HIGH SCHOOL EDITION
Journal of Student Research
Volume 13 Issue 2 (2024)

Exploring A Hypothetical Design of a Nanoparticle-Based Cancer Vaccine for Skin Cancer Melanoma

Reenie Cao[1] and Carcia Carson[#]

[#]Advisor

ABSTRACT

Melanoma is a skin cancer, in which cancer cells form in the melanocytes. It can occur anywhere on the skin but is hard to spot due to its only signs being a change in the way a specific mole or pigmented area looks. It is usually curable. Still, once it has bypassed stage IV, it can become fatal and deadly. The stages of melanoma depend on how thick the tumor is and whether it has broken through the skin. The most deadly is stage IV, in which the cancer has spread to numerous parts of the body, including but not limited to the lungs, liver, and brain. Studies have shown that the average 5-year survival rate for melanoma skin cancer is 94%; however, only 32% of people survive once the cancer has spread to distant parts of the body (The American Cancer Society et al., n.d.). Treatments for stage IV melanoma include surgery or radiation therapy. However, newer forms of immunotherapy and targeted drugs have shown to be more effective than chemotherapy. This paper will explore both the benefits and drawbacks of the immune checkpoint inhibitor atezolizumab and the BRAF inhibitor dabrafenib, both of which are FDA-approved. Furthermore, the paper will also explore the use of the PLGA nanoparticle in drug delivery as well as the possible future direction of this cancer treatment.

Introduction

The skin is the body's largest organ and is our body's first line of defense, protecting us from heat, sunlight, injury, and infection. It is composed of many layers, but two of the most important are the epidermis and the dermis.

The epidermis hosts three kinds of cells: squamous, basal, and melanocytes (National Cancer Institute et al., 2021). It is in the melanocytes where cancerous cells first appear and lead to melanoma. While melanoma can occur anywhere on the body, it is found most commonly on the trunk, head, and neck for men or on the arms and legs for women (National Cancer Institute et al., 2021).

Melanoma is a rare form of skin cancer and is usually curable when detected and treated early, but once it has spread deeper into the skin or other parts of the body, it can become deadly (National Cancer Institute et al., 2021). In the past decade, new invasive melanoma cases diagnosed increased by 27 percent. It can occur in the skin, which is known as cutaneous melanoma, or in the eye, which is called intraocular or ocular melanoma (National Cancer Institute et al., 2021). Melanoma is very dangerous because it is hard to detect its symptoms. The cancer can emerge through already existing moles or new growth on the skin, which many would not find alarming enough to report. This makes it harder to treat the disease, as when it progresses through stages, it spreads deeper and deeper into the skin, reaching the lymph nodes or other parts of the body in later stages. In Stage I, the tumor is only one millimeter thick and can be seen with or without ulcerations, but as the tumor grows, it spreads all over the skin and it becomes hard to identify where the original tumor formed (National Cancer Institute et al., 2021). The US Food and Drug Administration (FDA) has released 13 new approved melanoma therapies since 2007, but many can result in the damage of healthy cells alongside cancer cells (Melanoma Research Alliance et al., n.d.).

Around half of all melanomas have cancer cells that have BRAF gene changes, which are mutations that can cause the gene to turn on the BRAF protein and keep it on, causing normal cells to become cancerous (The American Cancer Society et al., n.d.). The protein signals for the cells to divide uncontrollably, pushing the cancer to grow faster and spread through further parts of the body. Dabrafenib specifically targets the V600E mutated BRAF protein and has shown more promising results than that of a chemotherapy drug, DTIC (dacarbazine) (National Cancer Institute et al., 2015).

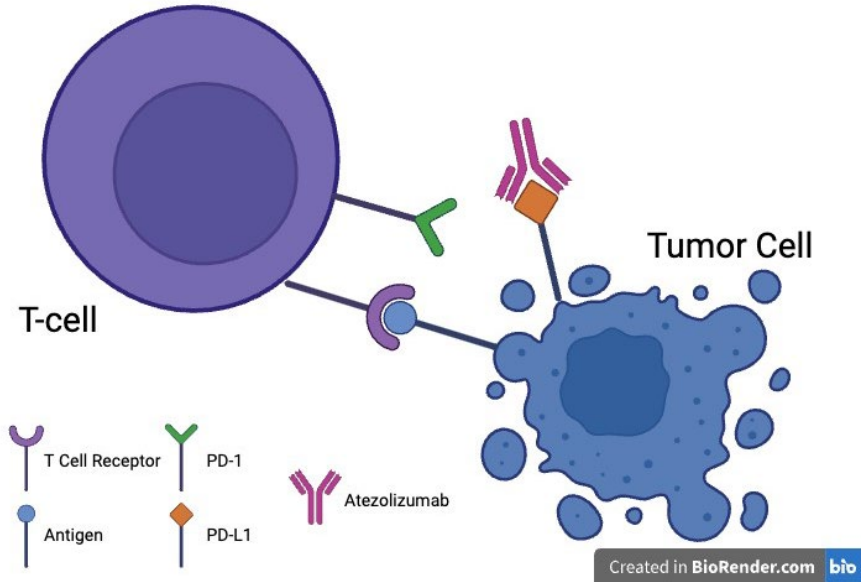

Figure 1. Mechanism of Action of Atezolizumab The immune checkpoint inhibitor atezolizumab stops the binding of PD-L1 and its receptor PD-1 by selectively binding to PD-L1. Blocking PD-1 or PD-L1 leads to tumor death. (Adapted from UCIR, 22)

However, most targeted therapies do not solely rely on BRAF inhibitors to remove melanoma because it does not get rid of any already existing tumor cells but only stop the production of them. An immune checkpoint inhibitor is needed because it can stop tumor cells from interfering with T-cell anti-tumor responses (Creative Biolabs et al., n.d.). The immune checkpoint inhibitor atezolizumab (Tecentriq) can block a protein that stops the immune system from working properly to attack cancer cells, making the immune system able to find and kill cancer cells (The American Cancer Society et al., 2022). As shown in Figure 1, it binds to the programmed cell death ligand PD-L1 to stop the binding between it and PD-1. An inhibitory signal is produced in the lymph nodes when PD-L1 binds to its receptors on activated T cells. This prevents the immune system from reacting to situations, allowing cancer cells to evade anti-tumor T-cell responses. Besides leading to tumor death, the blockage of PD-1 and PD-L1 may also enhance T-cell priming, leading to prolonged response and survival (Creative Biolabs et al., n.d.).

Paired with the BRAF inhibitor dabrafenib (Tafinlar), which blocks the action of an abnormal protein that signals cancer cells to multiply, the two drugs can help decrease the amount of cancer cells and get rid of the remaining ones, effectively treating the cancer and also preventing its possible return. Immunotherapy drugs called checkpoint inhibitors can shrink tumors for long periods but are more likely to result in serious side effects. These side effects usually occur due to the immune system attacking normal body parts in addition to cancer cells. However, by using nanoparticles as delivery vehicles, the immune system is less likely to attack healthy cells and more likely to target tumor cells. The PLGA nanoparticle has been used to develop nanoparticle-based gene delivery systems with numerous cancer-related drugs incorporated within (Acharya et al., 2011).

The Use of Atezeolizumab to Treat Cancer Cells

Atezolizumab is a monoclonal antibody that binds to the protein PD-L1 on the surface of some cancer cells, which can prevent cancer cells from suppressing the immune system. It has been found to work alone or with other drugs as treatment. Specifically, for the treatment of Melanoma, Atezolizumab has been previously paired with cobimetinib fumarate and vemurafenib (National Cancer Institute et al., 2016). A previous study has shown that atezolizumab can shrink and even completely get rid of tumors. In this study, 52 people in the trial were treated with atezolizumab. In said study, 37% of participants saw their tumor shrink by at least 30% and one person's tumor completely disappeared. Furthermore, imaging scans two years later of seven patients have shown no signs of the tumor growing again. In 2022, the Food and Drug Administration (FDA) approved Atezolizumab for adults and children 2 years and older for treatment of advanced alveolar soft part sarcoma (National Cancer Institute et al., 2023).

Primary analysis of the phase 3 IMspire150 study has shown improved progression-free survival with first-line atezolizumab, vemurafenib, and cobimetinib versus placebo, vemurafenib, and cobimetinib in patients with BRAF mutation-positive melanoma (Ascierto et al., 2023). 514 patients, median age of 54 years, were assigned to the atezolizumab group or the control group. Patients were randomly assigned to receive either drug. Those who received atezolizumab took 840 mg intravenously on days 1 and 15. Randomization was done centrally based on a permuted block randomization scheme, which utilized an interactive web-based response system. The intention-to-treat population's overall survival was examined, and each patient who took at least one dosage of the study medication had their safety evaluated about the actual care they received. Results show that by the data cutoff, Sept 8, 2021, 273 patients had died (126 in the atezolizumab group and 147 in the control group). Comparing the median overall survival rate, the atezolizumab group showed 39-0 months while the control group showed 25-8 months. However, interpretation shows that the overall survival was not significantly improved with atezolizumab (Ascierto et al., 2023).

Different *in vivo/in vitro* studies can be held to test drug effectiveness. One method includes modifying two alkalescence groups onto naphthalimide and tuning the DNA affinity, and a fluorescence probe enabling visualization of cell death via subcellular immigration between lysosomes and the nucleus is formed (Ge et al., 2021). This assay is important because it marks the number of dead cells and live cells. Furthermore, methods can be used to test the number of cancer cells surviving. Cancer cells typically outrun surrounding cells for nutrients, such as glucose. In diagnostics, the increased glucose metabolism of cancer cells can be revealed through a post-emission tomography (PET) scan, which uses a radioactive drug called a tracer to show both typical and atypical metabolic activity.

Although, there are limitations to the use of atezolizumab. A study of the use of atezolizumab has shown that there is a disadvantage for people who have a metastatic tumor in their liver. 85 out of 100 people who were given atezolizumab had severe side effects, which include disorders of the blood and lymphatic system, shortness of breath, and circulatory collapse. In comparison, 74 out of 100 people who had the standard treatment demonstrated these side effects (IQWiG et al., 2020). However, no difference was found in life expectancy, loss of appetite, pain, exhaustion, etc; there are still unknown details about immune-mediated severe side effects (IQWiG et al., 2020).

The Use of Dabrafenib to Treat Cancer Cells

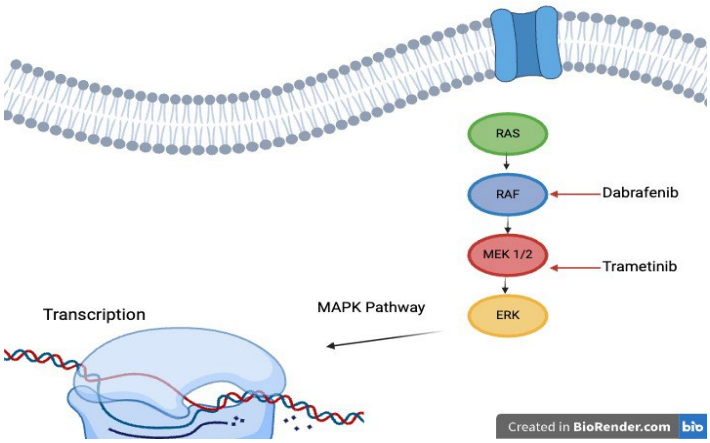

Figure 2. Mechanism of Action of Dabrafenib + Trametinib The BRAF inhibitor Dabrafenib in combination with kinase inhibitor Trametinib successfully stops the transcription of mutated BRAF genes. (Adapted from Shin, 23)

Around half of all melanomas have a BRAF mutation. The BRAF inhibitor dabrafenib (Tafinlar) focuses specifically on the V600E mutated BRAF Protein by interfering with the BRAF signals to slow or stop uncontrollable cell growth (Melanoma Research Alliance et al., n.d.). As seen in Figure 2, the BRAF gene is part of the RAS/MAPK pathway, which controls several important cell functions, and provides instructions for making a protein that helps transmit chemical signals from outside the cell into the cell's nucleus (Medline Plus et al., n.d.). When mutated, this means that the signal it sends provides instructions for uncontrollable cell growth, leading to cancer cells that have the ability to infiltrate and destroy normal body tissue. In 2013, the FDA approved the use of dabrafenib for patients with advanced stages, stages three to four, of melanoma. In a trial held by Melanoma Institute Australia, the treatment of dabrafenib accompanied by trametinib daily led to an overall response rate of 67% and a 6-month survival rate of 93% while the treatment of dabrafenib and placebo had a 51% response rate and a 6-month survival rate of 85% (National Cancer Institute et al., 2015). Such results are promising for the future treatment of Melanoma, and they also showcase the ability of dabrafenib in combination with another drug.

Another study of 563 patients also demonstrated the effects of combination therapy with BRAF and MEK inhibitors on patients with unresectable or metastatic melanoma, meaning that the cancer cells had already broken away from primary cancer and spread throughout the body (Robert et al., 2019). Dabraenib with trametinib was randomly assigned to all 563 patients, producing in progression-free survival rates of 19% at 5 years and 21% at 4 years. At 4 years, the overall survival rate was 37%, and at 5 years, it was 34%. Out of 109 patients (19%), 109 had a full response, which was linked to a better long-term result. At five years, the overall survival rate was 71% (95% CI, 62 to 79). Several baseline factors were associated with both progression-free survival and overall survival, including performance status, age sex, etc). In conclusion, a third of patients with unresectable or metastatic melanoma benefited from dabrafenib plus trametinib through long-term benefits (Melanoma Research Alliance et al., n.d.). This treatment shows promising results because the findings have shown stabilized progression-free survival and overall survival. According to the article on the five-year outcomes with Dabraneib plus Trametinib, compared to the general population, a greater percentage of patients who remained progression-free or alive five years after randomization had baseline characteristics linked to a lower tumor load and less aggressive tumor kinetics (Robert et al., 2019).

Different methods can be used to test the efficiency of dabrafenib. Flow cytometry rapidly analyzes single cells or particles as they flow past single or multiple lasers while suspended in a buffered salt-based solution. It is useful for revealing a percentage of a cell population in each phase of the cell cycle, which can

determine the drug's ability to induce cell cycle arrest (National Cancer Institute et al., 2015). Furthermore, cell proliferation assays quantify the rate at which a population of cells increases in number over time. Ethynyl deoxyuridine assays measure the incorporation of EdU into newly synthesized DNA during DNA replication (Melanoma Research Alliance et al., n.d.).

However, there are limitations to the use of dabrafenib in cancer treatment. In a trial involving dabrafenib and another treatment, serious febrile drug reactions, such as hypotension, dehydration, or renal failure, occurred in 3.7% of patients treated with dabrafenib and none in patients treated with dacarbazine. Furthermore, hyperglycemia occurred in 6% of patients treated with dabrafenib compared to dacarbazine-treated patients.

The Use of PLGA-Based Nanoparticles in Cancer Treatment

Nanoparticles has become a popular method of drug delivery due to their many features. It allows for a wide variety of drugs to be delivered as well as a targeted direction to particular organs or cells (Sadat Tabatabaei Mirakabad et al., 2014). However, nanoparticles must have some requirements, such as biocompatibility, drug compatibility, and proper biodegradation kinetics to properly and safely deliver the drug. Specific size and shape are very important for the efficiency of drug delivery. Nanoparticles can be created through the salting out/diffusion method, which can minimize the problem of unfolding or inactivation of protein during encapsulation (Dubey et al., 2016). Salting out is completed after the polymer and protein are dissolved in a water-miscible solvent, which separates from the aqueous solution when ions like calcium and magnesium chloride are added, which is then diluted with water to allow the diffusion of the organic solvent into the water and formation of polymer and drug containing forming-nanospheres (Dubey et al., 2016). The salting-out agent is then removed through cross-flow filtration (Dubey et al., 2016).

Polylactic Co-glycolic acid (PLGA) is one of the most effectively used biodegradable polymers (Sadat Tabatabaei Mirakabad et al., 2014). Furthermore, it has been approved as a nanoparticle by the US FDA for drug delivery. This is because PLGA undergoes hydrolysis in the body to produce the biodegradable metabolite monomers, lactic acid, and glycolic acid, which can then be metabolized in the body through the Krebs Cycle, meaning that it undergoes chemical reactions to convert into energy, and removed as carbon dioxide and water (Sadat Tabatabaei Mirakabad et al., 2014). This results in very minimal toxicity, which is important because it means that it will result in less inflammation and harm to the organs. Furthermore, it belongs to the synthetic biodegradable polymer category, which mainly includes hydrophobic materials that can be eliminated through normal metabolic pathways (Makadia et al., 2011). This is important because it plays a role in controlled drug delivery, though it is also important to note that a material's biodegradability depends on its biological environment. Particles that are 50 nm and shaped in an ellipsoidal shape can enhance circulation time to promote immunity (National Cancer Institute et al., 2016).

However, one barrier to drug delivery by nanoparticles is that the body identifies hydrophobic particles as alien, causing the reticuloendothelial system (RES) to remove them from the bloodstream (Sadat Tabatabaei Mirakabad et al., 2014). This affects nanoparticles because hydrophobicity is required for nanoparticles to sufficiently interact with the cell membrane. Furthermore, nanoparticles are likely to elicit a molecular response that may have a toxic effect and lead to a susceptibility to infectious diseases, including cancer development. According to several studies, this is because nanoparticle interactions with biological systems can stimulate inflammatory or allergic reactions, activating the complement system (Kononenko et al., 2015). However, this has been studied and methods to prevent this have been formed. Surface modification through the attachment of opsonized particles to macrophages as well as their internalization by phagocytosis can protect nanoparticles from being eliminated from the blood vascular system after intravenous injections (Kononenko et al., 2015).

Conclusion

The proposed skin cancer vaccine is a combination of the immune checkpoint inhibitor atezolizumab (Tecentriq) and the BRAF inhibitor dabrafenib (Tafinlar), all delivered on the biodegradable polymer PLGA nanoparticle. The atezolizumab will block a protein that disrupts the immune system from working and attacking cancer cells, which then allows the immune system to function properly. The dabrafenib blocks the action of an abnormal protein that signals for cancer cells to multiply. Combined, both will help significantly decrease the amount of cancer cells as well as stop the production of more. The PLGA nanoparticle ensures a smooth delivery as well as therapeutic compound protection and sustained and controlled drug release. Furthermore, it is biodegradable, biocompatible, and has strong mechanical strength. The expected results may be promising for the treatment of melanoma, one of the rarest yet most dangerous skin cancers.

Limitations

However, the amount of information we have on the BRAF inhibitor dabrafenib is limited due to its many studies featuring its combination with another drug, trametinib, rather than on dabrafenib alone. It is unsure whether dabrafenib would result in the same results if it were tested alone or with a different drug that is not trametinib. Furthermore, trametinib and atezolizumab are two different kinds of inhibitors. Trametinib is a MEK inhibitor while atezolizumab is an immune checkpoint inhibitor. It is unsure whether atezolizumab would be able to pair as well with dabrafenib as trametinib because a MEK inhibitor blocks two different proteins, MEK1 and MEK2, while an immune checkpoint inhibitor blocks the checkpoints made by immune system cells. While both can help kill cancer cells, they function in different ways.

Atezolizumab is also only approved by the FDA for adult and pediatric patients 2 years of age and older with unresectable or metastatic alveolar soft part sarcoma. Melanoma and Sarcoma differ in the fact that tumors develop in the skin in melanoma while sarcoma usually has soft tissue tumors, developed in the connective tissue. This changed treatment and may also change the way atezolizumab functions for melanoma treatment rather than sarcoma treatment.

Furthermore, the process of collecting results may be limited. Because the vaccine can only be tested on those with active melanoma, as well as those willing to try the combination, the number of participants may be less than enough to show statistical significance. Clinical trials are also very complicated processes, as most take 10-15 years to complete. They must also go through a set of rigid requirements that often pose a challenge for investigators. Furthermore, the combination would need to be first approved by the FDA before, which takes a long and arduous process consisting of the data on the drug's effects being reviewed by CDER as well as the drug's benefits that outweigh its potential risks (FDA et al., 2022). Though the process of this review is very structured, it can become complicated because many aspects of a new and untested drug are difficult to predict and may have unclear benefits and drawbacks. This is why the FDA approval process can take almost decades.

Data Collection Process

The topic of cancer research is personal to me because I have personally seen what it can do to families and friends. Because of this, I applied for a mentorship that allowed me to experience the biomedical engineering of cancer research from an expert in the field. It was through this that I formulated my paper, further expanding on it even after the mentorship ended. I scoured different public databases, exploring the articles that I could access through the internet and using that information to expand my cancer vaccine idea. After I had written up a general paper, I contacted my mentor who had given me the initial idea, Dr. Carcia Carson, and asked her to help me look over the changes that I had made after participating in her mentorship program. My goal for this

paper was to explore possible cancer vaccine treatments that could be formulated through already created and FDA-approved drugs as well as new technology such as nanoparticle-based drug delivery.

Acknowledgments

I would like to thank my advisor for the valuable insight provided to me on this topic.

References

Acharya, S., & Sahoo, S. K. (2011). PLGA nanoparticles containing various anticancer agents and tumour delivery by EPR effect. Advanced Drug Delivery Reviews, 63(3), 170–183. https://doi.org/10.1016/j.addr.2010.10.008

Ascierto, P. A., Stroyakovskiy, D., Gogas, H., Robert, C., Lewis, K., Protsenko, S., Pereira, R. P., Eigentler, T.,

Rutkowski, P., Demidov, L., Zhukova, N., Schachter, J., Yan, Y., Caro, I., Hertig, C., Xue, C., Kusters, L., McArthur, G. A., & Gutzmer, R. (2023). Overall survival with first-line atezolizumab in combination with vemurafenib and cobimetinib in BRAFV600 mutation-positive advanced melanoma (IMspire150): second interim analysis of a multicentre, randomised, phase 3 study. The Lancet. Oncology, 24(1), 33–44. https://doi.org/10.1016/S1470-2045(UCIR et al., n.d.)00687-8

Creative Biolabs. (n.d.). Atezolizumab Overview - Creative Biolabs. Www.creativebiolabs.net. https://www.creativebiolabs.net/atezolizumab-overview.htm

Dubey, S., Mody, N., Sharma, R., Agrawal, U., & Vyas, S. P. (2016, January 1). Chapter 4 - Nanobiomaterials:

Novel nanoplatforms for protein and peptide delivery (A. M. Grumezescu, Ed.). ScienceDirect; William Andrew Publishing. https://www.sciencedirect.com/science/article/pii/B9780323428668000046

FDA. (2022, August 8). Development & Approval Process (Drugs). U.S. Food and Drug Administration; www.fda.gov. https://www.fda.gov/drugs/development-approval-process-drugs

Ge, E., Tian, M., & Lin, W. (2021). A unique fluorescent probe for visualization of cell death via its subcellular immigration from lysosomes to nucleus. Sensors and Actuators B: Chemical, 347(0925-4005), 130656. https://doi.org/10.1016/j.snb.2021.130656

Hines, D. J., & Kaplan, D. L. (2013). Poly(lactic-co-glycolic) Acid-Controlled-Release Systems: Experimental and Modeling Insights. Critical Reviews in Therapeutic Drug Carrier Systems, 30(The American Cancer Society et al., n.d.), 257–276. https://doi.org/10.1615/critrevtherdrugcarriersyst.2013006475

IQWiG (Institute for Quality and Efficiency in Health Care. (2020, January 30). Atezolizumab (Tecentriq) for the first-line treatment of advanced lung cancer: Atezolizumab (Tecentriq) for the first-line treatment of advanced non-small-cell lung cancer. Www.ncbi.nlm.nih.gov; Institute for Quality and Efficiency in Health Care (IQWiG). https://www.ncbi.nlm.nih.gov/books/NBK553382/

Kononenko, V., Narat, M., & Drobne, D. (2015). Nanoparticle interaction with the immune system. Arhiv za higijenu rada i toksikologiju, 66(2.), 97–108. https://doi.org/10.1515/aiht-2015-66-2582

Makadia, H. K., & Siegel, S. J. (2011). Poly Lactic-co-Glycolic Acid (PLGA) as Biodegradable Controlled Drug Delivery Carrier. Polymers, 3(3), 1377–1397. https://doi.org/10.3390/polym3031377

MedlinePlus. (n.d.). BRAF gene: MedlinePlus Genetics. Medlineplus.gov. https://medlineplus.gov/genetics/gene/braf/

Melanoma Research Alliance. (n.d.). Tafinlar (Dabrafenib) for Metastatic BRAF+ Melanoma. Melanoma Research Alliance. https://www.curemelanoma.org/patient-eng/melanoma-treatment/targeted-therapy/dabrafenib-tafinlar
Melanoma Research Alliance. (n.d.-a). Melanoma: Facts & Stats About Skin Cancer. Melanoma Research Alliance. https://www.curemelanoma.org/about-melanoma/melanoma-101/melanoma-statistics-2#:~:text=Overall%2C%20the %20lifetime%20risk%20of
National Cancer Institute. (2015, January 6). Dabrafenib Plus Trametinib for Advanced Melanoma - NCI. Www.cancer.gov. https://www.cancer.gov/types/skin/research/dabrafenib-trametinib
National Cancer Institute. (2016, May 20). Atezolizumab - NCI. Www.cancer.gov. https://www.cancer.gov/about-cancer/treatment/drugs/atezolizumab#:~:text=Atezolizumab%20is%20a%20type%20 of
National Cancer Institute. (2021, August 6). Melanoma Treatment (PDQ®)–Patient Version - National Cancer Institute. Www.cancer.gov. https://www.cancer.gov/types/skin/patient/melanoma-treatment-pdq#:~:text=Melanoma%20is%20a%20disease%20i n
National Cancer Institute. (2023, October 20). Atezolizumab Shrinks Alveolar Soft Part Sarcomas - NCI. Www.cancer.gov. https://www.cancer.gov/news-events/cancer-currents-blog/2023/atezolizumab-effective-alveolar-soft-part-sarcoma
Robert, C., Grob, J. J., Stroyakovskiy, D., Karaszewska, B., Hauschild, A., Levchenko, E., Chiarion Sileni, V.,
Schachter, J., Garbe, C., Bondarenko, I., Gogas, H., Mandalá, M., Haanen, J. B. A. G., Lebbé, C., Mackiewicz, A.,
Rutkowski, P., Nathan, P. D., Ribas, A., Davies, M. A., & Flaherty, K. T. (2019). Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma. New England Journal of Medicine, 381(7), 626–636. https://doi.org/10.1056/nejmoa1904059
Sadat Tabatabaei Mirakabad, F., Nejati-Koshki, K., Akbarzadeh, A., Yamchi, M. R., Milani, M., Zarghami, N., Zeighamian, V., Rahimzadeh, A., Alimohammadi, S., Hanifehpour, Y., & Joo, S. W. (2014). PLGA-based nanoparticles as cancer drug delivery systems. Asian Pacific Journal of Cancer Prevention : APJCP, 15(2), 517–535. https://doi.org/10.7314/apjcp.2014.15.2.517
Shin, M. H., Kim, J., Lim, S. A., Kim, J., & Lee, K.-M. (2020b). Current Insights into Combination Therapies with MAPK Inhibitors and Immune Checkpoint Blockade. International Journal of Molecular Sciences, 21(7), 2531. https://doi.org/10.3390/ijms21072531
The American Cancer Society medical and editorial content team . (n.d.). Melanoma Survival Rates | Melanoma Survival Statistics. Www.cancer.org. https://www.cancer.org/cancer/types/melanoma-skin-cancer/detection-diagnosis-staging/survival-rates-for-melanom a-skin-cancer-by-stage.html
The American Cancer Society medical and editorial content team. (2022, March 22). Treatment of Melanoma by Stage. Www.cancer.org. https://www.cancer.org/cancer/types/melanoma-skin-cancer/treating/by-stage.html
The American Cancer Society medical and editorial content team. (n.d.). Melanoma Targeted Therapy | Targeted Drugs for Melanoma. Www.cancer.org. https://www.cancer.org/cancer/melanoma-skin-cancer/treating/targeted-therapy.html#:~:text=either%20one%20alon e.-
UCIR. (n.d.). Atezolizumab (Tecentriq) Drug Information. Www.ucir.org. https://www.ucir.org/immunotherapy-drugs/atezolizumab