September 4, 2025

Dear Commissioner Makary and Director Prasad,

We, the undersigned patient advocacy organizations, write to you on behalf of many thousands of patients with melanoma and their loved ones to express our **extreme disappointment** in the decision to deny approval of RP1 (vusolimogene oderparepvec) in combination with nivolumab for treatment of advanced melanoma in the second line setting. **We ask that you revisit the CRL and consider conditional approval of RP1 for patients in urgent need of more treatment options while you resolve any remaining issues with the sponsor. There are thousands of patients who desperately need this treatment.**

Before 2011, when ipilimumab (Yervoy) was approved for Stage IV melanoma, there were no effective treatment options for advanced melanoma, and the survival rate hovered in the single digits. This drug approval ushered in the era of immunotherapy, a game-changing breakthrough for melanoma and many other cancers. Today, approximately half of patients with metastatic melanoma see a response to anti-PD1 or anti-CTLA-4 immunotherapies, and many are alive 10+ years after they first began treatment.

But for the other half who don't see a response—and for those whose response is not durable—dismal survival statistics are still their reality. The average lifespan of a patient with advanced melanoma who does not benefit from first-line immunotherapy is about 12 months. It is estimated that 8,430 people with melanoma will die in the United States this year alone. The options for second-line treatment are few, and all have limited success, availability, and durability—one of these treatments requires a patient to travel to and/or remain at only a limited number of geographic locations. **There is a vast, unmet, and urgent need in this patient population, and we urge you to consider the denial of RP1 from the perspective of a patient who has not benefited from first-line therapy options.**

Investigators have been working steadily over the last decade to understand why some patients' immune systems do not respond to currently approved immunotherapies and to develop treatments that prime them to do so. There is still so much we don't know about provoking immune system response and converting immune-resistant tumors to immune-responsive, but we seem to be on the right track with treatments like RP1. The IGNYTE trial found that RP1 with nivolumab achieved an objective response rate of 32.9% and a complete response rate of 15.0% in 140 patients with advanced melanoma that no longer responded to other treatments.

Yes, the patients in the IGNYTE trial received PD-1 inhibitors in their unsuccessful first-line treatment, and yes, they received nivolumab with their RP1, which makes attribution vague, but it is nonetheless a positive therapeutic attribution. And that is precisely the point: RP1 with nivolumab in second-line treatment has been shown to be successful *in combination and in this situation*. **Exactly why the combination is successful—the individual attribution—should be less relevant than the fact that it is successful.**

Further, a randomized clinical trial assigning some patients to receive anti-PD1 alone, after they had not responded to it in first-line treatment, would be impossible to accrue patients for and could be perceived as ethically questionable.

Finally, we want you to consider this denial from the perspective of patients with melanoma who participated in the RP1 clinical trials—indeed, patients in any disease who participate in clinical trials. FDA's change of mind after years of agreement with the parameters and design of all phases of the RP1 clinical trials is a massive blindside hit. Patients put themselves out to join trials. They often travel long distances, make financial sacrifices, and put their own health at risk by participating. Their caregivers make similar sacrifices. They are aware that the treatment in their trial may not benefit them, but they participate hoping to advance research and help others who are suffering. In return for their participation, they count on the approval of a treatment that is deemed safe and effective. **Patients in all diseases will be less likely to participate in trials if the rules are changed in the 11th hour. Such behavior makes patients feel like their participation was meaningless.**

Ipilimumab was hailed by the melanoma community as miraculous at its approval. Fourteen years later, its real value is not in its use as a single agent, but its use in combination with nivolumab, and, more broadly, its status as the drug that sparked the immunotherapy revolution. Put more generally, treatment approval begets the next generation of more effective treatment. In the meantime, many patients survive with the initially approved treatment. This was true for ipilimumab, and it would be true for RP1.

We've received hundreds of messages from patients—many of whom have failed first-line treatment—and their loved ones, about this decision. We've included many of them with this letter, all urging you to make RP1 available. Please take a moment to read their words and appreciate the desperate and urgent need within the melanoma patient community for a drug with an objective response rate of 32.9%, which is comparable to the already FDA-approved lifileucel (Amtagvi).

Thousands of lives are at stake every day we wait. We ask you to please make RP1 available while you work out the remaining issues with the sponsor.

Sincerely,

aCURE INSIGHT.org ocular melanoma

AIM AT MELANOMA FOUNDATION

Claire Marie FOUNDATION

MAC MELANOMA ACTION COALITION

Melanoma Research Alliance

MRF Melanoma Research Foundation