"IMMUNOTHERAPY IN MELANOMA SKIN CANCER"

PROJECT/ THESIS WORK

NEIL M. SHAH (16BPH061)

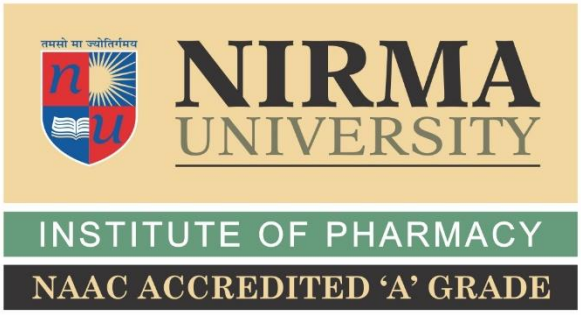
B. Pharm. Semester VII

UNDER THE GUIDANCE OF

Guide

Dr. BHOOMIKA M. PATEL

Dept. of Pharmacology



INSTITUTE OF PHARMACY
NIRMA UNIVERSITY
SARKHEJ-GANDHINAGAR HIGHWAY
AHMEDABAD-382481
GUJARAT, INDIA

MAY 2020

CERTIFICATE

This is to certify that ***"CTLA4: A NOVEL TARGET IN NON SMALL CELL LUNG CANCER"*** *is the bonafide work carried out by* ***SAHIL SHAH****(16BPH087), B.Pharm semester VIII under our guidance and supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 2019-2020. This work is up to my satisfaction*.

Guide: Dr Bhoomika M. Patel

Dr. Bhoomika M. Patel

M. Pharm., Ph.D., DPMM, DPQCQAM
Assistant Professor,
Department of Pharmacology,
Institute of Pharmacy,
Nirma University.

Prof. Jigna Shah

M.Pharm, Ph.D.,
HOD,
Department of Pharmacology
Institute of Pharmacy,
Nirma University.

Dr. Manjunath Ghate

M.Pharm, Ph.D.,
Director,
Department of Medicinal Chemistry,
Institute of Pharmacy,
Nirma University.

Date: 05 / 05 / 2020

CERTIFICATE

This is to certify that ***"CTLA4: A NOVEL TARGET IN NON SMALL CELL LUNG CANCER"*** *is the bonafide work carried out by* ***SAHIL SHAH****(16BPH087), B.Pharm semester VIII under our guidance and supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 2019-2020. This work is up to my satisfaction.*

Guide: Dr Bhoomika M. Patel

Dr. Bhoomika M. Patel

M. Pharm., Ph.D., DPMM, DPQCQAM
Assistant Professor,
Department of Pharmacology,
Institute of Pharmacy,
Nirma University.

Prof. Jigna Shah

M.Pharm, Ph.D.,
HOD,
Department of Pharmacology
Institute of Pharmacy,
Nirma University.

Dr. Manjunath Ghate 15/7/2020

M.Pharm, Ph.D.,
Director,
Department of Medicinal Chemistry,
Institute of Pharmacy,
Nirma University.

Date: 05 / 05 / 2020

CERTIFICATE OF SIMILARITY OF WORK

*This is to undertake that the B.Pharm. Project work entitled **"IMMUNOTHERAPY IN MELANOMA SKIN CANCER"** Submitted by **NEIL SHAH** (16BPH061), B.Pharm. Semester VIII is a bonafide review/research work carried out by me at the Institute of Pharmacy, Nirma University under the guidance of "Dr. Bhoomika M. Patel". I am aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad. According to that, the review/research work carried out by me is not reported anywhere as per best of my Knowledge.*

Neil Shah (16BPH061),
Institute of Pharmacy
Nirma University
Sarkhej - Gandhinagar Highway
Ahmedabad-382481
Gujarat, India

Guide: Dr Bhoomika M. Patel

Dr. Bhoomika M. Patel

M. Pharm., Ph.D., DPMM, DPQCQAM
Assistant Professor,
Department of Pharmacology,
Institute of Pharmacy,
Nirma University.

Prof. Jigna Shah

M.Pharm, Ph.D.,
HOD,
Department of Pharmacology
Institute of Pharmacy,
Nirma University.

Dr. Manjunath Ghate

M.Pharm, Ph.D.,
Director,
Department of Medicinal Chemistry,
Institute of Pharmacy,
Nirma University.

Date: 05 / 05 /2020

CERTIFICATE OF SIMILARITY OF WORK

This is to undertake that the B.Pharm. Project work entitled ***"IMMUNOTHERAPY IN MELANOMA SKIN CANCER"*** *Submitted by* ***NEIL SHAH*** *(16BPH061), B.Pharm. Semester VIII is a bonafide review/research work carried out by me at the Institute of Pharmacy, Nirma University under the guidance of "Dr. Bhoomika M. Patel". I am aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad. According to that, the review/research work carried out by me is not reported anywhere as per best of my Knowledge.*

Neil Shah (16BPH061),
Institute of Pharmacy
Nirma University
Sarkhej - Gandhinagar Highway
Ahmedabad-382481
Gujarat, India

Guide: Dr Bhoomika M. Patel

Dr. Bhoomika M. Patel

M. Pharm., Ph.D., DPMM, DPQCQAM
Assistant Professor,
Department of Pharmacology,
Institute of Pharmacy,
Nirma University.

Prof. Jigna Shah

M.Pharm, Ph.D.,
HOD,
Department of Pharmacology
Institute of Pharmacy,
Nirma University.

Dr. Manjunath Ghate 5/7/2020

M.Pharm, Ph.D.,
Director,
Department of Medicinal Chemistry,
Institute of Pharmacy,
Nirma University.

Date: 05 / 05 /2020

DECLARATION

*I,**NEIL SHAH(16BPH061),** student of VIIIth Semester of B.Pharm at Institute of Pharmacy, Nirma University, hereby declare that my project entitled **"IMMUNOTHERAPY IN MELANOMA SKIN CANCER"** is a result of culmination of my sincere efforts. I declare that the submitted project is done solely by me and to the best of my knowledge, no such work is done by any other person for the award of degree or diploma or for any other means. I also declare that all the information was collected from various primary sources (journals, patents, etc.) has been duly acknowledged in this project report*.

Neil Shah (16BPH061),
Institute of Pharmacy
Nirma University
Sarkhej - Gandhinagar Highway
Ahmedabad-382481
Gujarat, India

Date: 05 / 05 / 2020

DECLARATION

*I,**NEIL SHAH(16BPH061)**, student of VIIIth Semester of B.Pharm at Institute of Pharmacy, Nirma University, hereby declare that my project entitled **"IMMUNOTHERAPY IN MELANOMA SKIN CANCER"** is a result of culmination of my sincere efforts. I declare that the submitted project is done solely by me and to the best of my knowledge, no such work is done by any other person for the award of degree or diploma or for any other means. I also declare that all the information was collected from various primary sources (journals, patents, etc.) has been duly acknowledged in this project report.*

Neil Shah (16BPH061),
Institute of Pharmacy
Nirma University
Sarkhej - Gandhinagar Highway
Ahmedabad-382481
Gujarat, India

Date: 05 / 05 / 2020

ACKNOWLEDGEMENT:

Firstly, I would like to thank Dr.Bhoomika M. Patel for her guidance and counselling during the course of my thesis work, for her patience, motivation, enthusiasm and most importantly immense knowledge, which made the process easier and smooth.

Secondly, I would like to show my appreciation towards my colleague, Mr. Sahil Shah who has helped me throughout this entire project.

Also, I would like to thank Dr.Manjunath Ghate, Director, Institute of Pharmacy, Nirma University for providing all the resources and help needed to complete this project at our institute.

Lastly, I would like to thank my parents for supporting and encouraging me in all my decisions.

ACKNOWLEDGEMENT:

Firstly, I would like to thank Dr.Bhoomika M. Patel for her guidance and counselling during the course of my thesis work, for her patience, motivation, enthusiasm and most importantly immense knowledge, which made the process easier and smooth.

Secondly, I would like to show my appreciation towards my colleague, Mr. Sahil Shah who has helped me throughout this entire project.

Also, I would like to thank Dr.Manjunath Ghate, Director, Institute of Pharmacy, Nirma University for providing all the resources and help needed to complete this project at our institute.

Lastly, I would like to thank my parents for supporting and encouraging me in all my decisions.

Neil Sk

Table of content

Abstract

Malignant melanoma is one of the leading causes of death due to skin cancer. It's incidences have increased in the past few years. Early diagnosis and treatment is still a challenge for doctors. Due to recent advancement in technology and better interpretation of our nervous system, several immunotherapies have been developed and have been supported. Monoclonal antibodies against different immune checkpoints have been revolutionary. Antibodies against programmed death receptor-1 (pd-1) and cytotoxic-t lymphocyte antigen-4 (ctla-4) have shown to increase the life of patients after detection. Combination therapy has also proven useful. Additional modern approaches for ctl immunotherapy activation induction, ctl transition and tumour microenvironment alteration to promote ctl activation. In this review, information and data on these approved immunotherapies is presented.

Table of content

Abstract

Malignant melanoma is one of the leading causes of death due to skin cancer. It's incidences have increased in the past few years. Early diagnosis and treatment is still a challenge for doctors. Due to recent advancement in technology and better interpretation of our nervous system, several immunotherapies have been developed and have been supported. Monoclonal antibodies against different immune checkpoints have been revolutionary. Antibodies against programmed death receptor-1 (pd-1) and cytotoxic-t lymphocyte antigen-4 (ctla-4) have shown to increase the life of patients after detection. Combination therapy has also proven useful. Additional modern approaches for ctl immunotherapy activation induction, ctl transition and tumour microenvironment alteration to promote ctl activation. In this review, information and data on these approved immunotherapies is presented.

Introduction:

Melanoma is the 5th most prevalent cancer and is increasingly increasing, according to NIH SEER. The prevalence of non-melanoma and melanoma skin cancer has risen over the last few decades. There are estimates of 2 to 3 million cancers of the skin without melanoma and 132,000 cancers of the skin with melanoma per year around the globe. In 2018, about 1.2 million individuals were diagnosed in the United States with melanoma skin cancer. According to estimates by the Skin Cancer Foundation, one in three diseases diagnosed were skin cancer, and one in five People will experience skin cancer throughout their lifetime.

This is predicted that the amount of new melanoma patients reported will grow by about 2% in 2020. It is expected that in 2020 the number of melanoma deaths would decline by 5.3 points. Over the last decade (2010 – 2020), the rate of new invasive melanoma reported per year has increased by 47 per cent. It is projected that 6,850 will die of melanoma in 2020. Of all, 4,610 will be males and 2,240 will be females.

The sun light is mainly responsible for melanomas. In fact, 86 percent of melanomas are attributed to ultraviolet (UV) radiation damage from a UK test.

Melanoma patients are mainly divided into different stages:
Step 1 patients seek biopsy therapy within 30 days. The 5 percent greater probability of mortality relative to stage 1 in patients diagnosed within 30-59 days of biopsy. Patients diagnosed with a biopsy for 119 days are 41 percent more likely to die.
If detected early, melanoma can be cured by surgery if there are limited metastasis sites but melanoma of advanced stages (stage IV and stage V) have a much poorer scenario. Historically, the only drug used for treatment was decarbazine which is a chemotherapeutic agent. It was the only chemotherapeutic agent approved by US Food And Drug Administration and was used for curing stage IV melanoma. But it's success rate was only 5% and hence better therapies were desperately needed.

Immunotherapy is vastly different than chemotherapy and radiation with the former targeting the individual's own immune system while the latter interfering with tumor growth and survival. Breakthrough came in 1998 when the first immunotherapy for melanoma was

approved. High dose interleukin-2 was used as monotherapy or was used as combination therapy with chemotherapy. However, continuous usage showed toxicity. [1]

More modern immunotherapy is easily accepted. Melanoma immunotherapy now has four types. Immunotherapy

1) Strategies to restore T-cells' restricted function.
2) Methods used to trigger antigen-specific T-cell responses (accelerators)
3) Methods used to move tumor-specific triggered T-cells.
4) Strategies for the removal of tumor microenvironmental immunosuppressive causes.[2]

Immunotherapy Overview:

Immunotherapy is a form of cancer treatment that helps combat cancer with the help of our immune system. Infections and other diseases are fought by our body through our immune system. The immune system is made up of WBCs and organs and tissues of the lymph system. Immunotherapy is a biological form of treatment. Biological therapy is a method of therapy used to cure cancer by using substances created from living organisms.

When part of its regular operation, the immune system detects and destroys faulty cells, which most certainly prevents or curbs several cancers' growth. For eg, immune cells are commonly seen in and around tumors. These cells, called lymphocytes of the tumor or TIL, inform of an immune system attack from the tumor. People whose tumors are influenced by TILs sometimes perform better than those without TILs.

The different types of immunotherapy used to treat cancer include:

1) Immune Checkpoint Inhibitors - Immune checkpoint proteins form a natural part of the immune system. Their function is to avoid such a strong immune response that it kills healthy cells within the body. Immune tests arise as proteins in immune cell surfaces, known as tumor cells, recognise certain cells and attach to partner proteins such as some tumor cells. These proteins are referred to as immune control level proteins. The "down" signal of T cells is provided to protect the cancer from being destroyed by the immune system by linking the control point and partner proteins. Immunotherapy drugs called inhibitors of the immune control level work by stopping protein from interfering

with their partner proteins. This stops the "down" signal from being transmitted such that T cells will kill cancer cells. One of those drugs works against a checkpoint protein is called CTLA-4. PD-1 and PD-L1 are other proteins on which checkpoint inhibitors act against.

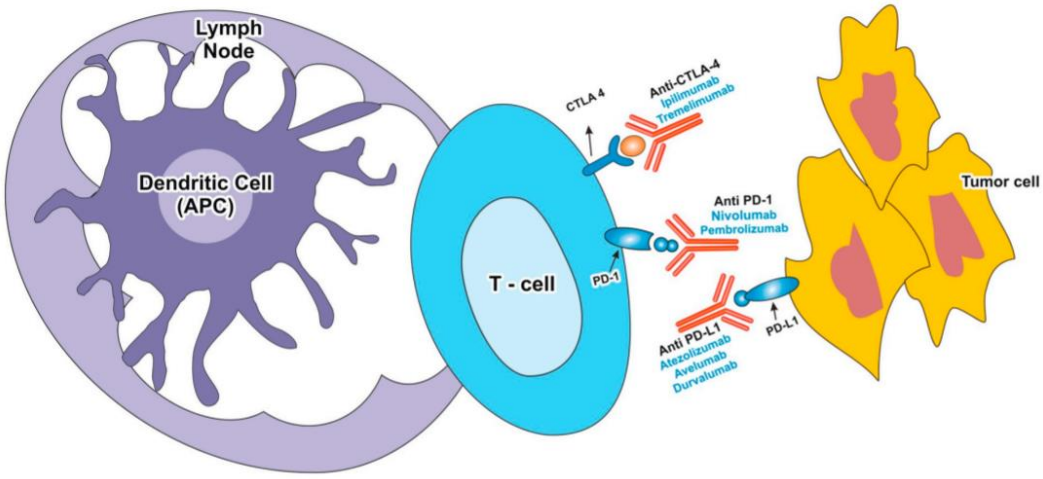


Fig 1. Figure depicts the working mechanism of Immune checkpoint inhibitors. [3]

2) T-cell Transfer Therapy - Transfer therapy with T-cells is a type of immunotherapy that increases your own immune cells' ability to combat cancer. Bridge treatment for T-cells includes two primary types: lymphocyte tumor infiltration (TIL) and CAR T-cell therapy, respectively. Which involve the isolation of your own immune cells, creation of huge quantities in your laboratory and finally a needle in your vein to restore the cells to you. The development of your T cells in the laboratory can take 2 to 8 weeks. You may be offered chemotherapy and, maybe, radiation treatment to kill your immune cells during this period. Reducing the immune cells helps make the T cells that are transferred more effective. After these treatments you will be given back the T cells that were developed in the laboratory through a needle in your vein.

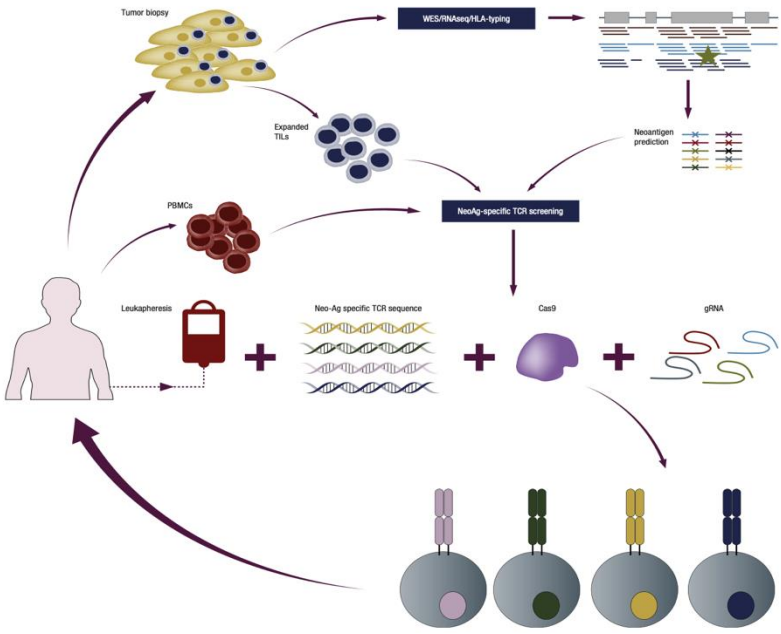


Fig 2. Personalized adoptive T-cell Therapy using gene editing. [4]

3) Monoclonal Antibodies - The immune system proteins generated in the laboratory are monoclonal antibodies. Antibodies are spontaneously formed in our body to assist the immune system in detecting and killing germs causing diseases such as bacteria and viruses. Monoclonal antibodies recognize specific targets, including the antibodies in the own body. Some monoclonal antibodies are used to combat cancer. This is a type of cancer therapy, which implies that it is designed to function for particular targets. Such monoclonal antibodies often tend to improve the immune response against cancer. They are immunotherapy. For instance, some monoclonal antibodies label cancer cells so that they are better identified and killed by the immune system. An example is rituximab, which binds B cells and other forms of cancer cells to a protein called CD20, which allows them to be destroyed by the immune system. B-cells are type of WBCs.[5]

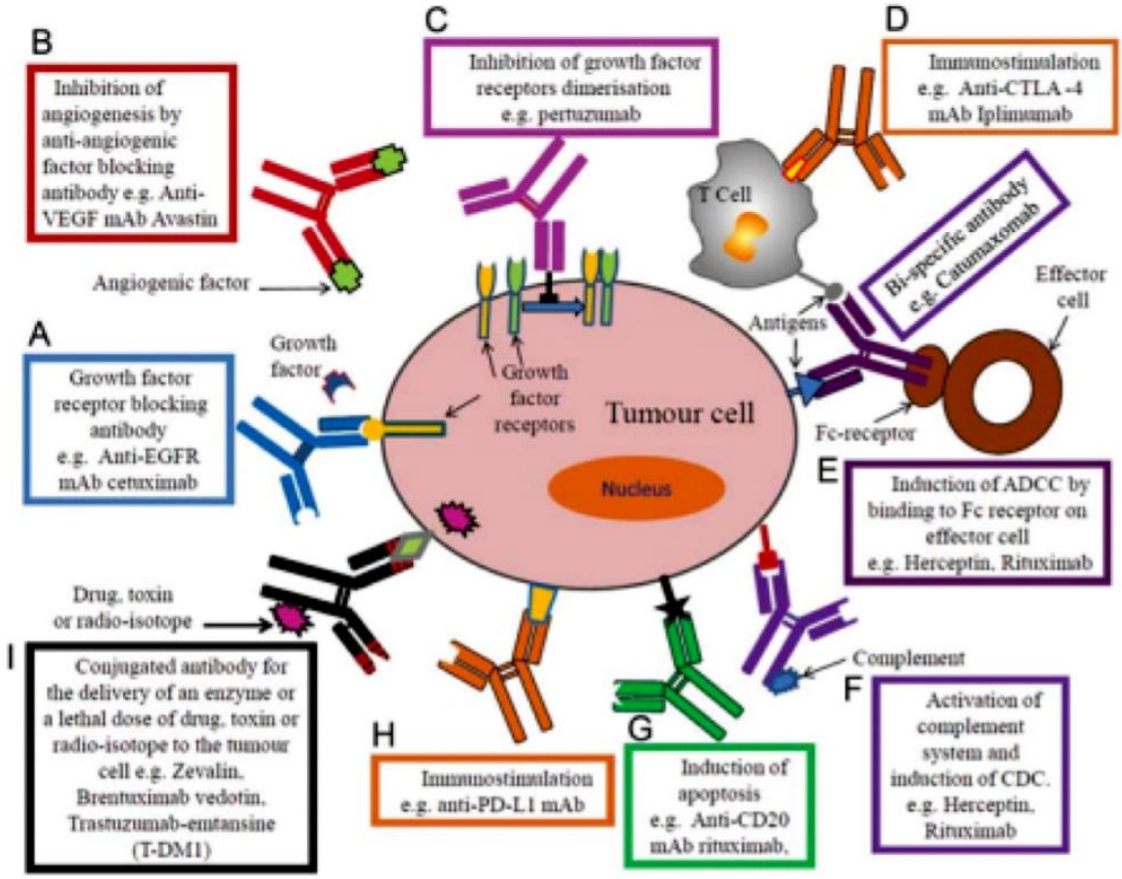


Fig 3. How monoclonal antibodies work is depicted in this picture. [6]

4) Treatment Vaccines - Protect yourself from cancer by strengthening the immune system reaction to cancer cells. Therapeutic vaccinations are not the same as those to avoid illness.

5) Immune System Modulators - Enhances immune reaction to cancer in the body. Many of such factors influence other areas of the immune system, while some impact the immune system more regularly. In modern cancer treatments, the bulk of immune modulating agents are used. Others are used to better combat side effects.

***Immunotherapy for Melanoma*:**

1) Brake release/Immune checkpoint blockade - Immune control points are particles on external surface of molecule that augment an immune reaction's strength and efficiency. The molecules of the relaxing checkpoint (e.g. CD28, OX-40 and 4-1BB) upregulate your immune response and the downregulate your immune reaction by the inhibitory checkpoint particles (i.e. CTLA-4, PD-1, and LAG-4). In the development of the immune system, immune regulation play an essential function. Usually tumor cells by-pass the system and avoid T cells identification. Inhibitor regulation molecules therapeutic blocking promotes T-cell reaction and enhances the function of the antitumor.

1.1) CTLA-4 - Tumors are identified and killed by Effector T Lymphocytes. The activation of T cells is usually synchronized by two consecutive signals: the T unit receptor (T cells recognise TCR antigens in unification with the main histocompatibility complex (MHC) antigen-presenting cell(APCs) molecules and co-stimulating / repressive signal. The contact amongst T-cell and APC is controlled by immune checkpoint molecules. The molecule with the control positions to relax. [7] For e.g., CD28 connects to APC CD80 on T cells. On the T-surface of the cell after a CD28 co-stimulating signal has been activated the receptor CTL-associated antigen4 (CTLA-4) control point molecule is released. CTLA-4 prevents co-stimulation by interacting with CD28 to bind to CD80 on the APC. CTLA-4 prevents T-cell activity by triggering the regulating cells CD4+/CD25+/FoxP3 + T. [8]

PD-1 – Effector T-cells also release controlled immune response point molecule (PD-1), Unit Death-1 (PD-1). The PD-L1 and PD-L2 programmed death cells all bind with the PD-1 ligand. The B7 family contains both PD-L1 and PD-L2. Although treg cells constitutively express PD-L1, interferon-y secreted by active T-effector cells induces melanoma cell production. PD-L1 binding with PD-1 stimulates the cells of the effector T along with the disruption of glucose metabolism and the secretion of IL-2. The PD-L1 interaction with PD-1 therefore inhibits the immune organization from targeting the lump. Monoclonal antibodies that target PD-1 and PD-L1 enhance resistant reaction to

the anti-tumor by blocking PD-1 binding to PD-L. In July 2014, nivolumab, a PD-1-specific monoclonal antibody, was authorized for the healing of ineradicable skin cancer in Japan (the sanction came later in the world). The average reaction rate for melanoma patients was 28 percent (26 of 94 patients), while for non-small unit lung cancer patients it was 18 percent (14 of 76 patients), and for renal cell cancer casualties it was 27 percent (9 of 33 patients). In comparison, following nivolumab, the one-year rate of survival of formerly not treated patients with secondary melanoma with no BRAF mutation was 72.9% greater than that of dacarbazine-treated patients (42.1 percent). With the mean progression-free survival and neutral reaction rate (40.0 vs. 13.9 percent), Nivolumab was superior than dacarbazine. A further important study found that median progression free survival was 11.5 months rivalled with 2.9 months for ipilimumab and 6.9 months for the nivolumab treatment of patients with previously untreated nivolumab, indicating that the additive effect of the immune blocker was immune regulation point blocker. Nevertheless, 55.0 percent of patients in the nivolumab plus ipilimumab group reported adverse effects associated with grade 3 or 4 medication, more than those in the nivolumab (16.3 percent) or ipilimumab (27.3 percent) categories. But physicians should pay particular attention in using combination treatments to treat adverse events.[9]

FDA approved agents - Ipilimumab is a human FDA licensed CTLA-4 blocking antibody for patients who acquire unresectable or metastatic melanoma or as a phase III resected adjuvant.

Nivolumab (Opdivo) and pembrolizumab (Keytruda) are both PD-1 blocking antibodies that were approved in 2014 by FDA for use in melanoma. Nivolumab is recommended as a single agent for the diagnosis of unresectable or metastatic melanoma, or in conjunction with ipilimumab. This is also indicated as adjuvant therapy for patients with stage IIIB, IIIC, or IV cutaneous melanoma completely resected.

Other Immune Checkpoints - The gene-3 activation of lymphocytes (LAG-3) and the immunoglobulin and mucin domain-3 T cells (TIM-3) are both repressive barrier particles. Both inhibit energizing signals in effector T cells, identical to CTLA-4 and PD-1. These are articulated by Treg cells, which are active in the immuncompromised process. Medications that obstruct these particles are presently under clinical trials.

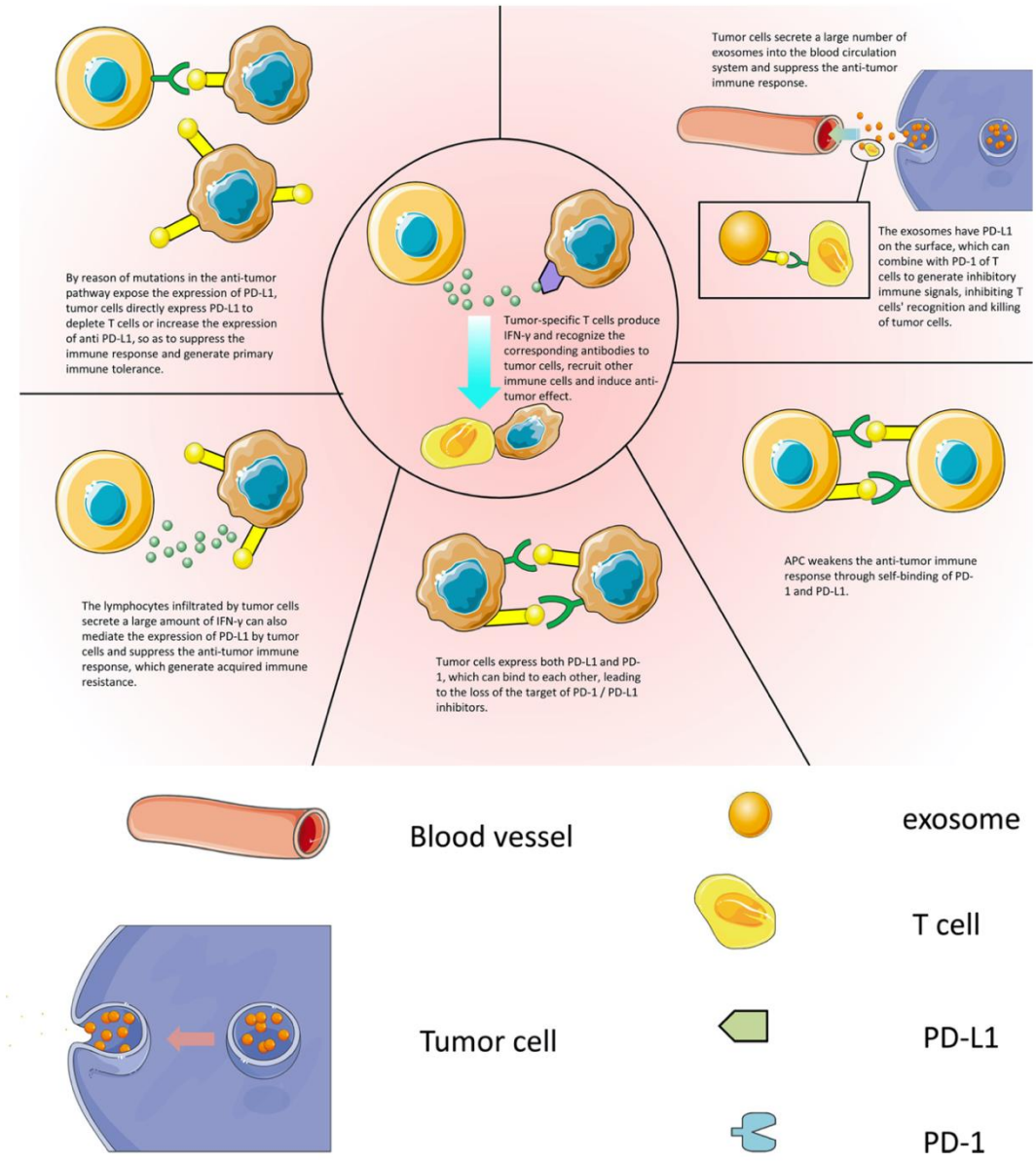


Fig 4. Mechanism of drug resistance in immunotherapy. [10]

Table 1. Immunological target molecules expressed by melanoma cells

Target	Agent	Current development	Function
CTLA-4	Ipilimumab	FDA approved	Checkpoint blockers
	Tremelimumab	Phase II	
PD-1	Nivolumab	FDA approved	
	Pembrolizumab	FDA approved	
	AMP-224	Phase I	
	PDR001	Phase II	
PD-L1	Atezolizumab	Phase I	
	Durvalumab	Phase I-II	
	Avelumab	Phase I	
	BMS-936559 (MDX1105)	Phase I	
LAG-3	IMP321	Phase I	
	BMS-986016	Phase I	
	LAG525	Phase I	
TIM-3	MBG453	Phase I	
4-1BB (CD137)	Urelumab	Phase II	Co-stimulatory agents
	PF-05082566	Phase I	
GITR	TRX518	Phase I	
CD40	CP-870893	Phase I	
	Dacetuzumab	Phase I	
CD27	Varlilumab	Phase I-II	
IDO	Indoximod	Phase I-II	Immunomodulators
	Epacadostat	Phase I-II	
VEGF	Bevacizumab	Phase I-II	

Abbreviations: CTLA-4, cytotoxic T lymphocyte-associated antigen 4; GITR, glucocorticoid-induced TNFR-related gene; IDO, indoleamine 2,3-dioxigenase; LAG-3, lymphocyte activation gene-3; PD-1, programmed cell death-1; PD-L1, programmed cell death-1 ligand-1; TIM-3, T cell immunoglobulin and mucin domain-3; VEGF, vascular endothelial growth factor.

Table 2. Combination immunotherapy for advanced melanoma

Target	Agent	Number	CR	ORR	Ref
CTLA-4 PD-1	Ipilimumab Nivolumab	314	36%	57%	[13]
CTLA-4 IDO	Ipilimumab Epacadostat	30	10%	30%	NCT01604889
PD-1 IDO	Pembrolizumab Epacadostat	7	29%	57%	NCT02178722
CTLA-4 Virus	Ipilimumab T-VEC	18	33%	56%	NCT01740297
PD-1 Virus	Pembrolizumab Talimogene laherparepvec	16		56%	NCT02263508

Abbreviations: CR, complete response; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; IDO, indoleamine 2,3-dioxigenase; ORR, overall response rate; PD-1, programmed cell death-1.

2) Stimulation of CTLs –

2.1) IL-2 remedy - IL-2 aims to transform ingenuous T cells into active T cells. The high IL-2 effects in a comprehensive reaction rate of 7 per cent and a partial response rates of 10 per cent for treating melanoma were suggested by Rosenberg.[11] As the high dose of IL-2 frequently triggers severe side consequences with various organs, combined therapies with the little dosage iL-2 and iL-2 is of considerable concern.

2.2) Cancer Vaccines (Peptides and Dendritic Unit Therapy) - CTLs recognize and target cancer-derivative antigenic peptides, encompassing 8–10 amino acid residues, which can be found on the surface of the cancer cell of MHC mols. For cancer vaccinations, mRNA, DNA, peptides, antibodies should be identified. MAGE-A3 was used for multiple melanoma vaccinations, consisting of peptides from the Wilms 1 gene, glycoprotein 100 (gp100), and melanoma-assisted antigen 3. Unfortunately, the primary endpoints were not reached in a phase-3I study of MAGE-A3 vaccine based therapy. Separate from the usage of cancer-definite antigens, ancillary are likely to be significant; this is due to adjuvants improve allergen identification and enhance immune responses. Although conventional vaccine ancillary, such as incomplete Freund's, have been used in many initial experiments, the potential of DCs to serve as an immune adjuvant has drawn significant interest. To achieve this, in the occurrence of cytokines such as "granulocyte macrophage colony-stimulating factor" (GM-CSF), DCs are insulated and flexible ex vivo (ex vivo DC therapy), either from monocytes or hematopoietic stem cells; cells grow through exposure to cancer specific antigens. Subsequently administer patients with the advanced DCs. Although in ex vivo DC therapy, immune answers to cancer unit were detected, tenacious tumor deterioration was limited to just a few instances. In vivo DC treatment, in vivo DCs are enabled to promote development and successful absorption of tumor antigens, has been investigated in several studies. A recent research described CD103 + DCs as potentially effective CTL stimulators. CD103 + DCs cause T-cell-dependent regression of tumors, and the excess of CD103 + DCs is consistent with quantifiable outcomes.[12]

2.3) Neo-Antigens - Non-self-specific peptides utilized by cancer cells are neo-antigens. Technological advances including sequencing for the next decade have allowed highly immunogenic neoantigens expressed across multiple cancers to be identified. The therapeutic role of immune-reaction antagonists, such as anti-CTLA-4 and anti-PD-1, is gaining attention from neo-antigens. [13] Furthermore, the immunogenicity of neoantigens often influences the outcomes of the shift treatment of tumor infiltration lymphocytes (TIL). Vaccine diagnosis utilizing individualized neo-antigens is now under review for clinical trials.

2.4) Oncolytic Virus Therapy - Underneath oncolytic virus remedy, restorative viruses rapidly and effectively replicate inside cancer cells to kill disease. Oncolytic viruses are potentially part of cancer vaccine as virus-induced type I interferon efficient in antigen-specific protection against cancer cell components. Produced not only in open cell death, but also indirect stimulation of specific cancer immune responses, the effects of oncolytic virus therapy.[14]

2.5) Co-Stimulatory Agents - The activation of T cells includes co-stimulatory signals (including TCR signals). Effector T cells produce many stimulatory power molecules, including the TNFR associated gene Glucocorticoid (GITR) and OX40. OX40 plays a part in stimulating, maintaining and growing T-cells in cytokines. Through preventing apoptosis of activated T cells, GITR promotes the production of and proliferation of T cells. Cells from Treg also generate OX40 and GITR, and their suppressive function is mitigated. Clinical experiments are also studying proteins that are specific to such molecules.

3) Adoptive Unit Therapy-- The running of autokinetic or allogeneic tumor-sensitive T or NK cells in order to improve tolerance to the anti-tumor is necessary for assumptive cell therapy.

3.1) TIL Therapy - Cellulite T, cancer-reactive, is sometimes stored both in TILs and in blood cells in the periphery. Relevant antigens comprising cancer-antigenic peptides and tumor units are then triggered by the in vitro stimulation and pass to the patients. Rosenberg also created a form of TIL conversion treatment, utilizing immunosuppressants and whole body radiation, in vitro-activated TILs, following lymphocyte elimination. Surprisingly, the rate of answer is over 70%. T-cells triggered by neo-antigens tend to have the therapeutic effect.[15]

3.2) TCR gene therapy - TCR tumor receptor genetic material are emulated from TILs and then passed to lymphocytes for these cloned TCR genes. A variety of studies have been carried out to date. Usage of melanocyte-specific TCRs contribute to harmful effects in the face, hair, and internal ears (melanin demonstrated at all locations in the head, as well as at the last two locations). Thus, TCR-gene therapy physicians should be vigilant of cross-reactions in ordinary tissue.[16]

4) Inhibiting Immunosuppression with Tumor Microenvironment - Several reports have confirmed the therapeutic efficacy of cancer immunotherapy. However, only small therapeutic responses can be seen in immunotherapies. The reality that cancer patients are still immune compromised may be one of the main factors for immunotherapy resistance. To boost clinical results, we also need to build approaches to overcome immunosuppression.

4.1) BRAF Inhibitors - Mutations found in 30-60% of melanomas of BRAF promote a micro-environmental immunosuppression by triggering MAPK that entails malignant transformations and proliferation of the mitogen-active protein kinase. In-vitro studies indicate melanoma units secreting immunosuppressive cytokines, comprising IL-10, IL-6, and VEGF. Of special interest is the decreased development of immunosuppressive cytokines by an inhibiting MAPK signalling in Melanoma Cells. Supernaturated cultivators from skin cancer units avoid DCs from developing T cell

invigorate cytokines I nevertheless, these are diminished by MAPK-inhibitor therapy which supports the finding that MAPK-signalling activation promotes immunosuppressive status. In fact, histopathologic study of the tissue in casualties with metastatic skin cancer exposes that BRAF, vemurafenib, enhances development of melanoma-precise allergens as well as reducing the output of immunosuppressive cytokines, contributes to tumor penetration with CD8 + T cells. The amount of CD4 + T cells that have tumor penetration also decreases with vemurafenib. Therefore, the results of BRAF inhibition include reductions in immunosuppressive signals that facilitate T and NK tumor infiltration, reduce the amount of immunosuppressive cells and restore the expression and demonstration of tumor antigen through Class 1 molecules.[17]

4.2) Anti-CCR4 Antibodies - CCR4 is the chemical receptor that controls leukocyte transport and other cells for many chemokines, for example CCL-2, -4 and -5. The diagnosis of adult T cell leukaemia is focused on anti-CCR4 antibodies. When CCR4 is expressed by Tregs, tumour tolerance is improved by the elimination of certain cells through anti-CCR4 antibodies. Present clinical studies for melanoma are performed in antibodies.[18]

4.3) Chemotherapy – Immunity is affected by Anti-Cancer Agents. Cyclophosphamide, gemcitabine, and docetaxel, for example, are fewer than Treg cells, while gemcitabine, docetaxel and doxorubicine are less than suppressive myeloid cells (SDCs).[19] The dosage and timing of distribution of anti-cancer agents are therefore likely to be not significant. It is worth remembering that certain anticancer agents such as cyclophosphamide, doxorubicin, mitoxantrone and oxaliplatin induce immunogenic cell death (ICD). Unlike necrosis and apoptosis, an immune reaction is more likely to occur via ICD. ICD induction has a range of advantages about the immune response to antitumor, including increased cancer cell-derived DC antigen accumulation, augmented activation of DCs and T cells, and augmented tumor invasion of these cells. ICD produces calreticulin, a signal known as 'eat me,' on the exterior of the carcinogenic cell, which contributes to enhanced DC phagocytosis. Moreover, ICD causes the release in extracellular space of an adenosine triphosphate (ATP), which draws immune cells into tumor tissue, as a so called "find me" signal. The secretion of the ATP also stimulates the inflammasome by binding to a purine receiver and hence

promotes the IL-1β secretion. However, release from tumor cells with strong activity community box 1 stimulates DCs as a ligand for toll-like receptor 4. Owing to the absence of heat shock protein (HSP), like HSP70 and HSP90, antigen absorption is often enhanced in the context of a tumor-derived antigen complex.

4.4) Anti-VEGF Antibodies - VEGF is a vital intermediary of immune suppression and, as a consequence, vegetable blockage may have a beneficial influence on anti-tumour immune response, as well as direct effects on the tumor vasculature, by inhibiting Treg cells and MDSC[43]. Blocking VEGF is an important treatment for various cancers. Present clinical studies for melanoma are performed in antibodies.

5) Predictive bio-markers for Immune Checkpoint Obstruction - Many reports show that an immune-active microtumour may associate with better endurance and/or answers in melanoma patients to PD-1/PD-L1 receptor inhibitors. CD8 + T unit tumor intrusion heads an anti-PD-1 antibody melanoma response. In fact, expression of PD-L1 can be a strong tumor reaction marker for anti-PD-L1 antibodies. Moreover, antibodies of PD-1 and PD-L1 can also be utilized for patients with no PD-L1 expression. The expression of PD-L1 can differ since interferon-μ is caused by the T cell secretion. To order to be reliable, immunostaining approaches that are unique to PD-L1 must also be standardized. Moreover, a descriptive measure of clinical action is the amount of monocytic MDSCs. A limited number of monocytic MDSCs are likely to be related to an ipilimumab clinical reaction. Tumors that have large numbers of corporal mutations typically lead to blockers at immune sites, such as PD-1 and CTLA-4 antibodies. These transformations allow neo-antigens to be present. The DNA repair gene 2 (BRCA2), is sometimes defective in a tumor that responds to the blocker of the immune control stage. In total, the increased survival is related to strong mutational loads. Neo-antigen heterogeneity often can influence tumor cell immune responses; clonal neo-antigens, in addition, may be a stronger target than heterogeneous neo-antigens[20]. In addition, these findings indicate that immunotherapy may be an successful cure for melanomas possessing large concentrations of somatic mutations; that is because neoantigens that promote the tumor invasion of CD8 + T cells are more prone to manifest such tumors. In tumors with a limited quantity of genetic transformations, however, immunotherapy

may also be successful. To enhance immunotherapy for melanoma, a more thorough analysis of the underlying mechanism is needed.

***Information about Clinical Trials in Tabular Form*:**

1) Study of Combination of Ipilimumab and Nivolumab in Patients With Melanoma

---

1) Tracking Information –

First Submitted – November 18, 2016
First Posted –November 2, 2016
Results first submitted – February 13, 2020
Results first posted– March 11, 2020
Last update posted – March 11, 2020
Actual Study Start —November 29, 2016
Actual Primary Completion – November 2018

Current Primary Outcomes - The adverse events are assessed in a specific language criterion for adverse events (CTCAE) V4 during a trial [time framework: 12 weeks after care start], which involves the adverse events.

Original Primary Outcomes - The efficacy of protocol therapy (adverse events) [Time Frame: From the start of protocol therapy to 12 weeks]
The adverse effects are measured in compliance with Standard Adverse Impact Terminology Guidelines (CTCAE) V4.

Current Secondary Outcomes - In the process of a study [time framework: 12 weeks after beginning treatment] the harmful effects are measured according to the harmful incidents language standard (CTCAE).

Original Secondary Outcome - • Assessment of immune response [Time framework: up to 3 months]
• Relapse period [Time Frame: up to 4 years]

2) Description Information –

Title - Ipilimumab and Nivolumab Combination Analysis in Melanoma Patients. A Experimental Ipilimumab Study With Nivolumab for participants with IIIB / IIIC / IV resected phases.

Brief Abstract - The goal of this research is to assess the efficacy of care for resected type IIIB / IIIC / IV melanoma with Nivolumab in conjunction with Ipilimumab.

Detailed Report - Researchers believe that blocking the CD8 + T cytotoxic lymphocytes in human beings (CTLs), particular for tumors associated antigens (i.e. self antigens), will have a beneficial impact in the proliferation and operation of CD8 + T cytotoxic lymphocytes (CTLs), which would result in enhanced anticancer therapying.

Phase of Study – Phase 2

Disease – Melanoma

Study Arms - Nivolumab and Ipilimumab.
Dosage of Nivolumab+ Ipilimumab in cycle 1 will consist of 3 mg / kg and 1 mg / kg respectively. There are 4 dosages of Nivolumab and 4 doses of Ipilimumab-induction treatment period, given every three weeks for 12 weeks (stage 1) in total. The 2-5 dosage would be 480 mg Nivolumab flat in 4 weeks daily (Q4W) for 48 hours, respectively.

3) Employment Information –

Employment Status – Currently not employing.

Eligibility Principles –

• Age at least 16;
• Resect process IIIB / IIIC / IV melanoma histologic evaluation without proof of clinical and radiological illness and harmful surgical margins. ;
Eastern Cooperative Oncology Community (ECOG) is permitted to participate in all melanomas irrespective of the primary location of the disease;
• Radiation or immunotherapy prior to prescribing the test medication, (such as tumor vaccination, cytokine, or cancer-control growth factor). All adverse effects must have either recovered to normal or have stabled.
• Previous-treated brain or meningeal metastases should be gradually demonstrated for a total of 8 weeks without magnetic resonance imaging (MRI) and off-immunosuppressive systemic steroid doses (> 10mg / day prednisone or equivalent) for a least 2weeks previous to the medication administration study;
• Routine radiation treatment must be performed at least four weeks prior to delivery of the drug. Once the treatment was prescribed, previous focus rehabilitation was performed for least 2 weeks. None of the medications (strontium and samarium) within 8 weeks of the test study;
• Immunosuppressive amounts of chronic pharmaceutical drugs, such as steroids or topical steroids ingested (amounts > 10 /day prednisone, or equivalent), must be halted for at least two weeks until the medication administration of the study;
• Nitrosourea therapy performed at least 6 weeks before any medicines were given;
• Before treatment, a period of 4 weeks must be done until the medication is actually delivered. Surgery involving local / epidural anaesthesia must be performed at least 72 hours prior to the execution of the medication test and participants recovered;
• Childbearing future females must: use effective contraceptive method(s). WOCBP will use an effective abortion procedure for 23 weeks after the last dosage

of investigative pharmaceutical products (30 days plus the period needed for 5 half-lives of nivolumab).

• Women with childbearing ability must have an unfavourable serum or urinary pregnancy check within 24 hours of nivolumab initiation (minimum sensitivities 25IU / L or equivalent units of HCG).

•In women that are deemed not to be mothers, the following requirements must be met:

- postmenopausal for at least 24 consecutive months;
- surgically sterile (i.e. hysterectomy or bilateral oophorectomy);
- females with menstrual irregularity or hormonal substituting therapy must be recorded with serum follicle enhancing hormone care.

• People who have intercourse with WOCBP and use some preventive treatment at a failure rate less than 1% a year Nivolumab is being adhered to for 31 weeks after the final dose of the investigating drug Women who are not of childbearing age (i.e. post-menopausal or surgically sterile) people who have sexually involved WOCBP males are to adhere to contraceptives.

• Participants will, after having thoroughly clarified the essence of their studies and readiness to comply with the schedule of study access and any limitations and constraints put out under this Procedure, have read, recognized and given their written informed consent and HIPAA approval.

4) Criteria for Exclusion –

• All participants that satisfy all of the following requirements during the evaluation will be considered eligible for research admission.

• Past of serious responses to certain mAbs;

• Prior malignancy non-melanoma diagnosed during the last 2 years but locally curable carcinoma that seems to have been treated, such as basal and squamous skin cancer, superficial bladder cancer, or in situ prostate, cervical and breast carcinoma;

• participants with an advanced autoimmune disorder, or with a recorded history of autoimmune disease or body syndrome.

• Established HIV or suspected HIV-positive tests with hepatitis B virus surface antigen (HBV SAg) or HCV RNA suggesting ongoing or persistent infection;

- Prior treatment with anti-PD-1, anti-PDL-2, anti-CTLA-4 antibodies (or some other antibody targeting T antibody),
- Proven experience with positive results on HIV or documented AIDS (acquired immune deficiency symbols);
- Concurrent health status which might include the usage of immunosuppressive or immunosuppressive treatments with systemic or absorbable topical corticosteroids;
- The underlying medical disease (e.g. diarrhoea disease) which, in the view of the Investigator, may risk the administration of the research product or both test drugs;
- Pregnant
- Present presence with any drug, chemotherapy or medical procedure or previous interest in the case.
- If aggressive brain metastases or leptomeningeal metastases exist, patients shall be removed. Brain metastases participants are suitable for diagnosis of metastases with no worsening symptoms from MRI for [the duration of 4 weeks or more] after therapy has been completed, within 28 days of the original dose of nivolumab. No immunosuppressive doses (> 10 mg / day prednisone equivalents) of systemic corticosteroids (> 2 weeks prior to the administration of the medication) must also be needed.
- As the mixture of nivolumab or nivolumab / ipilimumab is likely to contribute to liver toxicity, medications with hepatoxicity predisposition should be used with caution in nivolumab-containing patients.
- Adverse medication effects and allergies

1. Knowledge of medication ingredients allergy analysis
2. Knowledge of severe responses against monoclonal antibodies

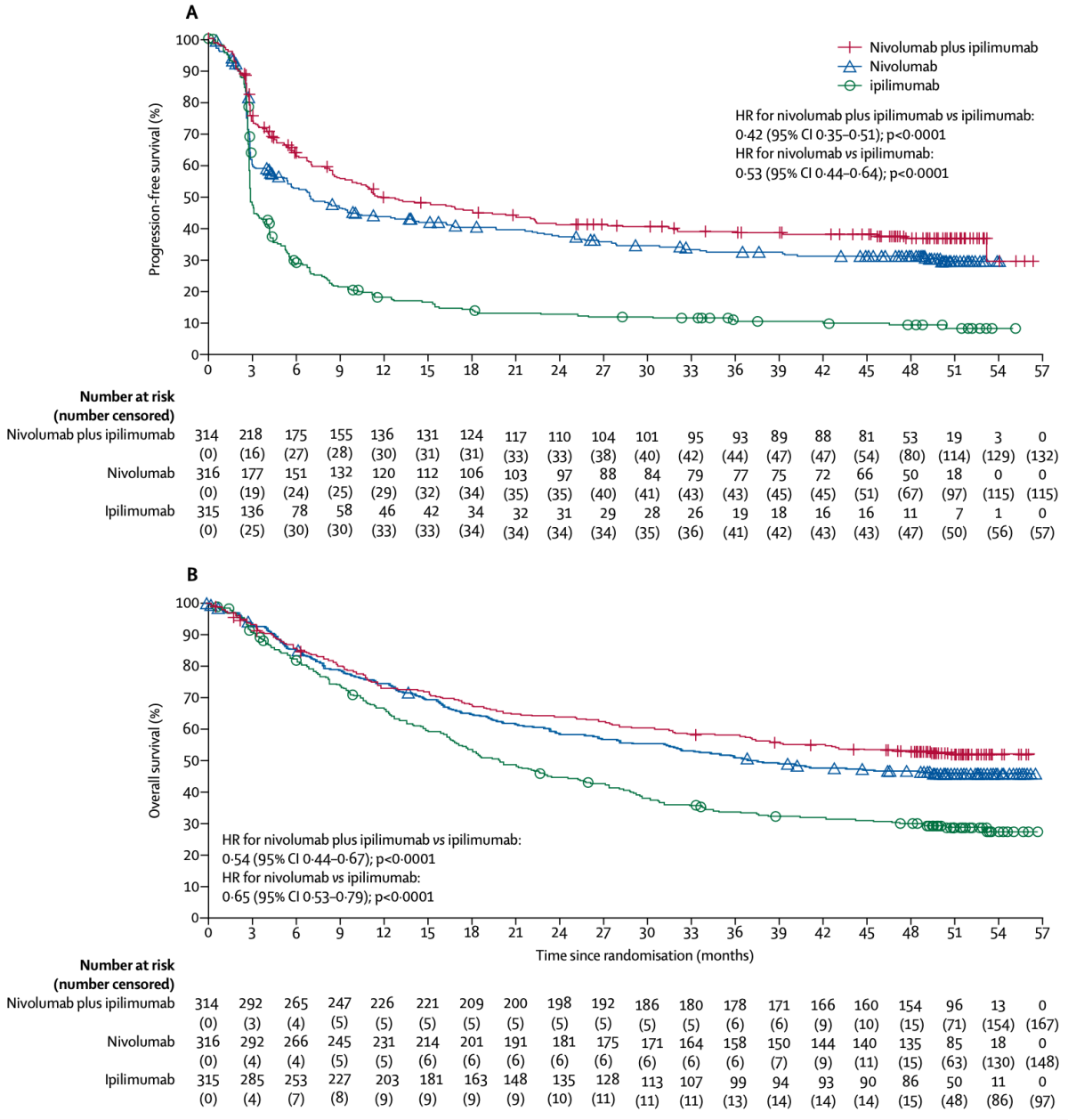


Fig 5. Graphical representation of the clinical trial findings. [21]

2) Phase 3 Trial in Subjects With Metastatic Melanoma Comparing 3 mg/kg Ipilimumab Versus 10 mg/kg Ipilimumab

---

1) Tracking Information –

   Presentation Date – January 18, 2012
   Publication Date –January 24, 2012
   Date of submission – February 3, 2017
   Date of results– March 24, 2017
   Final review date – July 31, 2019
   Date of definite onset —February 17, 2012
   Date of primary conclusion– February 6, 2016.

2) Current Primary Outcome - Overall Survival (OS) is established between the date of randomization and the cause of death for each person [Time Frame: Roughly speaking 48 months (evaluated up to February 2016)]. At the latest documented date of survival, Recovery period for non-dead subjects was censored. 95% intervals of trust were measured using the Brookmeyer and Crowley test, both median and linked.

3) Original Primary Outcome - The OS is described as the period between randomisation and death in each subject [Time Frame: Approximately 44 months after the first subject is randomised]. If a person has not died, the topic is censored until the last documented (last identified) date of touch (last documented) OS is calculated after 540 deaths. Interim review despite 360 deaths

4) Current Secondary Outcome –

   • Progression Free Survival (PFS) by MWHO Criteria [Time Frame: Randomised to 540 (approximately 48 months) deaths]

PFS was described as the period between the day on which a randomization occurred and the day on which it continued or expired. A person who had expired without prior advancement was contemplated to have proceeded on the date of death. PFS was censored on the last tumor evaluation day before resection for a patient who was exposed to resection after randomization. PFS was blocked on the last evaluable date for those who were alive and had not progressed. On the day of the randomization applicants who were not killed and who had no post-baseline test is amended.

The date of PD following the answer was taken in PFS analysis for accomplices who suffered from progressive disease (PD) previous to the Week 12 and the resulting Stable Disease (SD), Partial Answer (PR), or Full Response, otherwise censored on a tumor check. The Brookmeyer Crowley equation was used to measure mean and 2-sided CI 95%.

• Highest Overall Responses Ratio (BORR) by mWHO Criteria [Randomization Timeframe: 540 fatalities (around 48 months)]

The BORR was defined by a clinical arm as the total number of RPPs with the CR or PR BOR separated by the total number of RPMs. Each person who was not of BOR's interest, e.g. because of the absence of or 'non-evaluable' evaluations, was encompassed in the measurement denominator (i.e. was called a BORR outcome non-responder). The Clopper and Pearson process determined 95 percent two-sided exact trust intervals.

• mWHO Criterion for Disease Prevention Levels (DCR). [Time Frame: Randomization Period up to 540 deaths (around 48 months)]

The DCR was described by medication arm as the overall number of unplanned arm accomplices with CR, PR or SD separated by the overall number of random arm applicants. Each person who was of little benefit to Disease Control (DC), e.g. due to incomplete or "unevaluable" assessment was included in the measurement denominator (i.e. a DCR Outcome non-responder). The Clopper and Pearson approach was used to measure 95 percent of 2-side exact trust intervals.

• Reaction duration (RD) by mWHO [Time Frame: from RDD to 540 mortality incidents (around 48 months)] requirements

Length of reaction for applicants whose BOR was CR or PR was calculated, since the period was first defined for the total PR or CR answer (whichever

condition was first documented) and the date of illness or demise (whichever first took place) within the date determines criteria. The length of responses was censored on the last evaluation tumor evaluation date before the resection of participants who were tumor resected after reaction but before disease progression. The PD date following the corresponding (when available) in the study of answer period was used for a member who had SD, PR or CR BOR at Week 12 or a verified PR or CR answer before Week 12. The length of the reaction was suppressed on the date of the last evaluable tump evaluation, for those participants who stayed alive and did not advance after responding. The Brookmeyer Crowley approach was used to measure the median and associated 2-side 95 percent trust intervals.

• Stable diseases period by mWHO Standards [Time Frame: From randomization date to 540 deaths (about 48 months)]

The stable disease period was defined for participants with an SD BOR between the recording of first SD and the PD or death date (where applicable). The length of a controlled disease was suppressed at the last tumor evaluation before resection for patients who had undergone tumor resection after week 12 but before the disease advancement. The date of the post-week PD (if accessible), was used in the study of the length of the steady disease in applicants who had SD BOR at weeks 12. The period of stable disease was censored on the date of the final tumor evaluation for patients with BOR in SD who had not advanced afterwards and were still living. 95% intervals of confidence were measured using the Brookmeyer and Crowley processes, medium and linked two-sided.

• Time Period [From time: around 66 months] Total survival rate.

OS is described as the period between the date of randomisation and the death attributable to some cause for each participant. At the latest documented date of survival, Recovery period for non-dead subjects was censored. Calculations of survival levels were rendered using the log-log confidence intervals dependent on Kaplan-Meier calculations. The rate of survival at x year(s) is outlined as the likelihood of an person surviving after randomization at x year(s).

• Time Frame: Randomization period up to 540 mortality incidents (about 48 months) [Participant average recovery with Baseline brain metastasizing]

OS was calculated between a randomization date and mortality attributable to every trigger for any person with underlying brain metastasis. At the latest

documented date of survival, Recovery period for non-dead subjects was censored. The Brookmeyer and Crowley Method measured median OS and related 2-sided intervals of 95 percent confidence.

5) Original Secondary Outcome –

• [Time frame: Approximately 44 months after the randomization of the first subject] Progression Free Survival (PFS).

The PFS shall be specified for each topic between the randomization date and the advancement or death date, whichever first occurs after the incidence of 540 deaths.

• [Time Frame: Roughly 44 months after the first topic randomization] Best Overall Answer Rate (BORR)

BORR is classified as the total sum of arbitrary people in arm with a Complete Response (CR) or Partial Responsibility (PR) best overall answer (BOR), divided into the total number of random BORR items, after 540 mortality events have occurred.

• [Time Frame: Roughly 44 months after randomisation of the first subject] Disease Control Intensity (DCR)

In each arm of CR, PR, or Stable Disease (SD) BOR the total number of randomized subjects separated by the average number of random subjects in the arm of the DCR is calculated after 540 death cases.

• [Time Frame: approx. 44 months after randomization of the first subject]

The period of a response topic is determined by the time between the date estimation evaluation criterion and the date of success or death, which happens in the first place and after 540 deaths, for the first time the response length is assessed.

• Safe disease period [time framework: about 44 months after randomization of the first subject]

The period of the stable disease shall be specified for subjects with SD BOR between the first diagnosis of SD and the first date of Progressive Disease (PD) or death (whatever the first occurs).

6) Descriptive Information –

Title - Ipilimumab randomised double-blind phase III analysis prescribed at 3 mg / kg vs 10 mg / kg in participants with unresectable or metastatic Melanoma never diagnosed or untreated.

Brief Description - The goal of this research is to establish if Ipilimumab at dose 10 mg / kg is more life-long than Ipilimumab at dose 3 mg / Kg for individuals with unresectable skin cancer.

Phase – Phase 3 Study.

Disease – Melanoma

7) Recruitment Information –

Employment Principles – Melanoma of Stage 3 or Stage 4.
Quality score of 0 or 1 of the Eastern Cooperative Oncology Group (ECOG)

Criteria for Exclusion - Metastases in the brain that are symptomatic or require care.
Autoimmune disorder history.

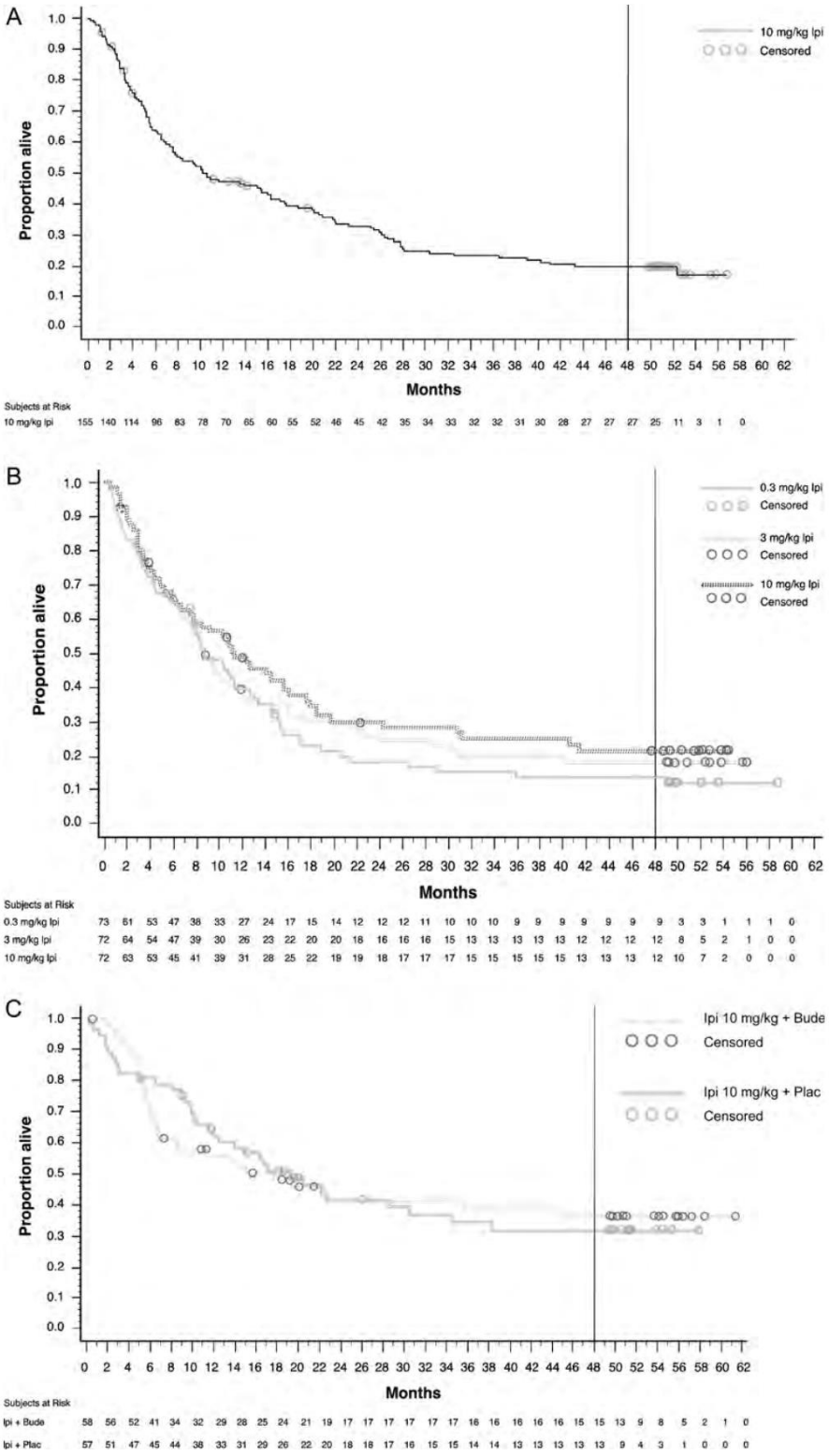


Fig 6. Graphical representation of the findings of the clinical trial. [22]

***Conclusion*:**

Many immunotherapies have recently been licensed for metastatic melanoma and various clinical trials are ongoing. Nevertheless, monotherapy's therapeutic results remain negligible, and the reaction rate is typically between 20% and 30%. They expect the advancement of patient-specific immunotherapy and combination therapies with more positive results. Future research will also explore in more depth the clinical impact of immunotherapy. Particularly brake release is necessary when a tumor-specific T-cell antigen is present in combination with the liberation of immunosuppression in the tumor micro atmosphere. Without unique T cells, the release of the brake and the activation of T cells and/or the importation of activated T cells in tumor materials is essential.

***References*:**

[1] S. Moriwaki, Human DNA repair disorders in dermatology: A historical perspective, current concepts and new insight, J. Dermatol. Sci. 81 (2016) 77–84. doi:10.1016/j.jdermsci.2015.09.008.

[2] K. Nakamura, R. Okuyama, Immunotherapy for advanced melanoma: Current knowledge and future directions, J. Dermatol. Sci. 83 (2016) 87–94. doi:10.1016/j.jdermsci.2016.05.009.

[3] H. Memon, B.M. Patel, Immune checkpoint inhibitors in non-small cell lung cancer: A bird's eye view, Life Sci. 233 (2019) 116713. doi:10.1016/j.lfs.2019.116713.

[4] C. Puig-Saus, A. Ribas, Gene editing: Towards the third generation of adoptive T-cell transfer therapies, Immuno-Oncology Technol. 1 (2019) 19–26. doi:10.1016/j.iotech.2019.06.001.

[5] I. Melero, S. Hervas-Stubbs, M. Glennie, D.M. Pardoll, L. Chen, Immunostimulatory monoclonal antibodies for cancer therapy, Nat. Rev. Cancer. 7 (2007) 95–106. doi:10.1038/nrc2051.

[6] V. Bayer, An Overview of Monoclonal Antibodies, Semin. Oncol. Nurs. 35 (2019) 150927. doi:10.1016/j.soncn.2019.08.006.

[7] L.S.K. Walker, D.M. Sansom, The emerging role of CTLA4 as a cell-extrinsic regulator of T cell responses, Nat. Rev. Immunol. 11 (2011) 852–863. doi:10.1038/nri3108.

[8] F.S. Hodi, M. Butler, D.A. Oble, M. V. Seiden, F.G. Haluska, A. Kruse, S. MacRae, M. Nelson, C. Canning, I. Lowy, A. Korman, D. Lautz, S. Russell, M.T. Jaklitsch, N. Ramaiya, T.C. Chen, D. Neuberg, J.P. Allison, M.C. Mihm, G. Dranoff, Immunologic and clinical effects of antibody blockade of cytotoxic T lymphocyte-associated antigen 4 in previously vaccinated cancer patients, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 3005–3010. doi:10.1073/pnas.0712237105.

[9] S.S. Taneja, Re: Safety, activity, and immune correlates of anti-PD-1 antibody in cancer: Editorial comment, J. Urol. 188 (2012) 2148–2149. doi:10.1016/j.juro.2012.08.169.

[10] S. Tan, D. Li, X. Zhu, Cancer immunotherapy: Pros, cons and beyond, Biomed. Pharmacother. 124 (2020). doi:10.1016/j.biopha.2020.109821.

[11] S.A. Rosenberg, J.C. Yang, S.L. Topalian, D.J. Schwartzentruber, J.S. Weber, D.R.

Parkinson, C.A. Seipp, J.H. Einhorn, D.E. White, Treatment of 283 Consecutive Patients With Metastatic Melanoma or Renal Cell Cancer Using High-Dose Bolus Interleukin 2, JAMA J. Am. Med. Assoc. 271 (1994) 907–913. doi:10.1001/jama.1994.03510360033032.

[12] R.H. Vonderheide, K.L. Nathanson, Immunotherapy at Large: The road to personalized cancer vaccines, Nat. Med. 19 (2013) 1098–1100. doi:10.1038/nm.3317.

[13] M.M. Gubin, X. Zhang, H. Schuster, E. Caron, J.P. Ward, T. Noguchi, Y. Ivanova, J. Hundal, C.D. Arthur, W.J. Krebber, G.E. Mulder, M. Toebes, M.D. Vesely, S.S.K. Lam, A.J. Korman, J.P. Allison, G.J. Freeman, A.H. Sharpe, E.L. Pearce, T.N. Schumacher, R. Aebersold, H.G. Rammensee, C.J.M. Melief, E.R. Mardis, W.E. Gillanders, M.N. Artyomov, R.D. Schreiber, Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens, Nature. 515 (2014) 577–581. doi:10.1038/nature13988.

[14] B.D. Lichty, C.J. Breitbach, D.F. Stojdl, J.C. Bell, Going viral with cancer immunotherapy, Nat. Rev. Cancer. 14 (2014) 559–567. doi:10.1038/nrc3770.

[15] S.A. Rosenberg, M.E. Dudley, Adoptive cell therapy for the treatment of patients with metastatic melanoma, Curr. Opin. Immunol. 21 (2009) 233–240. doi:10.1016/j.coi.2009.03.002.

[16] L.A. Johnson, R.A. Morgan, M.E. Dudley, L. Cassard, J.C. Yang, M.S. Hughes, U.S. Kammula, R.E. Royal, R.M. Sherry, J.R. Wunderlich, C.C.R. Lee, N.P. Restifo, S.L. Schwarz, A.P. Cogdill, R.J. Bishop, H. Kim, C.C. Brewer, S.F. Rudy, C. VanWaes, J.L. Davis, A. Mathur, R.T. Ripley, D.A. Nathan, C.M. Laurencot, S.A. Rosenberg, Gene therapy with human and mouse T-cell receptors mediates cancer regression and targets normal tissues expressing cognate antigen, Blood. 114 (2009) 535–546. doi:10.1182/blood-2009-03-211714.

[17] C. Robert, G. V. Long, B. Brady, C. Dutriaux, M. Maio, L. Mortier, J.C. Hassel, P. Rutkowski, C. McNeil, E. Kalinka-Warzocha, K.J. Savage, M.M. Hernberg, C. Lebbé, J. Charles, C. Mihalcioiu, V. Chiarion-Sileni, C. Mauch, F. Cognetti, A. Arance, H. Schmidt, D. Schadendorf, H. Gogas, L. Lundgren-Eriksson, C. Horak, B. Sharkey, I.M. Waxman, V. Atkinson, P.A. Ascierto, Nivolumab in previously untreated melanoma without BRAF mutation, N. Engl. J. Med. 372 (2015) 320–330. doi:10.1056/NEJMoa1412082.

[18] D. Sugiyama, H. Nishikawa, Y. Maeda, M. Nishioka, A. Tanemura, I. Katayama, S. Ezoe, Y. Kanakura, E. Sato, Y. Fukumori, J. Karbach, E. Jäger, S. Sakaguchi, Anti-

CCR4 mAb selectively depletes effector-Type FoxP3+CD4+ regulatory T cells, evoking antitumor immune responses in humans, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 17945–17950. doi:10.1073/pnas.1316796110.

[19] A. Sistigu, S. Viaud, N. Chaput, L. Bracci, E. Proietti, L. Zitvogel, Immunomodulatory effects of cyclophosphamide and implementations for vaccine design., Semin. Immunopathol. 33 (2011) 369–383. doi:10.1007/s00281-011-0245-0.

[20] C. Meyer, L. Cagnon, C.M. Costa-Nunes, P. Baumgaertner, N. Montandon, L. Leyvraz, O. Michielin, E. Romano, D.E. Speiser, Frequencies of circulating MDSC correlate with clinical outcome of melanoma patients treated with ipilimumab, Cancer Immunol. Immunother. 63 (2014) 247–257. doi:10.1007/s00262-013-1508-5.

[21] F.S. Hodi, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, P. Rutkowski, C.L. Cowey, C.D. Lao, D. Schadendorf, J. Wagstaff, R. Dummer, P.F. Ferrucci, M. Smylie, A. Hill, D. Hogg, I. Marquez-Rodas, J. Jiang, J. Rizzo, J. Larkin, J.D. Wolchok, Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial, Lancet Oncol. 19 (2018) 1480–1492. doi:10.1016/S1470-2045(18)30700-9.

[22] J.D. Wolchok, J.S. Weber, M. Maio, B. Neyns, K. Harmankaya, K. Chin, L. Cykowski, V. de Pril, R. Humphrey, C. Lebbé, Four-year survival rates for patients with metastatic melanoma who received ipilimumab in phase II clinical trials, Ann. Oncol. 24 (2013) 2174–2180. doi:10.1093/annonc/mdt161.

[1] S. Moriwaki, Human DNA repair disorders in dermatology: A historical perspective, current concepts and new insight, J. Dermatol. Sci. 81 (2016) 77–84. doi:10.1016/j.jdermsci.2015.09.008.

[2] K. Nakamura, R. Okuyama, Immunotherapy for advanced melanoma: Current knowledge and future directions, J. Dermatol. Sci. 83 (2016) 87–94. doi:10.1016/j.jdermsci.2016.05.009.

[3] H. Memon, B.M. Patel, Immune checkpoint inhibitors in non-small cell lung cancer: A bird's eye view, Life Sci. 233 (2019) 116713. doi:10.1016/j.lfs.2019.116713.

[4] C. Puig-Saus, A. Ribas, Gene editing: Towards the third generation of adoptive T-cell transfer therapies, Immuno-Oncology Technol. 1 (2019) 19–26. doi:10.1016/j.iotech.2019.06.001.

[5] I. Melero, S. Hervas-Stubbs, M. Glennie, D.M. Pardoll, L. Chen, Immunostimulatory monoclonal antibodies for cancer therapy, Nat. Rev. Cancer. 7 (2007) 95–106. doi:10.1038/nrc2051.

[6] V. Bayer, An Overview of Monoclonal Antibodies, Semin. Oncol. Nurs. 35 (2019) 150927. doi:10.1016/j.soncn.2019.08.006.

[7] L.S.K. Walker, D.M. Sansom, The emerging role of CTLA4 as a cell-extrinsic regulator of T cell responses, Nat. Rev. Immunol. 11 (2011) 852–863. doi:10.1038/nri3108.

[8] F.S. Hodi, M. Butler, D.A. Oble, M. V. Seiden, F.G. Haluska, A. Kruse, S. MacRae, M. Nelson, C. Canning, I. Lowy, A. Korman, D. Lautz, S. Russell, M.T. Jaklitsch, N. Ramaiya, T.C. Chen, D. Neuberg, J.P. Allison, M.C. Mihm, G. Dranoff, Immunologic and clinical effects of antibody blockade of cytotoxic T lymphocyte-associated antigen 4 in previously vaccinated cancer patients, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 3005–3010. doi:10.1073/pnas.0712237105.

[9] S.S. Taneja, Re: Safety, activity, and immune correlates of anti-PD-1 antibody in cancer: Editorial comment, J. Urol. 188 (2012) 2148–2149. doi:10.1016/j.juro.2012.08.169.

[10] S. Tan, D. Li, X. Zhu, Cancer immunotherapy: Pros, cons and beyond, Biomed. Pharmacother. 124 (2020). doi:10.1016/j.biopha.2020.109821.

[11] S.A. Rosenberg, J.C. Yang, S.L. Topalian, D.J. Schwartzentruber, J.S. Weber, D.R. Parkinson, C.A. Seipp, J.H. Einhorn, D.E. White, Treatment of 283 Consecutive Patients With Metastatic Melanoma or Renal Cell Cancer Using High-Dose Bolus Interleukin 2, JAMA J. Am. Med. Assoc. 271 (1994) 907–913. doi:10.1001/jama.1994.03510360033032.

[12] R.H. Vonderheide, K.L. Nathanson, Immunotherapy at Large: The road to personalized cancer vaccines, Nat. Med. 19 (2013) 1098–1100. doi:10.1038/nm.3317.

[13] M.M. Gubin, X. Zhang, H. Schuster, E. Caron, J.P. Ward, T. Noguchi, Y. Ivanova, J. Hundal, C.D. Arthur, W.J. Krebber, G.E. Mulder, M. Toebes, M.D. Vesely, S.S.K. Lam, A.J. Korman, J.P. Allison, G.J. Freeman, A.H. Sharpe, E.L. Pearce, T.N. Schumacher, R. Aebersold, H.G. Rammensee, C.J.M. Melief, E.R. Mardis, W.E. Gillanders, M.N. Artyomov, R.D. Schreiber, Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens, Nature. 515 (2014) 577–581. doi:10.1038/nature13988.

[14] B.D. Lichty, C.J. Breitbach, D.F. Stojdl, J.C. Bell, Going viral with cancer immunotherapy, Nat. Rev. Cancer. 14 (2014) 559–567. doi:10.1038/nrc3770.

[15] S.A. Rosenberg, M.E. Dudley, Adoptive cell therapy for the treatment of patients with metastatic melanoma, Curr. Opin. Immunol. 21 (2009) 233–240.

doi:10.1016/j.coi.2009.03.002.

[16] L.A. Johnson, R.A. Morgan, M.E. Dudley, L. Cassard, J.C. Yang, M.S. Hughes, U.S. Kammula, R.E. Royal, R.M. Sherry, J.R. Wunderlich, C.C.R. Lee, N.P. Restifo, S.L. Schwarz, A.P. Cogdill, R.J. Bishop, H. Kim, C.C. Brewer, S.F. Rudy, C. VanWaes, J.L. Davis, A. Mathur, R.T. Ripley, D.A. Nathan, C.M. Laurencot, S.A. Rosenberg, Gene therapy with human and mouse T-cell receptors mediates cancer regression and targets normal tissues expressing cognate antigen, Blood. 114 (2009) 535–546. doi:10.1182/blood-2009-03-211714.

[17] C. Robert, G. V. Long, B. Brady, C. Dutriaux, M. Maio, L. Mortier, J.C. Hassel, P. Rutkowski, C. McNeil, E. Kalinka-Warzocha, K.J. Savage, M.M. Hernberg, C. Lebbé, J. Charles, C. Mihalcioiu, V. Chiarion-Sileni, C. Mauch, F. Cognetti, A. Arance, H. Schmidt, D. Schadendorf, H. Gogas, L. Lundgren-Eriksson, C. Horak, B. Sharkey, I.M. Waxman, V. Atkinson, P.A. Ascierto, Nivolumab in previously untreated melanoma without BRAF mutation, N. Engl. J. Med. 372 (2015) 320–330. doi:10.1056/NEJMoa1412082.

[18] D. Sugiyama, H. Nishikawa, Y. Maeda, M. Nishioka, A. Tanemura, I. Katayama, S. Ezoe, Y. Kanakura, E. Sato, Y. Fukumori, J. Karbach, E. Jäger, S. Sakaguchi, Anti-CCR4 mAb selectively depletes effector-Type FoxP3+CD4+ regulatory T cells, evoking antitumor immune responses in humans, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 17945–17950. doi:10.1073/pnas.1316796110.

[19] A. Sistigu, S. Viaud, N. Chaput, L. Bracci, E. Proietti, L. Zitvogel, Immunomodulatory effects of cyclophosphamide and implementations for vaccine design., Semin. Immunopathol. 33 (2011) 369–383. doi:10.1007/s00281-011-0245-0.

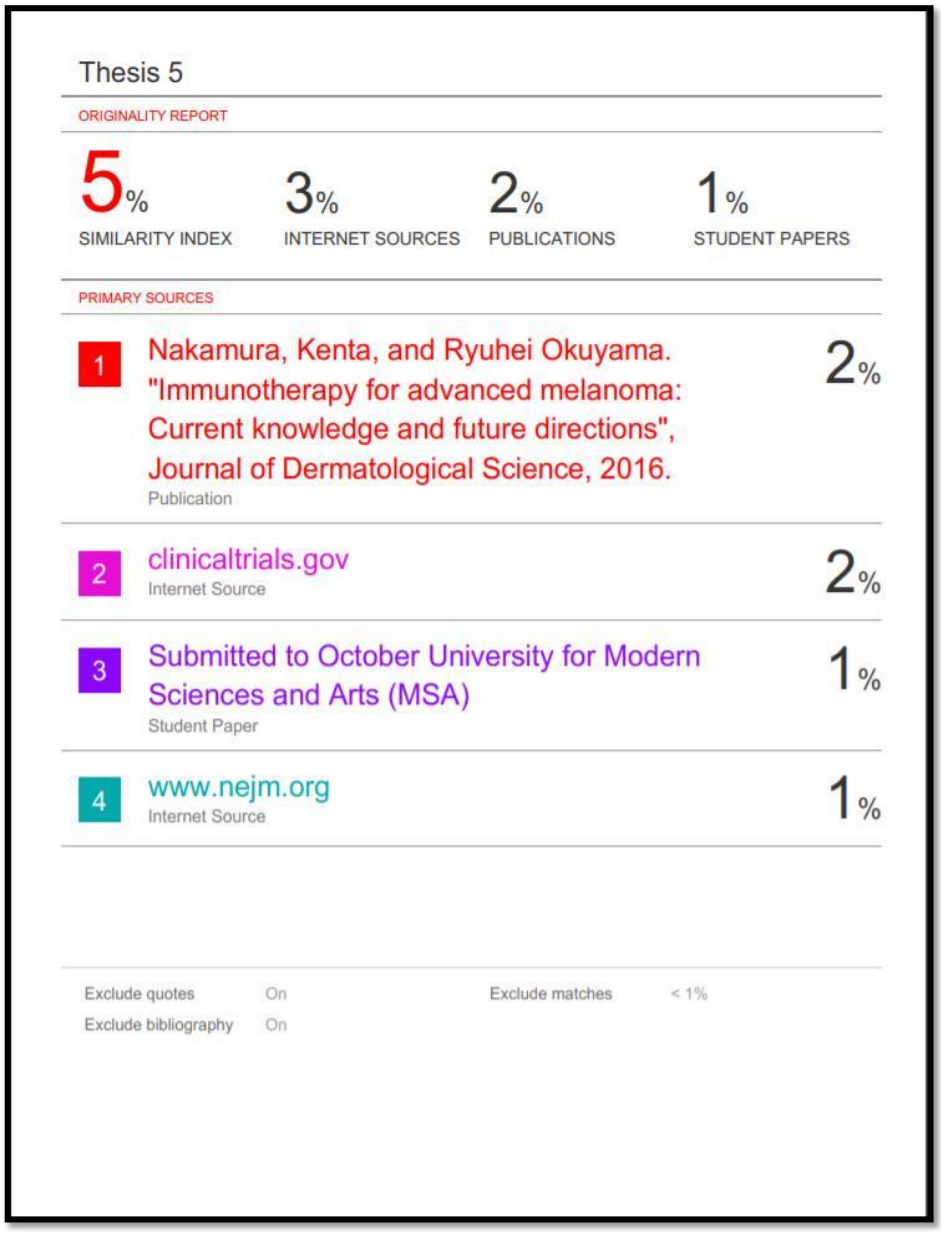
[20] C. Meyer, L. Cagnon, C.M. Costa-Nunes, P. Baumgaertner, N. Montandon, L. Leyvraz, O. Michielin, E. Romano, D.E. Speiser, Frequencies of circulating MDSC correlate with clinical outcome of melanoma patients treated with ipilimumab, Cancer Immunol. Immunother. 63 (2014) 247–257. doi:10.1007/s00262-013-1508-5.

[21] F.S. Hodi, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, P. Rutkowski, C.L. Cowey, C.D. Lao, D. Schadendorf, J. Wagstaff, R. Dummer, P.F. Ferrucci, M. Smylie, A. Hill, D. Hogg, I. Marquez-Rodas, J. Jiang, J. Rizzo, J. Larkin, J.D. Wolchok, Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial, Lancet Oncol. 19 (2018) 1480–1492. doi:10.1016/S1470-2045(18)30700-9.

[22] J.D. Wolchok, J.S. Weber, M. Maio, B. Neyns, K. Harmankaya, K. Chin, L.

Cykowski, V. de Pril, R. Humphrey, C. Lebbé, Four-year survival rates for patients with metastatic melanoma who received ipilimumab in phase II clinical trials, Ann. Oncol. 24 (2013) 2174–2180. doi:10.1093/annonc/mdt161.

"IMMUNOTHERAPY IN MELANOMA SKIN CANCER"



Thesis 5

ORIGINALITY REPORT

5%	3%	2%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Nakamura, Kenta, and Ryuhei Okuyama. "Immunotherapy for advanced melanoma: Current knowledge and future directions", Journal of Dermatological Science, 2016. Publication	2%
2	clinicaltrials.gov Internet Source	2%
3	Submitted to October University for Modern Sciences and Arts (MSA) Student Paper	1%
4	www.nejm.org Internet Source	1%

Exclude quotes	On	Exclude matches	< 1%
Exclude bibliography	On		

Neil Shah, Institute of Pharmacy, Nirma University

38