Replimune®

Igniting a Systemic Immune Response to Cancer

June 2023

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 overview

- Industry leader in tumor directed oncolytic immunotherapy (TDOI)
  - Potential to be a cornerstone treatment in immuno-oncology; 3 wholly owned programs (RP1, RP2, RP3)
- RP1 data supports the emergence of a major skin cancer franchise; two registrational studies ongoing
  - 211 patient 1L CSCC randomized controlled study fully enrolled; primary analysis Q3 2023
    - 47% CR rate / 65% ORR with strong durability in prior study
  - 141 patient study in anti-PD1 failed melanoma fully enrolled
    - 20% CR rate / 37% ORR in first 75 patients with activity across all disease stages and strong durability
- Broad mid-stage development planned with RP2 and RP3; responses shown in multiple unmet need indications
  - Several potential fast to market opportunities
    - Cost sharing collaboration with Roche in 3L CRC and 2L HCC
- Potential for the portfolio to deliver substantial commercial revenues beginning in 2025
- Capitalized to build a fully integrated biotech company; US commercial infrastructure, in-house manufacturing
  - March 31 2023, cash & short-term investments c. $583m

Tumor directed oncolytic immunotherapy mechanism of action

Replimune®

Injected tumor

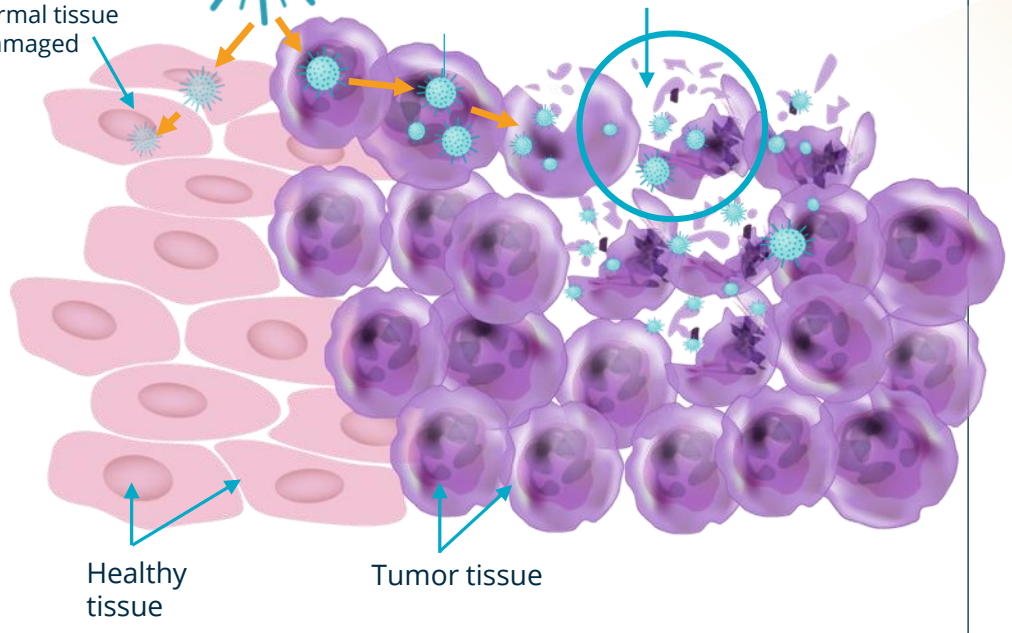
MECHANISM 1

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

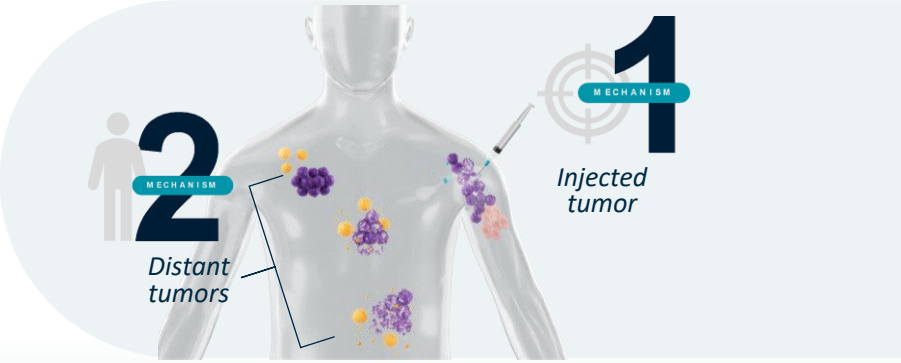
Local Inflammation

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

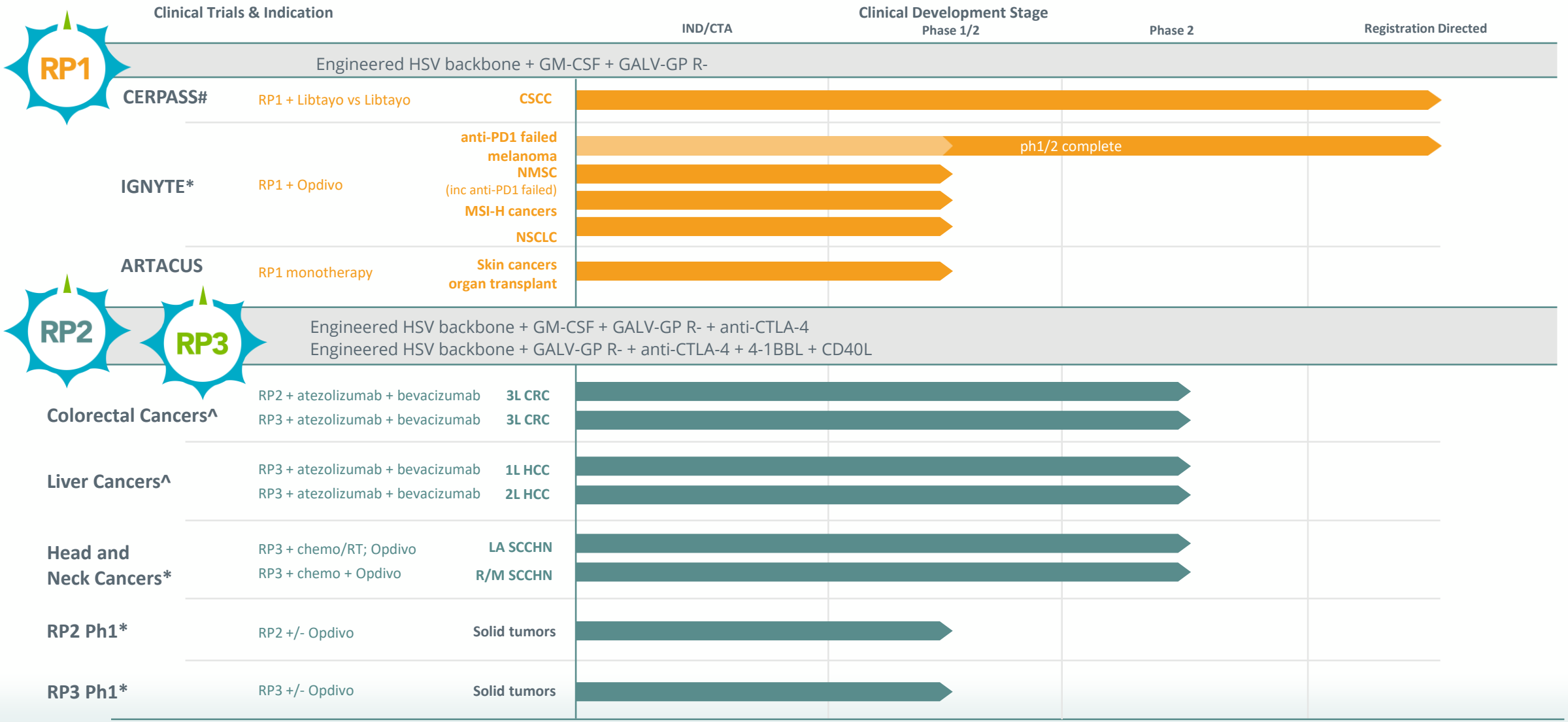


Bommareddy PK et al AJCD. 2016

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

	RP1	RP2	RP3
Payloads	GALV-GP R-, GM-CSF	GALV-GP R-, anti-CTLA-4, GM-CSF	GALV-GP R-, anti-CTLA-4, CD40L, 4-1BBL
Target	Immunologically responsive tumor types, including anti-PD1 failed	Less immunologically responsive tumor types	Less immunologically responsive tumor types (anticipated further improved compared to RP2)
Intended indication(s)	Skin cancers (CSCC, anti-PD1 failed melanoma, anti-PD1 failed CSCC, other NMSCs, etc)	Various solid tumors including primary liver cancers and/or those with a high prevalence of liver metastases e.g. HCC, CRC; Early disease (neoadjuvant/LA opportunities) e.g. SCCHN	
Clinical activity in anti-PD1 failed patients demonstrated	✓	✓	Ongoing
Safety & good tolerability demonstrated	✓	✓	Ongoing
Injection location	Superficial, nodal & visceral	Superficial, nodal & visceral	Superficial, nodal & visceral
Systemic activity	***Clear systemic effects seen in responding patients (un-injected tumor responses, responses are generally highly durable)***		Ongoing
Other design considerations	Designed for more I-O sensitive tumor types with excellent safety alone & in combination	Increased I-O systemic activity, also with excellent safety alone & in combination	Designed to maximize systemic I-O activity & potency

Company Pipeline



* Under a clinical trial collaboration & supply agreement with BMS for the supply of Opdivo where needed – full commercial rights retained by Replimune; SCCHN initiating mid 2023
# Under a clinical trial collaboration agreement with Regeneron; 50:50 sharing of clinical trial costs – full commercial rights retained by Replimune
^ Under clinical trial collaboration & supply agreement with Roche for atezolizumab & bevacizumab supply and 50:50 cost sharing in select indications – full commercial rights retained by Replimune; initiating mid 2023

RP1: Establishing a major skin cancer franchise

AGENDA

Establishing a broad skin cancer franchise

1	**IGNYTE anti-PD1 failed melanoma registrational cohort** *N=125*	Impressive response rate in first 75 patients, 20% CR rate, 37% ORR, full data with 6 month follow up expected Q4 2023
2	**CERPASS – first-line CSCC randomized controlled pivotal trial** *N=211*	Fully accrued, primary data Q3 2023; 47% CR rate and 65% ORR in prior study (N=17) **Initial approval sought in anti-PD1 naïve CSCC**
3	**IGNYTE initial NMSC cohort (anti-PD1 naïve)** *N=30 (fully accrued)*	Demonstrated activity in other NMSCs; Commercialization in MCC, BCC, angiosarcoma likely to be based on compendia listing
4	**IGNYTE anti-PD1-failed NMSC cohort** *N=30*	With signal can expand for registrational purposes; label expansion; 33% ORR to date (N=12)
5	**ARTACUS skin cancers in solid organ transplant recipients** *N=65*	Potential registration or compendia listing; 33% ORR to date as monotherapy (N=6)
6	**Neoadjuvant CSCC**	***Study being planned**: expected to capture significant high- risk patient population*

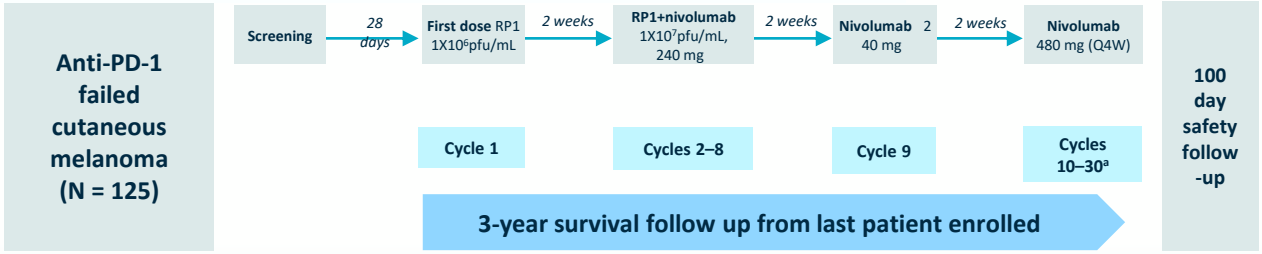
- RP1 establishes confidence in easy-to-administer settings
- Deep and durable responses across multiple settings in skin cancer, including high CRs in 1L CSCC
- Responses in anti-PD1 failed patients with melanoma & a range of NMSCs
- Development to provide proof-of-concept in neoadjuvant setting

IGNYTE melanoma patient demographics

RP1 plus nivo in anti-PD1 failed melanoma 125 patient registration study

- Registration-directed single arm cohort of patients with anti-PD1 failed cutaneous melanoma (n=125) treated with RP1 combined with nivolumab
- Initial data from the first 75 of these combined with 16 patients from a prior cohort was presented (n=91)
- Key inclusion criteria
  - Cutaneous melanoma patients having confirmed progression on the immediate prior line of anti-PD1 therapy as single agent or in combination
  - At least 8 weeks treatment with anti-PD1
  - Patients who progressed on prior adjuvant therapy (biopsy confirmed) were eligible
  - Not required to have received anti-CTLA-4 or BRAF directed therapy for BRAF mut patients
- **Primary endpoint: ORR**

IGNYTE Study Design



Enrollment objectives

To enroll a population representative of the different settings in which melanoma patients progress on anti-PD1 therapy, & would therefore benefit from a new treatment option

Key patient demographics (n=91)	n/%
Stage	
• IIIb/IIIc/IVM1a	45/49.4
• IVM1b/c	46/50.6
Prior therapy	
• Anti-PD1 as adjuvant therapy	32/35.2
• Anti-PD1 as 1L or beyond therapy	59/64.8
• Also received anti-CTLA-4 therapy	32/35.2
• Also received BRAF directed therapy	8/8.8
Other disease characteristics	
• Primary resistance* to prior anti-PD1	50/54.9
• Secondary resistance* to prior anti-PD1	38/41.8
• PD-L1 ≥1%**	26/28.6
• PD-L1 <1%	51/56.0
• BRAF wild-type	64/70.3
• BRAF mutant	27/29.7
• LDH ≤ULN**	64/70.3
• LDH >ULN	26/28.6

* Primary resistance = PD, or SD for <6 months on the prior course of anti-PD1; for adjuvant, progressed within 6 months: secondary resistance = PR, CR, or SD >6months on the prior course of anti-PD1; for adjuvant, progressed after 6 months
**PD-L1 status UNK n=14; LDH status UNK n=1

IGNYTE melanoma data: 37% ORR in first 75 patients

RP1 plus nivo in anti-PD1 failed melanoma 125 patient registration study

n (%)	N=16 Prior patients (n=16)	N=75 Data snapshot patients (n=75)	N=91 All patients (n=91)	Prior adjuvant anti–PD-1 only (n=32)	Prior anti–PD-1 other than adjuvant (n=59)	Prior anti–PD-1 & anti–CTLA-4 (n=32)	Stage IIIb/IIIc/IVa (n=45)	Stage IVb/IVc (n=46)	Primary resistance to anti-PD1 (n=50)**	Secondary resistance to anti-PD1 (n=38)**
Best overall response										
CR	2 (12.5)	15 (20.0)	17 (18.7)	9 (28.1)	8 (13.6)	3 (9.4)	13 (28.9)	4 (8.7)	12 (24.0)	5 (13.2)
PR	4 (25.0)	13 (17.3)*	17 (18.7)	7 (21.9)	10 (16.9)	8 (25.0)	8 (17.8)	9 (19.6)	6 (12.0)	11 (28.9)
SD	1 (6.3)	13 (17.3)	14 (15.4)	6 (18.8)	8 (13.6)	5 (15.6)	5 (11.1)	9 (19.6)	7 (14.0)	7 (18.4)
PD	8 (50.0)	31 (41.3)	39 (42.9)	10 (31.3)	29 (49.2)	13 (40.6)	19 (42.2)	20 (43.5)	24 (48.0)	12 (31.6)
ORR	**37.5%**	**37.3%**	**37.4%**	**50.0%**	**30.5%**	**34.4%**	**46.7%**	**28.3%**	**36.0%**	**42.1%**

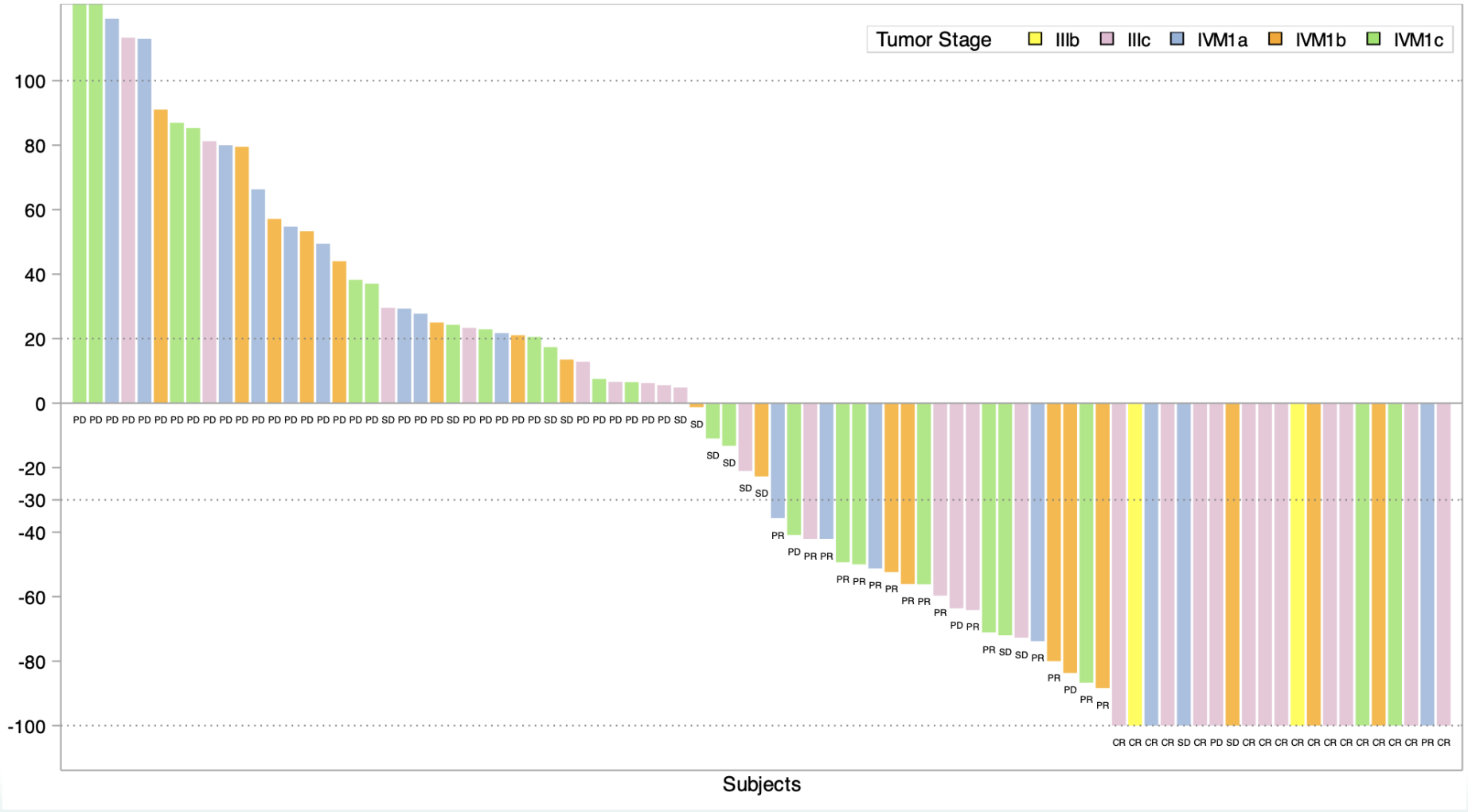
Key Snapshot Takeaways

- Data from the 75-patient snapshot are consistent with the 16 patients enrolled into the prior melanoma cohort
  - Majority of patients were primary refractory to anti-PD1
- At least 28% ORR in all sub-groups analyzed
- Particularly high ORR (50%) and CR rate (28%) in patients who progressed while on prior adjuvant anti-PD1 therapy

*One PR not confirmed. **Resistance type is unknown for 3 patients. Response data presented is by investigator assessment; the primary analysis from the study will be by blinded, independent central review.

Waterfall plots: All patients

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

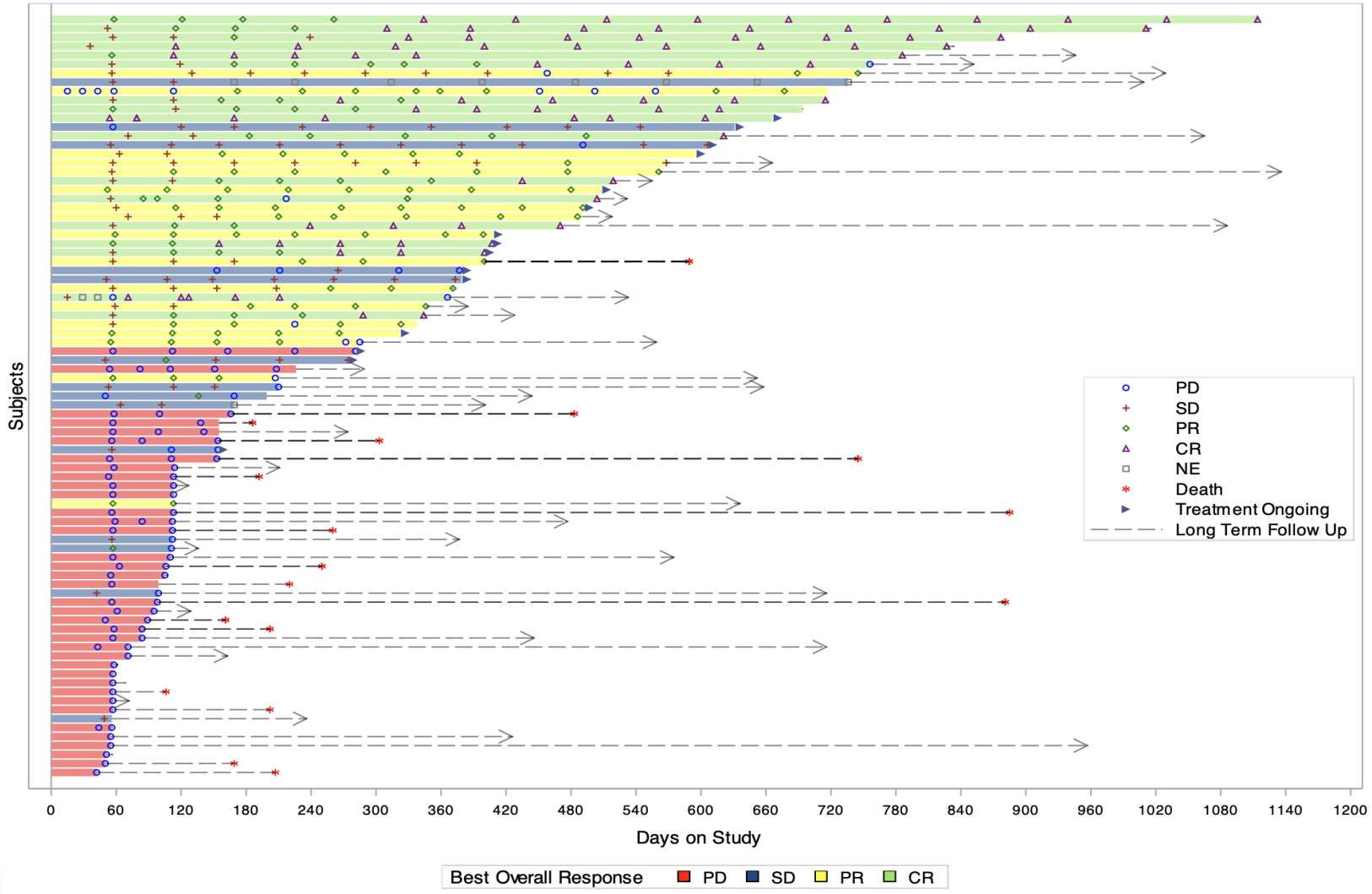


Key Takeaways

- >50% of patients have target (RECIST) tumor reduction
- Deep responses observed
- Includes CRs in patients with Stage IV M1b/c disease

Swimmer's plots: All patients

Patients with at least one follow up assessment



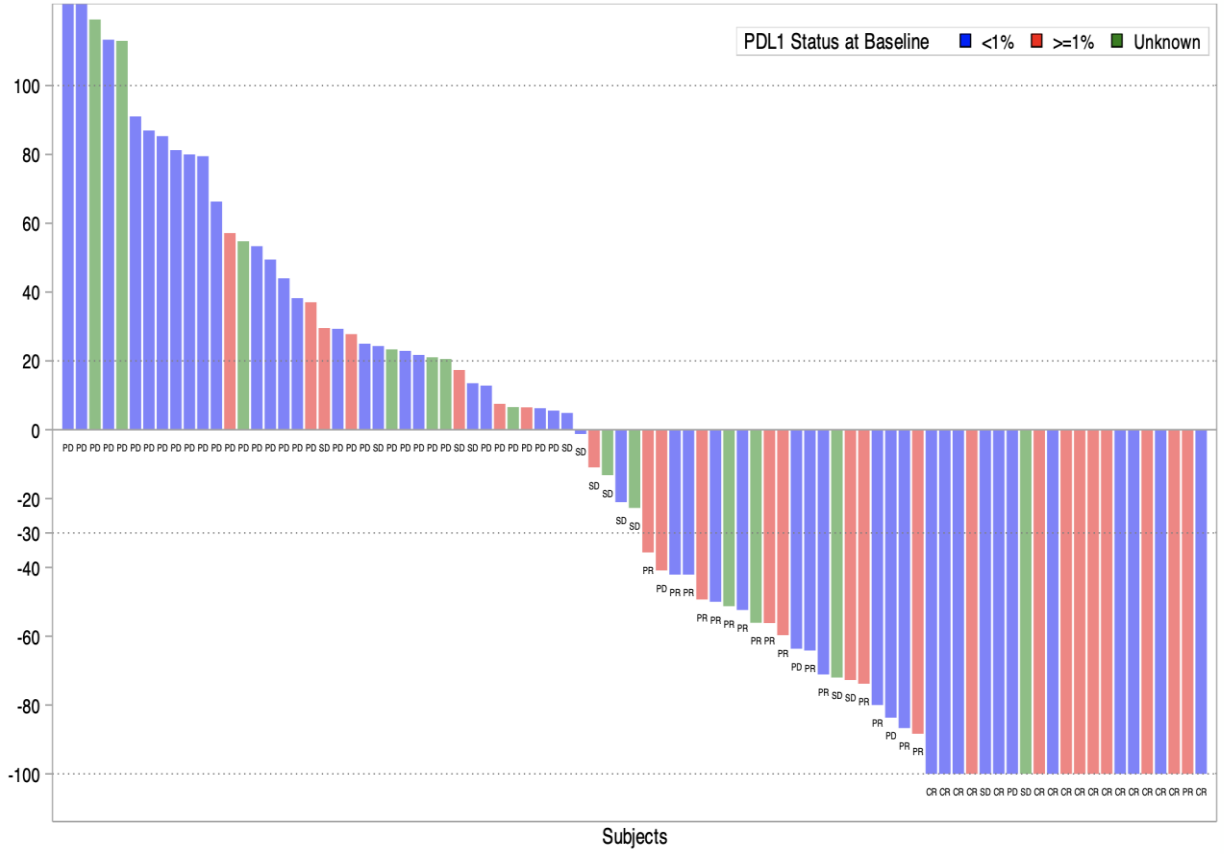
Key Takeaway

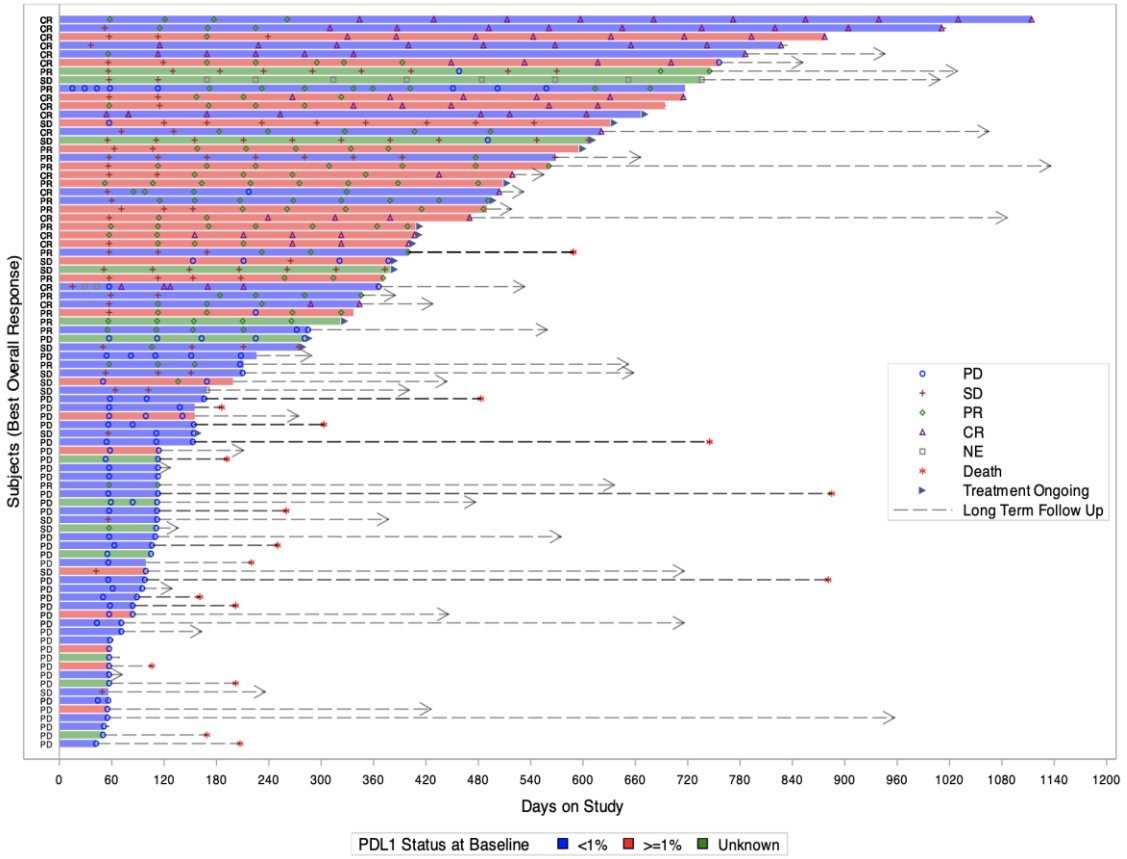
Responses are durable, indicating systemic overall benefit

- 85% of responses are ongoing
- 71% of responders are out over one year from starting therapy

IGNYTE Translational Data

Patients with at least one follow up assessment, by PD-L1 Status at Baseline





Key Takeaway

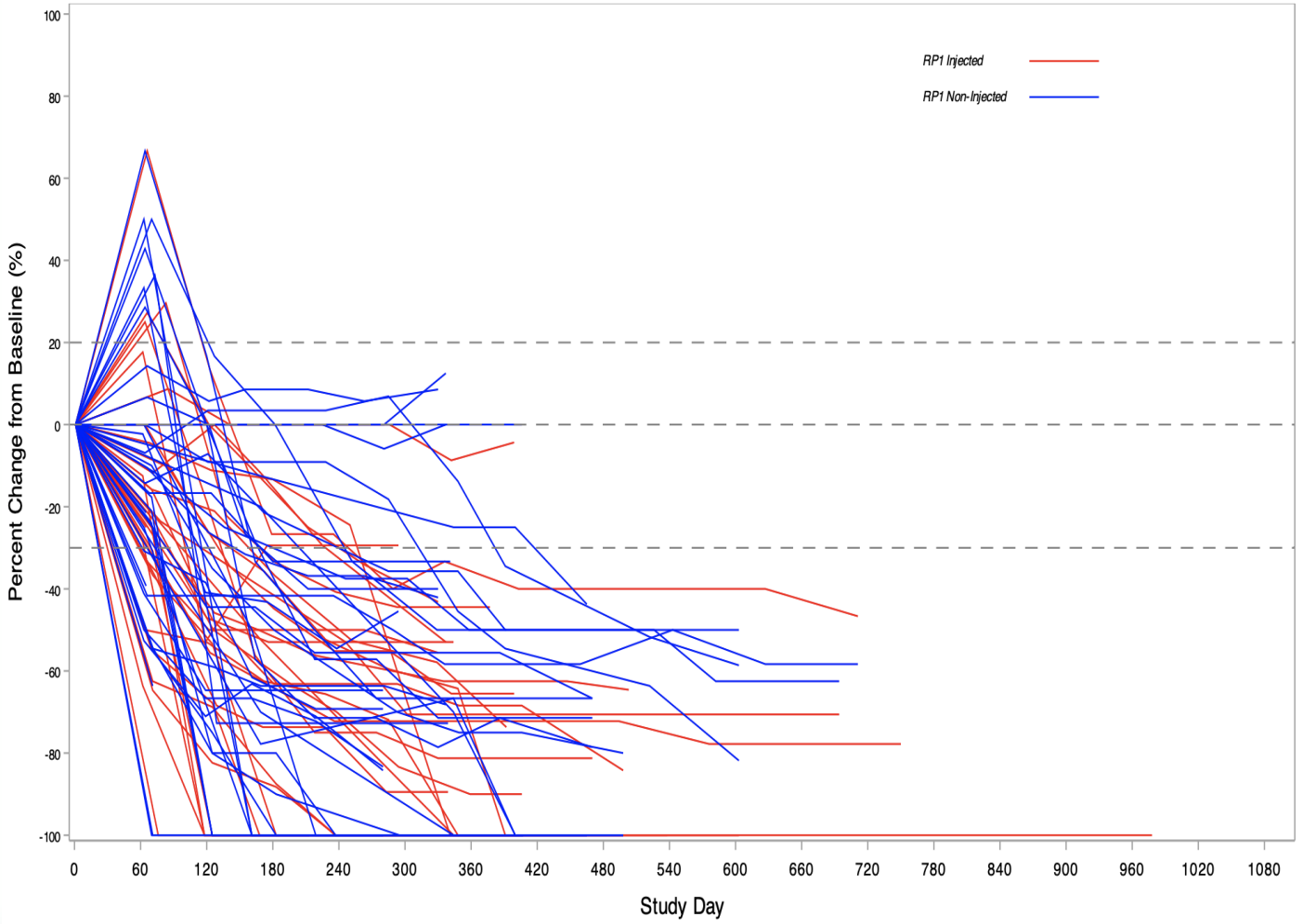
Responses are deep and durable, independent of baseline PD-L1 status

- RP1 efficacy demonstrated in PD-L1 low patients (33% ORR, 17/52 patients responding)

n=26 PD-L1 ≥1%; n= 51 PD-L1 <1%; n=14 PD-L1 status UNK

IGNYTE Kinetics of Response

Change in size of individual injected and uninjected lesions



Key Takeaways

- Systemic effects including in patients with:
  - Visceral lesions, after both deep and superficial injection
  - Bulky lesions
  - Up to >20cm of total tumor burden and up to >10cm of uninjected disease
- 70.4% of responding patients had uninjected lesions
  - Responders include patients with minority of lesions injected
- Large number of uninjected lesions respond supporting systemic benefit
- Injected and uninjected lesions respond with similar durability and kinetics
  - Depth of response independent whether injected

Includes both target and non-target lesions for RECIST assessment, measured from CT/MRI scans for radiologically assessable lesions (n=75 group). 58/75 patients had at ≥ 1 uninjected lesion, of whom 15 achieved a response based on those lesions (excludes possible response in injected lesions); ORR of 25.9% on the basis of uninjected lesions only

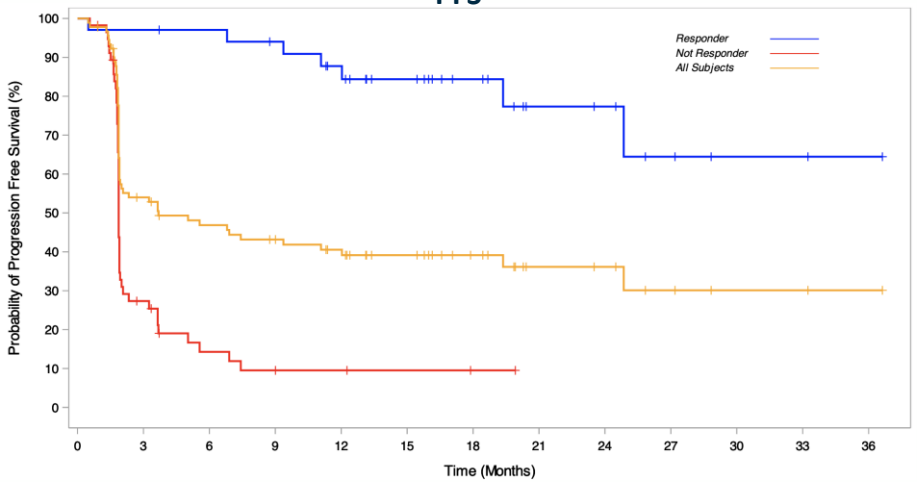
IGNYTE PFS & OS Data

Early PFS and OS; patients with at least one follow up assessment

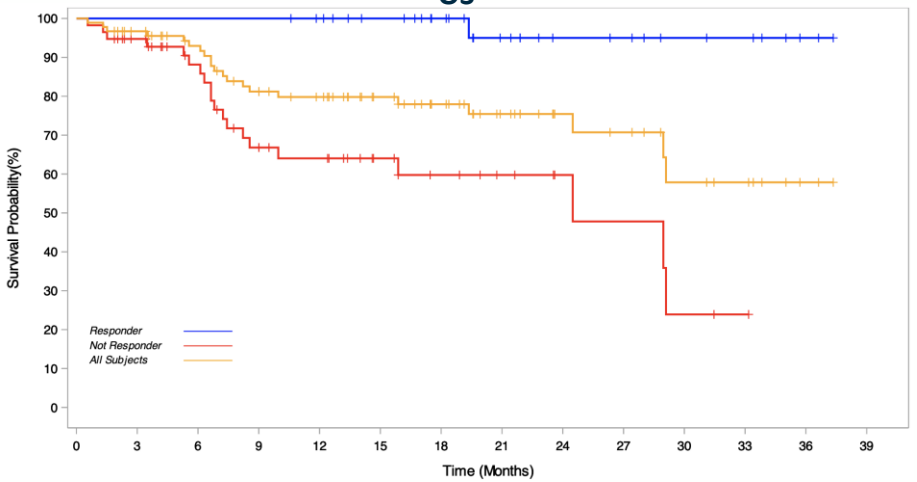
Response status to RP1 combined with nivolumab

(Responder [CR or PR] vs. non-responder)

PFS



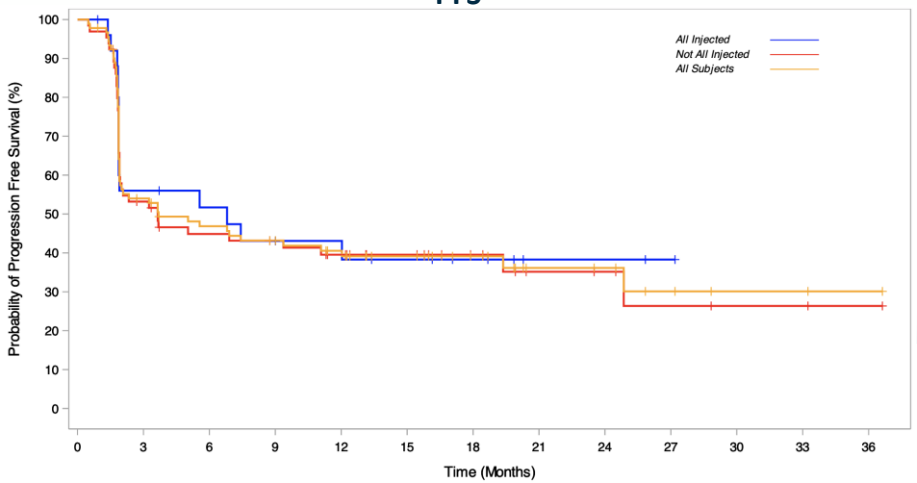
OS



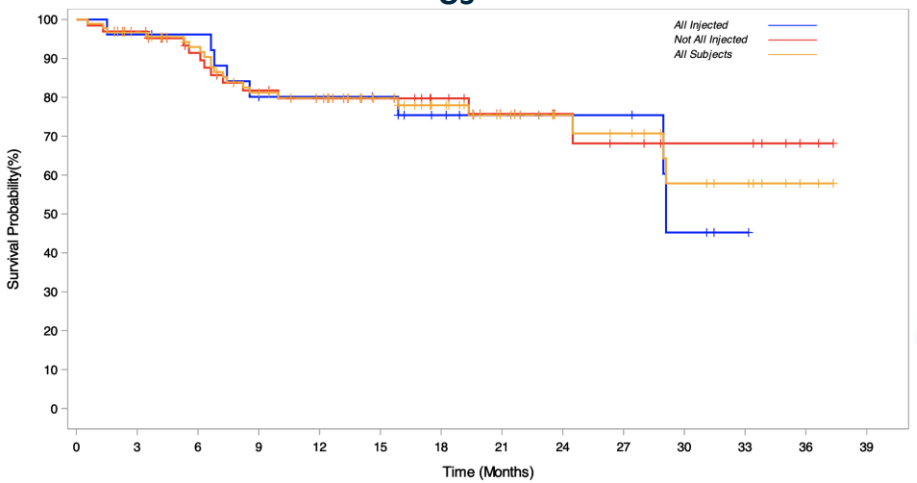
Lesion injection status

(all lesions injected vs. not all lesions injected with RP1)

PFS



OS



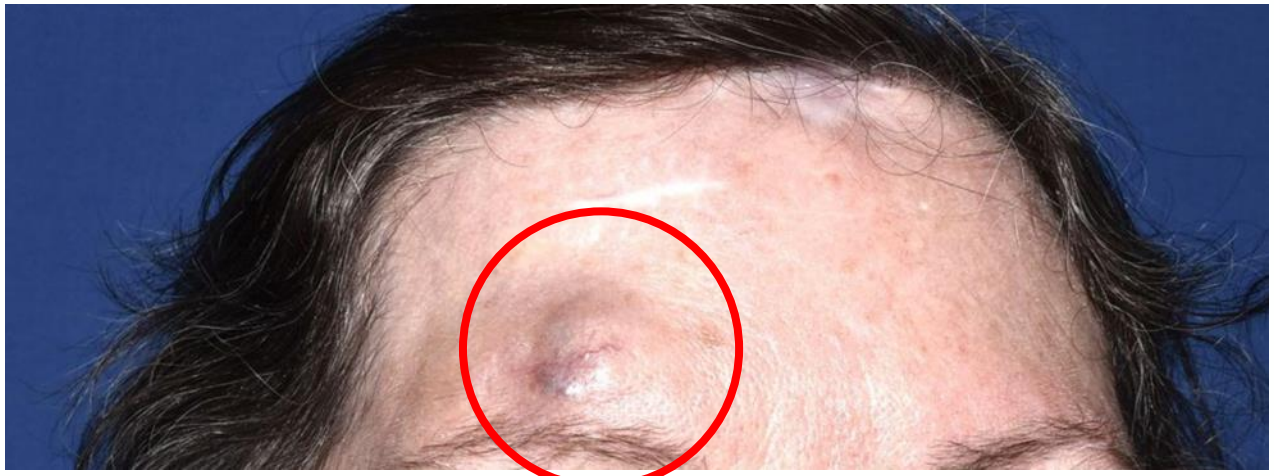
Key Takeaway

- Both PFS and OS appear promising for the population enrolled
- This includes when broken down by prognostic and other factors
  - By far the greatest impact on PFS & OS was response to RP1 combined with nivolumab
  - There was no impact whether or not all lesions were injected with RP1
  - Other subgroups not shown (see ASCO 2023 poster)

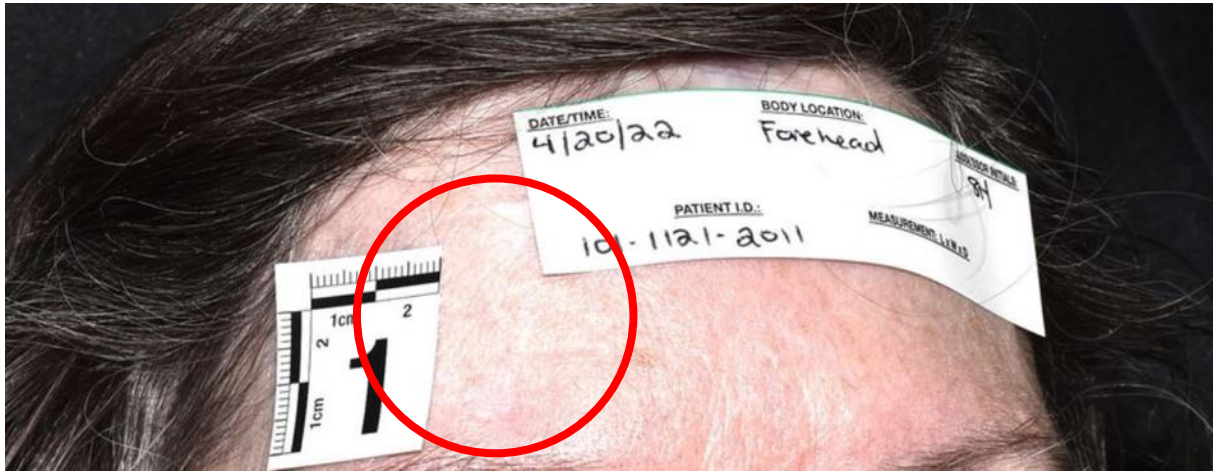
Patient 1121-2011:

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

29 JUL 2021 / Screening



20 APRIL 2022



Injected Un-injected

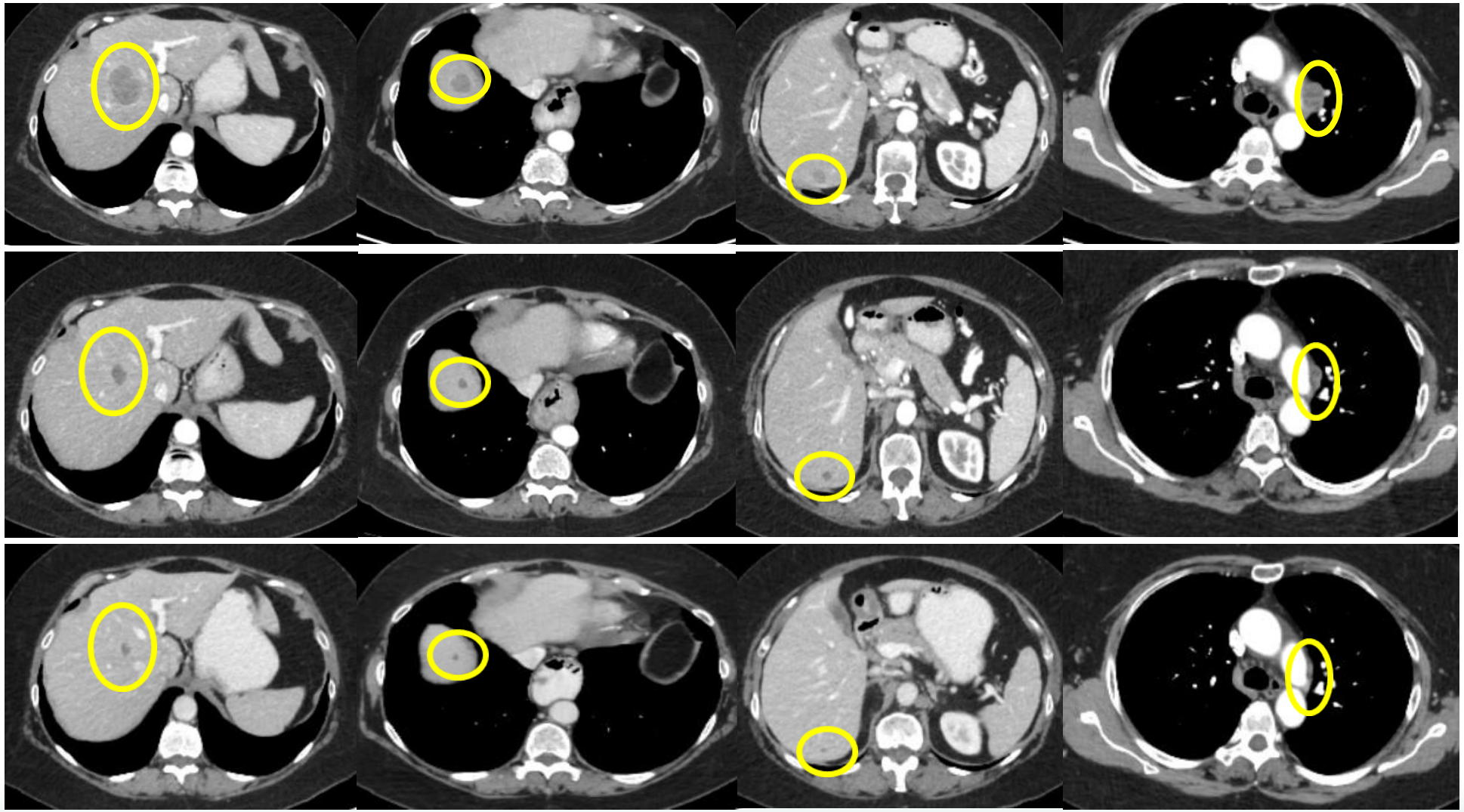
Patient 1121-2011 Cont'd:

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

22 Jul 2021/
Baseline

22 Sep 2021/
Day 57

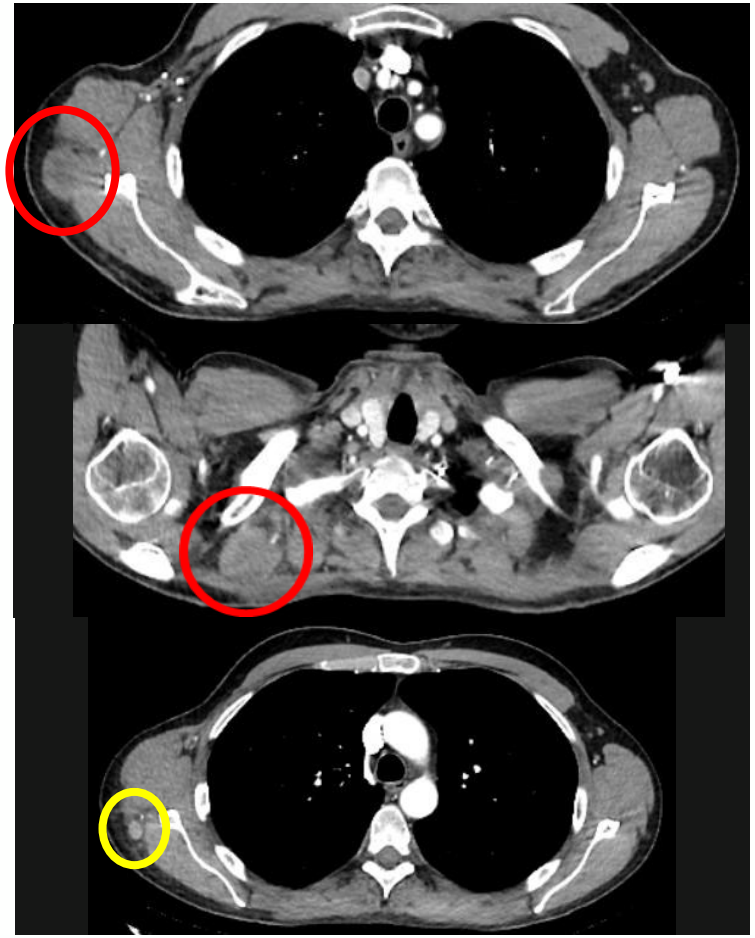
29 Dec 2021/
Day 155



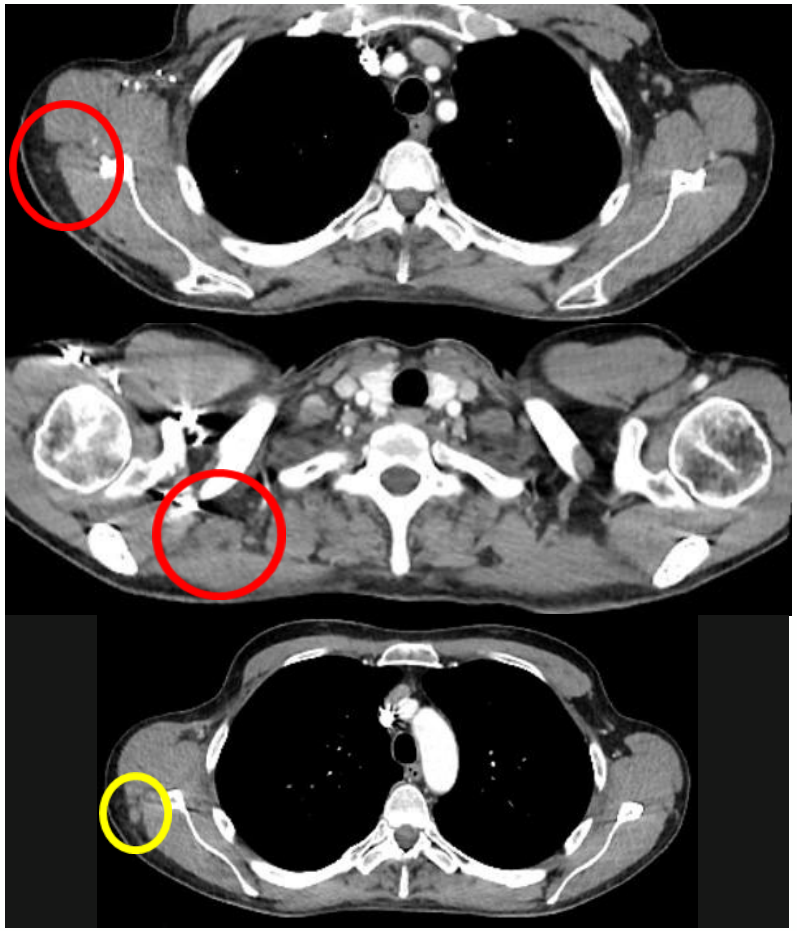
Injected Un-injected

Patient 4405-2007:
Prior Keytruda, Yervoy/Opdivo: Stage IVM1b

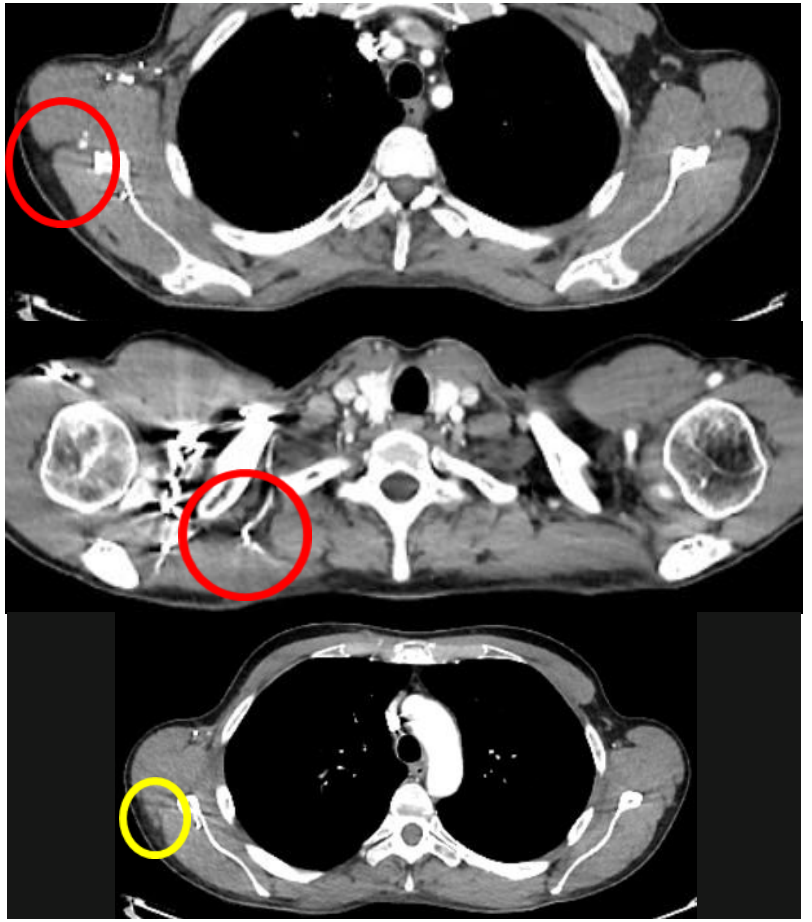
6 Aug 2021/Baseline



24 Jan 2022



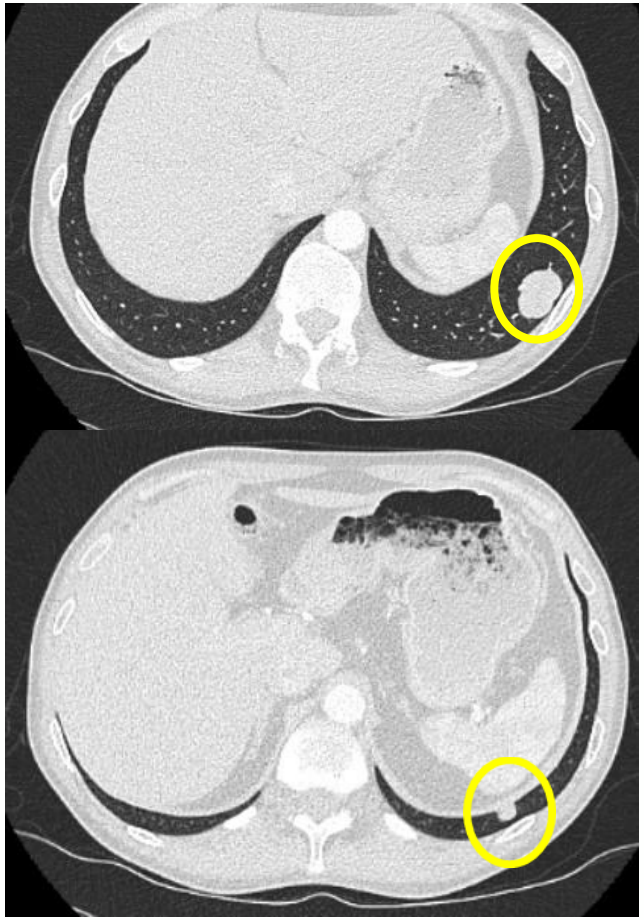
31 Aug 2022



Injected *Un-injected*

Patient 4405-2007 Cont'd:
Prior Keytruda, Yervoy/Opdivo: Stage IVM1b

6 Aug 2021/Baseline



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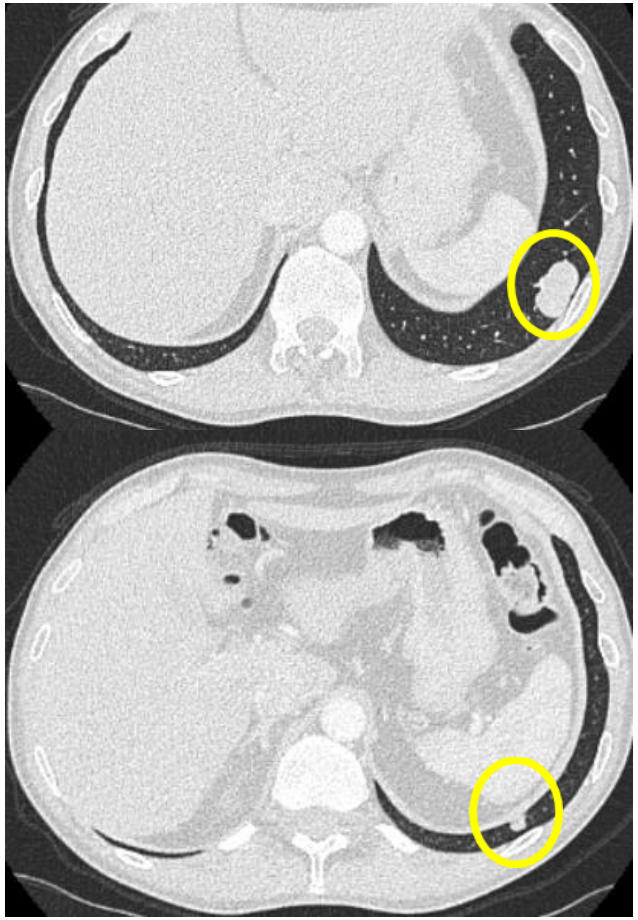
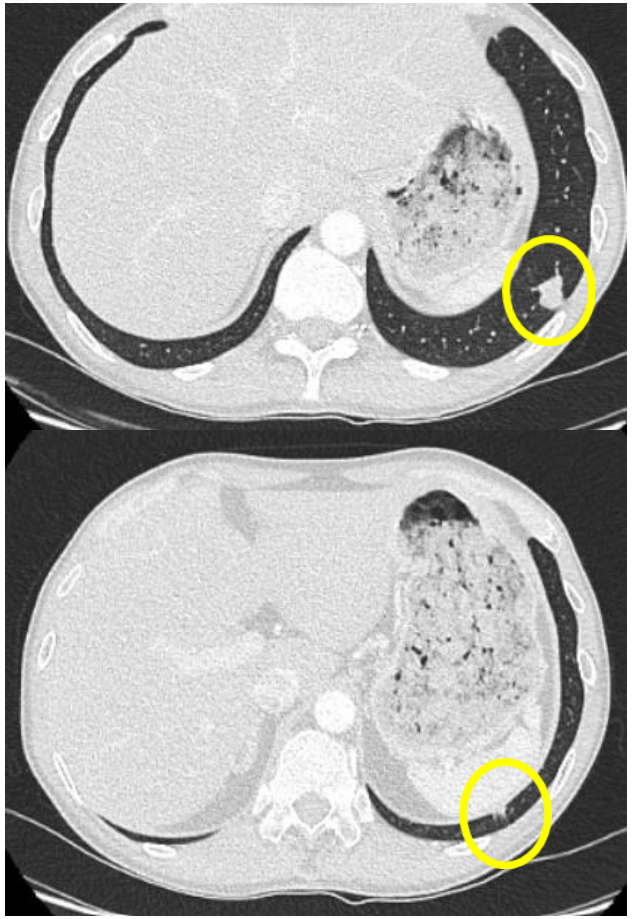


31 Aug 2022



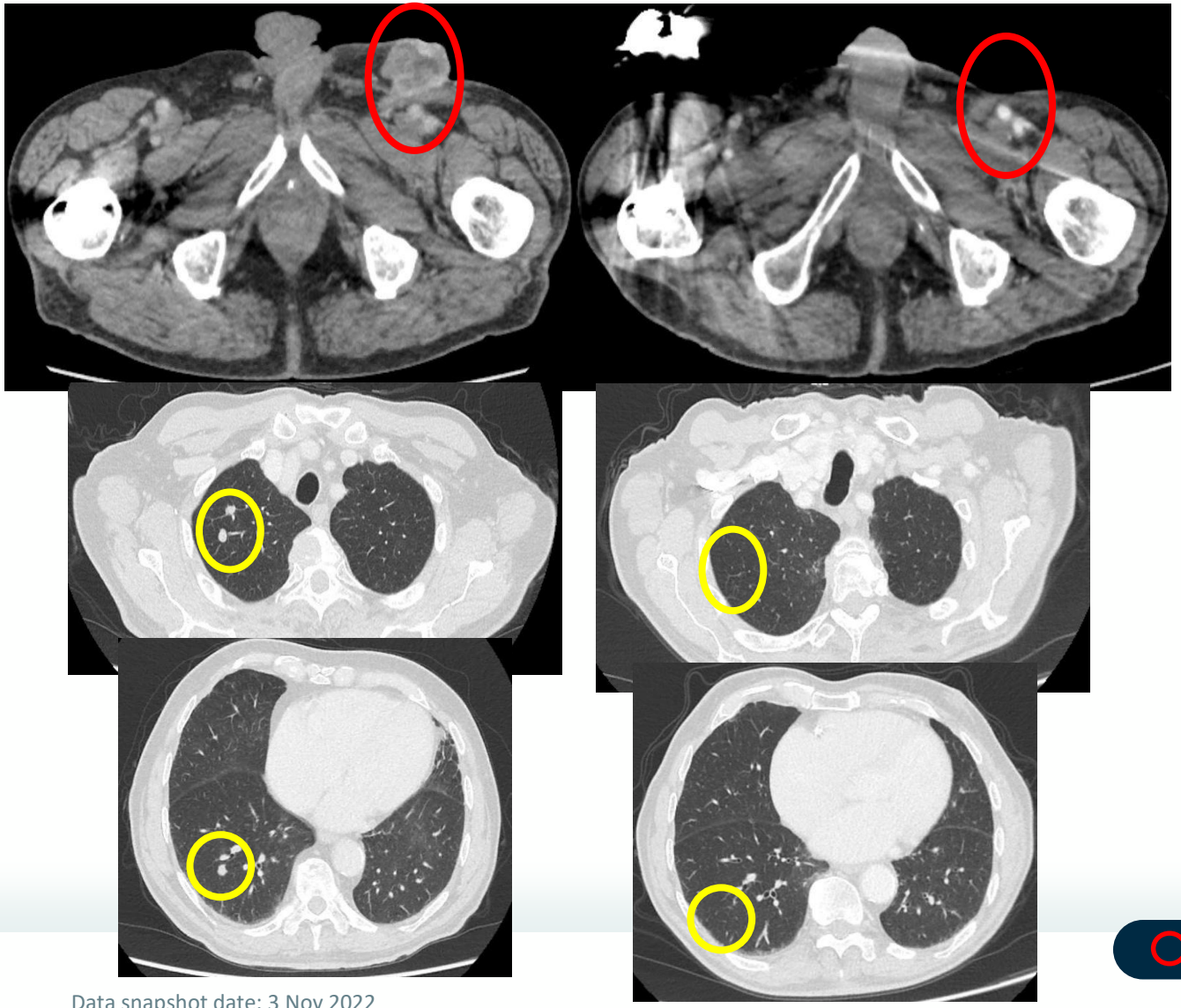
Injected *Un-injected*

Patient 4401-2021: Prior Tafinlar/Mekinist, Keytruda

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

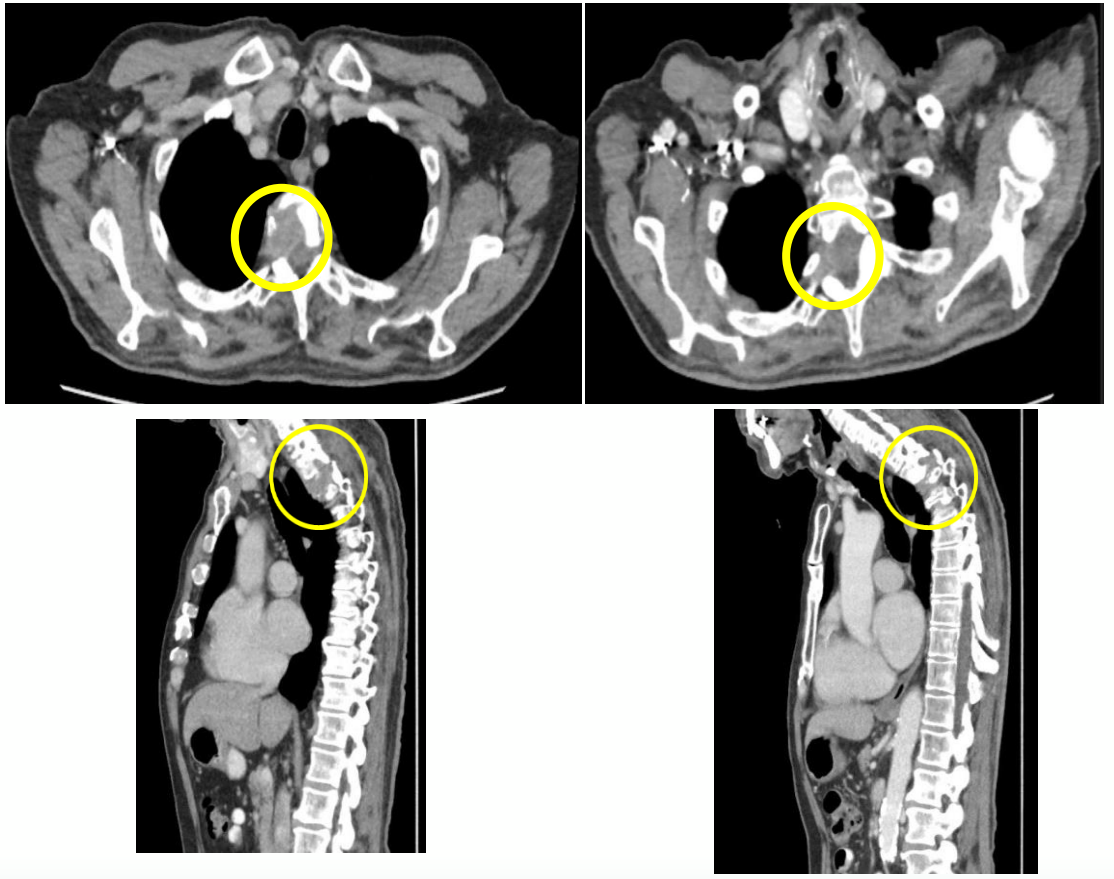
12JAN2021/Baseline

15FEB2022/Day 368



12JAN2021/Baseline

15FEB2022/Day 368

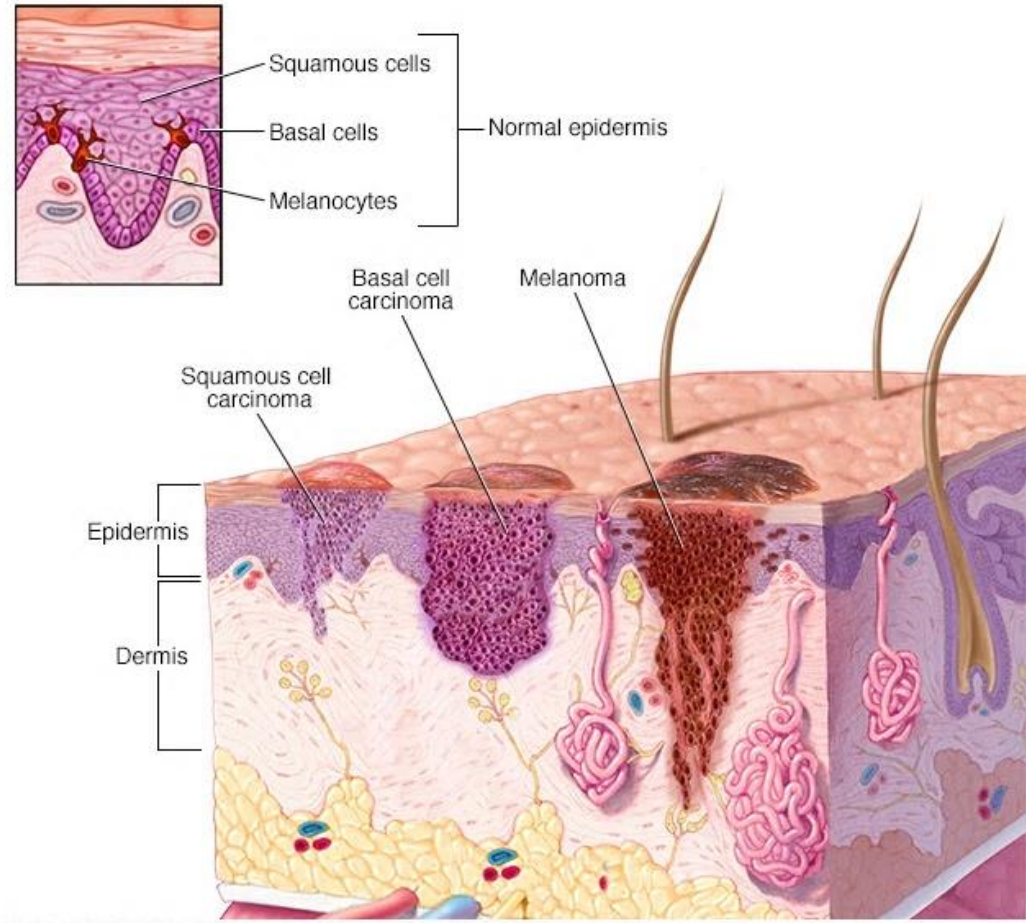


Injected *Un-injected*

Data snapshot date: 3 Nov 2022

CSCC disease characteristics, largely superficial/local issue

- Second most common skin cancer with ≈700,000 patients annually in the U.S.[1], caused by exposure to ultraviolet radiation
- ~up to **10% of CSCC patients are high risk (neo-adj opportunity)**
- Approximately 7,000-15,000 US deaths annually[1-3]
  - ***80% of patients die from locoregional progression**, not metastatic disease*[4,5]
- **CSCC is an outward growing disease with large, painful, superficial tumors, almost all (~90%) CSCC have superficial tumors**
- Majority of systemic treated patients have **prior surgery and/or radiation**
- First systemic treatment, cemiplimab, approved in 2018 followed by pembrolizumab in 2020
  - **(ORR: ~35-45%, CRR: ~5-15%)**



[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

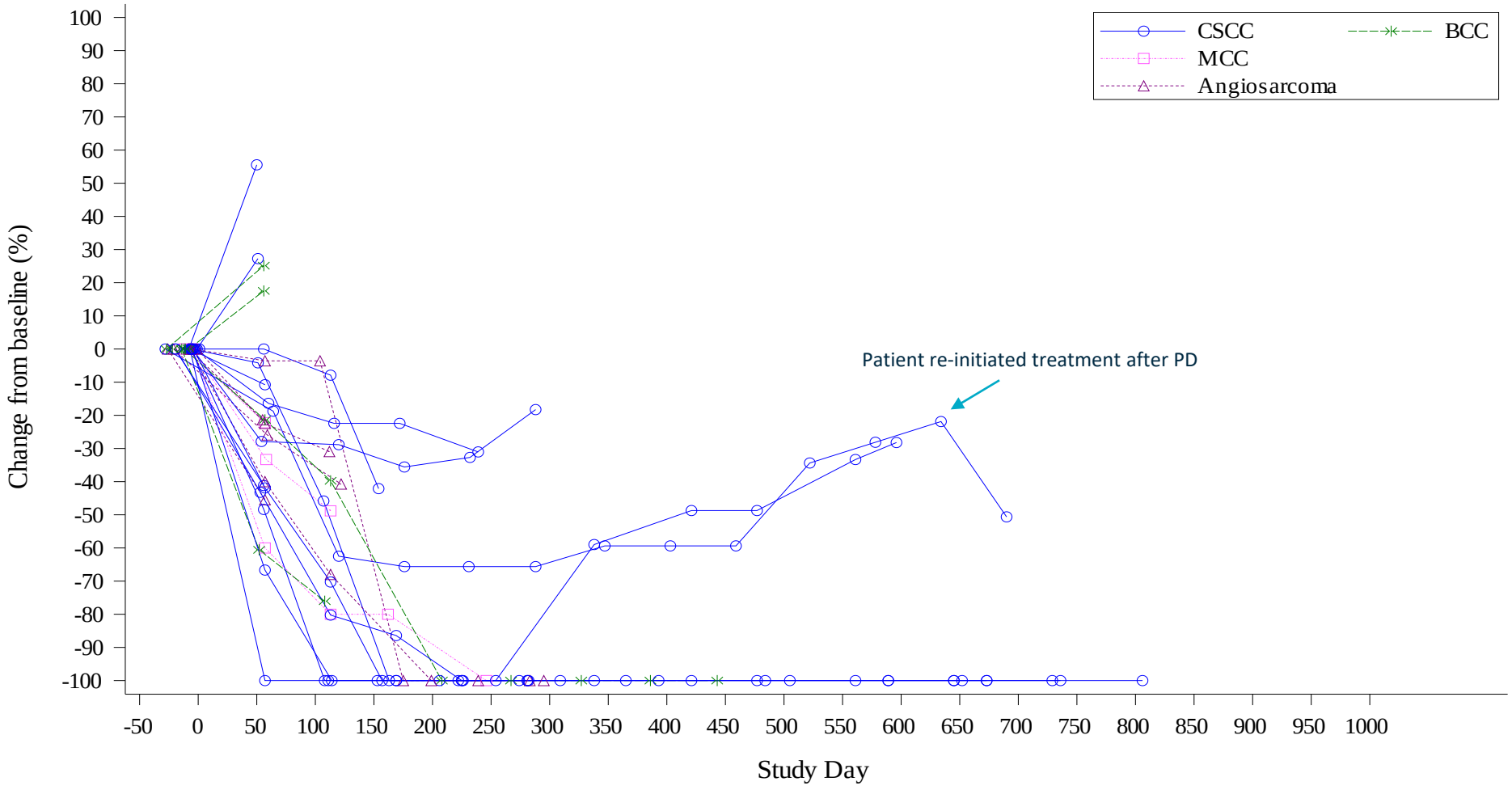
High rates of CR in CSCC in IL study in combo with Nivo

n (%)	CSCC (n=17)	BCC (n=4)	MCC (n=4)	Angio (n=6)
Best overall response				
CR	8 (47.1)	1 (25.0)	2 (50.0)	1 (16.7)
PR	3 (17.6)	0	1 (25.0)	3 (50.0)
SD	1 (5.9)	2 (50.0)	0	1 (16.7)
PD	4 (23.5)	1 (25.0)	1 (25.0)	1 (16.7)
ORR	11 (64.7)	1 (25.0)	3 (75.0)	4 (66.7)
DCR	12 (70.6)	3 (75.0)	3 (75.0)	5 (83.3)

Patients with follow up assessments (n=31), as presented at ASCO 2022; DCR = disease control rate (CR + PR + SD)
Note: Data snapshot date: 11th March 2022

Anti-PD1 naïve NMSC: Deep/durable responses in CSCC

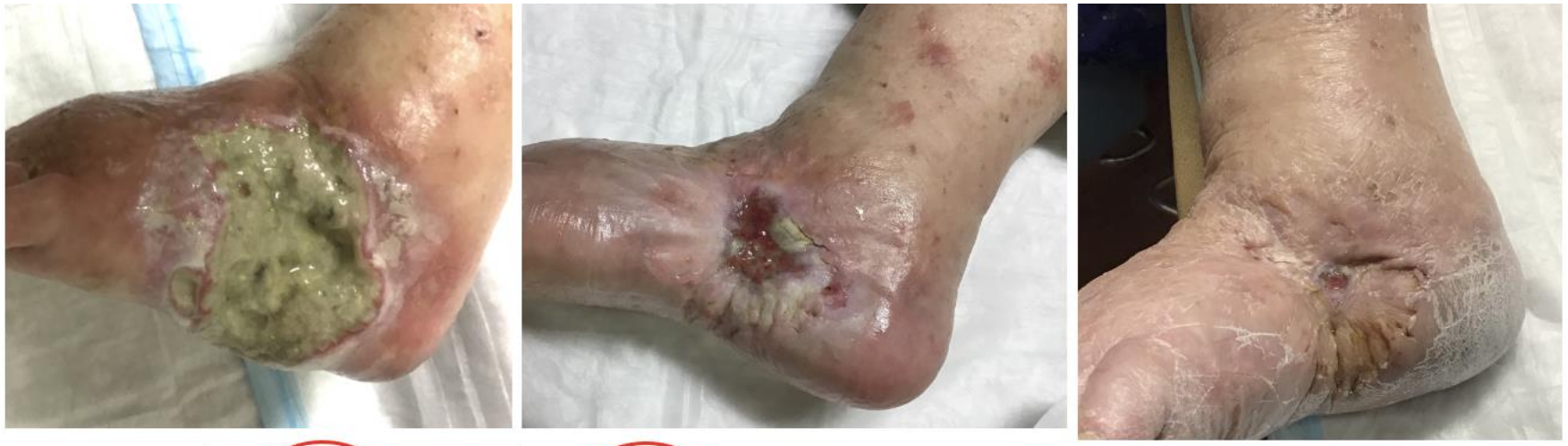
A high frequency of durable responses continues to be observed

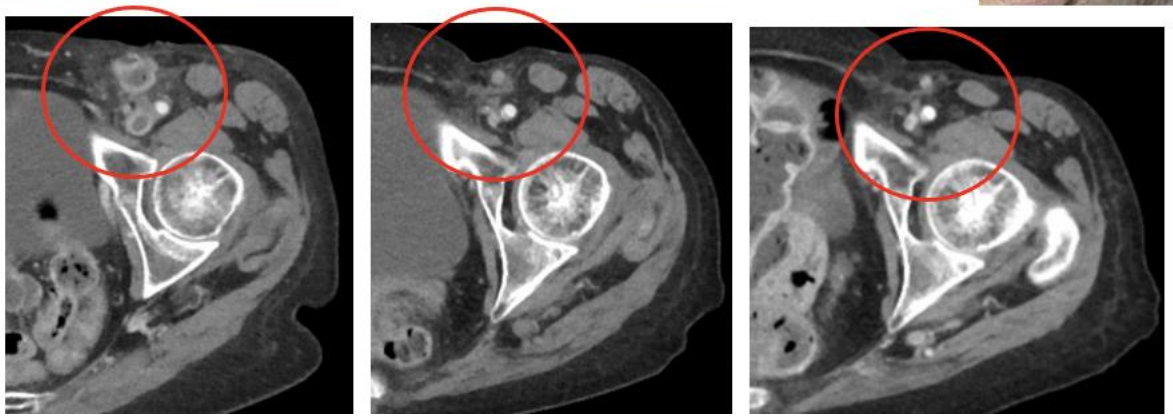


2 CR's are not represented in spider plot as only scheduled visits were programmatically captured
Note: Data snapshot date: 11th March 2022

Example complete resolution of aggressive locoregional disease

22ND MAY 2020 | 12TH OCT 2020 (PR) | 12TH FEB 2021 (CR)





SCREENING | 17TH AUG 2020 | 18TH DEC 2020

Injected | Un-injected

Pt 1122-2014 - CR

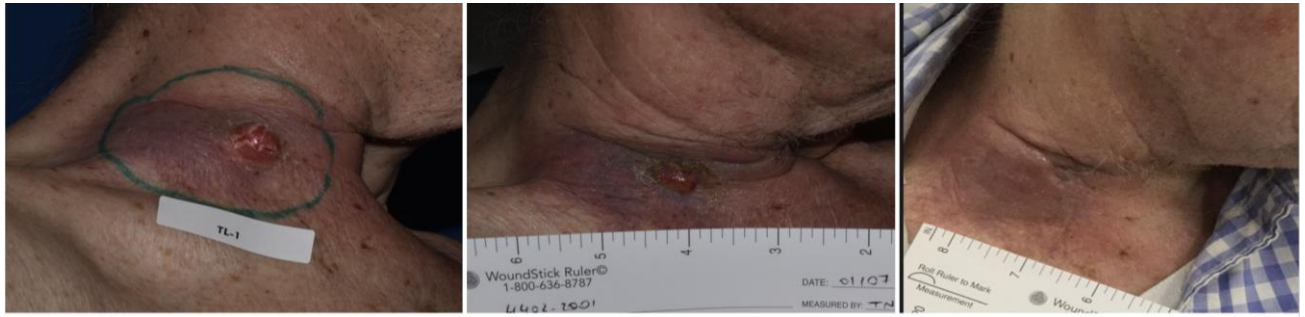
- Patient had groin node metastases that were initially injected & responded
- Response observed in **distant tumor in the foot**, allowing for subsequent injection

Robust effects observed, with complete resolution of uninjected metastases, including bone

June 16, 2019
(baseline)

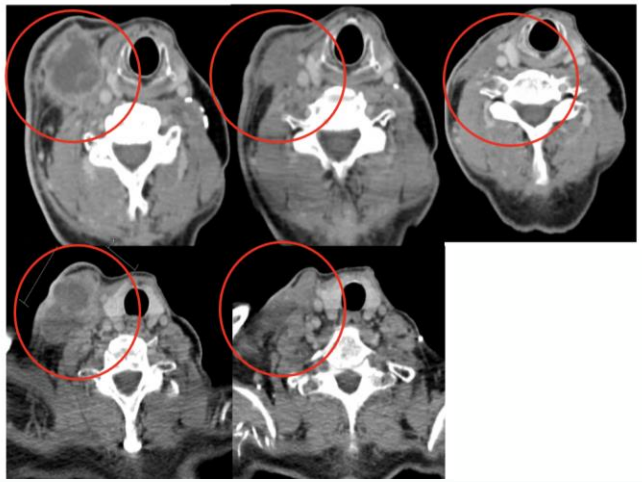
July 1, 2019
(post 1 dose RP1, no Opdivo)

July 16, 2019
(post 2 doses RP1, 1 dose Opdivo)



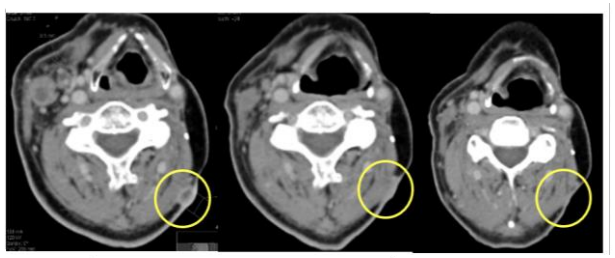
Right neck (injected)

Baseline 8 weeks 24 weeks

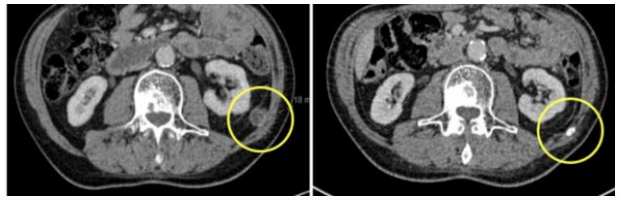


Left neck (un-injected)

Baseline 8 weeks 16 weeks



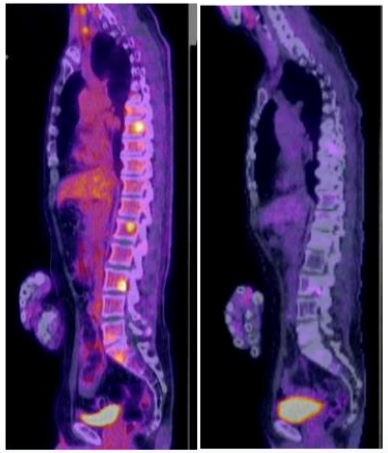
Retroperitoneal lymph nodes (un-injected)



Pt 4402-2001 - CR

- Recurrent CSCC of the neck (bilateral)
- Previously treated with cisplatin-based chemoradiation & six cycles of carboplatin/5-FU
- Both the large injected tumor & the contralateral tumor in the neck reduced before first Opdivo dose
- Resolution of bone metastases

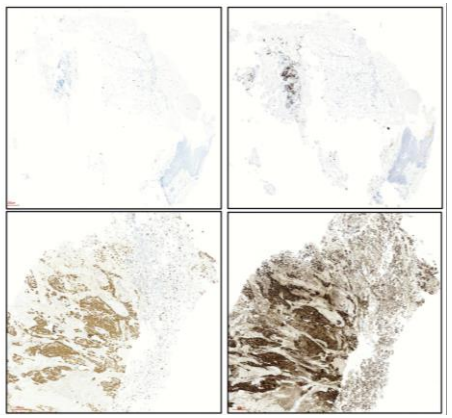
June 2018 Feb 2020



CD8 PD-L1

Baseline

Day 43



Injected Un-injected

Increasing CRs:
An opportunity to transform the CSCC market

CSCC Characteristics

- Large, outward, fast-growing tumors
- Disease can cause social isolation — disfiguring, painful, oozing
- **Directly tackling the problem** via tumor injection

Market Research / KOL Feedback

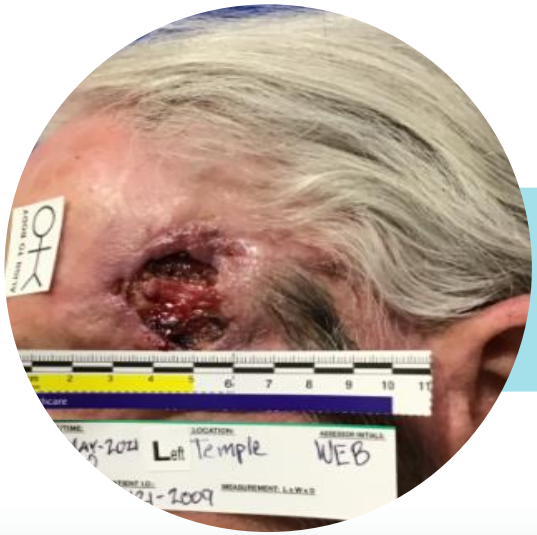
- Despite CPIs impressive outcomes, there is still need for improvement in ORR, and particularly CR
- RP1 profile seen as compelling especially **doubling CRs vs. SOC** with good tolerability

"CRs are very important in this setting, as they usually lead to long-term survival and also have a huge impact on the patient's quality of life"

KOL in market research

Future Market Impact

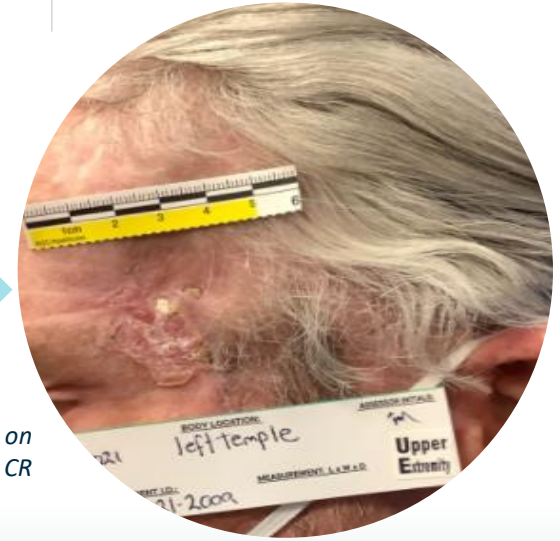
- Potential to change existing mindset and treatment approach to treat more earlier stage patients
- **Driving CRs key to success in neoadjuvant** allowing many more patients to be treated and cured



Ability to see a fast (even prior to CPI admin), deep and durable response

5 months

Latest response ; PR - still on study with potential for CR



CERPASS registration-directed Ph2 study in CSCC

Top line primary analysis of randomized, controlled CERPASS trial expected in Q3 2023

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

†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

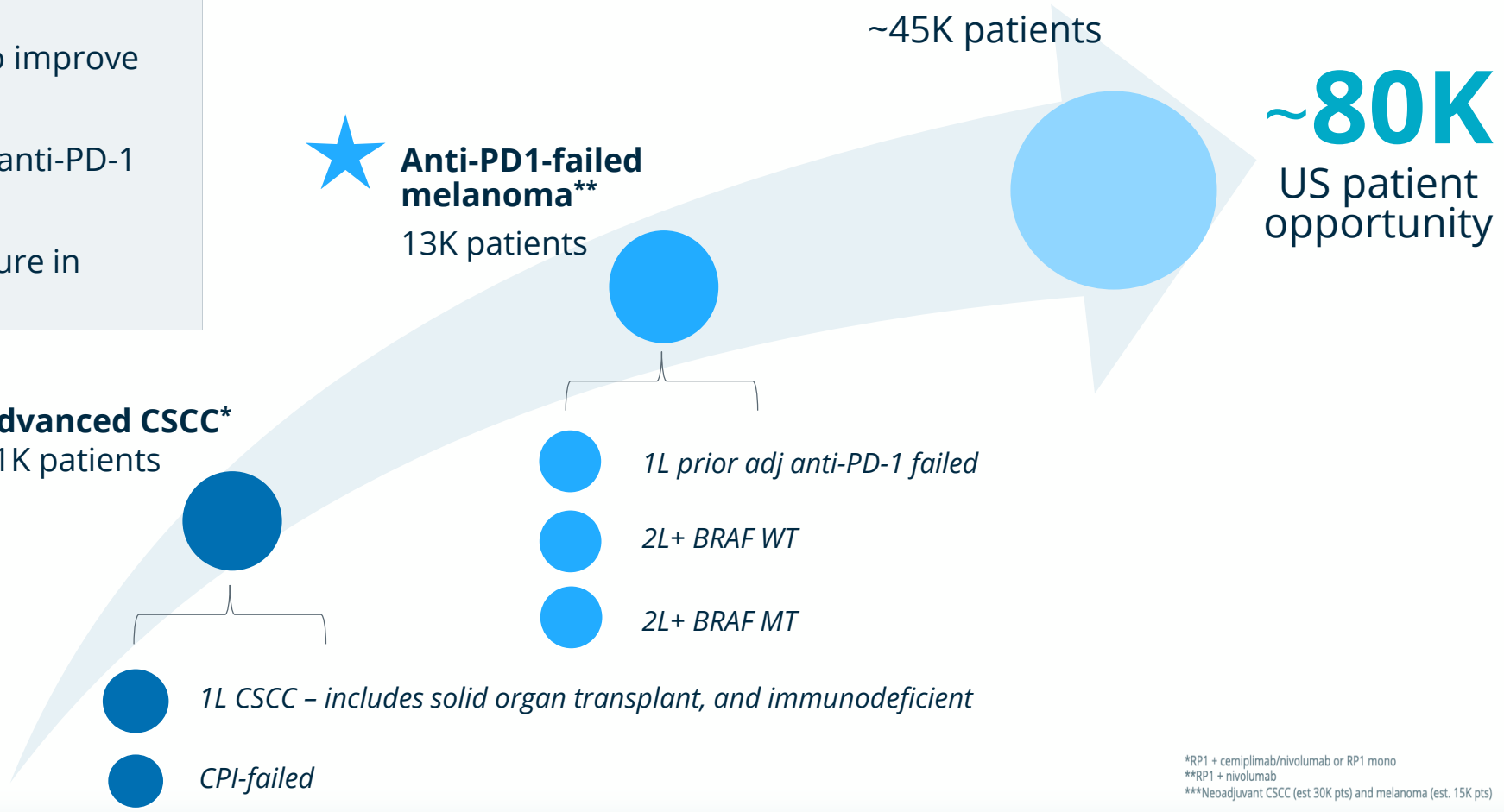
RP1 Commercial Opportunity

AGENDA

RP1: A significant skin franchise opportunity

Aiming to transform skin cancer care with RP1

- RP1 + anti-PD1 intended to improve on SOC
- Address high unmet need anti-PD-1 failed settings
- Provides opportunity for cure in early-stage patients



*RP1 + cemiplimab/nivolumab or RP1 mono
**RP1 + nivolumab
***Neoadjuvant CSCC (est 30K pts) and melanoma (est. 15K pts)

Note: CSCC US treated patient population for 2029 based on multiple sources including IQVIA claims, primary market research, and company data.
Melanoma US treated patient population for 2029 based on CancerMPact® Patient Metrics, Cerner Enviza (available from www.cancermpact.com Accessed 11 Oct 2022), with adjustments to future 2L+ treatment rates based on primary market research

RP1: Initial launch in skin cancers maximizes the chance of commercial success due to high unmet need & tumor directed administration feasibility

Replimune®

Feasible 80-90% of CSCC pts and 50-60% of melanoma pts

Image guidance increases eligible pool to up to 100% of CSCC patients and 80% of all melanoma pts

1 **Superficial lesions**

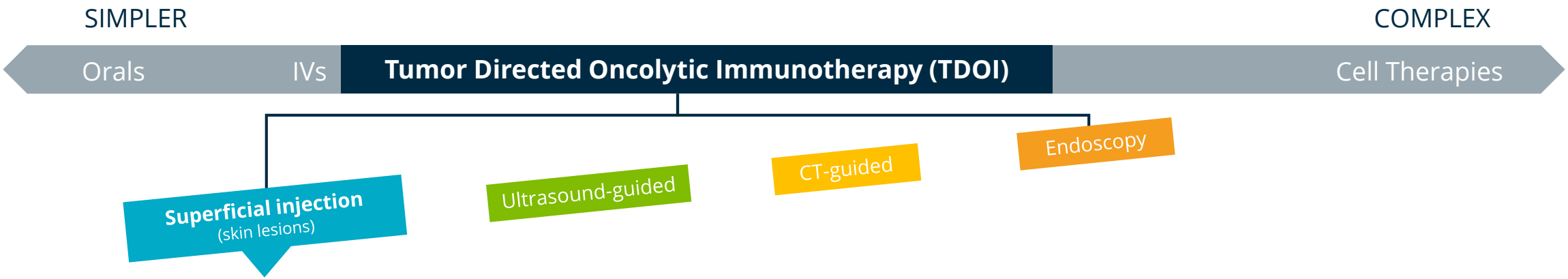
Where delivery can be easy and routine and doesn't need imaging guidance: *Superficial/palpable lesions and sub cutaneous nodes via portable ultrasound*

2 **Deeper nodes/liver lesions**

Where delivery is routine via ultrasound but requires IR/Rad to conduct *e.g., deeper nodes or visceral organs such as liver metastases*

Increasing Administration Intricacy

Superficial skin lesion injections are feasible and can routinely be incorporated across the majority of practice settings



3 Key Focus Areas*

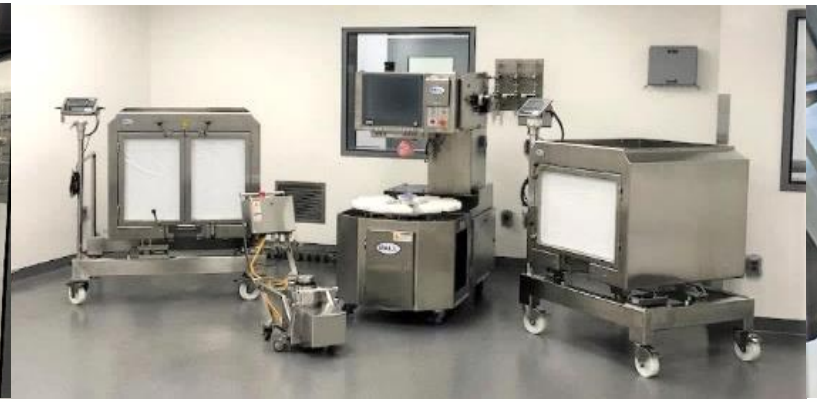
Scheduling & Logistics	• **Ability to refrigerate (2-8^{0}C) RP1 for an extended period enables broad community adoption** • RP1 dosage / admin is readily incorporated into existing workflows
Injection	• **Majority of CSCC and many melanoma lesions won't require image guidance** • Identifying and training injectors e.g., APPs (NP/PA's) at accounts is feasible
Biosafety	• **Biosafety data generation / publications in progress to increase HCP confidence** • Extensive RP1 safety data (>350 pts treated)

*Buying process market research

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
  - *RP1-3 technology transfer from CMO successfully completed*
  - *RP1 released to clinic post comparability analysis*
  - *RP1 BLA consistency lot runs underway*
- 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 and RP3 Update

AGENDA

RP2 & RP3 leverage Replimune's platform to express additional potent immune stimulators

- Focus on the delivery of molecules which function at the time & place of immune activation, i.e. in tumors & draining lymph nodes

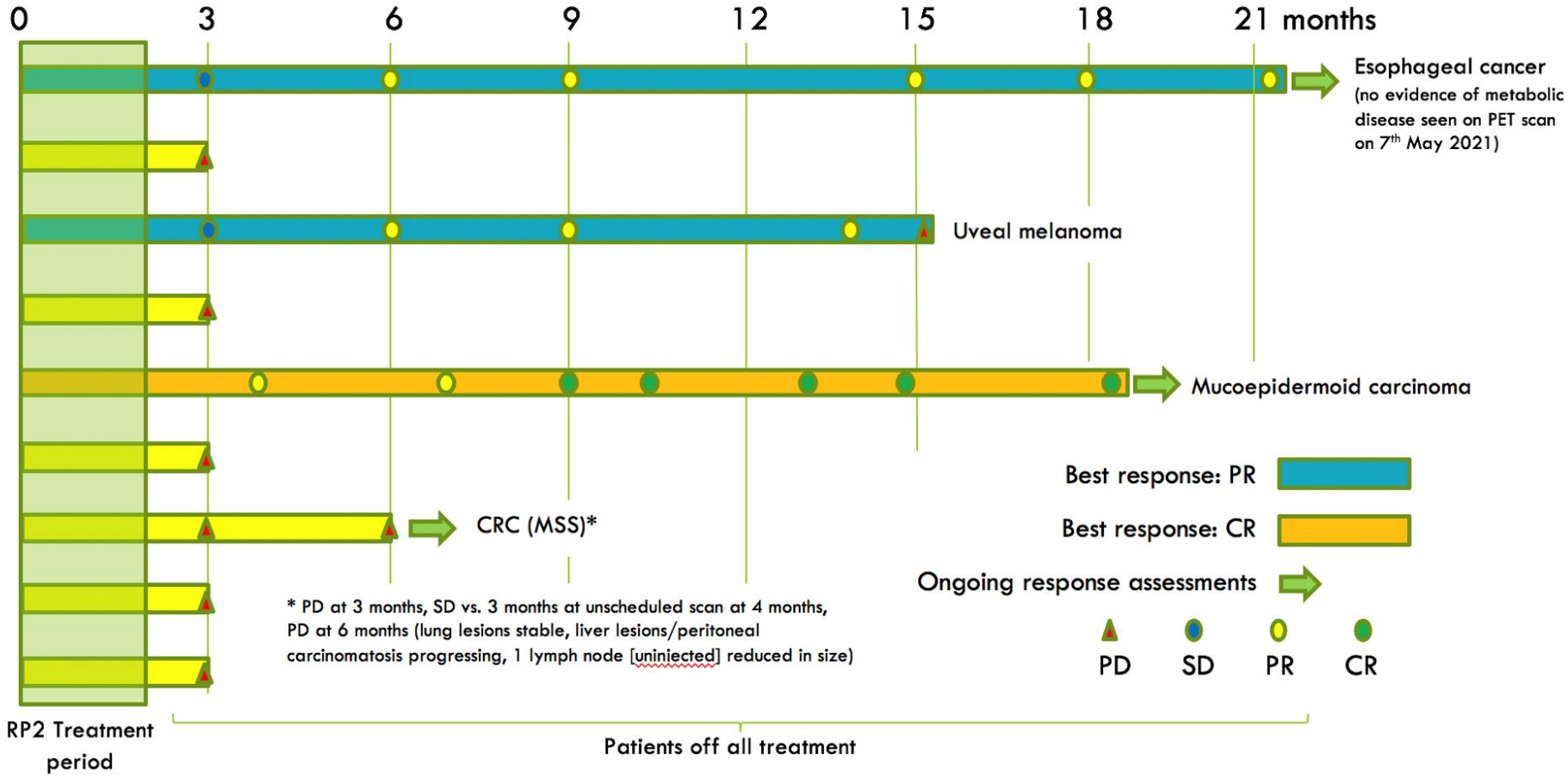
- Delivered mechanisms are clinically validated:
  - *Anti-CTLA-4 – ipilimumab, tremelimumab*
  - *CD40L, 4-1BBL – agonistic antibodies against CD40 & 4-1BB (CD137) have shown clinical activity*

- The RP1 backbone maximizes antigen presentation & T cell activation to kickstart an immune response
  - *CTLA-4 inhibits the effectiveness of antigen presentation and T cell activation (immunogenic 'Signal 1' & 'Signal 2')*
  - *CD40L & 4-1BBL provide immune co-stimulation (immunogenic 'Signal 2') needed for full immune activation — this leads to the expression of inflammatory cytokines – immunogenic 'Signal 3'*

- **Local expression of each of anti-CTLA-4, CD40L & 4-1BBL optimal**, both mechanistically, and to reduce systemic toxicity

Single agent activity demonstrated in traditionally ‘cold’ tumor types

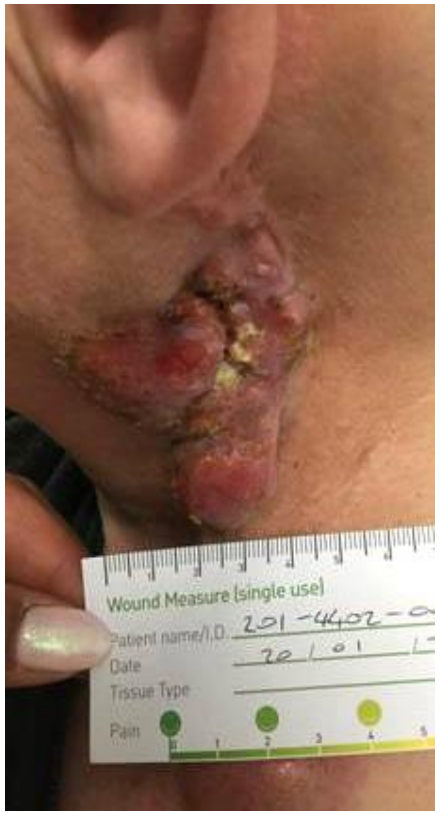
Kinetics of response following treatment with single agent RP2



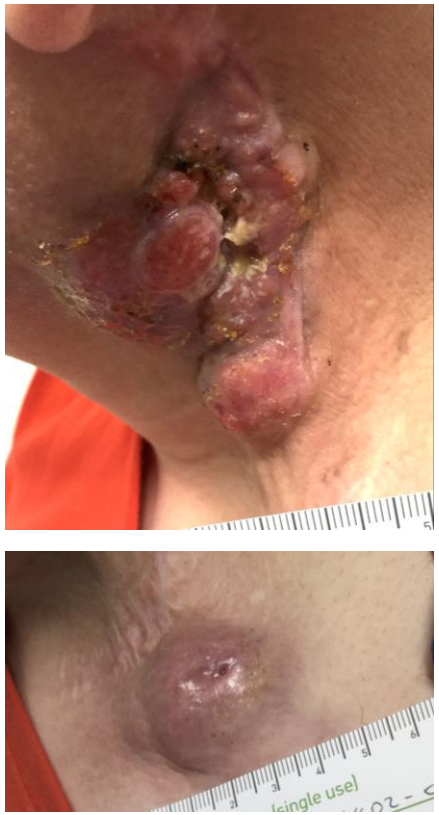
Data as of Oct 12th 2021

Ongoing CR in mucoepidermoid carcinoma following monotherapy RP2

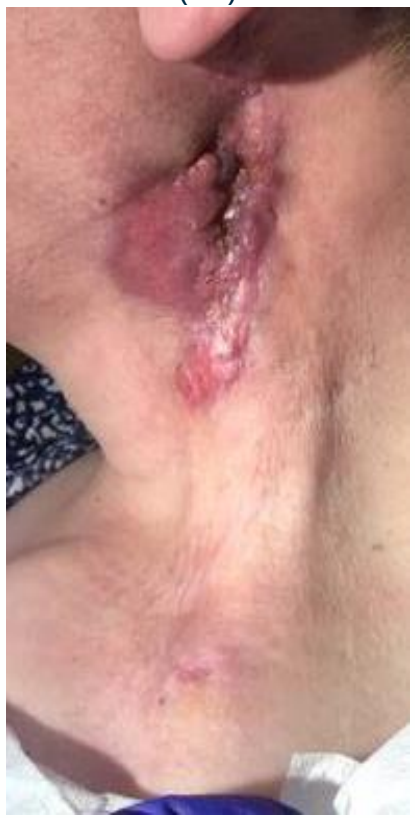
Baseline



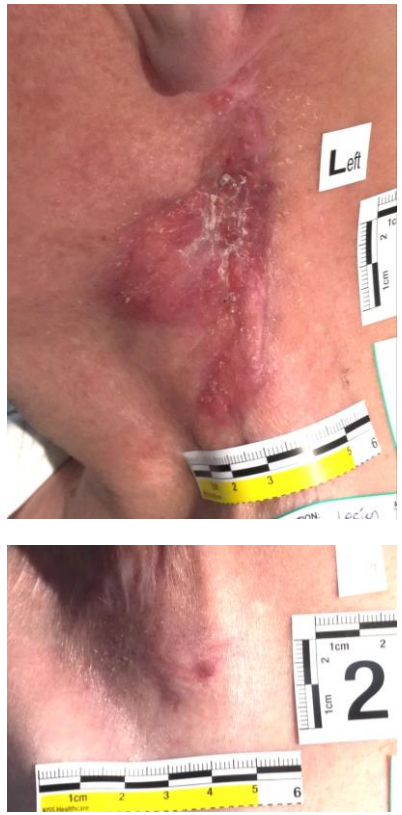
1 month



3 months (PR)



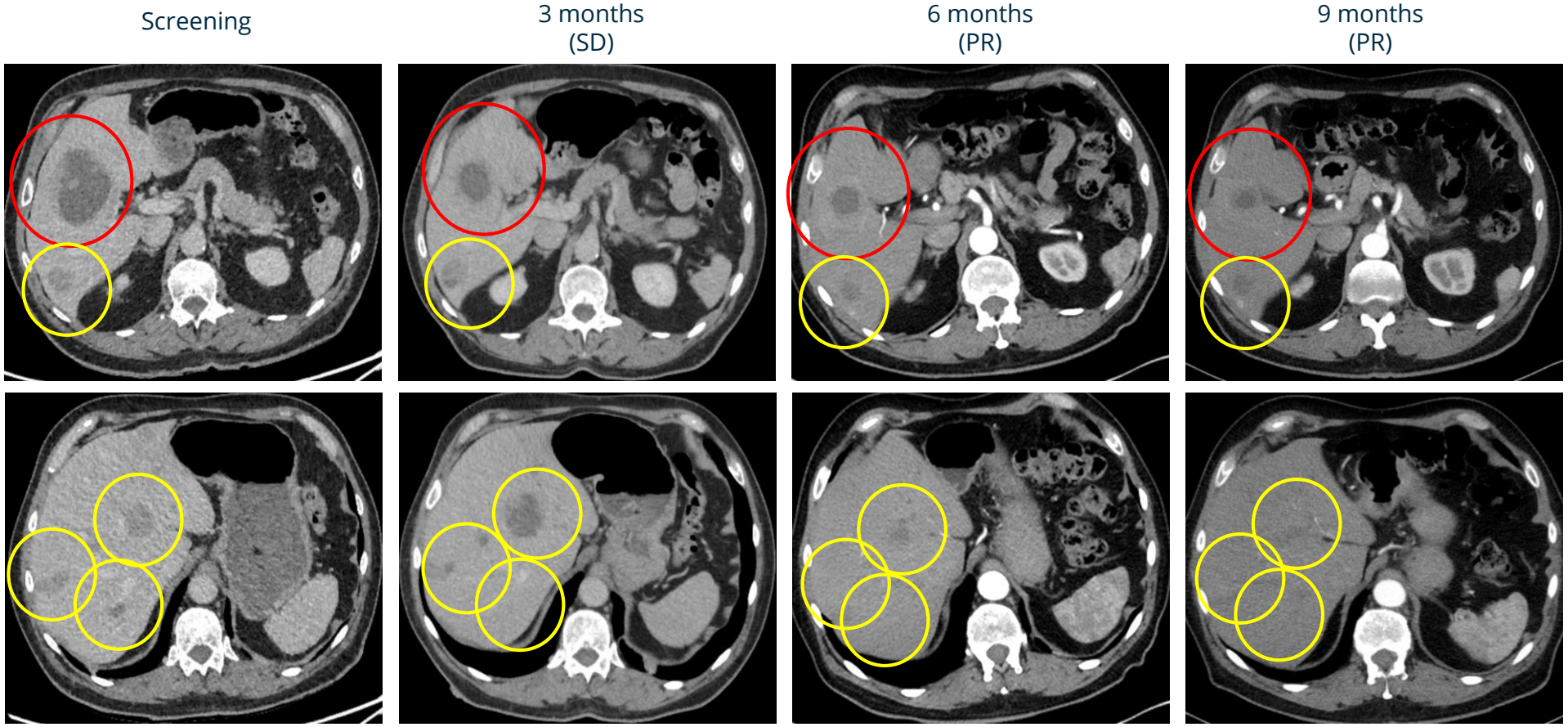
4 months



Pt 4402-0001 - ongoing CR

- Mucoepidermoid carcinoma of the parotid gland
- Prior therapies: carboplatin/ paclitaxel, bicalutamide, ceralasertib
- Cervical lymph node & supraclavicular fossa lesions injected

Example patient with liver metastases treated with RP2 monotherapy – uveal melanoma



Pt 4401-0003 - PR

- Uveal melanoma
- Extensive liver metastases (others not shown)
- Prior therapies: Ipilimumab/ nivolumab
- Patient progressed at 15 months

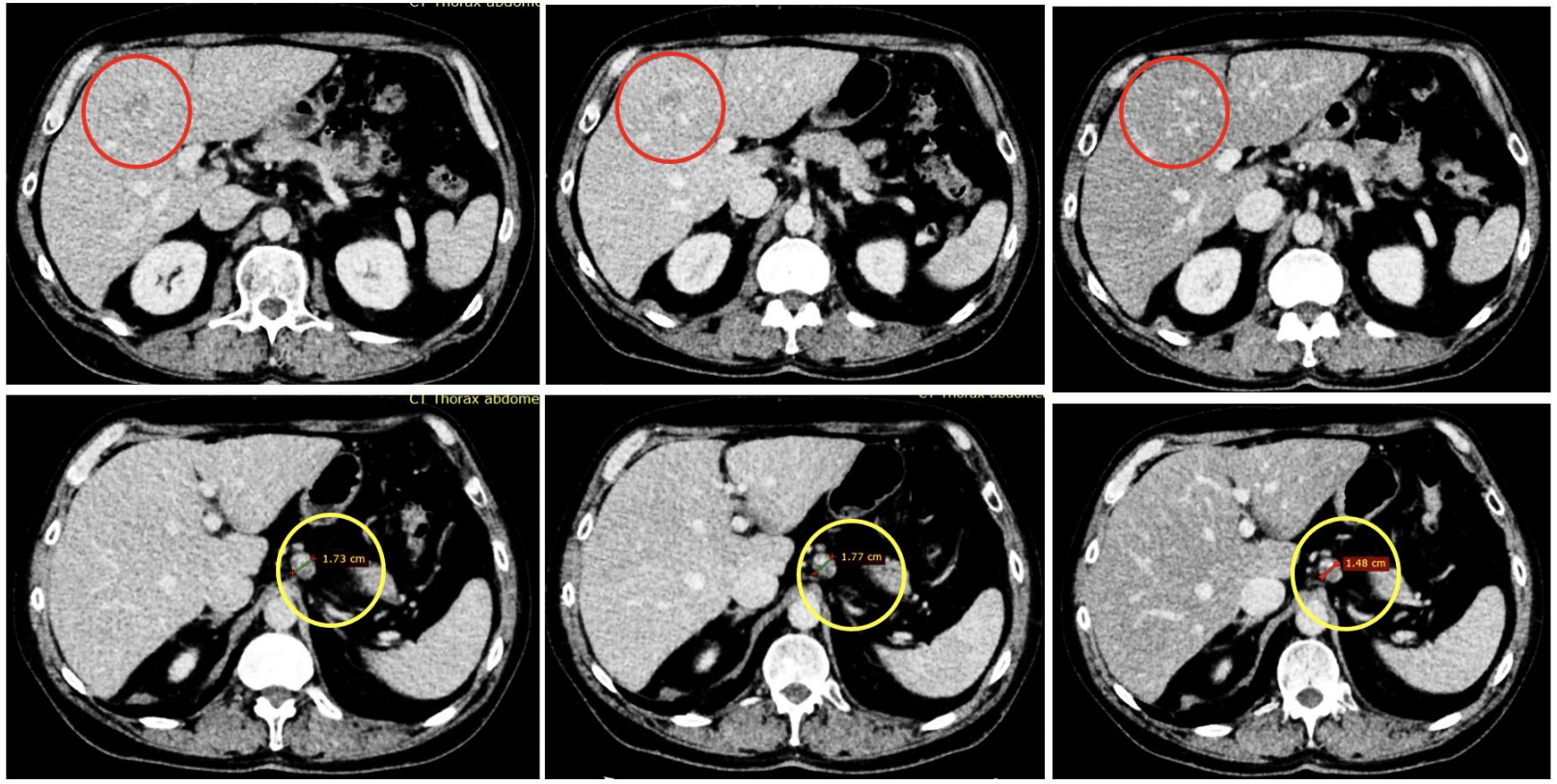
Injected *Un-injected*

Example patient with liver metastases treated with RP2 monotherapy – esophageal cancer

Baseline

3 months
(SD)

6 months
(PR, CR by PET scan at 18 months)



Pt 4401-0001 - ongoing PR

- Esophageal cancer
- Liver & abdominal lymph node metastases
- Prior therapies: Durvalumab (anti-PD-L1), M6620 (ATR kinase inhibitor), capecitabine, oxaliplatin, cisplatin, chemoradiation
- Liver lesion injected

Injected *Un-injected*

RP2 vs. RP3 positioning and ph2 development plan

Liver/liver mets driven post Roche collaboration

Replimune®

RP3 — LA/1L SCCHN

RP3+ chemoradiation followed by nivolumab

LA SCCHN 100 pts randomized → Expand to registrational n

Randomized safety response & RFS data | *Potentially registrational dataset*

RP3+chemo+nivolumab

1L CPS <20 SCCHN Ph2 ≈30 pts → Expand single arm or RCT for approval (N=TBD)*

Open label safety, response & PFS data | *Potentially registrational dataset*

RP3 — 1L/2L HCC

RP3+atezo/bev

1L HCC Ph2 ≈30 pts → 1L RCT

Open label safety, response & PFS data (confirm safety & initial evidence if activity) | *Potentially registrational dataset*

RP3+atezo/bev

2L HCC Ph2 ≈30 pts → Expand single arm or RCT for approval (N=TBD)*

Open label safety, response & PFS data | *Potentially registrational dataset*

RP2 + RP3 — 3L CRC

RP2+atezo/bev & RP3+atezo/bev

3L CRC Ph2 ≈30 pts each → Expand single arm or RCT for approval (N=TBD)*

Open label safety, response & PFS data | *Potentially registrational dataset*

Highlighted green box=potential FTM opportunities

*Pending FDA discussion; Note: Replimune has a clinical trial collaboration & supply agreement with BMS for the supply of Opdivo in its clinical trial program with RP2/3

Unmet need in liver cancer/liver mets remains

Unmet need[1]

- Liver is a common site of metastasis across tumor types
- Patients with liver mets have a poor prognosis
- IO has a particularly poor outcome in pts with liver mets
- Liver mets are often the primary driver of mortality

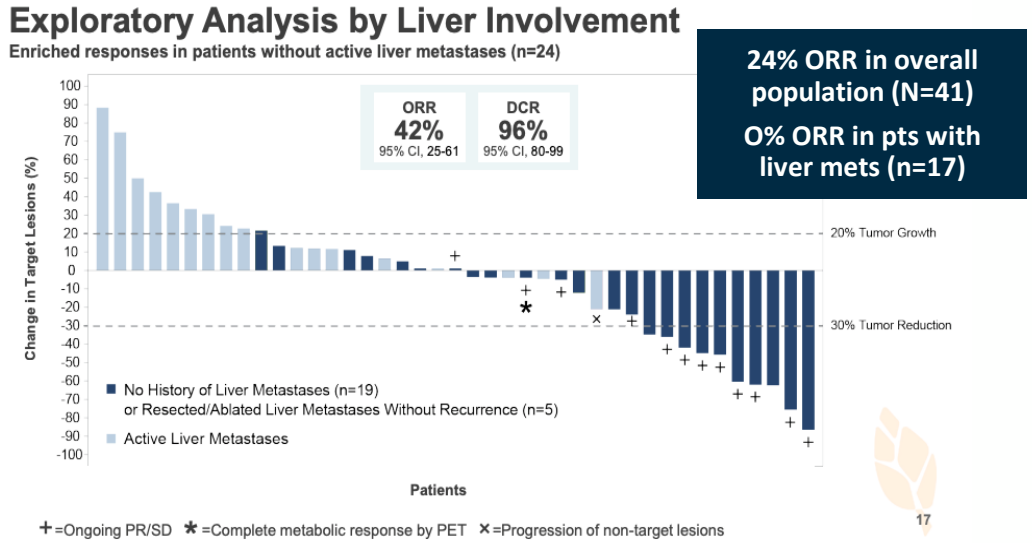
Scientific rationale[2]

- Liver metastases are associated with the antigen-specific elimination of T cells from the circulation by macrophages
  - *Leads to systemic loss of T cells and diminished immunotherapy efficacy*

"OI" rationale/ feasibility

- RPx MOA - powerful direct tumor killing & systemic immune activation
  - *Relief of organ (liver) symptoms & systemic disease control*
- Liver/liver mets are routinely injected by ultrasound and IR/Rads already play a key role in patient management

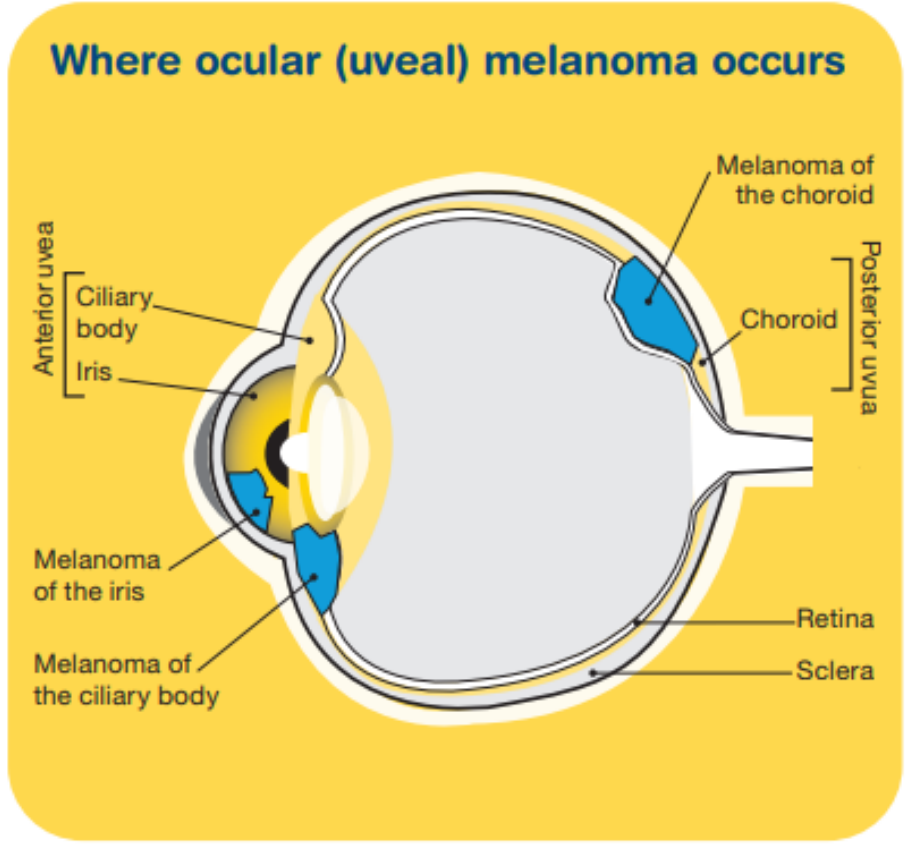
Agenus: 2L+ MSS CRC – Botensilimab (CTLA4)+PD-1
EMSO 2022



[1]SEER 2021 Estimated Deaths. From SEER Cancer Stat Facts by indication; Riihimaki et al Cancer Med 2018
[2]Yu et al Nat Med Jan 2021; IR=interventional radiologists, Rads=radiologists

RP2: Uveal melanoma; proxy for treating immune insensitive disease with liver mets

- 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

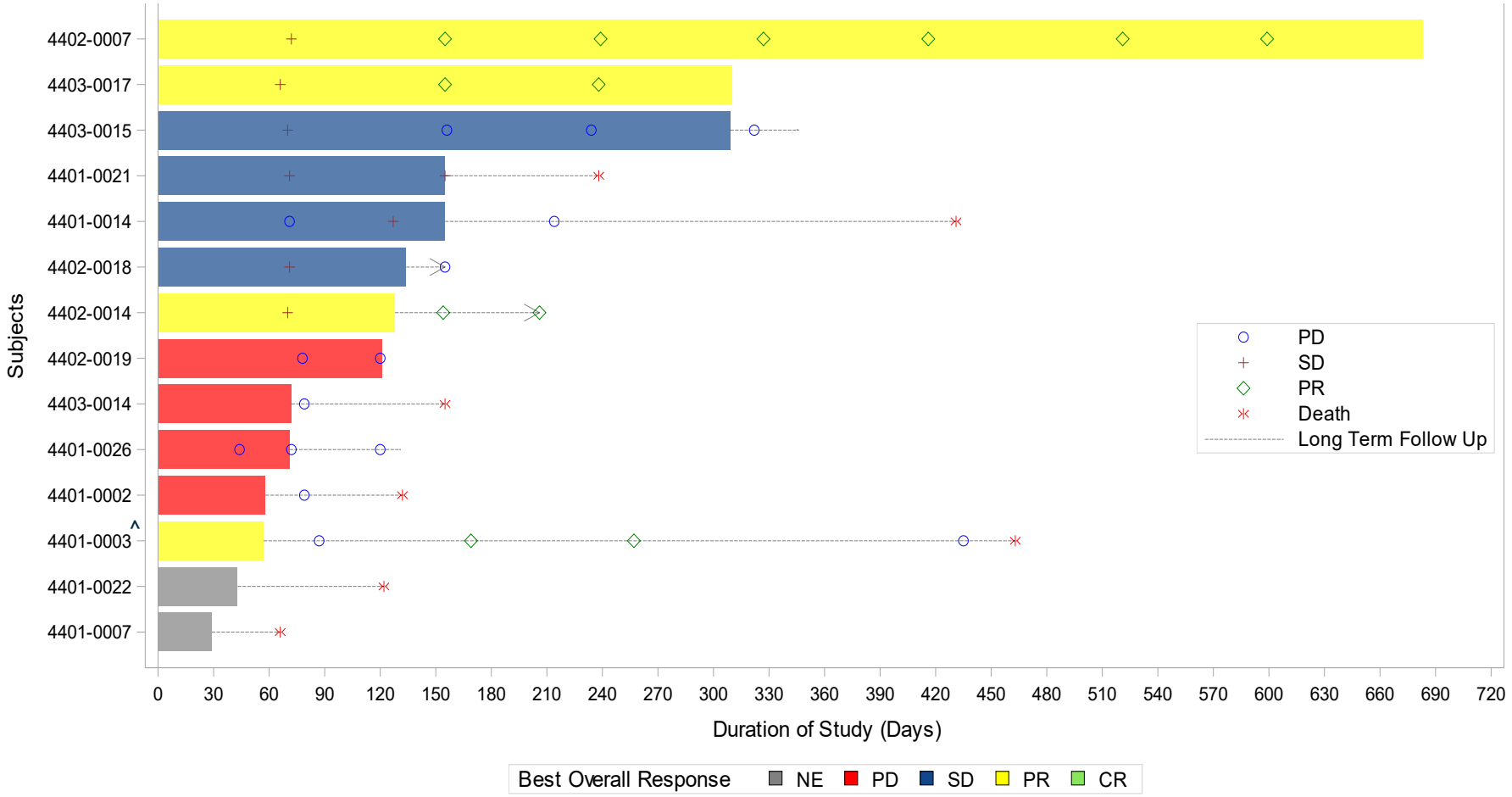
RP2 uveal melanoma

Heavily pre-treated population; all responders anti-PD1 failed, 3/4 double refractory

Patient #	RP2 monotherapy or combination w/ nivolumab	Prior therapies	Sites of disease	Best response
4401-0002	Monotherapy	Ipilimumab + nivolumab, temozolomide, selumetinib + vistusertib, carboplatin	Lung, liver, abdomen, chest, lymph nodes, subcutaneous, bone	PD
4401-0003	Monotherapy	Ipilimumab + nivolumab	Liver	**PR**
4401-0007	Monotherapy	Ipilimumab + nivolumab, intratumoral AGI-134	Liver, kidney, head and neck, peritoneal, intramuscular, subcutaneous, bone	Not done (non-evaluable)
4401-0014	Combination	None	Liver	**SD**
4402-0007	Combination	Nivolumab	Orbital mass, bone (pelvis, vertebral), cheek	**PR**
4401-0021	Combination	Selumetinib + paclitaxel, pembrolizumab, ipilimumab, melphalan intrahepatic chemoperfusion	Liver, gastrointestinal, lymph nodes, abdominal wall, leg	**SD**
4401-0022	Combination	Ipilimumab, dacarbazine	Liver	Not captured
4402-0014	Combination	Ipilimumab, pembrolizumab	Retroperitoneal, SCF	**PR**
4403-0014	Combination	Tebentafusp	Liver	PD
4403-0015	Combination	Tebentafusp, nivolumab + ipilimumab	Lung, liver, vertebra	**SD**
4401-0026	Combination	Ipilimumab + nivolumab, chemosaturation	Liver	PD
4403-0017	Combination	Ipilimumab + nivolumab	Liver	**PR**
4402-0018	Combination	None	Liver	**SD**
4402-0019	Combination	Ipilimumab, pembrolizumab	Liver, perirenal	PD
4403-0018	*Combination*	*Nivolumab + ipilimumab*	*Liver*	**SD**
4403-0019	*Combination*	*Ipilimumab + nivolumab*	*Liver*	*Not done yet*
3412-0001	*Combination*	*Ipilimumab + nivolumab, IL-2, carboplatin, paclitaxel*	*Liver, lung*	*Not done yet*

RP2 uveal melanoma

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



Key Takeaways

- 4/14 (28.6%) evaluable patient responders
- Heavily pre-treated population, with all responders having failed prior CPI

Durable responses represent compelling initial signal

- Median DOR 5.8 months at data cutoff
- Longest ongoing response over 21 months
- Responses deepen over time, after limited RP2 treatment course

^ indicates objective response from monotherapy treatment

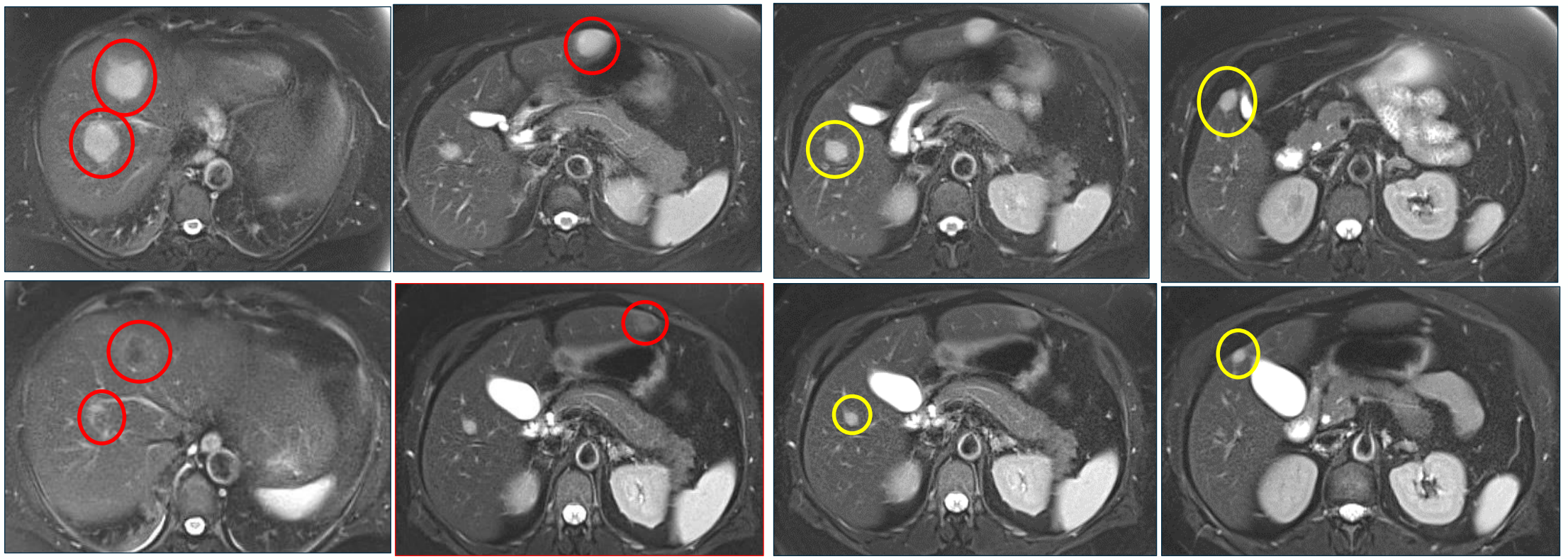
Patient 201-4403-0017: Uveal melanoma

Yervoy/Opdivo failed – PR (RP2+Opdivo)

Replimune®

24th Dec 2021
(Screening)

5th Sept 2022



Injected Un-injected

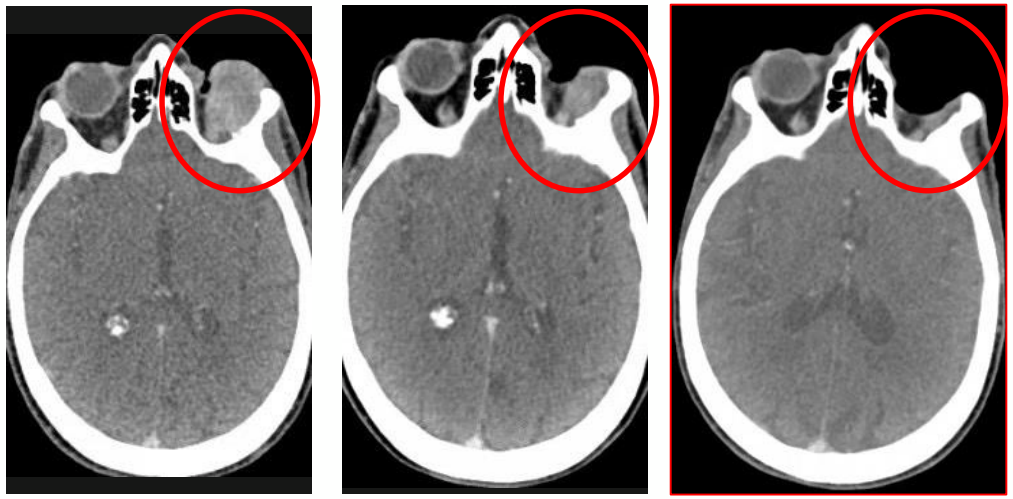
Patient 201-4402-0007: Uveal melanoma

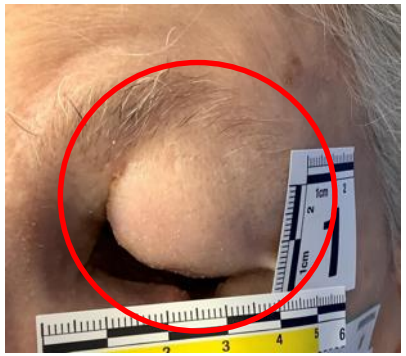
Opdivo failed – PR (RP2+Opdivo)

30th Sept 2020 (Screening)

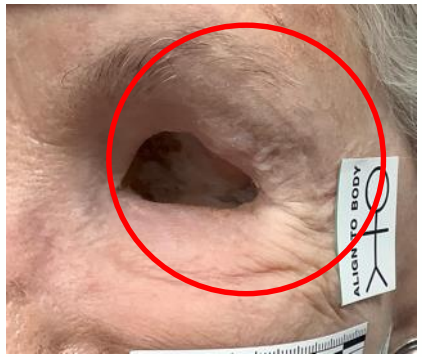
29th Dec 2020

9th June2022





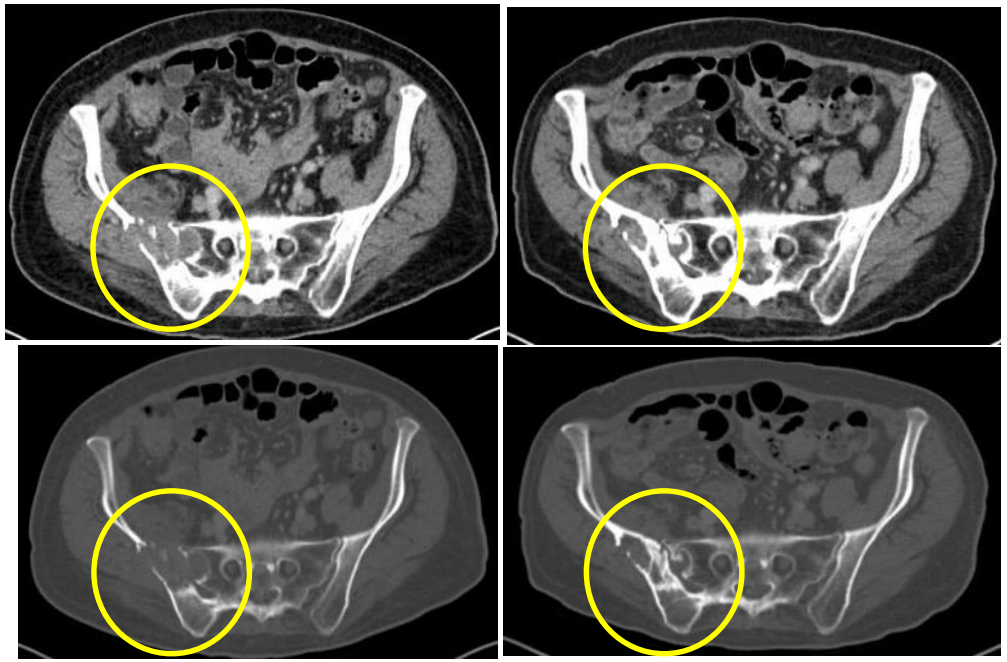
19th Oct 2020 (Baseline)



27th Jan 2021

30th Sept 2020 (Screening)

9th June2022



Notes:

- Ongoing metabolic CR at 21 months

Injected Un-injected

Overall summary

Major skin cancer franchise planned with RP1

- Strong data to date in multiple skin cancers in both the PD1 naïve and failed setting
  - *Anti-PD1 failed data presented to date potentially transformative in anti-PD1 failed melanoma*
  - *CERPASS registrational data in CSCC expected Q3 2023*
- Scale manufacturing in place
  - *To serve worldwide market at attractive COGS*
- Commercial planning ramping up for intended US launch in H2 2024*

RP2 and RP3 mid-stage pipeline

- Focused on easily injected tumor types with high commercial value, such as SCCHN, HCC, & CRC
- Fast routes to randomized controlled trials or expansion of single arm trials for approval
- Early signal emerging in uveal melanoma and other cold tumor types

Strong cash position to execute on our vision

- Cash and Investments of $583M as of March 31, 2023
- Availability of $200M non-dilutive debt facility

With catalyst rich 2023

- RP1 CERPASS primary read out
- RP1 ARTACUS update
- RP1 NMSC anti-PD1 failed update
- RP1 IGNYTE anti-PD1 failed melanoma 6 month read out from the fully enrolled population
- RP2/3 further Phase 1 expansion data
- Initiation of RP2/3 Phase 2 trial program

* Subject to submission & approval of a BLA

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®