Checkpoint Inhibitors: A New and Promising Melanoma Treatment

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ABSTRACT

Melanoma is the most common and severe form of skin cancer, known for its rapid progression and high potential for metastasis. Over the past decade, melanoma cases have increased by more than 40%, making it a significant public health concern. There are several proven methods to reduce tumors. Chemotherapy, a commonly used treatment, employs drugs to kill cancerous cells and prevent their spread. While effective, chemotherapy can have significant side effects and limitations. Recent advances in immunotherapy, particularly the development of checkpoint inhibitors, show promise in harnessing the immune system to combat cancer cells under various conditions. Checkpoint inhibitors work by blocking proteins that prevent the immune system from attacking cancer cells, thereby enhancing the body's natural immune response against the tumor. In doing this, T cells are allowed to kill the cancer cells. This review will highlight the current state of checkpoint inhibitors, exploring their mechanisms and interactions with biomarkers. Biomarkers help predict which patients are most likely to benefit from this therapy, optimizing treatment outcomes. As checkpoint inhibitors are a relatively new treatment, it is important to address other issues that could be limiting this treatment such as cost, accessibility, and long-term effectiveness. Understanding these factors helps to integrate checkpoint inhibitors into standard melanoma treatment protocols and improves patient care.

MELANOMA

- The number of melanoma deaths is expected to increase by 3.8 % in 2024 (ACS, 2024)
- Only 20—30% of melanomas double if they have had more than 5 sunburns (ACS, 2024)
- Only 20-30% of melanomas are found in existing moles, while 70-80 percent arise on apparently normal skin(ACS, 2024)
- Overall, one in 28 white men and one in 41 women will develop melanoma in their lifetime. (ACS, 2024)

METHODS

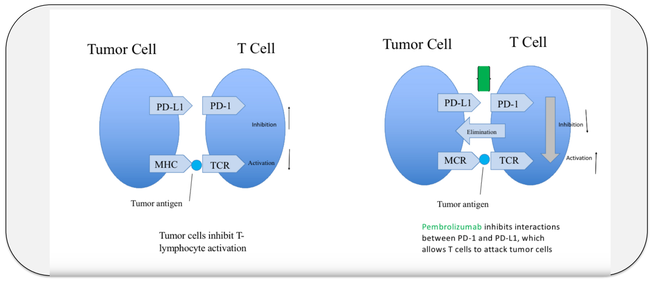
A systematic search of 20 scientific sources was conducted using predetermined research studies related to immunotherapies using checkpoint inhibitors. Specifically analyzing primary and secondary literature

CHEMOTHERAPY VS IMMUNOTHERAPY

- Chemotherapy drugs attack and kill rapidly growing cancer cells
- May kill healthy cells
- Side effects include hair loss , nausea (FDA, 2012)

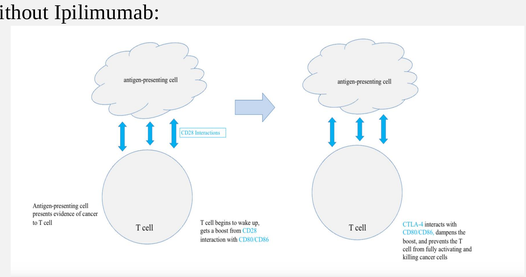
- Immunotherapy uses the body's immune system to eliminate cancer cells
- Side effects are less severe since fewer healthy cells are damaged
- T-cell therapy and other vaccines are part of other approaches in immunotherapy (FDA, 2012)

Figure 1. Pembrolizumab mechanism of action, Left shows without the inhibitor present and right shows inhibitor present . (Figure adapted from Ribas et al 2017)



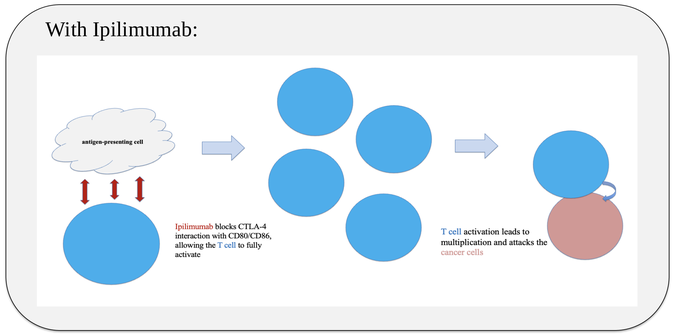
<u>Pembrolizumab:</u> Stimulates the body's immune system to fight cancer cells. It blocks PD-1 on the surface of certain immune cells

Without Ipilimumab:



With Ipilimumab:

Figure 2. Ipilimumab mechanism of action, above is without inhibitor and right shows inhibitor present. (Figure adapted from Ribas et al 2017)



<u>Ipilimumab</u>: Antibody that blocks CTLA- 4. a protein receptor on the surface of T cells that normally inhibit prolonged activation of T cells

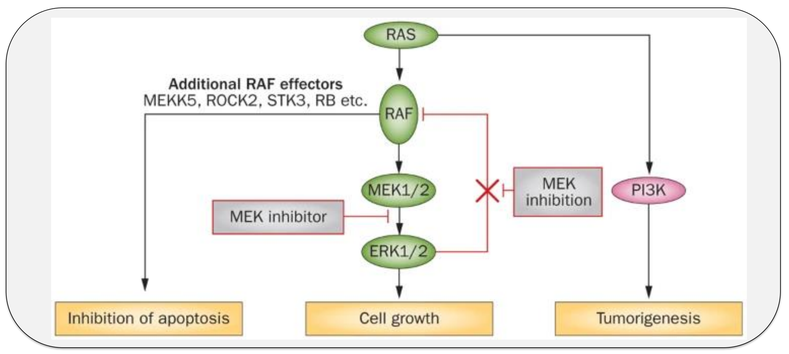


Figure 3. Abrogation of negative feedback pathways between ERK and RAF. Taken from (Adejei, 2014)

MEK: Blocks the MEK protein which slows the growth of cancer cells

COMBINATION THERAPIES

- Strategic use of multiple inhibitors targeting various signaling pathways or immune checkpoints to enhance efficacy and reduce the chances of resistance development (Ribas et al. 2017)
- Different drugs have a different molecular target within melanoma cells
- Target and block checkpoints which lead to immune activation (Ribas et al. 2017)

BIOMARKERS

Predictive:

- Identify individuals who are more likely than others to experience a favorable or unfavorable effect
- Help assist in informing on patient care decisions
- Can characterize a disease process by viewing mutations in tumors

Prognostic:

- Disease Stage Analysis
- Depth of Invasion
- Ulceration
- Lymph Node Involvement
- Presence of Microsatellites
- Predict Course of Disease

FUTURE DIRECTIONS/ CONCLUSIONS

- Public health campaigns emphasizing sun safety practices, educational initiatives targeting at-risk populations, and advancements in medical research and technologies (Ward et al, 2008)
- Raising awareness about prevention and early detection
- Promoting sun-safe behaviors and create a better understanding of the skin cancer risk and warning signs.
- Improving access to immunotherapy

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