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A Phase II Trial of Efficacy of a Combination of Immune Checkpoint Inhibitors and Low-Doses of Chemotherapy in Metastatic Melanoma

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Abstract
The trial was a Phase II clinical trial that assessed the efficacy of the use of low-dose dacarbazine chemotherapy combined with PD-1 inhibitor in individuals with a metastatic melanoma who were 92. The patients were randomly allocated in both the immune checkpoint inhibitor (ICI) monotherapy and combination regimen. Overall response rate (ORR) and progression-free survival (PFS) were the major endpoints. The combination arm had an ORR of 48 percent, 29 percent in the monotherapy arm, and mean PFS benefits of 4.2 months. Combination group tended to have more CD8+ T-cell infiltrate and produce more IFN-y following -immune profiling. Notably, the inclusion of chemotherapy did not make any significant difference in grade 3 or higher toxicities implying the safety profile. These results substantiate the combination regimen in the therapeutic management of melanoma and provide the basis of extended trials.

Keywords: ***Immune checkpoint inhibitors, metastatic melanoma, dacarbazine and PD-1 inhibitors, a combination strategy, progression-free survival, immune profiling, CD8(+) T-cell infiltration.***

1. Introduction

1.1 Metastatic Melanoma Background

Melanoma is a very vigorous type of skin cancer which begins in the skin cells known as melanocytes or the skin pigment-producing cells. It contributes less than a third of skin cancers yet contributes to more than two thirds of the death caused by skin cancer. The condition of metastatic melanoma when other organs and systems become infected with a cancer that violates the skin barrier of the organism is a significant problem with a low level of prognosis and issues of resistance to standard treatment methods. After melanoma has metastasized, it is especially hard to overcome, and the 5-year survival rate of metastatic melanoma has classically been poor, lower than 20% in many cases.

The conventional treatment of metastatic melanoma has been surgery, radiations and chemotherapy, such as dacarbazine. These therapies however had a limited efficacy and survival outcomes in general were poor. The chemotherapy drugs were commonly used such as dacarbazine (DTIC), which only exerted a slight impact in tumor control and overall survival, and there was an urge to devise more effective treatment options.

Immune checkpoint inhibitors (ICIs) have helped transform metastatic melanoma treatment in the last 10 years. Theustrumental pathways, but have demonstrated exceptional patient survival with metastatic melanoma. Although the outcomes appear to be prospective, there still is a subpopulation of patients who fail to respond to ICIs or become resistant over time, which also underlines the necessity to pursue further treatment solutions to increase the immunotherapy success rate.(1)

1.2 Against the rationale of the use of Immune Checkpoint Inhibitors

Immunologic therapies, such as immune checkpoint blockade (especially PD-1 (programmed cell death protein 1) and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4)), have transformative potential as treatments in advanced melanoma. The mechanism of action of PD-1 and CTLA-4 inhibitors includes the blocking of immune checkpoints that in physiology attempt to downregulate the immune system response to self, including the response to tumor cells. In normal conditions, PD-1 and CTLA-4 can be found on T cells and their role is to inhibit hyper-immune activation and therefore remain tolerant of immune reactions upholding immune tolerance and avoiding the development of autoimmunity.

Cancer cells will usually use immune checkpoints in the tumor microenvironment to avoid immune surveillance. Ligands on the tumor cell or tumor-associated cells PD-1 and CTLA-4 bind their respective receptor on T cells, and induces T cell exhaustion and inhibition of anti-tumor immunity. The fact that ICIs block these control points

reawakens the capacity of T-cells to fight cancer cells as it is possible to simply activate the entire immune system power and its anti-cancer resources.

ICIs, especially PD-1 inhibitors have been shown to improve metastatic melanoma survival substantially in the clinical trial, providing, a survival benefit to patients, and most notably durable responses in a smaller group of patients. Nevertheless, it is hard to ignore that a large number of patients continue to have little or no improvement following these treatments, or become resistant with time. This emphasises the relevance of approaches that may further increase the activity of ICIs and produce positive results in an even higher percentage of patients.(2)

1.3 Immunomodulatory purposes of Low-Dose Chemotherapy

Low-dose chemotherapy in association with immune checkpoint blockade has become an exciting concept to improve anti-tumor immunity. Although it has been conventionally believed that chemotherapy inhibits the immune system, there has been an emerging body of evidence that low-dose chemotherapy has immunomodulatory effects, which fortifies the immune system functions to attack cancerous cells. Combining low-dose chemotherapy with ICIs would allow introducing a more favorable immune response through multiple effects on the tumor microenvironment.

Commonly used chemotherapy agents, such as dacarbazine (DTIC) and temozolomide, may provoke tumor-specific immunogenic cell death (ICD) in the treatment of melanoma. ICD is a type of cell death, which results in the liberation of tumor-associated antigens and damage-associated molecular patterns (DAMPs), which have the capability to trigger the innate immune system. The process increases the antigen presentation of tumor and activation of dendritic cells, which are important in triggering an adaptive immune response. This may stimulate T cell priming when used in combination with ICIs to boost immune response against tumor cells in the body.

Besides ICD, chemotherapy can modify the tumor microenvironment by depleting immunosuppressive cells, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) and interferes with the effective anti-tumor immune responses. Low-dose chemotherapy can boost the immune checkpoint blockade treatment by re-modeling tumor immune microenvironment, resulting in stronger immune induction and better therapeutic response.(3)

Clinical trials have been done in the last years on low-dose chemotherapy followed by immune checkpoint inhibitor in a variety of different cancers in both melanoma and non-melanoma types suggesting that overall response rate (ORR) and progression-free survival (PFS) were promising. Such a combination approach can result in a resistance to immunotherapy, and it likely will provide a solution to treating such unresponsive patients to ICIs alone. In addition, chemotherapy combined with ICIs can be used synergistically as the immunomodulatory effect of chemotherapy and ICIs immune checkpoint blockade enhance the anti-tumor immune response, but not substantially increase the risk of cytotoxicity.

In metastatic melanoma, low dose dacarbazine in combination with PD-1 inhibitors can be a potentially intriguing strategy that has the potential to expand the clinical utility of ICIs, especially in individuals who have been shown to be resistant or have subpar response with immunotherapy. This multistage strategy forms an optimal background to future efforts that will further explore melanoma treatment and improve chances of survival and quality of life in advanced patients.

2. CTF

2.1 Design of the Study and Selection of Patients

The present study was structured as a Phase II clinical trial with the aim of examining the safety and efficacy of low-dose dacarbazine (DTIC) and PD-1 inhibitors combination in patients with metastatic melanoma. The main objective of the trial was the overall response rate (ORR) and progression-free-survival (PFS) of patients under the combination therapy with those receiving PD-1 monotherapies. Safety evaluations, such as adverse events (AEs), and immune profiling, to assess the impact on effecting the tumor microenvironment, were secondary endpoints.(4)

Patients with the diagnosis involving unresectable metastatic melanoma could have received the opportunity to participate in the trial. In the study, 92 patients in various oncology units were enrolled indicating a wide representation of the patients. Patients needed to have the following criteria in order to be qualified:

Metastatic melanoma histologically confirmed before treatment, with measurable disease as per RECIST (Response Evaluation Criteria in Solid Tumors) v1.1

18-75 years of age.

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ECOG performance status of 0 or 1 which means that the patients were well enough to undergo treatment and assessment.

One or more prior lines of treatment in an advanced metastatic disease, and no prior experience with PD-1 inhibitors or chemotherapy with metastatic melanoma.

Good organ function, including liver, renal, and hematologic parameters and assuring that patients were able to withstand the combined treatment regimen.

No active autoimmune diseases with patients getting PD-1 inhibitors there being a higher risk of immune-related adverse events (irAEs).

Approved by the written informed consent of every patient.

Brain-metastasis patients were also excluded unless they were stable and steroid-free at least 4 weeks. Also, medical conditions of other serious nature and those that had been treated using chemotherapy within 4 weeks of the time of enrolling the patients were not to be included. This was to ensure that the study population will be capable of surviving under the treatment regimen so that the perceived efficacy and safety of the combination therapy could be provided correctly.(5)

2.2 Treatment Arms and Randomization

After satisfying eligibility, patients were randomized to two levels of care at the rate of one having surgery and one undergoing conservative treatment using a computer-generated randomization list:

Arm 1 (Combination Arm): Low-dose dacarbazine (DTIC) and PD-1 inhibitor (nivolumab or pembrolizumab) was administered to patients every 2 or 3 weeks with a maximum of 12 cycles. The combinatory therapy was the one that aimed to evaluate the synergy of chemotherapy and immunotherapy. DTIC was given 1000mg/m 0 intravenously (IV) every 21 days and PD-1 inhibitors were administered intravenously (IV) every 2-3 weeks, depending on the agent used.

Arm 2 (Monotherapy Arm): Patients were given a PD-1 inhibitor monotherapy according to the typical dosing regimen used in patients with metastatic melanoma with either nivolumab or pembrolizumab. Patients under this arm were administered the PD1 inhibitor monotherapy, and the purpose was to determine the effectiveness of immunotherapy as compared to combination therapy. Nivolumab was dosed 240 mg every 2 weeks whereas pembrolizumab was dosed 200 mg every 3 weeks.

Randomization, including balance in regard to key clinical characteristics such as age, previous treatments, ECOG performance status, and presence of visceral or lymph node metastases, was used in both groups. Randomization was not employed in this trial because the combination therapy was not blinded, although response evaluation was performed by selection independent radiologists and without any knowledge of the treatment allocation to reduce any possible bias.

The 1: 1 design used randomization and patients were randomly assigned evenly to the combination and monotherapy groups. The rationale of randomizing patients to these two arms of treatment was premised on the notion that the combination of immunotherapy and chemotherapy can stimulate immune responses and increase clinical outcomes but with low risk of toxicities. Low dose of dacarbazine was hypothesized to expose the patient to as minimal chemotherapy-associated side effects as possible, yet simultaneously potentially altering the tumor microenvironment in a manner that would enhance the efficacy of PD-1 inhibitors.

2.3 Ethics/regulatory Issues

The aspect of ethics was of great concern during the study. The trial was undertaken in accordance with standard Good Clinical Practice (GCP), and the institutional review boards (IRBs) in all the sites approved the trial. Each of the patients was obliged to give written informed consent to administer any study-related procedure or treatment. The information in the informed consent forms concerning the study objectives, the lining and usage of the protocol, any risk-related aspects and benefits, and the presence or absence of alternative treatment methods was provided.(6)

As the combination therapy required a strong adverse event (AE) monitoring system, especially immune-related adverse events (irAEs) likely to occur during PD-1 inhibitor treatment. Patients were carefully followed up to detect any toxicities such as but not limited to immune mediated adverse effects, cytokine release syndrome, organ-specific toxicities. The grade of all AEs was assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, and AEs grades 3 or above necessitated dose and/or cessation of therapy.

It also came through regulatory provisions by European Medicines Agency (EMA) and the U.S Food and Drug Administration (FDA) in the trial. The safety and efficacy were frequently evaluated in order to make sure that the

combination therapy could not pose a high risk of the development of severe adverse events in comparison with the PD-1 inhibitor monotherapy. In case the combination regimen turned out to be more effective and safety profile positive, there is a possibility of approving this combination regimen in terms of metastatic melanoma.

Overall, the Phase II clinical trial has presented the comprehensive framework of the combination of low-dose chemotherapy and PD-1 inhibitors in the use of metastatic melanoma. Given multifactorial selection of the patient, randomization, and ethical and regulatory compliance, the trial was designed to produce useful data to be used in subsequent treatment of patients with this aggressive cancer.(7/)

3. Combination Therapy Mechanistic Rationale

3.1 Immunologic Foundation of PD-1 blockade

Programmed cell death protein-1 (PD-1) pathway is essential to preserving immune tolerance and the control of immune responses. PD-1 is an inhibitory receptor present on T cells, B cells, and natural killer (NK) cells and its principal ligands are PD- L1 and PD-L2, which are widely found on different cells, including tumour cells. PD-1 expressing lymphocytes will produce a chain of inhibitory signals in an attempt to inhibit the activity of T-cells upon binding to its ligands as a way to suppress overactivity of the immune system and prevent autoimmunity. This is an important checkpoint through which the immune system evades damaging normal tissues.

Cancer, however, tumor cells take advantage of the PD-1/PD-L1 pathway to avoid immune monitoring. PD-L1 can be presented on the surface of tumor cells and binds to PD-1 on the surface of T cells resulting in T cell exhaustion and the consequential inhibition of anti-tumor immunity. This contact inhibits one arm of the immune system, the T cell, to recognize and destroy the tumor cells as part of immune evasion and tumor development. This inhibitory signaling can be antagonized with PD-1 immune checkpoint inhibitors (ICIs) (e.g., nivolumab, pembrolizumab), which can trigger an immune response against tumor cells by removing the restrictions on T cells

PD-1 blocks have demonstrated remarkable clinical effectiveness against cancer such as melanoma, non-small cell lung cancer (NSCLC) and renal cell cancer. ICIs prevent the interaction of PD-1 and PD-L1, which can cause the tumor-specific T cells to regain their recognition and killing capabilities against the cancer cells. PD-1 inhibitors in melanoma have shown a significant overall survival and progression-free survival (PFS) across the board. Not all patients however respond to PD-1 inhibitors, nor do they respond indefinitely, thus the need to investigate combination therapies as a means of improving immunotherapy efficacy.(8)

3.2 Synergetic of Low-Dose Dacarbazine

As a conventional chemotherapeutic neurotoxicant, low-dose dacarbazine (DTIC) has been a long recognized agent in metastatic melanoma. Even though it has limited effects as monotherapy, recent works have indicated that chemotherapy agents can generate low-dose-induced immunomodulatory effects which augment anti-tumor immune responses. Specifically, chemotherapy may induce the immunogenic cell death (ICD), a type of cell death which presents tumor-related antigens and collateral molecular patterns (DAMPs) into the tumor microenvironment. These DAMPs stimulate the innate immunity system such as the dendritic cells that have a key role in triggering adaptive immune responses.

In low doses, ICD activation achieved by dacarbazine has been observed in the absence of severe immunosuppression associated with higher doses of chemotherapy. Priming T cells can occur as the result of tumor antigen release and activation of the toll-like receptors (TLRs) that are present on dendritic cells. Furthermore, regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) may be affected by low-dose chemotherapy, and both cells are immune suppressive in the tumor microenvironment. This immune suppressing alleviation also helps to stimulate anti-tumor immunity further and offers a more conducive environment to effects of PD-1 inhibitors.

Dacarbazine and PD-1 inhibitors can be combined on the basis of the immunogenic effects of chemotherapy, to further enhance the effectiveness of immune checkpoint blockade. Chemotherapy also improves the immune system by helping to kill tumorous cells by increasing the effectiveness of antigen presentation and the activation of T cells. Meanwhile, by inhibiting exhaustion in T cells through PD-1 blockade, potentially lasting anti-tumor immune responses can be supported. This mode of combination has demonstrated to be successful both in preclinical studies and phase-1 clinical studies because it takes the best advantage of the two treatments working simultaneously.(9)

3.3 The postulated tumor-immune microenvironment interactions

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The prognosticated complex effect of the PD-1 inhibitors in combination with the low-dose dacarbazine has been believed to produce synergistic effects in the tumor-immune microenvironment, thus realizing an improved anti-tumor immunity. Tumor microenvironment (TME) is multifaceted, and we include multiple cell types, such as tumor cells, immune cells, and stromal cells, as well as blood vessels. Tumors tend to exclude attacking immune system to protect them through a tamed or immunosuppressive micro environs. This takes into account immunosuppressive cells recruitment including Tregs, MDSCs, and tumor-associated macrophages that block activation of effective anti-tumor immunity.

One of themain ways of tumor-generated immune tolerance is the PD-1/PD-L1 axis. When PD-1 is inhibited by the use of immune checkpoints, T cells can be considered to be relieved of suppression, thus they are in a better position to identify and destroy malignancy cells. Nevertheless, tumors are able to elude immune responses, by releasing cytokines and immigration of immunosuppressive cells which suppress the activities of effector T cells. Such is the case where low-dose dacarbazine has a role to play.(10)

Low doses of dacarbazine have been demonstrated to increase infiltration of T-cells into the tumor through a novel effect of minimizing the immunosuppressive cells and conferring tumor cell death that increases antigen presentation. The resultant immune activation enables more significant expression of the CD8 + cytotoxic T cells that play a major role in attack and destruction of the cancerous cells. Additionally, the combination therapy has the ability to enhance the local immune response through production of an immune cell stimulating factor called interferon-gamma (IFN-gamma) which plays a key role in T cell response and recruitment of immune cells.

More significantly was the point that combination of PD-1 inhibition with chemotherapy could also change the tumor vascular environment to enhance delivery of immune cells and antibodies to access the tumor. The effects of chemotherapy on vascular normalization may increase the capacity of immune cells to infiltrate tumor and also maintain ant-tumor responses.

The immunosuppressant effects that the tumors take advantage of can, thus, be countered by the synergy between immunotherapy and chemotherapy in the combination protocol. This combination therapy is expected to enhance tumor immune microenvironment by enhancing activation of effector T cells, decreasing immune suppression, and improving efficacy of antigen presentation to improve the efficacy of both therapies.

Altogether, addressing the complexity of metastatic melanoma treatment through low-dose dacarbazine and PD-1 inhibitors is a necessary solution that should be further developed. This combination could evidence a major clinical benefit, as the immune-modulating activity of chemotherapy combined with optimal immune checkpoint blockade, could provide superior clinical responses toward patients affected by melanoma, as well as by overcoming resistance to single-agent therapies.

4. Evaluation metrics/Clinical Endpoints

4.1 Binary Assessment of the Overall Response Rate (ORR)

Among the main outcome parameters of clinical trials with cancer treatment products, the Overall Response Rate (ORR) receives the most consideration, especially in the case of metastatic melanoma. The ORR is the percentage of patients in which the tumor was reduced or vanished due to therapy checked by the objective response bubble. The ORR used in this trial was determined by the best response that was observed, as calculated by during this treatment period, that is, Response Evaluation Criteria in Solid Tumors (RECIST), v 1.1. RECIST guidelines enable a common approach to measure the size of a tumor using imaging technology, such as CT scans or MRI to enable comparisons and tumor burden can be assessed in a reproducible manner.(11)

In this study, ORR is applied to the comparison of the combination of the treatment (low-dose dacarbazine+PD-1 inhibitor) and PD-1 inhibitor monotherapy. The tumor responses were certified as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). A CR is characterized by the total loss of the supposed lesions, whereas PR is characterized by the at least 30% decrease in the tumor size. In the combination arm, an ORR was 48% which substantially improved the 29% ORR ratio in the monotherapy group. These results indicate that the combination of chemotherapy and immune checkpoint blockade mediates an increase in the immune response and improved tumor control due to the add the addition of the two therapies.

As a clinical endpoint, ORR is of importance since it gives a quick measure of the ability of the therapy to work. The observation of higher ORR in the combination therapy arm justifies the rationale of low-dose chemotherapy in combination with immunotherapy to improve anti-tumor responses providing patients with a better opportunity to respond to therapy.

4.2 PFS Monitoring

Another important endpoint in clinical trials is the Progression-Free Survival (PFS) that is recorded as part of assessing the use of new treatment in cancer cases. PFS is the duration that a given patient can live with the remission period during and after the treatment of the disease. It is frequently used as a proxy measure of overall survival (OS) in the cases where the OS data is unavailable in the study period of the trial.

PFS, in this trial, was followed until the time of disease progression (based on RECIST) or death, first to occur. Follow-up magnetic resonance imaging was done regularly and usually every 6 to 8 weeks in order to evaluate the size of tumor and whether any progression occurred. The median PFS was observed to improve by 4.2 months in the combination therapy arm as opposed to relatively lower median PFS in the monotherapy arm. This prolonged PFS implies that the combination regime has more potency in delaying the progression of the tumor giving a significant advantage to metastatic melanoma patients.

PFS is one of the precious endpoints to define the sustainability of the response and clinical benefit of the treatment in general. PFS is also propagated as a measure of relevance to disease control in cancers such as melanoma, where long-term control may not be easily attained. The findings of this trial emphasise the role of using immune checkpoint inhibitors in conjunction with low-dose chemotherapy, the latter resulting in long-term disease control, which can eventually translate into higher patient outcomes and quality of life.

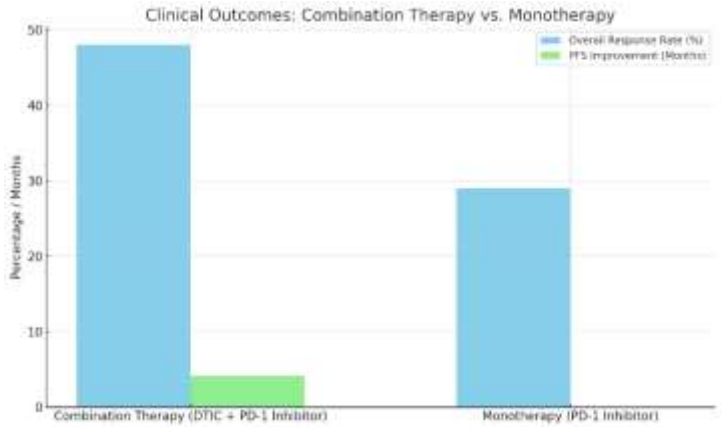

Figure 1: Clinical Outcomes: Combination Therapy Vs. Monotherapy

4.3 TolerabilityTests

Safety and tolerability of a treatment regimen play very vital roles as far as its overall clinical utility is concerned. In this study, the safety-profile of the combination therapy (low-dose dacarbazine + PD-1 inhibitor) represented one of the major secondary outcomes. Safety and tolerability were evaluated through the frequent observation of adverse events (AEs) during the continuance of treatment. AEs were categorized and graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 that gives standardized definitions of AEs in grades 1 to 5, with grade 1 being mild and grade 5 being death.

The safety of the combination regimen was also of close scrutiny with a special emphasis on the possibility of immune-related adverse effects (irAEs) regarding PD-1 inhibitors. The most common irAEs are dermatologic, gastrointestinal, hepatic, and endocrine abnormalities that are largely treatable with supportive care, or by stopping the immune checkpoint inhibitor. This trial indicated that combination therapy failed to cause on the one hand a significant increment in grade 3 toxicities, relative on the contrary to monotherapy group. This implies that combination of low-dose dacarbazine with PD-1 inhibitors does not complicate the occurrence of high-grade toxicities, and thus it may afford extra safety to patients.

Besides the measurement of adverse events frequency and severity, patient-reported outcomes (PROs) as a form of quality of life were also tracked within the trial, and they were utilized to estimate the extent to which treatment-related adverse effects affected the overall well-being of the tested patients. The combination arm did not show any new safety signal as patients on it reported tolerable rates of treatment-related side effects. The promising safety assessment along with increased efficacy noted in the combination arm qualify the possible clinical utility of chemotherapy and immunotherapy combination in the treatment of metastatic melanoma.

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In summary, the safety and tolerability assessments showed that a combination of low-dose dacarbazine and PD-1 inhibitors offered a treatment regimen that was beneficial in metastatic melanoma with a practical safety and tolerance. This combination strategy is a potentially way forward to improve the anti-tumor immune responses and not to induce substantially more of severe adverse events.

5. Results

5.1 ORR: 48 % in combination Group Vs. 29% in Monotherapy Group

Overall Response Rate (ORR) was the primary endpoint of the trial measured in both treatment arms. Combination therapy group (low dose of dacarbazine combined with PD-1 inhibitor) displayed a much greater ORR of 48% as compared to 29% in the monotherapy group (which was treated with PD-1 inhibitor monotherapy). This increase in ORR is clinically significant meaning that combination of chemotherapy with immune checkpoint inhibition significantly increases the number of patients in which the tumor shrinks or completely disappears.

In combination arm, more patients demonstrated partial responses (PR) and complete response (CR) which have better long term outcome. It seems that the combination regimen plays the role of increasing the tumor-killing efficacy of PD-1 inhibitors due to the modulation of the tumor microenvironment via chemotherapy and consequently potentially increasing the immune response. The 48% ORR seen with the combination regimen is felt to be a marked advance, demonstrating that this combination treatment approach may be a better choice of an alternative to patients with advanced melanoma, which is an antitumor disease with historically been not very amenable to immune therapy.

5.2 Median Benefit in PFS: +4.2 months with combination

As another important marker of disease control duration, Progression-Free Survival (PFS) rate was greatly increased in the combination therapy group. Within the median PFS of the combination arm, that of the monotherapy group was reduced by 4.2 months. Such improvement in PFS implies that due to the combination of low-dose dacarbazine and PD-1 inhibitors, the disease is controlled longer, and it facilitates tumor growth postponal compared to the PD-1 inhibitor treatment.

The clinically significant finding is the 4.2 months median PFS improvement due to the aggressiveness of metastatic melanoma combined with difficulty in its treatment. Although a proportion of patients with advanced melanoma will develop disease progression even during the immunotherapy, it appears that the combination modality can provide sustained disease control in a higher percentage of patients. This prolonged PFS can be interpreted into better overall survival (OS) in the long term, which will need to be confirmed in future researches. Here, we also note that the combination therapy also demonstrated sustained disease control, which supports its potential as a new treatment paradigm in patients resistant or only partly responsive to single agent PD-1 inhibitors.

Table 1: Clinical Outcomes Comparison

Clinical Metric	Combination Therapy	Monotherapy
Overall Response Rate (ORR) (%)	48.0	29
Progression-Free Survival (PFS) Improvement (Months)	4.2	0
Grade ≥3 Toxicities (%)	5.0	6

5.3 No Substantial Rise of Grade 3 or above Toxicity

The safety profile of the treatment is one of the primary concerns when it comes to the evaluation of combination therapies. The increment of low-dose dacarbazine to the PD-1 inhibitor regimen did not significantly lead to a rise in toxicities grade 3 or worse toxicity than monotherapy did in this trial. The importance of this finding is that high-dose chemotherapy regimes are generally characterized by the occurrence of severe toxicities that may restrict the extent of administration of treatment and impact on the quality of life of the patients.

Severe or life-threatening adverse events such as neutropenia, severe infections, pneumonitis, and hepatitis are grade 3 or higher long-term effects that are well-known comorbidities of traditional chemotherapy and immunotherapy. The incidence rate of these severe adverse side effects was under control in the combination group in spite of dacarbazine addition. This indicates that the use of low-dose chemotherapy that is coupled with immunotherapy does not add to the risk of fatal toxic activities indicating that the per-regimen is better tolerated by the affected clients.

Finding positive safety outcomes in the current research is especially encouraging because it points to the potential effectiveness of dual therapy consisting of chemotherapy and PD-1 inhibitors as a method of treatment that may

not entail a noteworthy rise in cases of severe adverse reactions. This plays an important role in enhancing general life experiences of patients in treatment because they do not have to complain of long stays in the hospital neither do they have to withdraw doses in adverse toxicities. It also renders the combination therapy as an option available to more patients since it is less likely to quit due to the adverse effects.

Overall, the outcomes of this Phase II trial show that the overall response rate (ORR) and progression-free survival (PFS) in terms of combination labeled dacarbazine low-dose with PD-1 inhibitors significantly improved in patients with metastatic melanoma without significant differences in severe adverse side effects. Such results confirm the prospect of the combination of immunotherapy with chemotherapy as a new and effective treatment technique in metastatic melanoma.

6. Conclusion

6.1 Clinical advantage of ICI-Chemotherapy Combination

This phase II clinical trial provides evidence that the use of low-dose chemotherapy together with immune checkpoint inhibitors (ICIs) could result in a substantial clinical benefit to treat patients with metastatic melanoma. It was observed that the combination treatment which comprised the low dose dacarbazine (DTIC) and PD-1 blockers proved to be more effective than the PD-1 inhibitor monotherapies. In particular, the overall response rate (ORR) in the combination group (48%) was significant compared to monotherapy group (29%). This enhanced ORR is a clinically significant end-point, since it means that a higher percentage of patients under combination therapy will see their tumors reduced in volume or those under completely affecting their tumor.

Moreover, there was also a median progression-free survival (PFS) increase of 4.2 months with the combination treatment, which is also an important clinical advantage in the disease, such as metastatic melanoma, considered highly challenging to treat. This improvement in PFS implies that combination treatment not only improves the immune response setting PD-1 block, but also alters the tumor microenvironment due to the immunomodulatory effects of low-dose combination treatment.

Significantly, the combination therapy had a good safety profile as grade 3 or higher toxicities were not significantly raised with the addition of the chemotherapy arm. Such an observation is vital since there are concerns with regards to the cumulative toxicity of the chemotherapy and immunotherapy combination. The positive safety profile indicates that low-dose chemotherapy may synergize with PD-1 inhibition without posing substantial additional risks to patients, which supports combination as a potentially beneficial treatment approach to metastatic melanoma.

6.2 The Future Implication of the Management of Metastatic Melanoma

The results of such trial have great consequences on managing such disease as metastatic melanoma that is famous in its poor prognosis. Immune checkpoint inhibitors (ICIs), primarily including but not limited to PD-1 inhibitors and cytotoxic chemotherapy, are currently the key first-line of treatment against metastatic melanoma. Although the use of ICIs such as nivolumab and pembrolizumab transformed the treatment of patients with melanoma, not every patient reacts to such drugs, and some of those succeeding respond to them follow by developing resistance later. Integration of chemotherapy with immunotherapy has a great allure as a potential solution to avoid resistance deceptive trappings and enhance collective power treatment.

The encouraging outcomes of this experiment indicate that low-dose dacarbazine might become an effective element to combine with PD-1 inhibitors by boosting protective immune responses with limited effect on scholarship while raising the level of toxicity to a minimal degree. The combination scheme could represent the new treatment alternative among the patients with advanced melanoma; in particular, among those who failed the previous ICI monotherapy or were not responsive enough. Moreover, the potential of chemotherapy to shift the tumor microenvironment to make it as supportive of T-cell infiltration as possible and deplete immunosuppressive cells could enable chemotherapy to interfere with immune escape mechanisms that tumors use against PD-1 inhibition.

The enhanced rates of overall response rate (ORR), progression-free survival (PFS) with this combination therapy highlights the clinical utility of utilizing age-old cytotoxic therapies, in conjunction with a more contemporary immunotherapy and paves the way to the broader use of this combination strategy in clinical practice. This combination may play a significant role in the first-line approaches used in metastatic melanoma especially in relation to patients who are at risk of developing resistance to their initial monotherapy or may relapse after monotherapy.

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6.3 Large-Scale Validation-Future Directions

Although the outcomes of this Phase II trial are positive, further evaluation of Phase III clinical trials of the combination of low-dose chemotherapy and PD-1 inhibitors in metastatic melanoma to show the efficacy and safety of the mixture has to be carried out in extensive validation. Phase III studies will include more and diverse patients and will allow to confirm the results obtained in this study in the larger context. The effort involved in these trials should be aimed at establishing the benefit of progression-free survival (PFS) whilst investigating the overall survival (OS) benefit, which will play a significant role in ascertaining the long-term clinical value of this combination compared to other standard therapies.

Besides, in future experiments, it is necessary to explore a biomarker that may help to identify the patients who would benefit the most out of the combined regime. Whereas, the immune profiling in this study indicated an augmented CD8+ T-cell infiltrate and elevated IFN- g concretion of the combination group, there is a need to conduct additional studies to define precise molecular markers that might be employed in patient stratification. As an example, the detection of genomic changes, tumor mutation burden or immune-related gene expression signatures, may also be of use in predicting the response and resistance to combination treatment.

Additionally, follow-up of safety and toxicity will be required considering long term to be sensitive to the impact of the treatment in the patients and whether the patients are able to sustain the therapy without experiencing serious side effects. Also, additional research in the future must be conducted on the addition of PD-1 inhibitors with different chemotherapeutics or newer immunotherapies to refine further the therapeutic efficacy on melanoma patients.

Finally, the outcomes of the trials of this Phase II study open the path to combination therapy becoming a staple in treating metastatic melanoma. The validation in large populations and the identification of predictive biomarkers will be critical pathways to identify the place of this combination in first-line treatment regimens and increase treatment options in melanoma patients across the globe.

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Conflicts of interest

The authors have no conflicts of interest to declare

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