Replimune®

Igniting a Systemic Immune Response to Cancer

September 2024

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.

Industry Leader in Oncolytic Immunotherapy

RP1 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

RP2 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

Replimune®

Injected tumor

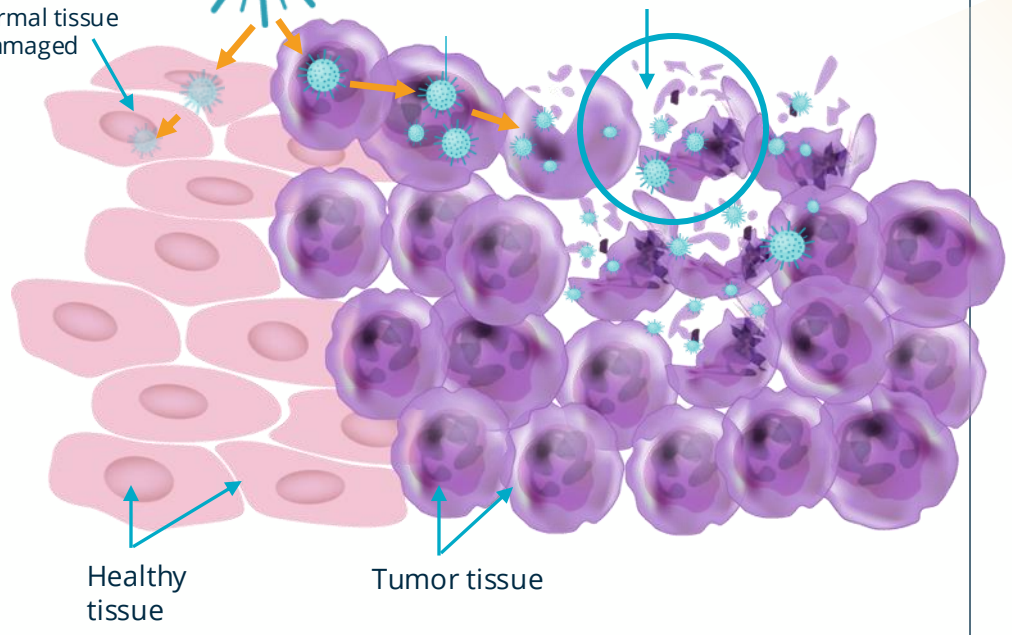
MECHANISM 1

Attenuated potent new clinical isolate of HSV-1 modified to express a fusogenic glycoprotein and immune stimulating proteins

Oncolytic immunotherapy

Dysregulated host antiviral response allows robust virus replication and tumor lysis

Intact host antiviral response: Normal tissue remains undamaged



Healthy tissue

Tumor tissue

Immune response

MECHANISM 2

Release of virus progeny

Infection of more tumor cells

Tumor cell death and release of tumor antigens

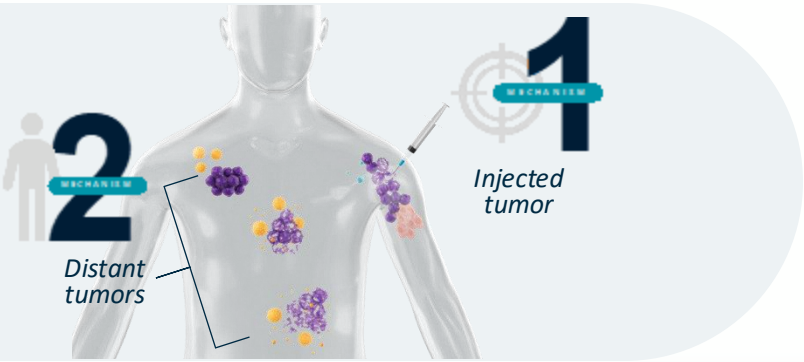
Local Inflammation

Altering of tumor microenvironment

Enhanced T cell priming and activation

T cell infiltration and killing of distant, uninjected tumors

Generating a strong and durable systemic anti-tumor immune response



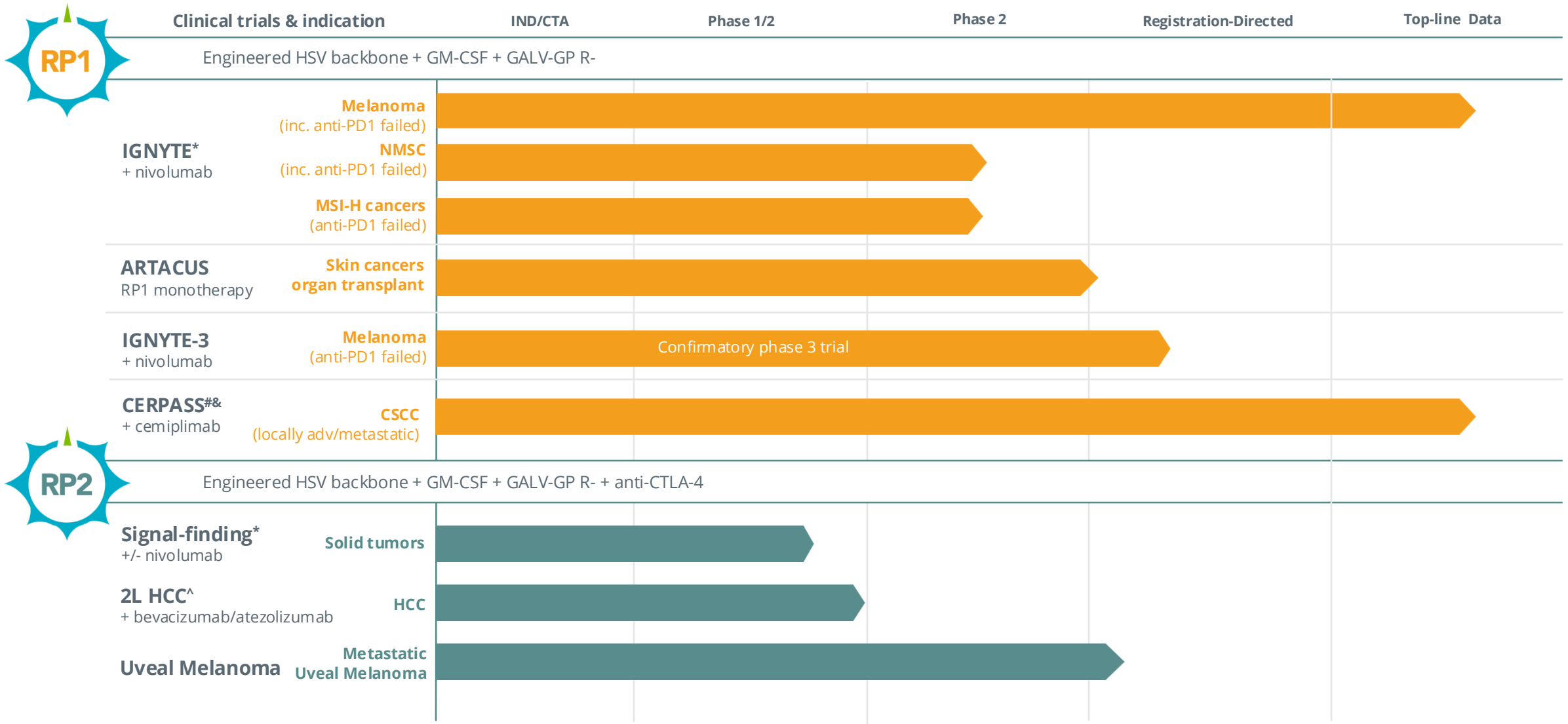
Bommareddy PK et al AJCD. 2016

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

	RP1	RP2
Payloads	GALV-GP R-, GM-CSF	GALV-GP R-, anti-CTLA-4, GM-CSF
Target	Immunologically responsive tumor types, including anti-PD1 failed	Less immunologically responsive tumor types
Intended indication(s)	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
Clinical activity in anti-PD1 failed patients demonstrated	✓	✓
Good tolerability and Safety profile demonstrated	✓	✓
Injection location	Superficial, nodal & visceral	Superficial, nodal & visceral
Systemic activity	***Clear systemic effects seen in responding patients (un-injected tumor responses, responses are generally highly durable)***	
Other design considerations	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%[1]
- Nivolumab + ipilimumab is a potential option[2,] but toxicity is high[3,4]
- Anti-LAG3 plus anti–PD1 has not demonstrated meaningful efficacy in the anti–PD1 failed setting[5]
- For BRAF mutant tumors, BRAF-targeted therapy responses are generally transient[6]
- TIL therapy for select patients gives response rates of ~30%, but comes with toxicity (nearly all patients have grade 4 toxicity)[7]
- T-VEC + pembrolizumab has limited activity outside of the adjuvant setting, with no responses seen in patients with visceral disease[8,9]

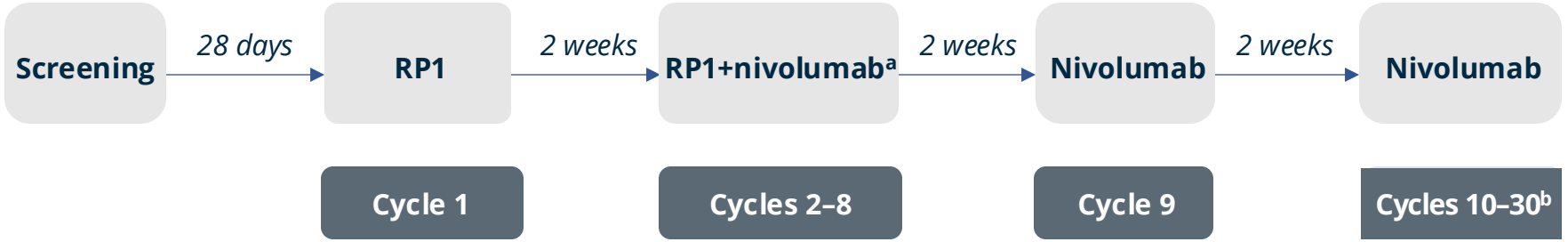
CTLA-4, cytotoxic T-lymphocyte antigen 4; LAG3, lymphocyte-activation gene 3; PD-1, programmed cell death protein 1; TIL, tumor infiltrating lymphocyte

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

Anti–PD1 failed melanoma cohort

(140 pts; 16 pts treated in prior cohorts: Total=156)



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[c]

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

[a]Dosing with nivolumab begins at dose 2 of RP1 (C2D15). [b]Option to reinitiate RP1 for 8 cycles if criteria are met. c. 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.

ESMO 2024: Baseline Clinical Characteristics

Real-world anti-PD1 failed melanoma population was enrolled

Patients, n (%)	N = 140
Age, median (range), y	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)
Baseline PD-L1 tumor expression	
Positive (≥1%)	44 (31.4)
Negative (<1%)	79 (56.4)
Undetermined or missing	17 (12.1)

Patients, n (%)	N = 140
Prior therapy	
Anti–PD-1	
Anti–PD-1 only as adjuvant therapy	36 (25.7)
Anti–PD-1 other than as adjuvant 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)
Received BRAF/MEK therapy	17 (12.1)
Anti–PD-1 resistance category	
Primary resistance[a]	92 (65.7)
Secondary resistance[b,c]	48 (34.3)

Due to the requirement that patients must have confirmed PD on an immediate prior anti–PD-1–based therapy, most patients had 1 or 2 prior lines of therapy

The median (range) follow-up at the time of the primary analysis was 15.4 months (0.5–47.6 months)

[a]Primary resistance: Progressed within 6 months of starting the immediate prior course of anti–PD-1 therapy. [b]Secondary resistance: Progressed after 6 months of treatment on the immediate prior course of anti–PD-1 therapy. [c]Includes one patient with unknown resistance status. CTLA-4, cytotoxic T-lymphocyte antigen 4; LDH, lactate dehydrogenase; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ULN, upper limit of normal.

ESMO 2024: Primary Efficacy Analysis
By blinded independent central review

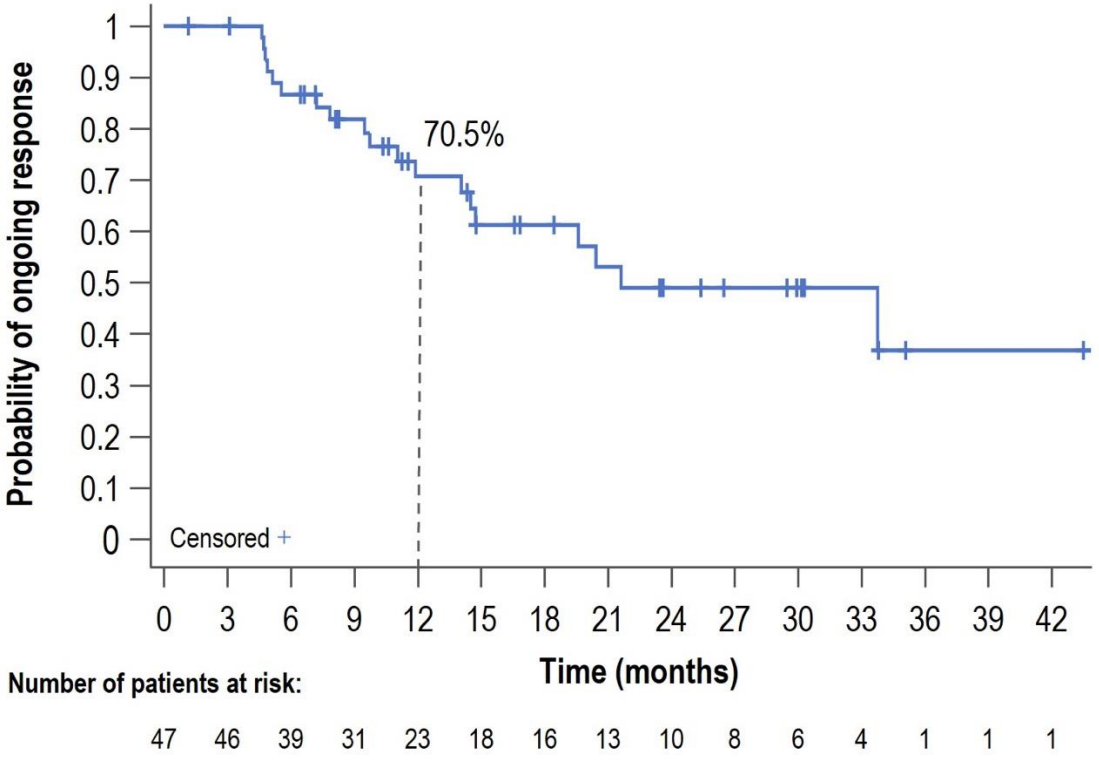
	Primary endpoint mRECIST v1.1 (N = 140)	Sensitivity analysis RECIST v1.1 (N = 140)
Confirmed best response, n (%)		
CR	21 (15.0)	21 (15.0)
PR	26 (18.6)	25 (17.9)
SD	41 (29.3)	31 (22.1)
PD	43 (30.7)	54 (38.6)
ORR (confirmed CR+PR), n (%)	**47 (33.6)**	**46 (32.9)**
95% CI	(25.8, 42.0)	(25.2, 41.3)

1 in 3 patients (33.6%) experienced a confirmed objective response,15.0% CR

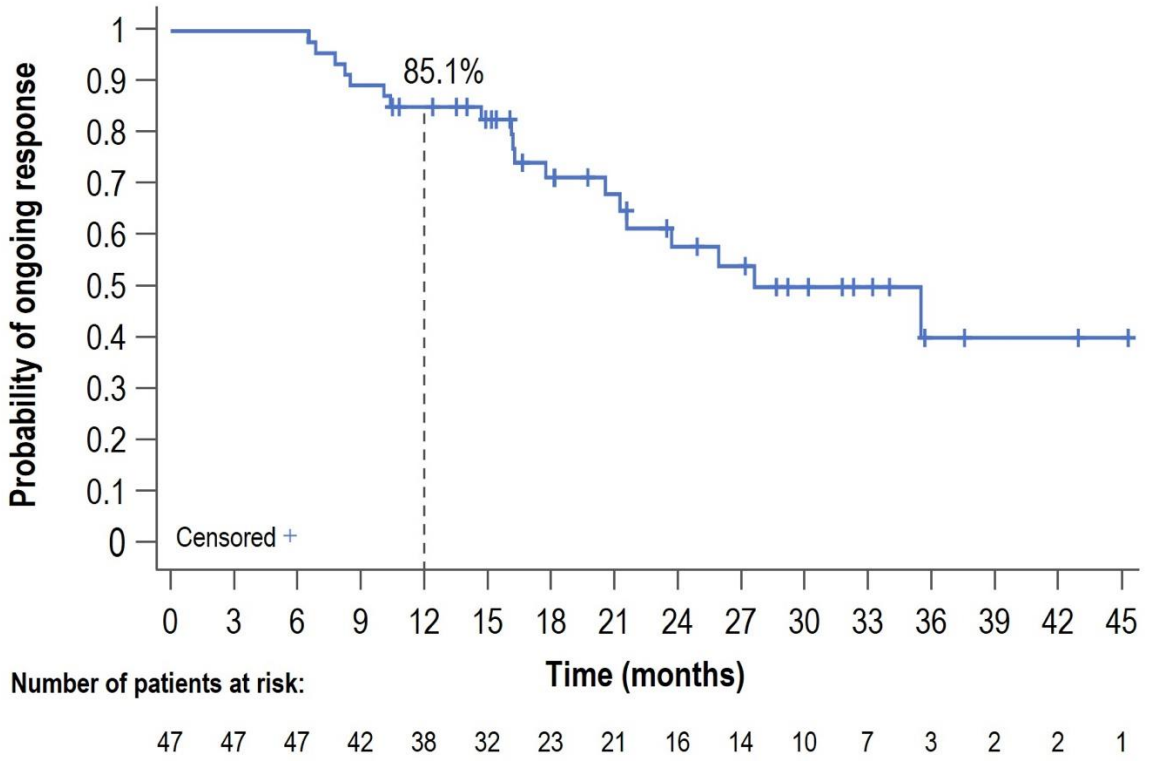
CR, complete response; mRECIST, modified RECIST; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

ESMO 2024: Duration of Response (by mRECIST v1.1)

Duration from response initiation



Duration from treatment initiation



- Median (range) duration from response initiation was 21.6 months (1.2+ to 43.5+ months)
- Median (range) duration from baseline was 27.6 months (6.6+ to 45.3+ months)
- ***85% of responses were ongoing ≥1 year from starting treatment***

ESMO 2024: Efficacy

Centrally reviewed mRECIST v1.1 responses (per protocol); all patients have ≥12 months follow up

BOR n (%)	All patients (N = 140)	Single-agent anti–PD-1 (n = 75)	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])	Anti–PD-1 adjuvant (n = 36)	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)**

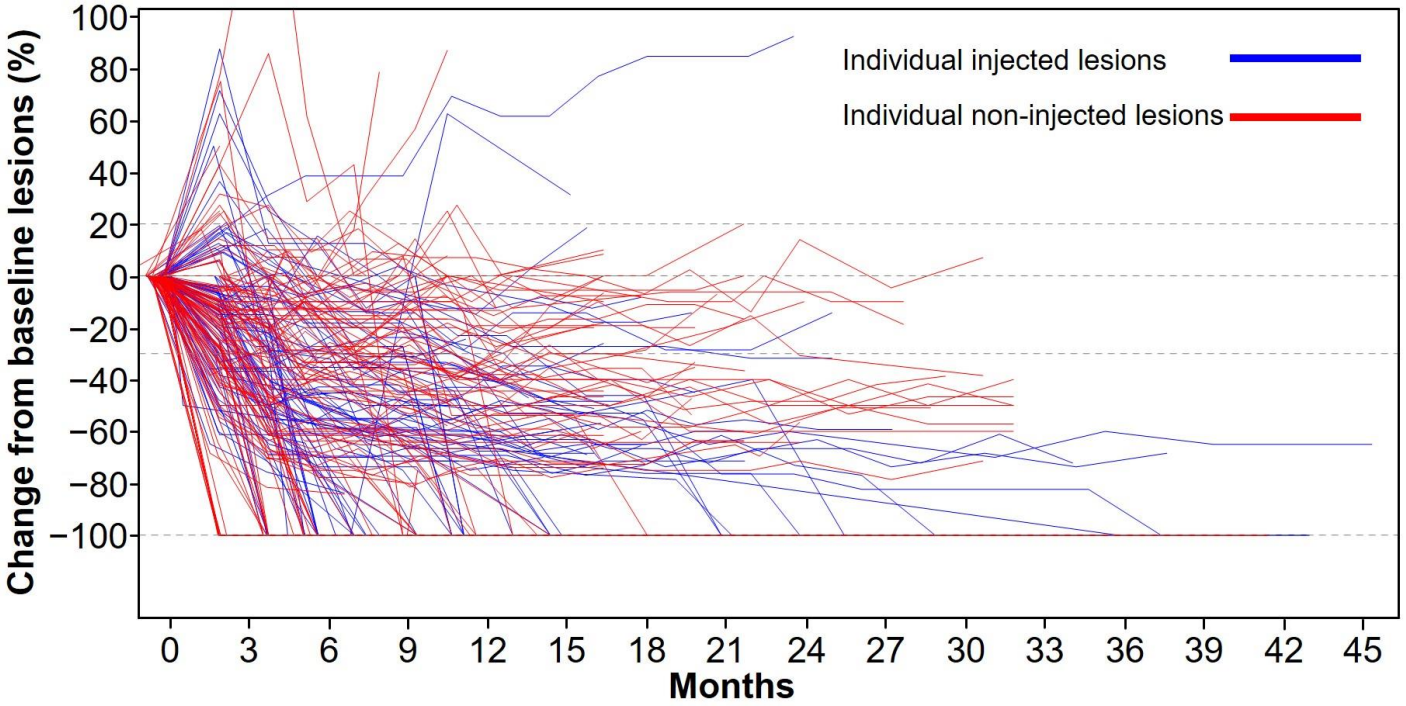
Consistent response rates were seen across patient subgroups, including:

- **27.7% ORR** in patients who had **prior anti–PD-1 and anti–CTLA-4**
- **35.9% ORR** in patients who had **primary resistance to anti–PD-1**

[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.

ESMO 2024: Change in Size of Individual Injected and Non-injected Lesions Over Time (mRECIST v1.1)

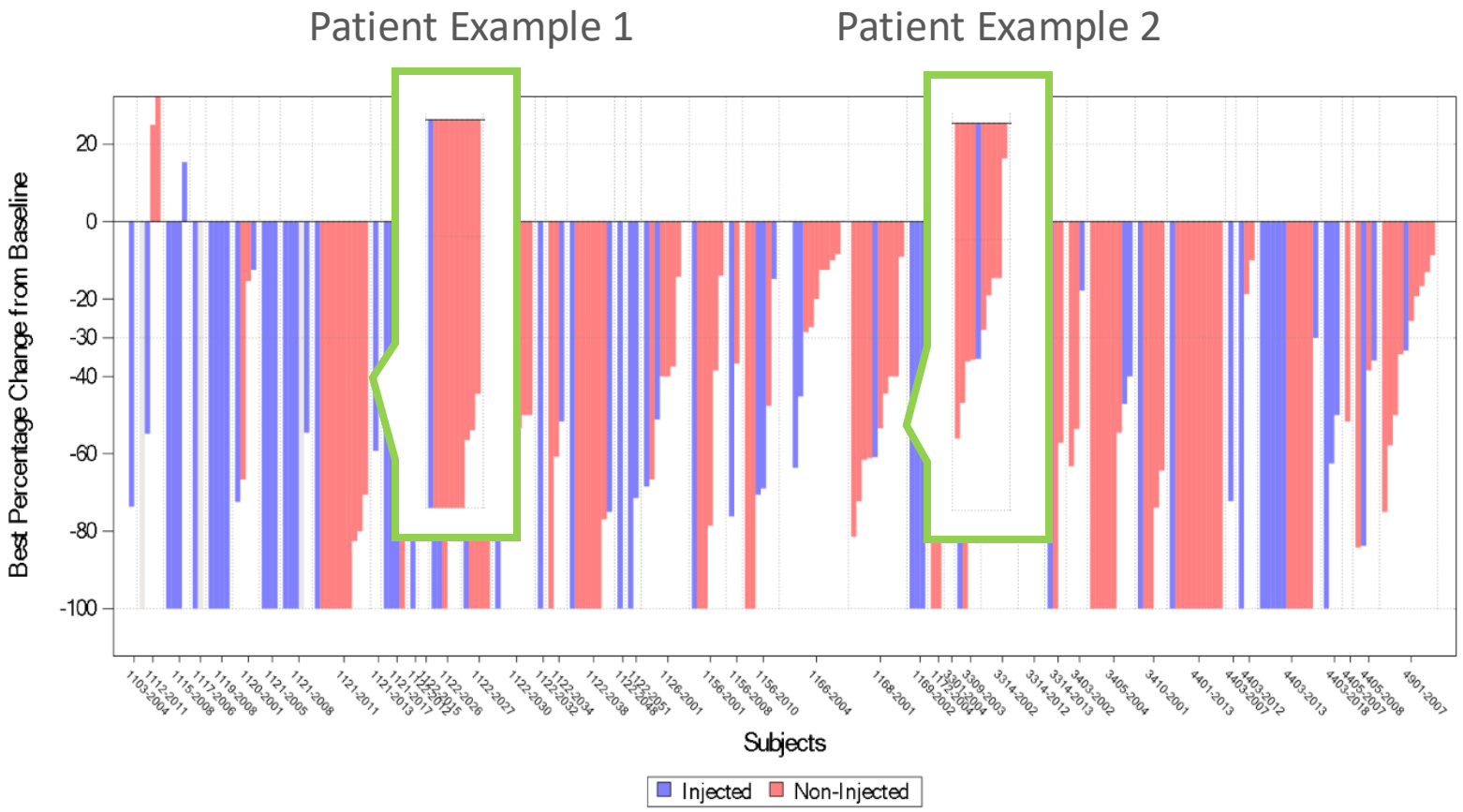


	Number (%) of measured lesions for responders (CR or PR; N = 47)	
	Injected (n = 79)	Non-injected (n = 123)
Number of lesions with:		
No reduction	1 (1.3)	2 (1.6)
Any reduction	78 (98.7)	121 (98.4)
Best reduction >0 to <30%	4 (5.1)	23 (18.7)
Best reduction ≥30 to <100%	31 (39.2)	48 (39.0)
Best reduction of 100%	43 (54.4)	50 (40.7)

Injected and non-injected lesions responded with similar frequency, depth, duration, and kinetics

All measurable lesions (10 max if >10 were present) measured by central review for each patient with a best response of confirmed CR or PR. Central reviewers were blinded to lesion injection status. CR, complete response; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PR, partial response.

ESMO 2024: Responses in Injected and Non-Injected Lesions

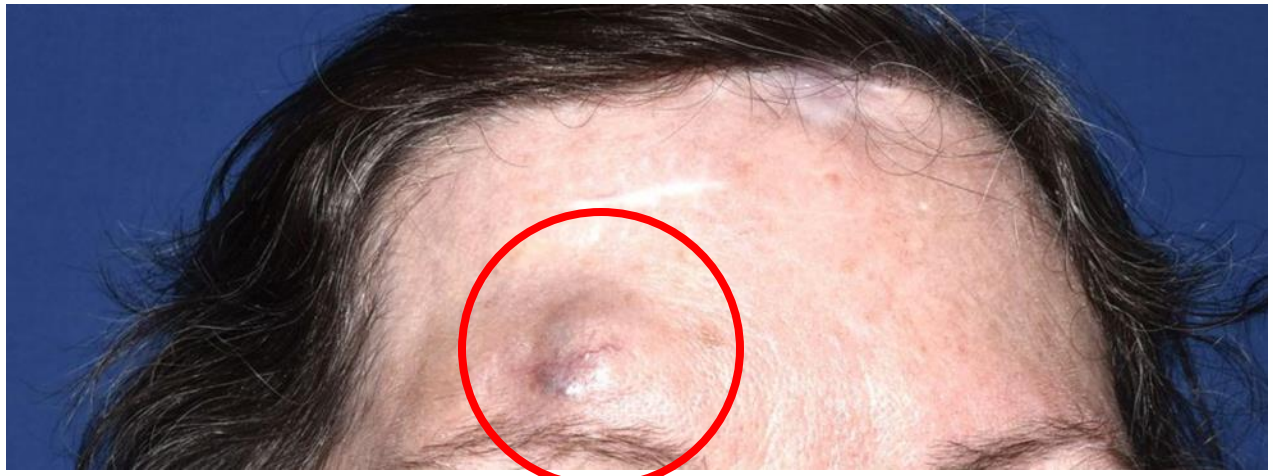


- Tumor reduction seen in 53 out of 60 non-injected visceral organ lesions
- Injected and non-injected lesions responded with similar frequency, depth and duration
- Responses not driven by injected lesions alone

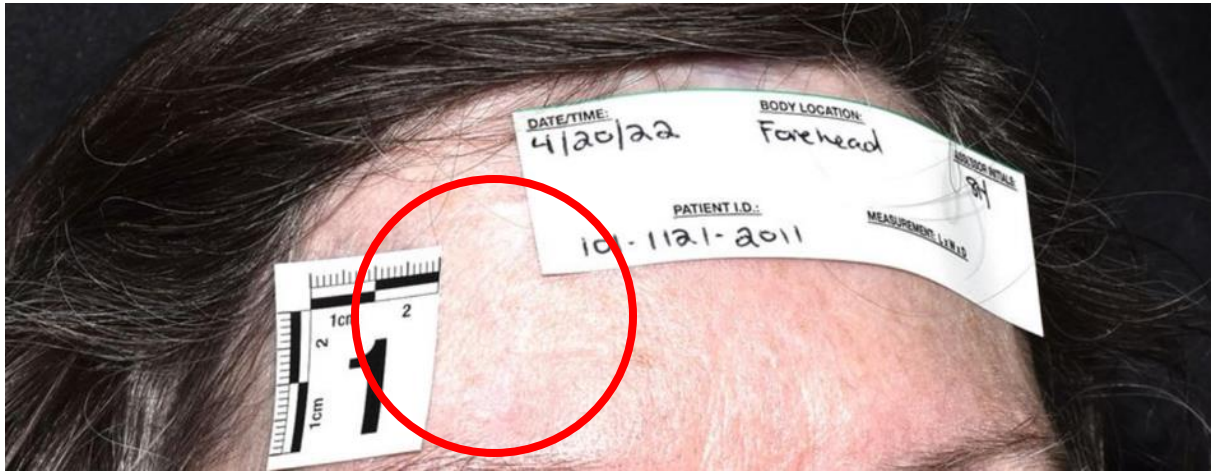
All measurable lesions (10 max if >10 were present) measured by central review for each patient with a best response of confirmed CR or PR. Central reviewers were blinded to lesion injection status.

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

29 JUL 2021 / Screening



20 APRIL 2022



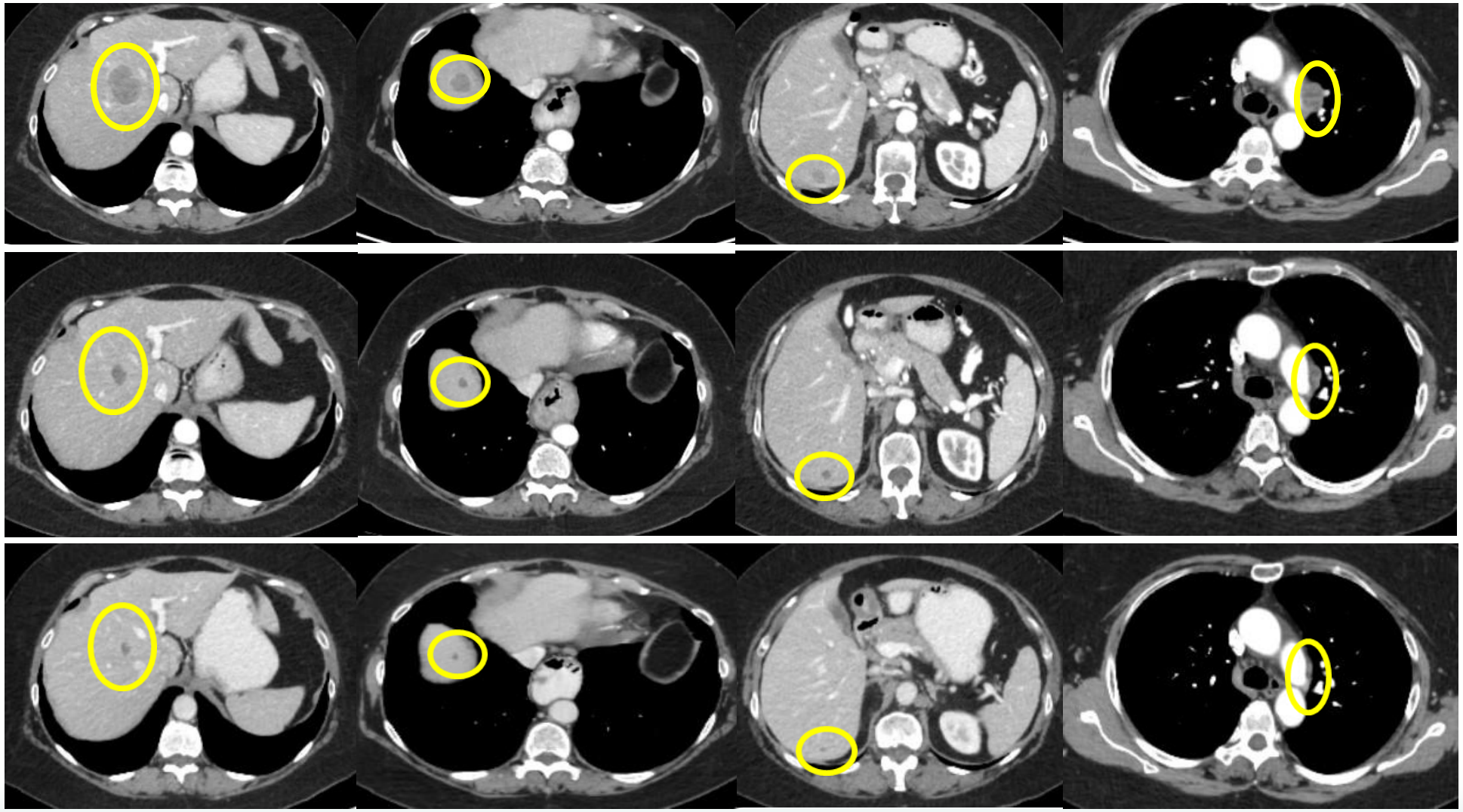
Injected Un-injected

Patient Example Cont'd:
Prior Opdivo (adjuvant) and Keytruda (first line for metastatic disease), Stage IVM1c

22 Jul 2021/
Baseline

22 Sep 2021/
Day 57

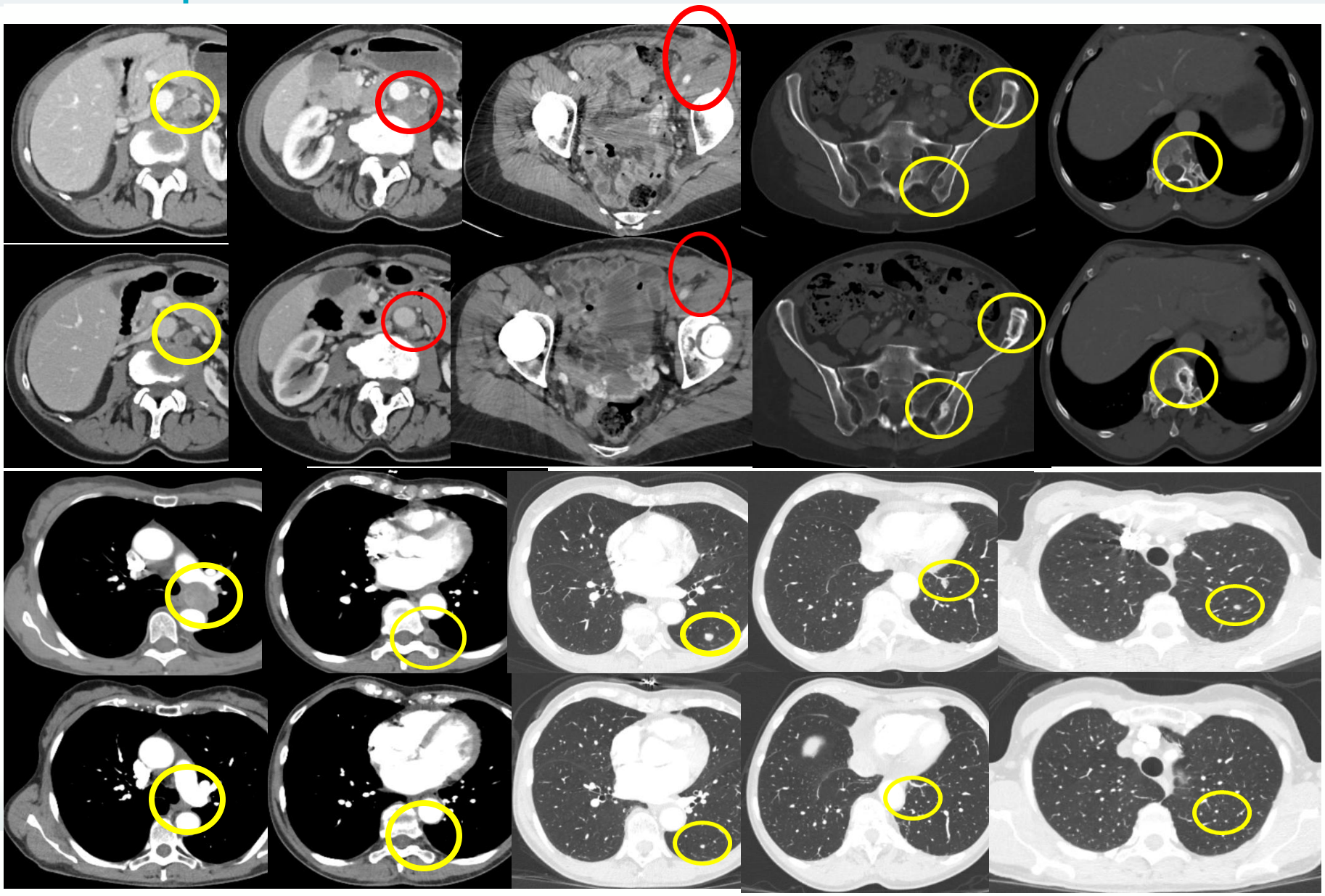
29 Dec 2021/
Day 155



Injected Un-injected

Patient Example

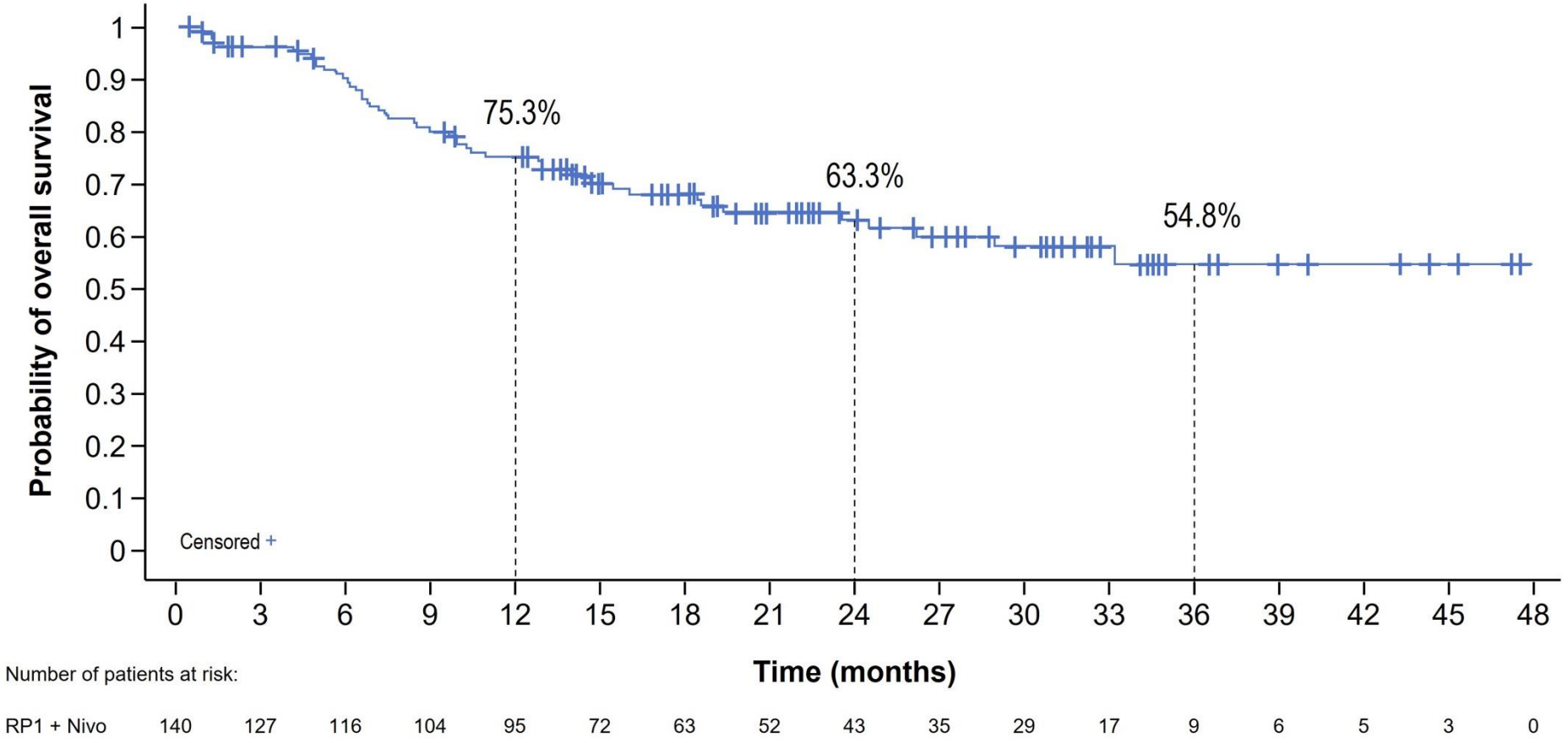
Prior atezolizumab+cobimetinib, ipilimumab, SX682 (CXCR-inhibitor)+ atezolizumab, ipilimumab+nivolumab



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

Injected Un-injected

ESMO 2024: Overall Survival



- One-, two-, and three-year survival rates were 75.3%, 63.3%, and 54.8%, respectively
- Median overall survival has not been reached

ESMO 2024: Safety/Treatment-Related AEs (N=141)

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)

RP1 combined with nivolumab is generally well tolerated

- 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

IGNYTE Data Shows Clinically Meaningful Benefit

- One third of patients respond by independent central review (ORR: 33.6%*)
  - Clinically meaningful activity seen across all subgroups, including patients who had prior combined anti-PD1/anti-CTLA-4 and those with primary anti-PD1 resistance
- Responses are durable
  - Median DOR of 21.6 months with 85% of responses ongoing ≥1 year from starting treatment
- 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
- While median OS has not been reached, 1-(75.3%), 2- (63.3%) and 3-year (54.8%) survival rates are promising

*By modified RECIST 1.1 (protocol defined endpoint)

CTLA-4, cytotoxic T-lymphocyte antigen 4; DOR, duration of response; PD-1, programmed cell death protein 1; ORR, objective response rate; OS, overall survival

IGNYTE-3: Confirmatory Phase 3 Trial Design*

RP1 and Nivolumab in Ipi-Nivo Pretreated Patients

Advanced cutaneous melanoma

Progressed on anti-PD1 AND anti-CTLA-4 OR not candidates for anti-CTLA-4

Up to 2 prior lines of systemic therapy for advanced disease

BRAF mutant patients must have been treated with BRAF/MEK-directed therapy[1]

N=~400

Randomized 1:1

RP1 + Nivolumab

Treatment of Physician's Choice (TPC)

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

Primary Endpoint
Overall Survival

Key Secondary Endpoints
Progression Free Survival and Objective Response Rate

[1] 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

RP1 as monotherapy shows clear clinical activity with promising ORR/CRR

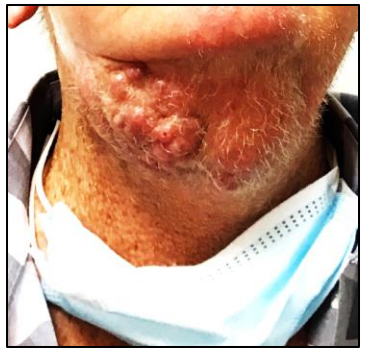
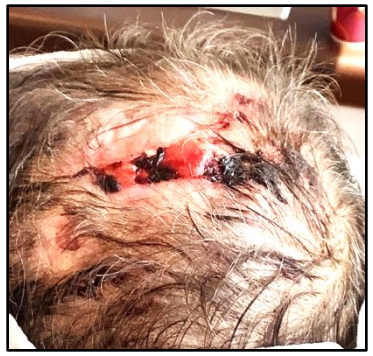
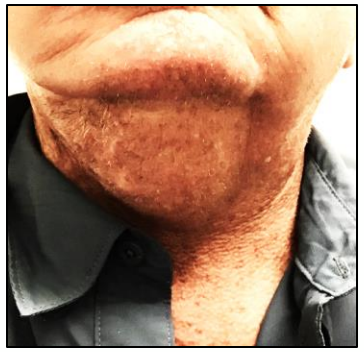
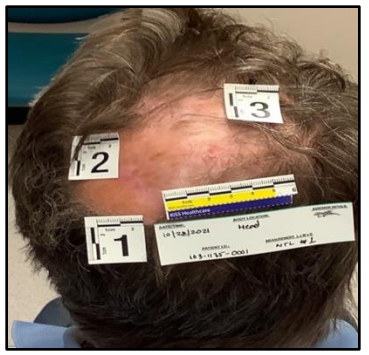
Characteristic	All patients (N = 27)
Age, years, median (range)	68.0 (48–86)
Male, n (%)	21 (77.8)
Race, n (%)	
White	26 (96.3)
Native Hawaiian/Pacific Islander	1 (3.7)
Allograft type, n (%)	
Kidney	22 (81.5)
Liver	4 (14.8)
Lung	1 (3.7)
Heart	0
Cutaneous malignancies, n (%)	
CSCC	24 (88.9)
MCC	3 (11.1)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

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

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

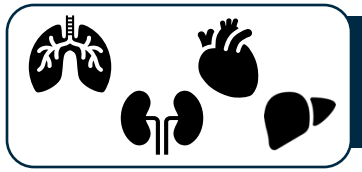
[a]Per protocol, metastatic to skin, soft tissue, or lymph nodes.
CSCC, cutaneous squamous cell carcinoma; MCC, Merkel cell carcinoma
Migden et al, AACR 2024, Presentation CT003.

ARTACUS: Examples of Patients With Confirmed Response

	1143-0002	1143-0001	1135-0001
	May 2022	June 2021	July 2021
Baseline			
	August 2022 (3 months)	December 2021 (6 months)	October 2021 (3 months)
Best response			
	Complete response	Complete response	Complete response

Migden et al, AACR 2024, Presentation CT003

High Risk of Skin Cancer in Organ Transplant Patients Drives the RP1 ARTACUS Opportunity



~1.5K Addressable* Solid Organ Transplant Patients with skin cancer[6]

50%↑ Growth in transplants over the last 8 years[1]

Significant Unmet Need

UP TO 53x **Increased Risk of Cancer**
Increased risk of SoT patients developing skin cancer, with a high rate of metastasis[2]

35% **High Rate of Multiple Primary Lesions**
Percentage of patients developing multiple primary lessions[4,5]

30% **Treatment Options Risk Loss of Organ**
Rate of organ rejection, due to treatment with ICIs for skin cancer[3]

ARTACUS Data

RP1 showed an **35% ORR and a 22% CRR[7]** 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[7]**

*Addressable defined as locally advanced or metastatic SoT (solid organ transplant) skin cancer patients
[a]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	
n/%	Cemiplimab n=72	RP1+ cemiplimab n=139
PR	19 (26.4)	20 (14.4)
SD	14 (19.4)	18* (12.9)
PD	12 (16.7)	27 (19.4)
OR	**37 (51.4%)**	**73 (52.5%)**
	P=0.692[1]	
CR	**18 (25.0%)**	**53 (38.1%)**
	P=0.040[1]	

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

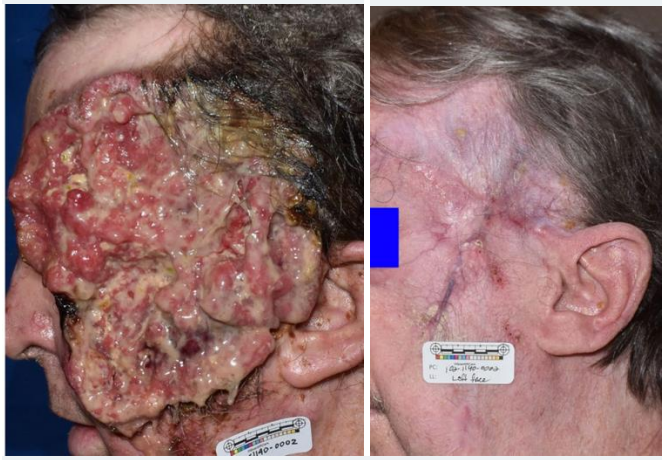
[1]Per the protocol p≤0.025 is required for formal statistical success in CERPASS for CRR or ORR alone and p≤0.05 if both endpoints were met

BOR=best overall response

Five of the Most Visually Impactful CRs with RP1+cemiplimab

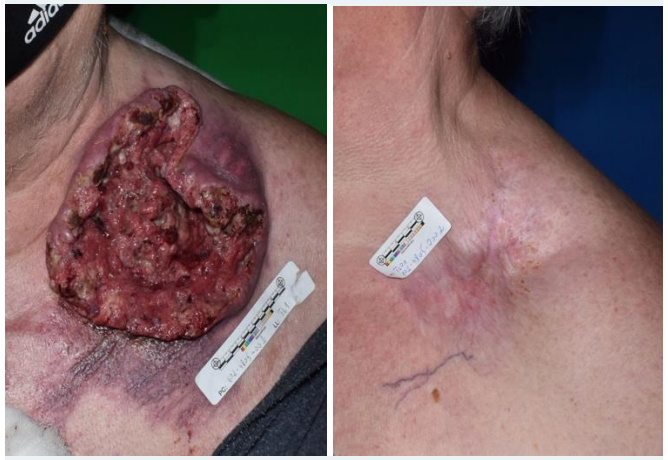
Replimune®

Baseline | 81 weeks



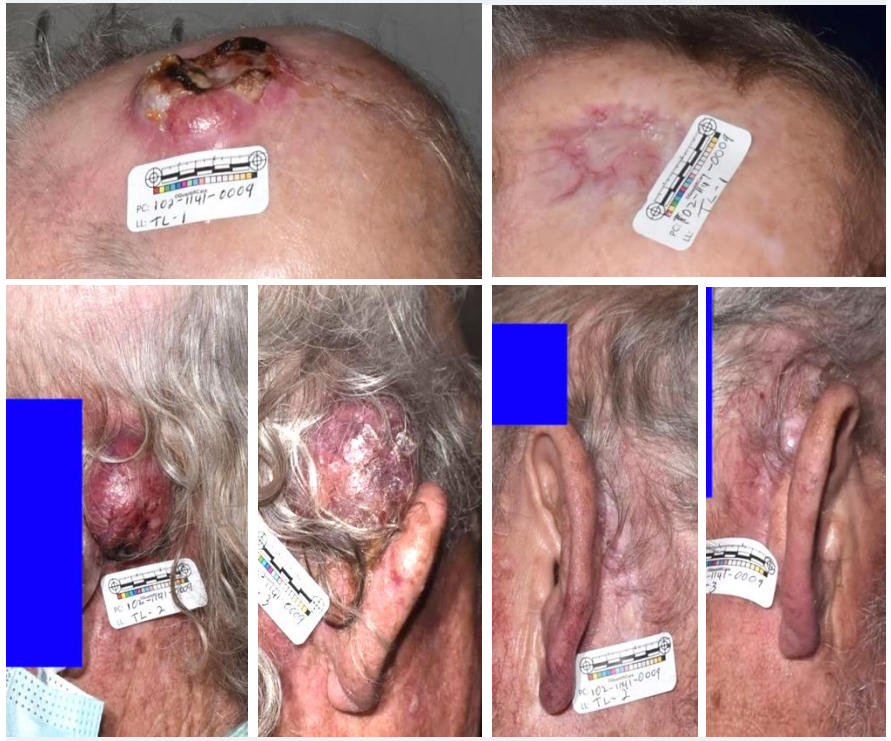
1140-0002

Baseline | 81 weeks



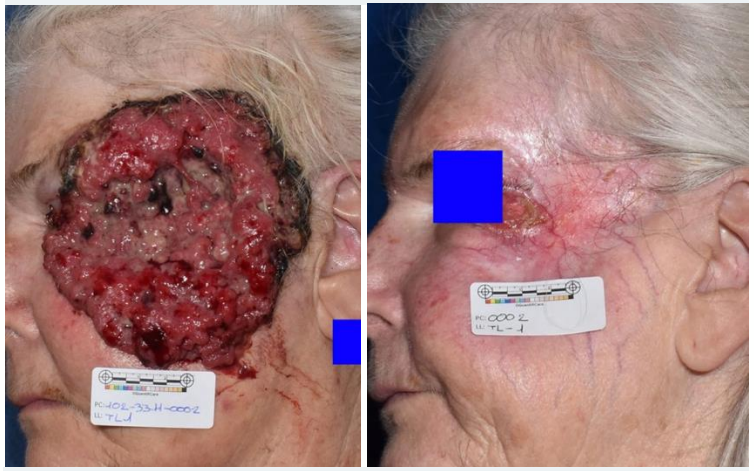
4805-0002

Baseline | 54 weeks



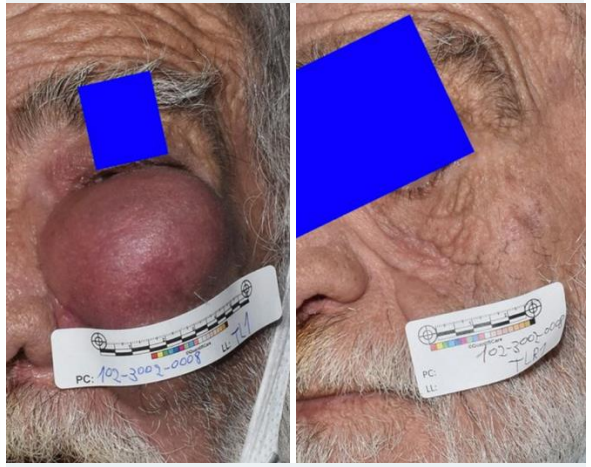
1141-0009

Baseline | 63 weeks



3311-0002

Baseline | 63 weeks



3002-0008

RP1 Commercial Opportunity

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

RP1 near-term opportunity

Anti-PD1-failed melanoma

~13K patients[1]

1L prior adjuvant

2L+ BRAF WT

2L+ BRAF MT

GOAL

Address high unmet need in anti-PD-1 failed settings

Potential NMSC* access via compendia+

~11K patients[2]

1L CSCC

SOT NMSC

Anti-PD1 failed

Immuno-compromised (other)

GOAL

Improve upon the SOC either as combo or as monotherapy

Future growth driver

Neoadjuvant skin cancers**

~45K patients

Neoadjuvant CSCC

Neoadjuvant melanoma

GOAL

Improve cure rates in early-stage patients

~70,000 treatable patients in the US

"Opportunity to change the treatment paradigm and ensure all appropriate patients can benefit from RP1"

+Spontaneous use will not be promoted

Source: [1]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. [2]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

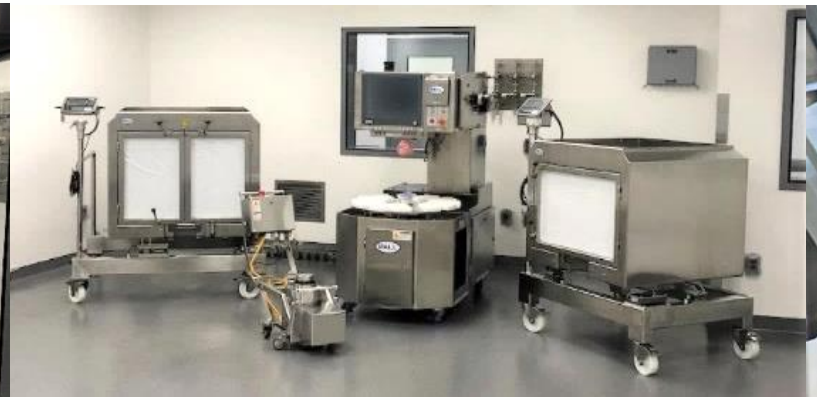
- RP1+nivolumab is well positioned to be the first option for melanoma patients who progress on a PD1-based regimen (in adjuvant or 1L setting), given:
  - Deep & durable responses
  - Safety profile
  - Ease of administration
- RP1+nivolumab provides a potentially compelling option for a broad range 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

*Source: IPSOS Oncology Monitor (chart audit, 2023) and Replimune primary market research

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

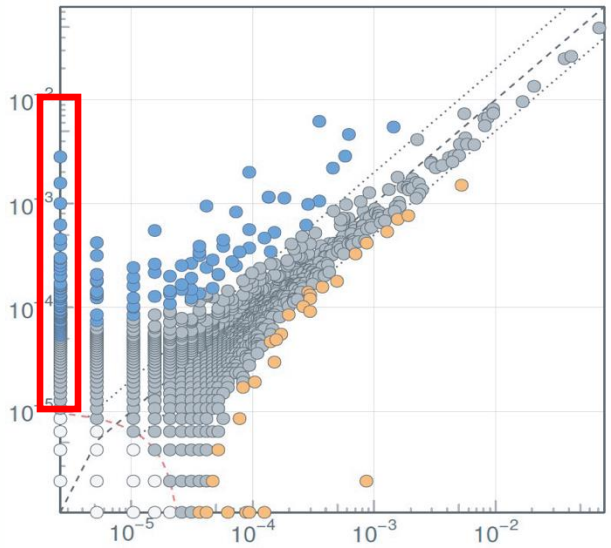


RP2: Focused on Rare Cancers

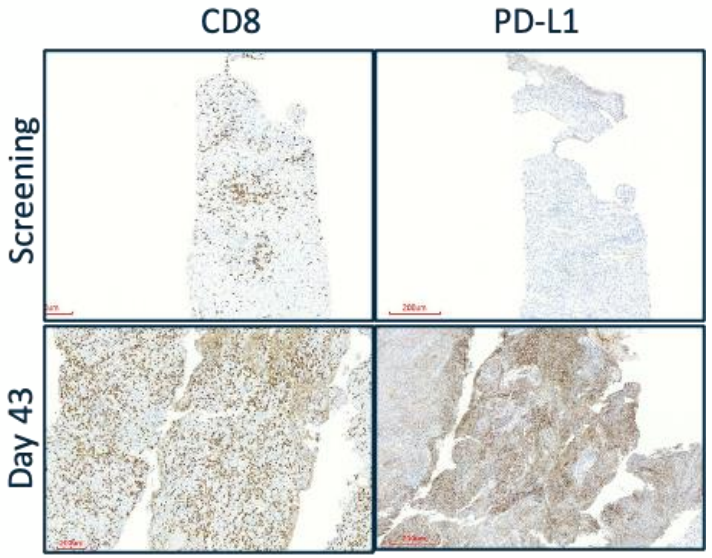
RP2: Fusion Enhanced Oncolytic HSV Expressing Anti-CTLA-4

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)*

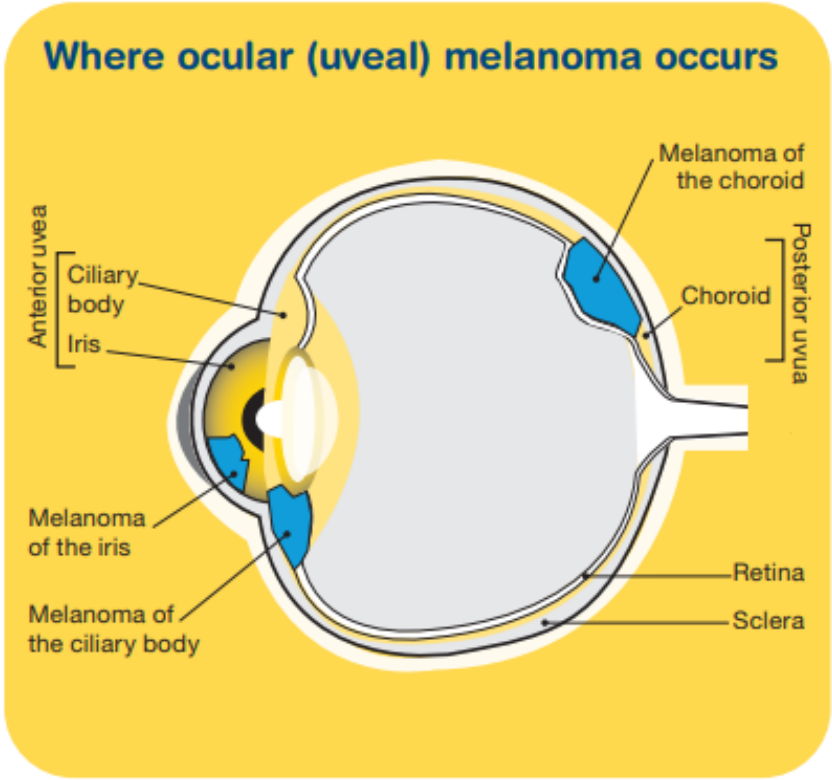
*Bommareddy P et al AACR 2024, # https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4400238/

Uveal Melanoma and Unmet Need

- Ocular or “uveal” melanoma is a rare cancer with approx. 1,000 cases in the US per year[1]
  - The historic median OS is approx. 12 months[1]

- 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[2,3,4]
  - 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



[1]Carvajal RD et al. Br J Ophthalmol 2017; [2]Nathan P et al. N Engl J Med. 2021;385(13):1196-1206; [3]PelsterMS et al. J Clin Oncol. 2021;39(6):599-607; [4]Lukzky J et al SMR 2022; [5]Sacco et al, 20th 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)[a] months

	RP2 monotherapy (n = 3)	RP2 + nivolumab (n = 14)	Total (N = 17)
Best overall response, n (%)			
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[b]	1 (33.3)	1 (33.3)	2 (11.8)
ORR (CR + PR)	**1 (33.3)**	**4 (28.6)**	**5 (29.4)**
DCR (CR + PR + SD)	**1 (33.3)**	**9 (64.3)**	**10 (58.8)**

HLA-A*02:01 status	Positive (n = 6)	Negative (n = 11)	Total (N = 17)
Best overall response, n (%)			
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

[a]From first dose to disease progression; response is ongoing. [b]Two patients died before any assessment.
CR, complete response; DCR, disease control rate; DOR, duration of response; HLA, human leukocyte antigen; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

ASCO 2024 Results: Safety Profile in Uveal Melanoma

Patients with TRAEs	Grade 1–2[a]	Grade 3	Grade 4–5
RP2 monotherapy (n = 3)	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
RP2 + nivolumab (n = 14)	13 (92.9)	6 (42.9)[b]	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.[a]Grade 1 or 2 TRAEs occurring in >10% of patients are shown.[b]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

Metastatic Uveal Melanoma

Immune-checkpoint inhibitor naïve

≤1 prior line

Randomized 1:1

RP2 + Nivolumab (n=140)

Ipilimumab + Nivolumab (n=140)

Dual Primary Independent Endpoints
Progression Free Survival
Overall Survival

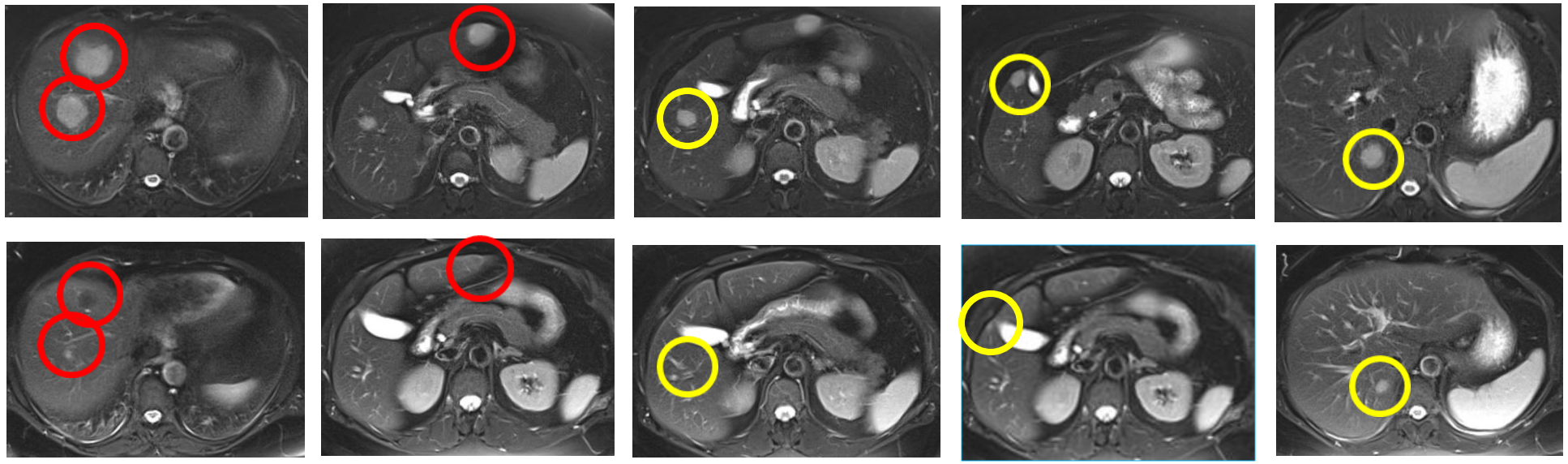
Key Secondary Endpoints
Objective Response Rate, Duration of Response and Disease Control Rate

Note : Go/No-Go safety/efficacy decision for phase 3 (after ~90 pts)

NCT04336241; https://clinicaltrials.gov/study/NCT04336241?a=6

Uveal Melanoma Patient Featured in ITV News

Prior nivolumab+ipilimumab – PR (RP2+nivolumab)



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)

BBC

Home News Sport Business Innovation Culture Travel Earth Video Live

Krzysztof's cancer is no longer detectable

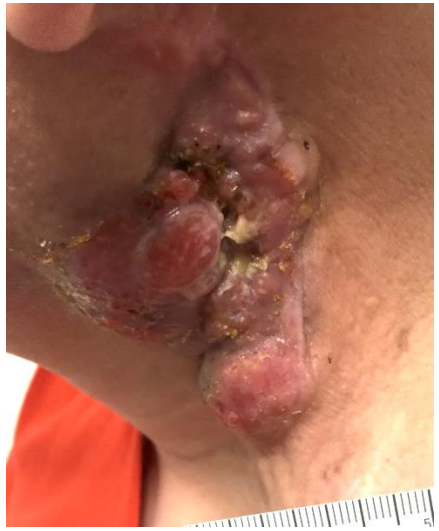
ICR The Institute of Cancer Research

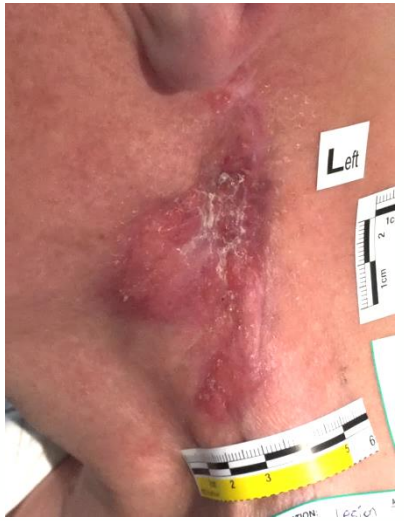
"My final lifeline"

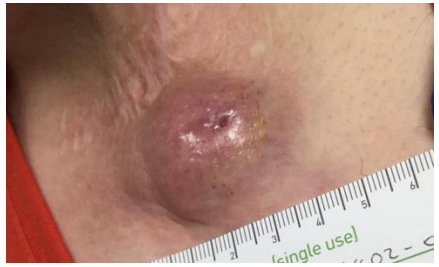
"I had injections every two weeks for five weeks which completely eradicated my cancer. I've been cancer-free for two years now."

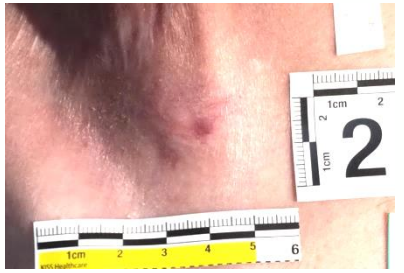
1 month

4 months







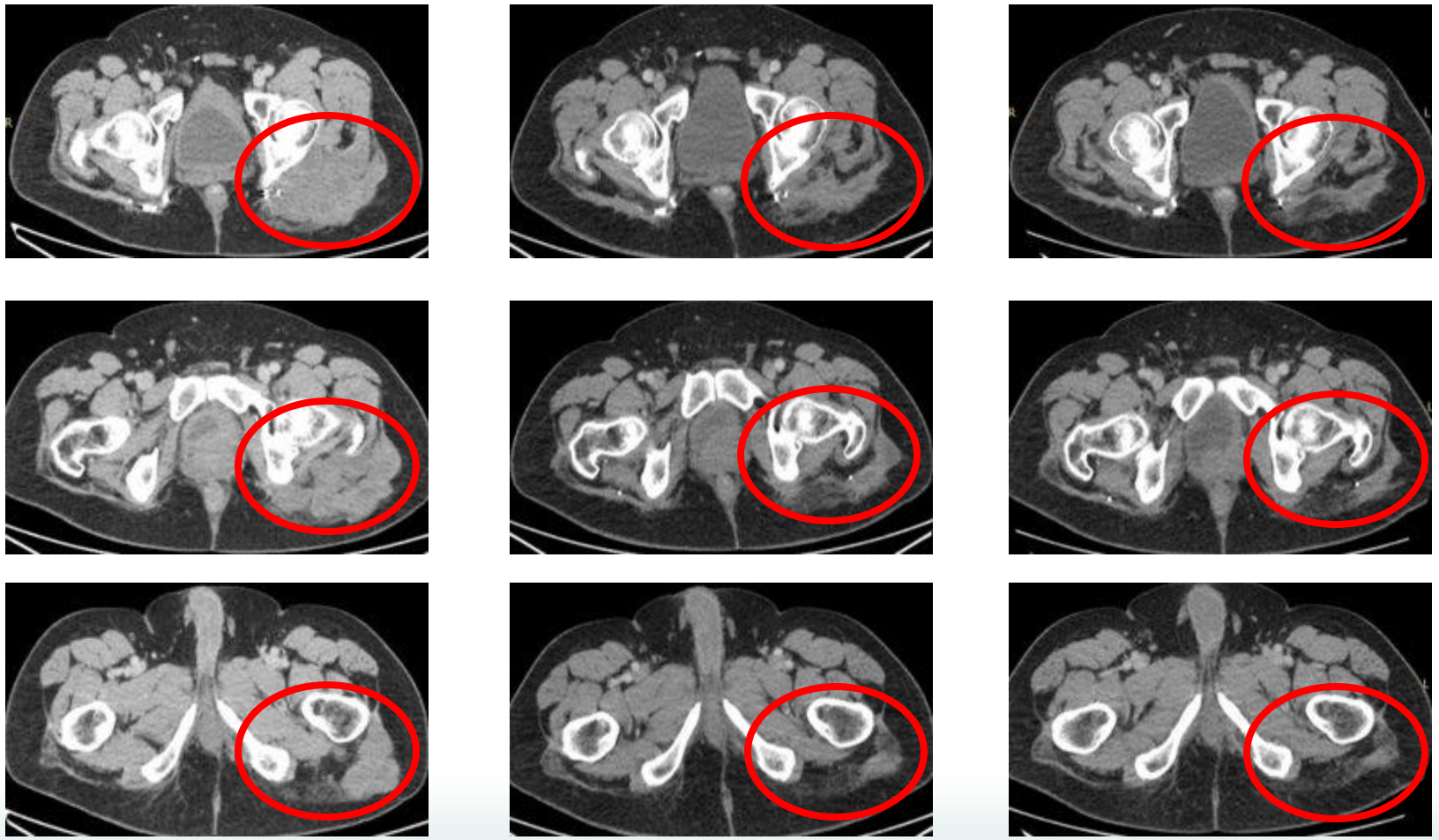


"It's a true miracle, there is no other word to describe it. I've been able to work as a builder again and spend time with my family, there's nothing I can't do."

RP2 Monotherapy Patient with Chordoma

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

Screening | 3 months | 6 months



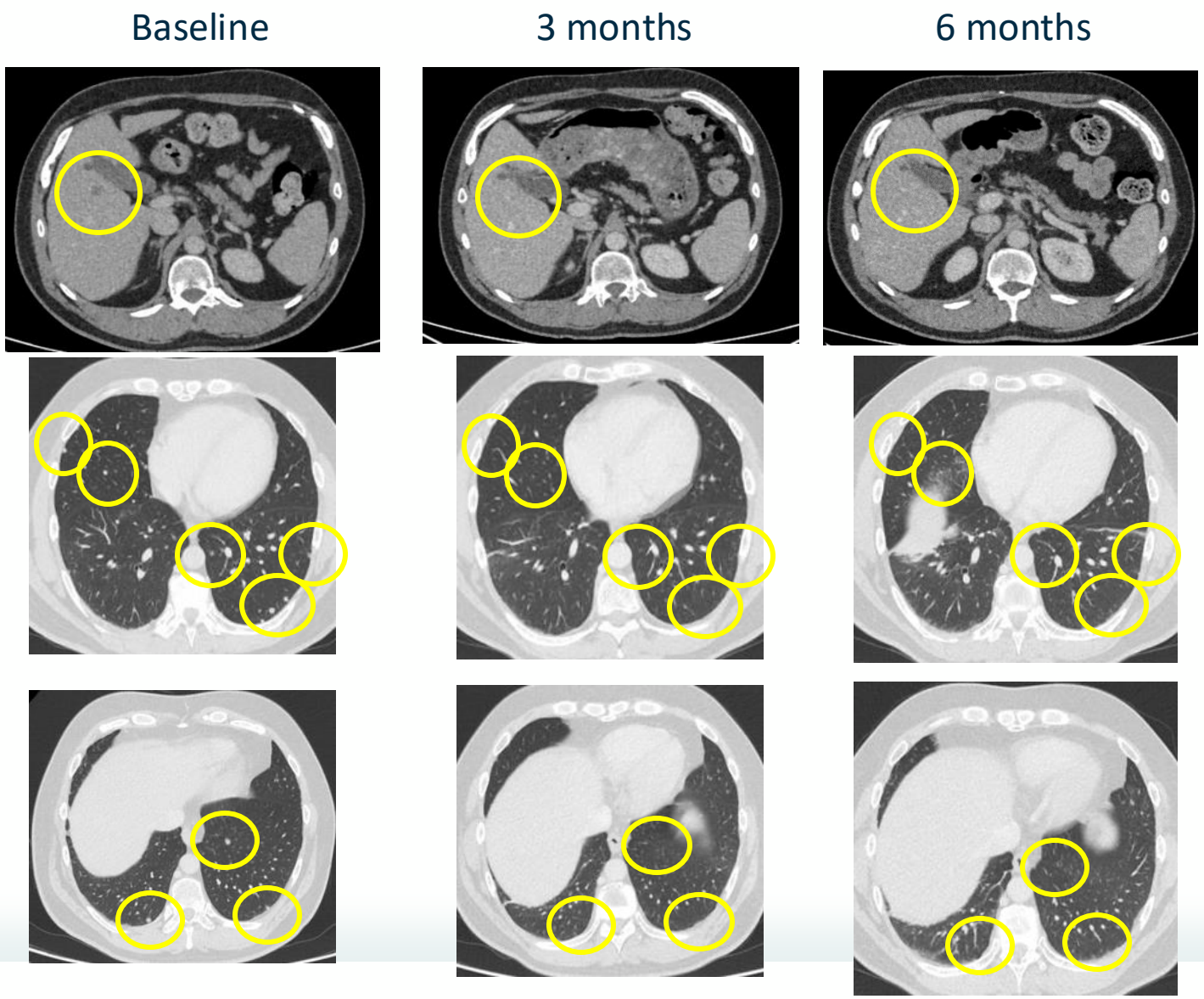
Pt 4401-0029 - ongoing PR

- 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)



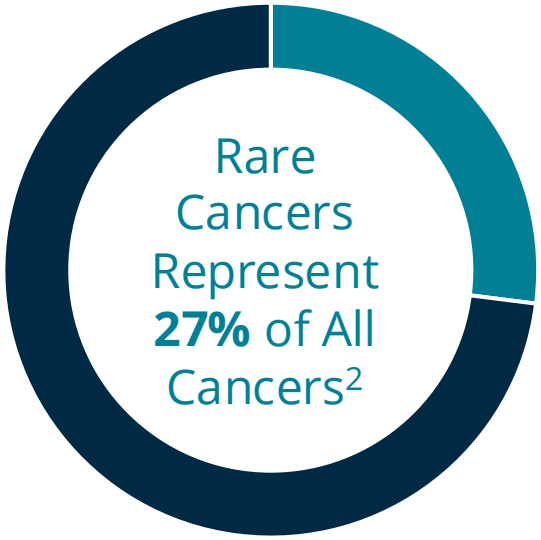
Pt 4401-0029 - ongoing PR

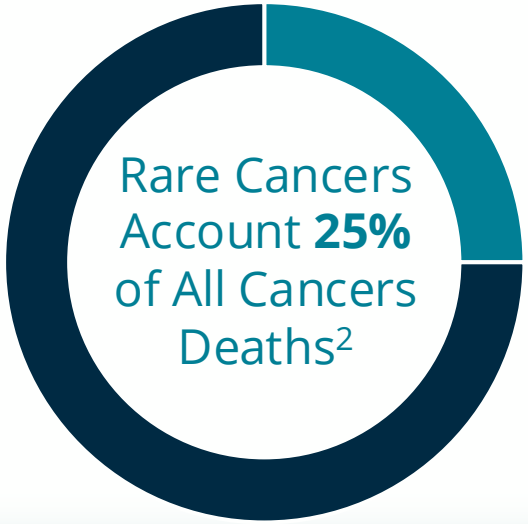
- Left gluteal muscle lesion injected
- Liver & >50 small lung lesions also disappeared during treatment

Injected *Un-injected*

Uveal Melanoma is the Foundation for a Potential Rare Cancer Franchise

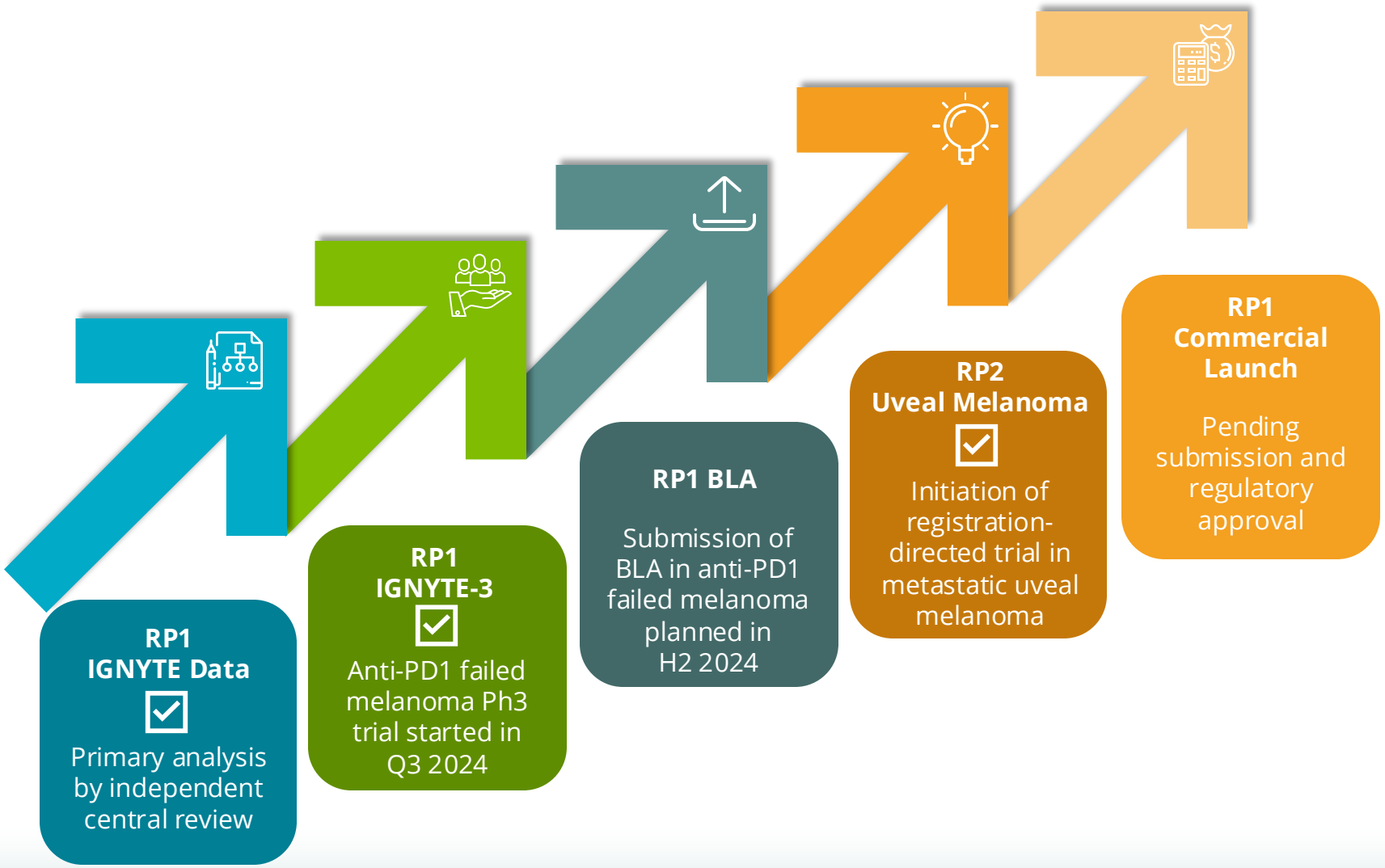
- Treatment with RP2 has led to responses in rare cancer settings including uveal, chordoma, and mucoepidermoid carcinoma[1]
  - Durable monotherapy and combination responses demonstrated in multiple immune insensitive tumor types[1]
- Rare cancers present a significant unmet need and potential for paths 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.)[1]





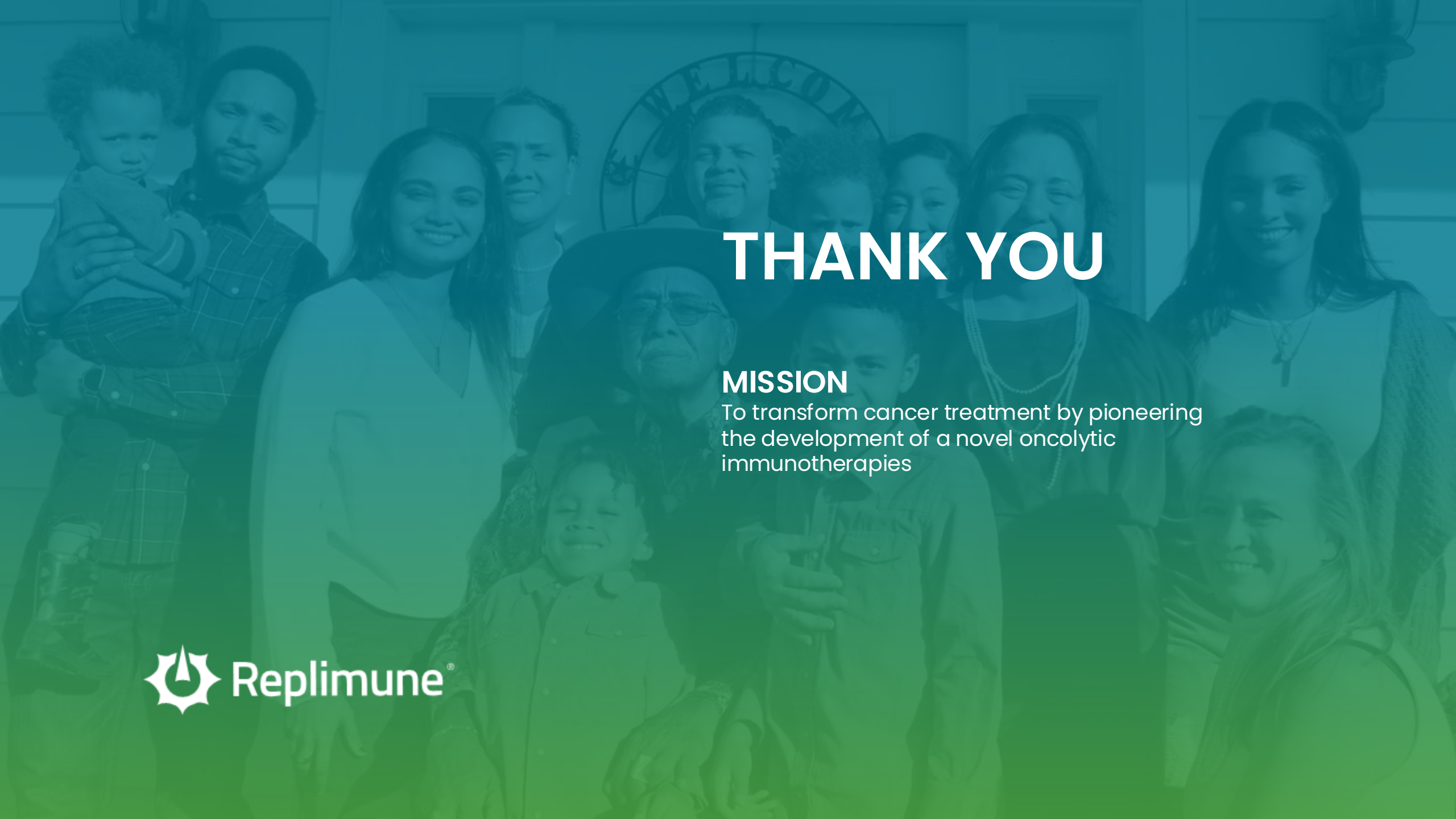
1) Data on file
2) https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/about-rare-cancers

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 oncolytic immunotherapies

Replimune®