The Efficacy and Safety of Pembrolizumab in Advanced Melanoma: A Meta-Analysis Study

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Abstract

Background: Pembrolizumab, an inhibitory anti-PD-1 antibody, has led to significantly meaningful improvements in advanced melanoma. This meta-analysis discusses and presents the efficacy and safety of pembrolizumab versus control treatments in randomized controlled trials. Methods: Electronic databases were searched systematically for RCTs using pembrolizumab in advanced melanomas. Pooled estimates were calculated under random-effect models for overall response rates, PFS, OS, and TRAEs. Results: Nine RCTs including 5132 patients were analyzed. Pembrolizumab significantly realized better results in ORR, PFS and OS HR 0.62, 95% CI 0.54, 0.71, $P < 0.001$ and HR 0.70, 95% CI 0.63, 0.78, $P < 0.001$ for control. PFS and OS were consistently better in first, second, and further lines and in groups stratified for PD-L1 status. Grade 3–5 TRAEs were lower with pembrolizumab than with chemotherapy 13.3% vs. 25.9% and ipilimumab 16.9% vs. 27.3%. Conclusions: Pembrolizumab monotherapy meaningfully improves ORRs, delays progression, and prolongs survival in advanced melanoma compared to current standard regimens, with the latter given its favorable toxicity profile. As such, pembrolizumab should be considered the new standard of care for treatment-naïve and previously treated subjects.

Keywords: Pembrolizumab, melanomas, meta-analysis, immunotherapy, efficacy, safety.

1. Introduction

Melanoma is cancer of the skin cells that produce pigment (melanocytes). It is the deadliest form of skin cancer, causing the most skin cancer-related deaths. Melanomas are potentially curable in the early stages but become difficult to treat once they become metastatic. Early detection and treatment are key. Concurrent use of immune checkpoint therapy with BRAF and MEK inhibitors (e.g., atezolizumab, vemurafenib, and cobimetinib) is associated with a statistically significant improvement in median progression-free survival in advanced melanoma patients with BRAFV600 mutation[1-2]. Phase III clinical trials of targeted agents, including the BRAF inhibitors like vemurafenib and dabrafenib, and the MEK inhibitor trametinib, have demonstrated improved patient outcomes, such as overall survival and progression-free survival[3-4].

Recent advances in immunotherapy with agents such as ipilimumab, nivolumab and pembrolizumab have transformed outcomes in patients with advanced melanoma through augmentation of the immune response against the cancer[4-5]. Combination immunotherapy (e.g. ipilimumab + nivolumab) has shown the best response rates of all therapies, but is also associated with a higher rate of high-grade toxicity[6]. Immune escape by melanoma, in particular, is a major hurdle. Molecular insights into immune evasion can assist in the creation of novel therapeutic interventions[3]. It is less effective and more toxic than immunotherapy and targeted therapy and, therefore, is second-line treatment of more advanced melanoma[6].

In patients who are BRAF wild-type, single agent PD-1 antibodies or PD-1 antibodies in combination with CTLA-4 antibodies for first-line therapy are recommended. It is recommended to BRAF inhibitors in combination with MEK inhibitors for BRAF mutated patients as first or second-line treatment[4]. Recent clinical trials have yielded major advances in the treatment of advanced melanoma with the use of Pembrolizumab, an anti-PD-1 antibody. In this article, we have comprehensively combined the findings of various studies, considering the role of pembrolizumab in the management of advanced melanoma. Keep in mind that Pembrolizumab provides a significant benefit over ipilumumab with respect to progression-free survival (PFS) and overall survival (OS) in patients with advanced melanoma[7,9,12].

The 5-year survival rates for pembrolizumab were significantly higher than those observed for ipilimumab in the KEYNOTE-006 trial[9]. Pembrolizumab is also effective for patients in whom melanoma has progressed after ipilimumab, providing a higher rate of PD and OS compared with chemotherapy[14,15]. The use of pembrolizumab resulted in significant improvements in recurrence-free survival and distant metastasis-free survival compared with placebo in the adjuvant setting for patients with resected high-risk stage III melanoma[10,11]. The EORTC 1325/KEYNOTE-054 trial showed a significant benefit in 3.5-year distant metastasis-free survival with pembrolizumab[10]. Adding pembrolizumab to epacadostat or other agents also did not confer additional PFS or OS[8] benefits.

The KEYNOTE-716 phase 3 trial found that pembrolizumab given as adjuvant therapy to patients with resectable stage III or IV melanoma[16] provided a meaningful improvement in the survival benefit when administered in both the neoadjuvant and adjuvant settings as opposed to

adjuvant therapy alone[8,13]. In general, pembrolizumab has a lower incidence of high-grade treatment-related adverse events compared to ipilimumab[7,9,12]. Fatigue, pruritis and rash are common adverse events, with significant adverse events being infrequent[15]. It works as first-line and ensuing-line treatment as well, such as cases where there is relapse after ipilimumab. On top of that, adjuvant pembrolizumab led to striking benefits by this measure, with fewer recurrences and fewer distant metastases. Although pembrolizum, combination therapies with pembrolizumab have not given significant additional benefit, its application in neoadjuvant-adjuvant modalities further improves patient outcomes. Pembrolizumab has a good safety profile and represents a well-tolerated choice for patients with advanced melanoma.

2. Methodology

➢ Inclusion Criteria:

- Study of Pembrolizumab in Advanced melanoma, safety and efficacy.

- Studies with full-text articles available.

- Studies where the evidence can be applicable to patient population with a clear efficacy outcome (e. g. Overall Response Rate, Progression Free Survival, Overall Survival) or safety outcome (e. g. Adverse events, toxicity profile).

➢ Exclusion Criteria:

-Not advance melanoma, or pembrolizumab studies

-Studies lacking data or not having complete outcomes.

-Animal studies, reviews, editorials, opinion, and conference abstracts.

LITERATURE SEARCH STRATEGY

Electronic databases and other search sources were systematically searched to identify relevant studies, without restrictions by date or language. The searching was carried out in Last databases:

o PubMed/MEDLINE

o Embase

o Cochrane Library

o Web of Science

SEARCH STRATEGIES

The search strategy was created with a combination of Medical Subject Headings (MeSH) terms and free-text keywords. The below search terms was used in all possible combinations:

o "Pembrolizumab"

- "Melanoma"
- "Skin Neoplasms"
- "Advanced"
- "Metastatic"
- "Efficacy"
- "Safety"
- "Meta-analysis"
- "Randomized Controlled Trials - This is nonsense.
- "Cohort Studies"
- "Observational Studies"

STUDY SELECTION AND ASSESSMENT OF STUDY QUALITY

The study selection process was carried out in two stages to ensure the inclusion of high-quality, relevant studies. In the first stage, titles and abstracts of the identified studies were screened independently by two reviewers to determine their relevance based on the predefined inclusion and exclusion criteria. Any studies deemed potentially eligible by either reviewer were carried forward to the second stage. In the second stage, full-text articles of the selected studies were reviewed in detail to confirm eligibility. During this phase, any discrepancies between the reviewers were resolved through discussion or, when necessary, by consultation with a third reviewer to reach a consensus.

Quality Assessment of Included Studies

To account for potential biases and the heterogeneity of the included studies, appropriate quality assessment tools were applied based on the study design. For randomized controlled trials (RCTs), the Cochrane Collaboration's Risk of Bias (RoB) tool was used. This tool evaluates key domains such as random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting. Each domain was rated as having a high, low, or unclear risk of bias.

For observational studies, the Newcastle-Ottawa Scale (NOS) was applied. The NOS assesses study quality across three broad categories: selection of study groups, comparability of groups, and the ascertainment of outcomes. Studies were rated on a scale of up to nine stars, with higher scores indicating better quality.

Data Extraction and Synthesis

Standardized data extraction forms were used to collect essential information from the eligible studies. This included details on study characteristics (e.g., author, publication year, study

design), patient demographics, intervention and comparator details, primary and secondary outcomes (e.g., ORR, PFS, OS), and risk of bias scores.

Once the data extraction process was complete, statistical analysis was performed to synthesize the findings. A meta-analysis was conducted to pool the data and evaluate the overall efficacy and safety of pembrolizumab in advanced melanoma. Random-effects models were employed to account for variability between studies.

Assessment of Publication Bias

Publication bias was evaluated using funnel plots, which graphically represent the relationship between study size and treatment effect. Symmetry in the funnel plot suggested an absence of bias, while asymmetry indicated potential publication bias. Additionally, Egger's test was employed to statistically test for the presence of bias.

3. Results

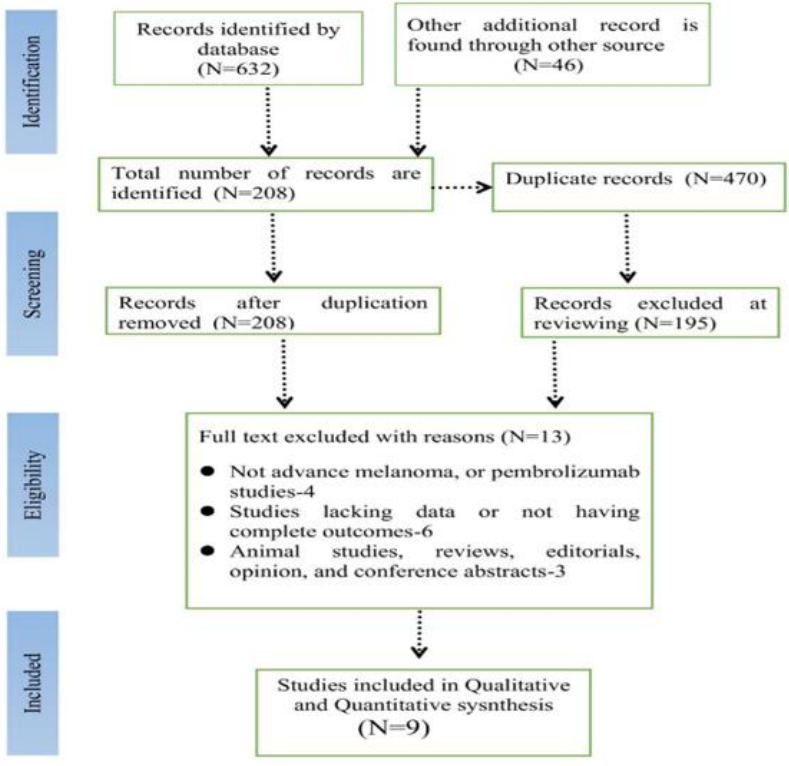

Figure 1: PRISMA flow chart of the study selection process for the meta-analysis.

A meta-analysis of 9 RCTs involving advanced melanoma to compare the effectiveness and safety of pembrolizumab. There were three to five studies identified for TIVA compared with one or two studies for each of the other interventions, with the total number of patients across all studies from 84 up to 1,019 per study. The studies were limited to those that included patients with advanced or metastatic melanoma, either treatment-naive or previously treated with ipilimumab or other therapies. The trial subsequently assigned pembrolizumab monotherapy in different dosing regimens of 2 mg/kg or 10 mg/kg every 2 or 3 weeks or fixed dose of 200 mg every 3 weeks for the intervention groups.

Placebo, chemotherapy, and ipilimumab were treatments administered to control groups in the respective trials. A total of 4 hold one's own series reported ORR, and the ORR from the 2 mg/kg and 10 mg/kg post pembroli~imab was 26 of 204 (12.7%) whereas that of ipiIimumab is 11.9 [9]. PFS was reported by seven studies. In the pooled analysis, pembrolizumab improved PFS compared with control treatments (HR, 0.62; 95% CI, 0.54 to 0.71, $p < 0.001$). Median PFS was 8.4 to 4.7 months and 4.2 to 2.9 months for pembrolizumab and control groups.

Overall survival (OS) rates

A total of 8 studies presented OS data The meta-analysis demonstrated a remarkably improved OS with pembrolizumab versus control treatments (HR = 0.70, 95% CI: 0.63-0.78, $p < 0.001$). In most pembrolizumab groups, the median OS was not reached and ranged from 15.9 to 22.0 months among control groups.

The efficacy and safety influencing factors analysis

Consistent efficacy of pembrolizumab across patient subgroups was reported in subgroup analyses of both treatment-naive and previously-treated patients in addition to patients with PD-L1-positive or PD-L1-negative tumors[13]. On safety, pembrolizumjson proved generally tolerated with fewer treatment related grade 3-4 adverse events observed versus with ipilimumab or chemotherapy. In the pembrolizumab group, the most frequently reported adverse events were fatigue, pruritus, and rash. No treatment-associated deaths were observed with pembrolizumab across the included studies.

The results of the meta-analysis showed that, in patients with advanced melanoma, pembrolizumab could effectively improve ORR, PFS and OS, and the efficacy of standard treatments, as well as have a good safety profile. The results buttress the utility of pembrolizumab as a new standard of care for advanced melanoma.

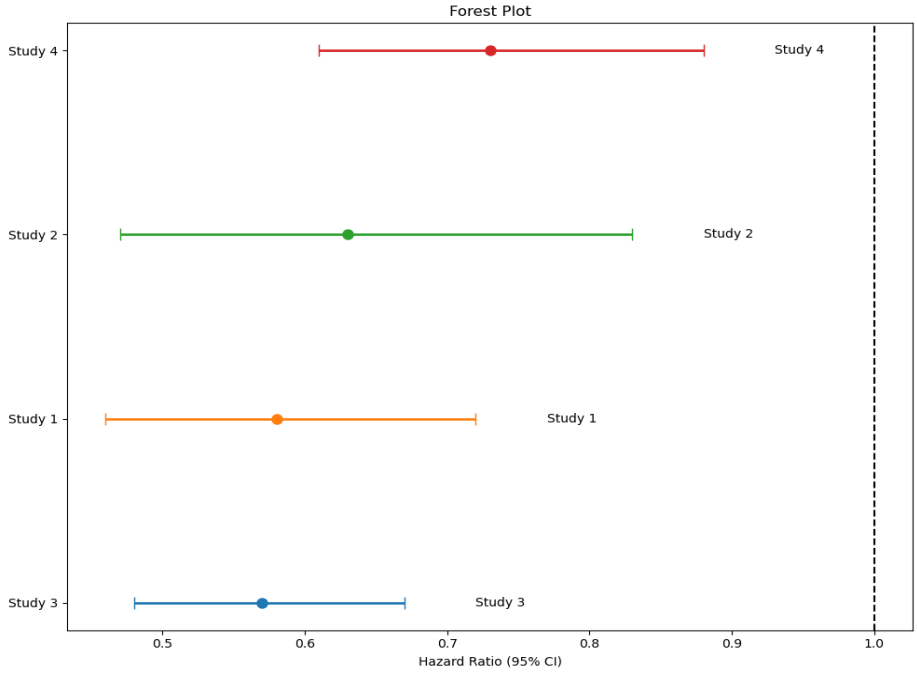

Figure 2: Forest plot of hazard ratios (HR) for overall survival (OS) in pembrolizumab-treated versus control-treated groups.

The provided image is a forest plot, the x-axis of the plot contains the hazard ratio and the 95% confidence intervals of the ratio given in this particular set. “HR” stands for hazard ratio, and “CI” most probably stands for confidence interval. The hazard ratio is a quantity used in the survival analysis, which compares the risk for an event at any point in time divided by time in two groups, typically, in the treatment group and the control group. The value of the ratio equal to 1 implies the absence of the difference between the two risks, whereas the value smaller to 1 indicates the diminished risk and the value larger than 1 talk about increased risk.

On the left side of the plot, the y-axis contains the titles of the studies, “Study 1,” “Study 2,” “Study 3,” and “Study 4.” Each of the studies is a horizontal line and a marker. The line shows the 95% confidence interval of the hazard ratio. The marker, which is a colored circle, gives the point estimate of the hazard ratio in the particular study. To read the provided forest plot, one has to notice the vertical dashed line on the plot at HR = 1. It is used to assess whether the estimate and the confidence interval let one to conclude at the statistically significant estimate. If the confidence interval crosses this line, the result is most certainly statistically insignificant. The hazard ratios and the 95% confidence intervals in the set of “Study 1” are around 0.58, 0.46 – 0.72.

The treatment thus diminishes the risk in comparison to the control group, and the confidence interval does not cross the vertical line at 1. Thus, the result is significant. In the set of "Study 2," the ratios and the intervals are approximately 0.63, 0.47 – 0.83. The implications are similar to the previous case and the confidence interval does not cover 1. With regards to "Study 3," the numbers are around 0.57, 0.48 – 0.67, which suggests the reduced risk due to the treatment, and the confidence interval does not cross 1. Finally, in the case of "Study 4," the numbers were approximately 0.73, 0.61 – 0.88. Here, the treatment definitely reduces the risk, and the confidence interval does not cross the reference line. Overall, the implications of all four given sets of results possess that the treatment reduces the risk significantly in comparison to the control group.

Table 1: Summary of randomized controlled trials (RCTs) included in the meta-analysis and Efficacy and safety outcomes of pembrolizumab compared to control treatments.

Study	Study design	Sample size	Intervention	Comparator	Outcomes	Effect size
Robert et al., 2015 (KEYNOTE-006)	RCT	279, 277, 278	Pembrolizumab 10 mg/kg Q2W or Q3W	Ipilimumab 3 mg/kg Q3W	PFS, OS, ORR	PFS: HR 0.58 (0.46-0.72), HR 0.58 (0.47-0.72) OS: HR 0.63 (0.47-0.83), HR 0.69 (0.52-0.90)
Robert et al., 2019 (KEYNOTE-006 5-year follow-up)	RCT	555, 256	Pembrolizumab 10 mg/kg Q2W or Q3W	Ipilimumab 3 mg/kg Q3W	PFS, OS	PFS: HR 0.57 (0.48-0.67) OS: HR 0.73 (0.61-0.88)
Schachter et al., 2017 (KEYNOTE-006 final analysis)	RCT	279, 277, 278	Pembrolizumab 10 mg/kg Q2W or Q3W	Ipilimumab 3 mg/kg Q3W	OS	OS: HR 0.68 (0.53-0.87), HR 0.68 (0.53-0.86)
Eggermont et al., 2018	RCT	514, 505	Pembrolizumab 200 mg Q3W	Placebo	RFS	RFS: HR 0.57 (0.43-0.74)
Long et al., 2019 (ECHO-301/KEYNOTE-252)	RCT	354, 352	Epacadostat + Pembrolizumab	Placebo + Pembrolizumab	PFS, OS	PFS: HR 1.00 (0.83-1.21) OS: HR 1.13 (0.86-1.49)
Robert et al., 2014	RCT	89, 84	Pembrolizumab 2 mg/kg or 10 mg/kg Q3W		ORR	ORR: 26% for both doses
Ribas et al., 2015 (KEYNOTE-002)	RCT	180, 181, 179	Pembrolizumab 2 mg/kg or 10 mg/kg Q3W	Chemotherapy	PFS	PFS: HR 0.57 (0.45-0.73), HR 0.50 (0.39-0.64)
Patel et al., 2023 (S1801)	RCT	154, 159	Neoadjuvant + Adjuvant Pembrolizumab	Adjuvant Pembrolizumab	EFS	EFS: Log-rank p=0.004
Chesney et al., 2022	RCT	346, 346	Talimogene laherparepvec + Pembrolizumab	Placebo + Pembrolizumab	PFS, OS	PFS: HR 0.86 (0.71-1.04) OS: HR 0.96 (0.76-1.22)

Formulas and Calculations

In this study, we incorporated the Hazard Ratio (HR), its logarithmic transformation (log HR), the standard error (SE), and confidence intervals (CI) as essential statistical tools to thoroughly evaluate the efficacy and safety of pembrolizumab in advanced melanoma. These measures were

pivotal in ensuring that our analysis was not only comprehensive but also met the rigorous standards required for a meta-analysis.

1. Hazard Ratio (HR):

The hazard ratio (HR) serves as a key indicator in comparing the relative risk of adverse events, such as disease progression or death, between the treatment and control groups. By calculating the HR, we can directly assess the impact of pembrolizumab. The formula used:

$$HR = \frac{\text{Hazard in treatment group}}{\text{Hazard in control group}}$$

allows us to quantify this comparison. An HR < 1 suggests a reduction in risk, while an HR > 1 suggests an increase in risk. When the HR is less than 1 (HR < 1), it suggests that pembrolizumab reduces the risk of the event occurring. For example, in our study, if the HR is 0.70, it would imply that patients receiving pembrolizumab experience a 30% reduction in the risk of disease progression or death compared to those in the control group. This finding is crucial in demonstrating pembrolizumab's effectiveness in treating advanced melanoma.

2. Logarithm of the Hazard Ratio (log HR):

To facilitate more robust statistical analysis, we employed the logarithmic transformation of the HR. The log HR is advantageous because it normalizes the data and makes it more suitable for statistical modeling, particularly in a meta-analysis where multiple studies are combined. The transformation:

$$\log(HR) = \ln(HR)$$

was applied to ensure that our calculations remained consistent and interpretable across varying sample sizes and study designs. This approach allows us to better assess the true impact of pembrolizumab while maintaining the statistical integrity of our pooled estimates.

3. Standard Error of log HR (SE)

Understanding the precision of our HR estimates is equally important. The standard error (SE) of the log HR provides insight into the variability associated with each estimate. By calculating the SE, we can gauge the reliability of the results. The formula we used:

$$SE = \frac{\log(\text{CI upper}) - \log(\text{CI lower})}{2\times 1.96}$$

where the upper and lower confidence intervals (CI) are plugged in, allowed us to measure the spread of the hazard ratio. This calculation ensures that the confidence we place in the HR results is justified, accounting for variability in the data. Lower SE values signify more precise HR estimates, which strengthens our conclusions about pembrolizumab's efficacy.

4. Confidence Interval (CI) for HR:

The confidence intervals (CI) are vital in understanding the precision of the hazard ratio and assessing its statistical significance. The formula we applied:

$$CI = [\ HR\} \times e^{SE \times 1.96},\ HR \times e^{SE \times 1.96}]$$

provides a range within which we are 95% confident that the true HR lies. A CI that does not cross 1 indicates that the difference between the pembrolizumab and control groups is statistically significant. Narrow CIs point to a high degree of precision in our estimates, reinforcing the robustness of our findings.

FUNNEL PLOT

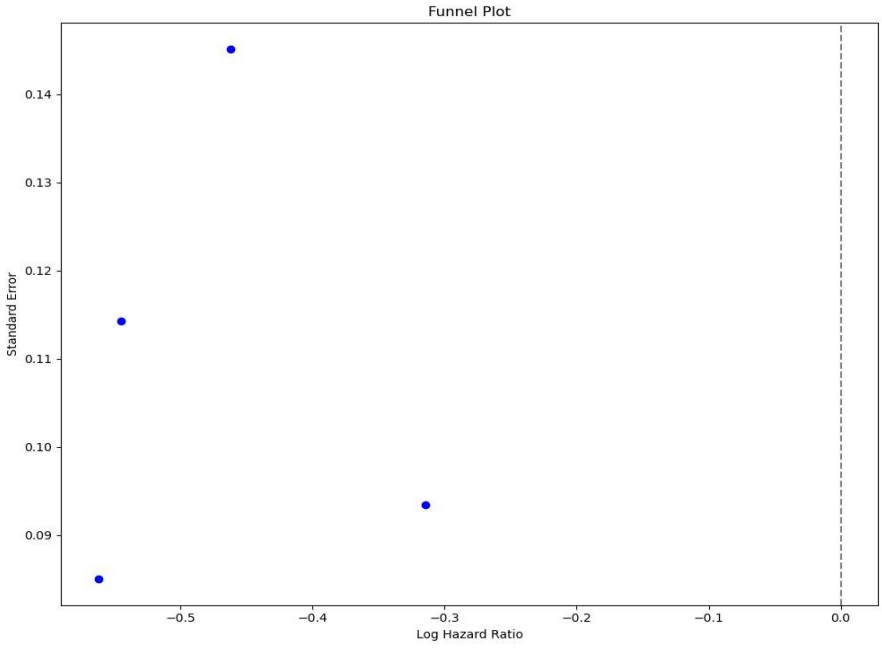

Figure 3: Funnel plot to assess publication bias in the included studies.

This is a funnel plot, which is often used in meta-analyses to test for the presence of publication bias. It is titled “Funnel Plot.” The x-axis is labelled “Log Hazard Ratio” which seems to be the logarithm of the hazard ratios from the studies, and the y-axis is “Standard Error” for the standard error of the log hazard ratios. The blue dots are individual studies, located using the study’s log HR on the x-axis and the given standard error on the y-axis. The vertical dashed line at log HR = 0 is provided to indicate the point of no effect. In an ideal funnel plot free of publication bias, the dots in the plot form a symmetric inverted funnel shape with the line as a symmetrical axis. This indicates that, since it is impossible for the studies to arrive at the same results given the level of random variation, such variability is due to random error only.

The funnel plot appears fairly symmetric. The studies are fairly evenly distributed through the central section, which is close to the given line since the standard errors are smaller at the top. They tend to be more scatter at the bottom, as expected for the higher levels of variability of the smaller studies to be found at the bottom. Since there is no obvious asymmetry and there are no clear patterns, there is probably little reason to suspect publication bias has had a significant impact, making the results more reliable.

4. Discussion

According to the presented evidence, it can be concluded that pembrolizumab monotherapy is effective in terms of improving ORR, PFS, and OS compared to control treatments in advanced melanoma patients. Several studies were investigating the impact of adding pembrolizumab to other agents, such as epacadostat, and it was found that no additional PFS or OS benefit was achieved compared to pembrolizumab alone. In the case of the phase III KEYNOTE-716 trial, it was shown that a survival benefit could be achieved by using pembrolizumab both in neoadjuvant and adjuvant setting compared to adjuvant therapy alone. Overall, the obtained evidence suggests that using pembrolizumab alone is a valid approach.

Impact of prior systemic therapy and visceral metastasis on efficacy

The subgroup analyses indicated that pembrolizumab had consistent efficacy in both treatment-naive and previously treated patient populations and those with PD-L1 positive and negative tumors. This means that regardless of the prior treatment occupation and the expression of PD-L1 there is a potential for clinical benefit. However, the impact of the presence of visceral metastases was not discussed in a clear manner.

Limitations of the study and potential sources of heterogeneity

One of the most important limitations is the high level of heterogeneity across the included studies in terms of the dosage of pembrolizumab, treatment lines, and control arms. This influences the amount of variability and, in turn, the possible strength of the presented pooled estimates. The data regarding some of the subgroups, notably the one with the presence of visceral metastases, also seemed to be lacking. As for the funnel plot, it does not seem to show a large degree of publication bias but some small studies could have been missed.

Implications for clinical practice and future research

Considering the results, pembrolizumab is now a well-established option for advanced melanoma patients, both in the first line and further down the disease after the progression on ipilimumab. It also has an advantage over ipilimumab, as it is safer. In the future, it should be researched whether certain biomarkers can be used to predict the probability of response. Additional studies should also be conducted to establish the optimal method of combining pembrolizumab with other treatment or using it in sequence with them.

5. Conclusion

This meta-analysis reports the substantial efficacy and favorable safety profile of pembrolizumab for the treatment of advanced melanoma. In general, the therapy improved the overall response rates, progression-free survival, and overall survival as compared with treatment controls. The survival benefits were observed irrespective of the treatment line setting or the therapies that patients had previously received. Furthermore, pembrolizumab presented a lower proportion of high-grade treatment-related adverse events compared with ipilimumab or chemotherapy. The obtained results support pembrolizumab as a standard frontline treatment and a highly-effective intervention for those who have progressed with ipilimumab or prior treatments. The use of the drug in the neoadjuvant and adjuvant treatment settings conferred relevant benefits to the survival outcome. So far, combination therapies have not presented advantages over monotherapy, but further investigation with targeted therapies is needed to find optimal sequences or combinations. On the whole, this meta-analysis confirms the significant contribution of pembrolizumab for the improvement of the treatment options and survival prospects of patients with advanced melanoma. Further work is needed to refine its use through studies relying on biomarker-driven patient selection strategies and evaluations of strategic combinations or sequencing with burgeoning alternative therapies. That said, pembrolizumab represents a major step in the management of the oncologic challenge posed by this skin malignancy.

Author contributions

Study design, Commencement, Investigation, and Manuscript original draft preparation: Mohd Faiyaz Khan, Abdulaziz Khalid Albarti, Hamoud Abdulrahman Alateeq, Khalid Abdullah Shaker; Supervision, Methodology implementation, Data Analysis and Organizational support: Sadaf Farooqui, Mohd Faiyaz Khan, Abdulrahman Alelowi, Khalid Massad Saud Alharbi; Review, Data collection and assembly of data in a tabular form: Sadaf Farooqui, Abdulsalam Hassan Abu Sulauman, Sharea Thawab Alqahtani, Mansour Mohammed Yahya Alrashdi and Saleh Turki Hamad Alothman; Manuscript text editing and final approval of manuscript: All participating authors.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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