

## Advances of FDA Approved Drugs that Target PD-1 and PD-L1 for Cancer Immunotherapy

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### Abstract:

Cancer is a lethal disease and is one of the leading causes of death in the world. Though there have been enormous leaps in the field of cancer treatment and prolonged patient survival rate, new therapies are still in high demand. Cancer immunotherapy is an emerging field in cancer treatment especially for patients with late stage cancers that had few options previously. Cancer immunotherapy is composed of CAR-T cell therapy, immune checkpoint inhibitors (ICI), and cancer vaccines. ICIs are monoclonal antibodies, which are used to block certain immune checkpoint from binding with tumor cells, preventing the shutdown of the T-cell. As of now, there have been 6 ICIs approved for many different cancer indications that target the proteins, PD-1, PD-L1 and CTLA-4 that have significantly increased patient response rates in recent years. In this review, the concept, history, recent advances in ICIs, and existing commercial drugs and their response rates in different cancer indications were summarized; the advantages and disadvantages of ICI treatment in cancer were also discussed.

**Keywords:** Immunotherapy; Immune checkpoint inhibitor; PD-1; PD-L1; CTLA-4

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## 1. Introduction

Cancer is a collection of related diseases in which the body's cells have mutated and grow abnormally that can invade and spread to the rest of the body. It is a leading cause of death with an estimated amount of 1.76 million new cases and 606,880 deaths in 2019 [1]. Cancer can be broken down into four major types which are carcinomas, sarcomas, leukemias, and lymphomas [2]. There are many treatments for cancer. The early treatments for cancer involved fancy medicines such as fox lungs and ground white coral or barber-surgeons performing mastectomies without anesthetics in extremely unsanitary conditions. Later on with the discovery of general anesthetics, surgeons were able to perform radical surgery ensuring the removal of the tumor, but uncertain if they had truly cured the patient. In 1896, Emil Grubbe pioneered the usage of x-rays and other forms of radiation to kill the tumors. Grubbe did not understand why radiotherapy worked, but now we know that radiation broke the DNA that controlled cell division killing both healthy and cancer cells. During the 1940s, anticancer drugs made their appearance, the first of which was nitrogen mustard and rechristened mustine which were the first chemotherapy licensed agent. The principles of chemotherapy are that it can seek cancer cells out regardless of their location in the body even if it had spread. Now immune checkpoint inhibitors (ICI) have taken over the market of cancer treatment. ICIs are able to block the tumor from attacking T cells from the checkpoint proteins [3,4].

The immune system is critical in the fight against cancer. The immune system consists of many cells to fight off threats. Macrophages are cells that have flexible tendrils that they use to snag and attack their targets. Dendritic cells give directions to the T-cells and B-cells to where their targets are. NK cells are rapid response cells that attack viruses and are aggressive in attacking cancerous and precancerous cells. The B-cells create antibodies that help fight off viruses and bacteria while the T-cells are divided into helper T-cells that stimulate the B-cells into producing antibodies and killer T-cells that attack harmful cells directly. There is a fine balance between the cell mutation burden and the effectiveness of the immune system. When the immune system is overwhelmed by the tumor, it fails to respond to the threat. The tipping point is thought to be when the cancer cell recruits immune cells to aid the cancer cells growth and travel [5].

Immunotherapy drugs allow the immune system to work harder making it eliminate cancer cells. ICIs are different compared to conventional therapies such as radiotherapy and chemotherapy as it activates the immune system to kill the cancer cells. Immunotherapy offers many benefits that other treatments can not offer [6]. The immune system has memory, which can be used to go after cancer cells if it does come back. It is proven to help other treatments work better, and also causes fewer side effects because it targets only the immune system and not all the cells in your body [7-9]. The risks include bad reactions to the medications, not working for every individual and the start-up of the immune system, making you feel like you have the flu [10,11].

Immune checkpoint inhibitors first started when a clinical trial consisting of patients with unresectable stage III/IV melanoma, demonstrated improved survival after receiving treatment with a fully human IgG1 $\kappa$  anti-CTLA-4 monoclonal antibody [12]. This study allowed for the FDA approval of ipilimumab, the first immune checkpoint inhibitor approved for cancer therapy, in 2011. Since 2011

there have been 6 ICIs approved for numerous cancer indications that target CTLA-4 PD-1 and PD-L1 have had unparalleled and lasting responses in a majority of cancer patients in recent years [13]. It is also noteworthy that ICIs take a shorter duration of time to be approved by the FDA compared to other anticancer agents. This allows ICIs to benefit from access to FDA programs for accelerated development [14].

PD-1 and PD-L1 inhibitors are a group of checkpoint inhibitors, currently being developed for cancer treatment. PD-1 and PD-L1 are proteins found on the surface of cells and the interaction of the two proteins causes the suppression of the immune system or prevention of autoimmune disease. Over the years, patient eligibility for immune checkpoint inhibitors has increased from 1.54% to 43.63% while patient response rates have also skyrocketed from 0.14% to 12.46% from 2011 to 2018 [15]. Even though ICI have revolutionized cancer treatment due to their durable remissions in many patients who have failed prior treatment and effectiveness against a large number of cancers, it does not work for everyone [16]. The patient responses to ICI vary tremendously such as melanoma having a much higher response rate when compared to prostate cancer [17]. Combination therapy is a new trend in the field of immunology because it can increase efficacy [18-20]. As mentioned prior, not all patients benefit from single-agent ICI therapy, which prompts the idea of combination therapy improving patient response outcomes [21-24]. Ideally, the combination of drugs should complement the mechanisms of each drug to maximize benefit and minimize toxicity [25-27].

## **Programmed cell death protein 1 (PD-1)**

### **Biology of PD-1**

In the year 1992, Tasuko Honjo, Yasumasa Ishida and colleagues at Kyoto University, were performing screenings of genes involved in apoptosis, when they discovered and named PD-1 (also known as CD279) [28]. Seven years later, the same team established that when PD-1 was knocked out of a mouse, they were prone to autoimmune disease and thus determined PD-1 was a negative regulator of immune responses [29].

PD-1 is expressed on a vast scale of immune cells, such as monocytes, T cells, B cells, dendritic cells and tumor-infiltrating lymphocytes (TILs). RNA is expressed on almost all human tissues and particularly, the appendix, bone marrow, lymph nodes, tonsils, spleen, and small intestine are expressed in greater quantities [30,31].

PD-1 is a protein on the cell's surface that suppresses both the immune system's response to human cells and the T-cell's inflammatory activity, by bolstering the body's ability to tolerate foreign cells. This process prevents autoimmune diseases, but also prevents the immune system from recognizing and killing cancer cells [32]. It is able to prevent autoimmunity through two mechanisms. First, in lymph nodes, PD-1 promotes apoptosis of antigen-specific T cells and second, it lessens apoptosis in regulatory T-cells [33,34].

PD-1 is a type 1 membrane protein, which contains 268 amino acids and is a member of the T cell regulator family [28]. The protein's arrangement comprises an extracellular IgV domain, a transmembrane region, and an intracellular tail. Located in an immunoreceptor tyrosine-based

inhibitory motif and immunoreceptor tyrosine-based switch motif, the intracellular tail contains two phosphorylation sites which suggest that PD-1 suppresses the T-cell receptor(TCR) signals. Furthermore, PD-1 ligation stimulates E3-ubiquitin ligases CBL-b and c-CBL that sparks TCR down-modulation. Since PD-1 is expressed on the surface of activated T cells, B cells, and macrophages, it suggests PD-1 provides a broader suppression of immune response than CTLA-4 [35].

PD-1 is an immune checkpoint that allows the T cell to check for foreign cells, but is rendered useless when bound with the tumor cell's PD-L1. When a cancer cell detects high levels of interferon-gamma, an expression of PD-L1 will be induced. Then when a CD8+ T cell checks the cancer cell, the CD8+ T cell's PD-1 will bind with PD-L1, causing the exhaustion of the CD8+ T cell, reducing the secretion of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-2 (IL-2) and interferon-gamma (IFN- $\gamma$ ), unlike the active CD8+ T cell, which secretes TNF- $\alpha$ , IL-2 and IFN- $\gamma$  to kill the mutated cell. Contrarily, when there is either an upregulation of PI3K-Akt kinases or secretion of IFN- $\gamma$ , it causes more expression of PD-L1, in which two general types of immune resistance is created, specifically, innate immune resistance, and adaptive immune resistance [36].

### PD-1 inhibitor drugs

Merck, a pharmaceutical company based in New Jersey, developed a drug called Keytruda(pembrolizumab) which has been FDA approved for applications of melanoma, advanced non-small cell lung cancer, head and neck squamous cell cancer, advanced urothelial bladder cancer, classical Hodgkin lymphoma, advanced gastric cancer, advanced Merkel cell carcinoma, advanced cervical cancer, advanced hepatocellular carcinoma, primary mediastinal B-cell lymphoma and advanced kidney cancer, which have been approved between 2014 and 2019. Overall the response rate for those cancer's ranges from 13.3% for advanced gastric cancer to 69% of classical Hodgkin lymphoma (Table 1).

Lung cancer is the leading cause of cancer death among both men and women, which has 228,150 diagnosed each year and a 5-year survival rate of 19%. NSCLC(Non-Small Cell Lung Cancer), a form of epithelial lung cancer accounts for roughly 84% of the lung cancer population [1]. Recently Merck has produced a drug called Keytruda, which was approved by the FDA in 2015 to reduce the number of deaths and increase the survival rate of the patients diagnosed with advanced NSCLC [37]. So far, the treatments for early NSCLC is surgery sometimes with chemotherapy, but for advanced NSCLC it is treated with chemotherapy, targeted drugs or immunotherapy [38]. According to the clinical trial results, with 410 participants for the Keytruda and chemotherapy study and 206 for the chemotherapy study, the median survival rate for Keytruda combination therapy with chemotherapy was 8.8 months compared to chemotherapy alone of 4.9 months, patient's partial response was 47% and full response was 0.5% when combined with chemotherapy (Table 1).

As of June 2019, Keytruda was approved for the usage of small cell lung cancer, which accounts for 10% to 15% of all lung cancers. The disease is commonly attributed to smoking and develops in the bronchi. According to keynote 158, which composed of 83 total patients, all received Keytruda monotherapy after failed previous treatments, had an overall response rate of 19%, 17% of which were partial and 2% were full responses [39-41].

Kidney cancer, also called renal cell carcinoma, is a urinary disease that is estimated to have 73,820 new cases, 14,770 deaths in 2019 and a 5-year survival rate of 75% [42]. The conventional treatments for kidney cancer were either surgery or ablation therapy, which uses extreme temperature to destroy the tumor cells, but in 2019 the FDA approved Keytruda for the usage of advanced kidney cancer, which has increased the patient response rate [1]. As shown by Keytruda's clinical trials, there is a median survival rate of 15 months when combined with chemotherapy, 4 months more than chemotherapy alone, and a 59% response rate which has a 53% partial response and a 6% full response rate for a clinical study that involved 432 participants using Keytruda combined with chemotherapy and 429 using chemotherapy alone [43].

Opdivo(Nivolumab), developed by Bristol-Myers Squibb(BMS) was among the first immune checkpoint inhibitors(ICIs) to hit the PD-1 market. From 2014 to 2018, the FDA has approved multiple usages of this drug for several cancer indications. Those cancer indications are melanoma, NSCLC, advanced kidney cancer, advanced bladder cancer, advanced liver cancer ,and small cell lung cancer. The patient response rates to these cancers range from 11% for small cell lung cancer to 50% for melanoma (Table 1).

The most dangerous form of skin cancer, melanoma develops in the cells that produce melanin and can form in your eyes and in rare cases in internal organs. Melanoma is estimated to have 96,480 new cases in 2019 and about 7000 people are expected to die of this disease [44]. As Opdivo's first FDA approval for cancer treatment, it is used most effectively when combined with Yervoy having a 50% response rate which is a 33% partial response and a 17% full response with the study containing 314 participants as shown by the Checkmate-067 study. Currently, the treatments available for melanoma are surgery, immunotherapy, chemotherapy, radiation therapy and BRAF targeted therapy, which is able to slow down the growth of melanoma, but later on, the tumor cell develops resistance to the drug allowing for a relapse. On the other hand, ICIs develop memory that allow it to prevent the relapse of melanoma [45].

Bladder cancer, which will have 80,470 new cases and 17,670 deaths in 2019 [46]. This form of cancer occurs when bladder cells become abnormal, which can spread to nearby lymph nodes, organs and in severe cases, can spread to the bones, lungs ,and liver. Smoking is the most established risk factor of bladder cancer contributing to 47% of the cases and bladder cancer as a whole has a high tumor mutation burden, which can potentially have a higher patient response rate for immunotherapy. Opdivo was approved by the FDA in 2017 and during the Checkmate-275 study, the response rate of patients who failed prior treatment was 19.6%, composed of 17% partial and 2.6 full response rate found from a study containing 270 participants (Table 1).

## **Programmed death-ligand 1 (PD-L1)**

### **Biology of PD-L1**

Programmed death-ligand 1(PD-L1 or B7H1) is a protein present in humans that is encoded by the CD274 gene. It was first characterized by the Mayo Clinic as an immune regulatory molecule B7H1. Later on, this molecule was renamed PD-L1 as it was identified as a ligand to PD-1 [47]. It is expressed in multiple human tissues like the lung, placenta, lymph nodes and spleen [31,48]. There are several

human cancer cells such as thyroid, urothelial and lung cancers that express high levels of PD-L1 [30]. PD-L1 was then shown to be expressed on Myeloid cells as a checkpoint protein and was suggested as a potential target in cancer immunotherapy [49].

PD-L1 is a type 1 transmembrane glycoprotein composed of both IgC- and IgV- type extracellular domains [50]. It is believed to have a major role in the suppression of the acquired immune system during certain events such as autoimmune disease. The binding between PD-L1 and PD-1 transmits a suppressive signal based on interaction with phosphatases through Immunoreceptor Tyrosine-Based Switch Motif (ITSM) [51]. This signal reduces the buildup of antigen-specific T-cells in regulatory T cells, which is mediated by a lower regulation of the gene Bcl-2.

PD-L1 expressed is induced in cancer response over-express of cytokines like INF- $\gamma$ , and TNF- $\alpha$ . In 2003, Curriel et.al showed that a blockade of PD-L1 led to a reduction to the growth of tumors in the presence of immune cells, and it was then concluded that PD-L1 helps tumor cells evade anti-tumor immunity. When bound together with its receptor PD-1, PD-L1 is able to neutralize the T-cell's activating signals. Expression of PD-L1 on tumor cells in the tumor microenvironment is of major clinical applicability, due to the fact that antibody-based PD-1 and PD-L1 inhibitors can activate durable tumor remissions in patients with various advanced cancers [49].

### **PD-L1 inhibitor drugs**

Tecentriq(Atezolimumab) was developed by Roche(Genentech), a Swiss multinational healthcare company is a new drug on the PD-L1 market. From 2016 to 2019, there have been 4 FDA approvals for the usage of advanced bladder cancer, metastatic non-small cell lung cancer, extensive stage small cell lung cancer, and metastatic triple negative breast cancer. The patient response rates range from 23.5% for advanced bladder cancer to 53% for TNBC (Table 1).

Triple Negative Breast Cancer, a form of breast cancer that accounts for 10 - 20% of all breast cancers, occurs when the three most common receptors that fuel breast cancer growth, estrogen, progesterone, and HER-2 are not present in the tumor [52]. Due to the tumors lack of necessary receptors, common treatments such as hormone therapy and drugs that specifically target estrogen, progesterone and HER-2 are ineffective. Compared with hormone receptor-positive breast cancers, triple negative breast cancer has a worse patient outcome and an aggressive history. In 2019, Tecentriq(Atezolizumab) was approved by the FD for patients with Triple Negative Breast Cancer. In a clinical study of 902 total participants, patients that received Tecentriq and Chemotherapy had a median survival rate of 21.3 months, while patients that received placebo and chemotherapy had a median survival rate of 17.6 months. The objective response rate of the patients was 53% for the Tecentriq group and 33% for the placebo group (Table 1).

Extensive stage small cell lung cancer is a form of lung cancer that does not fit into the criteria set by the International Association for the Study of Lung Cancer “disease restricted to one hemithorax with regional lymph node metastases, including hilar, ipsilateral and contralateral mediastinal, and ipsilateral and contralateral supraclavicular nodes and should also include patients with ipsilateral pleural effusion independent of whether cytology is positive or negative” [53]. The disease accounts for 60% to 70% of all small cell lung cancer cases at the time of diagnosis [54]. Tecentriq's usage for

extensive stage small cell lung cancer was not FDA approved until 2019. Roche's clinical study of 403 total patients, showed that when Tecentriq is combined with chemotherapy, the median survival rate is 12.3 months, but when the patient receives only chemotherapy the median survival rate is 10.3 months (Table 1).

In 2018, AstraZeneca's drug Imfinzi, a PD-L1 inhibitor was FDA approved allowing for the treatment of NSCLC. In their clinical trial of 476 patients on Imfinzi and 237 on placebo, the median survival rate was not reached and there was a 95% CI of (34.7, NR). On the other hand, the placebo group's median survival rate was 28.7 months and a 95% CI of (22.9, NR) (Table 1).

Merkel cells are found in the basal epidermal layer of the skin. Merkel cell carcinoma or neuroendocrine carcinoma is a rare form of skin cancer that forms in areas of skin commonly exposed to the sun [55]. Bavencio developed by Pfizer was FDA approved for the usage of metastatic Merkel cell carcinoma in 2017. Through a clinical study of 88 patients receiving Bavencio combined with chemotherapy, there was a 33% response rate, 22% of which were partial response and 11% were full responses (Table 1).

## Summary

Since nivolumab's clinical trial in 2006, there have been 6 new monoclonal antibodies (mAbs) targeting PD-1 and its ligand PD-L1 approved by the FDA to treat 14 different cancer indications. Furthermore, there has been a dramatic surge of active clinical trials testing anti PD-1 and PD-L1 agents, starting with 1 in 2006 and 2,250 as of September 2018. Of the 2,250 active trials, 1,716 are trials testing combination therapy. Though combination therapy only has two FDA approvals, there are 240 different targets that can be assessed anti PD-1 and PD-L1 agents. With so many clinical trials active, the need for patient volunteers has increased greatly. These trials have recruited patients at a rate of 1.15 patients per site per month in 2014 and is now slowing down to 0.35 patients per site per month in 2018. This suggests that combination therapy trials will face difficulty in their recruitment process in the near future for certain cancer types. Patient response rates have also been on the rise, such as the usage of Keytruda for Hodgkin lymphoma reaching a 69% patient response rate and Opdivo used with Yervoy for melanoma reaching a 50% patient response rate. But not all indications of cancer have a high patient response rate like gastric cancer where the response rate is only 13.3%. These statistics show that the fight against cancer is nowhere near finished [56]. New combination therapies or ICIs may potentially help increase patient response rates [57-60].

Given only a subset of patients deriving clinical benefit, it is crucial to understand and define a group of biomarkers, which is predictive of patient response and resistance [61-63]. So far many biomarkers have been discovered such as tumor mutation burden (TMB) [64,65], PDL1 expression, DNA mismatch repair deficiency [66], gut microbial diversity [67], HLA class genotype [68], and T cell-inflamed microenvironment [69]. TMB can affect the development of immunogenic peptides, thus affecting the ICI response in patients [70]. The best initial ICI response rates were found in cancers such as melanoma and NSCLC, which typically has a high TMB, owing to the mutagenic effects of ultraviolet light and cigarette smoke. In two melanoma studies, patients who had, on average a higher pre-therapy TMB than others, tended to experience durable clinical benefit from ipilimumab [71]. A

second study of melanoma patients only establishes an association between a high TMB and response to ipilimumab that patients with a TMB greater than 100 had a statistically higher overall survival (OS) percentage [72,73]. There have already been many biomarkers discovered [74], but more biomarkers are needed to improve patient response rates [75-78]. Patient response rates can also be improved through the discovery of an effective combination of biomarkers. Beside PD-1 and PD-L1, new ICIs targeting new targets such as Siglec-15 are under development [79].

Despite approvals of PD-1 and PD-L1 drugs in the United States and Europe, China is developing its own drugs towards these targets. In China, immuno-oncology remains at a preliminary stage. Although there are 26 active phase I studies investigating 14 ICIs, early phase designs incorporating the characteristics of Chinese patients are lackluster. Currently, there are 15 companies developing new ICIs in China. As of June 1, 2018, there has not been an ICI approved by the CFDA. Besides ICIs, there are several other fields of immunotherapy currently being developed such as T-cell therapy and cancer vaccines [80-82]. In the field of immuno-oncology, ICIs are a breakthrough in cancer treatment that shows extreme promise.

**Table 1. Immune checkpoint inhibitors approved by the US FDA**

Drugs	FDA approved Indications	Patient number	MedianOS (month)	Patient Response Rate	Year	Reference
Keytruda	Melanoma	277	4.1	33%(27%;6%)*	2014	[83]
Pembrolizumab	Advanced NSCLC	410	8.8	48%(47%;0.5%)**	2015	[84]
	Advanced Bladder Cancer	270	2.1	29%(22%;7%)*	2017	[85]
	Hodgkin Lymphoma	210	n/a	69%(47%;22%)**	2017	[86]
	PMBCL	53	31.4	45%(34%;11%)**	2018	[87]
	Advanced Kidney Cancer	432	15	59%(53%;6%)**	2019	[43]
	Advanced Gastric Cancer	143	n/a	13.3%(11.9%;1.4%)**	2017	[88]
	Advanced Liver Cancer	104	12.9	17%(16%;1%)*	2018	[89]
	HNSCC	174	n/a	16%(11%;5%)*	2016	[90]
	Advanced Cervical Cancer	77	9.4	14.3%(11.7%;2.6%)**	2018	[40]
	Advanced MCC	50	16.8 <sup>a</sup>	56%(32%;24%)*	2018	[91]
	Advanced SCLC	83	n/a	19%(17%;2%)*	2019	[40]
Opdivo	Melanoma	314	11.1 <sup>a</sup>	50%(33%;17%)**	2014	[92]



Nivolumab	NSCLC	135	9.2	19%**	2015 [93]
	SCLC	109	5.6	11%(10%;0.9%)**	2018 [92]
	Advanced Liver Cancer	154	NR	14.3%(12.3%;2%)**	2017 [94]
	RCC	425	NR	41.6%(32.2%;9.4%)**	2015 [95]
	Colorectal Cancer dMMR	82	n/a	46%(43%;3.7%)**	2018 [96]
	Advanced Bladder Cancer	270	8.74	19.6%(17%;2.6%)**	2017 [97]
Tecentriq	Metastatic NSCLC	850	13.8	n/a	2018 [98]
Atezolizumab	Extensive Stage SCLC	403	12.3	n/a	2019 [99]
	Metastatic TNBC	902	21.3	53%*	2019 [100]
	Advanced Bladder Cancer	119	5.9	23.5%*	2016 [101]
Imfinzi	Unresectable	476	34.7NR	n/a	2018 [102]
Durvalumab	Stage 3 NSCLC				
	Metastatic UC	191	18.2	17%(14.3%;2.7%)**	2017 [103]
Bavencio	RCC	886	13.8	51.4%**	2019 [104]
Avelumab	Metastatic UC	161	6.5	16.1%(10.6%;5.6%)**	2017 [105]
	Metastatic MCC	88	n/a	33%(22%;11%)**	2017 [106]

\* = monotherapy,

\*\* = combined therapy

a = PFS and MedianOS-NR

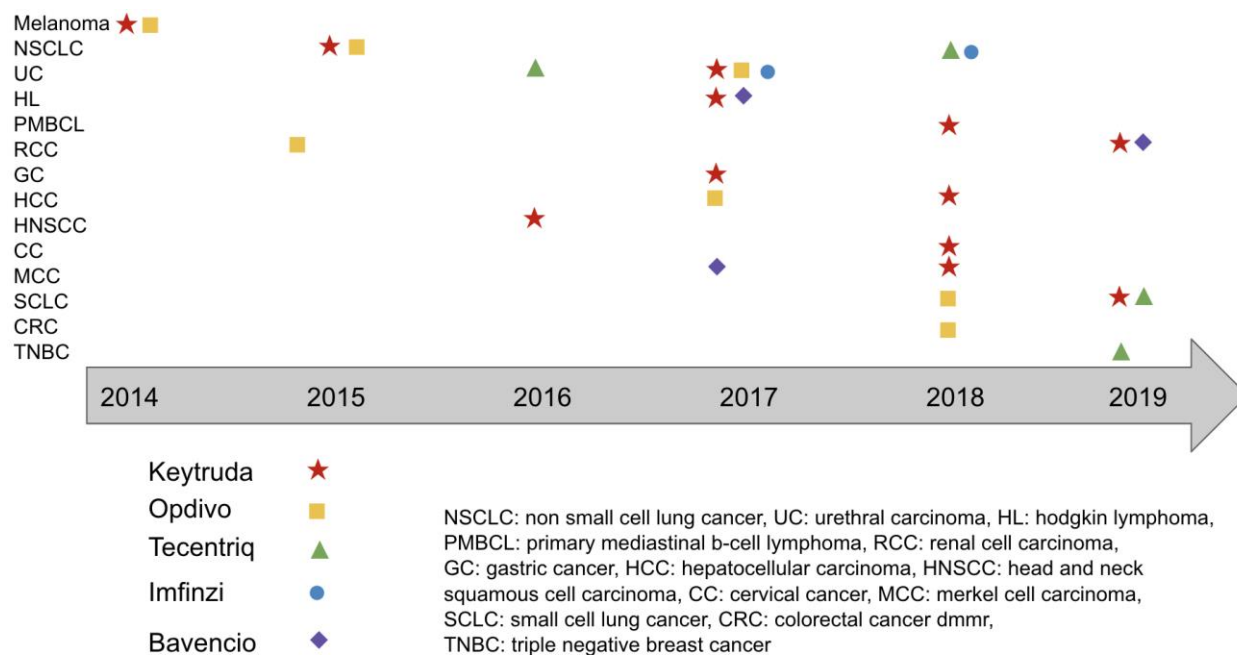
PMBCL = Primary Mediastinal B-Cell Lymphoma,

HNSCC = Head and Neck Squamous Cell Cancer,

TNBC = Triple Negative Breast Cancer,

UC = Urethral Carcinoma,

MCC = Merkel Cell Carcinoma

**Figure 1. FDA approval years for ICI product in different indications**

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