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FDA Briefing Document

BLA 125827

Drug name: vusolimogene oderparepvec

Applicant: Replimune, Inc.

Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

07/30/2026

Office of Therapeutic Products

Center for Biologics Evaluation and Research

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office.

We have brought the reliability and interpretability of the efficacy data from the IGNYTE study (RPL-001-016) for vusolimogene oderparepvec in combination with nivolumab for the treatment of adult patients with unresectable advanced cutaneous melanoma who experienced disease progression with a programmed death receptor-1 (PD-1)-blocking antibody-based therapy to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered, and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

AC	Advisory Committee
AE	adverse event
BLA	Biologics License Application
BOR	best overall response
BRAF	B-Raf proto-oncogene Serine/threonine kinase
CFR	Code of Federal Regulations
CI	confidence interval
CR	complete response
CRL	Complete Response Letter
CSCC	cutaneous squamous cell carcinoma
CTLA-4	cytotoxic T-lymphocyte Antigen 4
DOR	duration of response
FDA	Food and Drug Administration
GM-CSF	granulocyte-macrophage colony-stimulating factor
HSV	herpes simplex virus
ICI	immune checkpoint inhibitor
IND	Investigational New Drug
IRC	Independent Review Committee
IT	intratumoral
LAG-3	Lymphocyte Activation Gene-3
MEK	mitogen-activated protein kinase kinase
NCCN	National Comprehensive Cancer Network
NE	not evaluable
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PFS	progression-free survival
PFU	plaque-forming units
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SITC	Society for Immunotherapy of Cancer
TEAE	treatment-emergent adverse event
VO	vusolimogene oderparepvec

1. Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The FDA is convening this meeting to publicly discuss review issues associated with Replimune's application for its investigational product, vusolimogene oderparepvec (VO, also known as RP1), for the following proposed indication: vusolimogene oderparepvec in combination with nivolumab for the treatment of adult patients with unresectable advanced cutaneous melanoma who experienced disease progression with a programmed cell death protein 1 (PD-1)-blocking antibody-based therapy. The data submitted by the Applicant that is intended to provide substantial evidence of effectiveness to seek Accelerated Approval are derived from the IGNYTE study, also known as Study RPL-001-16.

The key FDA review issues include the following:

- In the IGNYTE study, the Applicant's application of Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) criteria for response assessment confounds interpretation of the reported efficacy results and limits FDA's ability to verify the reported results.
- The objective response data from the single-arm IGNYTE study are not of sufficient magnitude to overcome concerns about the contribution of effect, particularly in the absence of a reliable historical control, and therefore it cannot be determined whether RP1 contributes to any observed effect when administered in combination with nivolumab.
- The overall survival analysis from the single-arm IGNYTE study is not interpretable.

1.2 Context for Issues to Be Discussed at the AC

Disease Setting

Advanced unresectable cutaneous melanoma is a serious and life-threatening disease. The outcome in patients with this disease depends on the stage at presentation. In recent years, the expected prognosis of patients with advanced/metastatic melanoma has improved considerably compared to historical data. For example, the CheckMate 067 trial (Wolchok et al. 2025) established nivolumab and ipilimumab in combination as a first-line treatment for patients with metastatic melanoma, and long-term outcomes reported 71.9 months median overall survival for the combination (Wolchok et al. 2025). Other commonly used first-line therapies include nivolumab and relatlimab-rmbw combination therapy, nivolumab monotherapy, pembrolizumab monotherapy, and, for patients with B-Raf proto-oncogene serine/threonine kinase (BRAF) V600 mutation positivity, BRAF/ mitogen-activated protein kinase kinase (MEK) targeted therapies. Selection of second-line or later subsequent therapies is challenging due to the lack of prospective, randomized comparisons in this setting. National Comprehensive Cancer Network (NCCN) guidelines state that if a patient experienced progression of melanoma during or shortly after a systemic therapy, rechallenge with the same therapy or a therapy of the same class is unlikely to yield a response and is not recommended (NCCN 2026). However, the "exception to this rule" is that, for patients who progressed on a single-agent immune checkpoint therapy, nivolumab and ipilimumab combination therapy is a reasonable treatment option. In select cases, such as late progression or relapse following treatment discontinuation, reinduction with the same agent or same class of agents may be considered. Other professional guidelines (e.g., Society for Immunotherapy of

Cancer [SITC]) (Pavlick et al. 2023) have varying recommendations on the management of patients with advanced/metastatic cutaneous melanoma.

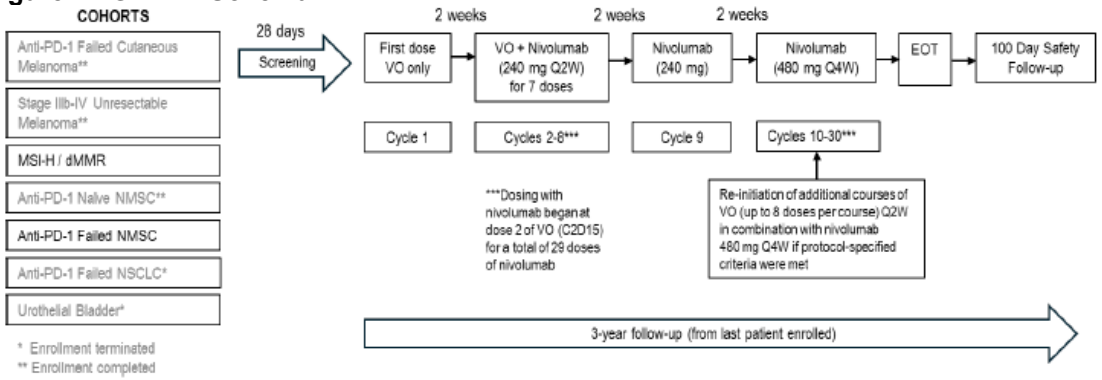
Following progression on anti-programmed cell death protein 1 (anti-PD-1) therapy, expected outcomes can vary based on factors such as disease stage, tumor BRAF mutation status, type and setting of prior therapies received, and other factors. The optimal treatment for this population is not well-defined and may include rechallenge with single or dual immune checkpoint inhibitors, BRAF/MEK inhibitors, chemotherapy, the intratumoral oncolytic viral therapy talimogene laherparepvec, or lifileucel (granted FDA accelerated approval in 2024). The expected outcomes following progression on anti-PD-1 therapy, including response rates to therapies such as immune checkpoint inhibitor rechallenge, are poorly characterized in the literature.

IGNYTE (Study RPL-001-16)

The primary evidence of effectiveness to support this BLA is based on results from IGNYTE, a single-arm, multicenter, Phase 1/2 study. This study was initiated as an exploratory study evaluating RP1 either as a single agent or in combination with anti-PD-1 therapy for the treatment of a variety of solid tumors. The study was later amended to evaluate RP1 in combination with nivolumab in a cohort of patients with unresectable advanced cutaneous melanoma who had progressed on anti-PD1 therapy (N=140), rather than being prospectively designed as a pivotal cohort from the study's outset. The study protocol underwent several subsequent amendments that materially changed the cohort's eligibility criteria and conduct.

Figure 1 depicts the IGNYTE schema. The "Anti-PD-1 Failed Cutaneous Melanoma" cohort (N=140) comprises the efficacy-evaluable population. The primary endpoint of IGNYTE is objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1), assessed by blinded Independent Review Committee (IRC).

Figure 1. IGNYTE Schema



Source: Adapted from Applicant's Assessment Aid Review Document
Abbreviations: EOT, end of time; NMSC, non-melanoma skin cancer; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; Q2W, every 2 weeks; Q4W, every 4 weeks; VO, vusolimogene oderparepvec

IGNYTE enrolled patients with unresectable Stage IIIB to IV cutaneous melanoma who had confirmed disease progression after at least 8 weeks of anti-PD-1 therapy (e.g., nivolumab or pembrolizumab). Prior therapy may have been administered either alone or in combination with anti-cytotoxic T-lymphocyte Antigen 4 (CTLA-4; e.g., ipilimumab) or other therapies. Anti-PD-1 therapy must have been the last line of prior therapy. Patients must have also had measurable disease per RECIST v1.1 and at

least one measurable tumor of 1 cm or greater in longest diameter, or 1.5 cm or greater in shortest diameter for lymph nodes and injectable lesions. Treatment was administered as follows:

- RP1 was injected at a first dose of 1×10^6 plaque-forming units (PFU)/mL, followed by subsequent doses of 1×10^7 PFU/mL every 2 weeks for up to 8 total cycles (~4 months), starting at Day 1.
- Nivolumab 240 mg was administered every 2 weeks for Cycles 2 to 9 (~4 months), followed by 480 mg every 4 weeks for Cycles 10 to 30 (~20 months), or 240 mg every 2 weeks at the discretion of the investigator, until confirmed progression or intolerable toxicity occurred or for a total of 29 cycles (~2 years).

At the investigators' discretion, treatment with RP1 could be continued beyond progression. Both superficial and deep/visceral intratumoral (IT) injections of RP1 were allowed. Multiple tumors could be injected until all injectable tumors had been treated or 10 mL of RP1 had been used. New tumors were eligible for injection. There was no minimum size for injectable lesions.

Use of Response Rate as an Endpoint

The statutory standard for approval of drugs and biologics requires, among other things, substantial evidence of effectiveness, consisting of adequate and well-controlled investigations. Drugs and biologics granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval. The accelerated approval pathway may be considered for products that treat serious conditions, provide a meaningful advantage over available therapies, and demonstrate an effect on an endpoint that is reasonably likely to predict clinical benefit.

FDA has accepted response rate as an endpoint for accelerated approval, and in certain cases, for traditional approval. FDA interprets response rates together with duration of response results. Response rate has been used as the approval endpoint, while duration of response is used to support the response rate results to demonstrate that effects are not short-lived or transient. However, duration of response has limitations in interpretation when these data are generated in a single-arm trial (e.g., confounding effects of the natural history of the disease). Response rate has been used as the primary endpoint to support traditional approvals in rare diseases and considerations for whether this is appropriate include, but are not limited to, the rarity of the population, a mechanism of action supported by strong scientific rationale, the intended use in a well-defined population, the degree of unmet need, a high and durable response rate, the location of the tumor and likelihood of symptom or functional improvement, and other context-dependent considerations associated with an overall positive benefit-risk profile.

Response rate has more commonly supported FDA accelerated approvals, as this clinical endpoint can be measured earlier than irreversible morbidity or mortality and is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit when taking into account the severity and rarity of the condition, the lack of alternative treatment options, and the overall benefit-risk profile. Response rate can be used to reasonably predict an effect in this manner because of the presumption that a systemic response to an investigational therapy may be disease-modifying. However, obtaining a response to therapy may not necessarily be indicative of clinical benefit. For example, if patients' tumors shrink on imaging studies consistent with a response but patients suffer toxicity from the treatment and/or do not live any longer, the benefit of a transient reduction in tumor burden is unclear and may not represent clinical benefit. Thus, reducing tumor size may be reasonably likely to predict benefit if

supported by duration of response, the safety profile is acceptable for the proposed population, and if clinical benefit is confirmed.

Response Criteria

For approval of oncology therapeutics, FDA generally requires that standardized response criteria be used to ascertain response in order to minimize bias, measurement error, and variability in response methods. Response rate for solid tumors is most commonly assessed using RECIST v1.1 criteria (Eisenhauer et al. 2009), which were developed and validated specifically to assess response to systemic therapies. Other response criteria may be used based on the disease setting and circumstance. RECIST v1.1 specifies that tumor lesions subjected to loco-regional therapies are generally not considered measurable for response assessment unless documented progression has occurred, as local treatment effects may confound radiographic measurements of tumor burden. Other groups have also stated that current oncology response criteria, including RECIST v1.1, were designed to only assess response to systemic therapy and are considered unsuitable for IT therapy trials (Goldmacher et al. 2020). Notably, RP1 is a local therapy administered intratumorally. Currently, there are no consensus guidelines for the use of imaging criteria to assess response specific to IT therapies. Proposed frameworks such as itRECIST (Goldmacher et al. 2020) have been described in the literature but have not been broadly adopted or validated for regulatory decision-making. SITC guidance (Luke et al. 2024) recommends using RECIST criteria, albeit with modifications regarding confirmation of progressive disease. Given the lack of consensus on response criteria to use for IT administered therapies, RECISTv1.1 may be considered if a systemic effect can be demonstrated and the magnitude of benefit is large to account for residual uncertainty.

We acknowledge a prior FDA approval of an IT administered therapy, the oncolytic viral therapy talimogene laherparepvec, which was approved in 2015 for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with recurrent melanoma after initial surgery. This approval was based on a randomized controlled trial of talimogene laherparepvec monotherapy versus granulocyte-macrophage colony-stimulating factor (GM-CSF) control in patients with unresectable stage IIIB, IIIC, and IV melanoma, with a primary endpoint of durable response rate (DRR) of at least 6 months as assessed by the World Health Organization response criteria. While the study demonstrated a DRR of 16.3% in the investigational arm versus 2.1% of the control arm, there was limited evidence of a systemic effect. Prior to approval, a joint meeting of the Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC) and the Oncologic Drugs Advisory Committee (ODAC) was convened on April 29, 2015, in part to examine this question. Committee panelists acknowledged the challenge of interpreting systemic activity for intratumorally administered agents, noting that, historically, multiple intratumoral agents have caused regression of injected tumors, yet evidence of activity in distant, non-injected lesions remains difficult to characterize (FDA 2015). Although the Applicant's proposed indication was for treatment of injectable regionally or distantly metastatic melanoma, following the AC, the indication was restricted to local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with recurrent melanoma after initial surgery. Additionally, a limitation of use was included in the United States Prescribing Information stating that talimogene laherparepvec has not been shown to improve overall survival or have an effect on visceral metastases. Of note, the treatment landscape for metastatic cutaneous melanoma has evolved considerably since this approval.

This underscores how currently available response assessment criteria were not developed to capture the distinct mechanisms and local effects of intratumorally administered therapies, making it difficult to reliably determine systemic antitumor activity. The challenge in reliably differentiating systemic antitumor activity from local antitumor effects using standard response criteria is particularly relevant to the IGNYTE study, where the combination of an intratumoral agent of RP1 with a systemic therapy of nivolumab in a single arm trial further complicates the assessment of whether RP1 contributes to a systemic response in patients with advanced/metastatic cutaneous melanoma.

Assessing the Contribution of Effect of Each Product to the Combination of RP1 and Nivolumab

When drugs are used in combination, it is important to determine the need for (i.e., contribution of) each drug component because each drug may cause toxicity and subjecting patients to unnecessary toxicity is not recommended. The IGNYTE study was not designed to assess the contribution of RP1 when administered in combination with nivolumab. To assess the contribution of RP1 to the combination, FDA recommended that the Applicant conduct a randomized trial to establish the contribution of effect of RP1 when added to nivolumab; however, the Applicant proceeded with BLA submission based on the single-arm IGNYTE study. FDA acknowledges that there may be a perceived lack of equipoise in this disease setting, as it may not be ethical to randomize patients who progressed on prior checkpoint inhibitor therapy to single-agent nivolumab. However, determining the need for each component of the RP1 and nivolumab combination remains important because both products can cause toxicity.

Due to the lack of a concurrent control, the Applicant instead relies on cross-trial comparisons of response rates from the IGNYTE study to historical controls to ascertain the expected response to immune checkpoint rechallenge (i.e., nivolumab monotherapy) in this population. Based on these data, the Applicant cites the reported response rates from the IGNYTE study in an attempt to demonstrate that the combination of RP1 and nivolumab results in a higher response rate than would be expected from monotherapy immune checkpoint rechallenge, as reported in the literature (Table 12). The presumption is then that RP1 contributes to the combination if the response rates reported for the combination of RP1 and nivolumab exceed those of monotherapy immune checkpoint rechallenge in the historical literature.

This is a challenging approach to establishing the activity of RP1 because of the heterogeneity of the patient population in the IGNYTE study, as well as in the historical literature. For example, several patient and disease factors may affect the expected outcome (i.e., response) in this population of patients with advanced/metastatic cutaneous melanoma that has progressed after prior checkpoint inhibitor therapy. Such factors include the type of prior therapy received, such as single agent anti-PD-1 or combination checkpoint inhibitor, duration of prior therapy, setting of prior anti-PD-1 therapy (adjuvant versus advanced/metastatic setting), extent of disease at baseline, and other unknown factors.

It is not possible to identify a well-established historical control benchmark for response rate and duration of response for comparison to the IGNYTE study population, and the expected response to immunotherapy rechallenge (i.e., nivolumab monotherapy) cannot be reliably determined in this patient population. The additional issues with the response assessment methodology in the IGNYTE study, discussed further below, also affect the ability to reliably determine the objective response rate and the

ability to compare these data to historical controls. This, in turn, results in uncertainty about whether the observed responses are due to nivolumab alone.

1.3 Brief Description of Issues for Discussion at the AC

The following key efficacy issues have been identified by FDA and form the basis for deliberation at this Advisory Committee (AC) meeting:

1. In the IGNYTE study, unreliable response assessment methods confound interpretation of the reported efficacy results, limit FDA's ability to verify the reported results, and do not support the conclusion that this trial is adequate and well-controlled.

FDA review of the IGNYTE study data identified significant concerns regarding the assessment of the Applicant-reported ORR and duration of response (DOR). The application of RECIST v1.1 criteria for response assessment in the IGNYTE study confounds the interpretability and clinical meaningfulness of the reported ORR and DOR. The FDA review team determined that the response methodology employed by the Applicant in the IGNYTE study does not allow for a reliable estimate of the treatment effect of RP1 when combined with nivolumab, and that it artificially increased the reported ORR and DOR. Given the uncertainty in the expected response rate to nivolumab monotherapy in this setting, this results in further challenges in determining whether RP1 meaningfully contributes to any observed effect.

These issues are further compounded by the fundamental challenge that RECIST v1.1 was intended to assess response to systemic therapies and may not be suitable for assessing response to IT therapies. The responses observed may represent local effects due to direct injection of RP1 rather than a true systemic disease-modifying effect; therefore, the reported response rate may not be considered reasonably likely to predict clinical benefit.

2. The objective response data from the single-arm IGNYTE study is not of sufficient magnitude to overcome concerns about the contribution of effect, particularly in the absence of a reliable historical control, and therefore it cannot be determined whether RP1 contributes to any observed effect when administered in combination with nivolumab.

The IGNYTE study was not designed to isolate the contribution of RP1 or nivolumab when used in combination. The lack of a concurrent control in the IGNYTE study necessitates comparison to historical controls of immune checkpoint rechallenge to determine what the expected response to nivolumab alone would be in the IGNYTE study population and whether RP1 contributes to any observed effect.

Given the unmet need in the indicated population, the FDA exercised flexibility by agreeing to review data from a single-arm trial. However, the magnitude of the observed effect, considered in the context of response assessment limitations and the lack of a reliable historical control, is not sufficient to overcome the uncertainties about the contribution of effect.

Comparing response rates cross-trial from the IGNYTE study to historical controls is challenging due to the heterogeneity of the enrolled patient population in the IGNYTE study and historical controls. Examples of potential confounders include, but are not limited to, the type of prior therapy received, such as single-agent anti-PD-1 or combination checkpoint inhibitor, duration of prior therapy, setting of prior anti-PD-1 therapy (adjuvant versus advanced/metastatic setting), and extent of disease at baseline. This heterogeneity, combined with the variability in response rates reported in the published literature,

precludes establishment of a reliable historical control benchmark for immune checkpoint rechallenge (i.e., nivolumab monotherapy).

The absence of a concurrent randomized control arm, combined with the unreliable response assessment and population heterogeneity described above, makes it impossible to determine whether RP1 contributes to any observed effect when administered in combination with nivolumab.

3. The overall survival analysis from the single-arm IGNYTE study is not interpretable.

The Applicant submitted a 3-year overall survival (OS) analysis from the IGNYTE study as supportive evidence of effectiveness for its BLA. OS data from a single-arm trial without a concurrent randomized control arm are not interpretable for establishing a treatment effect, as time-to-event endpoints in the absence of a concurrent control do not allow for distinguishing between a potential treatment effect on observed outcomes versus the natural history of the disease or other factors.

1.4 Draft Points for Consideration

1. Discuss whether the single-arm IGNYTE study, as designed and conducted, allows for a reliable determination of the expected response rate and durability of response in the proposed population.

2. Discuss the clinical meaningfulness of the response rate and duration of response reported in the IGNYTE study, and whether the observed responses are indicative of systemic antitumor activity attributable to RP1.

1.5 Draft Voting Questions

1. Are the efficacy results from IGNYTE evaluable and clinically meaningful?

2. Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Advanced unresectable cutaneous melanoma is a serious and life-threatening disease. Cutaneous melanoma is the fifth most common cancer in the United States, with an estimated 112,000 new diagnoses and 8,510 deaths in 2026 (NCCN 2026). The outcome in patients with this disease depends on the stage at presentation. In recent years, the expected prognosis of patients with advanced/metastatic melanoma has improved considerably compared to historical data. For example, the CheckMate 067 trial established nivolumab and ipilimumab in combination as a first-line treatment for patients with metastatic melanoma, and long-term outcomes reported 71.9 months median overall survival for the combination (Wolchok et al. 2025). Major advances in systemic immunotherapy over the past decade have resulted in increased survival and observations of long-term remissions; however, many patients with advanced melanoma do not achieve long-term disease control. At least 50% of patients treated with frontline anti-PD-1-based therapy experience disease progression within 1 year.

Commonly used first-line therapies include nivolumab and ipilimumab, nivolumab and relatlimab-rmbw, nivolumab monotherapy, pembrolizumab monotherapy, and for patients with BRAF V600 mutation

positivity, BRAF/MEK-targeted therapies. Selection of second-line or later subsequent therapies after disease progression on immunotherapy is challenging due to the lack of prospective, randomized comparisons in this setting (NCCN 2026). NCCN guidelines state that if a patient experienced progression of melanoma during or shortly after a systemic therapy, rechallenge with the same therapy or a therapy of the same class is unlikely to yield a response and is not recommended. However, NCCN guidelines also note that for patients who progressed on a single-agent immune checkpoint therapy, nivolumab and ipilimumab combination therapy remains a reasonable treatment option. Additionally, reinduction with the same agent or same class of agents may be considered in select cases, such as late progression or relapse following treatment discontinuation. While FDA acknowledges that NCCN is only one professional guideline, this expert consensus opinion underscores the uncertainty and challenges in determining the optimal sequencing and selection of therapies for patients with metastatic melanoma who progressed after treatment with a prior anti-PD-1 therapy (i.e., checkpoint inhibitor).

Following progression on anti-PD-1 therapy, expected outcomes can vary based on factors such as disease stage, BRAF mutation status, type and setting of prior therapies received, and other factors. The optimal treatment for this population is not well-defined and may include rechallenge with single or dual immune checkpoint inhibitors, BRAF/MEK inhibitors, chemotherapy, the intratumoral oncolytic viral therapy talimogene laherparepvec, or lifileucel (granted accelerated approval in 2024). The expected response to therapies following progression on anti-PD-1 therapy, including immune checkpoint inhibitor rechallenge, is poorly characterized in the literature.

This condition represents an area of unmet medical need.

2.2 Pertinent Drug Development and Regulatory History

Product

RP1 is a genetically modified human herpes simplex virus type 1 (HSV-1) with deletions of the neurovirulence factor ICP34.5 and the transport associated with antigen presentation inhibitor ICP47, and insertions of transgenes encoding a fusogenic glycoprotein derived from gibbon ape leukemia virus with the R sequence deleted (GALV-GP-R-) and human granulocyte-macrophage colony-stimulating factor (hGM-CSF). GM-CSF is a cytokine intended to activate and mature dendritic cells and monocytes. GALV-GP-R- is a fusion protein intended to promote viral spreading in tumors to enhance tumor killing.

RP1 is administered by intratumoral injection at a dose of 1 mL per cm of the largest tumor dimension (maximum 10 mL per injection visit) every 2 weeks for 8 doses, starting at 10^6 PFU/mL and escalating to 10^7 PFU/mL from Week 3.

Regulatory History

The original IND 17922 was submitted to FDA in February 2018, including an exploratory Phase 1/2 IGNYTE study evaluating RP1 either as a single agent or in combination with anti-PD-1 therapy for the treatment of a variety of solid tumors. The Phase 2 portion of the IGNYTE study was initiated in May 2019 with multiple cohorts, and the anti-PD-1 refractory cutaneous melanoma cohort was added in December 2019. Patients enrolled in this cohort were treated with repeated RP1 doses administered intratumorally in combination with nivolumab, which was administered intravenously. Key eligibility criteria included Stage IIIB, IIIC, or IV unresectable advanced cutaneous melanoma with confirmed

progressive disease after at least 8 weeks of nivolumab or pembrolizumab received either alone or in combination with other treatments (prior immune checkpoint inhibitor [ICI] treatment in the adjuvant setting was allowed). The primary study endpoint was ORR. The study underwent several subsequent amendments that materially changed the cohort's eligibility criteria and conduct. See Table 1 for a summary of major protocol amendments.

Table 1. Summary of Key Changes Implemented in Protocol Amendments for IGNYTE Study per Applicant

Amendment Number /Date/Country	Key Changes
Amendment 7 December 17, 2019 Global	• Added the anti-PD-1 refractory melanoma cohort of patients with melanoma who had progressed on anti-PD-1 therapy. • Updated inclusion criteria for injectable lesions to include tumors of shortest diameter ≥1.5 cm in lymph nodes and injectable lesions which in aggregate comprise ≥1 cm in longest diameter.
Amendment 8 December 14, 2020 Global	• Permitted patients who met specific criteria to reinitiate dosing with RP1 for up to 8 additional doses. • Established an independent response assessment committee for the anti-PD-1 refractory melanoma cohort. • Updated the primary objectives to state that the efficacy of RP1 in combination with nivolumab would be determined by ORR per modified RECIST, as assessed by the investigator, except for the anti-PD-1 refractory melanoma cohort, in which ORR would be assessed by independent review.
Amendment 10 August 24, 2021 Global	• Further defined the specific subpopulation to be enrolled in the anti-PD-1 refractory cutaneous melanoma cohort, including a specified number of patients with Stage IVB-D disease and with deep/visceral lesions. • Changed inclusion criteria for the anti-PD-1 refractory cutaneous melanoma cohort to allow treatment of patients with >1 prior line of anti-PD-1 therapy. • Increased survival follow-up for all Phase 2 patients to a total of 3 years after initial RP1 dosing.* • Established 12 months after the last patient's first study drug dose as the timepoint for the primary analysis of the anti-PD-1 refractory melanoma cohort.
Amendment 11 July 22, 2022 Global	• Submitted to FDA but not implemented before additional changes to sample sizes of Phase 2 cohorts were made to Protocol Amendment 12. • Changed survival follow-up for all Phase 2 patients to a total of 3 years from the date of last patient enrolled.* • Clarified that approximately 138 patients would be enrolled in the anti-PD-1 refractory melanoma cohort to achieve a target sample size of 125 treated patients, given a 10% early dropout rate.
Amendment 12 Current: September 2, 2022 Global	• Removed the requirement for a specific number of patients to be enrolled with Stage IVB-D disease and with deep/visceral lesions in the anti-PD-1 refractory cutaneous melanoma cohort.

Source: Adapted from Applicant Submission in Assessment Aid, BLA Clinical Review and Evaluation Memo (Section 8.1.2, Table 24)
* As the survival follow-up period was different from amendment to amendment, patients who had completed the study based on older amendments were not followed afterwards because they were not consented to the most current amendment.
Abbreviations: ORR, objective response rate; PD-1, programmed cell death protein 1; RECIST, Response Evaluation Criteria in Solid Tumors

A brief summary of key revisions is provided below:

- Amendment 8 (December 2020) retrospectively established the IRC for this cohort after enrollment had begun and reduced the minimum required duration of immediate prior anti-PD-1 therapy from 12 weeks to 8 weeks, increasing the risk of enrolling patients who may have had pseudoprogression rather than true refractory disease. Amendment 8 also permitted reinitiation of RP1 for up to eight additional doses beyond the initially planned treatment schedule and expanded the allowed lactate dehydrogenase level.
- Amendment 10 (August 2021) introduced a minimum enrollment target for patients with visceral lesions suitable for intratumoral injection and patients with Stage IVB to IVD disease, while also allowing patients with more than one prior line of anti-PD-1 therapy, further broadening the study population.
- Amendments 11 and 12 (2022) subsequently removed the visceral lesion enrollment requirement and changed the survival follow-up window.

Taken together, these amendments introduced heterogeneity into the IGNYTE study population and raised important questions about the consistency of the response assessment methodology and the representativeness of the cohort for the proposed indication.

Thereafter, multiple meetings between FDA and the Applicant were held between 2021 and 2024. Notably, during a Type B meeting held on March 25, 2021, FDA emphasized that the proposed single-arm design would not be able to isolate the contribution of RP1 to the treatment effect (e.g., the response rate) from the combination regimen, and that the proposed target overall response rate of 30 to 40% may not translate into improved clinical benefit for the intended population. FDA also noted that "interpretation of responses in the setting of the intra-tumoral route of administration to be problematic in the lesions which have been injected." Therefore, FDA recommended that the Applicant conduct a randomized controlled trial to establish the efficacy of RP1. Additionally, in subsequent meetings, FDA emphasized that the primary efficacy analysis to support the BLA should be per RECIST v1.1 (unmodified), as assessed by IRC.

In September 2024, FDA stated that it does not object to the Applicant's proposal to submit a BLA based primarily on data from the IGNYTE study. However, FDA noted that in the BLA submission, the Applicant should provide evidence to demonstrate that there is a compelling reason that both RP1 and nivolumab are necessary to achieve the observed treatment effect and also provide evidence that RP1-injected and noninjected tumors achieved objective responses.

The initial BLA was submitted on November 21, 2024, based on clinical data from the single-arm Phase 2 IGNYTE study's anti-PD-1 refractory cutaneous melanoma cohort (N=140), with the primary efficacy endpoint of ORR per RECIST v1.1 by IRC. The primary efficacy analysis was performed in 140 patients, and the Applicant's reported ORR was 33.6% (95% confidence interval [CI]: 25.8%, 42.0%), including complete responses (CRs) in 23 (16.4%) patients and partial responses (PRs) in 24 (17.1%) patients. The Applicant's reported median DOR was 24.8 months (95% CI: 14.1, not reached). The Applicant reports that responses were observed in 80.9%, 59.6%, 42.6%, and 29.8% of responders at 6, 12, 18, and 24 months, respectively.

A Complete Response Letter (CRL) was issued on July 21, 2025. FDA concluded that the IGNYTE trial was not an adequate and well-controlled study. Key deficiencies cited in the CRL included:

- Inability to adequately interpret the response rate due to heterogeneity of the IGNYTE trial population, including the type of prior therapy received, such as single-agent anti-PD-1 or combination checkpoint inhibitor, duration and setting of prior anti-PD-1 therapy, and extent of disease at baseline, as well as heterogeneity of the patient population reported in the literature.
- The IGNYTE trial was not designed to isolate the contribution of RP1 to the observed ORR when administered in combination with nivolumab.

FDA stated that the Applicant must conduct and provide results from adequate and well-controlled clinical trial(s) demonstrating substantial evidence of effectiveness.

During a follow-up Type A meeting held on September 16, 2025, after the Complete Response, FDA reiterated these issues and also communicated that the response criteria used in IGNYTE were not consistent with RECIST v1.1 and raised concerns regarding the response methods used in IGNYTE that confound interpretation of the reported trial results.

FDA acknowledged the unmet need in this patient population. To address these concerns while still allowing for potential accelerated approval to meet patients' unmet need, FDA recommended that the Applicant consider amending their ongoing Phase 3 trial, IGNYTE-03, to potentially support accelerated approval by conducting an interim analysis of response rate and duration of response between arms, while using further follow-up OS data to potentially confirm benefit to support conversion to traditional approval. FDA recommended that the Applicant generate a proposal for using interim analyses from the ongoing IGNYTE-03 trial to potentially support resubmission of a BLA and also recommended that they request a meeting with FDA to discuss any such proposal further. However, the Applicant did not heed this advice and instead resubmitted the BLA on October 9, 2025, shortly after the Type A meeting.

To support this first resubmission of the BLA, the Applicant provided ORR data from an early unplanned analysis of their ongoing, randomized, Phase 3 trial RP1-104 (IGNYTE-03), including 22 patients in the investigational arm of RP1 with nivolumab and 18 patients in the control arm, representing 10% of the planned enrollment of 400 patients. The Applicant:

- Reported three confirmed investigator-assessed responses in the RP1 and nivolumab arm and none in the physician's choice of therapy control arm. Follow-up was insufficient to assess duration of response, these responses were not reviewed by an independent radiology committee, and FDA found that these data did not address the issues outlined in the CRL.
- Reported that for progression-free survival (PFS), 59.3% of patients in the RP1 and nivolumab arm remained progression-free at 6 months compared to 24.2% in the control arm, with a hazard ratio of 0.44. Unplanned PFS analyses that are not controlled for type I error and conducted in a small number of patients were not considered interpretable by FDA.
- Noted one death in the RP1 and nivolumab arm and four deaths in the control arm.
- Provided results from additional exploratory analyses of the IGNYTE trial, including analyses in which the Applicant assessed patients' response to immediate prior therapy and compared this to their response to RP1 and nivolumab. The Applicant reported that in responding patients (n=47), PFS with

RP1 and nivolumab was 30.6 months versus a median PFS of 4.4 months on immediate prior anti-PD-1 therapy. FDA found this comparison to be uninterpretable.

- Provided an analysis of injected versus noninjected lesions, which was also part of the first BLA, in an attempt to demonstrate the systemic effect of RP1 when added to nivolumab. This is discussed further below.

The Applicant stated that they proposed to use these data to "provide confidence that the IGNYTE-03 study is tracking consistently with expectations from the literature for the control arm and with the data from the IGNYTE" study.

The FDA review team determined that the additional data submitted by the Applicant were insufficient to support an efficacy claim due to the limited number of patients treated, a lack of duration of response data, and the other aforementioned reasons. These preliminary efficacy data were limited in their interpretability and the FDA review team concluded that they did not substantively add to the Applicant's initial data and submission package. The additional analyses submitted by the Applicant did not alter the initial conclusion drawn by the FDA review team, and this resubmission did not address FDA's concerns as outlined in the CRL. A second CRL was issued on April 10, 2026. In this CRL, FDA stated that issues in response assessment confound efficacy results, heterogeneity of the IGNYTE patient population and lack of a well-established historical control limit comparisons of response rate, and the trial design was inadequate to establish contribution of effect.

Table 2 summarizes key regulatory interactions and pertinent FDA clinical comments related to the IGNYTE study prior to and during BLA submissions.

Table 2. FDA Summary of Key Regulatory Interactions and Pertinent FDA Clinical Comments

Date	Interaction Type	Pertinent Comments/Agreements
March 25, 2021	Type B meeting CRTMS #13148 (IGNYTE [RPL-001-16])	• FDA did not agree that the results from the single-arm IGNYTE study could be used as the primary evidence to support effectiveness and safety for this BLA. • FDA stated that the proposed single-arm study would not enable identification of the contribution of each component of the combination to the overall response rate. • FDA stated that the proposed target of 30% to 40% ORR may not translate into unequivocally improved clinical benefit in this indication compared with the combination of nivolumab plus ipilimumab. • FDA recommended that the Applicant conduct a RCT to demonstrate the efficacy and safety of the combination and isolate the contribution of each component to the overall treatment effect. • FDA stated that the IGNYTE study population appears to be heterogeneous with respect to prior treatment regimens other than anti-PD-1, and noted that considerable differences in prior treatment regimens, timing of treatment, and burden of disease among study subjects may make it difficult to interpret efficacy results relative to available therapies. FDA recommended that the Applicant revise the inclusion criteria to include a more well-defined study population and reduce differences in baseline characteristics among study subjects. • FDA noted potential issues with interpreting efficacy results due to baseline heterogeneities among study subjects. FDA stated that it

Date	Interaction Type	Pertinent Comments/Agreements
		will interpret the results based on the study subjects including information on prior treatment regimens and timing of the prior treatment. FDA reiterated that it would not recommend that the Applicant submit a BLA based on the results of a single-arm study. • FDA noted that interpretation of responses in the setting of the intratumoral route of administration can be problematic in lesions that have been injected. In the absence of a randomized blinded, placebo-controlled trial, responses in small, injected lesions will be difficult to interpret and the observed response could potentially be attributed to mechanical effects of repeated injections. • FDA recommended measuring and tracking objective responses of both injected and noninjected lesions when reporting ORR.
September 12, 2023	Type C meeting CRMTS #15143 (Clinical meeting to discuss regulatory strategy for registration)	• FDA stated that it was unable to determine if the preliminary efficacy results from the IGNYTE trial could potentially meet the AA criteria. • FDA stated that it would be necessary to isolate the contribution of RP1 and nivolumab to the observed ORR using trial data within the clinical development program and/or data from published literature. • FDA requested revision of the IRC charter so that assessments of tumor responses by IRC follow the guidelines of RECIST v1.1. For any modifications to RECIST v1.1, the Applicant should provide detailed justification for doing so. • FDA requested a detailed IRC charter, including information about new lesions and PD. FDA stated that, per RECIST v1.1, new lesions considered “unequivocal” on the scan should be declared as PD; equivocal or small lesions should be confirmed at a later scan, but once confirmed: the new lesion should be declared as PD; radiographically confirmed PD should be documented as a progression event and PD; and the end time of DOR and PFS should be the earlier time point of the PD, not the time point when PD is confirmed.
March 5, 2024	FDA Clinical Information Request	• Following the Applicant’s submission of Independent Review Charter v1.0, dated February 12, 2024, FDA responded that tumor responses, including TPRs and BOR, as assessed by the IRC, according to the RECIST v1.1 guidelines, would be the basis of the primary and key secondary endpoints for regulatory approval purposes. Tumor responses derived from protocol-modified RECIST would be reviewed by FDA as supporting evidence.
September 3, 2024	Type B Pre-BLA meeting Meeting ID# 20461	• FDA did not object to the proposal to submit a BLA based primarily on data from the cohort of patients (N=140) in the Phase 2 IGNYTE trial. • FDA requested that the Applicant provide evidence demonstrating that there is a compelling reason that both RP1 and nivolumab are necessary to achieve the observed treatment effect. • FDA requested that the Applicant provide evidence that both RP1-injected and noninjected tumors achieved objective responses. • FDA clarified that the primary ORR and DOR data to support the BLA would be assessed by IRC per RECIST v1.1, and that results assessed by IRC per mRECIST may be presented as supportive evidence.

Date	Interaction Type	Pertinent Comments/Agreements
September 6, 2024	Type C Written Responses Only Meeting ID# 20441	• FDA confirmed that the primary efficacy analysis would be based on the study results from the SCE of the Phase 2 anti-PD-1 cohort (N=140), assessed using unmodified RECIST v1.1 by independent radiology review.
November 21, 2024	Initial BLA Submission	• Single-arm IGNYTE trial used to support this BLA. • ORR 33.6% (95% CI: 25.8, 42.0); median DOR 24.8 months.
July 21, 2025	First CRL	• IGNYTE not an adequate and well-controlled study. • Unable to assess contribution of effect of RP1. • Trial results difficult to interpret due to patient heterogeneity.
September 16, 2025	Type A Meeting	• Response criteria not consistent with RECIST v1.1. • Recommended amending Phase 3 trial to evaluate RR at interim analysis to generate more supportive data to potentially support AA.
October 9, 2025	BLA resubmission	• Minimal new data provided. • Resubmission essentially the same data package as initial submission.
April 10, 2026	Second CRL	• Inability to isolate the contribution of RP1 when administered in combination with nivolumab. • Heterogeneity of the study population. • Response assessment methodology issues leading to uncertainty in determining response, including ORR assessment not consistent with RECIST v1.1 and surgical interventions with potential for confounding response results. • To address these deficiencies, FDA stated that the Applicant must conduct and provide results from adequate and well-controlled clinical trial(s) demonstrating substantial evidence of effectiveness.
June 2, 2026	BLA resubmission	• Minimal new data provided. • Resubmission essentially same data package as the initial submission; included the 3-year survival analysis of the IGNYTE Phase 2 anti-PD-1 refractory melanoma patient cohort.

Source: FDA analysis
Abbreviations: AA, accelerated approval; BLA, biologics license application; BOR, best overall response; CI, confidence interval; DOR, duration of response; IRC, independent review committee; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PFS, progression-free survival; RCT, randomized controlled trial; RECIST, Response Evaluation Criteria in Solid Tumors; RR, response rate; SCE, Summary of Clinical Efficacy; TPR, tumor partial response

Summary of Interactions with Other Regulatory Authorities

(b)(3)

3. Summary of Issues for the AC

3.1 Efficacy Issues

Key efficacy issues:

- In the IGNYTE study, the Applicant's application of RECIST v1.1 criteria for response assessment confounds interpretation of the reported efficacy results, limits FDA's ability to verify the reported results, and does not support the conclusion that this is an adequate and well-controlled trial.
- The objective response data from the single-arm IGNYTE study is not of sufficient magnitude to overcome concerns about the contribution of effect, particularly in the absence of a reliable historical control, and therefore it cannot be determined whether RP1 contributes to any observed effect when administered in combination with nivolumab.
- The overall survival analysis from the single-arm IGNYTE study is not interpretable.

3.1.1 Sources of Data for Efficacy

The primary efficacy data submitted in support of BLA 125827 are derived from the Phase 2 anti-PD-1 refractory melanoma cohort of the IGNYTE study. Early interim data from the Phase 3 IGNYTE-03 trial were also provided in the first resubmission.

Table 3. Studies in Support of BLA 125827

Study	Design	Population	Primary Endpoint	N (Efficacy Cohort)
IGNYTE (RPL-001-16) Phase 2	Single-arm, open-label, multicenter, multicohort	Unresectable Stage IIIB-IV cutaneous melanoma; confirmed progression on prior anti-PD-1 as immediate prior line	ORR per RECIST v1.1 by IRC	140
RP1-104 (IGNYTE-3)	Randomized, open-label; RP1 and nivolumab vs. physician's choice	Unresectable advanced cutaneous melanoma; progression on anti-PD-1 and anti-CTLA-4	Overall Survival (primary); ORR (exploratory interim only)	41 randomized at data cutoff (10% of planned enrollment)

Source: FDA Clinical Review Memo (original BLA, July 15, 2025) and FDA Clinical Review Addendum (resubmission, April 7, 2026)
Abbreviations: CTLA-4, Cytotoxic T-lymphocyte Antigen 4; IRC, independent review committee; ORR, objective response rate; PD-1, programmed cell death protein 1; RECIST, Response Evaluation Criteria in Solid Tumors

3.1.2 Efficacy Summary

The Applicant-reported primary efficacy results from the IGNYTE study are as follows:

- ORR of 33.6% (95% CI: 25.8%, 42.0%), including 23 complete responses (16.4%) and 24 partial responses (17.1%).
- Median DOR of 24.8 months (95% CI: 14.1, not reached), as assessed by IRC per RECIST v1.1.

FDA identified the following specific key review issues:

- Application of RECIST v1.1 criteria in the IGNYTE study compromises the reliability and interpretability of the reported ORR and DOR.
- The responses observed may represent local effects due to direct injection of RP1 rather than a true systemic disease-modifying effect; therefore, the reported response rate may not be considered reasonably likely to predict clinical benefit.
- The ORR data from the single-arm IGNYTE study, considered in the context of the response assessment limitations and the lack of a reliable historical control, is not sufficient to overcome the uncertainties about the contribution of effect; thus, the contribution of RP1 to the combination cannot be established.
- OS analysis provided by the Applicant is not interpretable.

3.1.3 Efficacy Issues in Detail

The key efficacy issues to be discussed at the AC meeting are described in detail below.

Key Efficacy Issue 1: In the IGNYTE study, the Applicant's application of RECIST v1.1 criteria for response assessment methods confounds interpretation of the reported efficacy results, limits FDA's ability to verify the reported results, and does not support the conclusion that this is an adequate and well-controlled trial.

RP1 is an intratumorally injected therapy administered in combination with a systemic therapy, nivolumab. The criteria the Applicant purports to have used to assess tumor response in the IGNYTE study, called RECIST v1.1 (Eisenhauer et al. 2009), were designed for use to assess the response to systemic therapies. Application of these criteria is challenging for assessing response to IT therapies because:

- Focal intervention (e.g., injection of tumors with the investigational drug) renders treated lesions non-evaluable for response by definition.
- RECIST criteria do not allow separate response assessments in injected and noninjected lesions, which is important for assessing the systemic effect of the IT therapy.
- There is no consensus on injected lesion assessment when lesions chosen for injection may change during treatment because of regression, loss of accessibility, or growth of other lesions.

There are currently no consensus guidelines for use to assess response to IT therapies; however, different criteria have been proposed and published by the scientific community (Goldmacher et al. 2020). Given the lack of consensus response criteria to apply for IT therapies, RECIST v1.1, even with its limitations, may allow for estimating the drug activity of investigational IT therapies. FDA exercised flexibility when agreeing to the use of RECIST v1.1 criteria to assess response in the IGNYTE study, given the lack of other validated response criteria; however, uniform application of these criteria is critical to allow for interpretable and reliable response data. Whether RECIST v1.1 criteria are appropriate for this purpose depends on the application of the criteria, whether a systemic effect can be inferred, the magnitude of effect observed, and other context-specific considerations.

FDA review identified several issues in the assessment of the reported response rate and duration of response in the IGNYTE study that affect the reliability of the reported results and their clinical

meaningfulness. Review of the individual patient data also revealed potential deviations from standard RECIST v1.1 methodology that the Applicant claims to have used to report efficacy results.

1. **Lack of noninjected target lesions and assessment of systemic effect:** FDA review identified that almost half (49%) of patients that the Applicant deemed to have had a response had all of their target lesions injected with RP1. FDA review identified two additional patients deemed responders who did not have any target lesions per independent review at baseline. Thus, over half (53%) of patients with an Applicant-reported objective response did not have any noninjected target lesions to assess systemic antitumor activity. When these patients are excluded as responders from the analysis of the primary endpoint of ORR, the resulting response rate decreases from the reported response rate, with the lower bound of the 95% confidence interval falling to 10.1% (Table 4). The median DOR also decreases to 14.1 months. FDA's primary efficacy analysis retains all 140 patients in the denominator to maintain consistency with prespecified primary efficacy analysis set that follows the intent-to-treat principle.

   In addition to the FDA primary efficacy analysis cited above with ORR of 15.7% (95% CI: 10.1%, 22.8%), FDA also conducted a sensitivity analysis by excluding all patients (whether deemed an Applicant-responder or non-responder) who had all TLs injected or no TLs at baseline from the primary analysis (exclusion of n=51 patients). FDA notes that excluding these 51 patients may be a form of "informative censoring," such that certain characteristics in these patients may make them more or less likely to respond to the investigational therapy. In this sensitivity analysis, the resulting evaluable population includes 89 patients, of whom 22 were responders, yielding an ORR of 24.7% (95% CI: 16.2%, 35.0%) with a median DOR of 14.1 months (95% CI: 10.7, NR) (Table 4).

Table 4. FDA Efficacy Analysis of ORR and DOR per RECIST v1.1 by IRC, IGNYTE Study Anti-PD1 Refractory Cohort: Excluding Responders Who Had All TLs Injected With RP1 or Had no TLs at Baseline

Analysis	Responders (n)	ORR (95% CI, %)	Median DOR (Months) (95% CI)
Applicant	47	33.6 (25.8, 42.0)	24.8 (14.1, NR)
FDA Primary Analysis (n=140)	22	15.7 (10.1, 22.8)	14.1 (10.7, NR)
FDA Sensitivity Analysis (n=89)	22	24.7 (16.2, 35.0)	14.1 (10.7, NR)

Source: FDA analysis
Abbreviations: CI, confidence interval; IRC, independent review committee; ORR, objective response rate; TL, target lesion; RECIST, Response Evaluation Criteria in Solid Tumors

The FDA review team notes the following:

- RECIST criteria necessitate assessment of tumors that are designated as target lesions because response is defined as a change from a fixed reference point. That reference point is the baseline sum of diameters of preselected target lesions. Without a well-defined, measurable baseline, responses cannot be calculated. Therefore, the two patients that the Applicant enrolled in the IGNYTE study who were deemed to be responders but had no target lesions are not appropriate to include as responders.
  With respect to the patients who had target lesions, but for whom all target lesions were injected with RP1, RECIST criteria state that tumor lesions in areas subjected to loco-regional therapy are "usually not considered measurable unless there has been demonstrated progression in the lesion."

This is because, as noted earlier, RECIST criteria were designed to assess systemic therapies. Systemic therapies (e.g., intravenously administered chemotherapy, immunotherapy, oral small molecule drugs) allow for equal exposure to the drug that circulates throughout the body and presumably reaches all tumor sites. Therefore, any target lesions, regardless of their location, may be a valid measure of a drug's systemic effect. However, these assumptions do not hold for intratumorally administered therapies because injected lesions receive direct local drug exposure and there may be different biological phenomena involved with these therapies. For example, responses in injected lesions may be the result of local oncolytic activity, local immune activation, or injection-related volume changes rather than due to systemic immune activation, abscopal effects, or other indicators of a true systemic response.

- Notably, the SITC guidelines (Luke et al. 2024) that the Applicant has cited to the FDA review team also note that for response assessment, "target lesions must include noninjected lesions."
- This issue is further compounded by concomitant administration of systemic therapy, nivolumab, in the IGNYTE study.

The Applicant provides an exploratory analysis of injected versus noninjected lesions to support their claim of a systemic effect of the combination. The analysis is summarized in Table 5.

Table 5. Applicant's Summary of Response in Patients Who Had Both Injected and Noninjected Measured Lesions (IGNYTE Study Anti-PD1 Refractory Melanoma Cohort, N=108)

Best Response Category n (%)	Response Based on Injected Measured Lesions Only	Response Based on Noninjected Measured Lesions Only
CR	16 (14.8)	13 (12)
PR	18 (16.7)	18 (16.7)
SD	33 (30.6)	28 (25.9)
PD	32 (29.6)	35 (32.4)
NE	9 (8.3)	14 (13)
RR (CR + PR)	34 (31.5)	31 (28.7)
95% CI	22.9, 41.1	20.4, 38.2

Source: *Applicant's Clinical Overview Addendum Submitted October 9, 2025
Abbreviations: CI, confidence interval; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RR, response rate; SD, stable disease

The FDA review team notes the following:

- The Applicant acknowledged that their dataset only captured whether a lesion was ever injected or never injected. If a lesion was not present at baseline but appeared later and was then injected, it might be classified as injected later. Conversely, if a lesion was noninjected at baseline but later received an injection, it would be classified as injected retroactively. This creates the potential for temporal misalignment, as the classification at the time of the response assessment may not reflect the actual injection status at that time.
- Additionally, the noninjected group is a highly selected subgroup of lesions which investigators chose to never inject. This may be because these lesions were inaccessible, too small, or already responding, which introduces selection bias into the noninjected subgroup. The noninjected group is not a random sample of lesions and its response rate cannot be appropriately interpreted to determine RP1's measure of systemic immune activity. It is unclear why those lesions responded, when they responded relative to injections of other sites of disease, or whether the response was driven by RP1, nivolumab, or both.

- These uncertainties may have been partially mitigated by time-point specific data that the Applicant's dataset does not contain.
- Objective responses in anatomically distant, noninjected target lesions confirmed by independent radiologic review could have helped strengthen the evidence of a systemic effect.

The FDA review team also notes the following:

- During the Type A meeting held in September 2025, FDA pointed out that RECIST criteria state that tumor lesions situated in areas subjected to locoregional therapies are usually not considered measurable. The Applicant stated in response that this citation from the RECIST guidelines referred to measurement and assessment of lesions previously treated with loco-regional therapy and not to the applicability of RECIST to subsequent loco-regional therapy, and "since prior therapy with an oncolytic therapy was an exclusion criterion, this is not a confounding issue for Study RPL-001-16." FDA disagrees with the Applicant's interpretation of this RECIST guideline element. FDA contends that the issue is not whether patients received loco-regional therapy before study enrollment, but that they received loco-regional therapy before the response assessment on Study RPL-001-16 (IGNYTE) that confounds interpretation of the subsequent response in these lesions.
- The Applicant has also stated to FDA that "the requirement for noninjected target lesions in every patient was a new concept introduced only with the April 10, 2026 CRL" and was not identified as an issue prior to this. However, FDA communicated this issue to the Applicant in a meeting held on March 25, 2021. At that time, the FDA stated that it was not clear in the protocol whether target lesions would include both injected and noninjected lesions, and noted that responses in small injected lesions could be attributed to mechanical effects of repeated injections; thus, they recommended that the Applicant measure and track objective responses to both injected and noninjected lesions when reporting ORR. Further, FDA noted the challenge in interpreting responses in small lesions in the absence of a randomized study. FDA stated the importance of including both injected and noninjected lesions as target lesions for objective response assessment.

Summary of Issue: Without definitive evidence of systemic effect, the FDA review team cannot conclude that the response rate and duration of response reported by the Applicant are indicative of clinical benefit or are likely to predict clinical benefit for the indicated patient population.

2. **Re-injection of lesions and assessment of progression:** The IGNYTE study protocol allowed for retreatment with RP1 according to investigator discretion. FDA review identified patients with either new lesions or existing lesions that were identified as having enlarged, who were selected for retreatment with RP1 injections. Upon an FDA query, the Applicant reported 14 patients deemed responders by IRC that received study treatment with RP1 and/or nivolumab post-initial progressive disease (PD). Retreating patients after investigator-determined PD obscures the determination of response as assessed by the IRC. These patients may have had intervening progressive disease prior to their best overall response (BOR) as determined by IRC, which in turn would confound both the reported response rate (by counting responses that occurred after progression) and the reported duration of response (by extending the duration beyond progression events). Table 6 summarizes each patient treated beyond progression that was identified by the Applicant. Table 7 provides further details on two of these cases as examples to illustrate this issue.

Table 6. Summary of 14 Patients in the IGNYTE Study Treated Beyond Progression With Additional RP1 and/or Nivolumab

Patient	Narrative	Potential Implications on ORR/DOR
(b) (6)	• Patient achieved PR at first assessment based on biopsy pathology report • Had NE assessment in August 2021 • Began second course of RP1 in October 2021 to treat new right inguinal LN lesion • Called CR in March 2022 • Treated LN lesion eventually progressed.	DOR may be inflated due to disregarding new LN lesion that was retreated DOR changed from ~4 months to ~34 months
(b) (6)	• Patient achieved PR at first assessment • Had NE assessment in December 2021 • Had PD in February 2022 • Continued nivolumab until May 2022	No impact apparent; continued treatment occurred after PD
(b) (6)	• Patient had SD at first assessment • PR in January 2023 • Started second course of RP1 in March 2023 into a target lesion and multiple nontarget lesions • PD in April 2023	DOR may be inflated by ~1 month
(b) (6)	• Designated PD at first assessment in June 2021 but considered pseudoprogression by investigator • Had 2 assessments of SD until November 2021 • Had PR in November 2021	IRC states PD; however appears overturned to SD. Per RECIST, this patient may not be considered a responder
(b) (6)	• Had PD by IRC at first assessment in October 2021 • Next assessment was SD in November 2021 • PR in January 2022	IRC states PD; however appears overturned to SD. Per RECIST, this patient may not be considered a responder
(b) (6)	• Patient had SD for first 4 assessments • PR in April 2022 • PD in June 2023; continued to have PD assessment thereafter	No impact apparent; continued treatment occurred after PD
(b) (6)	• Patient had SD for first 2 assessments • Retreated with RP1 starting May 30, 2023, for unknown reason • PR determined in May 2023	Unclear why patient started a second course of RP1 in May 2023, at same time as PR assessment. Confounds interpretation of this response.
(b) (6)	• PR at first response assessment, November 2022 • Designated PD in October 2023 • Started second course of RP1 in January 2024	No impact apparent; continued treatment occurred after PD
(b) (6)	• Patient had SD at first assessment in April 2022 until January 2023 • PR in March 2023 • Began second course of RP1 in May 2023 into 2 existing lesions and a new subcutaneous left arm lesion • PD in August 2023	New subcutaneous left arm lesion appears to be PD but PD not called until 3 months later. May inflate actual DOR

Patient	Narrative	Potential Implications on ORR/DOR
(b) (6)	• PR at first assessment and then CR in March 2022 • PD in July 2023 • Began second course of RP1 in August 2023 into existing lesion	No impact apparent; continued treatment occurred after PD
(b) (6)	• Patient had PR in September 2020 • CR in April 2021 • PD in January 2022 • Continued treatment until May 2022	No impact apparent; continued treatment occurred after PD
(b) (6)	• PR in May 2022 until April 2023 • PD in April 2023 • Started second course of RP1 in September 2023 into two new lesions (right leg, distal femur)	No impact apparent; continued treatment occurred after PD
(b) (6)	• Had PD at first assessment in April 2021 • CR in July 2021 • Assessed as PD by investigator in intervening period in May 2021	IRC states PD; however appears overturned to SD. Per RECIST, this patient may not be considered a responder
(b) (6)	• PR by IRC at first assessment in April 2023 • PD by Investigator at first assessment due to appearance of two new lung nodules • Started second course of treatment in July 2023 into a lung lesion • PD by IRC called in December 2023	Patient had progressive disease in the lungs in April by investigator assessment. Treatment of lung lesion in July may have been progressing lesion that was intervened upon before next response assessment. Confounds interpretation of this response.

Source: FDA analysis
Abbreviations: CR, complete response; DOR, duration of response; IRC, independent review committee; LN, lymph node; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

Table 7. FDA-Detailed Examples of Reinjection of Lesions and Assessment of Progression

Patient	Narrative	Potential Impact on ORR/DOR
(b) (6)	• Initiated treatment on February 25, 2021 and subsequently had a PR by IRC on April 19, 2021 • Developed PD by both the IRC and the investigator on November 4, 2021, due to development of 2 new lesions. • The new lesions were injected with RP1 8 times over the following 3 months, indicating that these new lesions were not equivocal, and the injected lesions subsequently reduced in size. • The BOR was deemed a CR on March 10, 2022. • One of the new lesions eventually progressed, leading to another IRC assessment of PD on February 9, 2024, (nearly two years later) and confirming that the new lesion was not equivocal. • However, the Applicant designated the BOR for this patient as CR and claimed that this assessment was per RECIST v1.1. • The DOR per IRC, calculated from the initial response to the second PD, was 34 months. Following RECIST v1.1, this patient had a BOR of PR with a DOR of 4 months, as calculated from the initial PR to the first PD (when new lesions were first identified).	Reclassified the reported DOR from 4 months to 34 months

Patient	Narrative	Potential Impact on ORR/DOR
(b) (6)	• IRC determined PD at their first assessment, which would render them a nonresponder per RECIST. • However, the Applicant stated that this patient "developed new lesions early in the treatment which each resolved by the next assessment and were therefore not confirmed." • The patient was then deemed a CR at a later timepoint.	Appeared to have PD at first assessment, rendering them a nonresponder by the IRC

Source: FDA analysis
Abbreviations: BOR, best overall response; CR, complete response; DOR, duration of response; IRC, independent review committee; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RP1, vusolimogene oderparepvec

The FDA review team notes the following:

- RECIST criteria allow for continued therapy and follow-up evaluation of new lesions if they are considered equivocal. The SITC has published recommendations on IT clinical trials that recommend allowing treatment beyond progression to account for pseudo-progression (Luke et al. 2024).
- However, in IGNYTE, if new lesions or enlarging existing lesions were deemed equivocal because it could not be determined whether they represent progression of disease, it was unclear why these same lesions would then be deemed appropriate and large enough in size to inject and treat. This conduct suggests that these lesions may not have been equivocal, as reported by the Applicant.
- Injecting lesions that are new and considered equivocal, or enlarging existing lesions that have not yet met criteria for PD, obscures the development of PD and could impact the IRC assessment of these lesions in the context of a best overall response designation.
- FDA concludes that the Applicant's method of retreating patients with RP1 after investigator-determined progressive disease likely resulted in:
  - Some patients with investigator-assessed PD being retreated and then assessed as responders when they may have been deemed nonresponders per RECIST v1.1 criteria; and/or
  - Some patients with an initial response having progressed but who underwent retreatment with RP1 before PD was captured by IRC, artificially elongating the reported duration of response.

Summary of Issue: While allowing retreatment with RP1 per investigator discretion may be acceptable to provide potential therapy to patients, this protocol feature confounds interpretation of the IRC assessments of response. RECIST criteria allow for continued therapy and follow-up evaluation of new lesions if they are considered equivocal. FDA also acknowledges that immunotherapies, including IT therapies, may cause transient inflammatory reactions that could appear as new or enlarging lesions, and professional organizations such as the SITC has published recommendations on IT clinical trials that recommend allowing treatment beyond progression to account for this (Luke et al. 2024).

However, injecting new lesions or enlarging existing lesions confounds interpretation of the response assessment by IRC and may artifactually inflate the reported ORR and DOR results in some patients (Table 6). An FDA audit identified several cases in which it is unclear whether the new or enlarging lesions were transient inflammatory reactions or represented true sites of progressing disease, which confounds interpretation of ORR and DOR in these patients.

3. **Confounding effect of surgical procedures:** In the IGNYTE study, biopsies for exploratory biomarker analyses were required at baseline and at Study Day 43. Additional optional biopsies of injected lesions could also have been collected at predose during Cycle 2 Day 15 or at the end of treatment.

Biopsies could also be collected or the lesion excised if the investigator believed a patient had become tumor free, or to provide histological confirmation of response. For patients who were considered unresectable at screening but were subsequently deemed resectable during the course of the study, curative intent surgery was allowed.

Surgical procedures, including excisional biopsies and resections, were performed on target lesions during the treatment period and in some cases immediately preceded the next response assessment scheduled to determine a partial or complete response. Table 8 provides examples to illustrate this issue further.

Table 8. FDA Examples of Potential Impact of Surgical and Biopsy Procedures on Reported Efficacy Measures

Patient	Narrative	Potential Impact on ORR/DOR
(b) (6)	• First imaging assessment: SD • Second response assessment: NE. • Discontinued treatment due to an adverse event of myocarditis. • Approximately 3 months after treatment discontinuation, underwent radical resection of melanoma of the left posterior heel. Pathology reports no evidence of residual melanoma. • Approximately 5 months after treatment discontinuation, best overall response reported as CR.	CR appears to be determined based on pathology after discontinuing therapy. NE assessment, followed by surgery, then CR determination confounds determination of response.
(b) (6)	• One target lesion measuring 20 mm in the right inguinal lymph node was injected with RP1. • One month later, had core biopsy of the right inguinal lymph node target lesion. • Two weeks after core biopsy of target lesion, determined by the Applicant to have a PR.	Removal of lymph node tissue in relatively small 20 mm lesion via core biopsy 2 weeks prior to PR impacts response assessment.
(b) (6)	• Two target lesions, both on the left side of the head measuring 16 mm and 11 mm, respectively. • First imaging assessment: SD. • Two months later, new lesion on scalp identified. • The same day that new lesion is identified, underwent excisional biopsy of an unknown scalp lesion, which confirms “in transit melanoma”. • The next day, response assessment reported as PR by IRC, but PD by investigator (due to new lesion).	Excisional biopsy (i.e. lesion removal) of unknown scalp lesion the day before response assessment could have been of a new lesion or a relatively small target scalp lesion. This likely impacts response assessment.

Source: FDA analysis
Abbreviations: CR, complete response; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PR, partial response; RP1, vusolimogene oderparepvec; SD, stable disease

The FDA review team notes the following:

- Removal of tumor tissue can impact measurement of tumor lesions, particularly in patients with few or small lesions, and counting these patients as having responded to RP1 may not be appropriate, as reduction in tumor size may be due to removal of tumor tissue via surgery or excisional biopsy, rather than due to the antitumor activity of RP1.
- Among the 47 responders per the Applicant assessment, a total of 115 invasive procedures were performed on tumor lesions. Of these, 80 procedures were performed on target lesions, including

44 performed during the treatment period and 36 at screening. There were 7 excisional biopsies and 5 complete resections.

- It is also notable that many patients enrolled in the IGNYTE study had a relatively low burden of disease, with a median of only 2 target lesions at baseline and 26% of patients having only a single lesion. Of the 47 responders, 2 patients had no target lesions at baseline, 14 patients (30%) had 1 target lesion, 16 patients (34%) had 2 target lesions, 7 patients (15%) had 3 target lesions, and 8 patients (17%) had 4 target lesions.
- In patients with few or small lesions, measurement variability and the impact of local procedures such as biopsies and injections on lesion size may have had a disproportionate effect on the calculated sum of diameters, potentially introducing measurement bias into the response assessment.
- The FDA review team also evaluated response by tumor burden, as determined by the sum of diameters (in millimeters) of target lesions at baseline. Table 9 further summarizes response by disease burden at baseline.

Table 9. Responders by Disease Burden at Baseline

SOD[a]	N	Responders (CR+PR)	ORR	CR	CR Rate
≤20 mm[b]	19	12	63.2%	11	57.9%
21-50 mm	41	16	39.0%	7	17.1%
51-100 mm	37	13	35.1%	5	13.5%
101-150 mm	26	4	15.4%	0	0%
>150 mm	17	2	11.8%	0	0%

Source: FDA analysis
[a] FDA acknowledges that the SOD categories are arbitrarily defined based on size for the purposes of this analysis and what constitutes low, moderate, and high burden of disease may be subjective and/or depend on other factors.
[b] This includes 2 patients who had no target lesions at baseline.
Abbreviations: CR, complete response; ORR, objective response rate; PR, partial response; SOD, sum of diameters

FDA review notes the following:

- Two patients had no measurable lesions and therefore cannot be assessed for response per RECIST criteria.
- 14% of patients had a low burden of disease (≤20 mm), and these patients are particularly susceptible to having their response assessment impacted by removal of tissue.
- The ORR reported in Table 9 indicates the response rate for that subgroup of patients as defined by their disease burden.
- As disease burden increases, ORR and CR rates decrease in these subgroups. This may be due to several reasons, one of which is that patients with more tumor burden are less susceptible to having their response assessment impacted by the removal of tumor tissue. However, removal of tumor tissue may still have impacted their objective response designation.

With respect to prior communications with the Applicant regarding this potential issue, FDA notes the following:

- At the Type A meeting held in September 2025, FDA stated that the use of surgical intervention to resect or debulk disease and then count this as a response would not be appropriate. The Applicant

stated that they confirmed this criterion in the protocol did not lead to a response observed on study.

- In a communication dated June 2, 2026, the Applicant acknowledges patients that had an instance of change in response status following a biopsy but claims that "in no instances did a biopsy or excision of a lesion remnant result in an improved BOR."
- However, FDA's review findings, as noted in Table 11, are inconsistent with this representation. Several patients appear to have been reclassified from a partial response to a complete response after procedural interventions and at their next assessment. Other responders may have had their response assessment impacted by preceding surgical procedures.

Summary of this issue: FDA review identified patients deemed responders by the Applicant who underwent removal of tumor tissue via resection or biopsy while on study. Given the number of biopsies and procedures performed in the IGNYTE study, including on target lesions during the study, FDA cannot determine the full impact of these procedures on the reported results. However, an FDA audit identified several patients (with examples noted above) that likely had their response designation impacted by removal of tumor tissue. The FDA review team notes that Table 8 only summarizes a few select cases identified upon FDA audit, and given the number of procedures conducted on study, including mandatory biopsies done for exploratory purposes in the IGNYTE study, the total number of patients whose response assessment may have been affected is unknown and the true extent of the impact on ORR and DOR cannot be determined. This confounds interpretation of trial results, particularly in those patients with one or few target lesions and/or low disease burden (defined by sum of diameters) at baseline.

4. **Nonevaluable assessments:** Several patients had an assessment of not evaluable (NE) by independent radiologic review (i.e., IRC) in the IGNYTE study. The Applicant reported 13 such responders (27.6% of responders) who had at least 1 timepoint assessed as NE by IRC. For most patients, the reason for an assessment of NE was lack of imaging provided to the IRC. The IRC was added in Protocol Amendment 8 after the melanoma population in the IGNYTE study had enrolled; thus, this issue may have arisen or been compounded due to the retrospective implementation of the IRC.

The FDA review team notes the following:

- RECIST criteria state that repeated "NE" time point assessments may complicate best response determination.
- As an example, one patient had three consecutive NE response assessments at timepoints prior to a BOR of PR. Per the Applicant, these NE timepoints were due to a lack of radiologic/photographic images. Due to the prolonged period of missing disease assessments (over 8 months), it cannot be determined if the patient had intervening progression, biopsies, or other interventions prior to being declared a responder that may have affected this PR determination.
- Table 10 summarizes patients who had NE assessments by IRC in the IGNYTE study and the potential impact on the reported efficacy results.

Table 10. Patients Who Had an NE Assessment by IRC in the IGNYTE Study

Patient	Assessment Status	Potential Impact on ORR/DOR
(b) (6)	Patient had NE at same time as investigator PR, then subsequent CR on IRC assessment.	No impact apparent.
(b) (6)	NE by IRC at same time as PD by INV. Then next assessment was PD by IRC and INV.	Inflates DOR assessment.
(b) (6)	Had NE assessment by IRC but PD at next assessment.	Unclear if PD occurred earlier at the NE assessment. Had prior PR so ORR unaffected but DOR may be inflated.
(b) (6)	NE assessment between CR assessments.	No impact apparent.
(b) (6)	NE assessment prior to PR assessment.	No impact apparent.
(b) (6)	NE assessment at same time as PD by INV. PR at next assessment.	May not be a responder since NE was at first assessment that INV called PD.
(b) (6)	NE for first 4 assessments, including at time when INV called PD.	May not be a responder.
(b) (6)	Had 3 consecutive NE assessments prior to determination of response.	May have progressed during this long time period of NE assessments.
(b) (6)	NE assessment at first assessment followed by PR.	Unclear if patient had PD prior to PR.
(b) (6)	Had NE in between assessments of PR.	No impact apparent.
(b) (6)	Had NE assessment after CR.	No impact apparent.
(b) (6)	Had NE assessment after response.	No impact apparent.
(b) (6)	Had NE assessment at same time as PD by INV.	May inflate DOR.

Source: FDA analysis
Abbreviations: CR, complete response; DOR, duration of response; INV, investigator; IRC, independent review committee; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response

FDA review of these patients notes the following:

- Of the 13 patients noted in Table 10, 6 patients had NE assessments where no impact is apparent on their response designation.
- Four patients had NE assessments that raise concerns regarding whether the patient meets criteria for being a responder at subsequent timepoints.
- Three patients were identified as likely having responded; however, their DOR may be inflated due to the potential for having actually progressed earlier than determined by the Applicant.

Summary of this issue: The FDA review team cannot determine the full impact of NE assessments in patients classified as responders by the Applicant. However, FDA notes that there are several patients whose response designations and/or duration of response assessments are confounded by NE assessments in the IGNYTE study. This can result in patients who never truly responded being designated as responders and could also inflate the DOR of patients who did respond but had multiple or consecutive NE assessments.

5. **Histology assessments:** Histopathologic assessments were used to assess response, and in some cases, these results changed the radiologic response assessment of best overall response. RECIST criteria state that in some circumstances, it may be difficult to distinguish residual disease from normal tissue, and a residual lesion can be investigated via biopsy before assigning a status of complete response. However, these criteria also state that this approach may lead to false positive CR due to limitations of biopsy resolution/sensitivity. Histology can be used to differentiate between PR and CR in "rare cases if required by protocol."

The FDA review team identified, at minimum, seven patients (15%) that the Applicant designated as responders, all complete responses, whose IRC best overall response was impacted by histology, pathology, or biopsy results. These cases are summarized in Table 11.

Table 11. Patients Deemed Responders by Applicant That had BOR Impacted by Pathology, Biopsy, or Histology

Patient	Narrative	Impact on Response Assessment
(b) (6)	• No target lesions by IRC at baseline (presence of non-target lesions on scalp). • At first response assessment, deemed PD by IRC and investigator due to the presence of new cutaneous lesions by photography. • Underwent biopsies of scalp lesions 337 days after last RP1 and 309 days after last nivolumab showing "no viable melanocytic lesions." • Best Overall Response by IRC retrospectively changed to CR and all prior time point responses changed to NE.	Classified as CR based on pathology long after completing study treatment, despite initial prior IRC assessments indicating PD due to presence of new lesions.
(b) (6)	• Designated a PR beginning at third response assessment. • Underwent right axillary lymphadenectomy 15 months after completing RP1 injections. • Pathology reported as "extensive necrosis without viable melanoma." • Changed to CR at next assessment after surgery.	Reclassified PR to CR based on pathology.
(b) (6)	• No target lesions at baseline (presence of cutaneous non-target lesions in right forearm). • Designated as PD at first assessment due to new lesion. • One month later, underwent biopsy of a treated subcutaneous lesion in the right forearm. • Pathology reported as "no evidence of melanoma." • Counted as a CR at next assessment. • Multiple missing IRC time point responses by photography and radiology review due to "photographs not submitted by the Investigator".	Initially designated a PD due to new lesion. Subsequently designated a CR based on histology from biopsy. Multiple missing time point response assessments due to images not provided to IRC.
(b) (6)	• First two response assessments of SD and NE. • Discontinued therapy due to toxicity. • Approximately 3 months after treatment discontinuation, underwent radical resection of melanoma of left posterior heel. • Pathology reported as "no evidence of residual melanoma." • Designated a CR at next assessment.	No prior response on radiographic imaging; only designated a responder (CR) after radical resection of tumor.

Patient	Narrative	Impact on Response Assessment
(b) (6)	• First disease assessment designated as PD. • Third assessment designated as PR. • One month later, underwent surgical resection of injected lesion that showed no evidence of disease. • Designated a CR at next assessment.	Treated beyond IRC PD, then designated PR, then reclassified to CR after surgical resection.
(b) (6)	• Designated a PR at fourth response assessment. • Several weeks later, underwent resection of all lesions. • Pathology reported "regressed melanoma." • Designated CR at next assessment.	Reclassified PR to CR based on pathology.
(b) (6)	• One target lesion on skin of ear (15mm) • Designated PR at third response assessment. • Underwent biopsy of injected target lesion of ear. • Pathology reported as "no tumor was identified." • Best overall response changed to CR.	Reclassified PR to CR based on pathology.

Source: FDA analysis
Abbreviations: CR, complete response; IRC, independent review committee; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

The FDA review team notes the following:

- During the Type A meeting held in September 2025, FDA inquired into this issue. The Applicant stated that the IGNYTE study "was a multicohort study including nonmelanoma skin cancer cohorts. Replimune confirms that this strategy does not apply to the anti-PD-1 failed melanoma cohort of the IGNYTE study." However, FDA review identified several patients (Table 11) who had their response assessment changed based on pathology results.
- In the IGNYTE study, these histology specimens were not centrally reviewed (which could increase the possibility of reader variability and bias), there is potential for sampling error with respect to biopsy specimens that may result in false negatives, and there is the potential impact of intratumoral injections that could affect histology interpretation. It is also unclear whether a determination of tumor response based on pathology reflects local treatment effects at the injection site rather than systemic effects of the investigational therapy.

With respect to prior communications with the Applicant regarding this potential issue, the FDA notes the following:

- At the Type A meeting in September 2025, FDA inquired into whether histology was used to differentiate between partial and complete responses in the IGNYTE study. The Applicant stated "IGNYTE was a multicohort study including nonmelanoma skin cancer cohorts. Replimune confirms that this strategy does not apply to the anti-PD-1 failed melanoma cohort of the IGNYTE study."
- However, as noted in Table 11, FDA review identified that histology was used to reclassify several patients' responses. Thus, the Applicant's claim that this did not occur is not true.

Summary of this issue: FDA acknowledges that depending on the disease setting and context, RECIST v1.1 criteria allow for pathology findings to be used to adjudicate or confirm response assessments. However, in cases where patients had no prior radiologic assessment consistent with a response, or pathology was used to reclassify a response designation rather than confirm radiologic findings, this conduct introduces subjectivity and potential bias into the response assessments. The FDA review team finds it difficult to adjudicate these responses based on pathology reports and cannot rule out the

potential for false negatives that could result in an overestimation of the ORR and CR rate reported in the IGNYTE study.

Summary of Key Efficacy Issue 1

FDA acknowledges that allowing for investigator discretion in clinical trial protocols may be reasonable to allow for appropriate care and treatment of patients on clinical trials. However, it is important that efficacy results are reported according to the prespecified criteria (e.g., RECIST v1.1) to allow for consistent reporting and to reduce variability that may affect interpretation of trial outcomes. Sensitivity analyses may address different clinical scenarios; however, the primary efficacy evaluation should be per the prespecified criteria. FDA review determined that while RECIST v1.1 guidelines allow for latitude in several respects, the Applicant did not adhere to the principles of RECIST v1.1 to determine response in several patients; thus, the criteria used to report ORR and DOR are not consistent with the prespecified RECIST v1.1 criteria. This also raises concerns regarding trial conduct, including the use of a retrospective IRC review, and whether these data were collected in an adequate and well-controlled trial.

The independent review charter, or IRC, defines rules and procedures for how independent review of response is conducted. This is done to avoid or mitigate bias, and reviewers on these committees are generally blinded patient treatment details. FDA notes that the Applicant's IRC was established after initiating the IGNYTE trial and finalized 4 years after the trial started. The retrospective nature of the IRC review may have caused or compounded response assessment issues. FDA also notes that IRC design and conduct effects interpretation of trial outcomes. For example, the Applicant approved individual radiologists and oncologists to perform a review that was called "independent", provided clinical data to the IRC for review, including physical exam findings, clinical history, pathology results, and relevant clinical notes, and several IRC response designations were changed by the Applicant after receiving data from the IRC third party vendor. It is unclear how this conduct and design may have impacted response assessments, and FDA notes the potential for bias in these methods.

In prior correspondence with FDA, the Applicant acknowledged that independent authors have stated that RECIST v1.1 and iRECIST are unsuitable for IT immunotherapy trials for several reasons and then stated "Replimune also notes that this seems to be an opinion, as there are no data included in the paper to demonstrate that 'focal intervention renders treated lesions nonevaluable.'" FDA exercised flexibility when agreeing to the use of RECIST v1.1 criteria to assess response in the IGNYTE study given the lack of other validated response criteria; however, uniform application of these criteria is critical to allow for interpretable and reliable response data. FDA acknowledges that RECIST criteria are professional guidelines based on expert opinion; however, this does not justify the Applicant's flawed methodology and application of these criteria. Where RECIST criteria allow for latitude, the Applicant's implementation of the criteria raises questions regarding whether the responses reported are true measures of drug activity and attributable to the study intervention versus other factors.

During the Type A meeting held in September 2025, FDA pointed out that RECIST criteria state that tumor lesions situated in areas subjected to locoregional therapies are usually not considered measurable. The Applicant stated in response that this citation from the RECIST guidelines referred to measurement and assessment of lesions previously treated with loco-regional therapy and not to the applicability of RECIST to subsequent loco-regional therapy, and "since prior therapy with an oncolytic therapy was an exclusion criterion, this is not a confounding issue for IGNYTE." FDA disagrees with the

Applicant's interpretation of this RECIST guideline element. FDA contends that the issue is not whether patients received loco-regional therapy before study enrollment, but that they received loco-regional therapy before the response assessment on the IGNYTE study, which confounds interpretation of response in these lesions. Given the other issues with application of RECIST noted in this section, FDA concludes that the application of RECIST methodology suggest that the criteria were not uniformly understood or applied. The actual application of response criteria and reporting of results are the responsibility of the Applicant.

The Applicant has also stated to FDA that "the requirement for noninjected target lesions in every patient was a new concept introduced only with the April 10, 2026, CRL" and was not identified as an issue prior to this. However, FDA communicated this issue to the Applicant in a meeting held on March 25, 2021. At that time, FDA stated that it was not clear in the protocol whether target lesions would include both injected and noninjected lesions, and noted that responses in small injected lesions could be attributed to mechanical effects of repeated injections; thus, they recommended that the Applicant measure and track objective responses to both injected and noninjected lesions when reporting ORR. Further, FDA noted the challenge in interpreting responses in small lesions in the absence of a randomized study. FDA stated the importance of including both injected and noninjected lesions as target lesions for objective response assessment.

Due to these issues, the Applicant's reported results do not appear to be an accurate reflection of the application of RECIST v1.1 criteria and FDA does not agree with the Applicant's reported ORR and DOR. FDA acknowledges that RECIST guidelines allow for latitude and discretion with respect to several aspects of response assessment. FDA concludes that the Applicant's application of RECIST criteria, even where discretion is allowed, impacted the reported results and the extent of this impact cannot be determined. The FDA review team finds that conducting sensitivity analyses to ascertain an accurate estimation of the ORR and DOR per RECIST v1.1 is impossible due to the conduct of the IGNYTE study.

Key Efficacy Issue 2

The objective response data from the single**-arm IGNYTE study are not of sufficient magnitude to overcome concerns about the contribution of effect, particularly in the absence of a reliable historical control, and therefore it cannot be determined whether RP1 contributes to any observed effect when administered in combination with nivolumab.**

The IGNYTE study was not designed to isolate the contribution of RP1 when administered in combination with nivolumab. To assess the contribution of both components, a true factorial, randomized trial would be the ideal trial design. A randomized trial comparing RP1 and nivolumab to nivolumab monotherapy would aid in assessing whether RP1 adds to any nivolumab effect. FDA recommended that the Applicant conduct a randomized trial to establish the contribution of effect of RP1 when added to nivolumab; however, the Applicant proceeded with submission of their BLA based on the single-arm IGNYTE study.

FDA acknowledges that there may be a perceived lack of equipoise, and it may not be ethical to randomize patients who progressed on prior checkpoint inhibitor therapies to single-agent nivolumab. However, determining the need for each component of the RP1 and nivolumab combination is still important because both products can cause toxicity. Administering a drug to patients that can cause

toxicity but has not been demonstrated to contribute to efficacy in a combination regimen may be unethical.

To this end, in September 2024, FDA communicated to the Applicant that it did not object to submission of a BLA based on data from the IGNYTE study. However, the Applicant should still provide evidence to demonstrate that there is a compelling reason that both RP1 and nivolumab are necessary to achieve the observed treatment effect. FDA acknowledges the unmet need in this patient population and accordingly exercised regulatory flexibility; however, the review team contends the magnitude of the observed effect, considered in the context of response assessment limitations and the lack of a reliable historical control, is not sufficient to overcome the uncertainties about the contribution of effect, and the Applicant has not demonstrated that RP1 contributes to the observed effect.

FDA also notes that while the Applicant cited lack of equipoise as a reason why conducting such a randomized trial would be infeasible, they had designed and were enrolling their ongoing RP1-104 trial (IGNYTE-03). This is a randomized trial that includes a physician's choice of control therapies, which includes rechallenge with anti-PD-1 monotherapy. Thus, it is unclear to FDA why the Applicant cited an inability to conduct a randomized trial that would randomize patients to monotherapy nivolumab to potentially support approval while at the same time allowing anti-PD-1 monotherapy as a control therapy in their separate confirmatory trial, IGNYTE-03. The logical inconsistency of the equipoise argument weakens the rationale for not generating randomized data.

Given the challenge in conducting a randomized trial with a monotherapy checkpoint control arm, FDA communicated to the Applicant in September 2025 (after the first CRL was issued) that they could consider comparing RP1 and nivolumab to nivolumab and relatlimab in their ongoing IGNYTE-03 trial. While this would not directly address the contribution of effect issue in a factorial design, a large differential in response rates between these arms could potentially support the efficacy of RP1 and nivolumab in the indicated population. The data provided by the Applicant in the resubmission were based on exploratory, preliminary, and non-prespecified analyses of response rate and progression-free survival in a limited number of patients in the IGNYTE-03 trial. These data were not consistent with what was discussed at the Type A meeting in September 2025 with respect to resubmitting the BLA for potential accelerated approval.

Due to the lack of concurrent control, the Applicant instead relies on comparing response rates cross-trial from the IGNYTE study to historical controls to ascertain the expected response to immune checkpoint rechallenge (i.e., nivolumab monotherapy) in this population. Based on these data, they cite the reported response rates from the IGNYTE study in an attempt to demonstrate that RP1 and nivolumab result in higher response rates than would be expected from immune checkpoint rechallenge, as reported in the literature. The presumption then is that RP1 would be contributing to the combination if the response rates reported for RP1 and nivolumab exceed the response rates of immune checkpoint rechallenge in the historical literature.

This is a challenging approach to establishing the activity of RP1 because of the heterogeneity of the enrolled patient population in the IGNYTE study, as well as in the historical literature. For example, several patient and disease factors may affect the expected outcome (i.e., response) in this population of patients with advanced/metastatic cutaneous melanoma that has progressed after prior checkpoint inhibitor therapy (e.g., the type of prior therapy received, such as single-agent anti-PD-1 or combination

checkpoint inhibitor, duration of prior therapy, setting of prior anti-PD-1 therapy [adjuvant versus advanced/metastatic setting], extent of disease at baseline, or other unknown factors).

As an example of this challenge, NCCN guidelines state that if a patient experienced progression of melanoma during or shortly after a systemic therapy, rechallenge with the same therapy or a therapy of the same class is unlikely to yield a response and is not recommended. However, NCCN guidelines note that for patients who progressed on single-agent immune checkpoint therapy, nivolumab and ipilimumab combination therapy remains a reasonable option—an exception to this general recommendation. In select cases, reinduction with the same agent or same class of agents may be considered. FDA acknowledges that NCCN is only one consensus guideline, and others, such as SITC, have also published peer-reviewed guidelines; yet this provides an example that underscores the uncertainty in selecting subsequent therapies for patients who have progressed on immune checkpoint therapy (NCCN 2026).

Table 12 summarizes FDA review of publicly available literature that cites response rates to immune checkpoint inhibitor rechallenge in patients with advanced/metastatic melanoma with varying patient and disease characteristics.

Table 12. Response Rates Reported for Immune Checkpoint Rechallenge in Patients With Advanced Melanoma With Varying Patient and Disease Characteristics

Study	Patient Population	Reported Results
Beaver 2018 (pooled FDA analysis)* (Beaver et al. 2018)	Patients with unresectable or metastatic melanoma that were on trials which allowed for continuing PD-1 antibody beyond RECIST-defined progression (for products approved prior to 2017).	N=500 RR 19%
Nardin 2023 (retrospective multicenter national study) (Nardin et al. 2023)	Patients with progressive or recurrent advanced melanoma following previous disease control induced by ICI which was subsequently interrupted.	N=85 RR 54%
Olson 2021 (prospective trial) (Olson et al. 2021)	Patients with advanced melanoma who progressed on anti-PD-1/L1 antibody as immediate prior therapy and were treated with pembrolizumab and ipilimumab.	N=70 itRECIST RR 29%
Reschke 2020 (review of published literature) (Reschke and Ziemer 2020)	Patients with melanoma rechallenged after disease progression on prior immune checkpoint therapy (Group 1).	n=85 (first group) 15.5%
Simeone 2025 (single center, retrospective analysis) (Simeone et al. 2025)	Patients with melanoma who underwent anti-PD-1 rechallenge after disease progression after initial treatment. Could have initial response to immunotherapy.	N=84 21%
Ascierto 2023 (prospective study) (Ascierto et al. 2023)	Patients with advanced melanoma with prior progression on anti-PD-1/L1 containing regimens being treated with nivolumab and relatlimab in the RELATIVITY-020 trial (D1 Cohort patients progressed within 3 months 1 regimen and D2 cohorts progressed after 2 or more regimens).	Cohort D1 N=354 Cohort D2 N=164 D1 RR 9.2% D2 RR 12%

*The Applicant cites Ribas 2018, discussed further below in this section, that is a response to a manuscript published by Beaver et al. in Lancet Oncology 2018 (Beaver et al. 2018; Ribas et al. 2018)
Abbreviations: ICI, immune checkpoint inhibitor; PD-1/L1, programmed cell death protein 1/ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; RR, response rate

The FDA review team notes the following:

- FDA acknowledges that patient populations in the historical literature do not appear consistent with the IGNYTE study population; thus, comparisons of response rates across these studies are difficult to interpret.
- Review of these reports underscores the inherent heterogeneity in populations of patients with advanced/metastatic melanoma who have received prior immune checkpoint inhibitors. While this heterogeneity may reflect the real-world population, it makes cross-trial comparisons challenging for the purposes of establishing the expected response to nivolumab monotherapy in the IGNYTE study population to determine contribution of components. There is a lack of a well-established historical control benchmark for response rate and DOR in the population consistent with patients enrolled in the IGNYTE study, and this does not allow for a comparative analysis to be conducted to ascertain nivolumab's expected monotherapy activity in this population.
- Specific sources of heterogeneity in the IGNYTE study population that complicate historical control comparisons include:
  - Prior therapy type: 43.6% of patients had received anti-PD-1 in combination with anti-CTLA-4 therapy; 25.7% had received prior anti-PD-1 only in the adjuvant setting; and 40% had received more than one line of anti-PD-1-based therapy.
  - Disease stage: 29.2% of patients had Stage III disease, which may or may not be consistent with other trial populations, raising questions about the comparability of the study population to other reported cohorts.
  - Extent of disease: The disease burden and number of lesions in the enrolled IGNYTE study population may have a more favorable natural history and may be more susceptible to measurement bias in response assessment, as discussed above.
  - Lesion locations: 18.6% of patients had skin-only disease; 62.9% had lesions in lymph nodes; 35.0% had lung lesions; and 17.1% had liver lesions, as assessed by IRC.
  - Duration of prior anti-PD-1 therapy: Range of 1.0 to 55.2 months; patients with shorter prior anti-PD-1 exposure may have had pseudo-progression rather than true refractory disease prior to enrollment in the IGNYTE study.
- The Applicant has cited a ~7% expected ORR for nivolumab rechallenge, based primarily on a Ribas 2018 analysis published as a correspondence in Lancet Oncology that is itself derived from the Beaver 2018 pooled FDA analysis of patients treated beyond RECIST progression (Table 12) (Beaver et al. 2018; Ribas et al. 2018). The ~7% figure cited by the Applicant is not based on prospective data or a retrospective report of patient-level outcomes and may underestimate the expected response to nivolumab in the IGNYTE study population. FDA finds this analysis difficult to interpret.
- In correspondence to FDA, the Applicant stated that the RELATIVITY-020 trial (Ascierto et al. 2023) (Table 12) may serve as a contemporary, prospective historical control. They further state that this study shows that for patients with Lymphocyte Activation Gene-3 (LAG-3) expression <1% for whom only nivolumab but not relatlimab would have any clinical activity, the response rate was 5%, "consistent with the conclusions drawn from the other literature discussed in the BLA." However, FDA notes that the Applicant is citing a subgroup from the D1 cohort of this study that is defined by LAG-3 expression, and it is unclear how this population compares with the population enrolled in the IGNYTE study. Preliminary review by FDA comparing these populations, discussed further below,

suggests that these populations vary substantially and, therefore, use of these data as a historical control is limited and difficult to interpret.

- Published retrospective reviews of ICI rechallenge in anti-PD-1 refractory melanoma report widely variable response rates that reflect the heterogeneity of patient populations, definitions of prior treatment failure, and response assessment methods used across studies. This variability means that no single historical control ORR can be reliably compared to the IGNYTE study population.
- FDA acknowledges the data reported from populations most similar to the IGNYTE study population but notes that these are estimations and cannot be reliably extrapolated from published literature.
- Because the response rate and duration of response were not reliably assessed in the IGNYTE study (see FDA Review Issue #1) and RP1 is an IT therapy while the historical literature describes primarily intravenously administered systemic therapies, comparing the Applicant's reported ORR of 33.6% to external, historical control data are further compounded.
- FDA also considered the CERPASS trial, a randomized Phase 2 study of RP1 in combination with cemiplimab versus cemiplimab alone in patients with advanced cutaneous squamous cell carcinoma (CSCC), which did not demonstrate a statistically significant improvement in ORR for the combination arm over cemiplimab monotherapy. While CSCC is a different disease from melanoma, this result does not provide supportive evidence for synergy between RP1 and checkpoint inhibitor therapy and raises questions about the generalizability of the proposed mechanism of action.
- RP1 monotherapy data from the Phase 1 dose escalation portion of the IGNYTE study showed tumor shrinkage in patients with melanoma. However, these monotherapy data may be subject to the same methodological issues described under Key Efficacy Issue #1, and the small sample size limits interpretation. Notably, if RP1 as monotherapy has meaningful single-agent activity, this would further complicate the interpretation of the combination data and raise the question of whether nivolumab is necessary to achieve the observed responses.

The Applicant also provides an exploratory analysis in which they evaluated patients serving as an internal control. The Applicant compared ORR and progression-free survival in patients on immediate prior therapy to PFS on the IGNYTE study and claims that any additional response observed subsequently reflects the additional, add on, effect contributed by RP1 to nivolumab.

The Applicant created a subgroup of 104 patients out of the total 140 patients enrolled in IGNYTE where they stated the "add on effect is best seen" by excluding patients whose prior therapy was in the adjuvant setting. They reported a response rate of 11.5% in patients to prior therapy and approximately 30% in patients on IGNYTE. FDA identifies several issues with this analysis. This is an exploratory analysis with lack of pre-specification and no type 1 error control, which is further complicated by the applicant selecting 104 patients out of the total 140 patients enrolled for analysis and the aforementioned response assessment issues. Also, enrolling on IGNYTE required progression on prior treatment. These patients were guaranteed to have progressed. Thus, comparing patient responses on IGNYTE to patients who already progressed previously is not a valid internal control. Also, prior therapy ORR was assessed by investigator vs. by IRC in IGNYTE. In addition, it is unclear whether the within-subject correlation was properly accounted for in the analysis where patients serve as their own internal controls. Failing to account for this correlation leads to invalid statistical inferences, making the results difficult to interpret.

FDA concludes that this analysis is structurally flawed and favors the on-IGNYTE response group by design and is uninterpretable and not supportive of the contribution of RP1 to the combination. The Applicant also reports a median PFS in the 47 responding patients in IGNYTE as 30.6 months vs. time to progression on prior therapy as 4.4 months. FDA concludes that this analysis is uninterpretable because time to event endpoints assessed in single arm trials lack a concurrent control. Comparing responses to patients who already progressed is not a valid internal control and different response methods and investigator vs. IRC methods were used in the pre-IGNYTE vs. on-IGNYTE populations, respectively. Also, it is unclear why the Applicant notes PFS in the on-IGNYTE group but time to progression in the prior therapy group. These are technically different endpoints with different definitions. FDA also notes that in the full 140 patient cohort, the Applicant reports a median PFS of only 3.6 months. Thus, it is unclear how to interpret these analyses in the context of that short PFS in the overall population. And finally, the response assessment issues previously discussed also confound this analysis.

Summary of this issue: It remains unclear whether the observed responses in the IGNYTE study are due to nivolumab alone. FDA communicated these concerns to the Applicant during the Type B meeting on March 25, 2021, stating "FDA noted potential issues of interpreting efficacy results due to baseline heterogeneities among study subjects" and reiterated that it "would not recommend that the Sponsor submit a BLA based on the results of a single-arm study."

Comparisons to historical control are limited in interpretability for the aforementioned reasons, and FDA contends that the expected response to subsequent immune checkpoint inhibitor therapy after progression on such therapies are estimations and it may not be possible to reasonably extrapolate the expected ORR. Moreover, the Applicant reported ORR is confounded by the other response assessment flaws outlined under Key Review Issue 1 and may be an overestimation.

Key Efficacy Issue 3: OS Analysis Is Not Interpretable

The Applicant submitted a 3-year OS analysis from the IGNYTE study as part of the BLA resubmission (data cutoff March 8, 2026). The following OS data are Applicant-sourced and have not been independently verified by FDA.

The Applicant reports that as of a data cutoff of March 8, 2025, of the 140 patients in the IGNYTE study efficacy population, 71 patients (50.7%) had died. They calculated summary statistics using Kaplan-Meier analysis and 95% confidence intervals using the log-log method. They report a median OS of 32.9 months (95% CI: 25.76, 46.03), with 1-year, 2-year, and 3-year survival rates of 75.3%, 61.5%, and 47.8%, respectively. The Applicant compares these results to a median OS of 14.7 months in patients receiving nivolumab plus relatlimab in the RELATIVITY-020 trial (Ascierto et al. 2023).

OS data from a single-arm trial without a concurrent randomized control arm are not interpretable for establishing a treatment effect, as time-to-event endpoints in the absence of a concurrent control may reflect patient selection bias, the natural history of the disease or other factors rather than a treatment effect attributable to the study intervention. The Applicant's comparison of the IGNYTE study OS results to those from the RELATIVITY-020 trial is a cross-trial comparison subject to all of the limitations of nonrandomized historical comparisons, including the same population heterogeneity issues that limit interpretation of the primary ORR endpoint.

Comparing OS across trials in this disease setting is particularly challenging for the following reasons:

- The IGNYTE study enrolled a substantial proportion of patients with Stage III disease (29.2%) and patients with skin-only or limited nodal disease (18.6% skin-only), who are likely to have a more favorable prognosis than patients with visceral metastatic disease. Additionally, as noted under Key FDA Review Issue #1, patients in the IGNYTE study, including responders, had other characteristics (e.g., few target lesions, low burden of disease defined by the sum of diameters) that may portend more favorable prognostic characteristics compared to other externally derived populations of patients with advanced/metastatic melanoma. Comparing OS across these populations is not appropriate and cannot be reliably interpreted.
- The RELATIVITY-020 trial, cited by the Applicant as a historical OS comparator, enrolled a different patient population with different prior therapy requirements and disease characteristics, making cross-trial OS comparisons unreliable. For example, in comparison to the IGNYTE study, the RELATIVITY-020 trial enrolled patients with mucosal, acral, and other subtypes of melanoma that have been reported to have poorer prognostic features. This trial also enrolled <10% of patients with Stage III disease, and Stage IV patients comprised >90% of the study population. More than half of the patients enrolled had received two or more prior systemic regimens. Thus, the RELATIVITY-020 population and the IGNYTE study population vary substantially with respect to both known prognostic factors and unknown factors.
- The FDA review team concludes that the Applicant's proposed historical comparators for OS are composed of patients with poorer prognostic features than the IGNYTE study population and that cross-trial comparisons of survival between these populations are not appropriate or interpretable.
- Subsequent therapies received after progression on the IGNYTE study treatment are not accounted for in the OS analysis and may have contributed to the observed survival outcomes.
- Finally, both known and unknown factors can impact trial results. Randomization may account for this, but single arm trial designs do not.

The Applicant also provides an exploratory overall survival analysis comparing patients deemed responders vs non-responders on the IGNYTE trial. At the data cutoff for the 3-year survival update, the median OS in the 47 patients deemed responders was not reached, as compared to 18.5 months for those considered non-responders on IGNYTE. This analysis is confounded by responder selection bias.

- To be counted as a responder, a patient had to live long enough to have a response confirmed at a follow up scan; therefore, the responder group systematically excludes patients at highest risk of early death.
- Patients who responded may have more favorable disease characteristics, such as lower tumor burden, which may independently predict longer survival, regardless of treatment.
- This is non-pre-specified, exploratory analysis, that is not controlled for confounders or type 1 error.

Therefore, FDA does not consider this data interpretable or supportive of an efficacy claim.

It is important to consider context for interpreting overall survival in patients with advanced and metastatic melanoma. The Checkmate 067 study reported 10-year outcomes in overall survival in 2024 (Wolchok et al. 2025). This was a randomized trial in previously untreated advanced melanoma where patients were randomized to either nivolumab plus ipilimumab, nivolumab with placebo, or ipilimumab with placebo. The median OS was reported as 71.9 months, or 6 years, in patients treated with

nivolumab in combination with ipilimumab. Notably, the IGNYTE population received prior ICI therapies such as this. Also, in the Applicant's own OS analysis of patients who were non-responders, they report a median OS of 18.5 months. Meaning, of the 93 patients who did not even respond to RP1, half of these patients live longer than one and a half years. This illustrates that expected survival in populations of patients with advanced cutaneous melanoma can be in the range of several years.

Overall, substantial population heterogeneity confounds interpretation of these analyses. For example, the IGNYTE populations had better prognostic features than some historical controls, as previously discussed. Also, different therapies received after IGNYTE will impact OS. Ultimately, a randomized trial is necessary to evaluate OS as an endpoint and for results to be interpretable.

Accordingly, this OS analysis does not resolve the issues identified with the IGNYTE study design and does not constitute evidence that would address the previously identified deficiencies.

Summary and Conclusions

The key conclusions from FDA's review of the IGNYTE study efficacy data are as follows:

- Use of RECIST v1.1 criteria to assess drug effect for intratumoral therapies is challenging because these criteria were designed for systemic therapies and render injected lesions nonevaluable for response by definition. While there may be residual uncertainty about the magnitude of the true response rate assessed according to RECIST v1.1, a large magnitude in response rate may mitigate this uncertainty if the response assessment is reliable and the systemic nature of the response can be established. Neither condition was met in the IGNYTE study.
- Even when RECIST v1.1 was claimed to have been used, the actual methodology applied in the IGNYTE study was problematic. The reported ORR appears artifactually inflated, as does the reported DOR, due to the multiple methodological flaws described above.
- When responders who either had all of their target lesions injected or had no target lesions at baseline are excluded from the analysis of the primary endpoint of ORR to conduct a sensitivity analysis to more closely align with RECIST v1.1 criteria (Table 4), the resulting response rate decreases from the reported response rate of 33.6%. This adds uncertainty as to whether RP1 contributes to any observed effect when administered in combination with nivolumab and also does not take into account the other response assessment issues identified; thus, even a point estimate of 15.7% in the IGNYTE study may be artifactually increased.
- It is unclear whether nivolumab alone or the combination led to the observed results. The systemic effect of RP1 is not well-characterized, and the contribution of each component to the combination cannot be determined from the available data.
- Conducting a randomized trial to support the safety and efficacy of RP1 and nivolumab would not have mitigated all of the issues identified in the IGNYTE study, but having a concurrent control arm would have potentially allowed for demonstrating a clinically meaningful improvement in outcomes of RP1 and nivolumab over available therapies to support an efficacy claim. In the absence of such trial data, the FDA review team cannot conclude that the IGNYTE study results support an efficacy claim.
- Without definitive evidence of a systemic treatment effect, it cannot be presumed that the observed responses are likely to predict clinical benefit. The responses may represent local effects due to direct injection rather than a true systemic disease-modifying effect, and without evidence of

a systemic effect, the reported response rate cannot be considered reasonably likely to predict clinical benefit, per the statutory requirements for accelerated approval.

- Additional exploratory analyses conducted by the Applicant to support an efficacy claim are not sufficient to resolve the deficiencies identified by the FDA review team in their prior BLA submission.

3.2 Safety

A summary of the safety profile is provided for context.

3.2.1 Sources of Data for Safety

The primary safety evaluation is based on 140 patients treated with RP1 in combination with nivolumab in the Phase 2 anti-PD-1 refractory cutaneous melanoma cohort of the IGNYTE study. Supportive safety data are drawn from all patients in the IGNYTE study Phase 1 dose expansion and Phase 2 portions who received RP1 in combination with nivolumab (N=335), the ARTACUS study (RP1 monotherapy in transplant patients; N=50), and the CERPASS study (RP1 in combination with cemiplimab; N=137 randomized arm). Median duration of study follow-up in the primary safety population was 20.8 months.

3.2.2 Safety Summary

The safety profile of RP1 in combination with nivolumab is generally consistent with that of nivolumab monotherapy, with the addition of injection site-related and constitutional symptoms associated with intratumoral administration. However, these toxicities should be carefully considered in the context of the uncertain clinical benefit, as noted in the Efficacy Summary of this document.

Table 13. IGNYTE Study Safety Summary

Adverse Event Parameter	Phase 2 Anti-PD-1 Refractory Cutaneous Melanoma Cohort N=140	Pooled Phase 1/2 All Cohorts N=355
All Grade AEs	137 (98%)	329 (98%)
Grade ≥3 AEs	44 (31%)	130 (39%)
Deaths due to AE	5 (4%)	15 (4%)
Dose Discontinuation due to AE	22 (16%)	34 (10%)
Dose Interruption due to AE	32 (23%)	89 (27%)
Serious AEs	50 (36%)	158 (47%)

Source: ADAE dataset; data cutoff date 15 October 2024
Abbreviations: AE, adverse event; PD-1, programmed cell death protein 1

Table 14. Summary of Common (>10%) Adverse Reactions (Excluding Laboratory-Related Adverse Events) – IGNYTE Phase 2 Anti-PD-1 Refractory Cutaneous Melanoma Patients

Adverse Reactions	All Grades n (%)	Grade 3 n (%)
Gastrointestinal	-	-
Nausea	40 (29)	0 (0)
Diarrhea*	41 (29)	3 (2)
Vomiting	24 (17)	0 (0)
Constipation	22 (16)	0 (0)
Decreased appetite	18 (13)	2 (1)

Adverse Reactions	All Grades n (%)	Grade 3 n (%)
General disorders and administration site conditions	-	-
Fatigue	63 (45)	2 (1)
Pyrexia	54 (39)	0 (0)
Chills	45 (32)	0 (0)
Injection site reaction*	37 (26)	0 (0)
Asthenia	22 (16)	2 (1)
Influenza like illness	25 (18)	0 (0)
Infections and infestations	-	-
Infections*	47 (34)	8 (6)
Musculoskeletal and connective tissue disorders	-	-
Musculoskeletal pain	43 (31)	0 (0)
Arthralgia	23 (16)	2 (1)
Nervous system disorders	-	-
Headache	26 (19)	0 (0)
Dizziness	18 (13)	0 (0)
Respiratory, thoracic and mediastinal disorders	-	-
Cough	25 (18)	0 (0.0)
Dyspnea	16 (11)	1 (1)
Skin and subcutaneous tissue disorders	-	-
Pruritus	24 (17)	0 (0.0)

Source: FDA analysis
Graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. None of the common adverse reactions were Grade 4 or 5.
* A composite that includes multiple related terms.
Abbreviation: PD-1, programmed cell death protein 1

A narrative summary of these tables is provided below:

Deaths: Among the anti-PD-1 refractory cutaneous melanoma Phase 2 cohort treated on the IGNYTE study (N=140), 59 patients (42.1%) died during study follow-up; 47 (33.6%) were attributable to disease progression. Five deaths (4%) were due to treatment-emergent adverse events (TEAEs), two of which were considered possibly related to study treatment (RP1 or nivolumab) by FDA assessment. A 44-year-old patient with Stage IV melanoma developed infection of an injected tumor lesion, subsequently developed *Escherichia coli* bacteremia, and ultimately died of multiorgan dysfunction on Study Day 39 (11 days after the second dose of RP1). A 70-year-old patient with Stage IVb melanoma died of a massive myocardial infarction 87 days after the last dose of RP1 and 30 days after the last dose of nivolumab.

Among the pooled IGNYTE Phase 1/2 all cohorts group (N=335), 157 patients (47%) died during study follow-up, with 120 deaths (36%) due to disease progression and 15 deaths (4.5%) due to TEAEs. Several of these deaths were considered possibly related to study regimen by FDA assessment, including immune-mediated myocarditis, capillary leak syndrome, pneumonia, and pulmonary sepsis. In one case, the cause of death (capillary leak syndrome) was initially attributed to the study regimen by the investigator, but the cause of death was subsequently changed to disease progression by the Applicant. Additionally, a 75-year-old patient with nonmelanoma skin cancer involving multiple lymph nodes and tissue in the pericarotid and perimandibular regions developed tumor hemorrhage in the neck and ear area 10 days after the first RP1 injection and died 5 days later. The Applicant attributed this death to disease progression; however, by FDA analysis, tumor hemorrhage related to RP1 injection may have been a contributing factor.

Serious TEAEs: Among the anti-PD-1 refractory cutaneous melanoma Phase 2 cohort, serious TEAEs occurred in 50 (35.7%) patients. Events in two or more patients included disease progression (5.7%), pleural effusion (2.1%), and each occurring in 1.4%: acute kidney injury, arthralgia, atrial fibrillation, atrial flutter, cancer pain, hypophysitis, immune-mediated enterocolitis, myocardial infarction, pyrexia, sepsis, and urinary tract infection.

Common adverse reactions (>10% of patients): Fatigue (45.0%), pyrexia (38.6%), infections (33.6%), chills (32.1%), musculoskeletal pain (30.7%), diarrhea (29.3%), nausea (28.6%), injection site reaction (26.4%), influenza-like illness (20.0%), headache (18.6%), vomiting (17.1%), arthralgia (16.4%), constipation (15.7%), decreased appetite (12.9%), dizziness (12.9%), and dyspnea (11.4%). Grade 3 events observed in two patients each for arthralgia, asthenia, decreased appetite, diarrhea, and fatigue. No Grade 4 adverse events (AEs) in more than 10% of patients.

Treatment discontinuations, procedure-related events, and herpetic infections: In the anti-PD-1 refractory cutaneous melanoma Phase 2 cohort, adverse reactions leading to discontinuation of RP1 or nivolumab occurred in 22 patients (15.7%), including 9 (6.4%) who discontinued both. Low-grade pneumothorax occurred in three patients (2.1%) receiving lung lesion injections. Three patients (2.1%) experienced Grade 2 or less herpetic-like infections; no systemic HSV infections were observed. Immune-mediated events were consistent with nivolumab class effects.

Adverse Events of Special Interest

Other clinically significant adverse reactions associated with administration of RP1 occurring in less than 10% of patients in the primary safety population (N=140) include visceral injury including pneumothorax (n=3) associated with visceral lesion injection, tumor hemorrhage (n=3), sepsis (n=3), herpetic-like infection including oral herpes (n=2), herpes simplex (n=1), herpes simplex reactivation (n=1), and cytokine release syndrome (n=1).

FDA review notes the following adverse events of special interest associated with nivolumab:

- Immune-mediated toxicities: hypothyroidism (n=8, 5.7%), vitiligo (n=7, 5.0%), colitis (n=5, 3.6%), neuropathy peripheral (n=5, 3.6%), hepatitis (n=2, 1.4%), myocarditis (n=2, 1.4%), dermatitis (n=2, 1.4%), gastritis (n=2, 1.4%), hyperthyroidism (n=2, 1.4%). Grade 3 or greater immune-mediated events included colitis (n=2), hepatitis (n=1), myocarditis (n=1), and peripheral sensory neuropathy (n=1).
- Infusion-related reactions occurred in 3 (2.1%) patients, including 1 Grade 3 event.

Known AE Profile of Nivolumab

Nivolumab has several indications to treat patients with cancer. As the nivolumab USPI notes, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice. However, FDA notes that the existing database on patients who have received nivolumab is large, with several thousand patients' data considered in the nivolumab USPI.

Based on the USPI, FDA review notes that while several of the following AEs were not specifically observed in the IGNYTE trial, these events are known toxicities associated with nivolumab, and thus it is

reasonable to presume that patients receiving RP1 in combination with nivolumab are at risk of these same events.

The following are events listed as warnings and precautions in the nivolumab USPI: immune-mediated adverse reactions, which may be severe or fatal and can occur in any organ system or tissue, including immune-mediated pneumonitis, colitis, hepatitis or hepatotoxicity, endocrinopathies, dermatologic adverse reactions, and nephritis and renal dysfunction; and infusion-related reactions.

Summary of Safety

Overall, the FDA review team notes that toxicities known to occur with use of nivolumab occurred in studies of RP1 and nivolumab. Nivolumab itself carries a well-characterized and potentially serious toxicity burden, including immune-mediated adverse reactions that may be severe or fatal. Additionally, several serious and potentially life-threatening adverse events occurred in the IGNYTE study that may be related to RP1 administration, including tumor hemorrhage, sepsis, and capillary leak syndrome, underscoring that the combination regimen is not without meaningful risk. Due to the lack of a control arm in studies of RP1 and nivolumab, a robust comparative safety analysis cannot be conducted to ascertain the toxicity of this regimen in the context of nivolumab monotherapy or other available therapies. The observed toxicities, including serious toxicities potentially attributable to RP1, must be carefully weighed against the uncertain clinical benefit of this regimen in the context of the overall benefit-risk assessment.

4. Conclusions

Advanced unresectable and metastatic cutaneous melanoma that has progressed on anti-PD-1-based therapy is a serious and life-threatening condition. At least 50% of patients fail frontline anti-PD-1 therapy within 1 year. The unmet need is particularly high for patients who have progressed on anti-PD-1 combined with anti-CTLA-4 combination therapy, representing 43.6% of the IGNYTE study population. Treatment options with proven clinical benefit are limited. A well-tolerated, effective therapy would address an important gap. However, approval requires demonstration of substantial evidence of effectiveness. FDA identified several issues with the Applicant's application of RECIST v1.1 criteria that were used for response assessment. The FDA review team concludes that these artifactually inflated the primary endpoints of the IGNYTE trial, ORR and DOR. The contribution of RP1 to the combination effect cannot be determined, and it is unclear if RP1 contributes to any observed effect. Overall survival data from the single-arm trial are not interpretable for establishing a treatment effect. Without definitive evidence of systemic effect, the response rate cannot be considered reasonably likely to predict clinical benefit per the statutory requirements for accelerated approval.

Accelerated approval has the same statutory requirement for substantial evidence of effectiveness as traditional approval. The fundamental regulatory issue is whether the single-arm IGNYTE study provides substantial evidence of effectiveness. FDA identified deficiencies in three areas: (1) response assessment methodology that confounds the reported ORR and DOR; (2) the magnitude of the observed response rate from the single-arm IGNYTE study is not sufficient to overcome concerns regarding contribution of effect, particularly given the limitations in response assessment and the absence of a reliable historical control; and (3) the Applicant-submitted OS data from the single-arm IGNYTE study are not considered interpretable for establishing a treatment effect. While the risks of RP1 and nivolumab may be

acceptable for this population of patients, it is imperative that benefit is established to justify the risk of toxicity to patients. Ultimately, the FDA review team concludes that this BLA does not include an adequate and well-controlled investigation that demonstrates substantial evidence of effectiveness.

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