Atezolizumab and the PD-L1 Immune Checkpoint

Two Student Team

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Introduction

Immune checkpoints are essential for regulating our immune systems. However, in many cancers, the immune checkpoint is stimulated in a way that allows cancers to protect themselves against attack. This mechanism allows cancers to manifest and eventually spread, making it extremely difficult to surgically remove tumors from the human body. Oncology has progressed tremendously over the course of the 21st century, with more treatments becoming available for patients with various forms of metastatic cancer. Many of these metastatic cancers require inhibition at immune checkpoints in order to prevent them from growing. Between March 2011 and August 2018, the United States Food and Drug Administration (FDA) has approved many checkpoint inhibitors for these patients, with eligibility increasing from 1.54% in 2011 to 43.63% in 2018, as well as patients responding to treatment also increasing [1]. This improvement is attributed to immunotherapies such as Atezolizumab, which is used to treat certain urinary, breast, skin, lung, and liver cancers.

Bladder Cancer, Previous Treatments, and the "Game Changer"

Bladder cancer is a common form of cancer that is estimated to affect 83,730 people and lead to 17,200 deaths in the United States in 2021. Bladder cancer occurs more often in men than it does in women, and is the fourth most common form of cancer in men [2]. Some of the risk factors that can cause bladder cancer include smoking, exposure to certain chemicals, and having a family history of bladder cancer. Smoking, in particular, is the most apparent risk factor because the cancer causing chemicals from tobacco enter the bloodstream and are filtered through the kidneys and transferred to the bladder in order to be removed from the

body. This causes cancer to develop on the bladder's inner lining, which is known as urothelial carcinoma. A few signs for bladder cancer include blood in the urine, or hematuria, a feeling of urgency to urinate, frequent urination, fatigue, flank pain, and decreased appetite and weight. Bladder cancer can be detected through urine cytology, imaging of the urinary tract, or genetic analysis [3].

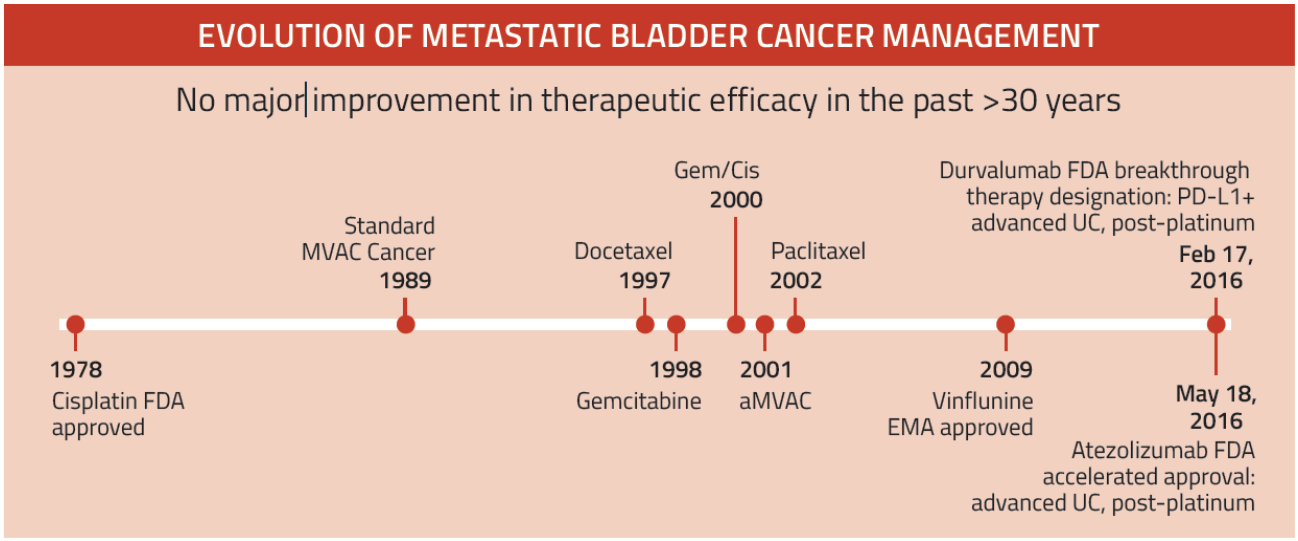


Figure 1: A timeline of the evolution of metastatic bladder cancer management over 30 yrs [4].

In 1978, Bristol-Myers Squibb's Cisplatin was approved by the FDA to treat metastatic bladder cancer, and has been one of the standard treatments for bladder cancer. During the late 1980s, a chemotherapy combination of methotrexate, vinblastine sulfate, adriamycin, and cisplatin, or MVAC, was used to treat advanced urothelial bladder cancer by destroying quickly dividing cancer cells. Using these medications has been shown to delay recurrence of bladder cancer after surgical removal of the tumor and extend life expectancy. Overtime, the development of treatment options for metastatic bladder cancer has shifted to more promising immunotherapies, such as the usage of Programmed Death-Ligand 1 (PD-L1) [5].

PD-L1 is an immune checkpoint protein that is expressed on the surface of tumor cells and PD-1 on tumor infiltrating cells. PD-1 and B7.1, both of which are proteins found on T lymphocytes, or T-cells, are part of the body's immune system. PD-L1 binds to PD-1 or B7.1, which downregulates antitumor T-cell function and protects cancer cells from an immune response. Atezolizumab, which is a humanized monoclonal antibody immune checkpoint inhibitor, binds to PD-L1 and prevents this interaction with PD-1 or B7.1 by inhibiting the inhibitory signals that the cancer cells project to the T-cell. This allows antitumor T-cells to effectively destroy cancer cells from proliferating [6, 7]. This immune checkpoint between PD-L1 and PD-1 is very common in many cancer forms. In order to diagnose these cancers, oncologists perform biopsies to test the cancer for PD-L1 expression before beginning treatment with immunotherapies such as Atezolizumab.

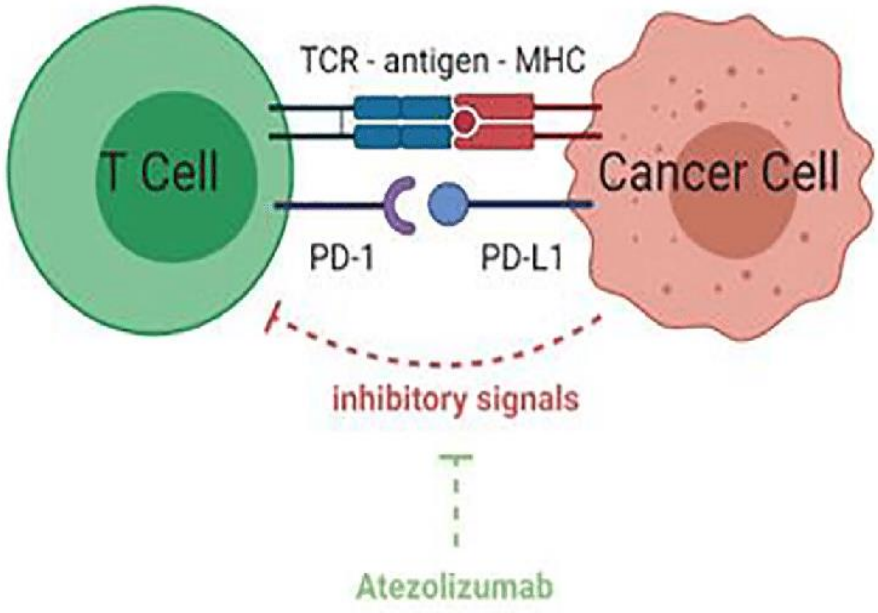
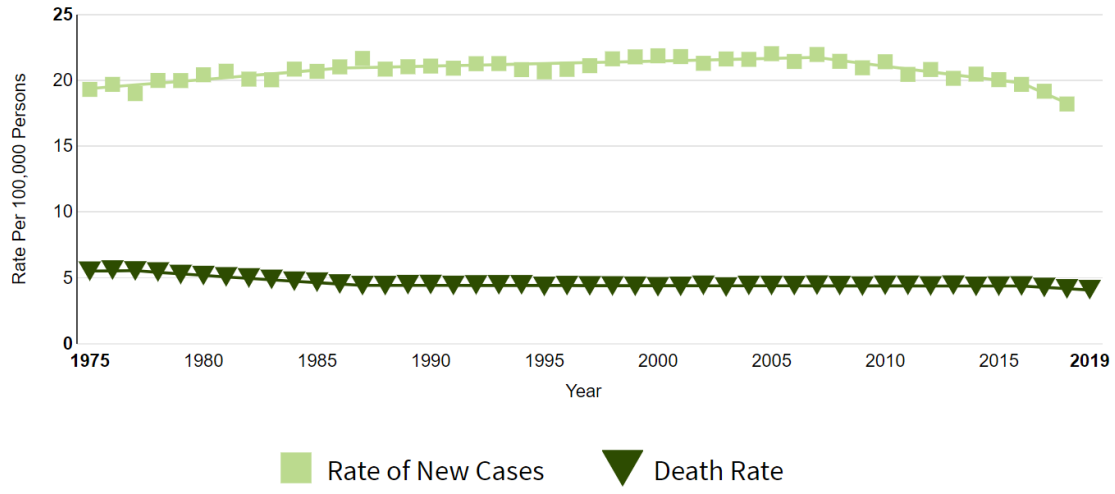


Figure 2: The mechanism that Atezolizumab uses involves inhibiting the inhibitory signal on T-cells that results from the binding of PD-L1 and PD-1 [7].

Tecentriq, which is the brand name for Atezolizumab, is the first FDA-approved PD-L1 inhibitor and a revolutionary innovation in the field of bladder cancer. It was approved to treat patients with locally advanced or metastatic urothelial carcinoma while or following chemotherapy [8]. The FDA coined Tecentriq as a "Game Changer" immunotherapy drug for bladder cancer because it is the first new treatment for this form of cancer in more than 20 years. The drug was given accelerated approval after its phase II trials because of its promising results and in order to help expedite the development of new drugs to benefit patients with serious or life-threatening conditions [3].



New cases come from SEER 9. Deaths come from U.S. Mortality.
All Races, Both Sexes. Rates are Age-Adjusted.
Modeled trend lines were calculated from the underlying rates using the Joinpoint Trend Analysis Software.

Figure 3: The graph shows a decrease in death rate after the release of new treatments [9].

Treatments for metastatic bladder cancer have affected the death rates over time. After 1978, when Cisplatin was approved by the FDA and used as a treatment, the death rate decreased from 5.4% in 1978 to 4.5% in 1989. The release of Tecentriq in 2016 and other immune checkpoint blockers decreased the death rate even more to 4.1% in 2019 [9]. This reveals how the innovative nature of the treatments for bladder cancer have improved chances of survival.

Clinical Trials, Patent Information, and Other Approvals

On May 18, 2016, Tecentriq became the first PD-L1 inhibitor approved by the FDA to treat metastatic urothelial carcinoma. The phase II clinical trial treated 310 patients with locally advanced or metastatic urothelial carcinoma. These patients were either treated or being treated with chemotherapy while receiving Atezolizumab. Scientists also analyzed the "positive" or "negative" expression of PD-L1 on patients' tumor-infiltrating immune cells, and found that Tecentriq had a greater tumor response on those who were classified as "positive" for PD-L1 expression. Specifically, the clinical trial showed the 12-month overall survival rate was 37% compared to 20% with past treatments; patients with higher levels of PD-L1 immune expression had an even greater benefit, as the 12-month overall survival was 50%. Additionally, the clinical trial showed that 14.8% of patients experienced some sort of tumor shrinkage, which lasted from 2.1 to more than 13.8 months [8]. This is shown in Figure 4 where the mean delay to see a response to Tecentriq was roughly 2 months but analysis was only done for patients that remained in the trial for at least 6 months. While it appears that overall response was good, only 27/119 (23%) patients reached statistical significance compared to baseline with

a 95% confidence interval [10]. The FDA also approved the Ventana PD-L1 assay, which detects PD-L1 expression levels in patients, in order to facilitate physicians' ability to treat patients with Tecentriq [4]. This highlights the advances in immunotherapy treatment for bladder cancer, and the effectiveness of checkpoint inhibitors in cancer.

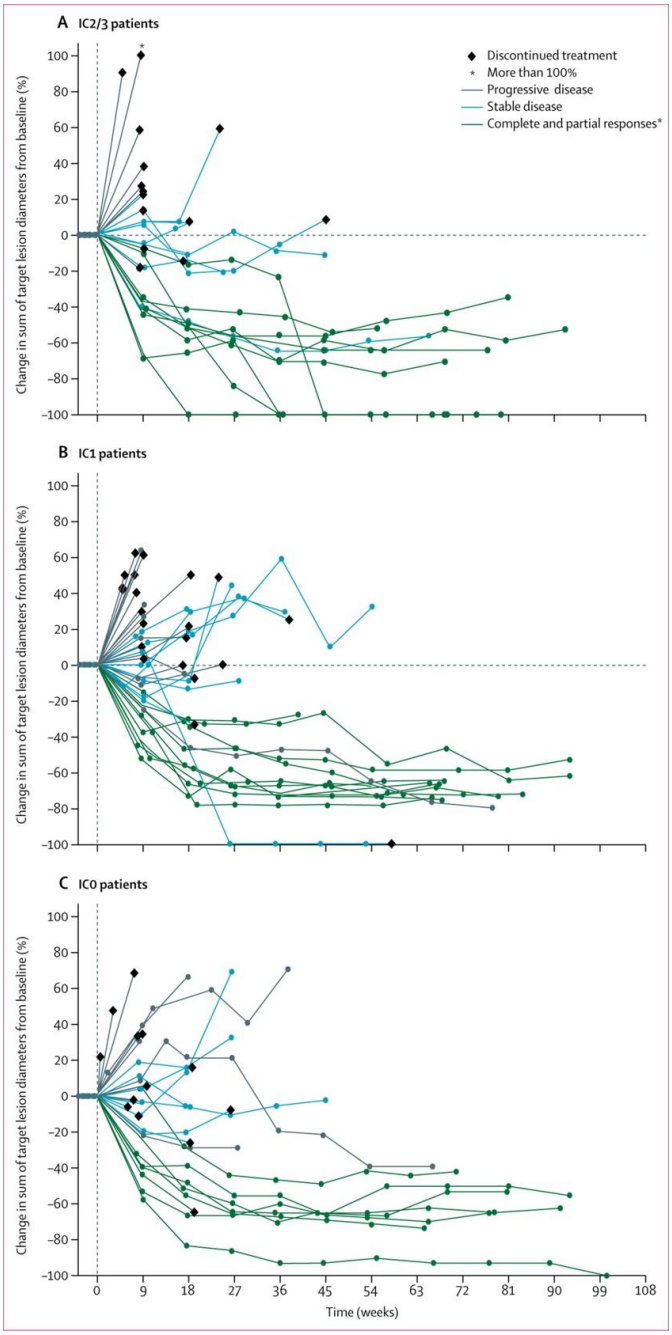


Figure 4: Patient response to Atezolizumab quantified by sum of change in target lesion diameter compared to baseline. Patients were split into subgroups by PD-L1 status on tumor-infiltrating immune cells (IC) Adapted from [10].

The development process of Tecentriq involved many patents, including one that patented PD-L1 antibodies and the methods of using it. The first patent was introduced in July 2014 and was officially published in January 2018. The expiration date for this patent is in March 2036. The amino acid sequence and antibody binding sites were a few aspects of the invention features described in the patent. Additionally, various methods of detecting PD-L1 expression levels, such as immunohistochemistry (IHC), flow cytometry, ELISA, or immunoblot, were listed as parts of the invention [11].

The current patent for Tecentriq is assigned to Ventana Medical Systems and Spring BioScience Corporation, subsidiaries of Roche. It was granted in 2020 and has and is expected to expire in 2036. Globally, the patent is active in Australia, China, and Russia with patents pending or in the process in Brazil, Canada, Mexico, Japan, the European Patent Office, Singapore, and South Africa [12].

Over the past five years, Tecentriq has also been given FDA approval for multiple different metastatic cancers, including non-small cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and advanced melanoma. This demonstrates how powerful the anti-PD-L1 drug is and the uprising implementation of immunology on cancer treatments [13].

Date	Article
Oct 15, 2021	Approval FDA Approves Genentech's Tecentriq as Adjuvant Treatment for Certain People With Early Non-Small Cell Lung Cancer
Mar 7, 2021	Genentech Provides Update on Tecentriq U.S. Indication in Prior-Platinum Treated Metastatic Bladder Cancer
Jul 30, 2020	Approval FDA Approves Genentech's Tecentriq plus Cotellic and Zelboraf for People With Advanced Melanoma
May 29, 2020	Approval FDA Approves Genentech's Tecentriq in Combination With Avastin for People With Hepatocellular Carcinoma
May 18, 2020	Approval FDA Approves Genentech's Tecentriq as a First-Line Monotherapy for Certain People With Metastatic Non-Small Cell Lung Cancer
Dec 3, 2019	Approval FDA Approves Genentech's Tecentriq Plus Chemotherapy (Abraxane and Carboplatin) for The Initial Treatment of Metastatic Non-Squamous Non-Small Cell Lung Cancer
Mar 18, 2019	Approval FDA Approves Genentech's Tecentriq in Combination With Chemotherapy for the Initial Treatment of Adults With Extensive-Stage Small Cell Lung Cancer
Mar 8, 2019	Approval FDA Grants Genentech's Tecentriq in Combination With Abraxane Accelerated Approval for People With PD-L1-Positive, Metastatic Triple-Negative Breast Cancer
Dec 6, 2018	Approval FDA Approves Genentech's Tecentriq in Combination With Avastin and Chemotherapy for the Initial Treatment of Metastatic Non-Squamous Non-Small Cell Lung Cancer
Apr 17, 2017	Approval FDA Grants Genentech's Tecentriq (atezolizumab) Accelerated Approval as Initial Treatment for Certain People with Advanced Bladder Cancer
Oct 18, 2016	Approval FDA Approves Genentech's Cancer Immunotherapy Tecentriq (Atezolizumab) for People with a Specific Type of Metastatic Lung Cancer
May 18, 2016	Approval FDA Approves Tecentriq (atezolizumab) for Urothelial Carcinoma

Figure 5: A detailed list of the different advanced cancers Tecentriq has been approved for after its first FDA approval in 2016 for urothelial carcinoma [13].

Figure 6: The stock prices of Roche have not drastically changed in accordance with the additional approvals for Tecentriq on various cancer forms [14].

Looking at the various approvals Tecentriq has acquired over the years against Roche's stock price, the stock price has had relatively negligible movements due to how large of a group Roche is. Genentech used to be publicly traded and that stock price would likely reflect news associated with Tecentriq; however, when Roche acquired them in 2009, their stock went private.

Pricing, Access to Treatment, and Insurance

MVAC, which was the traditional treatment used to treat bladder cancer, resulted in a 14% higher rate of complete remissions than the control groups [15]. However, MVAC administration came with other additional costs, including central line placements, ER visits, infusion visits, cardiac imaging, and hospitalization days, leading to a mean total cost per patient of $17,360 for this treatment [16].

The fixed cost for developing Tecentriq was convoluted with the rest of Roche's R&D budget, as the company reports its spendings in a total yearly figure; therefore, the specific cost to design Tecentriq across multiple years could not be extrapolated. Depending on the dosage schedule, Tecentriq has a sticker price of about $13,860 per month of treatment in the United States. Tecentriq is a Medicare part B drug and comes out to ~$74 per dose under that coverage with a total Medicare spending of $463 million in 2019; additionally, Genentech offers various financial support systems that can bring the price of copays as low as $5 and they even

offer free treatment to those who qualify. Eligibility requirements for Tecentriq include having commercial (private or non-governmental) insurance, not being a government beneficiary, at least 18 years old and a resident of the United States, must have a prescription for a Genentech Oncology product, and do not receive assistance from any co-pay assistance programs, including the Genentech Patient Foundation. Unfortunately, the Genentech oncology co-pay assistance program is limited to $25,000 per product per year which equates to $480.77 a week. In comparison to the weekly estimated cost of Tecentriq on a typical dodge schedule, this covers about 13.87% of the cost meaning most people would still require further financial assistance usually provided by insurance [17].

The UK information on cancer drugs is rather incomplete with the most recent figures report in 2017-18 reporting 100 patients were eligible for treatment with Tecentriq over a 5 month period. This number is difficult to extrapolate given the significant global adoption of checkpoint inhibitors in the years since. It is reported that average price in the UK is $7,270 per month of treatment but the UK's National Institute for Health and Care Excellence (NICE) did not deem it cost effective and thus was not recommended. In response, Roche offered the UK NHS an undisclosed discount that changed the decision [18].

Specifically looking at the dosage schedule for urothelial carcinoma, the schedules are 840mg intravenously every two weeks, 1200mg intravenously every three weeks, or 1680mg every four weeks. It can be seen that the dosages are equivalent to ~420 mg a week until disease progression or unacceptable toxicity. Tecentriq costs $6,930.06 per 840mg/14mL solution. This equates to Tecentriq costing $3,465.03 per week of treatment; however, most patients will pay reduced prices with insurance and other assistance programs [19].

Benefits and Side Effects

There are many benefits to taking Tecentriq over the traditional treatments, such as MVAC. Primarily, Atezolizumab is administered every three weeks as an IV drip at a given dose, whereas MVAC is given over the course of two days through a mixture of injections and drips [20]. Some of the advantages of Atezolizumab surprisingly favored those who had a low count of PD-L1 positive immune cells: these individuals experienced nausea and insomnia several months after the standard treatment group. Additionally, the study showed that compared to standard treatment, patients that took Atezolizumab experienced less inflammation of the mucous membranes, and not as severe constipation or febrile neutropenia. While these advantages were apparent, however, Atezolizumab did have some disadvantages compared to the traditional treatment. Because Atezolizumab used the body's immune system in order to help the T-cells attack the cancer cells, some patients experienced severe immune-mediated side effects. Moreover, some patients in this sample group experienced pneumonia, while no patients in the standard treatment group had difficulty with breathing. Both treatments caused very similar health-related issues, including exhaustion, body pain, a loss of appetite, and diarrhea [16, 20].

In the cost-benefit analysis done on Tecentriq for metastatic urothelial cancer, it was found that Tecentriq provided an additional 0.39 QALYs; while this may seem low, this treatment is for late stage cancer where that time is rather significant [22]. Another aspect that should be noted is that treatment with Tecentriq has less adverse events and a preserved quality of life compared to traditional treatment [23]. This results in an incremental cost of $170,759 per QALY compared with the placebo group and an incremental cost effectiveness

ratio (ICER) of $434,317 per QALY. With patients who have at least 5% expression of PD-L1 on their immune cells the ICER decreases to $325,236 per QALY [22]. Most of this cost is driven by the sticker price of Tecentriq but as noted, insurance and assistance programs are in place such that few patients are paying this much.

Policies and Ethical Concerns

One ethical concern that has arisen from Tecentriq is that the accelerated approvals for other cancer indications may be not well defined. Tecentriq was approved for PD-L1 positive breast cancer which also covered triple negative breast cancer, a cancer that is typically more aggressive and harder to treat. Tecentriq received the approval after the IMpassion130 study showed Tecentriq had notable improvement in progression free survival when paired with Abraxane however the follow up period was only one year and further studies were to be conducted in order to confirm its efficacy. In the follow up study IMpassion131 Tecentriq was paired with another chemotherapy drug Taxol and in this study there was no improvement in progression free survival [24]. For this reason Genetech voluntarily withdrew Tecentriq from breast cancer indications but only in the United States. This calls into question the ethics of accelerated approvals since if the IMpassion131 study was the study to acquire the initial approval, it likely would not have passed. Furthermore, the company did not withdraw the drug for breast cancer in other countries due to the ethical dilemma of wanting to provide a treatment for triple negative breast cancer since there is currently a void in that area [25].

Similarly, Tecentriq received accelerated approval for urothelial carcinoma based on the promising phase II trials of IMVigor210 in 2016. Tecentriq would receive continued approval

contingent on reaching primary objectives in the follow up phase III trial, IMVigor211. Unfortunately, Tecentriq did not satisfy the primary endpoint of overall survival improvement for metastatic bladder cancer compared to just chemotherapy with some subgroups showing worse survival and progression free survival across select time ranges [26]. For these reasons, Roche is voluntarily withdrawing Tecentriq from bladder cancer indications in the United States to remain in accordance with the FDA's guidelines; however, it is not clear if it will be withdrawn internationally.

Immunological Competition for Bladder Cancer

When Tecentriq was first approved for urothelial carcinoma it was the first effective treatment approved in 20 years. This gave Genentech a monopoly of the market for the first year until Pembrolizumab, otherwise known as Keytruda, from Merck entered the market as well. Keytruda is a PD-1 inhibitor so it will bind to the PD-1 receptor on the T-cell preventing it from binding to the PD-L1 ligand expressed on the cancer cell and thus allowing the T-cell to target the cancer cell [26]. This is in contrast to Tecentriq which binds to the PD-L1 ligand on the cancer cell similarly preventing the interaction and thus allowing the immune system to target the cancer cells. This concept is visualized in figure 7 where Tecentriq would be the yellow anti PD-L1 and Keytruda would be the orange anti PD-1. Both drugs have similar clinical trial results and are priced nearly the same with Keytruda costing an equivalent of $3,422.91 per week of treatment [27]. Ever since then, several other drugs including avelumab, durvalumab, erdafitinib, enfortumab vedotin-ejfv, and nivolumab have entered the bladder cancer space [28]. While there are some options, the market remains as an oligopoly since

Tecentriq and the other drugs have not seen significant price changes since it first came to market and are still under patent protection.

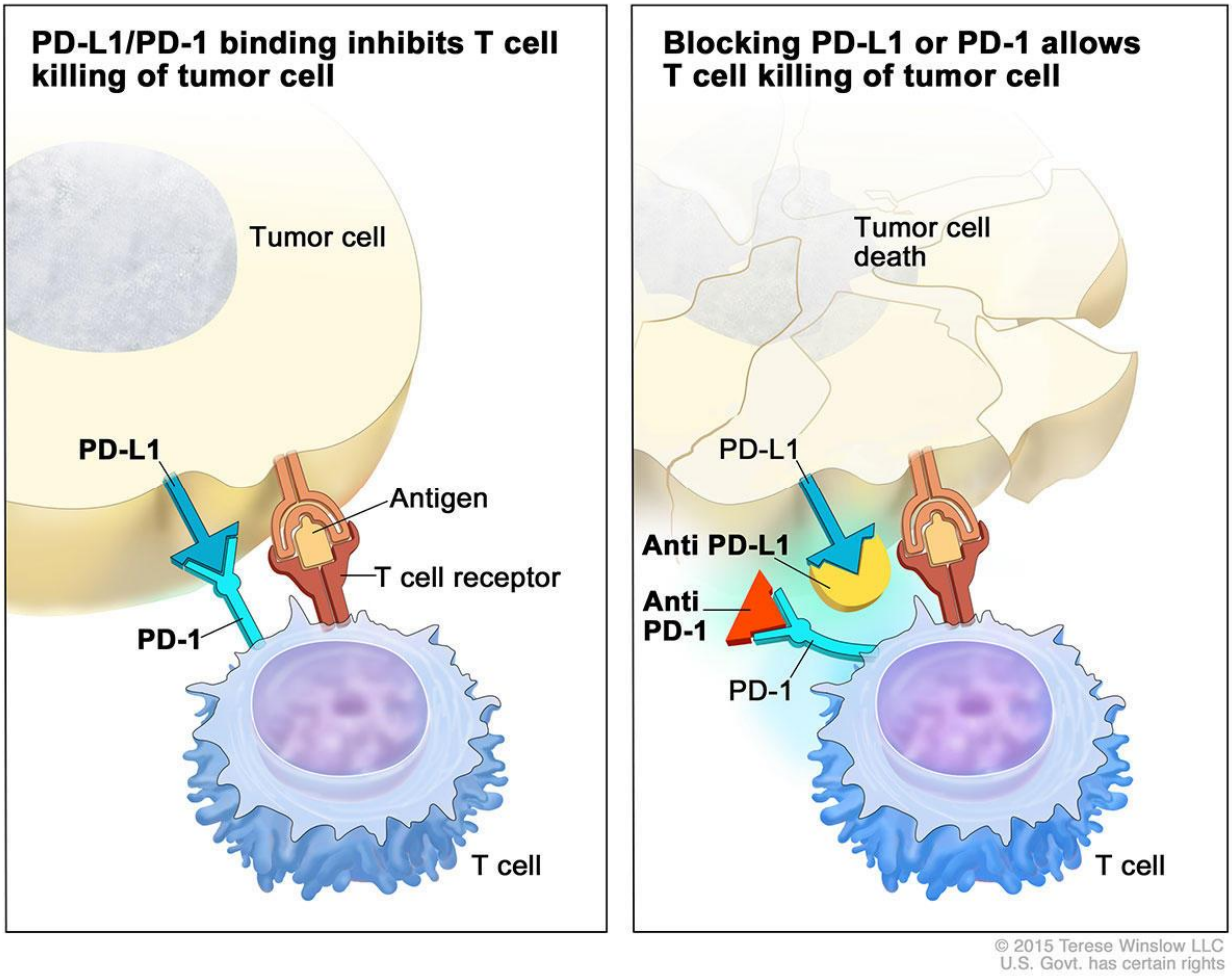


Figure 7: The image on the left illustrates the PD-L1 and PD-1 interaction and the inhibition of the T-cell. The image on the right illustrates how Anti PD-L1 in atezolizumab or Anti PD-1 in pembrolizumab blocks this interaction and allows the T-cell to attack the tumor cells.

Future Directions and Conclusion

Genentech only discusses their future plans for solid tumors in metastatic melanoma in their pipeline but looking at the clinical trials, there are currently 499 active studies that include

Tecentriq. Many of these studies are to complete FDA approval since many of the indications Tecentriq was approved for were accelerated approvals granted on phase II trials contingent on phase III trials being successful. Beyond that, many of the trials are to extend the indication Tecentriq can be applied to such as cutaneous melanoma, neoplasms of currently approved indication, thymic carcinoma, colorectal cancer, carcinoma of the head and neck, Non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, and thyroid cancer among the many other indications they have trials active or recruiting for [29].

The development of Atezolizumab has paved the way for many immunotherapy treatments of advanced cancers. Not only is the administration of this medication easier than previous treatments for bladder cancer, but it also has a much greater outcome for patients with this disease. While Tecentriq and checkpoint inhibitors remain relatively novel in oncology, the sticker prices of those drugs still lead to them being considered too expensive for the benefit. Fortunately, insurance and assistance programs make the treatments accessible to the general public, and as the field continues to develop rapidly, prices should come down to the point where immunotherapies become the preeminent option for late stage cancers.

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