WESTFIELD
CAPITAL MANAGEMENT

April 2019

Cancer Can Be Beaten:
Oncology's New Age

Yet the enchainment of past and future
Woven in the weakness of the changing body,
Protects mankind from heaven and damnation
Which flesh cannot endure.
-T. S. Eliot, Four Quartets

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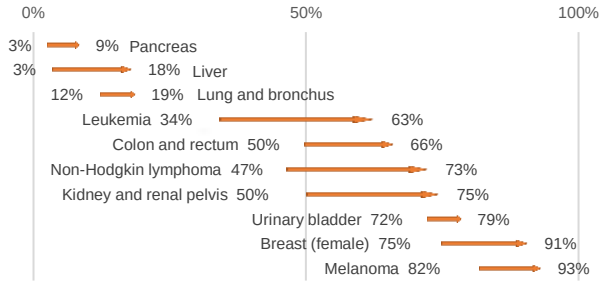
Oncology's New Age

Half of men and one third of women will get cancer in their lifetime, the dreaded disease that has shadowed humankind for all of its recorded history and was first referenced three thousand years ago in the time of the pharaohs. Few will be untouched by the sorrow of the "creeping ulcer" and the ancient, existential fear it engenders. And yet there is hope. Substantial progress in the fight against cancer has been made over the last forty years in the form of longer overall survival. In fact, average five-year survival rates for the ten most common tumors rose 16% over that period (fig. 1), but a tipping point may be at hand as a number of key scientific advances converge.

Figure 1: Change in cancer survival rates over the past ~40 years
Average five-year survival rates for the most common cancer sites for the years 1975-77 and 2006-12.



Source: Journal of the National Cancer Institute, Five Prime Therapeutics, Inc., 2019

Targeted Therapies

Prior to 1997, cancer treatment was largely limited to the time-worn treatment methods of surgery, radiation, and chemotherapy. These rather primitive approaches amount to cutting, burning, or poisoning tumors and patients often suffer debilitating side-effects.

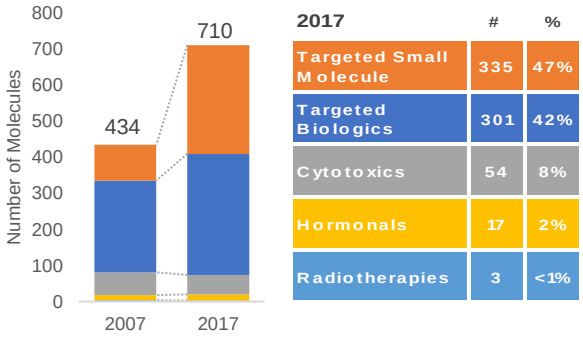
While the older methods still play a central role in many treatment plans today, the 1997 approval of Rituxan for the treatment of Non-Hodgkin's Lymphoma marked the beginning of the era of targeted therapies, so-called because these drugs more accurately target tumor tissue while sparing healthy tissue, ultimately improving patient outcomes.

These targeted therapies fall into two broad categories:

1. Targeted small-molecule drugs taken orally in pill form that modify biochemical pathways gone awry due to cancer-causing genetic mutations, and;
2. Targeted biologics delivered intravenously. While biologics are sometimes used to modify those same biochemical pathways through different means, they are often directed toward modifying the immune system in ways that enable it to kill cancer cells, commonly called "immuno-oncology".

The pharmaceutical industry has validated the notion of an inflection in the promise of the science by dramatically accelerating investment in oncology drug development, with almost all the incremental investment over the last 10 years falling into these two targeted therapy categories as shown in figure 2.

Figure 2: The pipeline of new medicines in late phase development rose over 60% since 2007 with incremental growth coming from targeted small molecules and biologics.
Pipeline of Late Phase Oncology Molecules, 2007 - 2017



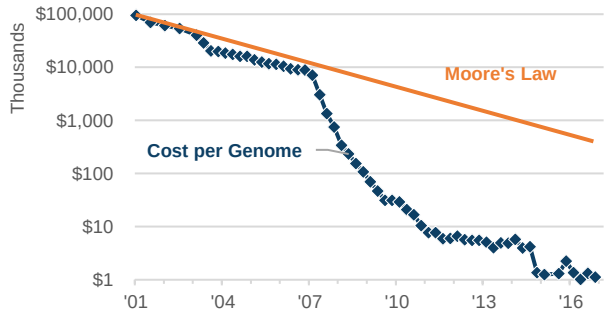
Source: IQVIA, ARK R&D Intelligence, December 2017; IQVIA Institute, March 2018

A brief history of each targeted therapy follows, highlighting that the tempo of innovation has accelerated meaningfully for both categories in recent years, and perhaps more importantly, that the two may converge in the future to bring us closer to a cure for cancer.

Targeted Small Molecules

The dramatic drop in the cost of sequencing the human genome as a result of Next Generation Sequencing (NGS) (fig. 3) has fueled targeted small molecule development in two important ways.

Figure 3: Cost per Genome



Source: National Human Genome Research Institute, March 2019

First, the reduction in time and cost to sequence the genome using NGS made it possible to examine the myriad variations between tens of thousands of cancer patients and healthy individuals, as well as compare the diseased and healthy tissue within cancer patients. Very rare mutations can be discovered, patterns of mutations discerned, and important insights into how tumors become resistant to treatment through constant mutation garnered, providing a vital roadmap to drug makers.

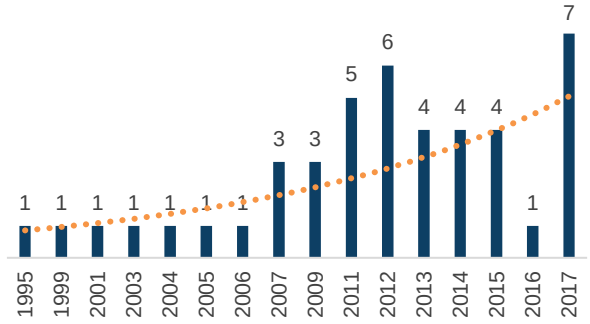
Second, by defining cancer patient populations based on genetic mutations, drugs to address those mutations can be tested in clinical trials on only those patients most likely to respond. Smaller clinical trials showing larger efficacy advantages resulting from testing the right patient populations are much faster and cheaper than conventional trials using unselected patients.

The November 2018 FDA approval of Vitrakvi was a milestone in this regard, as it was the first cancer drug approved to treat a specific cancer mutation rather than a specific tumor type such as lung or breast cancer. For those with the mutation, the efficacy of the drug was so pronounced that it was approved only two years after beginning human trials, cutting development time by more than half.

Lung cancer provides perhaps the best example of the refinement of our understanding of using distinct treatments within distinct patient populations. Non-small cell lung cancer (NSCLC) comprises about 80% of U.S. lung cancers and is among the most prevalent and deadliest tumors. As recently as twenty-five years ago, only three sub-types of NSCLC had been identified and all were treated with some combination of surgery, radiation, or chemotherapy. Fast forward to today and there are ten identified NSCLC mutations with almost forty drugs approved or in clinical development to treat these specific mutations.

Faster and cheaper trials combined with a new trove of NGS-derived raw data has accelerated the pace of innovation in targeted small molecules as clearly evidenced by the number of approved molecules shown in Figure 4. While half a dozen targeted small molecules were approved in the decade from 1995 to 2004, almost forty have been approved in the subsequent thirteen years with seven in 2017 alone.

Figure 4: Number of Approved Targeted Small Molecules



Source: Westfield, March 2019

Given the heightened level of R&D investment and the increasing frequency of drug approvals, the pace of innovation for targeted small molecules can only be expected to increase.

Targeted Biologics: Immuno-oncology

In 1796, English physician Edward Jenner inoculated his gardener's eight-year-old son with pus scraped from cowpox blisters on a milkmaid's hand. The boy was subsequently found to be immune to smallpox, the dreaded "Red Death" which gruesomely killed 10% of the population in Jenner's time. This invention of the vaccine, the word itself derived from the Latin *vacca*, or "cow", is the foundation of the science of immunology.

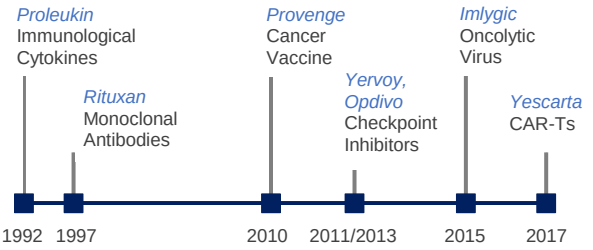
About a century later in 1891, William Coley observed that skin cancer patients who contracted a common skin infection sometimes saw complete resolution of their cancer. He tested his hypothesis by injecting bacteria into a cancer patient to induce that same infection and the patient's tumor disappeared. With that, immuno-oncology was born. Coley's methods subsequently fell into disrepute, and with the rise of radiation and chemotherapy, all but disappeared from use. It would take yet another century for Coley's central biologic principal to resurface in 2007 when the underlying mechanism of Coley's method, a TLR agonist, was tested in clinical trials. Ultimately, the phase 3 trials failed, but the nature of that failure is key to understanding the great advances soon to come. In hindsight, we now know that while Coley was

conceptually correct, our understanding of the biology at the time was insufficient to stimulate the immune system with enough specificity to elicit an immune response powerful enough to kill tumors.

All of that changed with the 2011 FDA approval of Yervoy and the 2013 approval of Opdivo, both of which are based on an idea that is almost the opposite of Coley's original insight. Rather than stimulating the immune system to fight cancer, these drugs counteract biological signals that dampen the immune response to tumors. This clever inversion of Coley's idea became possible as we began to understand immune system function at a molecular level, enabling the kind of specific intervention required to turn the immune system against tumors.

This increased understanding of the complexity of the immune system has resulted in rapid advancement of new immuno-oncology therapeutic applications. Consider below the tempo of landmark approvals for various immuno-oncology modalities.

Figure 5: FDA Approvals of New Immuno-oncology Modalities



Source: Westfield, March 2019

However, the initial approvals of many of these therapeutic applications demonstrated subpar risk-benefits such that their impact on clinical practice has been extremely limited. The notable exceptions are the checkpoint inhibitors Opdivo and Keytruda, which have radically altered clinical practice and become mega-blockbusters in a few short years. In short, checkpoint inhibitors unleash the power of the immune system to attack cancer cells by removing their disguise as healthy cells.

As was the case with targeted small molecules, NGS is beginning to transform immune-oncology drug development. While 2017 marked the first approval of an immuno-oncology agent based upon a genetic mutation, current clinical trials are testing a biomarker called TMB (tumor mutational burden) which tallies the number of mutations in a given tumor's genetic code, seeking to exploit the observation that highly mutated tumors such as melanoma and lung respond best to immuno-therapy.

This stratification of patient populations using genetic markers is ushering in an era when a majority of drugs might be approved for genetically-defined populations. A hallmark of these drugs is their unprecedented efficacy in these precisely-defined patient pools, and furthering immuno-oncology patient selection using NGS is one of the most promising horizons of the science.

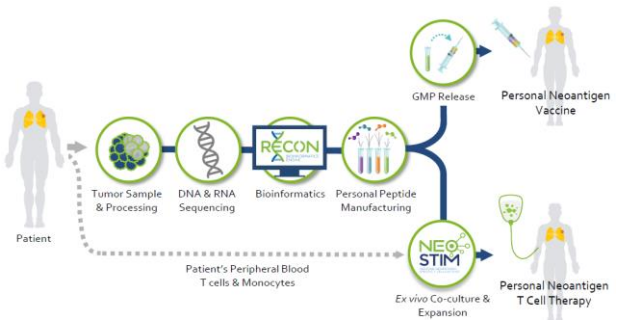
Putting It All Together: Neo-antigens

Thus NGS is advancing oncology drug development in two important ways: selecting patients based upon a tumor's genetic makeup and developing drugs that can target that genetic makeup. By taking such patient selection and tumor targeting to its logical extreme, the most highly selected patient "population" is a single individual and the most precisely targeted drug would key to the unique genetic code of that individual's tumor.

The immune system targets specific cells for elimination by homing in on beacons on the cell's surface. These beacons are called antigens and the genetic code of the cell contained in its DNA dictates the structure of these antigens. When cells in the body are dividing, their DNA must be copied over to the new cell. Copying errors are sometimes made giving rise to alterations in the genetic code which are called mutations. Thus these mutations can result in correlative changes to the antigens on the cell's surface, resulting in new antigens, or "neoantigens". The key here is that these mutations and thus these neoantigens occur randomly in each patient's tumor as that tumor grows such that no two patterns of neoantigens will be alike.

Following this line of reasoning, we begin to see for the first time the outlines of what might one day become a cure for cancer. As a patient's tumor mutates, its genetic makeup becomes as individualized as the patient, a kind of genetic "fingerprint" for that tumor. These neoantigens can then be used to either genetically engineer lymphocytes, the immune system cells which attack tumors, to target that tumor with exquisite specificity, or to make a "cancer vaccine" which will stimulate the patient's own immune system to attack that tumor with that same exquisite specificity. This is the realization of Coley's nineteenth-century vision which has been made possible by the dramatic advances in both immunology and genetics (fig. 6).

Figure 6: Personal neoantigen therapies



Source: Neon Therapeutics, 2018

In the same way that the vast amounts of genetic information provided by cheap NGS technology both

informs the design of chemical molecules and segments the patient population for the targeted therapy pills described earlier, that same information can be used to design immune-oncology agents. However, there is a crucial distinction that might one day allow immune-oncology agents to transcend anything that has come before: the genetic information can actually be incorporated into the structure of the drug itself, resulting in treatments where NGS is integral to manufacturing the drug rather than simply being a part of its early development in the lab.

In this application of NGS, a patient's tumor is biopsied and its genetic code is sequenced to determine mutations specific to that tumor. T-cells can then be genetically engineered to target the neoantigens caused by those specific mutations. Only by making the cost of sequencing a single human genome one hundred thousand times cheaper than it was twenty years ago is such a radical advance in the treatment of cancer even conceivable. Furthermore, methods for engineering and growing T-cells can be cumbersome, producing mixtures of incorrectly engineered T-cells that must be extensively purified, putting a practical limit on the degree to which the T-cells can be altered. These methods may soon be superseded by more precise genomic editing of a single cell that can be modified in almost innumerable ways to optimize it for targeting and killing tumors, perfect copies of which can then be grown using pluripotent stem cells that will require no further purification. Marshalling these technologies to target an individual patient's pattern of neoantigens represents a compelling new hope in the fight against cancer.

Looking Ahead

Our genetic code is quite literally what makes each individual unique, and mutations in that code result in a similarly unique expression of disease. However, with scientific advancement, treatments could become as distinct as the individual and the illness. There will come a time in the not too distant future where one of the first steps in cancer diagnosis will be genetic sequencing of a patient's tumor looking for genetic vulnerabilities that might be exploited. A little further still one can imagine identification of antigens unique to an individual patient, which can then be used to precisely genetically engineer immune cells that will home directly to the tumor and kill it.

Recently, the combination of the targeted pill Inlyta and the immune-oncology agent Keytuda demonstrated efficacy profound enough to become the new standard of care in advanced renal cancer. This almost brings us full circle in that a targeted pill designed in the lab to exploit genetic data derived from NGS is paired with an immune-oncology agent underpinned by our understanding of immune system function at the molecular level. Closing the circle may be at hand as those advances in immunology are deployed with lethal efficiency in the form of living cells targeted using that same NGS data. While drug development is inherently long-term in nature, even the near-term looks promising as a wave of important clinical data is expected over the next few years. As a result, we may be on the threshold of dramatic improvements in overall survival for many tumor types.

These developments coincide with demographic changes which will only accelerate the need for these innovative cancer therapeutics. Age is a significant risk factor for cancer and the aging of the global population will result in growth of cancer incidence well in excess of population growth. This combination of groundbreaking medical developments and a growing patient population creates a compelling backdrop for investment. That said, the expectations are as high as the science is promising. The skillful investor must navigate both the science and the hope around it to accurately assess value in this arena.