



NEXT-GENERATION ONCOLYTIC IMMUNOTHERAPY

June 2021

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 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, 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.

Proprietary ‘Immulytic’ 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 immune-responsive tumor types

- Registration directed development based on compelling efficacy and safety profile
 - CERPASS study in advanced cutaneous squamous cell carcinoma (CSCC) enrolling
 - IGYTE study in anti-PD1 failed melanoma enrolling
- 30 patient anti-PD1 failed non-small cell lung cancer cohort enrolling

Next generation oncolytic immunotherapies optimized for superior immune stimulation, intended to treat immunologically ‘cold’ tumors

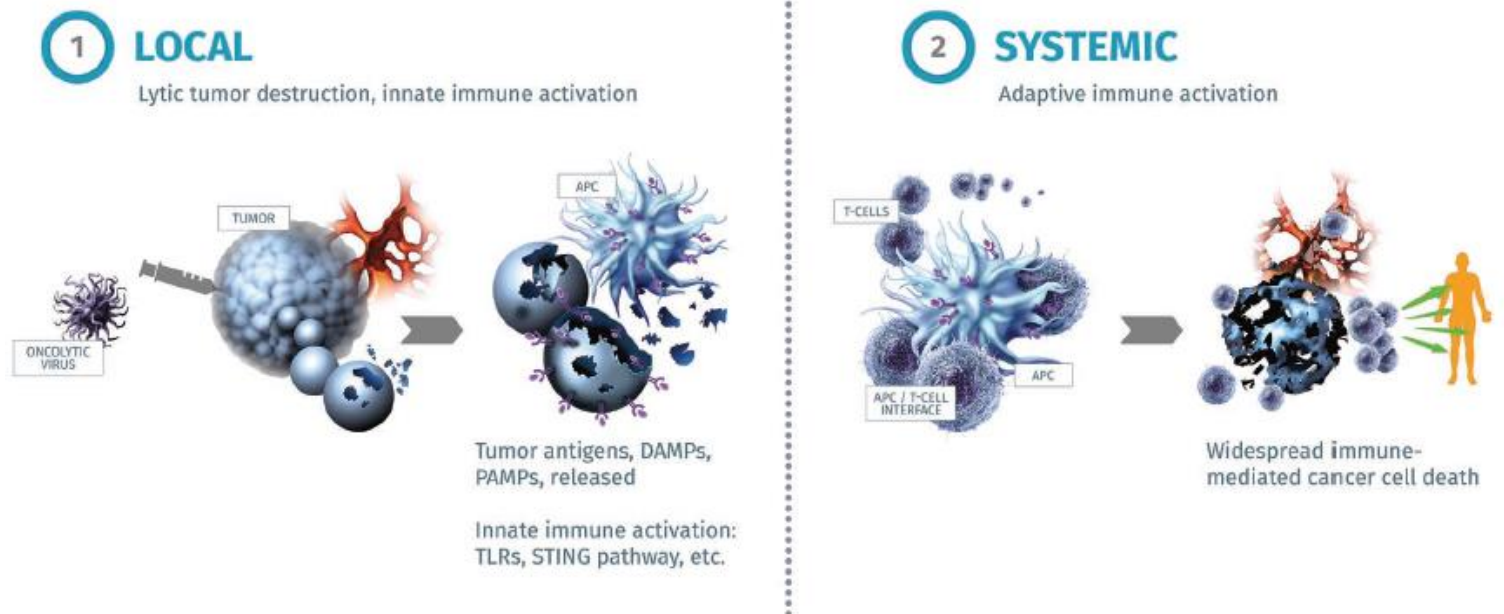
- RP2 – Single agent activity & activity in combination with Opdivo demonstrated in heavily pre-treated immune insensitive & anti-PD1 failed tumors
- RP3 – Single agent dosing underway

Company positioned for long term growth supporting 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 ~\$476m as of March 31st 2021, expected to fund current operational plan into H2 2024

Oncolytic immunotherapy




- The use of viruses that selectively replicate in & kill tumors to treat cancer
 - Highly inflammatory: Activates both innate and adaptive immunity
 - Systemically activates the immune system against the tumor antigens released
 - Can be 'armed' with additional genes to augment the natural properties of the virus with additional mechanisms of action
 - Off-the-shelf
- Single agent T-VEC is clinically validated & FDA approved



Replimune's best-in-class platform

- Optimized to infect, replicate in, and kill tumor cells – intended to maximize tumor destruction & immunogenic cell death (immunogenic 'Signal 1')
 - Potent clinical HSV strain selected from comprehensive screen for anti-cancer lytic activity
 - Modifications for selective replication in tumors sparing healthy tissue (ICP34.5 deleted for selectivity, US11 upregulated)
 - Fusogenic protein (GALV-GP R-) increases killing & immunogenic cell death 10-100 fold
- Further armed with immune activating transgenes intended to maximize T cell co-stimulation ('Signal 2') & systemic immune activation (including through induction of inflammatory cytokines: 'Signal 3')

programs:

				
<i>RH018A viral strain</i>	Optimized tumor infectivity and lytic activity, engineered for selective replication	✓	✓	✓
<i>GALV-GP R-</i>	Increased tumor killing & immunogenic cell death	✓	✓	✓
<i>GM-CSF</i>	DC expansion & maturation	✓	✓	
<i>Anti-CTLA-4</i>	APC/T-cell feedback loop blocking		✓	✓
<i>CD40L</i>	APC maturation, T-cell co-stimulation, inflammatory cytokine release (IFN-γ)			✓
<i>4-1BBL</i>	T-cell co-stimulation, NK-cell ADCC, APC maturation, inflammatory cytokines release (IL-2, IL-8, IL-12, IFN-γ)			✓

Practical and comprehensive activation of an anti-tumor immune response



Our platform offers <i>significant potential advantages compared to competing approaches,</i> 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	✓	✗	✗

Replimune Pipeline



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

Under a clinical trial collaboration agreement with Regeneron; 50:50 sharing of clinical trial costs – full commercial rights retained by Replimune

^ Planned – RP2 includes expansion in uveal melanoma; which anti-PD1 TBD

^^ Planned – To include specific cohorts of patients of tumor types where liver metastases are common; which anti-PD1 TBD



Lead indication overview: CSCC



- The second most common skin cancer with $\approx 700,000$ patients annually in the U.S.¹
- Approximately 7,000-15,000 US deaths annually¹⁻³
 - Most conservative addressable population
 - 80% of patients die from locoregional progression, not metastatic disease^{4,5}
- Potential US market estimated at 7,000-28,000 patients annually¹⁻⁴
- While effective, anti-PD1 therapy alone results in only a low rate of complete response

	Libtayo				Keytruda	Opdivo
<u>Patient population</u>	Locally advanced		Metastatic		47 locally advanced + 58 metastatic	4 locally advanced, 16 locoregional, 4 metastatic
<u>Number of patients</u>	33 (per label, 2018)	78 (ASCO 2020)	75 (per label, 2018)	59 (ASCO 2020)	105 (ESMO 2019)	24 (ASCO 2020)
<u>ORR</u>	48.5%	45%	46.7%	51%	34.3%	54.5%
<u>CR</u>	0%	13%	5.3%	20%	3.8%	0%

¹Rogers et al *JAMA Dermatol* 2015 (10); ²Clayman et al *JCO* 2005 (23); ³Mansouri et al *J Am Acad Dermatol* 2017 (153);

⁴Schmults et al *JAMA Dermatol* 2013 (149) ; ⁵Motaparathi et al *Adv Anat Pathol* 2017 (24)



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)

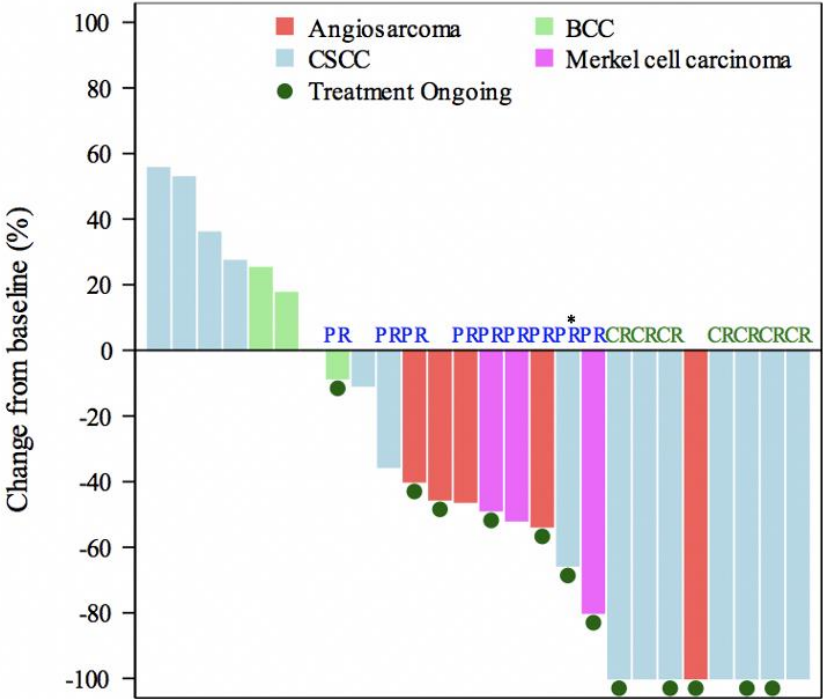
		CSCC	BCC	Merkel cell carcinoma	Angiosarcoma
<u>Number of patients</u>		15	4	4	5
<u>Best overall response</u> n (%)	CR	7 (46.6)	0	0	0
	PR	2* (13.2)	1 (25)	3** (75)	3** (60)
	SD	1 (6.7)	2 (50)	0	1 (20)
	PD	4 (26.7)	1 (25)	1 (25)	1 (20)
	ORR	9 (60)	0	0	3 (60)
	CR+PR+SD	10 (66.7)	3 (75)	3 (75)	4 (80)

* 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

Cohort expanded from 30 to 45 patients to include patients who have failed prior anti-PD1 therapy



Registration-directed development in CSCC: the CERPASS study



- Registration-directed randomized controlled Phase 2 clinical trial in collaboration with Regeneron*
 - Randomized 2:1 (RP1+ Libtayo vs. Libtayo alone) in patients with locally advanced or metastatic CSCC naïve to anti-PD1 therapy
 - Design based on the ongoing data with RP1 combined with nivolumab
 - Target enrollment: 180 patients
 - Independent dual primary endpoints: ORR & complete response rate (CRR)
 - Provides opportunity to 'win' on either or both endpoints
 - 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
 - Control arm ORR expectation based on anti-PD1 single agent data 34-51%
 - Control arm CR expectation based on anti-PD1 single agent data <10% at data cut off
 - Secondary endpoints include duration of response, PFS, OS

* Under a clinical trial collaboration agreement with Regeneron; 50:50 sharing of clinical trial costs – full commercial rights retained by Replimune



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

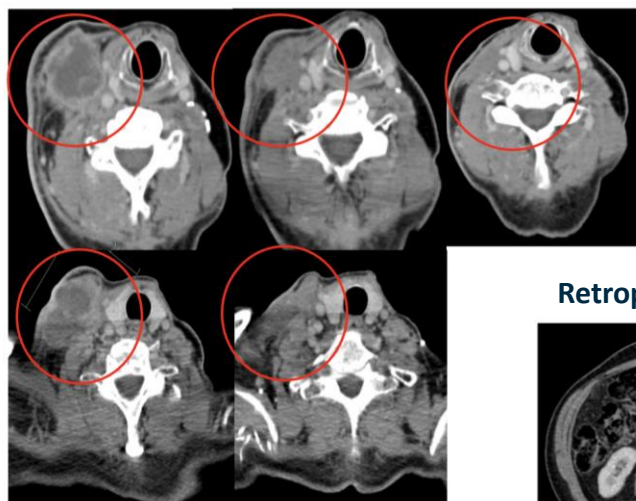
- Recurrent CSCC of the neck (bilateral)
- Previously treated with cisplatin-based chemoradiation & six cycles of carboplatin/5-FU
- Both the large injected tumor & the contralateral tumor in the neck reduced before first Opdivo dose
- Resolution of bone metastases

Right neck (injected)

Baseline

8 weeks

24 weeks

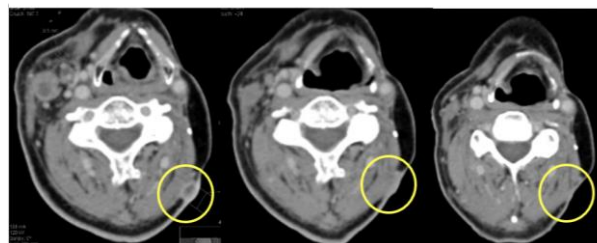


Left neck (un-injected)

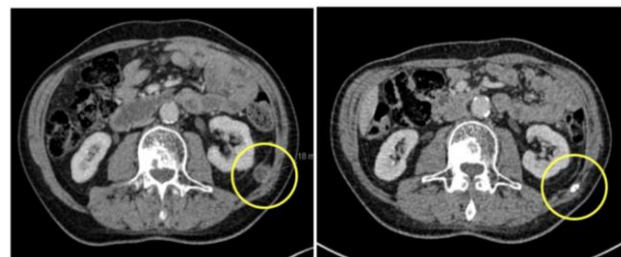
Baseline

8 weeks

16 weeks

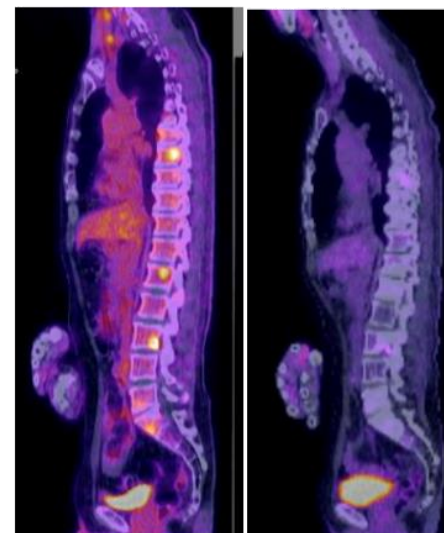


Retroperitoneal lymph nodes (un-injected)



June 2018

Feb 2020

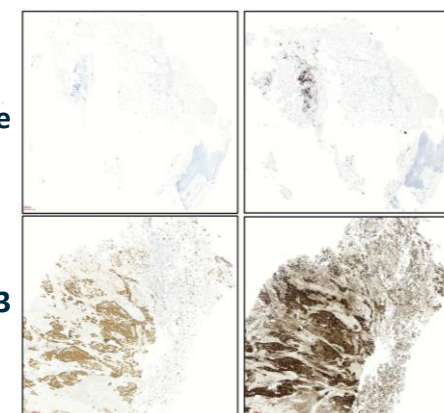


CD8

PD-L1

Baseline

Day 43





Resolution of aggressive locoregional disease



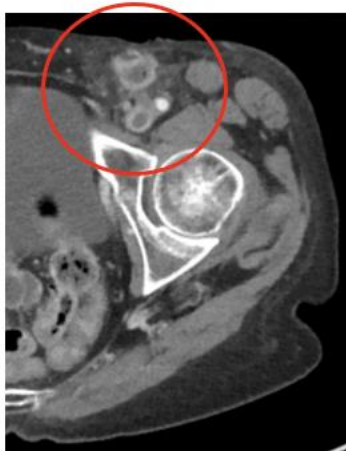
22nd May 2020



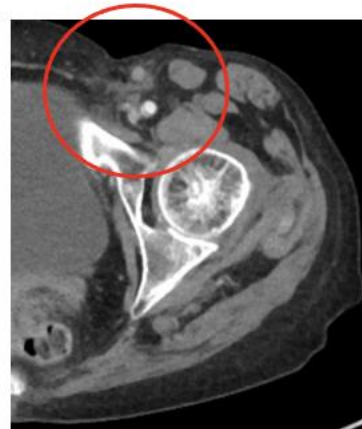
12th October 2020 (PR)



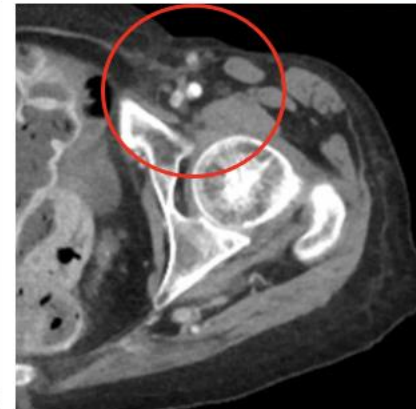
12th Feb 2021 (CR)



Screening



17th Aug 2020



18th Dec 2020

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

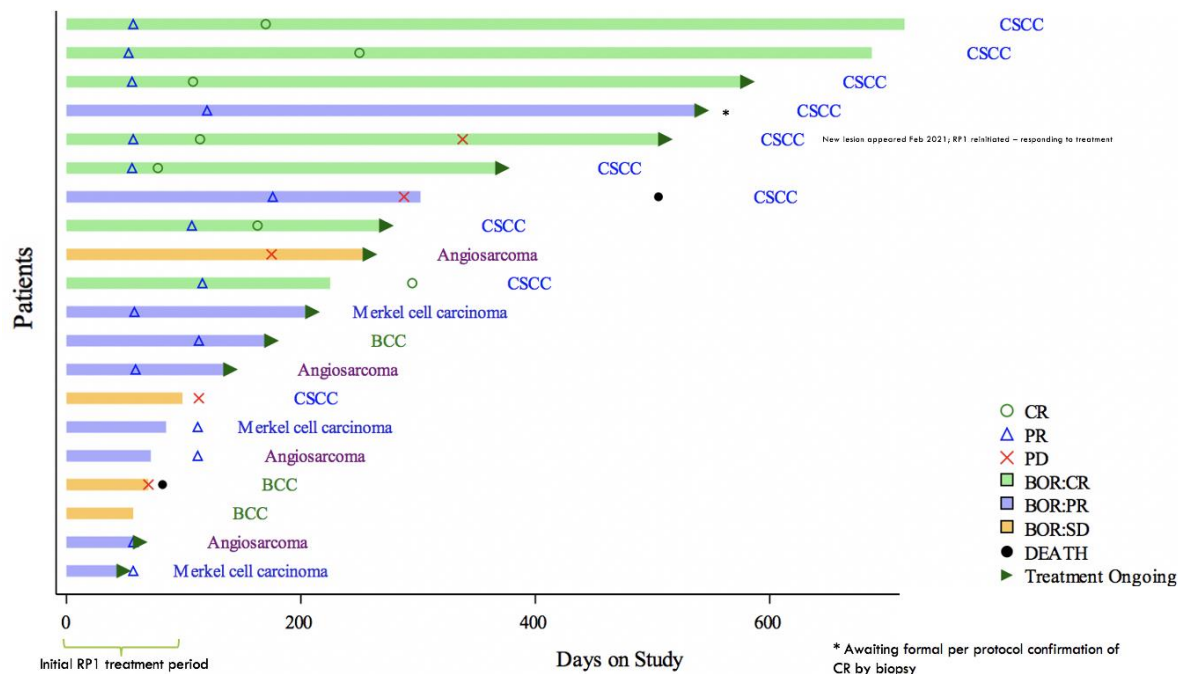


Responses in CSCC are deep & durable



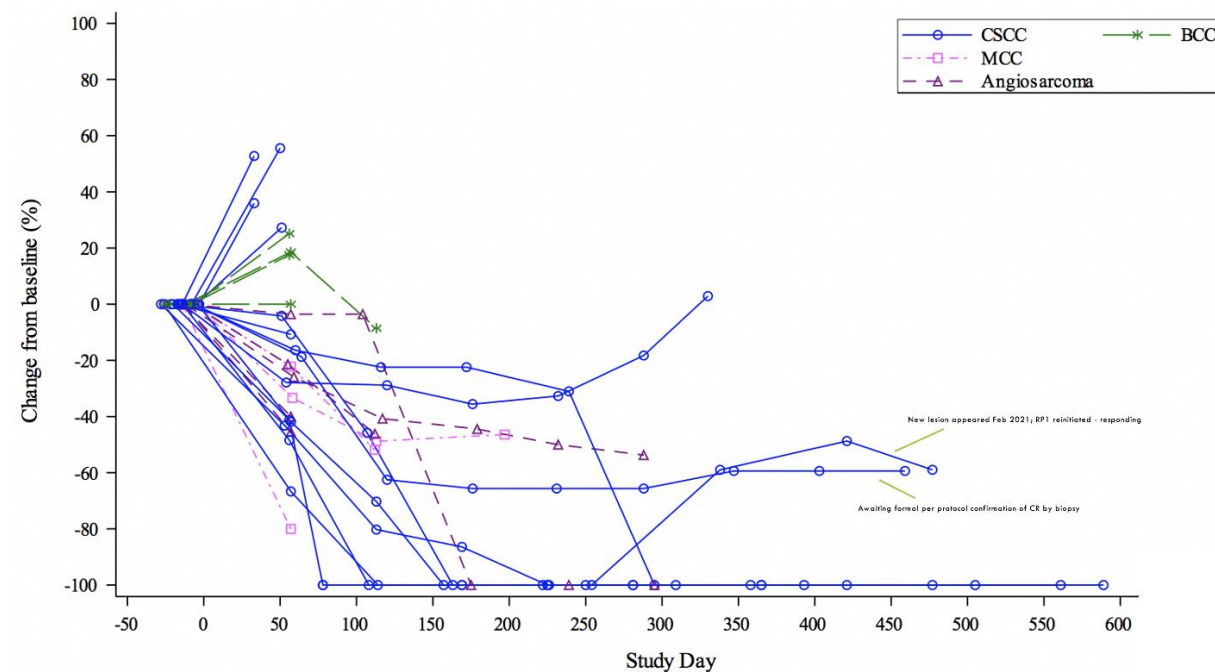
Duration of best response

Patients with a best response of at least SD



% Change from baseline in sum of tumor diameters over time

Patients with at least one follow up assessment



Based on the data to date, Replimune believes it is well positioned for success in the registration directed Phase 2 clinical trial of RP1 combined with Libtayo in CSCC



Anti-PD1 failed melanoma – market 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 melanoma¹
- Approximately 62,000 deaths annually world-wide²
- High unmet medical need for patients who fail anti-PD1 based therapy
- 40-65% of all metastatic melanoma are primary refractory to initial anti-PD1 therapy³
- Expected response rate to continued treatment with anti-PD1 therapy following confirmed progression on single agent anti-PD1 is 6-7%^{4,5}
- The expected response rate to Yervoy following failure of initial single agent anti-PD1 is 13%⁶

¹<https://seer.cancer.gov> (2019 data); ²Global Burden of Disease Cancer Collaboration *JAMA Oncol* 2019 (12); ³Gide et al *Clin. Cancer Res* 2018 (24)

⁴Ribas et al *Lancet Oncology* 2018 (19); ⁵Hodi et al *JCO* 2016 (34); ⁶Pires de Sliva et al *J Clin Onc* 2020 (38)



RP1 in anti-PD1 failed melanoma data

Based on May 2021 data cut of anti-PD1 failed cutaneous melanoma (N=16 patients)

- Advanced visceral disease population – **87.5% stage IVM1b/ M1c**
- Nine patients showed initial clinical benefit*
 - Five patients have met the formal criteria for response – **1 CR, 4 PR**
 - Four of which had previously failed both anti-PD1 and anti-CTLA-4 therapies
 - ORR at **31%**
 - Patients without formal response show clinical benefit from treatment
 - Ongoing surgical CR (counted as SD per study protocol definitions)
 - Ongoing CR by PET scan (no metabolic activity seen: PR by protocol definitions)
 - Ongoing SD, responding to recent reinitiation of RP1 treatment (28% reduction from baseline at latest scan)
- Responses are deep and durable – **80% ongoing at out to over 16 months**
- Clinical data supported by biomarker data, including reversal of T cell exclusion
- Activity also seen in melanoma subtypes with traditionally poor prognosis
 - Patients with uveal and mucosal melanoma who have failed prior anti-PD1 therapy



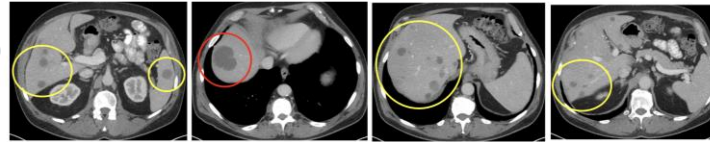
Local & distant responses observed in ipilimumab/nivolumab failed melanoma



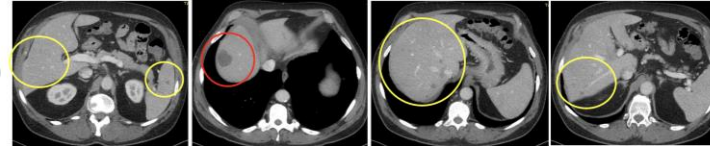
Pt 1122-2007 – PR
(ongoing at 19 months
from first RP1 dose)

- Ipi/nivo failed
cutaneous
melanoma

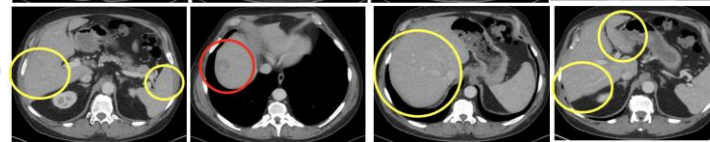
October 22, 2019
(baseline)



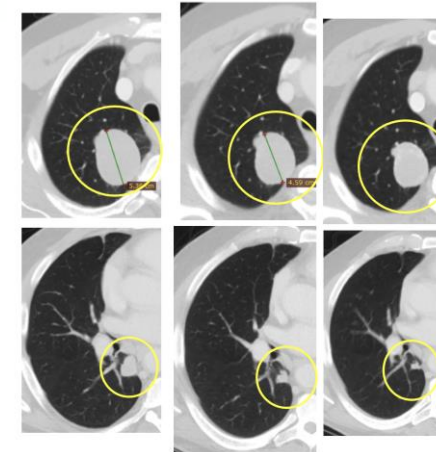
March 9, 2020



Dec 15, 2020



Oct 22, 2019 Mar 9, 2020 Dec 15, 2020



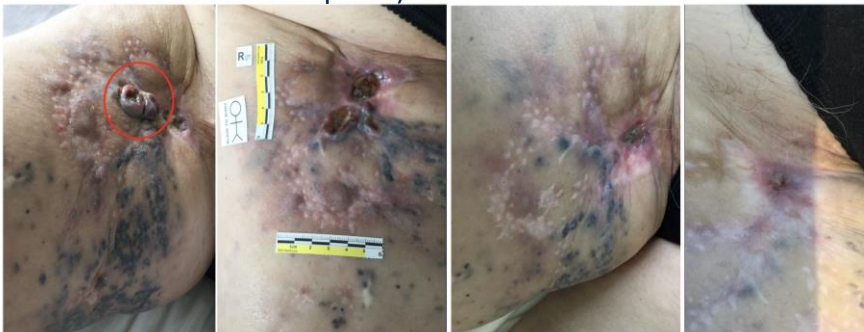
Pt 4403-1003 – PR (ongoing at 23
months from first RP1 dose)
• Ipi/nivo failed cutaneous melanoma

June 10, 2019

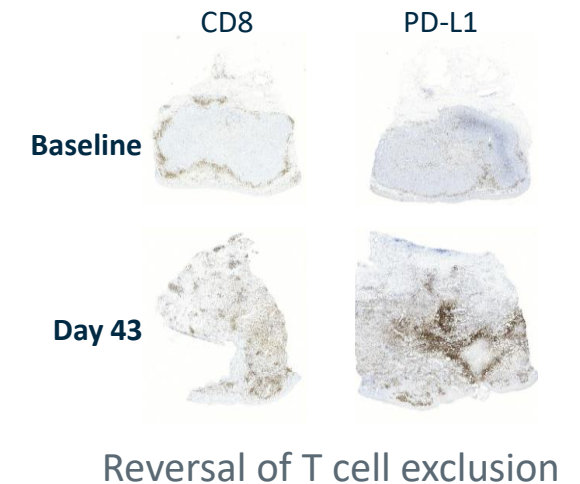
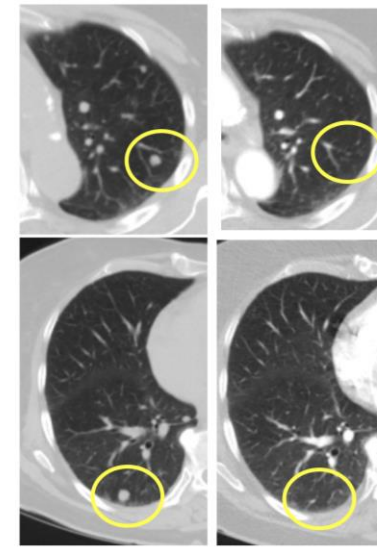
June 24, 2019
(post 1 dose RP1,
no Opdivo)

Sept 2, 2019

July 6, 2020

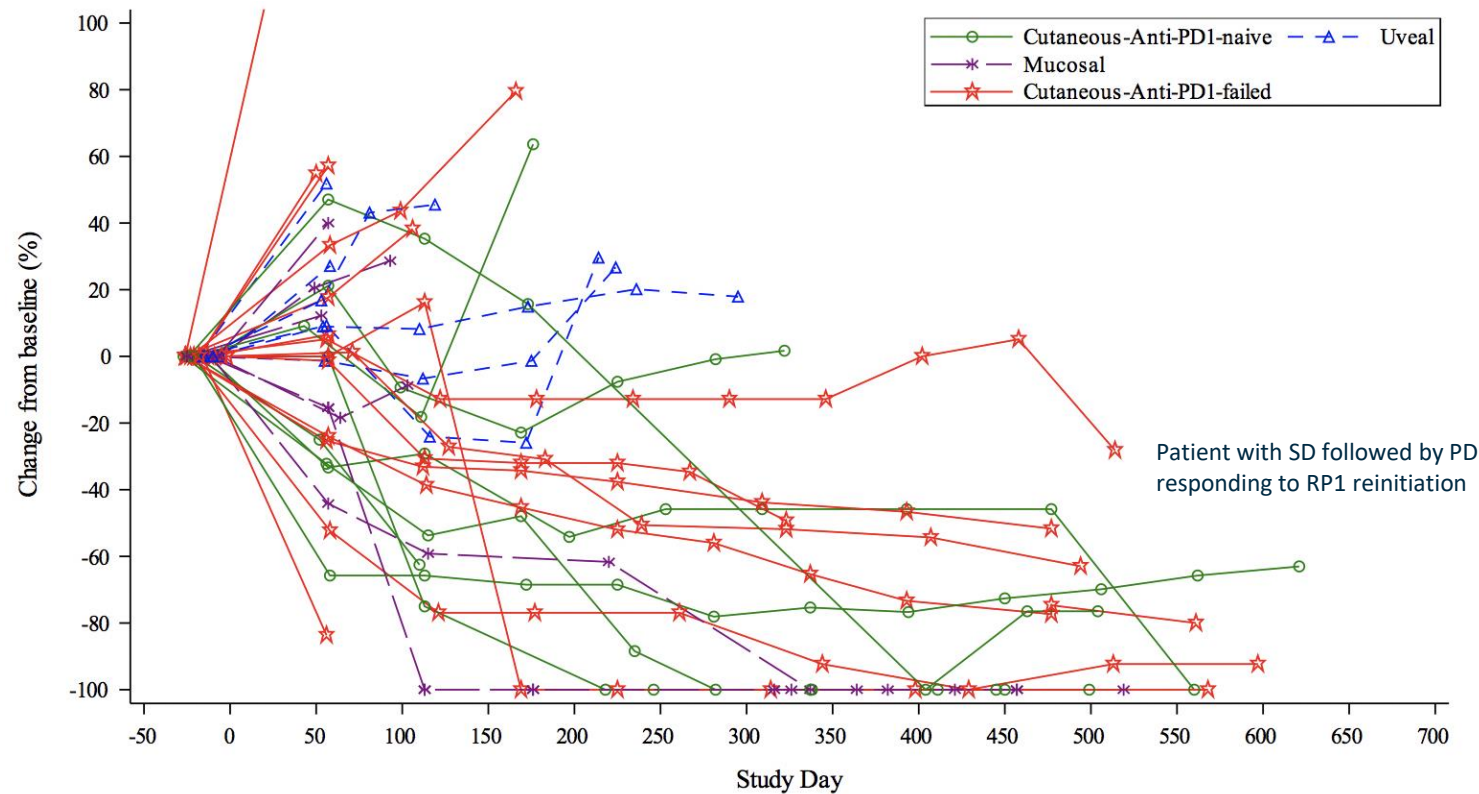


May 22, 2019 Mar 16, 2020 May 22, 2019 Mar 16, 2020





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



Extended clinical benefit also seen in patients with a best response of SD

Based on the data to date, Replimune believes it is well positioned for success in the registration directed 125 patient Phase 2 cohort of RP1 combined with nivolumab in anti-PD1 failed melanoma



Registration-directed development in melanoma – the IGNYTE study



- Registration-directed single arm 125 patient Phase 2 cohort of RP1 combined with Opdivo in anti-PD1 failed cutaneous melanoma*
 - Patients have either failed anti-PD1 alone, or anti-PD1 in combination (including with anti-CTLA-4)
 - Confirmed disease progression required while on prior anti-PD1 therapy
 - Anti-PD1 containing therapy must be the last therapy received
 - Primary endpoint: ORR by independent central review
 - Key secondary endpoints: Duration of response, CRR, PFS, OS
- 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 & needed for conversion to full approval
 - 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%

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



Single agent activity clearly demonstrated in traditionally 'cold' tumor types



- RP2 leverages Replimune's platform to additionally express an anti-CTLA-4 antibody
- Maximizes antigen presentation to kickstart an immune response
 - CTLA-4 inhibits antigen presentation and T cell activation (Immunogenic 'Signal 1' & 'Signal 2')
 - **Local expression optimal** mechanistically, and to reduce systemic toxicity
- Well tolerated – side effects consistent with RP1
- **Compelling single agent efficacy** (N=9) in heavily pre-treated patients with immune insensitive tumor types
 - CR – Mucoepidermoid carcinoma – ongoing at 15 months
 - PR – Uveal melanoma – maintained for 15 months before PD
 - PR – Esophageal cancer – ongoing at 18 months
- **Initial combination data further confirms activity**
 - 27 patients so far enrolled with RP2 combined with Opdivo
 - Six responses so far (1x uveal melanoma, 4x cutaneous melanoma, 1x SCCHN – all pts having had prior anti-PD1)
 - Continued demonstration of activity in anti-PD1 failed melanoma (i.e. following from that also seen with RP1+Opdivo)
 - Continued demonstration of activity in uveal melanoma (i.e. as was also seen with RP2 monotherapy)

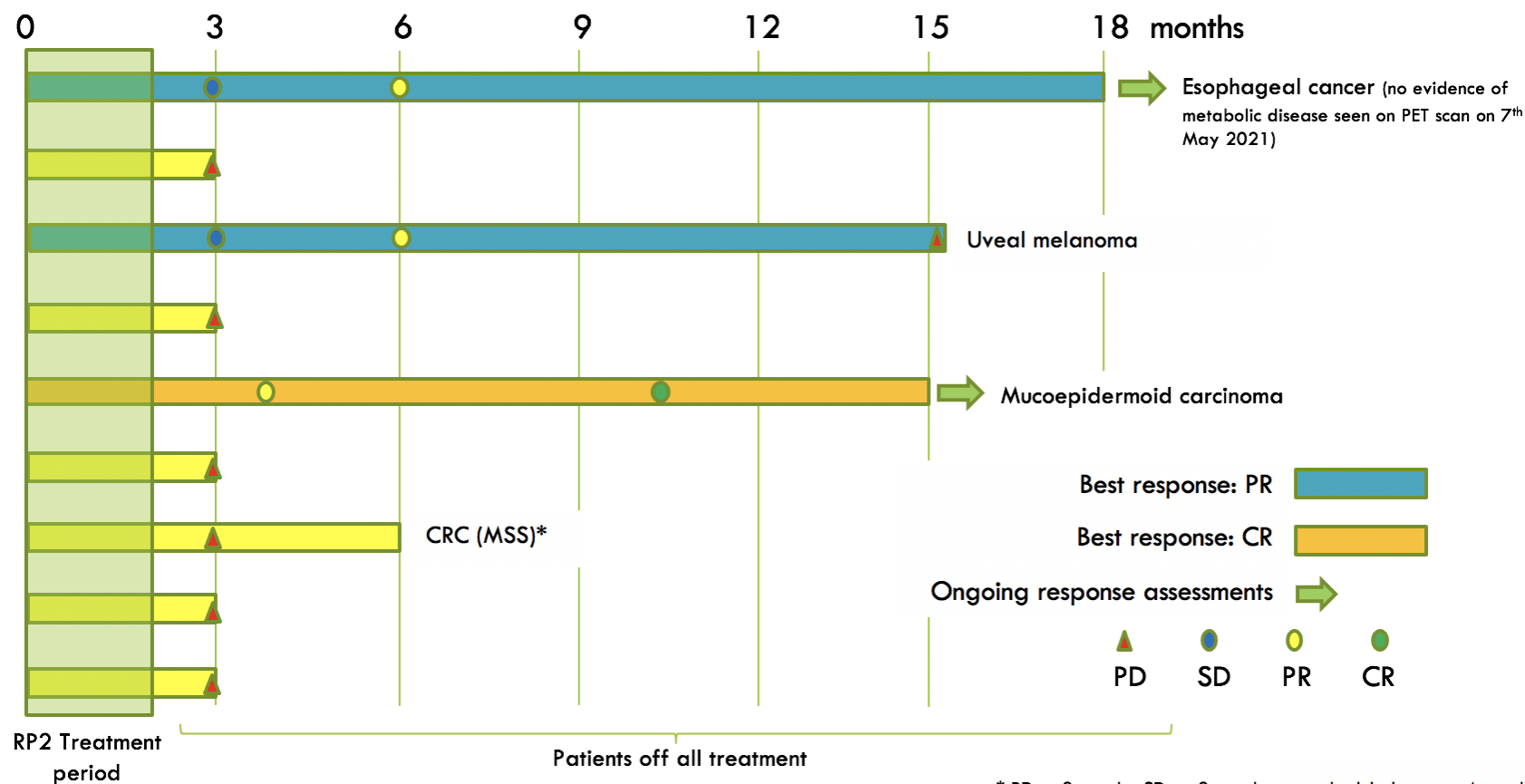


Deep and durable responses with RP2 monotherapy



Kinetics of response following treatment with single agent RP2

Other patients had advanced, heavily pre-treated uveal melanoma x2, head & neck cancer & cutaneous melanoma x2



* PD at 3 months, SD vs. 3 months at unscheduled scan at 4 months, PD at 6 months (lung lesions stable, liver lesions/peritoneal carcinomatosis progressing, 1 lymph node [uninjected] reduced in size)



Ongoing CR observed in mucoepidermoid carcinoma of the parotid (RP2 monotherapy)



Pt 4402-0001 - ongoing CR

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

Baseline



1 month



3 months
(PR)



4 months





Ongoing CR observed in mucoepidermoid carcinoma of the parotid (RP2 monotherapy)



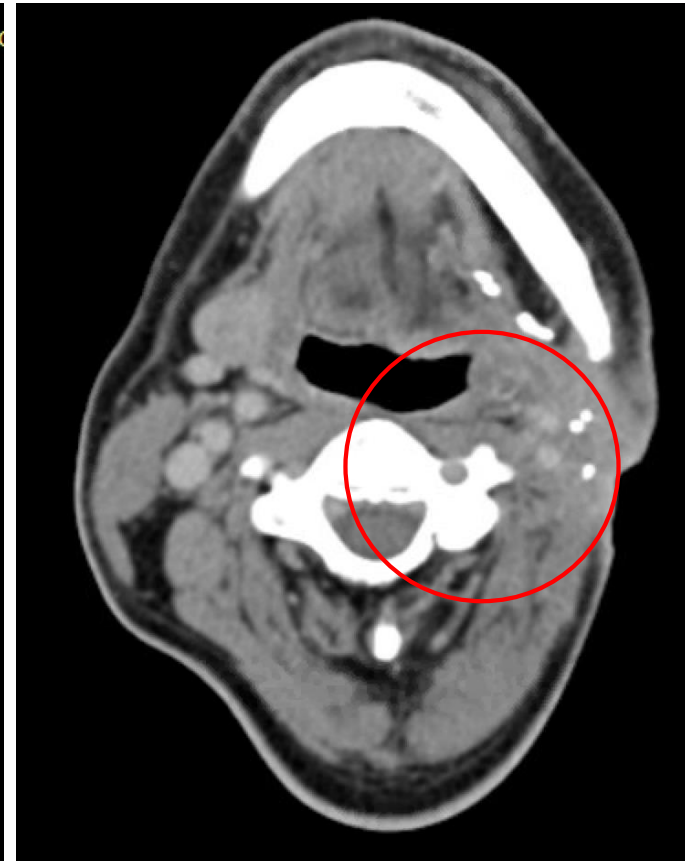
6 months



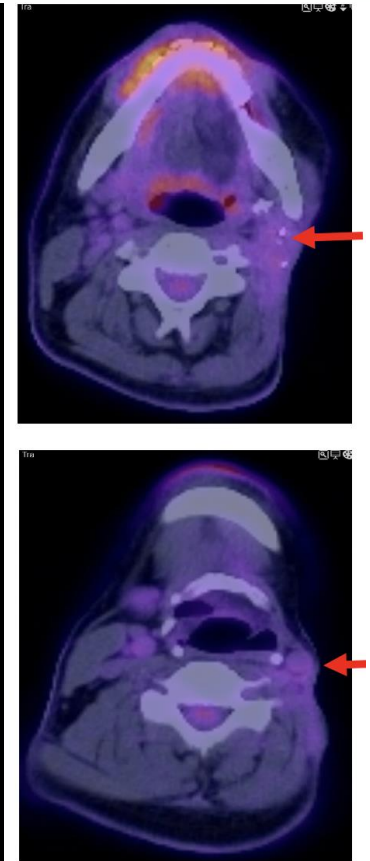
Screening



5 months



8 months
(PET scan to confirm CR)



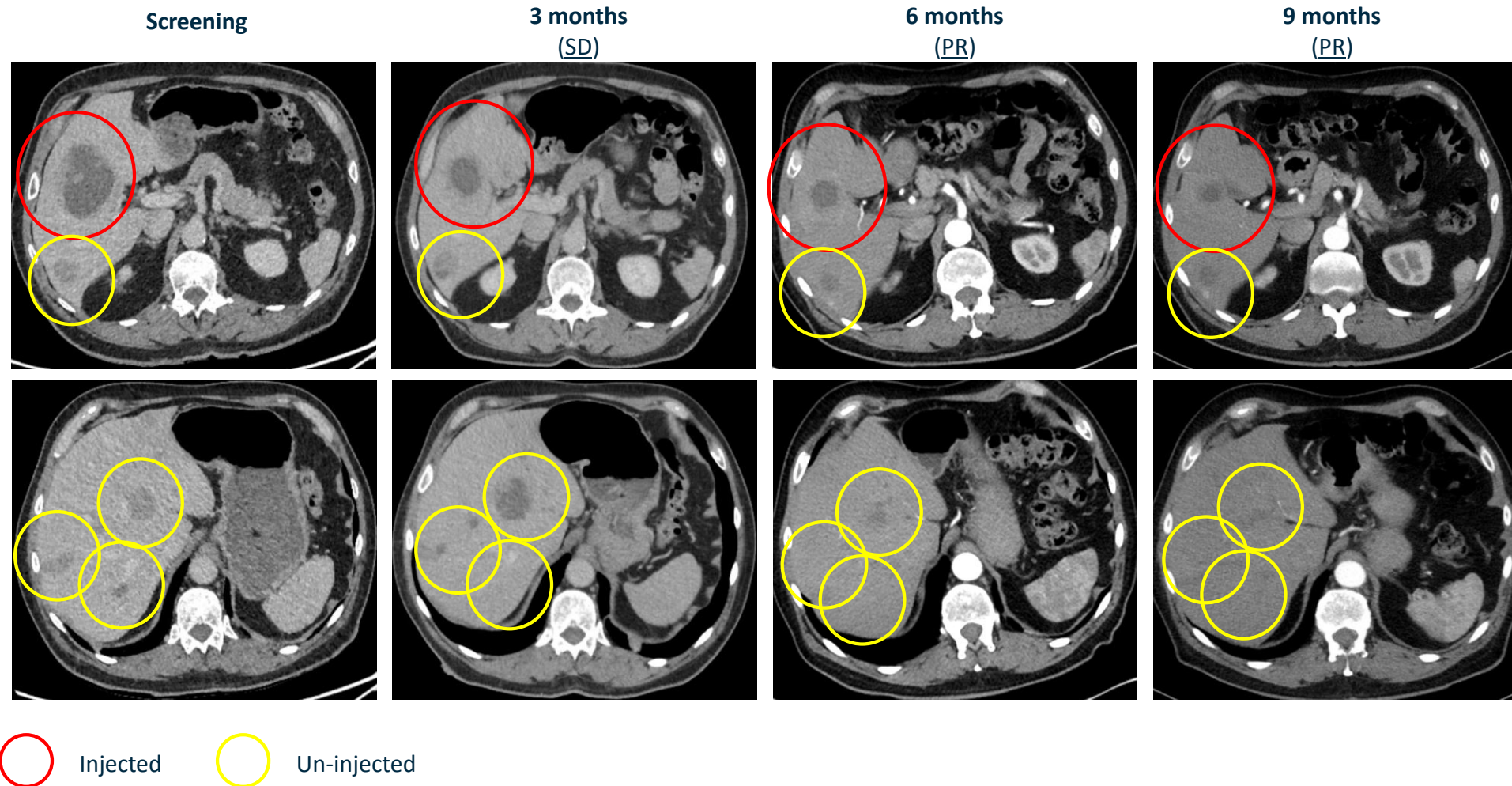


Resolution of injected and uninjected liver mets in uveal melanoma (RP2 monotherapy)



Pt 4401-0003 - PR

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

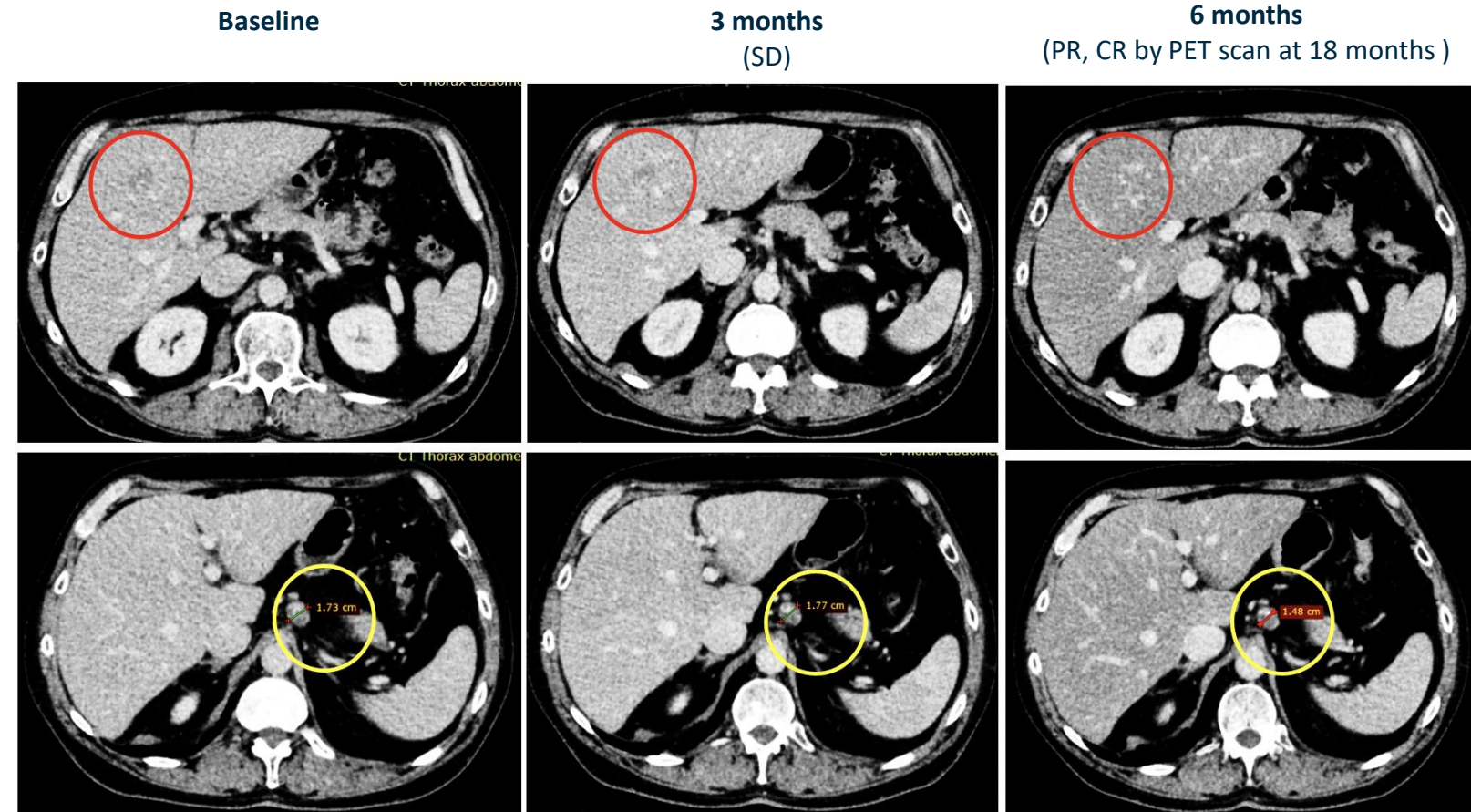




Deepening response over time in esophageal cancer (RP2 monotherapy)

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



Initial data with RP2 combined with Opdivo



Tumor type (Prior therapies)	All	Cutaneous melanoma (Anti-PD1 or anti- PD1/anti-CTLA-4 x9)	Uveal melanoma (IMCgp100 x1; anti-PD1 or anti-PD1/anti- CTLA-4 x2)	Uveal melanoma (Anti-PD1 naïve x2; prior therapy unknown x1)	SCCHN (Chemo/anti- PD1 failed x2; RT failed x1)	NPC (multiple chemo failed)	Salivary gland cancer (naïve; tipfarnib/RT failed)	Sarcoma/ sarcomatoid carcinoma (multi-chemo; multi- surgery/RT x2; brachytherapy)	Chordoma (OSI- 906/imetinib/ afatinib; afatinib/RT)
# of patients	27	9	3	3	3	1	2	4	2
Ongoing PR	6	4 ^a	1	-	1 ^b	-	-	-	-
Best response SD ^c	9	3	-	2	-	-	-	2	2
Ongoing SD	3		-	1	-	-	-	2	-
Best response PD	7	2	-	-	1	1	1	2	
Continuing treatment post initial progression	3	2	-	-	-	-	-	-	1
On treatment with no follow up	2	-	2	-	-	-	-	-	-
On study with the opportunity for response	8	2	2	1	0	0	0	2	1
Current ORR	22%	44%	33%	0%	33%	0%	0%	0%	0%

^aTwo not yet confirmed ^bNot yet confirmed; prior nivolumab, 5-FU/cisplatin, radiotherapy ^cOngoing SD or SD followed by PD



Activity further confirmed in anti-PD1 failed melanoma (RP2+Opdivo)



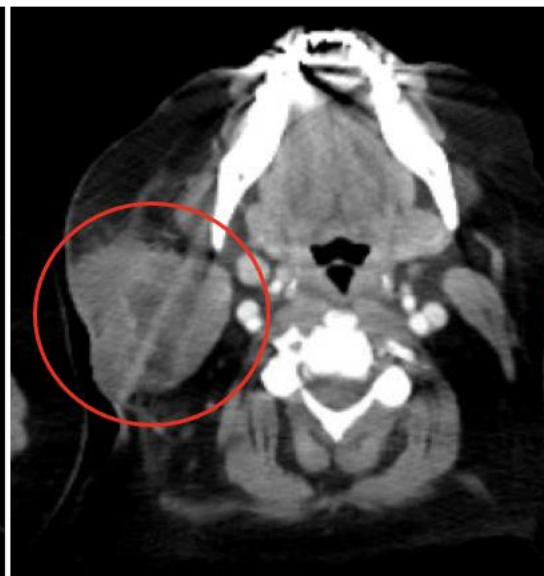
Pt 4403-0004 - PR

- Cutaneous melanoma
- Extensive liver metastases (others not shown)
- Prior therapies: Opdivo
- Had been off work for three years & in significant pain: Now off all pain meds & back at work

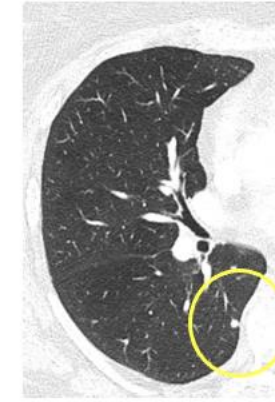
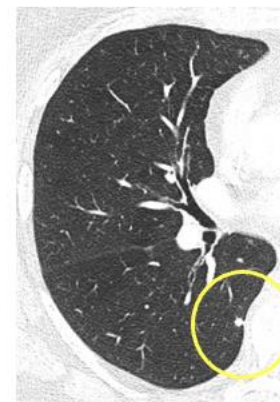
Screening



3 months
(SD)



6 months
(PR)



Injected



Un-injected



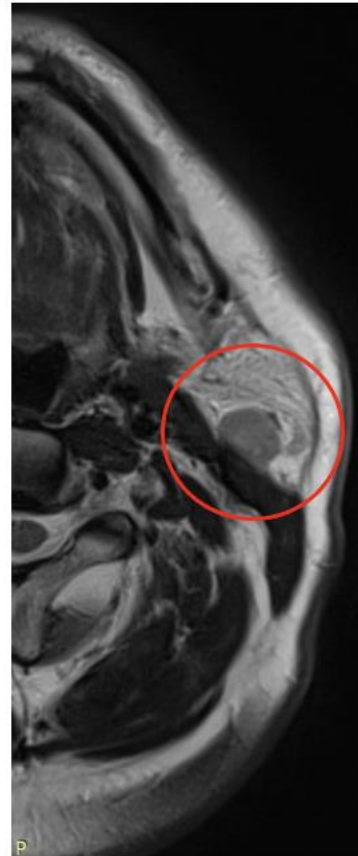
Activity in head & neck cancer (RP2+Opdivo)



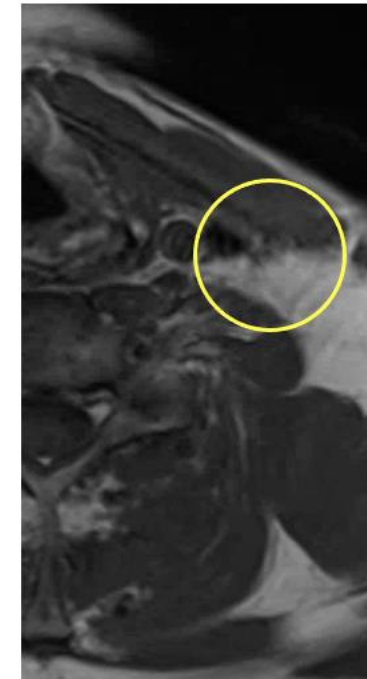
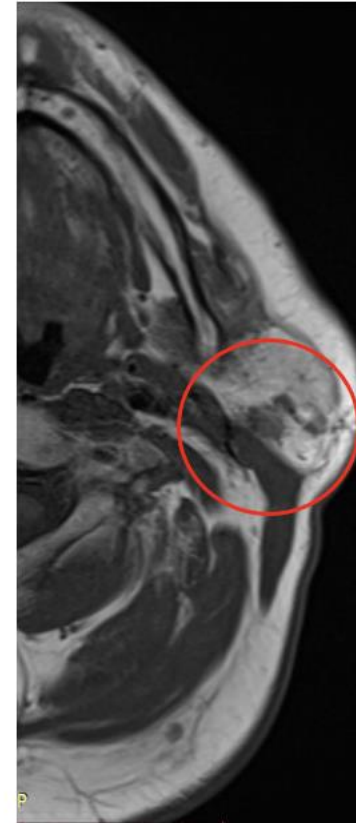
Pt 4403-0011 - PR

- Squamous cell carcinoma of the head and neck
- Prior therapies: 5-FU/cisplatin, radiation, Opdivo

Screening



2 months
(PR)



Injected



Un-injected

Beyond skin cancers – Background & rationale for development in patients with liver metastases



- Liver is one of the most common sites of metastases across tumors (including lung, breast, and colon cancer)
- Prognosis for patients with liver metastases is poor with limited effective treatment options
 - Liver metastases across tumor types are associated with systemic resistance to immune checkpoint blockade
- Liver metastases are associated with the antigen-specific elimination of T cells from the circulation by macrophages resident in the liver metastases
 - Leads to systemic loss of T cells and diminished immunotherapy efficacy
- The oncolytic immunotherapy MOA is intended to
 - Directly kill tumors
 - Induce systemic T cell mediated (& other) immune responses to the antigens released
- Intratumoral RP1 & RP2 alone & combined with anti-PD1 is well tolerated & has demonstrated compelling evidence of efficacy, including in liver mets

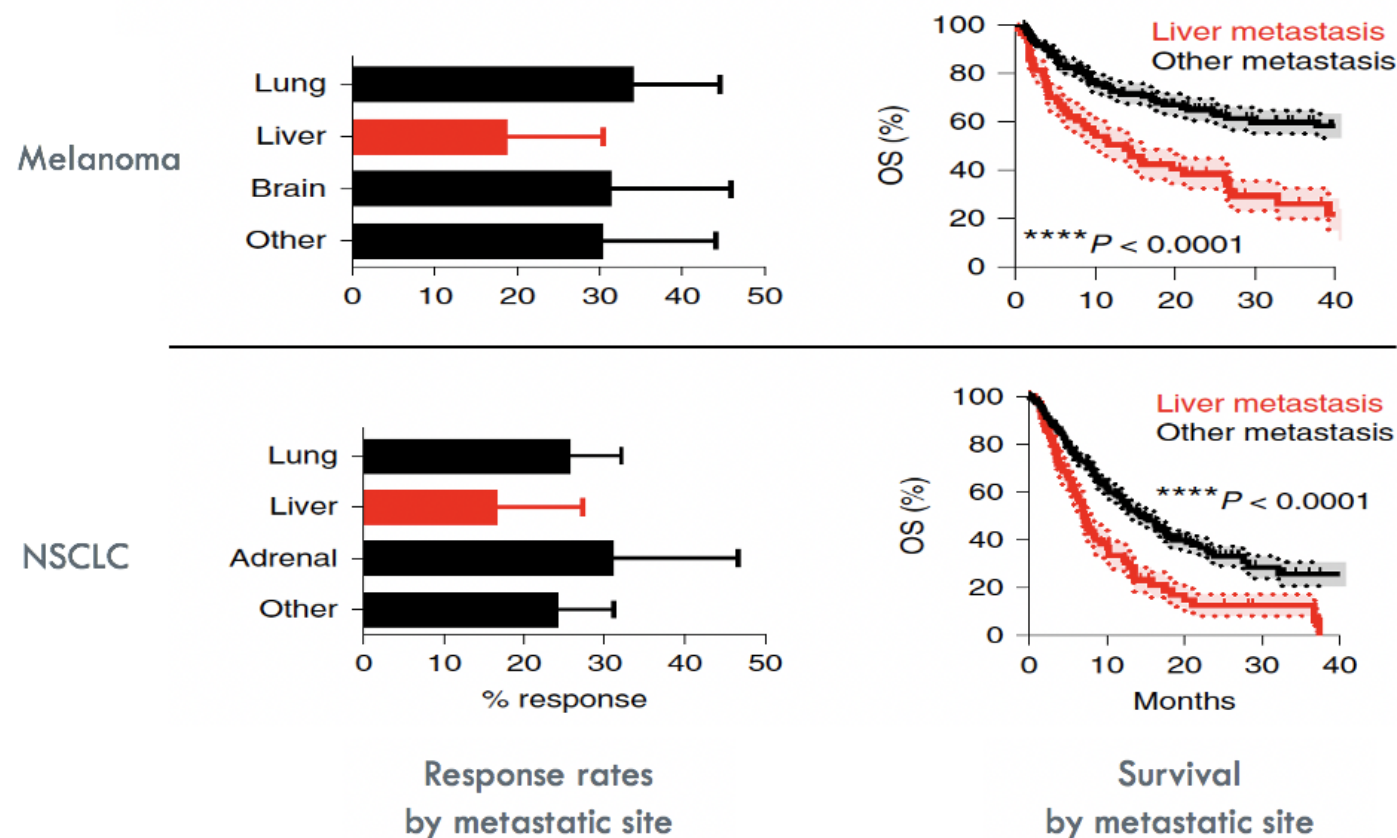
Sources: Riihimaki et al Cancer Med 2018; Yu et al Nat Med Jan 2021

There is a significant unmet need for patients with liver metastases

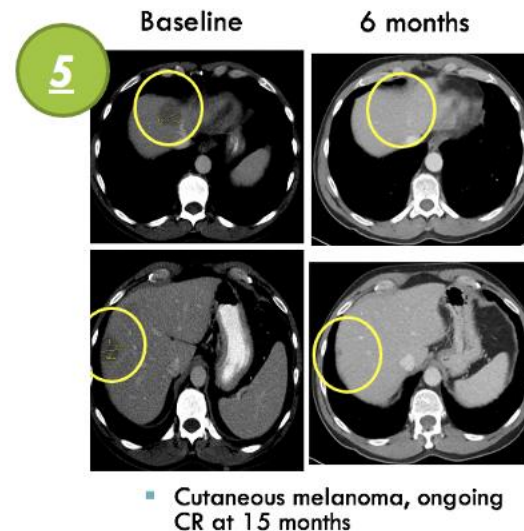
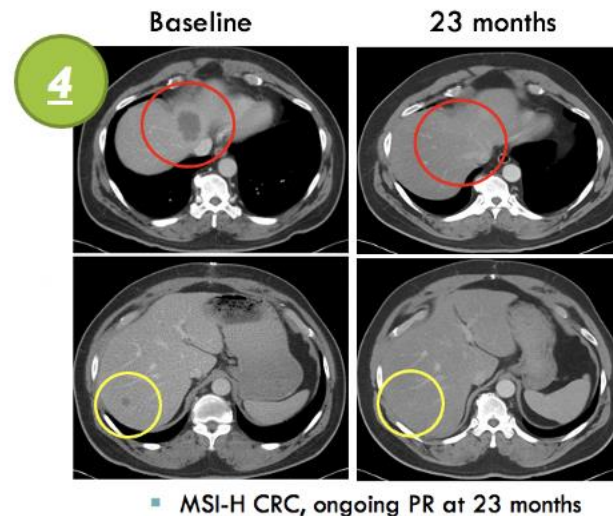
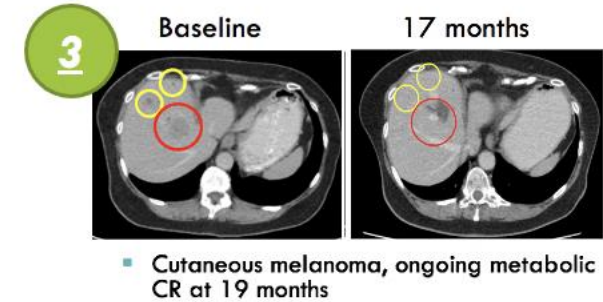
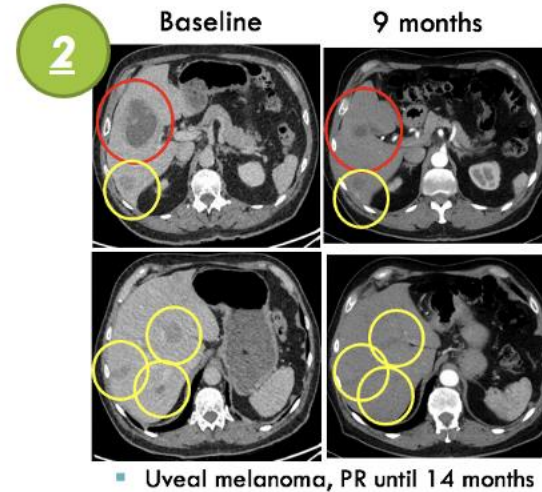
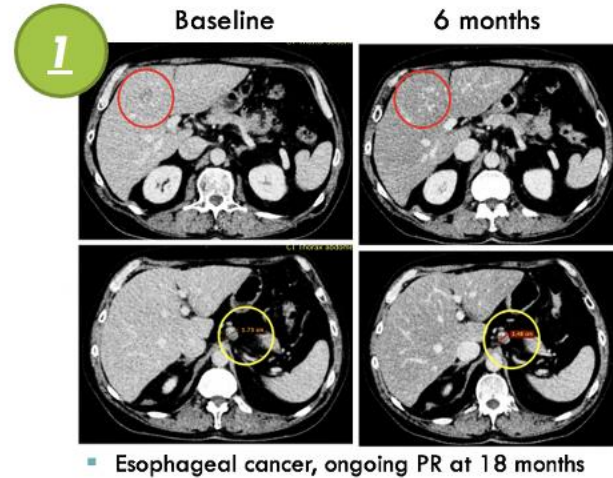
The presence of liver metastasis correlates with **poor outcomes** to immunotherapy

- Lower objective response rates
- Survival significantly reduced

Two illustrative tumor types show substantial outcome gap between patients with and without liver mets



Six example patients with liver metastases across tumor types responding to RP1 or RP2



Liver metastases – Development strategy

- Expand RP2 enrollment to include patients with liver metastases of defined tumor types
 - GI cancers, breast, lung & further signal confirmation in uveal melanoma
 - Further confirm the ability of RPx to treat patients with liver metastases
 - With signal confirmation in uveal melanoma, proceed to registration-directed development
- Determine safety of RP3, including when injected into liver metastases
 - Ongoing phase 1 clinical trial of RP3 alone & combined with anti-PD1 therapy
- Assess RP2 or RP3 (data dependent) in a multi-cohort phase 2 clinical trial in patients with liver metastases
 - N=20-40 per cohort
 - e.g. CRC (MSS), breast cancer, NSCLC, SCLC, SCCHN
 - Depending on activity & risk benefit, un-gate
 - Tumor type agnostic registration-directed clinical trial, &/or
 - Indication specific registration-directed clinical trial(s)

Investment in manufacturing facility to support global supply for patients



Commercial scale in-house manufacturing in the US

- 63,000 square foot state-of-the-art facility for GMP manufacturing
- RP1 technology transfer from CMO successfully completed; RP2 commenced

Complete supply chain 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, complete Replimune quality control

Low cost per dose to support sustainable, widespread treatment option for patients

- Per patient cost-of-goods significantly below TIL or CAR-T autologous manufacture costs
- Drug availability and stocking 'off-the-shelf' avoids manufacturing complexity and treatment delays



Upcoming data sets expected in 2021/22

End 2021

- RP2 + Opdivo updated data from combination cohort in all comers study
- RP3 phase 1 initial single agent data in all comers
- RP1 + Opdivo anti-PD1 failed NSCLC initial data
- RP1 ARTACUS single agent initial data in CSCC organ transplant patients
- Further granularity on RP2/3 development strategy

2022

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

Well capitalized to deliver on all potential catalysts with cash into H2 2024



THANK YOU

Replimune is developing a best-in-class platform for the treatment of solid tumors



<u>Viral Immunotherapy</u>	<u>HSV Type 1</u>	<u>RP Backbone</u>	<u>Payloads</u>
<ul style="list-style-type: none">• Infective – tumor tropism for viral infection of cancer cells• Selective – weakened tumor viral defense allows for preferred replication in tumor• Immunogenic – body immune system adapted for response to viral pathogens	<ul style="list-style-type: none">• Lytic – highly lytic virus to kill infected tumor cells• Large capacity – genome size for inserting payloads• Characterized – extensive in-human track record, treatable with antivirals• Validated – TVEC is only approved OI also based on HSV1	<ul style="list-style-type: none">• Viral Strain – clinical variants more potent than lab strains, 29 variants screened to select best tumor cell killing• ICP34.5 – deletion enhances tumor-specific selectivity based on impaired tumor IFN defense• US11 – upregulation of gene for resistance increases replication in cancerous cells	<ul style="list-style-type: none">• Local tumor destruction – GALV increases viral infectivity, killing, and immunogenicity• Innate immune response – enhances natural HSV stimulation of immune cells and inflammatory cytokines release• Adaptive & memory immune activation – transgenes local tumor expression for maximal antigen presentation and effector stimulation
Viruses, which naturally to infect cells and generate human immune response, <u>repurposed for novel function</u>	<u>Viral properties, human characterization, and regulatory precedent</u> make ideal for development of immunotherapy	Extensive <u>screening and engineering</u> of HSV to maximize therapy safety & efficacy	Diverse and intentional transgene insertion to <u>optimize immune activity over multiple pathways</u>

Areas of differentiation – unique to Replimune programs