

The Leading Edge

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In the arms race being waged to develop new cancer treatments, the competition is fierce and the prize enormous. In this edition, we examine the exciting field of Immuno-oncology and the companies that are vying for leadership in the treatment of 'mankind's greatest scourge'

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Justin BraitlingPortfolio Manager

Message from the CIO

Shares are expensive and risky at current levels. While many indices are poised to reach new highs as confidence and optimism abounds, markets are vulnerable to disappointment which may emerge along with softer data in the months ahead.

This time last year the picture was quite grim. The industrial economy was teetering on recession, China was looking at a hard landing, and deflationary forces were pervasive. Confidence and expectations hit a cycle low.

Responding to this weakness, policy stimulus fuelled a recovery in activity which started in earnest in the third quarter last year. Leading indicators surged through the second half of 2016. With expectations going into 2016 so low, the data has been stronger than forecast. For the first time in many years, analysts have been upgrading growth estimates. This of course has been positive for the share market which has rallied 12% in the last six months. Commodity prices and bonds yields have also pushed higher.

All the indicators are now either at or approaching cyclical highs. Confidence and sentiment are peaking, leading indicators are also peaking and valuations are back at elevated levels. Most of these measures are backward looking - history has shown that when confidence is highest we are often at the top of the cycle. As Sir John Templeton famously noted, bull markets are born in pessimism, grown in scepticism, mature in optimism and die on euphoria. While we may not be quite at euphoria, optimism certainly abounds. The VIX a measure of volatility (complacency) is at its lowest level in 19 years, the silence is deathly.

For the same reasons the economy abruptly changed course last year, we suspect activity is likely to slow in the months ahead. Stimulus has been withdrawn, interest rates are now rising across the yield structure, base money and credit growth is slowing as lenders tighten standards. As financial conditions constrict, leading indicators will roll over and the economy will slow. Market indicators are confirming this. Oil and bond yields have been falling since the start of the year while defensive and growth sectors have regained market leadership.

As this mini cycle rolls over, investors will once again be exposed to the same benign underlying trends of weak potential growth that have persisted since the financial crisis. However, with shares and valuations much higher, the risks are firmly to the downside.

Healthcare - Keeping track of exciting developments

With a combined market capitalisation of over US\$4 trillion and a wide variety of subsectors, spanning therapeutics, hospitals, service providers and insurers, we are spoilt for choice looking for investment opportunities in the global healthcare sector. Across the sector, rates of change and innovation are rapid as new advances in science and medicine are developed and commercialised. With ageing populations in much of the western world, healthcare companies also benefit from demographic tailwinds and structural growth that make the sector even more appealing from an investment perspective.

Along with these opportunities come risks. Biotechnology companies have one of the highest failure rates of any sector and operate at the cutting-edge of new developments in science and medicine. Governments around the world are grappling with ongoing problems associated with caring for their ageing populations, making the sector one of the most heavily regulated, and most susceptible to change and disruption via legislative reform. The costs to society (both social and economic) of failure in the healthcare system are vast, and both governments and payors (health insurers) are exerting pressure right across the value chain with one clear message deliver better outcomes or don't get paid. This has triggered significant consolidation across the sector, and the development of new reimbursement models. In this new paradigm, companies that cannot innovate or position themselves to respond to change will ultimately be left behind.

Our strategy in healthcare is to identify and invest in companies that are innovative with leading science. We also look for companies with strong competitive positions and a proven ability to pivot and adapt when the world changes. On the short side, we look to sell companies that are relatively undifferentiated, where the market has not adequately priced in the risks of greater competition or reimbursement pressures, which can emerge due to a failure to innovate.

In pharmaceuticals for example, we are circumspect on companies that have adopted a lower-risk approach to innovation in the 'post-patent-cliff' era by developing 'me too' drugs. We've also sold companies that have spent heavily merely extending established drugs through 'innovations in patient convenience' rather than making true progress in improving clinical outcomes; basal insulins in diabetes and recombinant proteins for treating haemophilia are key examples of this.

Immuno-oncology - Unleashing your immune system in the fight against cancer

A revolution in treating cancer is underway in 'immuno-oncology', boosting the immune system to identify and kill cancer cells. The last few years have been marked by successful launches of important new immuno-oncology drugs including Merck & Co.'s Keytruda, Bristol-Myers Squibb's Opdivo and Roche's Tecentriq. In certain cancers, these drugs are delivering profound improvements in patient survival and quality of life, particularly in difficult to treat cancers such as metastatic melanoma and Non-Small Cell Lung Carcinoma (referred to as NSCLC). Early successes in these and other smaller cancer groups have driven estimates for revenues from the immuno-oncology market to ~US\$25 billion by 2025; expectations are high as is the level of investment by leading pharma's in this space.

To help understand the appeal of immuno-oncology, it is first necessary to outline some basic principles of the immune system, given its importance at the core of how these therapies work.

Immune system basics

Our body has several defence mechanisms at its disposal to combat foreign bodies, pathogens (viruses, bacteria, fungi etc; disease-causing organisms) and even cancerous cells. To do so, our immune system must be able to distinguish antigens as being 'self' or 'non-self' and selectively eliminate 'non-self' pathogens from the body. Antigens are basically anything that causes an immune response, including whole pathogens (bacteria, viruses, fungi etc) and the proteins they make. Notably, antigens can also be present on the outer-surface of cells, which makes them attractive targets for developing drugs. It is also interesting to note that at some point in our life, our immune system will have identified and destroyed cancerous cells before they even became detectable or dangerous; implying that the immune system must also have a role in how the growth of cancers becomes uncontrolled.

There are two major systems make up the immune system; being the innate and the adaptive immune systems. They are quite different, but together form a complementary network of defence. In this piece, we focus on the adaptive immune system given it is currently the major focus for pharmaceutical/biotechnology companies developing immuno-oncology drugs.

Adaptive Immune System - A key ally for next generation cancer therapies

The adaptive immune system is not present at birth, it is learned. Adaptive immunity is 'antigen-dependent' and 'antigen-specific' and usually takes about 4-7 days to reach a maximal response. The adaptive immune system is usually activated if an invading pathogen becomes successful in evading or overcoming the

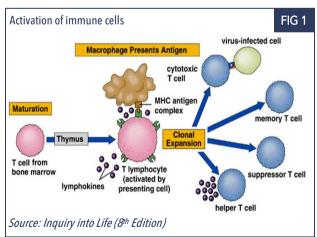
innate immune system's defences and an infection becomes established. The other unique aspect of the adaptive response is its ability to develop 'memory' of antigens (usually lasting for life). The concept of immune 'memory' is why you may only suffer from illnesses like Chicken Pox once in a lifetime and how immunisations can prevent you from ever becoming infected by viruses like Polio, Hepatitis B and Measles. Therefore, anytime the body is re-exposed to a known or 'remembered' antigen, the adaptive immune system is rapidly activated to clear it from the body.

The primary functions of the adaptive immune response are:

- 1) To recognise specific "non-self" antigens in the presence of "self" antigens (i.e. being able to tell the difference between your cells versus infected, foreign, or cancerous cells);
- 2) To generate 'pathogen-specific' killing pathways (also known as effector pathways) that eliminate specific pathogens or pathogen-infected cells; and
- 3) To develop immune memory that can quickly eliminate a specific pathogen should re-exposure occur.

Cells of the adaptive immune system are made up of 2 major cell types, T cells and B cells (both are white blood cells or lymphocytes).

<u>T cells</u> form initially in the bone marrow and then migrate to an organ in the chest called the Thymus (hence 'T' cell). In the thymus, T cells learn to distinguish 'self' antigens from 'non-self' antigens in order to prevent them from attacking the body's own tissues/cells (this is what can happen in autoimmune diseases). After learning not to attack 'self' antigens, T cells can leave the thymus and mostly reside in the lymphatic tissues. T cells then need to become activated before they can fight pathogens. Once activated, T cells multiply rapidly to make an army of identical T cells, including specialised 'cytoxic T cells' which directly 'kill' infected cells and eliminate them from the body (Fig 1).



<u>B cells</u>, on the other hand, are formed in the bone marrow and produce proteins called antibodies which cause 'antibodymediated' or humoral immune responses. Antibodies are soluble proteins (i.e. dissolve in the blood) which travel with the

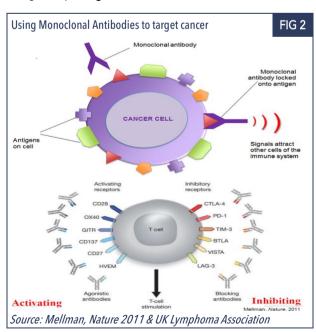
blood throughout the tissues of the body. Each antibody binds to a specific antigen. Upon binding of antibodies to a foreign antigen/pathogen, they can

- 1. Directly neutralise the ability of a pathogen to infect our body; and/or
- 2. Mark the pathogen for destruction by other immune cells. Our body's ability to produce antibodies to a specific pathogen is the hallmark of immune 'memory'.

Therapeutic Application

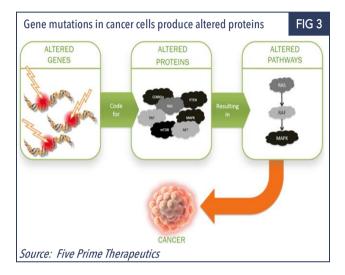
For decades, researchers have been designing antibodies to target specific antigens/proteins and producing them in vast quantities for therapeutic and research use. Known as 'monoclonal antibodies' these fall under a class of drugs called biologics. Dozens of monoclonal antibodies are currently approved for use in a variety of illnesses including cancer and autoimmune diseases. In the therapeutic context, monoclonal antibodies work by:

- 1) Physically blocking or boosting the actions of a specific antigen: By binding on at a critical place required for activity, the antibody causes its target to stop functioning. For example, a monoclonal antibody could be designed to block signals sent by cancer cells. Just as they can be designed to block a signal, antibodies may also be designed to augment/boost a signal. For example, upon binding to a certain T cell antigen, the antibody causes the cell to become activated or 'revved up'.
- 2) Activating the immune system after it has attached to its target: Using a cancer cell for example, a monoclonal antibody may be designed to target a specific antigen present only on the surface of cancer cell; after binding, it then signals the immune system to come and destroy that cell. Scientists have identified numerous antigens linked to how cancer cells can evade the immune system, the target of Merck's Keytruda therapy is a fitting example (Fig 2).

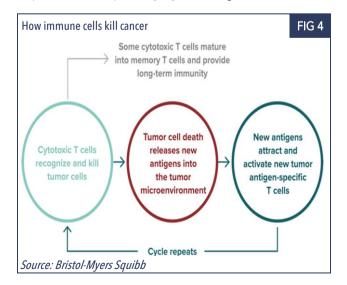


Putting it all together - Evidence that the immune system can respond to cancer

There is clear scientific evidence showing that the body can generate immune responses to solid tumours (e.g. lung, melanoma, breast, kidney etc) and hematologic cancers (blood cancers like leukaemia, lymphomas) with potential to impede the cancer's growth or destroy it completely; this is known as 'tumour immunogenicity'. Studies of more 'immunogenic' tumour types (e.g. melanoma) have shown that their constituent cancer cells carry a greater number of mutations in their genes, causing tumour cells to produce more 'tumour-specific' antigens which then may be recognised by the immune system (Fig 3).



Researchers have detected the immune cells residing within many solid tumours (known as 'tumour-infiltrating' immune cells), highlighting immune cells' ability to identify and migrate to a tumour. Finally, in the early stages of tumour growth there have been many reported cases of 'spontaneous regression' suggesting the immune system has developed an anti-tumour response - an example is highlighted in (Fig 4).

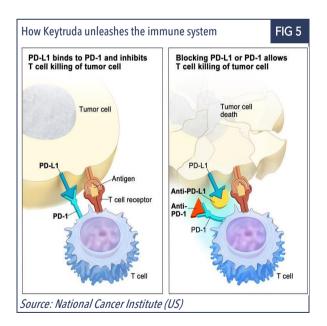


Evading the immune system; as discussed above, we know tumours can attract immune responses. Equally important, is how tumours can then develop ways to evade immune detection, allowing uncontrolled or 'unchecked' growth to ensue. Major efforts are underway to identify how tumours are avoiding the immune system and develop drugs to block them. At the same time, researchers are looking at ways to 're-activate' the immune system's ability to kill cancer cells. While this is a hugely complicated task there have been successes such as Merck's Keytruda. We will focus here on using the adaptive immune system (mainly T cells) to fight cancer.

Immuno-oncology drugs

So now we know a little more about the immune system, the question is how does a drug like Keytruda work? We know cancer cells can grow very rapidly by 'avoiding' the immune system. A cancer cell's ability to avoid immune detection is often caused by many mutations occurring in their genes – where mutations may cause a cell to inappropriately send 'avoidance' signals to your immune system. This process effectively 'tricks' your immune system into believing a cancer cell is 'OK' and to let it grow 'unchecked'.

With the benefit of decades of research that has identified some of these 'tricks', drugs such as Keytruda use monoclonal antibodies to block the avoidance signal from a cancer cell, thereby allowing the T cells to 're-recognise' cancers and destroy them (Fig 5).



Clinical evidence with Keytruda shows a strong correlation between the response to therapy (i.e. survival) and the proportion of cancer cells within a tumour which produces the avoidance signal (PD-L1 protein).

Since first being approved in metastatic melanoma 'checkpoint inhibitors' like Keytruda have been approved in multiple cancer settings at various lines of therapy. A 'line' of therapy refers to the number of prior chemotherapy treatments a patient has progressed through, where for example first line therapy (or 1L) refers to the first time a patient has been administered a systemic chemotherapy drug. Then it follows that second line (or 2L) therapy means a patient has failed 1L therapy (i.e. the tumour has not responded to the drugs) and is now being given a second chemotherapy regimen, and so it goes on.

Non-Small Cell Lung Carcinoma (NSCLC) - a big opportunity for successful immuno-oncology drugs

NSCLC is the most hotly contested immune-oncology market. In the USA, it is estimated that there will be approximately 178,000 new NSCLC patients this year. Lung and Bronchus cancer is the second largest source of new cancer patients each year and is the leading cause of death by cancer. **Fig 6** shows the 10 most common cancers by incidence, note NSCLC represents ~80% of the 'Lung and Bronchus Cancer" incidence of 222,500.

Common Types of Cancer		Estimated New Cases 2017	Estimated Deaths 2017	
1.	Breast Cancer (Female)	252,710	40,610	
2.	Lung and Bronchus Cancer	222,500	155,870	
3.	Prostate Cancer	161,360	26,730	
4.	Colon and Rectum Cancer	135,430	50,260	
5.	Melanoma of the skin	87,110	9,730	
6.	Bladder Cancer	79,030	16,870	
7.	Non-Hodgkin Lymphoma	72,240	20,140	
8.	Kidney & Renal Pelvis Cancer	63,990	14,400	
9.	Leukemia	62,130	24,500	
10.	Endometrial Cancer	61,380	10,920	
Cancer of A	Anv Site	1,688,780	600,920	

Given the ~US\$150,000 per year price tag of some of these therapies, the prize is big. There are currently 'checkpoint inhibitor' therapies approved for the second line treatment of NSCLC and beyond - Merck's Keytruda, Bristol-Myers Squibb's (BMS) Opdivo and Roche's Tecentriq.

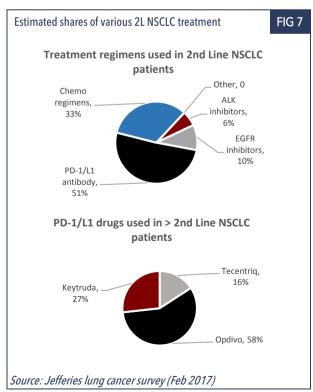
BMS took the lead in the NSCLC arms race in March 2015, with the approval of Opdivo by the US FDA. On the back of this success, the market was valuing the company on the basis that it would go on to secure the same dominant position in first line treatment and was ascribing a very generous valuation on BMY's pipeline, which would benefit from the use of Opdivo in combination with other drugs.

Historic data from NSCLC patients tells us that treating with standard care chemotherapy in the first line setting (i.e. the first time a patient is treated with any systemic drug) gives a median overall survival time of 8-10 months with 10-19% of patients being alive more than 2 years later.

In October 2015 Merck made a major breakthrough, when it showed that NSCLC patients with tumours with elevated activity in producing avoidance signals, and who had already failed multiple lines of chemotherapy, treatment with Keytruda provided a median overall survival time of 17.3 months, with more than 60% of patients remaining alive after 2 years. These were compelling results, given these patients had failed multiple therapies and had limited options left.

The obvious aim for clinical trials of cancer treatments are to prolong survival for as long as possible (overall survival) and to prevent tumour growth for as long as possible (progression-free survival). For clarity, Progression-Free Survival (PFS) refers to time from when therapy commences until disease progression (i.e. tumour grows or death). Overall Survival (OS) refers to the time from when therapy commences until death from any cause.

Because of these results, and those of competitors, the standard of care has now changed for patients with NSCLC who have failed two or more lines of therapy (or \geq 2L). A recent survey of lung cancer specialists in the US (published by Jeffries analyst Dr Jeffrey Holford) shows more than 50% of \geq 2L NSCLC patients are now being treated with a 'checkpoint' inhibitor (**Fig 7**). Bristol-Myers Squibb's Opdivo holds the market share advantage for now but this is expected to decline due to Merck's approval of Keytruda in the 1L setting in October 2016.



Merck's Keytruda is the only immuno-oncology drug approved in first line (1L) NSCLC

Approval of Keytruda in the 1L setting of NSCLC in the US in October 2016 was based on positive results reported in its Phase 3 clinical trial called KEYNOTE-024. Patients with metastatic NSCLC who had not received prior chemotherapy and whose tumours contain 50% or greater proportion of cells expressing PD-L1 are now eligible for Keytruda therapy in the US.

Just like in the 2L studies, the survival results in Merck KEYNOTE-024 study were impressive where Overall Survival (OS) at 12 months was 70%.

From a competitive perspective, it is interesting to note that results from this trial were announced in June 2016 and at this point the share market gave Merck very little credit for Keytruda's commercial prospects. The market widely expected results from Bristol-Myers Squibb's Checkmate 026 trial were imminent and that they would also be successful in the same setting. This coupled with Opdivo's dominance in the 2L setting made for a compelling bear case around Merck's prospects in 1L NSCLC. The market could not have been more wrong...

In one of the most spectacular biopharma blow-ups of 2016, Opdivo failed in 1L NSCLC. The results of the 'Checkmate-026' trial could not have been much worse for BMS, both from a commercial and medical standpoint. Unlike Merck's Keytruda, Opdivo delivered NO survival benefit versus chemotherapy, and in fact showed a trend towards a worse overall survival outcome. This baffled doctors, scientists and investors as not only did it fail spectacularly but this happened despite Opdivo already showing strong survival benefits in the 2L which led to its approval there in the first place! This setback was a big win for Merck, with Keytruda now the only PD-1 inhibitor approved for 1L treatment in NSCLC and growing share in the 2L setting.

Analysis of BMS' trial design provides some insight into how the trial failed so badly. In an attempt to almost double their addressable market and differentiate Opdivo's efficacy profile in an increasingly competitive market, BMS lowered the PD-L1 expression requirement to 5%, effectively bringing into the study, a patient population with tumours that were showing a much lower level of 'avoidance signalling'. Had BMS used the same threshold as Merck, the trial may well have been a success.

This takes us to the next leg in this story, combining PD-1/PD-L1 inhibitors with other therapies whether they be already approved drugs (like chemotherapy) or emerging immuno-oncology drug candidates. Again, NSCLC will be the main event in the race to develop next generation combination therapies, given its large incident population and success achieved with monotherapy treatment so far.

Combinations, and more combinations

Combination therapies are commonplace in medicine and have been used in chemotherapy treatments for decades. By combining two or more drugs together, the hope is to achieve an additive benefit to survival, in some cases drugs used in combination can have a synergistic effect on each other (ie 1+1=3). One of the strategies being explored now is combining multiple immuno-oncology drugs together, one drug would aim to block avoidance signals sent by tumours to the immune system (like Keytruda) and another would aim to stimulate a more powerful response by the immune system. Merck clearly has a head start in 1L NSCLC but it is not resting on its laurels, with the competition now hot on its heels. Combination therapy with immuno-oncology drugs has shown encouraging signs of delivering improvements above PD-1/PD-L1 monotherapy.

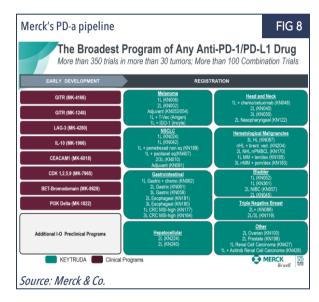
Combinations including PD-1/PD-L1 immuno-oncology drugs appear attractive because of the individual success these treatments have had to date. As knowledge of how cancer can avoid the immune system grows, more targets will be identified. The combination 'arms race' is on with Merck, Bristol-Myers Squibb, Roche and AstraZeneca leading the charge.

Two key approaches to combination therapy in NSCLC are being pursued with near-term results:

- Combining PD-1/PD-L1 monotherapy with well-established chemotherapy drugs this approach, commonly referred to as "I-O/Chemo combos" is being aggressively pursued by Merck and Roche. Following Merck's compelling data presented at a major cancer conference in October 2016 (Keynote 0219), AstraZeneca and BMS added chemotherapy combinations to their major trials, POSEIDON and Checkmate-227 respectively.
- Combining PD-1/PD-L1 monotherapy with other immuno-oncology drugs this is commonly referred to as "I-O/I-O combos". These are being pursued by all participants. The most anticipated results are coming from AstraZeneca and BMS, where they are combining their PD-1/PD-L1inhibitors (Durvalumab & Opdivo) with another immuno-oncology drug targeting CTLA-4.
- CTLA-4 (Cytotoxic T-Lymphocyte-Associated protein 4) is protein present on T cells. Activation of CTLA-4, by tumour cells, prevents T cells from initiating an immune response against the tumour. Therefore, using a monoclonal antibody to block CTLA-4 can boost a T-cell activation towards tumour cells. BMS's CTLA-4 inhibitor Yervoy has been approved for use in combination with Opdivo in unresectable (unable to be surgically removed) metastatic Melanoma since 2015. Yervoy monotherapy in late-stage Melanoma was approved in 2011.

Who will win the combination race? How are we investing in this rapidly evolving field?

In the near to medium term we see the early evidence for combination with chemotherapies, I-O/Chemo combo, as having compelling efficacy and a better safety profile. We also see potential for this combination to have a steeper adoption profile by doctors in the first instance, should it be approved. First-mover advantage will be very important in our view, particularly if efficacy and safety data from competitors' PD-1/PD-L1 inhibitors is largely comparable to incumbents' - i.e. they all work as well as each other. In this paradigm, companies with the deepest pipelines will clearly be in a better position, especially those developing drugs/combinations targeting the other aspects of the immune system (i.e. innate immune system).



In the longer term the outlook becomes cloudier, we believe the race will continue for decades! As newer immuno-oncology targets are identified, they will have to be tested against the leading PD-1/PD-L1 inhibitors or combination that is leading at the time. Additionally, we are anticipating a renaissance of small molecule drugs (chemotherapy drugs), which will also be thrown into the combination mix. We suspect it will become more difficult to develop new combinations as time goes on, given the high bar already set by PD-1/PD-L1 inhibitors the bar will continue to move higher as new therapies are added

Merck and Roche are key holdings across Watermark funds. We believe I-O/Chemo combos in NSCLC will be successful commercially as further results come through and approvals are forthcoming. We back Roche's deep experience and strong position in global oncology to drive commercial success of Tecentrig. Merck and Roche have very deep and diversified

pipelines in this space, reducing binary risk and providing multiple shots at goal.

Regarding our view that I-O/Chemo combos will be successful in 1L NSCLC. This is based on early data showing impressive response rates of tumours; notably most of the leaders have published small study results using chemotherapy combinations. While we have spoken with many sceptics of this combination, including oncologists and researchers, we have also spoken with many of the same fraternity whom have changed their minds.

We also sense that an I-O/Chemo combo would be more readily adopted in the community oncology setting, that is outside of the major academic cancer centres, given doctors have decades of experience managing patients on chemotherapy drugs and the side-effect are well understood. Outside of the major academic centres, the use of CTLA-4 inhibitors is less frequent and the known toxicity profile will make doctors more hesitant to use it in NSCLC.

Bristol-Myers Squibb - opportunity vs risk, balanced here?

We find it comforting that Bristol-Myers Squibb has added a chemotherapy combination for its key clinical trial called Checkmate-227, capitulating on the long-held and publicly stated view that chemotherapy combinations are unlikely to work and that I-O/I-O combinations are the only way forward. We are not short Bristol-Myers Squibb shares and see them as potentially undervalued post the setback of Checkmate-026, however there is now significant binary risk associated with any investment in Bristol-Myers Squibb which makes us cautious investing ahead of Merck's I-O/chemo combo potential approval in 1L NSCLC (due imminently at the time of writing) and considering AstraZeneca's I-O/I-O study called MYSTIC is due to read out results midway through this year.

AstraZeneca - very high risk, modest reward?

AstraZeneca's MYSTIC trial is testing an I-O/I-O combination in 1L NSCLC, we see a high-risk of disappointment for many reasons. The company has completely backflipped on its original thesis that its combination would work in 'all-comers' BUT work best in tumours that don't express PD-L1. The original thesis was flawed in our view and seemed more like an aggressive attempt to differentiate itself from Merck (and Bristol-Myers Squibb to a lesser extent) and target a much bigger population of patients. AstraZeneca has since parted ways with this thesis and is now prioritising patients with PD-L1 expressing tumours in its analysis. As a result, it has re-sized and changed the endpoints of the MYSTIC trial multiple times which

is always a red flag and can make rigorous statistical analysis more problematic. Put simply we believe the trial will not deliver an unequivocal 'yes' or 'no' result which could leave investors disappointed.

The others

After digging deep into the early data releases from all developers of PD-1/PD-L1 inhibitors we are becoming more convinced that not all are as good as each other; this is fully acknowledging the dangers of cross-trial comparisons particularly in small numbers of patients. For the reasons outlined above we believe these will struggle against the more progressed companies.

Final thought - immuno-oncology is a very dynamic, fast moving field. By the time you finish reading this, the world of immuno-oncology will likely be a different place. We will keep you posted.

BASIC INDUSTRIES

After a rapid advance in 2016, the outlook for resources was mixed coming in to the new year. While Chinese demand for commodities remains strong, the Government has enacted policies aimed at slowing credit growth. Mining shares began to waiver early in the year, in anticipation of a slowing in demand for commodities and economic conditions in China. Similarly, the energy sector rallied into Christmas following the OPEC agreement. However, higher prices were met with renewed enthusiasm from US shale producers, who have rapidly increased production. This has weighed on shares in the oil and gas sector, with many having given up their pre-Christmas gains.

We are short the mining sector. Further credit tightening in China will weigh on commodity prices and the broader resources sector. As we saw in 2012, deflation in the sector will likely be gradual - punctuated by occasional relief rallies, which will present opportunities to sell. With consensus that oil markets rebalance in 2017, investors have positioned themselves long both physical oil and energy companies. However, the wash out for share prices in the first quarter of 2017 has presented a more favourable entry point for an exposure to the sector. We are currently neutral in this part of the portfolio, but are exploring several compelling investment opportunities.

We continue to search for opportunities in the Agricultural Chemicals sector which remains at depressed levels. While we believe, it is still a touch early, there could be a nice set up approaching for an investment in this space in the year ahead.

We added *BHP Billiton* to the portfolio in Q1 2017 following significant underperformance versus its peers. We are attracted to the optionality in its portfolio, both within oil and mining. Recent shareholder agitation will not wane and this pressure will be beneficial for all shareholders. *Iluka* suffered a setback after their financial results in February. We took the opportunity to increase our holding and have benefitted in recent months from strength in zircon prices. We initiated a position in *Fletcher Building* when the company's shares fell on an earnings downgrade. The construction issues which caused the downgrade are likely to be transitory. The business has a privileged position in several sectors in New Zealand, an economy which continues to perform well.

Our short exposure in the mining sector has been built predominately through international companies who have benefitted from high coal, zinc and copper prices. These companies remain highly exposed to a slowdown in China. Furthermore, under-investment in their mining portfolios may result in some production underperformance.

Performance of the resources portfolio was mixed, with the continued rally in January impacting returns. These losses were recouped later in the quarter as the mining sector began to roll over.



INDUSTRIALS

The industrials sector globally has been buoyed by hopes of a pickup in economic growth. Leading indicators for the global economy recovered during the second half of 2016 following stimulus from central banks at the beginning of last year, driving a sharp rally in the sector. The Trump election also saw increased optimism for a reduction in corporate taxes for US companies, which helped the sector. Higher interest rates, oil prices, and more hawkish central banks should slow the pace of growth, which could see some disappointment in more cyclical parts of the market.

The funds are hedged in industrials, with long positions in higher quality, undervalued companies, and short exposures in lower quality names where valuations have fully captured the rapid economic pickup. A significant structural theme is the shift to digital platforms, where leading companies are upgrading their products to be digitally connected and monitorable (e.g. wind farms, jet engines) – with benefits to customers through better productivity and availability.

In Australia, the funds have benefitted from investments in quality industrials such as *Amcor* (an underappreciated global leader in packaging), and deep value plays such as *Qantas* (trading at a significant discount to foreign competitors). Valuation discrepancies were also exploited in the infrastructure sector, where positions were established opportunistically in

Sydney Airport, which became oversold on concerns around the impact of a second airport.

Internationally, core investments include *Deutsche Post*, a beneficiary of growing global e-commerce parcel delivery; *BMW*, a stand-out in the auto sector with strong brands and management; *Siemens*, an industrial powerhouse, benefitting from restructuring and a strong position in digitally connected factory automation; and *Airbus* which has a strong order book, and will benefit from the ramp in production of the A350 and the roll-off of currency hedges. On the short side, the funds have positions in companies facing structural pressures, such as growing competition from Chinese competitors, and the encroachment of e-commerce on traditional distribution models. Gains from industrial/manufacturing positions were partially offset by some weakness in automotive positions, with transport broadly neutral.

CONSUMER

The strength of the global consumer is presently inconsistent across both geographies and categories. Overall, we are seeing improving trends in Europe and Asia while the picture in the United States and Australia is better described as uneven. Despite accelerating store closures, there remains too many retail stores in the United States given the channel shift to ecommerce. Although the starting points in Australia, continental Europe and Asia look more favourable, retailers in these regions should not assume they will be immune. This quarter was most notable for the return of the high-end Chinese consumer with strong outperformance by luxury brand owners and casinos catering to Chinese VIP baccarat players.

The investable consumer universe can be roughly divided into retailers and brand owners. Watermark's strategy for the retail segment is primarily to invest in retailers in product categories that have a minor overlap with Amazon (or alternatively have a credible plan to deal with the behemoth). Retail categories that meet this criterion include home improvement, pharmacies, and supermarkets. Unfortunately, it is very easy to find retailers that are being threatened by Amazon and the market has already punished these names, making it difficult to find shorts that aren't crowded. To date our best successes on the short side have come from identifying companies with idiosyncratic problems rather than thematic shorts (e.g. department stores, stationary retailers). When investing in brand owners we are looking for sustainably managed brands in growing categories, balanced with short positions in overpriced securities which do not properly reflect the structural challenges that we have identified.

During the quarter our positions in domestic gaming companies (*Tabcorp, Star Entertainment* and *SkyCity Entertainment*) all benefited from stronger trading conditions. In the case of the casinos, electronic gaming machine revenues for pubs and clubs in Auckland, Sydney and the Gold Coast implied a supportive environment that would accommodate the self-help initiatives of each company. Separately, *Tabcorp's* share price has strengthened as momentum builds for a 'point of consumption' tax that would help level the playing field with online bookmakers.

Unilever and Heineken made important contributions to performance over the quarter. The Kraft Heinz bid for Unilever validated our view of the value of Unilever's strong brands, in attractive categories and markets. Heineken's share price recovered from the undue pessimism levelled at their Mexican beer business following the election of President Trump. Positions in United States domiciled supermarkets detracted from returns as deflationary conditions due to commodity weakness and an escalation of price competition hurt store profitability.

In aggregate Consumer positions provided a positive contribution to returns over the quarter.

FINANCIALS

Volatility in financial shares was heightened in the quarter as global interest rates shifted higher. Financial firms which typically borrow short and lend long, benefit from higher interest rates which are lifting across the yield structure as policy tightens and inflation expectations rise. We have targeted banks that can benefit from higher rates without suffering from adverse credit quality such as *UniCredit SpA* and *ING Groep*. Both companies have just reported excellent Q1' 2017 results. In the United States, we are seeing the emergence of some troubling credit quality issues in auto lending and credit cards, this is typical of a maturing cycle. In Japan and Europe where the economic recovery continues to be less vigorous, very low rates continue to weigh on margins, while credit quality is more benign.

In Australia - the first half bank results were disappointing. Soft revenue trends are set to continue as the property sector slows. Meanwhile, net interest margins are falling as the regulator APRA looks to strengthen bank funding. On the positive side, diminutive loan loss charges continue given low interest rates and strong employment conditions. Looking forward, revenue growth expectations appear too high given the limited capacity for Australian households to accumulate more debt. The tax on deposits announced with the Federal Budget was a complete

surprise. A reminder that banks are a lightning rod for public discord and a soft target given challenges with an inflated property sector.

In Insurance, we have added to our positions in the general insurer *Suncorp* and *IAG* as premiums firm up in home and motor policies, as challenger brands pull back and reach maturity. In commercial lines, we are also seeing premiums pick up, having fallen for many years.

In the listed Real Estate sector, we are long the super-regionals and short the lower quality sub-regional centres which are under pressure as specialty retailers in B and C grade locations close. Investments in *Charter Hall* and *Goodman* group performed particularly well in the quarter.

HEALTHCARE

We see current Healthcare valuations as unappealing and expect sentiment rather than earnings growth to drive valuations over the medium term, we maintain a net short bias.

In Pharmaceuticals, Biotechnology and Medical Devices we seek to own companies with science and innovation at their core, strong competitive positions and a proven ability to pivot when the world changes. On the short side, we sell companies with undifferentiated portfolios, facing risks of greater competition and reimbursement pressure. In Healthcare Services, we look to own companies developing integrated care models and employing 'value-based' or 'risk sharing' reimbursement models. We tend to sell Healthcare providers that are subscale and rely too heavily on single sources of funding.

Our key concern for pharmaceutical/biotech companies is that drug pricing headwinds will continue to surprise investors following major consolidation amongst US Managed Care Organisations and Pharmacy Benefit Managers - the ultimate payers for drugs in the US. Pricing power with drugs now resides with the top three players that control more than 75% of the US drug market. Innovation is the best counter for pharmaceutical/biotech companies however we believe too many 'me too' drugs with limited differentiation have been developed in recent years which again allows companies to flex their power. A step-change is absent in the innovation cycle (i.e. faster identification of novel drugs, shorter development times and higher probabilities of success) we suspect structural pricing pressures will drive more consolidation of pharmaceutical/biotech companies. Notwithstanding these pressures, consolidation is unlikely to emerge before clarity on US taxation reforms and repeal and replace of the Affordable Care Act (Obamacare) is provided. Valuations appear

reasonable, with upside from consolidation and US tax reform balanced by structural headwinds. Medical device companies on the other hand trade at elevated valuations and appear expensive, a hiding place to avoid drug pricing headwinds in Pharma/biotech. However, these companies have solid demand outlooks and would benefit from proposed US taxation reforms.

In the March guarter, Australian Healthcare shares rose by nearly 15%, outperforming the broader Industrials index by 9%. We used the 26% rally in Sirtex Medical to re-establish a short position ahead of the SARAH study readout in April. CSL added ~26% following upgraded FY17 guidance and a strong 1H result while Primary Health Care fell (down ~11%) following a disappointing 1H result and the resignation of the CEO. We continue to like Ramsay Healthcare, despite a fall in the share price following the resignation of long-serving CEO Chris Rex (announced February), elevated political scrutiny and fears a recent 'slowdown' in surgical volumes would become protracted. This provided a great opportunity to add to our position at depressed levels. We believe the market mistakenly extrapolated declining utilisation trends and poor operating results from competitor Healthscope. Overall, we believe Australian Healthcare shares are overvalued relative to their offshore peers.

Offshore, Pharmaceutical and Biotechnology shares rose ~7% and ~11% respectively, outperforming the S&P500 (+6%) in the March quarter. Strength was driven by in-line Q1 results and less drug pricing rhetoric in the US. Notable outperformers were small mid cap biotech names including *Kite* (+75%) and large cap Medical Device companies (+10%). We established a new long position in *Roche* and continued to build short positions in select European Healthcare businesses, which outperformed in the period.

The Healthcare segment of the portfolio detracted from returns in the March quarter. Strength in short positions, specifically in European shares, outweighed strong performances in core long positions such as *Roche*. Volatility in small mid cap biotechnology stocks modestly impacted returns in the quarter.

TECHNOLOGY/MEDIA/TELECOMMUNICATIONS

Technology shares continued to lead the market higher through the quarter, as results from leading companies met or exceeded expectations. Notably, the technology sector continues to make new highs, surpassing even the previous 'dot-com' peak during the quarter. We attended the largest annual global TMT conference in San Francisco, and found the level of positivity around the sector remarkable. We see semiconductor shares as expensive, particularly following a flurry of M&A activity in

recent years. We retain a preference for investments in analog semiconductor shares, with high barriers to entry and structural growth tailwinds, over logic which is pressured by enterprises transitioning to the cloud and heightened competition. Structural pressures remain in media, as advertising spend continues to shift to digital platforms. Content remains king, but competition is heating up as distribution companies move upstream to protect margins, amid an acceleration in (cable TV) cord-cutting. Telcos continue to struggle with price deflation and declining revenues for legacy voice and enterprise services. In the face of maturing broadband and mobile penetration, telcos are attempting to combat competitive pressures by stoking convergence across mobile/broadband/content.

We are short the technology sector; given its strong performance has resulted in lofty valuations, while cherrypicking core long holdings which still have plenty of runway for structural growth. Within semiconductors we are long analog semis, exposed to content growth particularly in industrial automation and connected devices, while shorting logic semiconductor manufacturers where returns are under pressure as businesses migrate workloads to the cloud. Growing penetration of high speed internet access is seeing most of us spend a greater portion of our day consuming content in various forms, be it Netflix streaming or a Facebook newsfeed. While the demand for premium video content is well understood by the market, we see this as an opportunity to invest in undervalued content such as video games and music. Meanwhile TV networks' role in distributing video remains vulnerable given declining audiences. Given the struggles across the sector, we are short Telcos that are over-earning or under competitive threat, while selectively investing in 'recovering' and growth markets.

There is a limited universe of Australian TMT companies to consider. We managed to avoid the capitulation in the telco sector during the quarter, as *TPG Telecom* confirmed their entry as the fourth mobile operator with an expensive spectrum purchase. Our core holding in *Fairfax Media* benefitted from plans to spin-off *Domain*, which we believe has been undervalued sitting among the company's legacy print newspaper assets – and more recently from competing takeover bids.

During the quarter, we increased our short on the technology sector globally. Premature excitement around new components rumoured to be present in the upcoming iPhone presented an opportunity to short one of the most expensive semiconductor shares in the world, *ST Microelectronics*. Standout results from all video game publishers gave us confidence to increase our holding in *Ubisoft* and re-introduce *Activision Blizzard* into the

portfolio. These companies will benefit from the tailwind of physical distribution moving to higher-margin digital sales for years to come. Our positioning in the telco sector was validated as the Chinese telcos (which we are long) reported accelerating growth, while the US telcos (which we were short) are challenged by intense competition.

The portfolio performed well following favourable earnings results during the quarter, with notable contributions from our core holdings in the video game publishers, German media company *Stroer* and French telco *Iliad*.

Performance Review

Performance across all Watermark Funds was flat in the quarter, with modest gains in the domestic portfolio offset by losses on international exposures. This was a reversal of the trend in the final quarter of 2016, where international positions did the heavy lifting in the portfolio.

It is clear from an analysis of fund returns across our long short peer group and the broader industry, that 2016 was a very tough year for stock pickers. Fig 10 shows the strong influence of value factors on returns, at the expense of quality and momentum, which have been the preferred factor biases for many active fund managers in recent years. This period also coincided with a range of macroeconomic and geopolitical events that have played a key role in shaping investor sentiment and the prevailing direction of markets. While we deliberately set out to eliminate such biases from our portfolios, we have not been able to avoid missteps along the way, which have weighed on performance in the period. The influence of 'factors' has been more benign in 2017, and while investors' focus remains in part on the impact of geopolitical shocks and tightening from central banks, it is earnings that will ultimately be the key determinant of share price returns, which suits fundamental investors such as ourselves.



While fund returns in the last 12 months have been weak by our standards, investors can take comfort from the fact that in every one of the last 9 years, we have created a positive 'spread' (difference in performance between longs and shorts) through security selection. Even during difficult periods for performance (2014, 2016), our long/short investment strategy has proven robust, and we have avoided losing our investors' capital. We look forward to a return to form and remain convinced of the important role that alternative investment strategies such as ours will play in our investors' portfolios.

Performance Attribution for the Quarter

Contributors

Domestic Positions	International Positions
Westpac Banking Corp	Hennes & Mauritz AB
Rio Tinto Limited	Nevro Corp
Charter Hall Group	Roche Holdings
Fairfax Media Limited	Stroeer & Co
Retail Food Group Limited	Allergan PLC

Detractors

Domestic Positions	International Positions
Fortescue Metals Group Ltd	Grifols SA
Independence Group NL	Hess Corp
Seven Group Holdings Ltd	Kroger Co
BHP Billiton Ltd	Tesla Inc
Australian & New Zealand Banking Group	Bluebird Bio Inc





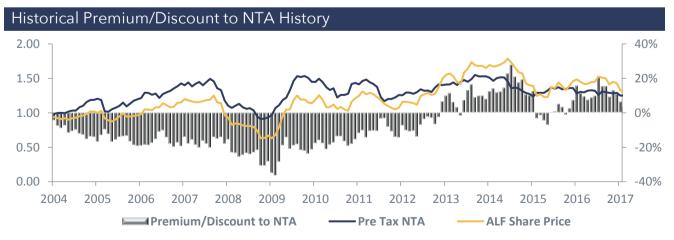
Fund at a Glance - April 2017	
ASX Code	ALF
Fund Size	AU\$342.4m
Fund Strategy	Variable Beta
Shares on Issue	272.5m
Dividend (HY17 Interim)	4 cents
Dividend Yield (annualised))	7.0%

Net Tangible Asset (NTA) Backing						
	Mar 17	Apr 17				
NTA Before Tax	\$1.29	\$1.26				
NTA After Tax & Dividend	\$1.26	\$1.27				
Gross Portfolio Structure	Э					
	Mar 17	Apr 17				
Long Exposure	107.3%	122.3%				
Short Exposure	-107.4%	-116.5%				
Gross Exposure	214.7%	238.8%				
Cash	100.1%	94.2%				

ALF Performance							
	1 Mth	6 Mths	1 Yr	2 Yrs (pa)	5 Yrs (pa)	7 yrs (pa)	S.I. (pa)
Portfolio Return (net)	1.2%	-0.6%	4.8%	7.8%	11.9%	9.9%	13.1%
All Ords Accum Index	0.8%	12.4%	16.6%	6.0%	10.6%	7.5%	9.1%
Outperformance (net)	0.4%	-13.0%	-11.8%	1.8%	1.3%	2.4%	4.0%

Net Equity Exposure







Fund at a Glance - April 2017

Outperformance

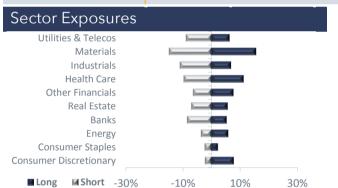
Market Neutral Trust

APIR: WMF0001AU

Roturn Characteristics

							Return Characteristics				
Fund Size		AU\$191	m P	ositive l	69.4%						
Strategy FUM		AU\$237	m P	ortfolio	-0.2						
Fund Inception Date		August 201	2 S	harpe R	atio		1.5				
Fund Strategy	Equi	ty Market Neutr	al S	ortino R	Ratio		4.4				
Application/Redemption		Dai	ly S	tandard	Deviation		7.1%				
Management Fee		1.5	% N	lo. Long		57					
Performance Fee		20% No. Short Positions		No. Short Positions			55				
Benchmark		RBA Cash Rat	te G	Gross Exposure			150%				
				International Exposure (% of Gross)			19%				
Performance ²											
	1 Mth	6 Mths	Fin. Y	TD	1 Yr	2 Yrs (pa)	S.I (pa)				
WMNT (net return)	1.1%	0.7%	1.79	%	4.6%	10.6%	12.8%				
RBA Cash Rate	0.1%	0.7%	1.39	%	1.6%	1.8%	2.3%				

0.4%



1.0%

0.0%



8.8%

10.5%

3.0%

Mont	onthly Net Performance (%)												
Cal. Yr	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	YTD
2012	-	-	-	-	-	-	-	1.36	0.97	0.00	6.51	2.88	11.72
2013	-0.71	0.21	4.60	1.55	5.83	5.31	1.11	2.57	1.43	1.86	0.35	-0.06	24.05
2014	1.71	1.45	-1.17	2.80	1.21	0.84	-4.38	-1.77	2.52	-1.57	-1.58	-1.32	-1.26
2015	-1.18	0.70	3.23	0.96	-0.61	3.39	3.82	4.04	2.73	-1.36	1.53	2.93	20.19
2016	-0.14	-1.92	1.13	0.53	1.08	1.76	0.60	-1.46	2.23	-0.34	-0.46	0.07	3.03
2017	-0.81	0.02	0.76	1.13									1.10

¹ Return Characteristics are in relation to the market neutral strategy using long/short return series recorded from April 2008.

 $^{^{\}rm 2}$ Performance data is net of all fees and expenses. The Fund's inception date is August 2012.

³ Long/Short spread shows the gross performance of the long and short portfolios. The Fund makes a profit where the long portfolio outperforms the short portfolio, after the payment of fees. Returns prior to the Fund's inception date are based on return series from the long and short portfolios of the Australian Leaders Fund Ltd in a market neutral structure.



Market Neutral Fund Ltd

Fund at a Glance - April 2017						
ASX Code	WMK					
Fund Size	AU\$87.5m					
Fund Strategy	Equity Market Neutral					
Shares on Issue	87.4m					
Dividend (HY17 Interim)	3 cents					
Dividend Yield (annualised)	5.7%					

Net Tangible Asset (NTA) Backing						
	Mar 17	Apr 17				
NTA Before Tax	\$1.03	\$0.99				
NTA After Tax & Dividend	\$1.00	\$1.01				
Gross Portfolio Structure						
	Mar 17	Apr 17				
Long Exposure	108.1%	125.3%				
Short Exposure	-107.9%	-118.4%				
Gross Exposure	216.0%	243.7%				
Cash	99.8%	93.1%				

WMK Performance						
	1 Mth	6 Mths	1 Yr	S.I. (pa)		
Portfolio Return (net)	0.9%	-0.9%	4.3%	6.9%		
RBA Cash Rate	0.1%	0.7%	1.6%	2.1%		
Outperformance (net)	0.8%	-1.6%	2.7%	4.8%		



^{*} Long Short spread shows the gross monthly performance of the Company's long and short portfolios. The difference between the two represents the gross performance of the portfolio as a whole. The company will make a profit where the long portfolio outperforms the short portfolio, after the payment of fees and expenses.





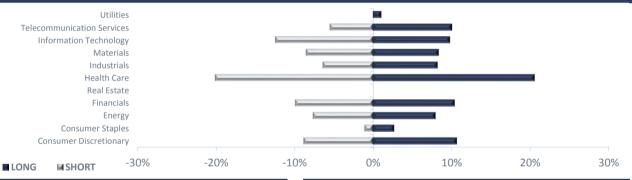
Global Leaders Fund Ltd

Fund at a Glance - April 2017				
ASX Code	WGF			
ASX Code Options	WGFO			
Fund Size	AU\$88.9m			
Fund Strategy	Global Market Neutral			
Share Price	\$0.99			
Shares on Issue	82.8m			
Option Price	2.6 cents			

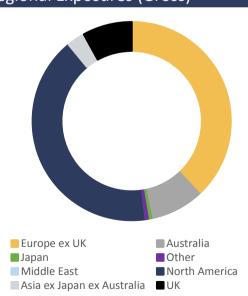
Net Tangible Asset (NTA) Backing					
	Mar 17	Apr 17			
NTA Before Tax	\$1.08	\$1.08			
NTA After Tax	\$1.07	\$1.08			
Gross Portfolio Structure					
	Mar 17	Apr 17			
Long Exposure	85.6%	89.8%			
Short Exposure	-79.5%	-80.7%			
Gross Exposure	165.1%	170.5%			
Cash	93.9%	90.9%			

WGF Performance						
	1 Mth	3 Mths	1 Yr	S.I. (pa)		
Portfolio Return (net)	0.4%	0.6%	%	0.6%		
RBA Cash Rate	0.1%	0.4%	%	0.5%		
Outperformance (net)	0.3%	0.2%	%	0.1%		

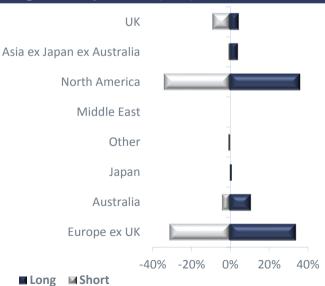
Sector Exposures



Regional Exposures (Gross)



Regional Exposures (Net)





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