



Fall 2018

Immune Checkpoints in Cancer Treatment

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Cherubino, Matthew A., "Immune Checkpoints in Cancer Treatment" (2018). *Student Publications*. 677.
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Immune Checkpoints in Cancer Treatment

Abstract

Despite the human immune system, cancer thrives in an extremely hostile environment. Cancer is the second most common cause of death in the U.S. with about 600,000 deaths every year, and cancer is expected to surpass heart disease as the most common cause of death in the U.S. Immune checkpoint inhibitors are a novel and promising therapeutic for treating cancer in its late stages.

Keywords

immune checkpoints, immune checkpoint inhibitors, cancer, ipilimumab, nivolumab

Disciplines

Cancer Biology | Cell and Developmental Biology | Cells | Hemic and Immune Systems

Comments

Created for FYS 155-2: Cancer in Society: A War Against Immortality and presented at the 2019 Celebration of Academic First-Year Engagement Symposium.

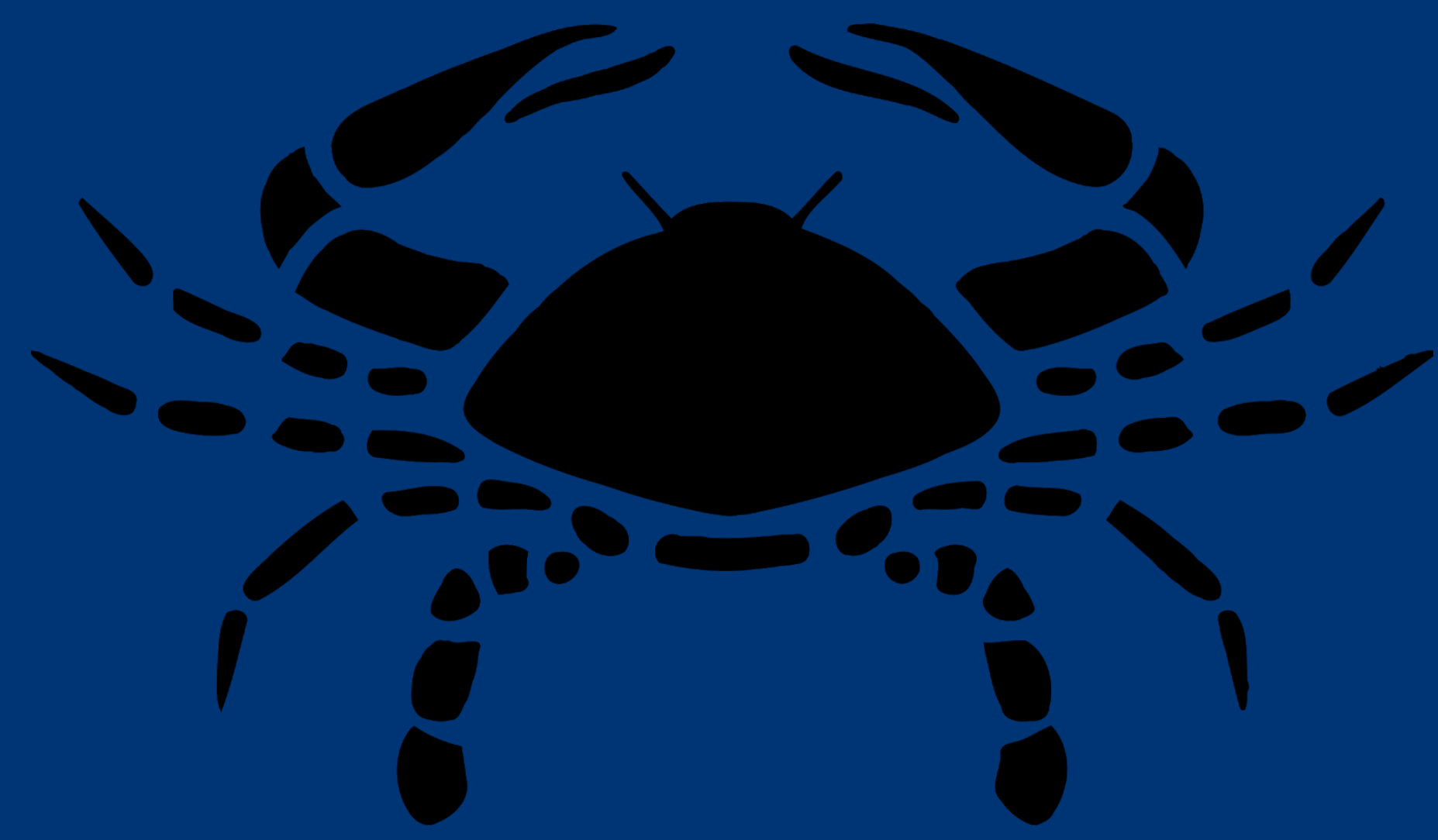
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Immune Checkpoints in Cancer Treatment

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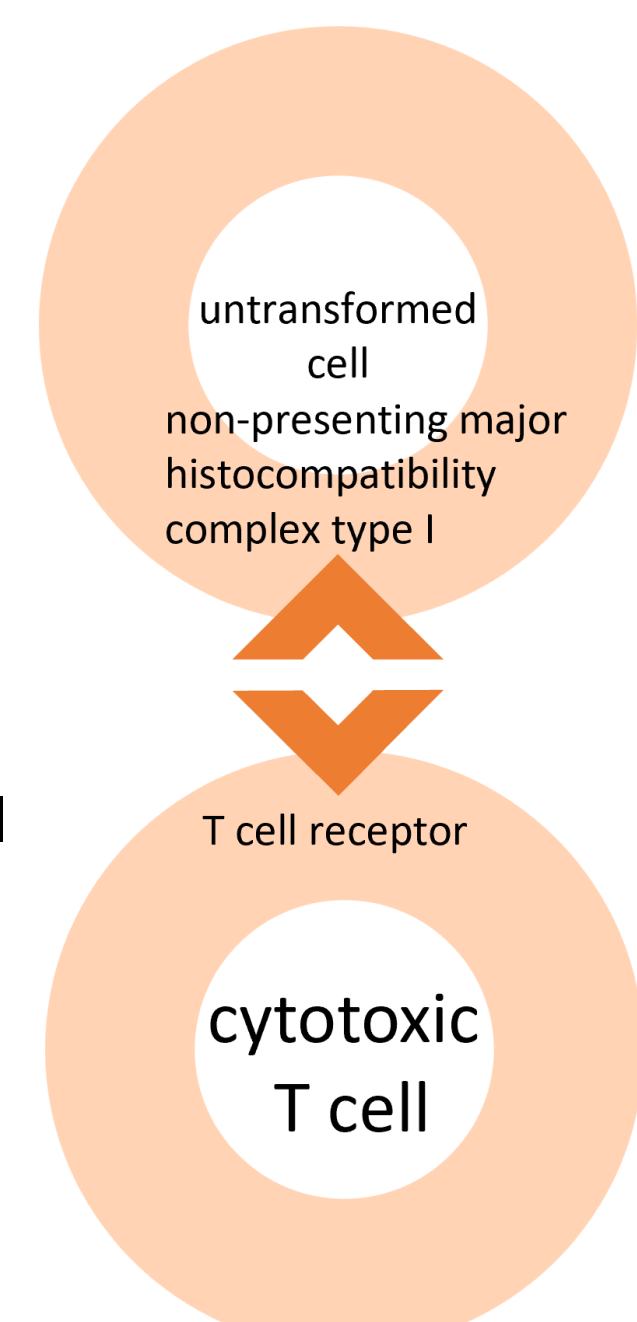
Overview

Despite the human immune system, cancer thrives in an extremely hostile environment. Cancer is the second most common cause of death in the U.S. with about 600,000 deaths every year, and cancer is expected to surpass heart disease as the most common cause of death in the U.S. Immune checkpoint inhibitors are a novel and promising therapeutic for treating cancer in its late stages.

Background

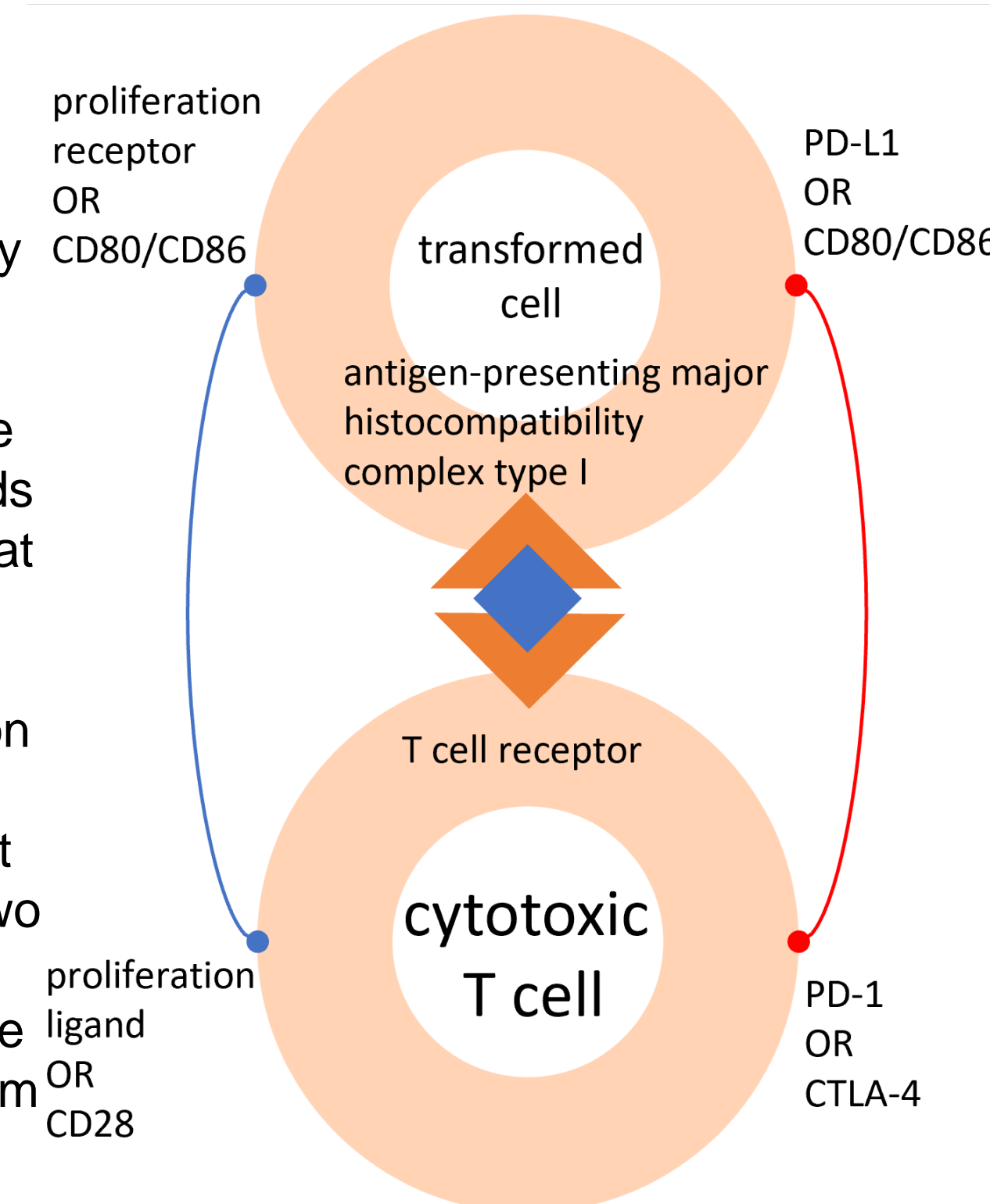
The human immune system evolved to detect and respond to antigens, or foreign insults. When a cell detects an antigen from within, through a series of events, the cell presents the antigen to the immune system via a major histocompatibility complex type I (MHC I). Most of the time, MHCs are non-presenting. When in this state, the immune system cannot detect foreign insults, thus the immune system does not mount an immune response. For example, when MHC I is non-presenting, a T cell receptor (TCR) will not bind to MHC I, thus no interaction occurs (see Figure 1.). For a long time, many researchers hypothesized that transformed cells, cancerous cells derived from within normal cells, used the host cell to disguise its insult from the immune system. Researchers now believe that in many cases, this hypothesis is false.

Figure 1. No interaction between a normal, untransformed cell and a cytotoxic T cell.



In cancer patients, the immune system often detects the insult by recognizing a cancer antigen in MHC I. A cytotoxic T lymphocyte (CTL), a staple component of the acquired immune response, binds to the antigen-presenting MHC I at the TCR. Cytokines, small molecules that assist in immune responses, facilitate the formation of a costimulatory pathway. Different cell types carry different surface proteins and ligands. Two such sets of surface protein and ligand are shown in Figure 2. The study of how these pathways form is an active research area. The CD80/CD86 and CD28 costimulatory pathway is as necessary as the MHC I and TCR pathway. This costimulatory pathway, referred to as the cell proliferative pathway, signals the cytotoxic T cell to clonally expand to around 10^{15} copies. If created, all of these copies would be programmed with the directive to kill cancer cells bearing a cancer antigen. However, cancer cells make use of the suppression pathway to silence instructions from the costimulatory pathway.

Figure 2. Immune response suppressed by immune suppression pathway.



One suppression pathway is the PD-L1 and PD-1 pathway. When both pathways are simultaneously delivering instructions to the CTL, the CTL becomes inactive or dies. In addition to dominance, when both pathways are active CD80/CD86 of the suppression pathway sometimes (if bonding attractions are strong enough) has the ability to break the costimulatory pathway in a process called transendocytosis.

Treatment Mechanism

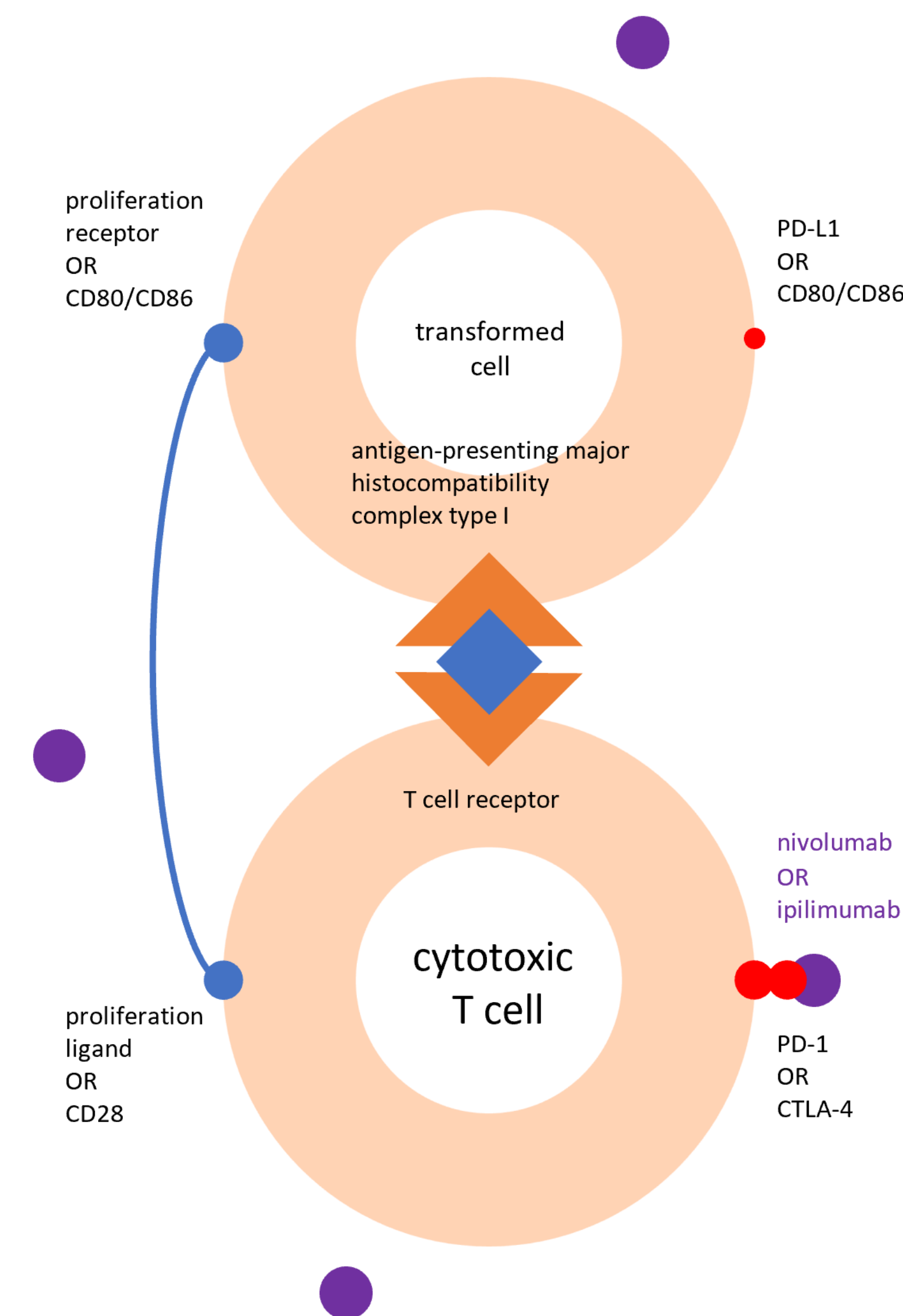


Figure 3. Immune response enabled by blocking of the immune suppression pathway.

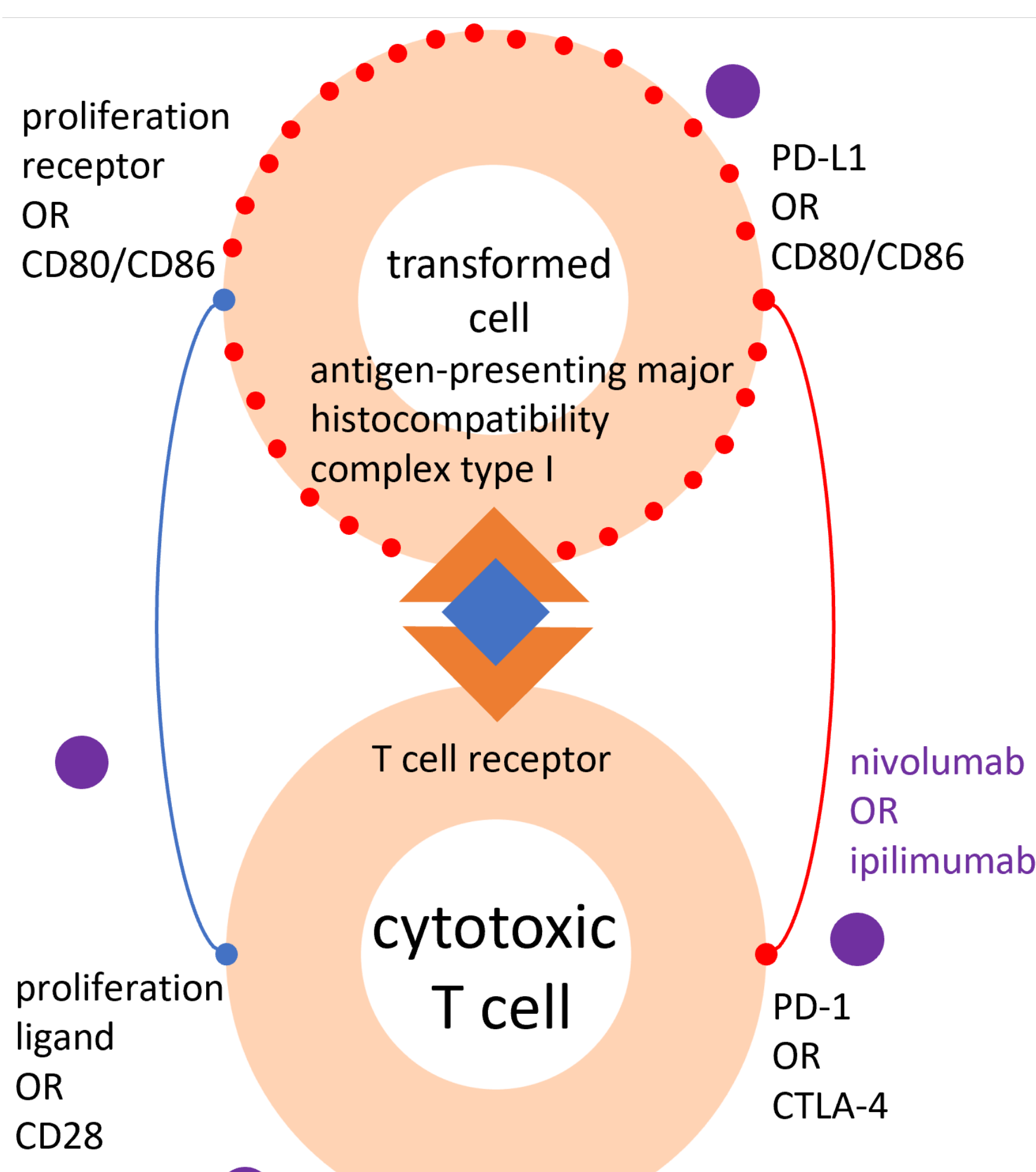


Figure 4. Immune response suppressed by immune suppression pathway, despite immune checkpoint cancer treatment.

The invention of ipilimumab, the first successful immune checkpoint inhibitor, marked the inception of a new era in cancer treatment. Immune checkpoint inhibitors like ipilimumab and nivolumab (anti-PD-1) block the immune suppression pathway by mimicking the suppression ligand that binds to either PD-1 or CTLA-4 (see Figure 3.). The binding of these antibodies is irreversible, thus allowing the bonded CTL to be uninterrupted as it carries out instructions from the costimulatory pathway. The resulting clonal expansion of CTLs specific to the cancer antigen leads to a robust immune response to the cancer cells. The randomness of which molecules bump into other molecules is a critical component to the success or failure of immune checkpoint cancer treatments. After all, both PD-L1 and CD80/CD86 and their mimicking antibodies bind irreversibly to their respective PD-1 or CTLA-4. Although several minor factors influence the probability that a protein will meet its ligand, the process is largely random. For the purpose of simplicity, the actual probabilities can be adequately represented by a random system. In order to best understand this situation, consider Figure 3. mathematically.

Given 1 PD-1, 1 PD-L1, and 4 anti-PD-1, what is the probability that the immune suppression pathway will be blocked? What is the probability that the pathway will be active?

PD-1 may bind to PD-L1 to activate the immune suppression pathway, or it may bind to one of the four anti-PD-1 ligands to block the pathway.

$$4 \text{ block} / 5 \text{ total} = 0.8 \text{ block}$$

$$1 \text{ activate} / 5 \text{ total} = 0.2 \text{ active}$$

In an environment with many transformed cells, some are likely to survive. The daughter cells of the survivors do not inherit PD-1, and are thus vulnerable to the effect of the drugs.

While this treatment shows promise by hindering cancer, it is very unlikely to cure cancer. Figure 4. illustrates a cancer cell's common and rapid adaptation to its new, hostile environment. Again, mathematics can be used to easily visualize the significance of the situation.

Given 1 PD-1, 30 PD-L1, and 4 anti-PD-1, what is the probability that the immune suppression pathway will be blocked? What is the probability that the pathway will be active?

PD-1 may bind to one of the thirty PD-L1 to activate the immune suppression pathway, or it may bind to one of the four anti-PD-1 ligands to block the pathway.

$$4 \text{ block} / 34 \text{ total} = 0.1 \text{ block}$$

$$30 \text{ activate} / 34 \text{ total} = 0.9 \text{ active}$$

Clearly, the adaptation is devastating to the success of anti-PD-1. In most cases, the adaptation is likely caused by a specific aneuploidy rather than by mutation, which would explain both its relatively large frequency and short lag time. Cancer cells without the adaptation are likely to die. Cancer cells with the adaptation are likely to survive. The drugged environment selects for cells with the adaptation and against the cells without the adaptation. This selection results in a bottleneck effect. Most survivors emerge resistant to the new environment, and their unhindered cell division leads to large populations of resistant cancer cells.

Treatment Information

Many immune checkpoint inhibitors are in clinics and development today. These inhibitors extend the life of a terminally ill patient or serve as a safeguard accompanying removal of cancerous tissue. Ipilimumab and nivolumab are most often used to extend life by treating late stage, metastatic melanoma and lung cancer. In a study, ipilimumab plus dacarbazine (a chemotherapeutic) were found to have a five-year survival rate of 18.2% versus the 8.8% five-year survival rate of placebo plus dacarbazine (see Figure 5.). Nivolumab and other immune checkpoint inhibitors offer similar results for their respective cell types. All approved immune checkpoint inhibitors have around a 20% five-year survival rate. Inhibitor cocktails can sometimes lead to better results at the cost of higher toxicity.

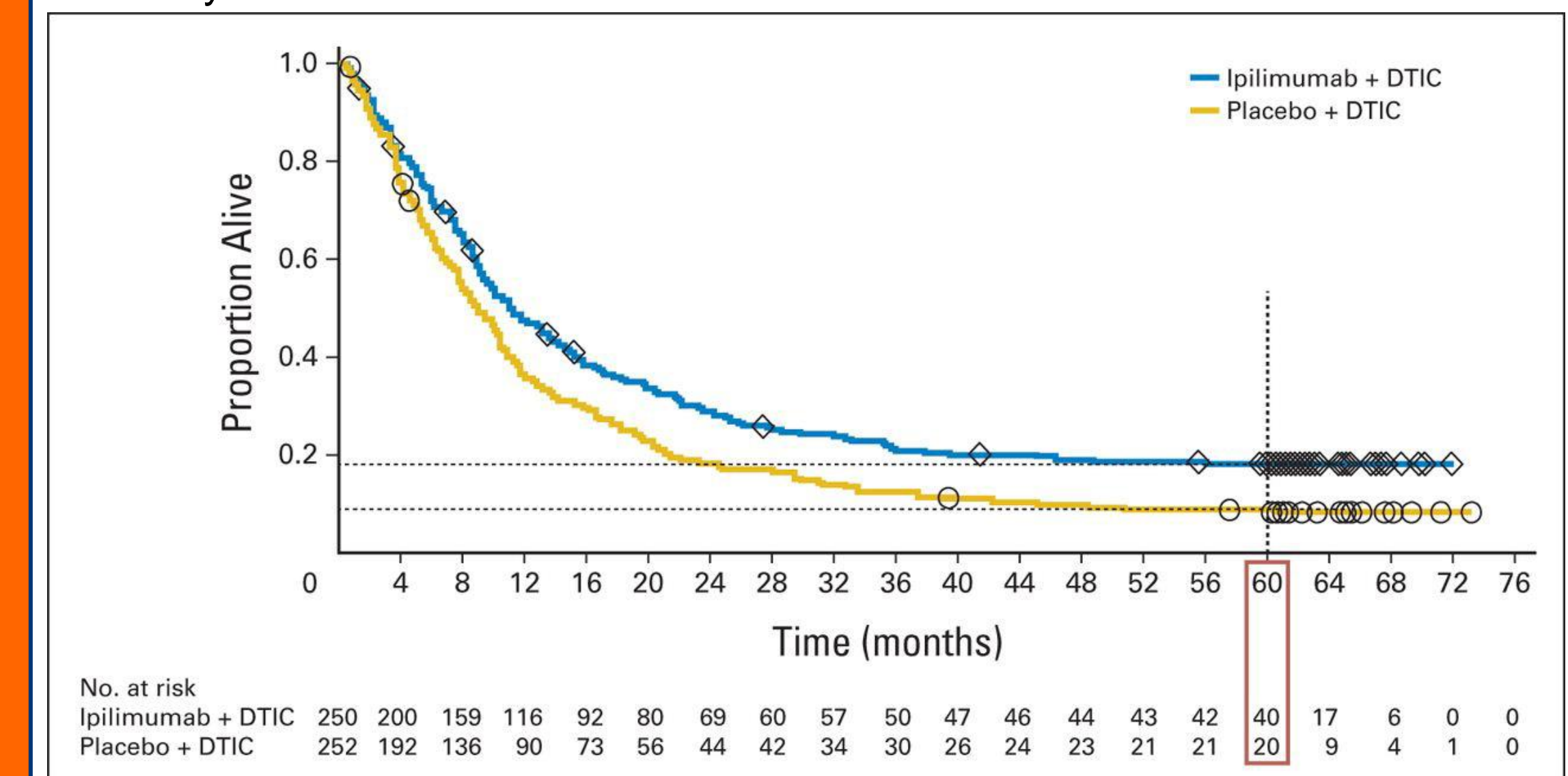


Figure 5. Phase III study compares the living proportion treated with ipilimumab plus dacarbazine (blue) and the living proportion treated with placebo plus dacarbazine (yellow), both vs. months elapsed. Symbols indicate censored observations. n=247, n=251.

Bristol-Myers Squibb is a major company in the development of these immune checkpoint inhibitors. Bristol-Myers Squibb prices ipilimumab (brand name YERVOY) at \$30,000 per dose. Each dose consists of 3mg/kg every three weeks. A regimen typically consists of four consecutive doses, which brings the total cost of treatment to \$120,000; however, a patient-assistance program may reduce the price to \$80,000. All immune checkpoint inhibitors cost around \$150,000 for one year of treatment. The medication is administered regularly until progression of the disease or until toxicity becomes intolerable.

Conclusions

Immune checkpoint inhibitors, such as ipilimumab and nivolumab, block the suppression pathway of cancer cell interaction with T cells. This mechanic stimulates the proliferation of T cells, which can result in a robust immune response to metastatic melanoma, among other cancers. Immune checkpoint inhibitors tend to produce around a 20% five-year survival rate.

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Acknowledgments

Special thanks to Robert Garrity for his knowledge and guidance throughout the creation of this project.