Replimune®

Igniting a Systemic Immune Response to Cancer

JP Morgan

January 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, 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 the SARS-COV-2 coronavirus as a global pandemic and related public health issues, the ongoing military conflict between Russia and Ukraine 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.

Replimune; Industry Leader in Oncolytic Immunotherapy

- **RP1 – activity across multiple skin cancers supports broad skin cancer strategy**
  - 140 patient registrational IGNYTE study in anti-PD1 failed melanoma
    - **~ 1 in 3 patients demonstrating durable response**
      - 100% of responses >6 months with median DOR >24 months
    - **BLA filing planned 2H 2024**
  - 211 patient 1L CSCC randomized controlled CERPASS study; primary analysis reported December 2023
    - Missed significance at P<0.025 for dual endpoints (ORR/CRR)
      - However, clear clinical benefit for RP1+cemiplimab was demonstrated
        - **CRR vs. cemplimab alone (38.1% vs 25.0%, p=0.040[1])**
        - Duration of response increased
  - Strong data in hard-to-treat solid organ transplant patients as **monotherapy**
  - Potential for the portfolio to deliver commercial revenues beginning in late 2025
- **RP2 has shown compelling monotherapy and combination activity**
  - Uveal melanoma RCT study in planning -> **potential for a rare cancer franchise**
- **Strong balance sheet** ~ $466m [(1)] as of 31 December 2023; runway into H2 2026

(1) Unaudited estimate

[1]Per the protocol p<0.025 is required for formal statistical success in CERPASS for CRR or ORR alone. *SOT=solid organ transplant

Oncolytic immunotherapy – mechanism of action

Injected tumor

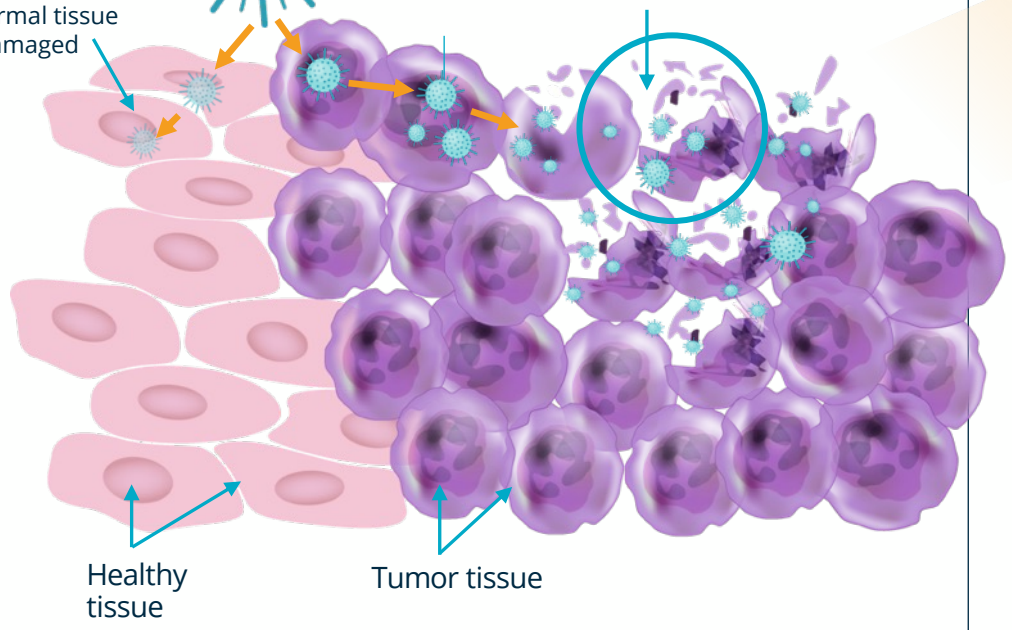
MECHANISM 1

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

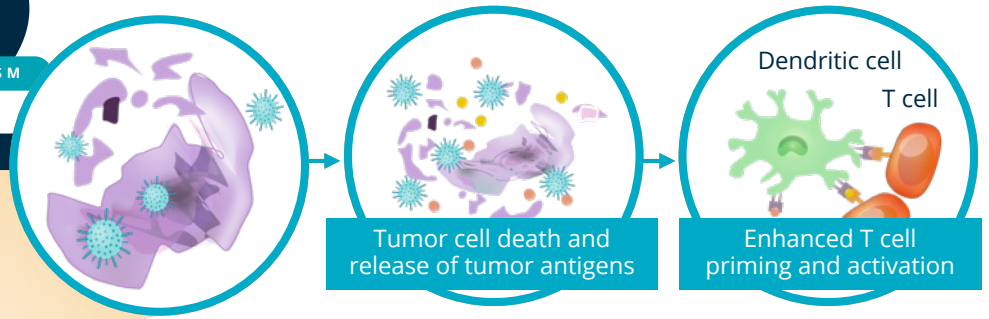


Healthy tissue

Tumor tissue

Immune response

MECHANISM 2



Release of virus progeny

Infection of more tumor cells

Tumor cell death and release of tumor antigens

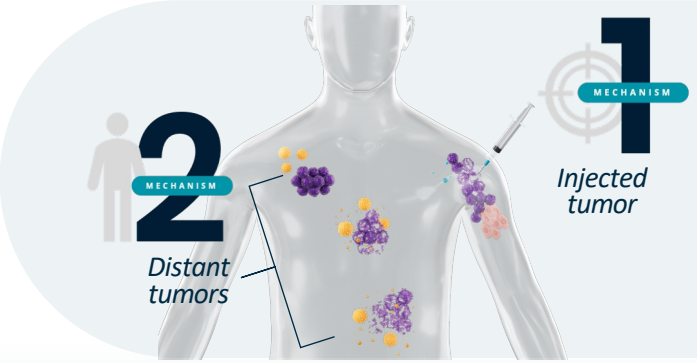
Local Inflammation

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



RPx positioning: Platform designed to address a range of tumor types with an optimal balance of potency & tolerability

	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 CSCC, 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

RP1: Establishing a major skin cancer franchise

IGNYTE RP1 + nivolumab in anti-PD1 failed melanoma registrational study data

Consistent ORR benefit across all subgroups

BOR n (%)	Prior cohort (n=16)	Anti-PD1 failed cohort (n=140)	All patients (n=156)						
			All patients (n=156)	Prior single agent anti-PD1 (n=84)	Prior combination anti–PD-1 & anti–CTLA-4* (n=72)	Stage IIIb/IIIc/IVa (n=76)	Stage IVb/c/d (n=80)	Primary resistance to anti-PD1 (n=91)	Secondary resistance to anti-PD1 (n=63)
CR	2 (12.5)	17 (12.1)	19 (12.2)	14 (16.7)	5 (6.9)	15 (19.7)	4 (5.0)	12 (13.2)	6 (9.5)
PR	4 (25.0)	26 (18.6)	30 (19.2)	16 (19.0)	14 (19.4)	14 (18.4)	16 (20.0)	19 (20.9)	11 (17.5)
SD	2 (12.5)	29 (20.7)	31 (19.9)^	21 (25.0)	10 (13.9)	18 (23.7)^	13 (16.3)	15 (16.5)^	16 (25.4)
PD	8 (50.0)	68 (48.6)	76 (48.7)	33 (39.3)	43 (59.7)	29 (38.2)	47 (58.8)	45 (49.5)	30 (47.6)
ORR	6 (37.5)	43 (30.7)	49 (31.4)	30 (35.7)	19 (26.4)	29 (38.2)	20 (25.0)	31 (34.1)	17 (27.0)

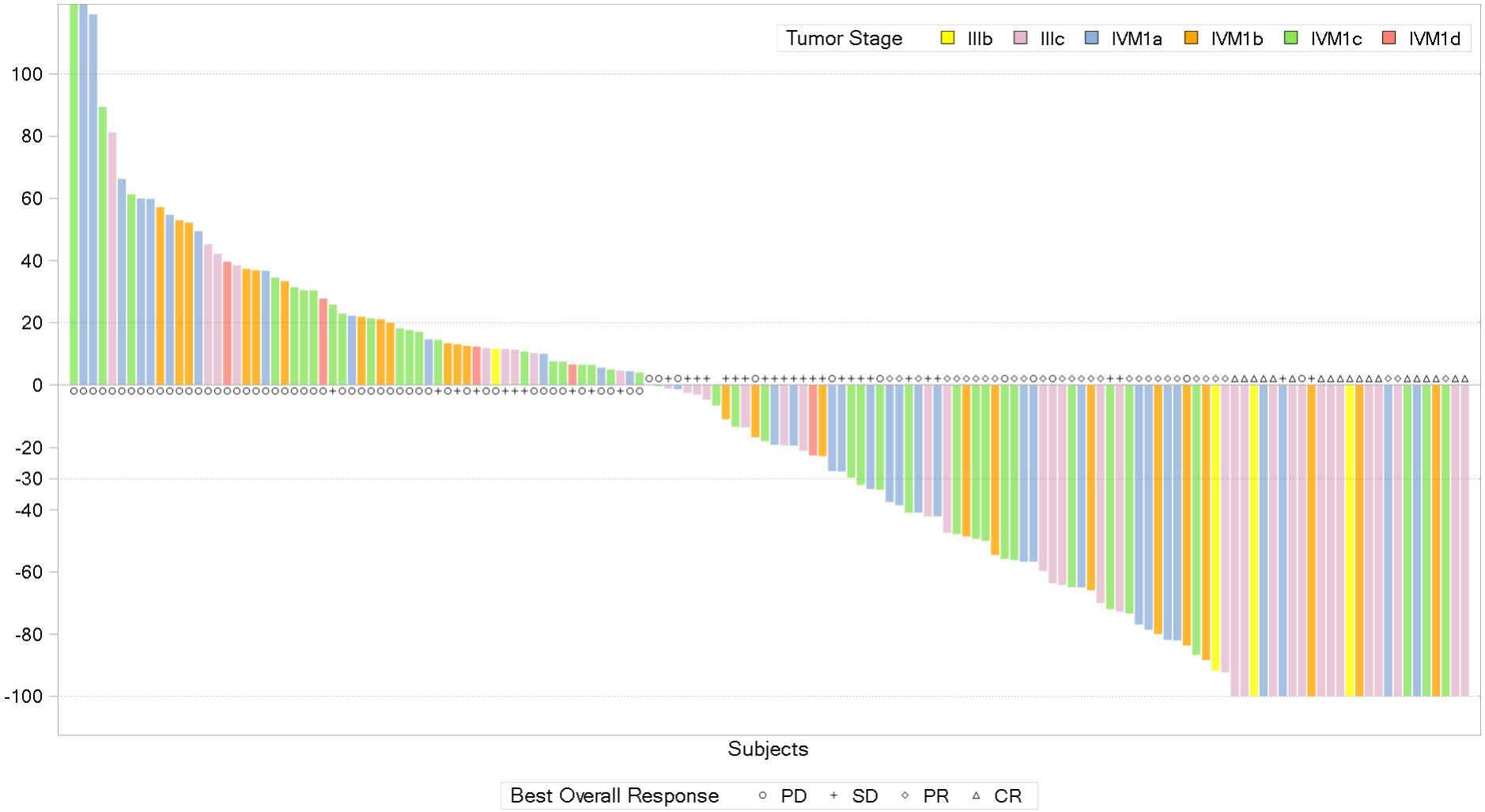
- 1 in 3 patients experienced a response
  - 26.4% ORR in hard-to-treat Ipi+Nivo failed patients (approx. 50% of the overall study population)
  - 100% of responses lasted >6 months, with median DOR >24 months

BOR=best overall response

^Includes 1 patient with a unconfirmed PR (uPR). **There are 5 patients still on study with the opportunity for response.**
Response data presented is by investigator assessment; the primary analysis from the study will be by blinded, independent central review.

Depth of response n=156

Maximum change in target lesions; patients with at least one follow up assessment

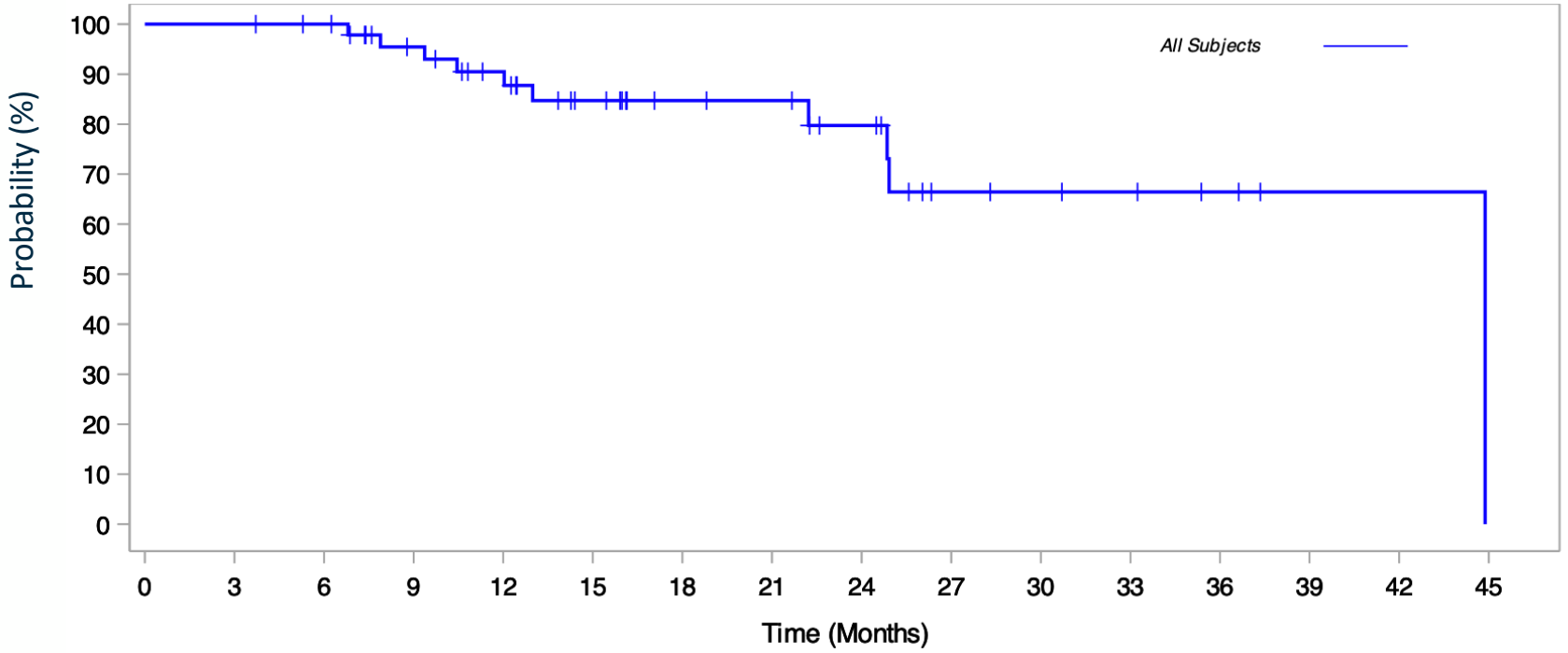


Key Takeaways

- 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

Patients with at least one post baseline assessment – target lesion response for each patient

Duration of response
(time from baseline to end of response for responders)



Key Takeaway

Responses are highly durable, with median DOR >24 months

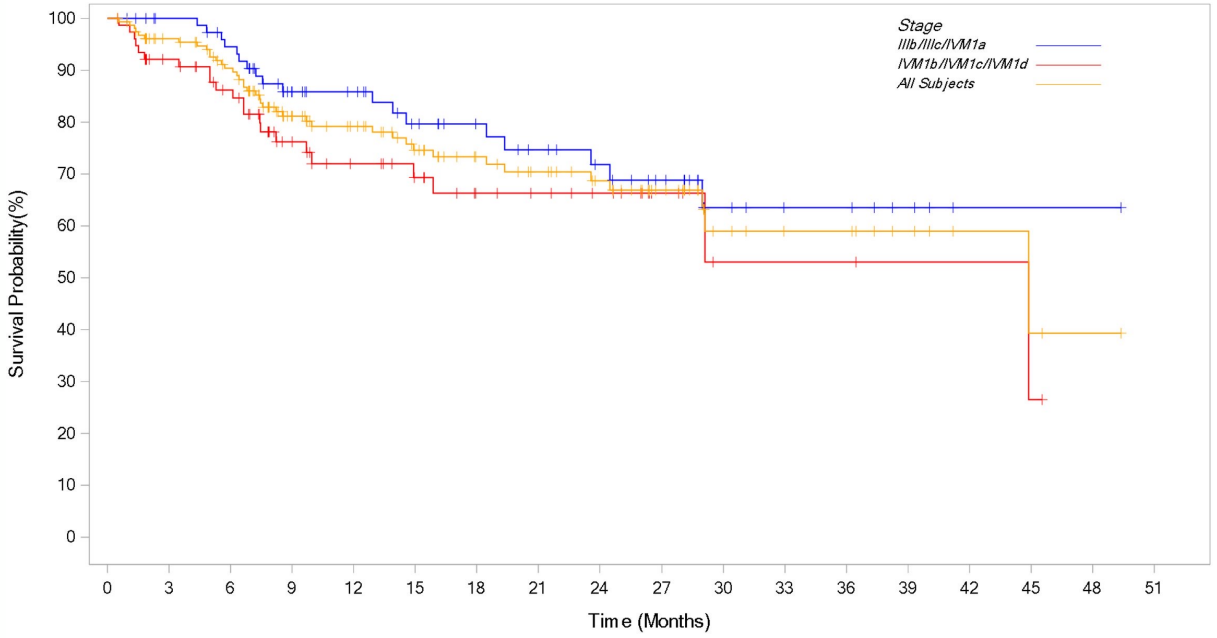
>6 months	>12 months	>18 months	>24 months
100%	90.5%	84.7%	79.7%

All patients have at least 6 months follow up, median follow up is 88.21 weeks

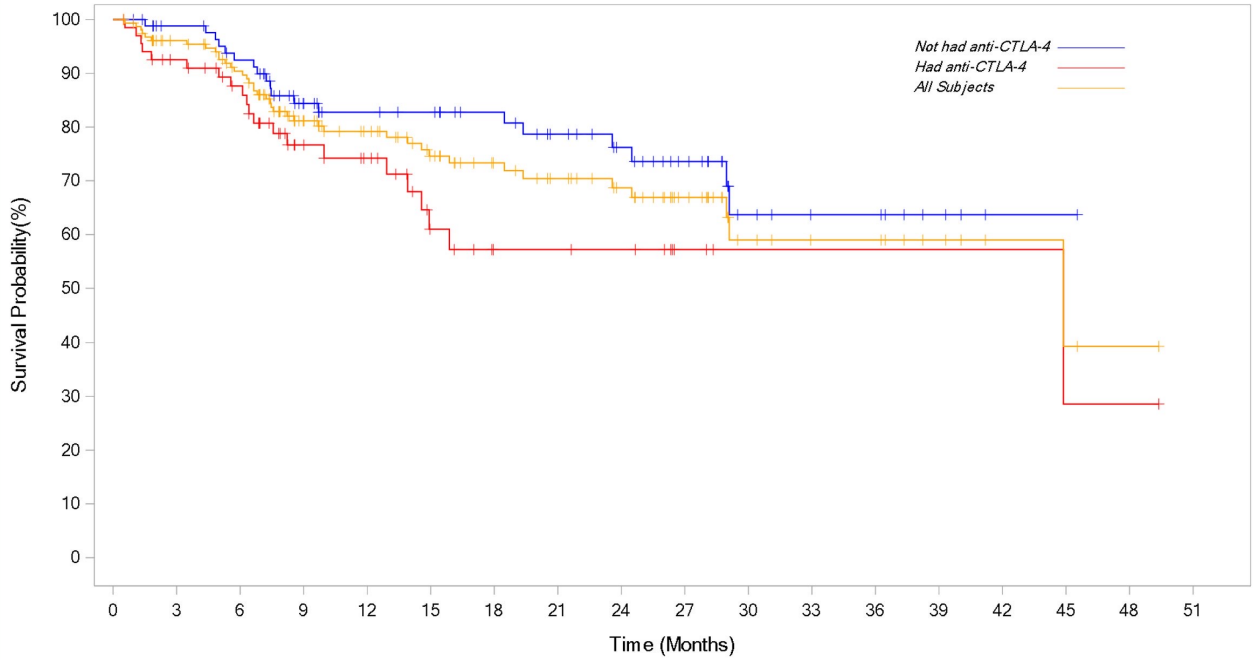
Promising OS is seen across disease subsets, including those with the greatest unmet need

Replimune®

Stage IIIb/IIIc/IVM1a vs Stage IV M1b/c/d



Prior anti-CTLA-4+anti-PD1 vs prior anti-PD1 alone



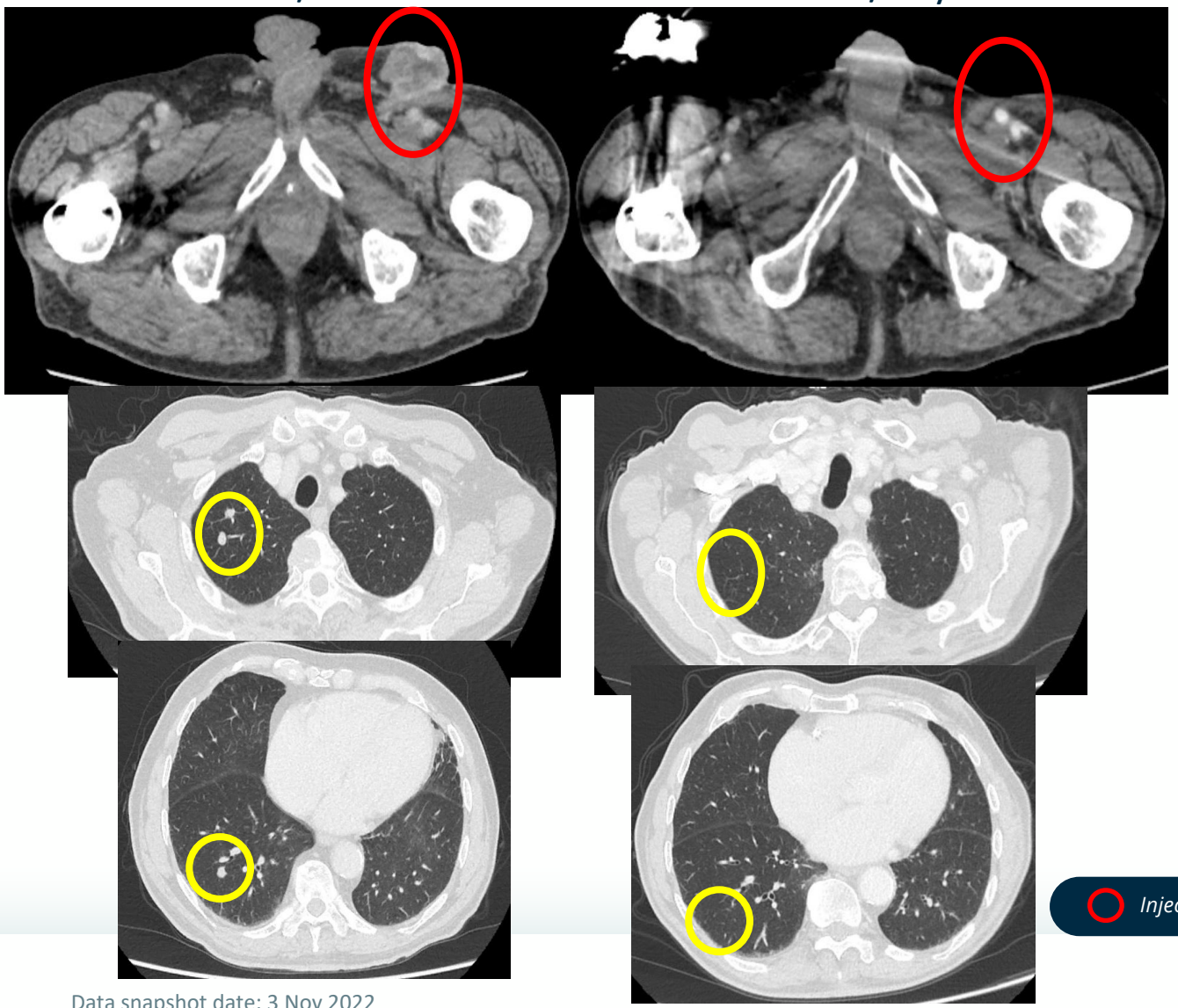
All patients have at least 6 months follow up, median follow up is 88.21 weeks

Patient 4401-2021: Prior Tafinlar/Mekinist, Keytruda

Prior BRAF/MEK as well as progressed on anti-PD1 Stage IVM1c

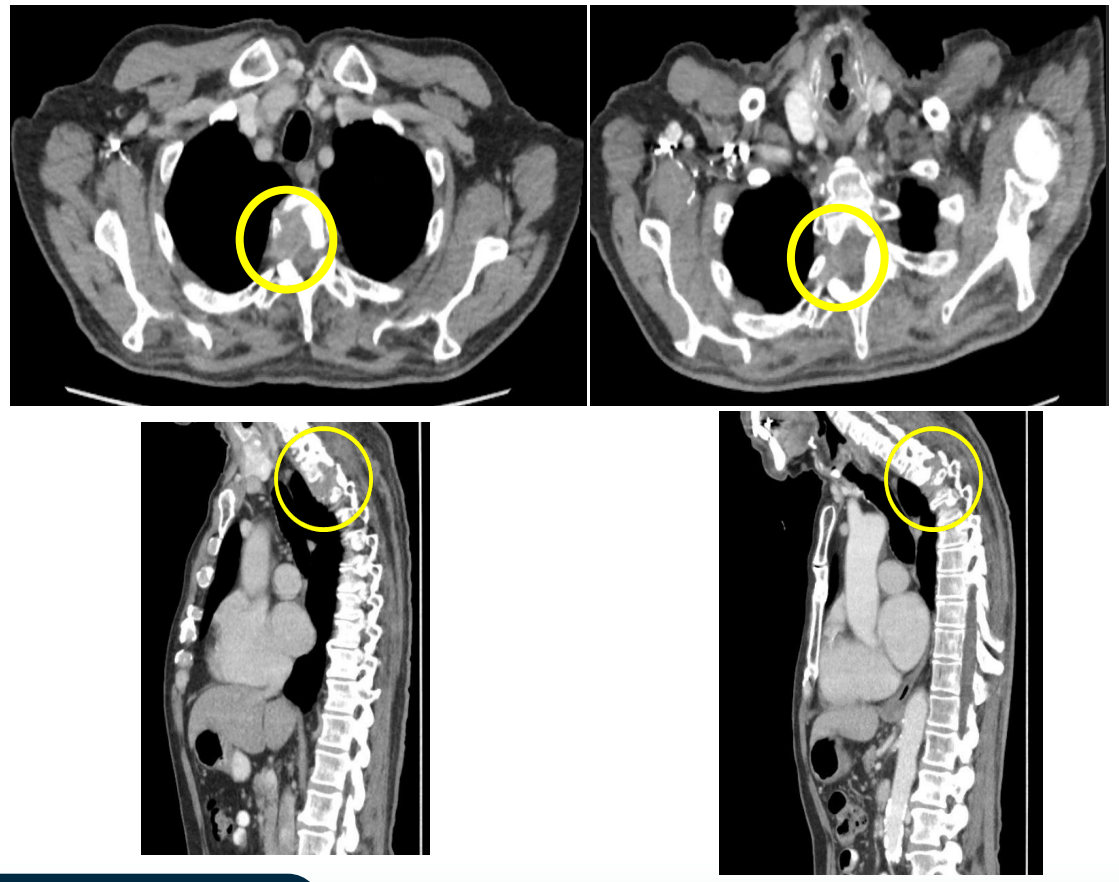
12JAN2021/Baseline

15FEB2022/Day 368



12JAN2021/Baseline

15FEB2022/Day 368



Injected

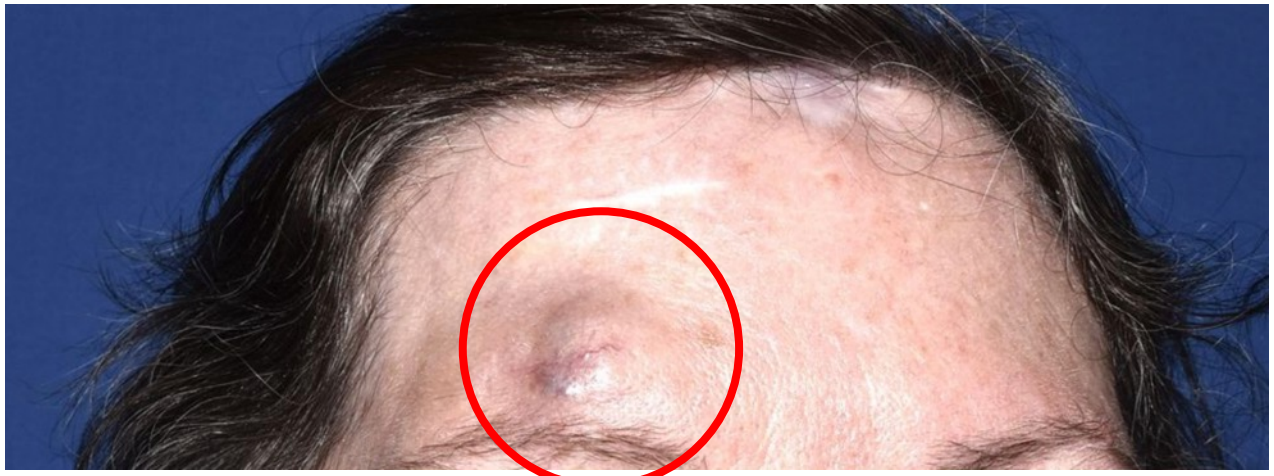
Un-injected

Data snapshot date: 3 Nov 2022

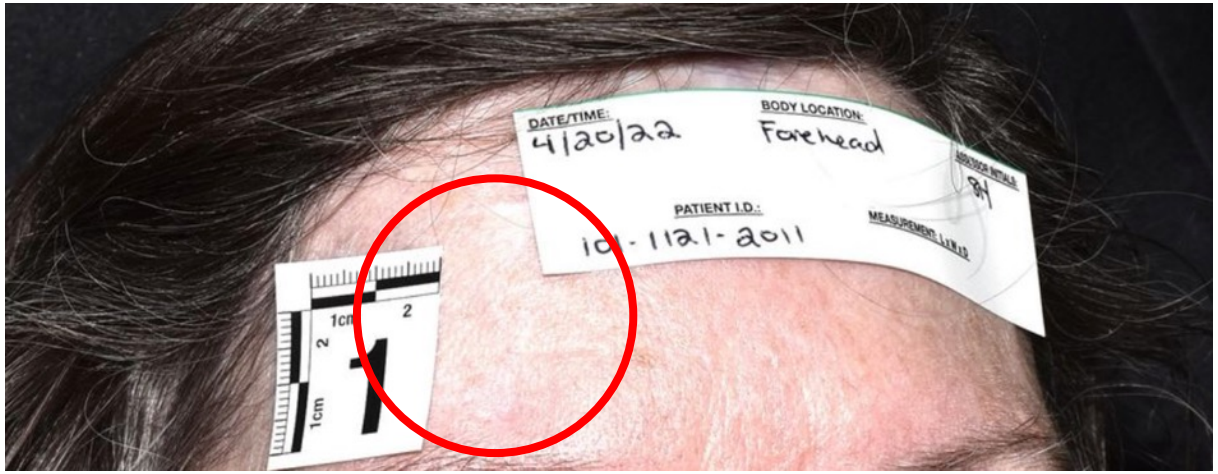
Patient 1121-2011:

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

29 JUL 2021 / Screening



20 APRIL 2022



Injected Un-injected

Patient 1121-2011 Cont'd:

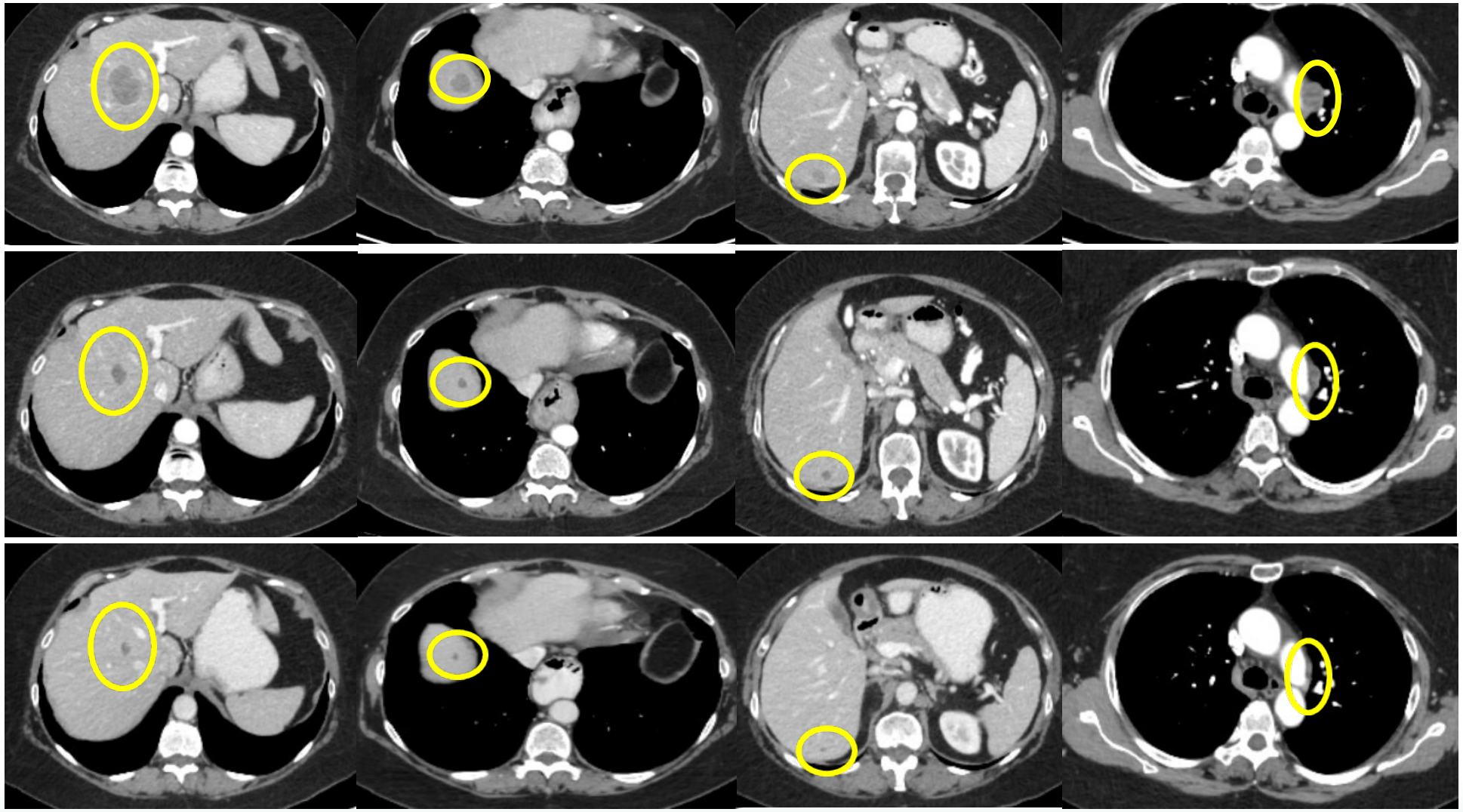
Prior Opdivo (adjuvant) and Keytruda (first line for metastatic disease), Stage IVM1c

Replimune®

22 Jul 2021/
Baseline

22 Sep 2021/
Day 57

29 Dec 2021/
Day 155



Injected Un-injected

IGNYTE – Regulatory summary/next steps

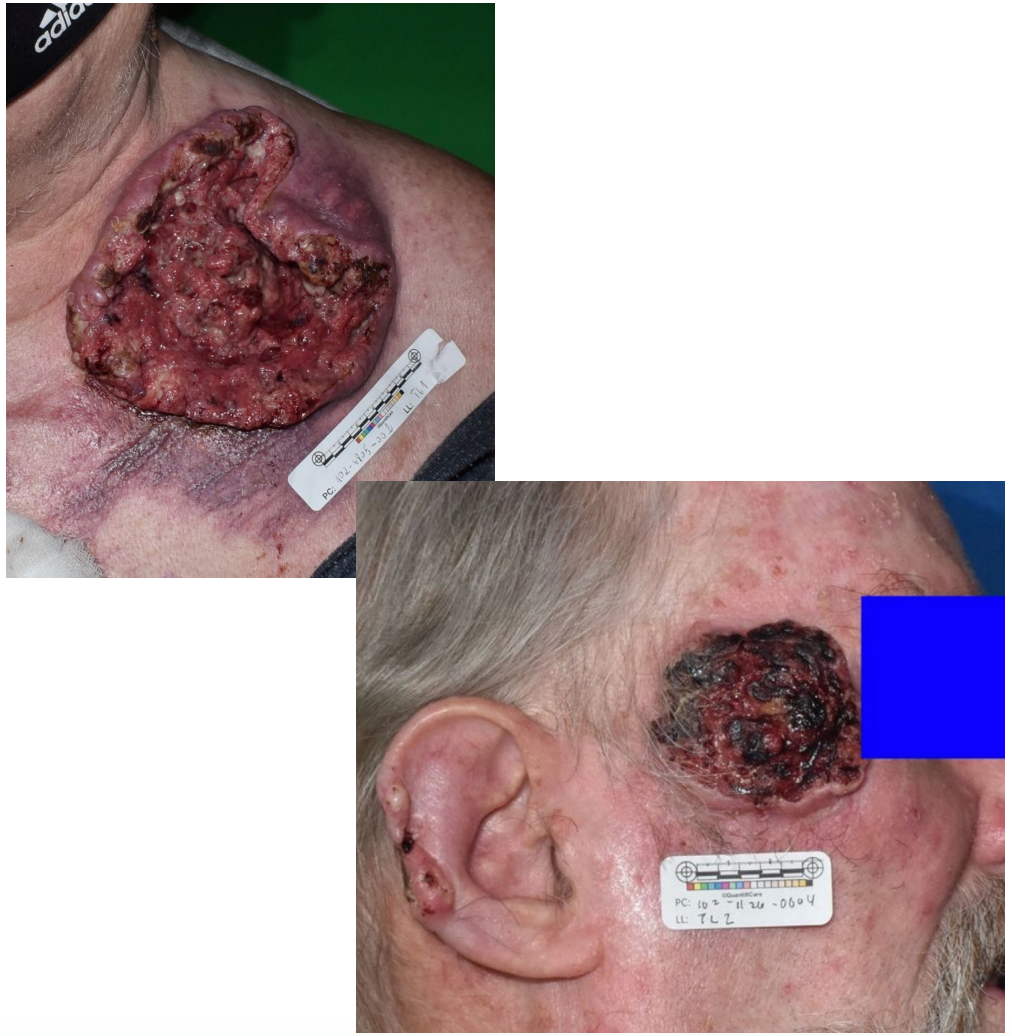
IGNYTE

IGNYTE FDA Type C meeting on anti-PD1 failed melanoma

- The FDA acknowledged that the IGNYTE population is one of unmet need
- The FDA agreed with a 2-arm randomized trial design in anti-PD1 failed melanoma with physician's choice as a comparator arm in the study population
  - The study should be underway at time of BLA submission
- A BLA submission for anti-PD1 failed melanoma is planned for 2H 2024 pending
  - Centrally reviewed data by RECIST v 1.1
  - All patients followed for at least 12 months (which is the per protocol primary analysis timepoint)
  - All responding patients followed for at least 6 months from response initiation

CSCC disease characteristics and typical patient presentation

- **Second most common skin cancer** with ≈700,000 patients annually in the U.S.[1]
- **Approximately 7,000-15,000 US deaths** annually[1-3]
  - 80% of patients die from locoregional progression, not metastatic disease[4,5]
- Usually develops from precursor lesions (actinic keratosis) but may be *de novo;* ***m*ajority (80–90%) occur on the head and neck**
- **CSCC** is a predominately outward growing disease with large, painful, superficial tumors which **can impact quality of life and contribute to social isolation**
  - Disfiguring, painful
  - Foul smelling drainage
  - Delay in seeking medical care
- Anti-PD1 SOC **~ 50% ORR, ~ 15-25% CRR**



[1]Rogers et al JAMA Dermatol 10 2015;
[2]Clayman et al JCO 23 2005;
[3]Mansouri et al J Am Acad Dermatol 153 2017;
[4]Schmults et al JAMA Dermatol 149 2013;
[5]Motaparthi et al Adv Anat Pathol 24 2017

CERPASS registration-directed Ph2 study in CSCC

Key Eligibility Criteria:

- Locally-advanced/metastatic CSCC
- ECOG PS 0 or 1
- No active autoimmune disease
- No prior treatment with a PD-1/PD-L1 inhibitor
- No untreated brain metastases

2:1
N=211

RP1 IT Q3W x 8 doses†
($1x10^6$ PFU/mL for one dose followed by $1x10^7$ PFU/mL for 7 doses)
+
Cemiplimab 350mg Q3W IV

Cemiplimab 350mg Q3W IV

57 weeks treatment‡

3-year survival follow up

Key Endpoints

- **Dual independent primary endpoints: Complete Response Rate & Overall Response Rate***
  - Approx. 15% absolute difference in CRR and/or ORR required
  - Secondary endpoints: DOR, PFS, OS, disease-specific survival, safety/tolerability

**Note $p \leq 0.05$ is required if both dual primary endpoints hit for statistical success, if only one of the dual endpoint hits need a $p \leq 0.025$ is needed*

†First dose of RP1 to be given as monotherapy with cemiplimab to be given with second dose of RP1
‡57 weeks treatment for the combination arm; treatment duration for cemiplimab-only arm is 54 weeks

Confirmed ORR & CRR (ITT population)

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

- While ORR was similar between the arms, the number of patients who achieved a CRR was substantially increased with RP1+cemiplimab (P=0.04)
- In LA CSCC, there was a more than doubling of the CR rate for RP1+cemiplimab vs cemiplimab alone (48.1% vs 22.6%)
- CRs are the key driver of long-term clinical benefit in CSCC

*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

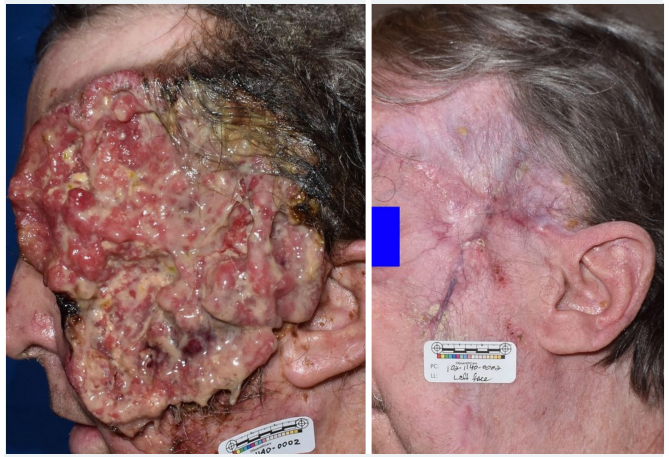
[1]Per the protocol p≤0.025 is required for formal statistical success in CERPASS for CRR or ORR alone and p≤0.05 if both endpoints were met

BOR=best overall response

Five of the most visually impactful CRs with RP1+cemiplimab

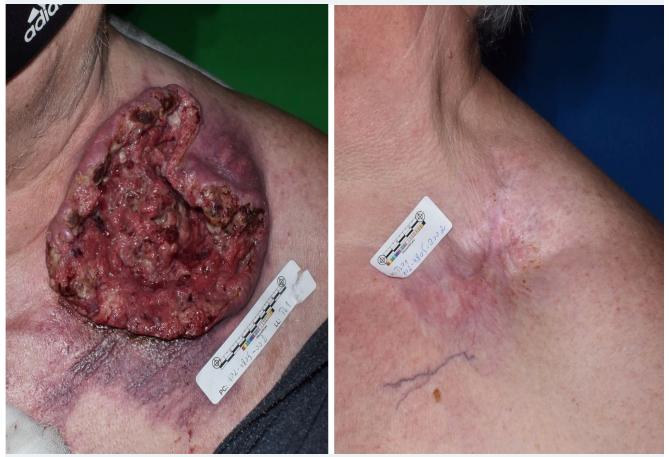
Replimune®

Baseline | 81 weeks



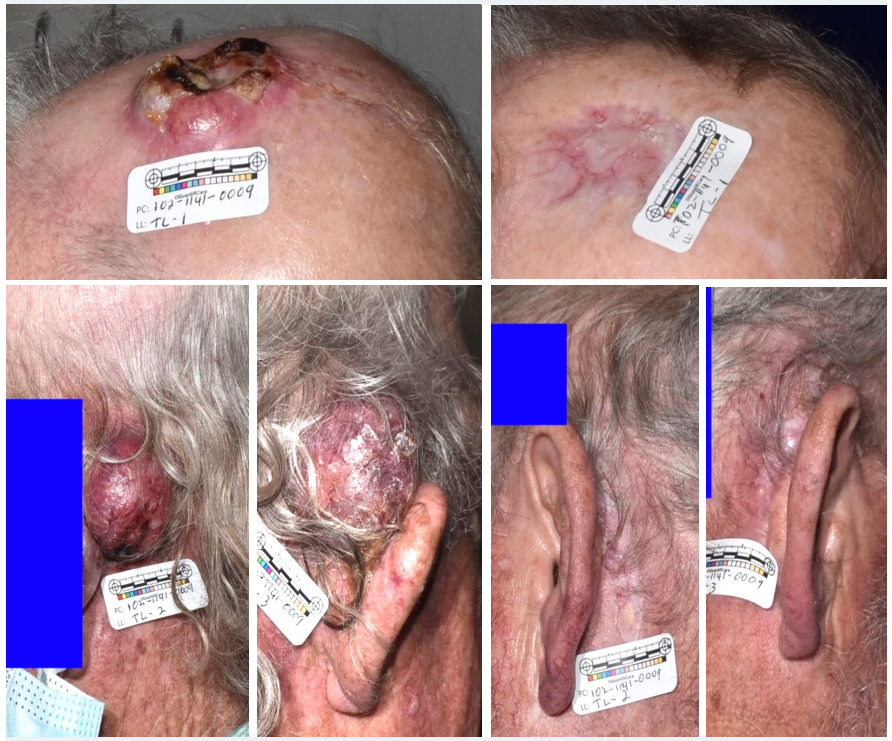
1140-0002

Baseline | 81 weeks



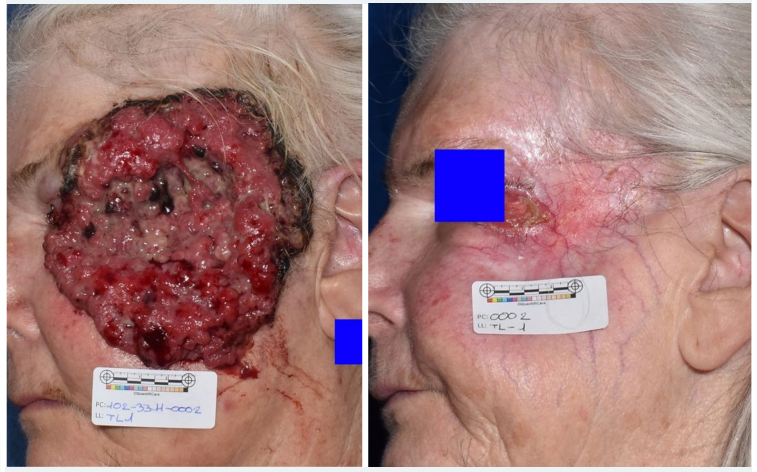
4805-0002

Baseline | 54 weeks



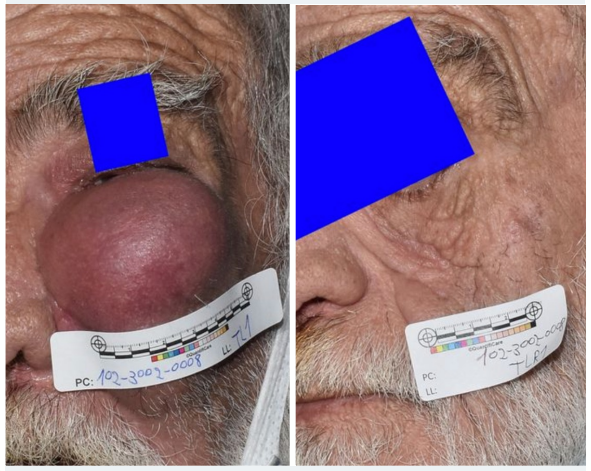
1141-0009

Baseline | 63 weeks



3311-0002

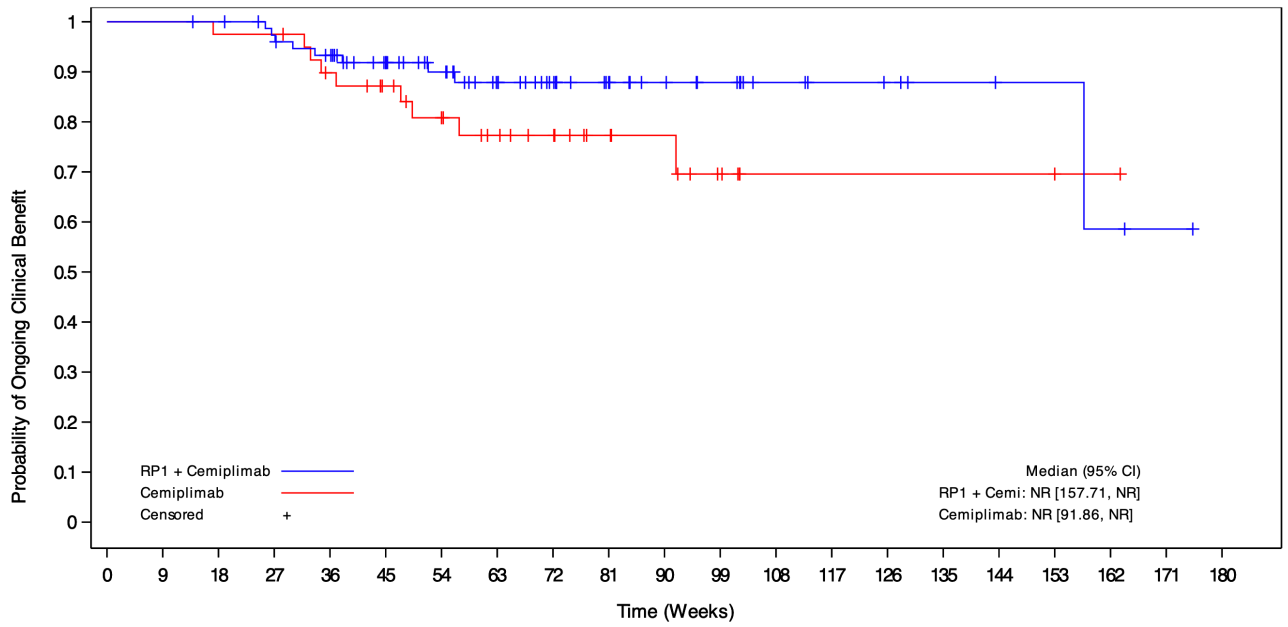
Baseline | 63 weeks



3002-0008

Duration of response (immature data)
Time from baseline to end of response for responders

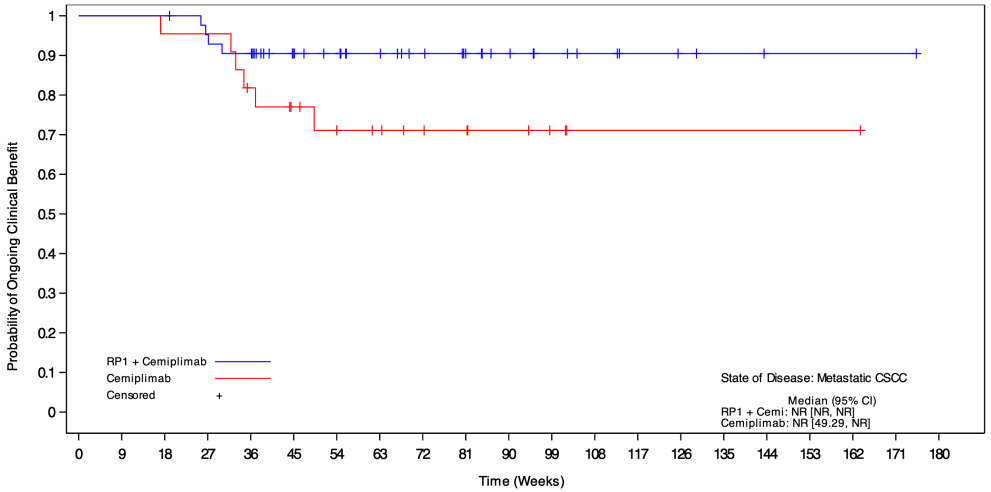
All responding patients



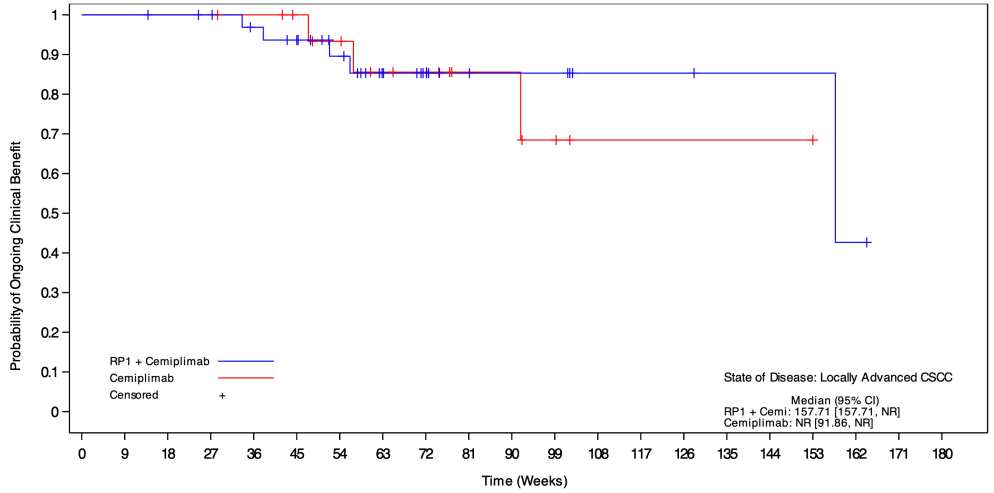
Number of subjects at risk:

RP1 + Cemi	78	78	77	73	68	58	48	37	29	22	17	14	9	7	6	4	3	3	2	1	0
Cemiplimab	40	40	39	39	34	29	25	20	17	12	10	6	2	2	2	2	2	2	1	0	

Metastatic patients



Locally advanced patients



Key Takeaway

Duration of response was improved with RP1+cemiplimab as compared to cemiplimab alone (HR 0.45 immature data). While the improvement is clear in metastatic disease, locally advanced patient data is currently too immature to draw conclusions. The study will continue to allow all endpoints to further mature, in particular for DOR, PFS & OS

CERPASS – next steps

CERPASS

- CERPASS missed its primary endpoints while demonstrating treatment effects suggesting clinical benefit
  - CR rate
  - Duration of response
- All time-based endpoints are immature (DOR, PFS and OS) and will be followed to maturity
- Mature data required to determine whether any filing or compendia listing strategy is warranted

Additional unmet needs in CSCC/NMSC

ARTACUS STUDY

- Treatment of high-risk immune compromised populations who develop skin cancers
- Anti-PD1 use can lead to loss of graft
- **RP1 monotherapy; 35% ORR (n=23)**

IGNYTE anti-PD1 failed NMSC

- No FDA approved options for anti-PD1-failed CSCC/NMSC; ~ 70% of treated patients still ultimately progress
- **RP1 + nivo 30% ORR (n=30)**

Lam JKS, et al. Head Neck. 2018;40:985-992.
Friman T, et al. Int J Cancer. 2022;150(11):1779-91.
Marin-Acevedo et al Cancers 2023, 15(12), 3180

RP1 Commercial Opportunity

Significant opportunity to establish a broad skin cancer franchise built upon strong foundation in melanoma

Replimune®

RP1 near-term opportunity is significant

Anti-PD1-failed melanoma

~13K patients[1]

1L prior adjuvant
2L+ BRAF WT
2L+ BRAF MT

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)

Ability to improve the SOC either as combo or as monotherapy

Future growth driver

Earlier stage skin cancers**

~45K patients

Neoadjuvant CSCC
Neoadjuvant melanoma

Improving 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"

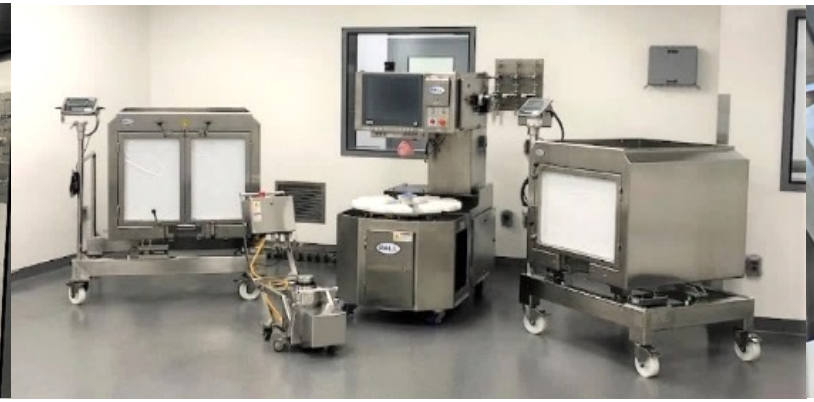
+Spontaneous use will not be promoted

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

Investment in manufacturing to support full commercialization

Commercial scale in-house manufacturing established

- 63,000 square foot state-of-the-art facility for GMP manufacturing
  - *RP1-2 technology transfer from CMO successfully completed*
  - *RP1 released to clinic post comparability analysis*
  - *RP1 BLA consistency lot runs complete*
- Scale expected to be sufficient to cover global commercialization of all Replimune's product candidates at full capacity
- Commercially attractive cost of goods & 'off the shelf' product practicality



RP2 update

RP2 leverages Replimune's platform to express anti-CTLA-4

- Anti-CTLA-4 prevents immune blockade at the APC / T cell interface
  - Anti-CTLA-4 is clinically validated; Ipilimumab, tremelimumab
- **RP2 has shown durable mono-therapy responses in multiple immune insensitive tumor types**
  - Salivary gland cancer
  - Chordoma
  - Uveal melanoma
  - Esophogeal cancer
- **30% ORR (N=17) in 2L uveal melanoma with impressive duration**
  - Randomized control trial planned ; foundation of rare disease strategy
    - Rare head and neck cancers
    - Sarcomas
    - HPV associated ; vulvar, anal

Mucoepidermoid carcinoma patient featured in BBC news

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

BBC

Home News Sport Business Innovation Culture Travel Earth Video Live

Krzysztof's cancer is no longer detectable

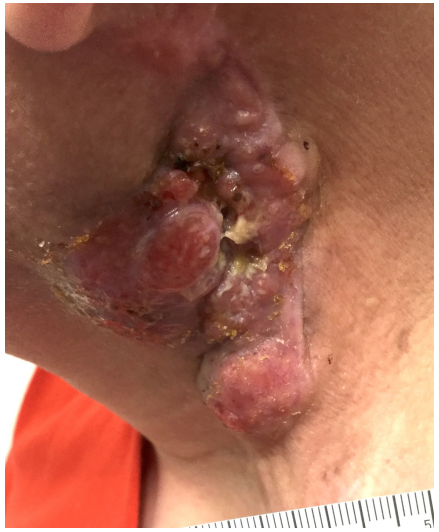
ICR The Institute of Cancer Research

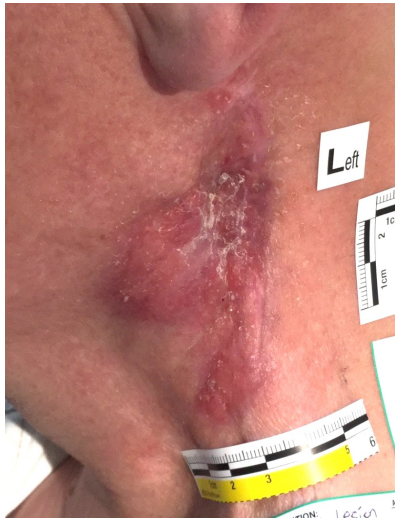
"My final lifeline"

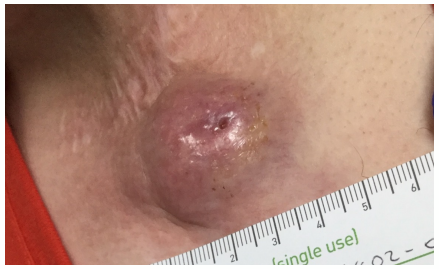
"I had injections every two weeks for five weeks which completely eradicated my cancer. I've been cancer-free for two years now."

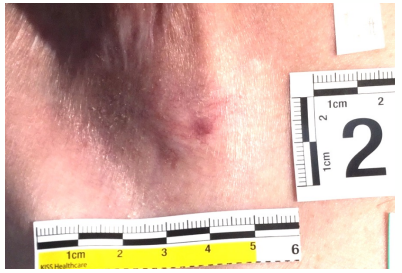
1 month

4 months







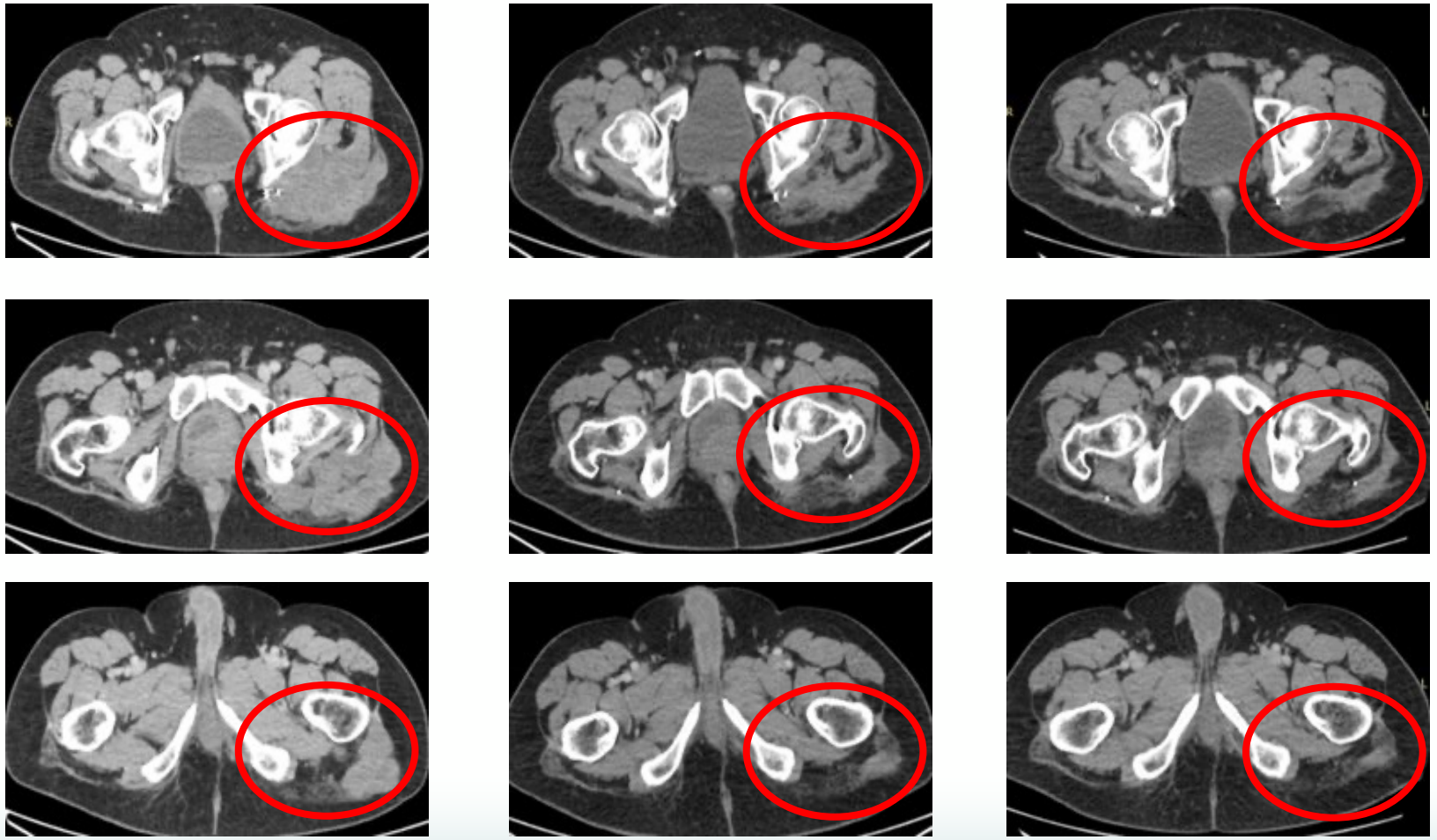


"It's a true miracle, there is no other word to describe it. I've been able to work as a builder again and spend time with my family, there's nothing I can't do."

Patient 4401-0029: Chordoma

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

Screening | 3 months | 6 months



Pt 4401-0029 - ongoing PR

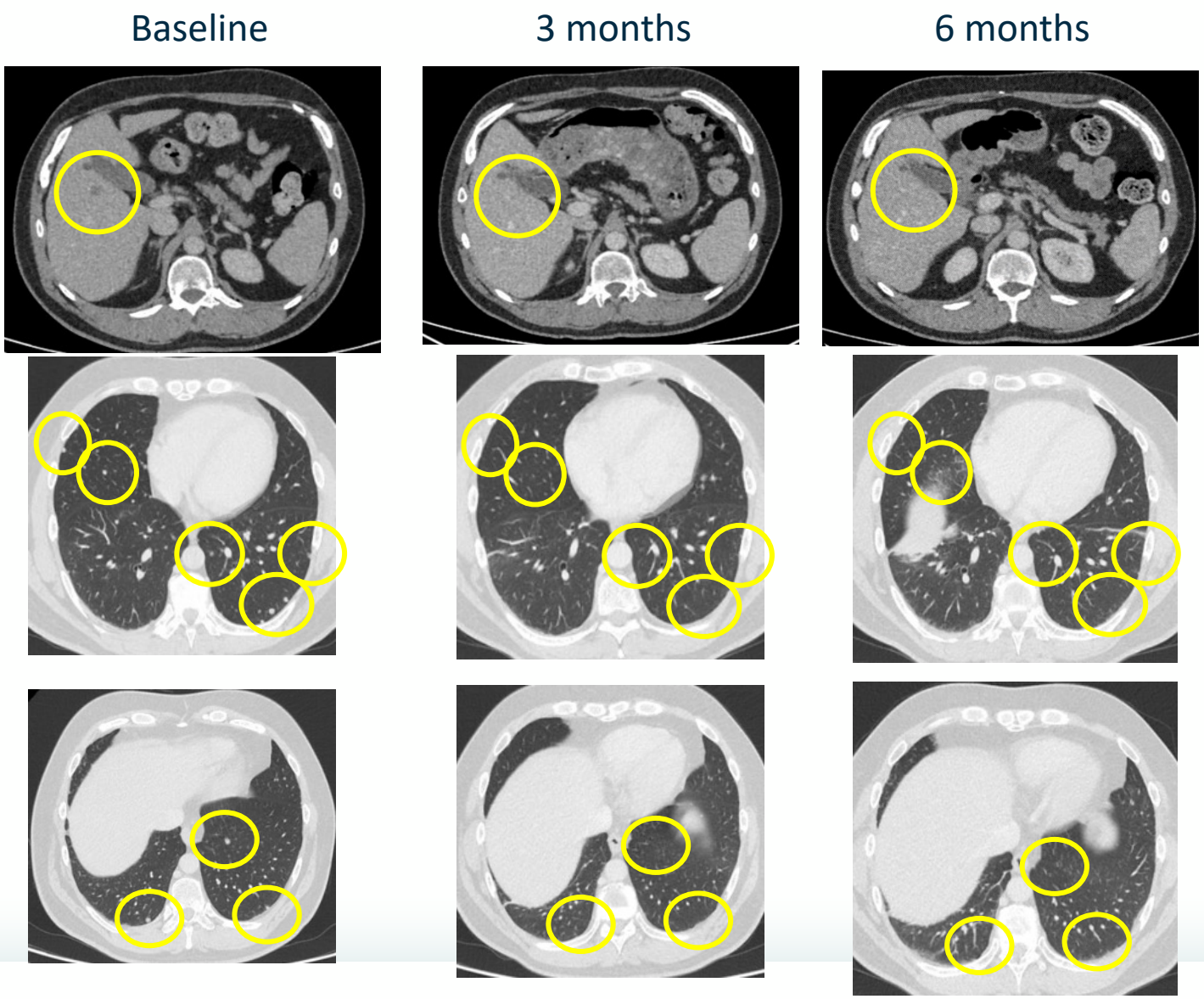
- Left gluteal muscle injected
- Liver & >50 small lung lesions also disappeared during treatment

Injected *Un-injected*

Patient 4401-0029: Chordoma

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

Replimune®



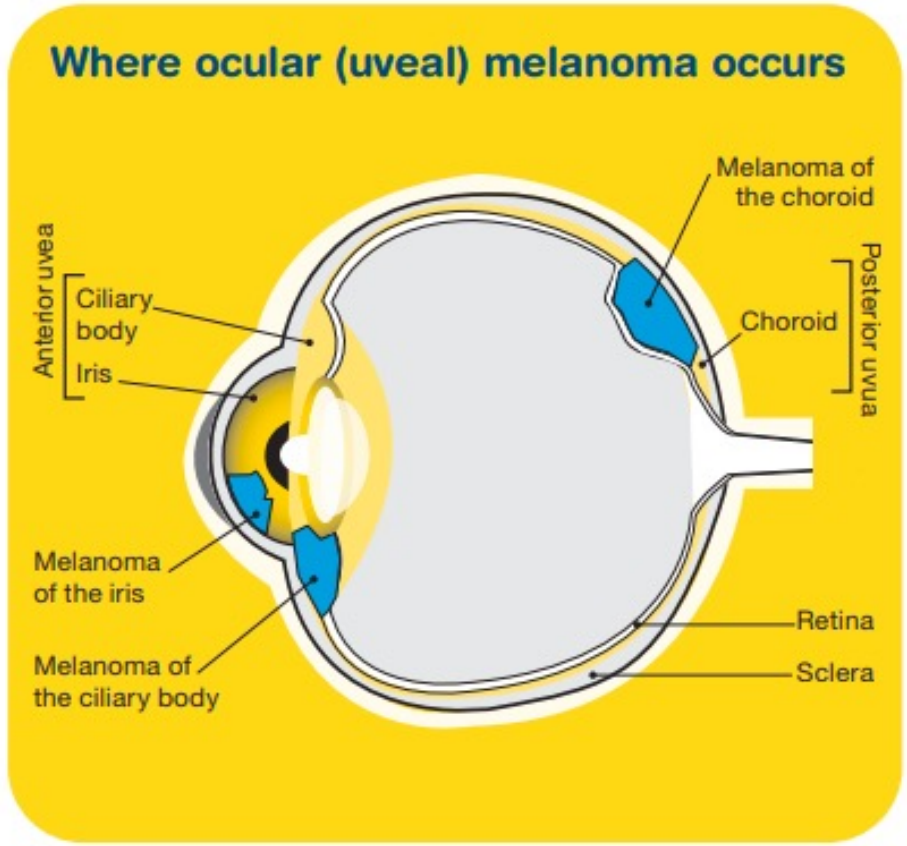
Pt 4401-0029 - ongoing PR

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

Injected *Un-injected*

RP2 in uveal melanoma

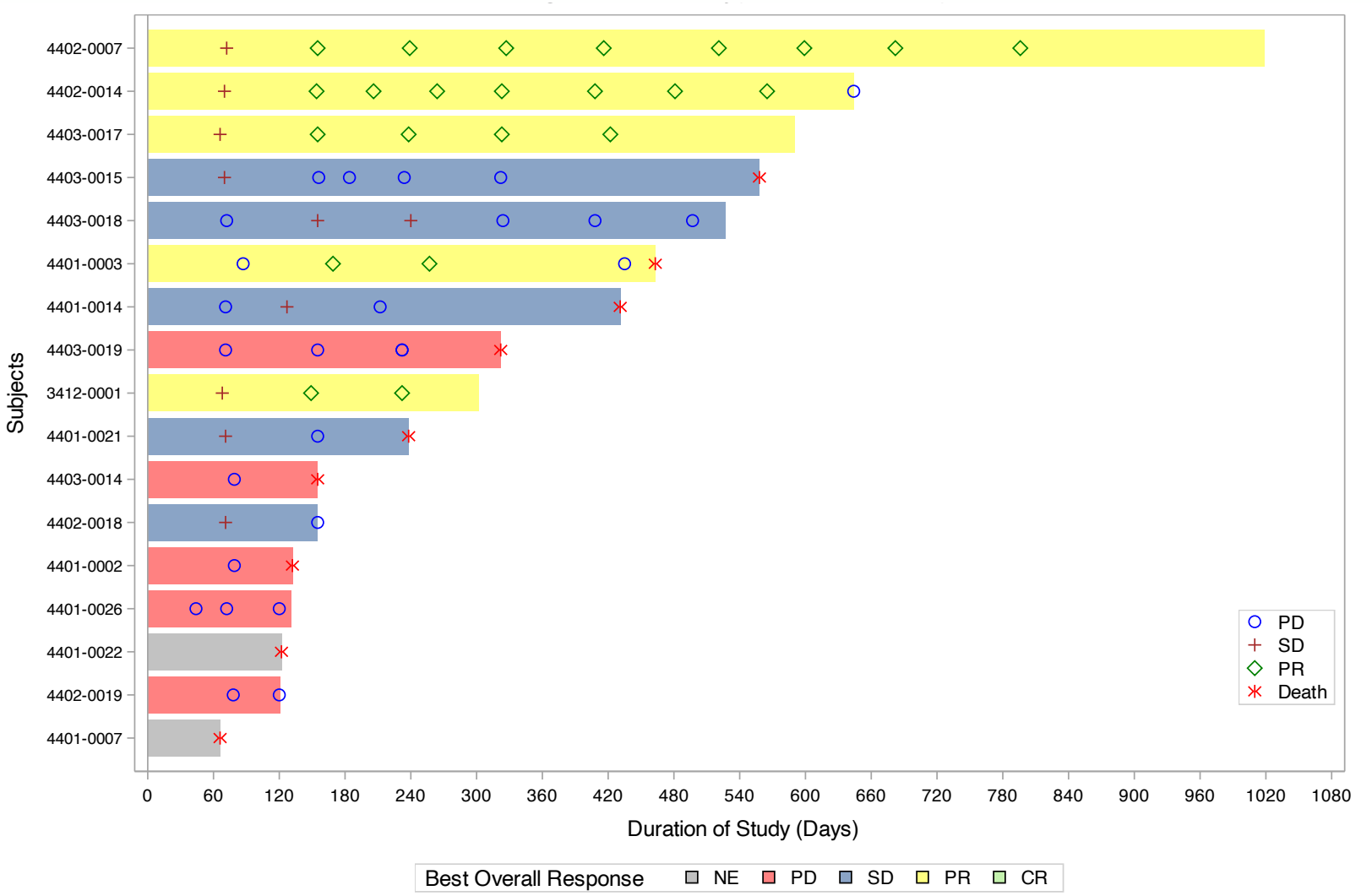
- Ocular or “uveal” melanoma is a rare cancer with approx. 1,000 cases in the US per year[1]
  - Originates from melanocytes and can occur in several eye locations
  - The historic median OS is approx. 12 months[1]
- Uveal melanoma **behaves quite differently from skin melanoma**
  - ***Mostly metastasizes to the liver*** *(approx. 70-90% of cases) and once this occurs only about 10% of these patients survive beyond a year*
  - *A difficult to treat tumor where* ***CPIs have previously 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 for uveal melanoma patients remains high, including improved efficacy/tolerability, effective options for HLA negative patients, and options for Kimmtrak and anti-PD1 failed patients**



[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;
* Versus investigator’s choice, pembrolizumab, ipilimumab, or dacarbazine

RP2 Uveal melanoma: Duration of response

Durable responses in small initial dataset, both monotherapy RP2 and RP2 + nivo



Key Takeaways

- 5/14 (29.4%) evaluable patient responders
- Heavily pre-treated population, with all responders having failed prior CPI

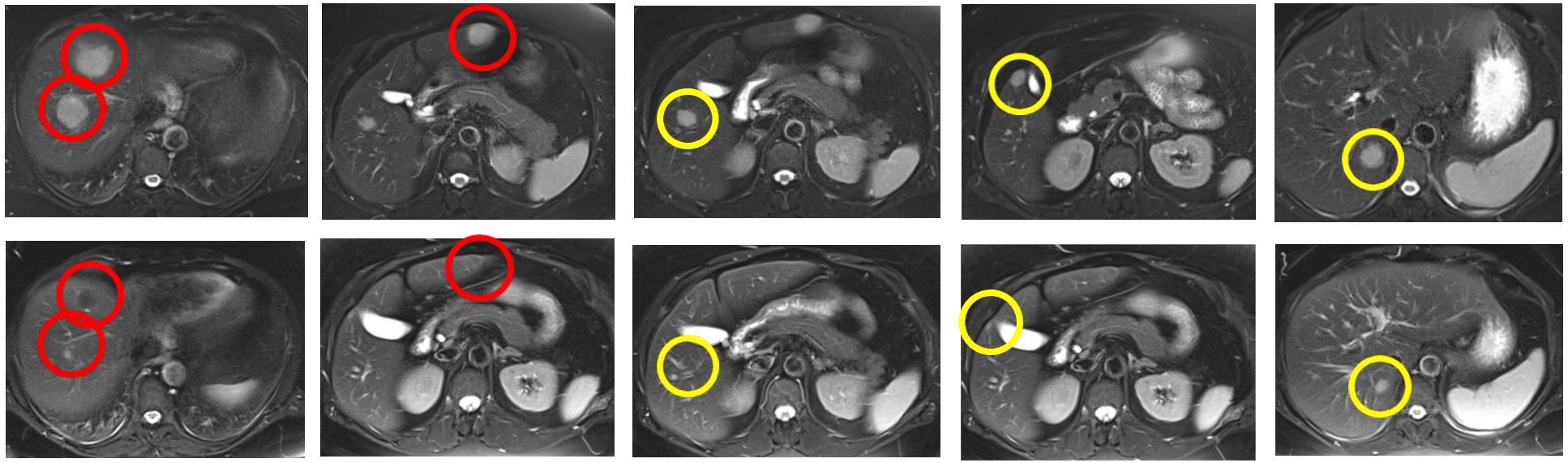
Durable responses represent compelling initial signal

- Longest ongoing response over 24 months

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease Data from SMR 2023

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

Summary

RP1 in skin cancer

- Initial snapshot of data from all 156 anti-PD1 failed melanoma patients demonstrate that RP1+nivolumab maintains transformative potential in this high unmet need setting
    - BLA submission planned for 2H 2024
- While CERPASSS missed its primary endpoints at P>0.025, a clinically meaningful benefit in CRR (P=0.04) and DOR in CSCC was demonstrated
- Other skin cancer data in hard-to-treat settings such as solid organ transplant recipients & anti-PD1 failed melanoma & NMSC demonstrate compelling clinical activity

Mid-stage pipeline

- Strong data with RP2 in uveal melanoma
- Planning for a randomized controlled pivotal study in uveal melanoma underway
    - Plan to investigate other rare cancer opportunities

Strong cash position

- Strong balance sheet; $466m [(1)] as of 31 December 2023
- Cash Runway into H2 2026

[(1)] Unaudited estimate

THANK YOU

MISSION

To enable tumor directed oncolytic immunotherapy (TDOI) to become a cornerstone in the treatment of cancer

VISION

To deliver **transformational** results for patients **across cancers** using tumor directed oncolytic immunotherapy to induce a powerful and durable systemic anti-tumor immune response resulting in **quality survival** and a **chance for a cure**

Replimune®