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Nivolumab with relatlimab in the treatment of melanoma patients — the position of the Section of Immuno-oncology of the Polish Society of Oncology

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ABSTRACT

Treatment of melanoma patients has undergone significant modification in recent years, resulting in improved outcomes. Still, the prognosis of patients with advanced stage or metastatic disease is not the best, and new therapeutic options are being sought. One direction of research is the combination of molecules with different mechanisms of action, the so-called fixed-dose combination (FDC) formulations, which are expected to improve the quality of life and safety of patients and provide improved treatment outcomes.

This article presents the position of the Immunooncology Section of the Polish Society of Oncology on the use of the combination of nivolumab and relatlimab in the treatment of patients with inoperable melanoma or metastatic disease.

Keywords: melanoma, relatlimab, nivolumab, immunotherapy

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Introduction

The management of melanoma patients has been significantly modified in recent years, leading to improved treatment outcomes. Nevertheless, the prognosis of patients with advanced or metastatic disease is still unfavorable, and new therapeutic options are being sought. One of the currently explored options is development of combined drugs, including molecules with different mechanisms of action, so-called fixed-dose combination (FDC) preparations, which are expected to improve the quality of life, safety, and finally, treatment outcomes [1]. Such formulations include a fixed-dose combination of nivolumab (NIVO), an inhibitor of programmed death receptor 1 (PD-1), and relatlimab (RELA), an inhibitor of the lymphocyte-activation gene-3 (LAG-3) [2]. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thus preventing inhibition of T cells and immune responses (including anti-tumor immune responses) driven by the PD-1-related pathway. Relatlimab is a first-in-class human IgG4 LAG-3 blocking antibody that binds to LAG-3 and blocks its interaction with ligands, including the major histocompatibility complex (MHC II), which reduces the inhibition of immune responses mediated by the LAG-3-related pathway. The antagonism of this pathway promotes T-cell proliferation and cytokine secretion. The combination of nivolumab and relatlimab (NIVO/RELA) results in increased activation of T lymphocytes compared to the activity of either antibody alone [3–5]. In March 2022, the U.S. Food and Drug Administration (FDA) granted a priority review for the application for NIVO/RELA registration for the treatment of adults and children over the age of 12 with inoperable or metastatic melanoma [3].

Efficacy and safety of nivolumab/relatlimab combination

NIVO/RELA pivotal trials

The efficacy and safety of NIVO/RELA was evaluated in two pivotal trials — the phase I/IIa CA224020 study (RELATIVITY-020) and the phase II/III CA224047 study (RELATIVITY-047) [6, 7]. The RELATIVITY-047 study (n = 714) evaluated NIVO/RELA as a fixed-dose combination vs. NIVO monotherapy in patients with previously untreated metastatic or unresectable melanoma. The primary endpoint was progression-free survival (PFS), while the secondary endpoints included overall survival (OS), objective response rate (ORR), and quality of life (QoL). In the primary analysis, a statistically significant improvement in PFS was observed, with median PFS of 10.1 months in the NIVO/RELA group compared to 4.6 months in the NIVO group (median follow-up of 13.2 months). The differences were statistically significant, with a hazard ratio (HR) of 0.75 and a 95% confidence interval (CI) of 0.62–0.92. A subsequent PFS analysis, after a median follow-up of 19.3 months, confirmed the primary results. Median OS was not reached in the NIVO/RELA arm but was 34.1 months in the NIVO monotherapy arm. Estimated OS rates at 12, 24, and 36 months were more than 5% higher for NIVO/RELA as compared to NIVO alone. The objective response rate was 43.1% in the NIVO/RELA arm vs. 32.6% for NIVO. A subgroup analysis of patients with PD-L1 expression on melanoma cells of less than 1% showed an additional statistically significant benefit of NIVO/RELA in terms of PFS (6.67 months vs. 2.96 months) [7]. These results supported the European Medicines Agency's (EMA) registration of NIVO/RELA only in patients with PD-L1 expression on melanoma cells below 1%, which does not seem to have been fully justified given the good results and statistically significant difference in PFS in the remaining patients. Subgroup analysis additionally showed that in patients treated with NIVO/RELA, the ORR benefit was independent of PD-L1 expression level [4]. The study also evaluated the safety of the therapy. Adverse events occurred in nearly every patient — 97% and 94% in the NIVO/RELA and NIVO groups, respectively, while grade 3/4 adverse events occurred in 40% and 33% of patients in the NIVO/RELA and NIVO arms, respectively. Grade 3/4 treatment-related adverse events (TRAEs) occurred in 18.9% of patients in the NIVO/RELA group and 9.7% of patients in the NIVO group. No new safety issues were reported during NIVO/RELA therapy [7]. The data presented at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting after 3 years of follow-up showed the continuing superiority of NIVO/RELA over NIVO in terms of PFS, OS, ORR, and melanoma-specific survival (MSS). OS and MSS rates showed sustained improvement. Efficacy results also continued to favor NIVO/RELA over NIVO in most pre-specified subgroups. The safety of NIVO/RELA remained consistent with previous reports, with no new or unexpected toxicities.

NIVO/RELA and NIVO/IPI indirect comparison

To date, there have been no randomized trials directly comparing the efficacy and safety of NIVO/RELA and nivolumab with ipilimumab (NIVO/IPI). The only available analyses are indirect comparisons based on two randomized trials: the RELATIVITY-047 study with NIVO/RELA and the CheckMate 067 study with NIVO/IPI [6, 8–11]. Both trials were conducted in patients with previously untreated, unresectable, or metastatic melanoma. CheckMate-067 was a randomized phase

III study comparing NIVO/IPI or NIVO monotherapy with IPI monotherapy. The RELATIVITY-047 study evaluated NIVO/RELA vs. NIVO monotherapy. The main inclusion and exclusion criteria, as well as baseline characteristics, were similar in both studies. It should be noted, however, that in the RELATIVITY-047 study, there were more patients with BRAF mutations and positive PD-L1 expression on melanoma cells [6, 8, 11].

The first indirect analysis by Zhao et al. [11] showed that PFS was similar for NIVO/RELA and NIVO/IPI. In addition, analyses conducted according to hierarchical models showed that patients treated with NIVO/RELA experienced PFS benefits earlier than those receiving NIVO/IPI. The toxicity of NIVO/RELA treatment was also shown to be lower than that of NIVO/IPI. Grade 3/4 TRAEs occurred in 18.9% of patients using NIVO/RELA and 55.0% of those receiving NIVO/IPI [11].

Another indirect analysis comparing NIVO/RELA and NIVO/IPI was conducted by Long et al. [10] and showed no difference in PFS (HR = 1.08; 95% CI 0.88–1.33). There was also no confirmed statistically significant difference between the two groups in terms of the ORR (HR = 0.91; 95% CI 0.73–1.14), OS (HR = 0.94; 95% CI 0.75–1.19) and MSS (HR = 0.86; 95% CI 0.67–1.12). However, a numerical difference in favor of NIVO/IPI was demonstrated for some subgroups: patients with acral melanoma, *BRAF* mutant melanoma, and serum lactate dehydrogenase (LDH) level above 2 times the upper limit of normal (ULN). Nevertheless, the results of these analyses should be interpreted with caution due to the small sample size of the subgroups studied. Safety analysis showed that NIVO/RELA, compared to NIVO/IPI, was associated with fewer grade 3/4 TRAEs (23% *vs*. 61%) and no TRAEs leading to treatment discontinuation (17% *vs*. 41%). Overall, it was concluded that NIVO/RELA showed similar efficacy to NIVO/IPI in the general population, including most (but not all) subgroups, but with a more favorable safety profile [10].

Meta-analyses with NIWO/RELA

The only meta-analysis to date that included NIVO/RELA therapy in melanoma patients was conducted by Boutros et al. [12]. It included randomized clinical trials that enrolled patients with previously untreated unresectable or metastatic melanoma, with at least one arm receiving BRAF/MEK inhibitor or immune checkpoint inhibitor (ICI). The purpose of the meta-analysis was to indirectly compare the activity and safety of NIVO/IPI versus NIVO/RELA and all other therapeutic options for the first-line treatment of patients with advanced/metastatic melanoma (regardless of *BRAF* mutation status). Patients were not stratified by PD-L1 expression on melanoma cells. The meta-analysis included a total of 9070 patients from 18 randomized clinical trials. No difference was observed in terms of PFS (HR = 0.99; 95% CI 0.75–1.31) and ORR [relative risk (RR) = 0.99; 95% CI 0.78–1.27] between NIVO/IPI and NIVO/RELA, while anti-PD-L1/BRAF/MEK triple therapies were more effective than NIVO/IPI in terms of PFS (HR = 0.56; 95% CI 0.37–0.84) and ORR (RR = 3.07; 95% CI 1.61–5.85). NIVO/IPI showed the highest risk of grade ≥ 3 TRAEs. There was a trend toward a lower risk of grade ≥ 3 TRAEs for NIVO/RELA compared to NIVO/IPI (RR = 0.71; 95% CI 0.30–1.67). Conclusions from the meta-analysis indicated that PFS and ORR are similar for NIVO/RELA and NIVO/IPI, with a trend toward a better safety profile of NIVO/RELA.

Real-world data for NIVO/RELA

Real-world data (RWD) is a valuable source of information on the efficacy and safety of therapies. Nevertheless, as of October 2024, no major RWD analyses of NIVO/RELA therapy have been published. The only available analyses are brief reports by Thakker et al. [13] and Jang et al. [14] on small groups of patients. These analyses showed that PFS and OS for first- and second-line therapy with NIVO/RELA were consistent with results from the pivotal studies.

Conclusions

I. In all patients with unresectable or metastatic melanoma, NIVO/IPI therapy should be considered as the first line of treatment, taking into account primarily the safety profile. The long-term efficacy of NIVO/IPI therapy in this regard has been confirmed in several clinical studies.
II. In particular, it is recommended to use NIVO/IPI in patients with the following unfavorable prognostic factors: central nervous system metastases, high LDH level, moderate or significant disease dynamics, positive *BRAF* mutation status, progression after previous adjuvant treatment, and mucosal or acral melanomas.
III. In all patients who cannot be treated with NIVO/ /IPI, NIVO/RELA should be considered. The efficacy of NIVO/RELA in terms of PFS and ORR is close to that of NIVO/IPI, with significantly lower toxicity.
IV. Due to the registered EU label and the reimbursement provision in the current drug program of the Ministry of Health, NIVO/RELA therapy can only be used in patients with PD-L1 expression below 1% on melanoma cells; it is recommended to perform PD-L1 testing in all patients who are planning to start immunotherapy as first-line treatment

(this does not apply to patients who are planning to start treatment with NIVO/IPI).

V. The use of anti-PD-1 monotherapy should currently be considered only in patients with PD-L1 expression above 1% if there are contraindications to NIVO/IPI (presence of autoimmune diseases, multimorbidity, old age, inability to provide support to the patient and cooperate with the medical team) or if the patient does not consent to NIVO/IPI therapy. The data regarding the efficacy of anti-PD-1 monotherapy indicates that currently, this therapy should not be considered as the first-line treatment of choice, taking into account the possibility of combined immunotherapy use according to its reimbursement.

VI. A small tumor burden and slow course of malignancy should not be the only criterion for abandoning NIVO/IPI treatment, and even more so, NIVO/RELA.

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Supplementary material

None.

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