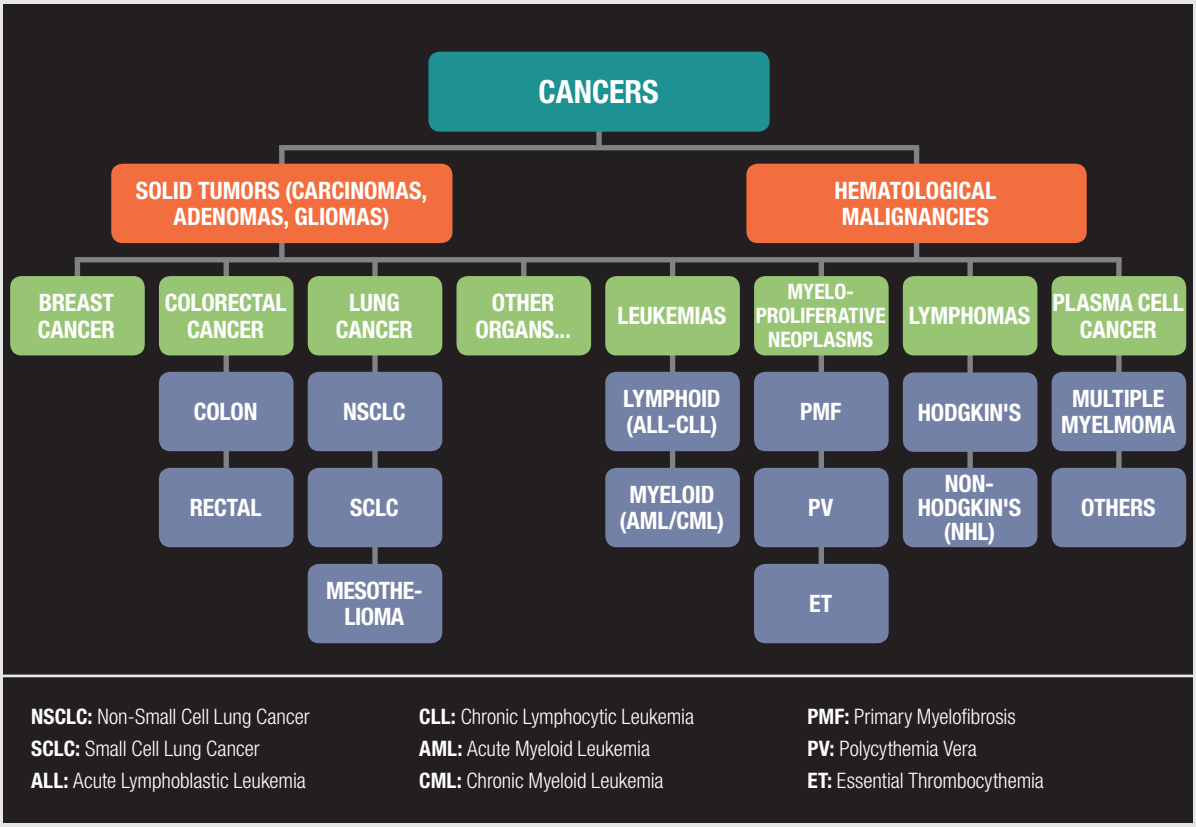
Source: National Cancer Institute (BRCA Mutations: Cancer Risk and Genetic Testing)[8]
https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet#r1

IPSOS REAL WORLD EVIDENCE

Cancer – One Disease or Many?

Each type of cancer is unique – a disease within itself, with its own causes, symptoms, and methods of treatment. Leukemias, lymphomas and myelomas are considered hematologic malignancies, while tumors affecting a specific organ are considered solid tumors. As with all groups of disease, some types of cancer are more common than others.

Figure 2: Tumor Types and Sub-Types



Classifying cancer becomes more comprehensive when linking it to the specific organ or system in the human body affected. The table on page 7 shows this classification.

Figure 3: Cancer Classifications

CNS	GENITOURINARY / GERM CELL	LEUKEMIA	SKIN CANCER
• Brain Stem Glioma • Cerebellar Astrocytoma • Cerebral Astrocytoma / Malignant Glioma • Ependymoma • Medulloblastoma • Supratentorial Primitive Neuroectodermal Tumors and Pineoblastoma • Visual Pathway, Hypothalamic Glioma • Neuroblastoma • Primary CNS Lymphoma	• Bladder Cancer • Kidney (Renal Cell) Cancer • Penile Cancer • Prostate Cancer • Renal Pelvis and Ureter Cancer • Testicular Cancer • Urethral Cancer • Wilms' Tumor • Germ Cell Tumor • Ovarian Germ Cell Tumor	• Acute Lymphoblastic Leukemia • Acute Myeloid Leukemia • Chronic Lymphocytic Leukemia • Chronic Myelogenous Leukemia • Hairy Cell Leukemia • Myelodysplastic Syndromes • Myeloproliferative Neoplasms	• Kaposi's Sarcoma • Melanoma • Merkel Cell Carcinoma • Basal Cell Skin Cancer • Squamous Cell Skin Cancer
ENDOCRINE	**GYNECOLOGIC**	**LUNG / RESPIRATORY**	**MUSCULOSKELETAL (SARCOMAS)**
• Adrenocortical Carcinoma • Parathyroid Cancer • Pheochromocytoma • Pituitary Tumor • Thyroid Cancer • Neuroendocrine Tumors • Thymoma / Thymic Carcinoma	• Cervical Cancer • Uterine/Endometrial Cancer • Gestational Trophoblastic Tumor • Ovarian Cancer • Vaginal Cancer • Vulvar Cancer	• Lung Cancer, Non-Small Cell • Lung Cancer, Small Cell • Malignant Mesothelioma	• Ewing's Family of Tumors • Osteosarcoma / Bone Histiocytoma • Rhabdomyosarcoma • Soft Tissue Sarcoma • Uterine Sarcoma
GASTROINTESTINAL	**HEAD AND NECK**	**LYMPHOMA / PLASMA CELL**	**BREAST CANCER**
• Anal Cancer • Bile Duct Cancer, Extrahepatic • Carcinoid Tumor, Gastrointestinal • Colon and Rectal Cancers • Esophageal Cancer • Gastric Cancer • Gallbladder Cancer • Pancreatic Cancer • Hepatobiliary Cancer	• Hypopharyngeal Cancer • Laryngeal Cancer • Lip and Oral Cavity Cancer • Nasopharyngeal Cancer • Oropharyngeal Cancer • Paranasal Sinus & Nasal Cavity Cancer • Salivary Gland Cancer • Melanoma, Intraocular • Retinoblastoma	• AIDS-Related Lymphoma • Cutaneous T-Cell Lymphoma • Cutaneous B-Cell Lymphoma • Hodgkin's Lymphoma • Mycosis Fungoides • Non-Hodgkin's Lymphoma • Sézary Syndrome • Waldenström's Macroglobulinemia • Multiple Myeloma	**UNKNOWN PRIMARY**

Once the cancer type is identified, there is still a need to understand the histology or cell type of the disease.

This process allows pathologists and physicians to understand which cells are being primarily impacted within the cancer.

For example, in NSCLC alone, there are different histological categories, the most common ones being:

- **Squamous cell**
- **Adenocarcinoma**
- **Large Cell**

Adenocarcinoma and Large Cell are often grouped together and referred to as “non-squamous” NSCLC. There are also several other rarer subtypes of NSCLC, such as pleomorphic, carcinoid tumor, adenosquamous, and salivary gland-type carcinoma.

NSCLC subtypes are further segmented by predictive biomarkers (which are discussed in a later section). All of this will ultimately inform the oncologist’s treatment approach and selection for the individual NSCLC patient.

Cancer Around the Globe

As cancer and treatment approaches vary significantly from country to country, it is important to understand not only the biology of each of the diseases but also the global differences.

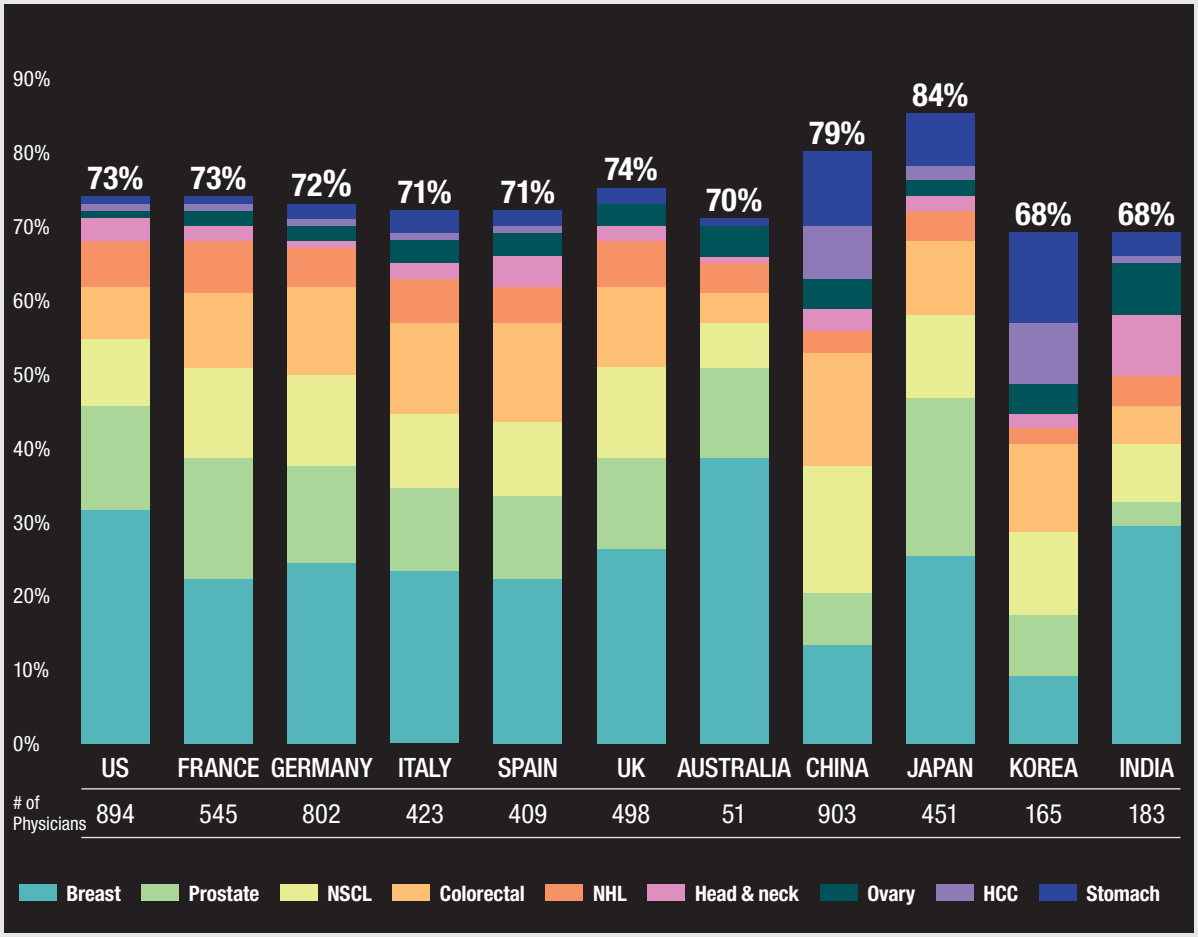
It is well documented that cancer incidence varies globally. For example, the incidence of prostate cancer is lower in certain Asian countries compared to America and Europe[9], while stomach cancer is more prevalent in Asia, particularly East Asia[10,11]. These differences stem from a multitude of factors including lifestyle, average age of the population and overall economic status of the region.

The Western diet, high in fat and refined sugar, but lower in fiber[12], has been linked to the increased risk of several cancers, including prostate, colorectal and breast[13], three of the top drug-treated cancers in the US and Europe according to Ipsos Global Oncology Monitor data. Meanwhile, NSCLC shows the highest drug-treated prevalence in China, likely attributable to pollution and higher smoking incidence, as smoking has the strongest cancer-lifestyle relationship and is responsible for nearly 90% of all lung cancers worldwide[14]. Additional evidence of lifestyle factors is seen in the higher proportion of drug-treated head and neck cancer in India, driven by use of smokeless tobacco products and the practice of chewing betel quid[15].

However, it is important to remember that actual drug-treatment rates will not correlate directly with incidence as additional variables come into play, including more prevalent screening, accessibility to medical care, and ability to afford treatment. Such socioeconomic factors often drive greater treatment of cancer in more developed countries.

When viewing cancer globally, it is vital to understand these local and regional considerations that impact incidence, prevalence and ultimately treatment of cancer.

Figure 4: Global Distribution of Drug-Treated Patients by Select Tumor Types (2017)



*Source: Ipsos Global Oncology Monitor, Jan – Dec 2017 (data collected online in US & EU; data collected both online and via pen & paper in all other markets) Note: *Data for China are not projected.*

Cancer – One Treater or Many?

When undertaking market research, great care needs to be taken when deciding what audience to survey – we need to think about the sample.

When conducting global research with cancer treaters, many researchers may believe it would be safe to focus only on Medical Oncologists and/or Hematologist/Oncologists. The reality is, there are multiple physician specialties treating cancer with drug therapy, with variability seen by cancer type as well as by region.

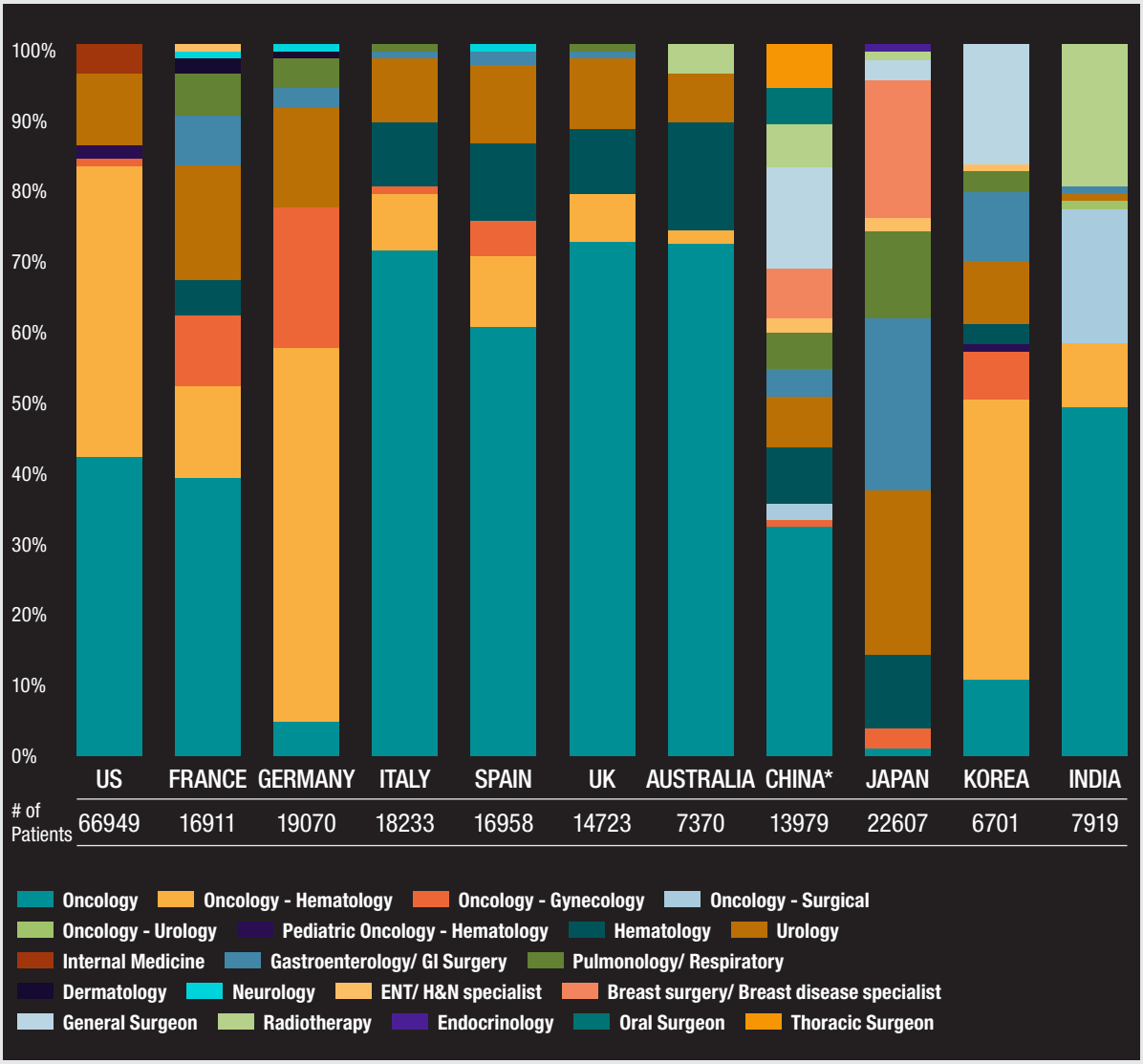
The vast majority of cancer treaters in the US are Oncologists, of which there is a relatively equal distribution between Medical Oncologists and Hematologist/Oncologists. The number of Hematologist/Oncologists in the US has more than doubled from 2004 to 2014[16] and is the fastest growing specialty of cancer treatment in the US since being recognized by the AMA in the mid-90s.

When comparing the US to a market such as Japan, however, there is a stark difference in the physician specialties that treat cancer with systemic therapy. Up until 2007, there was no "oncology" specialty in Japan. Although increasing, the latest figure given by the Japanese Board of Medical Oncology (JSMO) for the number of Oncologists in all of Japan is just 1,256[17] – lower per capita than the US. As such, the main cancer systemic treaters in Japan are either surgeons or physician specialties that treat a specific area of the body.

According to Ipsos Global Oncology Monitor data, Europe is somewhat of a hybrid of these markets. Medical Oncologists comprise 65% or more of cancer treaters in Italy, Spain and the UK, but only 2% in Germany. This difference can be attributed to the fact that in Europe, Medical Oncology is recognized as a distinct specialty in France, Italy, Spain and the UK, but as a mixed specialty with Hematology in Germany[18]. Further, in France and Germany, tumor-specific specialists, such as Gastro-Oncologists (stomach cancer), Pulmo-Oncologists (lung cancer), and Dermato-Oncologists (melanoma), treat with systemic drug therapy, aligning more with the Japanese approach.

Understanding the correct specialties of physician/treater to target and talk to globally can be as much of a challenge as understanding the nuances of cancer treatment. Ipsos conducts a market sizing study that enables us to identify the physician specialties treating cancer in each country.

Figure 5: Systemic Cancer Treating Specialties by Country – Overall (at patient level) (2017)



Source: Ipsos Market Sizing Study, data collected online in US & EU; data collected via mailing in other markets

Doctor level data

**China's data are not projected*

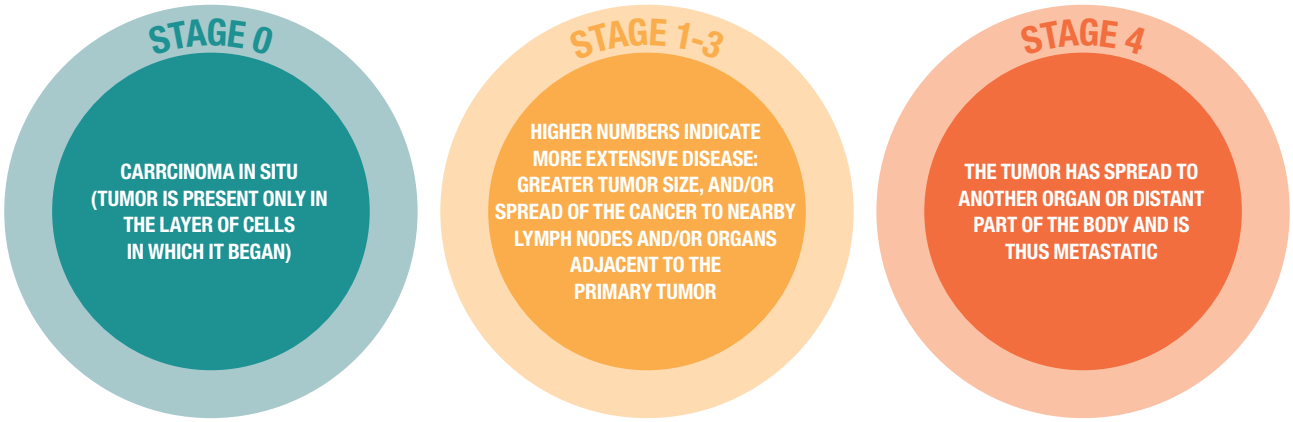
Treatment Challenges

Cancer staging – One system or many?

In order to determine the proper treatment for cancer, it is critical to assess the extent of the disease. Several staging systems have been developed to do this.

Solid tumors are commonly staged by a Roman numeric system that is related to the extent of disease, with 0 being least extensive and IV being the most extensive (metastatic) disease. However, gliomas and other CNS diseases are solid tumors that are exceptions to this system.

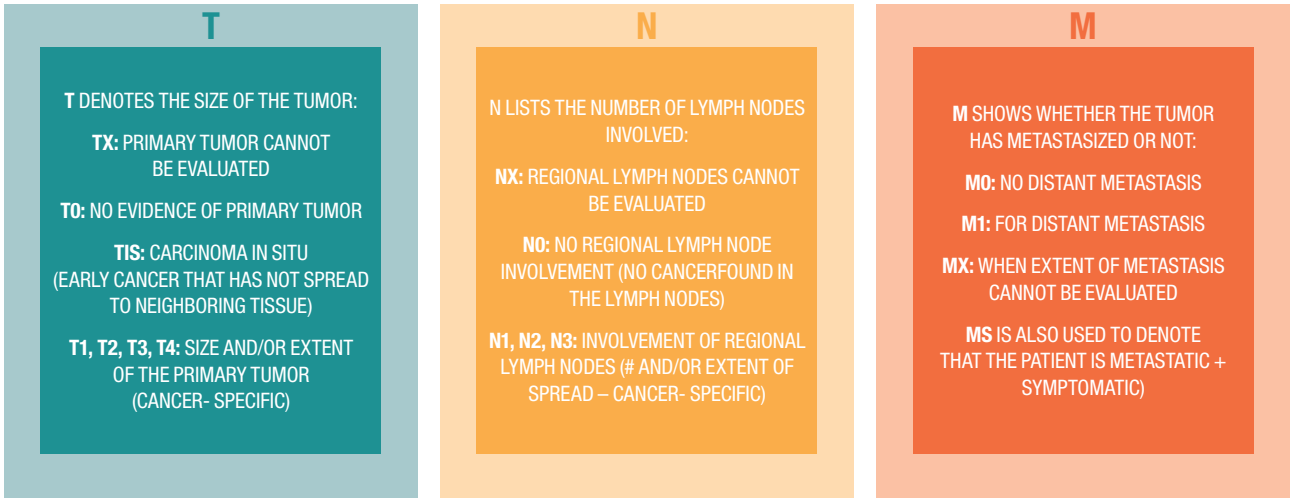
Figure 6: Roman Numeric Staging System for Solid Tumors



For most solid tumors, the TNM staging system is typically used to arrive at the Roman numeral stages. For each cancer type, the exact criteria for assigning these T, N and M values are different, as are the conversions from TNM into their respective Roman numeral stages.

These staging systems continue to evolve over time for any given cancer as our understanding grows. For example, the Cancer Staging System from the American Joint Committee on Cancer (AJCC) is now in its 8th edition[19].

Figure 7: TNM Staging System for Solid Tumors



Source: American Joint Committee on Cancer[20]

Alternative staging systems to TNM also exist for certain solid cancers, though their usage is generally on the decrease in favor of TNM.

Figure 8: Other Staging Systems for Solid Tumors

SYSTEM	TUMORS USED	DESCRIPTION
FIGO[21]	Ovarian	1. Malignancy of one or both ovaries, without ascites 2. Malignancy of one or both ovaries, with pelvic extension and ascites 3. Malignancy involves one/both ovaries, intraperitoneal metastases outside pelvis and/or positive retroperitoneal lymph nodes 4. Involvement of one/both ovaries with metastases and histologically confirmed extension to pleural cavity or liver
CIN[22]	Cervical	Cervical Intraepithelial Neoplasia – grading system for pre-cancerous cervical lesions
Dukes[23]	CRC	Stages A, B, C, and D roughly correspond with Stages I-IV
Jewett-Whitmore[24]	Prostate	Stages A and B cancers are considered curable. Stages C and D are treatable, but their prognoses are discouraging.
Breslow Depth / Clark Level[25]	Melanoma	Breslow thickness is defined as the total vertical height of the melanoma, from the very top (called the "granular layer") to the area of deepest penetration in to the skin. The Clark level refers to how deep the tumor has penetrated into the layers of the skin.

Due to the more diffuse and 'dimensionless' nature of these cancers, staging of hematological malignancies is generally very different to staging of solid tumors, and is also specific to each malignancy.

Figure 9: Staging Systems for Hematological Malignancies

SYSTEM	TUMORS USED	DESCRIPTION
Ann Arbor[26]	NHL, Hodgkin's Lymphoma	I. Cancer is located in a single region II. Cancer is located in two separate regions III. Cancer has spread to both sides of the diaphragm IV. Diffuse or disseminated involvement of one or more extralymphatic organs
International Staging System (ISS)[27]	Multiple Myeloma	I. ß2-microglobulin (ß2M) < 3.5 mg/L, albumin ³ 3.5 g/dL II. ß2M < 3.5 and albumin < 3.5; or ß2M ³ 3.5 and < 5.5 III. ß2M ³ 5.5
Binet Classification / RAI Staging System[28]	CLL	Clinical stage A characterized by no anemia or thrombocytopenia and fewer than three areas of lymphoid involvement (Rai stages 0, I, and II). Clinical stage B characterized by no anemia or thrombocytopenia with three or more areas of lymphoid involvement (Rai stages I and II). Clinical stage C characterized by anemia and/or thrombocytopenia regardless of the number of areas of lymphoid enlargement (Rai stages III and IV).
No staging system – PHASE used instead (which refers to aggressiveness)	CML	Chronic Phase. Fewer than ten percent of the cells in the blood and bone marrow are blast cells (immature white blood cells). Accelerated Phase. Ten to nineteen percent of the cells in the blood and bone marrow are blast cells. Blast Phase. Twenty percent or more of the cells in the blood or bone marrow are blast cells. When tiredness, fever and an enlarged spleen occur during this phase, it is called blast crisis.

Some hematological malignancies, such as AML and ALL are not commonly staged.

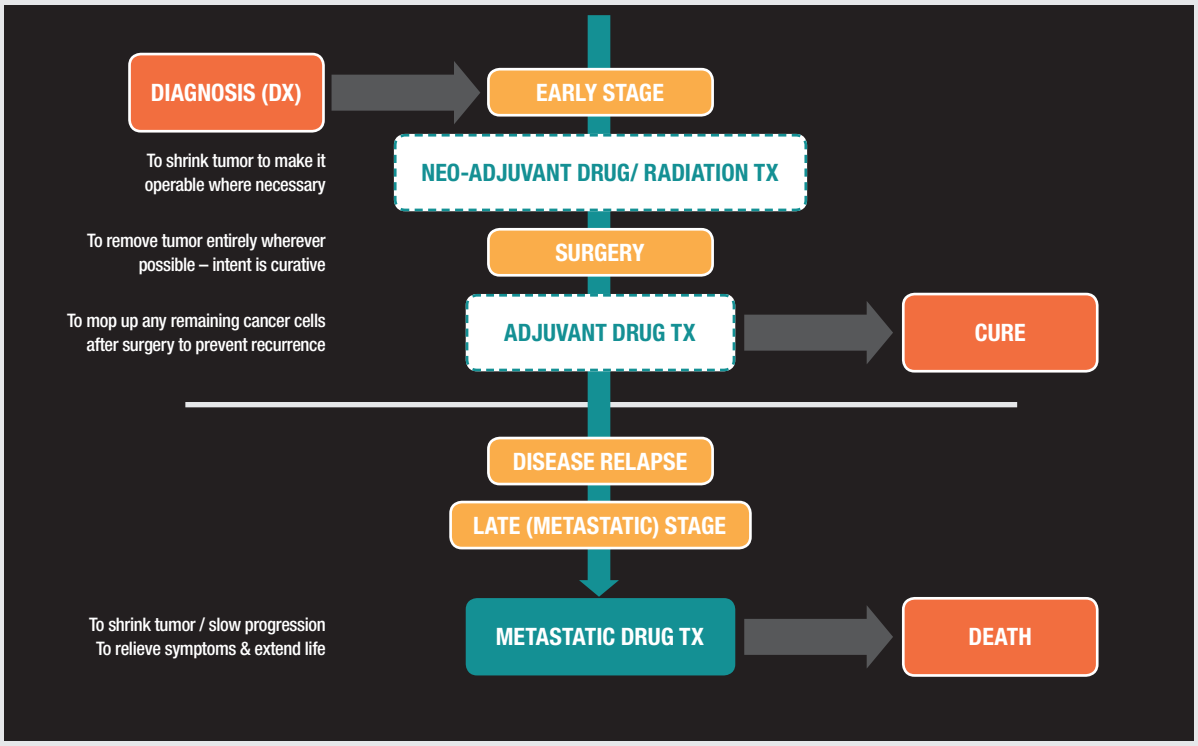
Cancer Treatment – Art or Science?

Solid tumors, like breast and lung cancer, begin as small groups of localized malignant cells in the primary organ in which they arose, but ultimately become much more dangerous to the host body by spreading to distant organs. Their relentless drive to replicate means that tumor cells often gain the ability to spread through the human body, in many cases (especially if not treated early enough) resulting in distant metastases. Cancer metastasizes by shedding cells from the primary tumor, which enter the lymphatic system and/or the bloodstream and travel to distant sites where they eventually take hold and replicate.

A significant challenge associated with cancer is that treatment is as much an art as it is a science. Even after the cell type, stage and grade (i.e. how aggressive is the tumor) have been determined, other variables such as the patient's general health, treatment history, preferences and support system, as well as the doctor's training, come into play to decide the appropriate treatment approach. Initial treatment modality may include surgery, radiation, drug therapy, or some combination of these approaches, with variability seen by tumor type.

Figure 10 shows two different patient diagnoses; one in which the cancer is detected early and another in which the cancer was detected late and had already metastasized (spread).

Figure 10: Solid Tumor Treatment – General Overview



- When cancer is detected early and the tumor is localized, surgery is generally the standard treatment modality of choice. By resecting the tumor and a margin of tissue surrounding it, a cure is possible. Surgery may also be combined with systemic drug or radiation therapy.

- **Neo-adjuvant** means that anti-cancer drugs are given before surgery. This aims to decrease the tumor size to make the tumor eligible for resection, improve the outcome, and/or make the resection easier to perform.

- **Adjuvant** means that anti-cancer drugs are given after surgery. This aims to kill any cancer cells that remain after surgery and prevent a recurrence/return of the cancer.

In some cases, surgery cannot be performed due to the location of the tumor or the patient's surgical ineligibility due to their general health and/or refusal. In this case, drug and/or radiation therapy may be used instead of surgery.

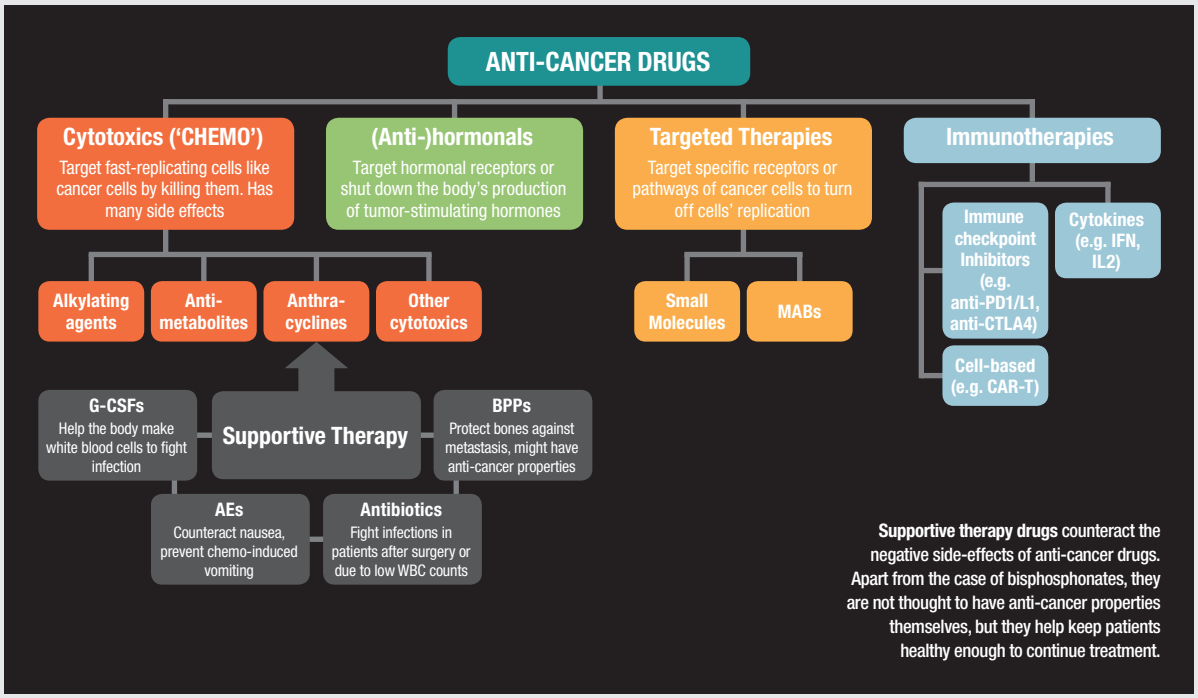
When cancer is diagnosed late, the treatment objective is to slow its progression in order to extend the patient's life. Cancer itself does not cause death; death occurs because the cancer cells crowd out the normal functioning cells and damage the organs of the body.

Cancer Treatment – A Plethora of Options

Adding to the complexity of cancer treatment is the fact that more drugs are approved for cancer than any other single disease[29]. With the advent of targeted therapies, some drugs have contributed to changing certain cancer types to more of a chronic condition with significantly longer survival.

Systemic drug therapy for cancer began with cytotoxic drugs and has since expanded to a number of different classes of drugs, as shown in Figure 11.

Figure 11: Systemic Therapy – Cancer Drug Treatment Class Overview



The oldest group of anti-cancer drugs is called cytotoxics; these drugs indiscriminately kill cells. Cytotoxic chemotherapy drugs interfere with DNA replication and/or cell division. They do not specifically target cancer cells, but instead rely on the fact that tumors are amongst the most rapidly dividing tissues in the body, hence affecting cancer cells to a larger degree than healthy cells. Because of this indiscriminate mode of action, they often have significant side-effects.

Then there are anti-hormonal therapies which are predominantly used in hormone-sensitive breast and prostate cancer. Some breast and prostate cancer cells have receptors on their surfaces that, when stimulated by hormones, result in the cells growing and dividing. Anti-hormonal therapies, sometimes referred to as hormonal agents, act by blocking the surface hormone receptors and preventing the cells from receiving a signal to grow and divide.

Biological/targeted therapies utilize the mechanisms of cancer and the pathways through which the cell signals. They can be divided into two sub-groups:

- **mAbs (monoclonal antibodies):** mAbs work at the level of the cell surface by blocking receptors that are involved in signalling cancer cells to keep dividing, keep growing and stop dying. They are large molecules and are typically administered by IV infusion.

- **Small molecules that target the cell signalling process within the cell:** These work within the cell by blocking the complex pathways involved in the cell cycle and apoptosis (programmed cell death). These are orally administered, which can also provide a patient convenience benefit.

There are also some mAbs that work not only by blocking the cell surface receptors, but also by delivering cytotoxic or radiological payloads directly to the cancer cells (sparing health cells). These so-called "smart bombs" are a new generation of targeted therapy called "antibody-drug conjugates" (ADC), and a number have now been approved across different tumor types.

Targeted therapies have created much excitement in the field of oncology and have transformed the way in which some cancers are treated.

Biomarkers – A Growing Influence on Treatment Selection

Whereas treatment decisions used to rely on a combination of clinical observations, various imaging techniques and general histopathological findings, Oncologists now have a range of biomarker tests at their disposal to make a more informed drug choice in a growing number of tumor types. Notwithstanding the complexity of such testing, this approach ultimately benefits physicians and patients alike: treatments which are likely to lead to better response rates and more prolonged responses can be selected based on molecular characteristics exhibited by the patient's tumor.

Many of the targeted therapies (as well as the hormonal therapies for breast cancer and some immunotherapies in certain tumor types) are linked to predictive biomarkers. For example, NSCLC patients who are EGFR (epithelial growth factor receptor) positive can be treated with targeted therapies (such as Tagrisso®, Tarceva®, etc.) that may provide these patients more benefits that the regular standard of care. Likewise, breast cancer patients who are HER-2 (human epidermal growth factor 2) positive should always be treated with targeted therapies such as Herceptin® and/or Perjeta® as they have been shown to extend survival vs. standard of care.

Biosimilars – the Future of Cancer Treatment?

Such is the context at a time when the first 'generics' of biologic targeted therapies are beginning to receive FDA/EMA approval to treat certain types of cancer.

As mentioned, targeted therapies such as mAbs are designed to recognize features specific to cancer cells and then target the specific areas of the cell that allow it to grow faster and/or abnormally. Copies of these targeted therapies are known not as generics but as 'biosimilars' – because it is impossible to replicate a biologic drug exactly. Manufacturing alone can modify its molecular structure. However, a biosimilar drug will have no clinically meaningful differences from the originator biological medicine in terms of quality, safety and efficacy.

Biosimilars themselves have been around for some time. Despite a slow initial uptake and ongoing debate over the concept of bio-similarity, the last few years have seen widespread use of biosimilars in autoimmune indications such as rheumatoid arthritis (RA) and ulcerative colitis (UC). Moving back to oncology, 2017 saw the approval of two mAb biosimilars to treat cancer, Truxima® and Rixathon®, both biosimilars of rituximab. In line with all biosimilar drugs, Truxima® was launched at a significantly cheaper cost than the branded version of rituximab, MabThera®. As of mid-2018, several additional rituximab biosimilars have become available, as well as biosimilar versions of Herceptin® and Avastin®.

Barriers to biosimilar uptake and similarities/differences across indications

Given the cost differential, it would be expected to see the same impact of biosimilars in oncology that has been seen so far in immunology – but the impact of potential barriers is quite different based on the indication of interest. There is big uncertainty around certain points, including:

1. **The impossibility of direct replication:** As mentioned, a 'biosimilar' is not an exact replica of a biologic drug. What's more, most companies who produce biosimilars are based in emerging countries, where regulations may be less stringent than those imposed by the FDA or EMA. Will Oncologists trust the companies behind their production and the manufacturing process?

2. **A lack of evidence:** If a biosimilar has been approved in another therapeutic category (i.e., the rituximab biosimilar in rheumatology), will physicians in a different field be convinced of the safety and efficacy of a drug which, on paper, seems equivalent to the branded version, but for which they don't have sufficient data?

3. **Patients' preference for brands:** In some countries, patients have a preference towards branded versions of a drug versus their generic counterparts. Will physicians ignore their patients' wishes or will patient preference influence the treatment decision?

Many different factors will determine the shape of biosimilar usage in oncology. Will different specialists welcome the learnings of peers focused on a completely different medical area? Will usage occur in specific patient types, or will it be driven by physicians' attitudes? Most importantly, will cancer patients have access to better healthcare? Only time will tell. However, Ipsos conducted physician research in 2017 that, together with the impossible financial equation facing the industry, leads us to expect biosimilars will play a significant role in the battle against cancer moving forwards[30].

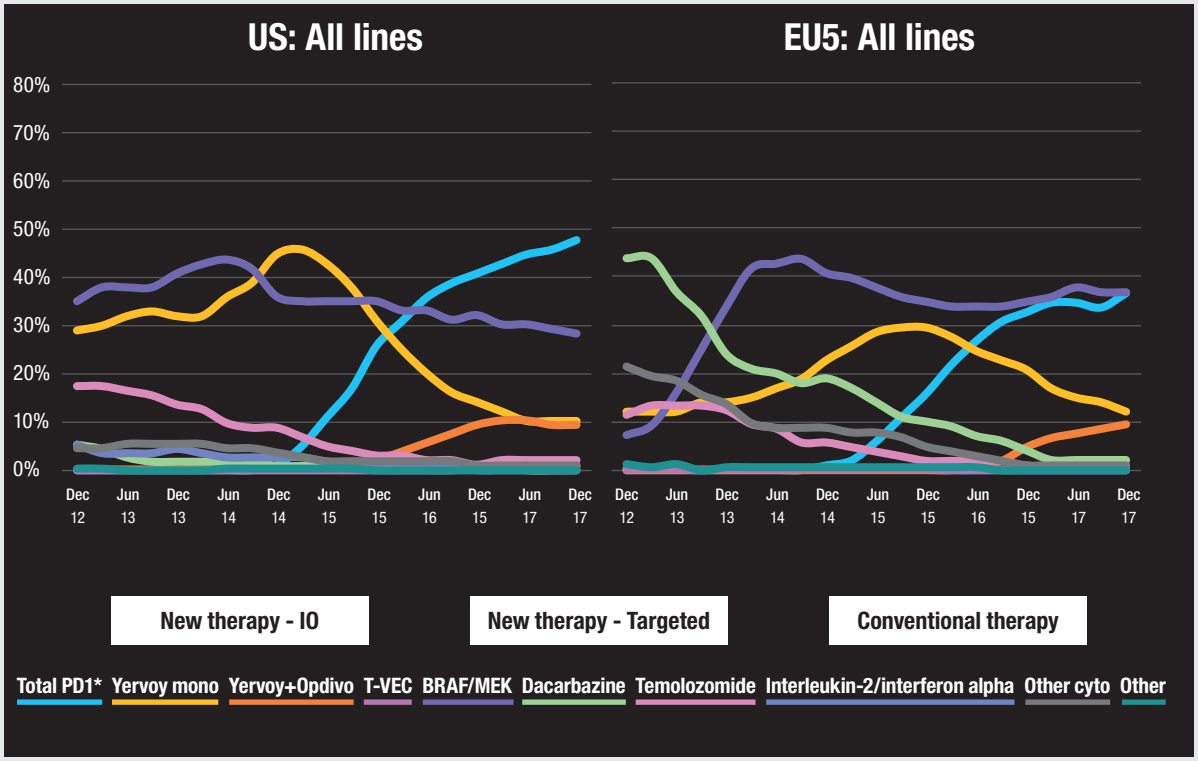
The rise of Immunotherapy

Immunotherapy – which includes checkpoint inhibitors, therapeutic cancer vaccines, oncolytic viruses, cell based therapies (e.g. CAR-Ts and TCR-Ts), and cytokines – deserves a section of its own. This treatment approach uses the body's own immune system to fight diseases; certain Immuno-Oncology (I-O) treatments, such as anti-CTLA-4s, anti PD-1s (programmed-death 1), anti PD-L1s (programmed-death ligand 1), and CAR-Ts (chimeric antigen receptor T-cell) have revolutionized cancer therapy in recent years.

In some indications, there are trends showing that anti PD-1 I-Os are now in very strong position to become the new standard of care in areas that used to be dominated by treatments such as chemotherapies or targeted therapies (see Figure 12).

Figure 12, based on recent data from the Ipsos Global Oncology Monitor, shows the dominance of new therapies versus traditional therapies in the treatment of melanoma. Chemotherapy using dacarbazine-based regimens used to be the standard of care in the EU5 prior to the arrival of targeted therapies such as the BRAF/MEK inhibitors and I-Os. Now, however, chemotherapies are rarely used for the treatment of advanced melanoma; anti PD-1s such as Opdivo® and Keytruda® are now the key treatment in both the US and EU5, alongside BRAF/MEK targeted therapies.

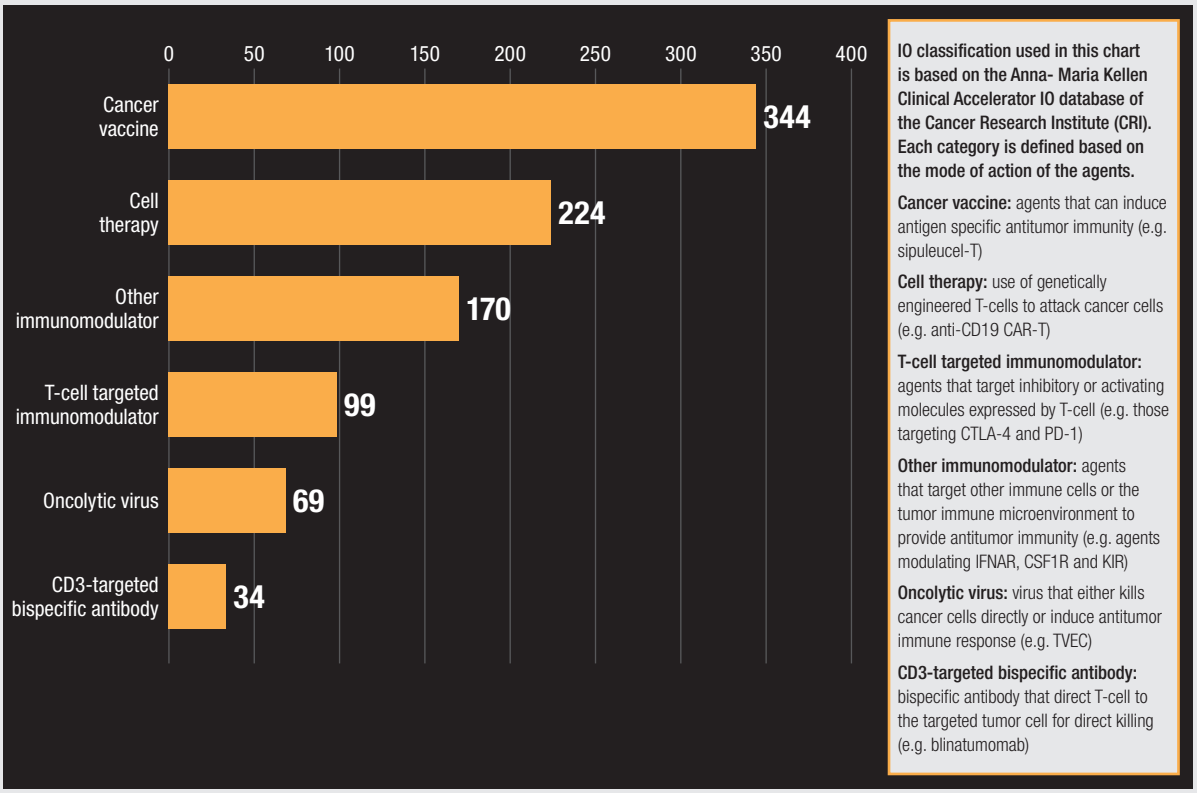
Figure 12: Conventional vs. new therapies in melanoma (as of end 2017)



Source: Ipsos Global Oncology Monitor, January 2012 - December 2017; all data collected online.
(avg. 183 doctors per wave in US and avg. 434 doctors per wave in EU5, providing a given number of patients record forms)
Base: Stage IIIb-c unresectable/ stage IV melanoma, excluding clinical trials
**Total PD1 is the sum of pembrolizumab and nivolumab*

As of April 2018, there were 26 I-O agents approved, and development is far from slowing down. The clinical research program of the Cancer Research Institute (CRI) has recorded 940 I-O agents that are in clinical development and tracked a total of 3,042 active clinical trials of these agents as of September 2017[31].

Figure 13: Number of I-O agents in clinical stage by I-O categories in US



Source: Annals of Oncology (Comprehensive analysis of the clinical immuno-oncology landscape)[32]

The Implications for Marketers

As we have tried to establish in this paper, the oncology market rarely stands still. This constant evolution affects oncology marketers and market researchers alike. Whatever specific challenges or objectives are in play – and these will be many and various – there are certain common challenges and look-outs for all of us working in oncology today:

Personalized medicine

The personalization of medicine has transformed the oncology treatment landscape. As established earlier on, we have tests today (e.g. BRCA 1/2 mutations) that can identify individuals with a higher lifetime risk of developing ovarian and/or breast cancer, enabling them to take early preventative action. Then, of course, we have biomarker tests to understand which therapy is likely to be most effective against that individual's particular cancer. Personalized medicine is set to evolve still further in the future, with cancer vaccines being developed and recent approvals of the first CAR-T therapies that use a patient's own genetically modified immune cells to fight cancer. For marketers, the implication of all this is clear: a catch-all approach is unlikely to succeed. As treatments become increasingly personalized, so too must the marketing strategies around them.

Proof of value

Cancer (and other) treatments have become so expensive in recent years that the overall value of each has been placed firmly in the spotlight. The industry's focus on value, and the dawn of value-based pricing, is another big change in the industry. Today's oncology marketers must create the right messages for *payers*; they must understand the importance of real world data and create a plan that showcases the product's value, efficacy and patient outcomes.

The proliferation of data

Today, data are literally everywhere. We have public data, claims data, syndicated data, patient record forms, electronic medical records, social media… What to *do* with all this data is still unclear to many. Ultimately, these datasets must all be analyzed in order to gain a full understanding of what's really happening in the market. For marketers, understanding how to integrate the data and use it to answer the commercial questions is critical – and a significant challenge they face.

Patient centricity

And what about patients themselves? Twenty years ago, oncology marketing and marketing research was all about the Oncologist. Today, it's about the physician, other healthcare providers such as nurses, the payor *and the patient*. After all, today's patients have a wealth of information at their fingertips and countless communities through which to share their experiences and ideas. As such, they are increasingly part of the decision-making team when it comes to their own care. Not only is this changing the dynamic between doctors and patients, it has also shifted the focus of pharma. Patient centricity is not only well documented in corporate visions and missions, it is at the top of many pharmaceutical company agendas. This is a big change in the industry, with marketers needing to heed the shift from product to patient centricity.

Achieving differentiation

One of the biggest challenges, and a lookout for marketers and market researchers, is differentiation. This is one area in which a patient centric approach can help. Looking beyond the mechanism of action, what is the patient's experience? What is their quality of life? What are their challenges? What are they frustrated with? Do they get enough specific information? Cancer is complicated and listening to the patient's voice and directing the right information and support to them – and their caregivers – could be a strong point of difference.

Closing

Of course, one of the biggest challenges of working in cancer is that we're focusing on diseases that, generally, do not yet have cures (unless they are diagnosed in early stages). However, there has been so much progress made in such a short space of time. The understanding that we now have of the pathogenesis and pathophysiology of cancer, the personalization of treatment via treatment selective biomarkers, the rise of immuno-oncology – all of this will lead to yet more advances in cancer treatment. As the industry continues to progress, we can expect for advanced cancer to potentially become chronic diseases rather than terminal ones, until eventually true cures are discovered. All of us currently working in cancer are waiting for the day this happens.

About the Research

Drug treatment patterns discussed in this paper were investigated using the Ipsos Global Oncology Monitor©, a patient record database. Specifically, a panel of cancer-treating physicians in over 20 countries worldwide reported on drug-treated cancer patients seen in consultation during the study period. Physicians taking part in the study were screened for specialty and level of seniority and had to be the main treatment decision-makers for their patients. The physicians provided a set number of patient records during the fieldwork period. Research was conducted online and through pen and paper diaries. In each market surveyed, Ipsos first conducts a market sizing study in order to identify which physician specialties treat cancer. Sample data are projected to the wider clinical population.

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At Ipsos we are passionately curious about people, markets, brands and society. We make our changing world easier and faster to navigate and inspire clients to make smarter decisions. Our Healthcare Service Line partners with pharmaceutical, bio-tech and medical device manufacturers to inspire better healthcare. Operating in over 50 countries, 1000+ experts support key business decisions for our clients throughout the commercial lifecycle, from early-stage strategy, to launch, to performance optimisation. We do this through a uniquely integrated combination of therapeutic and market expertise, gold standard real world evidence, and market-leading custom research approaches – all underpinned by a global footprint and unprecedented access to today's healthcare.