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## HEALTHCARE MARKET REVIEW AND OUTLOOK

The fourth quarter of 2018 marked a terrible end to what began as a decent year. During the quarter, markets in the developed world fell -12.8% (MSCI World AC Index), while the emerging one was down -7.5%. Developed-market healthcare, down -9.4%, was barely defensive, while emerging market healthcare (at -16.2%) was not defensive at all. Small- and mid-cap healthcare (-25.6%) and biotech (-20.5%, Nasdaq Biotech Index) fared the worst, with pharma (-6.4%) displaying characteristic defensiveness, while medtechs and services muddled along between these two extremes.

The macro and political landscape this quarter – with a flip-flopping Fed, a superpower tariff tiff, a zig-zagging 10-year, and a wall-induced shutdown showdown – did not create an environment ripe for positive returns. Most of the weakness in equities can be attributed to poor communication by the Federal Open Market Committee Chairman Jerome Powell. His contradictory and confusing statements increased monetary-policy uncertainty and amplified the concerns of an already jittery market. That said, the weakness in healthcare, and most especially, biotech and emerging markets was extreme.

| INDEX | CLOSE 12/31/2018 | RETURN | | | | | ANNUALIZED VOLATILITY | |
|---|---|---|---|---|---|---|---|---|
| | | 1 MONTH | 3 MONTH | 6 MONTH | 9 MONTH | 12 MONTH | 30 DAY | 90 DAY |
| MSCI World Index (all country) | 223.0 | -7.0% | -12.8% | -9.0% | -8.5% | -9.4% | 18% | 15% |
| MSC World Index | 5412.1 | -7.6% | -13.4% | -9.1% | -7.5% | -8.7% | 19% | 15% |
| MSCI World Healthcare Index | 309.2 | -8.1% | -9.4% | 1.0% | 3.8% | 2.5% | 20% | 16% |
| MSCI World Pharma | 216.0 | -7.6% | -6.4% | 4.5% | 4.2% | 1.6% | 17% | 14% |
| MSCI World Biotech | 1356.4 | -6.1% | -11.3% | -3.1% | -1.5% | -4.3% | 25% | 22% |
| MSCI World Equip and Supplies | 502.7 | -5.8% | -11.8% | -2.2% | 5.5% | 9.5% | 26% | 21% |
| MSCI World Healthcare Prov & Serv | 602.0 | -12.6% | -11.4% | -1.1% | 5.8% | 2.6% | 27% | 21% |
| MSCI Emerging Market Healthcare | 510.8 | -7.8% | -16.2% | -22.2% | -26.4% | -20.9% | 24% | 24% |
| MSCI Emerging Markets | 445.4 | -2.7% | -7.5% | -8.5% | -15.7% | -14.6% | 16% | 18% |

As bottom-up, fundamentals-driven stock pickers, what we are hearing from companies makes moves like this quarters' hard to explain. For example:

**The number of new drug approvals soared to 59 this year, a 20-year high. And among these approvals, one can find three revolutionary treatments for migraine sufferers, a drug that normalizes diets for pheynketanuria sufferers, and numerous drugs improving the plight of cancer patients.**

**The net price inflation of drugs fell to CPI, making continued fretting about drug-price increases inexplicable.**

**The CFO of a managed-care giant foresaw a 13-16% bottom line CAGR between now and 2028.**

**Mitral-heart disease patients, who have few treatment options, learned that a relatively new device reduces their disease mortality and hospitalizations rates by about 50%. For context, mitral-disease prevalence is 3.5 times larger than the multi-billion-dollar aortic-disease market.**

**A company is revolutionizing healthcare delivery by linking physicians directly to patients through apps and phones, reducing healthcare delivery costs dramatically.**

**Most biotechs are well capitalized, the result of a healthy multi-year funding environment.**

**Pharma companies have solid balance sheets, low leverage, strong cashflow generation and pipelines, and have seen earnings expectations rise.**

So, if sector fundamentals are not rotten, maybe the explanation for this quarter's rout lies with previously stretched valuations? The bookends in healthcare valuation are medtechs and biotechs. We have repeatedly highlighted that medtechs, at about 22x ntm P/E, trade at historic 10-year highs. That fact makes their almost -12% fall – an approximately in-line performance for the quarter – and the continuation of a mid-to-high single-digit premium difficult to understand, especially considering that the least expensive industry (biotech at 12.8x ntm PE, 10 points below medtech's P/E) was down about 25% over the same period. Multiples have been falling in biotech since the summer of 2015. Compared with the world, biotechs started and finished the quarter trading at just under a 1pnt discount; compared with healthcare, their discount remained flat. Thus, a coherent over-valuation argument is difficult to make when the most expensive industry (medtech, by almost 10 points,) outperformed the cheapest one (biotech) in the fourth quarter's market rout.

As we speculate about the causes of last quarter's perplexing healthcare weakness, a more important question remains: what are the best opportunities for 2019 and beyond? Despite a constructive macro backdrop in the US, with low risks of a recession in 2019/20, equity markets are nervous. The longevity of the current cycle, alongside a slowing US economy with fading fiscal stimulus and ongoing US/China trade concerns, is clouding the earnings outlook for 2019 and elevating recession fears. Powell's inconsistency may further erode his and the FOMC's credibility, and, in the process, risks turning the market's recession fears into a self-fulfilling prophecy. Uncertainty is likely to keep volatility elevated and financial conditions tight in the near term. That said, we continue to expect the central bank to err on the side of caution and pause for the first half of 2019. If so, we should see a modestly weaker USD, a steeper yield curve, and a loosening in financial conditions, which ultimately would favor cyclicals and small- and mid-caps over large. We also expect a more constructive backdrop for emerging markets in 2019, in which this sector outperforms developed markets. Emerging-market valuations are sitting close to 15-year lows and at a significant discount to developed markets; coupled with premium EPS earnings growth over developed markets, the risk of outperformance for emerging markets is to the upside. Trade concerns are a wild card and pose particularly negative headwinds to China. However, with recent news suggesting incremental progress and both Trump and Xi under pressure for an interim resolution,

trade risks are skewed to the downside. Looking to capture expected cyclical tailwinds, we favor exposure to China, where macro support and favorable healthcare sector dynamics, including new drug launches, increasing demand for innovative drugs, and higher discretionary incomes, should see healthcare bounce back strongly.

From a healthcare perspective, the most promising outlooks are for biotech, emerging-market healthcare, and disruptive-healthcare services, while the outlook for the other industries is less clear. Although we may sound like a broken record with our repeated caution for medtech, despite the sector's decent fundamentals, our reserve stems from two important facts: valuations remain near 10-year highs at 22x ntm P/E, and the regulatory environment is currently being revisited in the US, possibly creating disruption. Finally, the most interesting 2019 opportunities seem to lie largely in the diabetes and heart-valve spaces. Pharma's defensiveness this quarter sent this group of companies from a discount to the broad markets in the summer of 2018 (14.5x for pharma and 15.5x for the world ntm P/E) to a premium today, with the broad market's multiple sinking to 13.2x ntm, while pharma's remained largely flat. Years of bad corporate behaviour, especially in drug pricing, is being corrected (involuntarily and voluntarily) and creating more thoughtful corporate practices. At the same time, US government efforts to improve competitive drug dynamics (ie, President Trump's Drug Price Blueprint) will continue. The key R&D questions for 2019 are whether Bristol-Myers can recapture some of the immune-oncology opportunity lost to Merck in 2018 (irrespective of their planned acquisition of Celgene), and the ultimate clinical profiles of new drug classes in non-opioid pain management and oral diabetes, as well as for some novel treatments in rare diseases. Traditional healthcare-service companies, such as managed care, hospitals, and CROs, face external pressures and headwinds in 2019, making forecasting more complicated today. These difficulties include the recent Texas summary judgement invalidating Obamacare, the "Medicare for All" versus "Medicare for None" political debate, late-cycle worries for commercially oriented insurance companies, Amazon's post-Pillpack plans, and concerns regarding the execution of vertical-integration plans.

Unlike medtechs, pharmas and services, biotechs and emerging-market healthcare stocks suffered tremendously in the recent rout. Biotech innovation, as seen in its pipelines, approvals, and new-treatment modalities, remains robust. Most biotech companies are decently capitalized, and investors have continued to demonstrate a willingness to fund promising innovation, as is evidenced by Q4 raises of USD1.7bn in IPOs and USD2.3bn in secondaries, despite continually declining stock prices. In addition to a robust regulatory pipeline for 2019, we will learn the clinical profiles of novel therapeutic approaches to NASH (a liver disease), hepatitis B, achondroplasia, MTAP (a common mutation in cancer cells), and many other conditions. Positive clinical and regulatory catalysts and continued industry consolidation (in the context of attractive valuations) suggest biotech is well-positioned for a recovery, even if the timing is difficult to predict. In emerging-market healthcare, the biggest opportunity is with China's ongoing transformation to a science and innovation-based healthcare market. This quarter's governmental attacks on adjuvant drugs and new insurance quotas on non-drug items (eg, nutraceuticals and cosmeceuticals) reinforce efforts in insurance and regulatory reform; both will support the transition to innovative science-based drugs. In 2019, this transition will continue to gain steam through NRDL and centralized-tender expansions, the commercial roll-out of innovative domestic drugs, and, following 2018's teething troubles, an expansion of Hong Kong's nascent biotech IPO pipeline. Note that 10 companies already have filed and more than 20 have indicated an interest in following suit. Finally, improving corporate outcomes and efficiency in US healthcare-service delivery are certainly 'on the right side of history' and are well positioned. Giants such as Amazon, Google, and Berkshire-Hathaway have gotten some credit from grand pronouncements of top-down healthcare disruption, but a growing number of small and mid-cap companies are already transforming the sector from the

bottom up. The interesting investment opportunities certainly lie more with the latter than the former group of companies.

| GROWTH P.A. 2019-2021E | | | | | |
|---|---|---|---|---|---|
| | SALES | EPS | PE19E | EV/SALES18E | COGS |
| MSCI World Pharma | 6% | 10% | 15x | 4.0x | 26% |
| MSCI World Biotech | 7% | 12% | 14x | 5.4x | 16% |
| MSCI World Equip and Supplies | 6% | 12% | 22x | 4.2x | 38% |
| MSCI World Healthcare Providers | 4% | 9% | 13x | 0.5x | 81% |

Although the short-term outlook for healthcare is muddied by a number of macro uncertainties, the medium to long-term forecast certainly favors biotechs, emerging markets, and innovative services. Most pressing among the macro concerns is the timing of the next recession, which is overdue mathematically, if not economically, based on the average duration of recoveries. Its arrival in 2019, 2020, or beyond will adversely affect the more cyclically exposed segments of healthcare, such as parts of medtech and services, while supporting the more defensive sectors, among them pharmas and, on occasion, large-cap biotechs. Beyond the timing of this macroeconomic event, this quarter's sell off has provided a decent entry-point for medium- to long-term healthcare investors, particularly in biotech, emerging-market healthcare, and innovative-services names.

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## SOURCES

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# IS THE OPTIMISM ON IMMUNE THERAPIES JUSTIFIED?

After decades of basic research, the concept of harnessing the immune system to fight tumors has gained huge momentum in recent years. The impressive therapeutic benefits of antibodies that inhibit so-called immune checkpoints, which normally restrict the duration and extent of immune responses, has revolutionized the treatment of many forms of cancer. Particularly high response rates have been observed in Hodgkin's lymphoma, and in some patients with advanced metastatic melanoma, this strategy has resulted in durable responses over many years, suggesting that these patients may be cured. Two pioneers of this breakthrough in cancer therapy, which has been likened to "unleashing the breaks of the immune system," were recently awarded the 2018 Nobel Prize. These clinical successes are reflected in the US Food and Drug Administration's (FDA) approval of multiple immunotherapies for a broad range of cancer indications, a list that is likely to grow in the near future.

| TUMOUR TYPE | THERAPEUTIC AGENT | FDA APPROVAL DATE |
|---|---|---|
| Melanoma | Ipilimumab | 2011 |
| Melanoma | Nivolumab | 2014 |
| Melanoma | Pembrolizumab | 2014 |
| Non-small cell lung cancer | Nivolumab | 2015 |
| Non-small cell lung cancer | Pembrolizumab | 2015 |
| Melanoma (BRAF wild-type) | Ipilimumab + nivolumab | 2015 |
| Melanoma (adjuvant) | Ipilimumab | 2015 |
| Renal cell carcinoma | Nivolumab | 2015 |
| Hodgkin lymphoma | Nivolumab | 2016 |
| Urothelial carcinoma | Atezolizumab | 2016 |
| Head and neck squamous cell carcinoma | Nivolumab | 2016 |
| Head and neck squamous cell carcinoma | Pembrolizumab | 2016 |
| Melanoma (any BRAF status) | Ipilimumab + nivolumab | 2016 |
| Non-Small cell lung cancer | Atezolizumab | 2016 |
| Hodgkin lymphoma | Pembrolizumab | 2017 |
| Merkel Cell carcinoma | Avelumab | 2017 |
| Urothelial carcinoma | Avelumab | 2017 |
| Urothelial carcinoma | Durvalumab | 2017 |
| Urothelial carcinoma | Nivolumab | 2017 |
| Urothelial carcinoma | Pembrolizumab | 2017 |
| MSI-High or MMR-deficient metastatic colorectal cancer | Pembrolizumab | 2017 |
| Pediatric melanoma | Ipilimumab | 2017 |
| Hepatocellular carcinoma | Nivolumab | 2017 |
| Gastric and gastroesophageal carcinoma | Pembrolizumab | 2017 |
| Non-small cell lung cancer | Durvalumab | 2018 |
| Renal cell carcinoma | Ipilimumab + nivolumab | 2018 |

Figure 1. Summary of the tumor types for which immune checkpoint blockade therapies are FDA-approved [1]

Although the therapeutic benefit of checkpoint inhibitors has been observed across a number of tumor types, the rate of durable responses remains low and is often limited to small subsets of patients. The table below illustrates some of the drastically different response rates to the same agents:

| GROUP | INDICATION | OBJECTIVE RESPONSE RATE (%) | AGENTS APPROVED |
|---|---|---|---|
| High response rate | Hodgkin's Disease | 87 | Nivolumab<br>pembrolizumab |
| | Desmoplastic melanoma | 70 | Nivolumab<br>Pembrolizumab |
| | Merkel cell | 56 | Avelumab<br>Pembrolizumab |
| | MSI-h cancers | 53 | Nivolumab<br>Pembrolizumab |
| Intermediate response rate | Skin melanoma | 35 to 40 | Nivolumab<br>Pembrolizumab |
| | NSCLC | 20 | Atezolizumab<br>Nivolumab<br>Pembrolizumab |
| | Head and neck | 15 | Nivolumab<br>Pembrolizumab |
| | Gastroesophageal | 15 | Pembrolizumab |
| | Bladder and urinary tract | 15 | Atezolizumab<br>Avelumab<br>Durvalumab<br>Nivolumab<br>Pembrolizumab |
| | Renal cell carcinoma | 25 | Nivolumab<br>Pembrolizumab |
| | Hepatocellular carcinoma | 20 | Nivolumab |

*Alphabetical order

Figure 2. Major indications approved for the use of anti-PD-1 and anti-PD-L1 and associated response rate [2]

It is beyond the scope of this commentary to review the wide-ranging research efforts and ongoing trials aimed at extending the rate and duration of anti-tumoral immune responses. Still, it is interesting to note that among the approximately 3,000 immuno-oncology agents in

development, which were reported in a comprehensive survey conducted by the Cancer Research Institute [3], the global research effort is actually focused on only five main therapeutic strategies.

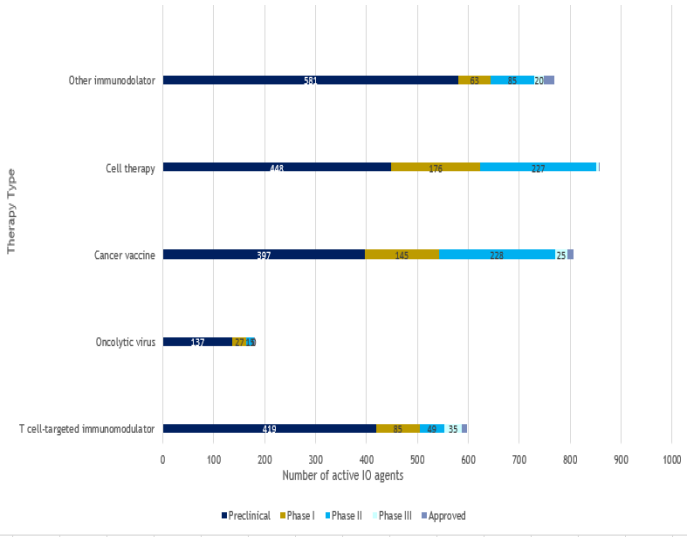


**Figure 3. Trends in the global immune-oncology (IO) pipeline as of September 2018 [3]. Chart created based on "Trends in the Global Immuno-oncology Landscape," *Nature Reviews Drug Discovery***

It is also clear that big pharma still dominates the clinical space, as the top 8 clinical pipelines belong to major pharmaceutical companies. [3]

The remainder of this article will cover some of the basic concepts in immunotherapy to illuminate the challenges that lie ahead.

A key question regarding anti-tumoral immune response relates to immune recognition. The mammalian immune system has evolved to recognize antigens, molecular motifs on proteins, that do not occur in the host. The purpose is to distinguish between "self" and "non-self." This principle, which lies at the core of how the immune system works, allows the body to combat foreign intruders, such as infectious agents (most notably viruses), while remaining tolerant of "self" and thereby avoiding self-destructive autoimmunity.

Tumors develop from host tissues and are therefore derived from the "self," raising the question as to what the immune system recognizes in patients whose tumors respond to checkpoint inhibitors. With the advent of large-scale DNA sequencing and comprehensive genomic profiling of large tumor-tissue collections, it became apparent that tumors can generate up to several hundred random mutations, in addition to the few, well-established genetic alterations that drive their progression. These mutations, which result from the genomic instability that is characteristic of many tumors, or as a consequence of tissue exposure to mutagens (e.g., UV light or tobacco smoke), may translate into aberrant proteins that are sufficiently different from their normal counterparts to be recognized as "non-self," or antigenic. In order to activate T lymphocytes, the main effector cells in an anti-tumoral immune response, tumor-derived antigens, similar to other antigens, need to be presented to the immune system, obeying its restrictive rules. Mounting evidence suggests that effective anti-tumoral immune responses are indeed directed at these neo-antigens [4]. However, the likelihood that a mutation becomes translated and appropriately processed to effectively activate T cells is low, as is suggested by the observation that, even in patients who mount durable anti-tumoral responses, this action seems directed at only a select few neo-antigens. This fact explains in part why such limited immune responses may become effective once amplified by checkpoint-inhibitor therapy.

Another critical point is tumor heterogeneity, which is driven by several mechanisms that generate a tumor mass composed of cells with vastly divergent properties, despite their having originated in a single tumor-initiating cell. One of these divergent properties is antigenicity, which may vary enormously among cells in the same tumor mass. Thus, one obvious shortcoming of current therapies aimed at stimulating anti-tumor immune responses is that they may be only partially

curative against antigens already present in the tumor-initiating cell. Among the main reasons why tumors escape immune attack are the lack of tumor-cell antigenicity and the capacity of tumor cells to turn off or mask antigen expression. Furthermore, tumors may elicit inflammatory reactions in the surrounding tissue that suppress the immune response.

A number of personalized strategies are currently being explored to improve immune recognition of tumor neo-antigens. For instance, samples from biopsies or surgery can be sequenced to comprehensively identify all mutations in a tumor. Using algorithms predictive of antigenicity and their appropriate presentation to the immune system, mutations that are more likely to elicit an immune response are selected. Then, peptides that contain several such potential neo-antigens are synthetically assembled to generate tumor vaccines. A conceptually interesting strategy is to make use of so-called oncolytic viruses, or viruses that have been engineered to preferentially replicate in, and kill, tumor cells. So far, only one oncolytic virus has been approved as a therapy, but numerous trials are underway to assess the extent to which virally mediated release of numerous cellular proteins, including potential tumor antigens, may initiate an anti-tumoral immune response (see the summary on Turnstone Biologics below).

Other approaches now in development aim at identifying immune-suppressive mechanisms that may provide therapeutic targets beyond the known immune checkpoints. Potential targets include other immunoregulatory molecules involved in T-cell activation and inactivation, as well as in signaling pathways and cellular components of the tumor microenvironment.

Whereas the concept of directing and enhancing immune responses against tumor neo-antigens is rationally appealing and clinically validated, it remains unclear how many patients actually respond to these treatments. So far, the best responses to checkpoint inhibitors have been observed in patients with tumors bearing relatively large numbers of mutations generated through exposure to mutagens such as those that induce skin and lung cancer (i.e. those having a high tumor-mutation burden). Nevertheless, it appears to be a matter of chance whether a randomly generated tumor mutation has the right attributes to be recognized by the host's immune system. In many cases, tumors may bear mutations that are simply not antigenic or capable of activating T cells and are therefore unresponsive to checkpoint inhibitors and other measures that enhance immune responses.

As might be anticipated, "releasing the breaks on the immune system" causes side effects, as immune cells attack normal tissues. Thus, as only a subset of patients responds to checkpoint inhibitors, it has become a priority to identify markers that predict response; doing so will enable clinicians to select only those patients with a high likelihood of response, preventing non-responders from receiving ineffective treatment and suffering severe side effects.

A conceptually different strategy directs the immune response towards tumor-associated antigens that are preferentially expressed in tumors but are typically non-mutated. Numerous trials are underway aiming at eliciting an immune response against such "self-antigens" using vaccination strategies, which aim to break immune tolerance. The clinical outcome has been disappointing thus far, but these approaches may benefit from the increasingly detailed understanding of immune recognition and become more promising, for example, when combined with checkpoint inhibitors.

Another series of alternative approaches makes use of engineered components of the immune system to incite a patient's own immune system to fight a tumor. In this scenario, tumor-associated self-antigens preferentially expressed in tumors may be targeted by antibodies raised specifically against such antigens. Such antibodies can be loaded with a toxin, which is then selectively enriched at the tumor site. Or, instead of adding a toxin, antibodies can be modified to target both the tumor antigen and host T cells that are activated upon contact with tumor cells. A third strategy to recruit the host's T cells to the

tumor tissue consists of fusing the antigen-binding portion of antibodies directed against tumor-associated antigens with receptors on T cells, thereby generating chimeric antigen receptors (CAR T-cells). These several strategies have already yielded approved drugs that have shown remarkable efficacy in some tumors that are notoriously difficult to treat, notably certain blood cancers. However, several challenges remain to be addressed to improve their efficacy against a broader range of tumors. Among them is the difficulty of enhancing the penetration of T cells into solid tumors. A major limitation is the relatively limited number of candidate antigens that are tumor-selective enough to avoid causing unwanted side effects.

The therapeutic effect of these various strategies, as well their limitations, has prompted substantial research in this field, leading to increasingly detailed knowledge of the complex relationship between tumors and the immune system. There is great hope that this knowledge can be translated into new treatments offering significant therapeutic benefit. Most major pharmaceutical companies have been trying to grab a piece of the immuno-oncology market, often by developing not very innovative "me-too" drugs. The extraordinary number of ongoing trials combining current and next-generation immune modulators with established cancer therapies, which, to be honest, are based on anecdotally validated rationales, shows that expectations to extend the effects of immunotherapies to larger patient populations are extremely high. To this date, however, the newer approaches have not equaled the potency of the anti-PD-1/PD-L1 and anti-CTLA-4 checkpoint inhibitors already available.

The present hype should not distract investors from the challenge common to most anti-tumor strategies: how to target differences between tumors and normal tissue. These differences, which allow tumors to anarchically escape the stringent rules of tissue building and renewal, and instead adopt Darwinist behavior, are typically subtle and difficult to target without causing unacceptable damage to normal tissue. The jury is still out regarding the ultimate clinical benefit of the wealth of ongoing immune-oncology research and clinical trials. It is unclear whether these novel approaches will prove superior to the current checkpoint inhibitors in enhancing the proportion of tumors that are effectively fought by the immune system. The lack of sufficiently potent antigens may prove a bridge too far for immune-modulators to cross.

When looking at investment opportunities in the IO space, in addition to the usual due diligence, a few specific questions are particularly important to consider. First, how supportive is the biology of synergies between newer agents and already approved IO drugs? As described above, companies often only rely on small datasets of animal and early clinical results before embarking on full pivotal clinical programs. Without a clear understanding of the interplay between the different pathways involved, the chance of success in humans is greatly reduced. Secondly, how satisfying is the company's strategy to account for the likely differential efficacy within a specific tumor subtype? As with other cancer therapies, understanding which subgroup of patients derive the most benefit is a major challenge in IO trials. Working with the appropriate efficacy endpoints and the right biomarker characteristics contribute to increasing the likelihood of success. Lastly, is there a good rational for activity in solid tumors? Incremental improvement in IO approaches in liquid tumors is foreseeable and desirable, but the largest untapped market is definitively in solid tumors where IO agents' results have been less inspiring.

## ILLUSTRATIVE CASE STUDY # 1: TURNSTONE BIOLOGICS (PRIVATE)

One emerging class of immune-oncology tools that offers a multimodal approach to target and destroy malignant cells makes use of oncolytic viruses. In principle, the mode of action of the oncolytic immunotherapies is simple. Upon infection with a virus selected for preferentially replicating in tumor cells, these molecules

get lysed, releasing virus particles that can spread further, as well as potential tumor antigens. The local inflammation caused by cell lysis provides conditions for exposing a vast array of potential tumor antigens to the immune system, operating as a patient-specific cancer vaccine.

Amgen's (NASDAQ: AMGN) IMLYGIC® is the only oncolytic virus now approved for advanced melanoma. And since its approval by the FDA, there has been a surge of development; in fact more than twenty-five different oncolytic virus are now in the pipeline. Moreover, large pharmas have been active with acquisitions and partnership in the sector, including Merck's (NYSE: MRK) acquisition of Viralytics (ASX: VLA) for USD394m; BMS' (NYSE: BMY) partnership with Psioxus (Private) for USD50m upfront and as much as USD886m in milestones; Janssen Biotech/JnJ's (NYSE: JNJ) acquisition of Benevir (Private) for USD140m and up to USD900m in milestones. Part of the excitement is justified by the widespread opinion that the IMLYGIC® approval, while a great achievement for the oncolytic virus field, left technological space for improvement. Ongoing research aims at engineering next-generation oncolytic viruses from the vast repertoire of viruses capable of infecting human cells. These newer viruses display improved tumor-lysis capacity and specificity, and can serve as cargos for genes capable of stimulating the immune response.

While scrutinizing the emerging competitive landscape, our attention was drawn to Turnstone Biologics (Private). In 2017, the company secured a global collaboration with AbbVie (NYSE: ABBV). The agreement gives AbbVie an exclusive option to license up to three of Turnstone's next-generation oncolytic viral immunotherapies. Financial terms were undisclosed. Turnstone' robust pipeline of early-stage investigational therapies, based on its Maraba (MG1) oncolytic-virus platform, are in development for solid tumors. Of note, Turnstone' founders screened hundreds of viruses before discovering that Maraba, a single-stranded RNA virus isolated from sand flies found in Brazil's Maraba region, was an optimal platform for cancer therapeutics. Maraba was engineered to MG1 to optimize its safety, selectivity, and potency, and a transgene capacity was added for targeted expression of tumor-associated antigens and immunomodulatory agents, according to the company website. It also is relatively easy to engineer and manufacture. We like the fact that MG1 is combining its oncolytic properties with an antigen-specific, cancer-vaccine potential. Based on this dual-mechanism and its favorable properties (safe, engineerable, large, and amenable for intravenous administration), we see Turnstone among the leaders in the next wave of oncolytic viruses. It may even top the field.

*Note that Sectoral led the Series-C financing of Turnstone in January 2019.*

## ILLUSTRATIVE CASE STUDY # 2: NEKTAR THERAPEUTICS (NASDAQ: NKTR)

As highlighted above, the large number of ongoing trials combining anticancer immunotherapy agents to increase the proportion of patients who benefit is based upon rationales that often lack vigorous validation. In this context, revisiting the biology of "older" immunotherapy approaches makes sense. This strategy also has the potential to mitigate risk. The renewed interest in long-established therapies is well illustrated by recent findings surrounding interleukin-2 (IL-2).

Before the identification of IL-2 in 1976, it was virtually impossible to culture lymphocytic cells outside the body. The discovery of IL-2's ability to grow T cells and sustain their functional activity represented a breakthrough that was rapidly translated to the clinic. In 1984, IL-2 became the first effective immunotherapy for human cancer, when it was administered to a 33-year-old woman with metastatic melanoma who had progressed despite multiple prior treatments. Within one month after treatment, a biopsy of one of her tumors showed extensive necrosis; after two months, all tumor sites were shrinking, and a few months, later there was no evidence of residual cancer. This patient has remained disease-free for the past 29 years [5]. This remarkable

success provided strong support for the concept of tumor immunotherapy and made IL-2 a key player as the approach moved into the mainstream of cancer treatment: the FDA approved IL-2 for the treatment of advanced renal-cell carcinoma in 1992 and metastatic melanoma in 1998. However, to be effective IL-2 must be given at doses that can cause severe adverse events; it also has a treatment-related mortality rate of 2-4% [6]. The conjunction between the low response rate and the emergence of newer immune-oncology agents has led to a reduction in the use of high-dose IL-2 [6].

With NKTR-214, Nektar Therapeutics (NASDAQ: NKTR) has been able to increase the half-life and biological activity of IL-2 by coupling polyethylene glycol (PEG) at critical sites, thereby directing the activity of this pegylated IL-2 to tumor-killing T cells. In animal models, NKTR-214 resulted in increased anti-tumor activity with a more tolerable safety profile. Likewise, Phase I data demonstrated safety and antitumor activity. However, this new formulation of IL-2 does not address the low response rate observed with previous IL-2 regimens. Based on the different mechanisms of action of checkpoint inhibitors, which enhance T cell activation, and IL-2, which stimulates T cell growth, Nektar set out to explore the potential synergy of combining the two approaches [7]. The initial results, which were presented at the 2017 Society for Immunotherapy of Cancer (SITC) annual meeting, reported both safety and efficacy data for patients with metastatic melanoma. Among the 11 evaluable patients, NKTR-214 plus nivolumab (an anti-PD-1 drug from BMS) led to an impressive response rate of 63% versus 40% for nivolumab alone. These results boosted Nektar's share price by almost 500%. Since then, the company has been providing updated data with more patients and, disappointingly, a reduced response rate. At this point, the jury is out on the value of combining a safer and potentially more efficacious IL-2 with established immune therapies. Answers are expected from the pivotal Phase III trial in treatment-naïve metastatic melanoma, which has started enrollment. Initial results should be released by mid-2020. As the Nektar case demonstrates, it is imperative to design immune-oncology trials based on validated rationales supporting synergistic effects.

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## APPENDIX

## TUMOR INITIATION AND PROGRESSION

Tumors emerge from a single cell that has undergone genetic damage, resulting in **DNA mutations** that may give rise to anomalies in proteins, which are critical for normal cell functions. Cell functions that become deregulated in tumors demonstrate uncontrolled **cell growth** and the propensity to invade normal tissue, forming metastases through dissemination to distant organs. The prognosis of tumors is primarily determined by the occurrence of **metastases**.

## THE ADAPTIVE IMMUNE SYSTEM

**Antibodies** are typically produced by the immune system to neutralize the action and propagation of infectious agents, such as viruses. The immune system remembers a first encounter with a virus and mounts a more rapid and stronger response to subsequent encounters with the same agent (**immunological memory**); this principle underlies the rationale for **vaccination**. Antibodies are typically Y-shaped molecules, with two identical binding sites at each tip of the Y, which selectively recognize a molecule, a so-called **antigen**, for example, a component of a virus.

Together with antibodies, **T-lymphocytes** form the key components of the **adaptive immune system**, which is critical for recognizing, neutralizing, and clearing pathogens. Whereas antibodies recognize antigens in the extracellular space, T-cells recognize antigens typically derived from intracellular proteins that are transported to the cell surface as complexes, with molecules specialized in antigen presentation and that follow restrictive rules. A key feature of the adaptive immune system is its ability to distinguish between the host's **"self-"**and **foreign "non-self" antigens**, thereby avoiding auto-immune responses against host tissues.

Tumors may elicit immune responses against **neo-antigens** derived from proteins that are altered as a consequence of DNA mutations. These neo-antigens may be recognized as "foreign," compared with their normal "self"-counterparts. Tumors may also express non-mutated "self" antigens, which are virtually absent from normal tissue. Numerous vaccination strategies that aim at prompting an immune response against such **tumor-associated antigens** are currently being explored**.**

In addition to self/non-self discrimination, immune responses are normally tightly regulated with regard to their extent and duration. Thus, once an antigen is recognized, T-cells become **effector cells** capable of killing these antigen-expressing target cells, such as virus-infected normal cells or neo-antigen expressing tumor cells. In the course of an immune response, effector T-cells start expressing **checkpoint molecules** (e.g., **PD-1)**, which upon their binding with cognate ligand **PD-L1,** trigger their inactivation. PD-L1 is normally expressed during chronic inflammation to prevent auto-immune damage to normal tissue. Tumors may also express PD-L1 and thereby suppress immune responses. Inhibition of such suppression by **immune-checkpoint inhibitors** has led to durable anti-tumoral immune responses in a number of cancer types (see main text).

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Sectoral Asset Management was founded in 2000 and is exclusively focused on managing global healthcare portfolios. Sectoral continuously aims to achieve superior returns for our investors by concentrating on primary research. Sectoral has one of the world's longest track records in managing biotech equities and is a sub-advisor of numerous healthcare and biotech funds offered by partners in Europe and Asia. The firm is employee owned and registered with the SEC, AMF, FINMA and the SFC.

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