Replimune®

Igniting a systemic immune response to cancer with oncolytic immunotherapy

JP Morgan Healthcare Conference
January 13, 2025

Safe Harbor

Any statements contained herein that are not statements of historical facts may be deemed to be forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, including statements regarding the advancement, timing and sufficiency of our clinical trials or financial status, patient enrollments in our existing and planned clinical trials and the timing thereof, the results of our clinical trials, the timing and release of our clinical data, statements regarding our expectations about our cash runway, our goals to develop and commercialize our product candidates, our expectations regarding the size of the patient populations for our product candidates if approved for commercial use and other statements identified by words such as "could," "expects," "intends," "may," "plans," "potential," "should," "will," "would," or similar expressions and the negatives of those terms. Forward-looking statements are not promises or guarantees of future performance, and are subject to a variety of risks and uncertainties, many of which are beyond our control, and which could cause actual results to differ materially from those contemplated in such forward-looking statements. These factors include risks related to our limited operating history, our ability to generate positive clinical trial results for our product candidates, the costs and timing of operating our in-house manufacturing facility, the timing and scope of regulatory approvals, changes in laws and regulations to which we are subject, competitive pressures, our ability to identify additional product candidates, political and global macro factors including the impact of global pandemics and related public health issues, the ongoing military conflicts between Russia-Ukraine and Israel-Hamas and the impact on the global economy and related governmental imposed sanctions, and other risks as may be detailed from time to time in our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, and other reports we file with the Securities and Exchange Commission. Our actual results could differ materially from the results described in or implied by such forward-looking statements. Forward-looking statements speak only as of the date hereof, and, except as required by law, we undertake no obligation to update or revise these forward-looking statements.

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3 Clinical Assets with >700 Patients Treated

7 Ongoing Clinical Trials

RP1 Establishing a Skin Cancer Franchise

Lead Indication: Anti-PD-1 Failed Melanoma

- RP1 + nivolumab showed **~34% ORR*; systemic activity** including in patients with **visceral** disease
- **Well-tolerated,** predominantly gr 1+2 AEs
- IGNYTE-3 **confirmatory trial underway**

Additional Data: Anti-PD-1 Failed NMSC and Solid Organ Transplant (SoT)

- **~30% ORR** in anti-PD-1 failed MCC, BCC, and LA CSCC
- **35% ORR** with **RP1 monotherapy** in SoT

RP2 RP3 Expanding RPx Opportunities

Uveal Melanoma

- RP2 + nivolumab **showed ~29% ORR**
- **Registrational trial ongoing#**

Hepatocellular Carcinoma (HCC)

- RP2 + atezolizumab + bevacizumab **Phase 2 trial in anti-PD-(L)1 failed HCC ongoing^**

Additional Signals

- **Clinical activity, including as monotherapy, in multiple challenging to treat tumors** (e.g., sarcomas, H&N subtypes, and esophageal cancer)

Positioned for Successful RP1 Independent Commercial Launch in 2H 2025

- Granted **Breakthrough Therapy Designation for RP1, BLA submitted for anti-PD-1 failed melanoma**
- **Strong financial position with cash of $536 million** as of 12/31/24 (unaudited)
- 63,000 ft^2 **US manufacturing facility enabling global supply with attractive COGs**
- **Wholly owned, unincumbered assets / RPx platform**

*modified RECIST; ORR=overall response rate; ^Trial being conducted under collaboration and supply agreement with Roche; #Trial being conducted under collaboration and supply agreement with BMS; H&N=head and neck; NMSC = Non melanoma skin cancers, COGs=cost of goods; SoT = solid organ transplant, LA = locally advanced, CSCC = cutaneous squamous cell carcinoma; BCC = basal cell carcinoma; MCC = Merkel cell carcinoma

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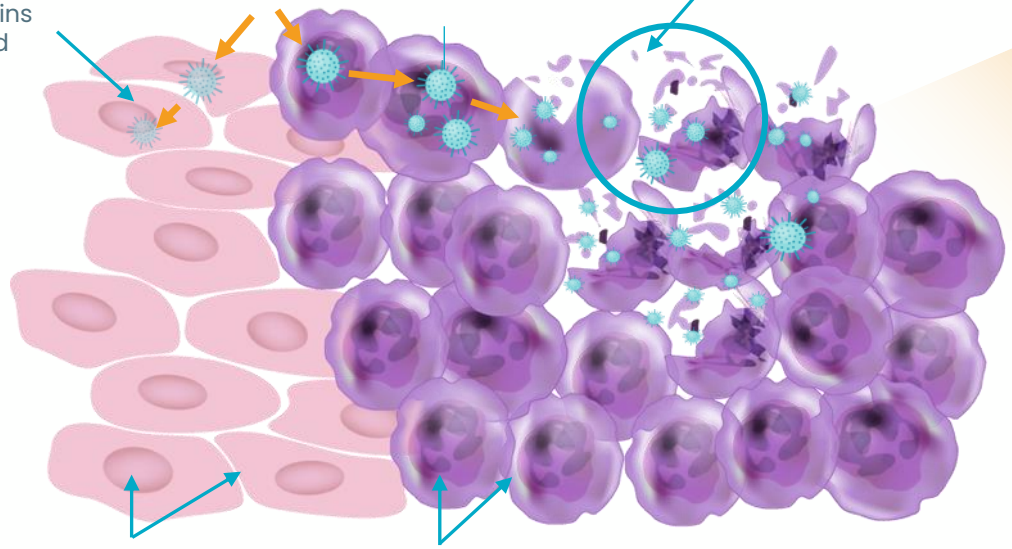
Oncolytic Immunotherapy Designed to Activate a Dual Local and Systemic Anti-Tumor Response

Oncolytic Immunotherapy - New clinical isolate of HSV-1 modified to express a fusogenic glycoprotein and immune stimulating proteins

Intact host antiviral response: Normal tissue remains undamaged

Dysregulated host antiviral response allows robust virus replication and tumor lysis



Injected Local Response

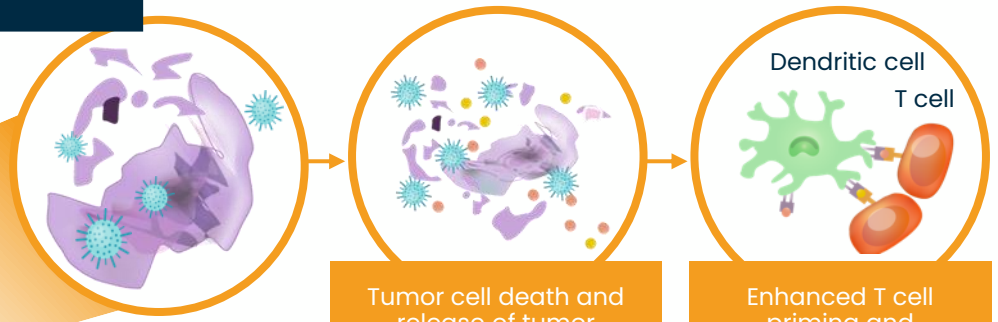
MECHANISM 1

Release of virus progeny

Infection of more tumor cells

Non-Injected Systemic Immune Response

MECHANISM 2



Tumor cell death and release of tumor antigens

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 anti-tumor immune response

Bommareddy PK et al AJCD. 2016

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Igniting a Systemic Immune Response via RPx Intra-tumoral (IT) Delivery

Replimune®

Expressed Payloads (Immune Stimulating)

RP1

GM-CSF (intended to mature antigen presenting cells, & **activate the immune system** against cancer)

GALV-GP R- (intended to **cause cell fusion and immunogenic cell death**, to enhance direct tumor killing & the adaptive and innate immune responses)

+

RP2

Anti-CTLA-4 (antibody intended to prevent immune blockade at the APC / T cell interface; **local expression limits systemic toxicity**)

Therapeutic Objective

Robust local and distant / systemic anti-tumor response

Limit adverse events and toxicities

Combinability and Rx synergy e.g., I-O, targeted therapies

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RP1: Delivering on the Promise of Oncolytic Immunotherapy

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Significant Unmet Need for Melanoma Patients that Progress on PD-1 Containing Regimens

~50% of patients on first line therapy progress within 6 months[1,2]

Few treatment options available[3,4]

Limited response rates/durability[5,6]

Current treatments have toxicity concerns[7,8,9]

Sources: . 1. Wolchok JD, et al. N Engl J Med. 2024. 2. Tawbi HA, et al. J Clin Oncol. 2024;42:16 suppl. 3. Mooradian MJ, et al. Oncology. 2019;33(4):141-8. 4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Melanoma: Cutaneous. Version 2. 2024. 5. Dixon-Douglas JR, et al. Curr Oncol Rep. 2022;24(8):1071-9. 6. Ascierto PA, et al. J Clin Oncol. 2023;41(15)2724-35. 7. Chesney J, et al. J Immunother Cancer. 2022;10(12):e005755. 8. US Food and Drug Administration. BLA clinical review and evaluation - AMTAGVI. BLA 125773. Updated February 6, 2024. Accessed May 31, 2024. https://www.fda.gov/media/176951/download. 9. Sarnaik AA, et al. J Clin Oncol. 2021;39(24):2656-66.

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RP1 + Nivolumab Delivers Consistent Responses Across Anti-PD-1 Failed Melanoma Subgroups

BOR n (%)	All patients (N = 140)	Prior single-agent anti–PD-1 (n = 75)	Prior anti–PD-1/ CTLA-4 (n = 65)	Stage IIIb–IVa (n = 72)	Stage IVb–IVd (n = 68)	Primary resistance (n = 92)	Secondary resistance (n = 48[a])	Prior anti–PD-1 adjuvant (n = 36)	Prior anti–PD-1 not adjuvant (n = 104)
CR	21 (15.0)	16 (21.3)	5 (7.7)	17 (23.6)	4 (5.9)	16 (17.4)	5 (10.4)	11 (30.6)	10 (9.6)
PR	26 (18.6)	13 (17.3)	13 (20.0)	12 (16.7)	14 (20.6)	17 (18.5)	9 (18.8)	5 (13.9)	21 (20.2)
SD	41 (29.3)	20 (26.7)	21 (32.3)	24 (33.3)	17 (25.0)	22 (23.9)	19 (39.6)	10 (27.8)	31 (29.8)
PD	43 (30.7)	24 (32.0)	19 (29.2)	18 (25.0)	25 (36.8)	31 (33.7)	12 (25.0)	9 (25.0)	34 (32.7)
ORR	**47 (33.6)**	**29 (38.7)**	**18 (27.7)**	**29 (40.3)**	**18 (26.5)**	**33 (35.9)**	**14 (29.2)**	**16 (44.4)**	**31 (29.8)**

Data presented at ESMO 2024, SITC 2024

[a]Includes one patient with unknown resistance status.
BOR, best overall response; CR, complete response; CTLA-4, cytotoxic T-lymphocyte antigen 4; mRECIST, modified response evaluation criteria in solid tumors; PD-1, programmed cell death protein 1; PD, progressive disease; PR, partial response; ORR, objective response rate; SD, stable disease.
Centrally reviewed mRECIST v1.1 responses (per protocol); all patients have ≥12 months follow up

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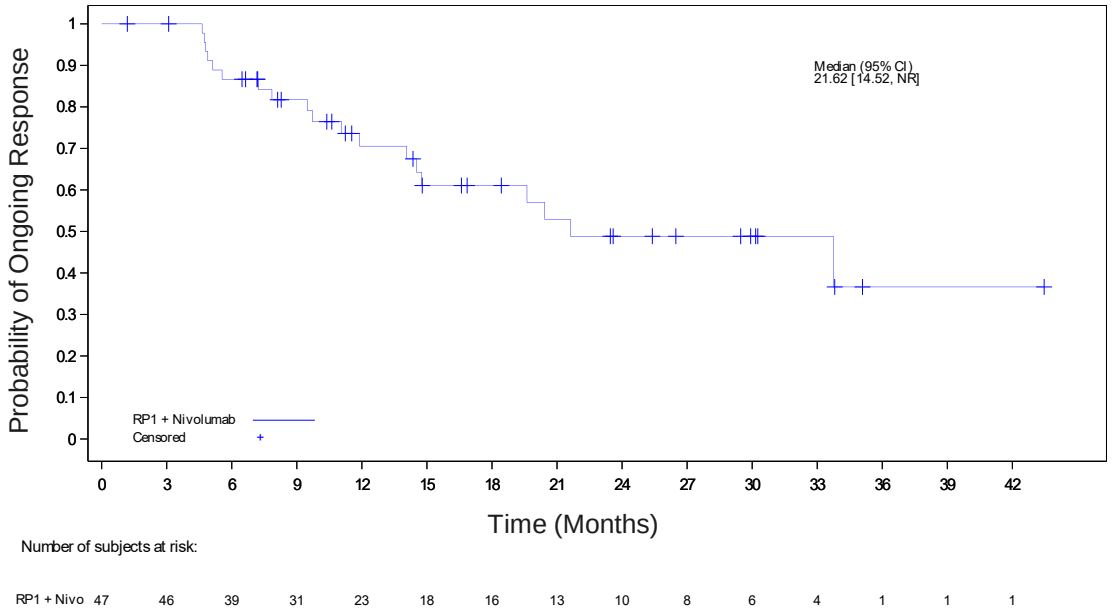
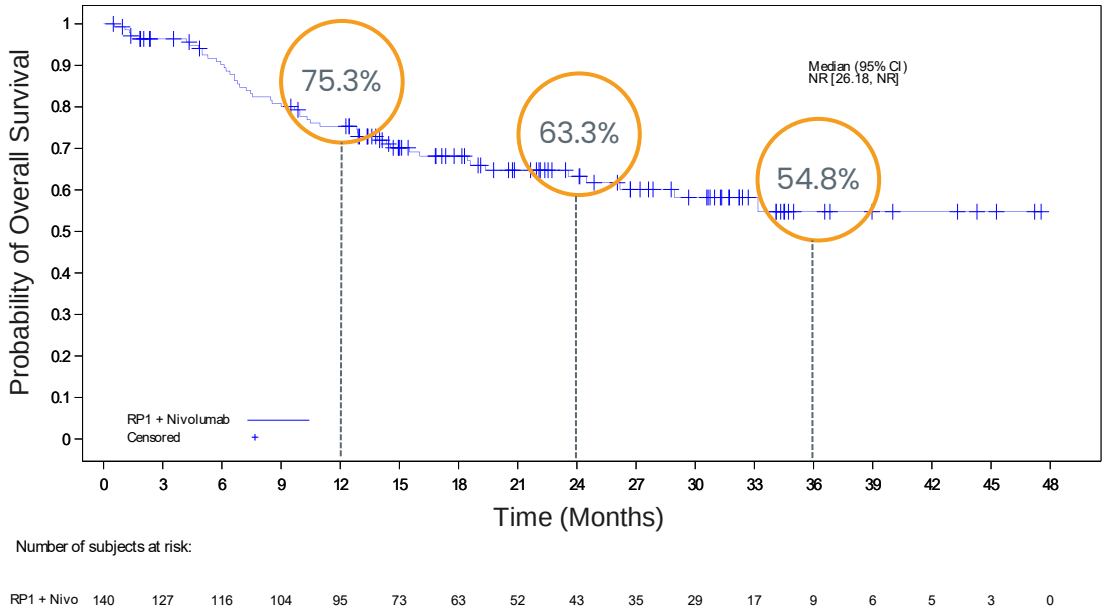
Durable Responses and Promising Overall Survival

Median Duration of Response - 21.6 months*



Overall Survival - Not Reached



Data presented at ESMO 2024, SITC 2024

*From response initiation; range (1.2+ to 43.5+ months)

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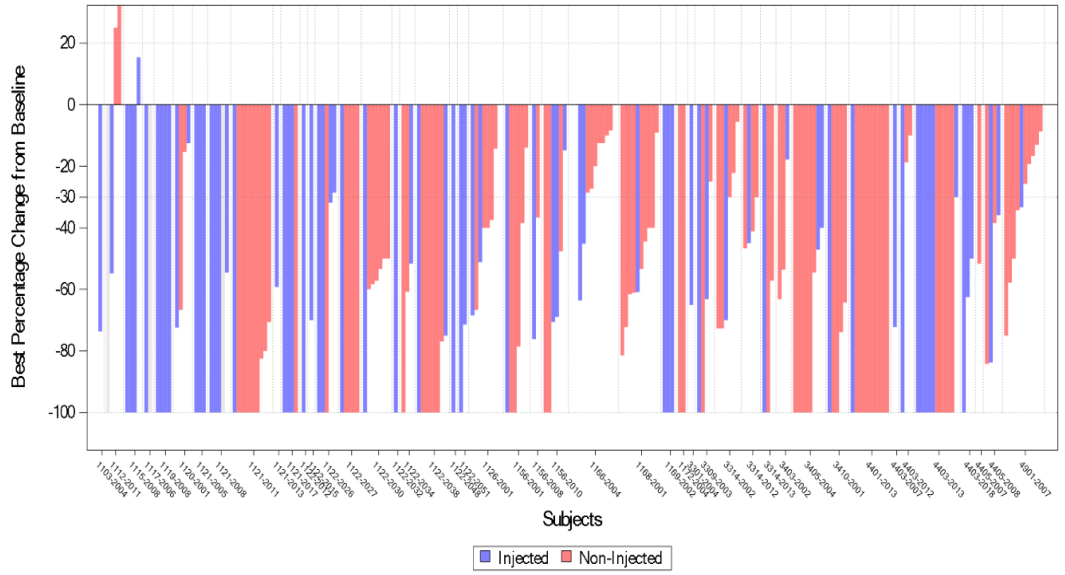
Systemic Benefit with Deep Responses in Visceral Lesions

Anti-tumor effect on non-injected visceral lesions*

Location of visceral lesions	n (Lesions)	Any Reduction	>0% to <30%	≥30% to <100%	100%
Lung	29	28 (96.6%)	7 (24.1%)	9 (31%)	12 (41.4%)
Liver	15	15 (100%)	4 (26.7%)	5 (33.3%)	6 (40%)
Adrenal	3	1 (33.3%)	0	0	1 (33.3%)
Ovary	1	1 (100%)	0	0	1 (100%)
Spleen	6	5 (83.3%)	5 (83.3%)	0	0
Pleura	2	2 (100%)	0	1 (50%)	1 (50%)
Brain	3	1 (33.3%)	1 (33.3%)	0	0
Pancreas	1	0	0	0	0
TOTAL	**60**	**53 (88.3%)**	**17 (28.3%)**	**15 (25%)**	**21 (35%)**

- Tumor reduction seen in 53 out of 60 non-injected visceral lesions

Responses in injected and non-injected lesions*



Data presented at SITC 2024
*in responding patients (N=47)

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Favorable Safety Profile of RP1 + Nivolumab

Preferred term, n (%)	TRAEs occurring in ≥5% of patients (N = 141)	
	All Grades	Grade 3-4
≥1 TRAE	**126 (89.4)**	**18 (12.8)**
Fatigue	46 (32.6)	1 (0.7)
Chills	45 (31.9)	0 (0.0)
Pyrexia	43 (30.5)	0 (0.0)
Nausea	31 (22.0)	0 (0.0)
Influenza-like illness	25 (17.7)	0 (0.0)
Injection-site pain	21 (14.9)	0 (0.0)
Diarrhoea	20 (14.2)	1 (0.7)
Vomiting	19 (13.5)	0 (0.0)
Headache	18 (12.8)	0 (0.0)
Pruritus	18 (12.8)	0 (0.0)
Asthenia	14 (9.9)	1 (0.7)
Arthralgia	10 (7.1)	1 (0.7)
Decreased appetite	9 (6.4)	1 (0.7)
Myalgia	9 (6.4)	0 (0.0)
Cough	8 (5.7)	0 (0.0)
Rash	8 (5.7)	0 (0.0)
Injection-site reaction	7 (5.0)	0 (0.0)
Vitiligo	7 (5.0)	0 (0.0)

Predominantly grade 1 and 2 constitutional-type side effects

Low incidence of grade 3 events (none occurring in >5% of patients); five grade 4 events in total

No grade 5 events

Additional grade 3/4 TRAEs (grade 4 italicized)**:**

Two events each (1.4%): Hypophysitis, rash maculo-popular

One event each (0.7%): Abdominal pain, acute left ventricular failure, amylase increased, cancer pain, *cytokine release syndrome*, eczema, enterocolitis, extranodal marginal zone B-cell lymphoma (MALT type), *hepatic cytolysis*, hyponatraemia, immune-mediated enterocolitis, infusion-related reaction, left ventricular dysfunction, *lipase increased*, memory impairment, meningitis aseptic, muscular weakness, *myocarditis*, palmar-plantar erythrodysaesthesia syndrome, paraesthesia, peripheral sensory neuropathy, radiculitis brachial, sinus arrhythmia, *splenic rupture*, tricuspid valve incompetence, tumor pain, type 1 diabetes mellitus

Data presented at ESMO 2024, SITC 2024

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IGNYTE-3 Confirmatory Study Underway and Expanded Access Program Initiated

Phase 3 confirmatory study

Advanced cutaneous melanoma

Progressed on anti-PD-1 AND anti-CTLA-4 OR not candidates for anti-CTLA-4

N=~400

Randomized 1:1

Interim Analysis – OS

RP1 + Nivolumab (n=200)

Treatment of Physician's Choice* (n=200)

Primary Analysis – OS

Secondary Endpoints - PFS/ORR

Expanded Access Program (RPL-EAP-001) in patients previously treated with an anti-PD-1 containing regimen and CTLA-4 naïve also initiated**

*Nivolumab-Relatlimab (Opdualag), Chemotherapy (DTIC, TMZ, paclitaxel/nab-paclitaxel), Rechallenge with anti-PD1 monotherapy (nivo or pembro)

**https://clinicaltrials.gov/study/NCT06590480

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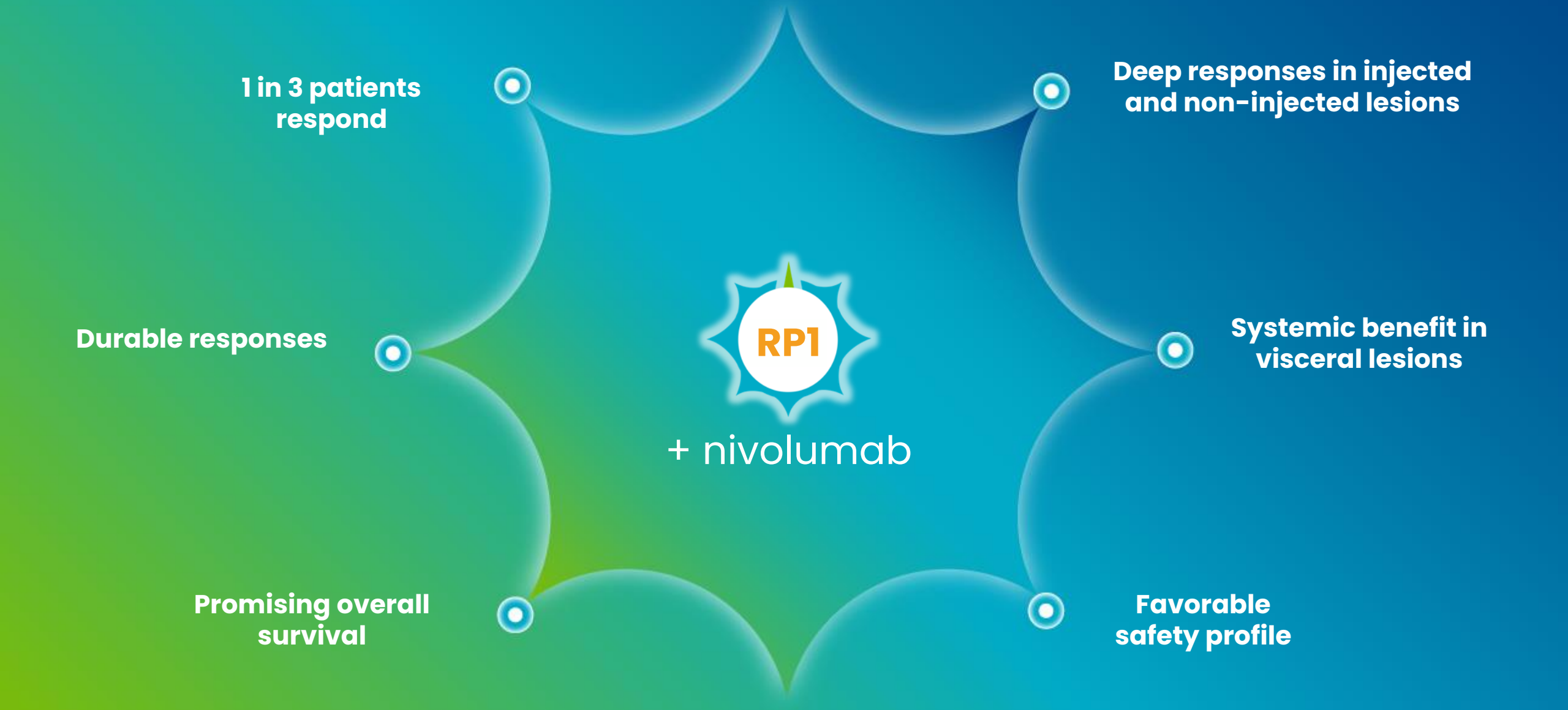
Anti-PD-1 Failed Data in Melanoma Drives Commercial Opportunity Upon Approval



Majority of Melanoma Patients Who Progress on Anti-PD-1 Therapy Are Addressable with RP1

~13K

patients who progress on/after PD-1 treatment (including ~2K from the adjuvant setting)

~80%

(~10.5K)

patients with injectable lesions

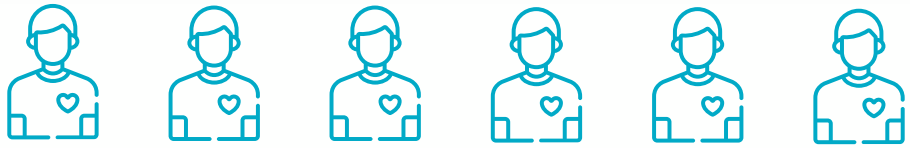
Outpatient Treatment

No Imaging

~2/10 pts require only superficial injections

Image Guidance for Deep Lesions*

~2/10 pts have superficial and deep lesions



~6/10 pts only have deep lesions (e.g., lymph, liver, lung, etc.)

*Image guided injections conducted by Interventional Radiology using ultra-sound, CT, or MRI
Source: Melanoma US treated patient population for 2030 based on CancerMPact Patient Metrics, Oct 2023 ; Injectability based on primary market research with IRs, Medical Oncologists and Surgical Oncologists

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Most Advanced Melanoma Patients Treated in Settings with Established Access to Interventional Radiology

Academic Centers/Hospital Based Systems

~50% of patients

Interventional Radiology on site / in-network
Many sites have intra-tumoral or RP1 trial experience

BJC HealthCare
BAPTIST HEALTH
MOFFITT CANCER CENTER
MAYO CLINIC
KAISER PERMANENTE
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

+

Large Community Networks

~30% of patients

Interventional Radiology relationships exist
Commercial model will support patient co-management

FLORIDA CANCER SPECIALISTS & Research Institute
TENNESSEE ONCOLOGY
TEXAS ONCOLOGY
More breakthroughs. More victories.®

Source: Analysis of Symphony Healthcare claims and IQVIA OneKey affiliations data

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Potential to Expand the Cancer Treatment Paradigm with RPx

- Interventional oncology is a key pillar of the oncology treatment paradigm with procedures expected to increase
- Interventional radiologists impressed with the systemic / visceral benefit observed
- RPx empowers interventional radiologists to play a new role in immunotherapy treatment

"There is a rising interest in intra-tumoral therapies with IRs…"

2H24 IR Market Research

"Seeing this level of RP1 activity in visceral, un-injected lesions is very motivating for IRs. This is not something we have seen with other intra-tumoral agents to date."

Rahul Sheth, M.D., F.S.I.R.

"If we can biopsy the tumor we can inject"

2H24 IR Market Research

Source: SEER 2021 Estimated Deaths. SEER Cancer Stat Facts by indication; Riihimaki et al Cancer Med 2018.

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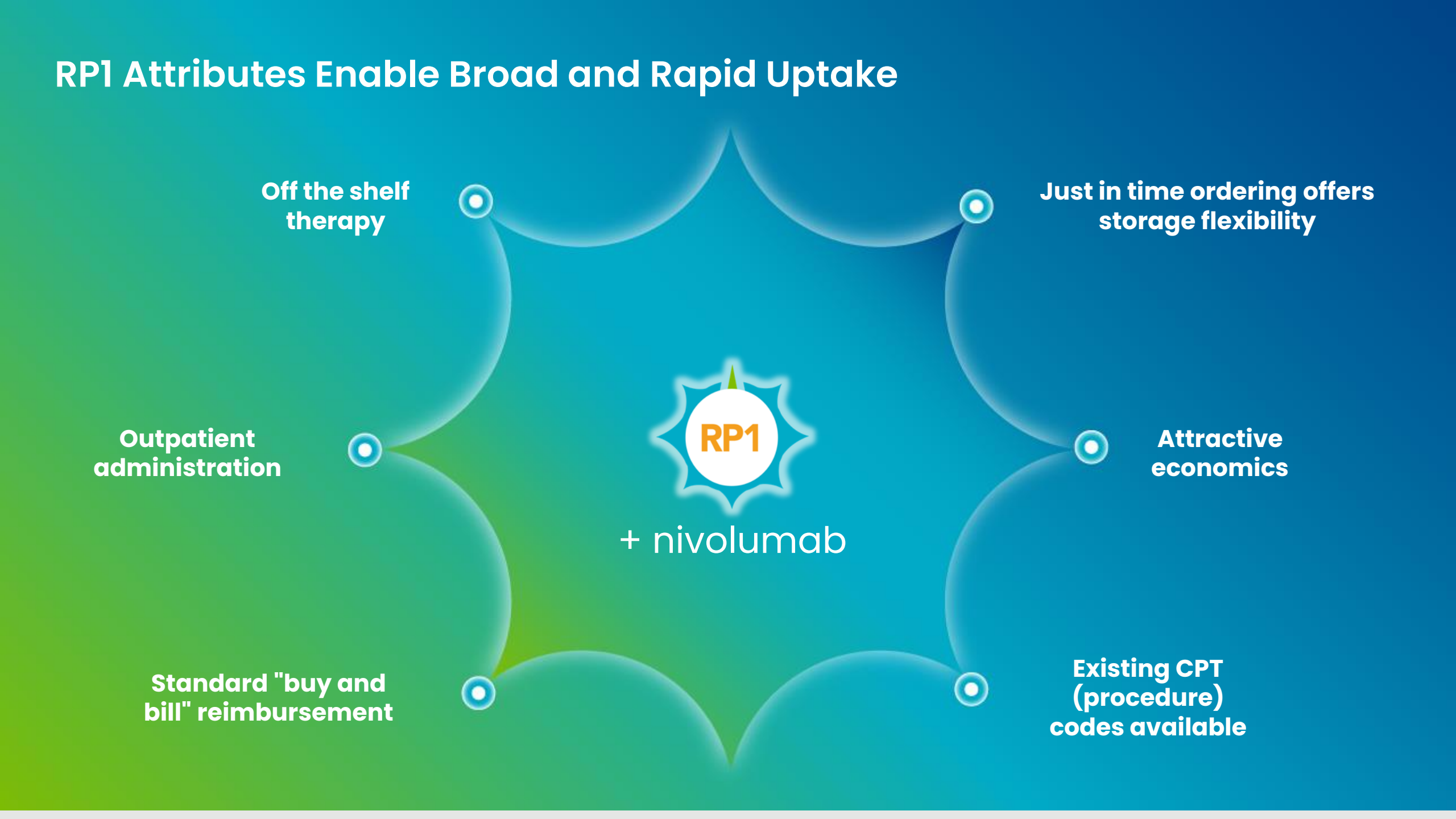
RP1 Attributes Enable Broad and Rapid Uptake



Well Positioned to be the 1st Choice after Anti-PD-1 Progression

Replimune®

- Compelling Data and Favorable Safety Profile
- Comprehensive Understanding of the Patient Population and Prescriber/IT Adoption
- Launch Model Prioritized For IT Adoption Across Key Account Settings
- Commercial-Scale In-House Manufacturing Established

Allows a significant commercial patient opportunity

Ability to meet demand

IT=Intra-tumoral

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RPx Expansion Opportunities

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Promising Data in Other Skin Cancers is the Foundation for RP1 Expansion

Anti-PD-1 failed NMSC

~30% ORR
(in MCC, BCC, & LA CSCC)

Response to RP1 + nivolumab (n=41)

- **~4,600* cases** of anti-PD-1 failed NMSC in the US per year
- No FDA approved treatments in anti-PD-1 failed NMSC
- Potential for compendia listing with additional patients enrolled

Solid Organ Transplant NMSC

~35% ORR, ~22% CRR

Response to RP1 monotherapy (n=23), with no cases of allograft rejection known to be caused by RP1[2]

- **~1,500 addressable** cases in the US** per year with 50% growth[1] in transplants over the last 8 years
- **Monotherapy dosing up to 26 times**, with the potential for retreatment
- Potential to seek indication (or compendia listing) with additional patients enrolled

Source: REPL Data on file and Replimune analysis (all epi numbers are for the year 2030) *Addressable defined as 2L CSCC, 2L MCC and 3L BCC patients, **Addressable defined as locally advanced or metastatic solid organ transplant NMSC patients; [1]Organ Procurement and Transplant Network; [2]Migden et al. Initial Results From an Open-Label Phase 1b/2 Study of RP1 Oncolytic Immunotherapy in Solid Organ Transplant Recipients With Advanced Cutaneous Malignancies (ARTACUS), AACR 2024; LA = locally advanced; CSCC, cutaneous squamous cell carcinoma; BCC, basal cell carcinoma; MCC, Merkel cell carcinoma; NMSC, non-melanoma skin cancer

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RP2 Shows Encouraging Activity in Metastatic Uveal Melanoma (mUM)

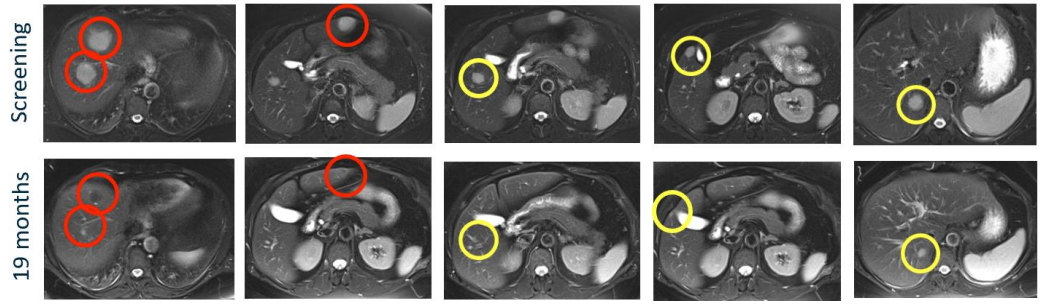
Unmet Need in uveal (ocular) melanoma

- ~1,000 cases in the US per year[1]
- No standard of care in 1L HLA-A2 neg or 2L[2]
- **70-90% of cases metastasize to liver only ~10% of patients survive > 1 year**[3,4]

RP1+Nivolumab (n=17) **has demonstrated promising clinical activity**

- **ORR of 29.4%* and DCR of 58.8%** with a median DOR of 11.5 (~2.8–21.2) months
- **Most common Grade 1/2 AEs (≥20%) were pyrexia, chills, fatigue, hypotension, and pruritus** with no clinically significant bleeding events

Durable activity in injected and non-injected liver lesions
Ipi/nivo failed metastatic uveal melanoma



Injected Un-injected

*70.6% [12/17] patients received prior anti–PD-1 and anti–CTLA-4 therapy, Sacco et al. ASCO 2024; 1. Carvajal RD et al. Br J Ophthalmol 2017; 2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Melanoma: Uveal. Version 1.2023.; 3. Jager MJ, et al. Nat Rev Dis Primers. 2020;6(1):24; 4. Khoja L, et al. Ann Oncol. 2019;30(8):1370-80.

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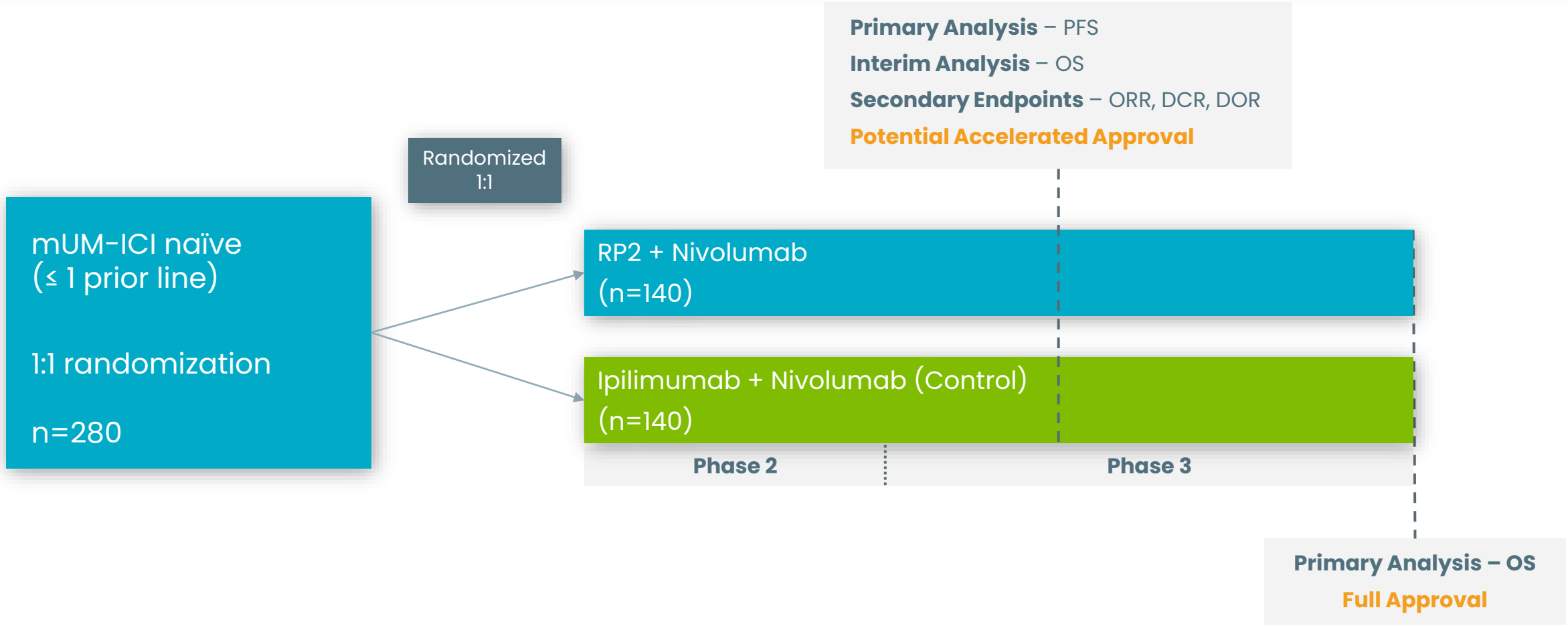
RP2 Pivotal Study in Metastatic Uveal Melanoma (mUM) Recently Enrolled First Patient



https://clinicaltrials.gov/study/NCT06581406

ICI = immune checkpoint inhibitor

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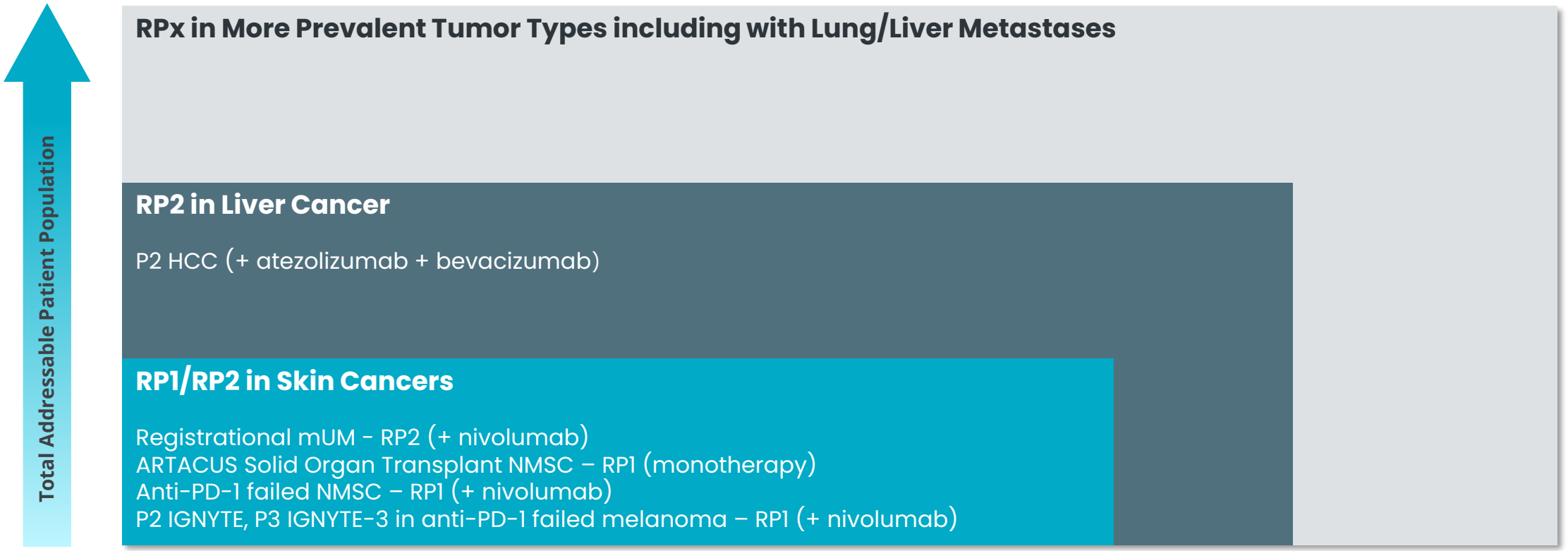
Systemic Benefit of RPx Supports Opportunity for Expansion Beyond Skin Cancers



NMSC, non-melanoma skin cancer; mUM, metastatic uveal melanoma

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2025 Value-driving Milestones

RP1 BLA Submitted, BTD Received, P3 IGNYTE-3 Enrolling

First Patients Enrolled
RP2 trials in metastatic uveal melanoma and HCC

RP1 BLA Acceptance

RPx R&D DAY
1H 2025

RP1 COMMERCIAL LAUNCH
Pending regulatory approval 2H 2025

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Thank you

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