Nivolumab and Relatlimab-rmbw (OPDUALAG) National Drug Monograph December 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Nivolumab is an anti-programmed death 1 (PD-1) antibody that binds PD-1 receptors and prevents binding to programmed death ligands 1 and 2 (PD-L1, PD-L2), reducing inhibition of the immune response, and leading to T-cell proliferation and up-regulation of the immune response. Relatlimab is an inhibitor of lymphocyte-activation gene 3 (LAG-3), an immune checkpoint, that blocks interaction between the LAG-3 receptor and its ligands, similarly leading to reduction of inhibition of the immune response.

Indication(s) Under Review in This Document

- This combination of medications is indicated for the treatment of unresectable metastatic melanoma.

Dosage Form(s) Under Review

- 240 mg of nivolumab and 80 mg of relatlimab per 20 mL (12 mg and 4 mg per mL) in a single-dose vial.

Clinical Evidence Summary

Efficacy Considerations

- The combination of a LAG-3 and a PD-1 inhibitor is a novel combination of medications and its role in previously untreated metastatic melanoma has yet to be determined.
- Efficacy data are summarized in Table 1.

Table 1: Efficacy results from clinical trials

Study	Design	PS	Treatment	Results
Tawbi et al. RELATIVITY-047[1]	• Phase 2-3, randomized, double-blinded, global study **Inclusion** • Age ≥ 12 • Untreated, Unresectable Stage III or IV melanoma • Measurable disease by RECIST v1.1 criteria • Brain metastases if treated and no MRI evidence of progression • BRAF status known or tested **Exclusion** • Requirement of >10 mg/day of prednisone equivalent for 2 weeks prior to study treatment administration • Prior immune checkpoint inhibitor therapy unless given as adjuvant or neoadjuvant therapy for melanoma • Radiotherapy within 2 weeks • Active brain or leptomeningeal metastases • Active, known , or suspected autoimmune disease • History of myocarditis • Pregnant or breastfeeding	Adults: ECOG 0-1	Group 1: n = 355 • Nivolumab 480 mg IV • Relatlimab 160 mg IV • Every 4 weeks Group 2: n = 359 • Nivolumab 480 mg IV • Every 4 weeks Treatment in both groups was continued until progression of disease, intolerable toxicity, or withdrawal of consent. Treatment beyond initial progression was allowed if investigators assessed that the patient had clinical benefit and if the patient did not have unacceptable toxicities.	Primary: PFS by BIRC Secondary: OS, objective response Exploratory: PFS in prespecified subgroups, health-related QOL NIVO+RELA/NIVO Median age: 63-62 Male: 59.2%-57.4% ECOG 0: 66.5%-67.4% LDH > ULN: 36.6%-35.7% LAG-3 expression ≥ 1%: 75.5%-74.9% PD-L1 expression ≥ 1%: 41.1%-40.9% Median follow-up: 13.2 months Median PFS NIVO+RELA/NIVO 10.1 months vs. 4.6 months (95% CI, 3.4 to 5.6), HR for progression or death, 0.75 (95% CI, 0.62 to 0.92, p = 0.006) 12-month PFS NIVO+RELA/NIVO 47.7% vs. 36% (95% CI, 30.5 to 41.6) Benefit was seen with NIVO+RELA over NIVO regardless of LAG-3 expression. In patients with PD-L1 expression ≥ 1%, median PFS was similar between groups. In patients with PD-L1 expression < 1%, median PFS with NIVO+RELA was 6.4 months (95% CI, 4.6 to 11.8) as compared with 2.9 months (95% CI, 2.8 to 4.5) with NIVO (HR, 0.66 [95% CI, 0.51 to 0.84])

RECIST = , MRI = magnetic resonance imaging; ECOG = Eastern Cooperative Oncology Group; PFS = progression-free survival; BIRC = blinded independent review committee; OS = overall survival; QOL = quality of life; NIVO+RELA = nivolumab and relatlimab; NIVO = nivolumab; LDH = lactate dehydrogenase; ULN = upper limit of normal; CI = confidence interval; HR = hazard ratio

- Purpose: To describe efficacy and safety endpoints of the RELATIVITY-047 trial comparing nivolumab + relatlimab-rmbw vs. nivolumab alone for the treatment of previously untreated unresectable melanoma.
- The majority of patients had LAG-3 expression ≥ 1% and PD-L1 expression < 1%.
- At the final analysis of progression-free survival (PFS), the data monitoring committee conducted a prespecified interim analysis of overall survival (OS) at which point in time had not reached significance; data on OS and objective response remain blinded.
- Health-related quality of life was reportedly similar between groups. Differences between the groups did not meet the minimal threshold for clinical importance.
- PFS favored nivolumab + relatlimab-rmbw in those with mutant BRAF with a hazard ratio (HR) of 0.74, however, the 95% confidence interval (CI) was not significant at 0.54-1.03. PFS favored nivolumab + relatlimab-rmbw in those with wild-type BRAF with a HR or 0.76 and a significant 95% CI at 0.59-0.98.
- The combination of nivolumab + relatlimab was also recently examined in 30 patients with resectable stage III or oligometastatic stage IV melanoma.[2] Neoadjuvant treatment followed by surgery and then additional adjuvant treatment was associated with a 57% pathologic complete response rate and a 70% overall pathologic response rate.[2]

Safety Considerations

Safety Results from Clinical Trials:

- Results from the RELATIVITY-047 trial

Table 2: Safety results from clinical trials

Study	Results
Tawbi et al. RELATIVITY-047[1]	NIVO+RELA vs. NIVO **Any grade ADE:** 97.2% vs. 94.4% **Grade 3-4 ADE:** 40.3% vs. 33.4% **Grade 3-4 treatment-related ADE:** 18.9% vs. 9.7% **ADE leading to discontinuation:** 14.6% vs. 6.7% **Treatment-related deaths:** 0.8% vs. 0.6%

NIVO + RELA = nivolumab and relatlimab; NIVO = nivolumab; ADE = adverse drug event

- **Boxed warnings:** none

- **Contraindications:** none
- **Other warnings / precautions**:
    - **Immune-mediated adverse reactions:** may cause dermatitis, immune-mediated rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, endocrinopathies, gastrointestinal toxicity, hepatotoxicity, infusion-related reactions, nephrotoxicity, ocular toxicity, and pulmonary toxicity, among others
    - **Cardiotoxicity**: may cause immune-mediated myocarditis, pericarditis and vasculitis have also been reported
    - **Disease-related concerns:** transplant-related complications including graft vs. host disease and hepatic veno-occlusive disease may occur in those who receive allogeneic hematopoietic stem cell transplant before or after treatment with an anti PD-L1/PD-1 antibody. Checkpoint inhibitors may also worsen or precipitate myasthenia gravis.
    - **Dosage form specific issues:** some dosage forms may contain polysorbate 80, known to induce hypersensitivity reactions
- **Adverse reactions**
    - **Common** (> 10%): pruritis, fatigue, rash, arthralgia, hypothyroidism, diarrhea, vitiligo
    - **Serious Adverse events / Deaths / Discontinuation:**
        - Any grade 3-4 toxicity: 10.3%
        - Deaths: 0.8%
        - Toxicity leading to discontinuation: 8.5%

Other Considerations

- **Adverse events more common with nivolumab + relatlimab than with nivolumab alone:** pruritis, fatigue, rash, arthralgia, hypothyroidism, diarrhea, vitiligo, hepatitis, adrenal insufficiency, pneumonitis, hypophysitis, nephritis
- **Adverse events more common with nivolumab alone than with nivolumab + relatlimab:** hyperthyroidism, grade 3-4 rash and diarrhea
- **Infusion:** administered over 30 minutes with a 0.2-1.2 micrometer in-line filter
- **Stability:**
    - Room temperature and room light: 8 hours
    - Refrigerated and protected from light: 24 hours

Risk-Benefit Assessment (for Oncology NMEs only)

- **Outcome in clinically significant area:** Median Progression-Free Survival
- **Effect Size:** HR for progression or death, 0.75 (95% CI, 0.62 to 0.92, p = 0.006)

- **Potential Harms:** Any grade 3-4 toxicity: 40.3%
- **Net Clinical Benefit:** Moderate (high risk of benefit/high risk of harm)

Other Therapeutic Options

Alternative treatments for untreated unresectable melanoma are listed in table 3 below

Table 3 Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
Nivolumab + Relatlimab	TBD	• NCCN-preferred category 2A recommendation for first-line treatment of metastatic or unresectable melanoma[2] • Versus nivolumab	• Unresectable/metastatic melanoma
Pembrolizumab	F	• NCCN-preferred category 1 recommendation for first-line treatment of metastatic or unresectable melanoma[2] • Versus ipilimumab	• Unresectable/metastatic melanoma • Adjuvant treatment of resected melanoma
Nivolumab	F	• NCCN-preferred category 1 recommendation for first-line treatment of metastatic or unresectable melanoma[2] • Versus ipilimumab and ipilimumab + nivolumab	• Unresectable/metastatic melanoma • Unresectable/metastatic melanoma in combination with ipilimumab • Metastatic melanoma with brain metastases • Adjuvant treatment of resected melanoma
Ipilimumab + Nivolumab	F	• NCCN-preferred category 1 recommendation for first-line treatment of metastatic or unresectable melanoma[2] • Versus nivolumab and ipilimumab + nivolumab	• Unresectable/metastatic melanoma • 6.5 Year OS for Ipilimumab + nivolumab vs. nivolumab vs. ipilimumab:[3] ◦ BRAF-mutant: 57%, 43%, 25% ◦ BRAF-WT: 46%, 42%, 22%
TBD = to be determined; NCCN = national comprehensive cancer network			

Projected Place in Therapy

- Melanoma is an aggressive form of skin cancer that can become invasive and invade organs other than the skin. Melanoma accounts for only 1% of skin cancers but is responsible for the majority of deaths related to skin cancer.[4] It is estimated that in 2022, there will be about 100,000 new diagnoses and approximately 7,650 deaths from melanoma.[4]
- The majority of melanomas are diagnosed at a local stage and intervened upon surgically, however, it is estimated that 5% of melanomas are diagnosed at the metastatic stage.[5]
- Standard of care for initial treatment of metastatic disease is immunotherapy, targeted therapy against BRAF V600-activating mutations, a combination of these, or single-agent immunotherapy.
- Nivolumab + relatlimab offers a potential new therapy option in patients with untreated metastatic or unresectable melanoma as a result of the phase 3 RELATIVITY-047 trial.
- Summary: for those 12 years of age and older with unresectable or untreated metastatic melanoma, up-front treatment with nivolumab + relatlimab was shown to produce a statistically significant benefit over nivolumab monotherapy in terms of PFS. In terms of safety, the combination of nivolumab + relatlimab was associated with higher rates of adverse drug events compared to nivolumab alone, although levels of significance were not reported.
- Median follow-up time for the current results was only 13.2 months, and overall survival data is immature.
- Median age was 63 (range 20-94), and the majority of patients were male, making the study overall generalizable to the Veteran population.
- As of November 2022, there were 17,947 Veterans within the VA system with an active diagnosis code for malignant melanoma of skin (C43). It is estimated that about 900 of these Veterans have metastatic disease.
- Recent results from the DREAMseq trial established an overall survival, progression-free survival, and duration of response benefit in favor of initiating treatment with combination ipilimumab + nivolumab, followed by dabrafenib + trametinib in BRAF-mutant melanoma rather the converse.[6]
- Treatment with nivolumab + relatlimab for unresectable or untreated metastatic melanoma is considered an alternative option for first-line combination immunotherapy if a patient is deemed eligible for immunotherapy receipt according to the VHA guidance on drug sequencing.
- Nivolumab + relatlimab as first-line therapy for metastatic or unresectable disease is a category 2A and one of the preferred regimens recommended per the NCCN guidelines.

References

[1]Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. *N Engl J Med*. 2022;386(1):24-34. doi:10.1056/NEJMoa2109970

[2]Amaria, R.N., Postow, M., Burton, E.M. et al. Neoadjuvant relatlimab and nivolumab in resectable melanoma. Nature 611, 155–160 (2022). https://doi.org/10.1038/s41586-022-05368-8[2]NCCN Guidelines. Melanoma: Cutaneous. Version 3.2022. Updated 11 April 2022.

[3]Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. J Clin Oncol. 2022 Jan 10;40(2):127-137. doi: 10.1200/JCO.21.02229. Epub 2021 Nov 24. PMID: 34818112; PMCID: PMC8718224.[4]American Cancer Society. *Key Statistics for Melanoma Skin Cancer.* 12 January 2022. https://www.cancer.org/cancer/melanoma-skin-cancer/about/key-statistics.html

[5]ASCO. *Melanoma: Statistics.* Updated February 2022. https://www.cancer.net/cancer-types/melanoma/statistics

[6]Atkins MB, Lee SJ, Chmielowski B, et al. Combination Dabrafenib and Trametinib Versus Combination Nivolumab and Ipilimumab for Patients With Advanced BRAF-Mutant Melanoma: The DREAMseq Trial-ECOG-ACRIN EA6134. J Clin Oncol. 2022 Sep 27:JCO2201763. doi: 10.1200/JCO.22.01763. Epub ahead of print. PMID: 36166727.

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Appendix A. Acquisition Prices and Cost Considerations

Refer to VA pricing resources for updated information