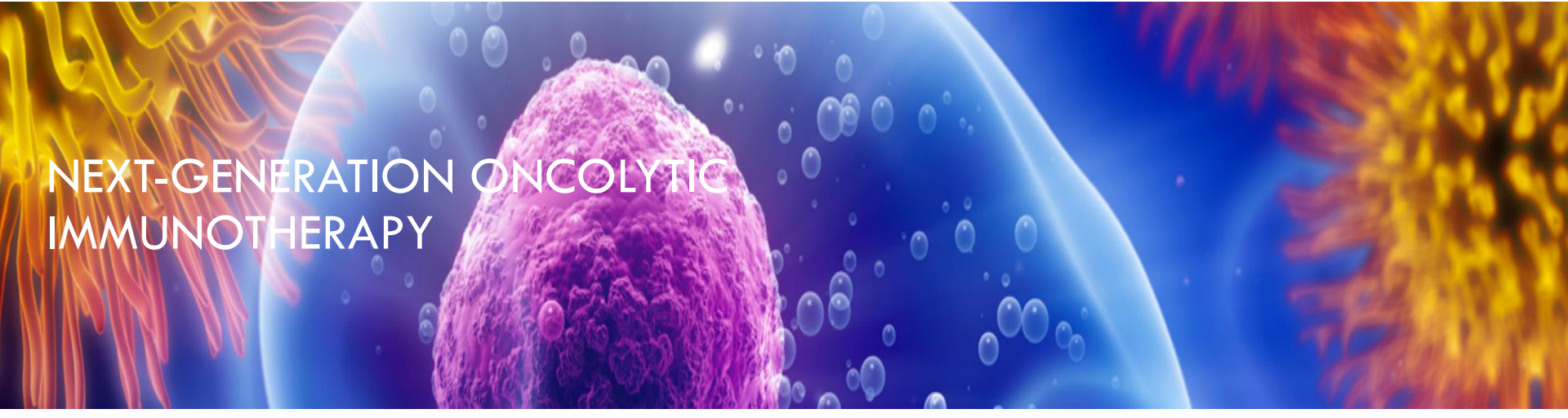
Replimune



SITC Investor Event Presentation

November 8th 2019

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 our expectations about our use of cash, our advancement of our clinical trials, our goals to develop and commercialize our product candidates, our plans to establish our own in-house manufacturing capabilities, our proposed scientific presentations, 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 establishing, equipping, and operating our planned 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, and other risks set forth under the heading "Risk Factors" of our Annual Report on Form 10-K for the year ended March 31, 2019. 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.

Schedule of events

- Introduction to the company and platform overview
- Clinical data & conclusions
- Q&A

Replimune mission statement

Replimune aims to transform the lives of cancer patients through the development of highly effective but low toxicity therapies that provide durable benefit across a broad range of tumor types

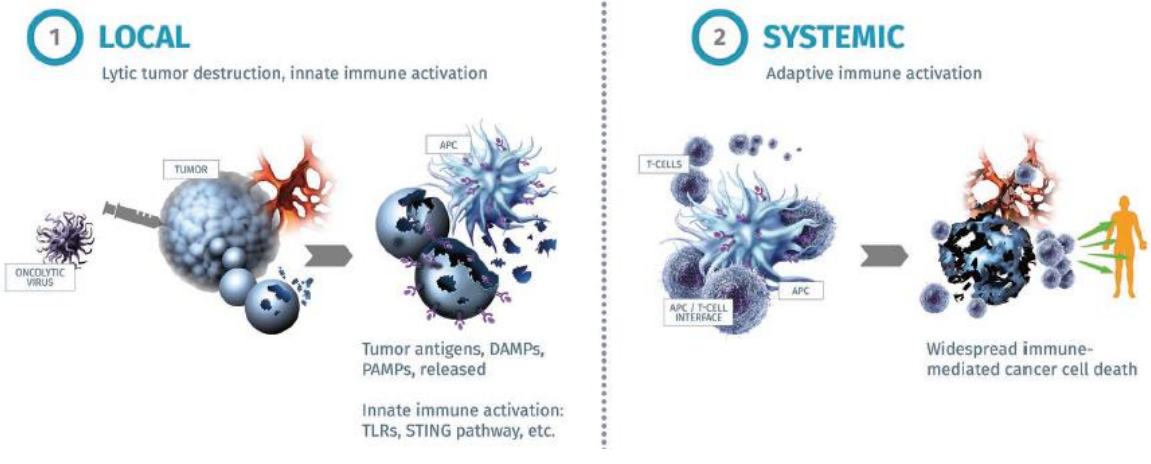
- Founded by the former BioVex management team that developed T-VEC
- Proprietary 'Immulytic' oncolytic immuno-gene therapy platform
  - *Intended to maximally activate the immune system against a patient's cancer*
  - *Establish Replimune's products as the second cornerstone of immuno-oncology*
- RP1 – in multiple clinical trials predominantly targeting skin cancers
  - *Skin cancer clinical trials underway & planned include*
    - *Ongoing Phase 2 trial including non-melanoma skin cancers in combination with nivolumab*
    - *Ongoing registration directed Phase 2 clinical trial in CSCC in combination with cemiplimab*
    - *Clinical trial of single agent RP1 in CSCC in organ transplant recipients (announced in October)*
    - *Clinical trial in anti-PD1 refractory melanoma patients (announced today)*
- RP2 & RP3 - intended to treat less immuno-responsive tumors, outside skin cancers
  - *Ongoing Phase 1 clinical trial of RP2 alone & combined with nivolumab*
  - *RP3 intended to enter the clinic in 2020*
- Commercial scale manufacturing capability expected to be operational H1 2020

Summary of data & conclusions to be presented

- RP1 alone & combined with nivolumab is well tolerated
- MOA of RP1 alone & in combination with nivolumab was confirmed
- Strong support was provided for Replimune's programs in melanoma & CSCC
  - Includes two of the three anti-PD1 refractory cutaneous melanoma patients enrolled in Phase 1 & the first ipi/nivo refractory Phase 2 patient with follow up scans treated in combination with nivolumab responding *(see separate melanoma-specific deck also released today)*
  - CSCC data previously disclosed & updated with further improvement today *(see separate CSCC-specific deck also released today)*
- Biomarker data also indicated robust virus replication & immune activation
- As a direct result of this clinical data, Replimune's clinical programs are being expanded in CSCC & melanoma
  - New clinical trial in CSCC in solid organ transplant patients with RP1 alone
  - New clinical trial in anti-PD1 refractory melanoma (RP1 combined with anti-PD1)
- Phase 2 data with RP1 combined with nivolumab in bladder cancer & MSI-H tumors is pending

Oncolytic immuno-gene therapy

- The use of viruses that selectively replicate in & kill tumors to treat cancer
  - Directly kills tumors
  - Highly inflammatory
  - Activates both innate and adaptive immunity
  - Releases the full array of tumor antigens into an inflamed environment
  - Systemically activates the immune system against the tumor & neo-antigens released
  - Armed with additional genes to increase efficacy
- Single agent T-VEC is FDA approved for the treatment of advanced melanoma

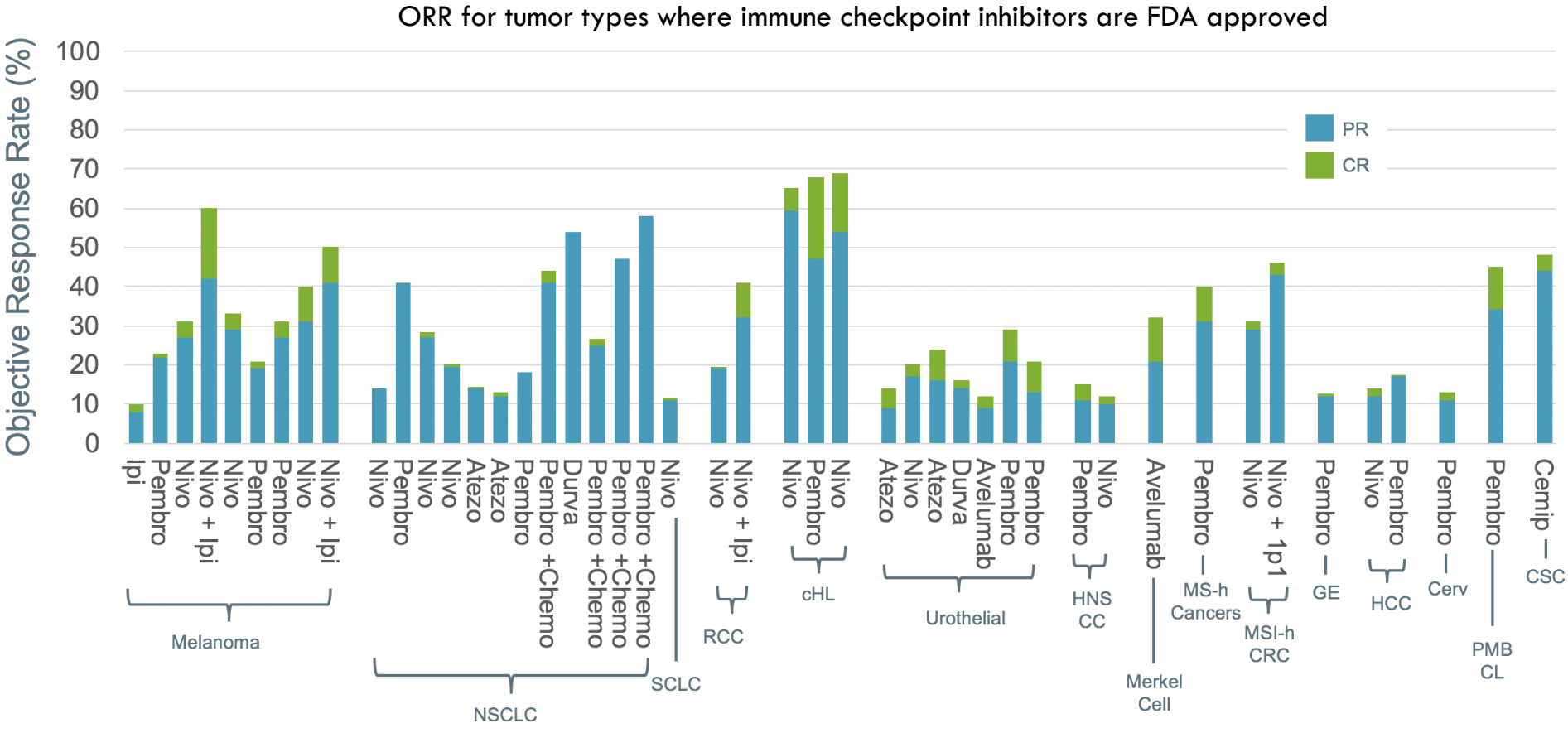


Replimune

Replimune's therapies are designed to be best in class

- Designed to maximize local tumor destruction
  - Clinically beneficial in its own right
  - Provides abundant release of tumor antigens to provide the systemic vaccination effect
- Designed to maximize the immunogenicity of cell death
  - Increases the potency of the immune response generated to tumor antigens as they are released
- Deliver potent immune stimulating proteins to the tumor to further amplify the immune response
  - Focus on proteins which act at the site and time of immune response initiation
  - In particular, such proteins often require ongoing antigen presentation (i.e. provision of Signal 1)
  - Virus mediated immunogenic killing provides a potent source of Signal 1, which is not usually present on an ongoing basis in cancer patients
- Thereby intended to convert immunologically 'cold' tumors to immunologically 'hot'
- Intended to maximize synergy with PD1 blockade

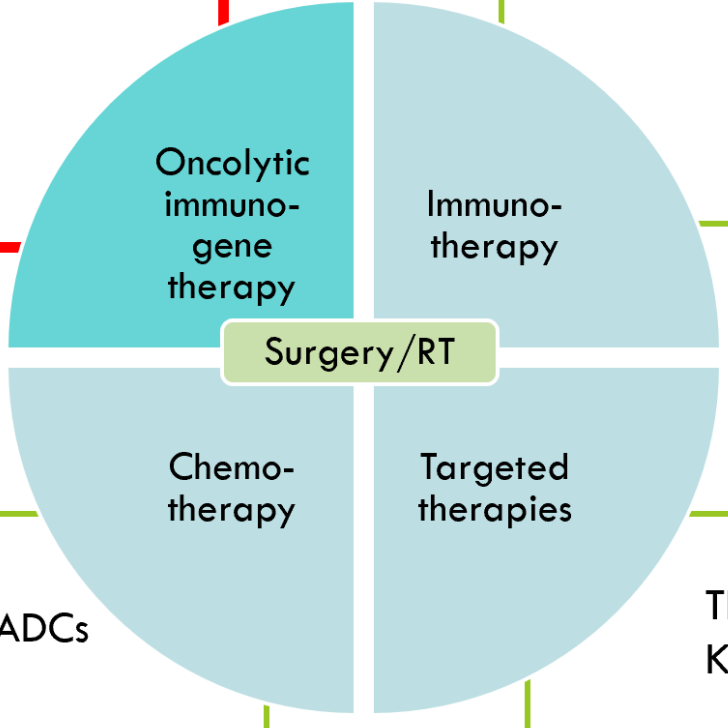
Most patients don't respond to immune checkpoint blockade



Source: re-drawn from FDA presentation at AAADV Workshop, 5/8/2019. Data as of 11/2018.

Intended to become the fourth cornerstone of cancer treatment

Immune activation: Currently missing from the cancer treatment paradigm



Overcome defenses to the host immune response – dominated by anti-PD1

Cell-based therapy

Traditional cytotoxics/ADCs

TKIs, PARPs, KRAS, various antibodies, etc

A pipeline designed to address specific needs in cancer therapy

- Need 1: Improve outcomes in immune sensitive cancers 

  - Tumors that already have a level of responsiveness to anti-PD1 blockade
  - In all cases there still remains a substantial unmet need
  - Intend to establish a franchise for the treatment of skin cancers, with initial clinical data-driven focus on
    - Cutaneous squamous cell carcinoma (CSCC)
    - Melanoma
  - Potential to expand to additional immune sensitive tumor types as clinical data warrants
    - Bladder cancer and MSI-H cancer

A pipeline designed to address specific needs in cancer therapy

- Need 2: Extend utility of immunotherapy in more immune resistant cancers

  - Tumors where anti-PD1 therapy is less effective, e.g. head & neck cancer, TNBC
  - Tumor types where anti-PD1 is not effective, e.g. colorectal cancer
  - Target tumor types for late stage development to be data-driven from earlier clinical trials

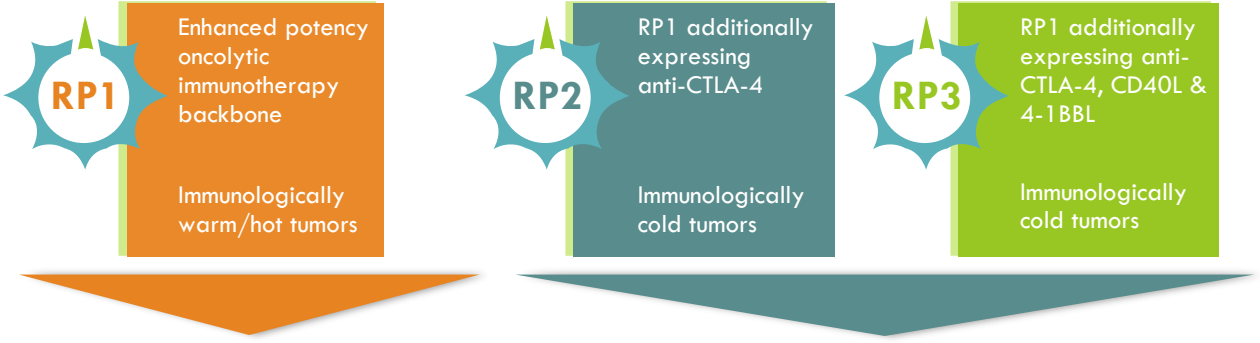
Replimune's Immulytic platform

1. A potent underlying HSV-1 strain

There is great diversity among clinical HSV strains

29 new clinical strains were tested & the most effective selected & engineered for oncolytic use

Our product candidates were then armed with two to four genes to augment tumor killing & the potency of immune activation



2. Increased tumor killing & spread

Armed with GM-CSF & a potent fusogenic protein (GALV-GP R-)

Provides a substantial increase in direct & immunogenic tumor killing potency

Intended for immune responsive tumor types, with focus on skin cancers

3. Delivery of potent immune stimulatory proteins

Focus on pathways where systemic engagement is sub-optimal

Further armed with anti-CTLA-4 & immune-costimulatory pathway activators

Intended for less & non-immune responsive tumor types

Replimune

Replimune has a robust & steadily advancing pipeline

	PRE-CLINICAL	PHASE 1	PHASE 2
RP1	Expresses GALV-GP R- & GM-CSF Phase 2 underway in 4 tumor types + nivolumab REGISTRATION DIRECTED 1. Randomized, controlled clinical trial in ≈240 patients with CSCC underway 2. Study in organ transplant recipients with CSCC to initiate Q1 2020 3. Study in PD1 refractory melanoma to initiate 2020	RP1 alone & with nivolumab Enrollment complete RP1 alone in organ transplant pts with CSCC Initiates Q1 2020*	Melanoma + nivolumab Enrolling Non-melanoma skin cancers + nivolumab Enrolling Bladder cancer + nivolumab Enrolling MSI high cancer + nivolumab Enrolling RP1+cemiplimab vs. cemiplimab in CSCC Enrolling RP1+antiPD1 in anti-PD1 refractory melanoma Initiates 2020
RP2	Additionally expresses an anti-CTLA-4 antibody. Phase 1 underway	RP2 alone & with anti-PD1 Enrolling	
RP3	Expresses GALV-GP R-, anti-CTLA-4, CD40L & 4-1BBL. Phase 1 initiates 2020	GXP activities underway	

*Trial expansion or additional trial expected to be needed for filing

Phase 1/2 clinical trial of RP1 alone & in combination with nivolumab

Key objectives of the RP1 Phase 1 part of the clinical trial

- Demonstrate safety of RP1, alone & combined with nivolumab
  - Via both superficial and deep injection routes
- Determine the recommended dose of RP1 for further development alone & combined with nivolumab
- Confirm the MOA of RP1 alone & in combination with nivolumab
- Provide support for Replimune's programs in the target tumor types for RP1
  - Initially skin cancers – melanoma & CSCC
  - With developing Phase 2 data, potentially bladder cancer & MSI-H tumors

Clinical trial design

- First in human two stage trial of RP1 alone and in combination with nivolumab
- Phase 1 part 1: Dose escalation of RP1 alone given up to 5 injections into a single tumor in three dose level cohorts each by either direct or imaging guided injection
  - Dose level 1: $1x10^4$ pfu/ml, $1x10^5$ pfu/ml, $1x10^6$ pfu/ml x 3
  - Dose level 2: $1x10^5$ pfu/ml, $1x10^6$ pfu/ml, $1x10^7$ pfu/ml x 3
  - Dose level 3: $1x10^6$ pfu/ml, $1x10^7$ pfu/ml, $1x10^8$ pfu/ml x 3
  - Samples taken for biodistribution & shedding
  - CT scan at baseline & 30 days post last dose
- Phase 1 part 2: RP1 given up to 8 times into multiple tumors at the recommended dose in combination with nivolumab starting from the second RP1 dose for up to two years
  - Serial biopsies taken for biomarker analysis & as clinically indicated

Data being presented today

- Phase 2: Four cohorts of 30 patients each with melanoma, non-melanoma skin cancers, bladder cancer and MSI-H tumors – *recruitment ongoing*

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Phase 1 key inclusion criteria (dose rising & combined with nivolumab)

Key inclusion criteria

- Advanced or metastatic non-neurological solid tumors, which have progressed on standard therapy or cannot tolerate standard therapy, or for which there is no standard therapy preferred to enrollment in a clinical trial
- At least one measurable and injectable (including use of image-guided injection) tumor of ≥ 1 cm in longest diameter
- Adequate hematologic, hepatic and renal function
- ECOG performance status 0 – 1
- No prior treatment with an oncolytic therapy
- No active CNS metastases

Phase 1 primary & secondary objectives (dose rising & combined with nivolumab)

Primary objectives

- To determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose of RP1
- To assess the safety and tolerability of RP1 alone and in combination with nivolumab

Secondary objectives

- To assess biological activity by changes in tumor size, inflammation, necrosis and erythema
- To assess RP1 biodistribution and shedding
- To assess the changes in levels of anti-HSV-1 antibodies

Phase 1 data summary

- The side effect profile was as expected alone & in combination
- Dose rising monotherapy phase
  - The recommended dose for further development was established
  - Tumor destruction was demonstrated, including delayed systemic tumor reductions without further therapy
  - Kinetics of detection of RP1 suggested robust virus replication
- Combination with nivolumab phase
  - Clinical activity seen in multiple patients with various tumor types
  - Two of the three anti-CTLA-4 + anti-PD-1 refractory cutaneous melanoma patients responding
    - The first ipilimumab/nivolumab refractory cutaneous melanoma patient in Phase 2 has also responded
  - Clear clinical activity seen in CSCC, including CR
    - Indications of activity in other tumor types also seen
  - Rapid tumor reduction seen before nivolumab, which is given from the second dose of RP1
- Abscopal effects were observed
- Increases in CD8 T cells, PD-L1 & inflammatory gene expression seen across tumor types
  - Including reversal of T cell exclusion

The patients enrolled

Patients enrolled - dose escalation

	Total	Melanoma	Colorectal	Head and neck	Breast	Esophageal	Pancreatic	CSCC	Cholangiocarcinoma
Number	22	8	5	2	2	2	1	1	1
Age: Range	22-81	22-71	30-59	61-78	55-65	66-81	58	58	68
ECOG performance status: 0, 1, 2 (%)	0: 13 1: 8 2: 1*	0: 4 1: 3 2: 1*	0: 4 1: 1	1: 2	0: 1 1: 1	0: 2	0: 1	1: 1	0: 1
Number of prior therapies: Range	1-13	1 – 5	2-5	3-5	8,13	1,2	5	2	1
Prior anti-PD1 therapy: Number (%)	8 (36.4)	7 (87.5)	0	1 (50)	0	0	0	0	0
Prior anti-PD1 + anti-CTLA-4 therapy: Number (%)	7 (31.8)	7 (87.5)	0	0	0	0	0	0	0
Baseline HSV serostatus: +ve, -ve (#)	14, 8	4, 4	3, 2	1, 1	1, 1	2, 0	1, 0	1, 0	1, 0

* The inclusion criteria were narrowed to exclude PS2 soon after the trial start

Patients enrolled - in combination with nivolumab

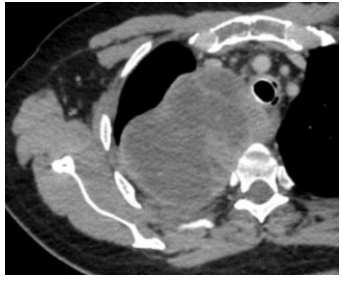
	Total	Cutaneous melanoma	Uveal melanoma	Mucosal melanoma	CRC	CSCC	BCC	Breast	Bladder	Adeno. of cecum	MSI-H (Colon)	Esepha geal
Number	14	3	2	1	1	1	1	1	1	1	1	1
Age: Range	28-74	28-67	53-64	74	70	61	56	59	51	41	50	70
ECOG performance status: 0, 1 (#)	0: 8 1: 6	0: 2 1: 1	0: 1 1: 1	0: 1	0: 1	1: 1	0: 1	0: 1	1: 1	1: 1	1: 1	0: 1
# of prior therapies: Range	1-8	2-3	1, 2	2	5	1	4	5	2	8	1	6
Prior anti-PD1 therapy: Number (%)	6 (42.9)	3 (100)	1 (50.0)	1 (100)	0	0	0	1 (100)	0	0	0	0
Prior anti-PD1 + anti-CTLA-4 therapy: Number (%)	5 (35.7)	3 (100)	1 (50.0)	1 (100)	0	0	0	0	0	0	0	0
Baseline HSV serostatus: +ve, -ve (#)	11, 3	1, 2	2, 0	1, 0	1, 0	1, 0	1, 0	0, 1	1, 0	1, 0	1, 0	1, 0

Patients enrolled - in combination with nivolumab

	Total	Cutaneous melanoma	Uveal melanoma	Mucosal melanoma	CRC	CSCC	BCC	Breast	Bladder	Adeno. of cecum	MSI-H (Colon)	Esepha geal
Number	14	3	2	1	1	1	1	1	1	1	1	1
Age: Range	28-74	28-67	53-64	74	70	61	56	59	51	41	50	70
ECOG performance status: 0, 1 (#)	0: 8 1: 6	0: 2 1: 1	0: 1 1: 1	0: 1	0: 1	1: 1	0: 1	0: 1	1: 1	1: 1	1: 1	0: 1
# of prior therapies: Range	1-8	2-3	1, 2	2	5	1	4	5	2	8	1	6
Prior anti-PD1 therapy: Number (%)	6 (42.9)	3 (100)	1 (50.0)	1 (100)	0	0	0	1 (100)	0	0	0	0
Prior anti-PD1 + anti-CTLA-4 therapy: Number (%)	5 (35.7)	3 (100)	1 (50.0)	1 (100)	0	0	0	0	0	0	0	0
Baseline HSV serostatus: +ve, -ve (#)	11, 3	1, 2	2, 0	1, 0	1, 0	1, 0	1, 0	0, 1	1, 0	1, 0	1, 0	1, 0

Current focus for registration directed clinical development

Advanced patients were enrolled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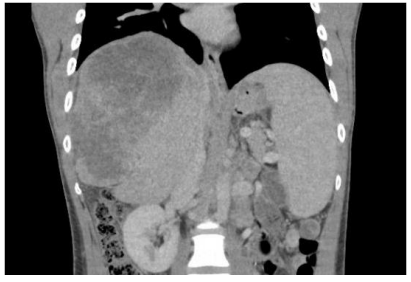
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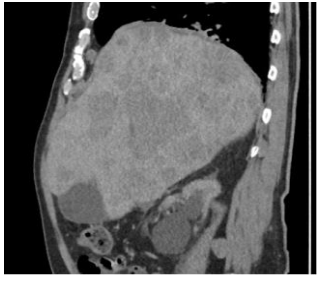
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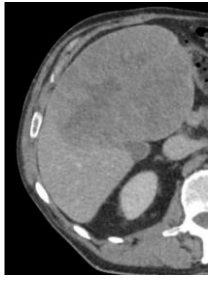
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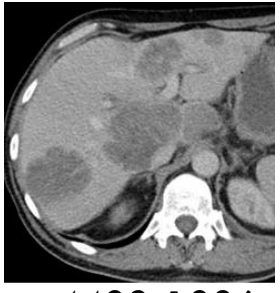
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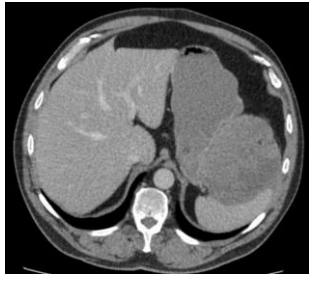
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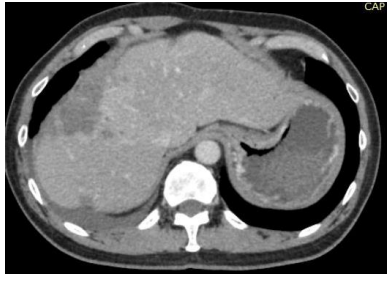

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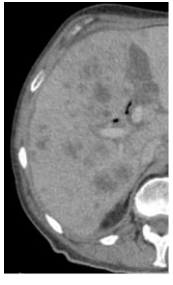
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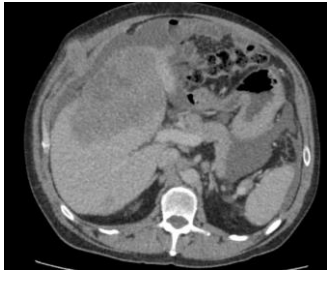
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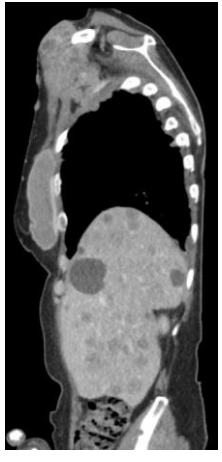
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Safety & tolerability

Treatment-related adverse events – dose escalation

N=22				
Preferred term	Grade 1-2 (>15%) # (%)	Grade 3 (all) # (%)	Grade 4 (all) # (%)	Grade 5 (all) # (%)
Pyrexia	16 (72.7)			
Fatigue	9 (40.9)			
Chills	7 (31.8)			
Vomiting	4 (18.2)			
Influenza like symptoms	4 (18.2)			
Headache	4 (18.2)			
Lipase increased			1 (4.5)	
Total	19 (86.4)		1 (4.5)	
Patients who discontinued due to TEAE	0			

- Side effects as expected for an oncolytic immunotherapy
- 'Flu-like constitutional symptoms, chills & rigors were the main side effects observed; self resolving within 72hrs of injection
- No obvious differences between deep & superficial dosing
- Modest increase in Grade 1-2 events with dose
- One DLT (elevated lipase) in the deep low dose cohort led to dose expansion to N=6
- No procedure-related AEs
- 32 SAEs reported, 8 related to RP1
  - 5 pyrexia, 2 vomiting, 1 tachycardia

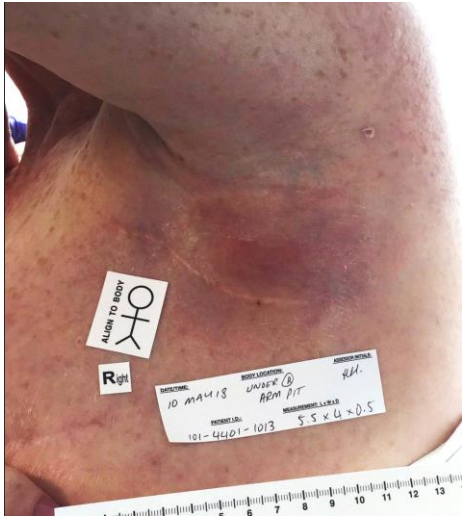
Treatment-related adverse events – with nivolumab

N=14				
Preferred term	Grade 1-2 (>15%) # (%)	Grade 3 (all) # (%)	Grade 4 (all) # (%)	Grade 5 (all) # (%)
Pyrexia	5 (35.7)			
Chills	5 (35.7)			
Nausea	4 (28.6)			
Tumour pain	4 (28.6)			
Influenza like illness	3 (21.4)			
Vomiting	3 (21.4)			
Fatigue	3 (21.4)			
Injection site pain	3 (21.4)			
Injection site necrosis		1 (7.1)		
Total	11 (78.6)	1 (7.1)	0	0
Patients who discontinued due to TEAE	0			

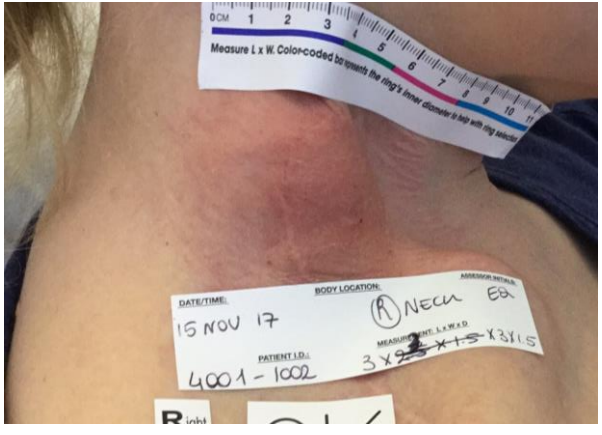
- No evidence of increased side effects as compared to that expected for either drug alone
- Two procedure-related AEs were seen (pneumothorax, n=2, self resolved)
- 10 SAEs seen, 0 related to RP1 or nivolumab
  - Procedure-related SAE: Pneumothorax
  - PD-related SAEs: 6
  - Co-morbid SAEs: 3
- <u>If anything, nivolumab related side effects appeared reduced</u>
  - No immune-related adverse events seen

Injection site erythema (24-48hrs post injection)

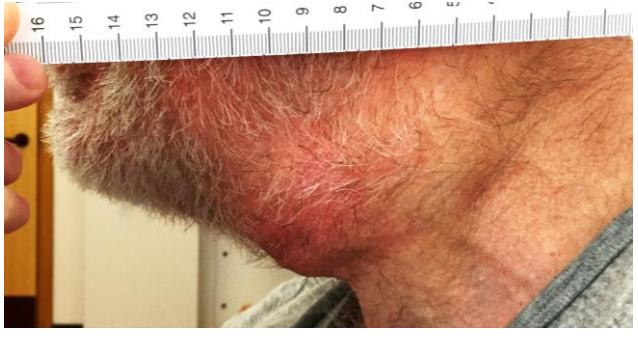
4401-1013
Breast cancer



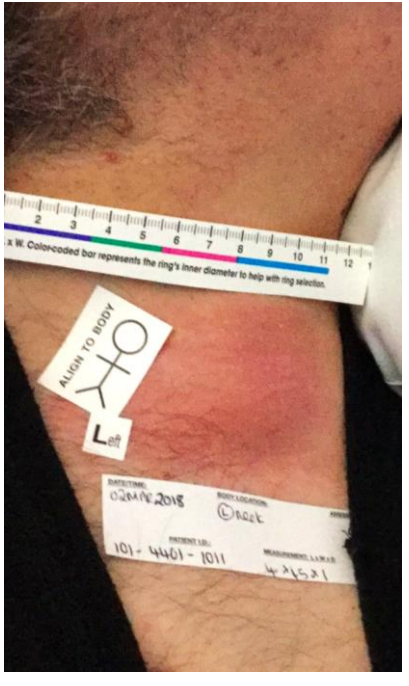
4401-1002
Melanoma



4402-1001
CSCC



4401-1011
Colorectal cancer

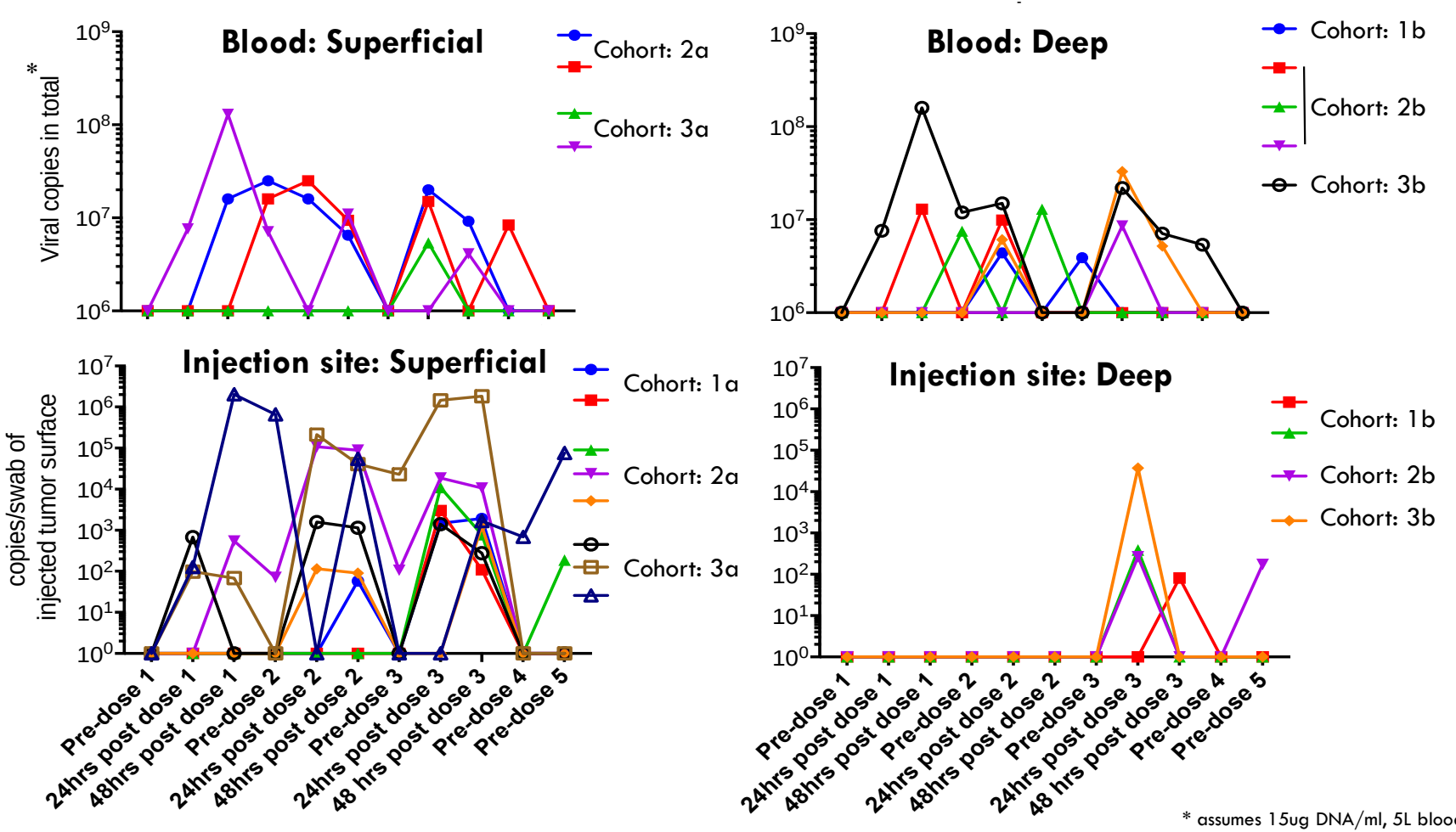


Safety & tolerability conclusions

- RP1 is well tolerated alone and in combination with nivolumab, with side effects as expected for each agent alone
- Both direct injection of superficial & nodal tumors, & imaging guided injection of deep/visceral tumors were well tolerated and practical
- The recommended Phase 2 dose by both dosing routes was:
  - A first dose of $1x10^6$ pfu/ml followed by multiple doses of $1x10^7$ pfu/ml
  - Up to 10mLs/injection day; Q2W or otherwise in line with cycles of anti-PD1 therapy

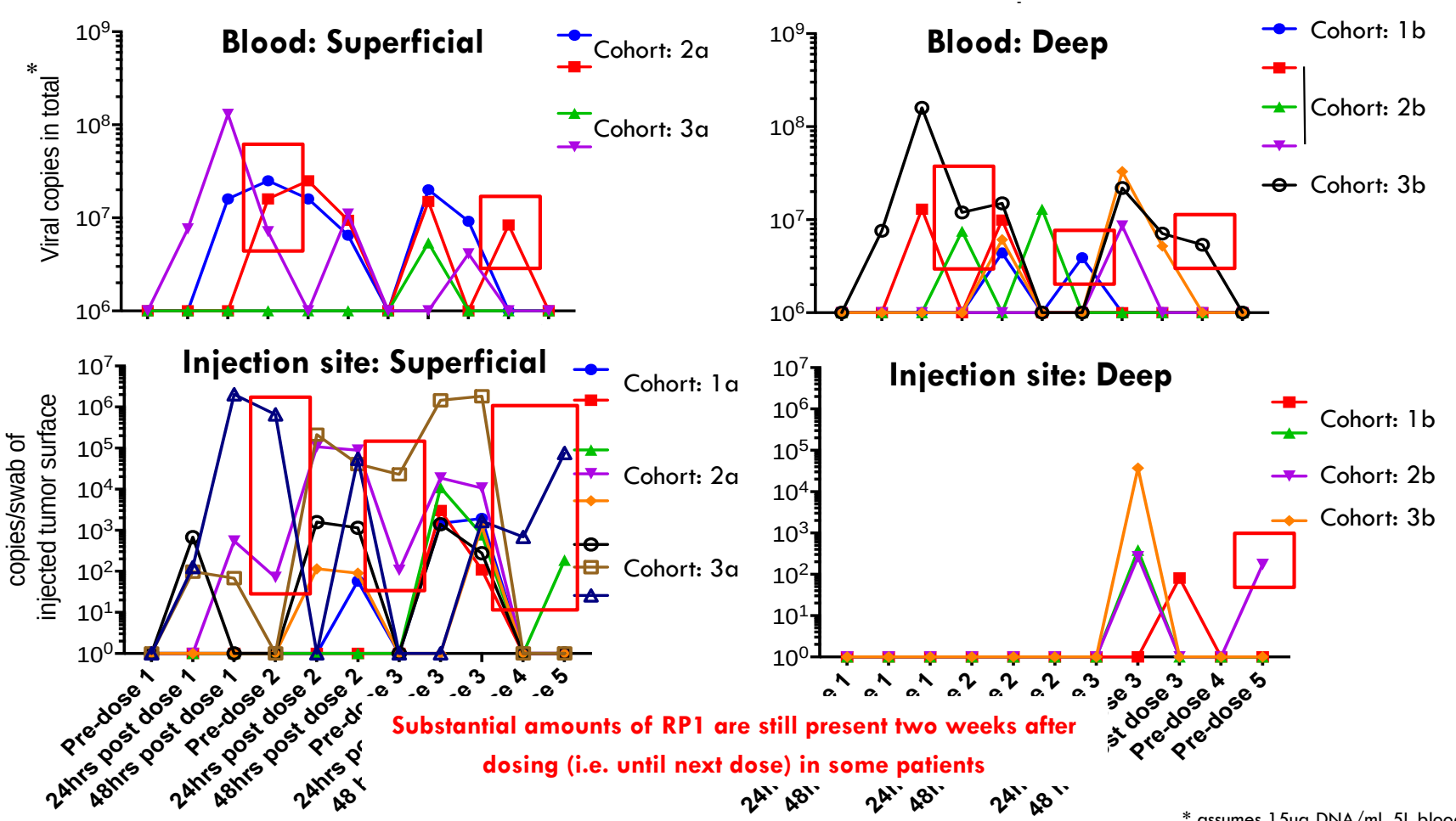
RP1 replication & seroconversion

Detection of RP1 in swab & blood samples: Dose Escalation



* assumes 15ug DNA/ml, 5L blood volume

Detection of RP1 in swab & blood samples: Dose Escalation



Substantial amounts of RP1 are still present two weeks after dosing (i.e. until next dose) in some patients

* assumes 15ug DNA/ml, 5L blood volume

RP1 detection & seroconversion conclusions

- RP1 was detected in the blood and on the injected tumor surface for up to two weeks (time of next dose) in some patients
- These kinetics are suggestive of robust virus replication*
- All HSV seronegative patients seroconverted by the third RP1 dose, and antibody titres increased in seropositive patients (*see Appendix*)

* In the T-VEC Phase 1 clinical trial, at the standard dose of $1x10^6$ pfu/ml followed by $1x10^8$ pfu/ml given twice, only low level virus was detected on the tumor surface of one patient (7.5pfu/swab), & never in the blood beyond 8 hours (Hu et al, CCR 2006 12: 6737-6747)

Biomarkers

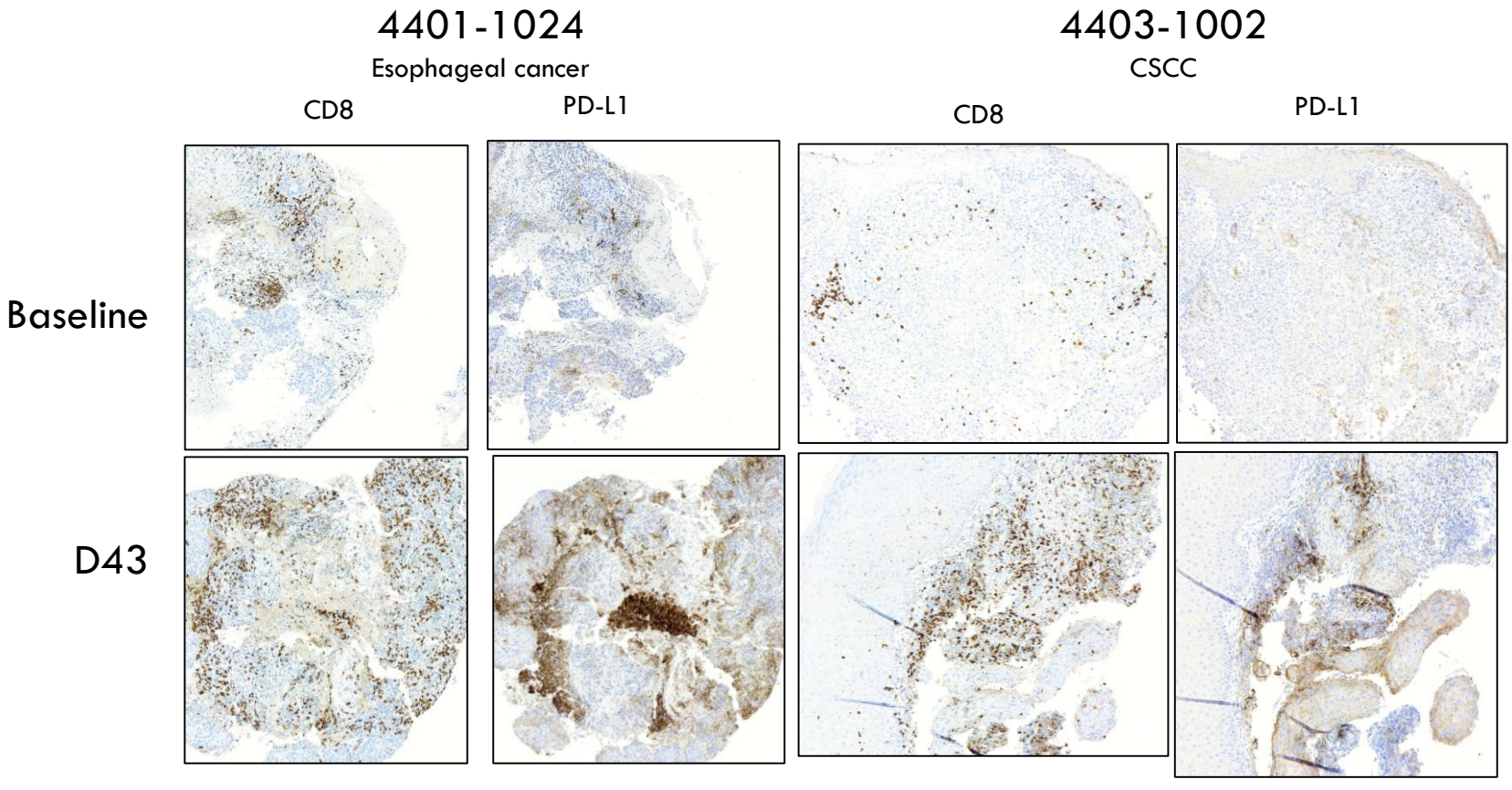
Biomarkers

- Tumor biopsies were taken at baseline & day 43 in the expansion cohort
- Assessed for the presence of tumor
- Stained for PD-L1 and CD8 T cells
- Subjected to Nanostring analysis
  - Inflammatory gene signature
  - Bespoke oncolytic virus specific panel of genes
- Blood samples were assessed for the generation of B cell responses in a subset of patients

PD-L1 & CD8 T cell staining & pathology summary

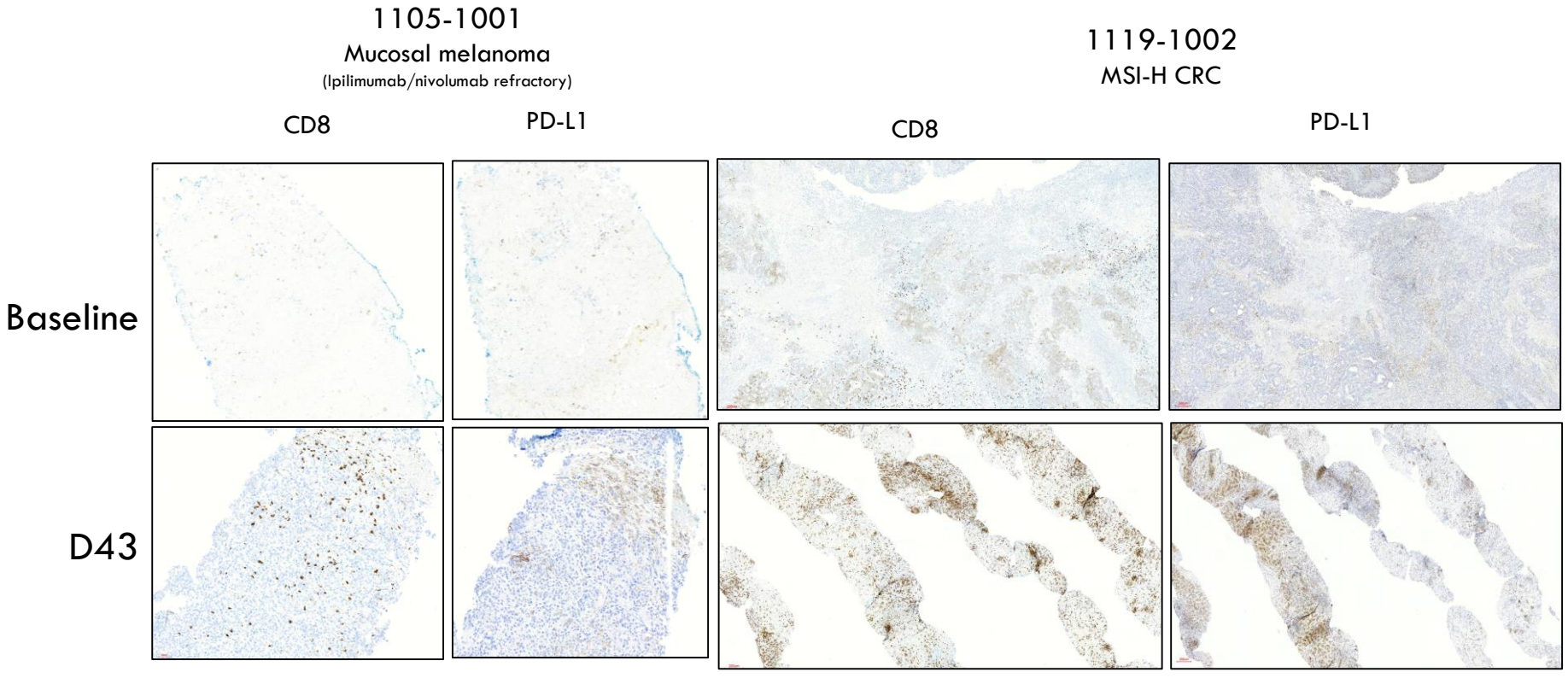
- Most post baseline biopsies showed extensive necrosis and/or were tumor free (*see Appendix for summary table*)
- Increases in both PD-L1 and CD8 T cells were seen across tumor types (*see Appendix for summary table*)
- Lack of tumor and/or necrosis in 50% of patients prevented assessment or quantification

CD8 T cell & PD-L1 staining is increased across tumor types



Replimune

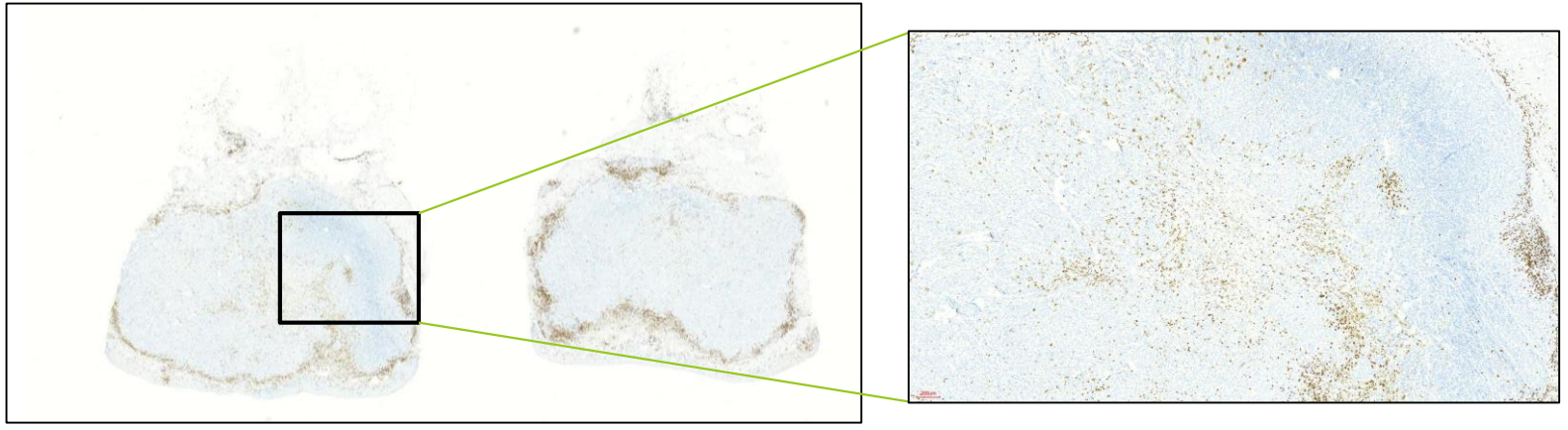
CD8 T cell & PD-L1 staining is increased across tumor types



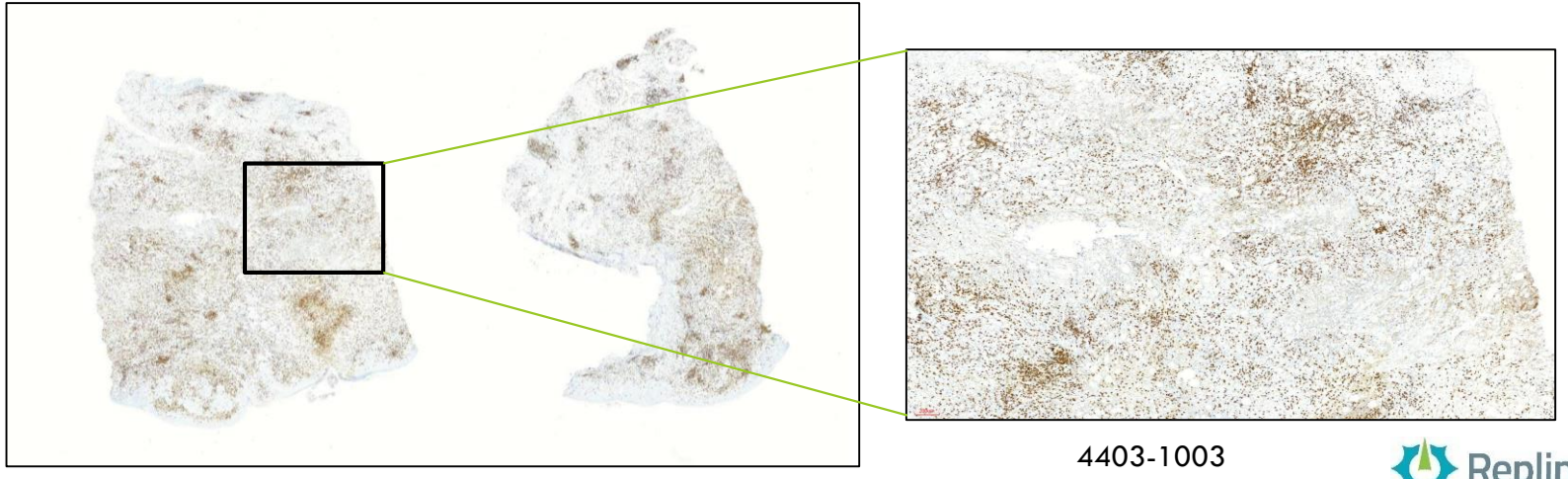
Replimune

Reversal of T cell exclusion with RP1 combined with nivolumab

CD8
Baseline



CD8
D43

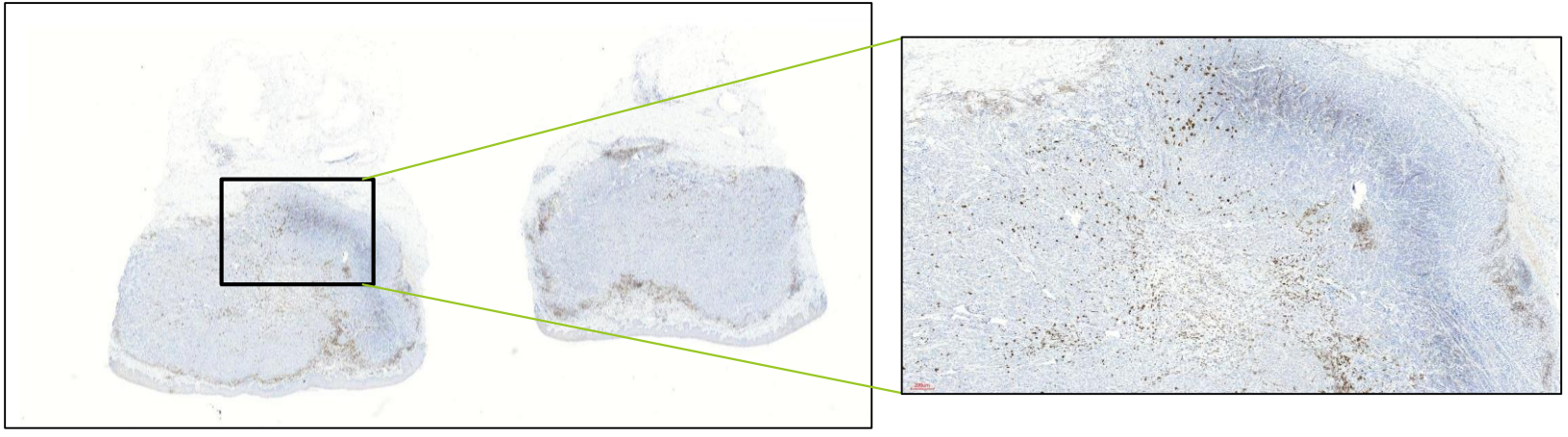


4403-1003
Cutaneous melanoma
(ipilimumab/nivolumab refractory)

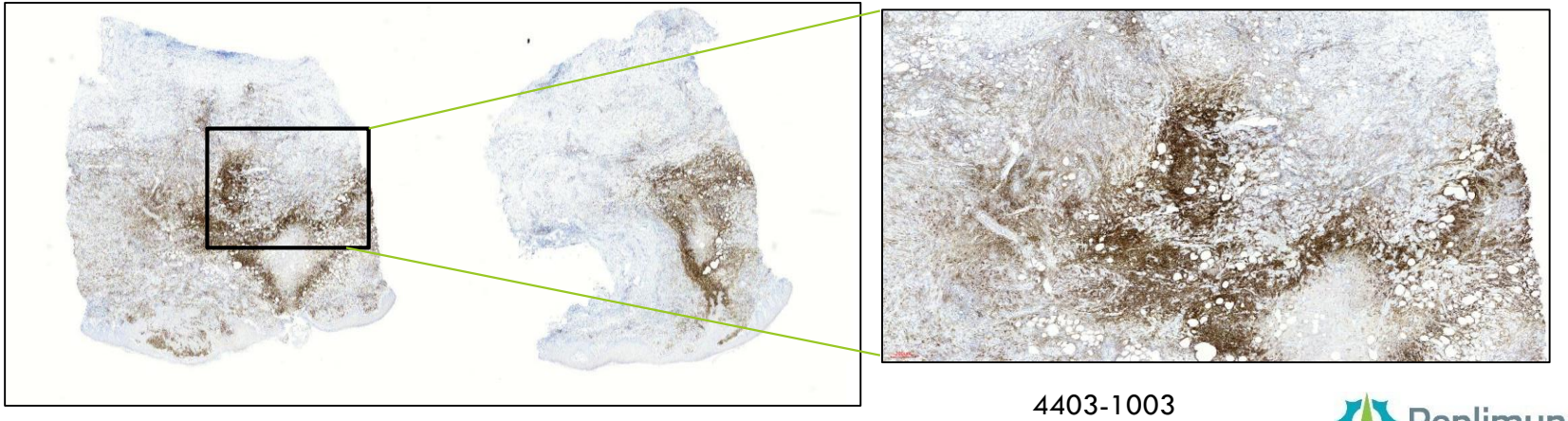
Replimune

Reversal of T cell exclusion with RP1 combined with nivolumab

PD-L1
Baseline



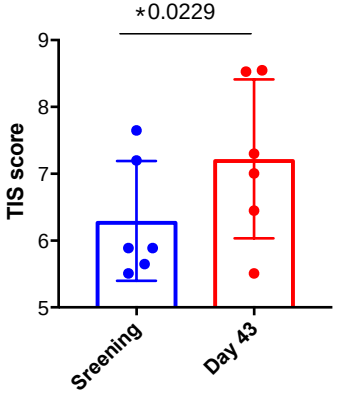
PD-L1
D43

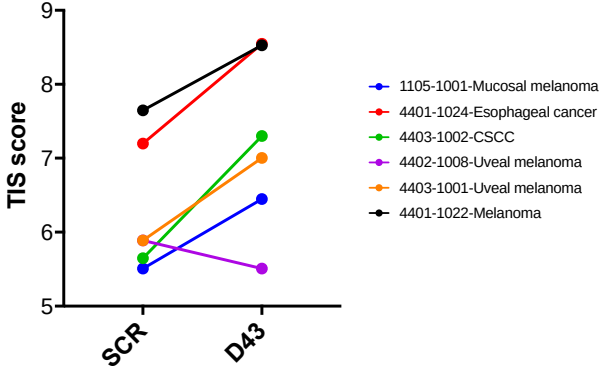


4403-1003
Cutaneous melanoma
(ipilimumab/nivolumab refractory)

Replimune

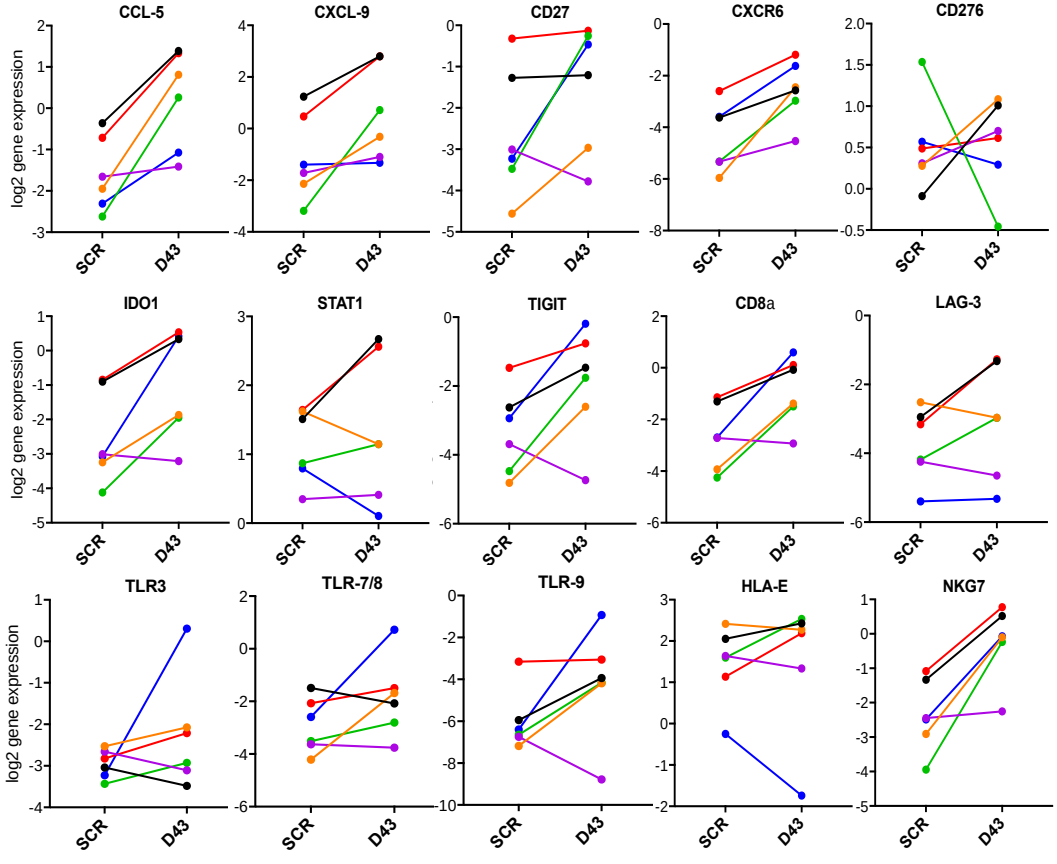
Nanostring analysis shows increased immune activation





Increased tumor inflammatory score

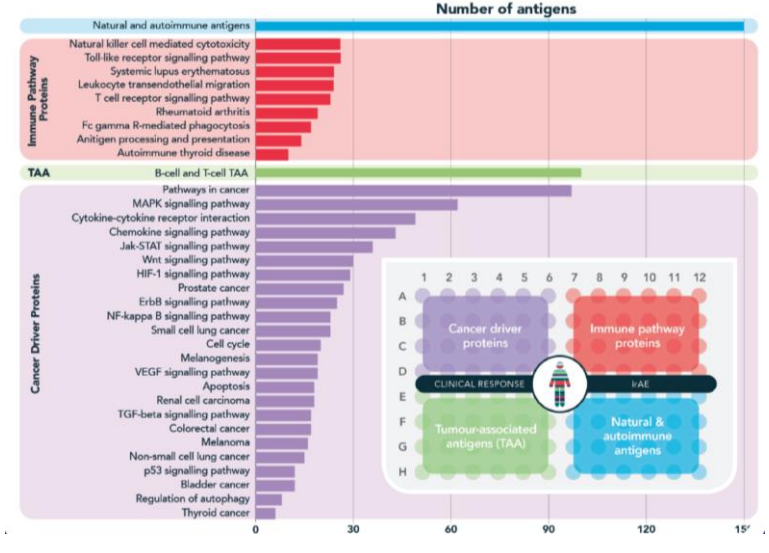
18 gene panel known to be associated with response to anti-PD1/L1 (Haddad R. Abstract 5009; ASCO 2017, Ayers et al 2017 JCI 127.8)



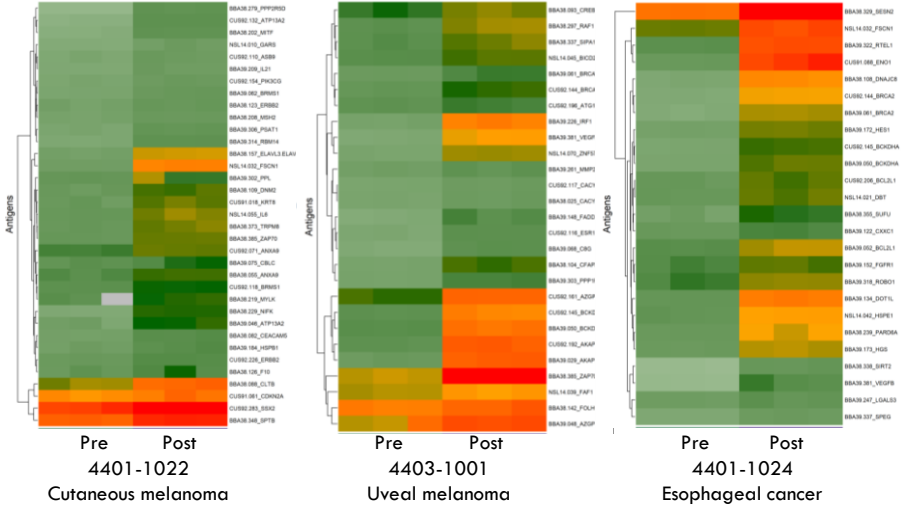
Selected genes showing increased expression

RP1+nivolumab increases autoimmune B cell responses

- Oncimmune have developed a high throughput approach to detecting autoimmune B cell responses which may be useful biomarkers for immuno-oncology
- Oncimmune used this platform to assess pre- and post- blood samples (29 days) from 4 RP1+nivolumab treated patients (4401-1022, 4401-1023, 4401-1024, 4403-1001)
- Increased reactivity was seen to 72 proteins: While there was some overlap, most were unique to each patient
- It was concluded that RP1+nivolumab treatment induces a broad autoantibody response in cancer patients

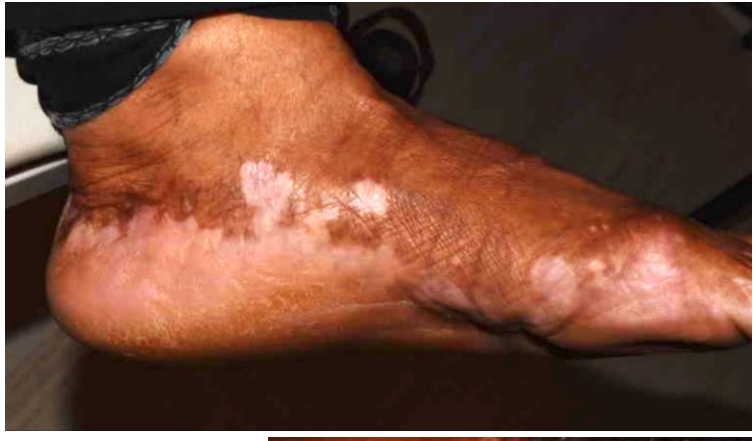


Oncimmune high-content cancer immunotherapy array



Clustered heatmap of top antigens, pre & post treatment

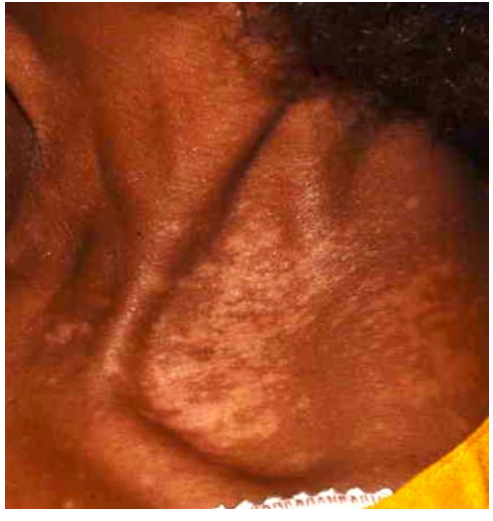
RP1 combined with nivolumab induces vitiligo (Phase 2 patient)



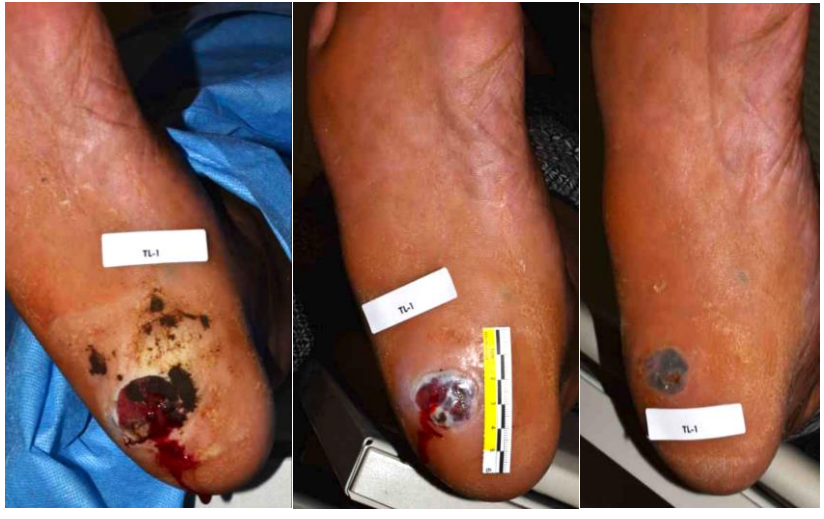
Left foot

Vitiligo D113

Left chest



Baseline D57 D113



Right heel

(injected once with RP1; subsequent injections into inguinal nodes)

1119-2001

Cutaneous melanoma

Replimune

Biomarker conclusions

- Increases in CD8 T cells & PD-L1 were seen across tumor types
- Reversal of T cell exclusion was observed
- Most biopsies showed extensive necrosis and/or were tumor free
- Increases in autoimmune B cell responses were seen, suggestive of broad immune activation
- Nanostring data demonstrates increases in the tumor inflammatory score & changes in expression levels of genes in the bespoke oncolytic virus gene panel
- Data suggests that RP1 is providing broad anti-tumor immune activation

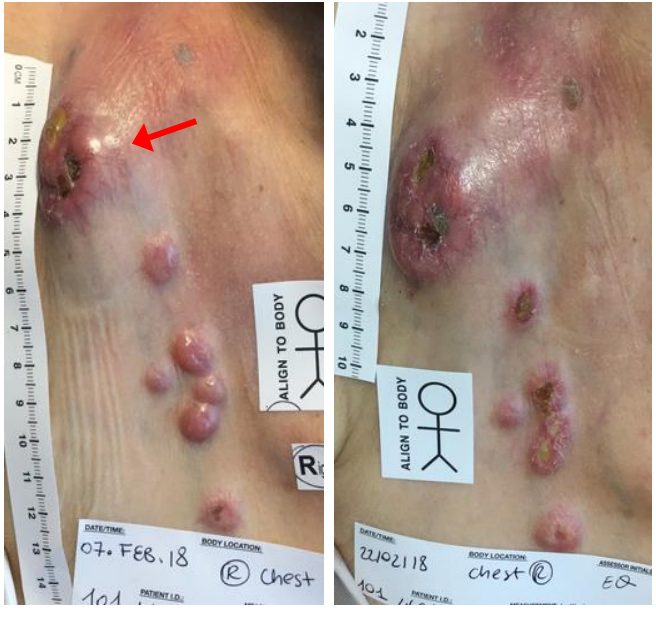
Anti-tumor activity

Anti-tumor activity - dose rising cohorts (single agent RP1)

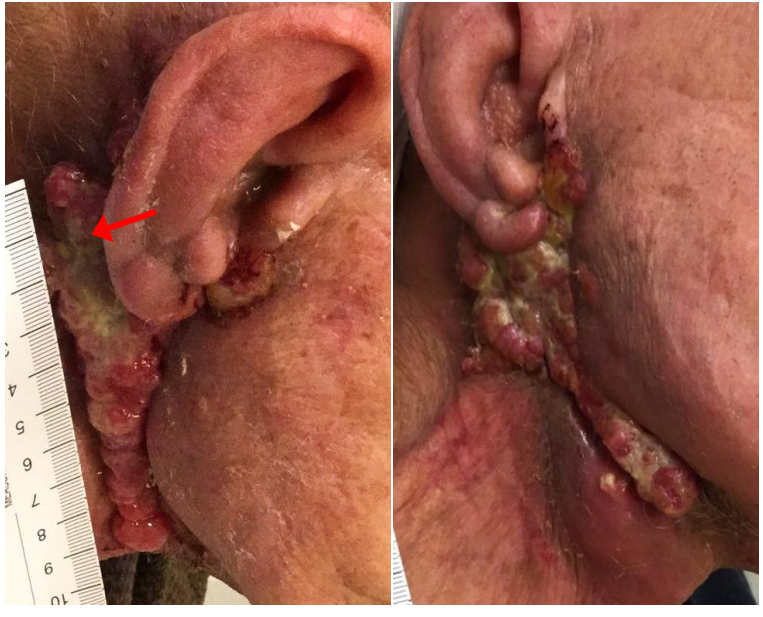
- CT scans per protocol were performed at baseline and at 30 days post the last RP1 dose for the dose rising cohort patients treated with single agent RP1
- Tumor shrinkage was seen in injected and uninjected tumors, including in the three patients with visible tumors
- Delayed systemic tumor reduction (post initial disease progression and beyond the 30 day cut off) without other therapy was seen in two patients
- One patient previously refractory to anti-PD1 therapy responded to further anti-PD1 therapy

Tumor necrosis in the visible tumors in the dose rising cohorts

4401-1008
Breast cancer

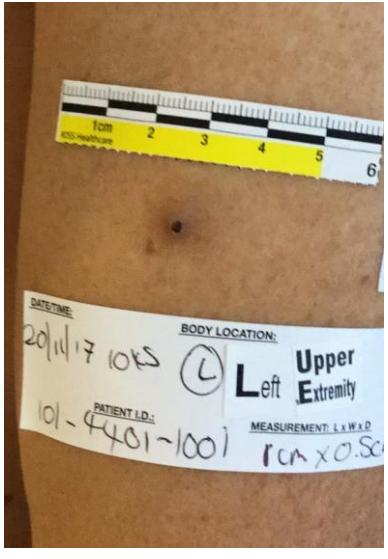


4402-1004
Salivary gland cancer



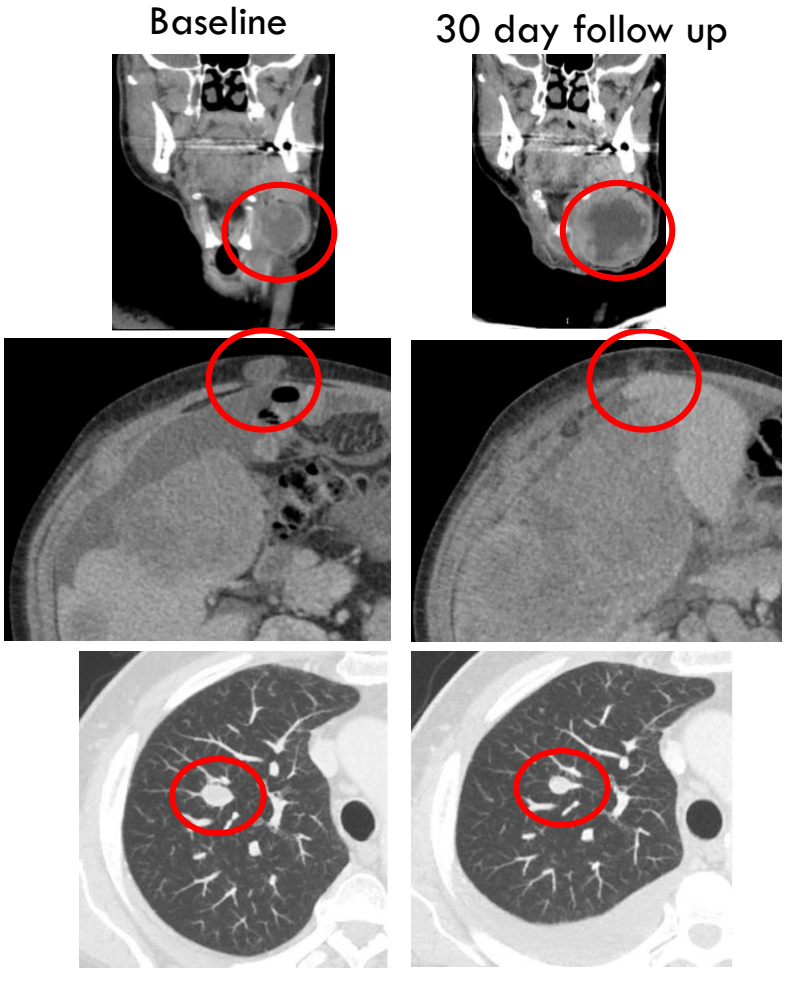
Only two patients in the dose rising cohorts had a superficially visible (i.e. cutaneous) tumor which was injected

4401-1001
Melanoma



The only other cutaneous tumor in the dose rising cohort patients (non-injected) became necrotic (injection site: axilla)

Shrinkage of injected tumors



4402-1001
CSCC
Central necrosis of a large injected tumor in the neck. The patient also had lung metastases

4401-1005
Colorectal cancer
Destruction of the injected tumor nodule. The patient also had extensive additional abdominal disease

4401-1015
Melanoma
The injected lung lesion reduced by ≈30%. The patient also had extensive additional disease in the lungs and pleura

Delayed systemic anti-tumor effects in the dose rising cohort

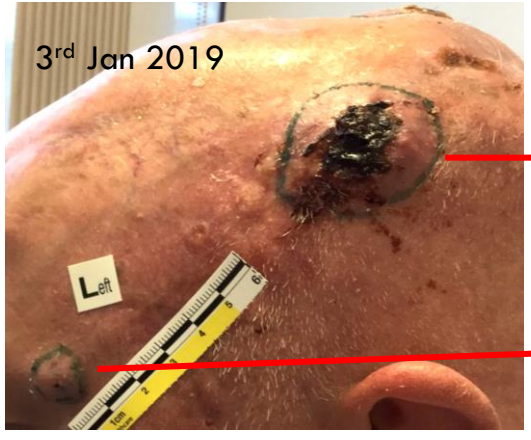
- Patients were followed per protocol in the dose rising for 30 days post the last RP1 dose to collect safety data, followed by a CT scan
- Delayed, post study (CT scans not available), anti-tumor effects (systemic reduction in disease burden) were seen in 2 patients following single agent RP1 injected into a single tumor:
  - 4401-1003 Melanoma, prior ipilimumab & nivolumab. Baseline disease: lung, pleura, lymph node & subcutaneous metastases. Five injections into the apical mass. Progression at the 30 day scan, then with no further therapy had reductions in the apical mass & hilar nodes, maintained for 8 months prior to PD
  - 4401-1018 Cholangiocarcinoma, prior chemotherapy. Baseline disease: multiple liver & lung metastases. Five injections into one liver lesion from September 2018. Progression at the 30 day scan, then with no further therapy had reductions in liver lesions, bone metastases & lymph nodes
- A pembrolizumab refractory melanoma patient responded to subsequent nivolumab:
  - 4401-1004 Melanoma, prior ipilumumab, pembrolizumab & clinical trial. Baseline disease: adrenal gland, liver, gluteal mass, subcutaneous deposits. Five injections into the 6.5cm gluteal mass. The injected lesion stabilized, others progressed, following which the patient received additional nivolumab followed by reduction in liver & subcutaneous metastases

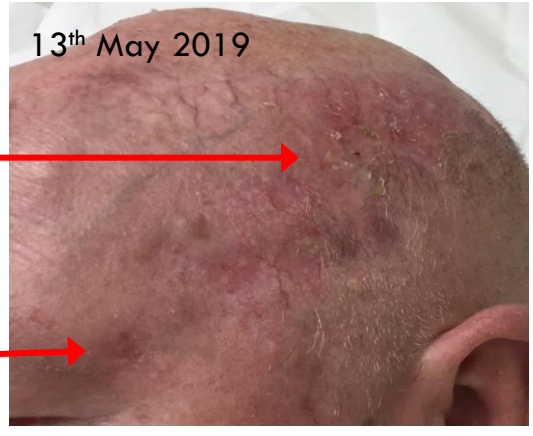
30 day follow up is likely too short for inflammatory & other effects mediated by RP1 to have resolved

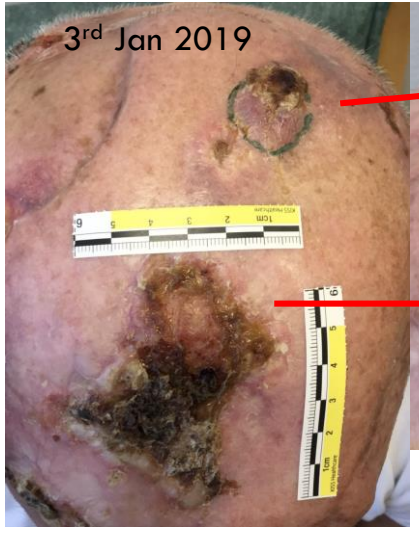
Anti-tumor activity – combination with nivolumab

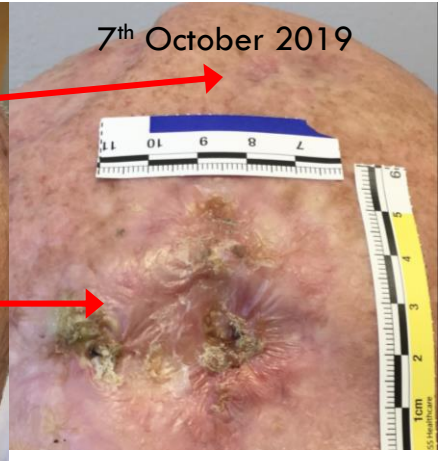
- Two of the three patients enrolled with cutaneous melanoma, all of whom were ipilimumab & pembrolizumab or ipilimumab/nivolumab refractory, are responding
  - The first ipilimumab/nivolumab patient in Phase 2 with follow up scans has also responded *(see melanoma-specific deck also released today)*
- CR in the patient with chemotherapy refractory CSCC enrolled into Phase 1
  - Further activity in CSCC seen in Phase 2 *(see CSCC-specific deck also released today)*
- Clear biologic activity seen in additional tumor types (including uveal melanoma) with two patients with esophageal and MSI-H cancer still ongoing with the opportunity to achieve response
- The majority of biopsies taken at Day 43 showed extensive necrosis and/or no remaining viable tumor

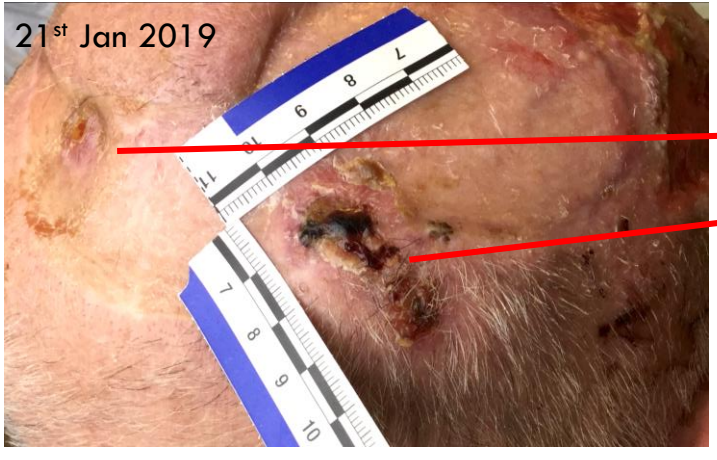
Patient #: 4403-1002 (chemotherapy refractory CSCC)

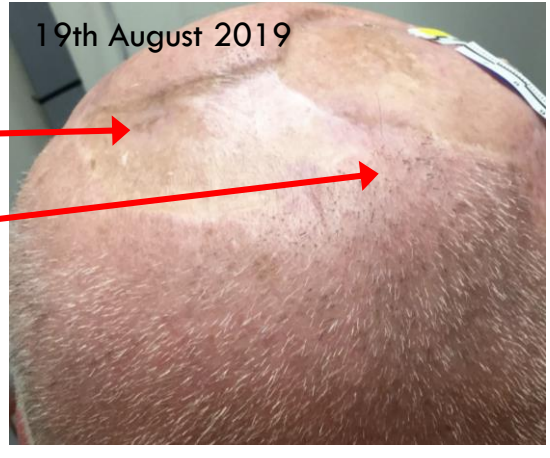








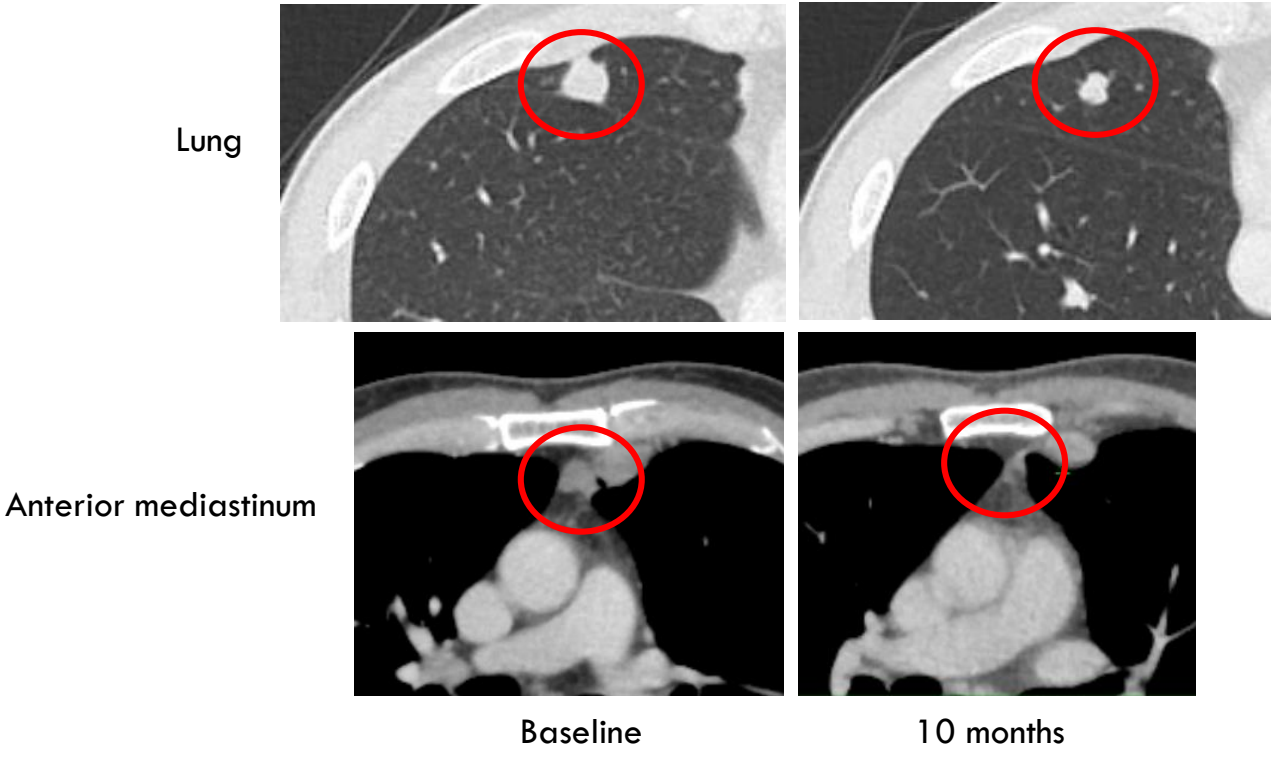




- Patient with extensive recurrent CSCC previously treated with surgery (including skin grafts), radiotherapy, cisplatin/5FU, then electrochemotherapy
- Now CR with residual areas tumor free by multiple biopsy & continuing to heal
- In addition to the complete tumor response, the patients' quality of life has been dramatically improved

Patient #: 4401-1022 (ipilimumab/pembrolizumab refractory melanoma)

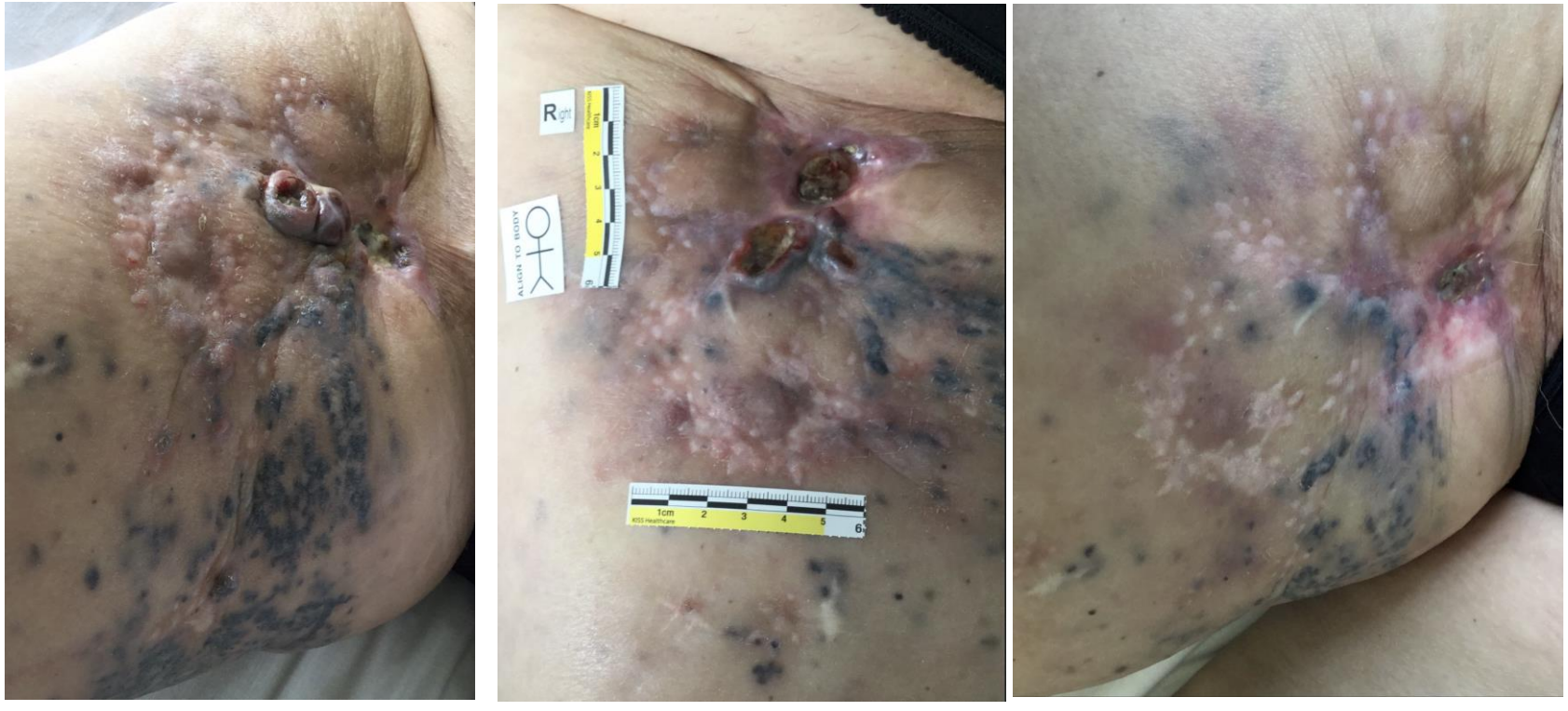
- Disease sites: Breast, lung, mediastinal and peritoneal anterior to the spleen
- RP1 injection site: Lesion behind the left ear



- Confirmed progression on prior immune checkpoint blockade, where two sequential PET scans demonstrated new lesions while also concurrently being treated with local therapy for the lesion behind the ear, then entry into the RP1 clinical trial
- PR with reduction in the breast, lung, mediastinum & anterior to the spleen
- Patient remains on nivolumab at 11 months

Patient #: 4403-1003 (ipilimumab/nivolumab refractory melanoma)

10th June 2019 | 24th June 2019 (pre nivolumab) | 2nd September 2019



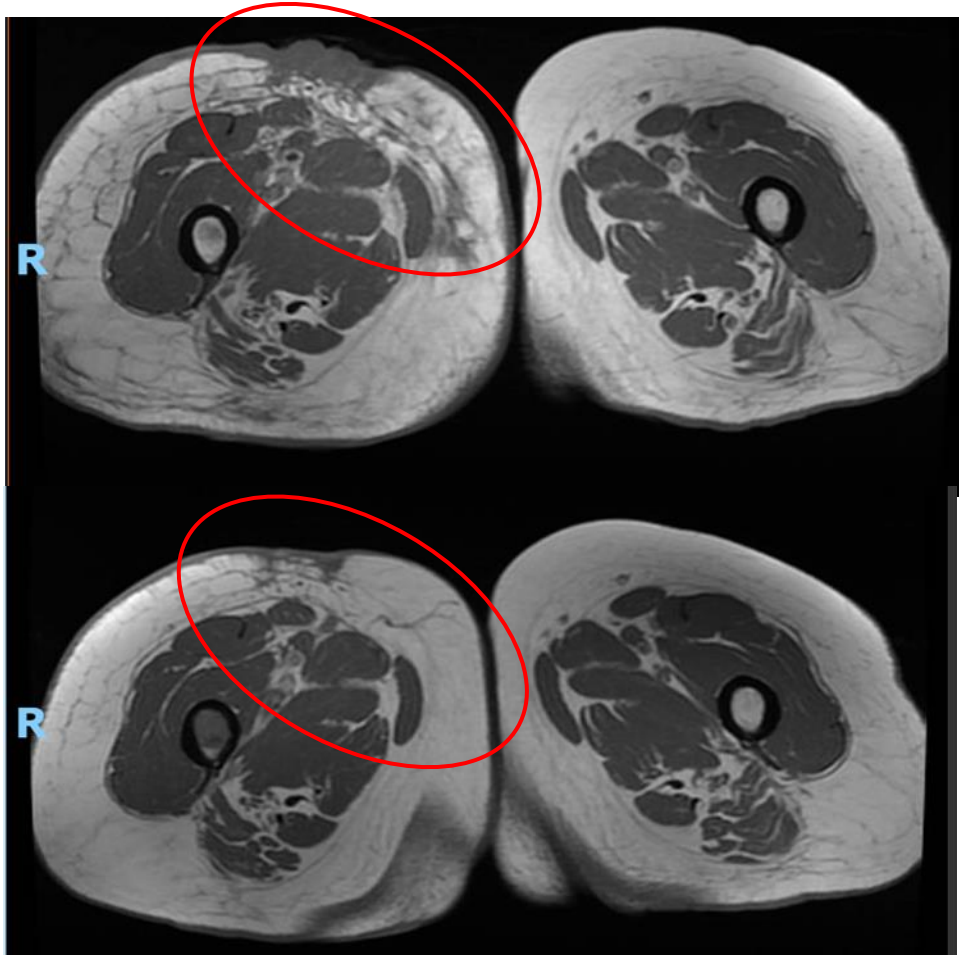
Patient history: Metastatic disease initially treated with ipili/nivo with best response of SD, then clear progression in the groin & thigh when radiotherapy followed by electrochemotherapy was added to continued nivolumab; following further clear progression, enrolled into the current trial

All tumors flattened after the first dose of RP1 ($1x10^6$ pfu/ml) & extensive oedema rapidly reduced

Patient #: 4403-1003 (ipilimumab/nivolumab refractory melanoma)

May 2019
(Baseline)

August
2019



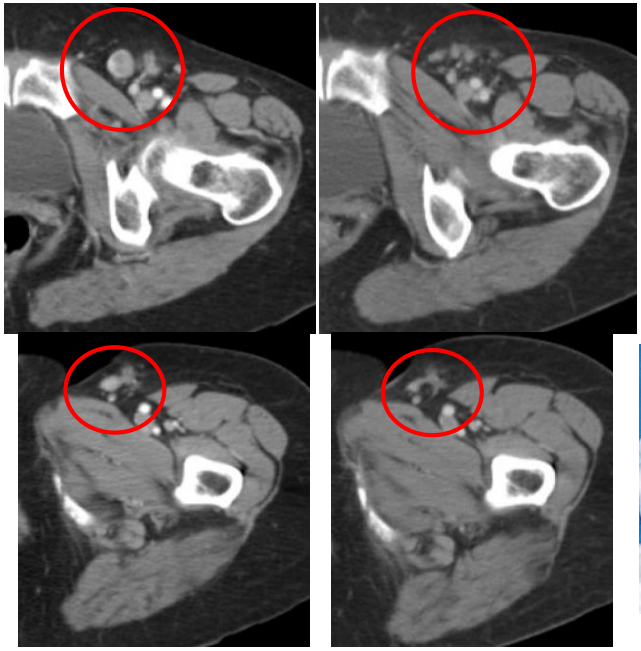
- Patient also had nodes in the groin which increased and are now reducing and lung metastases which following no change for prior 18 months are now reducing
- Patient quality of life has also greatly improved, from being essentially immobile at baseline to now able to go on long country walks
- Patient remains on treatment at >4 months

Replimune

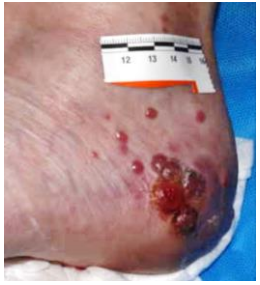
Patient #: 1119-2003 (ipilimumab/nivolumab refractory melanoma)

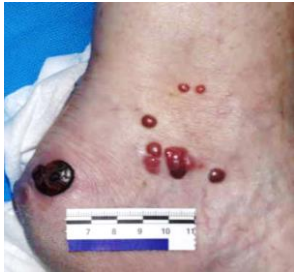
2nd July 2019 (screening)

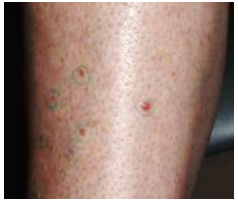
17th Sept 2019



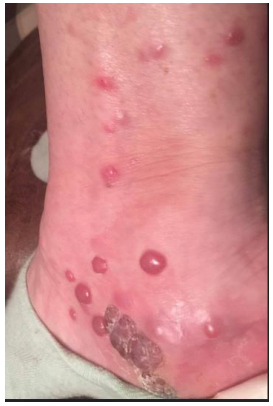
1st July 2019 (screening)

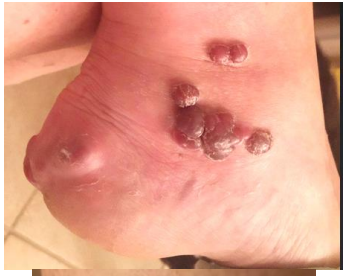


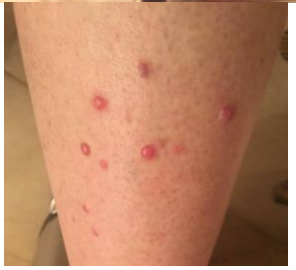




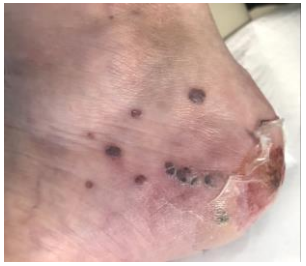
26th August 2019

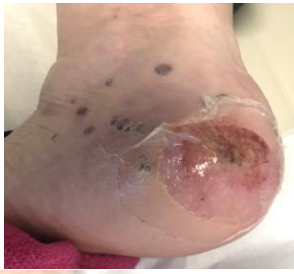


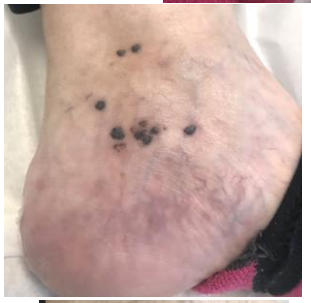


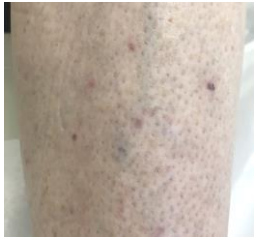


24th October 2019







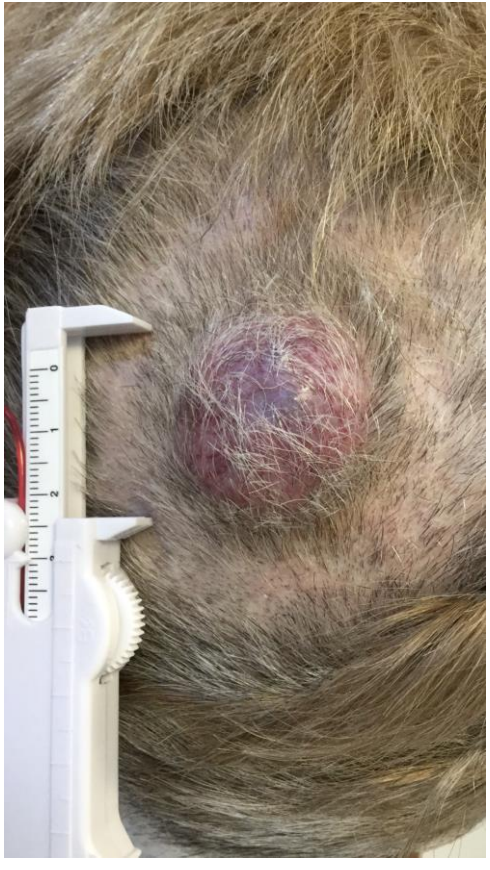


The first ipilimumab/nivolumab refractory melanoma patient enrolled into the Phase 2 part of the study. Other such patients do not have follow up scans.

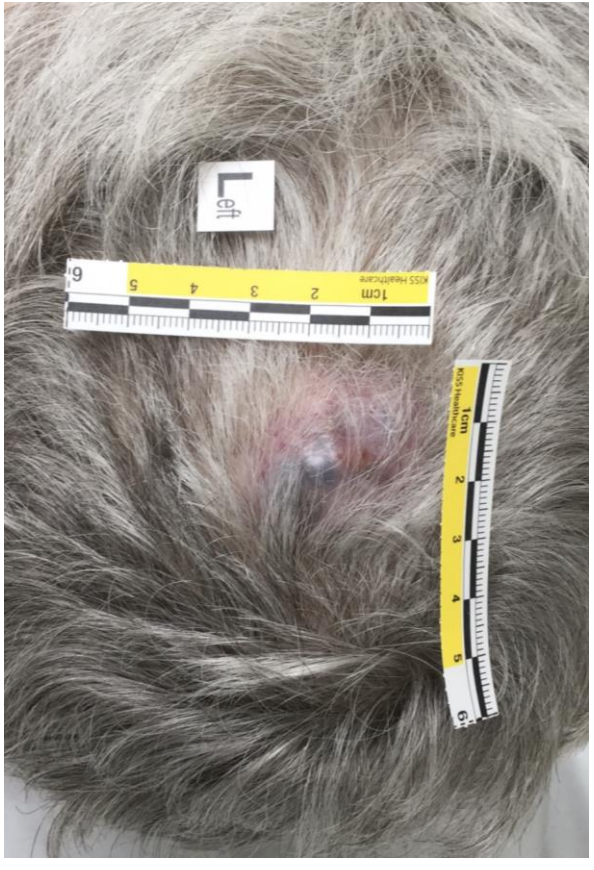
Current status: Ongoing partial response

Patient #: 4403-1001 (ipilimumab/nivolumab refractory uveal melanoma)

Baseline (2nd Jan 2019)



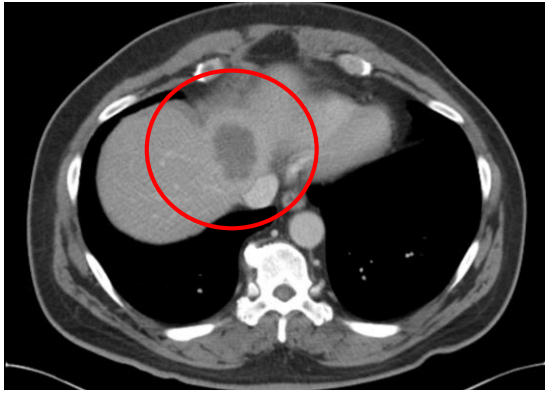
24th April 2019



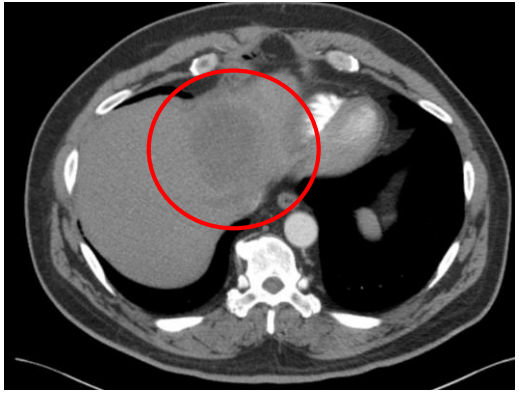
Patient has numerous additional subcutaneous lesions - remains on nivolumab at >9 months

Patient #: 1119-1002 (chemotherapy refractory MSI-H colorectal cancer)

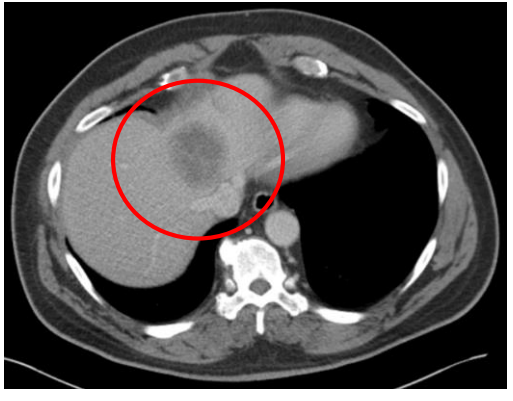
- Chemotherapy refractory MSI-H colorectal cancer
- 5cm liver metastasis and other liver metastases of around 1cm
- The liver lesions showed initial substantial increase (presumed inflammation), then reduction
- A biopsy taken at C4 demonstrated "A few viable glands of adenocarcinoma with extensive necrosis, fibrosis & chronic inflammation"
- Increases in PD-L1 and CD8 T cells were also seen
- Patient continues on therapy at 4 months



9th July 2019 (5.4x4.3cm)



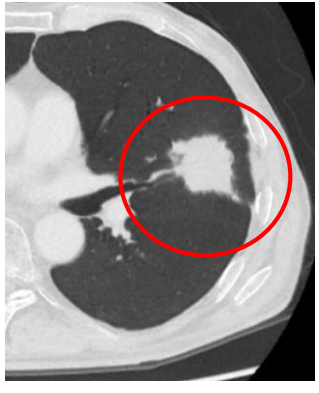
26th August 2019 (8x6cm)



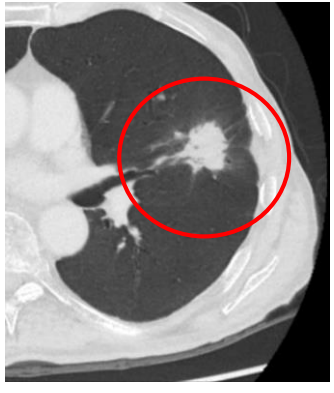
23rd September 2019 (5x5cm)
(Biopsy taken 9th Sept showed extensive necrosis & inflammation)

Patient #: 4401-1024 (esophageal cancer)

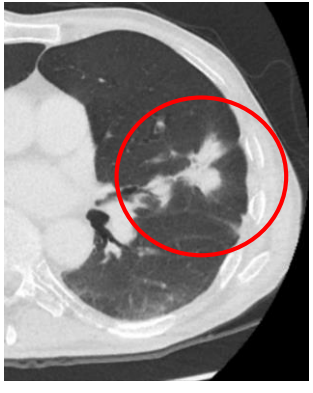
- Heavily pre-treated esophageal cancer (8 prior therapies)
- Lung lesions and lesions around the esophagus.
- Largest lung lesion injected 6 times after which too soft for further injections.
- Further smaller lung lesion injected once, but discomfort and self resolved pneumothorax. RP1 injections stopped at C7
- CT scan on 8th October 2019 (C11) showed overall disease reduction of 23%
- Patient continues on nivolumab treatment at 7 months



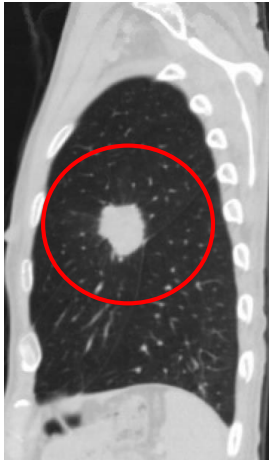
Baseline



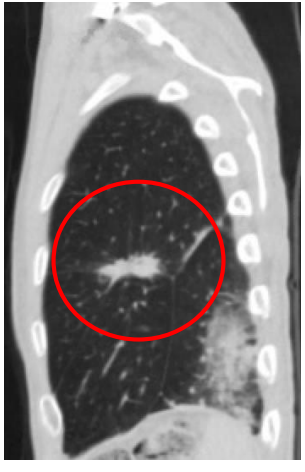
C5



C11



Baseline



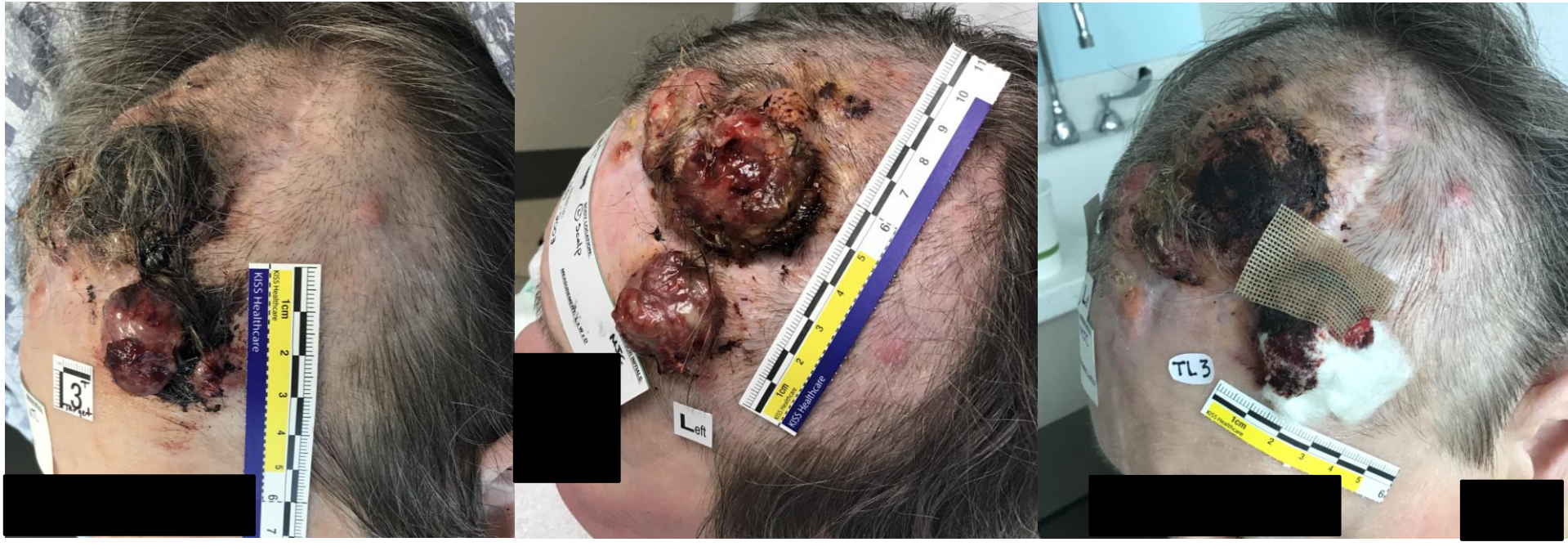
C11

Tumor shrinkage after one RP1 dose (1105-2003; pembrolizumab refractory melanoma)

10th October 2019

16th October 2019

23rd October2019
(pre-nivolumab)



- Increased drainage noted by D6 prior to tumors reducing by D13 (pre-nivolumab)
- Patient remains on treatment at 2-3 weeks

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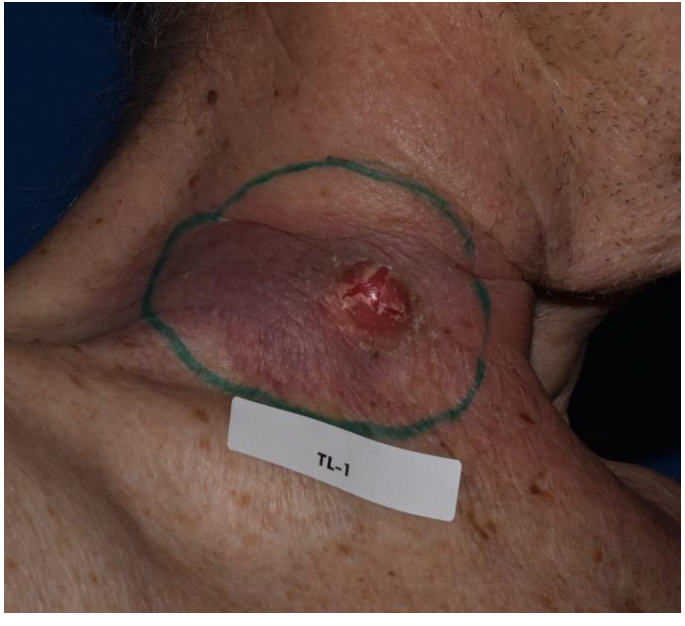
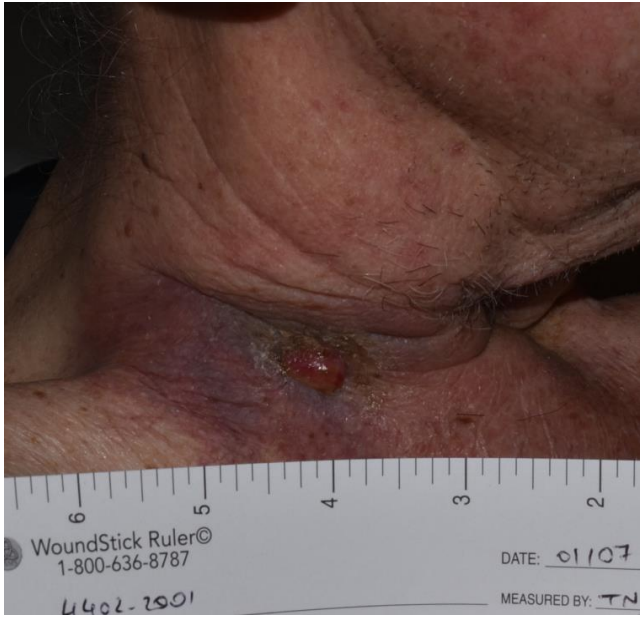
Tumor shrinkage after one RP1 dose (4402-2001; CSCC)

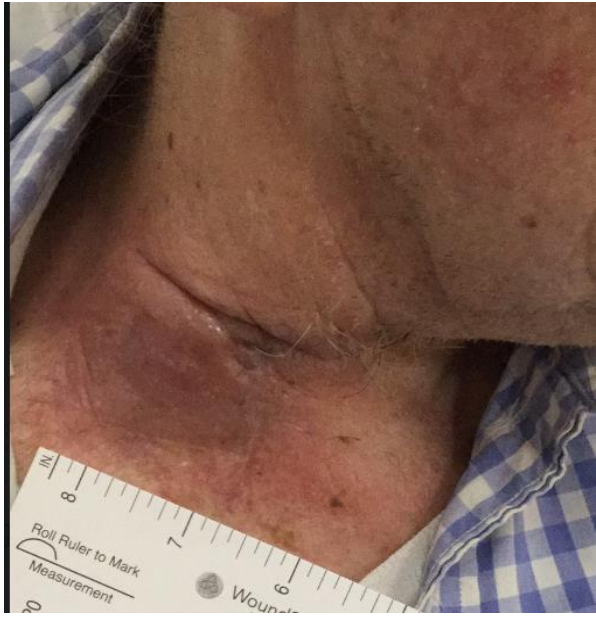
16th June 2019
(baseline)

1st July 2019
(post one dose of RP1, no nivolumab)

16th July 2019
(post 2 doses of RP1 & 1 dose of nivolumab)





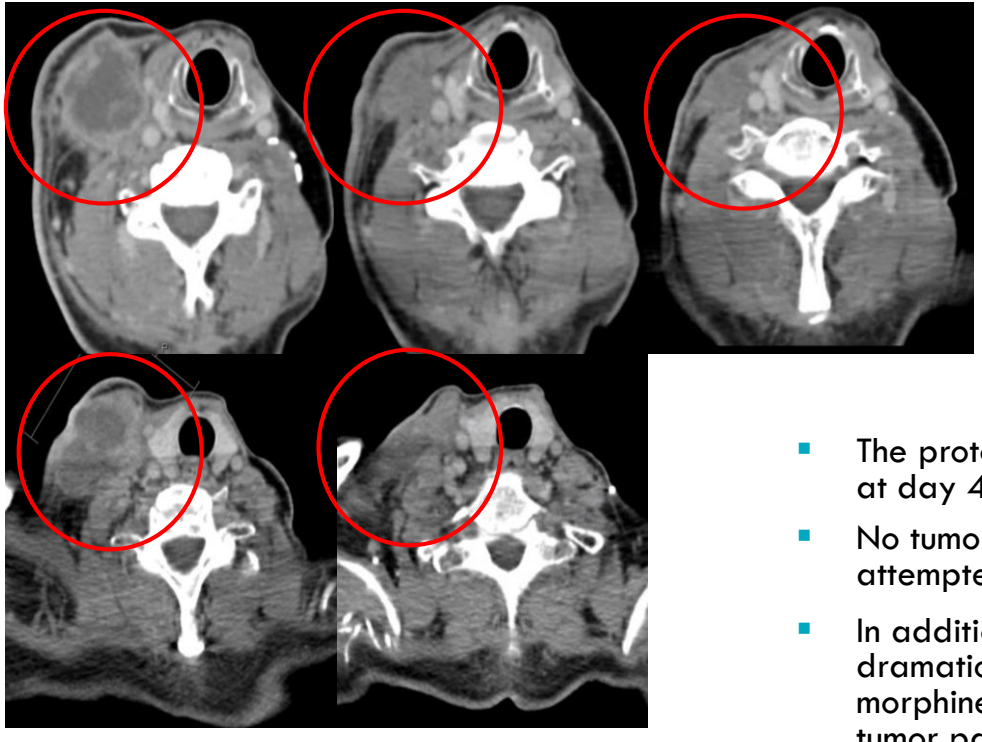


- Patient with recurrent CSCC of the neck (bilateral), previously treated with cisplatin-based chemoradiation & six cycles of carboplatin/5-FU, prior to entering the clinical trial
- Both the large injected tumor & the smaller contralateral tumor in the neck reduced considerably before the first nivolumab dose, i.e. after the first dose of RP1

Patient #: 4402-2001 (CSCC)

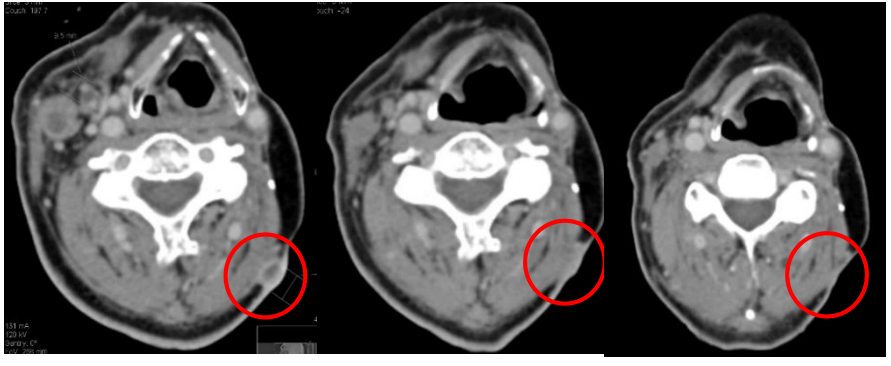
Right neck (injected)

Baseline 8 weeks 16 weeks



Left neck (not injected)

Baseline 8 weeks 16 weeks



- The protocol mandated biopsy of the injected tumor taken at day 43 was tumor free
- No tumor was found to remain when a biopsy was attempted from the left neck
- In addition to the tumor response, this patient has had a dramatic improvement in quality of life & is now off morphine which was previously necessary for substantial tumor pain

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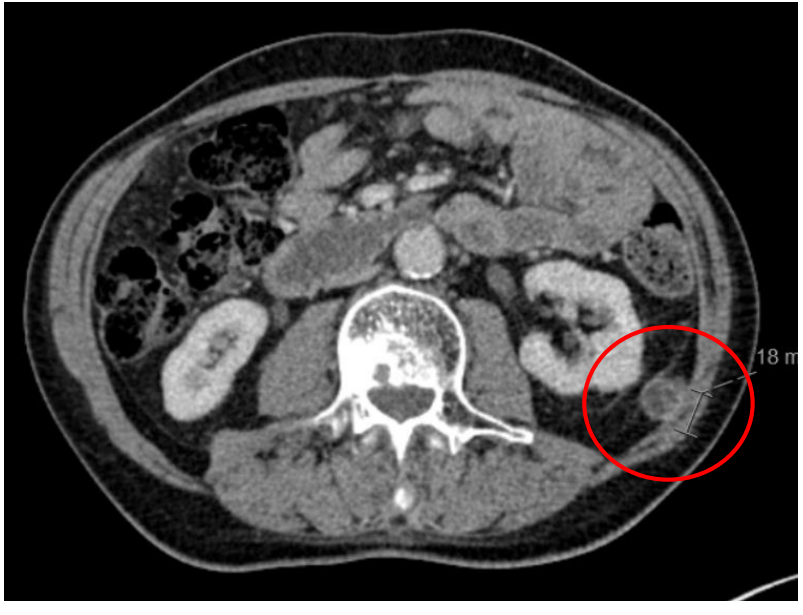
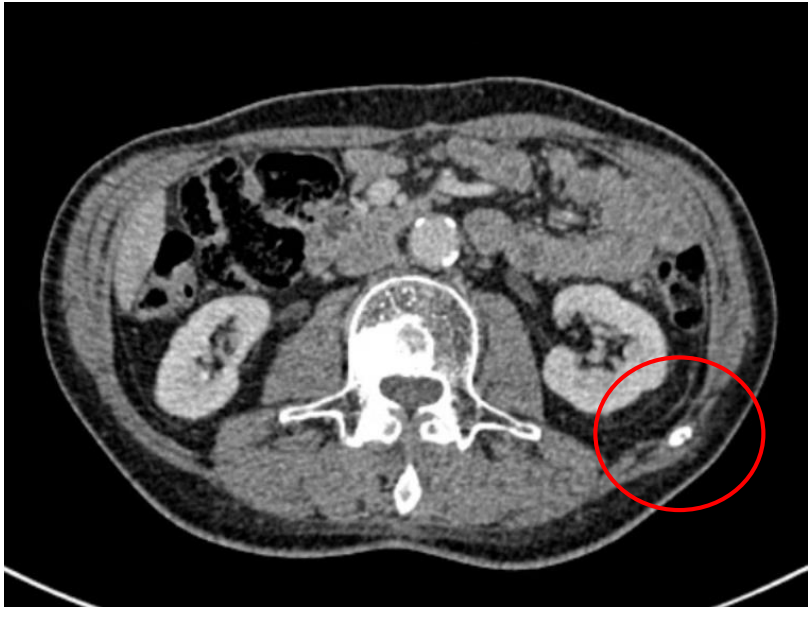
Patient #: 4402-2001 (CSCC)

Baseline



16 weeks



- The patient also had baseline retroperitoneal tumors which have completely resolved
- The only remaining disease are a number of non-measurable bone metastases, which were the main source of the cancer pain which has now resolved: These are now sclerotic, also suggestive of a treatment response, with Zometa also now having been withdrawn

Replimune

Anti-tumor activity conclusions

- Activity was seen with both RP1 alone and in combination with nivolumab
  - Including the rapid tumor reductions seen before the introduction of nivolumab
- In particular we saw clear clinical activity in CSCC and in anti-PD1 refractory melanoma
  - Provides strong support for our clinical programs in these tumor types
- Clinical activity in both tumor types has been further confirmed in initial patients enrolled in Phase 2
- Indications of clinical activity in additional tumor types was also seen

Overall conclusions from the clinical data so far

- RP1 is well tolerated alone & in combination with nivolumab
- Both direct injection & imaging guided injection were well tolerated and practical
- RP1 provides potent oncolytic activity & abscopal effects
- Clinical activity was seen for RP1 alone & in combination with nivolumab
- CD8 T cell levels and PD-L1 were increased across tumor types
- The kinetics of detection of RP1 in blood suggests robust virus replication
- The clear clinical activity in CSCC and immune checkpoint blockade refractory melanoma provides strong support for expanding Replimune's clinical programs with RP1 in these tumor types
  - New study intended in organ transplant recipients with CSCC (announced in October)
  - New study intended in anti-PD1 refractory melanoma (announced today)
- Anti-tumor effects were also seen in other tumor types
- Data with RP1 combined with nivolumab in bladder cancer & MSI-H tumors is pending

Q&A

Appendix

Administration site, volume & method used for each deep dose rising cohort patient

Patient #	Tumor type	Injection site	Volume/ injection (range in mL, given up to 5 times)	Imaging guidance used (CT or ultrasound)
4401-1003	Melanoma	Lung	5.0-10.0	Ultrasound
4401-1006	Colorectal	Liver	3.0	Ultrasound
4401-1007	Melanoma	Liver	6.0	Ultrasound
4401-1014	Esophageal	Liver	3.0 – 10.0	Ultrasound
4401-1015	Melanoma	Pleural deposit	2.5 – 3.0	Ultrasound
4401-1016	Head and Neck	Liver	8.0 – 10.0	Ultrasound
4401-1012	Melanoma	Lung	5.0 – 6.0	Ultrasound
4402-1006	Head and Neck	Liver	10.0	Ultrasound
4401-1019	Melanoma	Stomach	10.0	CT
4401-1020	Pancreatic	Liver	0.5	Ultrasound
4401-1017	Colorectal	Liver	3.0	Ultrasound
4401-1018	Cholangeocarcinoma	Liver	0.5 – 1.0	Ultrasound
4401-1021	Colorectal	Liver	4.0	Ultrasound

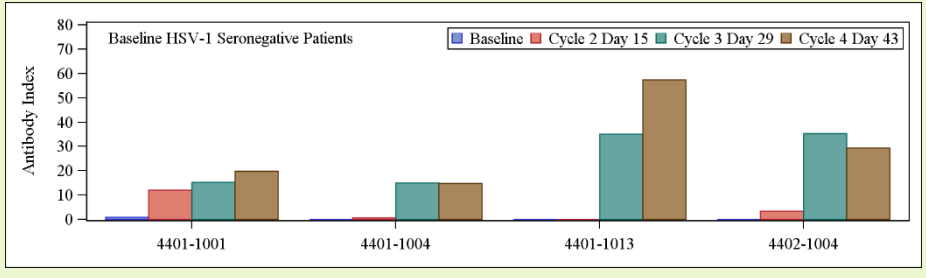
Administration site, volume & method used for each deep expansion cohort patient

Patient #	Tumor type	Injection site	Volume/ injection (range in mL, given up to 8 times)	Imaging guidance used (CT or ultrasound)
1105-1002	Melanoma	Liver	0.5-2.7	CT/Ultrasound
1110-1003	Colorectal	Liver	3.1	CT
1110-1004	Colorectal	Abdomen wall	3.1	CT
1119-1001	Bladder	Lung	0.1-6.0	CT
1119-1002	MSI-H colorectal	Liver	4.0-6.0	CT
4401-1024	Head and Neck	Lung	0.5-3.0	CT
4402-1008	Uveal Melanoma	Liver	10	Ultrasound

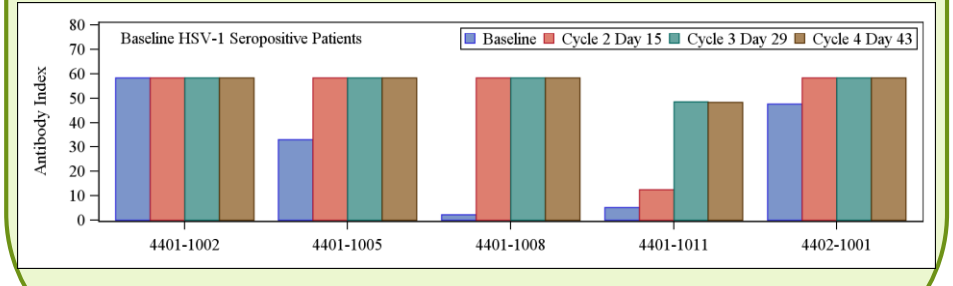
HSV antibody titres – dose rising cohorts

Superficial

HSV-1 Seronegative patients

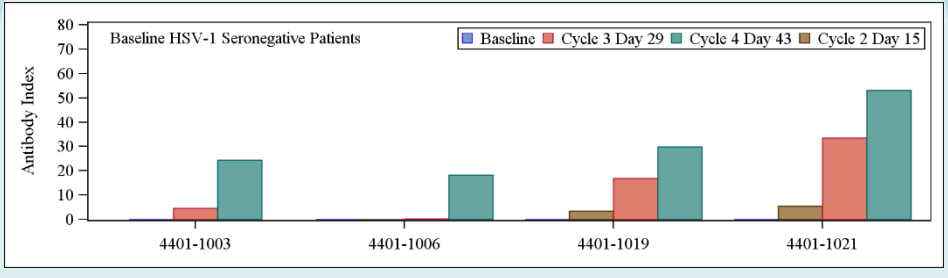


HSV-1 Seropositive patients

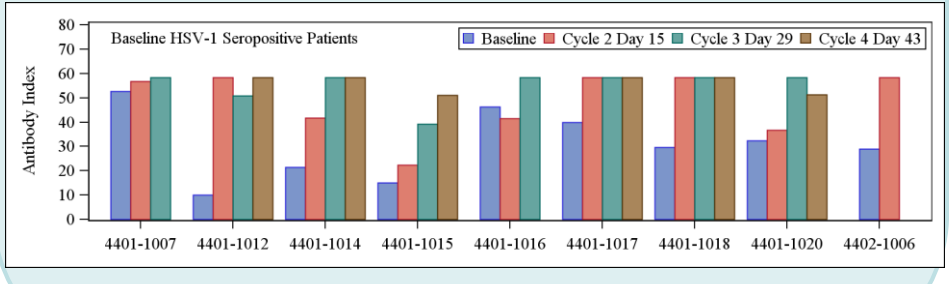


Deep

HSV-1 Seronegative patients



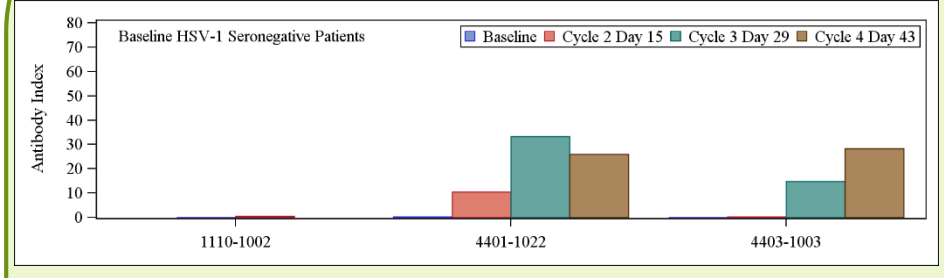
HSV-1 Seropositive patients



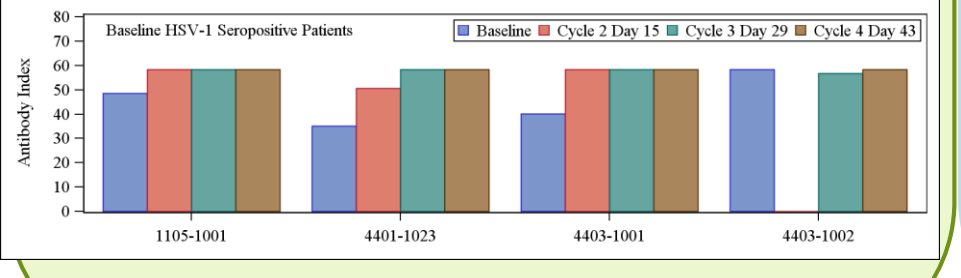
HSV antibody titres – expansion cohorts

Superficial

HSV-1 Seronegative patients



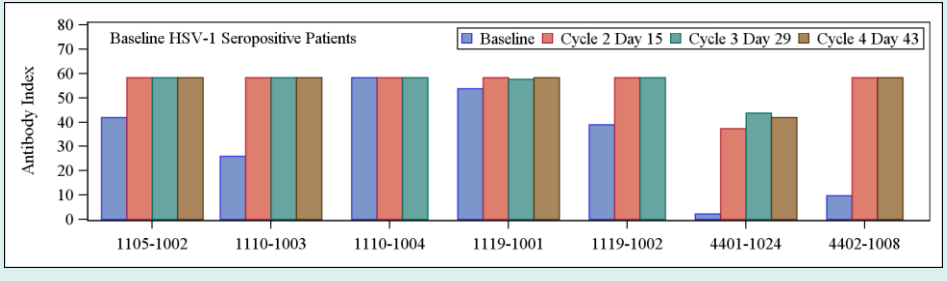
HSV-1 Seropositive patients



Deep

HSV-1 Seronegative patients
(no seronegative patients at baseline)

HSV-1 Seropositive patients



Most biopsies showed extensive necrosis and/or were tumor free

Patient #	Tumor type	Site of tumor for D43* biopsy	Baseline size of tumor for D43 biopsy	Biopsy results**
4403-1001	Uveal melanoma	Skin		D43: No evidence of melanoma. C6: No evidence of melanoma.
4403-1002	CSCC	Scalp	6.3cm	D43: Heavy chronic inflammatory infiltrate. Small foci of atypical epithelium suspicious for SCC. July 2019: 2 biopsies from last palpable area tumor free (confirmed CR)
4401-1022	Melanoma	Ear, left, behind	2.5cm	Information awaited
1105-1001	Mucosal melanoma	Lymph, right, inguinal	3.0cm	D43: Melanoma with extensive necrosis
4401-1024	Esophageal	Lung	3.1cm	Lesion too soft to inject by C6
1119-1001	Bladder cancer	Lymph node		D43: Tumor present
1110-1003	CRC	Liver	3.2cm	D43: Local pathology not performed
1105-1002	Melanoma	Liver, right, lobe	2.9cm	D43: No evidence of melanoma; Benign liver parenchyma with mild portal inflammation, inc rare pigmented foamy macrophages
4402-1008	Uveal melanoma	Liver	13.4cm	D43: Malignant melanoma
1110-1002	Breast cancer	Supraclavicular node		No biopsy taken (patient discontinued)
1110-1004	Adenocarcinoma of the cecum	Peritoneal mass	3.3cm	Patient refused biopsy
1119-1002	MSI-H CRC		4.6cm	D43: A few viable glands of adenocarcinoma with extensive necrosis, fibrosis & chronic inflammation
4403-1003	Melanoma	Thigh		D43: Necrosis with no obviously viable/intact melanocytes, junctional component with viable melanocytes, moderate to heavy chronic inflammation

* After three doses of RP1 & two doses of nivolumab ** Verbatim from site pathology reports

PD-L1 & CD8 T cell staining summary

Patient #	Tumor type	PD-L1 at baseline	PD-L1 at D43*	Peri and intra-tumoral CD8+ at baseline	Peri and intra-tumoral CD8+** at D43
4403-1001	Uveal melanoma	>5-10%	Skin without defined tumor	2+	Skin without defined tumor, skin without evident tumor, skin without evident tumor (three biopsies)
4403-1002	CSCC	>5-10%, >5-10% (two biopsies)	Skin without definitive tumor	1+, 4+ (two biopsies)	Skin without definitive tumor
4401-1022	Melanoma	**1-5%**	**>10%**	4+	4+
4401-1023	BCC	<1%	<1%	**1+**	**3+**
1105-1001	Mucosal melanoma	1-5%	Tumor is necrotic; limits interpretation	2+	Tumor is necrotic; limits interpretation
4401-1024	Esophageal cancer	**1-5%**	1-5%; **>10%** (two biopsies)	**4+**	4+; **6+** (two biopsies)
1119-1001	Bladder cancer	>10%	>10%	4+	2+
1110-1003	Colorectal cancer	UNK	<1%	UNK	0
1105-1002	Melanoma	>10%	No tumor identified	1+	No tumor identified
4402-1008	Uveal melanoma	**<1%**	**1- 5%**	**3+**	**6+**

IHC & assessment performed by DCL Pathology *After two doses of RP1 & one of nivolumab **Combined peritumoral (0-3+) & intra-tumoral (0-3+) CD8 staining intensity score. UNK = unknown (archival biopsy without tumor). Data from remaining patients awaited

- Quantifiable increases in both PD-L1 and CD8 T cells were seen in three of the ten*** patients for whom IHC results are currently available (although can be seen visually in other patients; see earlier slides)
- Lack of tumor and/or necrosis in 50% of patients prevented assessment and/or quantification

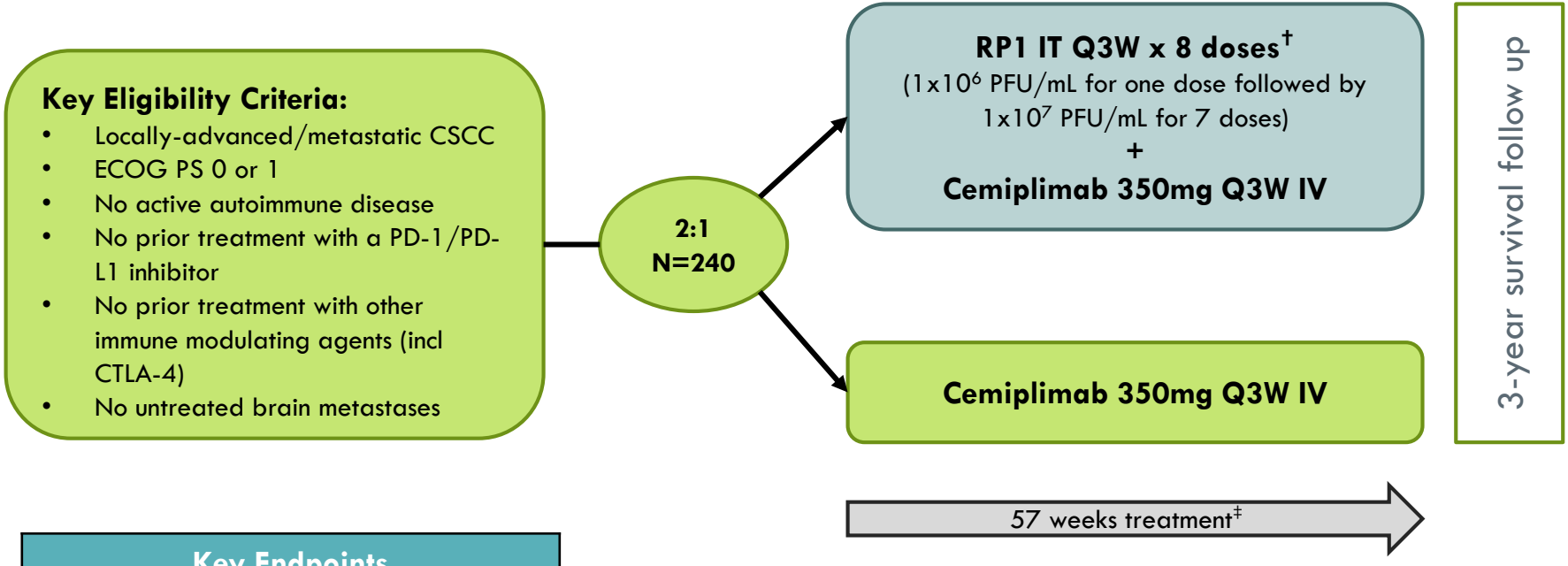
*** Excludes the patient with no baseline data

RP1 induces abscopal anti-tumor effects

Multiple patients showed abscopal (i.e. uninjected) tumor reduction, including:

- Reductions at multiple tumor sites (hilar nodes, liver tumors, bone lesions, lymph nodes) following injection of RP1 into a either a single lung or a single liver tumor up to 5 times (patients 4401-1003, 4401-1018)
- The three patients with visible disease in the dose rising phase saw anti-tumor activity in uninjected lesions (patients 4401-1001, 4401-1008, 4402-1004)
- All the lesions for patient 4403-1002 (CSCC) flattened after only the first dose of RP1, even though only some of the lesions were injected, before ultimately achieving an overall CR
- Patient 4401-1022 (ipilimumab/pembrolizumab refractory cutaneous melanoma) had systemic reduction in lesions (including in lung, mediastinum, peritoneum) following injections to only a lesion behind the ear, leading to PR
- Patient 4402-2001 (chemotherapy refractory CSCC) had reduction in an uninjected tumor in the neck, prior to the addition of nivolumab

Randomized controlled Phase 2 study in CSCC (CERPASS)



Key Endpoints

Primary: ORR (RECIST v1.1)
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

Phase 1b clinical trial in solid organ transplant recipients with CSCC

Key Eligibility Criteria:

- Locally-advanced/metastatic CSCC
- ECOG PS 0 or 1
- Renal or hepatic organ allograft recipients on stable immunosuppressive regimen for ≥12 mos
- No prior systemic anti-cancer treatment for CSCC
- No transplant-related viral infections (such as BK, EBV, CMV) within 3 months
- No untreated brain metastases

RP1 IT Q2W x 26 doses
($1x10^6$ PFU/mL for one dose followed by $1x10^7$ PFU/mL)

50 weeks treatment

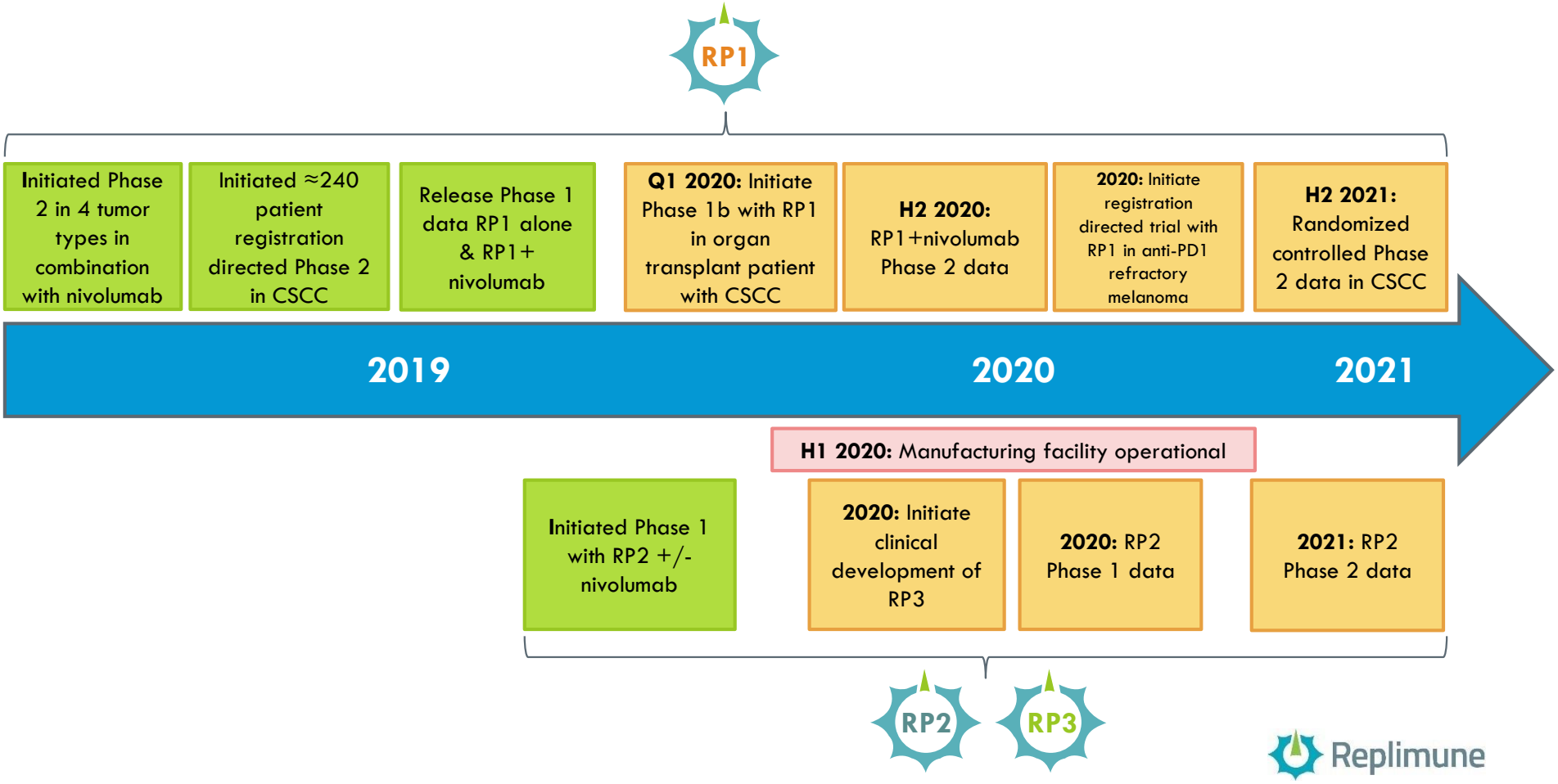
3-year survival follow up

Key Endpoints

Primary: Safety and tolerability
Secondary: ORR (RECIST v1.1), DOR, Disease-Free Survival, incidence/severity of graft rejection

Replimune

Replimune's key target milestones

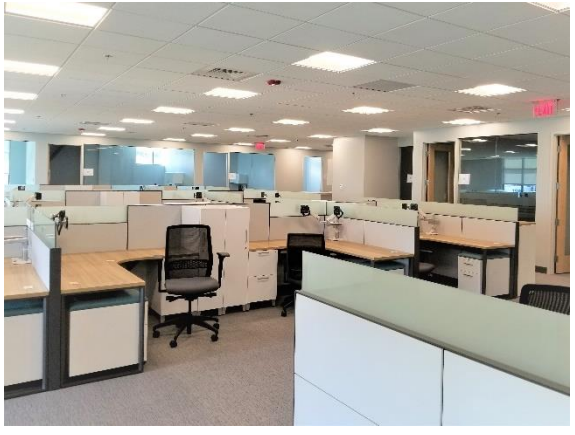


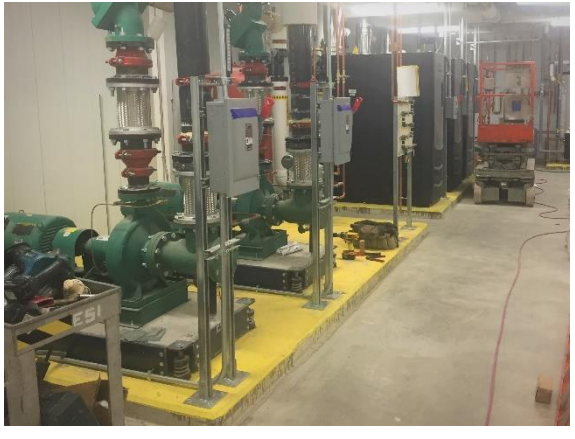
Replimune

Replimune's critical focus on manufacturing

- Product candidates currently manufactured by a CMO for ongoing clinical development
- For later stage development & commercialization, in-house manufacturing is preferable
- The team has extensive manufacturing experience
- 63,000 ft^2 manufacturing facility leased in July 2018 in Framingham, MA, appropriate for multi-product production – intended to include translational biomarker lab
- Of sufficient scale to cover full global commercialization of Replimune's products
- Expected to be on-line to produce clinical product in H1 2020

Reception, offices & utilities





Production areas