AstraZeneca's Bold and Potentially Risky New Cancer Drug R&D Portfolio Strategy

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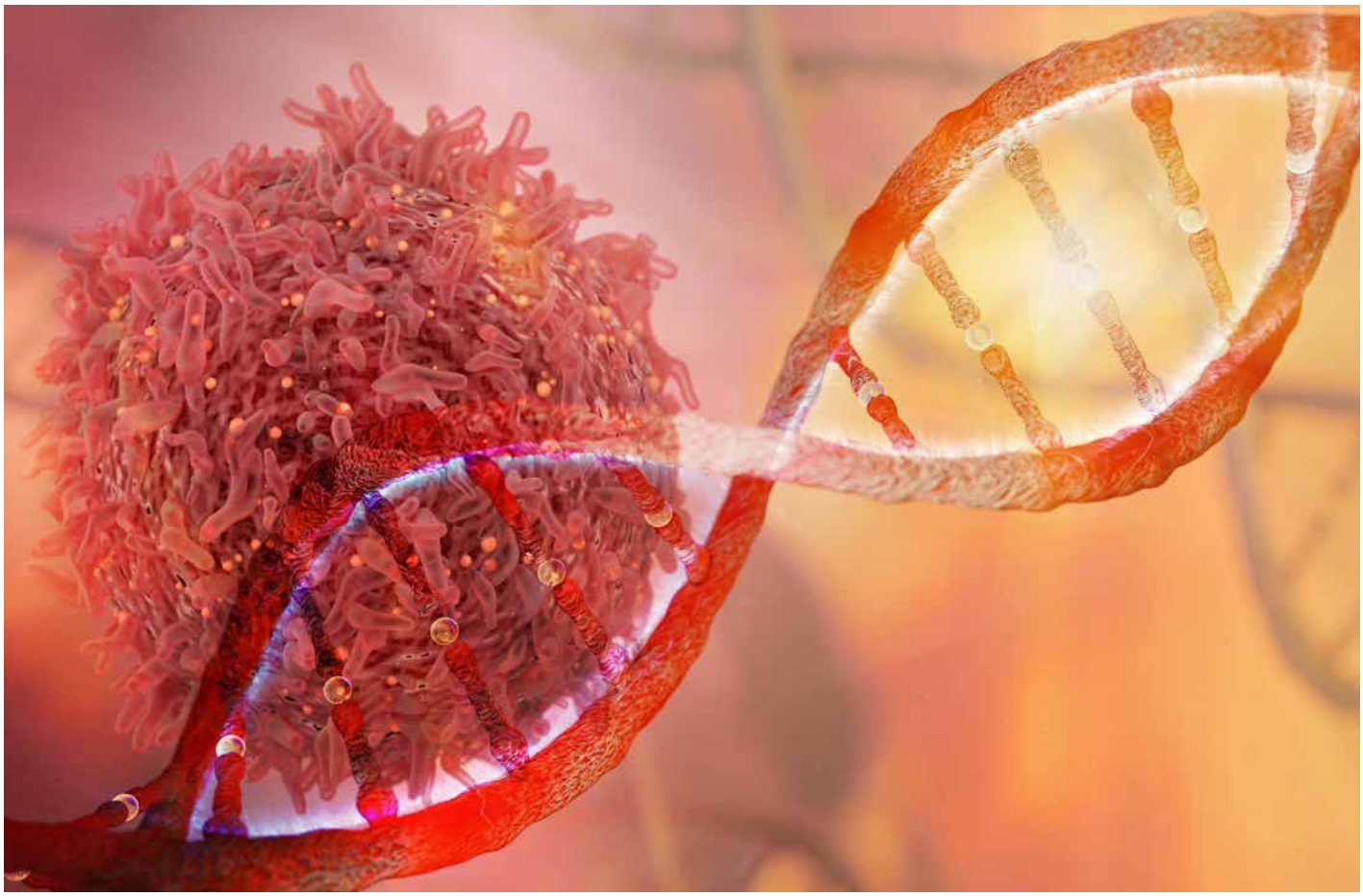
> Medicine is a science of uncertainty and an art of probability.
>
> ***Sir William Osler***
> *A Canadian physician, one of the four founding professors of Johns Hopkins Hospital, and frequently described as the Father of Modern Medicine*

1. AstraZeneca's Risky New Cancer Drug R&D Portfolio Strategy

The Wall Street Journal recently ran an interesting article about AstraZeneca (AZ) testing a bold new cancer drug R&D portfolio strategy.[1] AstraZeneca's new cancer research chief, Jose Baselga, wants the company to focus on *early-stage* cancers over *late-stage* (advanced) cancers for new drug development.[1] This shift in focus goes against the standard target development paradigm where companies focus on drugs for late-stage cancers where patients and their oncologists have exhausted all available treatment options.[1] The evidence from 34 new cancer drugs for solid tumors supports this current development approach as since 2014, 32 were for late-stage cancers and only two have targeted early-stage cancers.[1]

This approach can certainly reap substantial rewards for AZ by differentiating itself from the increasingly crowded field of companies in the cancer space IF AZ is able to deliver on this bold strategy.[2] That is a big IF as noted by industry insiders. Analysts note skepticism whether AZ can overcome a number of significant hurdles as listed below and noted in the *WSJ* article:[1]

1. The case for testing and patients taking new drugs for late-stage advanced cancers is clear where no further options exist. It is less clear for early-stage cancers where other alternatives may be available.
2. The analytics of measuring the value of new drugs for advanced cancers is also straightforward, such as additional survival time, often in months. This is not the case with early-stage cancers.
3. Patients are more willing to try and oncologists more willing to offer their patients new experimental drugs for advanced cancers. This is not the case with early-stage cancers where proven treatments that "cure" may already exist.
4. Regulators have also made it easier for treatments that can show additional survival time for patients through slowing the tumor growth of advanced cancers. This accommodating regulatory framework does not exist with early-stage cancers.
5. There are often clear-cut existing remedies when a cancer tumor is caught early, such as a mix of surgery, chemotherapy, and radiation.
6. The previous point means a very high bar for any new drug targeting an early-stage cancer, such as proving that the drug significantly lowers the odds of the tumor coming back. This is a difficult clinical endpoint to demonstrate.
7. Point 5. Also means that an early-stage new cancer drug for all intents and purposes would have to truly "cure" patients, while currently, the majority of drugs are designed to delay cancer growth.
8. The running of clinical trials and recruiting patients may be more difficult in testing early-stage cancer drugs. Why would patients try an experimental drug for an early-stage cancer if well-known and trusted treatments that can cure already exist? The counterpoint to this argument is that the patient pool may be larger.
9. There is also an empirical hurdle to measure drug effectiveness. It may take years to determine whether a new drug for an early-stage cancer actually produces extended survival, or the tumor did not return, thus making for very long (and thus expensive) clinical trials.



2. Will AstraZeneca's New Cancer Drug R&D Portfolio Strategy Succeed?

Time is needed to determine whether the new R&D cancer AZ strategy will succeed. **Table 1** shows AZ being a major player in an increasingly crowded and competitive oncology space. While AZ is shifting its focus to early-stage cancers, they are still keeping programs involved in the development of late-stage cancer drugs.[1]

Table 1: Top 10 Pharmaceutical Companies Based on Global Oncology Revenue in 2017 and 2024

Company	2017 $billion	2024* $billion
Roche	27.5	27.8
Celgene	11.6	18.6
Bristol-Myers Squibb	8.5	14.7
Johnson & Johnson	6.2	14.3
AstraZeneca	4.0	13.7
Merck	4.1	13.2
Novartis	7.9	9.7
AbbVie	3.1	8.5
Astellas Pharma	2.8	5.8

Source: Statista, The Statistics Portal, published online June 2018, available at https://www.statista.com/statistics/309705/oncology-revenue-by-top-ten-pharmaceutical-companies-worldwide/.[3] Notes: BMS and Celgene announced a merger in January 2019[4] and *: 2024 represents a projected figure as calculated by the source reference.[3]

Further, **Tables 2** and **3** illustrate the medical needs for developing new cancer drugs based on the number of annual new cases and deaths by site. So, the success of this new strategy can reap substantial rewards by beating the competition that is primarily focused on drugs to treat late-stage cancers.

Table 2: Leading Sites of New Cases, 2019 Estimates by Gender

Male New Cases			Female New Cases		
Prostate	174,650	20%	Breast	268,600	30%
Lung & bronchus	116,440	13%	Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%	Colon & rectum	67,100	7%
Urinary bladder	61,700	7%	Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%	Melanoma of the skin	39,260	5%
Kidney & renal pelvis	44,120	5%	Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%	Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%	Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%	Pancreas	26,830	3%
Pancreas	29,940	3%	Leukemia	25,860	3%
All sites	**870,970**		**All sites**	**891,480**	

Source: American Cancer Society, Inc., 2019. Surveillance Research, available at https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/leading-sites-of-new-cancer-cases-and-deaths-2019-estimates.pdf.[5] Percentages represent a fraction of all new cancer cases.

Table 3: Leading Sites of New Cancer Deaths, 2019 Estimates by Gender

Male			Female		
Lung & bronchus	76,550	24%	Lung & bronchus	66,020	23%
Prostate	31,620	10%	Breast	41,760	15%
Colon & rectum	27,640	9%	Colon & rectum	23,380	8%
Pancreas	23,800	7%	Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%	Ovary	13,980	5%
Leukemia	13,150	4%	Uterine corpus	12,160	4%
Esophagus	13,020	4%	Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%	Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%	Brain & other nervous system	7,850	3%
All sites	**321,670**		**All sites**	**285,210**	

Source: American Cancer Society, Inc., 2019. Surveillance Research, available at https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/leading-sites-of-new-cancer-cases-and-deaths-2019-estimates.pdf.[5] Percentages represent a fraction of all new cancer deaths.

Finally, the market opportunity is huge for the oncology therapy class based on US non-discounted spending. US spending on oncology drugs comprised $58.4BN (12.1%) in 2018 on a base of total non-discounted spending of $482.0BN.[6] Only the antidiabetics therapy class was greater in non-discounted spending for 2018 at $60.6BN (12.6%).[6] Thus, the preceding information demonstrates a clear medical need and financial opportunity to win big if the new R&D portfolio strategy succeeds. But what is the likelihood of success?

Recent data on the clinical development success rates for investigational drugs for the period 2003-2011 shows productivity rates are even lower than previous estimates.[7]

A comprehensive analysis of 'Phase Success' rates and the 'Likelihood of Approval' (LOA) for all oncology indications show very challenging productivity rates under the current paradigm approach.[7] The definitions of 'Phase Success' and LOA as provided by the authors are quoted below from their article:[7]

> "'Phase Success' is calculated as the number of drugs that moved from one phase to the next phase divided by the sum of the number of drugs that progressed to the next phase and the number of drugs that were suspended. The n value associated with the Phase Success represents the number of drugs that have advanced plus the number of drugs that have been suspended, which we label as phase transitions.
>
> LOA denotes the probability of reaching FDA approval from the current phase, and is also expressed as a percentage. LOA is calculated as the product of each Phase Success probability leading to FDA approval. The n value associated with LOA is the sum of the n values for each Phase Success included in the LOA calculation."

The trend showing very challenging productivity rates under the current paradigm approach holds across all indications and lead indications, oncology subgroups and cancer types, and FDA Special Protocol Assessment (SPA) or orphan drug designation.[7] Selected clinical development of Phase LOA for oncology are provided in **Table 4**. The Phase LOA for the top 3 leading sites for cancer by number of new cases and deaths by gender have also been provided. The Phase LOA using the new AZ approach would likely be even lower given the many R&D challenges noted earlier. The reader should go to the original source article and view Phase Success rates to see how increasingly challenging clinical development success has become under the current paradigm.

Table 4. Selected Clinical Development Phase LOA for Oncology Investigational Drugs

	Phase 1 LOA	Phase 2 LOA	Phase 3 LOA
Oncology – All indications	6.7%	10.5%	37.0%
Oncology – Lead indications	13.2%	19.1%	45.3%
Oncology – All indications by FDA classification	10.4%	16.2%	50.0%
Breast cancer	5.7%	8.4%	39.2%
Non-small cell lung cancer (NSCLC)	5.7%	6.5%	21.7%
Prostate cancer	5.6%	7.8%	37.5%
Colorectal cancer (CRC)	5.1%	8.2%	38.5%
SPA or orphan drug oncology	23.0%	27.1%	44.4%

Notes: See the source reference for the methodology to derive each selected clinical development Phase LOA. LOA means "Likelihood of Approval" and SPA means "Special Protocol Assessment."[7]
Source: Hay M, Thomas D, Craighead J, et al. Clinical development success rates for investigational drugs. *Nature Biotechnology* 2014; 32: 40-51.

3. What Should Pharma Companies Do When Faced with a Similar Situation?

The preceding analysis of oncology investigational drug success rates and the challenges of focusing on early-stage cancers leads one to ask an obvious question - how did AZ make this decision and/or what data did they collect that led them to believe a shift in portfolio strategy would be worth the cost and risk? Further, there is greater pricing pressure and payer resistance building in the healthcare system in response to the higher cost of new gene-therapy and immuno-oncology treatments. These higher drug costs will raise the bar on clinical outcomes necessary to improve cost-effectiveness and reach traditional threshold measures such as quality-adjusted life-years (QALYs) to justify adoption. This will further drive down the clinical development success rates of oncology investigational drugs, over and beyond what has been reported, by focusing on early-stage cancers.

Given the above-noted challenges, the author of this article asked two of his colleagues, both longtime experienced principals in the pharma industry, on their take of the decision by AZ and provide other thoughts.

David Wood, Ph.D., Senior Principal, Axtria

> "It seems to me that the AZ decision has many risks (which both the preceding analysis in this paper and the *WSJ* have summarized), and one big upside (much bigger markets to sell into) if this decision is successful. This is a high-risk gamble.
>
> Maybe another way to think about this decision is to try to answer the following question: What would AZ have to know (or believe) for this path to make sense? A few possibilities come to mind:
>
> 1. AZ has a super-promising molecule is in their pipeline (a "cure", or maybe just a "slam-dunk low-development risk" product).
> 2. AZ is anticipating significant regulatory changes? And if so, what are those changes?
> 3. AZ has a belief that new cancer incidence rates will increase, making 1st line therapy even more valuable?"

Randy Risser, Principal, Axtria

> "While we do not know at this time if the move by AZ will be a successful business strategy decision, I think it should be applauded and supported. This is a bold move – when pharma manufacturers have tended to adopt similar strategies (think blockbusters in the 1990s, line extensions in 2000s, and recent moves to oncology, specialty medicines, and orphan drugs for rare diseases). This decision has the potential to open up new lines of research, new approaches to treatment, new paths for approval of therapies – all of which can be good for innovation in the industry and good for patients. What if we can start to think, at the extreme, about prophylactic treatments that prevent cancer in broad patient populations, rather than late stage interventions that work for a limited set of patients and extend life by a few months?
>
> Also, one thing that stood out to me in the preceding analysis in this article was the estimate of global oncology revenue in 2024 for the top 10 manufacturers. This projection suggests a 70% increase in oncology revenue over the period until 2024! If this projection is true, this rise in revenue will put tremendous pressures on healthcare systems, payers, and patients while causing real affordability issues.
>
> Lastly, I recommend that Axtria thinks about how we can apply our analytics capabilities to help companies like AZ in making these bold decisions succeed. How can real-world evidence (RWE) be used to demonstrate the health economic value of early-stage interventions, and where there may be big opportunities and unmet needs? For example, can it be shown show how neo-adjuvant therapy for breast cancer patients (with the aim to shrink the tumor prior to resection) increases the success rate of surgery and results in improvement in patient outcomes with lower cost of care? Axtria can use analytics to size the opportunity of having better treatment options in this setting, along with broader adoption of these treatments."

Axtria can also help clients to develop empirical simulation models that can demonstrate variations in the likelihood of success based on changes in a set of predetermined salient factors based on prior research experience of not only individual investigational projects but also on the oncology clinical portfolio maximization problem. Axtria has the skillset and expertise in analytics and platforms needed to provide clients with needed dynamic insights to improve R&D portfolio decision-making. Axtria also has the intellectual talent to address any problems that have not been solved in the past.

Many pharma companies are shifting their clinical portfolio focus to oncology drugs as the opportunities diminish elsewhere.[2] Factors causing this shift to oncology drugs include but are not limited to the following trends affecting the pharma industry:

1. increased generic/biosimilar competition.
2. declining number of economically viable small molecule targets.
3. improvements in scientific advancements leading to novel drug treatments (especially on orphan drugs for rare diseases).
4. the continued existence of significant unmet medical needs that can be addressed by new drug treatments.
5. failure of companies in certain therapy areas to find effective treatments (e.g., Alzheimer's disease), thus looking to put those research dollars elsewhere.

Pharma companies need to make critically important well-informed analytically-supported clinical project portfolio optimization decisions. Axtria is available to work with pharma companies in the early-stages of these business decisions, while also leveraging our sales and marketing capabilities and experience as a proportion of those projects become drugs and thus will require commercialization expertise for a successful launch and beyond.

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