

Improving Treatment of Cutaneous Melanoma with Personalized Therapy: Get Ready for INTERPATH-001

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Article Summary: INTERPATH-001 is the first phase 3 trial evaluating a personalized mRNA therapy for high-risk melanoma. This represents a major shift in melanoma treatment, and potentially other cancers as well.



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What will INTERPATH tell us?

This phase 3 trial will tell us whether an individualized mRNA therapy called intismeran autogene can improve recurrence-free survival (RFS) in high-risk melanoma. The mRNA vaccine is paired with pembrolizumab and tested against pembrolizumab alone.

What is an individualized mRNA vaccine?

Mutated proteins on the surface of a cancer cell are called neoantigens. Next-generation sequencing, a technology only available in the last 20 years, is used to analyze cancer samples for neoantigens. The information is used to create an mRNA strand that is packaged into a lipid nanoparticle delivery system. After

administration, the mRNA is translated into proteins that stimulate T cells to attack the cancer. Each patient receives a unique therapy based on the neoantigens in the cancer sample.

Why do we need a combination mRNA + immune checkpoint inhibitor?

Immune checkpoint inhibitors like nivolumab and pembrolizumab have improved outcomes in high-risk melanoma.¹ At nine years, nivolumab demonstrated RFS of 44%.² At seven years, pembrolizumab demonstrated RFS of 50%.³ Despite these gains, disease recurrence remains common, and overall survival has not improved.^{4,5} Current

studies aim to improve outcomes using new mechanisms that do not significantly increase treatment-related adverse effects.

What are the trial details?

INTERPATH-001 is a randomized, double-blind trial enrolling 1,137 patients with stage IIB-IV melanoma. After a complete surgical resection, patients received treatment for about one year. The primary endpoint is recurrence-free survival. Secondary endpoints include overall survival and safety measures.

What was the phase 2 trial that got this started?

The phase 2b KEYNOTE-942⁶ study was published in 2024, with a 5-year update in 2026.⁷ Patients with stage IIIB-IV cutaneous melanoma were randomized to intismeran plus pembrolizumab every three weeks for 18 doses or pembrolizumab alone for 18 doses. The combination showed a four-year RFS of 72.4% (95% CI, 62.2%-80.2%) versus 49.1% (95% CI, 33.3%-63%) for pembrolizumab alone. The most common adverse effects attributed to intismeran were fatigue, pyrexia, and myalgias.

Conclusion

Melanoma still carries a high risk of recurrence even with current adjuvant therapies. Personalized mRNA technology is a promising new approach, and the first phase 3 results are expected within the

next year. This development represents a significant shift in cancer treatment.

Declaration of interests

The author holds a personal investment in Merck, one of the companies developing intismeran autogene.

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