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BLA 125827
Vusolimogene oderparepvec (RP1)

Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

July 30th, 2026

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Acting Branch Chief, Oncology Branch 2
Division of Clinical Evaluation Oncology, Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics Evaluation and Research, FDA

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Key Efficacy Issues

- Application of response criteria in the IGNYTE study compromise the reliability and interpretability of the primary efficacy outcome measures of objective response rate (ORR) and duration of response (DOR).

- Objective response data from the single-arm IGNYTE study are not of sufficient magnitude to overcome concerns regarding the contribution of effect, particularly in the absence of a reliable historical control.

- Applicant's submitted overall survival (OS) analysis is not interpretable.

Presentation Outline

- Background
  - Disease setting
  - Regulatory context and history
- Summary of efficacy
  - Overview of IGNYTE study
  - Efficacy issues in detail
- Summary of safety
- Considerations for Advisory Committee

Disease Setting:
Advanced Unresectable Cutaneous Melanoma

- Available therapies as initial treatment (first line) include:
  - Anti-PD-1 monotherapy
  - Combination checkpoint blockade (e.g., nivolumab + ipilimumab, nivolumab + relatlimab)
  - BRAF-targeted therapy (BRAF V600+)
- Subsequent therapy depends on several factors
  - Selection of therapies depend on patient characteristics, preferences, and prior therapies received
  - This is an area of unmet need

Prior Intratumoral Melanoma Therapy Approval: Talimogene laherparepvec (T-VEC)

- Intratumoral oncolytic viral therapy
- Granted traditional approval in 2015 based on durable response rate per WHO criteria
  - Randomized study vs GM-CSF control in unresectable advanced melanoma
  - Did not include coadministration of systemic product
- At advisory committee in 2015, concerns included:
  - Challenges in interpreting lesion level analyses to support claim of systemic effect
  - Other therapies, including benzene derivatives, can be injected “into virtually any lesion and have it go away”
  - Robust discussion regarding importance of characterizing systemic effect
- Indication restricted to local treatment of unresectable cutaneous, subcutaneous, and nodal lesions
  - Limitation of use: T-VEC has not been shown to improve overall survival or have an effect on visceral metastases

Key Regulatory History: IGNYTE Initiated as Exploratory Study

- Study RPL-001-16 (IGNYTE) initiated in 2018 as an exploratory Phase 1/2 study evaluating RP1 in multiple tumor types
  - Anti-PD-1 refractory cutaneous melanoma cohort added in 2019
  - Subsequent revisions materially changed the eligibility criteria and study conduct

Year	Key Changes
2020	- Established Independent Review Committee (IRC) - Decreased required duration of prior anti-PD1 exposure from 12 to 8 weeks - Removed prior eligibility criteria excluding patients with ≥10cm tumor burden
2021	- Required minimum 25% of patients with visceral metastases for injection
2022	- Removed visceral lesion enrollment requirement

FDA Conveyed Concerns With IGNYTE Study Design to Support BLA

- Multiple FDA / Applicant interactions between 2021 and 2024 regarding IGNYTE study concerns included:
  - Study not designed to isolate contribution of effect of RP1
  - Study population heterogeneity may affect interpretability
  - Proposed target of 30% to 40% ORR may not translate into unequivocally improved clinical benefit in this indication
  - Interpretation of responses in the setting of intra-tumoral route of administration may be problematic in lesions which have been injected
- FDA recommended
  - Randomized study design to support BLA
  - Use of RECIST v1.1 for response assessment

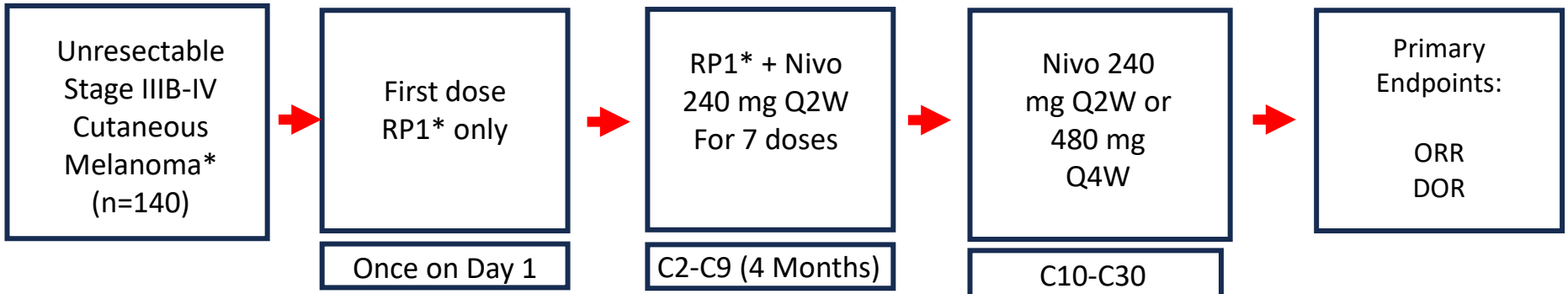
Study Designs Considerations

- RCTs mitigate bias, support time-to-event endpoints like OS, and allow comparative safety evaluation
- Others in oncology community support RCTs
  - SITC: “Single-arm data for any agent can be misleading and comparison” preferred when IT drug used “in combination with a systemic agent”
- Single arm studies may support FDA approvals when randomized trials are infeasible/unethical
- Applicant’s rationale for not conducting RCT was lack of equipoise
- FDA did “not object” to BLA submission based on single arm IGNYTE study
  - Applicant would need to demonstrate need for both products, systemic effect, and have large magnitude of effect in primary endpoint

Key Regulatory History

Interaction Date	Interaction Type	Key Regulatory Points
November 2024	Breakthrough Designation	• Granted based on IGNYTE Phase 2 anti-PD1 refractory cohort (n=140) • ORR 32.9% (95% CI: 25.2, 41.3), mDOR 33.7 months (95% CI: 14.1, NR)
November 2024	Initial BLA submission	• Single arm IGNYTE study used to support BLA
July 2025	CR Letter	• IGNYTE not adequate and well controlled study • Study results difficult to interpret due to pt heterogeneity • Unable to assess contribution of effect of RPI
September 2025	Type A meeting	• Response criteria not consistent with RECIST v1.1 • Recommended amending Phase 3 study to evaluate RR at interim analysis to generate more supportive data
October 2025	BLA resubmission	• Minimal new data provided (early unplanned analysis from IGNYTE 3, representing 10% of the planned enrollment) • Essentially same data package as initial submission
April 2026	CR Letter	• Issues from first CRL were not addressed • Response assessment methods confound efficacy results
June 2026	BLA resubmission #2	• Added IGNYTE 3-year Overall Survival analysis

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



- Stage IIIb to IV cutaneous melanoma
- Confirmed PD after ≥8 weeks of nivolumab or pembrolizumab, received either alone or in combination with other treatment
- ICI must have been last line of prior therapy
- Prior ICI treatment in adjuvant setting allowed

Re-initiation of RP1 (up to 8 doses per course) with Nivo allowed

*Injection Methods

- Superficial or visceral lesions
- Multiple tumors OK
- Largest tumors first
- New tumors eligible

IGNYTE Efficacy Results: Applicant Reported

Objective Response Rate (ORR) and Duration of Response (DOR)

Phase 2 Anti-PD-1 Refractory Cohort (N=140)	
Objective Response Rate by IRC	
ORR % (95% CI)	34 (26, 42)
Complete response rate, n (%)	23 (16)
Partial response rate, n (%)	24 (17)
Duration of response (DoR)	
Median DoR in months (95% CI)	24.8 (14.1, NR)
DoR range, months	3 to 49+

IGNYTE Efficacy Results: Applicant Reported

3-year Overall Survival Results

Phase 2 Anti-PD-1 Refractory Cohort (N=140)	
Number (%) of patients who died	71 (50.7%)
Median OS (months) (95% CI)	32.9 (25.76, 46.03)

*Data cutoff: March 8, 2026

Key Efficacy Issues

- Application of response criteria in the IGNYTE study compromise the reliability and interpretability of the reported ORR and DOR.

- Objective response data from the single-arm IGNYTE study is not of sufficient magnitude to overcome concerns about the contribution of effect, particularly in the absence of a reliable historical control.

- OS analysis is not interpretable.

Key Efficacy Issues

- Application of response criteria in the IGNYTE study compromise the reliability and interpretability of the reported ORR and DOR.

- Objective response data from the single-arm IGNYTE study is not of sufficient magnitude to overcome concerns about the contribution of effect, particularly in the absence of a reliable historical control.

- OS analysis is not interpretable.

Use of RECIST for Response Assessment

- Interpretation of responses to IT therapies is challenging
  - RECIST criteria designed to assess response to systemic therapies
  - Difficult to distinguish local from systemic effects
  - March 2021 meeting: FDA conveyed to the Applicant that responses in injected lesions would be difficult to interpret
- Lack of consensus response criteria for IT therapies
- 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
- FDA recommended response assessment by RECISTv1.1

Regulatory Context: RECIST Criteria

- Tumors are tracked using imaging (e.g., CT scans, MRIs) and other methods
- Up to 5 lesions total are selected as “target lesions”
  - Allow for reproducible repeated measurements
  - Longest diameter of each target lesion measured and added together (sum of diameters [SOD])
- Other abnormal areas tracked as “non-target lesions”
  - Noted if present or absent, not precisely measured
- At each scan, same lesions are re-measured to assess response

Regulatory Context: RECIST Criteria

Response Category	Criteria
Complete Response (CR)	All lesions have disappeared
Partial Response (PR)	Tumor burden decreased by ≥30%
Stable Disease (SD)	Neither enough decreased for response or enough growth for progressive disease
Progressive Disease (PD)	Tumor burden increased by ≥20% AND increased by at least 5 mm in absolute size, OR new lesions have appeared

- Responses should be confirmed at a follow up scan (~4 weeks later)
- Progressive disease does not require confirmation
- If unsure if new lesion is disease, can do follow up scan to confirm PD

Issues With the Application of Response Criteria

1. Lack of Noninjected Target Lesions (TLs) to Assess Systemic Effect
2. Re-injection of Lesions and Assessment of Progression
3. Confounding Effect of Procedures
4. Use of Histology Assessments to Reclassify Response
5. Non-evaluable Assessments

Issue #1: Lack of Noninjected Target Lesions (TLs) to Assess Systemic Effect

- RECISTv1.1 criteria:
  - Requires designation of Target Lesions at baseline
  - Focal intervention generally renders treated lesions non-evaluable
- SITC guidelines: "Target lesions must include noninjected lesions"
- Determining systemic response is critical to supporting efficacy claim
  - Responses in injected lesions may be the result of local oncolytic activity, immune activation, or injected-related volume changes
  - Rather than due to indicators of a true systemic response

Intratumoral Therapies for Cutaneous Melanoma

- Published clinical studies report ORR and CR up to 90% for other IT investigational products (non-approved) in various melanoma populations
  - IL-2, BCG, Rose Bengal, benzene derivatives
  - Unclear systemic effect
- Response to IT therapies may be due to local effects
- Clinical benefit of local responses in advanced/metastatic melanoma is uncertain
  - Other local interventions (e.g., metastasectomy, radiation) may be used in oligometastatic patients but unclear benefit

FDA Efficacy Analysis

ORR and DOR Excluding Patients Who Had All TLs Injected or No TLs at Baseline

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

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

FDA Sensitivity Analysis of ORR and DOR

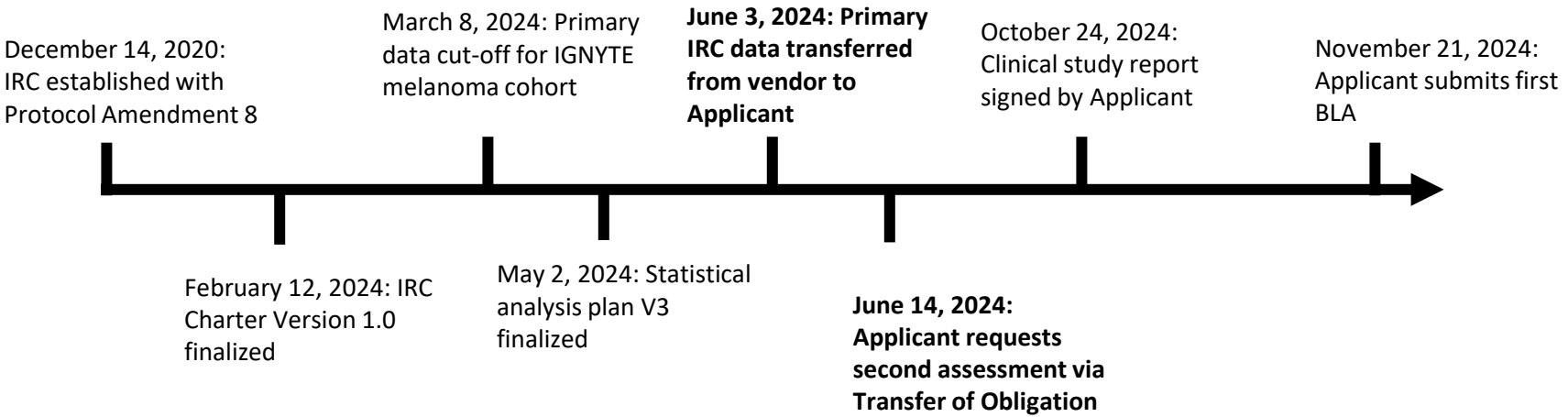
- Additional sensitivity analysis excludes patients with all injected lesions or no target lesions from total population
  - Efficacy evaluable population decreases to 89
  - ORR 24.7% (95% CI: 16.2, 35.0)
  - Median DOR 14.1 months (19.7, NR)
- Excluding these patients may be a form of “informative censoring”:
  - Characteristics in these patients may make them more or less likely to respond
- FDA concludes that reported ORR and DOR are confounded

Uncertain Systemic Effect of RP1

- Applicant provides multiple exploratory analyses of response in injected vs noninjected lesions to support claim of a systemic effect
- Analyses are challenging to interpret:

Selection Bias	Noninjected lesions are a highly selected subgroup (e.g., inaccessible, too small, or already responding).
Temporal Misalignment	Dataset only captured whether a lesion was ever injected vs. never injected.
Contribution of Effect	Responses in uninjected lesions may be due to nivolumab alone.
Uncertain Clinical Meaning	Mixed lesion-level responses may not correlate with patient-level objective response.

Applicant Exploratory Analyses: IRC Remeasurement after Data Transfer

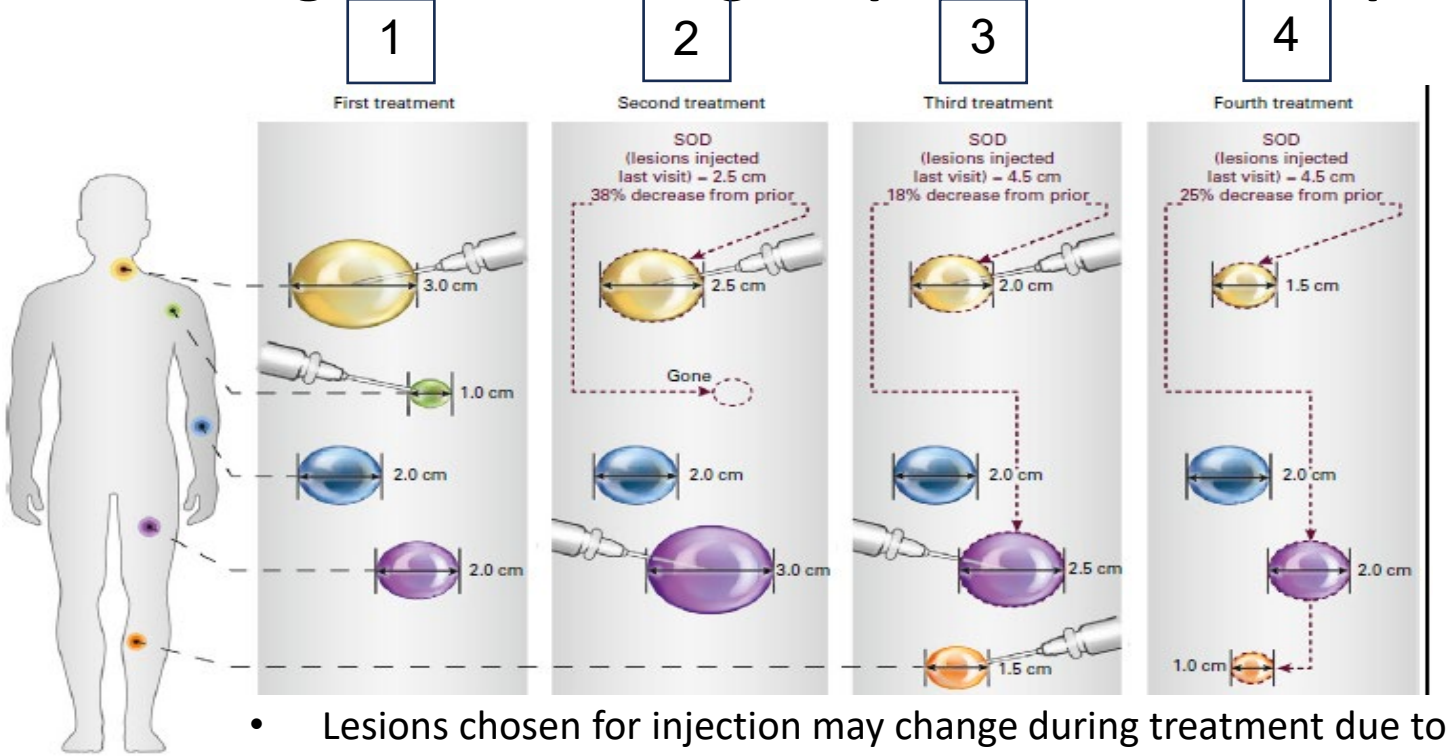


- Additional IRC assessment conducted 11 days after initial IRC data transmitted to Applicant
  - Includes additional lesion measurements using different minimum size thresholds beyond what is described within the final charter

Issue #2: Re-injection and Assessment of Progression

- IGNYTE study allowed for re-treatment with RP1 beyond progression per investigator discretion.
- FDA review identified patients with either new lesions or existing lesions identified as having enlarged that were selected for retreatment with RP1 injections.
- Injecting lesions that are new and considered equivocal, or enlarging existing lesions that have not yet met criteria for PD, obscures the development of PD and may impact the IRC assessment.
- If new lesions deemed appropriate and large enough in size to inject and treat, unclear why these would be deemed “equivocal.”

Challenges in Assessing Response to IT Therapies



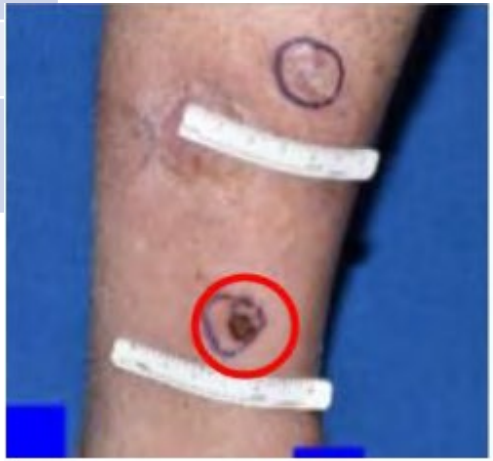
- Lesions chosen for injection may change during treatment due to regression, loss of accessibility, or growth of other lesions
- Injecting new lesions and enlarging lesions can obscure the development of progression

Goldmacher; Ascopubs.org/journal/jco 2020

Example: Confounding of New Lesions and Treatment Beyond Progressive Disease

Apr 2021	Partial Response
Aug 2021	2 new inguinal lymph nodes (16 mm each) New lesions injected ×8 over following 3 months
Nov 2021	Progressive Disease
Mar 2022	Complete Response
Feb 2024	2nd Progressive Disease

Target lesion (IRC):
skin (10mm)



Response assessment ignores intervening Progressive Disease
Applicant Best Overall Response: Complete Response
Applicant Duration of Response: 34 months (vs. 4 months)

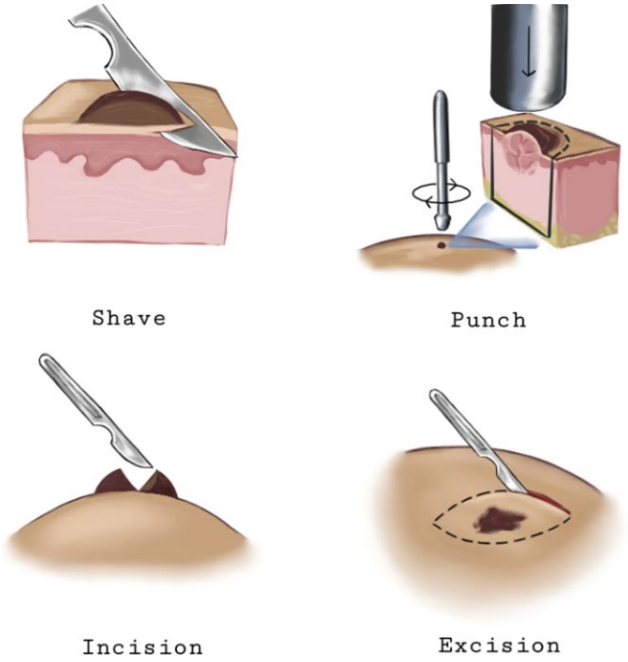
Treatment Beyond Progressive Disease

- Fourteen patients considered responders were treated beyond progression with additional RP1 and/or nivolumab
- For 6 patients, no impact apparent on reported results
  - Continued treatment occurred after documented PD
- For 5 patients, potential for patient being a non-responder
- For 3 patients, potential for inaccurate DOR determination
  - PD likely occurred earlier
  - Applicant-reported DOR may be artifactually inflated

Issue #3: Confounding Effect of Procedures

- IGNYTE allowed curative intent surgery for patients considered unresectable at screening but subsequently deemed resectable on study
- Required biopsies (core or excisional) for exploratory biomarker analyses at baseline and at Study Day 43, with additional optional biopsies allowed
- Among 47 patients deemed responders by Applicant:
  - 115 procedures performed on tumor lesions
  - 80 procedures on TLs (44 on treatment, 36 at screening)
  - Procedures included excisional biopsy (n=7), resection of lesions (n=5), core biopsy (n=57), punch biopsy (n=9), other biopsy (n=2)

Potential Impact of Biopsies and Procedures



- Surgical resection, excisional biopsies, and other biopsies of small lesions confounds response assessments

Alwahaibi et al. https://doi.org/10.3389/fmed.2025.1476685

Example: Confounding Excisional Biopsy Prior to Response Designation

Nov 21, 2022	Stable disease
Jan 17, 2023	New Lesion Identified Excisional biopsy of unknown scalp lesion → pathology confirms in-transit melanoma
Jan 18, 2023	Day after excisional biopsy, deemed a partial responder
Apr 2023	Progressive disease

- Baseline disease: two scalp target lesions (16mm, 11mm)
- Unclear if new or existing scalp lesion was excised
- Removal of lesion the day prior to response assessment confounds response

IGNYTE Population and Potential Impact of Procedures

Number of Target Lesions at Baseline in Responders	Number of "Responding" Patients (N=47), N (%)
No target lesions	2 (4)
1 target lesion	14 (30)
2 target lesions	16 (34)
3 target lesions	7 (15)
4 target lesions	8 (17)

Majority of patients deemed responders had 2 or fewer target lesions

Disproportionate Responses Observed Based on Baseline Disease Burden

Sum of Diameters (SOD)[a]	N	Responders (CR + PR)	% of Patients Responding Within Category	CR	CR Rate
≤20 mm	19*	12	**63%**	11	**58%**
21-50 mm	41	16	**39%**	7	**17%**
51-100 mm	37	13	**35%**	5	**13%**
101-150 mm	26	4	**15%**	0	**0%**
>150 mm	17	2	**12%**	0	**0%**

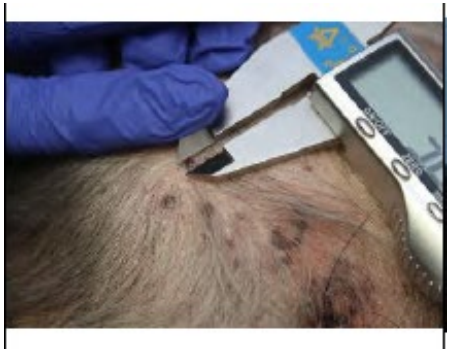
[a] FDA acknowledges that SOD categories are arbitrarily defined based on size for the purposes of this analysis.
*Includes 2 patients with no baseline target lesions at baseline

- In patients with few or small lesions procedures and local injection effects may have disproportionate effect on response assessment
- True extent of impact on ORR and DOR results cannot be determined

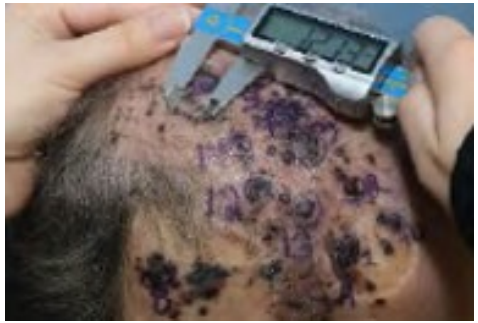
Issue #4: Histology Assessments to Reclassify Response

- Histopathologic assessments retrospectively changed the response assessment in some cases
- RECISTv1.1:
  - Histology can be used to differentiate between PR and CR in rare cases (e.g., germ cell tumors)
  - May lead to false positive CRs
- FDA identified seven patients designated as complete responses by Applicant based on histopathology results (15% of responders)
- Challenges with this approach include:
  - Histology was not centrally reviewed (potential reader variability/bias)
  - Potential for biopsy sampling error
  - Potential impact of IT administration affecting histology interpretation
  - May overestimate the ORR and CR rate

Example: Response Retrospectively Changed from PD to CR by Histology Assessment (>300 days later)



Baseline Disease: 2 non-target scalp lesions (no target)



First Assessment: Progression (new lesions)

Visit	IRC	IRC Retrospective
MAR2023	PD	NE
MAY2023	PD	NE
JUL2023	PD	NE
DEC2023	PD	NE
APR 2024	PD	CR
MAY2024	PD	CR

- > 300 days after last study dose, negative biopsy of scalp lesion
- Best Overall Response: Complete Response based on histology results
- **All prior Progressive Disease assessments retrospectively changed to 'Non-Evaluable'**

Issue #5: Non-Evaluable Assessments

- Repeated non-evaluable (NE) assessments can complicate best overall response and duration of response interpretation
- Several responders had repeated NE assessments because complete imaging was not provided to the IRC
- Issue may have been compounded due to the retrospective implementation of the IRC

Example: Confounding of Multiple NE Assessments

Independent Review (RECIST 1.1)	Investigator Assessment (mRECIST 1.1)
PD	PD
-	NE
-	NE
-	PD
-	CR
CR	CR
-	CR
CR	-
CR	CR
CR	CR
NE	PD

- No target lesions at baseline
- Non-target cutaneous lesions in right forearm
- PD at first assessment due to development of 7 new lesions in right forearm, several new lesions were injected
- Multiple NE timepoints because photos not submitted by Investigator to IRC
- Later underwent biopsy of injected lesion in right forearm leading to CR

Patients With NE Assessments in IGNYTE

- FDA review identified 13 patients deemed responders by Applicant with at least one NE assessment
- Four patients had NE assessments that raise concerns about Applicant's response designation
  - Unclear if patient should be classified as responder at subsequent timepoints
- Three patients likely responded, however DOR may be inflated
  - May have actually progressed earlier than determined by Applicant
- FDA cannot determine full impact of NE assessments
  - May result in overestimation of ORR and DOR

Applicant's Implementation of Independent Review Charter

- IRC established after initiating IGNYTE trial (finalized 4 years later)
  - 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 after receiving data
- Potential for bias because of these methods
  - Extent of impact on response assessments cannot be fully determined

Summary: Response Assessment

- Applicant's implementation of RECIST criteria in IGNYTE affects reliability and interpretability of the reported results
- Meaningful differences in application of response criteria result in:
  - Essentially a different endpoint than ORR per RECISTv1.1
  - Inability to compare to historical controls
  - Inability to determine if RP1 has systemic effect
- Conduct of the IRC further compounds these issues
  - Retrospective nature of review may have caused or compounded issues
  - Concerns with whether IRC was sufficiently "independent"
  - Potential for bias

Key Efficacy Issues

- Application of response criteria in the IGNYTE study compromise the reliability and interpretability of the reported ORR and DOR.

- Objective response data from the single-arm IGNYTE study is not of sufficient magnitude to overcome concerns about the contribution of effect, particularly in the absence of a reliable historical control.

- OS analysis is not interpretable.

Contribution of Effect

- Single arm IGYNTE study not designed to demonstrate the contribution of each product (RP1 + nivolumab)
  - FDA advised Applicant to conduct randomized study with nivolumab alone as control
  - Applicant stated that this may not be ethical due to lack of equipoise
- FDA exercised flexibility by agreeing to review data from a single-arm trial given the unmet medical need
  - Large magnitude of benefit, evidence of systemic effect, and strong scientific rationale could potentially mitigate these concerns
  - Applicant's responsibility to address these concerns with the data

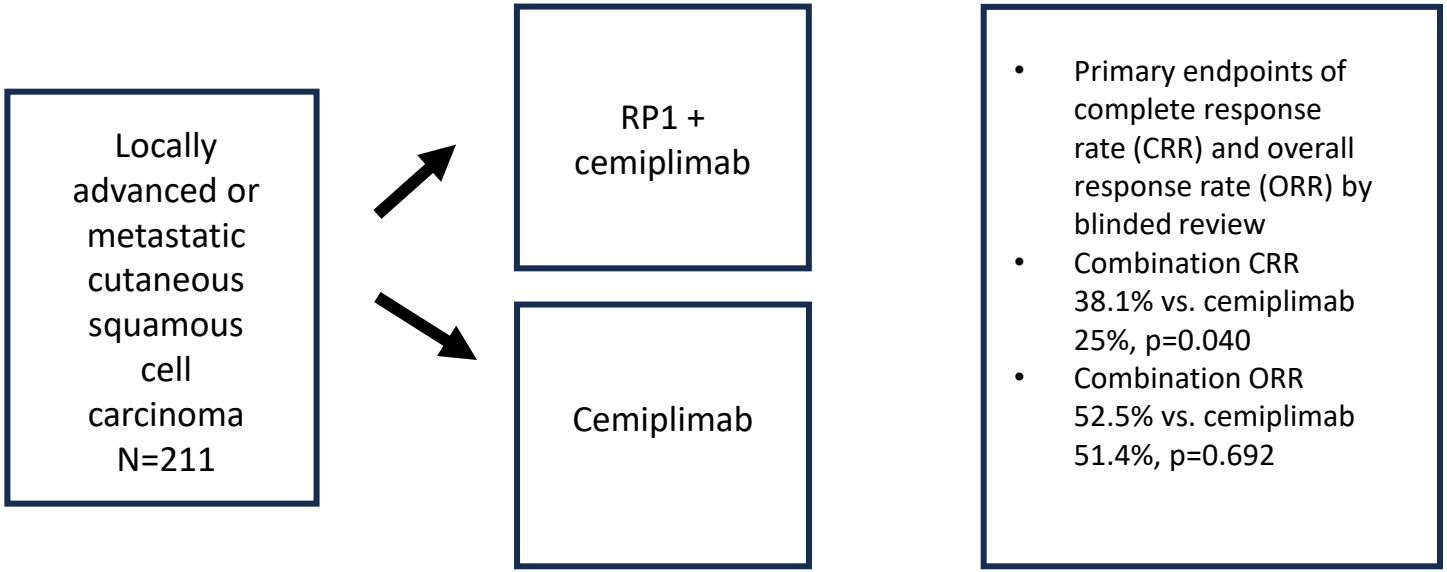
Heterogeneity in IGNYTE Population

Baseline Characteristic	Overall (n=140)
Disease stage	
Stage IIIB/IIIC	29% (41/140)
Lesion location	
Skin only	18.6% (26/140)
Involving lymph nodes	62.9% (80/140)
Liver	17.1% (24/140)
Lung	35.0% (49/140)
Median SOD of TL by IRC, mm	63 (range: 10-287, n=138)
Prior anti-PD1 based therapy Setting	
Adjuvant	25.7% (36/140)
Prior anti-PD1 based therapies	
More than one line	40% (56/140)
Prior anti-PD1 and anti-CTLA	44% (61/140)
Median duration of immediate prior anti-PD1, weeks (range)	20 (4-240)
Total prior anti-PD1 treatment duration, weeks (range)	34 (6-472)

Variable Historical Response Rates Reported for Immune Checkpoint Rechallenge

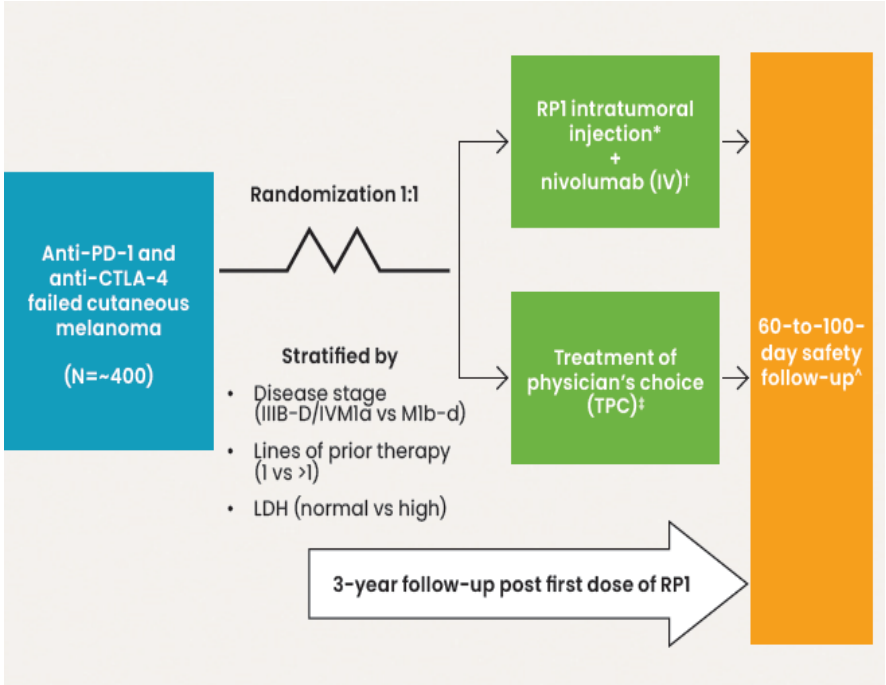
Study	Regimen	N	ORR	Notes
Beaver et al. 2018	Anti-PD-1 beyond RECIST progression	500	~19%	FDA-published pooled analysis
Ribas et al. 2018	Anti-PD-1 beyond RECIST progression	1361	~6-7%	Correspondence to Lancet in response to Beaver 2018
Nardin et al. 2023	ICI rechallenge (multiple regimens)	85	~54%	Multicenter retrospective
Olson et al. 2021	Pembro + ipilimumab post anti-PD-1	70	~29% (per irRECIST)	Dual ICI rechallenge
Reschke & Ziemer 2020	Anti-PD1 rechallenge (Group 1)	85 (Group 1)	15.5% (Group 1)	Retrospective review
Simeone et al. 2025	Anti-PD1 rechallenge	84	21%	Single center, retrospective
Ascierto 2023 (REL-020)	Nivo + relatlimab post anti-PD-1	164 (D2 Cohort)	~12% (D2 Cohort)	Prospective, randomized trial

Biological Plausibility: The CERPASS Study



- Neither primary endpoint was met
- FDA acknowledges SCC is a different disease than melanoma
- However, raises questions on generalizability of Applicant's proposed mechanism of action

Phase 3 Study IGNYTE-3 Data Insufficient to Establish Contribution of Effect



Physician's Choice Options:

1. Nivolumab + relatlimab
2. **ICI re-challenge (monotherapy nivolumab or pembrolizumab)**
3. Single-agent chemotherapy (dacarbazine, temozolomide, paclitaxel/nab-paclitaxel)

- Primary endpoint: OS
- Preliminary Data submitted = 10% of planned enrollment: (Data cutoff: Sept 24, 2025)
  - 41 patients randomized: 23 (RP1 + nivolumab) and 18 (PC) arm, all in US
  - **Preliminary response: more responders in RP1 + Nivo (3) than in PC (0)**

Applicant Exploratory Analysis: Patient Serving as an Internal Control (ORR)

- Applicant compared ORR in patients on immediate prior therapy to ORR on IGNYTE study
  - Claims “any additional response observed subsequently reflects the additional [“add on”] effect contributed by RP1 to nivolumab”
- Created subgroup of 104 patients where “add-on effect is best seen”
  - Excluded patients whose prior therapy was in adjuvant setting
- Reports the following results:
  - 12 of 104 patients had response to prior therapy (ORR 11.5%)
  - 31 out of 104 patients had response on IGNYTE (ORR 29.8%)

FDA Issues With Applicant's Exploratory Analysis of ORR

- Exploratory analysis with lack of pre-specification and no type 1 error control further complicated by
  - Applicant selecting subgroup (n=104) for analysis
  - Aforementioned response assessment issues
- Enrolling on IGNYTE required progression on prior treatment
  - These patients guaranteed to have progressed
  - Not a valid internal control
  - Prior therapy ORR assessed by investigator (vs. by IRC in IGNYTE)
  - Unclear if within-subject correlation was properly accounted for
- FDA conclusion:
  - This analysis is structurally flawed and favors on-IGNYTE group by design
  - Uninterpretable and not supportive of contribution of RP1 to combination

Applicant Exploratory Analysis: Patient Serving as an Internal Control (PFS)

- Median PFS in responding patients (n=47) of 30.6 months vs. time to progression (TTP) on prior therapy as 4.4 months
- FDA concludes that this analysis is uninterpretable:
  - Time to event endpoint assessed in single arm trial without control
  - Comparing response to patients who already progressed is not a valid internal control
  - Prior therapy response assessed by investigator (vs. by IRC in IGNYTE)
  - PFS and TTP are different endpoints with different event definitions
  - In the full 140 patient cohort, Applicant reports median PFS of only 3.6 months
  - Response assessment issues as previously discussed confound this analysis

FDA Concerns Regarding COE

- RP1 may have driven local responses in patients with few or small skin lesions
  - Population with better prognosis
  - May not be indicative of clinical benefit in the intended population
  - Should not be extrapolated to patients with higher disease burden/poorer prognosis
- Nivolumab may have driven responses in a few patients with higher disease burden
  - Potential prior pseudo-progression before trial entry
  - Delayed immunotherapy effect
- There may not be true synergy
  - Unable to determine which patient needs which component of combination
  - Yet all patients exposed to risks of both (hemorrhage, infection, systemic toxicity)

Summary: Contribution of Effect

- Published literature of anti-PD-1 rechallenge in melanoma patients report widely variable response rates
- Reflects inherent heterogeneity in:
  - Patient populations
  - Definitions of prior treatment failure
  - Response assessment methods used across studies
- Expected response to anti-PD-1 rechallenge cannot be reliably extrapolated
- Magnitude of the observed effect not sufficient to overcome the uncertainties about the contribution of effect

Key Efficacy Issues

- Application of response criteria in the IGNYTE study compromise the reliability and interpretability of the reported ORR and DOR.

- Objective response data from the single-arm IGNYTE study is not of sufficient magnitude to overcome concerns about the contribution of effect, particularly in the absence of a reliable historical control.

- OS analysis is not interpretable.

Applicant Provides Exploratory Analyses of Overall Survival to Support Efficacy Claim

Phase 2 Anti-PD1 Refractory Cohort

Parameter	Overall (N=140) N (%)
Number (%) of patients who died	71 (50.7)
Median OS, months	32.9 (25.8, 46.0)
OS 1-year survival rate	75.3 (66.9, 81.9)
OS 2-year survival rate	61.5 (52.4, 69.4)
OS 3-year survival rate	47.8 (38.6, 56.5)

Adapted from Applicant Submission, 3 year update, Data cutoff March 8, 2026

Challenges in Interpreting Applicant's Exploratory OS Analyses

- Time-to-event endpoints difficult to interpret in single arm studies
  - Absence of a concurrent control in single arm design
  - Necessitates comparison to external control for interpretation
- Apparent differences in outcome may be due to causes other than study intervention
  - Results may reflect patient selection, natural history of the disease, or other factors

Cross-Trial Comparisons Limited in Interpretability

- IGNYTE enrolled substantial proportion of patients with:
  - Stage III disease (29%), skin-only (19%) or limited nodal disease, prior treatment in adjuvant setting (25.7%)
  - Likely portends more favorable prognosis than historical controls
- Historical controls difficult to compare to:
  - Visceral metastatic disease and/or higher disease burden associated with poorer prognosis
  - Different disease subtypes across trials can influence results (e.g., acral, ocular, cutaneous)
- Both known and unknown factors can impact trial results
  - Randomization may account for this, but single arm trial designs do not

Applicant Exploratory Analysis: Responder vs. Non-Responder OS Analysis

Parameter	Responders	Non-Responders
	N=47	N=93
Number (%) or deaths	11 (23.4)	60 (64.5)
Median OS (95% CI) in months	NR (NR, NR)	18.5 (12.8, 24.5)

- Responder selection bias
  - Patients who responded lived long enough to have response confirmed→ systematically excludes patients at highest risk of early death
  - Confounding by disease biology→ Responders may have different prognostic characteristics
- Exploratory analysis with lack of pre-specification or type 1 error control
- Lack of concurrent randomization→ Unknown confounders
- FDA conclusion: These data are uninterpretable and not supportive of an efficacy claim

Challenges in Interpreting OS in Melanoma

- Checkmate-067 study reported 10-year outcomes in OS
  - Randomized trial in previously untreated advanced melanoma
  - Nivolumab + ipilimumab vs. nivolumab vs. ipilimumab
- Median OS 71.9 months (6 years) in patients treated with nivolumab + ipilimumab
  - IGNYTE patients received therapies such as this prior to enrollment
- Substantial population heterogeneity confound interpretation of these analyses
  - IGNYTE population had better prognostic features than some historical controls
  - Some melanoma populations have demonstrated survival measured in years
  - Randomized trial necessary to evaluate OS as an endpoint

Safety:
Anti-PD-1 Refractory Cutaneous Melanoma Cohort

Adverse Event Parameter	Phase 2 Anti-PD-1 Failed Cutaneous Melanoma N=140
All Grade AEs	137 (98%)
Grade ≥3 AEs	44 (31%)
Deaths due to AE	5 (4%)
Dose Discontinuation due to AE	22 (16%)
Dose Interruption due to AE	32 (23%)
Serious AEs	50 (36%)

- Most common TEAEs: (≥20% of patients): Fatigue (45.0%), pyrexia (38.6%), infections (33.6%), chills (32.1%), musculoskeletal pain (30.7%), diarrhea (29.3%), nausea (28.6%), injection site reaction (26.4%), influenza-like illness (20.0%)
- Other TEAEs of interest: herpes simplex or herpetic-like infection (n=4), visceral injury from injection including pneumothorax (n=3), tumor hemorrhage (n=3), sepsis (n=3)

Deaths

Case	Patient	Key Events (Study Days)	Attribution
Multi-Organ Failure	44 y/o Stage IVC Cutaneous Melanoma	Day 13: Injection-site infection Day 30: E. coli bacteremia; "over-infected tumoral lesions" Day 39 (11 days post 2nd RP1 dose): Death from multiorgan dysfunction	Disease progression (no imaging confirmation)
Tumor Hemorrhage	75 y/o Squamous Cell Carcinoma	Day 0: paratracheal, subcarinal, mandibular, pericarotid LNs injected Day 9: Tumor bleeding from neck/ear; worsened despite supportive care Day 14: Death	Disease progression (no imaging confirmation)
Capillary Leak Syndrome	78 y/o Merkel Cell Carcinoma	Day 28 (13 days post 2nd RP1 dose): Grade 4 AKI, sepsis, capillary leak Day 30: Death	Disputed: Investigator: RP1 + nivolumab Applicant: Disease progression

Safety Summary

- Several serious and potentially life-threatening adverse events occurred in the IGNYTE study that may be related to RP1 administration
  - Tumor hemorrhage
  - Sepsis
  - Capillary leak syndrome
- Nivolumab has a well-characterized safety profile with potentially severe or fatal toxicities, including immune-mediated adverse reactions
- Lack of concurrent control does not allow for robust comparative safety analysis

Summary

- Multiple IGNYTE study design and conduct issues despite FDA advice:
  - Response assessment methodology confounds and artifactually inflates ORR and DOR
  - Magnitude of ORR from single-arm IGNYTE study not sufficient to overcome concerns regarding contribution of effect
  - OS data from the single-arm IGNYTE study is not interpretable
- IGNYTE is not an adequate and well-controlled investigation that demonstrates substantial evidence of effectiveness
- Observed toxicities must be carefully weighed against uncertain clinical benefit

Considerations for the Committee

- Accelerated approval has the same statutory requirement for substantial evidence of effectiveness as traditional approval
- ORR and DOR results confounded by study design and conduct issues
- Systemic effect of RP1 not demonstrated
  - RP1 may have a local anti-tumor effect
  - Without evidence of clinically meaningful systemic effect, unclear if observed responses are likely to predict clinical benefit in patients with advanced/metastatic disease
- Administering a product that can cause toxicity without demonstrating contribution to efficacy in a combination regimen
  - Does not support a favorable risk-benefit assessment and
  - May not be justified

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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Backup

Advanced Cutaneous Melanoma: Available Therapies

Systemic Treatment Options for Advanced Melanoma after Treatment with Prior ICI	Objective Response Rate
Retreatment/rechallenge with single anti-PD1 agent	Poorly defined, most data suggest ~15-20%
Nivolumab + Ipilimumab	21%-31%
Nivolumab + Relatlimab	9-12%
Lenvatinib + Pembrolizumab	21% - 33%
Bevacizumab + Dacarbazine	19% in first-line setting
IL-2	16% in first-line setting
T-VEC	26.4% in first-line setting
BRAF/MEK Inhibitors (BRAF V600+)	Variable, most data suggest ~50-60%
Lifileucel* (accelerated approval)	31%

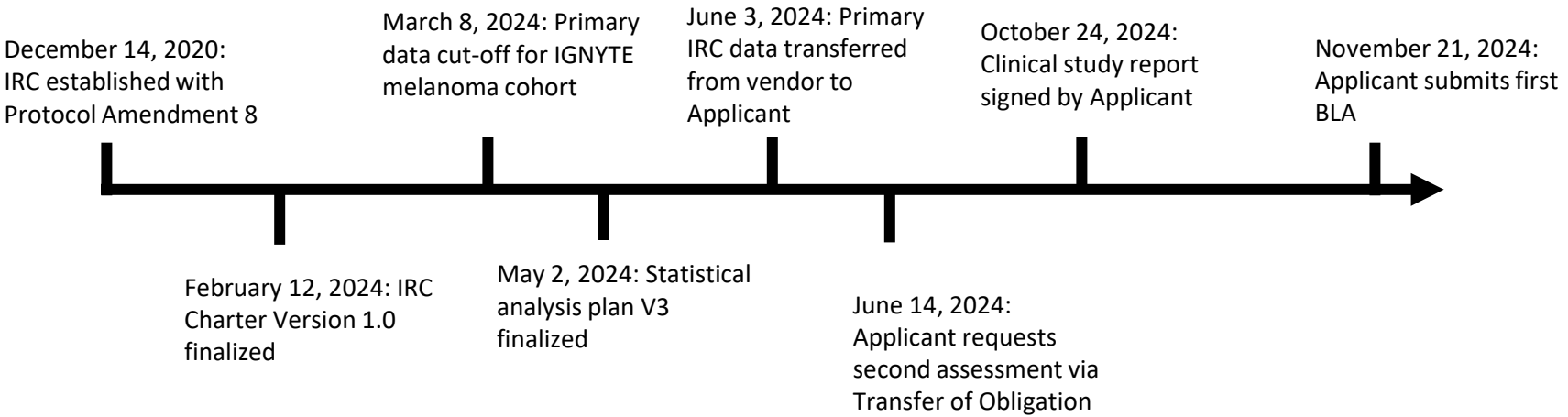
Breakthrough Therapy Designation

- Granted on November 20, 2024
  - Indication: treatment of adult patients with advanced melanoma, in combination with nivolumab, who have previously been treated with anti-PD1 containing therapy

- Preliminary efficacy based on single-arm Phase 1/2 study IGNYTE (n=140)
  - ORR 32.9% (95% CI: 25.2, 41.3) with mDOR 33.7 months (95% CI: 14.1, NR)

- Response assessment issues not apparent at time of BTD

Implementation of Independent Review Charter (IRC)



- IRC assessment was retrospective
- Unclear to FDA why statistical plan and IRC charter finalized 4 years after establishment of IRC in amendment 8
- Additional IRC assessment conducted 11 days after initial IRC data transmitted to Applicant

Applicant's Implementation of IRC

- Retrospective review nature of IRC may have caused or compounded aforementioned response assessment issues
- Several aspects of the IRC conduct may further complicate interpretation of trial results:
  - IRC Vendor cloned existing RECIST v1.1 data to perform additional lesion analyses at Applicant request after initial data was sent to Applicant but before submission of BLA
  - Applicant approved individual radiologists and oncologists to perform the "independent review"
  - Applicant provided clinical data to IRC oncologists for their overall review, including exam findings, clinical history, pathology results, relevant clinical notes
- FDA review cannot determine whether this conduct biased or impacted interpretation of response data to determine best overall response in IGNYTE

FDA Efficacy Analysis

ORR and DOR Excluding Patients Who Had All TLs Injected or No TLs at Baseline

	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)
DoR range, months	3.1 to 49.4+	3.9 to 34.6+	3.9 to 34.6+
DoR ≥ 12 months (%)	71.8%	54.6%	54.6%
DoR ≥ 24 months (%)	50.7%	23.0%	23.0%

- 46 patients out of 140 had all target lesions injected
- ORR 25% when excluding these patients from efficacy evaluable population

Disproportionate Responses Observed Based on Baseline Disease Burden

Response Rate by Disease Burden at Baseline

SOD[a]	N	ORR	CR	PR	SD	PD	CR Rate
≤20 mm	19	63.2%	11	1	2	5	57.9%
21-50 mm	41	39.0%	7	9	10	13	17.1%
51-100 mm	37	35.1%	5	8	9	15	13.5%
101-150 mm	26	15.4%	0	4	3	16	0%
>150 mm	17	11.8%	0	2	6	5	0%

[a] FDA acknowledges that SOD categories are arbitrarily defined based on size for the purposes of this analysis and what constitutes low, moderate, and high burden of disease may be subjective and/or depend on other factors.

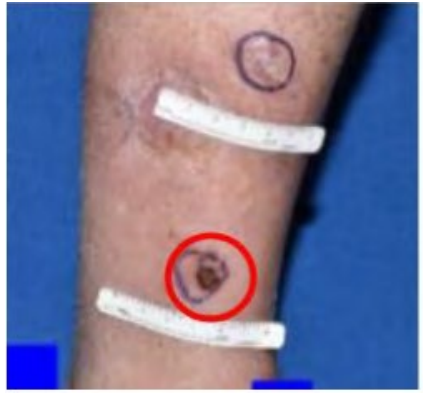
- In patients with few or small lesions procedures and local injection effects may have disproportionate effect on response assessment
- True extent of impact on ORR and DOR results cannot be determined

Example: Confounding of New Lesions and Treatment beyond PD

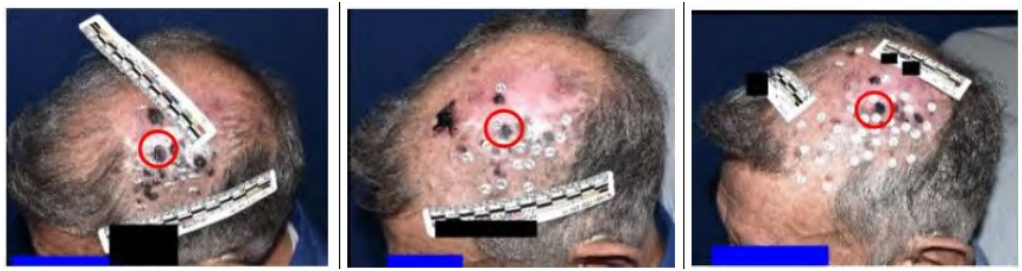
Apr 2021	PR based on TL biopsy pathology report (NT lesion still present)
Aug 2021	2 new inguinal LNs (16 mm each) New lesions injected ×8 over following 3 months PD by initial IRC review vs. NE by IRC retrospective review
Nov 2021	PD
Mar 2022	Discrepant overall response: • PD by initial IRC review • CR by IRC retrospective review (injected new LNs reduced)
Feb 2024	2nd PD BOR per Applicant recorded as CR (1st PD not counted) DOR per Applicant recorded as 34 months (to 2nd PD) DOR per RECISTv1.1 is <4 months (to 1st PD)

- Disease stage: IIIB
- Baseline disease (IRC):

Target: skin (10mm),
Non-target: skin lesion



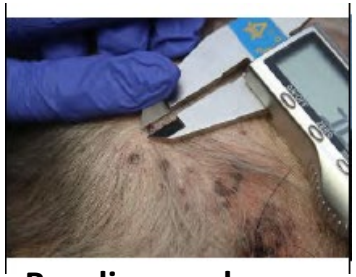
Example: Confounding Excisional Biopsy Prior to Response Designation



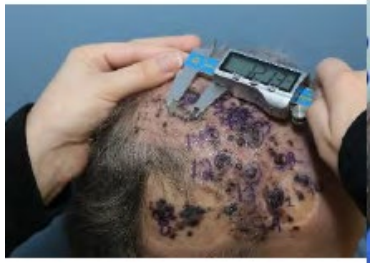
- Disease stage: Stage IIIC
- Target lesions (IRC): scalp (16mm), scalp (11mm)
- Non-target lesions (IRC): scalp (x3)

Sep 28, 2022	Treatment initiated
Nov 21, 2022	Stable disease
Jan 17, 2023	IRC dataset: New Lesion Identified Excisional biopsy of unknown scalp lesion → pathology confirms in-transit melanoma
Jan 18, 2023	Discrepant overall response: • PD by initial IRC review • PR by IRC retrospective review
Apr 2023	Progressive disease

Example: Response Retrospectively Changed from PD to CR by Histology Assessment (>300 days later)



Baseline: scalp lesion (non-target)



MAR2023: PD (IRC) by photography

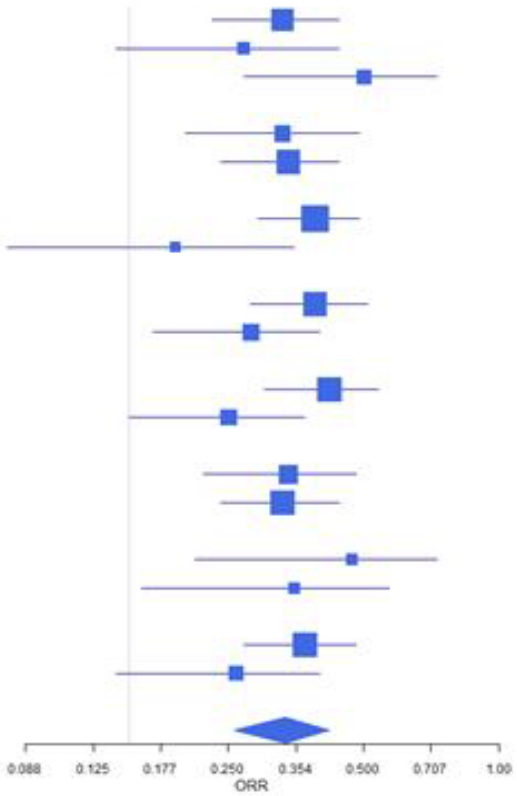
- Disease stage: Stage IV M1a
- Target lesions (IRC): NONE
- Non-target lesions (IRC): scalp (x2)

Visit	IRC Review	IRC Review Retrospective	Inv Review
MAR2023	PD	NE	PD
MAY2023	PD	NE	SD
JUL2023	PD	NE	SD
DEC2023	PD	NE	SD
APR 2024	PD	CR	CR
MAY2024	PD	CR	CR

- IRC assessed PD at 1st visit (new lesions)
- Retrospective review changes BOR to CR and converts previous PD assessments to 'NE' based on biopsies of scalp lesions 337 days after last RP1 and 309 days after last nivolumab showing "no viable melanocytic lesions"

FDA: ORR by Subgroups of Patients Treated on Anti-PD1 Failed Cohort

Subgroup	x/n	ORR (95% CI)
Age		
<65 Years	27/83	0.33(0.23,0.44)
>=65-<75 Years	10/37	0.27(0.14,0.44)
>=75 Years	10/20	0.50(0.27,0.73)
Sex		
Female	15/45	0.33(0.20,0.49)
Male	32/95	0.34(0.24,0.44)
Race		
White	40/103	0.39(0.29,0.49)
Non-White	7/37	0.19(0.08,0.35)
Region		
US	29/75	0.39(0.28,0.51)
Non-US	18/65	0.28(0.17,0.40)
Disease Stage		
IIIb-IVa	30/72	0.42(0.30,0.54)
IVb-IVd	17/68	0.25(0.15,0.37)
BRAF Mutation Status		
Mutated	18/53	0.34(0.22,0.48)
Wild Type	29/87	0.33(0.24,0.44)
PD-L1 Expression		
Positive	7/15	0.47(0.21,0.73)
Negative	8/23	0.35(0.16,0.57)
LDH Level		
<=ULN	34/92	0.37(0.27,0.48)
>ULN	12/47	0.26(0.14,0.40)
Overall	**47/140**	**0.336(0.258,0.420)**



Applicant's Summary of Response in Patients Who Had Both Injected and Noninjected Measured Lesions (IGNYTE study , N=108)

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

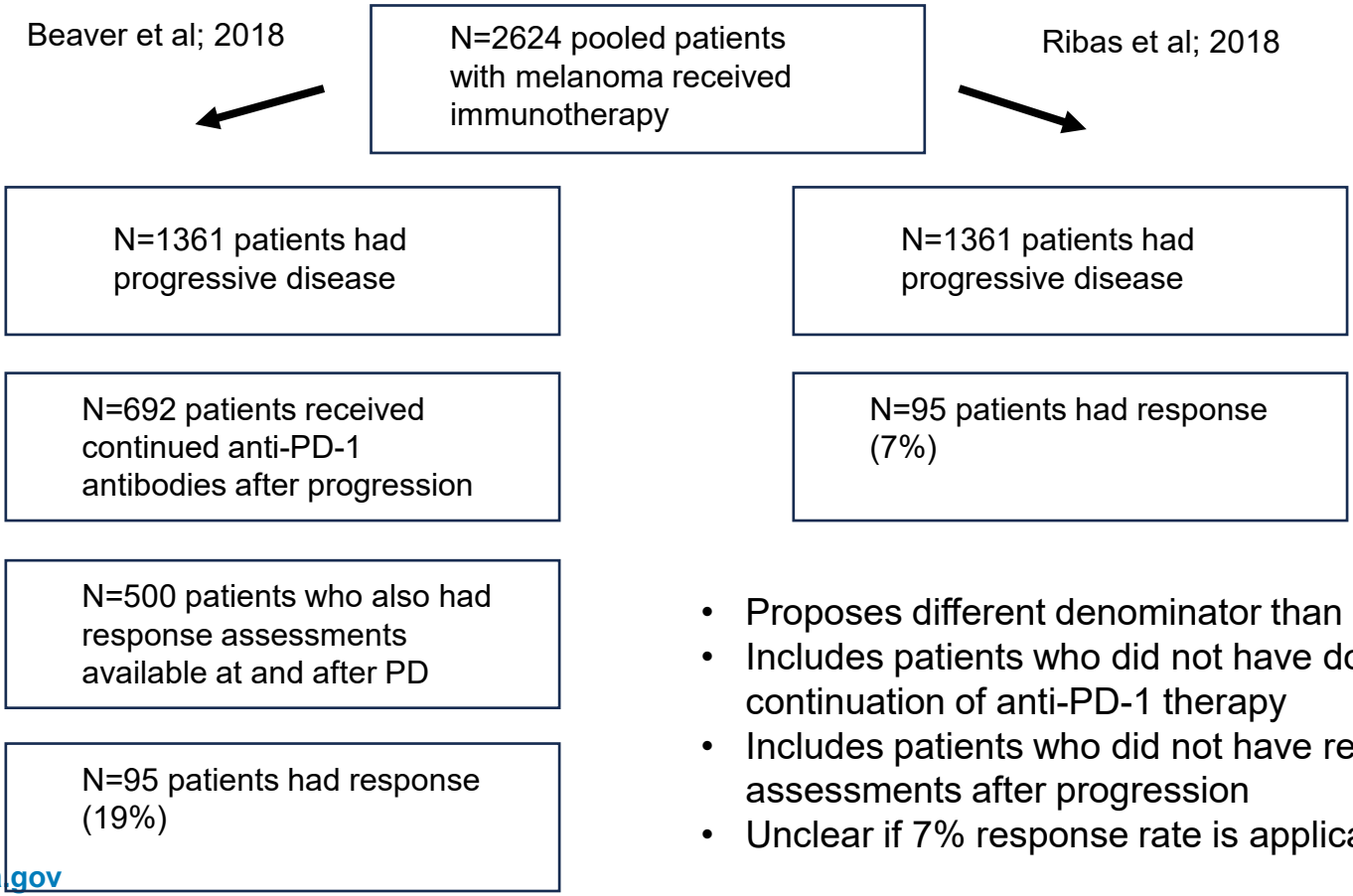
Applicant Provides Exploratory Analyses of Overall Survival to Support Efficacy Claim

Phase 2 Anti-PD1 Failed Cohort

Parameter	Overall (N=140) N (%)	Responders (n=47) N (%)	Non-Responders (n=93) N (%)
Number (%) of patients who died	71 (50.7)	11 (23.4)	60 (64.5)
Median OS, months	**32.9 (25.8, 46.0)**	**NR**	**18.5 (12.8. 24.5)**
OS 1-year survival rate	75.3 (66.9, 81.9)	97.9 (85.8, 99.7)	62.4 (51.0, 71.9)
OS 2-year survival rate	61.5 (52.4, 69.4)	95.7 (84.0, 98.9)	41.2 (30.2, 51.8)
OS 3-year survival rate	47.8 (38.6, 56.5)	83.5 (68.5, 91.8)	26.4 (16.9, 36.9)

Adapted from Applicant Submission, 3 year update, Data cutoff March 8, 2026

Evaluation of Beaver and Ribas Analyses



- Proposes different denominator than Beaver
- Includes patients who did not have documented continuation of anti-PD-1 therapy
- Includes patients who did not have response assessments after progression
- Unclear if 7% response rate is applicable

INGYTE Phase 1 RP1 Monotherapy Data

- IGNYTE Phase 1 Dose Escalation portion: N=22
- 3 dose levels
- 1 DLT in cohort 1b: grade 4 increased lipase
- Highest levels of RP1 DNA detection seen at the 1×10^8 PFU/mL dose level.
- RP2D:
  - 1×10^6 PFU/mL, followed by subsequent doses with a concentration of 1×10^7 PFU/mL
  - Maximum volume of RP1 across all tumors to be injected during any 1 day was 10 mL

Dose Level	RP1 Dose (PFU/mL)
DL1	1×10^4 to 1×10^6
DL2	1×10^5 to 1×10^7
DL3	1×10^6 to 1×10^8

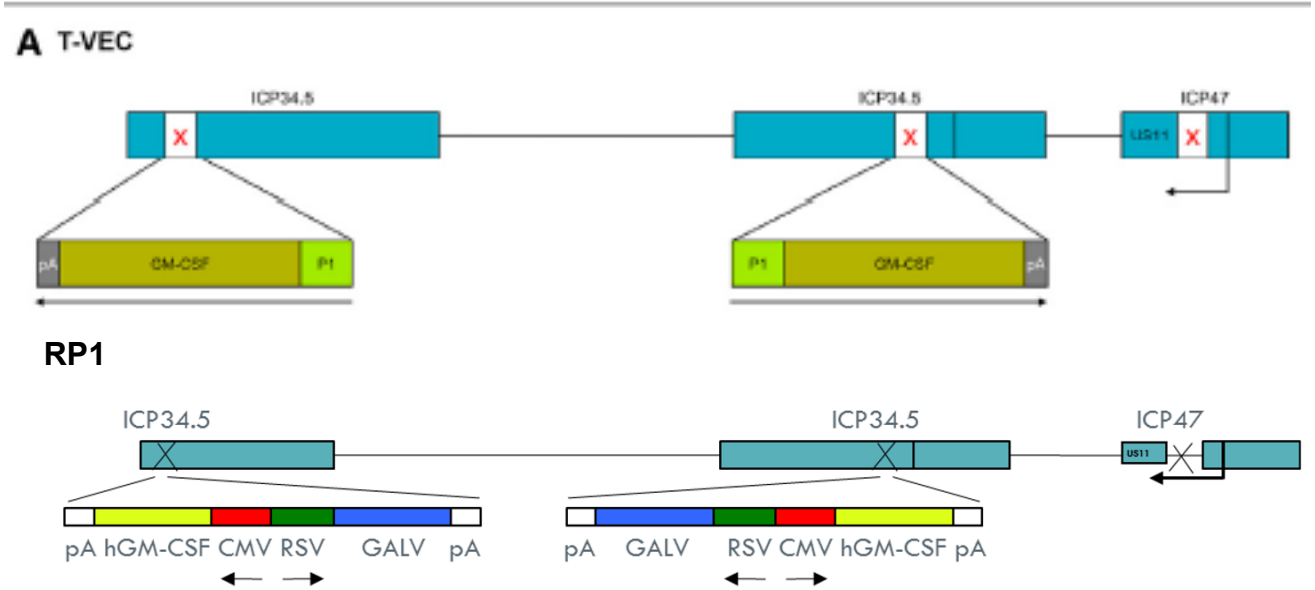
RP1 Monotherapy: Efficacy

- In early phase dose expansion (IGNYTE Phase 1), Applicant reports RP1 monotherapy data:
  - 4 patients had confirmed CR or PR with ORR 28.6% (95% CI: 8.4, 58.1)
  - In Cohort 4a (superficial tumors), ORR 42.9% (1 CR, 2 PRs)
  - In Cohort 4b (deep tumors), ORR 14.3% (1 CR, 2 PR)
  - Two out of four responders had cutaneous melanoma post-anti-PD-1
- ARTACUS study (cutaneous squamous cell carcinoma)
  - ORR by investigator modified RECIST (n=40) was 20%
  - Applicant states “in addition to clear and clinically meaningful activity in combination with nivolumab, VO (RP1) also has clinically meaningful activity as monotherapy”

IGNYTE PRO Data

- PROs were assessed as exploratory, not designed to provide primary or key secondary efficacy outcomes
- PRO for HRQoL were assessed using EORTC quality of life questionnaire (QLQ-C30)
- Patients completed QLQ-C30 prior to starting Cycle 1, Cycle 4 and Day 100 after the final dose of nivolumab or early termination
- Except for fatigue, most patients had no clinically meaningful change in the EORTC QLQ-C30 symptoms item score at Cycle 4 (57.5% to 87.3%) and 100 days after the final dose of nivolumab or early termination (46.4% to 78.6%)
- Per applicant: majority of the patients reported either a clinically meaningful improvement or no clinically meaningful changes in their QoL and symptom scores

RP1 and T-VEC



- T-VEC (IMLYGIC): recombinant oHSV1 expressing hGM-CSF
- RP1 introduced additional 2 copies of GALV-GP, may provide additional constitutive cell fusion activity to increase ability to spread from cell to cell

IT Therapies for Melanoma

T-VEC

- Single agent product
- Randomized trial
- Study population: Stage IIIB-IV melanoma
- Endpoint: durable response rate maintained for ≥6 months
- Indication for “local treatment”
- Limitation of use: doesn’t improve OS

RP1 + Nivolumab

- Combination therapy
- Single arm trial
- Study population: Stage IIIB-IV melanoma
- Endpoint: RECIST ORR and DOR
- Purports systemic effect
- Applicant provides uninterpretable OS analysis

T-VEC and Pembrolizumab

- Patients (n=692) with stage IIIB-IVM1c unresectable melanoma randomized to
  - T-VEC + pembrolizumab vs. placebo + pembrolizumab
- Endpoints not met
  - PFS HR 0.86 (95% CI, 0.71 to 1.04; p=.13)
  - OS HR 0.96 (95% CI, 0.76 to 1.22; p=.74)
  - ORR 48.6% with combination vs. 41.3% with placebo arm
- Notable differences in situation
  - Different HSV-1 based IT therapy
  - Different patient population (no prior immunotherapy)
- However, these results are not supportive of Applicant's proposed MOA

Chesney et al. JCO 2023

Summary of Nonclinical Data

- murine A20 melanoma and CT26 colorectal carcinoma models:
  - Repeat administrations of IT mRP1 and IP anti-PD-1 combination showed systemic anti-tumor activity, while administration of mRP1 or anti-PD-1 mAb single agents resulted in limited reduction of injected tumor volumes or no activity, respectively

- murine 4434 B-RAF mutant melanoma model:
  - mRP1 and anti-PD-1 mAb combination showed significant tumor volume reduction in both injected and contralateral flank tumors, compared to monotherapy groups and control
  - mRP1 alone showed tumor volume reduction only in injected tumors
  - RNAseq data for mRP1 and anti-PD-1 mAb combination suggests infiltration of both adaptive and innate immune effector cell types (e.g. T cells, NK cells and tumor associated macrophages) in injected tumors, and to a lesser extent in contralateral tumors

Clinical Biomarker Data Summary

- Biomarker data indicated induced immune response to the combo of RP1+nivolumab
  - CPS scores increased from baseline to Cycle 4 Day 43, numerically higher in responder groups than in non-responder group
  - gene expression signatures associated with CD8+ T cells, dendritic cells, macrophages, and TIS in responders is higher than those in non-responders
  - Immune response data from baseline to Cycle 4 Day 43 indicated that RP1+Nivo combo may help overcome anti-PD-1 resistance
  - However, given the single-arm study design and limited data, it is challenging to conclude that these data can demonstrate the contribution of RP1 to the clinical responses

Supportive Safety Data

Pooled from All IGNYTE Cohorts that Received RP1 and Nivolumab

	Pooled Phase 1/2 All Cohorts N=355
All Grade AEs	329 (98%)
Grade ≥3 AEs	130 (39%)
Deaths due to AE	15 (4%)
Dose Discontinuation due to AE	34 (10%)
Dose Interruption due to AE	89 (27%)
Serious AEs	158 (47%)