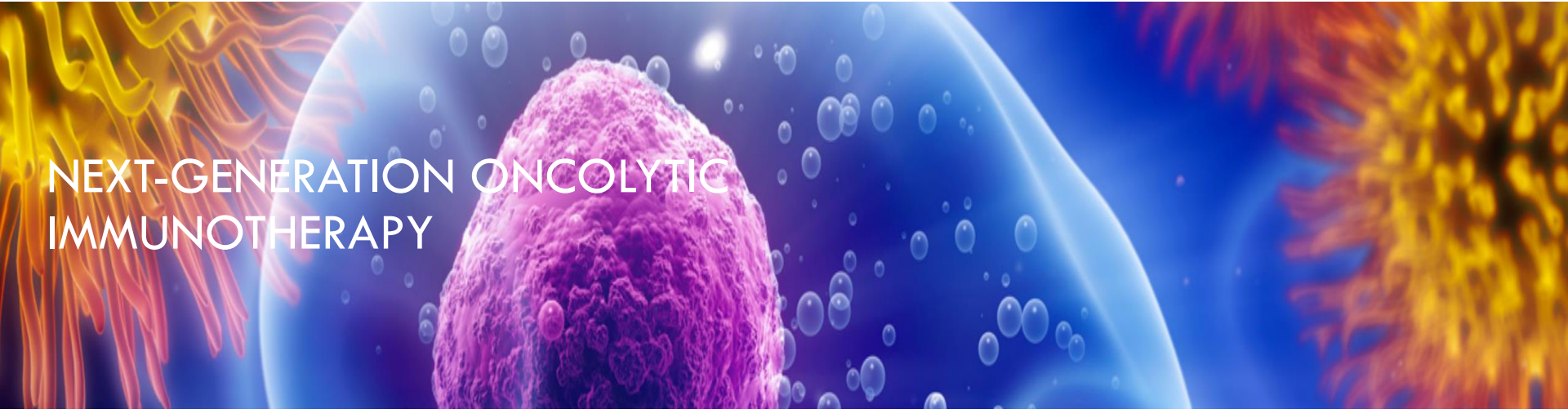
Replimune



February 2021

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 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 system against a patient's cancer
- Intended to establish Replimune's products as the second cornerstone of immuno-oncology

RP1 – in multiple clinical trials, with current focus on immune-responsive tumor types

- Registration directed development
  - CERPASS study in advanced cutaneous squamous cell carcinoma (CSCC) enrolling
  - IGNYTE study in anti-PD1 failed melanoma enrolling
- 30 patient anti-PD1 failed non-small cell lung cancer cohort open for enrolment

RP2/3 – intended to treat less immune-responsive tumor types

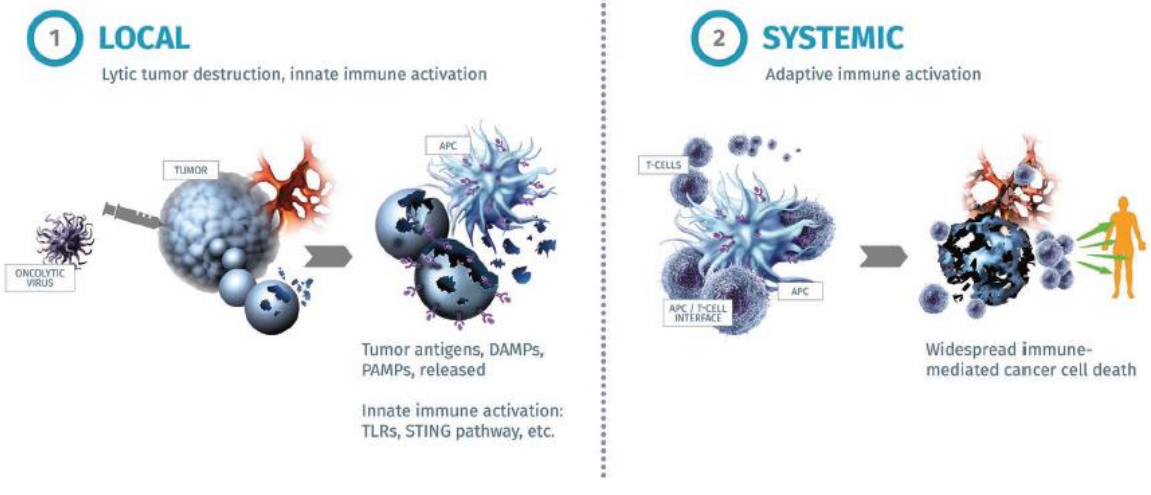
- RP2 – single agent utility demonstrated in heavily pre-treated immune insensitive tumor types ; anti-PD1combo arm enrolling
- RP3 – single agent dosing underway

- 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 ~$493m as of December 31st 2020, 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

Replimune's product design objectives & solutions

1. Maximize direct tumor destruction & immunogenic cell death through design and development of a virus with the best ability to infect, replicate in & kill tumor cells:
   - *Based on a potent new clinical HSV strain resulting from a comprehensive screen**
   - *ICP34.5 deleted for selectivity, US11 upregulated to retain near wild type replication in tumors**
   - *Encodes a potent fusogenic protein, increasing killing & immunogenic cell death 10-100 fold**
   - ➢ Together providing maximal antigen presentation ('Signal 1')
   - ➢ *Our platform for all our product candidates from which additional transgenes are then expressed*

2. Further arm with immune activating transgenes intended to maximize T cell co-stimulation ('Signal 2') & systemic immune activation (including through induction of inflammatory cytokines: 'Signal 3')
   - *GM-CSF – DC expansion & maturation:* ***RP1, RP2***
   - *Anti-CTLA-4 – block APC/T-cell feedback loop:* ***RP2, RP3***
   - *CD40L & 4-1BBL – Activate co-stimulation; induce inflammatory cytokines (IL-2, IL-8, IL-12):* ***RP3***

* Replimune's fusion-enhanced backbone virus is described in Thomas et al (2019) JITC 10; 214

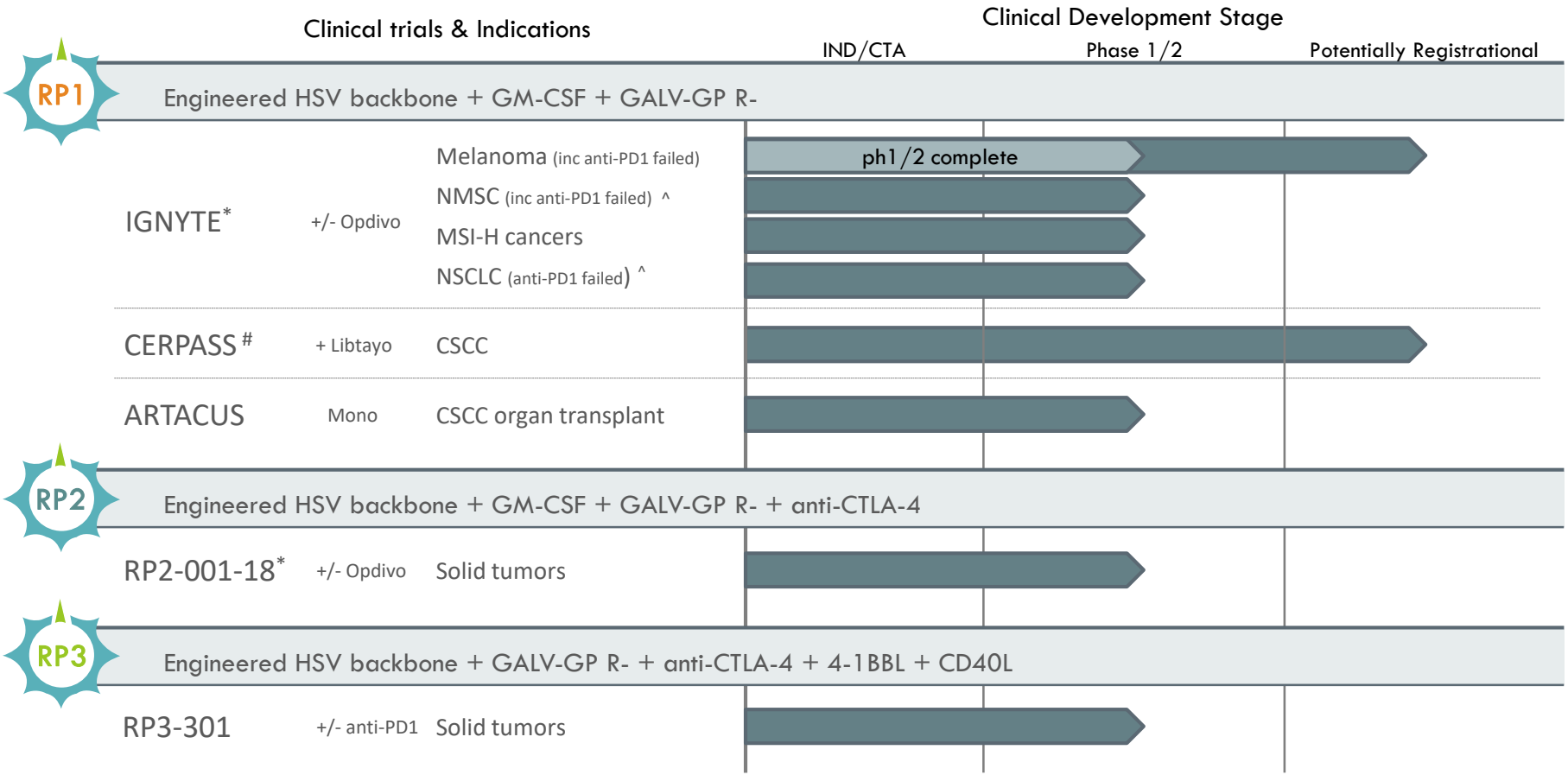
Practical and comprehensive activation of a tumor specific immune response

Our platform offers significant advantages compared to competing approaches, such as cell-based therapies, including TILs, 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	✓	✗	✗
Incorporates multiple modalities (incl. innate & adaptive immunity)	✓	✗	✗
Attractive safety profile, without a high frequency of high-grade side effects including death	✓	✗	✓
Potentially applicable to nearly all patients with solid tumors	✓	✗	✗

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
^ Assumes currently filed protocol amendment accepted by FDA

RP1 - Lead indication overview: CSCC

- The second most common skin cancer with ≈700,000 patients annually in the U.S.[1]
- Approximately 7,000-15,000 US deaths annually[1-3]
  - 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 annually[1-4]
- While effective, anti-PD1 therapy alone results in only a low rate of complete response

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

[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

RP1 - Lead indication: CSCC – the CERPASS study

- Registration-directed randomized controlled Phase 2 clinical trial in collaboration with Regeneron*
  - 240 patients (target enrollment) with locally advanced or metastatic CSCC naïve to anti-PD1 therapy
  - Randomized 2:1 (RP1+ Libtayo vs. Libtayo alone)
  - Primary endpoint ORR
  - Secondary endpoints include CR rate, duration of response, PFS, OS
- Aim to show ≥15% delta improvement in ORR
  - 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
- Aim to also improve durability and show multi-fold (2-3x) improvement in CR rate

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

Compelling activity with RP1 in combination with nivolumab in non-melanoma skin cancers, particularly CSCC

Best response

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

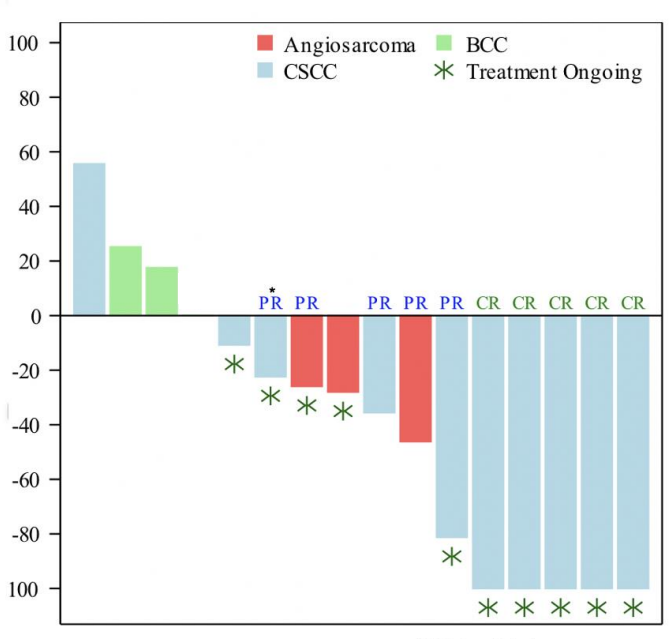
	CSCC	BCC	Merkel cell carcinoma	Angiosarcoma
Number of patients	11	3	1	3
Best overall response n (%)				
CR	5 (45.5)	0	0	0
PR	3* (27.3)	0	0	2 (66.7)
SD	1# (9.1)	2 (66.7)	0	1 (33.3)
PD	2 (18.2)	1 (33.3)	1 (100)	0
ORR	8 (72.7)	0	0	2 (66.7)
CR+PR+SD	9 (81.8)	2 (67.7)	0	3 (100)
DOR (mos.) Median Range	 >4.66 >0.03->16.93	 NA	 NA	 >0.03-NA^

*One patient PR by clinical assessment; CT pending #Just had first scan, newly added to the denominator
^Follow up for one patient not available post discontinuation for nivolumab-related side effects

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

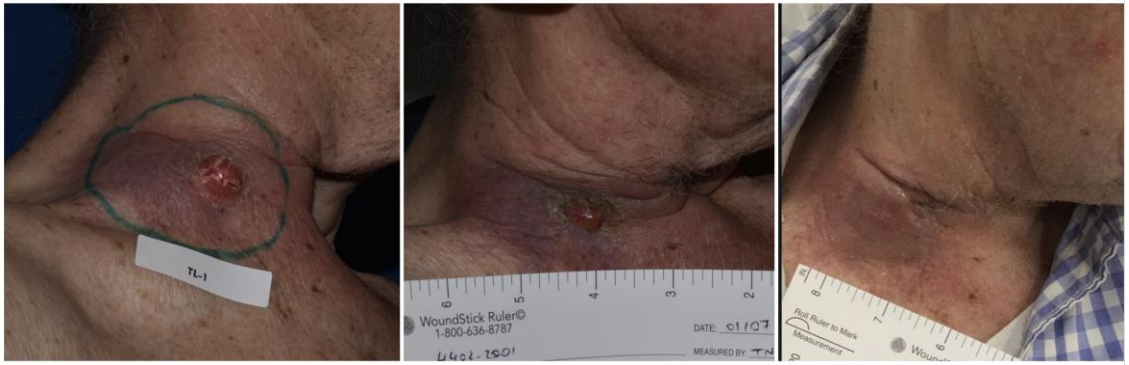
Maximum percent tumor reduction

Patients with follow up scans

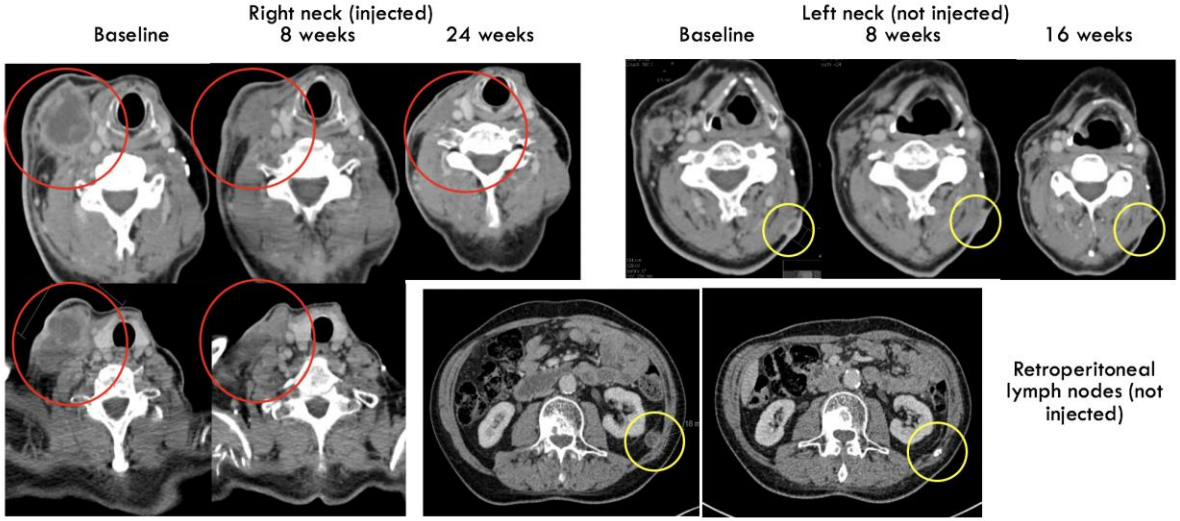


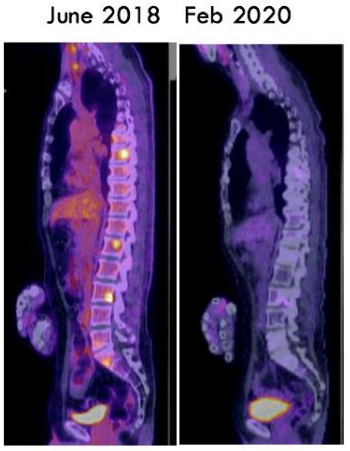
* PR by clinical assessment; CT pending

CSCC patient 4402-2001 - ongoing CR

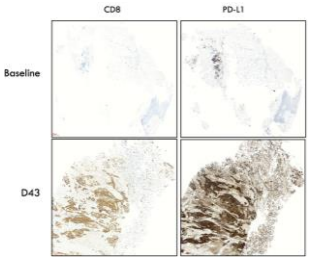


- Recurrent CSCC of the neck (bilateral), previously treated with cisplatin-based chemoradiation & six cycles of carboplatin/5-FU
- **Both the large injected tumor & the smaller contralateral tumor in the neck reduced considerably before the first Opdivo dose,** i.e. after the first dose of RP1

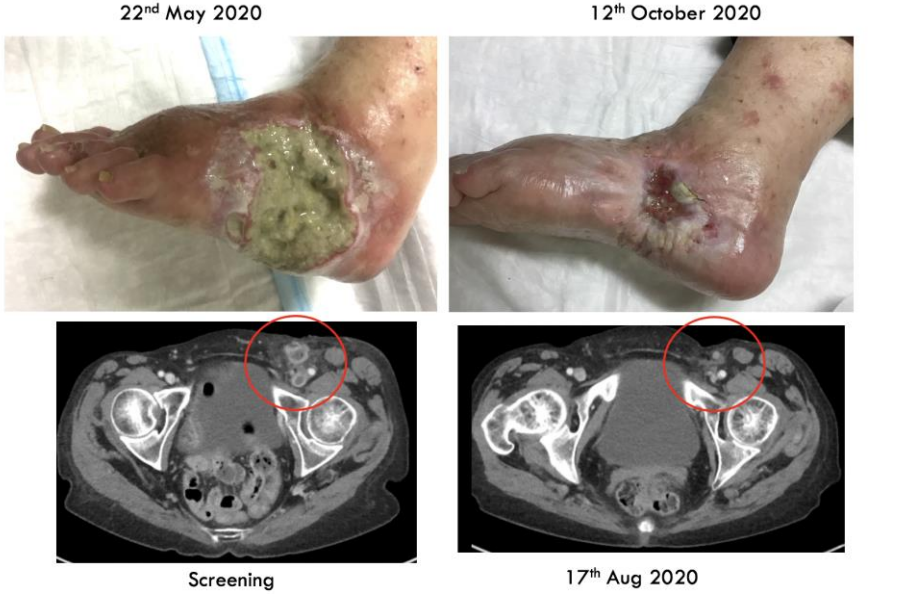


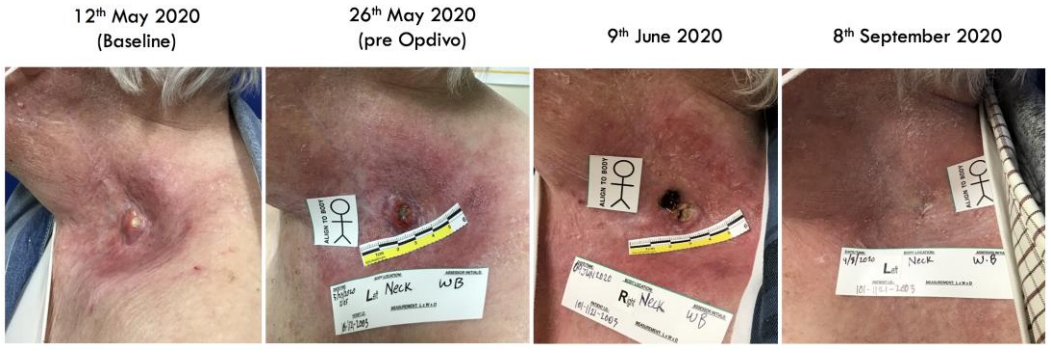


Bone metastases



New responses in CSCC reported in October 2020





Pt 1122-2014 - PR (clinically assessed October 12th 2020; October CT pending)

- Patient had enlarged groin node metastases that were initially injected & responded, as well as response in the distant foot tumor prior to its subsequent injection

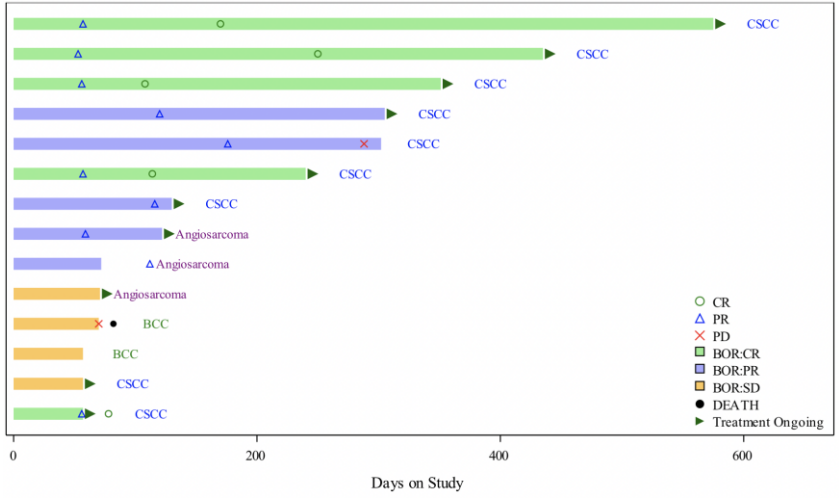
Pt 1121-2003 - CR

- Prior cetuximab
- Injections into left neck lesion

Responses in CSCC are deep & durable

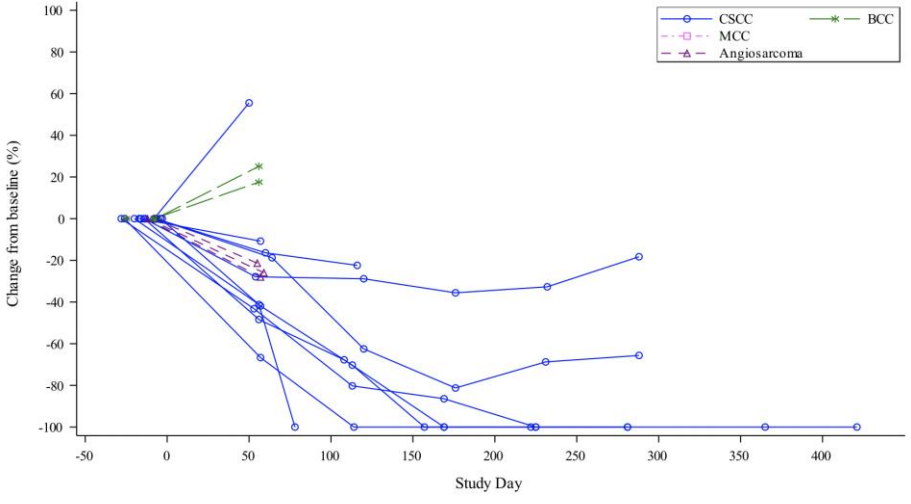
Duration of best response

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 potentially registrational 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 melanoma[1]
- Approximately 62,000 deaths annually world-wide[2]

- 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 therapy[3]
- Expected response rate to continued treatment with anti-PD1 therapy following confirmed progression on single agent anti-PD1 is 6-7%[4]
- The expected response rate to Yervoy following failure of initial single agent anti-PD1 is 13%[5]

[1] https://seer.cancer.gov (2019 data). [2]JAMA Oncol. 2019; 5(12):1749-1768. [3] Gide et al Clin. Cancer Res **24** 2018

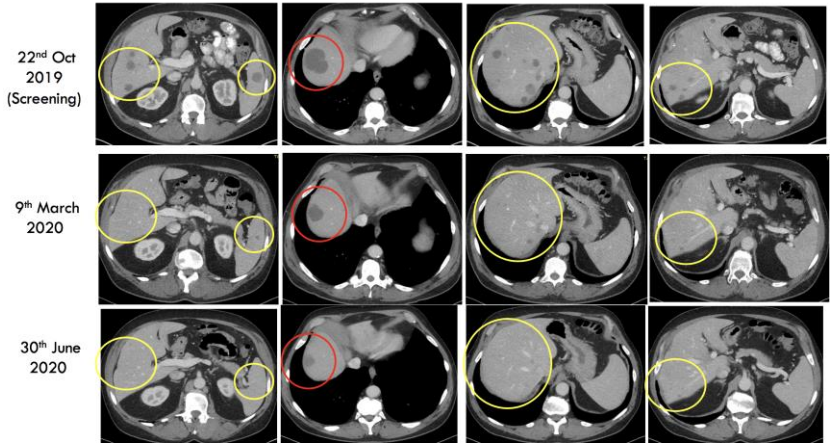
[4] Ribas et al Lancet Oncology **19** 2018; Hodi et al JCO **34** 2016 [5] Pires de Sliva et al ASCO 2020

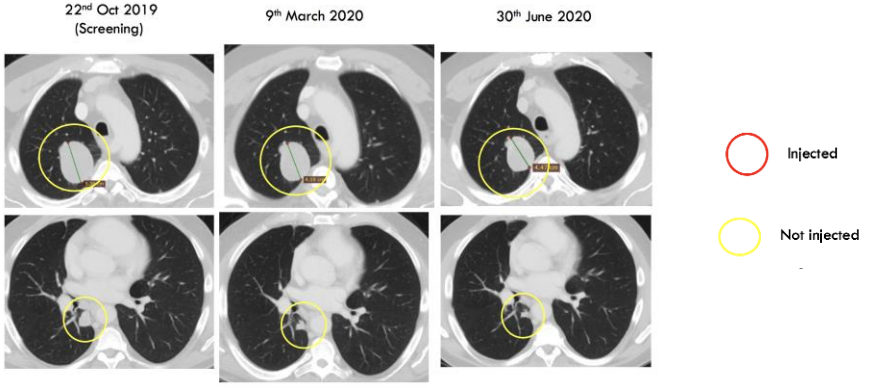
RP1 in anti-PD1 failed melanoma data

- October 15th 2020 status of the anti-PD1 failed cutaneous melanoma (N=16) patients dosed
  - 87.5% stage IVM1b/ M1c; very advanced visceral disease population
  - 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
  - Responses are deep and durable; 80% ongoing at out to over 12 months
  - Current ORR for these patients remains at 31%
    - Of two patients that had not responded or progressed as of June 2020 data disclosure
      - One is now an ongoing surgical CR (counted as SD per study protocol definitions)
      - One remains SD, with treatment ongoing
  - Clinical data supported by biomarker data, including reversal of T cell exclusion
- Activity also seen in patients who have failed prior anti-PD1 therapy with uveal and mucosal melanoma

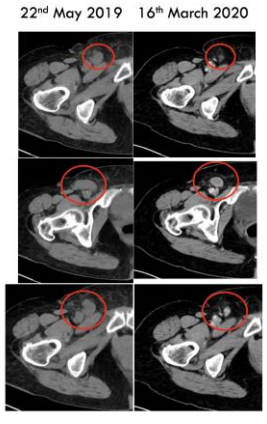
*SD or better with evidence of anti-tumor activity

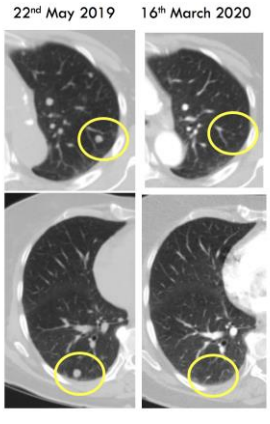
Local & distant responses in ipi/nivo failed melanoma

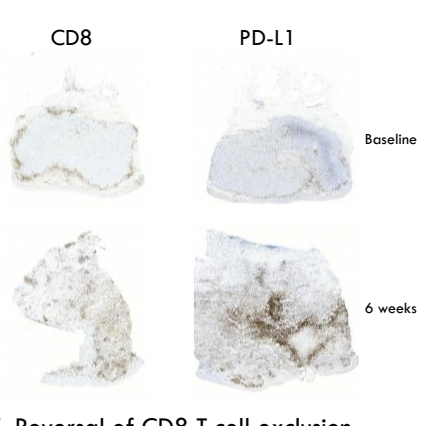




Pt 1122-2007 – ipi/nivo failed cutaneous melanoma (ongoing PR at 11 months from first RP1 dose)







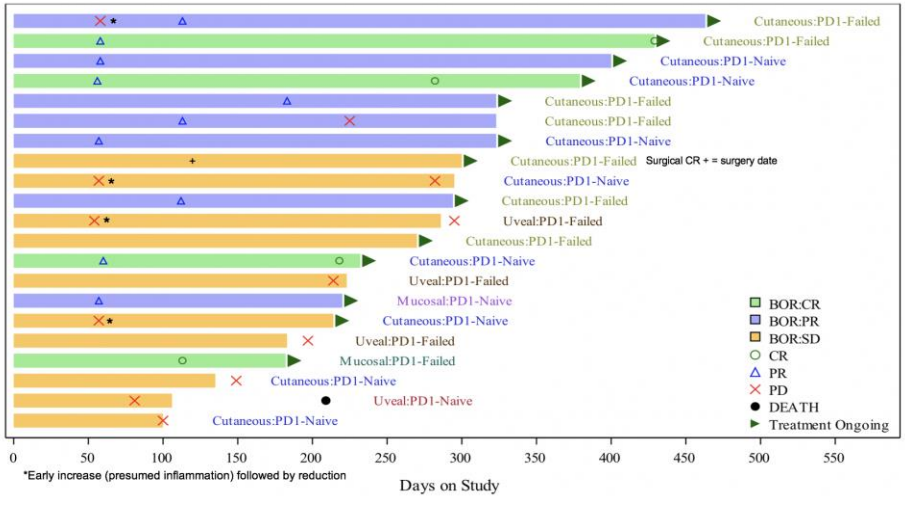
Pt 4403-1003 – ipi/nivo failed cutaneous melanoma (ongoing PR at 16 months from first RP1 dose)

Reversal of CD8 T cell exclusion

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

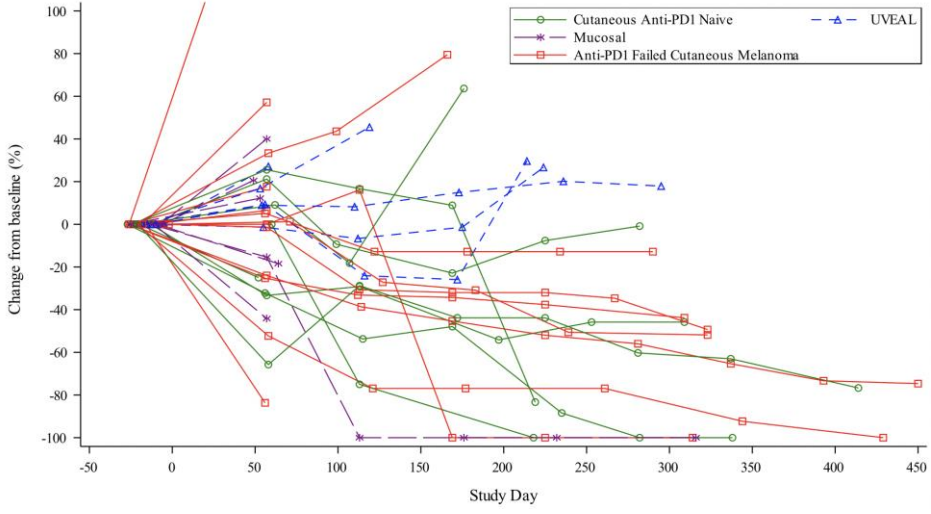
Duration of best response

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



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

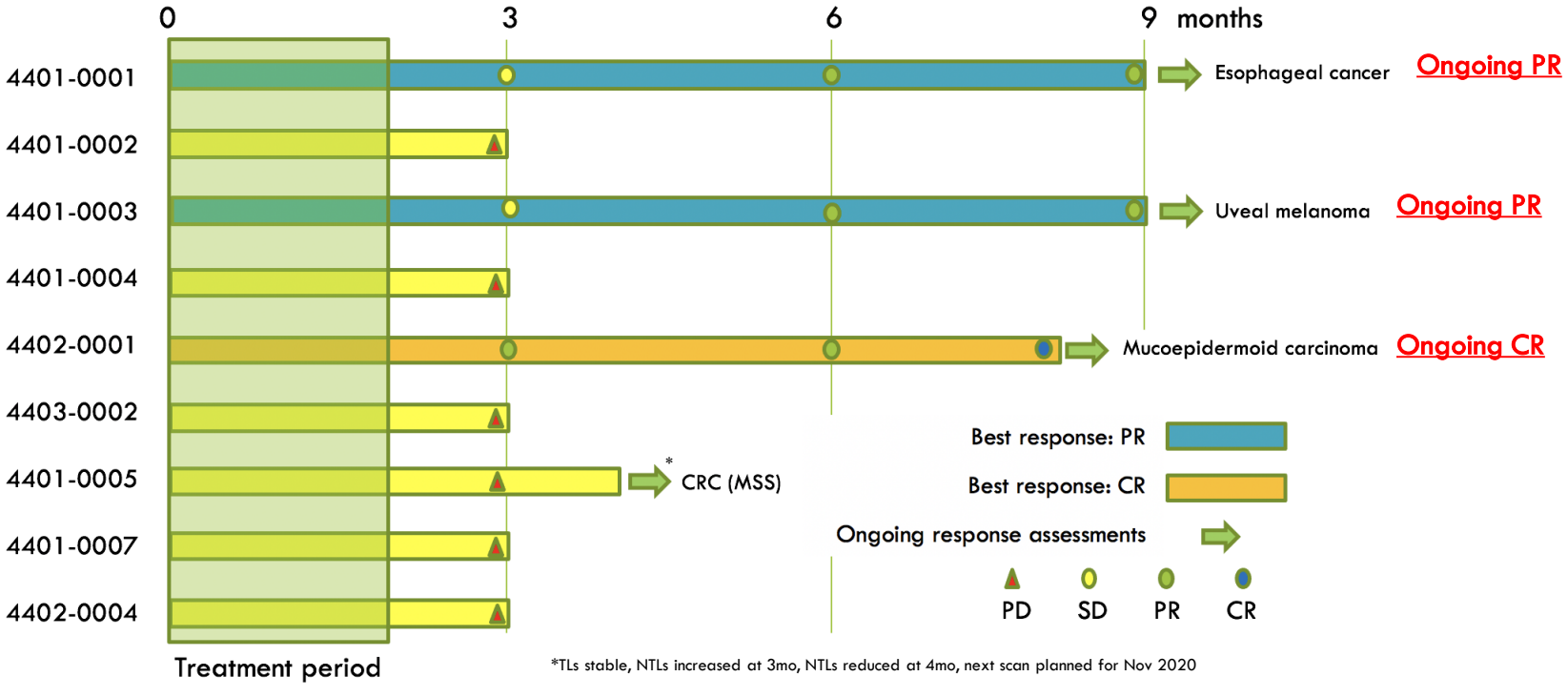
Based on the data to date, Replimune believes it is well positioned for success in the potentially registrational 125 patient Phase 2 cohort of RP1 combined with nivolumab in anti-PD1 failed melanoma

RP2 – Single agent activity clearly demonstrated

- RP2 – leverages Replimune's platform to additionally expresses an anti-CTLA-4 antibody
- Well tolerated; side effects consistent with RP1
- Compelling single agent efficacy in heavily pre-treated patients with less immune sensitive & immune insensitive tumor types
  - CR – Mucoepidermoid carcinoma
  - PR – Uveal melanoma
  - PR – Esophageal cancer
- Kinetics of response suggests initial tumor inflammation precedes response
  - Similar pattern may be developing in a further patient
    - MSS (immune insensitive) colorectal cancer
- Responses are durable & all are ongoing with patients at between 8 &11 months from first RP2 dose
- Treatment of patients with RP2 combined with Opdivo is underway
  - Patients not yet evaluable for efficacy but well tolerated so far

Replimune

RP2 single agent – Deep and durable responses



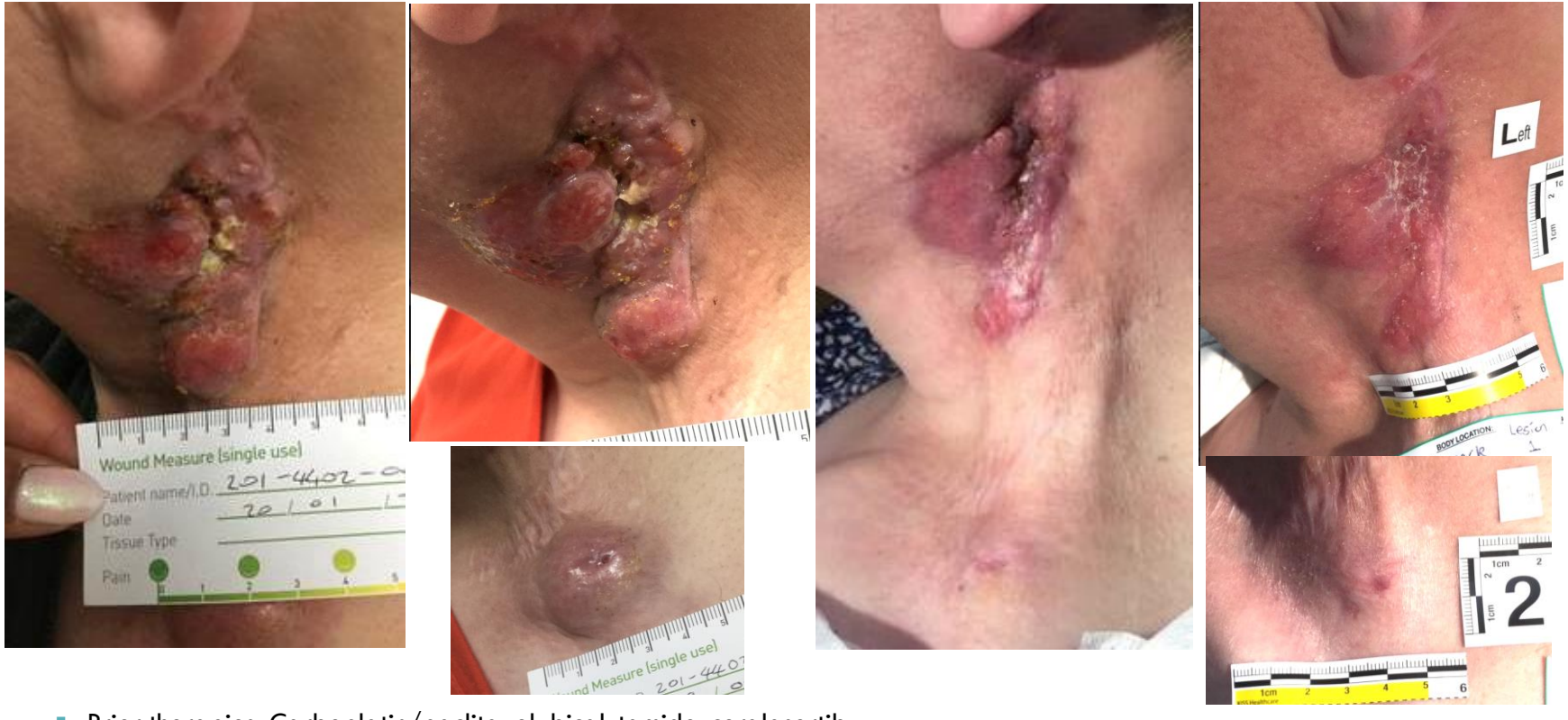
Kinetics of response following treatment with single agent RP2

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

Replimune

Patient #: 4402-0001: Mucoepidermoid carcinoma of the parotid – Ongoing CR

Baseline | 1 month | 3 months | 4 months

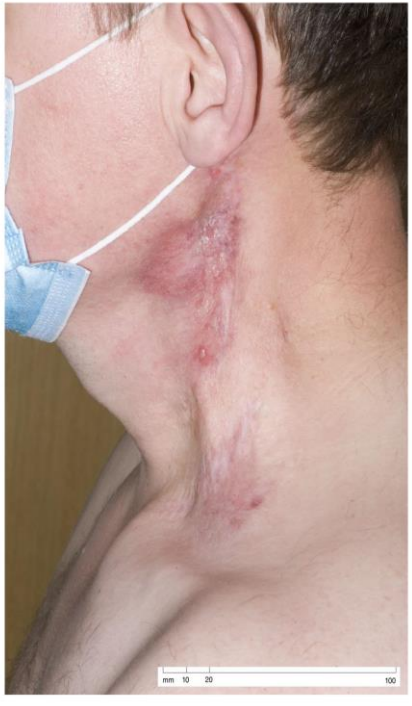


- Prior therapies: Carboplatin/paclitaxel, bicalutamide, ceralasertib
- Cervical lymph node & supraclavicular fossa injected with 10ml $1x10^6$ pfu/ml, then 10mL $1x10^7$ pfu/ml x4 Q2W
- CR confirmed by PET scan 16th Oct 2020

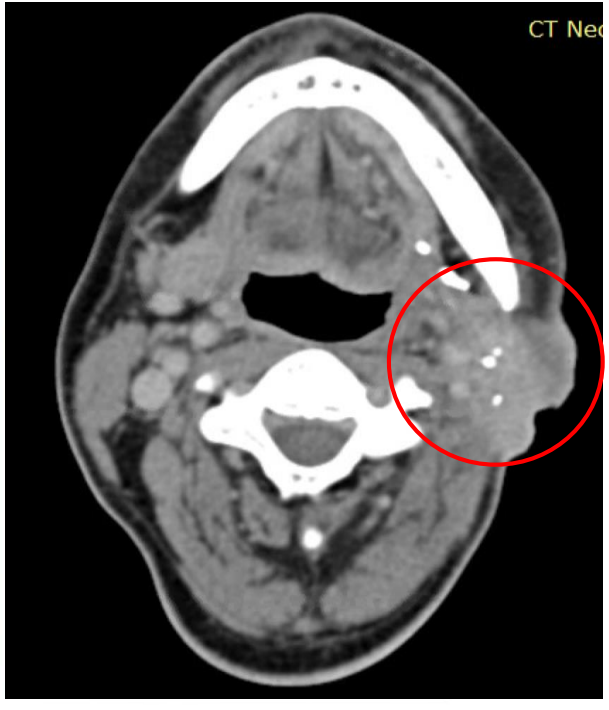
Replimune

Patient #: 4402-0001: Mucoepidermoid carcinoma of the parotid – Ongoing CR

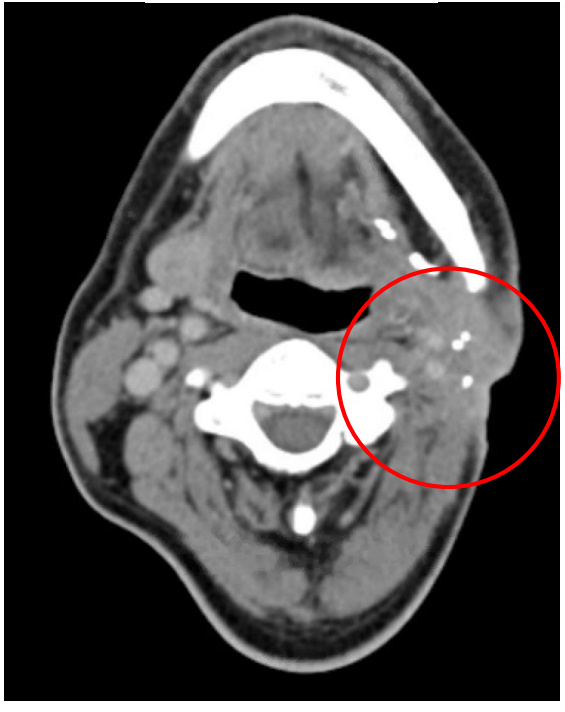
6 months



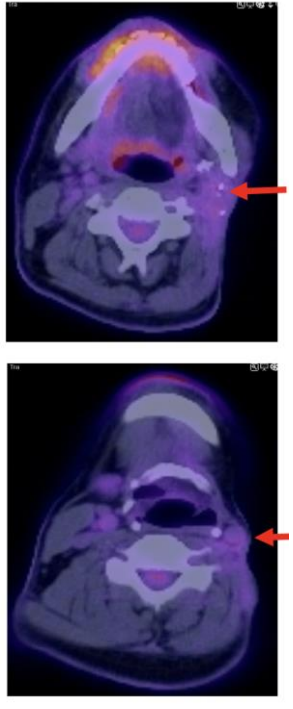
Screening



5 months

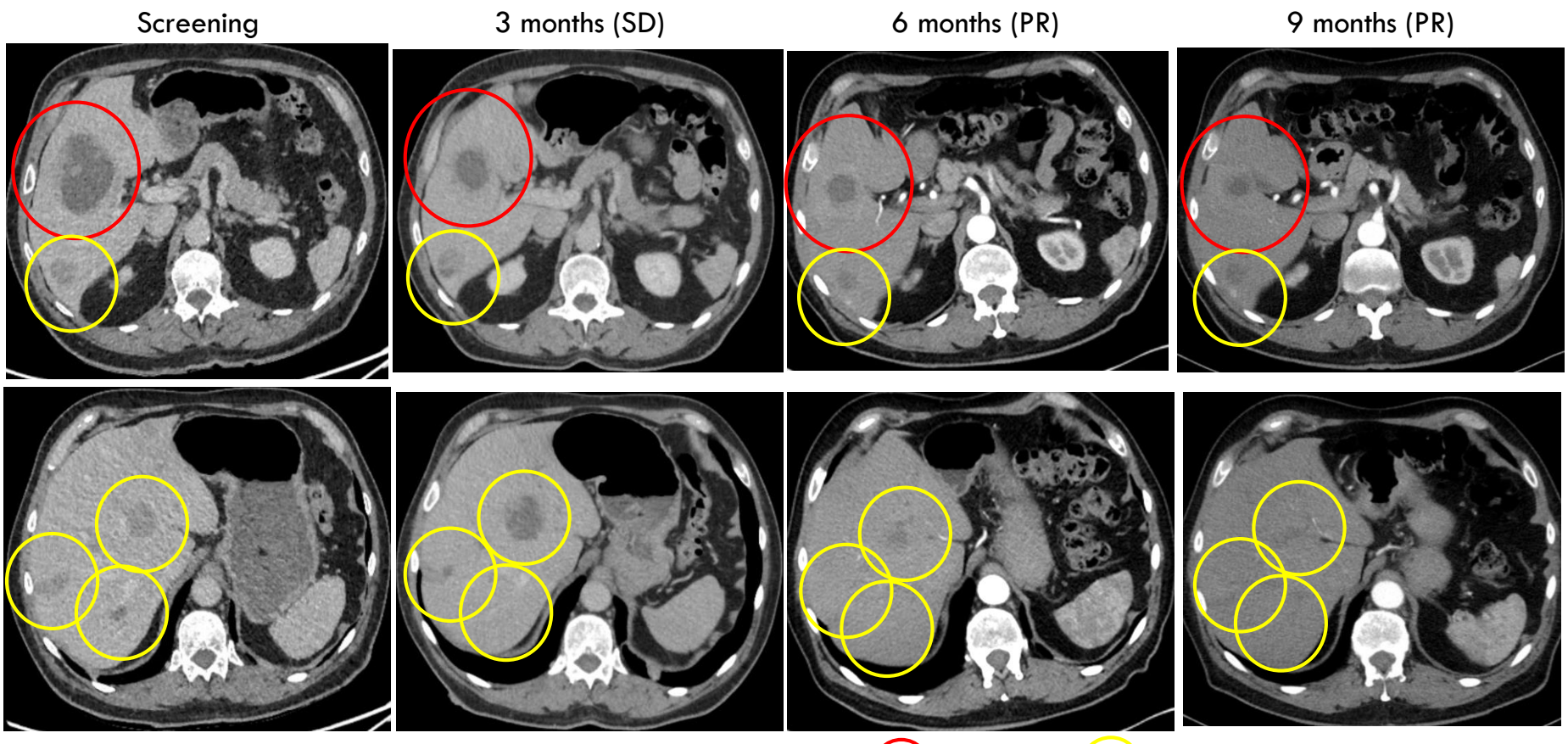


8 months
(PET scan to confirm CR)



Replimune

Patient #: 4401-0003: Uveal melanoma (ipi/nivo failed) – Ongoing PR



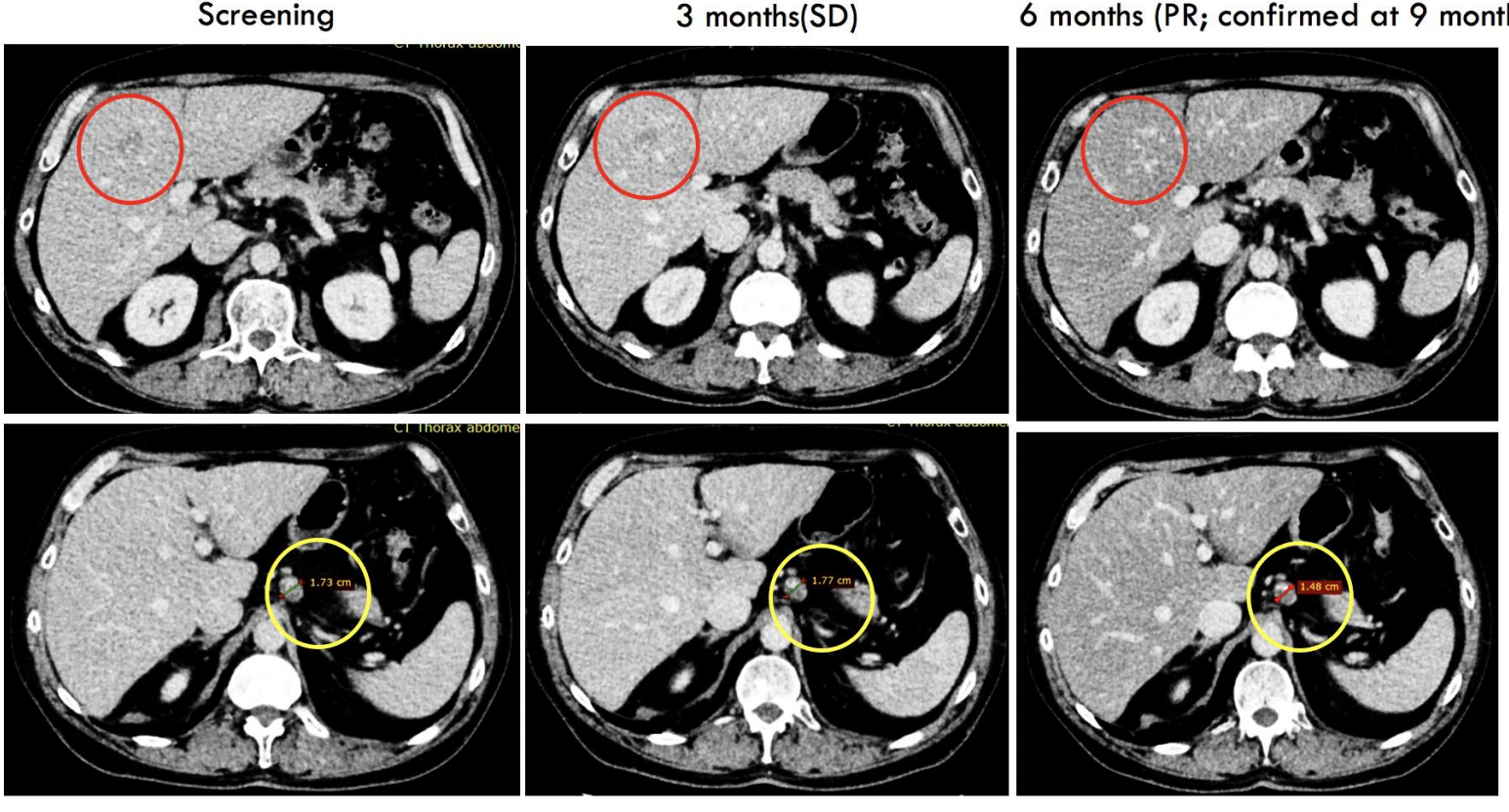
- Extensive liver metastases (others not shown)
- Prior therapies: Ipilimumab/nivolumab
- Largest liver lesion injected with 3ml 1x10^5 pfu/ml, then 3mL 1x10^7 pfu/ml x4 Q2W

Injected

Not injected

Replimune

Patient #: 4401-0001: Esophageal cancer (anti-PD-L1 failed) – Ongoing PR



- Liver & abdominal lymph node metastases
- Prior therapies: Durvalumab (anti-PD-L1), M6620 (ATR kinase inhibitor), capecitabine, oxaliplatin, cisplatin, chemoradiation
- Liver lesion injected with 1ml $1x10^5$ pfu/ml, then 0.5mL $1x10^6$ pfu/ml x4 Q2W

Completed and fully operational manufacturing facility

- Commercial scale in-house manufacturing in place
  - 63,000 ft^2 state of the art facility
  - RP1 technology transfer from CMO successfully completed ; RP2 commencing this quarter
  - Scale sufficient to cover global commercialization of Replimune's products at full capacity
- Operations management / CMC team has extensive manufacturing experience with HSV
- GMP manufacturing underway
  - First two RP1 comparability batches expected to be filled and complete QC testing this quarter

New & expanded data sets expected in 2021/22

- 2021
  - RP1 + Opdivo anti-PD1 failed NSCLC initial data
  - RP1 + Opdivo anti-PD1 failed CSCC initial data
  - RP1 ARTACUS single agent initial data in CSCC transplant patients
  - RP2 + Opdivo initial data in all comers study
  - RP3 phase 1 initial single agent data in all comers
  - Additional updates from all ongoing studies from which initial data has previously been released
- 2022
  - CERPASS (CSCC registration directed study) primary read out
  - IGNYTE (anti-PD1 failed melanoma registration directed study) primary read out
  - RP3 + Opdivo data in all comers study
  - Potential for initial readouts from other follow on studies with RP2/3
    - Indication prioritization analysis underway

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