Replimune®

Vusolimogene oderparepvec-wtpg (TUDRIQEV™) in Combination with Nivolumab for the Treatment of Adults with Unresectable Advanced Cutaneous Melanoma

United States Food and Drug Administration

Cellular, Tissue and Gene Therapies Advisory Committee

July 30, 2026

Introduction

Kari Jeschke, MA

Senior Vice President, Regulatory Affairs, Replimune, Inc.

Melanoma Community Support for Urgent Access to RP1

Proposed Indication Statement

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

Favorable Benefit-Risk for Accelerated Approval

UNMET NEED: SERIOUS, LIFE-THREATENING DISEASE

EFFICACY

Adequate and Well-controlled Trial

IGNYTE
- ORR: 33.6% (95% CI: 25.8, 42)
- DoR: 24.8 months (95% CI: 14.1, NE)

Supporting Evidence

MOA/Biological Plausibility | Preclinical | Biomarkers

SAFETY

Well-tolerated Safety Profile

IGNYTE
- Mainly Grade 1 and 2
- No treatment-related Grade 5

IGNYTE-3 randomized confirmatory trial ongoing with OS data expected in 2030

Melanoma Approvals Since Initiation of IGNYTE Study

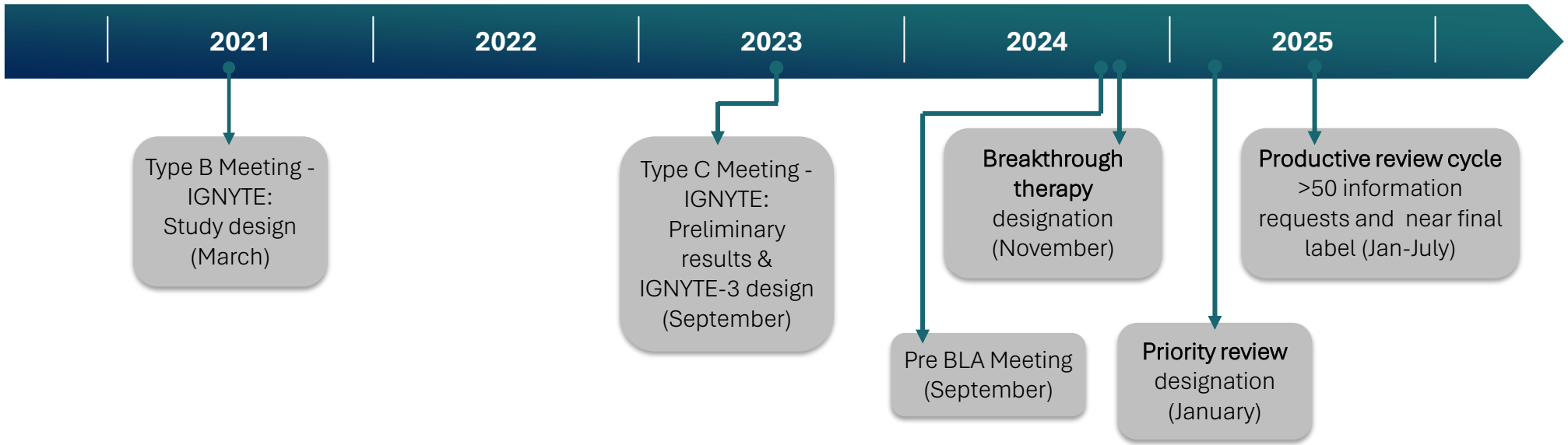
Recent FDA Approvals	Year	Basis of Approval	Relevance to RP1
Relatlimab + Nivolumab (OPDUALAG)	**2022**	• Randomized controlled trial • First-line treatment-naive patients • Now included in NCCN guidelines[1] for second line (ORR 9-12%)[2]	• Approved post IGNYTE • >95% selected option for IGNYTE-3 control arm
Lifileucel (AMTAGVI) + IL-2 regimen	**2024**	• Single arm • Previously treated with anti-PD-1 • ORR (31.5%, n=73); combination regimen with 7.5% mortality (n=160)[3]	• Precedent in similar setting (PD-1 failed melanoma) with single arm data

1. NCCN Guidelines Version 2.2026 Melanoma: Cutaneous. MELSYS 2 of 10.
2. Ascierto PA, et al. *J Clin Oncol*. 2023 May 20;41(15):2724-35.
3. AMTAGVI USPI. 2024 Iovance Biotherapeutics, Inc.

Ongoing Collaboration with FDA through 2025

Key alignments with FDA:

- Potential flexibility on single trial, pending compelling evidence (2021)
- Enroll real-world population (2021)
- RECIST 1.1 (2023)
- Analysis of all injected and non-injected lesions (2023)
- Literature to support contribution of effect (2023)
- IGNYTE-3 design (2023)
- SAP and Independent review charter for response assessment (2024)



Initial FDA Clinical Review: Basis for Approval

"…The reviewers acknowledge that the clinical benefit of VO in combination with nivolumab is based on results from a single arm trial with inherited biases including potential patient selection bias, like all single arm trials. However, **with over 30 clinical information requests including 27 efficacy related clinical information requests with over 136 questions, the reviewers did not find any study conduct or data integrity issues.**

The IGNYTE trial (RPL-001-16) Phase 2 portion is an adequate and well-controlled trial which provides substantial evidence of effectiveness…"

FDA BLA Clinical Review and Evaluation, July 15 2025 (obtained by Replimune through Freedom of Information Act)

Initial FDA Clinical Review: Recommended RP1 for Approval

"…Based on the IGNYTE trial results, a comprehensive literature review, the life-threatening condition of the intended patient population, the absence of treatment with proven clinical benefit in the standard of care setting, and the precedent cases using durable ORR to support drug approvals in this population, the reviewers conclude that the **efficacy and safety results from the IGNYTE trial have demonstrated substantial evidence of effectiveness of VO.** The benefits of VO, used in combination with nivolumab, outweigh risks, representing an improvement over standard of care. **The benefit over risk profile of VO in combination with nivolumab is superior to lifileucel treatment** which 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 high risks.

Therefore, the **reviewers recommend for accelerated approval of VO,** used in combinations with nivolumab, for adult patients with confirmed disease progression on anti-PD-1 based therapy…"

FDA BLA Clinical Review and Evaluation, July 15 2025 (obtained by Replimune through Freedom of Information Act)

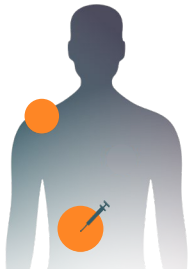
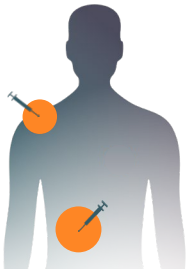
Regulatory Topics

Relevance of MOA to Response Assessment

LOCAL IMMUNE EFFECT + SYSTEMIC IMMUNE EFFECT

- Direct oncolytic virus-mediated tumor lysis attracts antigen-presenting cells
- Antigen-presenting cells internalize tumor antigens, leading to T cell activation
- Activated T cells traffic systemically, driving long-term durable responses in both injected and non-injected tumors

RECIST 1.1: Replimune vs. FDA Response Rate Analysis

	FDA ANALYSIS	REPLIMUNE ANALYSIS
NON-INJECTED TARGET LESION 	N=22	N=22
ALL TARGET LESIONS INJECTED 	N=0	N=25
	ORR 15.7%*, n/N=22/140	ORR 33.6%, n/N=47/140

Patients with all target lesions injected should be included

*If corrected for denominator = 25% (FDA sensitivity analysis)

Replimune Position: Response Assessment

FDA Issue	Replimune Position
Application of RECIST 1.1 confounds interpretation of efficacy results ***"RECIST 1.1 specifies that tumor lesions subjected to loco-regional therapies are generally not considered measurable for response assessment..."***	• IGNYTE study - injected lesions should not be excluded because the intervention is pre-specified in the protocol – Protocol details the conditions under which such lesions would be considered measurable (Eisenhauer 2009) • RP1 has a dual mechanism of action that stimulates a systemic T cell response to destroy injected and non-injected lesions

FDA Issues from briefing document

Replimune Position: Response Assessment

FDA Issue	Replimune Position
Other confounding factors:	Patient-by-patient analysis confirms appropriate response assessment – Per protocol – Blinded independent review – Confirmed by initial FDA clinical review team
Retreatment	• Aligned with FDA on approach for treatment beyond progression[1] • Protocol allows retreatment when in best interest of patients
Surgical procedures	• Majority were biomarker biopsies per protocol; protocol also allows tumor resections to confirm response • No evidence biopsies result in any clinically meaningful tumor reduction
Non-evaluable assessments	• Limited number of non-evaluable assessments were handled per charter • Investigator assessment confirms these did not impact BOR
Changes based on pathology	• Protocol and RECIST allows determination of response by pathology and histology • Complete responses were durable

1. FDA Type C meeting September 2023

FDA Issues from briefing document; BOR, best overall response; IRC, independent review committee

Replimune Position: Contribution of Effect

FDA Issue	Replimune Position
"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..."	• ORR of 33.6% (CR 16.4%) in IGNYTE is nearly 5x expected response for nivolumab alone and supports contribution of effect • FDA previously agreed to the use of literature to provide historical controls • Existing literature and expert opinions indicate patients who have definitively progressed on a prior anti-PD-1 are unlikely to respond to further anti-PD-1 monotherapy - yielding a 5-7% response rate[1] • FDA patient-by-patient analysis (July 2025) concluded prior anti-PD-1 exhaustion

FDA Issues from briefing document
1. NCCN, SITC, Ribas

What You Will Hear Today

Mechanism of Action	Dual mechanism of action	**Kevin Harrington, MD, PhD, FRCP, FRCR, FRSB** Professor of Biological Cancer Therapies Institute of Cancer Research
Unmet Need	Fills an unmet need Treats a serious, life-threatening condition	**Michael Wong, MD, PhD, FRCPc** Clinician, IGNYTE Study Advisory Board Former Physician in Chief, Roswell Park Cancer Center
Clinical Data	Substantial evidence of effectiveness Favorable safety profile	**Kostas Xynos, MD, PhD, MBA** Chief Medical Officer, Replimune, Inc.
Clinical Perspective	Positive benefit risk for approval	**Mohammed Milhem, MBBS** Professor of Internal Medicine Former Div. Chair and Holden Chair for Experimental Therapeutics Div. of Hematology and Oncology, University of Iowa

Additional Experts

RECIST/ itRECIST	**Greg Goldmacher** Chief Scientific & Medical Officer, Perceptive Inc.
Melanoma Oncologist	**Nikhil Khushalani** Vice Chair for the Department of Cutaneous Oncology, Moffitt Cancer Center
Melanoma Oncologist	**Yana Najjar** Associate Professor of Medicine and Director of the Clinical and Translational Research Center, UPMC Hillman Cancer Center
IGNYTE Response Assessment	**Steven Soignet** Medical Director, Clario
Senior Biostatistician	**Martin Roessner** Corporate Vice President Biostatistics, Parexel International

RP1 Mechanism of Action and Biological Plausibility

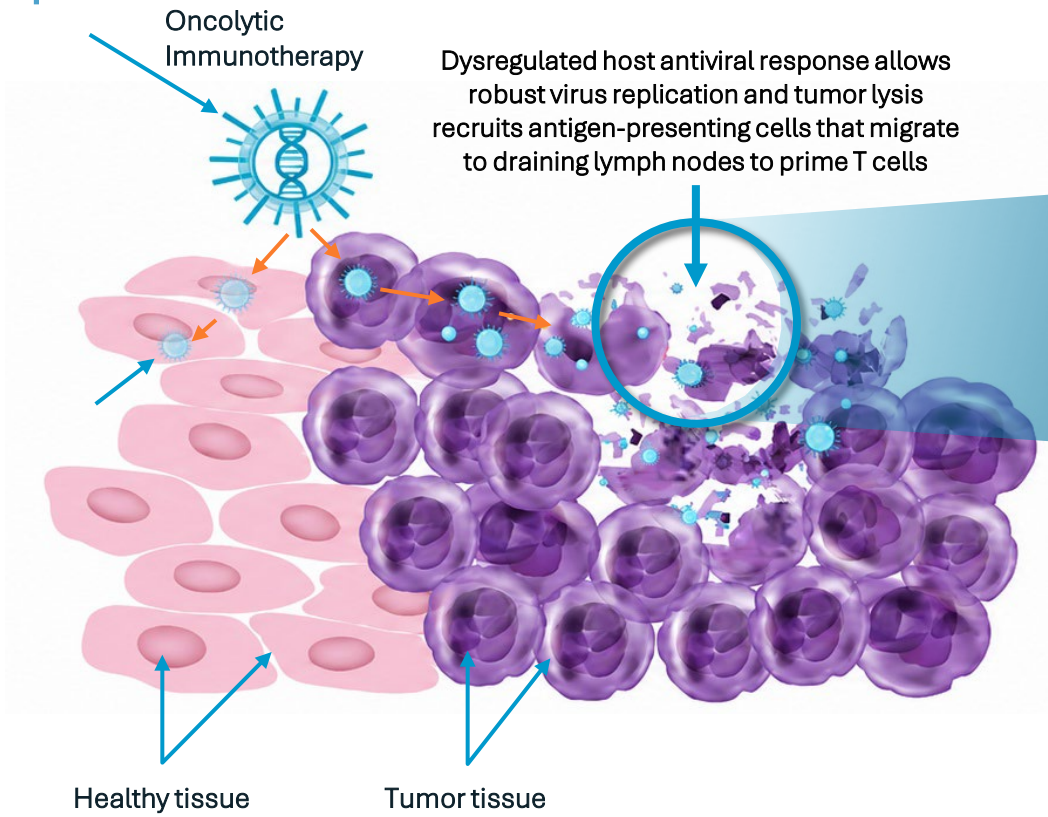
Kevin Harrington, MD, PhD, FRCP, FRCR, FRSB

Professor of Biological Cancer Therapies
Institute of Cancer Research

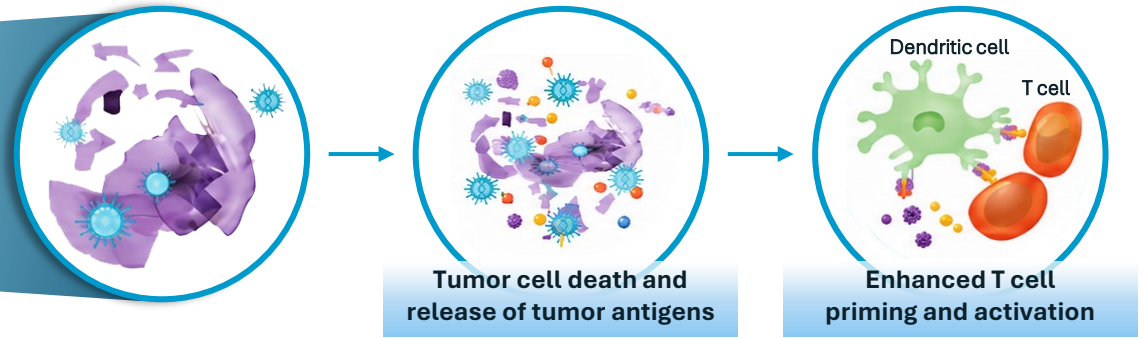
Dual MOA Drives Local and Systemic Antitumor Immune Responses

RP1 is an HSV-1 based oncolytic viral immunotherapy that expresses GM-CSF and a fusogenic glycoprotein GALV-GP-R[1]

1 LOCAL IMMUNE EFFECT



2 SYSTEMIC IMMUNE EFFECT



Tumor cell death and release of tumor antigens

Release of virus progeny

Infection of more tumor cells

Local inflammation

Altering of tumor microenvironment

Enhanced T cell priming and activation

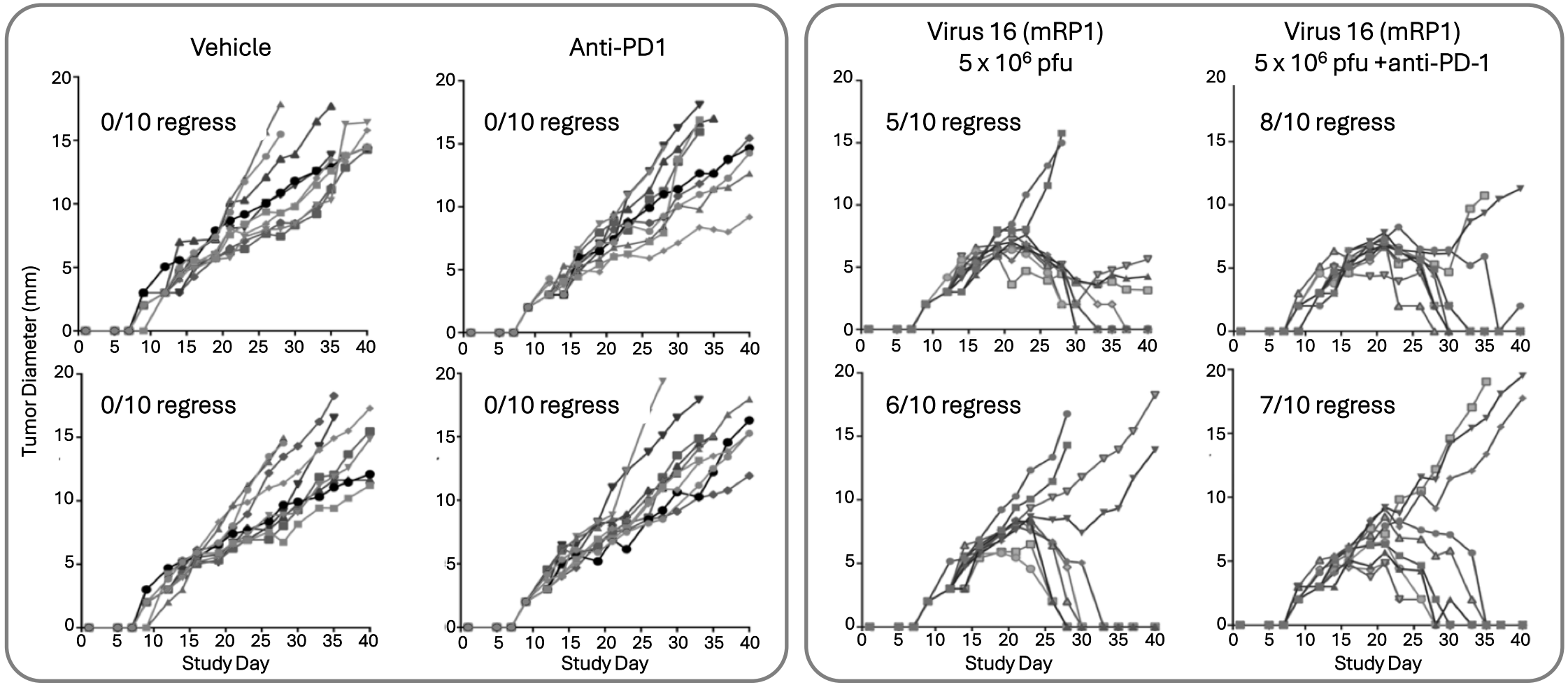
T cell infiltration and killing of distant, non-injected tumors

Generating a strong and durable systemic antitumor immune response

1. Thomas S, et al. *J Immunother Cancer*. 2019;7(1):214.

RP1 Combined with Anti-PD-1 Enhances Systemic Anti-tumor Activity

Anti-PD1-insensitive A20 Lymphoma Mouse Model



mRP1=mouse RP1
Thomas et al. JITC 2019

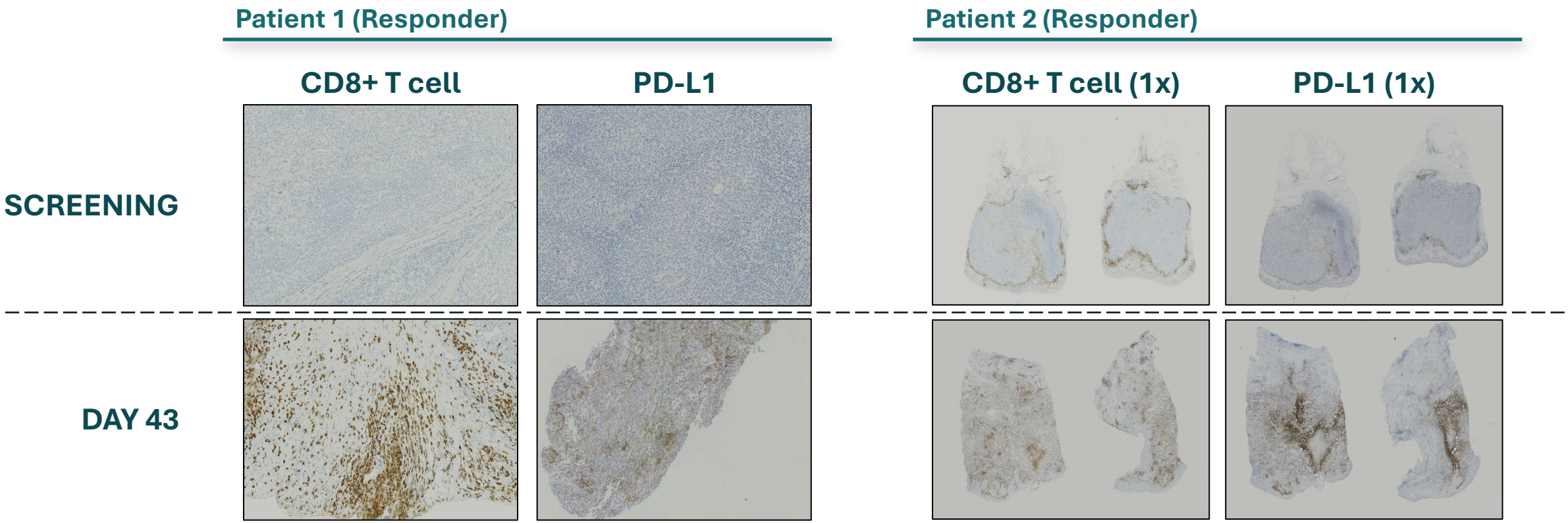
Mechanisms of Resistance to Anti-PD-1: Why Further Treatment is Minimally Effective

- Lack of T cell, PD-L1 expression and IFN gamma are known to be the resistance mechanisms of anti-PD-1 treatment[1]
- Patients who have drug holiday before progression on anti-PD-1: retreatment may be effective
  - Tumor microenvironment may still be immunologically active/sensitive
  - Memory CD8+ T cells can be reactivated
- Patients who progress while on anti–PD-1: retreatment is minimally effective
  - Tumor microenvironment is immune-suppressive, with low or absent T cell infiltration and PD-L1 expression
  - Low IFN-γ signature
  - Low antigen presentation

IGNYTE trial enrolled patients who progressed <u>while on treatment</u> with anti-PD-1

PMID: 29360728; 1. Nowiciki et al. *Cancer J* 2018

RP1+Nivolumab Increases CD8+ T Cells and PD-L1 Levels in IGNYTE Patients



Reversal of immune desert

Reversal of immune exclusion

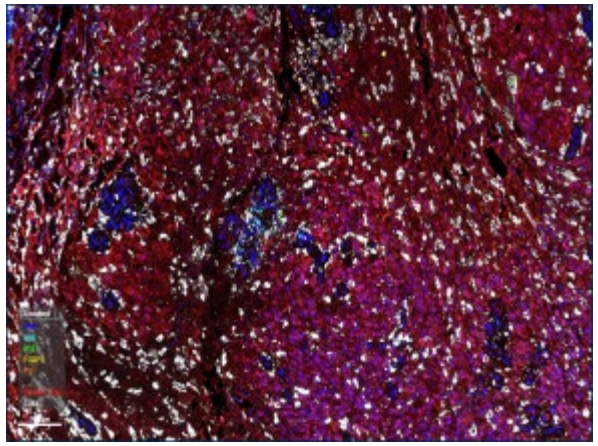
Additional analysis confirmed responding lesions exhibit significantly higher CD8+ and PD-L1 at Day 43 vs. screening (compared to lesions that do not respond)[1]

1. Data on file

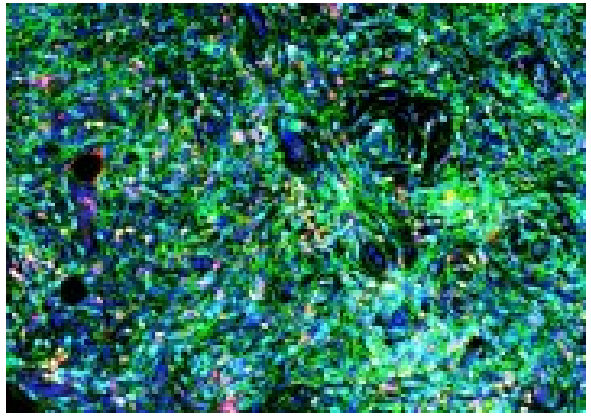
RP1 + Nivolumab Reprograms the Tumor Microenvironment (TME) in IGNYTE Melanoma Patients

8 paired biopsies

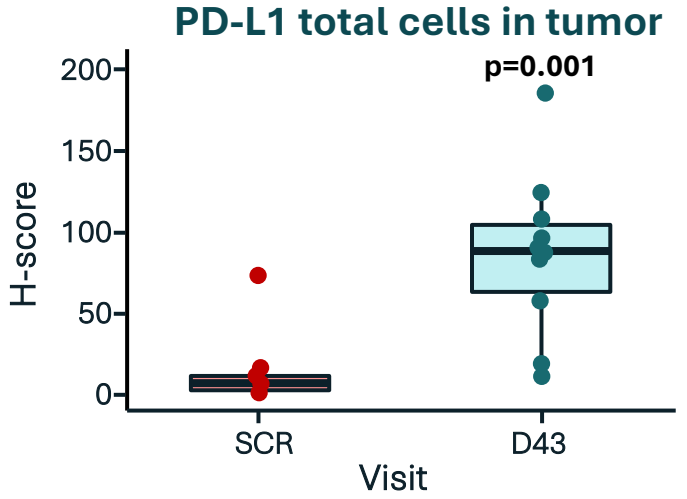
Screening:

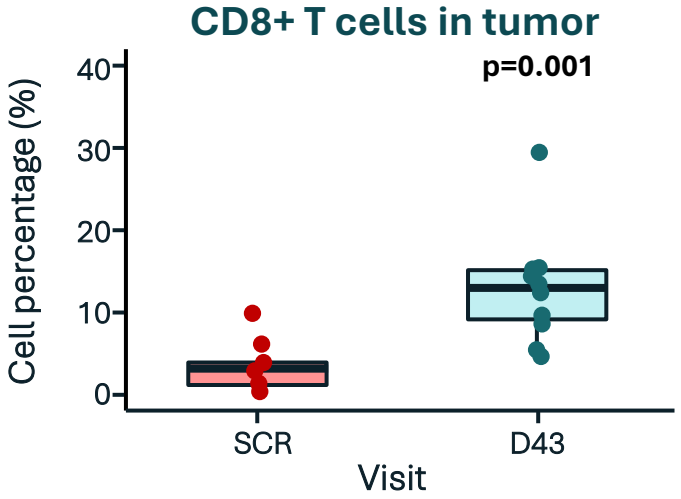


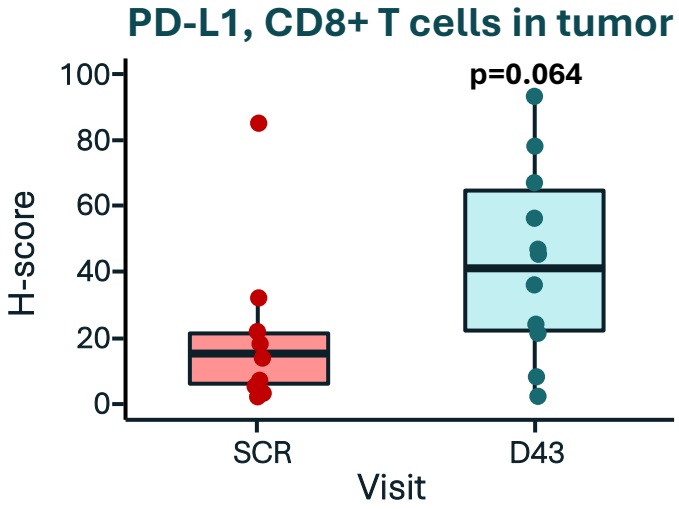
Day 43:

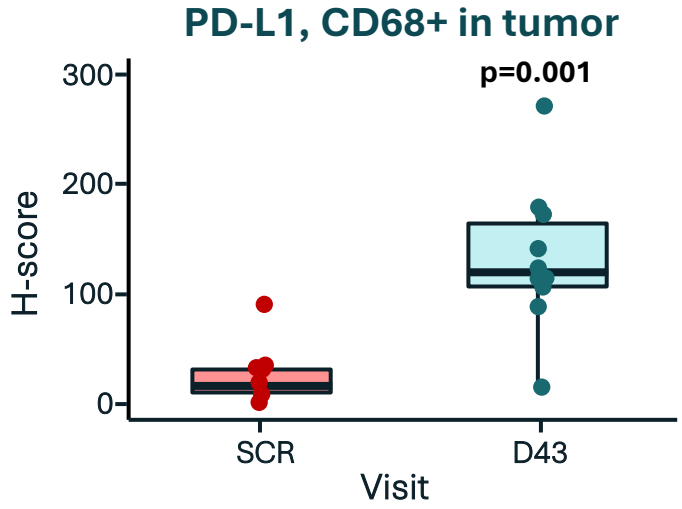


SOX10
FOXP3
DAPI
PD-L1
CD8
PD-1
CD68









P Value by Mann-Whitney U Test (Wilcoxon rank-sum test).
D, day; DAPI, 4',6-diamidino-2-phenylindole; FOXP3, forkhead box P3; nivo, nivolumab; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Scr, screening; SOX10, SRY-box transcription factor 10; TME, tumor microenvironment.

Melanoma: Unmet Need and Treatment Paradigm

Michael Wong, MD, PhD, FRCPc

Clinician, IGNYTE Study Advisory Board
Former Physician in Chief, Roswell Park Cancer Center

Significant Unmet Need Exists for Advanced Melanoma

- In the US, 110,000 new melanoma cases with ~8,500 related deaths projected in 2026[1]
- 50% of advanced melanoma patients progress in the first 12 months[2,3]
- Real-world 5-year OS among patients with distant metastatic disease is only 35%[1]

1. American Cancer Society 2026
2. Tawbi 2022
3. Robert 2015

Limited Options Post Immune Checkpoint Inhibitor (ICI) Progression in Advanced Melanoma

Neoadjuvant/
Adjuvant/
First line

Monotherapy

- Pembrolizumab (Keytruda)
- Nivolumab (Opdivo)
- Ipilimumab (Yervoy)

Combinations

- Ipilimumab + Nivolumab
- Relatlimab/Nivolumab (Opdualag)

Limited Options Post Immune Checkpoint Inhibitor (ICI) Progression in Advanced Melanoma

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On progression

Progression on Anti-PD-1 Based Regimen

Combinations

Lifileucel (AMTAGVI) + IL-2 is the only "FDA approved" treatment for anti-PD-1 failed therapy. Other combination treatments per NCCN

Lifileucel (AMTAGVI) is the Only FDA Approved Agent for Anti-PD-1 Failed Melanoma

Lifileucel (AMTAGVI)	
Efficacy (ORR)	• 31.5% (4.1% CR) • (n=73, primary efficacy data set)
Safety (Gr3+)	• 7.5% treatment-related mortality (n=160)
Considerations	• Multi-component approach: involving surgery, chemotherapy (fludarabine + cyclophosphamide), TIL infusion, high-dose IL-2 • Average time to TIL generation ~34 days (1 month)

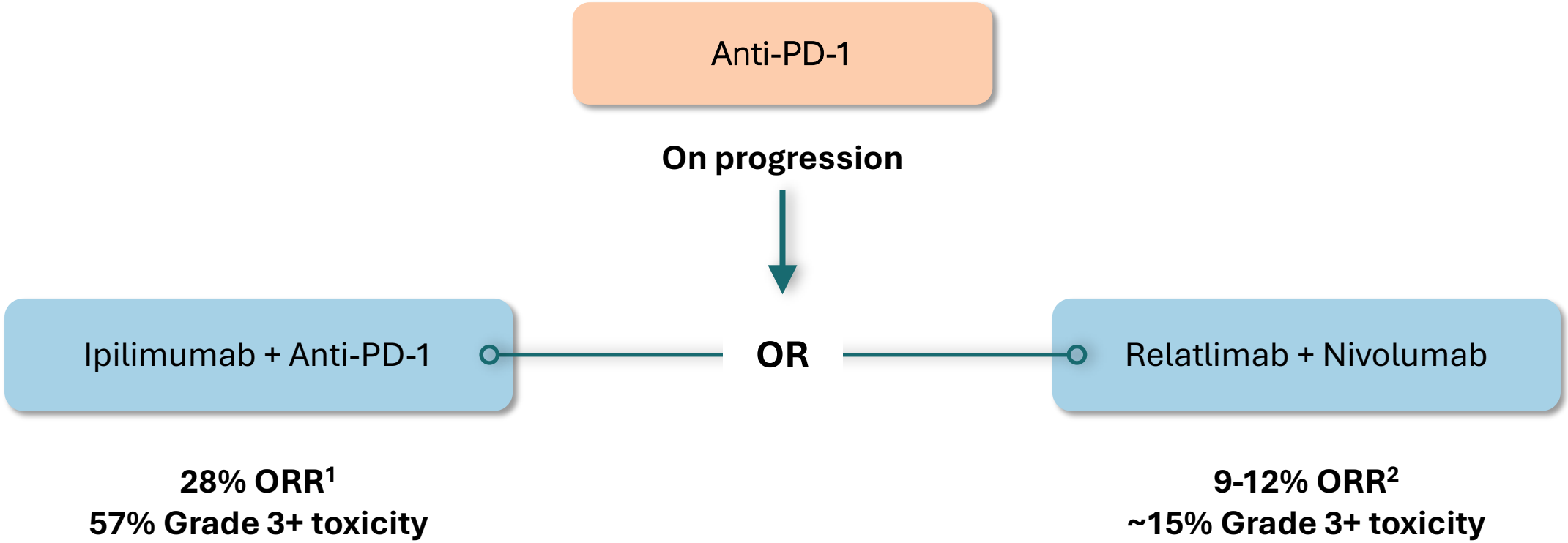
AMTAGVI (lifileucel) [package insert]; initial approval 2024

NCCN Recommendations:
PD-1 Retreatment Unlikely to Show Benefit

"if a patient experienced progression of melanoma during or shortly after a systemic therapy, **rechallenge with the same therapy or a therapy of the same class is unlikely to yield a response and is not recommended.**"

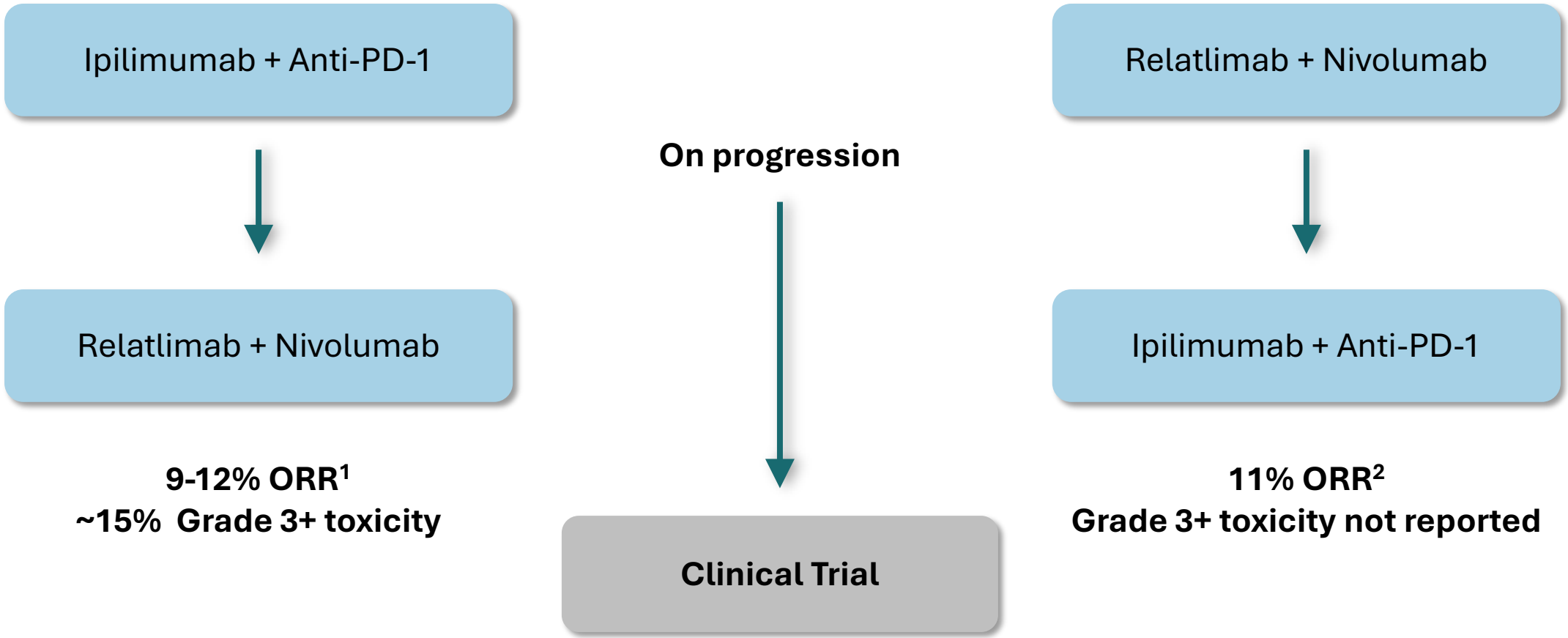
-NCCN Guidelines Version 2.2026. Melanoma: Cutaneous

Options Following Progression on Monotherapy Anti-PD-1 Progression



1. VanderWalde et al 2023 *Nat Med.* 2023 Sep;29(9):2278-85;
2. Ascierto et al RELATIVITY-020 trial. *J Clin Oncol.* 2023 May 20;41(15):2724-35.

Options Following Progression on Combination Immune Checkpoint Inhibitor (ICI)



1. Ascierto et al RELATIVITY-020 trial. *J Clin Oncol*. 2023 May 20;41(15):2724-35;
2. Menzies et al 2022 *N Engl J Med*. 2022;386(17):1668-9

Summary

- Based on the RELATIVITY-020 study a 9-12% ORR is a reasonable benchmark for the IGNYTE study data
- Limited existing options have significant toxicity and/or modest response rates
- Unmet need remains significant for patients who have failed anti-PD-1 based treatments

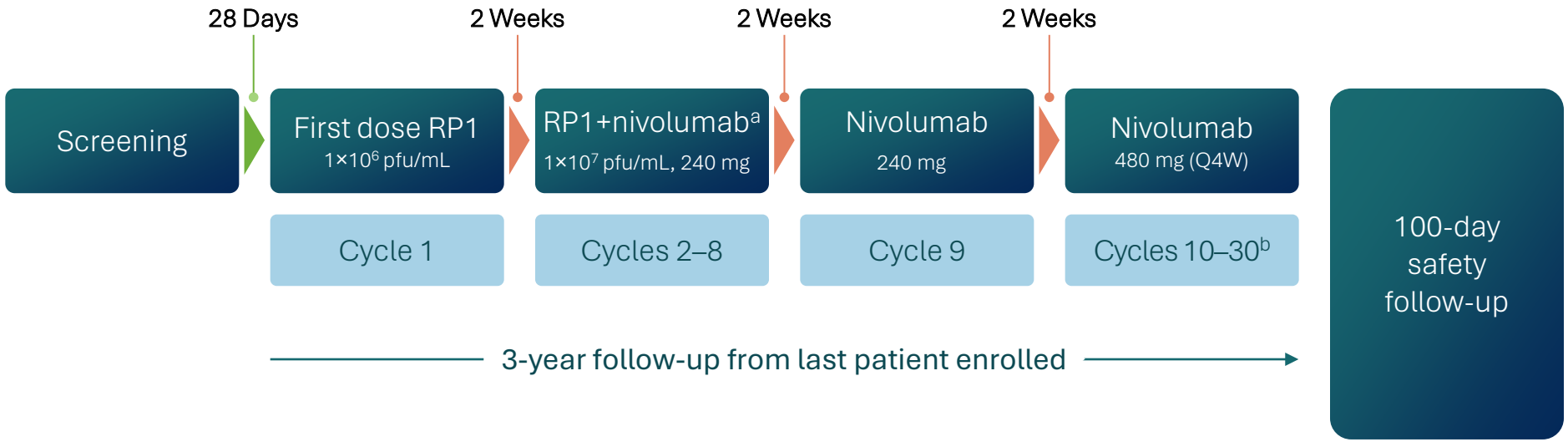
IGNYTE Study: Anti-PD-1 Failed Cutaneous Melanoma

Kostas Xynos, MD, PhD, MBA
Chief Medical Officer, Replimune, Inc.

IGNYTE Phase 2 Study Design: Anti–PD-1 Failed Cutaneous Melanoma Cohort

Anti–PD-1–failed cutaneous melanoma cohort
N=140

- Anti–PD-1–failed advanced melanoma
- Measurable disease
- Adequate organ function
- No prior oncolytic therapy
- ECOG performance status 0–1



Tumor response assessment: Radiographic imaging (CT) at baseline and every 8 weeks from first dose
Biopsy assessment: Day 1 and Day 43 biomarker analysis and confirmation of response were allowed

Primary endpoint:

- ORR by Independent Review per RECIST 1.1 (conducted when all patient had potential for at least 12 months follow up)

Secondary endpoints:

- DOR, CRR, DCR, PFS, and OS

CRR, complete response rate; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein-1; PFS, progression-free survival; PFU, plaque-forming units; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.
a. Nivolumab was given every 2 weeks (Q2W) from Cycle 2-9. b. RP1 can be reinitiated beyond 8 cycles if protocol-specified criteria are met.

Strict Criteria to Ensure Patients who are Enrolled Definitively Failed Anti–PD-1 Therapy

Adequate Prior Exposure to Anti-PD-1 Therapy

- Minimum exposure requirement: ≥8 weeks; 96% of patients received ≥12 weeks
- Anti–PD-1 therapy required as the immediate prior line of treatment

Confirmation of Disease Progression

- Confirmed progression while on anti-PD-1 treatment
- Confirmation based on two assessments ≥4 weeks apart

FDA and Sponsor concurred that patients had sufficient exposure and exhaustion to prior anti-PD-1 therapy[1]

1. FDA clinical review, July 15, 2025

Baseline Clinical Characteristics: A Real-World Population

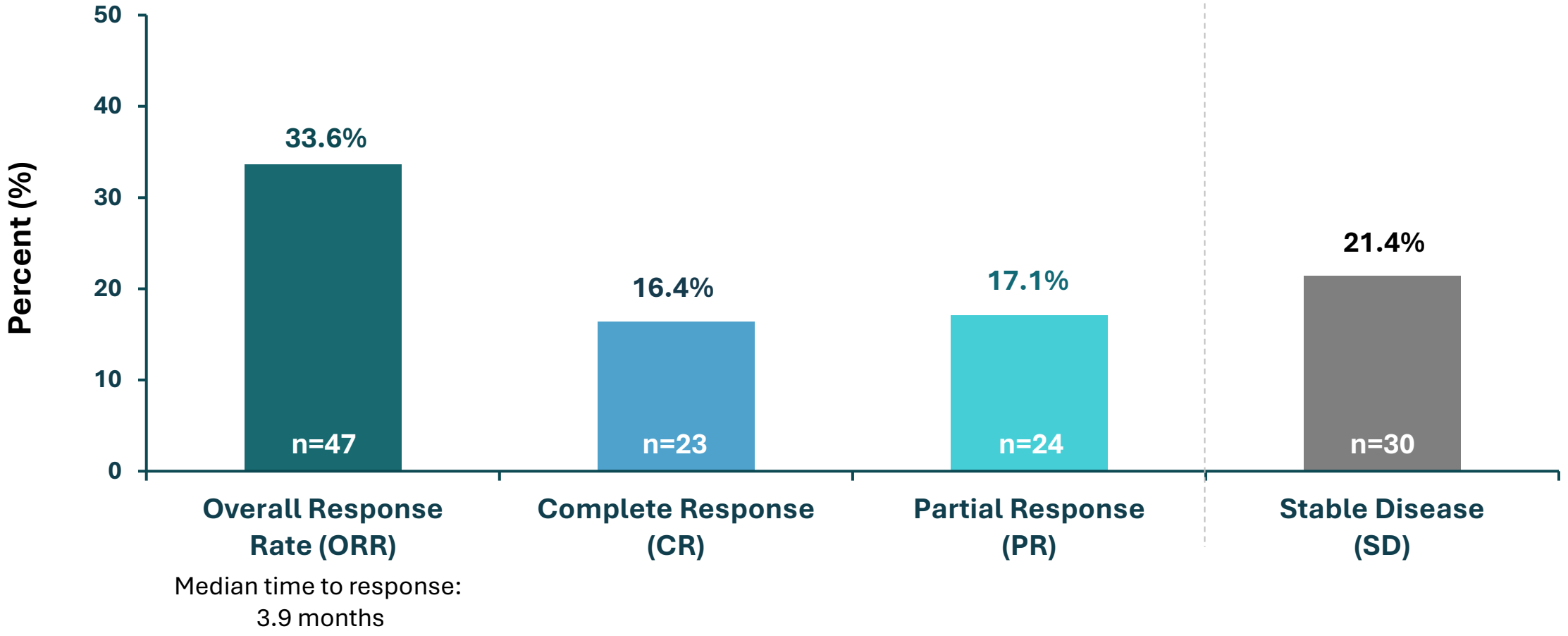
	Patients N=140 n (%)
Age, median (range), years	62 (21–91)
Sex	
Female	45 (32.1)
Male	95 (67.9)
Stage	
IIIB/IIIC/IVM1a	72 (51.4)
IVM1b/c/d	68 (48.6)
***BRAF* status**	
Wild-type	87 (62.1)
Mutant	53 (37.9)
LDH level	
LDH ≤ULN	92 (65.7)
LDH >ULN	47 (33.6)
Unknown	1 (0.7)

	Patients N=140 n (%)
PD-L1 tumor expression	
Positive (≥1%)	45 (32.1)
Negative (<1%)	78 (55.7)
Undetermined or missing	17 (12.1)
Prior therapy	
Anti–PD-1	
Anti–PD-1 only as adjuvant therapy	36 (25.7)
Anti–PD-1 as advanced/metastatic therapy	104 (74.3)
Anti–CTLA-4	
Anti–PD-1 combined with anti–CTLA-4	61 (43.6)
Anti–PD-1 treated with anti–CTLA-4 sequentially	4 (2.9)
BRAF/MEK therapy	17 (12.1)
Anti–PD-1 resistance category by SITC	
Primary resistance[a]	100 (71.4)
Secondary resistance[b]	40 (28.6)

Data cutoff: October 15, 2024. a Primary resistance: immediate prior anti-PD-1 exposure ≥6 weeks and best response of PD or SD for <6 months. b Secondary resistance: immediate prior anti-PD-1 exposure ≥6 months and best response of CR, PR, or SD for >6 months .
CTLA-4, cytotoxic T-lymphocyte antigen 4; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ULN, upper limit of normal.

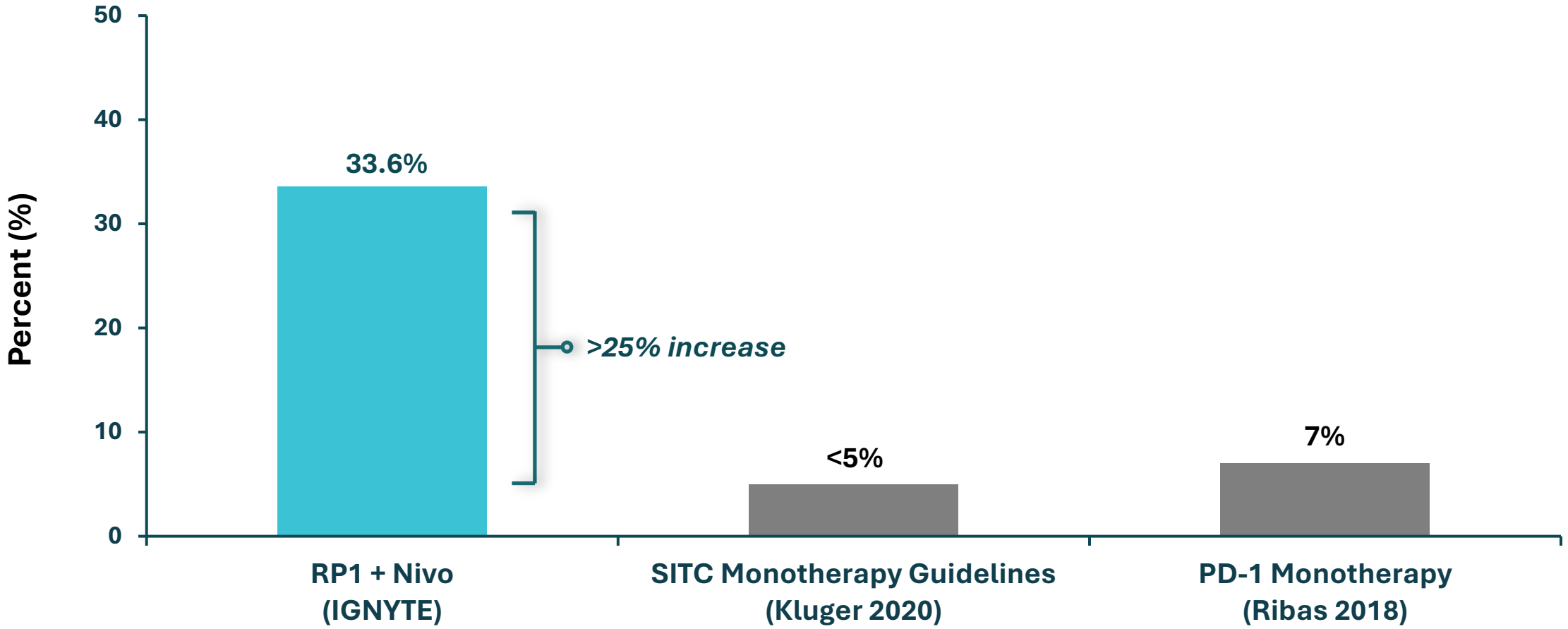
Efficacy

Clinically Meaningful Responses Observed in Anti-PD-1–Refractory Melanoma Population (IGNYTE Study)



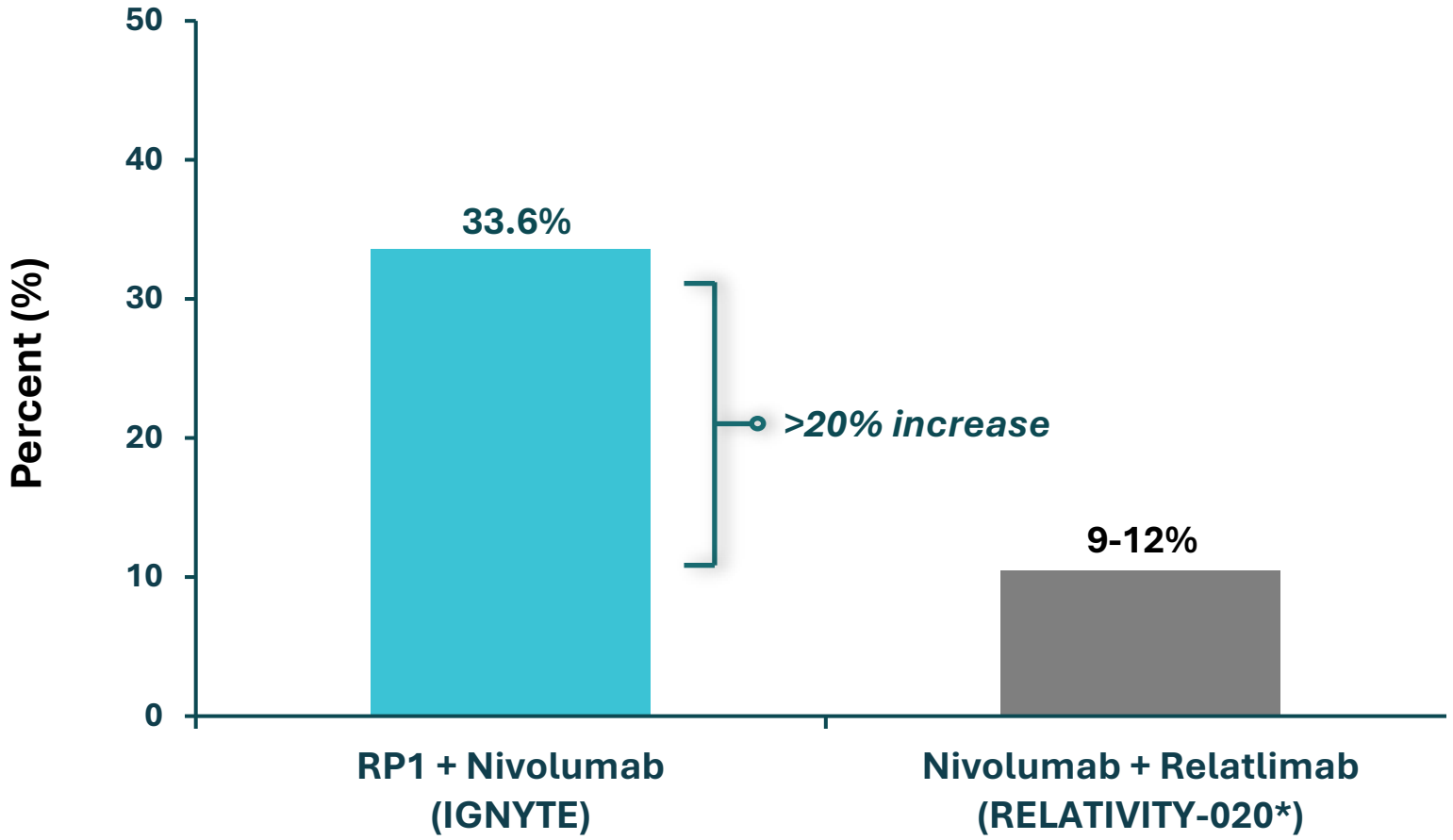
Data Cutoff: October 15, 2024

Only 5-7% ORR Expected with Further Anti-PD-1 Monotherapy Following Definitive Progression



Ribas A, et al. *Lancet Oncol*. 2018;19(5):e219;
Kluger HM, et al. *J Immunother Cancer*. 2020;8(1):e000398.

RELATIVITY-020 is a Reasonable Benchmark for Magnitude of Effect



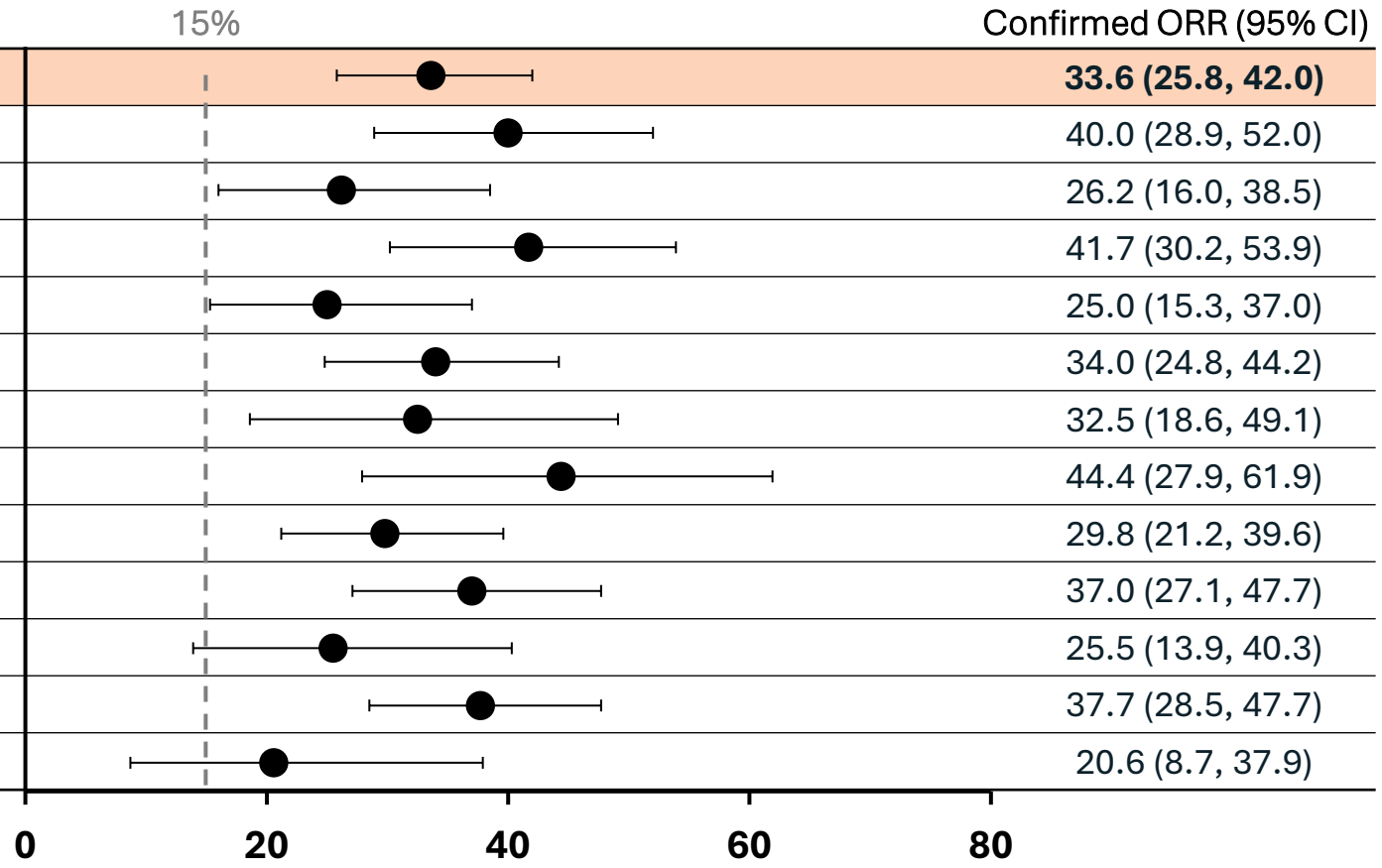
Similar study design

- Prospective study with broadly comparable resistant-disease populations
- Prior lines of therapy include anti-PD-1, CTLA-4, and BRAF
- ≥50% of patients received ≥2 prior lines of therapy
- Stage IV disease (~90% in RELATIVITY-020 and 84% in IGNYTE non-adjuvant)
- Rare subtypes included

Ascierto PA, et al. J Clin Oncol. 2023;41(15)2724-35.

RP1+ Nivolumab Delivers Meaningful Responses Across Clinically Relevant Subgroups

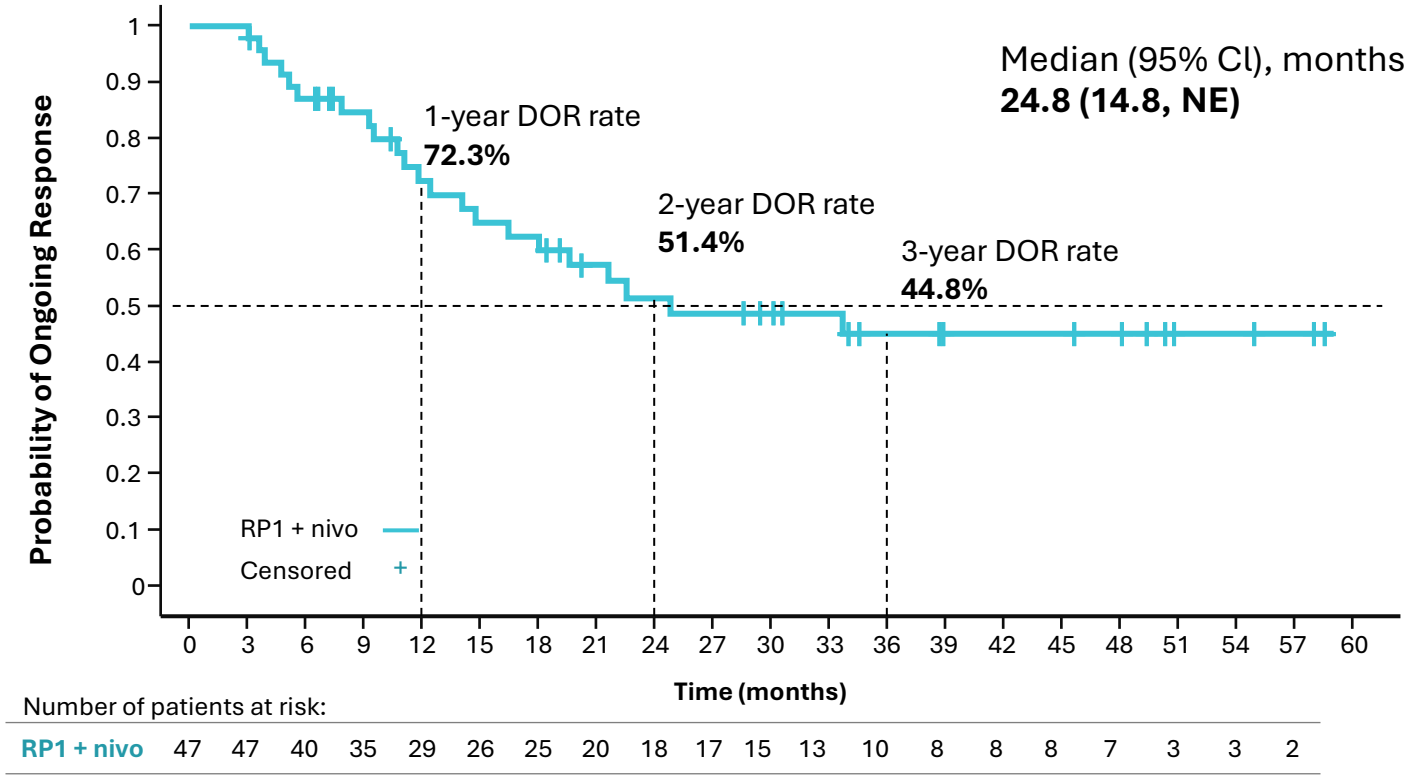
		n	Confirmed ORR (95% CI)
All patients		**140**	**33.6 (25.8, 42.0)**
Agent	Single-agent anti-PD-1	75	40.0 (28.9, 52.0)
	Anti–PD-1/CTLA-4	65	26.2 (16.0, 38.5)
Stage	Stage IIIb-IVM1a	72	41.7 (30.2, 53.9)
	Stage IVM1b-d	68	25.0 (15.3, 37.0)
Resistance	Primary resistance	100	34.0 (24.8, 44.2)
	Secondary resistance	40	32.5 (18.6, 49.1)
Adjuvant Status	Anti–PD-1 adjuvant	36	44.4 (27.9, 61.9)
	Anti–PD-1 not adjuvant	104	29.8 (21.2, 39.6)
LDH Level	≤ULN	92	37.0 (27.1, 47.7)
	>ULN	47	25.5 (13.9, 40.3)
Tumor Burden	≤10 cm	106	37.7 (28.5, 47.7)
	>10 cm	34	20.6 (8.7, 37.9)



FDA approved statistical analysis plan (SAP) required 95% CI to exclude 15% ORR, which was achieved for the primary analysis of ORR and for key clinical subgroups

Data cutoff: October 15, 2024
Centrally reviewed RECIST 1.1 responses; all patients have ≥12 months follow-up

Durable Response Supports Systemic Benefit



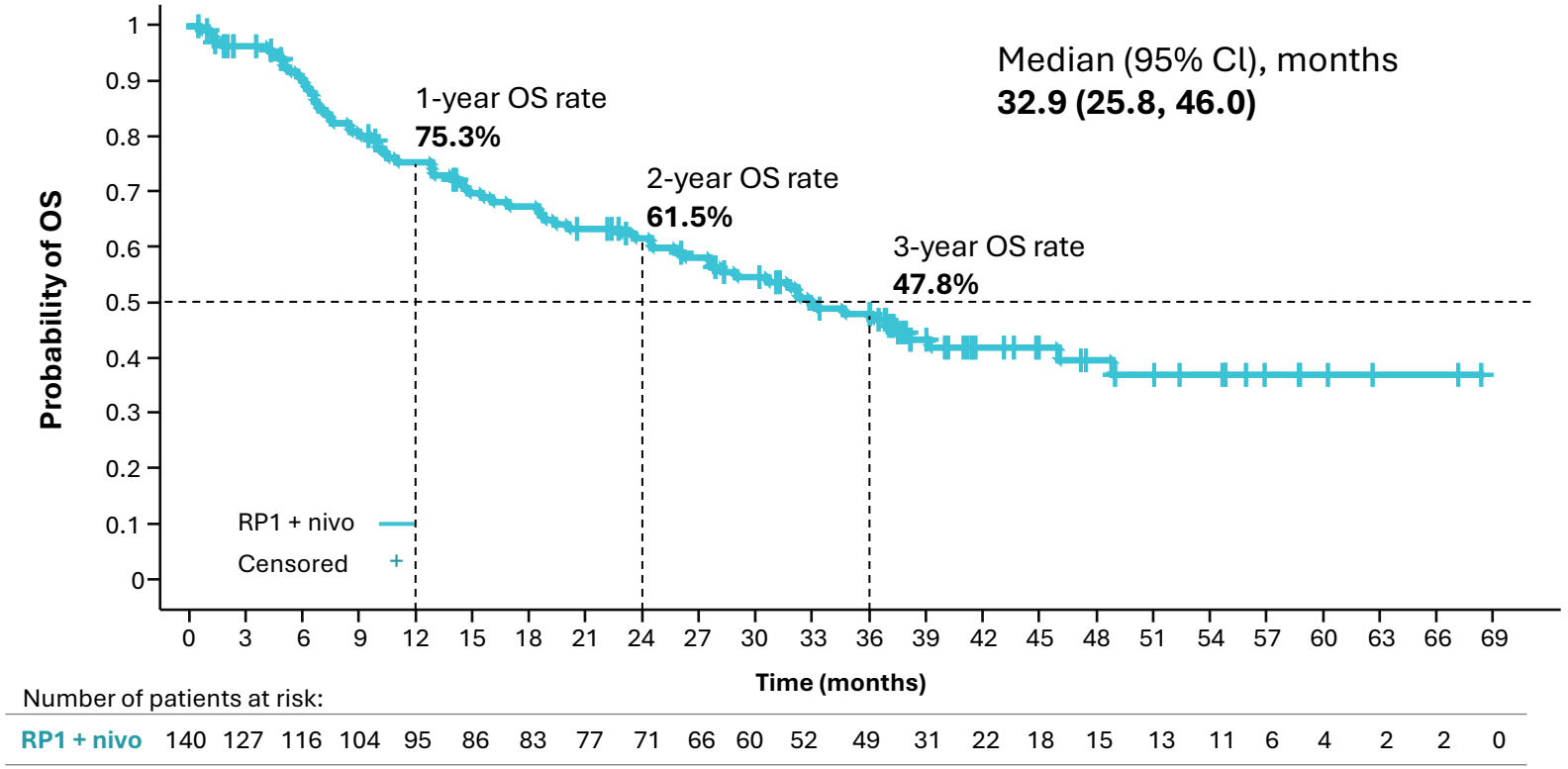
DOR rates, % (95% CI)	
1-year	**72.3** (56.2, 83.3)
2-year	**51.4** (35.0, 65.5)
3-year	**44.8** (28.5, 59.8)

ORR (95% CI) was 33.6% (25.8%, 42.0%), and the median DOR (95% CI) was 24.8 months (14.8, NE)

Note: Data previously not submitted to FDA

Cutoff: March 8, 2026.
CI, confidence interval; DOR, duration of response; nivo, nivolumab; NE, not estimable; ORR, objective response rate; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

3-Year Overall Survival Among All Patients



OS rates, % (95% CI)	
1-year	**75.3** (66.9, 81.9)
2-year	**61.5** (52.4, 69.4)
3-year	**47.8** (38.6, 56.5)

Median PFS (95% CI) per RECIST 1.1 by Independent Review was 3.6 months (2.0, 5.0); 34.9 months (22.0, NE) for responders

Data cutoff: March 8, 2026.
CI, confidence interval; nivo, nivolumab; OS, overall survival.

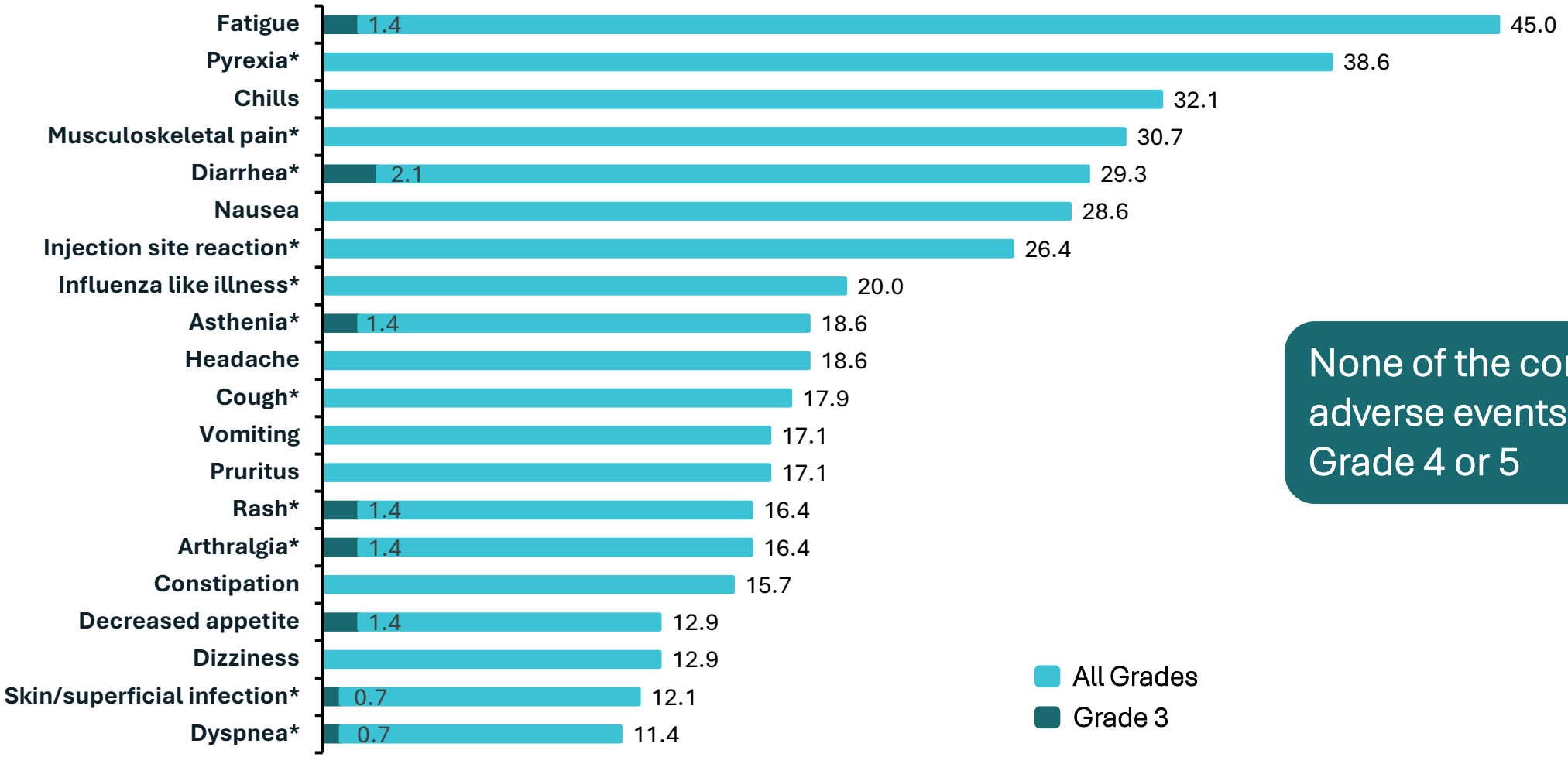
Clinical Safety Data

Overview of Safety for RP1 in Combination with Nivolumab

Patients with:	N=140 n (%)
Any TEAE	137 (97.9)
Any SAE	50 (35.7)
Any TEAE with outcome of death*	12 (8.6)
Any TEAE of CTCAE Grade 3 or higher	44 (31.4)
Any TEAE leading to dose interruption of RP1 or nivolumab	32 (22.9)
Any TEAE leading to discontinuation of RP1	11 (7.9)

*Includes reports of disease progression=8, death=1, head injury=1, multiple organ disfunction=1, myocardial infarction=1.

Adverse Events Occurring in >10% of Patients (Excluding Laboratory-Related Adverse Events) – IGNYTE Study (N=140)



None of the common adverse events were Grade 4 or 5

* A composite that includes multiple related terms
Data cutoff: October 15, 2024

Fatal Events Considered Possibly Related by FDA: Pooled Safety Analysis (N=335)

Patient ID	Age/Sex	Cohort (Malignancy)	Preferred Term	Related to RP1/Nivolumab	
				Investigator	Sponsor
1	70/M	Anti-PD-1 Failed **Cutaneous Melanoma**	Myocardial infarction (G5)	N/N	N/N
2	44/M	Anti-PD-1 Failed **Cutaneous Melanoma**	Multiple organ dysfunction syndrome (G5)	N/N	N/N
3	78/M	Anti-PD-1 Failed NMSC (MCC)	Capillary leak syndrome (G5)	Y/Y	N/N
4	87/M	Anti-PD-1 Naive NMSC (CSCC)	Immune-mediated myocarditis (G5)	N/Y	N/Y
5	90/M	Anti-PD-1 Failed NMSC (CSCC)	Pneumonia (G5)	N/N	N/N
6	75/M	Anti-PD-1 Failed NMSC (NMSC)	Tumor hemorrhage (G3) Disease progression (G5)	N/N	N/N
7	72/M	Anti-PD-1 Naive NMSC (CSCC)	Pulmonary sepsis (G3) Malignant neoplasm progression (G5)	N/N	N/N

Data cutoff: October 15, 2024
MCC, Merkel cell carcinoma; CSCC, cutaneous squamous cell carcinoma; NMSC, non-melanoma skin cancer

Assessment of Topics of Interest

- Contribution of Effect
- Response Assessment

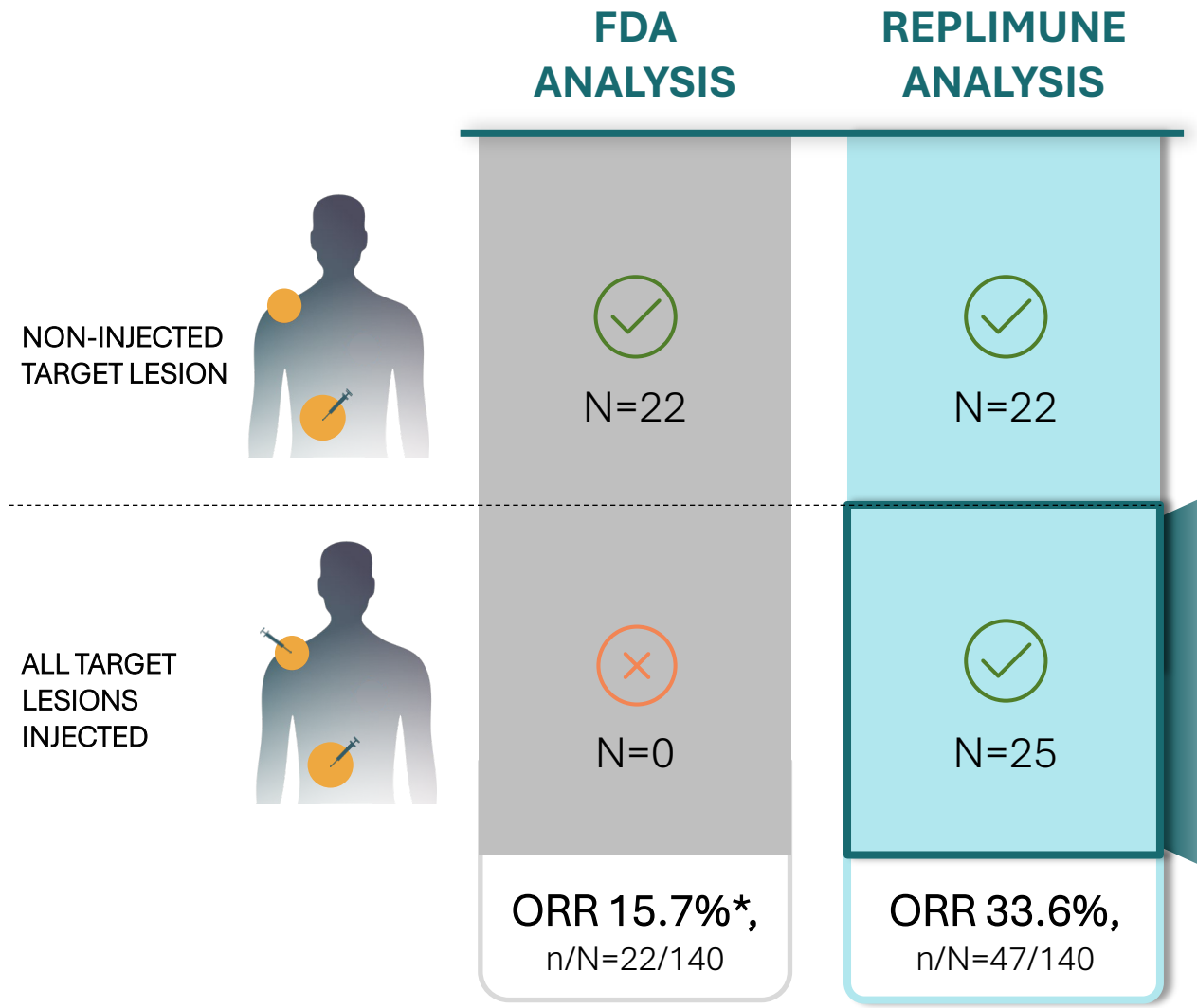
Patients Serving as Their Own Control Analysis Supports the Contribution of Effect (IGNYTE Study)

Patient Population	Time on Prior Treatment Months (Range)	ORR on Prior PD-1 Based Therapy % (n; 95% CI)	ORR During IGNYTE % (n; 95% CI)
All Patients (N=104) *Non-adjuvant*	5.6 (2.1, 60.0)	**11.5% (12; 6.1-19.3)**	**29.8% (31; 21.2-39.6)**
Responders Only (N=31) *Non-adjuvant*	5.6 (3.5, 46.9)	**12.9% (4; 3.6-29.8)**	**100% (31; 88.8-100)**

Replimune data on file. ORR analysis includes non-adjuvant patients only (cannot assess prior response to adjuvant treatment) n=104 for all patients and n=31 for responders.

Durability Supports Systemic Impact in IGNYTE Study

Response Assessment



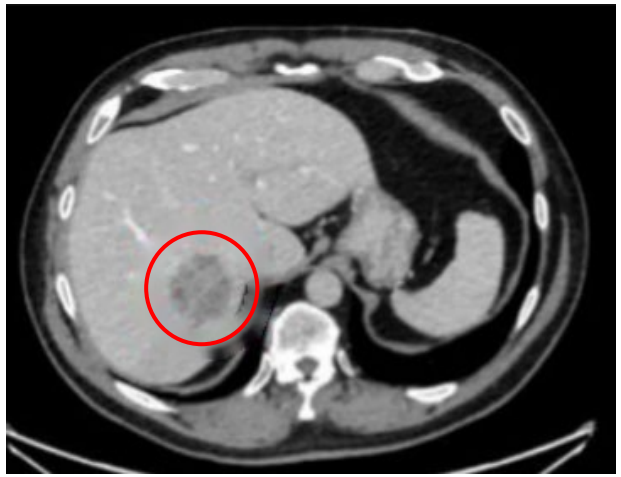
	Responder (n/N)	ORR (95% CI)	DOR, months (95% CI)
Patients who had all target lesions injected	**25/51**	**49.0 (34.8, 63.4)**	**NR (25.6, NE)**

*If corrected for denominator = 25% (FDA sensitivity analysis)
NE, not evaluable
NR, not reached

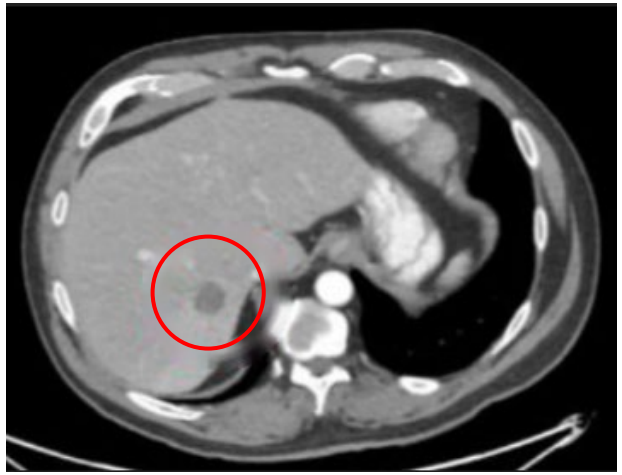
Patient Example With Injected Only Disease

Liver
INJECTED

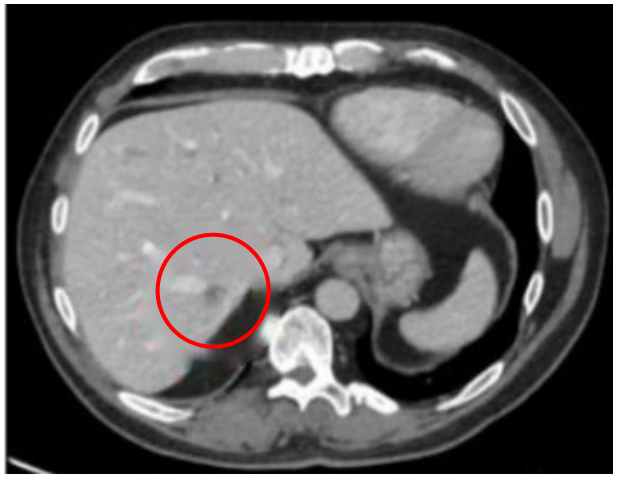
Baseline
NOV 2021



MAR 2022



FEB 2024



Disease Background:
- 68 yo M, Stage IVM1c

Prior line of therapy:
- Pembrolizumab (adjuvant)

Confirmed BOR per RECIST 1.1 by IRC = PR

DOR = 45.7mo

Injected

Response in All Lesions Measured is Consistent with RECIST 1.1 ORR 33.6%

Response in Patients Who Had Both Injected and Non-injected Measured Lesions (N=108)

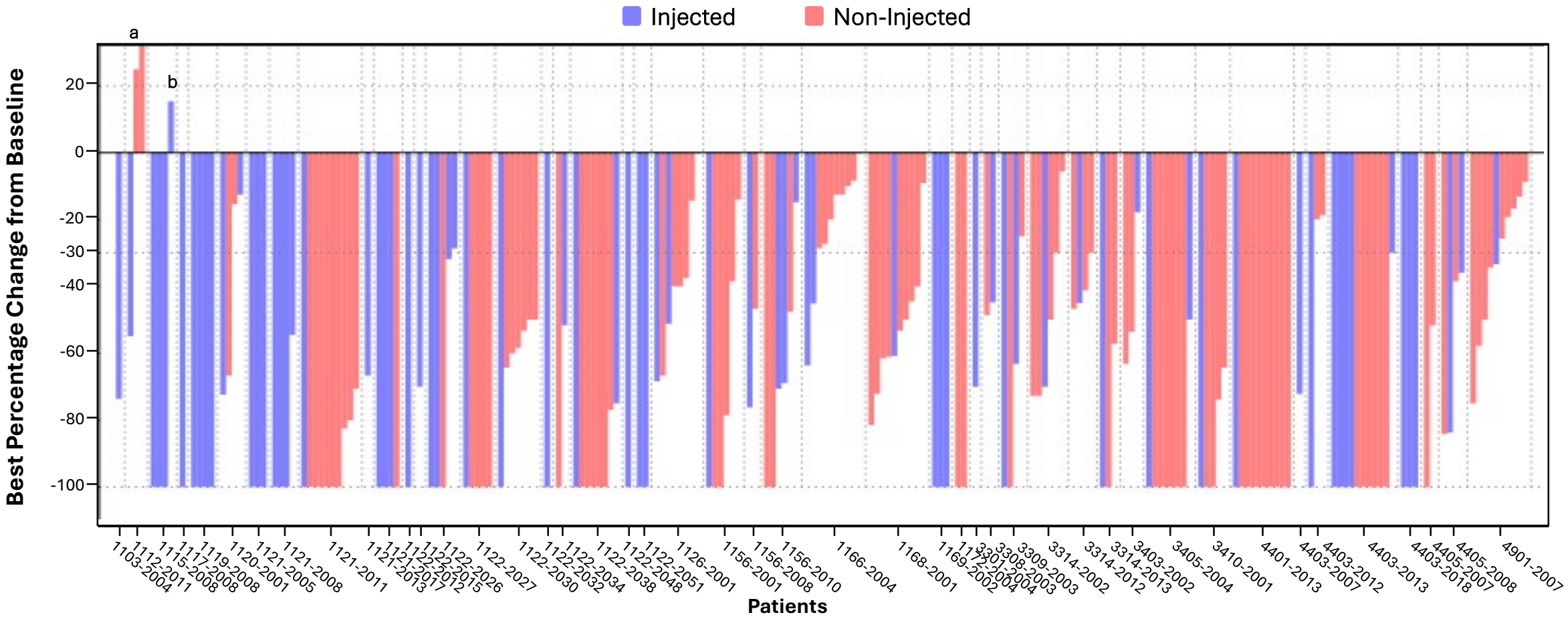
Best Response Category	Response Based on Injected Measured Lesions Only n (%)	Response Based on Non-injected Measured Lesions Only n (%)
CR	16 (14.8)	13 (12.0)
PR	18 (16.7)	18 (16.7)
SD	33 (30.6)	28 (25.9)
PD	32 (29.6)	35 (32.4)
NE	9 (8.3)	14 (13.0)
ORR	**34 (31.5)**	**31 (28.7)**
95% CI	22.9, 41.1	20.4, 38.2

All measured lesion analysis more comprehensive than RECIST 1.1*

*Only target lesions

Patient Level Analysis Supports Systemic Effect (Responders, All Measured Lesions)

Response Assessment



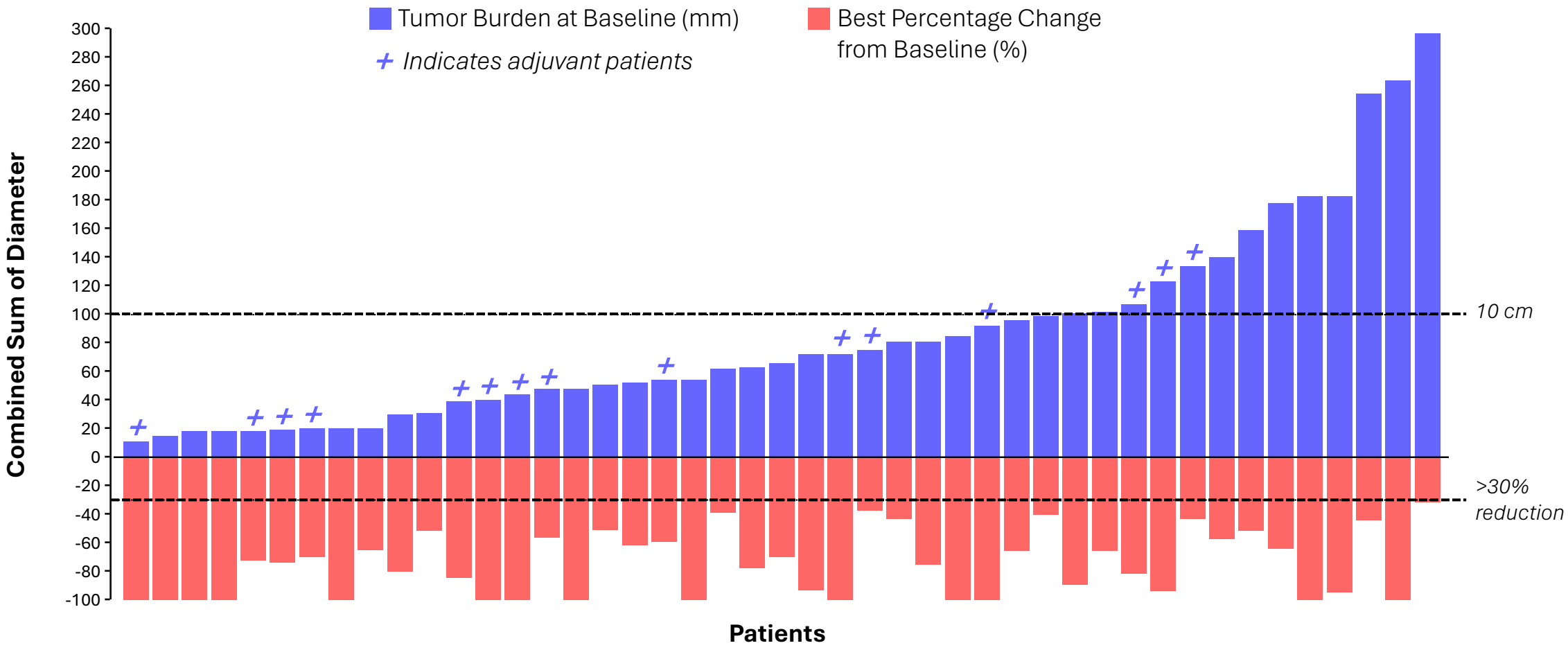
53 non-injected lesions were visceral (30 were lung lesions,14 were liver lesions)
66.0% (35/53) had a reduction of >30%

Data cutoff: October 15, 2024

a. Patient had a CR as a radical resection of all 3 lesions on the skin of the left foot confirmed full regression; b. The sum of diameters of 4 target lesions met the criteria for a PR

Deep Responses Across Tumor Burden Spectrum

All Measured Lesions



Cutoff: 8 March 2024

Summary

Favorable Benefit-Risk for Accelerated Approval

UNMET NEED: SERIOUS, LIFE-THREATENING DISEASE

EFFICACY

Adequate and Well-controlled Trial

IGNYTE
- ORR: 33.6% (95% CI: 25.8, 42)
- DoR: 24.8 months (95% CI: 14.1, NE)

Supporting Evidence

MOA/Biological Plausibility | Preclinical | Biomarkers

SAFETY

Well-tolerated Safety Profile

IGNYTE
- Mainly Grade 1 and 2
- No treatment-related Grade 5

IGNYTE-3 randomized confirmatory trial ongoing with OS data expected in 2030

Clinical Perspective and Case Studies

Mohammed Milhem, MBBS

Professor of Internal Medicine

Former Division Chair and Holden Chair for Experimental Therapeutics
Division of Hematology and Oncology, University of Iowa

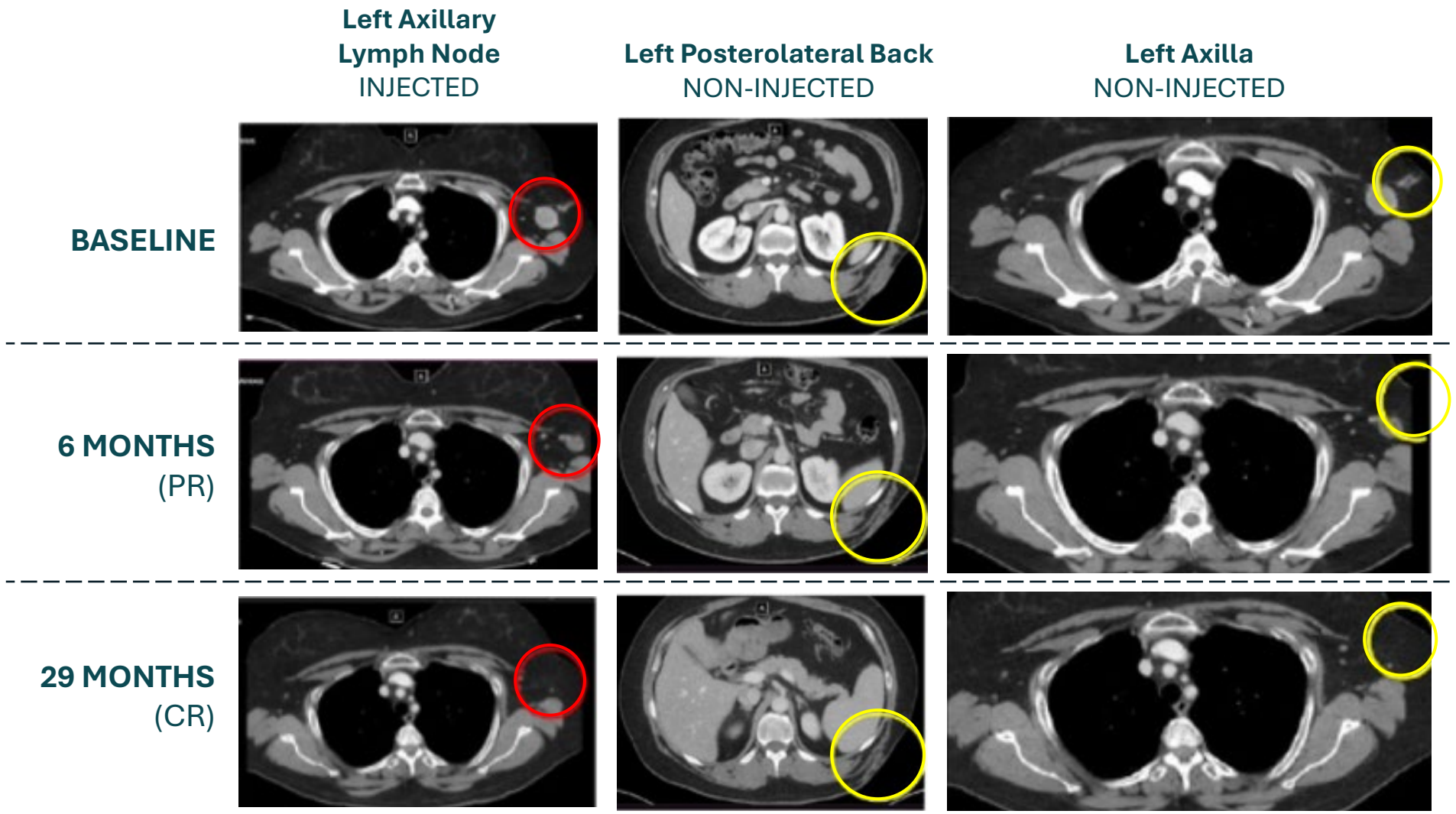
Clinical Reality Today

- **Patients whose disease progresses after PD-1 therapy have:**
  - Limited treatment options
  - Modest response rates
  - TILs treatment present logistical and safety challenges
- **What we need:**
  - New treatment options that can benefit patients whose disease has progressed on prior PD-1 therapy
  - Injection of tumors in different locations overcomes resistance mechanisms
  - Durable responses that will likely translate into survival
  - Manageable safety profile

RP1+Nivolumab Provides an Important Option for Difficult to Treat Patients

- Three patient examples
  - Adjuvant Failed
  - Failed Multiple Lines
  - Non-injected Visceral Responses

Patient Example: Adjuvant Failed



Disease Background:

- 50 yo F, Stage IIIC

Prior lines of therapy:

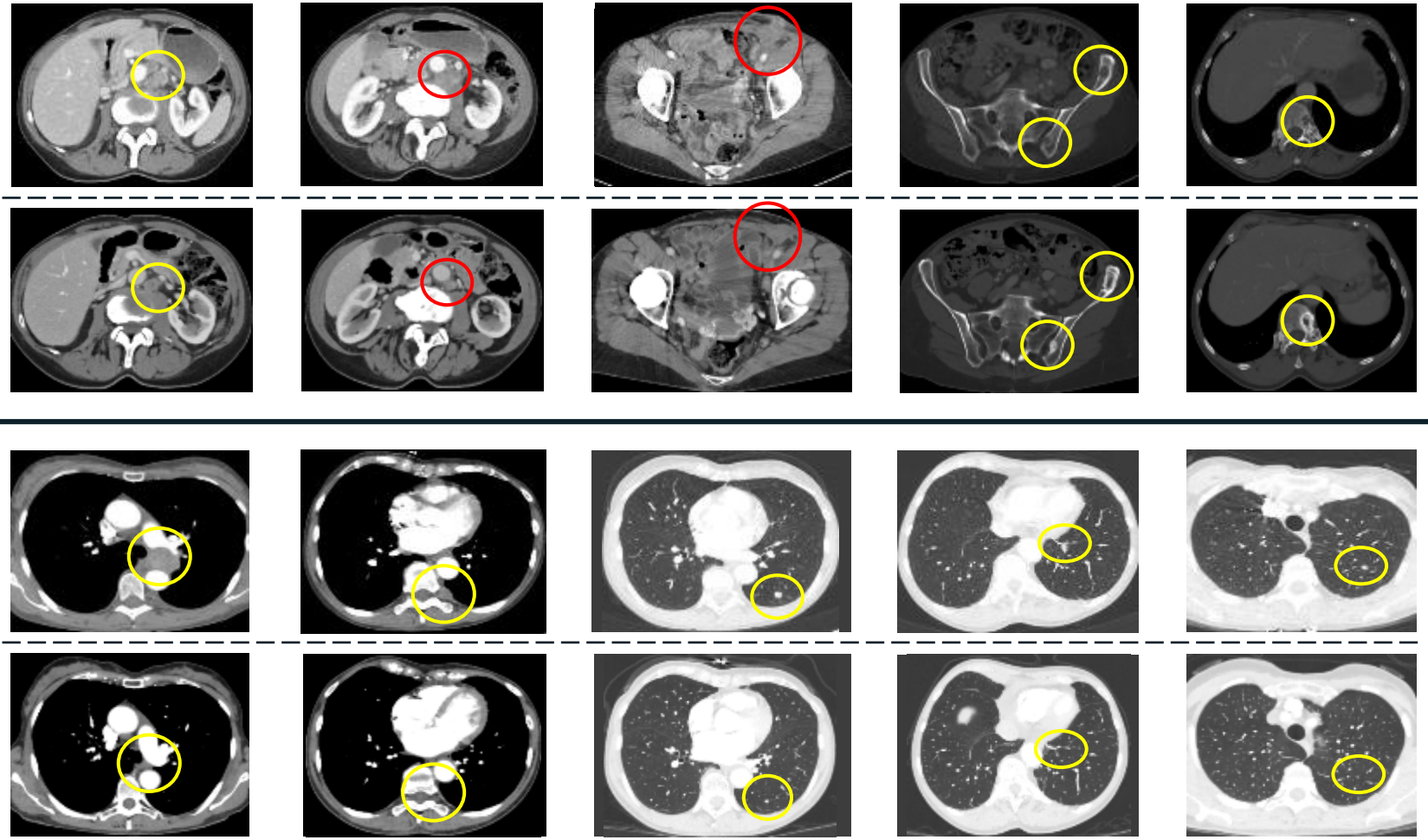
- Pembrolizumab
- Elevated LDH at baseline

Confirmed BOR per IRC = CR

Injected Non-injected

Patient Example: Failed Multiple Lines

Multiple sites of disease at baseline including chest, abdomen, and pelvis



Disease Background:

- 74 yo F, Stage IVM1b

Prior lines of therapy:

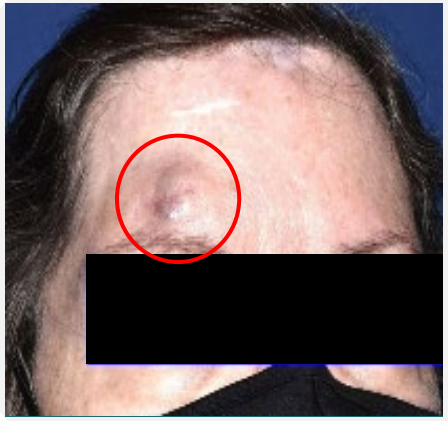
- Atezolizumab+ cobimetinib
- Atezolizumab
- Ipilimumab
- SX682 (CXCR-inhibitor)+ pembrolizumab
- Ipilimumab+ nivolumab
- Carboplatin+paclitaxel+ pembrolizumab

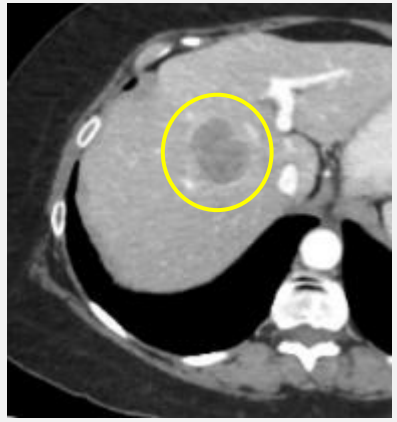
Confirmed BOR per IRC = PR

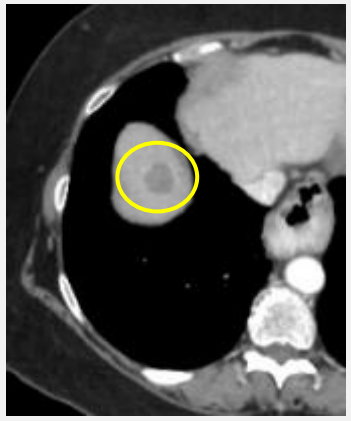
Injected Non-injected

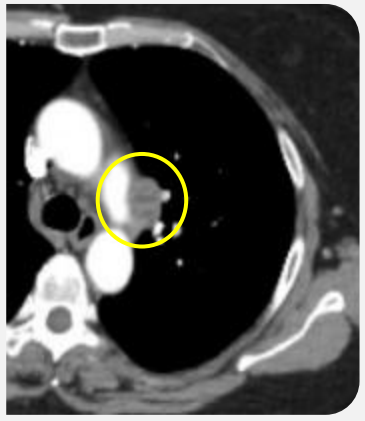
Patient Example: Non-injected Visceral Responses

BASELINE

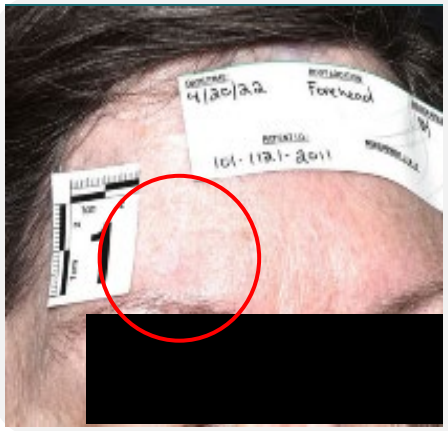


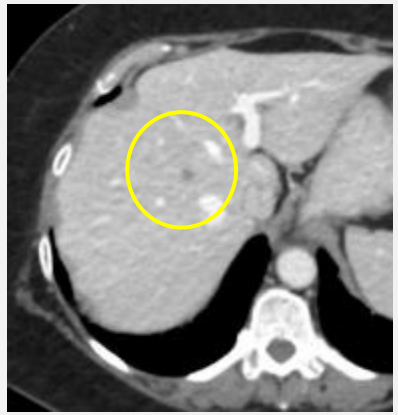


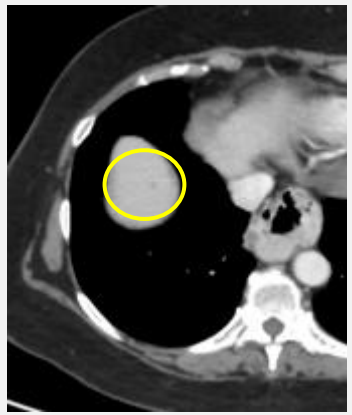


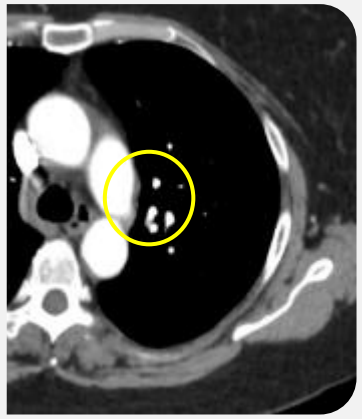


9 MONTHS









Disease Background:

- 62 yo F, Stage IVM1c

Prior lines of therapy:

- Nivolumab (adjuvant)
- Pembrolizumab (adv/met)
- Elevated LDH at baseline

Confirmed BOR per by IRC = PR

Injected Non-injected

RP1 Needed for Patients Now

- Urgent unmet need remains
- RP1 has a positive clinical benefit risk
  - Compelling efficacy
  - Favorable safety profile
- Innovative modalities require creative and pragmatic approaches to advance the field

Replimune®

Vusolimogene oderparepvec-wtpg (TUDRIQEV™) in combination with nivolumab for the treatment of adults with unresectable advanced cutaneous melanoma

United States Food and Drug Administration

Cellular, Tissue and Gene Therapies Advisory Committee

July 30, 2026