UBS

Longer Term Investments

Oncology

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- The aging of the global population will lead to rising incidence of cancer over the next 15 years and beyond, despite well-publicized initiatives to reduce exposure to cancer risks. We expect new cancer cases to outpace population growth by a factor of 3:1. The market for oncology drugs is currently around USD 100bn and should continue to grow well above GDP.
- Recent developments in understanding cancer biology and the immune system have led to the beginning of a new era in cancer treatment, with the first wave of immuno-oncology drugs now established in the market. Multiple new drug candidates are being studied that could be combined with these drugs.
- This investment theme can be accessed via investment in large biopharmaceutical companies with relatively predictable volume trends, high returns on capital and secure, growing dividends, or by earlier-stage investment in innovative biopharmaceutical companies. The latter approach has a different risk profile and can also be suitable for private market investments.
- In either approach we recommend a diversified portfolio and a long-term investment horizon.

Our View

According to the World Health Organization (WHO), over 14 million new cases of cancer occurred globally in 2012 and 8.8 million cancer deaths in 2015. Despite great strides made in diagnosis and treatment, cancer remains a leading cause of death.

Age is a significant risk factor for cancer; as global life expectancy rises, we expect the number of new cancer cases diagnosed to outpace population growth. According to American Cancer Society estimates there could be about 22 million new cases diagnosed annually by 2030.

We see innovative cancer therapeutics as the most investable way to benefit from the theme. The market for drugs to treat cancer is already around USD 100 billion and we expect this market to outpace global GDP growth over our long-term investment horizon.

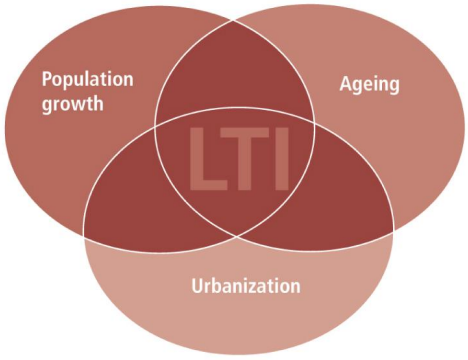
Companies with marketed drugs to treat cancer offer generally consistent sales trends, with earnings growth above GDP independent of the economic cycle. Strong cash returns on capital and well-covered dividends are also characteristic of pharma companies.

Introduction to the Longer Term Investments (LTI) series

› **The Longer Term Investments (LTI)** series contains thematic investment ideas based on long term structural developments.

› Secular trends such as population growth, ageing, and increased urbanization create a variety of longer term investment opportunities.

› Investors willing to invest over multiple business cycles can benefit from potential mispricings created by the typically shorter term focus of stock markets.



Related publications

- *Equity markets: Major advances in cancer therapeutics - update 8*, 4 April 2017

Some exciting innovation in oncology is found at smaller, development-stage biotech companies, whose returns depend on successful clinical development or commercial partnerships and represent a different risk profile to their established counterparts. In either case we advise a diversified portfolio approach given the risks inherent in drug development.

Summary – cancer still outpaces population growth

Despite great strides made in diagnosis and treatment over the past generation, cancer remains a leading cause of death globally, and we expect its incidence to keep rising as the population ages. The latest American Cancer Society (ACS) projections forecast 21.6m new cases of cancer annually by 2030, compared to about 14m in 2012. This suggests new cancer cases growing at around three times the expected rate of population growth over the same period. Put simply, age is a significant risk factor for the development of cancer (Fig. 1), and life expectancy is rising (Fig. 2).

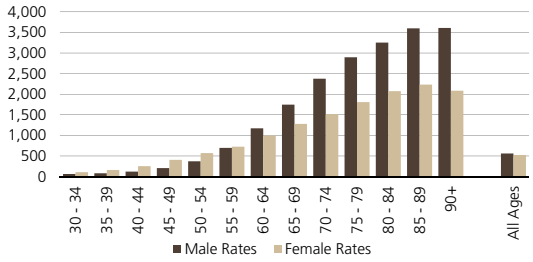
Recent progress and long-term goals

The emergence of targeted immuno-oncology has led to the beginning of a new era in cancer treatment. The first wave of a new generation of immuno-oncology drugs, known as checkpoint inhibitors, are now firmly established as the standard of care in advanced lung cancer and melanoma, and on their way to becoming the standard treatment for earlier-stage disease, following the approval of Merck's Keytruda as a "first-line" agent for use in previously untreated lung cancer patients last year. Combined sales of these drugs are already annualizing at nearly USD 8bn.

We expect checkpoint inhibitors to broaden their use as more data becomes available, including use in combination with other immuno-oncology approaches and with chemotherapy. This harnesses the synergistic effects of multiple mechanisms of action, taking advantage of checkpoint inhibitors' relatively benign side-effect profile. This year and 2018 will see several important studies read out data providing insight into which combinations are most effective and against which tumors. This new data will be key to determining the scientific and commercial potential for these drugs (see the detailed discussion in the appendix of this report).

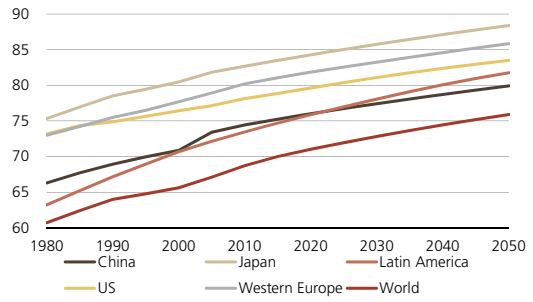
Additionally, even more advanced immuno-oncology therapies are in development, including personalized immunotherapy approaches such as CAR-Ts. Despite setbacks in some programs, the first of these treatment approaches may receive approval as early as this year, although their commercial potential is not yet clear.

Fig. 1: Cancer incidence rates by age, UK
New cancer cases per 100,000 population, selected age groups



Source: Cancer Research UK, as of March 2016

Fig. 2: Life expectancy rising globally
Life expectancy at birth, years



Source: UN, UBS, as of July 2015

While these new treatments are not a "cure," they represent a material improvement in ways of lengthening and bettering the quality of life for many patients. The complexity of cancer biology means it is highly unlikely that a single "golden bullet" will be found to cure the disease; rather several approaches will be needed and potentially will be used together. The good news is that early stage research continues to open new avenues of investigation.

Investment conclusion

We still see the most investable cancer-related opportunities in therapeutics; ongoing developments in immuno-oncology are indicative of the range of progress being made and support our belief that the market for cancer therapeutics could exceed USD 150bn by 2020, up from around USD 100bn currently. Longer-term, we see the market growing in the mid to high single digits beyond then, as a wider range of cancer types becomes treatable and patients survive longer. While it may be too early to pick winners in some therapeutic areas, a diversified portfolio of pharmaceutical and biotechnology companies with exposure to the theme should deliver above-GDP earnings growth over the medium to long term. The long-term nature of drug development also provides an opportunity for long-term investors to capture an illiquidity premium through private market investments in the area, including impact investment opportunities.

Risks

We recommend a diversified exposure to minimize stock-specific risks. Major risks to investing in the oncology theme include:

- **Clinical failure**. A new drug can fail at any point in clinical development, encounter regulatory issues or fail in post-approval commerce. This risk can be mitigated, but not eliminated, by focusing on drugs with demonstrated proof of concept. We therefore concentrate our theme on drugs in Phase II development or later.
- **Drug pricing**. Investors are increasingly concerned about perceived pressure on drug prices in the US, which remains the only major country where drug prices are set by the market, following widespread media and political criticism of drug price inflation. The legal and regulatory process surrounding drug price negotiation by the US government is complicated, but we believe is unlikely to change in the short to medium term, meaning manufacturers will remain free to charge the prices that the market will bear for drugs. Rising drug bills will undoubtedly lead to greater pressure from insurers and other payers, but in our view truly differentiated drugs are likely to go on commanding a premium. However, over the long term we cannot rule out changes to pricing dynamics.

- **Regulatory environment**. A key support of the recovery in R&D productivity seen by the pharma industry in the last five years has been a more supportive and pro-industry regulatory environment, particularly that of the US Food & Drug Administration (FDA). The FDA was seen as too risk-averse and reluctant to approve innovative new drugs, but has since introduced new approval pathways and financial incentives for innovation. In the event of an increase in reported adverse events perceived to be linked to these changes, the FDA could come under pressure to return to its earlier risk-averse days, particularly if its leadership or the political backdrop is less pro-industry in the future.
- **Market risks**. The biotechnology sector is sensitive to changes in risk attitude, in particular the availability of finance for development-stage companies, while the broader healthcare sector's performance has historically been negatively correlated to bond yields. However, over the long-term horizon of our theme, we expect fundamentals to dominate.

Oncology basics

Cancer is a leading cause of death and generates among the highest costs to healthcare systems around the globe. According to the WHO, over 14 million new cases of cancer (excluding non-melanoma skin cancers) occurred globally in 2012, and 8.8 million cancer deaths in 2015. The WHO further estimated the annual global financial cost of cancer at USD 1.16 trillion in 2010, with the cost and occurrence expected to rise steadily given the ever aging population worldwide.

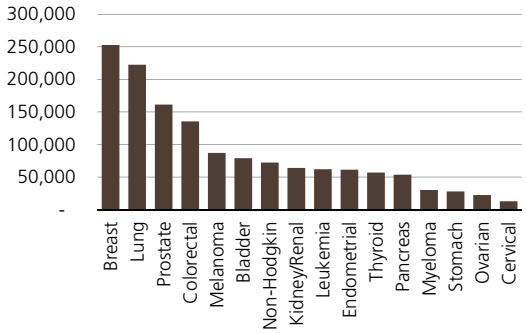
In its simplest terms, cancer is uncontrolled cell growth. It starts when cells, for genetic, environmental (e.g. sun exposure), life-style (smoking, diet) or even unknown factors, become abnormal and grow out of control. Some cancers, like leukemias and lymphomas, affect the blood stream and blood-forming organs, while other cancers invade normal tissues and can spread throughout the body.

The most common types of cancer in men are lung, prostate and colorectal cancer, and in women breast, colorectal and lung (Fig. 3), although less severe forms of skin cancer would dominate if also taken into account. These cancers, along with blood-borne cancers like leukemia and lymphoma, are among the largest therapeutic markets for pharmaceutical and biotechnology companies today.

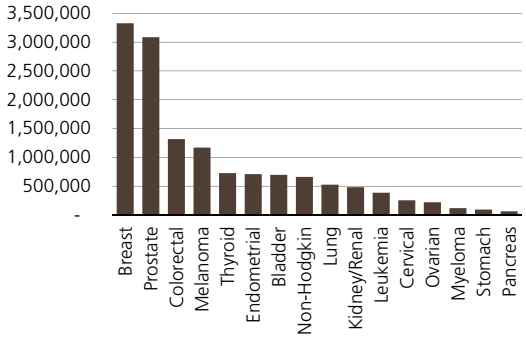
There are over 100 known forms of cancer, each with its own biological and life-altering characteristics. Treatment often requires multiple rounds of various combination therapies – surgery, chemotherapy, immunotherapy, targeted drug therapy, etc. – to modify disease progression, which commonly means increasing life expectancy by a matter of months.

Fig. 3: Cancer in the US – incidence, prevalence and five-year survival rates

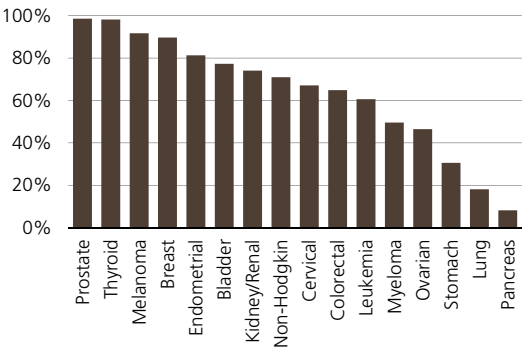
A) Incidence: new cancer cases in 2017



B) Prevalence: patients living with cancer



C) Five-year survival rates



Note: incidence - number of new cases estimated in 2017; Prevalence - cumulative number of patients alive with disease based on 2014 data; Survival rates based on 2007-13

Source: National Cancer Institute, SEER database, UBS, as of April 2017

Given the complexity of the disease, it is unlikely that we will ever find a "golden bullet" that cures cancer. However, scientific progress in both diagnosis and treatment has led to a better outlook for cancer patients over the past few decades. According to the American Cancer Society, the five-year survival rate for all cancers diagnosed between 2007 and 2013 was 67%, up from 49% in 1975 to 1977. While there are some notable success stories, such as prostate and breast cancer, survival rates for some hard-to-treat cancers remain low. Five-year relative survival rates for lung cancer are 18%, compared to 12% 40 years ago, while pancreatic cancer five-year survival is just 8% for patients diagnosed between 2007 and 2013, as compared to 3% for patients diagnosed between 1975 and 1977. Clearly, the need for new and better treatments for these cancer types is as great as ever.

The evolution of cancer treatment

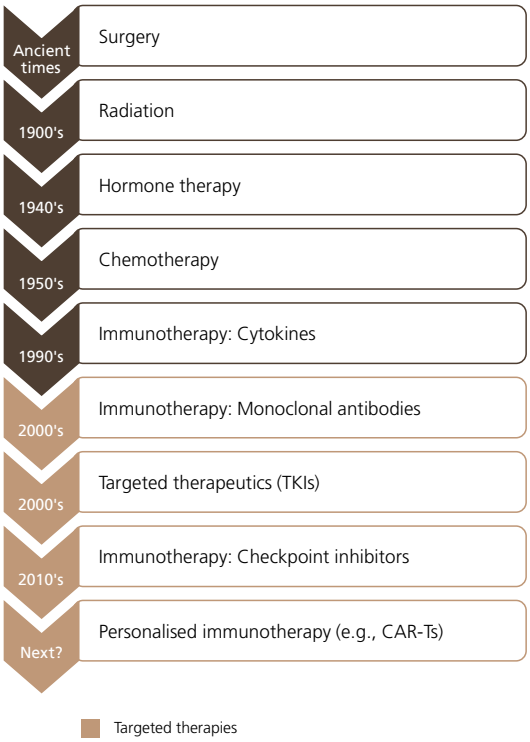
Cancer treatment evolved relatively slowly until the last two decades (Fig. 4), with most advances in surgery, radiotherapy and chemotherapy offering only incremental improvements in survival compared with previous treatments. More recently, a better understanding of cancer cell biology and the immune system has led to the development of immuno-oncology, an approach that uses the body's immune system to fight cancer. Immuno-oncology treatment offers the hope of more durable responses to treatment than conventional therapy (Fig. 5) but also has the benefit of significantly reducing the burden of side effects. The newest generation of immuno-oncology drugs to reach the market are the so-called checkpoint inhibitors. The benefits of these drugs include:

- **Improved patient survival rates**. For example, melanoma progression-free survival has improved from typically just a few weeks with traditional chemotherapy, to 2.9 months with Yervoy, 6.9 months with Opdivo, and more recently 11.5 months using Opdivo and Yervoy in combination.
- **Improved safety profile** compared to traditional chemotherapy.
- **Improved quality of life** during treatment.

These drugs have rapidly established themselves as the standard of care in advanced lung cancer and melanoma, and sales of the approved checkpoint inhibitors are already annualizing at nearly USD 8bn. Merck's Keytruda is now approved for use in previously untreated ("first-line") lung cancer, representing the next important step in the commercial evolution of checkpoint inhibitors.

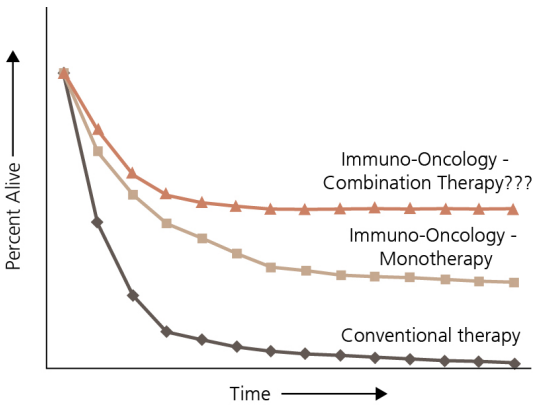
The PD-1 and related PD-L1 inhibitor drugs look set to become the backbone of treatment for many cancer types over the next few years. Their relatively benign safety profile suggests they could be used in combination with existing chemotherapies or other immuno-oncology drugs, which act to boost the immune system or suppress a tumor's ability to evade attack. This year and 2018 will see several important studies read out data providing insight into which combi-

Fig. 4: The evolution of cancer treatment
Several advances beyond traditional cancer treatment



Source: UBS

Fig. 5: The hope for immuno-oncology
Long, durable responses could transform survival rates



Note: for illustration only, not based on actual data
Source: Credit Suisse, UBS

nations are most effective and against which tumors. This new data will be key to determining the scientific and commercial potential for these drugs. Work is also ongoing to improve diagnostic procedures to identify the patients most likely to benefit from each drug and combination.

Checkpoint inhibitors do not work for all patients, but have been shown to produce deep and long-lasting responses to treatment in some cases. Beyond checkpoint inhibitors, research continues on a wide range of other approaches that could dramatically change the prognosis in certain cancer types. Personalized immuno-oncology using modified T-cells (known as CAR-Ts) has already demonstrated some success in the clinic, and could reach the market as soon as this year. Cancer vaccines and oncolytic viral therapies have seen limited success so far, but further developments are underway in both of these technically complex areas, and the emerging field of epigenetics could lead to new drugs able to augment treatment with checkpoint inhibitors.

We provide an updated discussion of some of these potential treatments in the Appendix below.

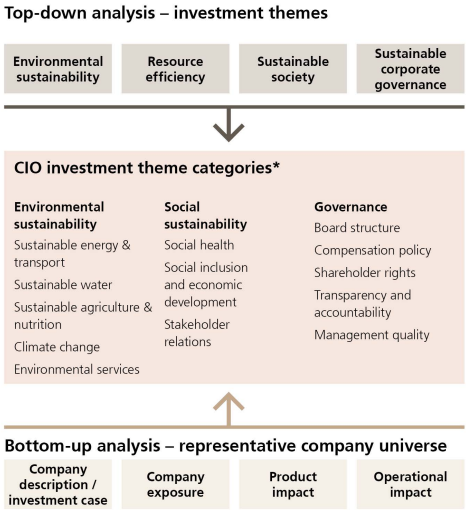
Link to Sustainable Investing

To identify whether a Longer Term Investment (LTI) theme qualifies as a Sustainable Investment (SI) theme, we follow a two-step process. The first works top-down. LTIs are assessed according to whether they match one or more of the sustainability topics within the environmental, social and governance (ESG) categories (Fig. 6). In general, these themes must contribute to environmental sustainability (e.g. a low-carbon economy), resource-efficiency (e.g. energy, water), sustainable society (e.g. health, education, poverty reduction, equality and social inclusion, etc.) or sustainable corporate governance. The second, bottom-up step, consists of considering a thematically aligned representative universe of companies. A large majority of included companies (80% or more) must align with one or more of the ESG categories. For each individual company, a minimum business involvement threshold is applied, e.g. 25% of revenues must be derived from the thematic activity under consideration.

In our view, investing in oncology therapeutics fits our sustainable investing framework. The theme exposes sustainable investors to one of our most exciting and innovative growth themes within our Longer Term Investment series. The global population is aging, which creates an increasing demand for healthcare products. Despite significant advances, cancer remains a leading cause of death and generates among the highest costs to healthcare systems around the globe. As with many serious diseases, the economic burden of cancer far exceeds the direct cost of treating the disease. Our oncology theme addresses the social aspect of ESG.

MSCI ESG Research ratings rank companies between AAA (best) and CCC (worst). The assessment encompasses the three ESG pillars. Each pillar has sub-categories: in the case of the environment, they are

Fig. 6: Overview of longer-term investment topic clusters



* For simplicity, all topic clusters include several subcategories not included in the graph. For example: sustainable water includes water utilities, treatment, desalination, infrastructure & technology, water efficiency and ballast-water treatment. Within each subcategory are further specifications; e.g. water treatment includes filtration, purification and waste treatment. In total, we have more than 100 categories (potential SI investment themes) in our thematic database.

Source: UBS

climate change, natural resources, pollution and waste, and environmental opportunities; in the social sphere, human capital, product liability, stakeholder opposition, and social opportunities; and for governance, corporate governance. The research also identifies 37 key ESG issues. For example, under climate change, companies are assessed based on their carbon emissions, energy efficiency and product carbon footprint.

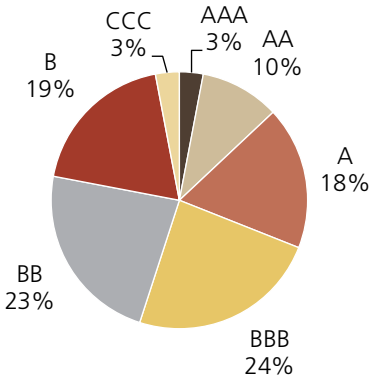
Oncology and the Sustainable Development Goals (SDGs)

The rising incidence of cancer globally is alarming. However, its pace in developing countries is of particular concern. According to the European Society of Medical Oncology, more than 66% of newly diagnosed cancer cases will occur in those regions with the least resources to tackle them[1]. Cancer and other non-communicable diseases constitutes a major health and development challenge, with cross-cutting implications for the United Nations' Sustainable Development Goals (SDGs). Impact investors can play a critical role in expanding both the quality of, and access to, oncology treatments. In particular, as long-term investors, impact investors can help address two key financing obstacles that are currently holding back progress in this field:

- The first hurdle concerns affordability, particularly in emerging markets where average incomes are lower. With public financing in emerging markets coming under increasing pressure, impact investors have a chance to step in and offer separate for-profit solutions to augment similar activity by listed companies.
- The second obstacle relates to the process of developing treatments. Studies have highlighted that the quarterly earnings cycle, real-time pricing and constant scrutiny of corporate performance by shareholders encourage listed pharmaceutical companies to focus on projects with clearer and more immediate payoffs at the expense of more speculative but potentially transformative and lucrative research[2]. As a result, funding for the riskiest segment of the drug-development process – the translational phase between basic research and human clinical trials – is severely limited. Impact investors can address this significant funding shortfall – known in the industry as the "valley of death" – by plugging intermediate gaps in the drug-development process.

Private market investors typically must commit capital for multi-year periods due to the nature of drug development, but these long-lockup investments can earn venture capital-type returns if a number of the funded drugs are successfully brought to market. Investors with this social impact objective can further commit to addressing the challenges in oncology by reinvesting a portion of any investment profits back into basic research and efforts to improve access to treatment in emerging markets. Impact investing can be a particularly attractive solution for ultra high net worth investors, who may have more risk capital than average and often less short-term need for their capital. As a result, they can afford to lock up more funds in longer-term

Fig. 7: MSCI ESG research corporate coverage
Rating distribution in %, 5,720 companies



Note: AAA = best possible ESG rating; CCC = worst.
Source: MSCI ESG Research, UBS, as of 23 Feb 2017

investment opportunities. Impact investing provides such investors with the opportunity to earn potentially compelling long-term returns while more closely aligning their portfolios with their personal values and social objectives.

Andrew Lee, Head Impact Investing and Private Markets
James Gifford, Senior Impact Investing Strategist
Nicole Neghaiwi, Impact Investing Analyst

[1] https://www.aeaweb.org/articles?id=10.1257/aer.103.3.406

[2] European Society for Medical Oncology: Developing Countries Oncology Survey (DC-OS report 2006

Appendix: Cancer treatment – past, present and future

Twentieth century cancer treatment

The first line of cancer treatment, from ancient times to the present day, has been to attempt surgical removal of malignant tumors (Fig. 4 above). The result, however, can be temporary; the tumor often grows back. For this reason, there is a pervasive belief that cancer cannot be cured. There are, however, many more cancer treatment options beyond surgery. In the late 19th century, radiation (x-rays) was discovered and subsequently used in cancer treatment. Also in the 19th century, the effect of specific hormones on certain cancers was discovered, establishing the groundwork for the modern use of hormone therapy that took off in the 20th century. During World War II, the impact of particular chemicals on cancer was observed, which translated into the development of the first chemotherapies. These treatment options – surgery, radiation, hormone therapy and chemotherapy – remain prevalent today, but much more effective treatments, with better survival outcomes and improved quality of life, have come to the fore. During the second half of the 20th century, the understanding of the immune system and the biology of cancer advanced significantly and led to what we now call immunotherapy. Initially this included biotechnological development of substances like interferons, interleukins, and other cytokines aimed at boosting a patient's immune system. Around the turn of the millennium, this approach was followed by the development of techniques that identified specific tumor targets and aimed antibodies at these tumors, thereby hindering tumor growth. These so-called recombinant monoclonal antibodies, and tyrosine kinase inhibitors (TKIs, small molecules targeting specific cancer cells) are now used routinely in cancer therapy, often in combination with older cancer therapies, and have led to better survival rates and improved quality of life.

The emergence of immuno-oncology

The common thread linking most recent developments in cancer care is a better understanding of the immune system. It has actually been known for a century or more that the immune system could play a role in cancer treatment, but the scientific developments allowing us to take advantage of this knowledge are much more recent. The inter-

ferons described above, developed in the 1980's and 1990's, were an early form of immunotherapy. Later, recombinant monoclonal antibodies were developed to target tumors directly, such as Roche's anti-B cell therapy Rituxan for non-Hodgkin's lymphoma. The most recent developments involve the T-cell part of the immune system, and appear to represent a step-change in treatment for some patients. In particular, the so-called checkpoint inhibitors, drugs that block a cancer cell's ability to defend itself from the immune system, have shown durable responses and improved survival rates in a subset of melanoma and lung cancer patients. Compared to traditional chemotherapy, the side effect profile of checkpoint inhibitors is relatively benign, offering improved quality of life for patients.

The first therapeutic checkpoint inhibitor was Bristol-Myers Squibb's CTLA-4 inhibitor Yervoy, approved to treat melanoma in 2011. In 2014, two checkpoint inhibitors targeting PD-1, Opdivo from Bristol-Myers Squibb and Keytruda from Merck & Co, were approved to treat late-stage melanoma. Since then, both of these approvals have been extended to treatment of earlier-stage melanoma, late-stage non-small cell lung cancer (NSCLC), head and neck (H&N) cancer, and Hodgkin's lymphoma. Opdivo is also approved for refractory kidney cancer and bladder cancer. Most recently, Keytruda was approved for first-line use in the treatment of NSCLC, and is currently the only checkpoint inhibitor with this important indication. Additionally, Roche's Tecentriq, a member of the related class of PD-L1 inhibitors, has been approved to treat bladder cancer and advanced NSCLC. Recently, a second PD-L1 inhibitor, Bavencia from Pfizer and Merck KGaA, was approved to treat a rare skin cancer known as Merkel cell carcinoma.

These drugs are rapidly establishing themselves as the standard of care, with combined sales already annualizing at nearly USD 8bn. Beyond the approved products, at least five more PD-1 and PD-L1 inhibitors are currently in clinical trials. Over 30 different cancer types are being targeted: beyond melanoma and lung cancer, checkpoint inhibitors have so far shown early evidence of benefit in bladder, ovarian, gastric, head and neck, and liver cancer, among others. Table 1 provides an overview of key immuno-oncology drugs in development, including checkpoint inhibitors. While the checkpoint inhibitors have demonstrated impressive efficacy in some patients, a key feature of these drugs is their relatively benign side effect profile. This allows them to be combined with almost any other type of treatment: chemotherapy, TKI's, cancer vaccines, and in particular other immuno-oncology drugs. Multiple mechanisms of action are used together routinely in oncology, due to the potential for synergistic effects. A similar benefit could be seen with the use of multiple immuno-oncology drugs: it is hypothesized that other treatments could stimulate the tumor to be in a more immunogenic state, increasing the tumor's sensitivity to treatment with checkpoint inhibitors. For example, Opdivo is approved for use along with Yervoy in melanoma treatment, and the past two years have seen an explosion of trials studying various combinations of immuno-oncology drugs, particularly of PD-1/PD-L1 inhibitors with newer

agents. We expect 2017 and 2018 to be pivotal years for checkpoint inhibitor development, with several important studies likely to read out data that will provide insight into which combinations are most effective and against which tumors. This new data will be key to determining the scientific, and commercial, potential for these drugs.

Immuno-oncology for the treatment of lung cancer

2016 saw many developments in the use of checkpoint inhibitors to treat lung cancer. Merck demonstrated, for the first time, that use of a single immuno-oncology agent is superior to chemotherapy in the treatment of first-line NSCLC, the single largest market for immuno-oncology drugs. Keytruda showed benefits in both progression free survival (PFS; 10.3 months vs. 6.0 months for chemotherapy) and overall survival (OS; 12-month OS of 70% vs 54% for chemotherapy) for patients shown to be PD-L1 positive (defined as PD-L1 > 50%, which represents about 25% of NSCLC patients). This is highly significant and will undoubtedly change the standard of care for many lung cancer patients. This data led to Keytruda's approval as a single agent for first-line NSCLC. On the other hand, Bristol-Myers Squibb's Opdivo failed to show a clinical benefit in a similar study comparing it to chemotherapy in first-line NSCLC. This surprising result highlights the risks inherent in cancer drug development: a drug can unexpectedly fail to produce a positive study result, despite apparently being similar to a successful product and having previously shown promising results in related disease areas. While the reasons for Opdivo's failure are still being debated by clinicians, one major difference between the two studies was in their design: Bristol-Myers tested patients with far lower levels of PD-L1 expression (PD-L1 > 1% or > 5%), while Merck tested high PD-L1 expressors (PD-L1 > 50%). Further studies will be required to determine how these results will influence checkpoint inhibitor development.

Table 1: Current and future immuno-oncology pipeline

Mechanism	Drug	Company	Status	Cancer type(s) where disclosed
First wave				
CTLA-4	Yervoy (ipilimumab)	Bristol-Myers Squibb	Approved	Melanoma, lung (phase III)
CTLA-4	tremelimumab	AstraZeneca	Phase III	NSCLC, others
CTLA-4	AGEN-1884	Agenus	Phase I	
PD-1	Opdivo (nivolumab)	Bristol-Myers Squibb	Approved	Melanoma, NSCLC, kidney, others
PD-1	Keytruda (pembrolizumab)	Merck & Co	Approved	Melanoma, NSCLC, others
PD-1	REGN2810 / SAR439684	Regeneron / Sanofi	Phase II	Skin cancer (non-melanoma)
PD-1	MEDI-0680	AstraZeneca	Phase I	
PD-1	SHR1210	Incyte / Jiangsu Hengrui	Phase I	
PD-L1	Tecentriq (atezolizumab)	Roche	Approved	NSCLC, bladder, others
PD-L1	durvalumab	AstraZeneca	Phase III	NSCLC, melanoma, others
PD-L1	Bavencio (avelumab)	Pfizer / Merck KGaA	Phase III	NSCLC, stomach, others
PD-L1	BMS-936559	Bristol-Myers Squibb	Phase I	
Potential second wave - key mechanisms of action				
IDO	epacadostat	Incyte *	Phase III	NSCLC, melanoma, others
IDO	indoximod	NewLink Genetics	Phase II	Breast, pancreatic, others
IDO	GDC0919 / RG6078	NewLink Genetics / Roche	Phase I	
IDO	BMS-986205	Bristol-Myers Squibb	Phase I	
IDO	PF-06840003	Pfizer / iTEOS	Phase I	
OX40	MEDI-0562	AstraZeneca	Phase I	
OX40	Anti-OX40	Pfizer/Merck KGaA	Phase I	
OX40	Anti-OX40	Bristol-Myers Squibb	Phase I	
OX40	RG7888	Roche	Phase I	
LAG3	BMS-986016	Bristol-Myers Squibb	Phase II	
LAG3	IMP321	Prima BioMed	Phase II	Breast, melanoma
LAG3	IMP701 (LAG525)	Novartis / Prima BioMed	Phase I	
CSF1R	pexidartinib	Daiichi Sankyo (Plexxikon)	Phase III	Breast, ovarian, others
CSF1R	cabiralizumab (FPA008)	Five Prime / Bristol-Myers Squibb	Phase II	NSCLC, melanoma, others
CSF1R	emactuzumab (RG7155)	Roche	Phase I/II	Synovial tumours, others
CSF1R	IMC-CS4	Lilly	Phase I	
CSF1R	ARRY-382	Array BioPharma	Phase I	
CSF1R	BLZ945	Novartis	Phase I	
KIR	lirilumab	Bristol-Myers Squibb / Innate Pharma	Phase II	Leukemia, others
KIR	IPH4102	Innate Pharma	Phase I	Lymphoma
GITR	TRX518	Leap Therapeutics	Phase I	
GITR	LKZ145	Novartis	Phase I	
GITR	Anti-GITR	Bristol-Myers Squibb	Phase I	
GITR	MK-4166	Merck & Co	Phase I	
GITR	MEDI-1873	AstraZeneca	Phase I	
GITR	INCAGN1876	Incyte / Agenus	Phase I	

Note: only clinical stage drug candidates shown. * Collaborations with Merck & Co, Bristol-Myers Squibb, Roche and AstraZeneca
Source: UBS, as of April 2017

Progress is continuing on combination therapies
As noted above, the real opportunity with immuno-oncology will probably rest on combination therapies. Currently, there are two major approaches:

- **IO/chemotherapy**: Use of an immuno-oncology agent (anti PD-1 or PD-L1) with chemotherapy
- **IO/IO therapy**: Two immuno-oncology agents combined (anti PD-1/CTLA-4 or anti PD-L1/CTLA-4 or anti PD-L1/IDO)

Currently, Merck and Roche are the leaders in the development of IO/chemo combinations, followed by Bristol-Myers Squibb, while Bristol-Myers and AstraZeneca are vying for the lead in IO/IO development. Current forecasts suggest that the largest market for these combination therapies, first-line NSCLC, could be a potential USD 10bn global opportunity. Both Merck and Roche have shown early data that suggests a benefit when adding their respective checkpoint inhibitors to chemotherapy. However, by 2018, we also expect read-outs from IO/IO combination trials that could show a more durable (i.e., longer-lasting) response, with less toxicity than chemotherapy combinations. At this point, it is far too early to call a winner, but the desired characteristics of a combination treatment are clear:

- Superior overall survival rates
- Acceptable toxicity (given OS rates)
- Efficacy in the broadest NSCLC population (ideally all PD-L1 negative and positive patients, not just PD-L1 positive patients)

Merck's Keytruda / chemotherapy combination for first line NSCLC is expected to be FDA approved for the US market by mid-2017. Roche's combination trial of Tecentriq with chemo now looks likely to produce data in late 2017 with filing in 2018. This would position Merck for the first approval, with Roche most likely following in 2018. So far, Roche's chemotherapy combination data has been the most promising, but ultimately it is likely that Roche's and Merck's combinations will prove to be virtually equivalent. With regard to IO/IO combinations, Bristol-Myers has released the most promising results in NSCLC, with the Opdivo/Yervoy combination showing improved progression free survival rates over time, as well as early evidence of complete responses in both PD-L1 negative and positive patients. For patients with PD-L1 > 1%, one-year overall survival was 87%, while for patients with PD-L1 > 50% it was 100%. However, these rates may fall as the data matures, an effect often seen in cancer studies. How new IO / IO combinations stack up against the more established PD-(L)1/CTLA-4 approaches is increasingly topical, with the potential for meaningful PD-L1/IDO data to be released by Incyte in mid-2017 (see below).

Bristol-Myers' most important combination trial (known as CHECKMATE-227), testing Opdivo with and without Yervoy or chemotherapy, may not report until early 2018, so this IO / IO combination is unlikely to be approved in this setting until late 2018, or a year behind approval for IO/chemotherapy combos from

Merck. AstraZeneca also has an IO/IO combination in development for first-line NSCLC (the so-called MYSTIC study of durvalumab/tremelimumab); however, AstraZeneca has disclosed relatively little on its study design, making it difficult to assess the potential outcome. We currently expect Astra's initial readout of progression-free survival (PFS) data in mid-2017 and overall survival (OS) data in 2018, potentially placing Astra just ahead of Bristol-Myers in the race to deliver an IO/IO combination for NSCLC. Table 2 presents an overview of various potential combination therapies for the leading checkpoint inhibitors in clinical development, showing the wide range of potential treatments. In general, it is still too early to determine which of these approaches will be successful.

While at this stage the outcome of these trials, and therefore the eventual evolution of the market, is unknown, given promising data to date for the various checkpoint inhibitors it seems reasonable to conclude that lung cancer treatment will evolve rapidly over the coming years. Most likely, first-line NSCLC will be treated with either a PD-1 or PD-L1 inhibitor in combination with either chemotherapy or another immuno-oncololgy agent. Chemotherapy combinations will be approved first, but IO/IO combinations have the potential to produce better patient survival rates and efficacy in a wider variety of patients, combined with cleaner safety profiles and an improved quality of life.

Table 2: Major trials for late-stage immuno-oncology pipeline

Cancer type	Use	Regimen	Launch
Opdivo (Bristol-Myers Squibb)			
Melanoma	1st line	With Yervoy	2015
Lung (NSCLC-PD-L1+/-)	2nd line	Single agent	2015
Kidney (RCC)	2nd line	Single agent	2015
Hodgkin's lymphoma (cHL)	1st line	With chemotherapy	2016
Lung (NSCLC-PD-L1>1%)	1st line	Single agent	Failed
Head & neck (SCCHN)	2nd line	Single agent	2016
Bladder	2nd line	Single agent	2017
Non-Hodgkin's-DLBCL	3rd line	Single agent	2017e
Non-Hodgkin's-Follicular	3rd line	Single agent	2017e
Brain (GBM)	2nd line	With Yervoy	2018e
Lung (NSCLC)	1st line	With Yervoy or chemotherapy	2018e
Lung (SCLC)	2nd line	Single agent	2018e
Lung (SCLC)	1st line	With Yervoy	2018e
Liver (HCC)	1st line	With Nexavar	2019e
Head & neck (SCCHN)	1st line	With Yervoy	2020e
Myeloma-relapse	2nd line	With chemotherapy	2020e
Keytruda (Merck & Co)			
Melanoma	1st line	Single agent	2015
Lung (NSCLC-PD-L1+)	2nd line	Single agent	2015
Head & neck (SCCHN)	2nd line	Single agent	2016
Lung (NSCLC)	1st line	Single agent	2016
Hodgkin's lymphoma (HL)	3rd line	Single agent	2017
Lung (NSCLC)	1st line	With chemotherapy	2017e
Gastric	3rd line	Single / with chemotherapy	2017e
Bladder	2nd line	Single agent	2017e
Breast (Triple negative)	2nd line	Single agent	2017e
Melanoma	Adjuvant	Adjuvant	2017e
Gastric	2nd line	Single agent	2017e
Colon (CRC)	2nd line	Single agent	2018e
Head & neck (SCCHN)	1st line	With chemotherapy	2018e
Hodgkin's lymphoma (cHL)	2nd line	Single agent	2018e
Esophageal	3rd line	Single agent	2019e
Liver (HCC)	2nd line	Single agent	2019e
Prostate	2nd line	Single agent	2019e
Melanoma	1st line	With IDO-inhibitor	2019e
Bladder	1st line	Single agent	2020e

Note: only clinical stage drug candidates shown
Source: clinicaltrials.gov, UBS, as of April 2017

Table 2: Major trials for late-stage immuno-oncology pipeline (continued)

Cancer type	Use	Regimen	Launch
Tecentriq (Roche)			
Bladder	2nd line	Single agent	2016
Lung (NSCLC-PD-L1+/-)	2nd line	Single agent	2016
Bladder (urothelial)	2nd line	Single agent	2017
Lung (NSCLC)	1st line	With Abraxane / chemotherapy	2018e
Kidney (RCC)	1st line	With Avastin	2019e
Lung (SCLC)	1st line	With chemotherapy	2019e
Breast (Triple negative)	1st line	With Abraxane	2019e
Bladder (muscle invasive)	Adjuvant	Single agent	2019e
Colon (CRC)	3rd line	With Cotellic	2019e
Lung (NSCLC)	1st line	Single agent	2020e
Urothelial	1st line	With chemotherapy	2020e
Prostate	1st line	With chemotherapy	2021e
Kidney (RCC)	Adjuvant	Adjuvant	2021e
Ovarian	1st line	With chemotherapy	2021e
Lung (NSCLC)	1st line	With Avastin / chemotherapy	2022e
Lung (NSCLC)	Adjuvant	Single agent	2023e
durvalumab (AstraZeneca)			
Bladder	2nd line	Single agent	2017e
Lung (NSCLC)	3rd line	Single agent	2018e
Head & neck (SCCHN)	2nd line	Single agent	2018e
Pancreatic	1st line	With tremelimumab (CTLA4)	2018e
Lung (NSCLC)	1st line	With tremelimumab (CTLA4)	2018e
Head & neck (SCCHN)	2nd line	With tremelimumab (CTLA4)	2018e
Head & neck (SCCHN)	1st line	With tremelimumab (CTLA4)	2018e
Bladder	1st line	With tremelimumab (CTLA4)	2019e
Lung (NSCLC)	2nd line	Single agent	2019e
Bavencio (Pfizer / Merck KGaA)			
Skin-Merkel cell carcinoma	2nd line	Single agent	2017
Lung (NSCLC)	2nd line	Single agent	2018e
Gastric	3rd line	Single agent	2018e
Ovarian	3rd line	Wtih chemotherapy	2018e
Kidney (RCC)	1st line	With Inlyta	2018e
Gastric	1st line	Single agent	2018e
Bladder (maintenance)	1st line	Combination	2019e
Ovarian	1st line	With chemotherapy	2019e
Lung (NSCLC)	1st line	Single agent	2020e

Note: only clinical stage drug candidates shown.
Source: clinicaltrials.gov, UBS, as of April 2017

IDO inhibitors: Potentially the next wave of immuno-oncology
The checkpoint inhibitors described above have demonstrated impressive response rates (i.e. reduction of tumor size) and are beginning to deliver survival benefits. However, many patients still do not respond, leading researchers to explore new mechanisms of boosting the immune system, or slowing down the cancer's ability to evade it. Unlike traditional chemotherapy, or even antibodies directly targeting tumors, which typically have severe toxicity that limits use in combinations, immuno-oncology's side effect profile is generally more benign. This allows many of these new drug candidates to be explored in combination with the checkpoint inhibitors. We expect some of these new drugs to emerge as the "next wave" of immuno-oncology drugs, potentially reaching the market over the next 3-5 years.

The first of the "next wave" of immuno-oncology drugs looks set to be the IDO inhibitors, led by Incyte's epacadostat. Epacadostat is currently in a range of studies across various cancer types in combination with most of the late-stage PD-1 and PD-L1 drugs (Table 1). Data from several of these Phase I/II trials should be presented at the ASCO cancer conference in June of this year, the first such data to be released. Importantly, Incyte has recently moved the drug into Phase III trials in combination with Merck's Keytruda in five key cancer types, namely NSCLC, melanoma, renal, bladder and H&N cancers.

Other companies with checkpoint inhibitors are also exploring combinations with IDO inhibitors, including Roche and Bristol-Myers Squibb, both of which are running combination trials with epacadostat. Interestingly, both companies also have "back-up" compounds in-house at earlier stages of development. None of these studies is likely to produce data until 2018 or later, however, making Incyte and Merck the clear leaders in PD-1/IDO combination development at this stage. Early data in melanoma (presented at ESMO in 2016) was encouraging, showing similar efficacy to Bristol-Myers' approved combination of Opdivo/Yervoy, but with a better side-effect profile. Interestingly, IDO inhibitors have shown disappointing efficacy as single agents. However, if these early data can be replicated in larger studies, IDO-containing combinations could be important in treating melanoma, and potentially other cancer types, and could even credibly challenge PD-(L)1/CTLA-4 combinations in some settings.

Novel personalized therapies: CAR-T getting closer to market
Despite the impressive improvement in survival seen so far with checkpoint inhibitors, these treatments and their follow-ons are not a "cure" for cancer. One area of development that could offer improvement over other IO approaches is the development of personalized cellular immunotherapy including CAR-T treatment and T-cell receptors (TCRs).

CAR-T treatment combines the cytotoxic (i.e. cell-killing) ability of T-cells (a type of white blood cell responsible for fighting infections) with the targeted nature of monoclonal antibodies. Treatment involves a three-step process:

1. T-cells are removed from the body
2. The T-cells are engineered to recognize the relevant cancer target
3. Engineered T-cells (CAR-T's) are reintroduced to the patient where they multiply and attack the targeted cancer cells

This approach showed remarkable evidence of efficacy in early studies in leukemia patients. For example, Novartis announced data from a Phase II trial of its CAR-T therapy CTL-019, showing that 55 out of 59 children (93%) with leukemia had complete responses to treatment, and 79% of patients were still alive a year after treatment. As is often the case with new therapies, as the data has matured survival rates have declined. However, CAR-T approaches have still shown the highest response rates of any therapies to date for these hard-to-treat blood-borne cancers. With the first CAR-T now filed with regulators, approval could come as soon as this year.

At present, it appears that Kite is closest to market with a CAR-T therapy. This March the company filed its lead product axicabtagene ciloleucel (KTE-C19) for approval in the broad indication of aggressive non-Hodgkin's lymphoma (NHL) in patients who are ineligible for autologous stem-cell transplant (ASCT). Given that KTE-C19 has Breakthrough Therapy Designation from the FDA, which allows a faster review time, it could be approved in 2H17 in the US market and 2018 in Europe. In terms of efficacy data, Kite has shown a three-month complete response (CR) rate of 33%, potentially a significant advance over slightly longer-term use of current therapy (CR~8% and overall survival of only 6.6 months based on SCHOLAR-1 study results), a seemingly low hurdle rate.

In acute lymphocytic leukemia (ALL), Novartis recently filed its product tisagenlecleucel-T (CTL-019) in the US and aims to submit in Europe later in 2017. This could see the product available commercially in late 2017 in the US. A filing in DLBCL is also planned for later in 2017. Unfortunately, Juno suffered a setback in its JCAR-015 program for ALL, and development of this program has ceased. Juno's DLBCL program (JCAR-017) should move into a pivotal trial this year. If approved, KTE-C19, CTL-019 and other CAR-T's have the potential to change the standard of care for many ALL and NHL patients. Table 3 presents an overview of key CAR-T and related T-cell-based therapies in development.

A number of issues need to be resolved before CAR-T therapy becomes a commercial reality. We expect safety to be a key challenge, particularly in solid tumor indications, due to the significant impact of CAR-T treatment on the patient's immune system (known as cytokine release syndrome or CRS). Clinical experience so far suggests that this is manageable, and that in the real world, where patients may be treated earlier than they have been so far in clinical trials, CRS could be more easily managed. Also, the nature of CAR-T treatment also introduces technical hurdles in manufacturing, notably consistency and security of supply, since each treatment is unique to a single patient. Several companies are developing new CAR-T approaches that could reduce these safety and manufacturing challenges, although we are

unaware of any to have reached the clinic as yet. Nevertheless, if these challenges can be overcome, the potential for personalized immunotherapies is great, in our view.

Table 3: Major CAR-T and T-cell therapy candidates

Mechanism	Drug	Company	Status	Cancer type(s) where disclosed
CAR-T approaches				
CD-19	JCAR-015	Juno Therapeutics	Dropped	Acute lymphoblastic leukemia (ALL)
CD-19	axicabtagene ciloleucel (KTE-C19)	Kite Pharma	Filed	Non-Hodgkins (DLBCL), ALL, MCL
CD-19	tisagenlecleucel-T (CTL-019)	Novartis	Filed	ALL, DLBCL
CD-19	JCAR-017	Juno Therapeutics	Phase II	Acute lymphoblastic leukemia (ALL)
CD-19	JCAR-017	Juno Therapeutics	Phase I	Non-Hodgkins (DLBCL)
CD-19	JCAR-014	Juno Therapeutics	Phase II	B-cell malignancies
CD-19	JCAR-014	Juno Therapeutics	Phase I	Non-Hodgkins (DLBCL)
CD-19	"Armored" CAR	Kite Pharma	Phase I	B-cell malignancies
CD-19	With PD-L1	Kite Pharma	Phase I	Non-Hodgkins lymphoma
CD-19	BPX	Bellicum	Phase I / II	Various
CD-19	bb2121	Bluebird	Phase I	Various
CD-19		Ziopharm / Intrexon	Phase I	Various
CD-19 (UCART)	UCART19	Cellectis	Phase I	B-cell malignancies
CD-22	JCAR-018	Juno Therapeutics	Phase I	ALL, non-Hodgkins lymphoma
Other TCR approaches				
NY-ESO TCR		Adaptimmune	Phase I/II	Synovial sarcoma, myeloma
NY-ESO TCR		Juno Therapeutics	Phase I/II	Synovial sarcoma, myeloma
MAGE A3 / A6		Kite Pharma	Phase I	Solid tumors
MAGE A10 TCR		Adaptimmune	Phase I/II	Lung (NSCLC), solid tumors
AFP TCR		Adaptimmune	Preclinical	Various
PRAME TCR		Bellicum	Phase I	Sarcoma, melanoma
HPV-16		Kite Pharma	Phase I	Cervical, head & neck
WT-1	JTCR016	Juno Therapeutics	Phase I	Lung (NSCLC)
WT-1	JTCR016	Juno Therapeutics	Phase I / II	Acute myeloid leukemia (AML)

Source: UBS, as of April 2017

Appendix

Terms and Abbreviations

Term / Abbreviation	Description / Definition	Term / Abbreviation	Description / Definition
1H, 2H, etc. or 1H11, 2H11, etc.	First half, second half, etc. or first half 2011, second half 2011, etc.	A	actual i.e. 2010A
COM	Common shares	CR	Combined ratio = ratio of claims and expenses as a percentage of premiums (for insurance companies)
E	expected i.e. 2011E	GDP	Gross domestic product
H	half year	Shares o/s	Shares outstanding
UP	Underperform: The stock is expected to underperform the sector benchmark	CIO	UBS WM Chief Investment Office
x	multiple / multiplicator		