RP1: The regulatory impasse of oncolytic virus therapy and the unmet needs in melanoma

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Received: August 4, 2026; Accepted: August 7, 2026; Published Online: August 7, 2026; https://doi.org/10.59717/j.xinn-oncol.2026.100032

Citation: Zhou G., Xie T., Jia W., et al. (2026). RP1: The regulatory impasse of oncolytic virus therapy and the unmet needs in melanoma. *The Innovation Oncology* **1**:100032.

The FDA's three BLA reviews of RP1 read like a condensed industry apocalypse. From receiving Priority Review in July 2025 to a split ODAC vote in July 2026, Replimune's oncolytic virus product RP1 endured two Complete Response Letters, an over 90% evaporation of market capitalization, and the layoff of 63 employees within a single year. At the heart of the controversy lies a fierce collision between the systematic tightening of regulatory science standards and the real-world constraints facing innovative therapies—this is not merely about one company's fate, but has profoundly reshaped the R&D, investment, and regulatory logic of the entire oncolytic virus field.

SCIENTIFIC MECHANISM: A SECOND-GENERATION ONCOLYTIC VIRUS

RP1 upon the foundation of T-VEC (approved in 2015), the only FDA-approved oncolytic virus—by adding a fusion protein GALV-GP R- (gibbon ape leukemia virus fusogenic glycoprotein, with R- denoting removal of the cytoplasmic tail) to induce syncytia formation in tumor cells, enhancing lytic efficiency. T-VEC deletes HSV-1 viral proteins ICP34.5 and ICP47 and inserts GM-CSF, representing an "attenuated + single immuno-stimulatory" design; RP1 additionally incorporates the fusogenic protein GALV-GP R- to achieve a triple mechanism of "attenuation + fusion-mediated killing + immune stimulation." More critically, the clinical positioning differs: T-VEC is approved as monotherapy via intratumoral injection for unresectable stage IIIB-IV melanoma (Phase 3 OPTiM trial, ORR ~26%), with indications limited to cutaneous and nodal lesions and a label note that it "may not extend overall survival." RP1, by contrast, targets a more urgent gap: advanced melanoma patients who have progressed on anti-PD-1 therapy, using a combination regimen with nivolumab.

CLINICAL DATA AND REGULATORY CONTROVERSY

The core grounds for the FDA's first CRL (July 2025) and second CRL (April 2026) centered on the single-arm design: lacking a randomized control, it was impossible to determine RP1's independent contribution to efficacy, and the heterogeneity of the patient population rendered the results "uninterpretable." T-VEC had been approved on the strength of a randomized controlled Phase III trial, whereas RP1 sought to navigate the accelerated approval pathway with single-arm Phase II data—the divergence in regulatory thresholds directly determined the contrasting fates of these two oncolytic virus products. The FDA's rejections were not driven by safety concerns, but rather targeted fundamental deficiencies in the clinical evidence. Even more controversial was the inconsistency between the FDA's successive review teams: the prior team had considered the evidence adequate, but leadership disagreed; the second review even saw the appointment of an entirely new review team. Replimune laid off 63 employees and warned that it would be unable to continue development. CEO Sushil Patel stated: "A treatment desperately needed by patients will not be available. Not because the medicine failed. Because the system did."

UNMET NEEDS AND IMPLICATIONS

Third ODAC review (July 2026): Replimune resubmitted the BLA, with a

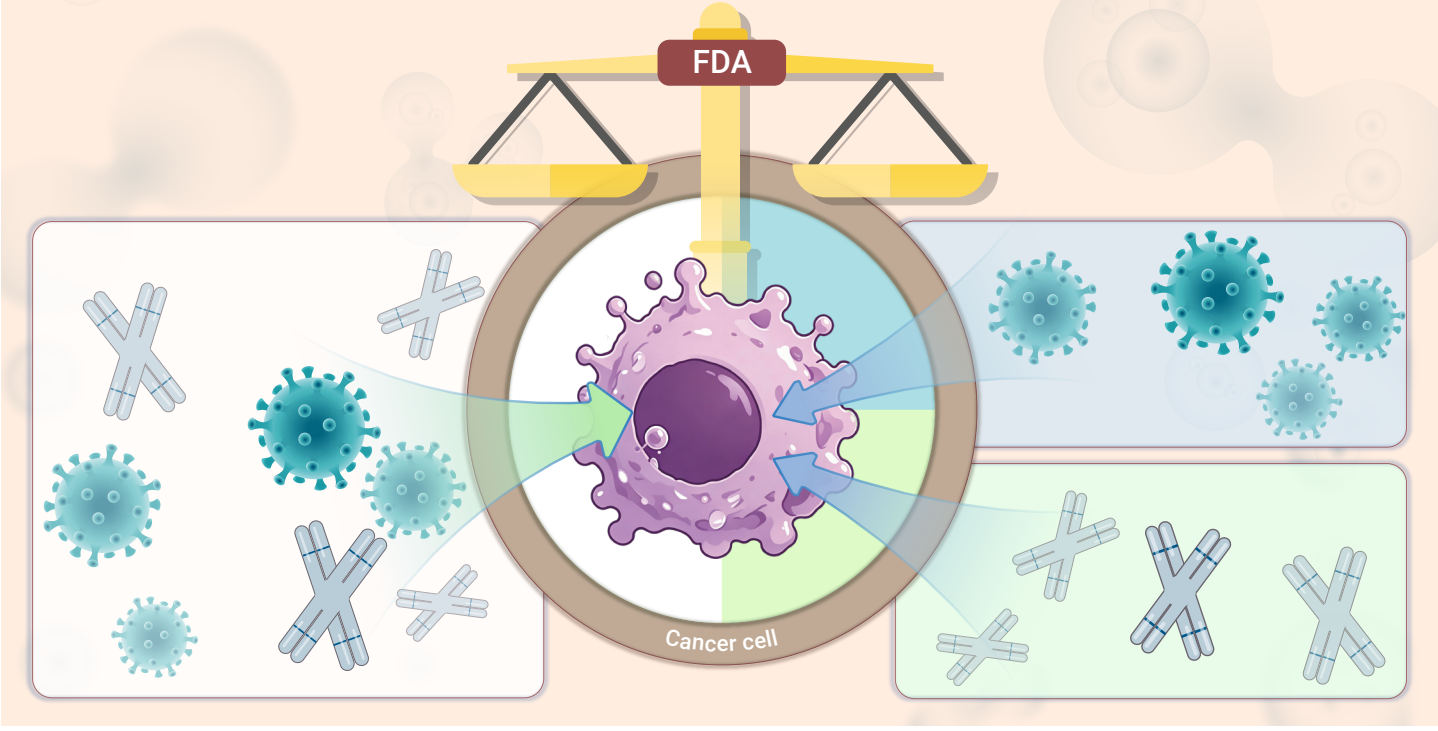

Figure 1. FDA approval of RP1 plus anti-PD1 FDA, Food and Drug Administration.

PDUFA target date set for August 2, 2026. The advisory committee vote was split—the committee unanimously recognized the substantial unmet need in PD-1-resistant melanoma and the impressive duration of response (median DOR >20 months). In the U.S., approximately 112,000 new melanoma cases are diagnosed annually; about half of patients do not respond to or eventually progress on anti-PD-1 therapy, leaving extremely limited subsequent options. Nearly twenty leading experts had jointly called for RP1's approval.

THE FDA'S THREE CORE CONCERNS

First, the "original sin" of the single-arm design. IGNYTE is a single-arm trial without a control group, making it impossible to disentangle RP1's contribution from that of nivolumab in the combination. The FDA's 2025 guidance on combination drugs explicitly requires demonstration of each component's independent contribution; the inability to deconvolute RP1's efficacy from the combination with nivolumab is the core bottleneck. By contrast, T-VEC was approved based on the rigorous randomized controlled Phase 3 OPTiM trial—a regulatory bar that is fundamentally different.

Second, the "heterogeneity" of the patient population. Enrolled patients had diverse prior treatment histories, ranging from pure PD-1 resistance to mixed PD-1 + CTLA-4 resistance. The FDA argued that this "melting pot" precluded attribution of efficacy. The sponsor countered that historical controls for PD-1-resistant melanoma show an ORR of only ~7%, while RP1 combination achieved an ORR of 33.6%, a CR rate of 15%, and a median DOR >20 months—a striking difference; moreover, real-world heterogeneous populations better reflect clinical practice, and forced stratification would disconnect from actual treatment scenarios.

Third, the "Rashomon" of efficacy assessment. Intratumoral injection lesions are inherently flawed under RECIST criteria—local procedures and biopsies can artificially inflate response rates. When all injected lesions were excluded, the ORR fell from 33.6% to 15.7%, a substantial shrinkage. This is the single-arm trial's most fatal weakness: it cannot rule out selection bias and measurement bias. Compounded by the failure of numerous confirmatory trials for accelerated-approved drugs in recent years, the FDA's Project Confirm has been steadily tightening, adopting a tougher stance toward innovative therapies with "weak signals."

THE SYSTEMATIC ELEVATION OF REGULATORY HURDLES FOR ONCOLYTIC VIRUSES

Tracing the evolution of FDA approval standards for oncolytic viruses reveals a clear upward trajectory: in the T-VEC era of 2015, randomized controlled monotherapy trials were accepted; after 2020, single-arm trials were limited to homogeneous, non-combination, localized tumor types; by 2025, combination ICI regimens essentially require randomized controls. A high ORR alone is no longer sufficient to unlock approval—the weight placed on evidentiary rigor continues to rise. The accelerated approval pathway has not been closed, but it now carries stronger constraints: confirmatory OS data must be submitted within a mandated post-approval timeline, and failure to meet the standard will trigger the indication withdrawal process.

This has crystallized into a three-tier industry consensus on approvability: the priority window points toward localized, intracavitary-delivered tumor types that have failed standard therapy (CG0070's intravesical instillation model in bladder cancer being the archetype); the cautious window covers injectable superficial melanoma monotherapy, which requires RCT support (replicating the T-VEC pathway); the high-barrier window is oncolytic virus combined with ICI for late-line solid tumors, where a randomized controlled design is mandatory—one arm ICI monotherapy, one arm combination, directly comparing incremental benefit to circumvent the attribution controversy. For efficacy assessment, injected lesions and non-injected distant lesions must be reported separately, with sensitivity analyses excluding the injected-lesion-only population.

U.S.-CHINA REGULATORY PATHWAYS: DIVERGENCE AND IMPLICATIONS

The RP1 episode highlights deep regulatory differences between the U.S. and China regarding oncolytic viruses.

In the U.S., no second oncolytic virus product has been approved in the decade since T-VEC. The FDA's new leadership places greater emphasis on evidence-based medicine, shifting from "encouraging innovation" to "strictly upholding evidentiary standards." RP1's two rejections have further chilled investment sentiment in an already cautious oncolytic virus space. Several biotech companies (uniQure, Capricor, Pierre Fabre/Atara) had previously accused the FDA of "flip-flopping" during reviews, and RP1 has become a landmark case in this controversy, even prompting Senator Ron Johnson to launch a formal investigation into the FDA's rare disease and oncology drug approval policies.

China, in contrast, presents a distinctly different landscape. China hosts one of the world's most active oncolytic virus pipelines, with over 50 candidates in clinical stages. The NMPA has not yet established precedent or written guidance as stringent as the FDA's in the oncolytic virus + ICI combination space, objectively providing a differentiated development window for local companies. However, RP1's lessons are equally cautionary: for indications such as gastrointestinal tumors, prioritizing randomized controlled designs and demonstrating added benefit is the only sustainable path; endoscopic or intracavitary administration can reduce RECIST assessment interference and may face a smoother review than superficial intratumoral injections. Companies should avoid relying on single-arm combination regimens for direct BLA submission—Phase 2 should serve only for signal validation, while the registrational stage must employ randomized controlled designs.

The red lines drawn by the FDA through two CRLs are clear and firm: in the context of combination with ICI, single-arm trials are no longer sufficient to support accelerated approval; randomized controls, independent contribution demonstration, and stratified efficacy assessments are three insurmountable thresholds. While this brings short-term pain, it helps steer the industry toward a healthier and more sustainable path. For Chinese oncolytic virus developers, the RP1 lesson is not that "regulation is too strict," but that "evidence design must stay ahead of regulation"—and this may be the most valuable legacy of this year-long regulatory tug-of-war for the industry.

Another broader lesson from the RP1 discussion is the challenge of applying conventional response criteria to new therapeutic modalities. RECIST 1.1 was developed primarily for systemic therapies, where tumor shrinkage serves as a surrogate for treatment activity. However, intratumoral immunotherapies can induce inflammation, immune-cell infiltration, and necrosis, complicating radiographic interpretation of injected lesions. The question is not whether RECIST should be abandoned, but whether it is always the right ruler for therapies with different mechanisms of action. For these approaches, meaningful benefit may extend beyond injected lesions to include systemic responses and durable disease control. Same dilemma was met in CART therapies, how to count the PFS during bridging when disease was still progressing, while the control arm has been treated already. The solution is not less rigorous evaluation, but better tools designed for emerging therapeutic platforms.

FINALE: ACCELERATED APPROVAL WITH STRINGS ATTACHED

After much controversy, RP1 has finally made its breakthrough. On August 6, 2026, the FDA granted accelerated approval to RP1 (brand name Tudriqev) for advanced melanoma—but with a catch: it is approved for marketing now, yet post-marketing clinical data must be submitted; if the predefined endpoints are not met, the approval could still be withdrawn.

The purpose of drug development is to bring meaningful therapies to patients who need them. A truly patient-centered approach requires both scientific rigor and humility about why we develop medicines in the first place. The more interesting lesson is that innovative therapeutic platforms often expose weaknesses in existing evaluation frameworks before they expose weaknesses in biology.

AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

Lin Shen is an Editorial Board member of *The Innovation Oncology* and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group. The other authors report no conflict of interest.