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ADVISORY COMMITTEE MEETING
BRIEFING MATERIALS
AVAILABLE FOR PUBLIC RELEASE

BLA 125827
TUDRIQEV™ (vusolimogene oderparepvec-wtpg, RP1)

Sponsor:

Replimune, Inc.

500 Unicorn Park, Third Floor

Woburn, MA 01801

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
BOR	best overall response
BLA	Biologics License Application
CD8+	cluster of differentiation 8
CI	confidence interval
CR	complete response
CRR	complete response rate
CRS	cytokine release syndrome
CSF	colony-stimulating factor
CSR	clinical study report
CTGTAC	Cellular, Tissue, and Gene Therapies Advisory Committee
CTLA-4	cytotoxic T-lymphocyte antigen 4
DCR	disease control rate
DNA	deoxyribonucleic acid
DOR	duration of response
DP	drug product
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GM	granulocyte-macrophage
HSV-1	herpes simplex virus type 1
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICI	immune checkpoint inhibitor
IL	interleukin
IND	Investigational New Drug
ITT	intent to treat
LAG-3	lymphocyte activation gene-3
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
mRECIST	Response Evaluation Criteria in Solid Tumors version 1.1 as modified for use in the IGNYTE study
NCCN	National Comprehensive Cancer Network
NMSC	nonmelanoma skin cancer
NR	not reached
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death protein 1 (receptor)
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PFU	plaque-forming units
PMC / PMR	post-marketing commitment / post-marketing requirement
PR	partial response
PS	performance score
qPCR	quantitative polymerase chain reaction
RECIST	Response Evaluation Criteria in Solid Tumors version 1.1
RP2D	recommended Phase 2 dose
SAP	Statistical Analysis Plan
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results Program
TCID50	tissue culture infection dose
TEAE	treatment-emergent adverse event
TME	tumor microenvironment
TRAE	treatment related adverse event
TTR	time to response
T-VEC	talimogene laherparepvec
ULN	upper limit of normal
US	United States
USPI	United States package insert

1. EXECUTIVE SUMMARY

Replimune, Inc. (Replimune) submitted BLA 125827 on 21 November 2024 for the accelerated approval of TUDRIQEV™ (vusolimogene oderparepvec, VO, RP1) in combination with nivolumab for the treatment of adults with unresectable advanced cutaneous melanoma who experienced disease progression with a programmed death receptor-1 (PD-1)-blocking antibody-based regimen. Safety and efficacy of RP1 in combination with nivolumab was demonstrated through the Phase 2 trial, RPL-001-16, known as IGNYTE. On the basis of the IGNYTE data, FDA granted Breakthrough Therapy Designation for RP1 in combination with nivolumab, for the treatment of adult patients with advanced melanoma that has progressed on an anti-PD-1 containing regimen and Priority Review to BLA 125827. This briefing document summarizes data included in the Biologics License Application (BLA) submitted to the US FDA in support of this indication.

1.1. Unmet Need with Limited Treatment Options

Advanced melanoma is a serious and life-threatening disease characterized by the spread of cancer beyond the primary site to regional or distant tissues and organs. The American Cancer Society estimates that 112,000 new melanomas will be diagnosed, and 8510 people will die from the disease in the US during 2026 (American Cancer Society 2026). Despite advances made with immune checkpoint inhibitor (ICI) therapies over the last decade, over 50% of advanced melanoma patients progress within the first 12 months (Robert 2015). Patients with advanced melanoma therefore remain at a substantial risk of disease progression and death (American Cancer Society 2026).

Immune checkpoint inhibitor (ICI)-based therapies such as nivolumab and pembrolizumab (anti-PD-1) with or without an anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) were approved and are considered standard of care options for treatment naïve patients with advanced melanoma (Knight 2023) since 2014 and 2015. Most patients in the US now receive either ipilimumab combined with nivolumab or relatlimab (anti-LAG3) combined with nivolumab in the first line setting (NCCN 2026). However, there are patients who are still treated with anti-PD-1 monotherapy due to toxicity of the combination regimens. After progression on anti-PD-1 based combination therapies, treatments options are very limited and provide generally poor outcomes (Section 3.3).

There is currently no FDA-approved therapy for patients with unresectable advanced melanoma whose disease has progressed after receiving anti-PD-1 based therapy, except for lifileucel (tumor infiltrating lymphocyte [TIL] therapy combined with IL2). Lifileucel was granted accelerated approval in 2024 based on a single arm trial with 82 patients treated in the primary efficacy cohort. However, nearly all patients experienced Grade 4 treatment related events, and the treatment-related mortality rate was 7.5% (AMTAGVI USPI). Consequently, there remains a critical unmet need for therapies that are both safe and effective for patients with advanced melanoma whose disease progresses on anti-PD-1–based treatment.

1.2. Rationale for Single Arm Study Design

The IGNYTE study was designed as a single-arm trial to evaluate the safety and efficacy of RP1 in combination with nivolumab in patients with unresectable advanced cutaneous melanoma who had confirmed disease progression while being treated with their prior anti-PD-1 regimen.

According to melanoma expert testimony, it is not **feasible or ethical** to randomize this patient population to a comparator arm of anti-PD-1 monotherapy that offered no hope for response, therefore a study comparing RP1 in combination with nivolumab, to nivolumab monotherapy in patients whose disease progressed while on nivolumab or other anti-PD-1 was not conducted.

At the time the IGNYTE study was designed, there were no approved therapies for anti-PD-1 failed melanoma. There is no evidence that continued anti-PD-1 monotherapy provides any level of clinical benefit to patients after definitive progression on prior anti-PD-1 therapy has been established. Consequently, there is very little literature evaluating this specific scenario, as continuing a therapy that has definitively failed would generally not be considered appropriate clinical practice.

The literature reports a range of response rates associated with retreatment of patients with anti-PD-1 based therapy, however, none of these studies employed inclusion/exclusion criteria, like what was done in IGNYTE, to ensure patients were truly anti-PD-1 resistant. These reports include retrospective analyses of treatment beyond progression or pseudoprogression (Beaver, Hodi), small prospective studies including patients without confirmed progression or required continuous treatment, and single site case reviews lacking pretreatment description. Therefore, when interpreting response rates reported in the literature after prior anti-PD-1 failure, it is important to consider the design and eligibility criteria of each study. Simply put, the reasons why responses may be observed in historical literature include:

- Patients had responded to prior anti-PD1, stopped therapy, and were then re-treated upon disease progression
- Patients received intervening treatment after stopping prior therapy
- Confirmed progression was not required allowing delayed response or pseudoprogression to inform treatment decisions
- No minimum treatment period of prior anti-PD1 therapy was required (ie, exposure not adequate for response)
- Responses were not independently and centrally reviewed.

The literature most relevant to patients who continue anti-PD-1 **monotherapy** after progression on prior anti-PD-1 therapy includes the analysis by Beaver et al. (2018), as further evaluated by Ribas et al. (2018). These analyses suggested that an **ORR of no more than 7%** would be expected in this setting. This finding is consistent with Hodi et al. (2016), in which delayed responses following initial disease progression were observed in approximately 6% of patients.

Subsequently in 2019, the Society for the Immunotherapy of Cancer (SITC) assembled a task force of 35 melanoma and immunotherapy experts aimed at defining the definitions of resistance on anti-PD-1 therapy after which no further benefit would be expected (Kluger 2020) and further supplemented in 2023 (Kluger 2023). There was general consensus that late responses after rapid and confirmed radiographic progression even at short time intervals such as 4 weeks, likely

occur in **no more than 5% of patients**, and are unlikely to significantly affect results of subsequent clinical trials in which a patient may enroll.

Therefore, using anti-PD-1 monotherapy (eg, nivolumab) in a control arm in patients whose disease had already definitively progressed while on their prior anti-PD-1 containing therapy (ie, either monotherapy or combination therapy) was not feasible or ethical. Therefore, a randomized trial in this setting comparing RP1 in combination with nivolumab to nivolumab was not conducted.

IGNYTE included patients who had adequate exposure to anti-PD-1 treatment (≥8 weeks) on their immediate prior therapy followed by confirmation of disease progression at least 4 weeks after the initial scan showing progressive disease (nearly all [96.4%] patients and all responders actually received 12 or more weeks of prior anti-PD-1 treatment), and therefore, Replimune considers that any ORR that exceeds 5% demonstrates that RP1 is contributing to the response effect.

FDA routinely grants accelerated approval for oncology products and specifically for melanoma on the basis of single-arm trials, including most recently Amtagvi (lifileucel; 2024) for unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody (as discussed above). The initial approvals for both Keytruda (pembrolizumab; 2014) and Opdivo (nivolumab; 2014) for unresectable or metastatic melanoma following ipilimumab were based on data from a single study arm. During the approval process, FDA reviewers noted that study populations for both Keytruda and Amtagvi were heterogeneous, which is common for later stage treatments (AMTAGVI Clinical Review and Evaluation 2025, KEYTRUDA BLA Clinical Review 2014).

1.3. IGNYTE Enrolled a Real-World US Patient Population

The benefit of RP1 in combination with nivolumab in the proposed indication was established in the Phase 2 Anti-PD-1 Failed Cutaneous Melanoma cohort of the IGNYTE trial, which enrolled a total of 140 patients with advanced melanoma who had **confirmed disease progression while being treated with anti-PD-1 therapy** (either alone or in combination, mainly with ipilimumab) either in the adjuvant or recurrent/metastatic setting as their most recent therapy. Patients enrolled in this primary efficacy cohort represent a real-world, unresectable cutaneous melanoma patient population with high unmet medical need.

Heterogeneity of the study population was controlled though robust inclusion criteria requiring each patient to have disease that progressed **during** (ongoing treatment) a minimum of 8 weeks of continuous anti-PD-1 treatment with **confirmation of progression** at least 4 weeks after the first observation. These criteria ensured that patients received adequate exposure to anti-PD-1 therapy and that there was no opportunity for a late response to the ongoing therapy.

During the review of the original BLA, Replimune conducted a patient-by-patient review to ensure all patients had received adequate exposure to their prior anti-PD-1 therapy prior to enrollment in IGNYTE and confirmed that in fact, nearly all of the patients (135/140; 96.4%) received 12 or more weeks of prior anti-PD-1 therapy.

Similarly, Replimune also confirmed that all patients had disease progression confirmed at least 4 weeks after their first observed progression, or had a confirmatory biopsy (ie, for adjuvant patients).

Because the study enrolled patients from 20 Mar 2020 through 8 Mar 2023, the study population includes patients who had confirmed progression while on PD-1 therapy either as monotherapy or combination with CTLA 4 or other immunotherapy in the neoadjuvant, adjuvant as well as advanced/metastatic setting. This reflects the current US treatment landscape and patients with limited safe and effective treatment options. This is also aligned with FDA advice to "not limit the patient population too much such that a real-world patient population was represented."

The current NCCN melanoma guidelines (version 2.2026) show multiple treatment pathways in both the adjuvant and advanced disease setting all converging to the IGNYTE study eligibility in the case of refractory disease. This means that this real-world patient population will be, by necessity, heterogeneous. Sub-segmenting these patients to artificially obtain statistical homogeneity would not reflect the US population of patients with refractory melanoma and would deny treatment opportunity to those in great need.

These points are echoed by global melanoma experts in the many letters written to the FDA by melanoma experts post issuance of the CRL, which universally make this point. Importantly, these patients are homogenous as they converge into the common biologic entity known as PD-1 refractory disease and require a therapeutic option with a MOA that sensitizes these patients to further anti-PD-1 treatment.

1.4. IGNYTE is an Adequate and Well-Controlled Trial that Provides Substantial Evidence of Effectiveness

IGNYTE is an adequate and well-controlled clinical trial that provides substantial evidence of effectiveness of RP1 in combination with nivolumab for the treatment of adult patients with unresectable advanced melanoma who experience disease progression with a programmed death receptor-1 (PD-1)-blocking antibody-based regimen.

The RECIST analysis by Independent Review constitutes the primary efficacy evidence for this submission. The objective response rate (ORR) was 33.6% (95% CI: 25.8%, 42.0%) and nearly half of the responding patients (23/47) achieved a CR, which is a particularly notable finding in the anti-PD-1 refractory melanoma setting where complete eradication of detectable disease is uncommon. Responses were durable with a median duration of response (DOR) of 24.8 months (95% CI: 14.1, not estimable); 50.7% of patients maintained responses at 24 months, including 1 patient whose response was ongoing for over 4 years. Together, the ORR, CR rate, and durability of response demonstrate clinically meaningful and sustained antitumor activity in a patient population with limited treatment options.

After all IGNYTE patients had the potential to be followed for at least 3 years, an updated analysis of overall survival (OS) was completed. The 3-year updated analysis of OS further confirms that overall durability of response is associated with longer survival. It is noteworthy that 7 of the 10 patients who were followed for more than 36 months remain in response beyond 48 months. Survival curves from melanoma studies that include long-term follow-up show a plateau at 3 to 4 years and suggest that patients who are alive at 3 years are likely to have further prolonged benefit from prior therapy (Michielin 2020).

Prospective studies benchmarking single agent anti-PD-1 activity in patients with advanced melanoma that progressed on a prior anti-PD-1 regimen are limited. However the RELATIVITY-020 study (Ascierto 2023) evaluating a combination therapy with nivolumab is

clinically relevant for IGNYTE because both studies evaluated patients with advanced melanoma whose disease had progressed on or after prior anti–PD-(L)1 therapy. RELATIVITY-020 enrolled advanced melanoma patients including those who previously received a single prior line of anti-PD 1–based therapy with or without anti-CTLA-4 (D1), as well as patients who had received one or more prior lines of anti- PD-(L)1 therapy, including in the adjuvant setting (D2). In this setting, Opdualag (relatlimab in combination with nivolumab) achieved objective response rates of 12% (D1) and 9% (D2). The ORR of 33.6% achieved in IGNYTE study is not only clinically meaningful, but is also substantially higher than the ORR observed with the combination treatment Opdualag.

Evaluation of the Contribution of the Effect

In the anti-PD-1 resistant setting, the mechanism of action of RP1 complements that of anti-PD-1 therapy by increasing the number of tumor reactive T cells leading to an immune inflamed tumor microenvironment (TME) and increased PD-L1 expression and thereby re-sensitizing tumors to anti–PD-1 therapy.

A nivolumab monotherapy control arm would not have been feasible or ethical in this anti-PD-1 refractory population as no benefit to patients would be expected as explained in Section 1.2.

The ORR of nearly 34% is **unlikely to be attributed to treatment with** nivolumab alone considering the following:

- Clinical trials leading to the approval of single-agent anti-PD-1 (nivolumab or pembrolizumab) consistently reported ORR of 32% to 34% in patients with melanoma who had never received prior treatment with anti-PD-1 (anti-PD-1 **treatment-naïve** patients) (Robert 2015a, Robert 2015b)
- Replimune maintains that continuation of anti-PD-1 monotherapy is not an effective option in the advanced setting in patients with metastatic or unresectable disease whose disease has already progressed while on an anti-PD-1 containing regimen. There is no credible literature evidence that continued therapy with anti-PD-1 would achieve clinical benefit in this population.
    - The available literature demonstrates that retreatment with anti-PD-1 monotherapy following definitive progression while being treated with any prior anti-PD-1 containing regimen would not be expected to result in any meaningful response rate, with the literature indicating that a response rate of no more than 7% would be seen (Hodi 2016, Ribas 2018).
    - The SITC taskforce concluded that patients meeting the SITC definition of definitive progression were unlikely to derive further benefit from continued anti-PD-1 therapy, with an expected ORR of <5% (Kluger 2020).
- Replimune conducted a patient-by-patient review to ensure all patients had received adequate exposure to their immediate prior anti-PD-1 therapy and had confirmation of disease progression (2 assessments, at least 4 weeks apart) while still being treated, prior to their enrollment in IGNYTE. The FDA Clinical Review (15 July 2025) concurred that these and their own analysis supported both sufficient exposure and exhaustion to prior anti-PD-1 therapy.

To further define the contribution of effect, Replimune also performed an exploratory analysis of patients in the IGNYTE trial where patients served as their own control (Section 4.4.2.1). Because each patient enrolled in IGNYTE had confirmed progression while on the prior anti-PD-1 therapy, any additional response observed subsequently reflects the additional ("add on") effect contributed by RP1 to nivolumab. This "add-on" effect is best seen in 104 patients who progressed while on prior anti-PD-1 therapy in the advanced (unresectable/metastatic) setting in the IGNYTE study.

Using their immediate prior therapy as the control, the contribution of RP1 can be estimated by comparing the ORR (as reported by the Investigator) on prior therapy to the ORR per RECIST by IRC observed in IGNYTE (RP1 in combination with nivolumab).

- Only 12 of 104 patients in IGNYTE had a **response to their immediate prior anti-PD-1** therapy in the advanced/metastatic setting; ORR of **11.5%** (95% CI: 6.1-19.3)
- In comparison, when treated with **RP1 in combination with nivolumab**, 31 of 104 patients had an **ORR of 29.8%** (95% CI: 21.2-39.6)

A remarkably improved PFS is also observed in responding patients (N=47) following **RP1 in combination with nivolumab (median PFS 30.6 months)** as compared to the time to progression (TTP) of those same patients on the immediate prior anti-PD-1 therapy upon which confirmed progression had just occurred (median **TTP 4.4 months**).

The body of evidence from the IGNYTE trial including clinically meaningful and substantially improved durable ORR in comparison with the historical literature in this setting, comparison of response and PFS from patients in IGNYTE to that of their immediate prior anti-PD-1 therapy, and the biologic mechanism of RP1 support that the IGNYTE trial is an adequate and well-controlled trial that can be used to provide substantial evidence of effectiveness in patients with anti-PD-1 refractory disease.

1.5. IGNYTE Demonstrates Safety and Tolerability of RP1 In Combination with Nivolumab

In the Anti-PD-1 Failed Cutaneous Melanoma cohort (N=140), TEAEs with the highest incidence (≥20% of patients) were fatigue, pyrexia, chills, nausea, and diarrhea. Most of the common TEAEs (ie, occurring in ≥10% of patients) were Grade 1 or 2, and all the common Grade 3-4 TEAEs were Grade 3 (Table 14). No treatment-related Grade 5 TEAEs have been reported for the IGNYTE Anti-PD-1 Failed Cutaneous Melanoma patient cohort.

The safety profile of RP1 in combination with nivolumab is consistent in nature and severity with clinical experience of nivolumab alone with an increase in only Grade 1 and 2 events expected with systemic immune activation and a low incidence of Grade 3 and 4 events. A summary of safety is provided in Section 5. Overall, there were no systemic HSV infections observed in the IGNYTE study (Section 5.2.2). Cumulatively, across the RP1 development program, there have been no reports of herpetic infection were reported for healthcare providers, patients' caregivers, or close contacts.

In addition to the RP1 safety data from IGNYTE Anti-PD-1 Cutaneous Melanoma cohort (primary efficacy cohort), the totality of the safety data across the RP1 program (Phase 1 and

Phase 2 portions of IGNYTE, the ARTACUS trial, and the CERPASS trial), along with the comprehensive toxicological program show that RP1 has a manageable safety profile.

These safety and efficacy findings provide the basis of a favorable benefit-risk assessment in support of accelerated approval.

1.6. IGNYTE-3, A Randomized, Controlled, Confirmatory Trial is Ongoing

IGNYTE-3 is a randomized, controlled, multicenter, open-label, Phase 3 clinical study comparing RP1 in combination with nivolumab to a physician's choice of treatment in patients with unresectable or metastatic melanoma. Following FDA consultation, the study protocol was finalized and the first patient was enrolled on 09 August 2024 to ensure that the study "was well underway" at the time of potential accelerated approval based on the IGNYTE Anti-PD-1 Failed Melanoma cohort.

All options listed in the Physician's Choice comparator arm are included in NCCN guidelines and with no other choices, even chemotherapy is sometimes used for these patients; however most patients (93%) in the IGNYTE-3 comparator arm are receiving Opdualag® (relatlimab in combination with nivolumab). During the 16 September 2025 Type A meeting FDA agreed that while it was not direct, an analysis of IGNYTE-3 patients comparing RP1 in combination with nivolumab to Opdualag could demonstrate the contribution of RP1 to the overall treatment effect. Opdualag (relatlimab in combination with nivolumab) has been shown to be superior to anti-PD-1 monotherapy (nivolumab) in first line treatment; therefore, superiority of RP1 in combination with nivolumab over Opdualag would show support for the contribution of RP1to the overall treatment effect.

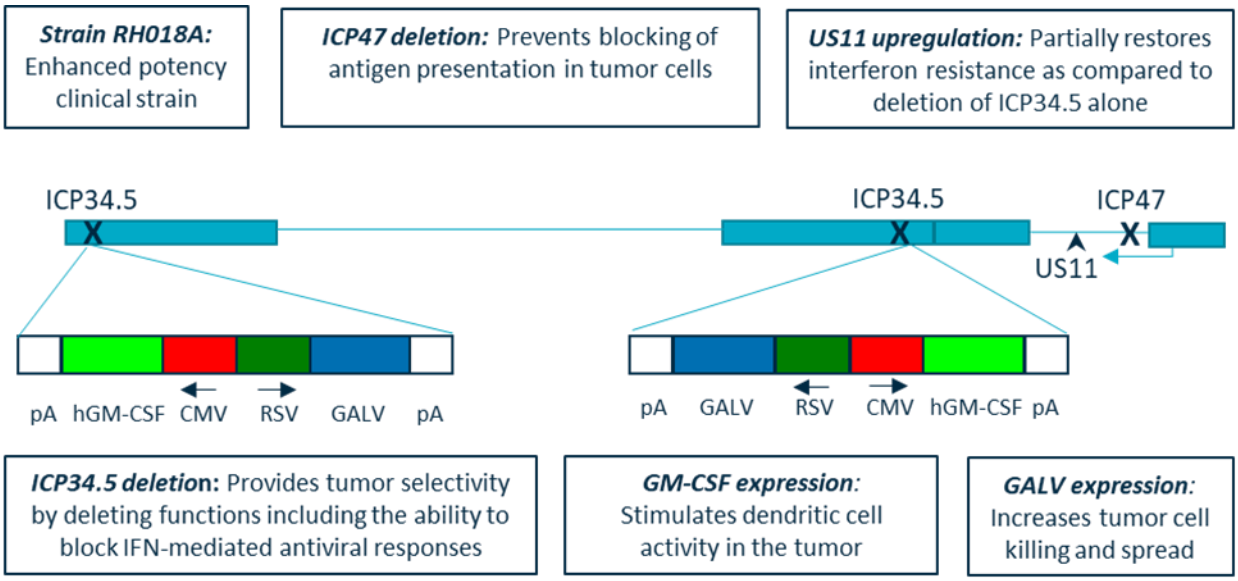
2. INTRODUCTION

2.1. Vusolimogene Oderparepvec (RP1)

2.1.1. Product Description

Vusolimogene oderparepvec (also referred to as RP1) is a fusion-enhanced genetically modified herpes simplex virus, type 1 (HSV-1) oncolytic viral therapy. RP1 encodes a fusogenic glycoprotein derived from gibbon ape leukemia vims with the R sequence deleted (GALV-GP-R$^-$) and human granulocyte-macrophage colony-stimulating factor (GM-CSF). The genes encoding the HSV-1 neurovirulence factor ICP34.5 and the transporter associated with antigen presentation inhibitor ICP47 are deleted from RP1.

Figure 1: Schematic Representation of the Vusolimogene Oderparepvec (RP1/RP1) Genome



2.1.2. Recommended Dosage

RP1 is administered by intratumor injection. The recommended dosage of RP1 is 1 mL/cm of the largest dimension of the tumor for a maximum of 10 mL across all lesions at a single injection visit. RP1 is administered every 2 weeks for 8 consecutive doses, starting with an initial concentration of 10^6 plaque-forming units (PFU) per mL at Week 1, followed by 10^7 PFU per mL at subsequent doses. Nivolumab is administered intravenously starting at Week 3 and is dosed according to the nivolumab prescribing information.

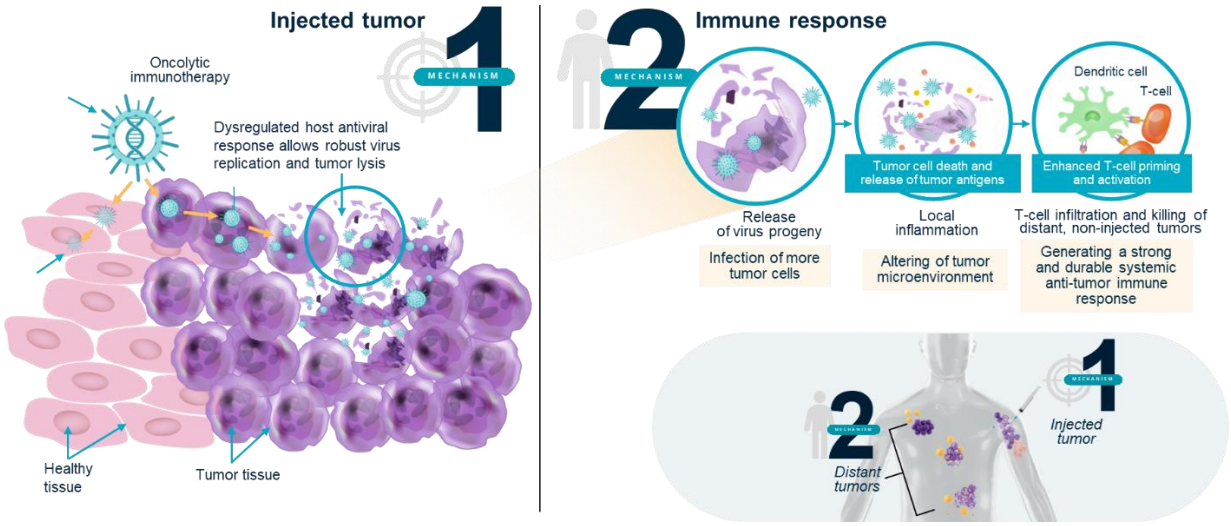
2.1.3. Mechanism of Action

RP1 is a selectively replication-competent herpes simplex virus, type 1 (HSV-1) that expresses human granulocyte-macrophage colony-stimulating factor (hGM-CSF) and the gibbon ape leukemia virus fusogenic glycoprotein with the R-sequence deleted (GALV-GP R$^-$). RP1 is administered by intratumoral injection and has a 2-pronged mechanism of action. Once injected into a tumor, RP1 replicates in and directly kills tumor cells, resulting in the release of tumor and

viral antigens which indirectly leads to T cells being activated to systemically destroy cancer deposits through-out the body. This mechanism is enhanced by the two transgenes encoded with RP1. GALV-GP R$^-$ is a fusogenic membrane glycoprotein, which markedly enhances immunogenic cell death, while hGM-CSF amplifies the immune response to newly released antigens. Nonclinical evidence demonstrates that the efficacy of RP1 combined with anti-PD-1 therapy is enhanced compared to that seen with either RP1 or anti-PD-1 across multiple tumor types.

In the anti-PD-1 resistant setting, a range of clinical biomarker data from the IGNTYE trial demonstrates that RP1 alters the tumor microenvironment (TME), converting immunologically silent TMEs to an inflamed phenotype, which is known to result in a far higher likelihood of clinical benefit from anti-PD-1-based treatment. Notably, this TME phenotype was not present in most of the enrolled patients following the patient's prior treatment with anti-PD1 therapy, but was only induced following treatment with RP1. Tumor biopsies collected from patients at baseline and Day 43 confirmed an increase in PD-L1 expression and CD8 T cell infiltration and T cell receptor sequencing from peripheral blood also demonstrated that RP1 in combination with nivolumab not only expands the existing CD8+ T cell clones but also generates new clones, demonstrating the induction of enhanced systemic anti-tumor immunity.

Figure 2: Oncolytic Immunotherapy Is Intended to Activate a Systemic Anti-Tumor Response



Constructed from Bommareddy PK, et al. *Am J Clin Dermatol*. 2017;18(1):1-15.

2.2. Proposed Indication

TUDRIQEV™ is indicated in combination with nivolumab for the treatment of adults with unresectable advanced cutaneous melanoma who experienced disease progression with programmed death receptor-1 (PD-1)-blocking antibody-based regimen.

2.3. Purpose of the Advisory Committee Meeting

The FDA convenes this meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC), scheduled for 30 July 2026. The committee will meet in open session to discuss and make recommendations on the Biologics License Application (BLA) 125827, from Replimune, Inc. for Vusolimogene oderparepvec.

Do the data provide substantial evidence of effectiveness in the proposed indication?

2.4. Regulatory History

Table 1: Key Regulatory Interactions

Date Interaction Type	Pertinent Comments/Agreements
25 March 2021 Type B meeting CRTMS #13148 (RPL-001-16 [IGNYTE])	FDA provided feedback on the clinical development plan for RP1 in anti-PD-1 failed melanoma: • Stated preference for a randomized, controlled trial • Indicated that if the results from the single-arm trial were compelling enough to support accelerated approval, a confirmatory trial with randomization would be required. • Regarding heterogeneity of the study population, FDA stated that they will interpret the results based on the study patients including information on prior treatment regimens and timing of the prior treatment. • Recommended that not too many restrictions be placed on the population to ensure that a real-world population representative of the unmet need was enrolled. • Agreed that the study population as defined represented a population of unmet need. • Noted that ORR together with response durability data (DOR) assessed by a blinded independent review committee could potentially support a claim of efficacy of the proposed treatment depending on a benefit-risk assessment of the study results. • Recommended to measure and track objective responses of both injected and noninjected lesions when reporting ORR.
12 September 2023 Type C meeting CRMTS #15143 (Clinical meeting to discuss regulatory strategy for registration)	FDA provided guidance on requirements for product registration: • FDA recognized the unmet medical need in the anti-PD-1 failed melanoma population. • Stated that tumor response as assessed by independent review per Response Evaluation Criteria in Solid Tumors version 1.1 is required for FDA to make a regulatory decision for accelerated approval. • Requested an updated independent review charter and Statistical Analysis Plan. • Recommended to provide 6 months of follow-up for each patient and 6 months of follow-up for each responder following the initial response or follow all responders until the median DOR is reached. • Stated that contribution of components could be demonstrated through the use of literature. • Advised on the information expected for a pre-BLA meeting and the BLA submission. • Generally agreed with the overall 2-arm randomized, controlled trial design with physician's choice as the comparator arm in the intended study population for a confirmatory study (IGNYTE-3).

Date Interaction Type	Pertinent Comments/Agreements
03 September 2024 Type B Pre-BLA meeting Meeting ID# 20461	• At the pre-BLA meeting, FDA indicated that an accelerated approval pathway is feasible. • Replimune and FDA agreed on the contents of a full BLA application. • FDA agreed to Replimune's proposal for late components submission a) submit real-time stability data for primary and supportive stability batches for RP1 Drug Substance and Drug Product and b) primary label validation study data and report no later than 60 days prior to Prescription Drug User Fee Act goal date. • The FDA commented that the labeling validation study report can be submitted as a late component, but the labeling validation protocol should be included in the initial BLA submission.
20 November 2024 Breakthrough Therapy Designation (BTD)	On the basis of the primary analysis data (n=140) per independent review, breakthrough designation was granted for "vusolimogene oderparepvec (VO also known as RP1) administered intratumorally, when used in combination with nivolumab, for the treatment of adult patients with advanced melanoma that has progressed on an anti-PD-1 containing regimen."
21 November 2024 BLA Submission	Replimune submitted BLA 125827 for the accelerated approval of TUDRIQEV™ in combination with nivolumab for the treatment of adults with unresectable advanced cutaneous melanoma who experienced disease progression with programmed death receptor-1 (PD-1)-blocking antibody-based regimen.
21 March 2025 Mid-Cycle Meeting held on	• FDA noted that the review of the clinical information was ongoing. No substantive clinical review issues had been identified. • FDA inquired about the status of the IGNYTE-3 trial, emphasizing that the trial should be underway prior to approval.
15 May 2025 Late-Cycle Meeting	No substantive clinical review issues were raised during the Late-Cycle Meeting.
End of BLA review activities	• On 30 May 2025, FDA conditionally accepted -wtpg as the suffix for inclusion in the proper name. • On 10 June 2025, FDA accepted the proposed proprietary name, TUDRIQEV. • On 13 June 2025, Replimune received comments to the draft labeling. Replimune addressed these comments and submitted revised labeling on 20 June 2025. FDA sent further comments on 26 June 2025. Replimune generally concurred with the remaining updates and provided an updated draft USPI on 01 July 2025. • On 13 June 2025, FDA sent proposed post marketing requirements and post marketing commitments (PMRs/PMCs) to Replimune. Replimune provided agreement to these on 17 June 2025.

Date Interaction Type	Pertinent Comments/Agreements
21 July 2025 CRL	FDA issued a Complete Response for BLA 125827 concluding that: • The prespecified response rate in the RPL-001-16 trial appears numerically higher compared to the proposed historical control rate from literature reports. However, the numerically higher response rate cannot be adequately interpreted due to heterogeneity of the RPL-001-16 trial patient 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, and due to the heterogeneity of the patient population reported in the literature. • The RPL-001-16 trial was also not designed to isolate the contribution of vusolimogene oderparepvec to the observed ORR when administered in combination with nivolumab. While vusolimogene oderparepvec is not expected to demonstrate significant single-agent activity based on its mechanism of action, its specific contribution to the observed ORR cannot be determined.
16 September 2025 Post CRL Type A Meeting	• FDA stated that they "continue to recommend a randomized comparison of vusolimogene oderparepvec + nivolumab to nivolumab monotherapy as a concurrent control to establish the contribution of components." • FDA expressed concern about the impact of intratumor injection on the ability to see changes between scans and suggested that an analysis of response between injected and noninjected tumors would be helpful. • FDA suggested that Replimune consider an interim analysis of response rate and duration of response between these arms and further follow up from the same trial assessing overall survival may potentially support conversion to traditional approval. • FDA suggested that they were open to an alternative analysis which may include conducting a descriptive interim analysis comparing response rates, with supportive duration of response data, between the investigational arm and the control arm of the ongoing Phase 3 trial.
10 October 2025 BLA Resubmission	Replimune submitted BLA 125827 for the accelerated approval of TUDRIQEV™ in combination with nivolumab with • An updated analysis using IGNYTE patients as their own control, comparing the time to progression on their immediate prior anti-PD-1 therapy to the progression-free survival. • A snapshot of early data from IGNYTE-3, which showed consistency with both the historical data cited in the BLA (comparator arm) and with the activity observed in the Phase 2 IGNYTE Anti-PD-1Failed Melanoma patient cohort that formed the basis of the BLA. This was in response to the Type A meeting when FDA suggested that a descriptive analysis from IGNYTE-3 could be considered for accelerated approval. • Further discussion and literature were included to address open items from the Type A meeting.
10 April 2026 CRL	FDA issued a Complete Response for BLA 125827 repeating the same 2 concerns (21 July 2026) and adding "Uncertainty of response assessments including surgical interventions with potential for confounding response results".
29 May 2026	• Aligned with FDA on a path forward for resubmission and reconsideration of the BLA for RP1 (vusolimogene oderparepvec) in combination with nivolumab for the treatment of advanced melanoma.

Date Interaction Type	Pertinent Comments/Agreements
02 June 2026 BLA Resubmission	• Replimune resubmitted BLA 125827 with 3-year survival update from the IGNYTE Anti-PD-1 Failed Melanoma cohort. • All CRL issues were addressed in a document based on FDA's letter.

Complete Response Concerns

With the July 21, 2025 Complete Response, FDA identified 2 areas of concern with one additional area identified with the April 10, 2026 Complete Response. None of these issues were raised as outstanding issues at either the mid-cycle (March 27, 2025) or late-cycle (May 15, 2025) review meetings.

1. Heterogeneity of the RPL-001-16 trial patient population and in the referenced literature.

   Replimune's position: The IGNYTE Phase 2 Anti-PD-1 Failed Melanoma cohort enrolled a real-world advanced melanoma population with confirmed progression while on their prior therapy, and clear unmet need. The consistent level of response across clinically important subgroups mitigates any concern relating to the heterogeneity of the study population. Prior to study enrollment, the inclusion/exclusion criteria were discussed with FDA (resistance types, disease stage, prior therapies) and FDA recommended to "not limit the patient population too much such that a real world patient population was represented". Further, eligibility criteria for this cohort were designed to ensure that patients had received adequate exposure to their prior anti-PD-1 therapy, followed by confirmed progression while still on treatment, to ensure that responses observed during the IGNYTE trial were not due to late response to their prior therapy.

   Additionally, in an August 1, 2025 open letter to the FDA, the Clinical Trial Investigators of RPL-001-16 (IGNYTE) and members of the Steering Committee for IGNYTE-3 wrote that, "The current NCCN melanoma guidelines (version 2.2025) show multiple treatment pathways in both the adjuvant and advanced disease setting funneling to the point of IGNYTE eligibility in the case of refractory disease. This means that this real-world patient population will be, by necessity, heterogeneous. Importantly, these patients converge into the common biologic entity known as 'PD-1 refractory disease' in which there is global consensus amongst treating immunotherapists that follow-on treatment responses are unlikely and prognosis is poor. Sub-segmenting these patients to artificially obtain statistical homogeneity serves no practical purpose and denies treatment opportunity to those in great need."

2. Isolation of the contribution of vusolimogene oderparepvec to the observed ORR.

   Replimune's position: BLA 125827 included a comprehensive review of response rates of available therapies in patient populations similar to the IGNYTE Anti-PD-1 Failed Melanoma cohort, demonstrating that retreatment with an anti-PD-1 monotherapy following confirmed progression while being treated with any prior anti-PD-1 containing regimen would not be expected to result in any clinically meaningful response rate. The literature most relevant to patients who continue anti-PD-1 monotherapy after progression on prior anti-PD-1 therapy includes the analysis

by Beaver et al. (2018), as further evaluated by Ribas et al. (2018). These analyses suggested that an ORR of no more than 7% would be expected in this setting. This finding is consistent with Hodi et al. (2016), in which delayed responses following initial disease progression were observed in approximately 6% of patients.

Nearly half (46.4%) of the patients treated in the primary efficacy cohort of the IGNYTE trial had confirmed disease progression while being treated with anti-PD-1 in combination with anti-CTLA or anti-LAG3 combination therapy. For such very-difficult-to-treat melanoma patients, no credible clinical evidence in the literature supports that anti-PD-1 single agent could achieve any clinically meaningful ORR indicating that RP1 makes a significant contribution to the responses observed.

The ORR of over 30% shown in the primary efficacy cohort is unlikely due to nivolumab alone considering that clinical trials leading to the approval of anti-PD-1 singe agent (nivolumab or pembrolizumab) consistently reported ORR of 32%-34% in anti-PD-1 treatment naïve melanoma patients.

3. Uncertainty of response assessments including surgical interventions.

Replimune's position: Biopsies for exploratory biomarker analyses were required at baseline and at Study Day 43 (during treatment cycle 4). Additional optional biopsies or the lesion excised if the Investigator believed a patient had become tumor free or to provide histological confirmation of response. These are common clinical practices and a patient-by-patient review shows **that in no instances did a biopsy or excision of a lesion remnant result in an improved BOR**.

Replimune prospectively planned for and conducted an assessment to show the systemic treatment effect on noninjected tumors. Measurements were completed by the independent review vendor using the same rigor as for the primary analysis. This analysis was submitted to FDA during the BLA review. Over half (57.7%) of the injected lesions and 41.3% of noninjected lesions completely resolved (100% reduction). A similar proportion of injected lesions (35.9%) and noninjected lesions (38.8%) had a maximum reduction of ≥30% to <100%. Considering that most patients received their RP1 injections during the first 16 weeks of study participation, the observed 24.8 (14.1, NR) months duration of response should address any remaining concerns for the uncertainty of response assessments. Additionally, Replimune notes that ILLUMINATE-301, the study that evaluated tilsotolimod administered intratumorally in combination with ipilimumab compared to ipilimumab alone, showed no difference between arms (ORRs were 8.8% in the tilsotolimod arm and 8.6% in the ipilimumab arm), further supporting that injection of a tumor does not impact the response rate (Diab 2025).

3. DESCRIPTION OF CLINICAL SETTING

3.1. Serious Nature of Advanced Melanoma

Advanced melanoma is a serious and life-threatening disease characterized by the spread of cancer beyond the primary site to regional or distant tissues and organs. The American Cancer Society estimates that 112,000 new melanomas will be diagnosed, and 8510 people will die from the disease in the US during 2026 (American Cancer Society 2026). Melanoma of the skin represents 5.3% of all new cancer cases in the United States (US) and is most frequently diagnosed in people 65 to 74 years of age (SEER 2026).

Despite advances in treatment with immune checkpoint inhibitor (ICI) therapies over the last decade, 50% of advanced melanoma patients progress within the first 12 months (Larkin 2019, Robert 2015). Patients with advanced melanoma remain at substantial risk of disease progression and death, with a reported 5-year relative survival rate of approximately 35% for distant metastatic disease (American Cancer Society 2026). A substantial proportion of patients continue to face progression despite currently available therapies.

3.2. Treatment Landscape

Since the approval of the immune checkpoint inhibitors (ICIs), nivolumab and pembrolizumab in 2014 and 2015, respectively, for treatment-naïve patients with advanced melanoma, ICI-based regimens have become a standard of care for treatment of advanced melanoma (Knight 2023). Treatment options have expanded to include nivolumab plus ipilimumab in the neoadjuvant setting (eg, prior to surgery to reduce the size or extent of a tumor), which demonstrated an 18-month event-free survival rate of 80.8% in Stage III melanoma (Blank et al 2024) and is recommended in the NCCN Guidelines (version 2.2026). Additional approved therapies include talimogene laherparepvec (T-VEC; 2015) for recurrent melanoma after surgery and nivolumab plus relatlimab (2022) for unresectable or metastatic melanoma. Historically, first line therapy for patients with BRAFV600-mutated melanoma also included BRAF/MEK inhibitor combinations. However, the reduced level of response observed when checkpoint inhibitor-based ipilimumab/nivolumab treatment follows BRAFi/MEKi therapy in the DREAMseq study (Atkins 2023) prompted a change in NCCN guidelines to note the superiority of first-line immunotherapy regardless of BRAF mutation status.

There are currently no FDA-approved therapies for patients with unresectable advanced melanoma whose disease has progressed after receiving anti-PD-1 based therapy, except for lifileucel. Lifileucel, a tumor-derived autologous T cell immunotherapy, was granted accelerated approval in 2024 for adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody and if BRAF V600 mutation positive, a BRAF inhibitor with or without an MEK inhibitor based on a 31.5% ORR with a 4.1% complete response rate from a single arm trial with patients treated in the primary efficacy cohort (AMTAGVI USPI). Lifileucel treatment is a multi-component regimen (preconditioning chemotherapy with cyclophosphamide and fludarabine followed by infusions of lifileucel and up to 6 doses of high dose IL-2) that is associated with 7.5% treatment related mortality.

These limitations underscore the need for additional safe and treatment options for patients with anti-PD-1–refractory advanced melanoma.

3.3. Unmet Medical Need in Advanced Melanoma

Despite significant advances in the treatment of melanoma with PD-1 inhibitors, a substantial unmet need remains for patients who experience disease progression on or after ICI treatment. While immunotherapies have transformed the landscape of care, a large proportion of patients either do not respond to initial treatment (primary resistance) or respond initially but later relapse (acquired or secondary resistance). Patients with melanoma whose disease progresses following frontline anti-PD-1–based therapy face a significant treatment challenge, as available subsequent therapies generally produce low response rates, limited durability of benefit, increased treatment-related toxicity, and, in some cases, substantial logistical complexities, highlighting a persistent unmet medical need in this setting.

For patients who progressed after anti-PD-1 monotherapy, the next step is likely to be a combination treatment. Following progression on anti-PD-1 based combination therapies, treatments options are very limited and are generally associated with poor outcomes. Patients typically receive the regimen they haven't previously received as 1L therapy.

However, many patients in the US now receive either ipilimumab combined with nivolumab or relatlimab (anti-LAG3) plus nivolumab (Opdualag) as first line (1L) therapy. Furthermore, since the publication of the NADINA study, which evaluated neoadjuvant ipilimumab plus nivolumab in patients with resectable stage III melanoma (Blank 2024), use of both ipilimumab plus nivolumab and relatlimab plus nivolumab has increasingly expanded into the neoadjuvant setting (NCCN 2026). As a result, treatments options after progression on anti-PD-1 based combination regimens have become increasingly limited and provide generally poor outcomes, highlighting a significant unmet need in this population.

In the clinic, patients that progress typically receive a regimen they haven't received previously. As such, in the adjuvant setting, most patients who progressed on or after anti-PD-1 monotherapy would receive anti-PD-1 combination therapy (eg, anti-CLTA4/anti-PD-1 antibody or nivolumab/relatlimab); in the advanced setting a patient progressing on an anti-PD-1 monotherapy will receive similar treatment; however, as the majority of patients currently received anti-PD-1 combination therapy (either with anti-CLTA4/ anti-PD-1 antibody or nivolumab/relatlimab) in front line, upon progression the patient would receive the alternative regimen they haven't experienced previously.

For instance, after progression on ipilimumab + nivolumab patients will often receive relatlimab + nivolumab and would expect to see a 9% to 12% ORR based on the RELATIVITY 020 study (Ascierto 2023). After progression on relatlimab + nivolumab, patients could receive ipilimumab + nivolumab, where an 11% ORR might be expected (Menzies 2022).

As described above (Section 3.2), tumor-infiltrating lymphocyte (TIL) therapy (lifileucel) combined with IL2 is the only US Food and Drug Administration (FDA)–approved therapy for melanoma in patients previously treated with anti–PD-1 therapy (Amtagvi USPI 2024).

As a result, many patients are left with limited options, which can include retreating with a prior therapy or using BRAF and MEK inhibitors for patients with a BRAF V600 mutation. However,

the effect of these options is generally reduced in the second-line setting, and many patients will receive very limited benefit.

Overall, the evolution in the use of checkpoint inhibitors, alone or in combination as standard of care in the advanced disease setting as well as in the neoadjuvant/adjuvant setting makes the need for new therapies even more critical for patients who progress on anti-PD-1 therapies. Currently, treatment options are very limited for these patients, and/or come with high toxicity.

Previously, FDA has acknowledged that patients treated in the primary efficacy cohort (ie, the Anti-PD-1 Failed Cutaneous Melanoma cohort) of the IGNYTE Phase 2 study represent a patient population with high unmet medical need.

3.4. Scientific Rationale for RP1 in Combination with Nivolumab

Replimune hypothesized that the combination of RP1 and nivolumab could provide systemic antitumor efficacy in both injected and noninjected tumors leading to immunological memory and a durable clinical benefit. The therapeutic strategy for RP1 is to induce direct "oncolytic" destruction of tumors that is enhanced compared to previous oncolytic agents, combined with induction of a systemic anti-tumor immune response to provide overall and long-term clinical benefit. RP1 has a dual mechanism of action. Once injected into a tumor, RP1 replicates in and directly kills tumor cells, resulting in the release of tumor and viral antigens which indirectly leads to T cells being activated to systemically destroy cancer deposits through-out the body.

This mechanism is enhanced by the two transgenes encoded with RP1. GALV-GP R- is a fusogenic membrane glycoprotein, which markedly enhances immunogenic cell death, while GM-CSF amplifies the immune response to newly released antigens (Section 2.1.3).

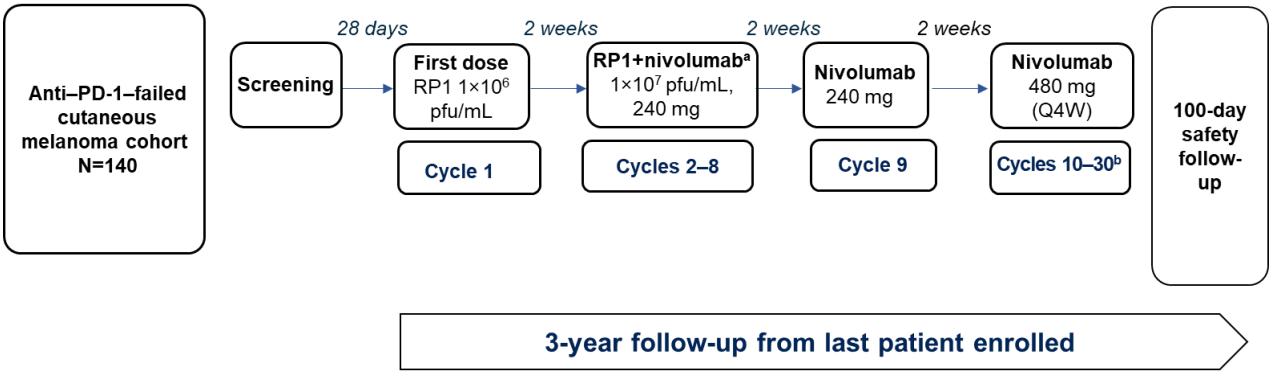
As described above (Section 3.2 and Section 3.3), while immune checkpoint inhibitors (ICIs) have revolutionized the treatment landscape for a wide range of tumor types leading to durable therapeutic benefit compared with conventional cancer therapies (Robert 2020), a significant number of patients do not respond, and many initial responders eventually develop resistance and progress (Schadendorf 2015, Sharma 2017). Tumors either inherently exhibit or can develop several resistance mechanisms such as lack of tumor-infiltrating lymphocytes, lack of programmed death ligand 1 (PD-L1) expression, loss of T cell function, or disruption of antigen presentation (Nowicki 2018) that can help evade the immune response. PD-L1 expression on cancer and other cells inhibits activated T cells (Garcia-Diaz 2017). PD-1 inhibitors, such as nivolumab, can bind to PD-1 on exhausted T cells leading to their reactivation (Brahmer 2015).

In the anti-PD-1 resistant setting, the mechanism of action of RP1 complements that of anti-PD-1 therapy by increasing the number of tumor reactive T cells leading to an immune inflamed tumor microenvironment (TME) and increased PD-L1 expression (refer to Section 2.1.3). Anti-PD-1 therapy reactivates both new and pre-existing T cells as they become exhausted by blocking the interaction of PD-1 and PD-L1, complementing the activity of RP1.

4. SUMMARY OF CLINICAL TRIAL SUPPORTING EFFICACY IGNYTE STUDY DESIGN AND METHODS

The primary evidence of efficacy and safety of RP1 in combination with nivolumab in BLA 125827 was based on a specific registration-directed cohort of patients with melanoma who had progressed while still on anti-PD-1 therapy (Anti-PD-1 Failed Cutaneous Melanoma cohort, N=140) in the Phase 2 part of the study. This cohort included adults with unresectable advanced cutaneous melanoma who had confirmed disease progression while on their prior anti-PD-1 regimen (see Section 4.1.1 and Section 4.2.2 for addition description of the patient population).

Figure 3: Phase 2 Study Flow for Anti-PD-1 Failed Cutaneous Melanoma Cohort (RPL-001-16, IGNYTE)



***Tumor response assessment**: Radiographic imaging (CT) at baseline and every 8 weeks from first dose and every 12 weeks after confirmation of response*

Following patient screening, all patients received a first dose of RP1 at a concentration of 10^6 plaque-forming units (PFU) per mL at Week 1 for seroconversion, followed by 10^7 PFU per mL Q2W for subsequent weeks, up to 8 total cycles. RP1 was injected directly into the largest and most rapidly growing tumors suitable for injection. The volume injected is based on the size of the injected tumors, up to a total of 10 mL for each treatment cycle.

Nivolumab was administered at the standard dose of 240 mg Q2W for Cycles 2 to 9 (~4 months) followed by 480 mg Q4W for Cycles 10 to 30 (~20 months) or 240 mg Q2W at the discretion of the Investigator until confirmed progression or intolerable toxicity occurred or for a total of 29 cycles (~2 years). At the Investigator's discretion, treatment with nivolumab may have continued at 240 mg Q2W.

Patients also had the opportunity to receive additional doses of RP1 if they met the protocol specified criteria. Dosing with RP1 continued until disease progression, as long as injectable lesions remained. If no injectable lesions remained, treatment with nivolumab may have continued for up to a total of 29 cycles of nivolumab (~2 years). Treatment beyond disease progression may have continued if the Investigator believed the patient was still benefiting.

RP1 was administered by intratumoral injection using 2 administration methods.

- **Superficial**: Direct injection to administer RP1 to any visible or palpable cutaneous, subcutaneous (SC), nodal (eg, inguinal, sub/supraclavicular, cervical lymph nodes) or mucosal lesion (eg, oral, anal, and cervical mucosa).

- **Deep/Visceral**: Image-guided injection to administer RP1 to deep lesions including deep lymph nodes (eg, retroperitoneal, pelvic, thoracic) and visceral lesions (eg, lung lesions, liver lesions, mesentery lesions).

For all patients, multiple tumors may have been injected until all injectable tumors had been injected or 10 mL of RP1 had been used. Where multiple tumors could be injected, the largest, then next largest injectable tumor, etc., present on each injection day were recommended to be injected until either no more RP1 remained, or no more injectable tumors remained. Different tumors could be injected on different injection days. New tumors were eligible for injection. There was no minimum size for injectable lesions. Detailed guidance for IT injection of RP1 was provided to the sites.

Completion of nivolumab treatment was defined as patients who completed all 29 cycles of nivolumab (although total of 30 cycles in study, first cycle in study was RP1 only).

After completion of study treatment, patients were followed every 3 months for a total of up to 3 years after the last patient was enrolled in the IGNYTE study.

4.1.1. Patient Population

Patients enrolled in the Anti-PD-1 Failed Cutaneous Melanoma cohort of the IGNYTE trial (primary efficacy cohort for registration) represent a real-world, unresectable Stage IIIb-IV cutaneous melanoma patient population with high unmet medical need.

Key eligibility criteria for this cohort were designed to ensure that patients had received adequate exposure to their prior anti-PD-1 therapy to allow for the possibility of response, followed by confirmed progression to ensure that responses observed during the IGNYTE trial were not due to late response in their prior therapy.

These include:

- Treatment with prior anti-PD-1 therapy must have continued from the time of initial tumor progression until confirmation of PD to ensure that patients were unlikely to respond to further anti-PD-1 single agent therapy.
- Disease progression must have been confirmed and documented using clinical or radiological assessment by 2 assessments at least 4 weeks apart to rule out late response to prior therapy or pseudoprogression.
- Anti-PD-1 therapy must have been the last line of prior therapy, to prevent re-sensitization to PD-1 blockade by intervening therapies.

Patients treated with anti-PD-1 therapy in the adjuvant setting with documented disease progression while on adjuvant therapy were eligible for the study. In this case, a confirmatory biopsy showing recurrence of melanoma could have been used in place of a confirmatory scan.

These rigorous criteria provide a truly anti-PD-1 resistant study population and ensure that response observed on study treatment is the result of the addition of RP1 to nivolumab therapy.

In patients with confirmed disease progression, there is no clear consensus supported by strong clinical evidence as to when to discontinue the ongoing anti-PD-1 therapy and consider a new anti-cancer therapy. FDA has not endorsed commonly used guidelines for determining whether a patient's disease is refractory or resistant to anti-PD-1 therapy. However, when the anti-PD-1

failed cutaneous melanoma cohort was added to the IGNYTE trial, the protocol's definition of "anti-PD-1 failed melanoma" and requirement for minimal anti-PD-1 treatment duration appeared to be consistent with the general clinical practice and the definitions of anti-PD(L)-1 resistance or refractory cancer at the time (Kluger et al 2020). FDA agreed to the requirement for the minimum treatment duration (8 weeks) for prior anti-PD-1. However, nearly all patients in the IGNTYE efficacy cohort (135/140; 96.4%) actually received ≥12 weeks of prior anti-PD-1 therapy.

4.1.2. Efficacy Endpoints

For the Anti-PD-1 Failed Melanoma Cohort, the primary efficacy analysis was based on objective response assessments performed by Independent Review according to RECIST 1.1, consistent with feedback from FDA at the 12 September 2023 Type C meeting. Investigator assessments using a modified RECIST v1.1 (mRECIST) methodology were also conducted prospectively during the study.

Time point responses for each patient at each response assessment timepoint were determined by Independent Review for the purpose of assessing the primary and secondary endpoints for the Anti-PD-1 Failed Cutaneous Melanoma cohort by RECIST v1.1.

Tumor imaging was performed every 8 weeks from the date of the first dose of RP1. Once a response was confirmed, tumor imaging could be performed every 12 weeks. Imaging continued to be performed until confirmed disease progression was identified by the Investigator (unless the Investigator elected to continue treatment), the start of new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurred first. Objective response and PD were confirmed by a repeat imaging assessment. Tumor imaging to confirm CR or PR was performed ≥4 weeks after the first assessment of a response; similarly, tumor imaging to confirm disease progression was performed ≥4 weeks after disease progression was initially observed.

Additionally, a comprehensive lesion-level analysis was conducted to evaluate the systemic effect of RP1 in combination with nivolumab (Section 4.4.1). Unlike most melanoma clinical trials, which typically assess only RECIST-defined target lesions, this analysis prospectively measured all lesions, up to 10 per patient, including target, non-target, and other evaluable lesions, regardless of injection status. All lesion measurements were performed by independent review using the same principles and processes applied for efficacy assessments by RECIST 1.1, with independent reviewers blinded to tumor injection status. This rigorous and unbiased methodology enabled a more detailed evaluation of local and systemic antitumor activity across a broad range of lesions than has been reported, as far as Replimune is aware, in any comparable study.

4.1.2.1. Primary Endpoint:

The primary endpoint for regulatory purposes was overall response rate (ORR).

- ORR was defined as the proportion of confirmed responders with best overall response (BOR) of complete response (CR) or partial response (PR) per RECIST v1.1 as assessed by Independent Review.

4.1.2.2. Secondary Endpoints:

This summary focuses on assessment of these secondary endpoints as assessed by Independent Review per RECIST v1.1.

- Duration of response (DOR) was defined as the time from when response (CR or PR, whichever was recorded first) was first documented (in patients who achieved a confirmed response) to first documentation of disease progression where PD was subsequently confirmed or death, whichever occurred first. The date of PD was determined by Independent Review.
- Complete response rate (CRR) was defined as the proportion of confirmed responders with a BOR of CR.
- Disease control rate (DCR) was defined as the proportion of patients achieving confirmed response (CR or PR), or stable disease (SD) of ≥6 months.
- Progression-free survival (PFS) was defined as the time from first dose to the earlier date of assessment of PD where PD was subsequently confirmed per RECIST v1.1 or there was death by any cause.
- Overall survival (OS) was defined as the interval between the date of first dose and the date of death from any cause

4.1.2.3. Exploratory Endpoints

Time-to-response (TTR) was not defined in the protocol as a secondary endpoint, but was calculated for confirmed responders (CR or PR).

- TTR was defined as the time from first dose to the first documented evidence of CR or PR.

4.1.2.4. Rationale for Selection of Endpoints

Under accelerated approval for a serious or life-threatening disease or condition, FDA can assess efficacy based on an effect on a surrogate endpoint or intermediate clinical endpoint reasonably likely to predict clinical benefit and require one or more postmarketing studies to verify clinical benefit (21 USC 356(c)). When discussing the IGNYTE Anti-PD-1 Failed Melanoma cohort, FDA agreed that depending on a benefit/risk assessment of the study results, ORR together with response durability data (DOR) assessed by a blinded independent review committee could potentially support a claim of efficacy of IGNYTE in combination with nivolumab.

ORR per RECIST 1.1 as assessed by independent review, is the regulatory standard for assessing response in solid tumors and with durable ORR, is considered an acceptable intermediate endpoint that is reasonably likely to predict clinical benefit. Durable ORR has been used as a basis for accelerated approvals in oncology for decades, including the accelerated approval of lifileucel in advanced melanoma in 2024 and traditional approval of Imlygic in 2015 for local treatment of unresectable lesions in patients with recurrent melanoma after initial surgery.

The Phase 3 randomized study (IGNYTE-3) is currently ongoing. The primary endpoint is designed to verify the OS benefit of RP1 + nivolumab compared with Physician's Choice (PC)

of treatment, in patients who had confirmed disease progression on anti-PD-1 and anti-CTLA therapy.

4.1.3. Statistical Methodology

The Anti-PD-1 Failed Cutaneous Melanoma cohort was analyzed separately for efficacy and included all eligible patients who received at least 1 dose of study treatment (RP1 or nivolumab) as specified in the study protocol and Statistical Analysis Plan (SAP).

At the time the IGNYTE study was designed, there were no available therapies for anti-PD-1 failed melanoma. Based on the literature, retreatment response was limited to 6%-7% (Beaver, Ribas, Hodi), therefore an effect >15% would be clinically meaningful. The study intended to enroll approximately 125 treated adult patients. The sample size was determined based on 2 considerations: the ability to produce a CI that would exclude an ORR of 15%, which is not considered clinically relevant, and provide sufficient information for a reliable understanding of the safety profile. Assuming the true ORR is 30%, the study has >97% power to reject the null hypothesis that the true ORR is <15%, considering a two-sided 5% alpha.

All efficacy analyses were based on the Full Analysis Set (FAS), which included all patients who received at least 1 dose of study treatment (RP1 or nivolumab).

Safety was assessed for all patients treated in IGNYTE Phase 2 (Phase 2 All Cohorts) based on the Safety Analysis Set, which included all patients who received at least 1 dose of study treatment (RP1 or nivolumab).

The primary efficacy endpoint of ORR was estimated with its corresponding 2-sided 95% confidence interval (CI) based on the Clopper-Pearson exact method. Patients who did not meet the criteria for confirmed CR or PR were considered nonresponders. Patients who did not have any postbaseline tumor assessments were considered non-evaluable (NE). Tumor assessments after the initiation of further anticancer therapy were excluded for the assessment of BOR.

DOR was estimated by using the Kaplan-Meier method for confirmed responders. Point estimates (minimum, 25th, 50th [median], and 75th percentiles, and maximum) were provided, along with a 2-sided 95% CI. Patients who had not progressed or died at the time of analysis were censored. Censoring rules for DOR were implemented following FDA guidance (FDA Guidance: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics). DOR was also calculated based on actual observed response time.

CRR and DCR were estimated by using the same method described above for ORR.

For the other time-to-event endpoints (eg, PFS, OS), the Kaplan-Meier method was used. For PFS, patients who did not have a PFS event (ie, had not progressed or died) were censored based on FDA guidance. For OS, patients who were alive as of their last known status were censored at their date of last contact.

4.2. IGNYTE Efficacy Results

4.2.1. Patient Disposition

Enrollment in the Anti-PD-1 Failed Melanoma cohort was complete prior to the initial data cutoff (DCO) date for the original BLA of 08 March 2024. There were 140 patients in this

cohort. In the original BLA submission, all patients had completed their initial course of RP1 treatment (up to 8 doses) and 2 patients continued RP1 treatment in additional course(s).

As of the 90-day efficacy and safety updates (DCO: 15 October 2024), no new patients were treated in Anti-PD-1 Failed Cutaneous Melanoma cohort and 3 patients received additional RP1 doses. As of the 15 October 2024 data cut, 6 patients were ongoing treatment with nivolumab and 46 patients were ongoing in the study. The most common reasons for discontinuation of treatment with RP1 or nivolumab were physician decision and progressive disease.

4.2.2. Patient Characteristics

The Phase 2 portion of the IGNYTE study was a global study. More than half of patients in the Anti-PD-1 Failed Melanoma cohort were treated at sites in the US (75 patients), with the remainder treated at sites in the EU (28 patients in France, 10 patients in Spain, 4 patients in Germany), and UK (23 patients).

In general, a highly PD-1 resistant population was enrolled in the IGNYTE study. A majority of these patients were PD-L1 negative at baseline with <1% of tumor expressing PD-L1 (Table 3). Most of the patients were considered primary resistant (71.4%, 100 of 140 patients; all 36 in the adjuvant setting and 64 in the advanced/metastatic patient), meaning that these patients had achieved a best response of PD or SD while on PD-1 blockade therapy and progressing in <6 months. These patients did not respond to their immediate prior PD-1 therapy. In the 36 patients who progressed while on anti-PD-1 therapy given with adjuvant intent, the tumor recurred while on anti-PD-1 therapy rather than after adjuvant therapy was completed, as required by the IGNYTE protocol. Only 12 of 104 patients who were treated in the advanced (unresectable/metastatic) setting had a response to their immediate prior therapy; ORR of 11.5% (95% CI: 6.1-19.3).

4.2.2.1. Demographics

Melanoma predominantly occurs in the White population. Having lighter skin color is a major risk factor for melanoma and the risk of melanoma increases with age. Most patients in the Anti-PD-1 Failed Melanoma cohort were White (73.6%). The average age at diagnosis is 66 years (American Cancer Society 2026) and the median age in the IGNYTE Phase 2 Anti-PD-1 Failed Melanoma cohort was 62 years (range: 21-91 years). The incidence of melanoma is higher in males than females (based on SEER 2026) and in the IGNYTE Phase 2 Anti-PD-1 Failed Melanoma cohort there was a higher proportion of males (67.9%) than females (32.1%).

Patients enrolled in this cohort were generally representative of the US melanoma patient population and allow for informed assessment of the efficacy and safety of RP1 in combination with nivolumab.

Table 2: Demographic and Baseline Characteristics (Full Analysis Set)

Characteristic	Number (%) of Patients Anti-PD-1 Failed Cutaneous Melanoma (N=140)
Age (years)	
Median (min, max)	62.0 (21.0, 91.0)
Mean (StD)	61.1 (13.95)
Age group (years), n (%)	
18 to 64	83 (59.3)
65 to 74	37 (26.4)
≥75	20 (14.3)
Sex, n (%)	
Male	95 (67.9)
Female	45 (32.1)
Race, n (%)	
White	103 (73.6)
Not reported	35 (25.0)
Black or African American	1 (0.7)
Asian	1 (0.7)
Ethnicity, n (%)	
Hispanic or Latino	8 (5.7)
Not Hispanic or Latino	97 (69.3)
Not reported	31 (22.1)
Unknown	4 (2.9)
Region, n (%)	
US	75 (53.6)
non-US	65 (46.4)
ECOG Performance Status, n (%)	
0	96 (68.6)
1	43 (30.7)
2[a]	1 (0.7)

Source: IGNYTE Phase 2 CSR, Table 14.1.3. Data cutoff date: 15 October 2024

[a] Patient (b) (6) had an ECOG status of 0 during the Screening period, which changed to 2 on Cycle 1 Day 1 (C1D1); based on the SAP, the last valid ECOG score prior to or on C1D1 was considered as Baseline.

4.2.2.2. Baseline Disease Characteristics

The baseline disease characteristics for the Anti-PD-1 Failed Cutaneous Melanoma cohort were consistent with those of patients with advanced disease treated with multiple prior therapies including at least 1 anti-PD-1-containing therapy.

In this cohort, approximately half of patients (48.6%) had visceral disease (Stage IVB to IVD). A total of 18.6% of patients had disease Stage IVB, 25.7% had disease Stage IVC, and 4.3% had disease Stage IVD. At Baseline, the proportion of patients with lung, liver, and brain lesions present was 32.9%, 20.7%, and 3.6%, respectively. Approximately one-third of patients (33.6%) had an LDH level >ULN, and 37.9% had BRAF mutant tumors. Additionally, more than half of patients (55.7%) had negative (<1%) PD-L1 tumor expression. Most patients (97/140; 69.3%) had seropositive HSV-1 status at Baseline.

Table 3: Baseline Disease Characteristics in the Anti-PD-1 Failed Cutaneous Melanoma Cohort (Full Analysis Set)

Characteristic	Anti-PD-1 Failed Cutaneous Melanoma (N=140)
Baseline LDH level, n (%)	
≤ULN	92 (65.7)
>ULN[a]	47 (33.6)
Unknown	1 (0.7)
BRAF status, n (%)	
Mutant	53 (37.9)
Wild type	87 (62.1)
Stage	
IIIB/IIIC/IVM1a	72 (51.4)
IVM1b/c/d	68 (48.6)
Baseline PD-L1 tumor expression, n (%)	
Positive (≥1%)	45 (32.1)
Negative (<1%)	78 (55.7)
Undetermined/missing	17 (12.1)
Time from initial diagnosis, years[b]	
Median (min, max)	2.3 (0.3, 37.1)
Mean (StD)	4.2 (5.77)
HSV-1 status at Baseline, n (%)	
Positive	97 (69.3)
Negative	40 (28.6)
Unknown	3 (2.1)

Source: Phase 2 IGNYTE CSR, Table 14.1.4.1. Data cutoff date: 15 October 2024
[a] >ULN includes 9 anti-PD-1 failed cutaneous melanoma patients with LDH level ≥2×ULN (Listing 16.3.2).
[b] Time from initial diagnosis was relative to the first dose date.

The IGNYTE study enrolled a difficult to treat, real-world population, utilizing robust anti-PD-1 progression criteria to ensure definitive anti-PD-1 failure in the immediate prior therapy

4.2.2.3. Prior Anticancer Therapy

The IGNYTE Phase 2 inclusion/exclusion criteria used were intended to exclude patients who had inadequate exposure to anti-PD-1 therapy, who progressed after completion of anti-PD-1 treatment, or who had pseudoprogression, by implementing a rigorous adaptation of the Society for Immunotherapy of Cancer (SITC) guidelines (Kluger 2020) for prior anti-PD-1 exposure and confirmed progression as inclusion criteria. Thus, all patients had prior treatment with anti-PD-1 therapy as their last line of treatment prior to enrollment: 25.7% as adjuvant therapy only and 74.3% received in settings other than adjuvant therapy (described as not adjuvant).

The majority (71.4%) of patients were primary resistant (achieved a best response of PD or SD while on PD-1 blockade therapy and progressed in <6 months) to their immediate prior line of anti-PD-1 therapy at the start of RP1, including all 36 patients who received prior anti-PD-1 in the adjuvant setting. Nearly half of patients (43.6%) having prior treatment with anti-PD-1 combined with anti-CTLA-4 therapy. In this cohort, 46.4% of patients had 1 prior regimen of systemic advanced/metastatic anticancer therapy, and 18.6% of patients had 2 prior regimens of systemic advanced/metastatic anticancer therapy. This is reflective of the fact that patients were

required to have anti-PD-1 as the last prior line of therapy prior to entering the clinical trial, and that anti-PD-1 containing therapy is the standard of care in first-line and/or second-line therapy for patients with advanced melanoma.

The median duration of the immediate prior anti-PD-1 therapy was 4.6 months (range: 1.0-55.2). Nearly all of the patients **(96%; 135/140)** were exposed **the prior course of anti–PD-1 for ≥12 weeks** (duration of actual immediate prior anti-PD-1 therapy) indicating that these patients had an adequate exposure on the immediate prior anti-PD-1 therapy per the NCCN criteria and further exposure to anti-PD-1 therapy was unlikely to result in a delayed response due only to anti-PD-1 therapy. The median time from end of the immediate prior anti-PD-1 therapy to the first dose of RP1 on IGNYTE was 1.7 months (range: 0.3-19.9), indicating that patients required additional treatment immediately as a result of rapidly progressing disease.

Protocol requirements for prior anti-PD-1 therapies and the methods used to confirm disease progression before trial enrollment ensure minimize heterogeneity so that primary efficacy outcomes of the IGNYTE trial are not significantly impacted.

4.2.3. Overview of Efficacy Results

The primary evidence of efficacy to support the proposed indication was based on data from 140 patients with cutaneous melanoma who had confirmed progression while being treated with prior anti-PD-1 therapy (ie, Anti-PD-1 Failed Cutaneous Melanoma cohort) from the Phase 2 IGNYTE study (RPL-001-16).

The original analysis of this cohort was conducted with a data cutoff of 08 March 2024. Wong 2025 recently reported the primary analysis of the Anti-PD-1 Failed Melanoma cohort in the Journal of Clinical Oncology.

The results presented here are based primarily on updated efficacy data submitted with the 90-day efficacy update (DCO: 15 October 2024) with updated data based on the 3-year update (DCO: 08 March 2026).

As of the 15 October 2024 data cutoff, the actual median duration of study follow-up was 20.8 months (range: 0.5-54.9 months) for patients in the Anti-PD-1 Failed Cutaneous Melanoma cohort and the median duration of RP1 treatment was 3.7 months (range: 0.5-14.4 months). The duration of follow-up and treatment was aligned with FDA's recommendation and adequate to assess durability of responses in this cohort.

4.2.4. Primary Efficacy Evidence – ORR and DOR

Consistent with FDA feedback, efficacy was evaluated using RECIST v1.1 criteria. Using RECIST v1.1 to facilitate comparison with other melanoma studies, the confirmed objective response rate (ORR) was 33.6% (95% CI: 25.8, 42.0) at the October 15, 2024 data cutoff, with the lower bound of the confidence interval substantially exceeding the prespecified 15% threshold. The median time to response of 3.9 months.

Complete responses (CRs) were achieved in 16.4% of patients, a notable finding in the post–anti-PD-1 melanoma setting where complete eradication of detectable disease is uncommon. CR rate is an important indicator of response depth and is associated with the potential for prolonged disease control.

The median DOR was 24.8 months (95% CI: 14.1, not estimable), and 50.7% of responders maintained their response at 24 months, including one patient with an ongoing response exceeding 4 years (Table 4). Together, the ORR, CR rate, and durability of response demonstrate clinically meaningful and sustained antitumor activity in a patient population with limited treatment options. An updated analysis of DOR as of the 3-year update (08 March 2026) is provided in Section 4.3.

RP1 enhances ORR beyond what would be expected with nivolumab single agent treatment for patients with disease progression on an anti-PD-1 based therapy. The observed ORR of 33.6% (95% CI: 25.8%, 42.0%) and a median DOR of 24.8 months (95% CI:14.1, NE), as assessed by IRC according to RECIST v1.1, demonstrate substantial evidence of effectiveness of RP1 in combination with nivolumab, which is reasonably likely to predict the clinical benefit of the treatment to patients with unresectable advanced cutaneous melanoma that has progressed on an anti-PD-1 based therapy.

Table 4: Primary Efficacy Results per Independent Review (RECIST v1.1) from Anti-PD-1 Failed Unresectable Advanced Cutaneous Melanoma Cohort of IGNYTE (FAS)

Parameter	Anti-PD-1 Failed Cutaneous Melanoma (N=140)
Best Overall Response, n (%)[a]	
CR	23 (16.4)
PR	24 (17.1)
SD	30 (21.4)
PD	54 (38.6)
NE[b]	9 (6.4)
ORR (cofirmed CR+PR), n (%)[a]	**47 (33.6)**
95% CI	25.8, 42.0
K-M Duration of Response (confirmed responders [CR+PR]), months[c]	
N	47
Median (95% CI)	24.8 (14.1, NR)
Min, Max	3.1, 49.4+
K-M estimate DOR (confirmed responder [CR+PR]), % (95% CI)[c]	
6 months	86.9 (73.2, 93.9)
9 months	84.5 (70.1, 92.3)
12 months	71.8 (55.5, 83.0)
24 months	50.7 (33.4, 65.6)
36 months	36.2 (18.1, 54.7)
Actual Duration of Follow-Up, months	
Median (min–max)	14.8 (3.1-49.4)

Source: Efficacy Update: IGNYTE Phase 2 CSR Table 14.2.2.1.2 (ORR, BOR RECIST). Data cutoff date: 15 October 2024.

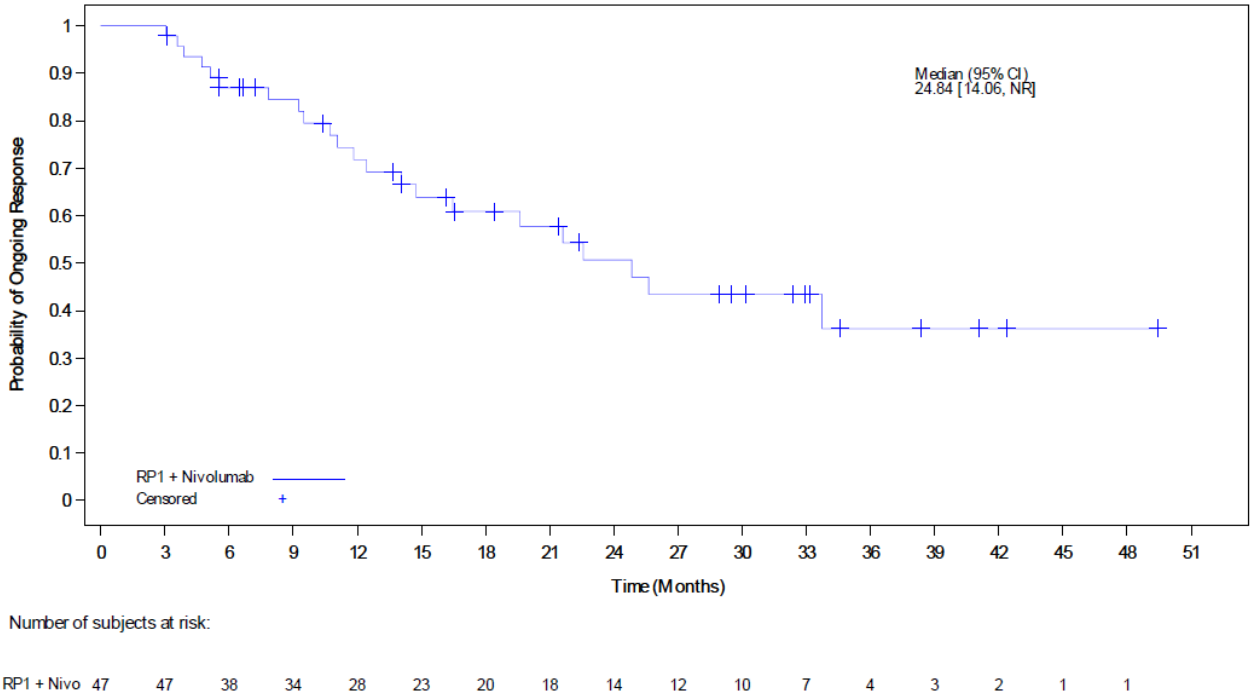
NE=not evaluable; NR=not reached/estimable

[a] Percentage was based on the number of patients in the Anti-PD-1 Failed Cutaneous Melanoma cohort (N=140). 95% CI for ORR was based on the Clopper-Pearson exact method.

[b] Includes patients who have response assessment categorized as NE, not done, or no response assessment after 4 weeks of first dose

[c] Summary statistics for DOR were calculated with Kaplan-Meier analysis and 95% CIs using the loglog method.

Figure 4: Kaplan-Meier Plot of DOR per RECIST as Assessed by Independent Review – Anti-PD-1 Failed Cutaneous Melanoma Cohort (N=140) (FAS) – IGNYTE Study



Source: Efficacy Update: IGNYTE Phase 2 CSR, Figure 14.2.4.1.2. Data cutoff date: 15 October 2024.
NR=not reached/estimable

4.2.4.1. Subgroup Analyses of ORR

RP1 combined with nivolumab provided clinically meaningful activity across each of the different settings after anti-PD-1 failure (Figure 5). The relative consistency of clinical activity observed across multiple relevant subgroups strengthens the overall evidence of treatment benefit.

Notably, responses were observed in patients with characteristics typically associated with poorer outcomes, including prior exposure to combined anti-PD-1/anti-CTLA-4 therapy, visceral metastatic disease (Stage IVb-IVd), and primary resistance to anti-PD-1 therapy. Across these higher-risk populations, objective response rates generally ranged from approximately 25% to 35%, supporting the robustness of treatment activity in a setting with limited therapeutic options.

Responses were observed regardless of age, sex, prior treatment history, or mechanism of anti-PD-1 resistance. ORR was similar in patients with primary and secondary anti-PD-1 resistance (34.0% and 32.5%, respectively), suggesting activity in populations that are often challenging to treat. Clinical activity was also maintained in patients previously treated with anti-PD-1 plus CTLA-4 therapy (ORR 26.2%), a population for whom effective treatment options are particularly limited.

The ORR in patients who received prior anti-PD-1 in the adjuvant setting was 44.4%. It is noteworthy that all 36 patients were primary resistant to anti-PD-1 therapy; therefore, the adjuvant patients in this study represent a more difficult to treat population (Eggermont 2021).

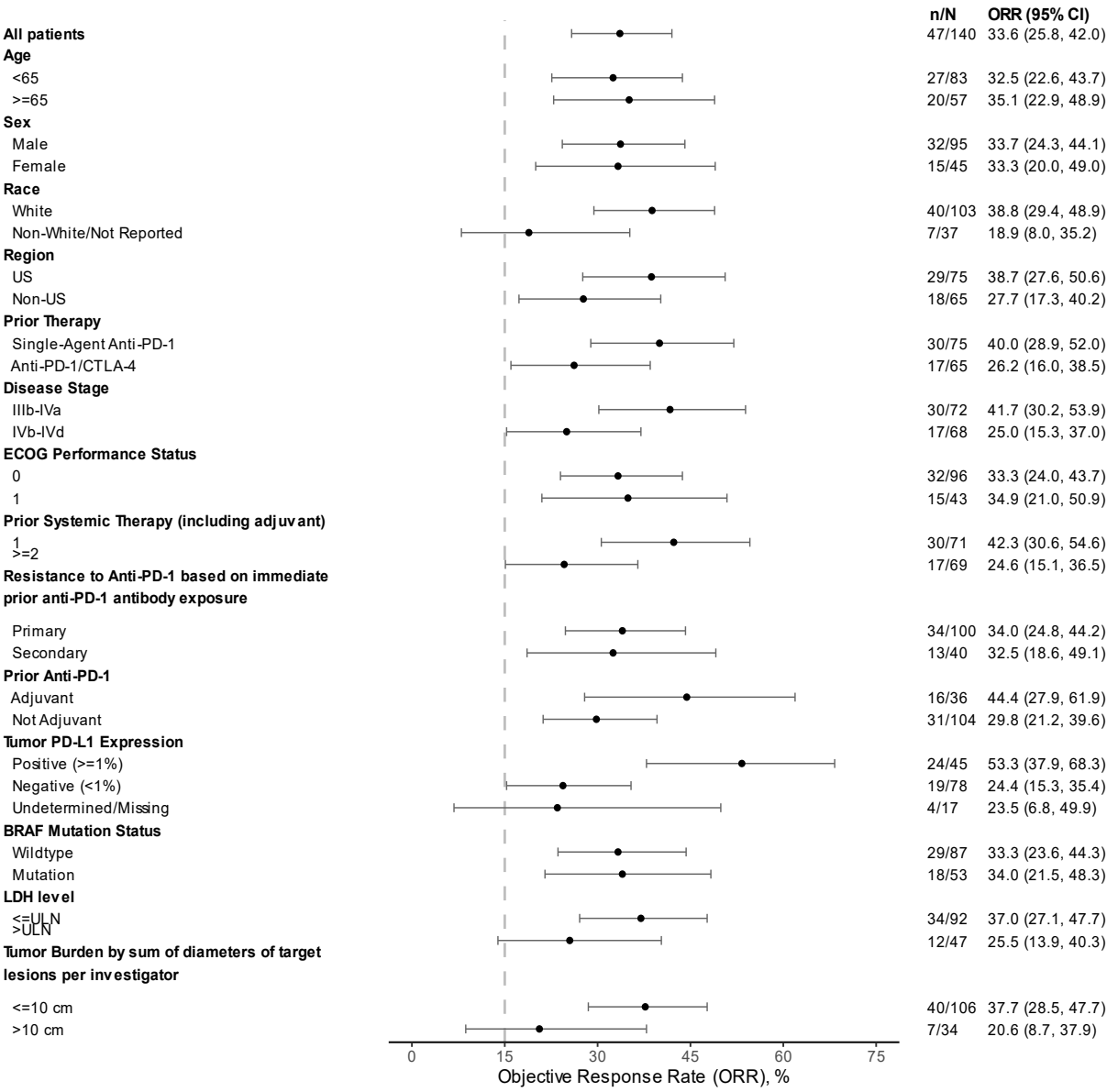
ORR was similar between the BRAF WT and mutant subgroups (33.3% and 34%) (Table 5). In this study, consistent with current clinical practice, the majority of patients with BRAF mutation did not receive prior BRAF therapy; therefore, no meaningful conclusions can be drawn for this subgroup.

Table 5: Summary of ORR by BRAF Mutation Status and Prior BRAF Therapy as Assessed by Independent Review per RECIST v1.1 (FAS)

	Patients With BRAF Wildtype (N=87)	Patients With BRAF Mutation (N=53)	Patients With BRAF Mutation	
			Prior BRAF Therapy (N=16)	No Prior BRAF Therapy (N=37)
ORR (confirmed CR+PR)				
n (%)	29 (33.3)	18 (34.0)	2 (12.5)	16 (43.2)
(95% CI)	(23.6, 44.3)	(21.5, 48.3)	(1.6, 38.3)	(27.1, 60.5)

Source: SCE Tables 14.2.5.3.2.2 and 14.2.5.3.4. Data cutoff date: 15 October 2024.
Note: 95% CI for ORR are based on the Clopper-Pearson exact method.

Figure 5: Forest Plot for Subgroup Analysis of Confirmed Objective Response Rate per Independent Review Based on RECIST 1.1 - Anti-PD-1 Failed Cutaneous Melanoma Cohort



Data cutoff date: 15 October 2024

4.2.5. Other Secondary and Supportive Efficacy Analyses

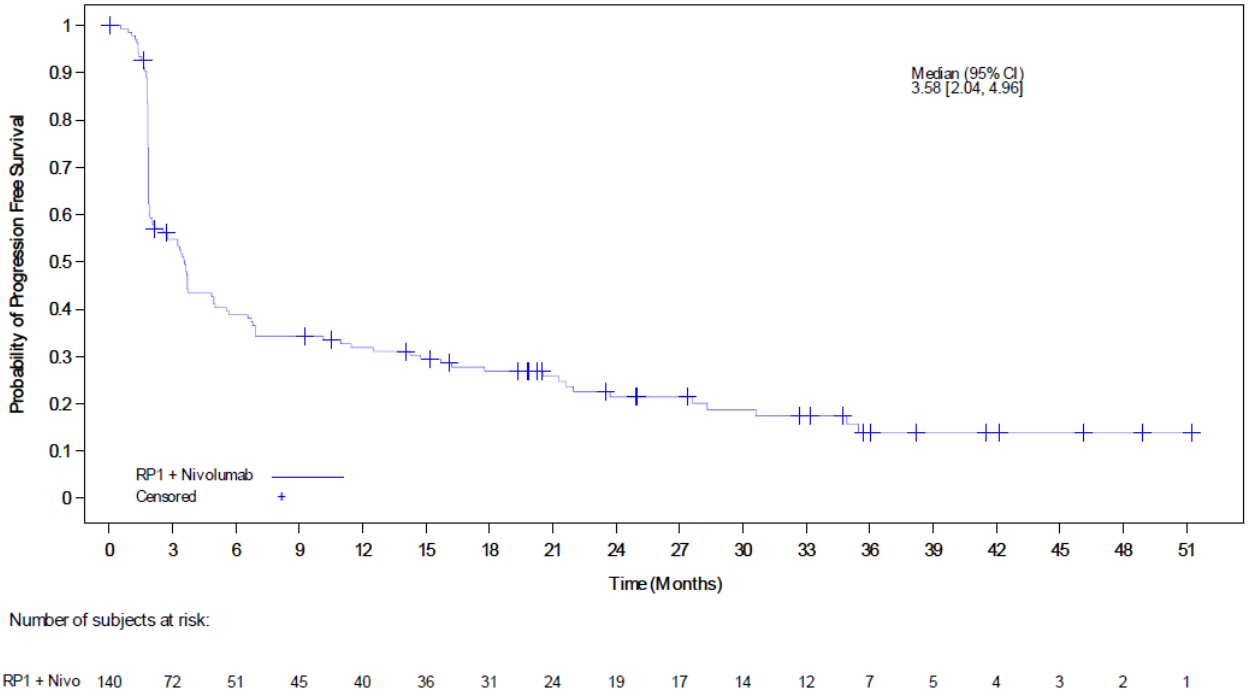
4.2.5.1. Complete Response and Disease Control Rate (15 October 2024)

In the Anti-PD-1 Failed Cutaneous Melanoma cohort (N=140), the CRR was 16.4% (95% CI: 10.7, 23.6) and the disease control rate (DCR; CR+PR+6 mo SD) was 35.7% (95% CI: 27.8, 44.3) as assessed by Independent Review per RECIST.

4.2.5.2. Progression-Free Survival (15 October 2024)

In the Anti-PD-1 Failed Cutaneous Melanoma cohort (N=140), median PFS was 3.6 months (95% CI: 2.0, 5.0) (Figure 6). At 12 months, 31.9% (95% CI: 24.1, 39.9) of patients were alive and progression free. At the time of analysis, 33 (23.6%) patients were censored; 18 (12.9%) were ongoing in the study.

Figure 6: Kaplan-Meier Plot of PFS (Full Analysis Set)



Source: Efficacy Update: IGNYTE Phase 2 CSR, Figure 14.2.6.1.2. Data cutoff date: 15 October 2024.

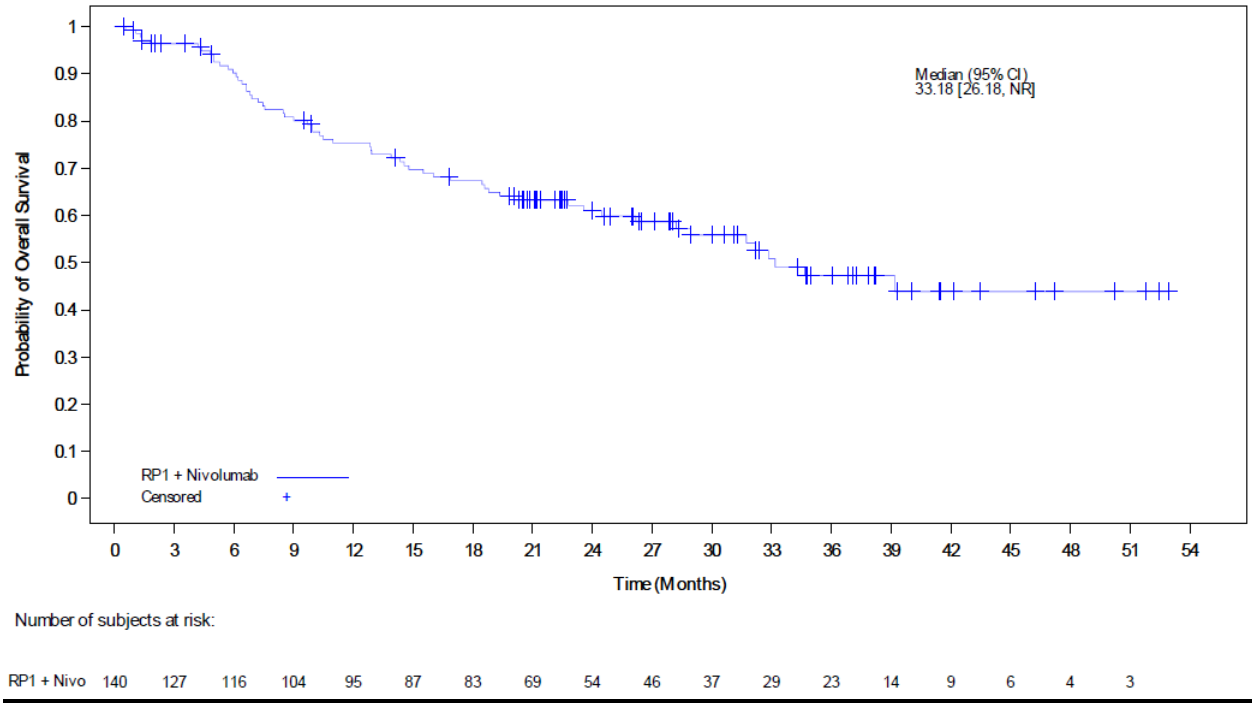
4.2.5.3. Overall Survival (15 October 2024)

As of the efficacy update (DCO: 15 October 2024), the median OS was 33.2 months and the lower bound of the 95% CI was 26.2 months (Figure 7). The 1-year, 2-year, and 3-year survival rates were 75.3%, 61.0%, and 47.2%, respectively.

While IGNYTE was a single-arm study, **the OS rates of 75.3% at 1 year, 61.0% at 2 years, and 47.2% at 3 years were supportive of the durable responses that were achieved having translated into survival benefit.**

An updated analysis of OS, as of the 3-year survival update is provided in Section 4.3, which further confirms that overall durability of response is associated with longer survival and suggest that treatment with RP1 in combination with nivolumab can lead to clinical benefit.

Figure 7: Kaplan-Meier Plot of Overall Survival (Full Analysis Set)



Source: Efficacy Update: IGNYE Phase 2 CSR, Figure 14.2.7.1. Data cutoff date: 15 October 2024.
NR=not reached/estimable

4.3. IGNYTE 3-Year Efficacy Update (08 March 2026)

The 3-year survival analysis was completed with an 08 March 2026 data cutoff, based on the last patient's first dose of RP1 in the IGNTYE Phase 2 Anti-PD-1 Failed Cutaneous Melanoma study cohort, allowing at least 36 months of potential follow-up for each patient. As of the data cutoff date, the actual median duration of follow-up was 24.5 months (range: 0.5-68.4) for patients in the Anti-PD-1 Failed Cutaneous Melanoma cohort. Using the reverse Kaplan-Meier method, the median duration of follow-up was 39.0 months (95% CI: 37.2, 41.6).

4.3.1. Patient Disposition

As of the data cutoff (08 March 2026), no patients were ongoing treatment with RP1.

No patients were ongoing treatment with nivolumab, 20 (14.3%) patients completed treatment, and 120 (85.7%) patients discontinued nivolumab treatment.

4.3.2. Overall Survival

As of the 3-year update, the median OS was 32.9 months (95% CI: 25.76, 46.03) for patients treated with RP1 in combination with nivolumab. The 1-year, 2-year, and 3-year survival rates were 75.3%, 61.5%, and 47.8.%, respectively (Table 6).

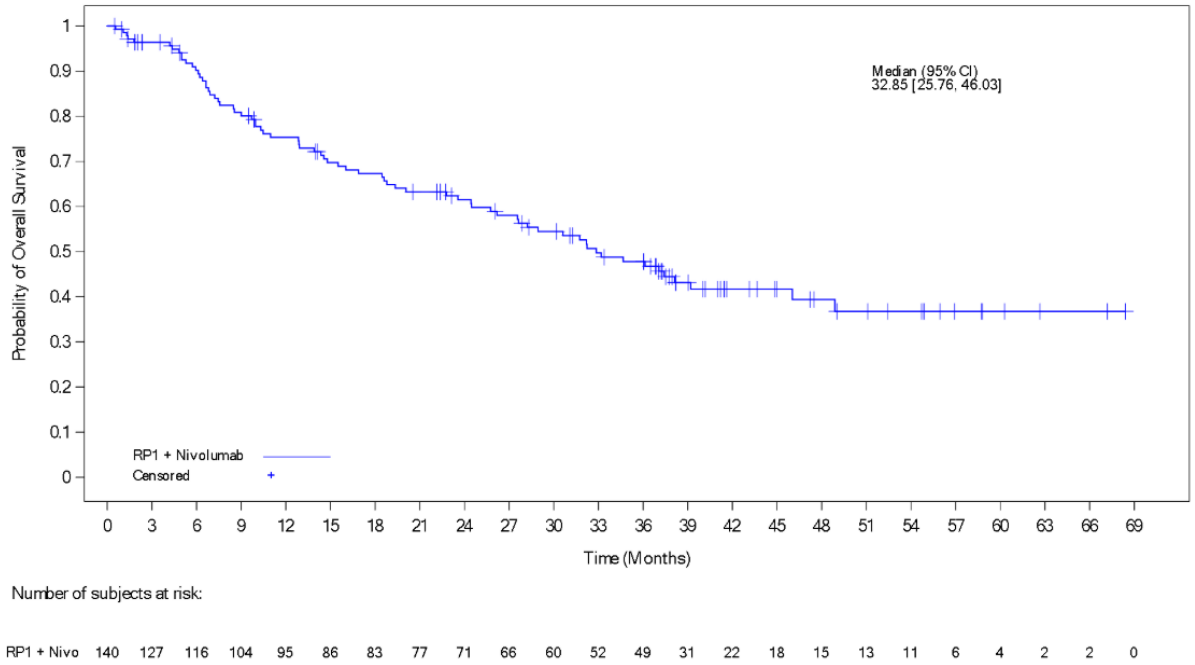
The Kaplan-Meier plot of OS is provided in Figure 8.

Table 6: Summary of OS – Anti-PD-1 Failed Cutaneous Melanoma – IGNYTE Study (FAS)

Parameter	Phase 2 Anti-PD-1 Failed Cohort (N=140)
Number (%) of patients who died	71 (50.7)
OS, months[a]	
Median (95% CI)	32.9 (25.8, 46.0)
Min, max	0.5+, 68.4+
OS, % (95% CI)	
1-year survival rate	75.3 (66.9, 81.9)
2-year survival rate	61.5 (52.4, 69.4)
3-year survival rate	47.8 (38.6, 56.5)

Source: 3-year update: Table 14.2.4.
Data cutoff date: 08 March 2026
Note: + indicates censored
[a] Summary statistics were calculated with Kaplan-Meier analysis and 95% CIs using the loglog method.

Figure 8: Kaplan-Meier Plot of Overall Survival – Anti-PD-1 Failed Cutaneous Melanoma Cohort – IGNYTE Study (FAS)



Source: SCE Figure 14.2.7.1. Data cutoff date: 08 March 2026. FAS=Full Analysis Set

4.3.3. Responder and Nonresponder Analysis

In the Anti-PD-1 Failed Cutaneous Melanoma cohort (N=140), the ORR was 33.6% (per RECIST 1.1 as assessed by Independent Review, Table 4) and the responses were durable with a median DOR of 24.8 months. In order to assess whether this antitumor response translates into meaningful clinical benefit, a responder analysis was conducted.

At the data cutoff for the 3-year survival update, the median OS in the 47 patients with confirmed response (CR+PR) to study treatment was not reached (NR) compared to 18.5 months for those without a confirmed response (SD+PD+NE). Survival rates in responding patients (N=47) are 97.9%, 95.7%, and 83.5% at 1, 2, and 3 years, respectively, from the first dose of RP1 (Table 7).

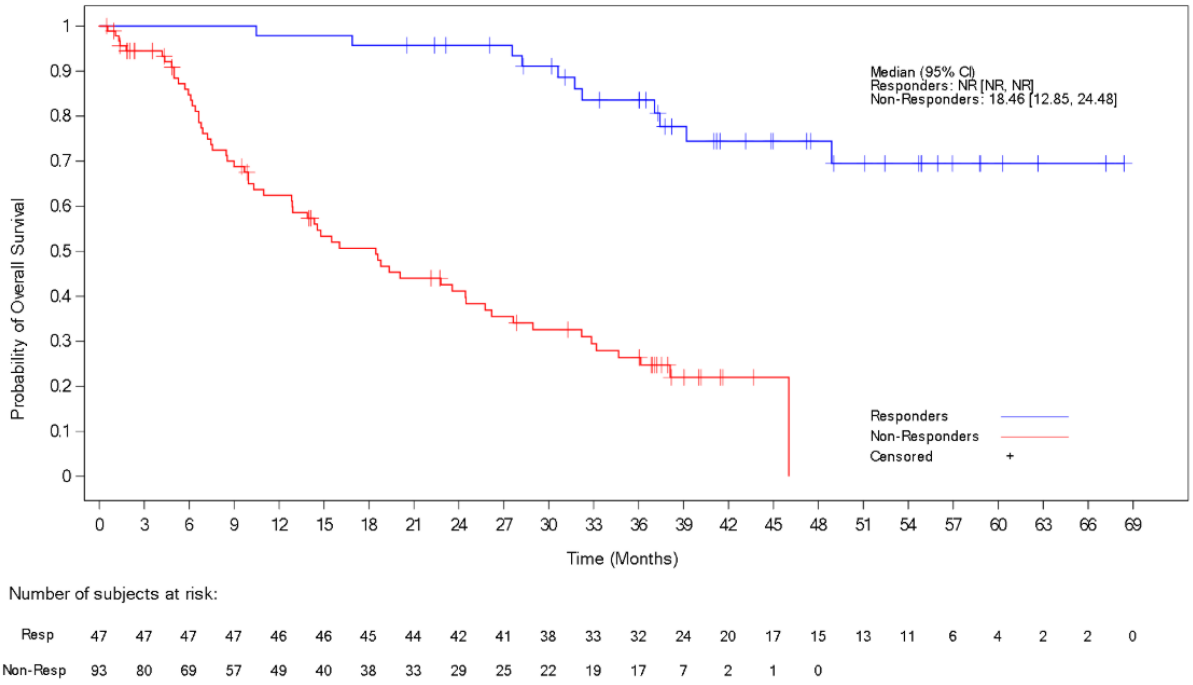
The Kaplan-Meier plot of OS and PFS in responders compared to nonresponders per RECIST are presented in Figure 9 and Figure 10.

Table 7: Summary of OS in Responders and Nonresponders – Anti-PD-1 Failed Cutaneous Melanoma Cohort – IGNYTE Study (FAS)

Parameter	Responders	Nonresponders
Number of patients	47	93
Number (%) of deaths	11 (23.4)	60 (64.5)
OS, months[a]		
Median (95% CI)	NR (NR, NR)	18.5 (12.8, 24.5)
Min, max	39.2, 68.4+	0.5+, 46.0
OS, % (95% CI)[a]		
1-year survival rate	97.9 (85.8, 99.7)	62.4 (51.0, 71.9)
2-year survival rate	95.7 (84.0, 98.9)	41.2 (30.2, 51.8)
3-year survival rate	83.5 (68.5, 91.8)	26.4 (16.9, 36.9)

Source: Table 14.2.5.6.3. Data cutoff: 08 March 2026.
NR= not reached/estimable
Note: + indicates censored
Summary statistics are calculated with Kaplan-Meier analysis and 95% CIs using the loglog method.

Figure 9: Kaplan-Meier Plot of OS in Confirmed Responders and Nonresponders – Anti-PD-1 Failed Cutaneous Melanoma Cohort (FAS) – IGNYTE Study

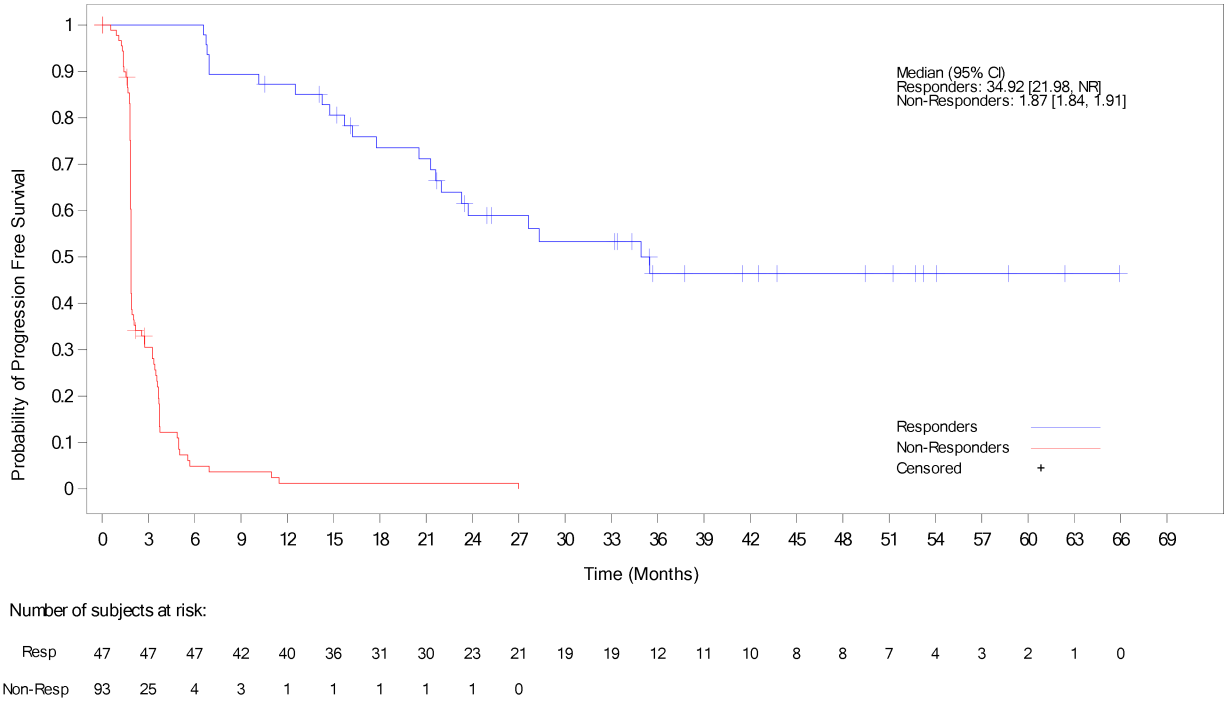


Number of subjects at risk:

Resp	47	47	47	47	46	46	45	44	42	41	38	33	32	24	20	17	15	13	11	6	4	2	2	0
Non-Resp	93	80	69	57	49	40	38	33	29	25	22	19	17	7	2	1	0							

Data cutoff: 08 March 2026.
NR= not reached/estimable

Figure 10: Kaplan-Meier Plot of PFS in Confirmed Responders and Nonresponders – Anti-PD-1 Failed Cutaneous Melanoma Cohort (FAS) – IGNYTE Study



Data cutoff: 08 March 2026.
NR= not reached/estimable

4.4. . Other Supportive Efficacy Analyses

4.4.1. Systemic Effect of Intratumoral Injection

In IGNYTE, patients received RP1 injections every 2 weeks up to 8 doses, with continued treatment if injectable lesions were still present or new lesions appeared. In order to assess the systemic effect of intratumoral injection, Replimune conducted a comprehensive analysis of injected and noninjected lesions by independent review.

A systemic treatment response was observed as evidenced by the injected vs noninjected analysis and duration of response.

To comprehensively characterize the activity of RP1 across the full burden of disease, Independent Review prospectively measured all evaluable lesions, up to a maximum of 10 (ie, not only target lesions), for each patient (n=140) using the same general principles as were applied during the Independent Review for response per RECIST 1.1.

This approach enabled assessment of treatment effect at the individual lesion level across both injected and noninjected tumors, providing a broader evaluation of antitumor activity than is typically captured through aggregate target and non-target lesion assessments alone. Independent readers were blinded to lesion injection status and investigator assessments, allowing objective evaluation of lesion responses regardless of whether lesions were injected or noninjected. Given the proposed mechanism of RP1, which is intended to induce both local

oncolytic activity and a systemic antitumor immune response, assessment of all evaluable lesions provided an important opportunity to characterize the consistency and extent of treatment activity throughout the patient's disease burden.

4.4.1.1. Responder Analysis

A total of 97.5 % of the 199 lesions measured for **responders** showed some reduction from Baseline, and 85.4% (170/199) had a tumor reduction of ≥30% (Table 8). Over half (57.7%) of the injected lesions and 41.3% of noninjected lesions completely resolved (100% reduction). A similar proportion of injected lesions (35.9%) and noninjected lesions (38.8%) had a maximum reduction of ≥30% to <100%.

Table 8: Summary of Best (Maximum) Reduction in Measured Lesions for Patients With a Confirmed Response per RECIST as Assessed by Independent Review (Full Analysis Set)

Number of Measured Lesions[b] With:	Number (%) of Measured Lesions for Responders (CR or PR) (N=47)[a]		
	Injected Lesions (N=78)	Noninjected Lesions (N=121)	Total Injected/ Noninjected Lesions (N=199)[c]
Any reduction	77 (98.7)	117 (96.7)	194 (97.5)
Best reduction >0 to <30%	4 (5.1)	20 (16.5)	24 (12.1)
Best reduction ≥30 to <100%	28 (35.9)	47 (38.8)	75 (37.7)
Best reduction of 100%	45 (57.7)	50 (41.3)	95 (47.7)

Source: Table 25 in the Assessment Aid. IGNYTE Phase 2 CSR, Table 14.2.12.2.3.1. Data cutoff date: 15 October 2024.
Up to 10 lesions (includes target, nontarget, and other lesions) were measured by Independent Review.
[a] Includes updated injected/noninjected lesions for the additional responder per the Efficacy Update.
[b] Includes target/non-target/other lesions at baseline.
[c] This is the total of injected and noninjected lesions.

Among patients who were **not responders**, both injected and noninjected lesions experienced some tumor reduction (Table 9).

Table 9: Summary of Best (Maximum) Reduction in Measured Lesions for Patients With a Confirmed Response per RECIST as Assessed by Independent Review (Full Analysis Set)

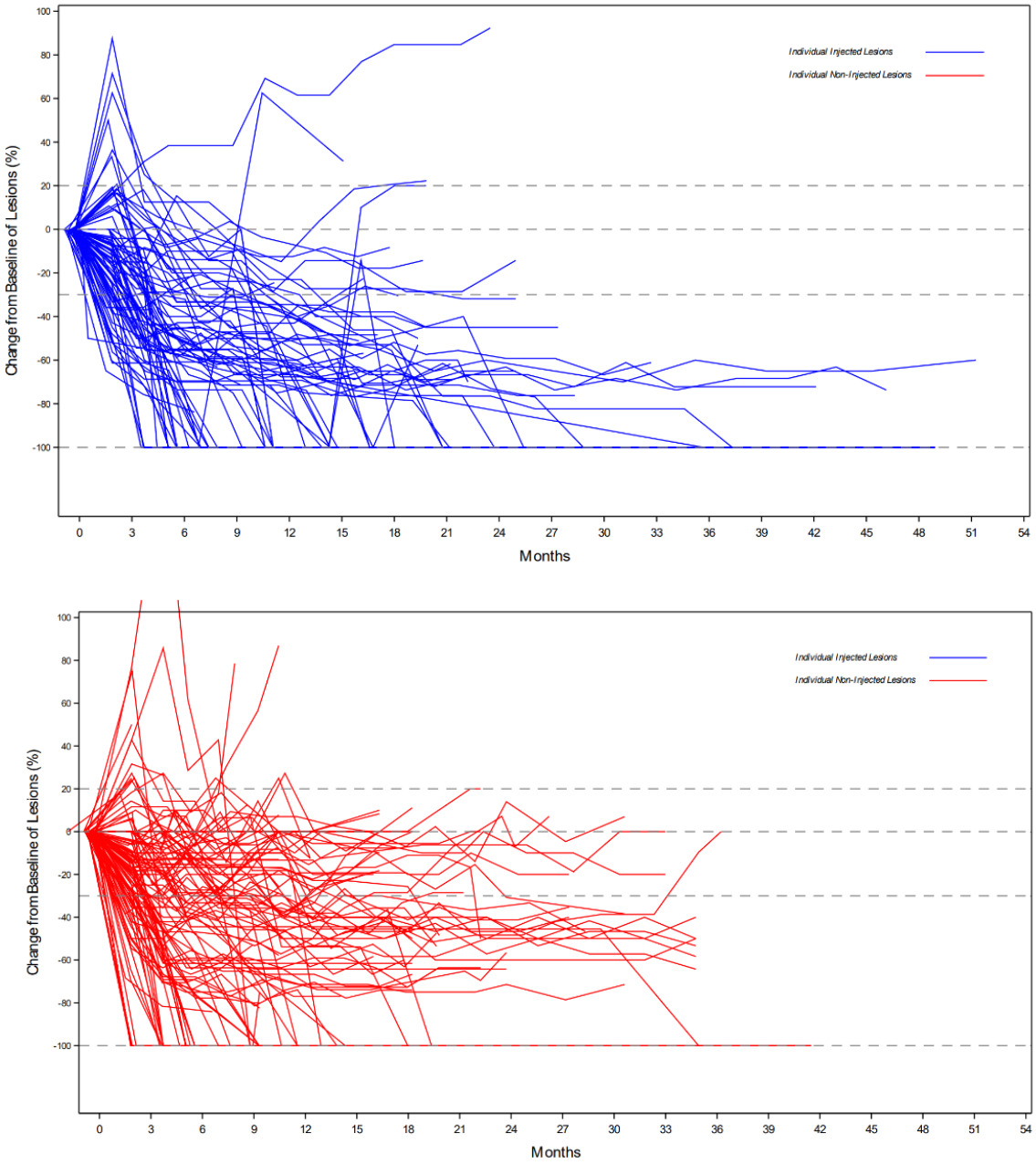
Number of Measured Lesions With:	Number (%) of Measured Lesions for Nonresponders (N=93)	
	Injected Lesions (N=138)	Noninjected Lesions (N=383)
Any reduction	55 (39.8)	131 (34.2)
Best reduction >0 to <30%	36 (26.1)	83 (21.7)
Best reduction ≥30 to <100%	16 (11.6)	36 (9.4)
Best reduction of 100%	3 (2.2)	12 (3.1)

Source: CSR Table 14.2.12.3.2
Data cutoff date: 15 October 2024
Note: 14 (2.6%) had injection lesion status unknown

At the lesion level, these analyses in Table 8 and Table 9 indicate that noninjected lesions behaved similarly to injected lesions in both responders and nonresponders demonstrating a systemic nature of RP1 in combination with nivolumab IT. Further look at responding patients (n=47) in Figure 12 shows the maximum percentage decrease of each measured lesion per RECIST as waterfall plots, sorted by patient. Each blue bar represents an injected tumor and each red bar represents a tumor that was not injected. The consistency in the pattern of the responses (frequency and magnitude) of the injected and noninjected lesions demonstrates that responses observed with RP1 in combination with nivolumab are systemic in nature, are not driven primarily or only by those lesions that were injected.

Additionally, these responses are unlikely a result of the intratumoral injection procedure. As Table 8 and Table 9 shows, lesion reduction in injected lesions were different in both the depth and kinetics when compared between the responders and nonresponders demonstrating that the reduction observed in the responders were not the result of the intratumoral injection procedure.

Figure 11: Spider Plot of Measured Lesions (Injected vs Noninjected) by Independent Review over Time; Full Analysis Set - Confirmed Responders per RECIST v1.1 by Independent Review in Anti-PD-1 Failed Cutaneous Melanoma Cohort



Note: The top panel with blue lines represents individual injected lesions and the bottom panel with red lines represents individual noninjected lesions.

4.4.1.2. Injected and Noninjected Measured Lesions

At the request of the FDA, modified intratumoral (it) RECIST (based on Goldmacher 2020) was also used to evaluate the patient level overall response based on injected and noninjected lesions using all available measured lesions (vs only target lesions; Table 10). Replimune considers such an assessment by target lesions only to be limited as patients may have nontarget lesions that were measurable and could also be used to assess the effect of the RP1in combination with nivolumab in noninjected lesions. However, even when looking at injected and noninjected target lesions a consistent ORR (34.8% vs 30.4%) is observed (Table 11).

Table 10: Summary of Response in Patients Who Had Both Injected and Noninjected Measured Lesions – Anti-PD-1 Failed Melanoma Cohort (FAS)

Parameter	Patients who Had Both Injected and Noninjected Measured Lesions (N=108)	
	Response Based on Injected Measured Lesions	Response Based on Noninjected Measured Lesions
Best Response Category, n (%)		
CR	16 (14.8)	13 (12.0)
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 (13.0)
RR (CR+PR), n (%)	**34 (31.5)**	**31 (28.7)**
95% CI	22.9, 41.1	20.4, 38.2

Source: Table 14.2.13.3.1.1.2 (submitted with response to IR #28). Data cutoff date: 15 October 2024.
95% CI for ORR was based on the Clopper-Pearson exact method.

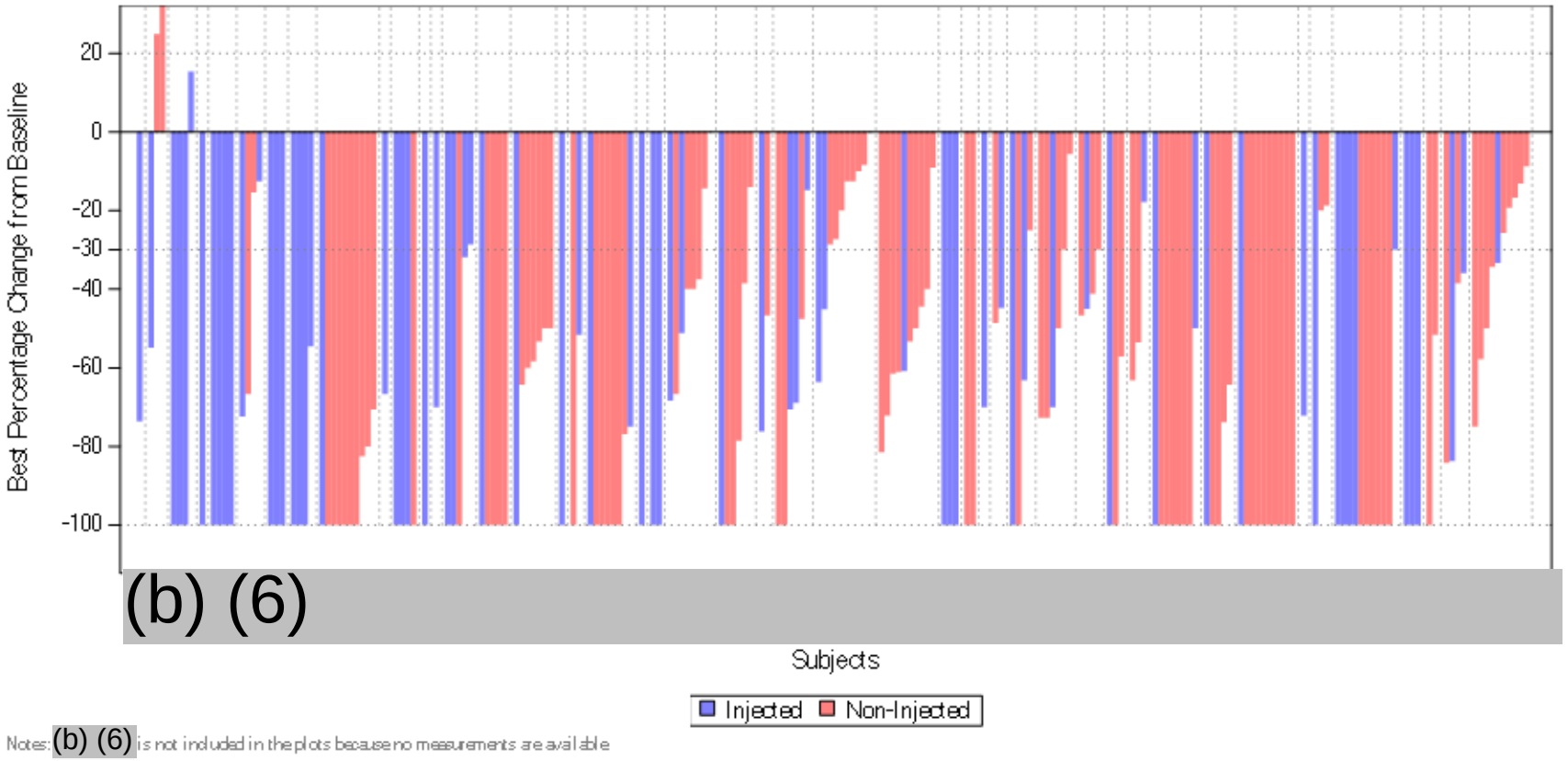
Table 11: Summary of Responses in Patients Who Had Both Injected and Noninjected Target Lesions – Anti-PD-1 Failed Melanoma Cohort (FAS)

Parameter	Patients who had Both Injected and Noninjected Target Lesions (N=69)	
	Response based on Injected TL(s)	Response based on Noninjected TL(s)
Best Response Category, n (%)		
CR	13 (18.8)	11 (15.9)
PR	11 (15.9)	10 (14.5)
SD	18 (26.1)	20 (29.0)
PD	24 (34.8)	25 (36.2)
NE	3 (4.3)	3 (4.3)
RR (CR+PR), n (%)[a]	**24 (34.8)**	**21 (30.4)**
95% CI	(23.7, 47.2)	(19.9, 42.7)

Source: Table 14.2.13.3.1.1.2 (submitted with response to IR #28). Data cutoff date: 15 October 2024.
95% CI for ORR was based on the Clopper-Pearson exact method.

Figure 12 shows the maximum percentage decrease of each measured lesion for responding patients (n=47) per RECIST as waterfall plots, sorted by patient. Each blue bar represents an injected tumor and the associated response. Each red bar represents a tumor that was not injected and the associated response. The consistency in the pattern of the responses (frequency and magnitude) of the injected and noninjected lesions demonstrates that responses observed with RP1 in combination with nivolumab are systemic in nature, and relate to the patient's entire disease burden, and are not driven primarily or only by those lesions that were injected.

Figure 12: Waterfall Plot of Maximum Percentage Decrease From Baseline of Measured Injected and Noninjected Lesions for Patients With a Confirmed Response (N=47) per RECIST (Independent Review) Sorted by Patient (FAS Set)



Source: IGNYTE Phase 2 CSR, Figure 14.2.1.1. Data cutoff date: 15 October 2024.

4.4.1.3. Systemic Effect on Noninjected Visceral Lesions

The systemic effect of RP1 in combination with nivolumab can be further observed in the effect on noninjected visceral lesions. Table 12 provides a summary of the response observed in noninjected visceral organ lesions for the 47 patients with a confirmed response per RECIST as assessed by Independent Review in the Phase 2 Anti-PD-1 Failed Cutaneous Melanoma cohort (N=140). Nearly all (50/52 lesions; 96.2%) of the noninjected visceral organ lesions measured had a reduction from Baseline, with 65.4% of noninjected lesions having a reduction of at least 30%. These results further demonstrate the systemic effect of RP1 in combination with nivolumab, even in tumors located in visceral organs.

Table 12: Summary of the Response of Noninjected Visceral Organ Lesions – Patients With a Confirmed Response per RECIST as Assessed by Independent Review (Full Analysis Set)

Number of Measured Lesions With:	Number (%) of Noninjected Visceral Organ Lesions for Responders (confirmed CR or PR) (N=47)					
	Lung	Liver	Spleen	Pleura	Brain	Total
Number of lesions	30	14	6	2	1	53
Any reduction	29 (96.7)	14 (100)	5 (83.3)	2 (100)	1 (100)	51 (96.2)
Best reduction >0 to <30%	7 (23.3)	3 (21.4)	5 (83.3)	0	1 (100)	16 (30.2)
Best reduction ≥30 to <100%	9 (30.0)	5 (35.7)	0	1 (50.0)	0	15 (28.3)
Best reduction of 100%	13 (43.3)	6 (42.9)	0	1 (50.0)	0	20 (37.7)

Source: SCE Table 14.2.12.2.5. Data cutoff date: 15 October 2024.

4.4.1.4. Overall Summary of Injected and Noninjected Lesions

Overall, the consistency in the pattern of the responses (frequency and magnitude) of the injected and noninjected lesions demonstrates that responses observed with RP1 in combination with nivolumab are systemic in nature, relate to the patient's entire disease burden, and are not driven by only those lesions that were injected. Injected and noninjected lesions responded with similar frequency, durability, depth, and kinetics. The similar durability of effect between injected and noninjected lesions further demonstrates that the responses observed are systemic.

4.4.2. Contribution of Effect

Replimune recognizes the need to assess the contribution of RP1 in this combination therapy (RP1 in combination with nivolumab) to the effect observed in this single-arm study. As a nivolumab monotherapy control arm would not have been feasible or ethical in this anti-PD-1 refractory population, historic literature has been utilized, as well as exploratory analyses from IGNYTE, and the confirmed biologic rationale to demonstrate the contribution of RP1 to the overall effect of RP1 in combination with nivolumab.

A summary of the relevant literature in this setting and how it supports the contribution of RP1 to the effect is provided in Section 1.4 and Section 7.1.

4.4.2.1. Each Patient Serving as an Internal Control for the Effect of RP1

To support the assessment of the contribution of effect for RP1 and nivolumab in this single-arm study, an exploratory analysis comparing patient response and PFS to that on their immediate prior anti-PD-1 therapy to their response on IGNYTE was performed.

Because each patient had confirmed progression while on the prior anti-PD-1 therapy, any additional response observed subsequently reflects the additional ("add on") effect contributed by RP1 to nivolumab.

This "add-on" effect is best seen in 104 patients who progressed while on prior anti-PD-1 therapy in the advanced (unresectable/metastatic) setting in the IGNYTE study. Using the immediate prior therapy as the control, the contribution of RP1 can be isolated by comparing the ORR (as reported by the Investigator) on prior therapy to the ORR per RECIST by IRC observed in IGNYTE (RP1 in combination with nivolumab) (Table 13).

- Only 12 of 104 patients had a response to their immediate prior therapy; ORR of 11.5% (95% CI: 6.1-19.3)
- With the addition of RP1, 31 of 104 patients had an ORR of 29.8% (95% CI: 21.2-39.6)

Figure 14 shows the "add-on" effect for patients who responded to RP1 in combination with nivolumab (31/47). These patients received their first dose of RP1 within a median of 1.58 months (Table 14.2.5.4.2.14.1) of their last dose of immediate prior anti-PD-1 therapy, and went on to respond with either a CR or PR.

Replimune provided detailed patient narratives for each of the patients who responded to study therapy per Independent Review by RECIST 1.1. These narratives provided detailed information for all prior systemic therapies, including the type of treatment, dates of first and last dose, and the best response (BOR) for each. During the BLA review, Replimune confirmed that each patient complied with the very rigorous study inclusion criteria that required patients to have at least 8 weeks of an anti-PD-1 containing therapy as their immediate prior treatment and had confirmed progression prior to enrolling in the study. These criteria ensured that patients were unlikely to respond to additional single-agent anti-PD-1 therapy without the addition of RP1.

A remarkably improved PFS was also observed in responding patients (N=47) following RP1 + nivolumab (median PFS 30.6 months) as compared to the TTP of those patients on the immediate prior anti-PD-1 therapy upon which confirmed progression had just occurred (median PFS 4.4 months) (Figure 13).

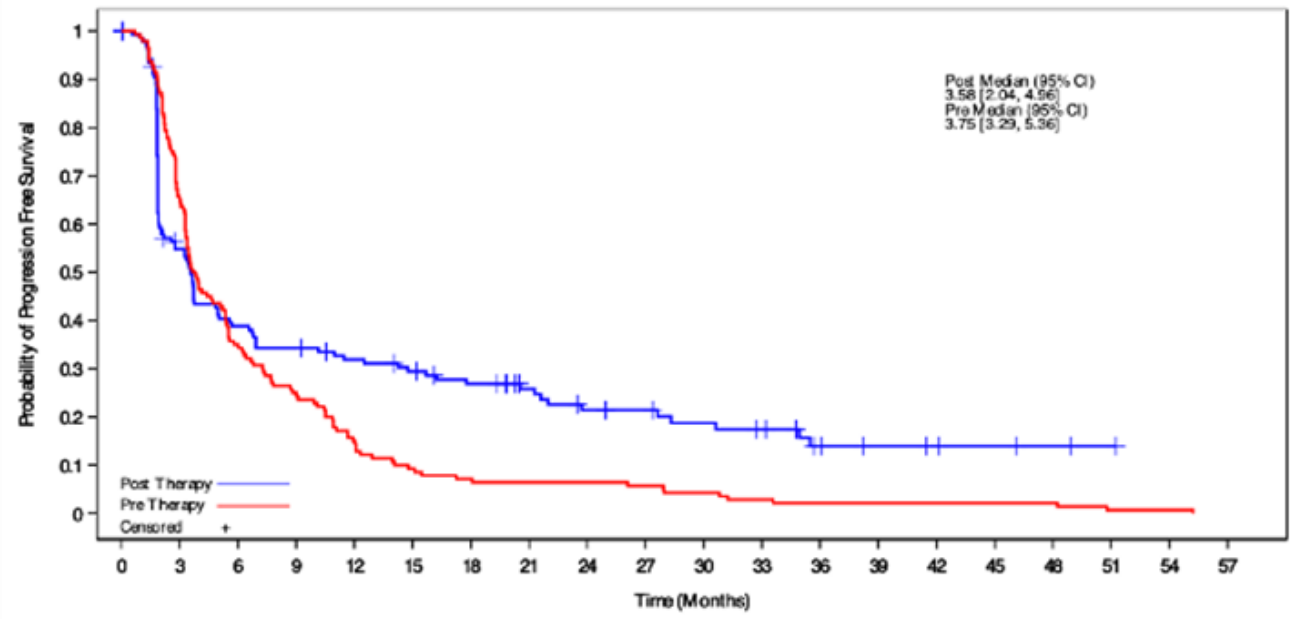
Table 13: Summary of Response on Immediate Prior Anti-PD-1 and on the IGNYTE Study - (N=104)[a]

IGNYTE Non-Adjuvant Patient Population	Time on Prior Treatment [b] months (Range)	ORR [c] on prior PD-1 based therapy (n; 95% CI)	ORR [d] during IGNYTE (n; 95% CI)
All Patients (N=104)	5.59 (2.14, 55.96)	11.5% (12; 6.1-19.3)	29.8% (31; 21.2-39.6)
Responders Only (N=31)	5.56 (2.53, 46.85)	12.9% (4; 3.6-29.8)	100% (31; 88.8-100)
Primary Resistance (N=64)	3.95 (2.14, 19.10)	0% (0; 0.0-5.6)	28.1% (18; 17.6-40.8)

IGNYTE Non-Adjuvant Patient Population	Time on Prior Treatment [b] months (Range)	ORR [c] on prior PD-1 based therapy (n; 95% CI)	ORR [d] during IGNYTE (n; 95% CI)
Secondary Resistance (N=40)	13.96 (5.33, 55.96)	30.0% (12; 16.6-46.5)	32.5% (13; 18.6-49.1)
PD-L1 Negative (<1%) (N=53)	5.62 (2.14, 55.96)	9.4% (5; 3.1-20.7)	18.9% (10; 9.4-32.0)
Stage (IVb-d) (N=59)	6.51 (2.17, 54.02)	13.6% (8; 6.0-25.0)	22.0% (13; 12.3-34.7)

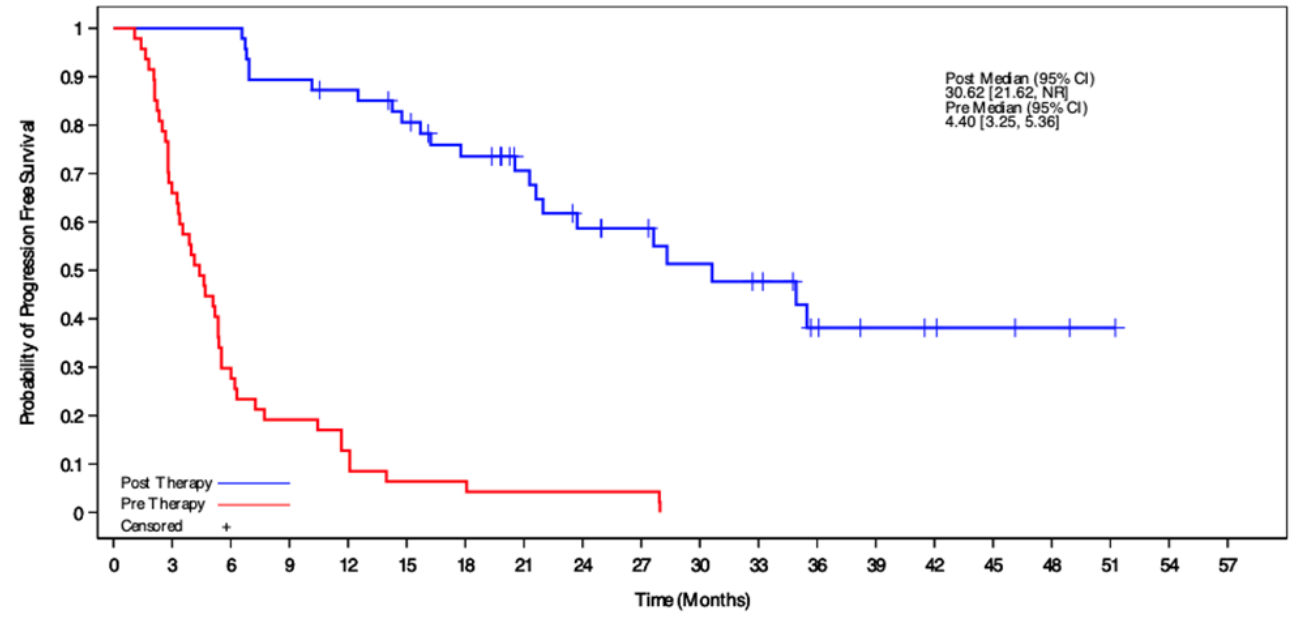
[a] Excludes patients who progressed while on anti-PD-1 in the adjuvant setting
[b] Time on immediate prior anti-PD-1 is the time from first dose to the last dose plus the interval of treatment (eg, every 2, 4, or 6 weeks, accordingly).
[c] ORR is based on Investigator reported BOR of the immediate prior therapy.
[d] ORR is based on Independent Review per RECIST 1.1.
Note: Primary and secondary resistance determined based on SITC criteria (Kluger 2018)
Source: Table 14.2.5.4.2.21.1, Table 14.2.5.4.2.14, Table 14.2.5.4.2.14.1, Table 14.2.5.4.2.14.2, Table 14.2.5.4.2.14.3, Table 14.2.5.4.2.14.4, Table 14.2.5.4.2.14.5, and Table 14.2.5.4.2.14.6

Figure 13: Time to Progression on Prior Anti-PD-1 Compared to RP1 in Combination with Nivolumab - IGNYTE Phase 2 Anti-PD-1 Failed Melanoma Cohort: All Patients (N=104)



Pre Therapy (red line)=time to progression on immediate prior anti-PD-1 containing regimen;
IGNYTE Study (blue line)=progression free survival on RP1 in combination with nivolumab.
Source: Data on file (DCO: 15 October 2024)

Figure 14: Time to Progression on Prior Anti-PD-1 Compared to RP1 in Combination with Nivolumab - IGNYTE Phase 2 Anti-PD-1 Failed Melanoma Cohort: Responding Patients (N=47)



Pre Therapy (red line)=time to progression on immediate prior anti-PD-1 containing regimen;
IGNYTE Study (blue line)=progression free survival on RP1 in combination with nivolumab.

Source: Data on file (DCO: 15 October 2024)

4.4.2.2. Biological Plausibility

RP1 has a dual mechanism of action (MOA). Following injection into tumors, RP1 replicates, leading to tumor lysis and local destruction of tumor cells. In the anti-PD-1 resistant setting, the RP1 mechanism increases the number of tumor reactive T cells leading to an immune inflamed tumor microenvironment and increases PD-L1 expression and other markers necessary for responsiveness to anti-PD-1 therapy. It is through this mechanism that RP1 allows further contribution of nivolumab to the treatment effect in anti-PD-1 resistant patients and why Replimune chose to develop RP1 in the high unmet need area of anti-PD-1 failed melanoma. For these same reasons, the contribution of components/effect is not easily demonstrated within a clinical trial, as treating patients with nivolumab monotherapy would be neither feasible nor ethical.

Data previously presented during initial BLA review response to IRR-18 confirms that RP1 combined with anti-PD-1 therapy demonstrates enhanced antitumor activity across three syngeneic tumor models of lymphoma (A20), colorectal cancer (CT-26), and melanoma (4434). In an immune-incompetent human xenograft model (SKMEL-28), RP1 alone shows direct antitumor efficacy that is superior to a virus lacking GALV-GP R^- expression, confirming the contribution of GALV-GP R^- to oncolytic potency independent of immune context. Importantly, none of the immune-competent syngeneic models tested exhibit notable tumor reduction with anti-PD-1 therapy alone, establishing them as genuine models of checkpoint resistance. The consistent superior antitumor activity observed with the combination across all three models therefore demonstrates that RP1 can reverse mechanisms of resistance to anti-PD-1 treatment.

Analysis of paired tumor biopsies from patients in the anti-PD-1–failed melanoma cohort, collected at screening (SCR) and Cycle 4 (Day 43) revealed an increase in PD-L1 combined positive score (CPS) in 55% (27/49) and CD8+ T-cell intensity score in 41% (21/51) of paired biopsies. Multiplex immunofluorescence of the available paired biopsies (n=8) further confirmed that RP1 plus nivolumab reprograms the tumor microenvironment (TME) from an immunosuppressive to an immune-active phenotype, marked by significant increases in PD-L1 expression; CD8+ T cells; PD-1, CD8+ T cells; and PD-L1, CD68+ macrophages (Figure 16). Notably, these changes were not detected after prolonged prior anti-PD-1 therapy but appeared within 6 weeks of starting the RP1 plus nivolumab combination therapy. RNA-sequencing analysis of paired biopsies at baseline and Cycle 4 demonstrated an increase in a broad range of genes responsible for T-cell function and cytokine signaling confirming the conversion of an immunologically silent tumor to an immune-inflamed microenvironment more so in responding lesions supporting the mechanism of action of sensitizing tumors to anti-PD-1 treatment (Wong et al 2025).

Resistance to anti-PD-1 therapy in this population is characterized by an immune-excluded, immunosuppressive tumor microenvironment with limited CD8+ T-cell infiltration and low PD-L1 expression. The changes observed following treatment with RP1 and nivolumab are consistent with conversion of this resistant phenotype into one permissive to PD-1 blockade. Together, these findings provide a mechanistic rationale for RP1's ability to reverse mechanism

of resistance to anti-PD-1 therapy and to re-sensitize previously refractory tumors to nivolumab and are consistent with the clinical responses observed in this population.

Figure 15: Multiplex Immunofluorescence of Paired Biopsies (n=8) Confirmed that RP1 plus Nivolumab Reprograms the Tumor Microenvironment from an Immunosuppressive to an Immune-Active Phenotype

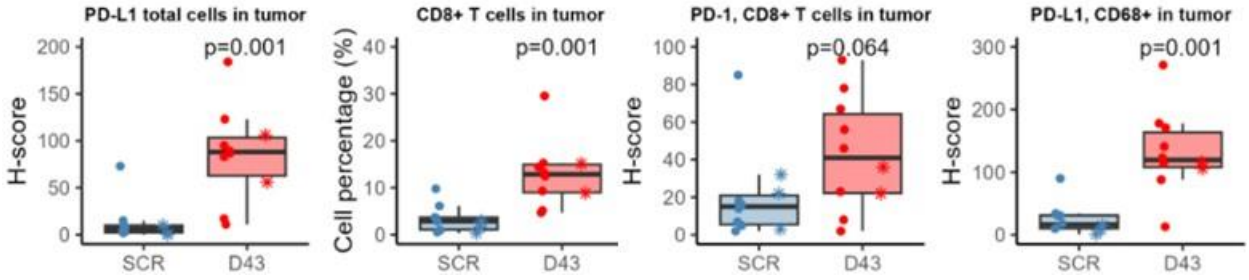


Figure legend: Bar plots showing PD-L1; CD8+ T cells; PD-1, CD8+ T cells (activated); PD-L1, CD68+ (activated macrophages) at baseline (SCR) and 6 weeks / Day 43 (D43) after RP1 and nivolumab combination. Location shift in distributions at each timepoint were performed using the Mann-Whitney U test. H-score = intensity of expression. Paired biopsy = same lesion biopsied at Screening (SCR) and Day 43 (D43)

5. SAFETY

The primary safety data supporting this BLA submission for vusolimogene oderparepvec is based on the cohort of patients with cutaneous melanoma who had progressed while on anti-PD-1 therapy (N=140) and were treated with RP1 in combination with nivolumab in the Phase 2 portion of the IGNYTE study.

Additional safety evidence is provided based on all pooled data from patients from the Phase 1 Dose Expansion and Phase 2 portions of the IGNYTE study who received RP1 in combination with nivolumab (N=335), which includes the 140 patients treated in the Phase 2 Anti-PD-1 Failed Cutaneous Melanoma cohort and 195 additional patients with other melanoma, non-melanoma skin cancer [NMSC], and non-skin cancer who received RP1 in combination with nivolumab in the Phase 1 Dose Expansion and Phase 2 portions of the IGNYTE study.

The summary of safety in Section 5.1 and Section 5.2 provides a summary of safety submitted to the BLA as of the Day 90 Safety Update (DCO: 15 October 2024). Section 5.3 provides a high-level summary of safety as of the 3-year update.

5.1. Safety Profile (15 October 2024)

Overall, the safety profile of RP1 in combination with nivolumab was consistent with established clinical experience for nivolumab alone, with only an increase in expected Grade 1–2 events associated with systemic immune activation

In the Anti-PD-1 Failed Cutaneous Melanoma cohort (N=140), TEAEs with the highest incidence (≥20% of patients) were fatigue, pyrexia, chills, nausea, and diarrhea (Table 14). Most of the common TEAEs (ie, occurring in ≥10% of patients) were Grade 1 or 2, and all the common Grade 3-4 TEAEs listed in Table 14 were Grade 3. No treatment-related Grade 5 TEAEs have been reported for the IGNYTE Anti-PD-1 Failed Cutaneous Melanoma patient cohort.

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

	Number (%) of Patients (N=140)			
	Within 30 Days of RP1 Treatment		Safety Reporting Period	
Adverse Reaction	**All Grades**	**Grade 3[a]**	**All Grades**	**Grade 3[a]**
Gastrointestinal disorders				
Nausea	38 (27.1)	0 (0.0)	40 (28.6)	0 (0.0)
Diarrhea [l]	33 (23.6)	2 (1.4)	41 (29.3)	3 (2.1)
Vomiting	21 (15.0)	0 (0.0)	24 (17.1)	0 (0.0)
Constipation	20 (14.3)	0 (0.0)	22 (15.7)	0 (0.0)
General disorders and administration site conditions				
Fatigue	62 (44.3)	1 (0.7)	63 (45.0)	2 (1.4)
Pyrexia[c]	51 (36.4)	0 (0.0)	54 (38.6)	0 (0.0)
Chills	44 (31.4)	0 (0.0)	45 (32.1)	0 (0.0)
Injection site reaction[d]	36 (25.7)	0 (0.0)	37 (26.4)	0 (0.0)
Asthenia[b]	26 (18.6)	1 (0.7)	26 (18.6)	2 (1.4)
Influenza like illness [m]	27 (19.3)	0 (0.0)	28 (20.0)	0 (0.0)

Adverse Reaction	Number (%) of Patients (N=140)			
	Within 30 Days of RP1 Treatment		Safety Reporting Period	
	All Grades	Grade 3[a]	All Grades	Grade 3[a]
Metabolism and nutrition disorders				
Decreased appetite	13 (9.3)	0 (0.0)	18 (12.9)	2 (1.4)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[f]	38 (27.1)	0 (0.0)	43 (30.7)	0 (0.0)
Arthralgia[e]	18 (12.9)	1 (0.7)	23 (16.4)	2 (1.4)
Nervous system disorders				
Headache[g]	24 (17.1)	0 (0.0)	26 (18.6)	0 (0.0)
Dizziness	11 (7.9)	0 (0.0)	18 (12.9)	0 (0.0)
Respiratory, thoracic and mediastinal disorders				
Cough[h]	19 (13.6)	0 (0.0)	25 (17.9)	0 (0.0)
Dyspnoea[i]	12 (8.6)	1 (0.7)	16 (11.4)	1 (0.7)
Skin and subcutaneous tissue disorders				
Pruritus	21 (15.0)	0 (0.0)	24 (17.1)	0 (0.0)
Rash[j]	15 (10.7)	1 (0.7)	23 (16.4)	2 (1.4)
Infections and infestations				
Skin/superficial infection [k]	11 (7.9)	0 (0.0)	17 (12.1)	1 (0.7)

Source: Safety Update: SCS Table 2.1.3.3.1 (PTs during the safety reporting period), SCS Table 2.1.5.3.1 (grouped terms within 30 days), SCS Table 2.1.3.5.1.1 (grouped terms during safety reporting period), SCS Table 2.1.5.1.1 (PTs within 30 days). Data cutoff date: 15 October 2024.
CTCAE=Common Terminology Criteria for Adverse Events; IGNYTE=Phase 1/2 RPL-001-16 study; NCI=National Cancer Institute; PD-1=programmed cell death protein 1 (receptor); PT=preferred term; SCS=Summary of Clinical Safety.
Note: A patient was counted once by maximum CTCAE grade within each system organ class and preferred term.
NCI CTCAE Version 5.0.

[a] None of the common adverse reactions were Grade 4 or 5 (Safety Update: SCS Tables 2.1.3.2.1 and 2.1.3.5.3.1.1).
[b] Includes asthenia and malaise.
[c] Includes pyrexia and hyperthermia.
[d] Includes injection site discharge, injection site erythema, injection site hematoma, injection site hemorrhage, injection site oedema, injection site pain, injection site pruritus, injection site reaction, injection site swelling, and injection site ulcer.
[e] Includes arthralgia and arthritis.
[f] Includes back pain, flank pain, muscle spasms, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, and pain in extremity.
[g] Includes headache.
[h] Includes cough, upper-airway cough syndrome, and productive cough.
[i] Includes dyspnea and dyspnea exertional.
[j] Includes eczema, erythema, rash, rash maculo-papular, and rash pruritic.
[k] Includes skin infection, cellulitis, fungal infection, abdominal infection, dermatophytosis, fungal skin infection, herpes simples, herpes simplex reactivation, injection site infection, parametritis (verbatim term: right wrist cellulitis)
[l] Includes diarrhoea, colitis, immune-mediated enterocolitis
[m] Includes influenza like illness and influenza

5.1.1. Deaths

In the Anti-PD-1 Failed Cutaneous Melanoma Phase 2 cohort (N=140), 59 (42.1%) patients died during the study: 45 (32.1%) due to disease progression, 5 (3.6%) due to TEAEs, 5 (3.6%) due to other reasons, and for 4 patients (2.9%) the cause of death was unknown. Most (53/59) patients died more than 30 days after the last dose of study treatment (RP1 or nivolumab). Of the 6 patients in this cohort who died within 30 days of the last dose of study treatment (RP1 or nivolumab), the cause of death was disease progression for 2 patients, due to an AE for 3 patients, and due to other reasons for 1 patient. The cause of death for the 3 patients who died within 30 days of the last dose of study treatment were AEs, which included head injury (b) (6) , multiple organ dysfunction syndrome (b) (6) , and disease progression (b) (6)

reported as an AE for this patient); none of these events were considered related to either study treatment (RP1 or nivolumab) by the Investigator or Sponsor.

5.1.2. Serious Adverse Events

In the Anti-PD-1 Failed Cutaneous Melanoma cohort (N=140), the incidence of patients with serious TEAEs was 35.7%. Serious TEAEs reported in more than 2 patients included disease progression (3.6%) and pleural effusion (2.1%); all other serious TEAEs occurred in 1 or 2 patients. The treatment-related serious TEAEs of hypophysitis, immune-mediated enterocolitis, and pyrexia were reported in 2 (1.4%) patients each; all other treatment-related serious TEAEs occurred in 1 patient each. Serious TEAEs reported in more than 1 patient within 30 days of the last dose of RP1 included disease progression (2.1% of patients), cancer pain, pyrexia, and pleural effusion (1.4% each); all other serious TEAEs occurred in 1 patient each.

Events the Sponsor considered serious adverse reactions include arthralgia, hypophysitis, immune-mediated enterocolitis, myocardial infarction, and pyrexia. Other serious TEAEs were not considered adverse reactions because they were either attributed to the underlying disease, confounded by concurrent illness or medical history, or lacked temporal relationship or biologic plausibility.

5.1.3. Discontinuation of Treatment Due to Adverse Events

TEAEs that led to discontinuation of RP1 that the Sponsor considered as adverse reactions included increased amylase, lipase increased, myocarditis, and pneumonitis, which only occurred in 1 patient each. The reason the other events were not considered adverse reactions is because they were either attributed to the underlying disease or study procedure, confounded by concurrent illness or medical history, or lacked temporal relationship (ie, occurred more than 60 days after RP1 discontinuation in patients).

5.2. Other Safety Topics of Interest (15 October 2024)

5.2.1. Procedural-Related Events

RP1 can be given under imaging guidance into deep tumors, including those involving visceral organs. Additional TEAEs may be observed as a result of these procedures. A thorough review of patients who were injected into liver and lung tumors was performed. While a Grade 2 or higher AST, ALT, or bilirubin with liver injection and Grade 2 or higher pneumothorax with lung injection were considered AEs of interest per protocol, analysis of liver function test (LFT) abnormalities and iatrogenic pneumothorax was conducted considering all grades.

Liver Injection

Overall, the incidence of LFT abnormalities was low: 0% (0/48) and 4.9% (10/204) of liver injections were associated with any LFT abnormalities in the Anti-PD-1 Failed Cutaneous Melanoma cohort (N=140) and the Pooled Phase 1/2 All Cohorts group (N=335), respectively. The majority of events were Grade 1-2.

Lung Injection

Overall, the incidence of iatrogenic pneumothorax was low: 5.8% (3/52) and 11% (9/82) of lung injections were associated with a case of pneumothorax in the Anti-PD-1 Failed Cutaneous Melanoma cohort (N=140) and the Pooled Phase 1/2 All Cohorts group (N=335), respectively. All events were Grade 1-2 in the IGNYTE study.

5.2.2. Herpetic-Like Infection

Background on RP1

RP1 is an engineered oncolytic agent derived from herpes simplex virus type 1 (HSV-1), a pathogen that most adults have already encountered. HSV-1 is responsible for recurrent oral cold sores and is estimated to infect approximately 65% of the general adult population (Ageeb 2024). Two critical viral genes ICP34.5 and ICP47 have been deleted to make RP1 replication tumor selective. ICP34.5 normally counteracts the cellular antiviral response, allowing HSV-1 to replicate in healthy tissue; without it, the virus can only propagate in tumor cells, which carry defects in the same antiviral pathways that ICP34.5 would otherwise need to suppress. These modifications essentially render RP1 unable to cause productive infection in normal tissue while retaining its ability to replicate within, and ultimately kill malignant tissue. For patients who are HSV-1 seronegative at baseline meaning they have not previously been infected and carry no pre-existing neutralizing antibodies against HSV-1, treatment with RP1 induces seroconversion. The immune system mounts a humoral response to the virus, generating HSV-1-specific antibodies that persist beyond the course of treatment, this seroconversion is immunologically protective against future HSV-1 infections is seronegative patients.

At baseline, the HSV-1 IgG serostatus of patients enrolled in the IGNYTE skin cancer cohorts was assessed. Among the total 282 patients, consistent with expectations for the general population (13), 203 of 282 patients (72.0%) were found to be seropositive for HSV-1 IgG antibodies, while 73 patients (25.9%) tested seronegative. The serostatus of 6 patients (2.1%) was indeterminate or unknown at the time of baseline assessment. Most seronegative patients seroconverted by Cycle 3 Day 29 after treatment with RP1.

At baseline, the HSV-1 IgG serostatus of patients enrolled in the IGNYTE anti-PD-1 failed melanoma cohort was assessed. Among the total 141 patients, consistent with expectations for the general population (13), 98 patients (69.5.0%) were found to be seropositive for HSV-1 IgG antibodies, while 40 patients (28.4%) tested seronegative. The serostatus of 3 patients (2.1%) was indeterminate or unknown at the time of baseline assessment. Most seronegative patients seroconverted by Cycle 3 Day 29 after treatment with RP1 (84.4% seropositive).

Evaluation of Herpetic-Like Infections from RP1 Clinical Studies

Instances of herpetic-like infections (eg, cutaneous or mucosal manifestations) were monitored in the RP1 clinical studies. Grade 2 or higher herpes simplex virus infection, either new infection or reactivation, were considered AEs of special interest. For this analysis, PTs including oral herpes, herpes simplex, and herpes simplex reactivation of any severity grade were included. While herpes zoster and herpes simplex are alpha herpesviruses, herpes zoster is a distinct viral infection from HSV and was not included in the analysis.

In the Anti-PD-1 Failed Cutaneous Melanoma cohort (N=140), 3 (2.1%) patients experienced 4 events of herpetic-like infection: oral herpes (2 patients), herpes simplex (1 patient), and herpes simplex reactivation (1 patient). All events were Grade 1 except for HSV reactivation, which was Grade 2 and all events resolved.

In the Pooled Phase 1/2 All Cohorts group (N=335), 9 (2.7%) patients experienced herpetic-like infection: oral herpes (4 patients), herpes simplex reactivation (4 patients), and herpes simplex (2 patients). Most events were Grade 1-2 (SCS Listing 2.1.16.1). Baseline HSV status was seronegative for only 2 patients (in the NMSC cohort): for 1 patient ((b) (6)), RP1 DNA was detected in a swab test, however no live virus was detected upon further testing, and in 1 patient (b) (6)), an oral swab test did not detect any RP1 DNA.

Baseline HSV status was seropositive for 3 of these patients (b) (6) , and (b) (6) in the Anti-PD-1 Failed Cutaneous Melanoma cohort.

Overall, there were no systemic HSV infections observed in the IGNYTE study. The comprehensive biodistribution and shedding data of RP1 and risk of infection to close contacts and patient caregivers is reported (Wise-Draper 2026)

5.3. IGNYTE 3-Year Safety Update (08 March 2026)

As of the 08 March 2026 data cutoff, RP1 in combination with nivolumab continues to be well tolerated with no new safety signals identified during long-term follow-up, including no Grade 5 events related to study treatment. No new or significant safety findings have been identified from the ongoing RP1 studies beyond what was described in the original BLA and 90-day safety update.

Additionally, the safety of RP1 across the program has been reviewed and as of 06 June 2026, no new or significant safety findings or risks have been identified beyond what was described in the original BLA and 90-day safety update.

6. OVERALL BENEFIT-RISK

The benefit of RP1 in combination with nivolumab in the proposed indication was established in the Phase 2 Anti-PD-1 Failed Cutaneous Melanoma cohort of the IGNYTE trial, which enrolled a total of 140 patients with advanced melanoma and confirmed progression while being treated with anti-PD-1 therapy either in the adjuvant or recurrent/metastatic setting. In this anti-PD-1–refractory melanoma population with limited treatment options, RP1 in combination with nivolumab demonstrated substantial and clinically meaningful antitumor activity, achieving a confirmed objective response rate (ORR) of **33.6%** (95% CI: 25.8, 42.0), including a **16.4% complete response (CR) rate**, as assessed by blinded independent review per RECIST v1.1. Responses were durable, with a median duration of response of **24.8 months** (95% CI: 14.1, NR) with 50.7% of patients maintaining observed responses at 24 months from response initiation, including 1 patient (b) (6)) whose response was ongoing for over 4 years. The overall durability of response is further supported by the 3-year updated analysis, which showed that the DOR was maintained and that responses resulted in a median OS of 32.9 months, with 2- and 3-year survival rates of 61.5% and 47.8%.

These durable responses were accompanied by a favorable safety profile characterized predominantly by Grade 1–2 adverse events and **no treatment-related fatalities**. Collectively, these findings demonstrate a favorable benefit-risk profile and support the potential of RP1 plus nivolumab to address a significant unmet medical need in patients with anti-PD-1–refractory advanced melanoma.

In an exploratory analysis, only 12 of 104 patients in IGNYTE had a response to their immediate prior anti-PD-1 therapy in the advanced/metastatic setting; ORR of 11.5% (95% CI: 6.1-19.3) on prior therapy, compared to an ORR of 29.8% (95% CI: 21.2-39.6) on IGNYTE for RP1 in combination with nivolumab. Improved PFS was also observed in responding patients (N=47) following RP1 in combination with nivolumab (median PFS 30.6 months) as compared to the TTP of those patients on the immediate prior anti-PD-1 therapy (median PFS 4.4 months).

Additionally, RP1 combined with nivolumab provided clinically meaningful activity across each of the different settings after anti-PD-1 failure. Notably, responses were observed in patients with characteristics typically associated with poorer outcomes, including prior exposure to combined anti-PD-1/anti-CTLA-4 therapy, visceral metastatic disease (Stage IVb-IVd), and primary resistance to anti-PD-1 therapy. Across these higher-risk populations, objective response rates generally ranged from approximately 25% to 35%, supporting the robustness of treatment activity in a setting with limited therapeutic options. The consistency of clinical activity observed across multiple relevant subgroups strengthens the overall evidence of treatment benefit.

Further, Replimune has reviewed the literature in this setting and has provided context for interpretation of the IGNYTE data (refer to Section 7.1). The ORR of 33.6% and durable response after treatment with RP1 in combination with nivolumab after anti-PD-1 failure exceed the ORRs of available treatment options and is far better tolerated than other available therapies.

Approval of RP1 in combination with nivolumab is also supported by the strong mechanistic rationale for RP1 in combination with nivolumab and supportive data (in combination with nivolumab and as a monotherapy) in other advanced cutaneous malignancies. RP1 increases the numbers of tumor-reactive T cells, and the levels of PD-L1 expression and other markers of

responsiveness to anti-PD-1 therapy, as demonstrated in biopsies from treated patients on the IGNYTE trial, with anti-PD-1 therapy then reactivating both new and pre-existing T cells as they become exhausted. This effect has also been demonstrated in multiple syngeneic immune-competent murine models showing an increased reduction in tumor volume compared with either RP1 or anti-PD-1 monotherapy. Further, a study of RP1 monotherapy in solid organ and hematopoietic cell transplant recipients with advanced cutaneous malignancies (RPL-003-19 or ARTACUS) showed the antitumor effectiveness of RP1 with similar biomarker effects also being observed.

The IGNYTE trial together with this supportive evidence therefore provides substantial evidence of effectiveness for the proposed indication and the overall benefits outweigh the risks.

7. ISSUES FOR DISCUSSION

7.1. Do the data provide substantial evidence of effectiveness in the proposed indication?

Replimune believes the data from the Anti-PD-1 Failed Cutaneous Melanoma cohort of the IGNYTE study (RPL-001-16) provide substantial evidence of effectiveness in the proposed indication.

- RP1 in combination with nivolumab demonstrated an overall response rate (ORR, confirmed CR and PR) of **33.6% (95% CI: 25.8-42.0) -** per RECIST 1.1 as evaluated by Independent Review
  - The lower bound of the confidence interval substantially exceeding the prespecified 15% threshold
- **16.4%** (95% CI: 10.7, 23.6) **of patients achieved a complete response (CR) -** per RECIST 1.1 as evaluated by Independent Review
  - Nearly half of the responders (23/47) achieved a complete response
  - This is a particularly notable finding in the anti-PD-1 refractory melanoma setting where complete eradication of detectable disease is uncommon
  - CR rate is an important indicator of response depth and is associated with the potential for prolonged disease control
- The median time-to-response (TTR) was 3.9 months (range: 1.7-21.9 months) from the first dose of RP1
- Responses were durable with a median duration of response (DOR) of 24.8 months (95% CI: 14.1, NR)
  - 50.7% of patients maintained responses at 24 months, including 1 patient whose response was ongoing for over 4 years
- Median OS was 33.2 months and the lower bound of the 95% CI was 26.2 months (the upper bound was not estimable)
  - The 1-, 2-, and 3-year survival rate was 75.3%, 61.0%, and 47.2%, respectively

Together, the ORR, CR rate, and durability of response demonstrate clinically meaningful and sustained antitumor activity in a patient population with limited treatment options. The durability observed also demonstrates the systemic nature of the benefit achieved.

To further assess the contribution of effect, an exploratory analysis was performed comparing patient response to their immediate prior anti-PD-1 therapy to their response on IGNYTE (Section 4.4.2.1). Because each patient had confirmed progression while on the prior anti-PD-1 therapy, any additional response observed subsequently reflect the additional ("add on") effect contributed by RP1 to nivolumab. This "add-on" effect is best seen in 104 patients who progressed while on prior anti-PD-1 therapy in the advanced (unresectable/metastatic) setting in the IGNYTE study.

Using each patient's immediate prior therapy as the control, the contribution of RP1 can be isolated by comparing the ORR (as reported by the Investigator) on prior therapy to the ORR per RECIST by IRC observed in IGNYTE (RP1 in combination with nivolumab).

- Only 12 of 104 patients in IGNYTE had a **response to their immediate prior** anti-PD-1 therapy in the advanced/metastatic setting; ORR of **11.5%** (95% CI: 6.1-19.3)
- When treated with **RP1 in combination with nivolumab**, 31 of 104 patients had an ORR of **29.8%** (95% CI: 21.2-39.6)
- Improved PFS was also observed in responding patients (N=47) following RP1 in combination with nivolumab (median PFS 30.6 months) as compared to the TTP of those patients on the immediate prior anti-PD-1 therapy (median PFS 4.4 months).
- **IGNYTE 3-Year Update:**

The durability of response in the 47 responders is further supported by the 3-year updated analysis of DOR, PFS, and OS (08 March 2026).

- Median DOR of 24.8 months was maintained; the lower bound of the 95% CI increased slightly from 14.1 to 14.8 months and the upper bound of the 95% CI was still not estimable
  - 1-, 2-, and 3-year DOR rates were 72.3%, 51.4%, and 44.8%, respectively
- Median progression-free survival (PFS) was 3.6 months (95% CI: 3.4, 5.0)
- Median OS was 32.9 months (95% CI: 25.76, 46.03)
  - 1-, 2-, and 3-year survival rates were 75.3%, 61.5%, and 47.8%, respectively

The 3-year updated analysis of OS further confirms that overall durability of response is associated with longer survival and suggests that treatment with RP1 in combination with nivolumab can lead to clinical benefit. It is noteworthy that 7 of the 10 patients who were followed for more than 36 months remain in response beyond 48 months.

Survival curves from melanoma studies that include long-term follow-up show a plateau at 3 to 4 years and suggest that patients who are alive at 3 years are likely to have prolonged benefit from prior therapy (Michielin 2020). Therefore, the results of the IGNYTE study suggest that IGNYTE patients may have significant survival benefit.

Overall Conclusion

The body of evidence from the IGNYTE trial is clinically meaningful and substantially improved durable ORR in comparison with the historical literature in this setting, comparison of response and PFS from patients in IGNYTE to that of their immediate prior anti-PD-1 therapy, and the biologic mechanism of RP1 support that the IGNYTE trial is an adequate and well-controlled trial that can be used to determine substantial evidence of effectiveness in patients with anti-PD-1 refractory disease.

The durable response observed in IGNYTE following treatment with RP1 in combination with nivolumab exceeds the ORRs of available treatment options and is far better tolerated than other available therapies, allowing the treatment of a broad range of patients with melanoma that has progressed following anti-PD-1 therapy.

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