BLA 125827
Vusolimogene oderparepvec (RP1)

Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

July 30th, 2026

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Presentation Outline

- Background
  - Disease background, product description, and IGNYTE study design
- Regulatory context
  - Approval pathways, endpoints, and trial designs
- Key review issues
  - Assessment of response, contribution of effect, interpretation of survival data
- Considerations for committee and voting question

Disease Setting:
Advanced Unresectable Cutaneous Melanoma

- Fifth most common cancer in the U.S.*
- Treatment landscape is rapidly evolving
- Available first-line therapies include:
  - Anti-PD-1 monotherapy (checkpoint inhibitors)
  - Combination checkpoint blockade
  - BRAF-targeted therapy (BRAF V600+)

*SEER Data 2026

Disease Setting:
Second Line and Subsequent Therapies

- Selection of second-line or later treatment depends on several factors
  - Number/types of prior therapies, location/extent of disease, progression patterns
- Available therapies include:
  - Retreatment with anti-PD-1 based therapies
  - Chemotherapy
  - Other therapies (e.g., T-VEC, BRAF-targeted agents)
- Metastatic melanoma remains largely incurable and is area of unmet need

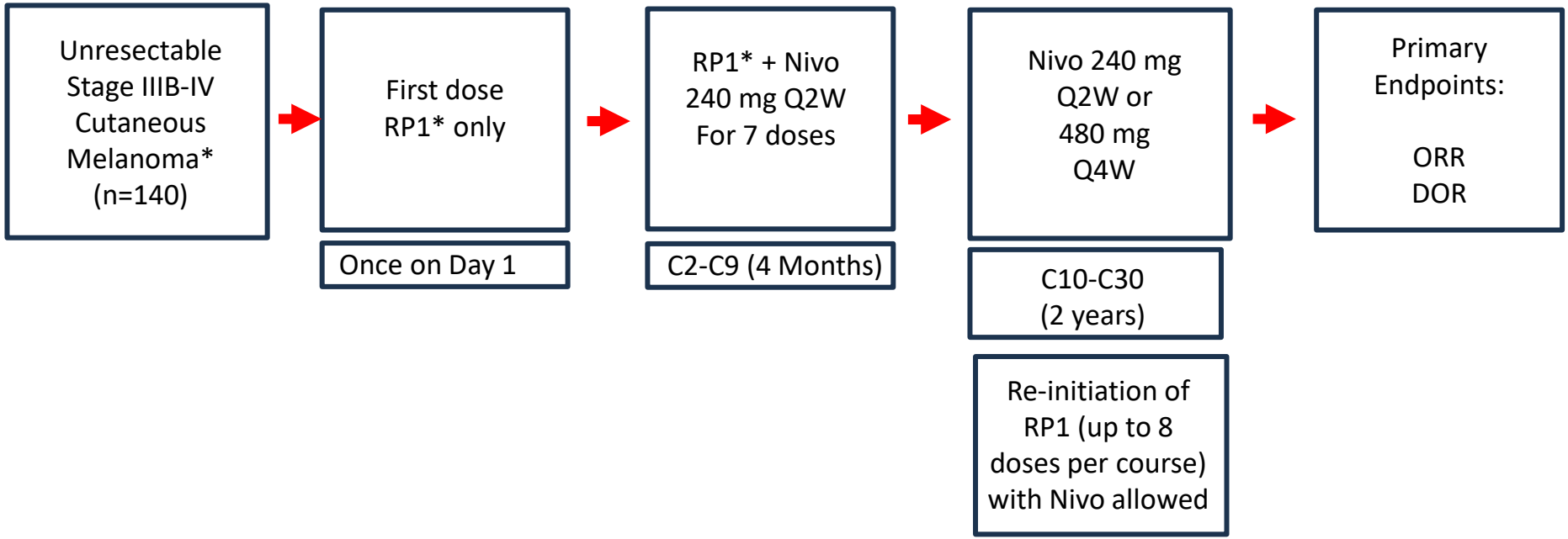
Product Description: Vusolimogene oderparepvec (RP1)

- Genetically modified, selectively replication-competent herpes simplex virus type-1 (HSV-1)
  - Expressing GM-CSF and a fusogenic glycoprotein
  - Administered intratumorally (IT)
- Proposed mechanism of action:
  - Selectively replicates in and directly kills tumors cells
  - Released tumor and viral antigens elicits systemic antitumor response
  - Complements anti-PD-1 by increasing # of tumor reactive T cells
- Proposed Indication:
  - In combination with nivolumab for treatment of adult patients with unresectable advanced cutaneous melanoma who experienced disease progression with PD-1-blocking antibody-based therapy

Product Description: Nivolumab

- Programmed death receptor-1 (PD-1) blocking antibody
  - Also referred to as anti-PD-1 therapy, immunotherapy, or checkpoint inhibitor therapy
- Has several indications including for the treatment of:
  - Unresectable or metastatic melanoma
  - Adjuvant, completely resected melanoma
- Toxicities include immune-mediated reactions
  - Can be severe or fatal
- Applicant proposes synergy between RP1 and nivolumab

IGNYTE Trial Design:
Anti-PD-1 Refractory Cutaneous Melanoma Cohort



FDA Conveyed Concerns with Study Design

- FDA conveyed concerns from 2021 to 2024 that included:
  - IGNYTE not designed to demonstrate contribution of components
  - Population heterogeneity may impact interpretability
  - Interpretation of responses to intra-tumoral (IT) therapies may be problematic in injected lesions
- FDA recommendations included:
  - A randomized clinical trial (RCT) design
  - Use of RECIST v1.1 for response assessment
- FDA ultimately did not object to submission based on IGNYTE
  - Consideration of unmet need

FDA Review Issues

1. Applicant's reported ORR and DOR are unreliable and difficult to interpret
2. Contribution of effect and need for each product not demonstrated
3. Applicant's submitted overall survival (OS) analysis not interpretable

Regulatory Context: FDA Approval Pathways

- Accelerated approval and traditional approval both require demonstration of substantial evidence of effectiveness
- Traditional approval
  - Based on direct measure of clinical benefit, or effect on a validated surrogate
- Accelerated approval (serious, life-threatening conditions)
  - Based on a surrogate or intermediate endpoint reasonably likely to predict clinical benefit
  - Requires meaningful improvement over available therapy
  - Post-approval clinical (confirmatory) trial(s) to verify benefit

Single Arm vs. Randomized Trial Designs

- Randomized trials preferred for evaluating cancer therapeutics
  - Mitigate bias by accounting for both known and unknown factors
  - Can evaluate time-to-event endpoints (OS)
  - Can assess contribution of effect in combinations
  - Allow robust comparative safety evaluation
- Single arm trials may support FDA approvals:
  - When randomized trials are infeasible/unethical
  - Most often used to support accelerated approvals with response-based endpoints
  - However, response not validated surrogate for other endpoints (e.g., OS)

ORR as an Endpoint

- Has supported traditional and accelerated approvals depending on context
- Considered a direct measure of drug antitumor activity
- Can be assessed in a single-arm trial design
- Duration of response (DOR) is used to support ORR
  - Important to demonstrate that the effects are not transient
  - Can be challenging to interpret without concurrent control
- Multiple variables impact the clinical meaningfulness of ORR and DOR:
  - Magnitude of effect observed
  - Likelihood of symptom or functional improvement
  - Degree of unmet need

Regulatory Context: Response Criteria

- Standardized response criteria minimize bias, measurement error, and variability that can impact interpretation of ORR and DOR
- **RECIST v1.1** commonly used for assessment of solid tumors:
  - Established to standardize tumor response assessment
  - Developed specifically to assess response to systemic therapies
  - Allows for latitude in certain circumstances, when clinically justified
  - Uniform and consistent application of criteria critical to interpret results

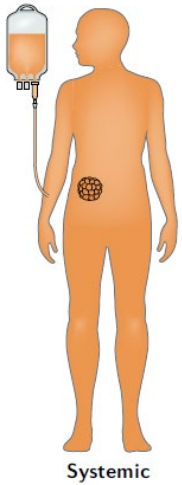
Eisenhaur 2009

Limitations of RECIST for Intratumoral Therapies

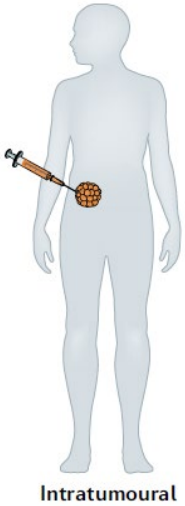
- RECIST criteria not designed to assess response to IT therapy
  - Lesions receiving local treatments “usually not considered” measurable unless tumor grows
  - Difficult to distinguish local from systemic effect
- No consensus on response criteria for IT therapies
  - itRECIST not broadly adopted or validated and difficult to implement
  - Society for Immunotherapy of Cancer (SITC) recommends RECIST with modification for confirming progression
- Interpreting ORR and DOR for intratumoral therapies is challenging

Goldmacher 2020; Luke 2024

Response Rate: Systemic vs. IT Therapies


Systemic

- Systemic therapies allow equal exposure to drug
- Target lesions, regardless of location, may be valid measure of drug's systemic effect


Intratumoural

- Injected lesions receive direct local drug exposure
- Responses may be result of
  - Local oncolytic activity
  - Local immune activation
  - Injection related volume changes

- Assumptions for use of response rate for systemic therapy may not apply to IT therapies

Melero et al., https://doi.org/10.1038/s41571-021-00507- y

Uncertainty in Response Assessments for IT Therapies

- Interpretation of responses to IT therapies challenging:
  - May represent local effect rather than systemic effect
  - Comparison to systemic therapies may not be valid
  - May effectively be different endpoints
- ORR per RECIST v1.1 may be considered for evaluating IT therapies if:
  - Systemic effect can be demonstrated
  - Magnitude of benefit is large to account for residual uncertainty
  - Uniform and consistent application of pre-specified criteria is critical

FDA Efficacy Analyses

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

*Excluding Patients Who Had All TLs Injected or No TLs at Baseline from Responders
**Excluding Patients Who Had All TLs Injected or No TLs at Baseline from Evaluable Population, including Responders

- 23 patients deemed responders had all target lesions injected
- 2 patients deemed responders had no target lesions at baseline

FDA Review Issue #1: Application of Response Criteria in IGNYTE

Response Assessment Element	Effect on Interpretation of Response
1. Lack of non-injected target lesions in patients	• Limits ability to establish systemic effect of RP1
2. New or growing tumors re-injected	• Some patients may not have had true response • Some response durations inaccurately inflated
3. Procedures on tumors before response assessment	• Response may be due to removal of tumor tissue instead of RP1 + nivolumab
4. Pathology used to reclassify responses	• May overestimate reported responses
5. Non-evaluable assessments on study	• Some patients may not have had true response • Some response durations inaccurately inflated

FDA Review of Applicant-Reported ORR/DOR

- Reported ORR and DOR results artifactually increased
- Full extent of impact cannot be determined
- Not consistent with principles of the pre-specified RECIST criteria
- Applicant reported ORR and DOR results are unreliable and difficult to interpret

Applicant's Implementation of Independent Review Charter

- Retrospective IRC review may have caused or compounded response assessment issues
- IRC design and conduct affects interpretation of trial outcomes
  - Applicant approved individual radiologists and oncologists to perform "independent review"
  - Applicant provided clinical data to IRC for review, including exam findings, clinical history, pathology results, and relevant clinical notes
  - Several IRC response designations changed
- FDA notes potential for bias in these methods
  - Unclear impact on reported results

FDA Review Issue #2: Contribution of Effect

- IGNYTE not designed to demonstrate the contribution of components
- FDA advised Applicant to conduct randomized trial
  - Applicant cited lack of equipoise in randomizing to nivolumab alone
  - However, Applicant subsequently did initiate such an RCT
  - IGNYTE-3 study is ongoing confirmatory study for RP1
- FDA did not object to reviewing single-arm trial data due to unmet need
  - Large magnitude of benefit, evidence of systemic effect, and strong scientific rationale could potentially mitigate these concerns
- FDA review determined that contribution of each component not demonstrated

FDA Review Issue #3: OS Data Not Interpretable

- Applicant reports estimated median OS of 32.9 months (95% CI: 25.7, 46.0)
- Time-to-event endpoints such as OS difficult to interpret from single arm trials
  - Absence of concurrent control necessitates comparison to external control
  - Apparent differences may be due to reasons other than study intervention
- Some populations of patients with advanced melanoma have demonstrated survival measured in years
- Randomized trial necessary to evaluate OS as an endpoint

FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics; December 2018

FDA Review Summary

- Several issues with application of response criteria:
  - Effects interpretability and reliability of ORR and DOR
  - Systemic effect of RP1 not demonstrated
- Contribution of RP1 and nivolumab not well characterized
  - Toxicity without contribution to efficacy may not be justified
- Overall survival exploratory analysis uninterpretable
- Clinical benefit of RP1 is unclear in the intended population

Considerations for the Committee

- Accelerated approval has the same statutory requirement for substantial evidence of effectiveness as traditional approval.
- Unclear if observed responses are likely to predict clinical benefit in patients with advanced/metastatic disease.
- Determining if results are clinically meaningful further confounded by trial design and conduct issues

Discussion Topics

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

- Discuss the clinical meaningfulness of the response rate and duration of response reported in Study IGNYTE and if the observed responses are indicative of systemic anti-tumor activity attributable to vusolimogene oderparepvec.

Voting Question

Are the efficacy results from IGNYTE evaluable and clinically meaningful?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