Replimune®

NEXT-GENERATION ONCOLYTIC IMMUNOTHERAPY

JP MORGAN - January 2022

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, 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 Corporate Overview

Proprietary oncolytic immunotherapy platform

- Intended to maximally activate a systemic immune response against a patient's cancer
- Intended to establish Replimune's products as the second cornerstone of immuno-oncology

RP1 in numerous clinical trials with focus on establishing a major skin cancer franchise

- Registration directed development based on compelling efficacy and safety profile
  - CERPASS clinical trial in advanced anti-PD1 naïve cutaneous squamous cell carcinoma (CSCC)
    - On track for last patient in mid year ; trigger for primary analysis late 2022
  - IGNYTE clinical trial in anti-PD1 failed melanoma
    - Interim results expected late 2022

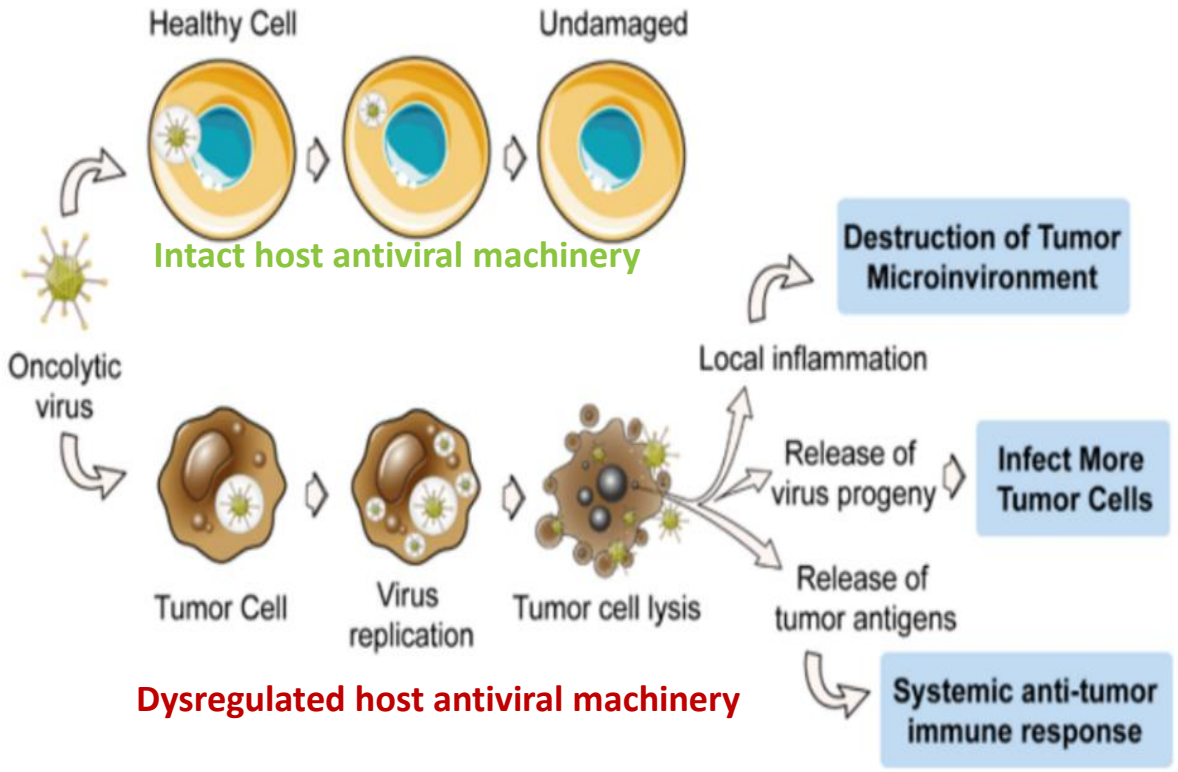
RP2/3 optimized for superior immune stimulation, intended to treat immunologically 'cold' tumors

- RP2 Phase 1 clinical trial
  - Durable single agent & combination with Opdivo activity demonstrated in heavily pre-treated immune insensitive & anti-PD1 failed tumors
- RP3 Phase 1 clinical trial – initial monotherapy data expected later in quarter
- RP2/3 – Broad Phase 1 expansion underway / planned, Phase 2 program expected to be presented later this quarter

Company positioned for long term growth supporting a new pillar of oncology

- Commercial scale manufacturing facility operational; GMP production underway
- Commercial planning activities underway
- Well capitalized to deliver, with cash, cash equivalents and short-term investments of ~$436m as of September 30th 2021

Tumor directed oncolytic immunotherapy provides a unique dual mechanism by which to kill tumors



1. Direct local killing of the tumor & altering the TME
2. Release of tumor antigens igniting a strong systemic anti-tumor immune response
3. Flexibility to combine with multiple modalities due to minimal additive side effects
4. Designed to deliver transformational results across tumor types

Bommareddy PK et al AJCD. 2016

Practical and comprehensive activation of an anti-tumor immune response

Our platform offers ***significant potential advantages compared to competing approaches***, including cell-based therapies and personalized cancer vaccines

	Replimune's Immulytic platform	Cell-based therapy (including TILs)	Personalized cancer vaccines
"Off the shelf" – no patient-specific manufacturing	✓	✗	✗
Commercially attractive COGS	✓	✗	✗
Efficacy from multiple immune modalities – both innate & adaptive immunity stimulated	✓	✗	✗
Attractive safety profile, with limited high-grade side effects	✓	✗	✓
Applicable to nearly all patients with solid tumors – not limited by surface markers or mutations	✓	✗	✗

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

Replimune®

CRITERIA	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)	Prevalent tumor types including those with tumors in the liver e.g. colon Various more superficial tumors e.g. SCCHN Other solid tumors including I-O resistant e.g. uveal melanoma	
Commercial opportunity	++	++++	
Clinical activity in anti-PD1 failed patients demonstrated	✓	✓	Ongoing
Safety & good tolerability demonstrated	✓	✓	Ongoing
Injection location	Superficial, nodal & visceral		
Systemic activity	Clear systemic effects seen in responding patients – uninjected tumors responding, responses generally highly durable		Ongoing
Other considerations	Optimally design for more I-O sensitive tumors with excellent safety in combination	Increased I-O systemic activity with good safety in combination	Maximized for systemic I-O activation & potency

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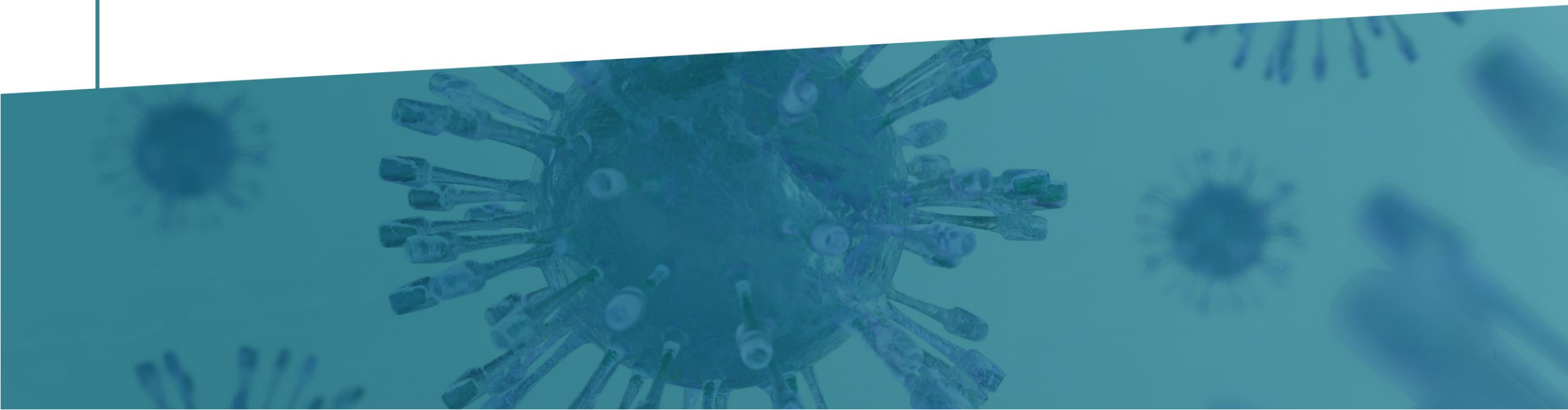
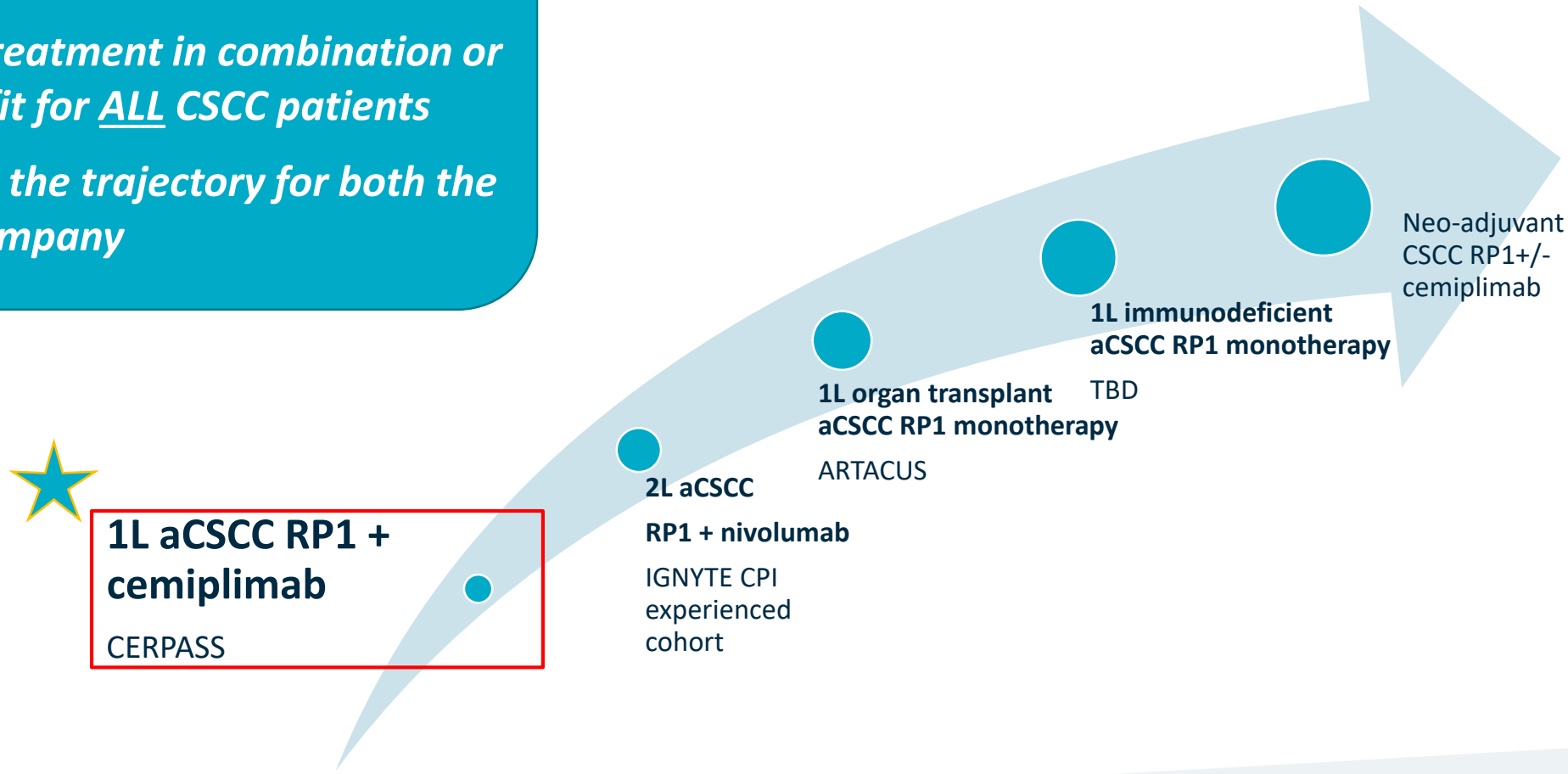
RP1



Building a skin cancer franchise & an overall RPx platform starts with the successful launch of RP1 in 1L advanced CSCC

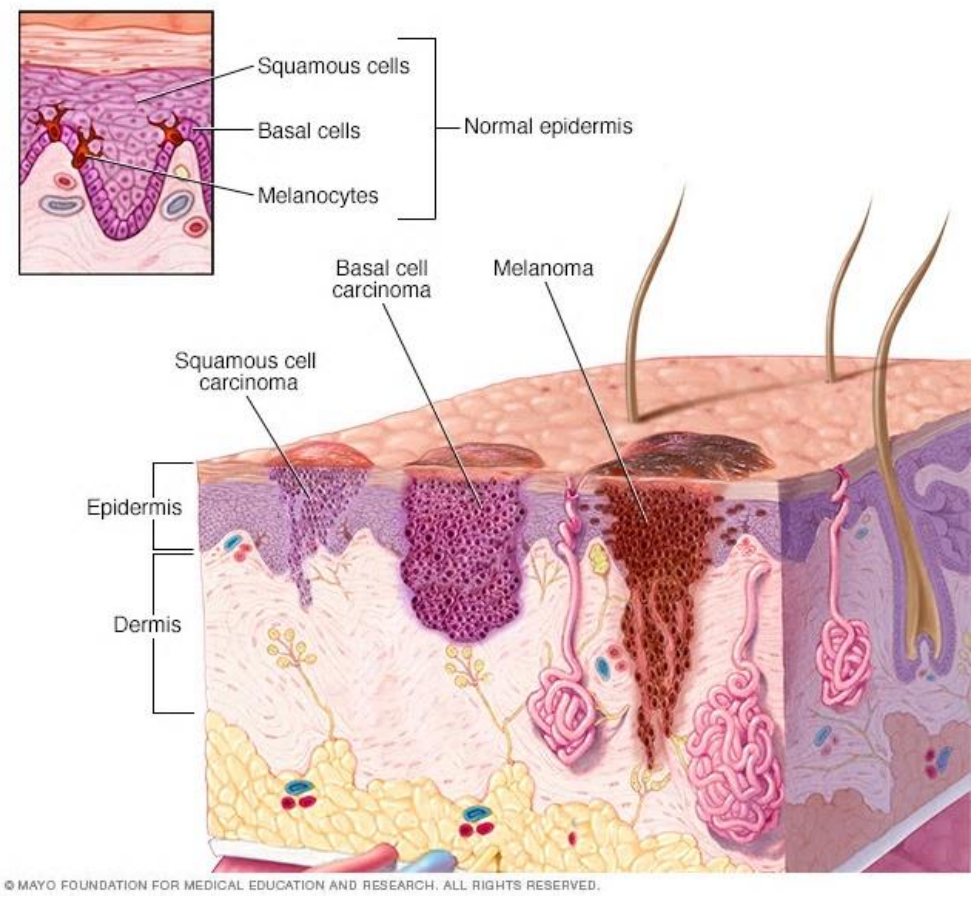
Owning CSCC:

- **Think CSCC, think RP1**
- ***RP1 to be the first treatment in combination or alone to offer benefit for ALL CSCC patients***
- ***The first launch sets the trajectory for both the portfolio and the company***



CSCC disease characteristics: largely a superficial/local issue

- The 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-aduvant 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 systemically treated patients have **prior surgery and/or radiation**
- First systemic treatment, cemiplimab, approved in 2018 followed by pembrolizumab in 2020. (ORR 35-50%, 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

Randomized controlled Phase 2 clinical trial in CSCC (CERPASS)

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 prior treatment with other immune modulating agents (incl CTLA-4)
- No untreated brain metastases

2:1
N=180

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 primary endpoints: CR& ORR (RECIST v1.1)
To win on both: An approximate 17% & 15% improvement for ORR & CRR, respectively is required
To win on ORR only: An approximate 19% improvement is required
To win on CRR only: An approximate 17% improvement is required
Secondary: 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

Signal finding study showed compelling activity of RP1 + nivolumab in non-melanoma skin cancers, including in CSCC

Best response

Efficacy evaluable population (Patients with follow up scans or PD)

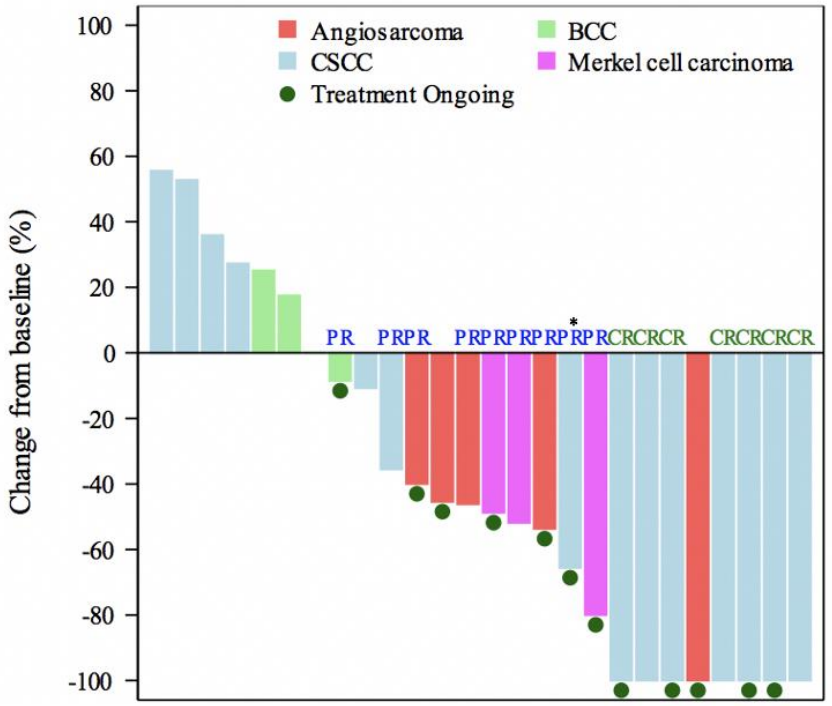
		CSCC	BCC	Merkel cell carcinoma	Angiosarcoma
Number of patients		15	4	4	5
Best overall response n (%)	**CR**	7 (46.6)	0	0	0
	PR	2* (13.2)	1 (25)	3** (75)	3** (60)
	SD	1 (6.7)	2 (50)	0	1 (20)
	PD	4 (26.7)	1 (25)	1 (25)	1 (20)
	ORR	9 (60)	1 (25)	3 (75)	3 (60)
	CR+PR+SD	10 (66.7)	3 (75)	3 (75)	4 (80)

* One PR patient awaiting formal per protocol confirmation of CR by biopsy

**One not yet confirmed

Maximum percent tumor reduction

Patients with follow up scans



* Awaiting formal per protocol confirmation of CR by biopsy

30 patient cohort of patients who have failed prior anti-PD1 therapy added

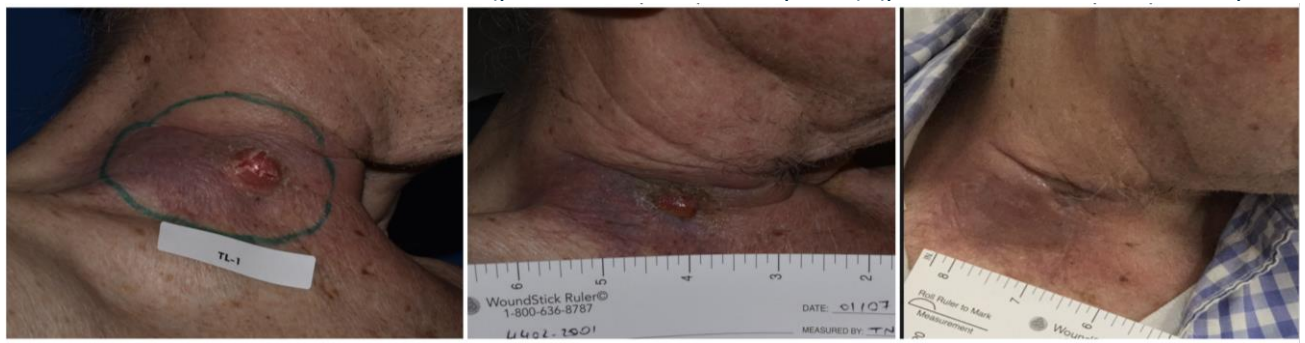
Data as of June 3 2021

Robust abscopal effects observed, with 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)

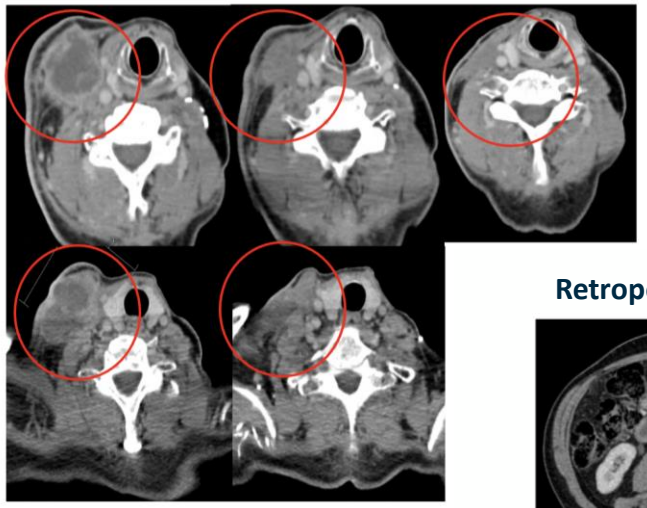


Pt 4402-2001 - CR

- 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

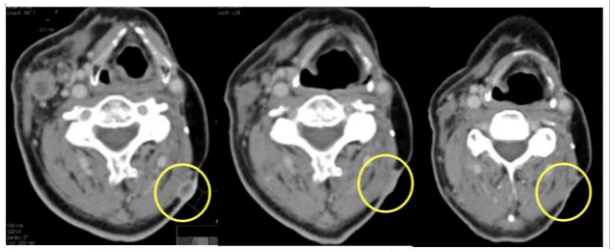
Right neck (injected)

Baseline 8 weeks 24 weeks

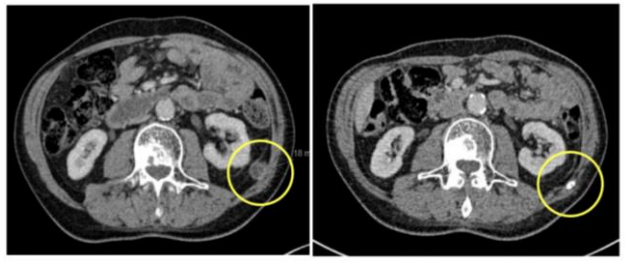


Left neck (un-injected)

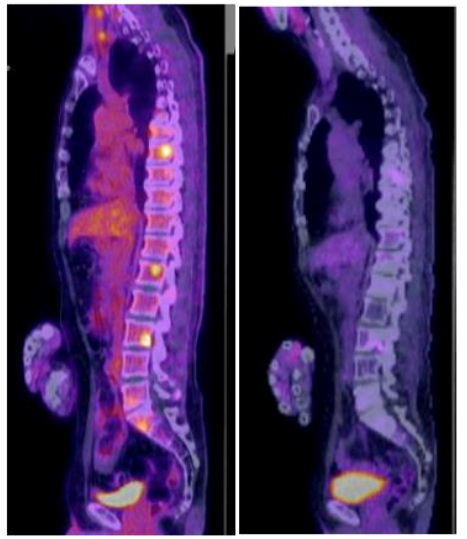
Baseline 8 weeks 16 weeks



Retroperitoneal lymph nodes (un-injected)



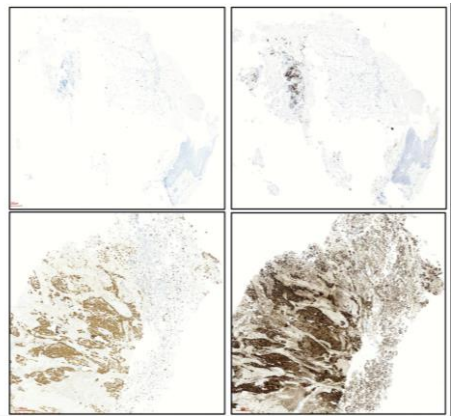
June 2018 **Feb 2020**



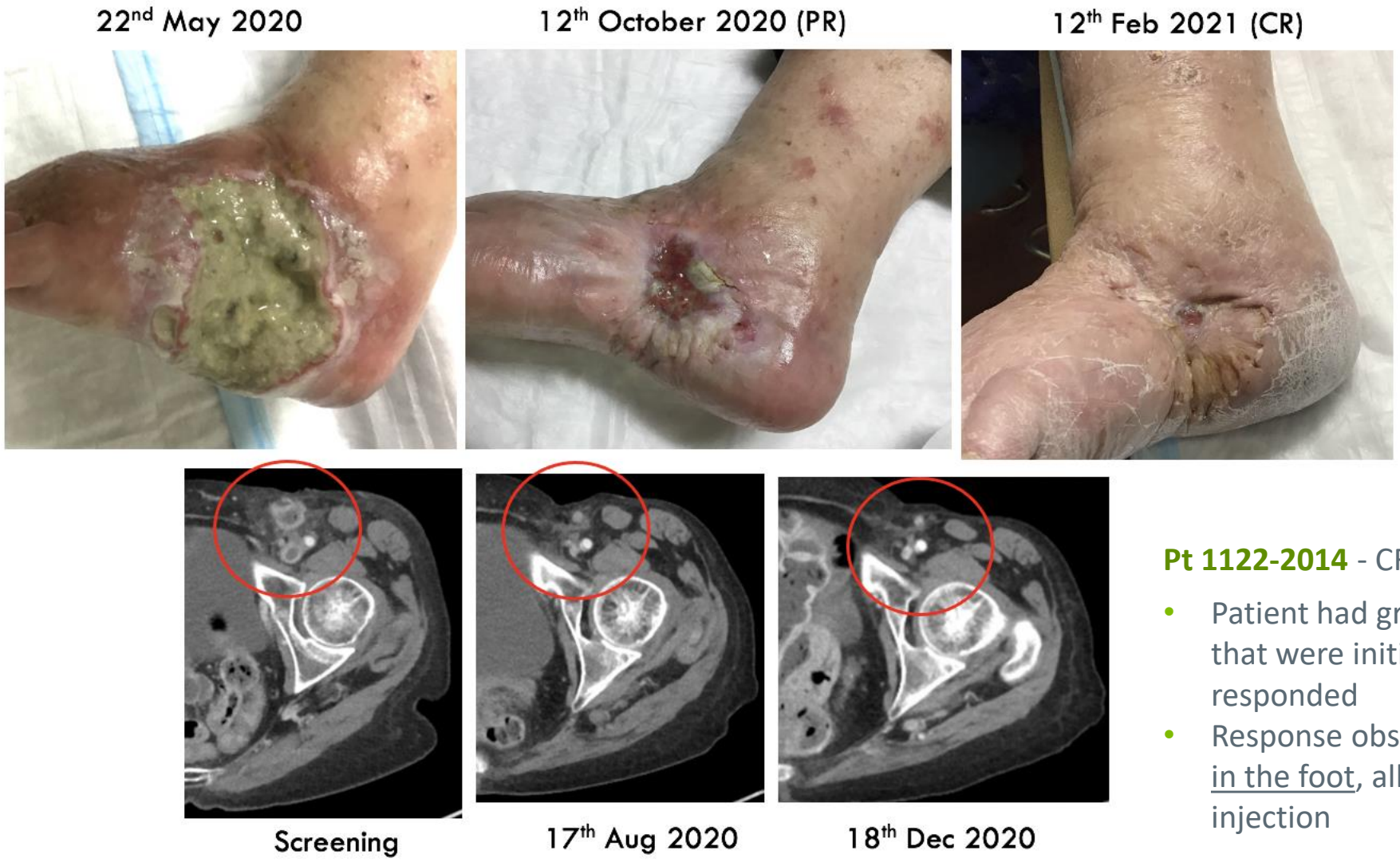
CD8 PD-L1

Baseline

Day 43



Resolution of aggressive locoregional disease



Pt 1122-2014 - CR

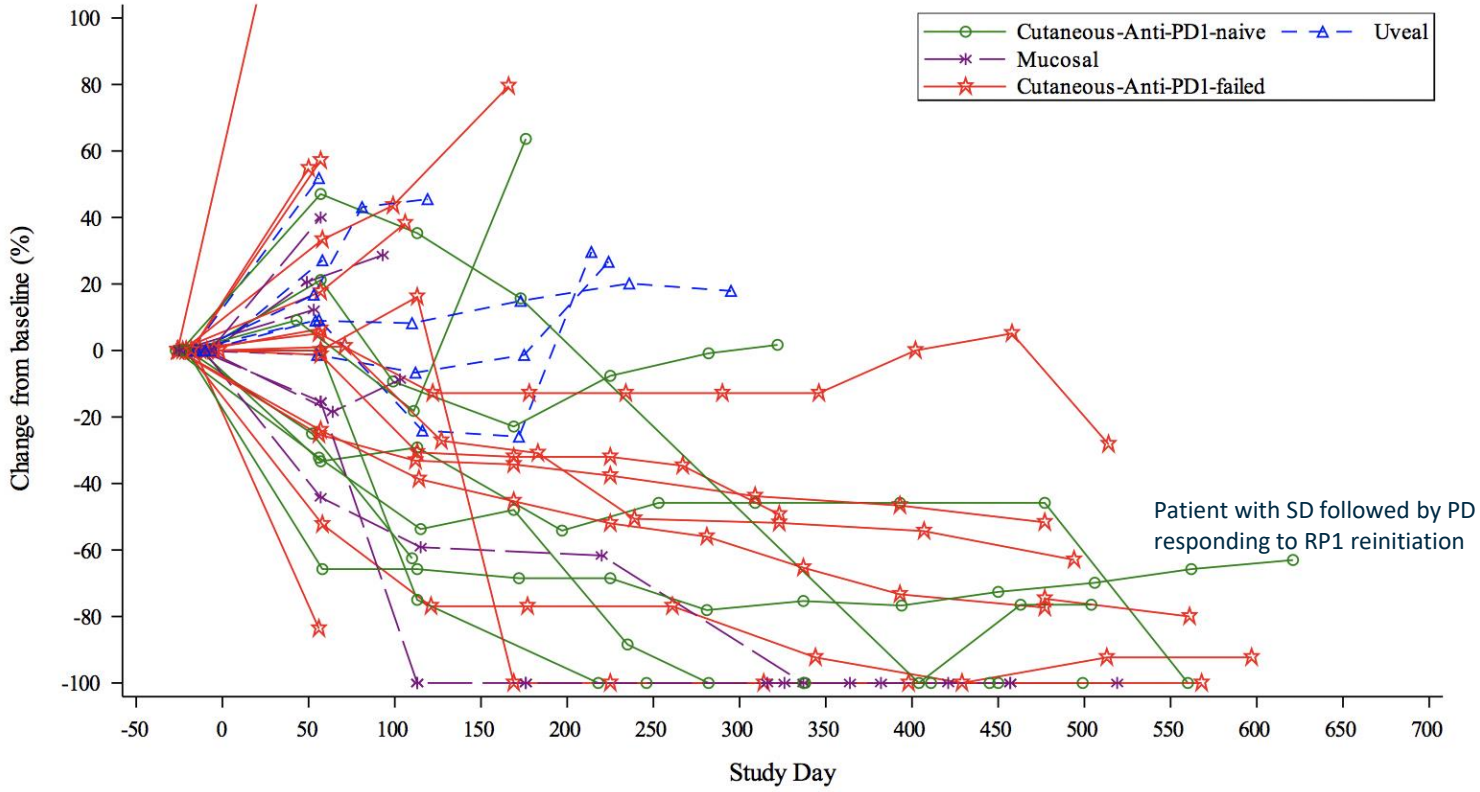
- Patient had groin node metastases that were initially injected & responded
- Response observed in distant tumor in the foot, allowing for subsequent injection

Anti-PD1 failed melanoma – opportunity

- Approximately half of advanced melanoma patients still die of their disease, despite multiple approved therapies now being available
  - Anti-PD1, anti-CTLA-4, combined anti-CTLA-4/anti-PD1, BRAF targeted agents
  - Approximately 7,230 US deaths annually from metastatic melanoma[1]
  - 40-65% of all metastatic melanoma are primary refractory to initial anti-PD1 therapy[3]
- Expected response rate to continued treatment with anti-PD1 therapy following confirmed progression on single agent anti-PD1 is 6-7%[4,5]
- Registration-directed single arm 125 patient Phase 2 cohort of RP1 combined with Opdivo in anti-PD1 failed cutaneous melanoma
  - Confirmed disease progression required while on prior anti-PD1 therapy
  - Primary endpoint: ORR by independent central review
- Design discussed with the FDA at a Type B meeting
  - Assuming clinically meaningful compelling data is generated, data able to be submitted for accelerated approval
  - As required for accelerated approval, a confirmatory clinical trial would also be needed to be underway at BLA filing
  - Study requires an observed ORR of 22% to discount a true response rate of <15% & an observed response rate of 28% to discount a true response rate of <20%

[1]https://seer.cancer.gov (2019 data); [2]Global Burden of Disease Cancer Collaboration *JAMA Oncol* 2019 (12); [3]Gide et al *Clin. Cancer Res* 2018 (24)
[4]Ribas et al *Lancet Oncology* 2018 (19); [5]Hodi et al *JCO* 2016 (34); [6]Pires de Sliva et al *J Clin Onc* 2020 (38)

Responses are deep & durable, including in anti-PD1 failed melanoma

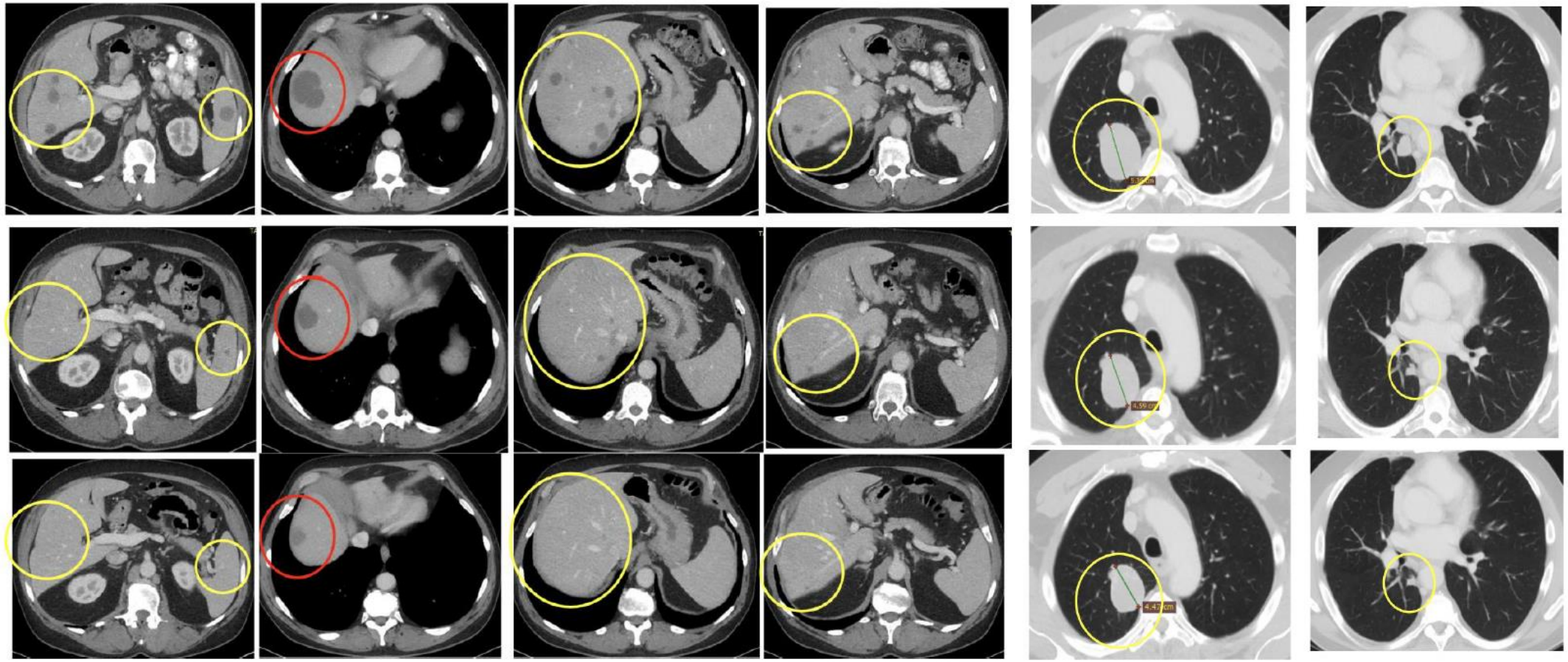


- ***31% ORR in patients with anti-PD1 failed cutaneous melanoma, in a very advanced population (87.5% Stage IV M1b/c), 75% of responders having also failed anti-CTLA-4***
- ***Responses are highly durable***
- ***Extended clinical benefit also seen in patients with a best response of SD***
- ***Other patients remain on study with the opportunity for response***

Data as of June 3 2021

Anti-PD1/anti-CTLA-4 failed melanoma: Systemic overall response

Pt 1122-2007 – PR (ongoing at 19 months from first RP1 dose)



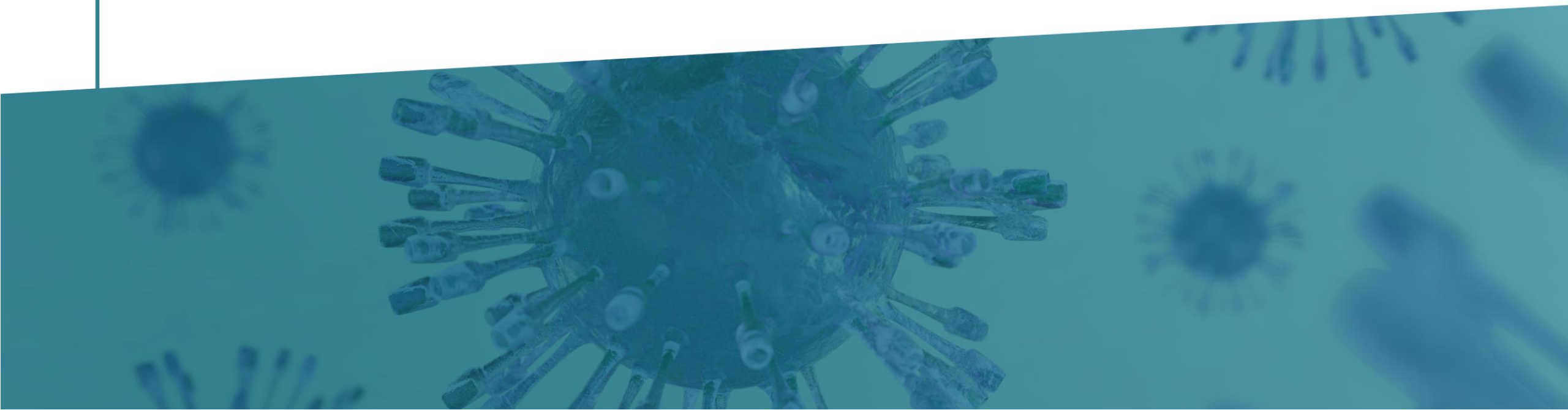
Injected

Not injected

All lesions show no evidence of metabolic activity by PET scan

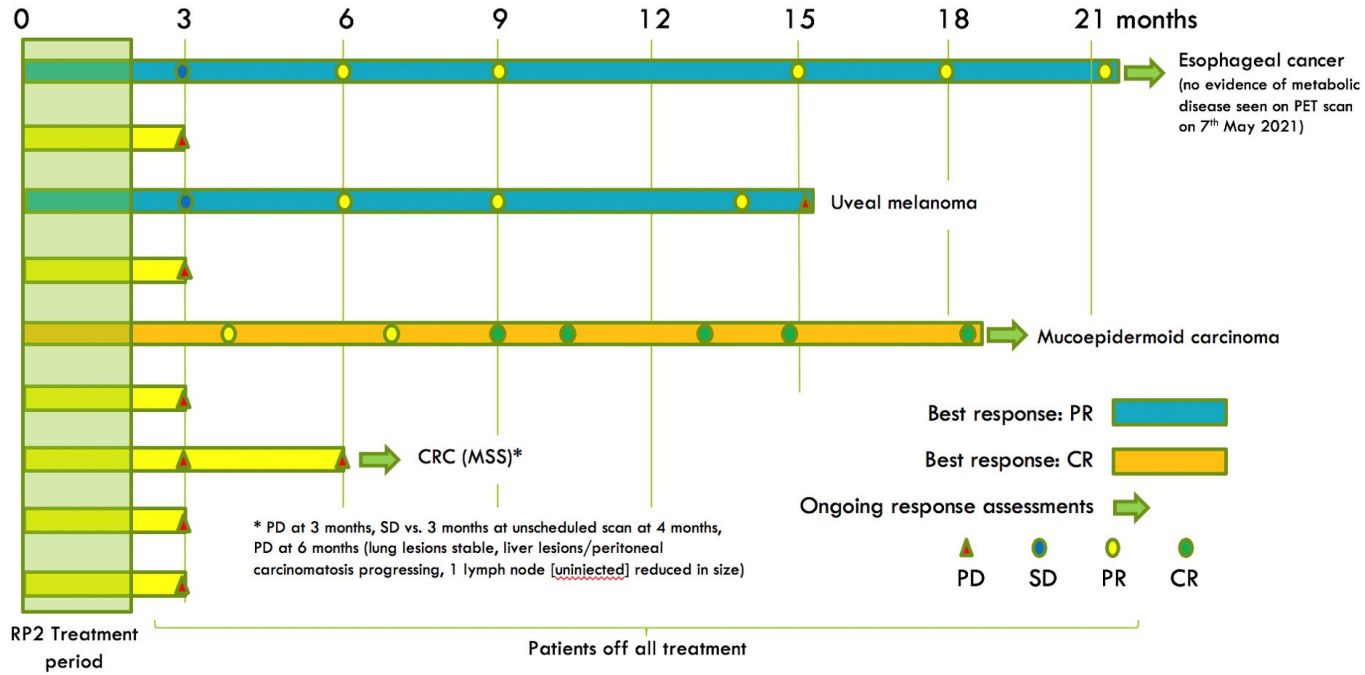
Replimune®

RP2/3



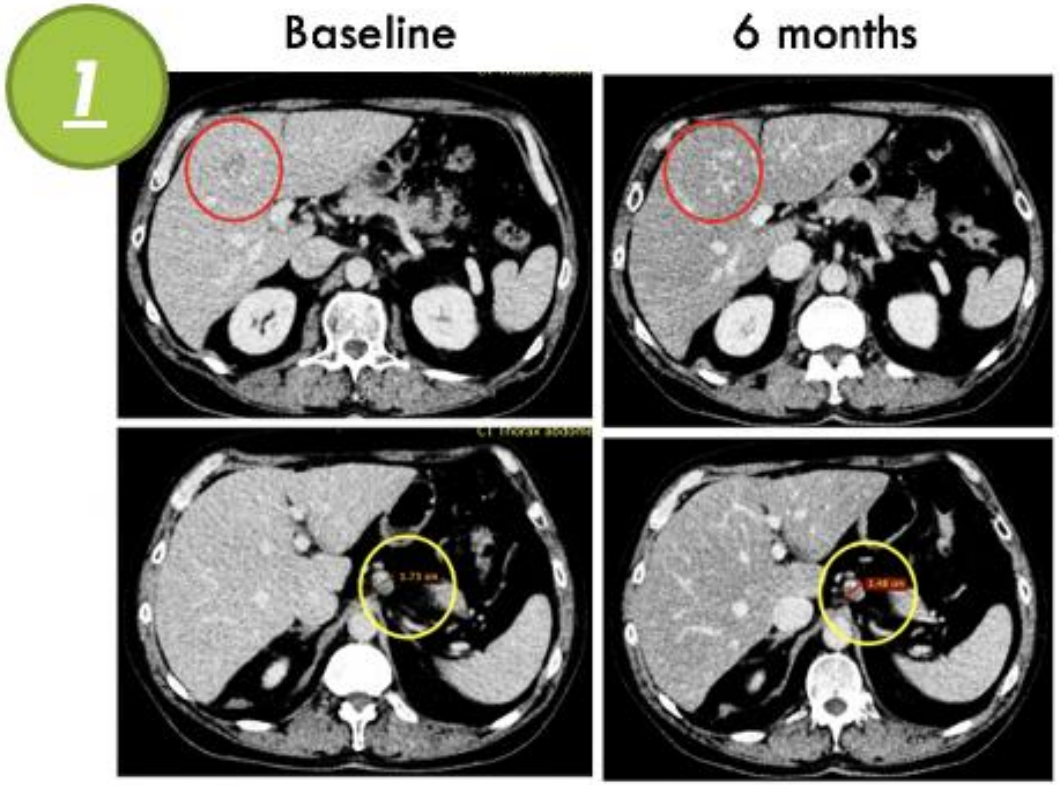
Single agent activity demonstrated in traditionally ‘cold’ tumor types

- RP2 leverages Replimune’s platform to additionally express an anti-CTLA-4 antibody
- 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’)
  - **Local expression optimal**, both mechanistically, and to reduce systemic toxicity
- Well tolerated – side effects consistent with RP1; compelling single agent activity



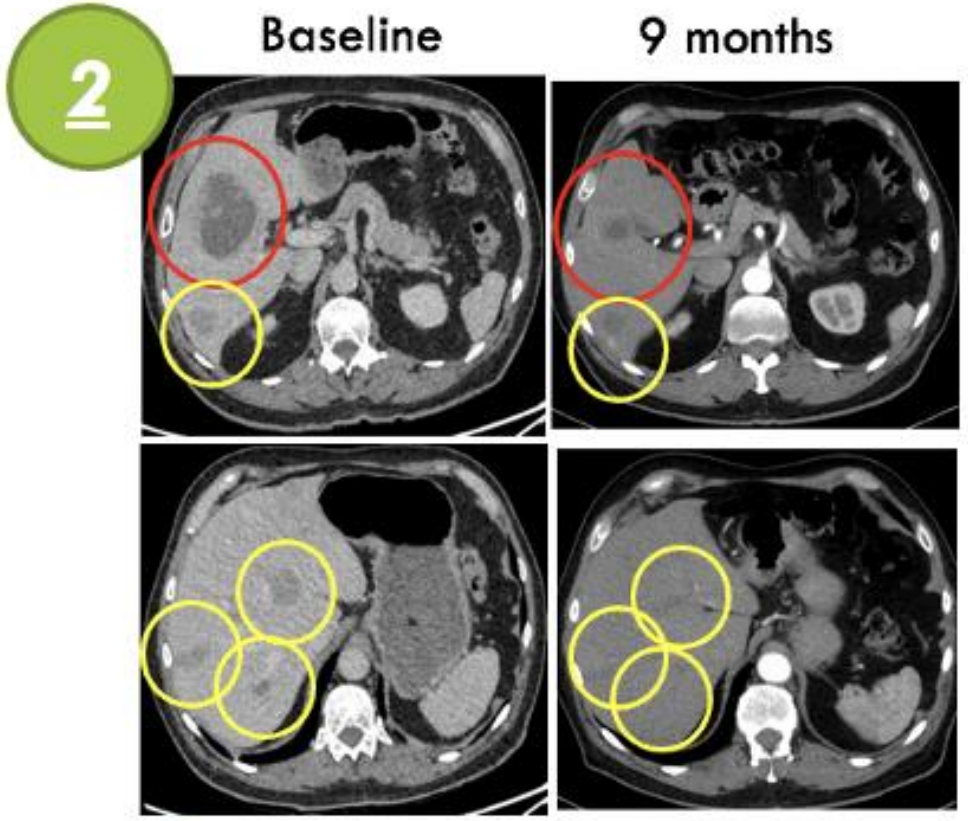
RP2 single agent activity in liver metastases

Single Agent RP2



- Esophageal cancer, ongoing PR at 21+ mos
- Previously treated w/ aPD-L1 and CTx

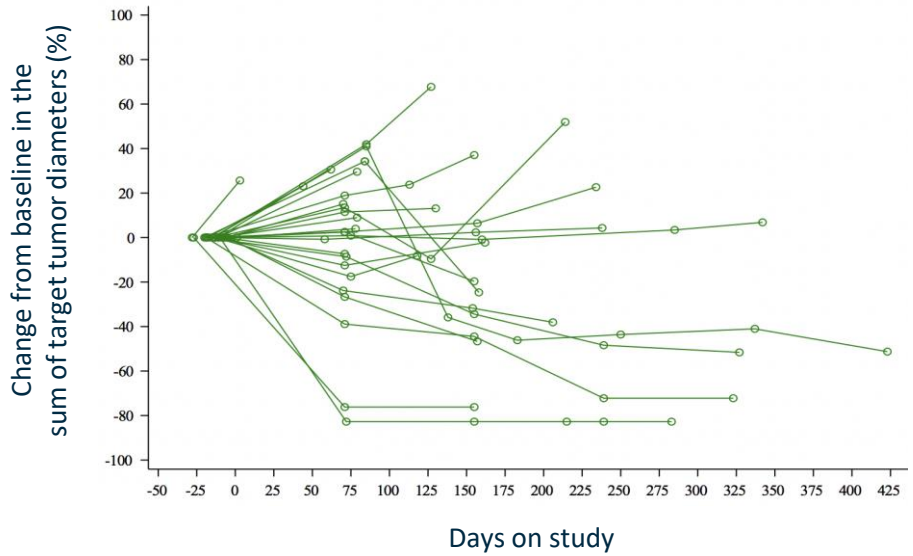
Single Agent RP2

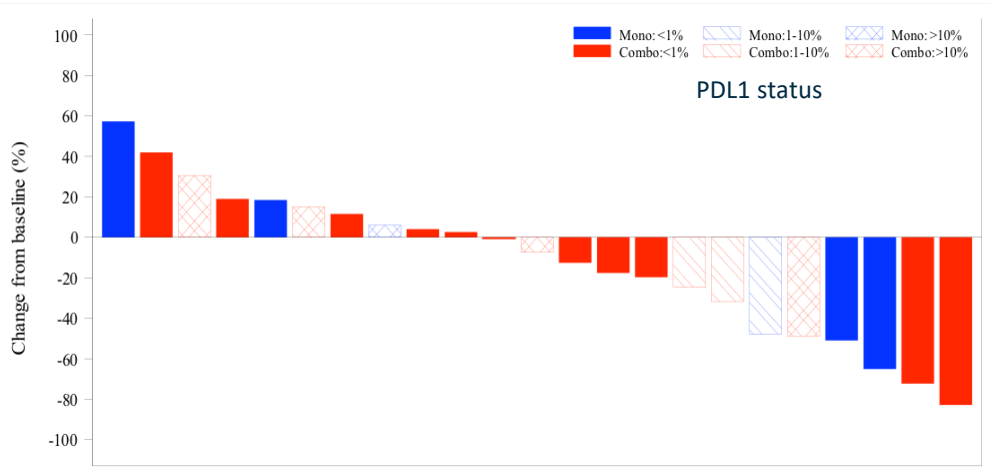


- Uveal melanoma, PR until 15 mos
- Previously treated w/ ipi-nivo

RP2 combination data further confirms activity

- 30 patients so far enrolled with RP2 combined with Opdivo
- Seven responses to date; all patients having failed anti-PD1
  - 2x uveal melanoma
  - 4x cutaneous melanoma
  - 1x SCCHN
- All but one response durable to date at out to >425 days
- ”Cold” tumors respond; responses seen irrespective of prior PD-L1 status



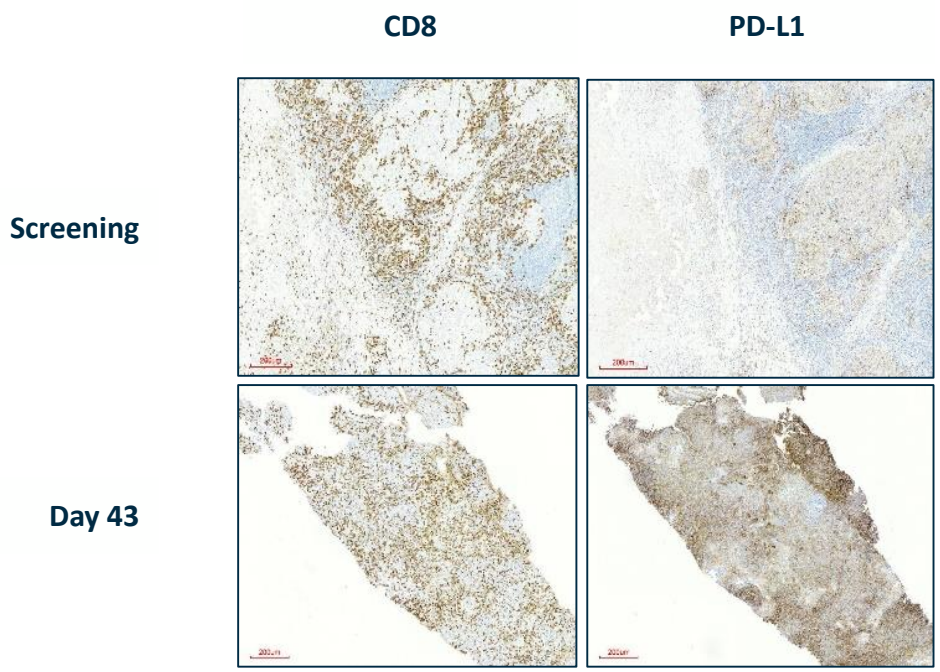


RP2 combined with Opdivo provides durable responses in advanced, heavily pre-treated phase 1 patients

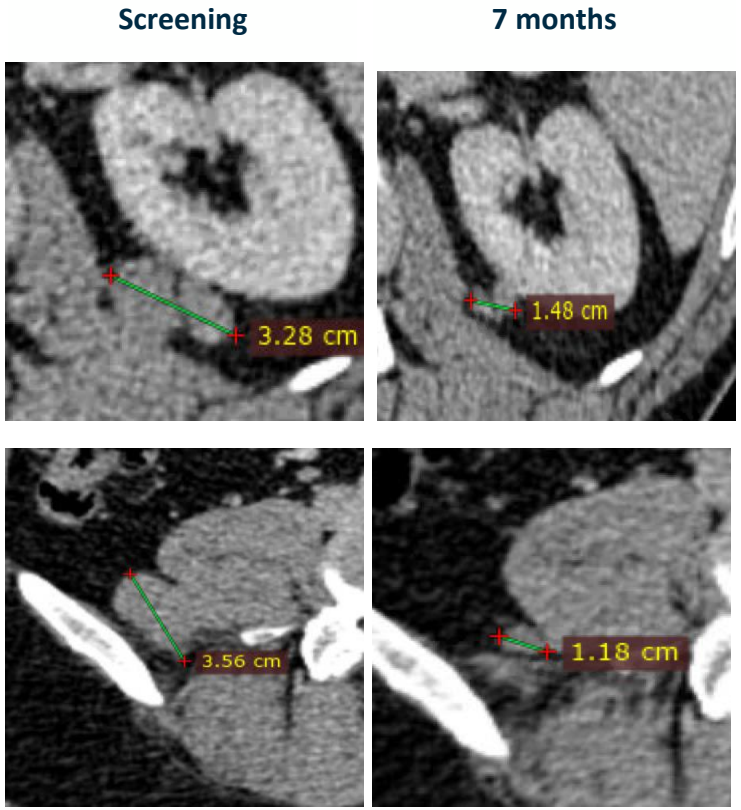
Ongoing partial response following deep nodal injection in ipi/pembro failed uveal melanoma

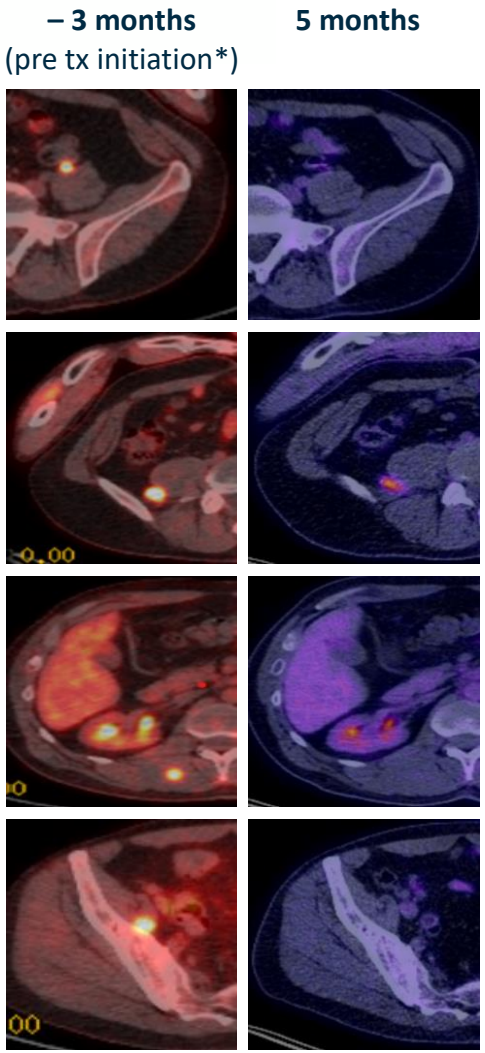
Pt 4402-0014 - PR

- Uveal melanoma
- Deep nodal lesion injected
- Prior therapies: ipilimumab, pembrolizumab



Discordant CD8 & PD-L1 staining at baseline changing to concordant staining at day 43





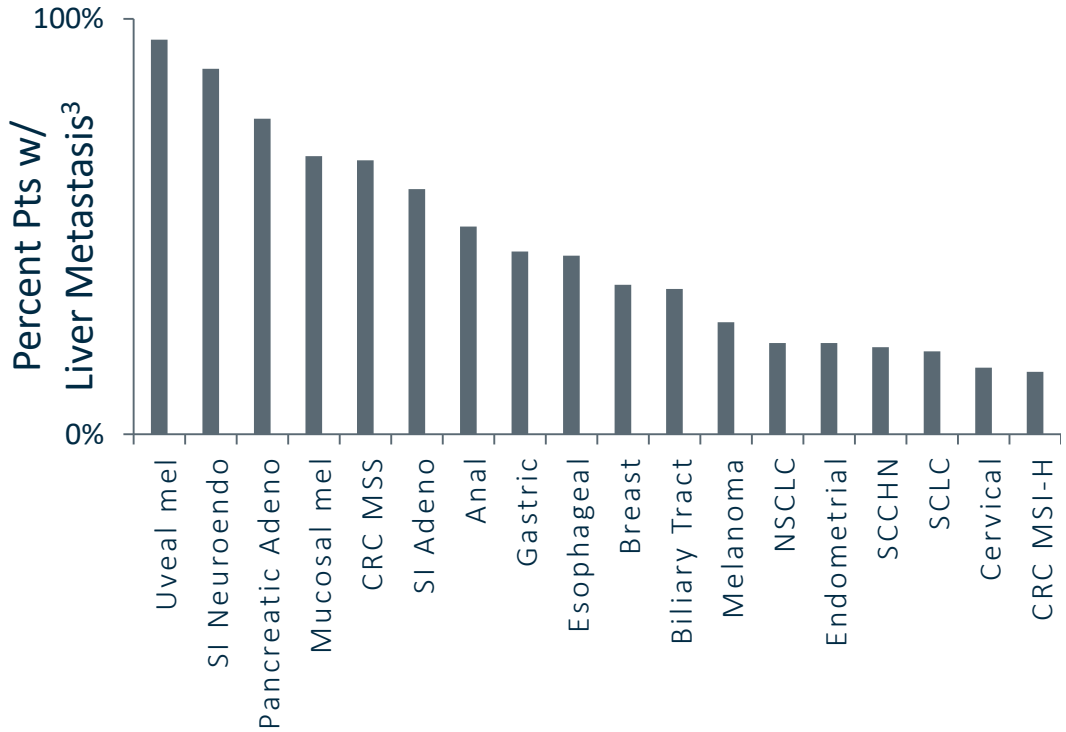
*No intervening therapy for patient in 3 months prior to screening, RP2 initiation

There is a large unmet need in patients with liver metastases

In three major indications, large numbers of patients with liver metastases could benefit from improved treatment

	Breast	Colon	Lung
Estimated Annual US Deaths[1]	43,600	52,980	131,880
Autopsy Liver Met. Rate[2]	36%	69%	23%
Rough Estimate of Amenable Patients	~16k	~37k	~30k

Numerous other cancer types also have a high frequency of liver metastases



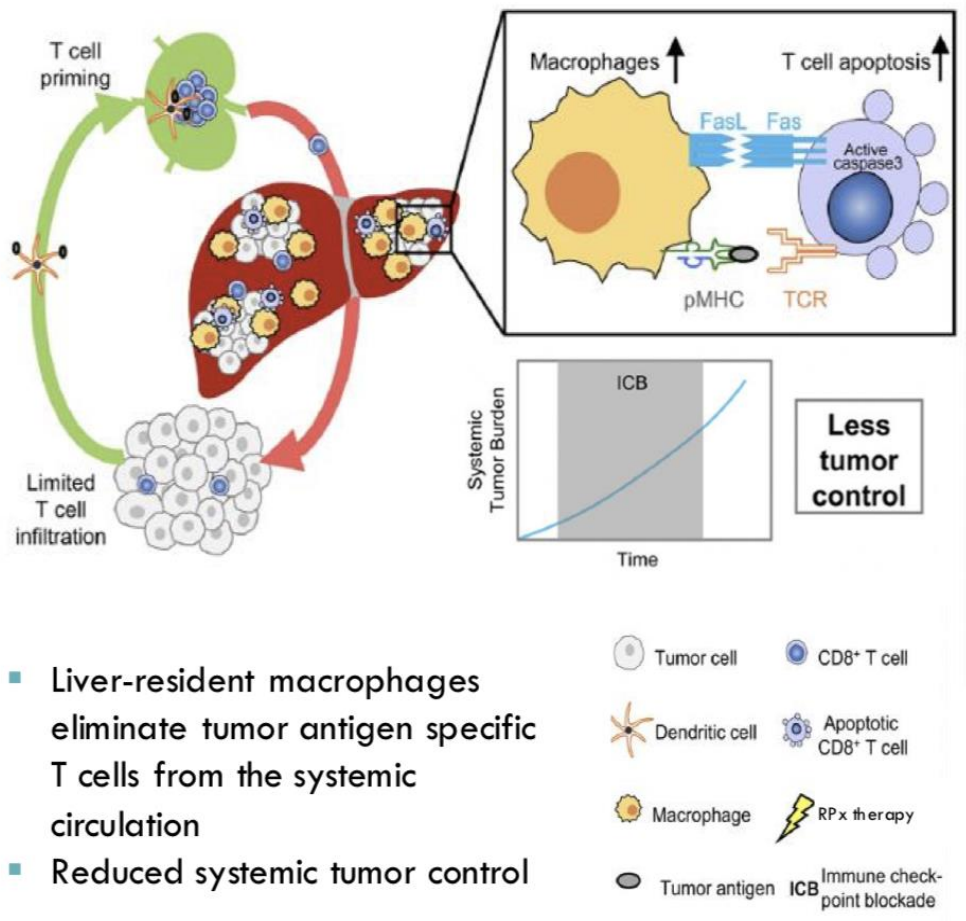
1) SEER 2021 Estimated Deaths. From SEER Cancer Stat Facts by indication

2) Riihimaki et al Cancer Med 2018

3) Data displays % of liver metastases at initial diagnosis or death Source: Independent analysis conducted on behalf of Replimune

RPx injection into liver metastases aims to re-ignite the immune response, clearing lesions locally and increasing T cells in circulation for systemic efficacy

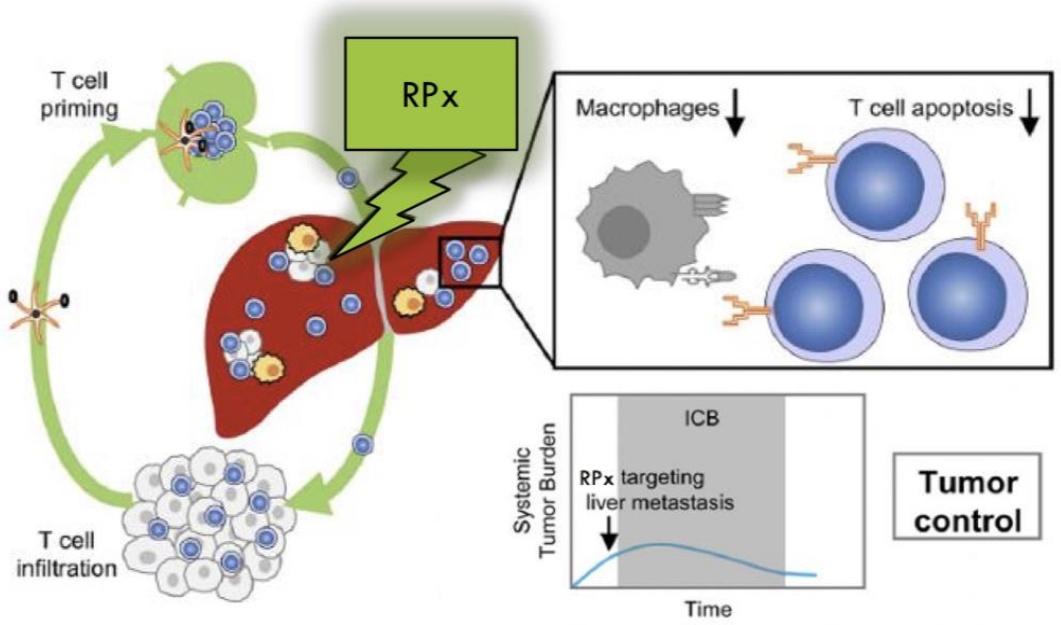
Immunotherapy with liver metastases



- Liver-resident macrophages eliminate tumor antigen specific T cells from the systemic circulation
- Reduced systemic tumor control

Modified from Yu et al Nat Med Jan 2021

Immunotherapy with liver metastasis depletion



- Liver metastases together with resident macrophages reduced by RPx
- Activation of innate & adaptive anti-tumor immunity – increased T cells
- CD40L/4-1BBL in RP3 also intended to reduce T cell apoptosis
- Restored/increased systemic tumor control

Development strategy for RP2/3

1. Expanded Phase 1 for RP2/3

RP2 expanded Phase 1

- Additional patients with liver metastases from lung, GI, breast & UM

RP3 expanded Phase 1

Dose escalation (3-6 patients /cohort)	Expansion @ RP3 RP2D
Cohort 1 (10^6 PFU/mL RP3 → HSV-1 neg (10^7 PFU/mL RP3)	RP3+nivo combo & translational cohorts with focus on SCCHN, lung cancer, BC (inc chest wall), GI & UM and pts with liver mets
Cohort 2 (10^7 PFU/ mL RP3)	

2. Follow on signal finding cohorts/studies in defined tumor types with RP2 or RP3 (n= 20-40pts each)

RP2/3 RP2D + anti-PD1 and/or other combo (example potential tumor types)

- Colorectal Cancer (MSS)
- HCC
- Lung cancer
- SCCHN
- Other GI cancers

Success criteria → Go/ No-Go

3. Registrational path

Indication specific OR Tumor agnostic OR Combination of the two

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 technology transfer from CMO successfully completed; RP2/3 underway

Complete manufacturing control to cover all clinical development and commercial needs

- Scale sufficient to cover global commercialization of Replimune's products at full capacity
- Avoids reliance on contract manufacturers

Attractive practicality & cost per dose

- Commercially attractive cost of goods & 'off the shelf' product practicality

Summary & milestones expected in 2022

RPx platform summary

- RP1: Compelling data in skin cancers including in PD1 failed patients; CERPASS study full enrollment expected mid year, trigger for primary analysis year end
- RP2: Single agent & combination activity seen in hard to treat (traditionally cold) tumors including PD1 failed uveal melanoma, SCCHN, & in patients with liver metastasis
- RP3: Opportunity to further enhance immune activation to address immunologically cold tumors

Q1 2022 milestones

- RP1 + Opdivo anti-PD1 failed CSCC initial data
- RP1 ARTACUS single agent initial data in CSCC organ transplant patients
- RP3 phase 1 initial single agent data in all comers
- Detail on RP1 commercialization strategy & RP2/3 development strategy

Q4 2022 milestones

- CERPASS (CSCC registration directed study) primary analysis trigger
- IGNYTE (anti-PD1 failed melanoma registration directed cohort) interim read out
- RP1 + Opdivo anti-PD1 failed NSCLC initial data
- RP1 + Opdivo anti-PD1 failed CSCC updated data
- RP1 ARTACUS single agent data in CSCC organ transplant patients updated data
- RP2 combined with Opdivo liver metastases expansion initial data
- RP3 anti-PD1 combination initial data

Well capitalized to deliver with cash into H2 2024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