



# Igniting a Systemic Immune Response to Cancer

September 2024



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## Establishing a Broad Skin Cancer Franchise

### Clinical activity demonstrated across multiple skin cancers and settings

- ✓ IGNYTE primary analysis by independent central review shows durable responses in difficult-to-treat population
- ✓ ARTACUS clinical trial of RP1 as monotherapy in solid organ transplant patients shows encouraging response rates
- ✓ IGNYTE-3 confirmatory phase 3 study in anti-PD1 melanoma enrolling
- ✓ Positive pre-BLA meeting completed; aligned with FDA on accelerated approval pathway for RP1 in anti-PD1 failed melanoma
- ✓ BLA submission in anti-PD1 failed melanoma on track for RP1 in 2H 2024

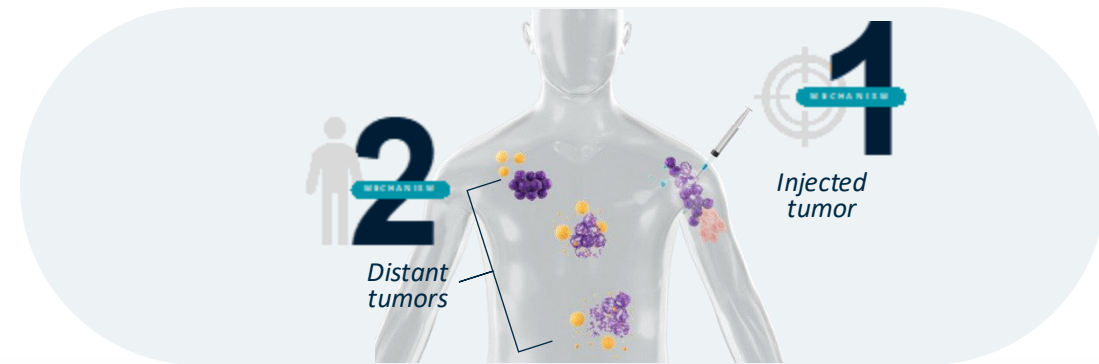
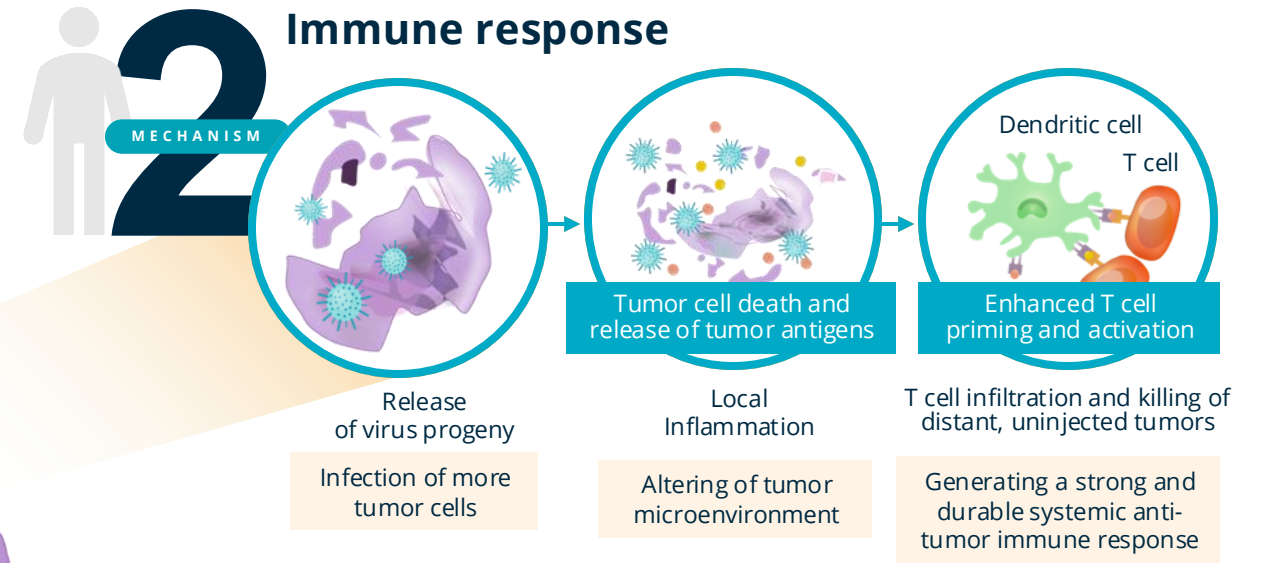
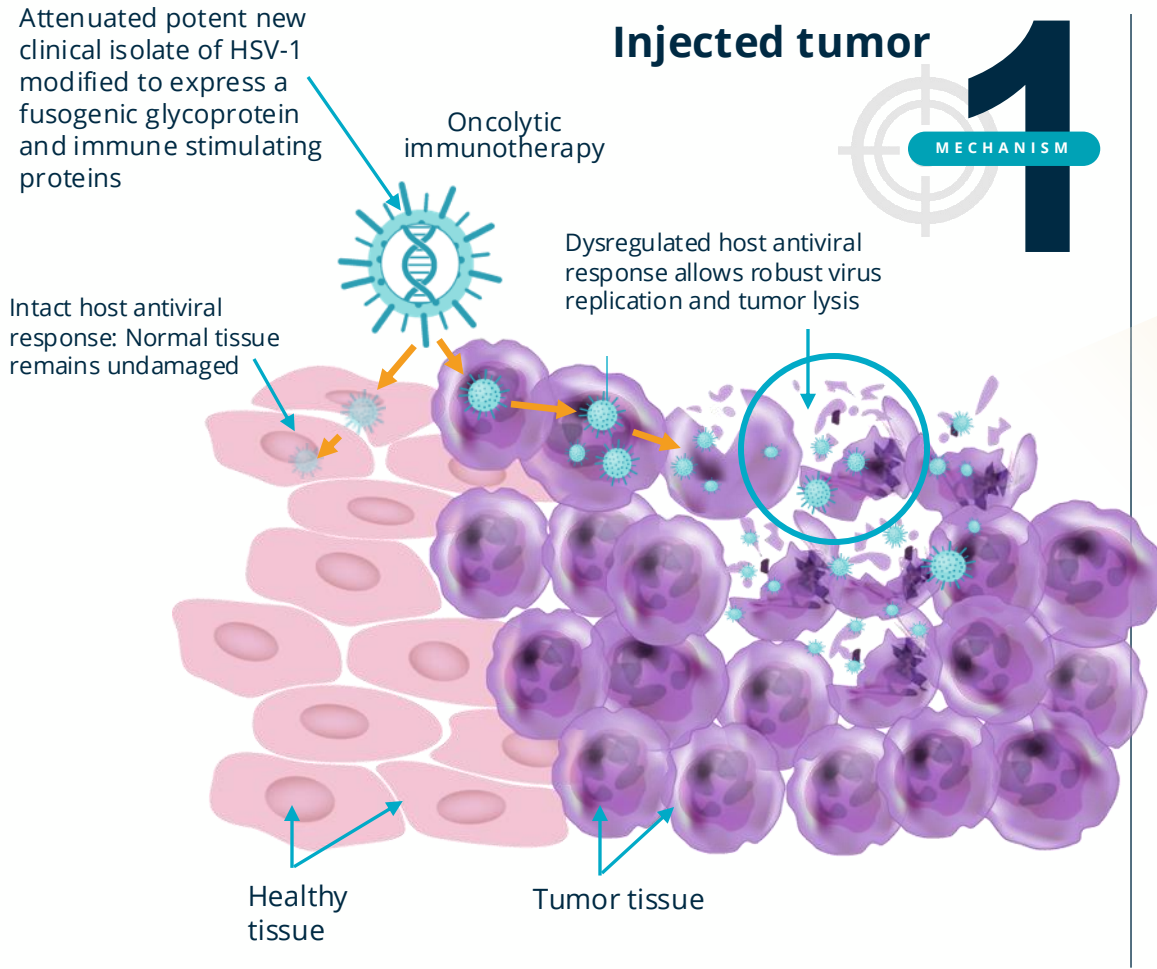


## Focused on Rare Cancers

### Clinical activity both as monotherapy and in combination with nivolumab

- ✓ Compelling phase 1 data in uveal melanoma
- ✓ Clinical activity seen in other rare tumors, including:
  - Sarcomas (e.g., chordoma)
  - Rare head & neck (e.g., mucoepidermoid)
- ✓ Aligned with FDA on pivotal study design in metastatic uveal melanoma
- ✓ On path to build rare cancer franchise

# Oncolytic Immunotherapy is Intended to Activate a Powerful and Durable Systemic Anti-Tumor Response



# RPx Platform Addresses a Range of Tumor Types Intending to Optimize Clinical Outcomes

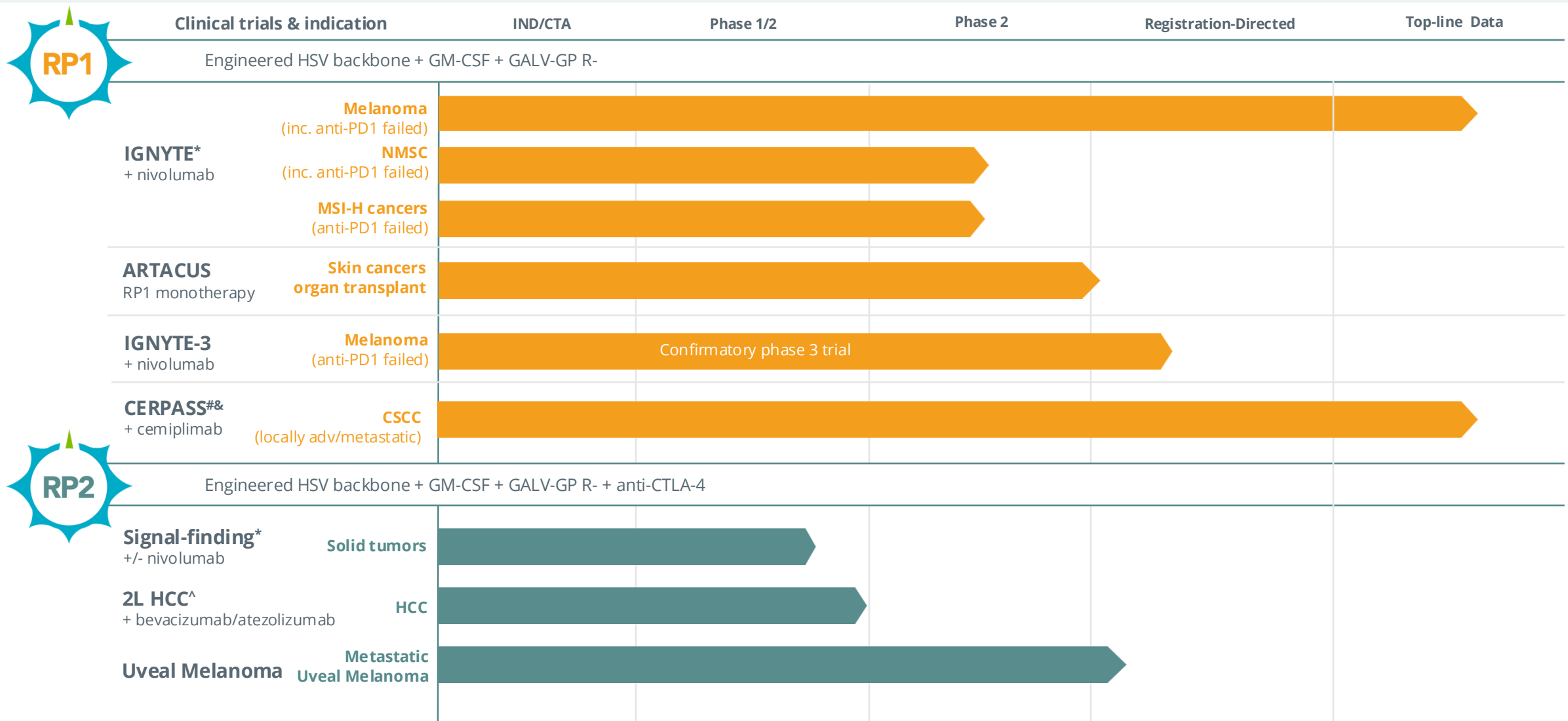


	RP1	RP2
<b>Payloads</b>	GALV-GP R-, GM-CSF	GALV-GP R-, anti-CTLA-4, GM-CSF
<b>Target</b>	Immunologically responsive tumor types, including anti-PD1 failed	Less immunologically responsive tumor types
<b>Intended indication(s)</b>	Skin cancers (CSCC inc. SOT*, anti-PD1 failed melanoma, anti-PD1 failed NMSC/other NMSCs, etc)	Rare cancers and neo adjuvant ; uveal melanoma registration study planned
<b>Clinical activity in anti-PD1 failed patients demonstrated</b>		
<b>Good tolerability and Safety profile demonstrated</b>		
<b>Injection location</b>	Superficial, nodal & visceral	Superficial, nodal & visceral
<b>Systemic activity</b>	<b><i>Clear systemic effects seen in responding patients (un-injected tumor responses, responses are generally highly durable)</i></b>	
<b>Other design considerations</b>	Designed for more I-O sensitive tumor types with excellent safety profile alone & in combination	Increased I-O systemic activity, also with excellent safety profile alone & in combination

\*SOT=solid organ transplant



# Pipeline



& CERPASS trial continuing to allow time-based endpoints to mature (DOR, PFS, OS), trial missed its primary endpoints (ORR, CRR)

\* Under a clinical trial collaboration & supply agreement with BMS for the supply of nivolumab— full commercial rights retained by Replimune

# Under a clinical trial collaboration agreement with Regeneron, includes certain sharing of clinical trial costs— full commercial rights retained by Replimune

^ Under clinical trial collaboration & supply agreement with Roche for atezolizumab & bevacizumab supply— full commercial rights retained by Replimune

# RP1: Establishing a Broad Skin Cancer Franchise

## IGNYTE Clinical Trial: RP1+Nivolumab in Anti-PD1 Failed Melanoma

# For Melanoma Patients that Progress on Anti-PD1 Therapy, Options are Limited



- Further single agent anti-PD1 for patients having confirmed PD on prior anti-PD1 gives a response rate of 6-7%<sup>1</sup>
- Nivolumab + ipilimumab is a potential option<sup>2</sup>, but toxicity is high<sup>3,4</sup>
- Anti-LAG3 plus anti-PD1 has not demonstrated meaningful efficacy in the anti-PD1 failed setting<sup>5</sup>
- For BRAF mutant tumors, BRAF-targeted therapy responses are generally transient<sup>6</sup>
- TIL therapy for select patients gives response rates of ~30%, but comes with toxicity (nearly all patients have grade 4 toxicity)<sup>7</sup>
- T-VEC + pembrolizumab has limited activity outside of the adjuvant setting, with no responses seen in patients with visceral disease<sup>8,9</sup>

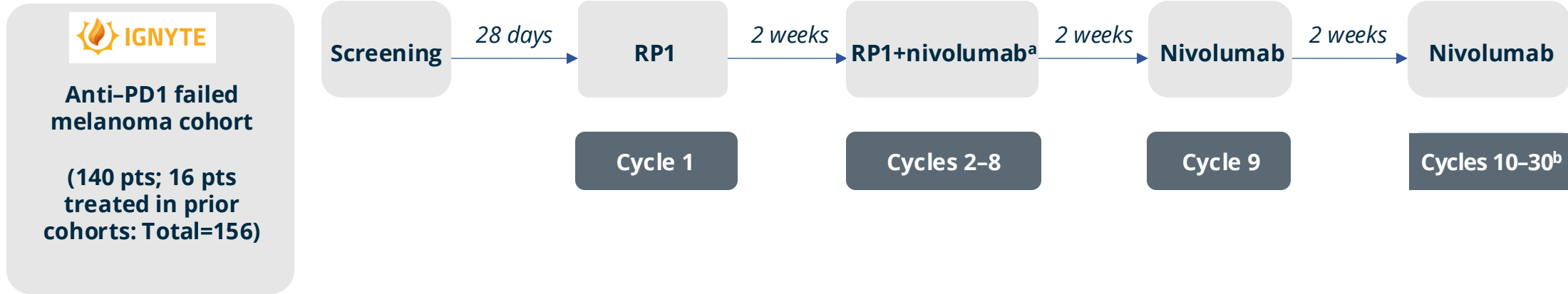
CTLA-4, cytotoxic T-lymphocyte antigen 4; LAG3, lymphocyte-activation gene 3; PD-1, programmed cell death protein 1; TIL, tumor infiltrating lymphocyte

1. Ribas A, Kirkwood JM, Flaherty KT. Lancet Oncology. 2018 May;10(5):e219. 2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Melanoma: Cutaneous. Version 2.2024. 3. Pires da Silva I, et al. Lancet Oncol. 2021;22(6):836-47. 4. VanderWalde AM, et al. Presented at the American Association of Cancer Research Annual Meeting 2022. New Orleans. 5. Ascierto PA, et al. J Clin Oncol. 2023;41(15):2724-35. 6. Dixon-Douglas JR, et al. Curr Oncol Rep. 2022;24(8):1071-9. 7. 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>. 8. Gastman B, et al. J Clin Oncol. 2022;40(16\_suppl):9518. 9. Hu-Lieskovan S, et al. Cancer Res. 2023;83(7\_suppl):3275.



# IGNYTE Study Design

## Anti-PD1 Failed Melanoma Cohort



### Primary objectives

- Safety and tolerability
- Efficacy as assessed by ORR using modified RECIST 1.1 criteria

### Secondary objective

DOR, CR rate, DCR, PFS, by central & investigator review, ORR by investigator review, and 1-year and 2-year OS

### Key eligibility criteria

**Confirmed progression while on prior anti-PD1 therapy<sup>c</sup>**

***At least 8 weeks of prior anti-PD1, confirmed progression while on anti-PD1; anti-PD1 must be the last therapy before clinical trial. Patients on prior adjuvant therapy must have progressed while on prior adjuvant treatment.***

***Primary analysis conducted when all patients have ≥ 12 months follow up***

<sup>a</sup>Dosing with nivolumab begins at dose 2 of RP1 (C2D15). <sup>b</sup>Option to reinitiate RP1 for 8 cycles if criteria are met. <sup>c</sup>Non-neurological solid tumors CR, complete response; CT, computed tomography; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; LD, longest diameter; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; pfu, plaque-forming unit; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

A 'real world' anti-PD1 failed melanoma population was enrolled

- Good representation of each of the sub-groups of patients who progress on prior anti-PD1 therapy

Patients, n (%)	All patients (N = 156)
Age (median [range])	62 (21-91)
Sex	
Female	52 (33.3)
Male	104 (66.7)
<b>Stage</b>	
IIIb/IIIc/IVM1a	75 (48.1)
IVM1b/c/d	81 (51.9)
<b>Prior therapy</b>	
Anti-PD1 only as adjuvant therapy	39 (25.0)
Anti-PD1 not as adjuvant therapy	117 (75.0)
Anti-PD1 & anti-CTLA-4	74 (47.4)
Received BRAF-directed therapy	17 (10.9)

Patients, n (%)	All patients (N = 156)
<b>Other disease characteristics</b>	
Primary resistance to prior anti-PD1 <sup>a</sup>	105 (67.3)
Secondary resistance to prior anti-PD1 <sup>b,c</sup>	51 (32.7)
BRAF wt	103 (66.0)
BRAF mutant	53 (34.0)
LDH ≤ULN	105 (67.3)
LDH >ULN	50 (32.1)
LDH unknown	1 (0.6)

Median follow up  
is 15.4 months (range 0.5-55.5)

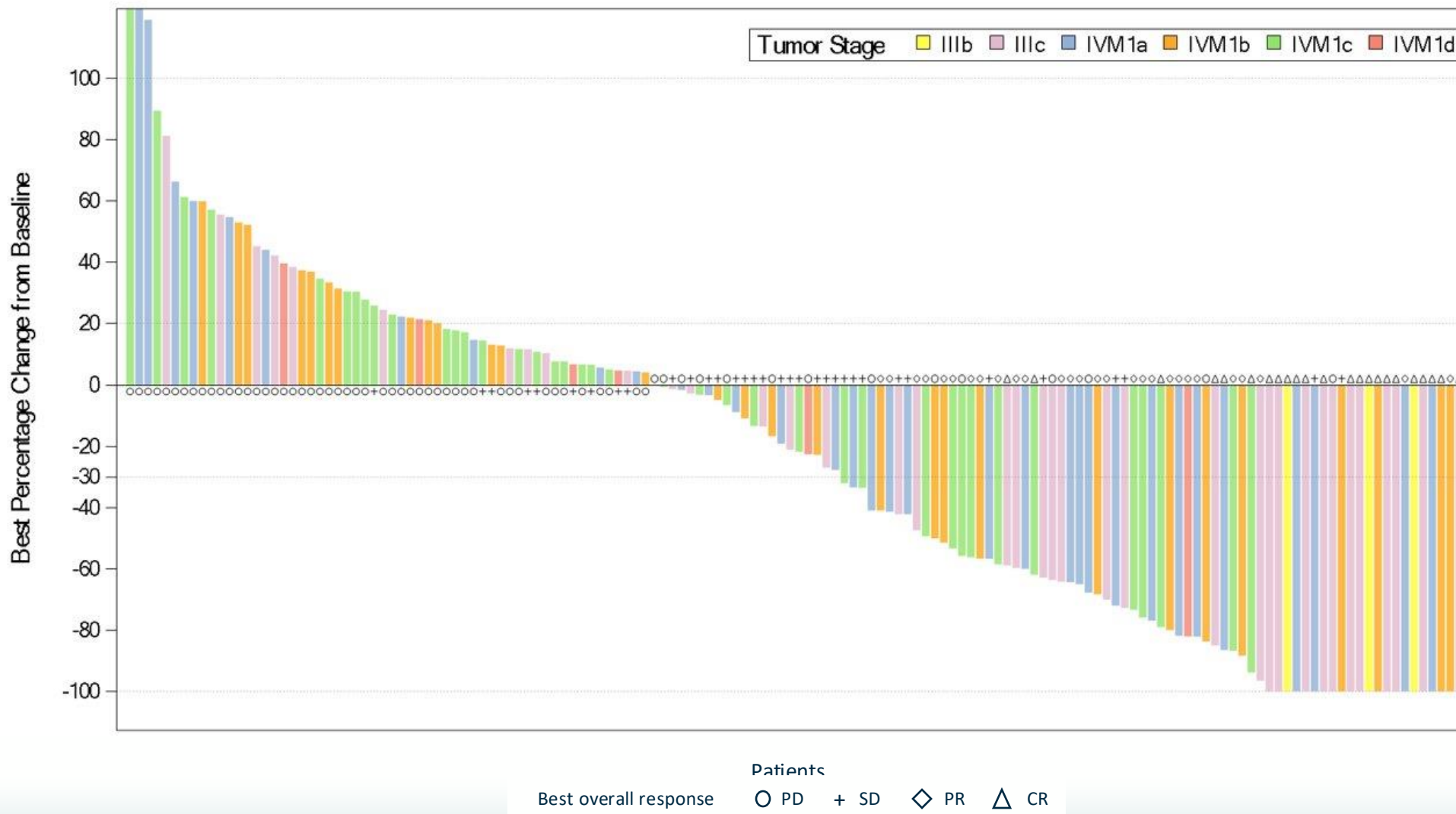
BOR n (%)	All patients enrolled in IGNYTE						
	All patients (n = 156)	Prior single- agent anti-PD1 (n = 82)	Prior anti- PD1/CTLA-4 (n = 74) <sup>a</sup>	Stage IIIb- IVM1a (n = 75)	Stage IVM1b-d (n = 81)	1 <sup>o</sup> resistance to anti-PD1 (n = 105)	2 <sup>o</sup> resistance to anti-PD1 (n = 51) <sup>b</sup>
CR	23 (14.7)	18 (22.0)	5 (6.8)	18 (24.0)	5 (6.2)	18 (17.1)	5 (9.8)
PR	28 (17.9)	13 (15.9)	15 (20.3)	13 (17.3)	15 (18.5)	18 (17.1)	10 (19.6)
SD	34 (21.8)	18 (22.0)	16 (21.6)	19 (25.3)	15 (18.5)	17 (16.2)	17 (33.3)
PD	63 (40.4)	31 (37.8)	32 (43.2)	24 (32.0)	39 (48.1)	47 (44.8)	16 (31.4)
<b>ORR</b>	<b>51 (32.7)<sup>c</sup></b>	<b>31 (37.8)</b>	<b>20 (27.0)</b>	<b>31 (41.3)</b>	<b>20 (24.7)</b>	<b>36 (34.3)</b>	<b>15 (29.4)</b>

<sup>a</sup>Eight patients were treated with sequential anti-CTLA-4 and anti-PD1 (ORR for prior combined anti-CTLA-4/anti-PD1 was 25.8%). <sup>b</sup>Includes one patient with unknown resistance status. <sup>c</sup>ORR for the 140-patient registration intended cohort was 32.1%

- 1 in 3 patients achieved an objective response (32.7%)
- Consistent ORR across subgroups, including:
  - 27% ORR in patients who had prior anti-PD1 & anti-CTLA-4
  - 34% ORR in patients who are primary resistant to their prior anti-PD1 therapy

# ASCO 2024: Depth of Response

Target tumor reduction seen in greater than 50 percent of patients (n=156)

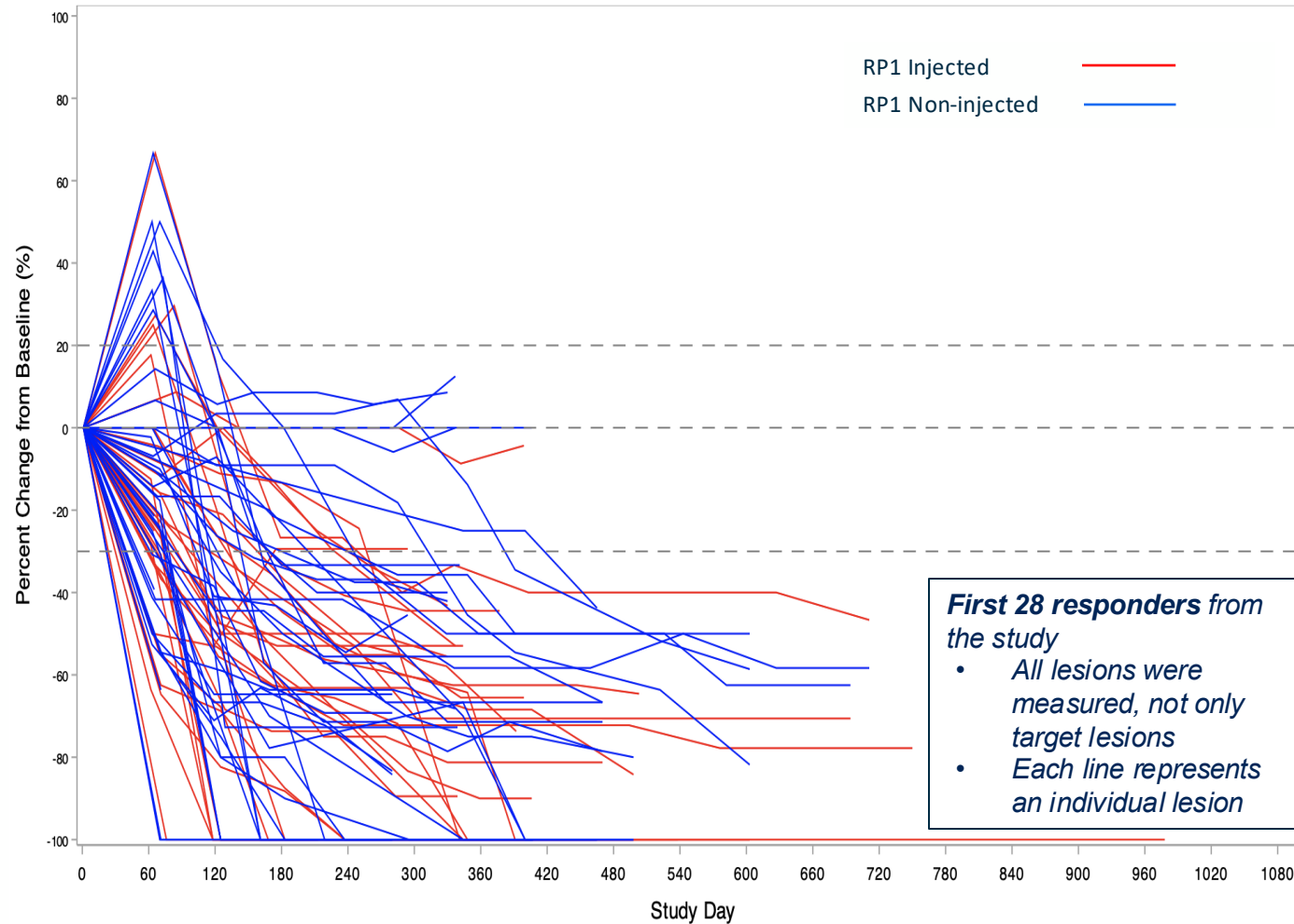


## Key Takeaways

- Target tumor reduction is seen in >50% of patients
- Responses were seen across disease stages, including complete responses in patients with stage IVM1b/c disease

# ASCO 2024: Responses are Systemic

## Change in size of individual injected and non-injected lesions



### Key Takeaways

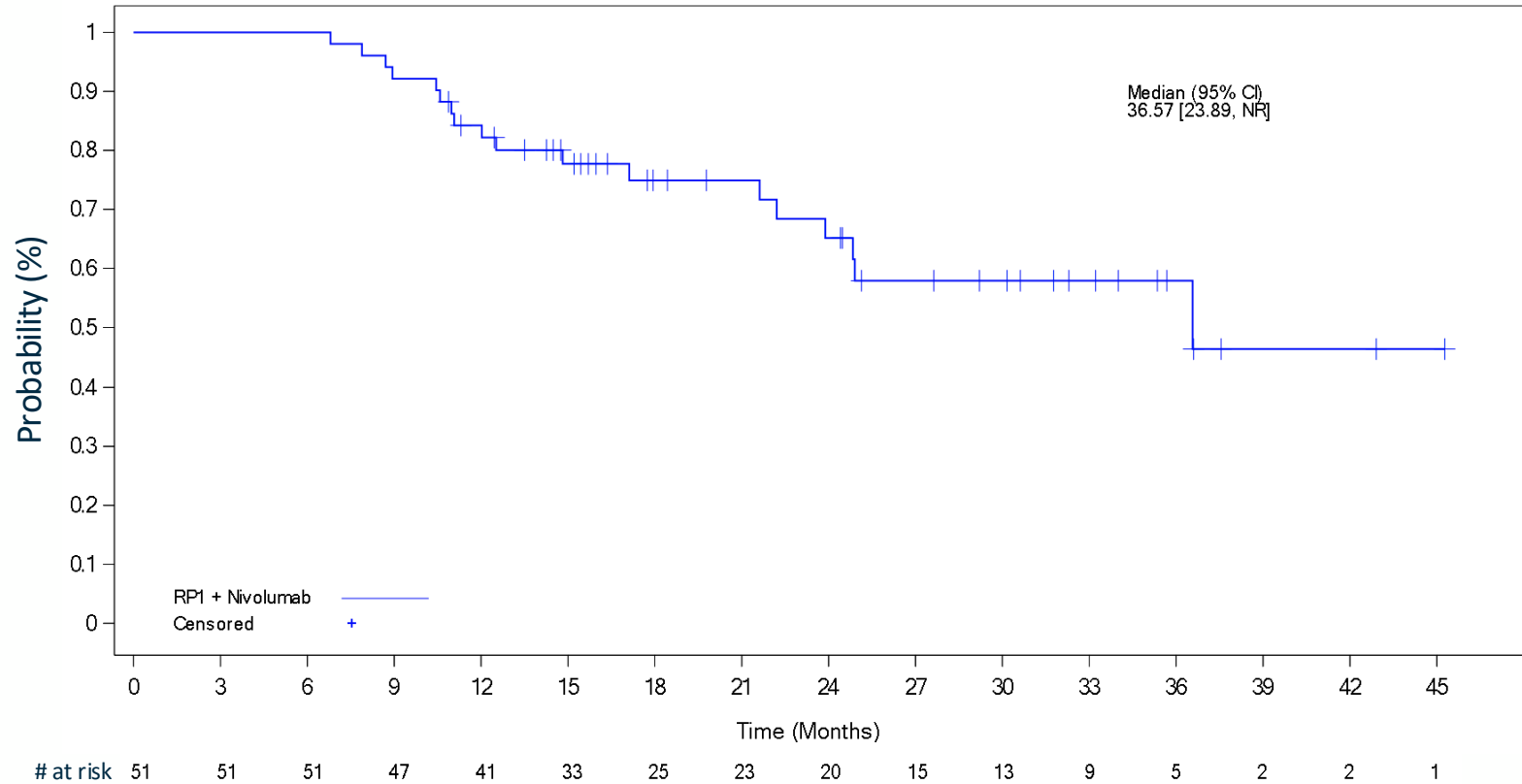
- 70.4% of responding patients had non-injected lesions
- Injected and non-injected lesions responded with similar duration and kinetics
- Depth of response independent of injection status

**Responses in non-injected lesions demonstrate systemic benefit**

Includes both target and non-target lesions for RECIST assessment, measured from CT/MRI scans for radiologically assessable lesions (responders from the first 75 patients enrolled into the registration intended cohort). 58/75 patients had at least 1 non-injected lesion, of whom 15 achieved a response based on those lesions only (excludes possible response in injected lesions); ORR of 25.9% on the basis of non-injected lesions only. First presented at ASCO 2023.



# ASCO 2024: Duration of Response From baseline



## Key Takeaway

- Responses are durable, with a **median DOR of 36.6 months**

>6 months	>12 months	>18 months	>24 months
100%	84.2%	74.9%	65.2%

The median follow up for responders is 27.9 months (range 10.5-55.5)

# ASCO 2024 Safety: Treatment-related AEs (N = 156)



Preferred term, n (%)	TRAEs occurring in >5% of patients				
	Grade 1–2	Grade 3	Grade 4	Grade 5	Total (N = 156)
Chills	53 (34.0)	1 (0.7)	0	0	53 (34.0)
Fatigue	51 (32.7)	2 (1.3)	0	0	52 (33.3)
Pyrexia	49 (31.4)	0	0	0	49 (31.4)
Nausea	35 (22.4)	0	0	0	35 (22.4)
Influenza-like illness	30 (19.2)	0	0	0	30 (19.2)
Injection-site pain	23 (14.7)	0	0	0	23 (14.7)
Diarrhea	21 (13.5)	1 (0.6)	0	0	21 (13.5)
Vomiting	21 (13.5)	0	0	0	21 (13.5)
Headache	20 (12.8)	0	0	0	20 (12.8)
Pruritus	20 (12.8)	0	0	0	20 (12.8)
Asthenia	13 (8.3)	1 (0.6)	0	0	14 (9.0)
Arthralgia	11 (7.1)	1 (0.7)	0	0	11 (7.1)
Myalgia	11 (7.1)	0	0	0	11 (7.1)
Decreased appetite	9 (5.8)	1 (0.6)	0	0	10 (6.4)
Rash	9 (5.8)	1 (0.6)	0	0	10 (6.4)

## Key Takeaway

RP1 combined with nivolumab continues to be a generally well tolerated regimen

- Predominantly grade 1 and 2 constitutional-type side effects
- Low incidence of grade 3 and 4 events
- No grade 5 events

### Additional grade 3 and 4 events <5%

**Grade 3:** Two each of rash maculo-papular and hypophysitis; 1 each of tumor pain, infusion-related reaction, muscular weakness, abdominal pain, amylase increased, dermatitis bullous, eczema, immune-mediated enterocolitis, immune-mediated hepatitis, paresthesia, acute left ventricular failure, arthritis, cancer pain, enterocolitis, extranodal marginal zone B-cell lymphoma (MALT type), hyponatremia, injection site necrosis, left ventricular dysfunction, memory impairment, meningitis aseptic, edema, palmar-plantar erythrodysesthesia syndrome, peripheral sensory neuropathy, radiculitis brachial, sinus arrhythmia, tricuspid valve incompetence, and type 1 diabetes mellitus

**Grade 4:** One each of lipase increased, alanine aminotransferase increased, blood bilirubin increased, cytokine release syndrome, myocarditis, and hepatic cytolysis, splenic rupture

# Topline Data for the IGNYTE Registrational Cohort Assessed by Independent Central Review:

## RPI+Nivolumab in Anti-PD1 Failed Melanoma

# Strong IGNYTE Primary Analysis Data by Independent Central Review



Overall Response Rate (registration-intended cohort: n=140) (%)		
Investigator Assessment	Independent Central Review <sup>1</sup>	
<b>Modified* RECIST 1.1</b> <b>32.1%</b>	<b>Primary Endpoint Modified* RECIST 1.1</b> <b>33.6%</b>	<b>RECIST 1.1**</b> <b>32.9%</b>

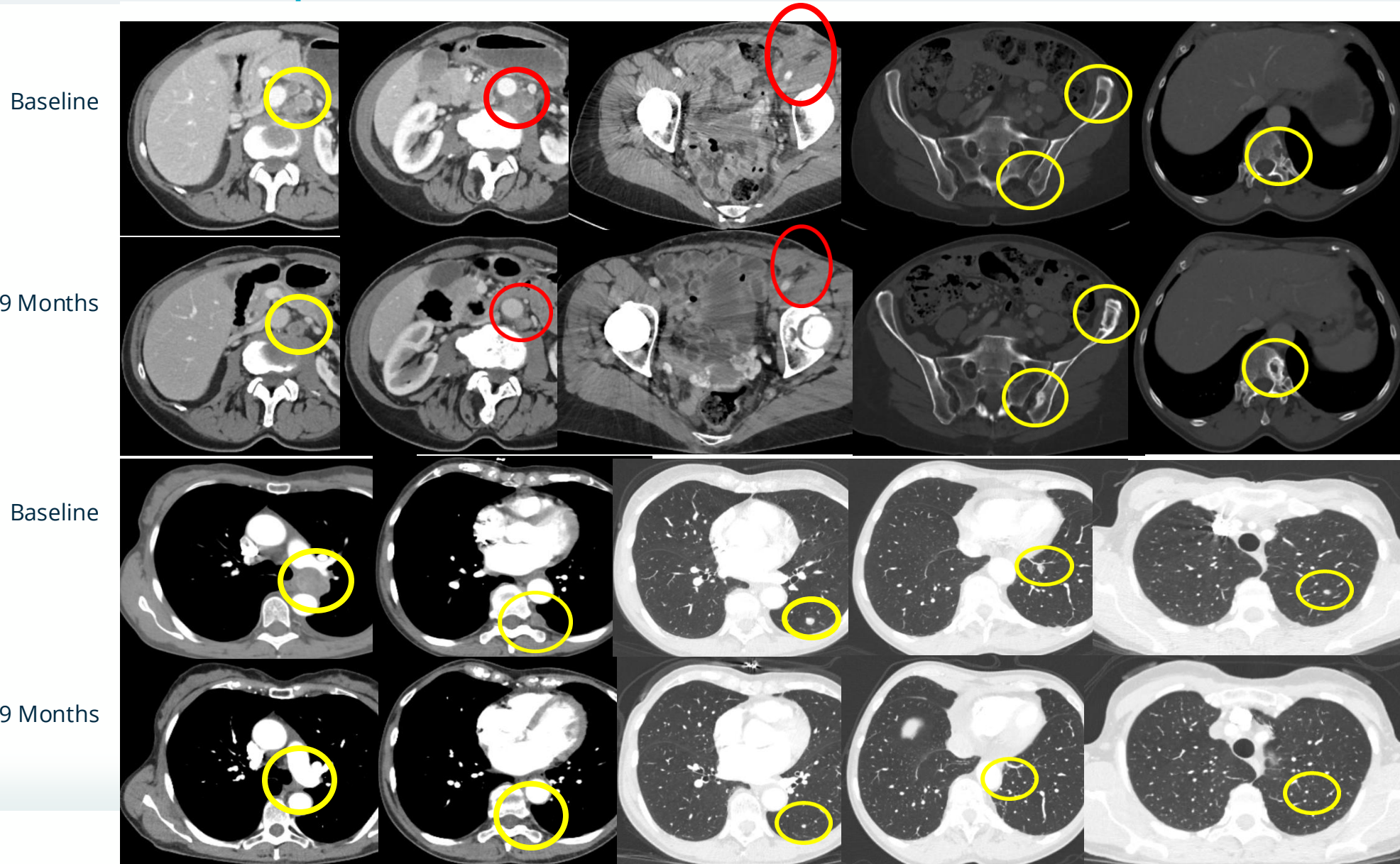
\* Confirmation of PD requires further tumor increase from the first observation of PD; responses can be captured at any time up until next anti-cancer therapy<sup>2</sup>

\*\* Requested by FDA, with confirmation of PD required; responses not included in ORR after the first confirmed PD

All patients with at least 12 months follow up

# Patient Example

Prior atezolizumab+cobimetinib, ipilimumab, SX682 (CXCR-inhibitor)+  
atezolizumab, ipilimumab+nivolumab



Responses in un-injected distant and visceral tumors including healing of lytic bone lesions (increasing sclerosis & new internal bone formation seen)





# Patient 1121-2011:

Prior Opdivo (adjuvant) and Keytruda (first line for metastatic disease), Stage IV M1c



29 JUL 2021 / Screening

20 APRIL 2022



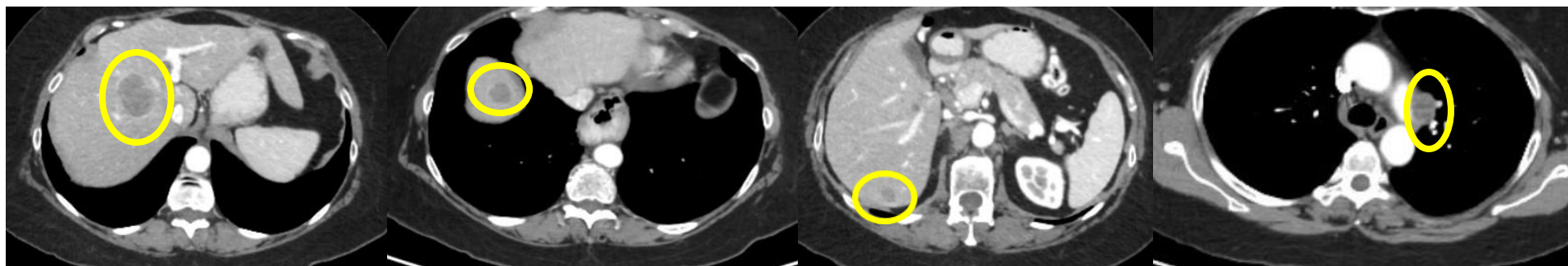
 Injected  Un-injected

# Patient 1121-2011 Cont'd:

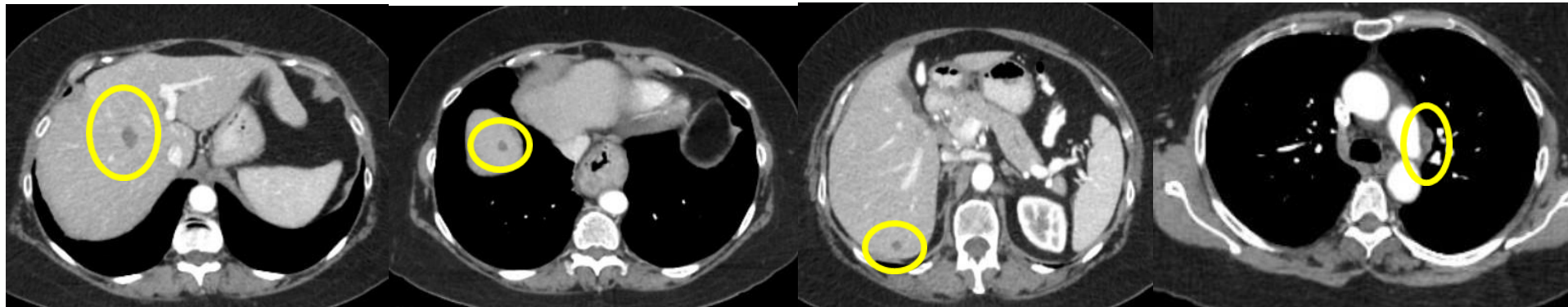
Prior Opdivo (adjuvant) and Keytruda (first line for metastatic disease), Stage IVM1c



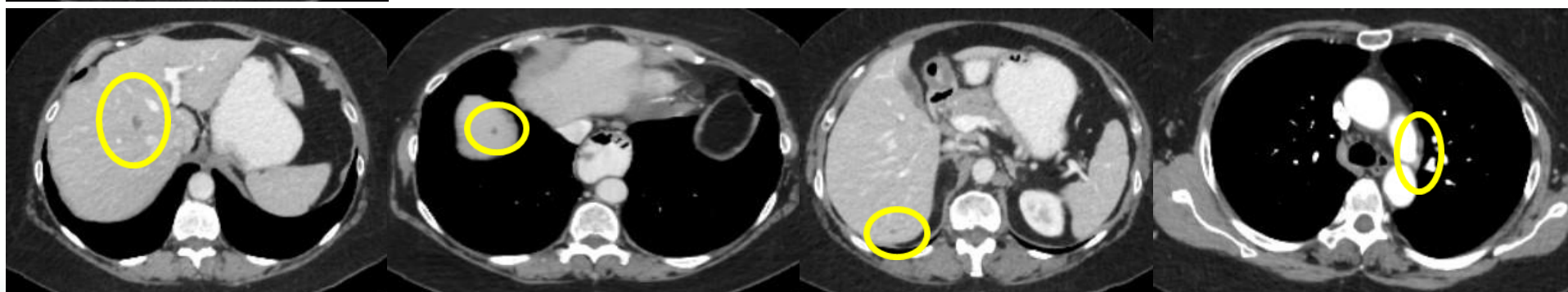
22 Jul 2021/  
Baseline



22 Sep 2021/  
Day 57



29 Dec 2021/  
Day 155



 Injected

 Un-injected

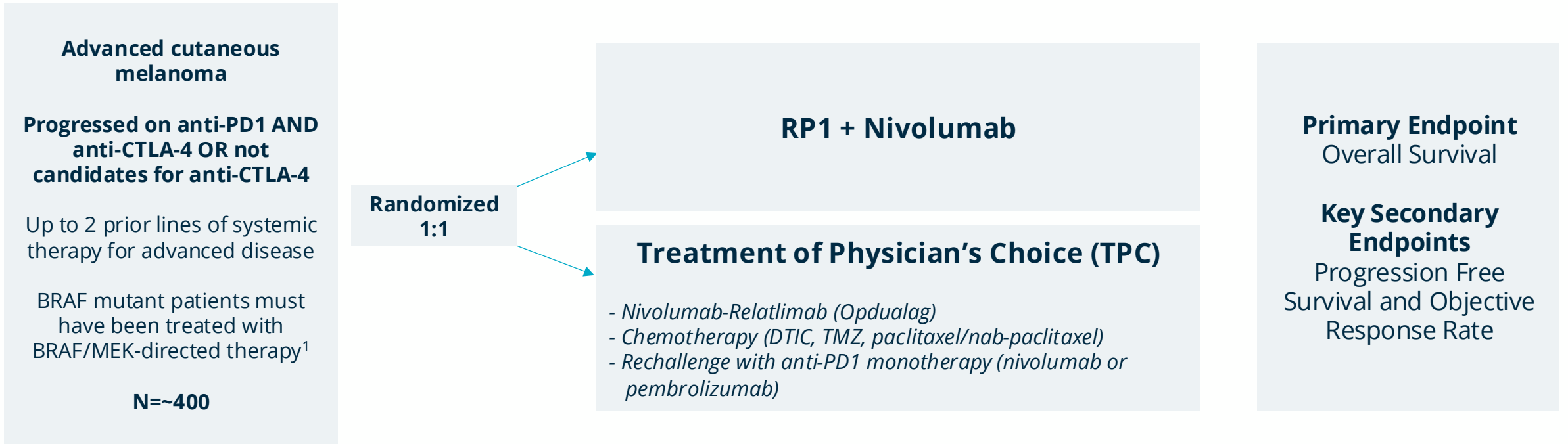
# IGNYTE Data Shows Clinically Meaningful Benefit



- One third of patients respond by independent central review (ORR: 33.6%\*)
- Responses are durable
  - 100% last >6 months, median DOR >35 months (from baseline)
- RP1 combined with nivolumab continues to be a generally well tolerated regimen
  - Predominantly grade 1/2 constitutional-type side effects
  - Low incidence of grade 3 and 4 events; no grade 5 events
- Full data to be submitted for presentation at an upcoming medical congress

# IGNYTE-3: Confirmatory Phase 3 Trial Design\*

## RP1 and Nivolumab in Ipi-Nivo Pretreated Patients



<sup>1</sup> For BRAF mutant patients prior BRAF/MEK-directed therapy is required unless deemed not clinically indicated at investigator's discretion due to documented concurrent medical condition or prior toxicity; \*ClinicalTrials.gov ID: NCT6264180



# ARTACUS Clinical Trial:

**RP1 Monotherapy in Solid Organ Transplant  
Non-Melanoma Skin Cancers (NMSC)**



# ARTACUS: Baseline Demographics, Characteristics, Activity



RPI as monotherapy shows clear clinical activity with promising ORR/CRR

Characteristic	All patients (N = 27)
Age, years, median (range)	68.0 (48–86)
Male, n (%)	21 (77.8)
Race, n (%)	
White	26 (96.3)
Native Hawaiian/Pacific Islander	1 (3.7)
Allograft type, n (%)	
Kidney	22 (81.5)
Liver	4 (14.8)
Lung	1 (3.7)
Heart	0
Cutaneous malignancies, n (%)	
CSCC	24 (88.9)
MCC	3 (11.1)
Stage at study baseline, n (%)	
Locally advanced	15 (55.6)
Metastatic <sup>a</sup>	12 (44.4)
Primary tumor location, n (%)	
Skin	26 (96.3)
Lymph node	1 (3.7)

	Evaluable patients <sup>a</sup> (N = 23)
Best overall response (modified RECIST 1.1)	n (%)
CR	5 (21.7) <sup>b</sup>
PR	3 (13.0) <sup>c</sup>
SD	1 (4.3)
PD	14 (60.9)
<b>ORR (CR + PR)</b>	<b>8 (34.8)</b>
<b>DCR (CR + PR + SD)</b>	<b>9 (39.1)</b>

	Responders (n = 8)
Characteristics of responders	n
Tumor type	
CSCC	6
MCC	2
Stage at study baseline	
Locally advanced	6
Metastatic	2

<sup>a</sup>Per protocol, metastatic to skin, soft tissue, or lymph nodes.  
CSCC, cutaneous squamous cell carcinoma; MCC, Merkel cell carcinoma  
Migden et al, AACR 2024, Presentation CT003.

# ARTACUS: Examples of Patients With Confirmed Response



Baseline

**1143-0002**  
May 2022



August 2022 (3 months)



**Complete response**

**1143-0001**  
June 2021



December 2021 (6 months)



**Complete response**

**1135-0001**  
July 2021

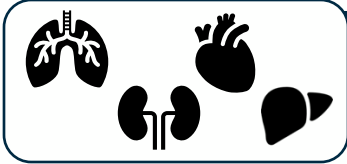


October 2021 (3 months)



**Complete response**

# High Risk of Skin Cancer in Organ Transplant Patients Drives the RPI ARTACUS Opportunity



**~1.5K** Addressable\* Solid Organ Transplant Patients with skin cancer<sup>6</sup>

**50%↑** Growth in transplants over the last 8 years<sup>1</sup>

## Significant Unmet Need

## ARTACUS Data

**UP TO 53X** **Increased Risk of Cancer**  
Increased risk of SoT patients developing skin cancer, with a high rate of metastasis<sup>2</sup>

**35%** **High Rate of Multiple Primary Lesions**  
Percentage of patients developing multiple primary lesions<sup>4,5</sup>

**30%** **Treatment Options Risk Loss of Organ**  
Rate of organ rejection, due to treatment with ICIs for skin cancer<sup>3</sup>

RP1 showed an **35% ORR** and a **22% CRR<sup>7</sup>** with safety similar to the profile seen in non-immunocompromised patients

RP1 has been **dosed up to 26 times to treat patients, with the potential for retreatment**

RP1 monotherapy has shown the ability to treat skin cancer with **no cases of allograft rejection<sup>7</sup>**

\*Addressable defined as locally advanced or metastatic SoT (solid organ transplant) skin cancer patients

<sup>2</sup>Standardized incidence ratios were calculated by dividing the observed number of NMSC cases by the expected number of cases based on the general population.

CSCC, cutaneous squamous cell carcinoma; NMSC, non-melanoma skin cancer; SOT, solid organ transplantation.

1. OPTN, 2. Friman T, et al. *Int J Cancer*. 2022;150(11):1779-91, 3. Ji et al. *Front Transplant* 2023 4. Eggermont, et al *JAAD* 2023 5. Gilbert et al. *Cureus*. 2022 6. Replimune Analysis 7) Midgen et al AACR 2024 Pres CT-003

# CERPASS Clinical Trial: 1L CSCC (RP1+Cemiplimab vs. Cemiplimab)

# CERPASS: Confirmed ORR & CRR (ITT population)

Number of patients achieving CR substantially increased with RP1;  
CR rate more than doubled for RP1 in locally advanced CSCC



BOR (confirmed response)	All N=211	
	Cemiplimab n=72	RP1+ cemiplimab n=139
n/%		
PR	19 (26.4)	20 (14.4)
SD	14 (19.4)	18* (12.9)
PD	12 (16.7)	27 (19.4)
OR	<b>37 (51.4%)</b>	<b>73 (52.5%)</b>
	P=0.692 <sup>1</sup>	
CR	<b>18 (25.0%)</b>	<b>53 (38.1%)</b>
	P=0.040 <sup>1</sup>	

BOR (confirmed response)	Locally advanced CSCC n=83		Metastatic CSCC n=128	
	Cemiplimab n=31	RP1+ cemiplimab n=52	Cemiplimab n=41	RP1+ cemiplimab n=87
n/%				
OR	18 (58.1%)	33 (63.3%)	19 (46.3%)	40 (46.0%)
CR	<b>7 (22.6%)</b>	<b>25 (48.1%)</b>	11 (26.6%)	28 (32.2%)

## Key Takeaways / Next Steps

- Study missed its primary endpoints (ORR/CRR)
- Study continuing to allow time-based endpoints to mature (DOR, PFS and OS)
- In locally advanced CSCC, CR rate more than doubled for RP1+cemiplimab vs cemiplimab alone (48.1% vs 22.6%)

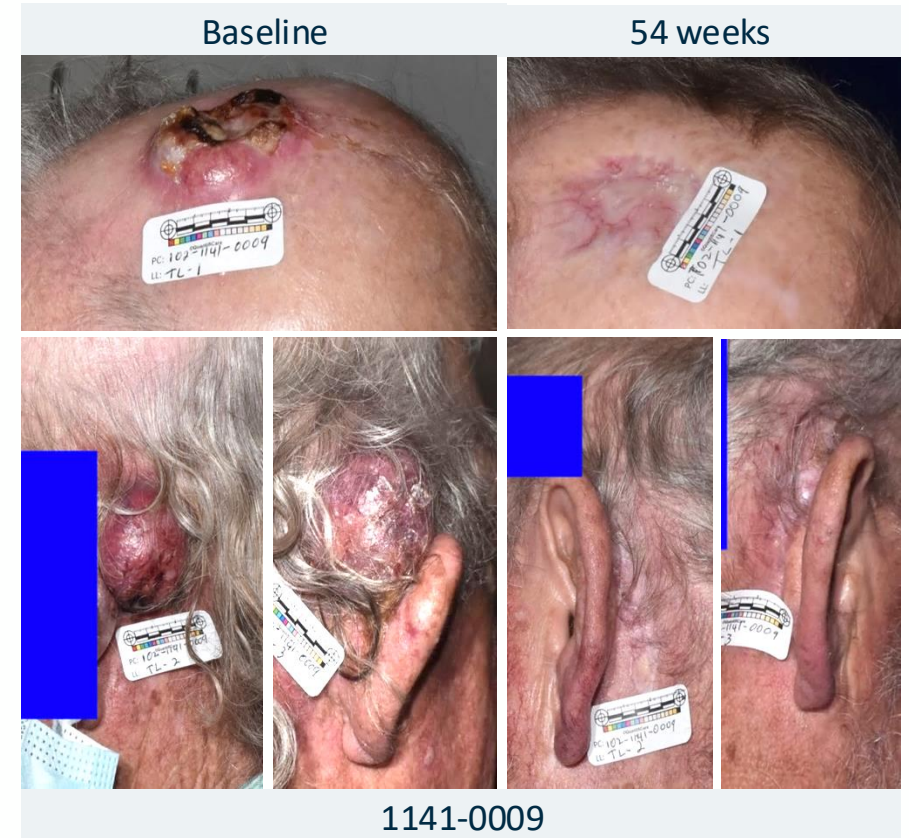
\*One patient shown as SD was a CR due to the confirmatory assessment happening 21 days rather than later 28 days as required per protocol (CRR if included = 38.8%; p=0.031); \*\*&Nominal p value 0.013

<sup>1</sup>Per the protocol p≤0.025 is required for formal statistical success in CERPASS for CRR or ORR alone and p≤0.05 if both endpoints were met

BOR=best overall response



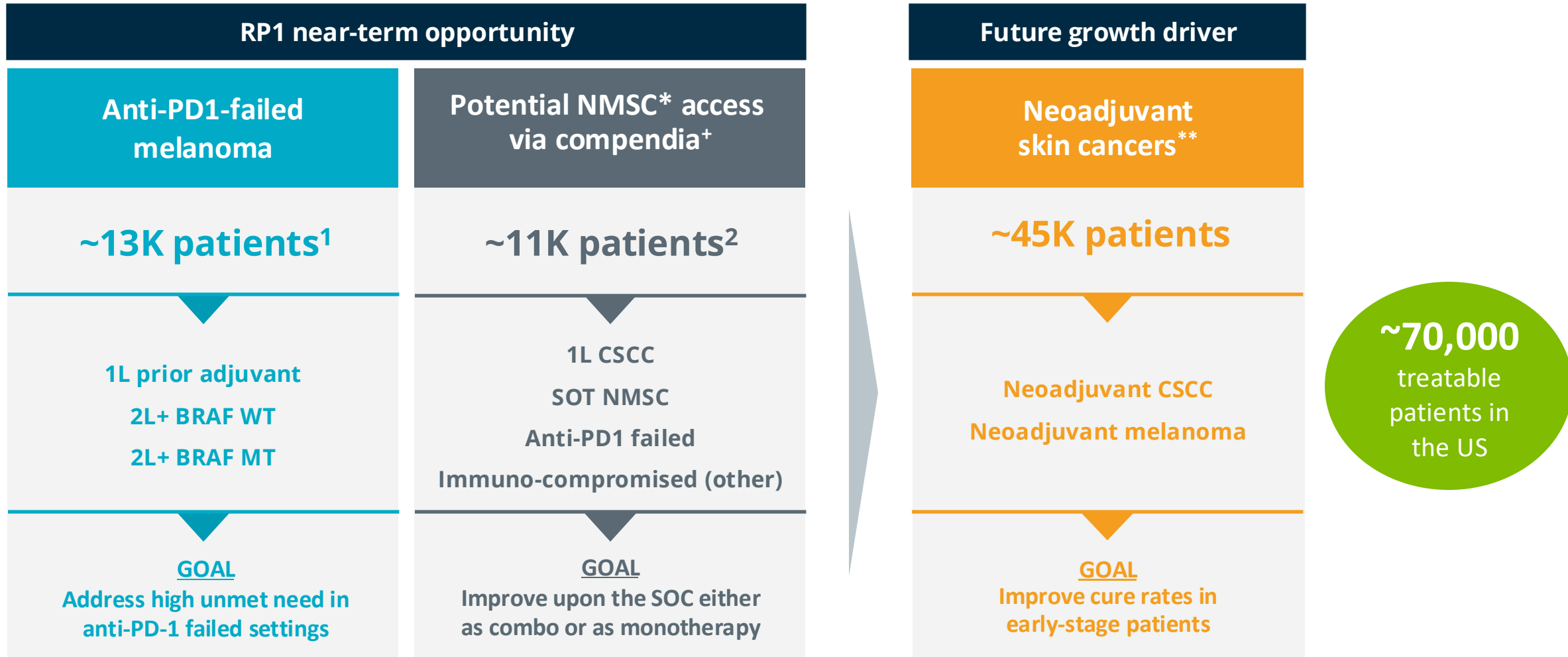
# Five of the Most Visually Impactful CRs with RP1+cemiplimab



# RP1 Commercial Opportunity



# Significant Opportunity to Establish a Broad Skin Cancer Franchise Built Upon Strong Foundation in Melanoma



**“Opportunity to change the treatment paradigm and ensure all appropriate patients can benefit from RP1”**

\*Spontaneous use will not be promoted

Source: <sup>1</sup>Melanoma US treated patient population for 2030 based on CancerMPact® Patient Metrics, Cerner Enviza (available from www.cancermpact.com Accessed 15 Oct 2023), with adjustments to future 2L+ treatment rates based on primary market research. <sup>2</sup>CSCC US treated patient population for 2030 based IQVIA claims, primary market research, and company data. \*NMSC (non-melanoma skin cancers); RP1+cemiplimab or RP1+nivolumab or RP1 mono \*\*Neoadjuvant CSCC (est. 30K patients) and melanoma (est. 15K patients). SOT=solid organ transplant

# RP1 Positioned to Enable Widespread Commercial Adoption

## Potential to treat a range of skin cancers across treatment settings



- RP1+nivolumab is well positioned to be the first option for melanoma patients who progress on a PD1-based regimen (in adjuvant or 1L setting), given:
  - Deep & durable responses
  - Safety profile
  - Ease of administration
- RP1+nivolumab provides a potentially compelling option for a broad range of anti-PD1 failed melanoma patients
  - Approx. 80%\* of all melanoma patients can be treated via either superficial and/or image guided deeper lesion injections requiring interventional radiology
  - Adoption feasible in most US healthcare settings including the community allowing practices to keep and treat patients locally
- RP1 has shown encouraging monotherapy activity in hard-to-treat solid organ transplant failed NMSC where patients have very limited options that don't risk graft rejection

# Manufacturing on Track to Support RP1 BLA and Commercialization



**Commercial  
scale in-house  
manufacturing  
established**

- Pre-BLA meeting with FDA confirmed alignment on Chemistry, Manufacturing and Controls (CMC) plans to support RP1 BLA submission
- 63,000 square foot state-of-the-art facility for GMP manufacturing in Framingham, MA
  - RP1 BLA consistency lot runs complete
  - Commercial inventory build underway
- Scale expected to be sufficient to cover global commercialization of RP1 and RP2
- Commercially attractive cost of goods & 'off the shelf' product practicality





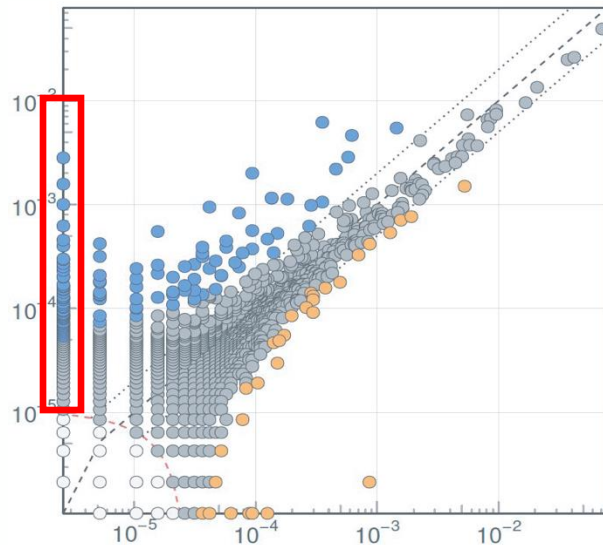
# RP2: Focused on Rare Cancers

# RP2: Fusion Enhanced Oncolytic HSV Expressing Anti-CTLA-4

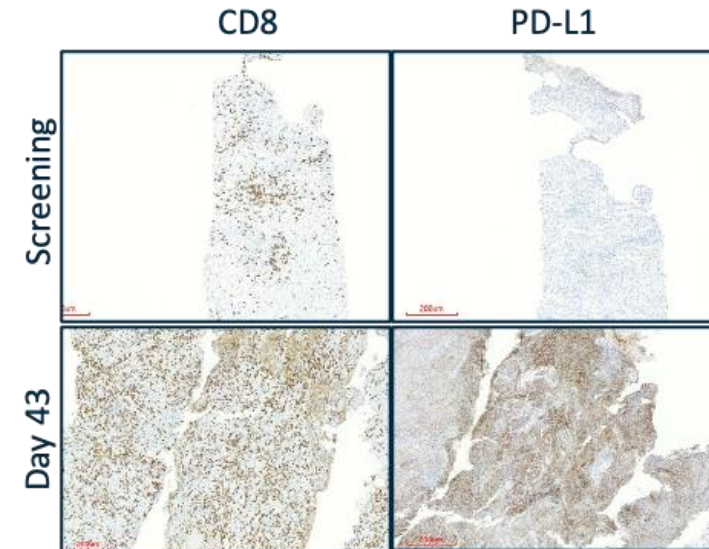
Durable monotherapy and combination responses demonstrated in multiple immune insensitive tumor types



- Designed to focus on the delivery of molecules which function at the time and place of immune activation, i.e. in tumors & draining lymph nodes
- Anti-CTLA-4 antibody prevents immune blockade at the APC / T cell interface
  - Anti-CTLA-4 is clinically validated; Ipilimumab, tremelimumab#
  - RP2 intends to deliver anti-CTLA-4 where it is needed (at the tumor) without systemic toxicity of other therapies



TCR sequencing of PBMCs demonstrated expansion of pre-existing and generation of new T cell clones following treatment with RP2 with nivolumab (Example: pt 3412-0001, uveal melanoma, PR)\*

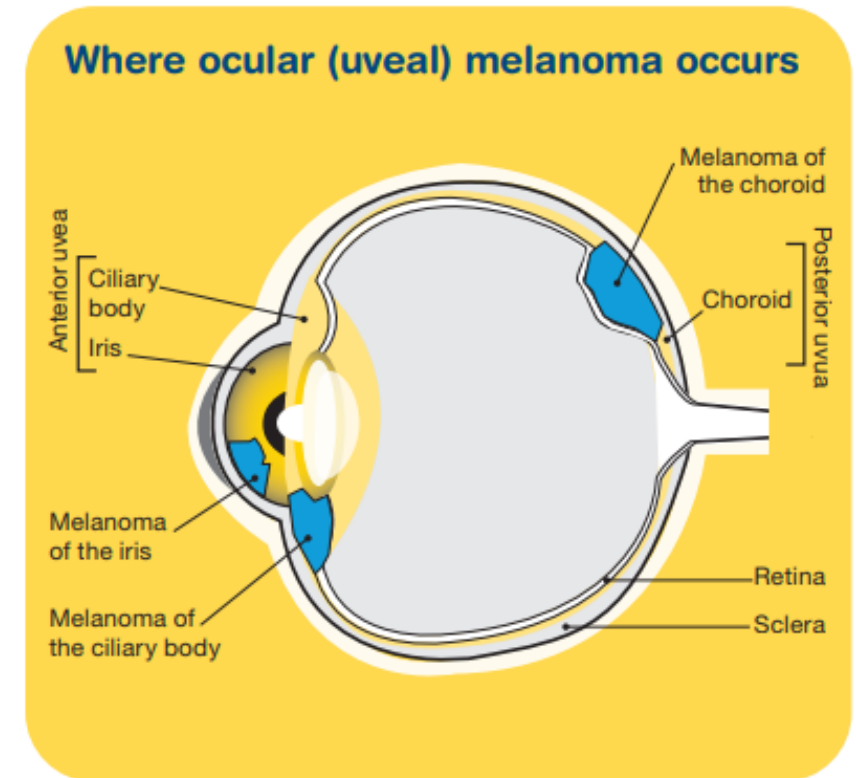


Substantial increases in CD8+ T cell infiltration and PD-L1 expression are seen (Example: pt 4403-0015, uveal melanoma SD)\*

\*Bommareddy P et al AACR 2024, # <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4400238/>

# Uveal Melanoma and Unmet Need

- Ocular or “uveal” melanoma is a rare cancer with approx. 1,000 cases in the US per year<sup>1</sup>
  - The historic median OS is approx. 12 months<sup>1</sup>
- Uveal melanoma behaves quite differently from skin melanoma
  - Mostly metastasizes to the liver (approx. 70-90% of cases) and once this occurs only about 10% of these patients survive beyond a year
  - Difficult to treat tumor where CPIs have demonstrated limited activity<sup>2,3,4</sup>
  - Kimmtrak (tebentafusp) is the 1st approved agent in uveal melanoma in HLA-A-02:01-positive adult patients (approx. 50% of the total population)\*
- Unmet need remains high, including improved efficacy and tolerability, effective options for HLA negative patients, and those who have progressed on Kimmtrak (HLA positive) and/or I-O combinations regardless of HLA status



<sup>1</sup>Carvajal RD et al. Br J Ophthalmol 2017; <sup>2</sup>Nathan P et al. N Engl J Med. 2021;385(13):1196-1206; <sup>3</sup>Pelster MS et al. J Clin Oncol. 2021;39(6):599-607; <sup>4</sup>Lukzky J et al SMR 2022; <sup>5</sup>Sacco et al, 20<sup>th</sup> International Congress of the Society for Melanoma Research, November 2023

\* Versus investigator's choice, pembrolizumab, ipilimumab, or dacarbazine

# ASCO 2024 Results: Clinical Activity in Uveal Melanoma



- The ORR was 29.4% (all PRs) and DCR was 58.8%
  - At data cutoff, median (range) DOR was 11.5 (2.8–21.2)<sup>a</sup> months

	RP2 monotherapy (n = 3)	RP2 + nivolumab (n = 14)	Total (N = 17)
<b>Best overall response, n (%)</b>			
CR	0	0	0
PR	1 (33.3)	4 (28.6)	5 (29.4)
SD	0	5 (35.7)	5 (29.4)
PD	1 (33.3)	4 (28.6)	5 (29.4)
NE <sup>b</sup>	1 (33.3)	1 (33.3)	2 (11.8)
<b>ORR (CR + PR)</b>	<b>1 (33.3)</b>	<b>4 (28.6)</b>	<b>5 (29.4)</b>
<b>DCR (CR + PR + SD)</b>	<b>1 (33.3)</b>	<b>9 (64.3)</b>	<b>10 (58.8)</b>

HLA-A*02:01 status	Positive (n = 6)	Negative (n = 11)	Total (N = 17)
<b>Best overall response, n (%)</b>			
PR	1 (16.7)	4 (36.4)	5 (29.4)
SD	2 (33.3)	3 (27.3)	5 (29.4)
PD/NE	3 (50.0)	4 (36.4)	7 (41.2)

- Responses were observed in both HLA-A2\*02:01-positive and -negative patients
- The majority of patients (70.6% [12/17]) received both prior anti-PD-1 and anti-CTLA-4 therapy

# ASCO 2024 Results: Safety Profile in Uveal Melanoma



Patients with TRAEs	Grade 1–2 <sup>a</sup>	Grade 3	Grade 4–5
<b>RP2 monotherapy (n = 3)</b>	2 (66.7)	0	0
Hypotension	2 (66.7)	0	0
Chills	1 (33.3)	0	0
Hyperhidrosis	1 (33.3)	0	0
Pyrexia	1 (33.3)	0	0
Rash	1 (33.3)	0	0
Vomiting	1 (33.3)	0	0
<b>RP2 + nivolumab (n = 14)</b>	13 (92.9)	6 (42.9) <sup>b</sup>	0
Pyrexia	10 (71.4)	0	0
Chills	7 (50.0)	0	0
Fatigue	4 (28.6)	0	0
Pruritus	4 (28.6)	0	0
Hypotension	2 (14.3)	2 (14.3)	0
Infusion-related reaction	2 (14.3)	1 (7.1)	0
Headache	2 (14.3)	0	0
Influenza-like illness	2 (14.3)	0	0
Nausea	2 (14.3)	0	0

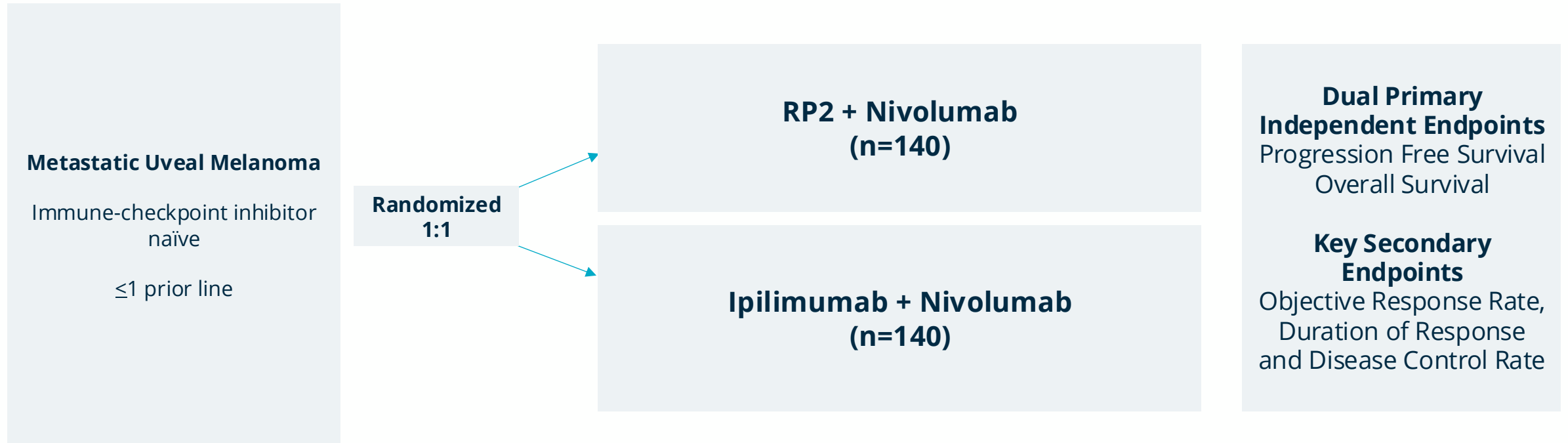
- The most common grade 1 or 2 TRAEs (≥20%) in both cohorts combined were pyrexia, chills, fatigue, hypotension, and pruritus
- Both cases of grade 3 hypotension were transient and readily managed with crystalloid repletion
- There were no grade 4 or 5 TRAEs
- In patients who underwent intrahepatic injections, there were no clinically significant bleeding events

All data presented as n (%). TRAEs include events deemed related to RP2 only, nivolumab only, or both RP2 and nivolumab.<sup>a</sup>Grade 1 or 2 TRAEs occurring in >10% of patients are shown.<sup>b</sup>For the combination therapy cohort, additional grade 3 TRAEs of alanine aminotransferase increase, arthralgia, diarrhea, gamma-glutamyltransferase increase, immune-mediated hepatitis, and lipase increase were reported in 1 patient each. TRAE, treatment-related adverse event.



# RP2-202: Metastatic Uveal Melanoma Study

## Registration-Directed Clinical Trial

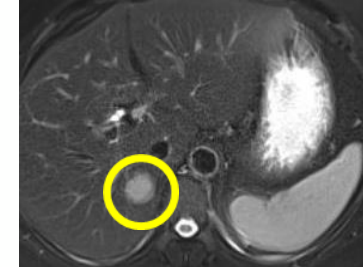
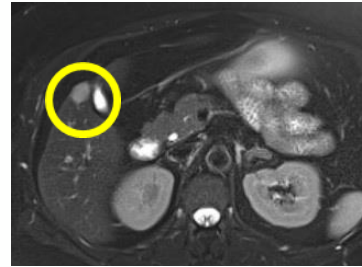
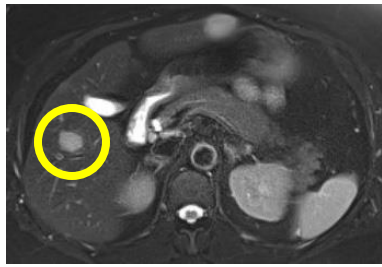
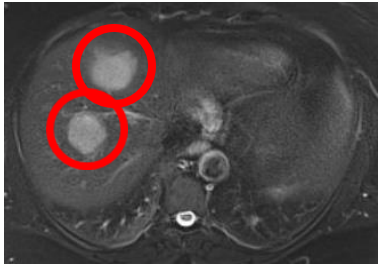


# Uveal Melanoma Patient Featured in ITV News

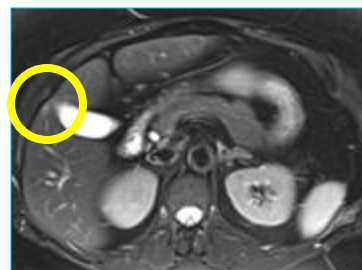
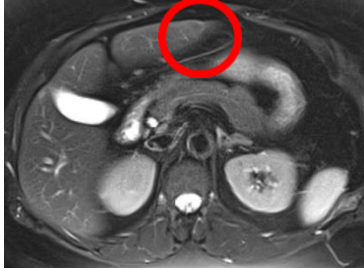
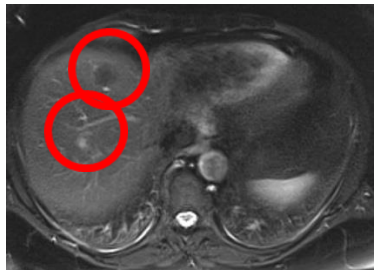
Prior nivolumab+ipilimumab – PR (RP2+nivolumab)



Screening



19 months



Pt 201-4403-0017 – ongoing PR

- Liver metastases
- Patient has ongoing PR at 19 months



"This trial has given me hope in the treatment, the trial, my care, and I'm happy. I don't think about dying anymore at all"

ITV, 03 November 2023

 *Injected*

 *Un-injected*

# Mucoepidermoid Carcinoma Monotherapy Patient Featured in BBC News

Prior carboplatin/paclitaxel, bicalutamide, ceralasertib – ongoing CR>2 years (RP2 mono)



**B B C**

Home News Sport Business Innovation Culture Travel Earth Video Live



Krzysztof's cancer is no longer detectable

**ICR** The Institute of Cancer Research

**“My final lifeline”**

“I had injections every two weeks for five weeks which completely eradicated my cancer. I've been cancer-free for two years now.”

1 month



4 months



**“It's a true miracle, there is no other word to describe it. I've been able to work as a builder again and spend time with my family, there's nothing I can't do.”**



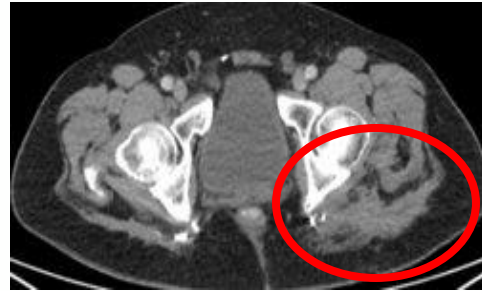
# RP2 Monotherapy Patient with Chordoma

Prior imatinib – ongoing PR at over 8 months (RP2 monotherapy)

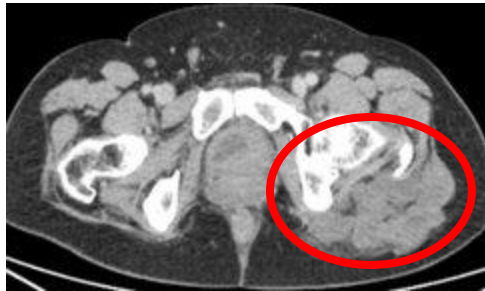
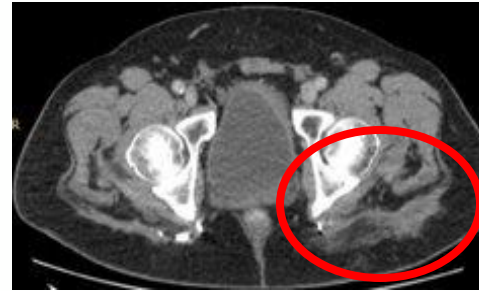
Screening



3 months



6 months



## Pt 4401-0029 - ongoing PR

- Left gluteal muscle injected
- Liver & >50 small lung lesions also disappeared during treatment

 Injected  Un-injected

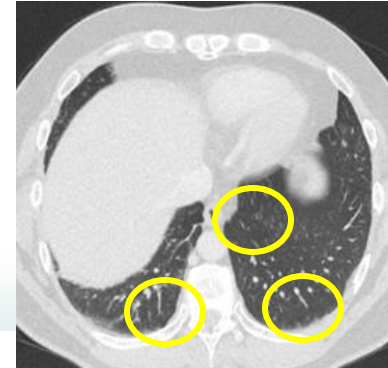
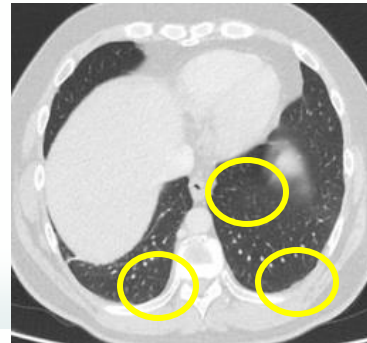
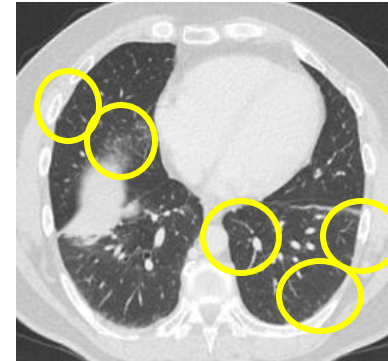
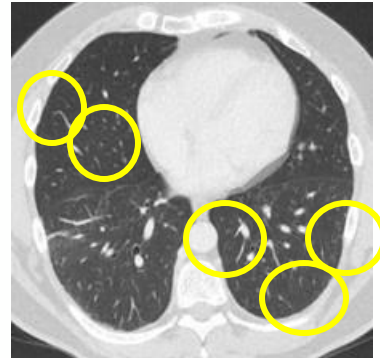
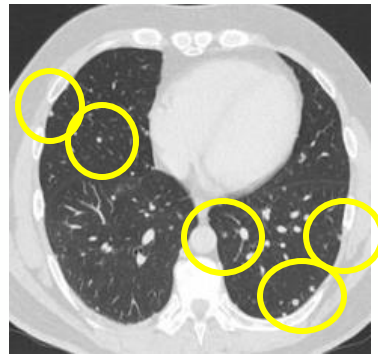
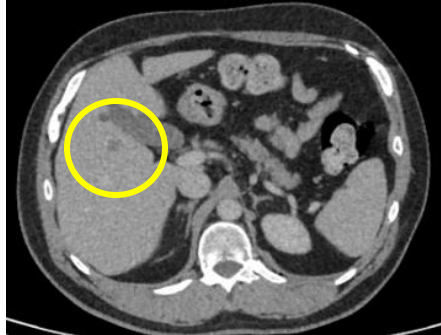
# RP2 Monotherapy Patient with Chordoma

Prior imatinib – ongoing PR at over 8 months (RP2 monotherapy)

Baseline

3 months

6 months



**Pt 4401-0029 -  
ongoing PR**

- Left gluteal muscle lesion injected
- Liver & >50 small lung lesions also disappeared during treatment

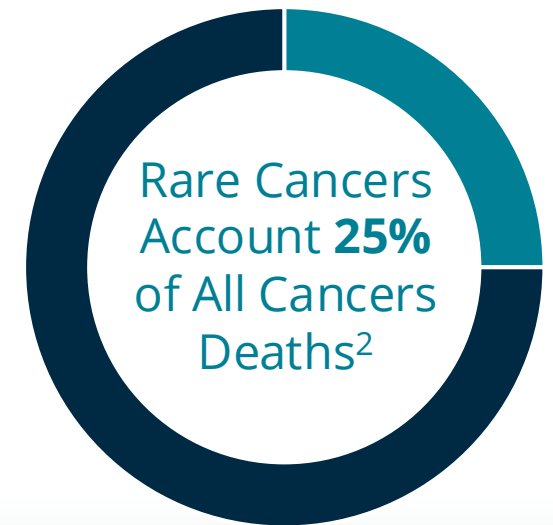
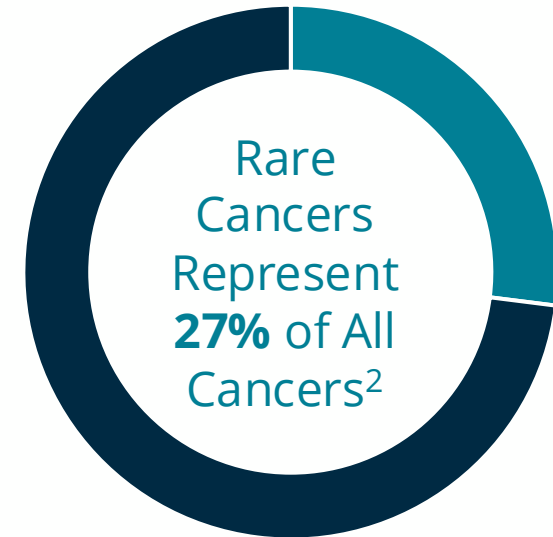
 *Injected*

 *Un-injected*

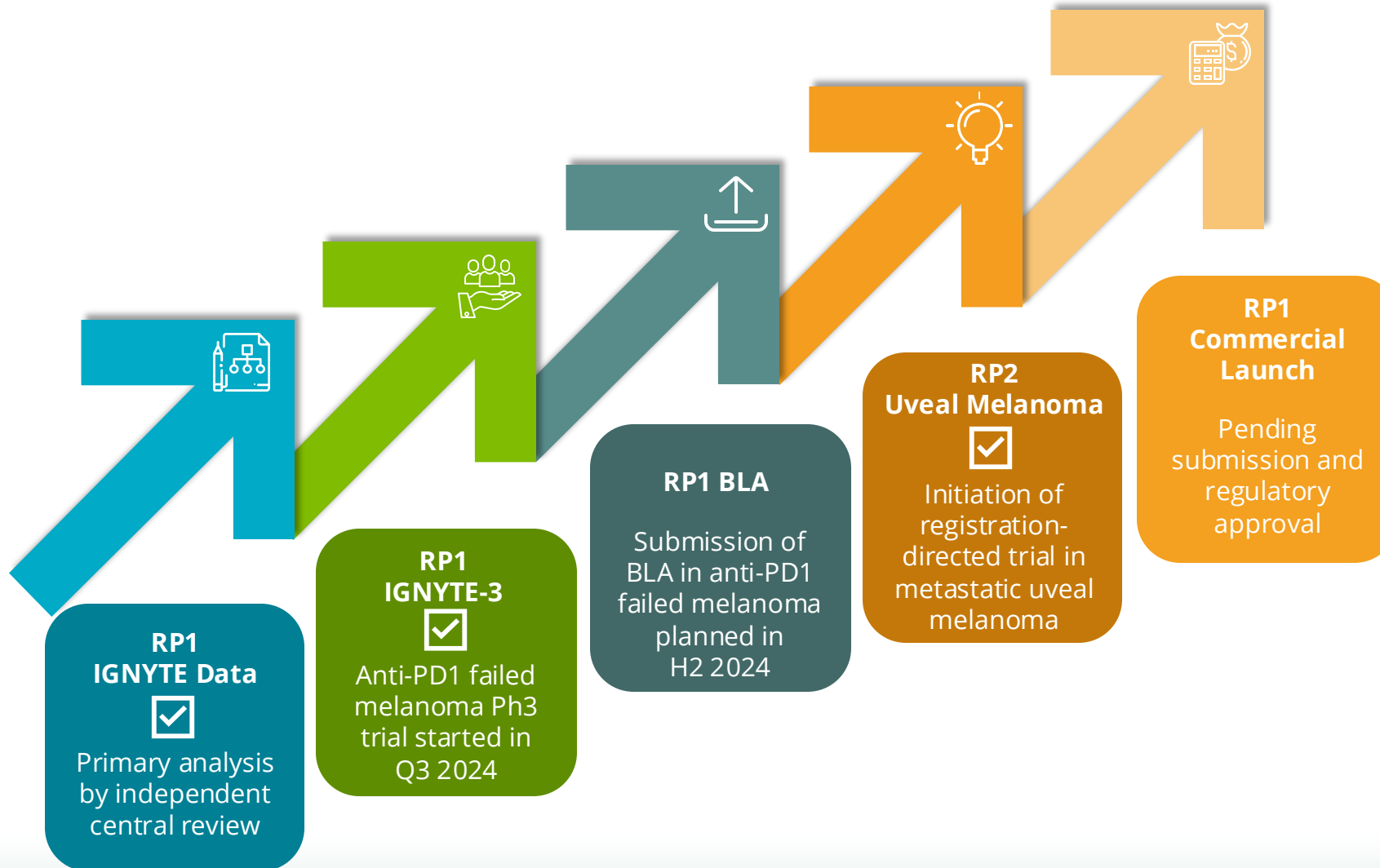


# Uveal Melanoma is the Foundation for a Potential Rare Cancer Franchise

- Treatment with RP2 has led to responses in rare cancer settings including uveal, chordoma, and mucoepidermoid carcinoma<sup>1</sup>
  - Durable monotherapy and combination responses demonstrated in multiple immune insensitive tumor types<sup>1</sup>
- Rare cancers present a significant unmet need and potential for paths to market for RP2
  - Uveal melanoma as a foundation; registration-directed clinical trial in metastatic uveal melanoma underway
  - Potential to expand to other rare cancers based on clinical activity observed with RP2 (soft tissue sarcomas, rare head and neck, etc.)<sup>1</sup>



# Upcoming Milestones to Drive Value



## Positioned to Bring our Oncolytic Immunotherapies to Market

- ✓ All programs wholly owned
- ✓ Potential to deliver substantial commercial revenues beginning in late 2025
- ✓ Strong financial position with cash of \$469.1 as of 30 June 2024
- ✓ Cash runway into 2H 2026



# THANK YOU

## MISSION

To transform cancer treatment by pioneering the development of a novel portfolio of oncolytic immunotherapies

